GUANIDINE COMPOUNDS AND USE THEREOF AS BINDING PARTNERS FOR 5-HT5 RECEPTORS

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Appl. No.: 15/332,744
Filed: Oct. 24, 2016

Related U.S. Application Data
Division of application No. 13/683,296, filed on Nov. 21, 2012, now Pat. No. 9,475,782, which is a continuation of application No. 13/021,336, filed on Feb. 4, 2011, now Pat. No. 8,481,576, which is a division of application No. 10/590,265, filed on Jun. 14, 2007, now Pat. No. 8,431,604, filed as application No. PCT/EP2005/001521 on Feb. 15, 2005.

Foreign Application Priority Data
Feb. 19, 2004 (DE) 102004008141.7

Publication Classification
Int. Cl.
C07D 277/48 (2006.01)
C07D 277/82 (2006.01)

The present invention relates to guanidine compounds of the general formula I

\[
\text{R}^1 \text{N} = \text{R}^2 \text{N} = \text{R}^3 \text{W}
\]

corresponding enantiomeric, diastereomeric and/or tautomeric forms thereof as well as pharmaceutically acceptable salts thereof. The present compound further relates to the use of guanidine compounds as binding partners for 5-HT5 receptors for the treatment of diseases which are modulated by a 5-HT5 receptor activity, in particular for the treatment of neurodegenerative and neuropsychiatric disorders as well as the associated signs, symptoms and dysfunctions.
GUANIDINE COMPOUNDS AND USE THEREOF AS BINDING PARTNERS FOR 5-HT5 RECEPTORS

FIELD OF THE INVENTION

[0001] The present invention relates to guanidine compounds and the use of guanidine compounds as binding partners for 5-HT5 receptors for the treatment of diseases that are modulated by a 5-HT5 receptor activity, in particular for the treatment of neurodegenerative and neuropsychiatric disorders as well as the signs, symptoms and dysfunctions associated therewith.

BACKGROUND OF THE INVENTION

[0002] At least seven different receptor classes mediate the physiological activities which are attributed to an involvement of the neurotransmitter serotonin (5-hydroxytryptamine, or 5-HT for short). They are designated according to an internationally recognized classification as 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6 and 5-HT7. The majority of these classes additionally include further distinguishable receptor sub-types. For example, receptors belonging to the 5-HT1 class can be further subdivided in at least five sub-classes and are termed 5-HT1A, 5-HT1B, 5-HT1C, 5-HT1D and 5-HT1E (Boess, Martin; Neuropharmacology 33:275-317 (1994)).

[0003] The 5-HT5-class was first described by Plassat et al., The EMBO Journal Bd. 11 Nr. 13, S. 4779-4786 (1992). One distinguishes between 5-HT5A and 5-HT5B receptors (Erlander et al., Proc. Natl. Acad. Sci. USA 90:3452-3456 (1993). There exists only minimal sequence homology between 5-HT5 and other 5-HT receptors, and the pharmacological profile of these receptors is markedly different. 5-HT5 receptors can be localized with the help of molecular biological techniques in the olfactory bulb, in the hippocampus, in the cortex, in the cerebral ventricles, in the corpus callosum and in the cerebellum. It was shown by immunohistochemical methods that 5-HT5 receptors are expressed in different regions of the brain (Oliver et al. Brain Res 2000, 867, 131-142; Pasqualetti et al. Mol Brain Res 1998, 56, 1-8)). These 5-HT5 receptors can on the one hand modulate functions of the brain directly or indirectly, but on the other hand they may also participate in mechanisms involved in neuropathological, neurodegenerative and neuropsychiatric diseases. 5-HT5 receptors were also localized in astrocytes (Carron et al., GLIA 17:317-326 (1996)). Astrocytes lie directly on the basal membrane of brain capillaries of the blood brain barrier and an abnormal astrocyte-endothelium-structure is associated with a loss of the blood brain barrier. The exact significance of astrocytes is unclear, but they seem to assume transport roles and connective functions. Reactive astrocytes were observed in connection with reactive gliosis in a series of pathological brain changes and neuropsychiatric diseases. These astrocytes modify their morphology as a result of brain injuries. The protein expression pattern changes and growth factors are produced. In-vitro studies on cultivated astrocytes showed 5-HT5 receptor mediated responses. For this reason, it is on the one hand assumed that the 5-HT5 receptor plays a role in recovery processes of the brain after disorders; on the other hand, it cannot be excluded that they contribute to the development of damage or even to an augmentation of damage.

[0004] Diseases of the CNS currently affect large sections of the population. The numbers of patients are continually rising, especially due to the increase of older people. Neuropathological conditions such as cerebral ischemia, stroke, epilepsy and seizures in general, chronic schizophrenia, other psychotic diseases, depression, states of anxiety, bipolar disorders, dementia, in particular Alzheimer dementia, demyelinating diseases, in particular multiple sclerosis, and brain tumors, lead to damage of the brain and to the neuronal deficits associated therewith. Up to now, therapeutic treatments of the neurodegenerative and neuropsychiatric disorders described have been directed to different membrane receptors with the goal of compensating deficits in neurotransmission processes. Neuroprotective effects with different serotoninergic compounds have been achieved in animal models for neuropathological conditions such as ischemia, stroke and excitotoxicity; in some cases beneficial effects on mood disorders, such as depression or states of anxiety, could be observed. For example 5-HT1A agonists such as buspiron, or the compound 8-hydroxy-2-(di-n-propylamino)tetraine (8-OH-DPAT), characterized as a selective 5-HT1A receptor-ligand, are noteworthy in this regard. However, these agents alleviate the neurological deficits described only under certain conditions; an effective therapy for these diseases does not yet exist at the present time.

[0005] A further neuropathological disease affecting large segments of the population, is migraine. In most cases, migraine manifests itself in recurring headaches, affecting an estimated 8 million people, i.e. 3-5% of all children, 7% of all men and 14% of all women. Although a genetic predisposition is propagated, the causes seem to be complex. (Diener H. C. et al., Arzneimitteltherapie 15:387-394 (1997)). Two hypotheses dominate. The vessel theory, known for a long time, suggests a dilation process of the inner and outer cerebral vessel system as a cause. The neurogenic theory is based on a release of vasoactive neurotransmitters, primarily neuropeptides, such as substance P and neuropepfin from axons of the vasculature, as a result of a stimulation of certain ganglia which innervate brain tissue, which supposedly leads to inflammatory reactions and thus to pain.

[0006] A causal therapy for the treatment of migraines does not yet exist at the present time. Two different treatment methods are currently employed: a first, prophylactic therapy for the prevention of recurning migraine attacks and a second, symptomatic therapy for suppressing acute symptoms during attacks. Migraine-specific agents such as Sumigran®, Noceront®, Desenil® and Vidor®, as well as other agents typically used for other indications, such as beta-blockers, anti-ematic agents such as Sibulium®, anti-depressives such as Laroxyl®, or anti-epileptic agents such as Depakin®, are prophylactically administered. In the context of acute therapy, one gives analgesics, such as Aspirin®, Paracetamol®or Opatilidon®, non-steroidal anti-inflammatory agents, such as Cebulic®, Voltaren®, Buften®, Ponstyl®, Profenid®, Aprumax® and Naprosin® against the pain and inflammation, ergotalkoids, such as ergotamine, dihydroergotamine, which can trigger a vasoconstriction, or substances of the triptan-family, such as sumatriptan, Narumig®, and AscoTop® with high affinity for 5-HT1D receptors. The latter substances function as agonists and block vasodilation.

[0007] The agents described are however not optimally suited for the treatment of migraines. Non-opioid analgesics often have side effects. The complex mode of action of
ergotalkaloids leads to side effects such as hypertension and gangrene due to the strong peripheral vasoconstriction. Compounds belonging to the triptan-family also are not completely satisfactory in their function. (Pfaffenrath V. Münch. Med. Wschr. 625-626 (1998)).

[0008] The use of 5-HT3 receptor ligands in general for the treatment of migraines and other cerebralvacular diseases, is described in WO 00/041472, and in WO 00/041696 for the treatment of neurodegenerative and neuropsychiatric diseases.

[0009] Guanidine compounds have not been used as 5-HT3 ligands up to now.

[0010] Substituted guanidines are generally known as H2-antagonists, as inhibitors of the H4K+/ATPase, inhibitors of the secretion of stomach acid, and in these capacities as a means for treating PUD-syndrome (Peptic Ulcer Disease). The most diversely substituted thiazole-guanidines are generally described in the literature as compounds with anti-viral, bacterioidal, anti-microbial and/or anti-inflammatory affect, as protease-inhibitors or vitronectin-antagonists.


SUMMARY OF THE INVENTION

[0015] The aim of the present invention is to provide compounds enabling the treatment of neuropathological, neuropsychiatric and neurodegenerative disorders with sufficient efficacy and low side-effects.

[0016] It was surprisingly found that substances of the general formula I or IA function as ligands of the 5-HT5 receptors, and a treatment of the above-described disease states associated therewith, as well as the symptoms and dysfunctions associated therewith, is thereby made possible.

[0017] The present invention therefore relates to a guanidine compound of the general formula I corresponding enantiomeric, diastereomeric and/or tautomer forms thereof, as well as pharmaceutically acceptable salts thereof, wherein the given moieties have the following definitions:

**W**:

[0019] a moiety of the general formula W1 or W2

**[0018]**

**[0019]**

**[0020]**

**[0021]**

**[0022]**

**[0023]**

wherein

C7-C7-alkyl, C7-C7-alkenyl, C7-C7-alkynyl, C7-C7-cycloalkyl, C7-C7-cycloalkene-
heterocyclo-alkyl, aryl, hetaryl, heterocycloalkyl, C_{1-2}C_{1-2}alkylene-hetaryl or C_{1-2}alkylenearyl, or
0024 or
0025 O—R_{3}^{1}, CO—R_{3}^{1}, S—R_{3}^{1}, SO—R_{3}^{1}, CO—O—R_{3}^{1}, NR_{3}^{1}—CO—O—R_{3}^{1}, O—CH=N—COO—
0026 R_{3}^{1}, NR_{3}^{1}—R_{3}^{1}, CONH, SO_{1-2}NH, NR_{3}^{1}—CO—
0027 each optionally substituted C_{1-2}alkyl, C_{1-2}alkenyl, C_{1-2}alkynyl, C_{1-2}C_{1-2}alkylene—C_{1-2}C_{1-2}alkylene—C_{1-2}C_{1-2}alkylene—hetarcylo—alkyl, aryl, heterocyclo—aryl, C_{1-2}alkylene—hetarcylo—alkyl, C_{1-2}alkylene—hetarcylo—aryl, 0028 or C_{1-2}alkylene—hetarcylo—hetarcylo—alkyl, hydrogen, OH, CN, or
0029 or each optionally substituted C_{1-2}alkyl, C_{1-2}alkenyl, C_{1-2}alkynyl, C_{1-2}alkylene—C_{1-2}alkylene—C_{1-2}C_{1-2}alkylene—hetarcylo—alkyl, aryl, heterocyclo—alkyl, C_{1-2}C_{1-2}alkylene—hetarcylo—hetarcylo—alkyl, CO—C_{1-2}alkyl, CO—hetacylo—alkyl, CO—C_{1-2}C_{1-2}alkylene—hetarcylo—hetarcylo—alkyl, CO—O—C_{1-2}alkyl, CO—O—hetacylo—alkyl, CO—O—C_{1-2}C_{1-2}alkylene—hetarcylo—hetarcylo—alkyl, SO_{2—C_{1-2}alkylene—hetarcylo—hetarcylo—alkyl, SO_{2—C_{1-2}alkylene—hetarcylo—hetarcylo—alkyl,}
0031 or
0032 or the moieties R_{3}^{2} and R_{3}^{4} form, together with the nitrogen, a 3 to 7-membered, optionally substituted, saturated or aromatic heterocycle, which may contain one, two or three further different or identical heteroatoms from the group O, N, S, wherein optionally two substituted moieties on this heterocycle can together form an anellated, saturated, or unsaturated carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S, and wherein the so-formed cycle can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;
0033 or
0034 R_{3}^{2}:
0035 hydrogen, or
0036 or each optionally substituted C_{1-2}alkyl, C_{1-2}C_{1-2}alkylene—C_{1-2}C_{1-2}alkylene—C_{1-2}alkylene—C_{1-2}alkylene—hetarcylo—alkyl, CO—C_{1-2}alkyl, CO—O—C_{1-2}alkyl, CO—O—C_{1-2}C_{1-2}alkylene—hetarcylo—hetarcylo—alkyl, CO—O—C_{1-2}C_{1-2}alkylene—hetarcylo—hetarcylo—alkyl, or
0037 B: hydrogen or as moiety A is defined,
0038 or each independently of one another, two of the moieties A, B or R_{3}^{2}, together form a 3 to 7-membered, optionally substituted, saturated or unsaturated carbocycle or an optionally substituted, saturated or unsaturated or aromatic heterocycle which may contain one, two or three further different or identical heteroatoms from the group O, N, S, wherein optionally two moieties substituted on this carbocycle or heterocycle may together form an anellated, saturated, or unsaturated carbocycle or heterocycle, wherein the heterocycle may contain up to three different or identical heteroatoms O, N, S, and wherein the formed cycle can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;
0039
0040 R_{3}^{2}:
0041 hydrogen, OH, halogen, NO_{2}, NH_{2}, CN, CF_{3}, CHF_{3}, O—CF_{3}, O—CHF_{2},
0042 or
0043 each optionally substituted C_{1-2}alkyl, C_{1-2}C_{1-2}alkylene—C_{1-2}C_{1-2}alkylene—hetarcylo—alkyl, CO—C_{1-2}alkyl, CO—hetacylo—alkyl, CO—O—C_{1-2}C_{1-2}alkylene—hetarcylo—hetarcylo—alkyl, SO_{2—C_{1-2}alkylene—hetarcylo—hetarcylo—alkyl,}
0044 or moiety A is defined;
0045 as
0046 Z: a moiety of the general formula Z1
0047 with the indices
0048
0049 a=0-4
0050 b=0, 1
0051 c=0-4
0052 wherein the sum of a, b and c is at least 1 and no more than 5;
0053 R_{2}^{1}, R_{2}^{2}, R_{2}^{3}, R_{2}^{4}, R_{2}^{5}, R_{2}^{6}, R_{2}^{7}, R_{2}^{8} independently of one another:
0054 hydrogen, OH, or
0055 each optionally substituted C_{1-2}alkyl, C_{1-2}C_{1-2}alkylene—C_{1-2}C_{1-2}alkylene—hetarcylo—alkyl, CO—C_{1-2}alkyl, CO—hetacylo—alkyl, or
0056 each independently of one another, two moieties are R_{2}^{1} and R_{2}^{2} or R_{2}^{3} and R_{2}^{4} together form a 3 to 7-membered, optionally substituted, saturated or unsaturated carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms from the group O, N or S;
0057 V_{2}:
0058 or
0059 CO—CO—NR_{5}^{5}, NR_{5}^{5}, CO—
0060 or
0061 S—SO_{2}, S—SO_{2}, S—SO_{2}, S—SO_{2},
0062 or
0063 or
0064 or
0065 or
0066 or
0067 or
0068 or
0069 or
0070 or
0071 or
0072 or
0073 or
0074 or
0075 or
0076 or
0077 or
0078 or
0079 or
0080 or
0081 or
0082 or
0083 or
0084 or
0085 or
0086 or
0087 or
0088 or
0089 or
0090 or
0091 or
0092 or
0093 or
0094 or
0095 or
0096 or
0097 or
[0059] R₂¹, R₂² independently of one another:

[0060] hydrogen or


[0062] R₂³, R₂⁴ independently of one another:

[0063] hydrogen, OH or


[0065] R³¹, R³², R³³ independently of one another:

[0066] hydrogen, OH, CN, or


[0068] each independently from the third moiety, two moieties of R³¹, R³² or R³³ together form a 5 to 7-membered, optionally substituted, saturated or unsaturated carbocycle or an optionally substituted, saturated or unsaturated heterocycle, which can contain one, two or three further different or identical heteroatoms from the group O, N, S, wherein optionally two moieties substituted on this carbo- or heterocycle together form an annelated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S, and wherein the cycle formed can optionally be substituted or a further optionally substituted cycle can be condensed onto this cycle;

[0069] Q:

[0070] a doubly substituted 5-membered hetaryl-moiety, chosen from Q1 to Q7

[0071] E: O, N—R₁¹ or S;

[0072] R₁¹:

[0073] hydrogen or


[0075] R³¹, R³² each independently of one another a moiety chosen from the groups 1.), 2.), 3.), 4.), 5.), 6.) or 7.);

[0076] 1.) hydrogen, halogen, CN, CF₃, CHF₂, or


[0078] 2.) Phenyl or napthyl, which are each substituted with R₂², R₂³ and R₂⁴,

[0079] wherein

[0080] R₂², R₂³ and R₂⁴ each independently of one another represent a substituent from the following group:

[0081] hydrogen, NO₂, NH₂, OH, CN, CF₃, CHF₂, OCF₃, OCTH₂, COOH, O—CH₂—COOH, SH, halogen, or
[0082] each optionally substituted aryl, hetaryl, heterocycloalkyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-5}-alkynyl, C_{2-6}-cycloalkyl, C_{1-6}-alkylene-C_{2-5}-cycloalkyl, C_{1-6}-alkylene-heterocycloalkyl, C_{1-6}-alkylene-aryl or C_{1-6}-alkylene-hetaryl, or

[0083] \text{O—R_4^5 \text{S—R}_2^5 \text{NR}_2^7 \text{R}_2^8, CO—OR_2^6, NR_2^7 \text{CO—OR}_2^6, CO—O—R_2^6, CO—OH, CO—SO_2^5, CO—SO_2^6, NR_2^7 \text{CO—O—R}_2^6, SO_2^—R_2^7, NR_2^7 \text{SO}—R_2^6, SO_2^—NR_2^7 \text{R}_2^8, CO—NR_2^7 \text{R}_2^8 \text{or CO—NR}_2^7 \text{R}_2^8, or}

[0084] two of the moieties R_2^2, R_2^3 or R_2^4 together form a 3 to 7-membered, optionally substituted, saturated, unsaturated or aromatic carbocycle or an optionally substituted, saturated, unsaturated aromatic heterocycle, which can contain up to three further different or identical heteroatoms O, N, S, and optionally two moieties substituted on this heterocycle can form an annelated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S, and the formed cycle can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

[0085] R_2^2 each optionally substituted C_{1-6}-alkenyl, C_{1-6}-alkynyl, C_{1-6}-alkylene-C_{1-6}-cycloalkyl, C_{1-6}-alkylene-heterocycloalkyl, heterecycloalkyl or hetaryl, or

[0086] C_{1-6}-alkyl, which is optionally substituted with a substituent from the group consisting of halogen, NO_2, NH_2, OH, CN, CF_3, CHF_3, OFC_3, OCHF_2, NH—(C_{1-6}-alkyl) and N(C_{1-6}-alkyl)_2;

[0087] R_2^3 each optionally substituted C_{1-6}-alkeny, C_{1-6}-alkynyl, C_{1-6}-alkylene-C_{1-6}-cycloalkyl, C_{1-6}-alkylene-heterocycloalkyl, heterecycloalkyl, or hetaryl; or

[0088] R_2^4 hydrogen, OH, CN, or

[0089] each optionally substituted C_{1-6}-alkenyl, C_{1-6}-alkynyl, C_{1-6}-cycloalkyl, C_{1-6}-alkylene-C_{1-6}-cycloalkyl, C_{1-6}-alkylene-heterocycloalkyl, ary, hetaryl, heterocycloalkyl, C_{1-6}-alkylene-O—C_{1-6}-alkyl, CO—C_{1-6}-alkenyl, C_{1-6}-alkylene-aryl, C_{1-6}-alkylene-hetaryl, CO—aryl, CO—hetaryl, CO—C_{1-6}-alkylene-aryl, CO—C_{1-6}-alkylene-hetaryl, CO—O—C_{1-6}-alkenyl, CO—O—aryl, CO—O—C_{1-6}-alkylene-aryl, CO—O—hetaryl, CO—O—C_{1-6}-alkylene-hetaryl, SO_2—C_{1-6}-alkenyl, SO_2—aryl, SO_2—hetaryl, SO_2—C_{1-6}-alkylene-aryl or SO_2—C_{1-6}-alkylene-hetaryl;

[0090] R_2^5 hydrogen or

[0091] each optionally substituted C_{1-6}-alkenyl, C_{1-6}-alkynyl, C_{1-6}-cycloalkyl, C_{1-6}-alkylene-C_{1-6}-cycloalkyl, C_{1-6}-alkylene-heterocycloalkyl, ary, hetaryl, heterocycloalkyl, C_{1-6}-alkylene-O—C_{1-6}-alkyl, CO—C_{1-6}-alkenyl, C_{1-6}-alkylene-aryl, C_{1-6}-alkylene-hetaryl, CO—aryl, CO—hetaryl, CO—C_{1-6}-alkylene-aryl, CO—C_{1-6}-alkylene-hetaryl, CO—O—C_{1-6}-alkenyl, CO—O—aryl, CO—O—C_{1-6}-alkylene-aryl, CO—O—hetaryl, CO—O—C_{1-6}-alkylene-hetaryl, SO_2—C_{1-6}-alkenyl, SO_2—aryl, SO_2—hetaryl, SO_2—C_{1-6}-alkylene-aryl or SO_2—C_{1-6}-alkylene-hetaryl, SO_2—C_{1-6}-alkenyl, SO_2—aryl, SO_2—hetaryl, SO_2—C_{1-6}-alkylene-aryl or SO_2—C_{1-6}-alkylene-hetaryl; or

[0092] the moieties R_2^7 and R_2^8 form, together with the nitrogen, a 3 to 7-membered, optionally substituted, saturated or aromatic heterocycle, which can contain one, two or three further different or identical heteroatoms O, N, S; and optionally two moieties substituted on this heterocycle can form an annelated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S, and the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

[0093] 3) a 5- or 6-membered hetaryl moiety, optionally substituted with 1 or 2 substituents, from the group consisting of:

[0094] 2-pyrolol, 3-pyrrolol, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 3-oxazolyl, 5-oxazolyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 6-pyrimidyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, thiadiazolyl, oxadiazolyl or triazinyl or their annelated derivatives indazolyl, benzothio phenyl, benzofuranyl, indoliny, benzimidazolyl, benzthiazolyl, benzoxazolyl, chinoliny and isochinoliny; or

[0095] 2-thienyl or 3-thienyl optionally substituted with one or two substituents,

[0096] wherein the substituents are chosen from the group consisting of halogen, NO_2, NH_2, OH, CN, CF_3, OFC_3, OCHF_2, O—CHF_2, C_{1-6}-alkenyl, C_{1-6}-alkenyl, NH—(C_{1-6}-alkenyl) and N(C_{1-6}-alkenyl)_2;

[0097] 4) both moieties R^4 and R^3 together form a 4 to 7-membered, optionally substituted, saturated or unsaturated or aromatic carbocycle or a 5- or 6-membered optionally substituted, saturated or unsaturated or aromatic heterocycle, which can contain up to three further different or identical heteroatoms O, N, S, and which can be substituted with up to two further moieties, wherein optionally two moieties substituted on this carbo- or heterocycle can together form an annelated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S and wherein the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

[0098] 5) a C_{3-5}-bi or tricyclic, saturated hydrocarbon moiety;

[0099] 6) each optionally substituted C_{1-6}-alkyl-NH_2, C_{1-6}-alkyl-NR_2^7, NR_2^7 C_{1-6}-alkyl-CO—NR_2^7, C_{1-6}-alkyl-CO—NR_2^7 R_2^8, C_{1-6}-alkyl-CO—NH_2, C_{1-6}-alkyl-CO—SO_2^5 NH_2, CO—NH_2, CO—NR_2^7 R_2^8, SO_2^—NH_2, SO_2^—NR_2^7 R_2^8, NR_2^7 R_2^8;

[0100] 7) a 4-7-membered mono- or bicyclic saturated or unsaturated heterocycle, which can contain up to two different or identical heteroatoms from the
The patent describes the invention of guanidine compounds of the formula (I), wherein a moiety W can be multiply substituted. The compounds can be saturated or aromatic heterocycles, and can contain one, two, or three different or identical heteroatoms O, N, S, or CH. Each compound can be optionally substituted with a moiety W1 or W2, which can be alkyl, alkenyl, or aryl. The compounds can form a saturated or unsaturated carbonyl or aromatic heterocycle, containing up to three different or identical heteroatoms O, N, S, or CH. Each compound can be optionally substituted or further, optionally substituted cycle can be condensed onto this cycle.

The patent also describes the invention of guanidine compounds of the formula (II), wherein D can be hydrogen or another moiety A. These compounds can be optionally substituted with a moiety Z, which can be alkyl, alkenyl, or aryl. The compounds can form a saturated or unsaturated carbonyl or aromatic heterocycle, containing up to three different or identical heteroatoms O, N, S, or CH. Each compound can be optionally substituted or further, optionally substituted cycle can be condensed onto this cycle.

The patent also describes the invention of guanidine compounds of the formula (III), wherein Z1 can be alkyl, alkenyl, or aryl. These compounds can be optionally substituted with a moiety Z, which can be alkyl, alkenyl, or aryl. The compounds can form a saturated or unsaturated carbonyl or aromatic heterocycle, containing up to three different or identical heteroatoms O, N, S, or CH. Each compound can be optionally substituted or further, optionally substituted cycle can be condensed onto this cycle.
R'1, R'2, R'3, R'4 independently of one another:

hydrogen, halogen, OH, or

each optionally substituted C1-C6-alkyl, C1-C6-alkenyl, C1-C6-alkynyl, C1-C6-alkylene-C5-C5-cycloalkyl, C5-C5-cycloalkyl, aryl, C1-C6-alkylene-aryl, or C1-C6-alkylene-hetaryl, or

each independently of one another two moieties R'1 and R'2 or R'3 and R'4 together form a 3 to 7-membered, optionally substituted, saturated or unsaturated carbocycle or heterocycle, wherein the heterocycle can contain up to three heteroatoms of the group O, N, or S;

V

CO, CO-NR, NO, NR-CO, O, -S-, SO, -SO2, -SO3

NR, NO, SO2, CS, CS-NR, -NR-CO, -CO-NR, -NR-

Q: a doubly substituted 5-membered hetaryl-moiety, chosen from Q1 to Q6

R'2, R'5 independently of one another:

hydrogen or

each optionally substituted C1-C6-alkyl, C1-C6-alkylene-O-C1-C6-alkyl, C2-C6-alkenyl, C2-C6-alkenyl, CO-C1-C6-alkyl, CO-O-C1-C6-alkyl, SO2-C1-C6-alkyl, C1-C6-alkylene-aryl, C1-C6-cycloalkyl, aryl, C1-C6-alkylene-aryl, aryl or C1-C6-alkylene-hetaryl,

R', R2, R3 independently of one another:

hydrogen, OH or

each optionally substituted C1-C6-alkyl, C1-C6-alkenyl, C1-C6-alkenyl, C1-C6-alkylene-C1-C6-cycloalkyl, C1-C6-cycloalkyl, aryl, C1-C6-alkylene-aryl, or C1-C6-alkylene-hetaryl,

R', R2, R3 independently of one another:

hydrogen, OH, CN, or

each optionally substituted C1-C6-alkyl, C1-C6-alkenyl, C1-C6-alkenyl, C1-C6-cycloalkyl, aryl, C1-C6-alkylene-aryl, C1-C6-cycloalkyl, aryl, C1-C6-alkylene-aryl, or C1-C6-alkylene-hetaryl,

E, O, N—R'2 or S;

hydrogen, or

each optionally substituted C1-C6-alkyl, C1-C6-alkenyl, C1-C6-alkenyl, C1-C6-cycloalkyl, aryl, C1-C6-alkylene-aryl, C1-C6-cycloalkyl, aryl, C1-C6-alkylene-aryl, or C1-C6-alkylene-hetaryl,

R', R5 each independently from one another 9 moieties chosen from the groups 1), 2), 3), 4) or 5):

hydrogen, halogen, CN, CF3, CHF2, or

each optionally substituted C1-C10-alkyl, C2-C10-alkenyl, C2-C10-alkenyl, C2-C10-cycloalkyl, C1-C6-alkylene-C1-C6-cycloalkyl, C1-C6-alkylene-aryl, C1-C6-alkylene-hetaryl,
C_{1-6}alkylene-O—C_{1-6}alkyl, C_{1-6}alkylene-O-aryl, COO—C_{1-6}alkyl or C_{1-6}alkylene-

SO_{2—C_{1-6}alkyl, SO_{2—C_{1-6}alkylene-aryl or SO_{2—C_{1-6}alkylene-hetaryl;}}

[0170] R^6 each optionally substituted C_{1-6}alkyl, C_{5-10}alkenyl, C_{5-10}alkyl, C_{3-6}cy-

cloalkyl, C_{1-6}alkylene-C_{3-6}alkyloalkyl, C_{1-6}alkylene-hetarycloalkyl, aryl, hetarya, heterycloalkyl, CO—C_{1-6}alkylene-aryl, CO—C_{1-6}alkylene-hetaryl, CO—C_{1-6}alkylene-aryl, CO—C_{1-6}alkyl, CO—O—C_{1-6}alkylene-aryl, CO—O—hetaryl, CO—O—C_{1-6}alkylene-hetaryl,}

[0171] or the moieties R^2 and R^3 form, together with the nitrogen, a 3 to 7-membered, optionally substituted, saturated or aromatic heterocycle, which can contain one, two or three further different or identical heteroatoms O, N, S; and optionally two moieties substituted on this heterocycle can together form an annelated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S, and the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle:

[0172] 3.) a 5- or 6-membered heteraryl moiety optionally substituted with one or two substituents from the group consisting of:

[0173] 2-pyrol, 3-pyrol, 2-thiazol, 4-thiazol, 5-thiazol, 2-oxazol, 4-oxazol, 5-ox-
azol, 2-pyrimid, 4-pyrimid, 5-pyrimid, 6-pyrimid, 3-pyrazol, 4-pyrazol, 5-pyra-
zol, 3-isothiazol, 4-isothiazol, 5-isothiazol, 2-imidazol, 4-imidazol, 5-imidazol, 3-pyrazin, 4-pyrazin, 5-pyrazin, 6-pyrazin, 3-isoxazol, 4-isoxazol, 5-isox-
azol, thiadiazol, oxadiazol or triazol or their annelated derivatives indazol, benzothio-
phenyl, benzofuranyl, indolyl, benzimidazolyl, benzthiazolyl, benzoazolyl, chinolinyl and iso-
chinolinyl; or

[0174] 2-thienyl or 3-thienyl optionally substituted with 1 or 2 substituents, wherein the substituents are chosen from the group consisting of halogen, NO_{2}, NH_{2}, OH, CN, CF_{3}, CHF_{2}, OCF_{3}, OCHF_{2}, NH—(C_{1-6}alkyl) and (N(C_{1-6}alkyl))

[0176] each optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkyl, C_{3-6}cy-
cloalkyl, C_{1-6}alkylene-aryl, CO—C_{1-6}alkylene-aryl, CO—C_{1-6}alkylene-hetaryl, CO—O—C_{1-6}alkylene-aryl, CO—O—hetaryl, CO—O—C_{1-6}alkylene-hetaryl,
O, N, S and wherein the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

[0176] 5) a C₃-C₁₈-bi- or tricyclic, saturated hydrocarbon.

[0177] Advantageously, the guanidine compounds have moieties with the following definitions:

[0178] W: W₁;

[0179] A: halogen, OH, CN, CF₃, CHF₂, OCF₃, OCHF₂, or each optionally substituted C₁-C₆-alkyl or C₂-C₆-alkenyl, O—CH—COO—R', O—R₁⁴, S—R₄⁰, NR₁⁴R₄⁰, NR₁⁴—CO—R₁⁴ or —CO—NR₁⁴R₄⁰;

[0180] R₁⁴: each optionally substituted C₁-C₆-alkyl, C₅-C₆-cycloalkyl, phenyl or benzyl;

[0181] R₄⁰: hydrogen, or

[0182] each optionally substituted C₁-C₆-alkyl, phenyl, benzyl, phenethyl, CO—C₁-C₆-alkyl, CO-aryl, CO—O—C₁-C₆-alkyl, SO₂—C₁-C₆-alkyl, SO₂-aryl, SO₂-hetaryl or SO₂—C₁-C₆-alkylene-aryl;

[0183] R₃: each optionally substituted C₁-C₆-alkyl, phenyl, benzyl, phenethyl, CO—C₁-C₆-alkyl, CO-aryl, CO—O—C₁-C₆-alkyl, SO₂—C₁-C₆-alkyl, SO₂-aryl, SO₂-hetaryl or SO₂—C₁-C₆-alkylene-aryl;

[0184] or both moieties R₃ and R₄ together form an optionally substituted 5- or 6-membered saturated or unsaturated ring, which can contain up to two identical or different heteroatoms from the group O and N;

[0185] R₈: hydrogen or an optionally substituted C₁-C₆-alkyl moiety;

[0186] B: hydrogen or as moieity A;

[0187] R₈: hydrogen, F, Cl, CN, CF₃, O—CF₃, or

[0188] each optionally substituted C₁-C₆-alkyl, ary1, C₅-C₆-alkylamino or C₁-C₆-dialkylamino;

in the formula Z1 the sum of a, b, c is 1, 2 or 3;

[0189] R₂⁵, R₂⁶, R₂⁷, R₂⁸ independently of one another;

[0190] hydrogen, halogen, OH, optionally substituted C₁-C₆-alkyl;


[0192] R₅⁰: hydrogen, CH₃;

[0193] R₅¹: R₅², R₅³ independently of one another;


[0195] Q is chosen from the group consisting of Q₁, Q₂ and Q₃;

[0196] R₂⁵: hydrogen, optionally substituted C₁-C₆-alkyl, in the aryl moiety optionally substituted benzyl, CO—C₁-C₆-alkyl, optionally substituted benzoyl, SO₂—C₁-C₆-alkyl or in the aryl moiety optionally substituted SO₂-aryl;

[0197] It is still more preferred that the guanidine compounds have moieties with the following definitions:

[0198] A: OH, F, Cl, OCF₃, OCHF₂, optionally substituted C₁-C₆-alkyl, O—C₁-C₆-alkyl or S—C₁-C₆-alkyl;

[0199] B: hydrogen, OH, F, Cl, CF₃, OCF₃, OCHF₂, optionally substituted C₁-C₆-alkyl, O—C₁-C₆-alkyl or S—C₁-C₆-alkyl;

[0200] R₃: hydrogen, F, Cl, CN, CF₃ or O—CF₃;

[0201] Z: each optionally substituted C₁-C₆-alkyl or C₁-C₆-alkylene—O—C₁-C₆-alkyl;

[0202] R₁⁴, R₂⁵, R₂⁶, R₂⁷, R₂⁸ each independently of one another hydrogen, F, CH₃;

[0203] R¹, R², R³ independently of one another:

[0204] hydrogen, OH, CN, O-methyl, O-phenyl, acetyl, benzoyl, O-acetyl, O-benzoyl;

[0205] Q is chosen from the group consisting of

[0206] R₉: hydrogen, CH₃, methanesulfonyl, phenylsulfonyl or tosyl.

[0207] In a further preferred embodiment the guanidine compounds have moieties with the following definitions:

[0208] A: OH, OCF₃, OCH₃, O-ethyl, O-propyl or O-i-propyl;

[0209] Z: —CH₂—, —CH₂—O—, —CH₂—CH₂— or

[0210] two of the moieties R¹, R², or R³, are hydrogen and the third moiety is hydrogen, OH, acetyl or benzoyl;

[0211] Q:

[0212] R₄⁰, R₅⁰, R₆⁰, each independently of one another, represent a moiety chosen from the groups 1), 2), 3), 4) or 5);

[0213] 1) hydrogen, F, CI, CN, CF₃ or

[0214] each optionally substituted C₁-C₆-alkyl, C₁-C₆-alkenyl, C₁-C₆-alkylene—O—C₁-C₆-alkyl or C₁-C₆-cycloalkyl;

[0215] 2) R₁⁴, R₂⁵, R₂⁶ and R₂⁷ independently of one another hydrogen, —CN, —CF₃, —CHF₂, —OCHF₂, —OCH₂F₂, F, Cl, OH or each optionally substituted phenyl or hetaryl, C₁-C₆-alkyl, C₁-C₆-cycloalkyl, O—R₇⁵, NR₅⁰R₆⁰, CO—OR₆⁰, NR₅⁰—CO—O—R₇⁵, O—CH₂—COO—R₇⁵, NR₅⁰—CO—O—R₇⁵, SO₂—R₇⁵, NR₅⁰—SO₂—R₆⁰, NR₅⁰—CO—O—R₆⁰, SO₂—NH₂R₆⁰, CONH₂R₆⁰, SO₂—NR₅⁰R₆⁰ or CO—NR₅⁰R₆⁰;

[0216] C₁-C₆-alkyl, which is optionally substituted with substituents from the group consisting of F, Cl, OH, CN, CF₃, OCF₃, NH—(C₁-C₆-alkyl) and N(C₁-C₆-alkyl);

[0217] R₉, each optionally substituted C₁-C₆-alkyl, aryl, hetaryl or phenyl;
[0218] R^3, hydrogen, each optionally substituted C_C-alkyl, allyl, aryl, hetaryl, benzyl, phenethyl or CH_hetero-
[0219] R^2, each optionally substituted C_C-alkyl, allyl, aryl, hetaryl, benzyl, phenethyl or CH_hetero-
[0220] or R^2 and R^3 form an optionally substituted 3- or 7-membered saturated or unsaturated ring which can contain up to two identical or different heteroatoms from the group O and N;
[0221] 3.) benzothiophenyl, benzo furanyl, chinolinyl or isoquinolinyl;
[0222] 4.) both moieties R^4 and R^5 together form one of the following rings:

![Image]

[0223] wherein R^2 and R^3 are as defined under 2.);
[0224] 5.) adamantyl.
[0225] It is preferred that a moiety from R^4 and R^5 is chosen from group 1 and that the other from R^4 and R^5 is chosen from group 1, 2 or 3.
[0226] The present invention further relates to the use of these guanidine compounds as medicaments as well as pharmaceutical compositions comprising at least one of these guanidine compounds as well as a pharmaceutically acceptable carrier or dilution agent.
[0227] The present invention further relates to the use of these guanidine compounds for the preparation of a medicament for the treatment of diseases, which are modulated by 5-HT_5 receptor activity, as is set out in detail below.
[0228] The present invention further relates to the use of compounds of the general formula 1A for the preparation of 5HT_5 receptor ligands:

![Image]

[0229] Here it is preferred that these compounds for the preparation of guanidine compounds, according to the invention, are used.
[0230] The present invention further relates to the use of a guanidine compound of the general formula IA

![Image]

corresponding enantiomeric, diastereomeric and/or tautomeric forms thereof, as well as pharmaceutically acceptable salts thereof,

wherein the given moieties have the following definitions:
[0231] W:
[0232] a moiety of the general formula W1 or W2

![Image]

[0233] A:
[0234] NO, NH, OH, CN, CF, OCF, CHF, OC=OH, O—CH=COOH, halogen, SH, or
[0235] each optionally substituted C_C-alkenyl, C_C-alkynyl, C_C-alkenoyl, C_C-alkenylene-C_C-alkenoyl or C_C-alkenylene-hetero-cycloalkyl, aryl, hetaryl, heterocyclo-
[0236] C_C-alkyl, C_C-alkenylene-hetaryl or C_C-alkenylene-
[0237] R^4, hydrogen, or
[0238] each optionally substituted C_C-alkenyl, C_C-alkenylene-C_C-alkenoyl, C_C-alkenylene-heterocycloalkyl, aryl, hetaryl, heterocyclo-
[0239] each optionally substituted C_C-alkenyl, C_C-alkenylene-C_C-alkenoyl, C_C-alkenylene-heterocycloalkyl, aryl, hetaryl, heterocyclo-
[0240] hydrogen, OH, CN, or
[0241] each optionally substituted C_C-alkenyl, C_C-alkenyl, C_C-alkenylene-C_C-
[0242] each optionally substituted C_C-alkenyl, C_C-alkenylene-C_C-
[0243] each optionally substituted C_C-alkenyl, C_C-alkenylene-C_C-
[0244] or the moieties R^2 and R^3 form, together with the nitrogen, a 3 to 7-membered, optionally substituted, saturated or aromatic heterocycle, which can contain one, two or three further different or identical heteroatoms from the group O, N, S; wherein optionally two moieties substituted on this heterocycle can together form an unsaturated, satu-
[0245] R^4, hydrogen, or
[0246] each optionally substituted C_C-alkenyl, C_C-alkenylene-C_C-
[0247] each optionally substituted C_C-alkenyl, C_C-alkenylene-C_C-
[0248] each optionally substituted C_C-alkenyl, C_C-alkenylene-C_C-

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C₃-C₁₀-alkynyl, CO—C₃-C₆-alkyl, CO—O—C₁-
C₆-alkyl, SO₂—C₃-C₆-alkyl, C₆-C₇-cycloalkenyl, aryI,
C₆-C₇-cycloalkenyl-aryl, CO—O—aryl, CO—aryl, heptyl, CO-hetaryl or SO₂—C₃-C₄-alkylene-aryl;

[0248] B: hydrogen or as moiety A is defined.

[0249] or each independently of each other, two of the moieties A, B or R₂⁴ together form a 3 to
7-membered, optionally substituted, saturated or unsaturated carbocycle or an optionally substituted,
saturated or unsaturated or aromatic heterocycle, which can contain one, two or three further different
or identical heteroatoms from the group O, N, S; wherein optionally two moieties substituted on this carbo-
or heterocycle can together form an anellated, saturated, unsaturated or aromatic carbocycle or het-
erocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S and
wherein the cycle formed can optionally be substituted or a further, optionally substituted cycle can be
condensed onto this cycle;

[0251] R₂⁴:

[0252] hydrogen, OH, halogen, NO₂, NH₂, CN, CF₃, CHF₂, OCF₃, OCHF₂, or each optionally substituted
C₆-C₇-alkyl, C₆-C₇-cycloalkyl, C₆-C₇-alkylene-O—
C₆-C₇-alkyl, C₆-C₇-alkylene-S—C₆-C₇-alkyl, aryI, heteryl, O—C₆-C₇-alkyl, O—aryI, O-benzyl, C₆-C₇-
alkylimino, C₆-C₇-diaxialamino, pyridinyl, py-
eridinyl, morpholinyl, CO—C₆-C₇-alkyl, SO₂—C₆-
C₇-alkyl, CO—aryl, SO₂—aryl, CO—C₆-C₇-alkylene-
aryl, SO₂—C₆-C₇-alkylene-aryl, COaryl, CONH₁,
CONH—C₆-C₇-alkyl, SO₃NH—C₆-C₇-alkyl, CON
(C₆-C₇-alkyl)₂, SO₃N(C₆-C₇-alkyl)₂, NH—SO₂—
C₆-C₇-alkyl or NH—CO—C₆-C₇-alkyl;

[0253] D:

[0254] as moiety A is defined;

[0255] Z:

[0256] a moiety of the general formula Z₁

[0257] with the indices

[0258] a=0-4

[0259] b=0, 1

[0260] c=0-4

[0261] wherein the sum of a, b and c is no more than

[0262] R₂⁴, R₂⁵, R₂⁶, R₂⁷ independently of one another:

[0263] hydrogen, halogen, OH, or

[0264] each optionally substituted C₆-C₇-alkyl, C₆-C₇-alkenyI, C₆-C₇-alkenyI, C₆-C₇-cycloalkenyl-C₆-
cycloalkenyl, C₆-C₇-cycloalkenyl, aryI, C₆-C₇-cyclo-
alkyI, heptyl or C₆-C₇-alkylene-heptyl, or

[0265] each independently of one another, two moieties R₂⁴ and R₂⁵ or R₂⁶ and R₂⁷ together form a 3 to
7-membered, optionally substituted, saturated or unsaturated carbo- or heterocycle, which can contain
up to three heteroatoms from the group O, N or S;

[0266] V₂⁵:

[0267] CO—, CO—NR₅—, NR₅—CO—,

[0268] O—, S—, SO₂—, SO₃—NR₅—,

[0269] NR₅—SO₂—, CS—, CS—O—, OCS—,

[0270] CO—, CO—, ethylene, or

[0271] R₂⁵, R₂⁶, R₂⁷ independently of one another:

[0272] hydrogen, OH, or

[0273] each optionally substituted C₆-C₇-alkyl, C₆-C₇-alkenyI, C₆-C₇-alkenyI, C₆-C₇-cycloalkenyl-C₆-
cycloalkenyl, C₆-C₇-cycloalkenyl, aryI, C₆-C₇-cyclo-
alkyI, aryI, C₆-C₇-alkylene-aryl, CO—O—C₆-C₇-alkylene-aryl, CO—C₆-C₇-alkylene-aryl, COaryl, SO₂—
aryl, heteryl, CO-hetaryl or SO₂—C₃-C₄-alkylene-aryl;

[0274] R₂⁴, R₂⁵, R₂⁶ independently of one another:

[0275] hydrogen, OH, CN, or

[0276] each optionally substituted C₆-C₇-alkyl, O—C₆-C₇-alkyl, C₆-C₇-alkenyI, C₆-C₇-cycloalkenyl
O—C₆-C₇-cycloalkenyl, aryI, heteroaryl, C₆-C₇-alkenyI, aryI, C₆-C₇-alkenyI, aryI, C₆-C₇-alkenyI
heteryl, aryI, O—C₆-C₇-alkenyI, aryI, O-hetaryl, O—C₆-
C₇-alkenyI-hetaryl, CO—C₆-C₇-alkenyI, COaryl,
CO-hetaryl, CO—C₆-C₇-alkenyI, aryI, CO—O—
C₆-C₇-alkenyI, aryI, CO—O—C₆-C₇-alkenyI
heteryl, CO—O—C₆-C₇-alkenyI, CO—O—
C₆-C₇-alkenyI, aryI, SO₂—C₆-C₇-alkenyI, aryI,
SO₂—C₆-C₇-alkenyI, aryI, SO₂—
hetaryl, SO₂—C₆-C₇-alkenyI-hetaryl, OCO—C₆-
C₇-alkenyI alkenyI, OCO—C₆-C₇-
alkenyI, OCO—C₆-C₇-alkenyI, aryI, OCO—C₆-
C₇-alkenyI, aryI, aryI, aryI, aryI,
aryI; or each independently from the third moiety, two moieties of R²⁴, R²⁵ or R²⁶ together
form a 3 to 7-membered, optionally substituted, saturated or unsaturated carbocycle, or an optionally
substituted, saturated or unsaturated, which can contain
two or three further different or identical het-
eroatoms from the group O, N, S, wherein optionally
two moieties substituted on this carbo- or hetero-
cycle can together form an anellated, saturated,
saturated or aromatic carbocycle or heterocycle,
wherein the heterocycle can contain up to three
different or identical heteroatoms O, N, S and
wherein the cycle formed can optionally be substituted
or a further, optionally substituted cycle can be
condensed onto this cycle;

[0277] Q:

[0278] a doubly substituted 5-membered hetaryl-
moiety, chosen from Q₁ to Q₆

Q₁
[0279] E: O, N—R_{Q}^{1} or S;
[0280] R_{Q}^{1};
[0281] hydrogen, or
[0282] each optionally substituted C_{1}-C_{8}-alkyl, CO—C_{1}-C_{8}-alkyl, SO_{2}—C_{1}-C_{8}-alkyl, CO—O—
C_{1}-C_{8}-alkyl, ary1, C_{1}-C_{8}-alkylene-aryl, CO-aryl, CO-hetary1, SO_{2}-aryl, SO_{2}-hetary1, CO—O-aryl,
CO—C_{1}-C_{8}-alkylene-aryl, SO_{2}—C_{1}-C_{8}-alkylene-aryl or CO—O—C_{1}-C_{8}-alkylene-aryl;
[0283] R^{4}, R^{5} each independently of one another a moiety chosen from the groups 1.), 2.), 3.), 4.) or 5.);
[0284] 1.) hydrogen, halogen, CN, CF_{3}, CHF_{2}, or
[0285] each optionally substituted C_{1}-C_{10}-alkyl, C_{2}-C_{10}-alkenyl, C_{2}-C_{10}-alkyl, C_{2}-C_{10}-cy-
claoxy1, C_{2}-C_{10}-alkylene-C_{2}-C_{10}-cyclaoxy1, C_{2}-C_{10}-alkylene-O—C_{2}-C_{10}-alkyl, C_{2}-C_{10}-alkylene-
O-ary1, COO—C_{2}-C_{10}-alkyl or C_{2}-C_{10}-alkylene-
COO—C_{2}-C_{10}-alkyl;
[0286] 2.) Phenyl or naphtyl, which are each substituted with R_{Q}^{2}, R_{Q}^{3} and R_{Q}^{4}, wherein
[0287] R_{Q}^{2}, R_{Q}^{3} and R_{Q}^{4} each independently of one another represent a substituent from the following group:
[0288] hydrogen, NO_{2}, NH_{2}, OH, CN, CF_{3}, CHF_{2},
OCF_{3}, OCFH_{2}, COOH, O—CH_{2}—COOH, SH, halogen, or
[0289] each optionally substituted ary1, hetary1, heterocyclaoxy1, C_{1}-C_{8}-alkyl, C_{2}-C_{8}-alkenyl,
C_{2}-C_{8}-alkenyl, C_{2}-C_{8}-cyclaoxy1, C_{1}-C_{8}-hetary1, C_{1}-C_{8}-hetary1.
erocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S, and the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle.

[0298] 3. a 5- or 6-membered hetaryl moiety optionally substituted with 1 or 2 substituents, from the group consisting of

[0299] 2-furyl, 3-furyl, 2-pyryl, 3-pyryl, 2-thienyl, 3-thienyl, 2-piretyl, 3-piretyl, 4-piretyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 6-pyrimidyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyridazines, 5-pyridazines, 6-pyridazines, 3-isopyrazolyl, 4-isopyrazolyl, thiadiazolyl, oxadiazolyl or triazolyl or their anellated derivatives indazolyl, indolyl, benzothiophenyl, benzofuranyl, indolinyI, benzimidazolyl, benzthiazolyl, benzoxazolyl, chinolinyI and isoquinolinyl;

[0300] 4.) both moieties R'5 and R52 together form a 4 to 7-membered, optionally substituted, saturated or unsaturated or aromatic carbocycle or a 5- or 6-membered optionally substituted, saturated or unsaturated or aromatic heterocycle which can contain up to three further different or identical heteroatoms O, N, S, and can be substituted with up to two further moieties, wherein optionally two moieties substituted on this carbo- or heterocycle can together form an anellated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the cycle formed can contain up to three different or identical heteroatoms O, N, S and wherein the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

[0301] 5. a C5-C10 bi- or tricyclic, saturated hydrocarbon moiety;

for the preparation of a medicament for the treatment of diseases which are modulated by a 5-HT5 receptor activity.

[0302] In this regard, the treatment of neuropathological, neuropsychiatric and neurodegenerative disorders, symptoms and dysfunctions is preferred, in particular the treatment of migraine and brain damage. Examples of brain damage and/or disorders can be cerebral ischemia, stroke, epilepsy and seizures in general, psychoses, schizophrenia, autism, OCD-syndrome, cognitive diseases, attention disorders, depressions, bipolar and/or unipolar depressions, conditions of anxiety, dementia, senile dementia, Alzheimer dementia, demyelinating diseases, multiple sclerosis and brain tumours. Also preferred is the treatment of cerebral vascular disorders, pain, disorders due to pain, addiction, disorders due to drugs, amnesia, alcohol abuse, drug abuse, disorders of the circadian rhythm and Cushing Syndrome.

DETAILED DESCRIPTION OF THE INVENTION

[0303] In preferred embodiments, the moieties of the formulae I or I'A have the following meanings;

[0304] W is defined as given above and preferably represents H.

[0305] A is defined as given above and preferably means halogen, OH, CN, CF3, CHF2, OCF3, OCF2 or each optionally substituted C1-C6 alkyl or C1-C6 alkenyl, —O—CH2—COO—R1, O—R1, S—R1, NR2R3, —NR4R5—CO—R6, SO2NH2, NR4—SO2—R4, SO2NR4R5, NR4R5—SO2R6 or —CO—NR4R5—R6.

[0306] In one embodiment A is preferably halogen, OH, CN, CF3, CHF2, OCF3, OCF2, or each optionally substituted C1-C6 alkyl or C1-C6 alkenyl, —O—CH2—COO—R1, O—R1, S—R1, NR2R3, —NR4R5—CO—R6 or —CO—NR4R5—R6.

[0307] It is especially preferred that A is halogen, OH, OCF3, OCF2, optionally substituted C1-C6 alkyl, O—R1 or S—R1. Even more preferred, A is halogen, OH, OCF3, OCF2, each optionally substituted C1-C6 alkyl, O—C1-C6 alkyl, O-benzyl, O-phenyl or S—C1-C6 alkyl. Of these, A is even more preferably OH, F, Cl, OCF3, OCF2, C1-C6 alkyl, O—C1-C6 alkyl or S—C1-C6 alkyl. Most preferred is A is OH, OCF3, OCF2, O-ethyl, O-n-propyl or O-i-propyl.

[0308] A is preferably located in the 2- or 4-position on the ring, more preferred, in the 2-position.

[0309] R5 is defined as given above and preferably means each optionally substituted C1-C6 alkyl, C1-C6-cycloalkyl, phenyl or benzyl. More preferred R5 is methyl, ethyl, n-propyl or i-propyl. Most preferred R5 is methyl or ethyl.

[0310] R52 is defined as given above and preferably means each optionally substituted C1-C6 alkyl, phenyl, benzyl, phenethyl, CO—C1-C6 alkyl, CO-aryl, CO—O—C1-C6 alkyl, SO2—C1-C6 alkyl, SO2-aryl, SO2-hetaryl, or SO2—C1-C6 alkenylene-aryl.

[0311] Even more preferred, R52 is hydrogen, C1-C4-alkyl, phenyl or benzyl.

[0312] In one embodiment, R52 is preferably hydrogen, methyl, ethyl, n-propyl or i-propyl.

[0313] R53 is defined as given above and preferably means each optionally substituted C1-C6 alkyl, phenyl, benzyl, phenethyl, CO—C1-C6 alkyl, CO-aryl, CO—O—C1-C6 alkyl, SO2—C1-C6 alkyl, SO2-aryl, SO2-hetaryl, or SO2—C1-C6 alkenylene-aryl.

[0314] Even more preferred, R53 is C1-C6 alkyl, phenyl or benzyl, most preferred methyl, ethyl, n-propyl or i-propyl or phenyl.

[0315] As described above, both of the moieties R52 and R53 can also form, together with the nitrogen, a 3-7-membered heterocycle. In this regard, both of the moieties R52 and R53 preferably together form an optionally substituted 5- or 6-membered, saturated or unsaturated ring which can contain one or two further or identical different heteroatoms from the group O, N and S.

[0316] R54 is defined as given above and preferably means hydrogen or an optionally substituted C1-C4-alkyl moiety. Most preferred, R54 is hydrogen, methyl, ethyl, n-propyl or i-propyl.

[0317] B is defined as given above and preferably means hydrogen, halogen, OH, CN, CF3, CHF2, OCF3, OCF2, each optionally substituted C1-C6 alkyl or C1-C6 alkenyl, —O—CH2—COO—R1, O—R1, S—R1, NR2R3, —NR4R5—CO—R6 or —CO—NR4R5—R6.

[0318] Especially preferred, B is hydrogen, halogen, OH, OCF3, OCF2, optionally substituted C1-C6 alkyl, O—R1 or S—R1.

[0319] Even more preferred, B is hydrogen, halogen, OH, OCF3, OCF2, each optionally substituted C1-C6 alkyl, O—C1-C6 alkyl, O-benzyl, O-phenyl or S—C1-C6 alkyl. Of these, B is even more preferably hydrogen, OH, F, Cl, OCF3,
halogen, OH or optionally substituted C₁–C₄-alkyl, even more preferably hydrogen, F or CH₃. Most preferably, R₂, R₂', R₂'' and R₂''' are simultaneously hydrogen.

[V₂] is defined as given above and preferably means —CO —CO—NR₃ NR₃ CO —O —S —CO —O —S —O —CO —O —S —O —S —O —S —O.

R₂, R₂', R₂'' and R₂''' are defined as given above and preferably mean independently of one another hydrogen or CH₃.

Most preferred, Q is

[0335] Q is defined as given above and preferably means a moiety of the formulae Q₁, Q₂, Q₃ or Q₅. In one embodiment, Q means a moiety of the formulae Q₁, Q₂ or Q₃. Especially preferred are the moieties of the formulae
In one embodiment, the moieties of the formulae
\[ \text{\textup{C}}_{n}\text{\textup{S}} \]
are preferred. In this embodiment, Q is most preferred.

\[ \text{E} \text{ is defined as given above and preferably means S or O, even more preferred, S.} \]

\[ \text{R}_{Q}^1 \text{ is defined as given above and preferably means hydrogen, optionally substituted C}_{1-4}\text{-alkyl, in the aryl moiey optionally substituted benzyll, CO—C}_{1-4}\text{-alkyl, optionally substituted benzyll, SO}_{2—C}_{1-4}\text{-alkyl or in the aryl moiey optionally substituted SO}_{2-aryl. Even more preferred, R}_{Q}^1 \text{ is hydrogen, CH}_{3}, \text{phenyl benzyl, methanesulfonyl, phenylsulfonyl or tosyl, most preferred, hydrogen.} \]

\[ \text{In a further embodiment, R}_{Q}^2 \text{ is defined as given above and preferably means hydrogen, optionally substituted C}_{1-4}\text{-alkyl, in the ary moiey optionally substituted benzyll, CO—C}_{1-4}\text{-alkyl, optionally substituted benzyll, SO}_{2—C}_{1-4}\text{-alkyl or in the ary moiey optionally substituted SO}_{2-aryl. Even more preferred, R}_{Q}^2 \text{ is hydrogen, CH}_{3}, \text{methanesulfonyl, phenylsulfonyl or tosyl, most preferred hydrogen.} \]

\[ \text{R}^4 \text{ and R}^5 \text{ are defined as given above and preferably have the following definitions:} \]

For the case 1.) \( \text{R}^4 \text{ and/or R}^5 \text{ are defined as given above, preferably each independently of one another, one moiety chosen from the group consisting of hydrogen, F, Cl, CN, CF}_{3}, \text{CHF}_{2}, \text{each optionally substituted C}_{1-4}\text{-alkyl, C}_{2-6}\text{-alkenyl, C}_{1-4}\text{-alkylene-O—C}_{1-4}\text{-alkyl or C}_{3-6}\text{-cycloalkyl. Especially preferred are hydrogen, C}_{1-4}\text{-alkyl, e.g. methyl, ethyl, n-propyl, i-propyl or tert-butyl, cyclohexyl or cyclopentyl.} \]

For the case 2.) \( \text{R}^4 \text{ and/or R}^5 \text{ are defined as given above, preferably phenyl, which is substituted with R}_{Q}^2, \text{R}_{Q}^3 \text{ and R}_{Q}^4.} \]

\[ \text{R}_{Q}^2, \text{R}_{Q}^3 \text{ and R}_{Q}^4 \text{ are defined as given above and preferably each independently of one another a substituent from the following group: hydrogen, —NO}_{2}, \text{—NH}_{2}, \text{—OH, —CN, —CF}_{3}, \text{—CHF}_{2}, \text{—OCHF}_{2}, \text{halogen, each optionally substituted aryl, hetaryl, C}_{1-4}\text{-alkyl, C}_{2-6}\text{-alkenyl, C}_{3-7}\text{-cycloalkyl, C}_{1-4}\text{-alkylene-C}_{3-7}\text{-cycloalkyl, C}_{1-4}\text{-alkylene-heterocycloalkyl, C}_{1-4}\text{-alkylene-aryl or C}_{1-4}\text{-alkylene-hetaryl; O—R}_{Q}^2, \text{NR}_{Q}^2 \text{—R}_{Q}^2, \text{—CO—OR}_{Q}^2, \text{—NR}_{Q}^2 \text{—CO—O—R}_{Q}^2, \text{—O—CHF}_{2}, \text{—CO—O—R}_{Q}^2, \text{—NR}_{Q}^2 \text{—SO}_{2—R}_{Q}^2, \text{—SO}_{2—R}_{Q}^2, \text{—NR}_{Q}^2 \text{—SO}_{2—R}_{Q}^2, \text{—CO—NR}_{Q}^2 \text{—R}_{Q}^2, \text{—SO}_{2—R}_{Q}^2, \text{—CONH}_{2}, \text{—SO}_{2—R}_{Q}^2, \text{—NR}_{Q}^2 \text{—R}_{Q}^2 \text{or —CO—NR}_{Q}^2 \text{—R}_{Q}^2. Especially preferred are hydrogen, NH}_{2}, \text{—CHF}_{2}, \text{—CF}_{3}, \text{—OCF}_{3}, \text{—O—R}_{Q}^2, \text{C}_{1-4}\text{-alkyl, —NR}_{Q}^2 \text{—R}_{Q}^2 \text{or halogen.} \]

In one embodiment, hydrogen, CF}_{3}, \text{—OCF}_{3}, \text{O—CH}_{3}, \text{—OCF}_{2}, \text{OH, N(CH}_{3})_{2}, \text{Cl and F are preferred. In another embodiment, hydrogen, CF}_{3}, \text{—OCF}_{3}, \text{O—CH}_{3}, \text{Cl and F are preferred.} \]

It is also possible that two of the moieties R}_{Q}^2, \text{R}_{Q}^3 \text{ or R}_{Q}^4 \text{ together form a 3 to 7-membered, optionally substituted, saturated, unsaturated or aromatic carbocycle or an optionally substituted, saturated, unsaturated, aromatic heterocycle, which can contain up to three further different or identical heteroatoms O, N, S and optionally two moieties substituted on this heterocycle can together form an annelated, saturated, unsaturated or aromatic carbocycle or heterocycle, which can contain up to three different or identical heteroatoms O, N, S and the cycle formed can optionally be substituted or further, optionally substituted cycle can be condensed onto this cycle. In this embodiment, R}_{Q}^2, \text{R}_{Q}^3 \text{ or R}_{Q}^4 \text{ preferably further together form a 5 or 6-membered, even more preferred 5-membered, heterocycle, which contains a further heterovatom O, N, S, preferably O. The heterocycle is preferably saturated.} \]

\[ \text{In one embodiment, R}_{Q}^5 \text{ is defined as given above, and preferably means hydrogen, or two of the substituents are hydrogen and the third substituent is a moiety other than hydrogen.} \]

\[ \text{R}_{Q}^5 \text{ is defined as given above and preferably means each optionally substituted C}_{1-4}\text{-alkyl, or C}_{2-6}\text{-alkenyl, even more preferred each optionally substituted C}_{1-4}\text{-alkyl, which is optionally substituted with a substituent from the group consisting of F, Cl, —OH, —CN, —CF}_{3}, \text{—CHF}_{2}, \text{—OCHF}_{2}, \text{NH—(C}_{1-4}\text{-alkyl) and N(C}_{1-4}\text{-alkyl)}}, \text{most preferred methyl or ethyl.} \]

\[ \text{In one embodiment, R}_{Q}^5 \text{ is C}_{1-4}\text{-alkyl-heterocycloalkyl, even more preferred C}_{1-4}\text{-alkyl-heterocycloalkyl, wherein the heterocycloalkyl is preferably a 5 or 6-membered ring with 1 to 3, even more preferred 1 to 2 heteroatoms, chosen from N, O or S, even more preferred, N or O. In one embodiment, R}_{Q}^5 \text{ is morpholinol.} \]

\[ \text{R}_{Q}^6 \text{ is defined as given above and preferably means each optionally substituted C}_{1-4}\text{-alkyl, C}_{2-6}\text{-alkenyl, C}_{1-4}\text{-cycloalkyl, ary, hetaryl or C}_{1-4}\text{-alkylene-O—C}_{1-4}\text{-alkyl, even more preferred each optionally substituted C}_{1-4}\text{-alkyl, ary, hetaryl, more preferred C}_{1-4}\text{-alkyl, C}_{1-4}\text{-cycloalkyl, ary, or C}_{1-4}\text{-alkylene-O—C}_{1-4}\text{-alkyl, most preferred methyl, ethyl, cyclohexyl or phenyl.} \]

\[ \text{R}_{Q}^7 \text{ is defined as given above and preferably means hydrogen, OH, or each optionally substituted C}_{1-4}\text{-alkyl, C}_{2-6}\text{-alkenyl, C}_{1-4}\text{-cycloalkyl, ary, hetaryl, C}_{1-4}\text{-alkylene-aryl or C}_{1-4}\text{-alkylene-hetaryl, more preferred hydrogen, each optionally substituted C}_{1-4}\text{-alkyl, ary, hetaryl, benzyl, phenethyl or CH}_{2}\text{-hetaryl.} \]

\[ \text{Of these, hydrogen, C}_{1-4}\text{-alkyl, phenyl, or benzyl is even more preferred, and most preferred is hydrogen, methyl, ethyl, or phenyl.} \]

\[ \text{R}_{Q}^8 \text{ is defined as given above and preferably means hydrogen, each optionally substituted C}_{1-4}\text{-alkyl, C}_{2-6}\text{-alkyl-
alkenyl, C₃-C₇-cycloalkyl, aryl, hetaryl, C₃-C₇-alkylenearyl, C₃-C₇-alkylene-hetaryl or C₃-C₇-alkylene-O-C₃-C₇-alkyl, CO—C₃-C₇-alkyl, SO₂—C₃-C₇-alkyl.

[0354] Even more preferred are hydrogen, each optionally substituted C₃-C₇-alkyl, aryl, hetaryl, benzyl, phenethyl or CH₃-hetaryl. Of these, even more preferred are hydrogen, C₃-C₇-alkyl, phenyl, or benzyl, and most preferred is hydrogen, methyl, ethyl, or phenyl.

[0355] It is likewise preferred that both of the moieties R⁷ and R₈ form, together with the nitrogen, an optionally substituted 3- or 7-membered, saturated or unsaturated ring, which can contain one N or two N or one O and one N. Even more preferred, both of the moieties R⁷ and R₈ form, together with the nitrogen, a 5- or 6-membered, optionally substituted, saturated heterocycle, which can contain a further heteroatom O, N or S, preferably O or N. Preferred are a 5-membered saturated heterocycle with one N and a 6-membered heterocycle with 2 N or 1 N and 1 O.

[0356] For the case 3.), R⁴ and/or R⁵ are preferably, each independent of one another, chosen from a group consisting of 2-pyridyl, 3-pyridyl, benzothiophenyl, benzo furanyl, chinoliny, isochinoliny, each optionally substituted with 1 or 2 substituents; or 2-thienyl or 3-thienyl each optionally substituted with 1 or 2 substituents, wherein the substituents are chosen from the group consisting of halogen, in particular Cl, NO₂, NH₂, —OH, —CN, —CF₃, —OCF₃, —CHF₂, O—CH₂₂, C₃-C₇-alkyl, in particular methyl or ethyl, O—C₃-C₇-alkyl, NH—(C₆H₅-alkyl) and N(C₆H₅-alkyl)₄, NHCO—C₃-C₇-alkyl, NHSO₂—C₃-C₇-alkyl and SO₂—C₃-C₇-alkyl.

[0357] Especially preferred are benzothiophenyl, benzo furanyl, chinoliny, isochinoliny, 2-thienyl, or 3-thienyl, wherein both of the latter are preferably substituted with halogen, in particular Cl, C₃-C₇-alkyl, in particular methyl or ethyl.

[0358] In one embodiment, R⁴ and/or R⁵ are preferably each independently of one another 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 6-pyrimidyl, 3-thienyl, 2-thienyl, benzothiophenyl, benzo furanyl, benzimidazolyl, chinoliny or isochinoliny, even more preferred 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-thienyl, benzothiophenyl, benzo furanyl, chinoliny, or isochinoliny, which can optionally be substituted with 1 or 2 moieties. The moieties are preferably chosen from the group consisting of halogen, in particular Cl or F, —NO₂, —NH₂, —OH, —CN, —CF₃, —OCF₃, —CHF₂, O—CH₂₂, C₃-C₇-alkyl, in particular methyl or ethyl, O—C₃-C₇-alkyl, NH—(C₆H₅-alkyl) and N(C₆H₅-alkyl)₄, NHCO—C₃-C₇-alkyl, NHSO₂—C₃-C₇-alkyl and SO₂—C₃-C₇-alkyl, most preferred halogen, in particular Cl or F, C₃-C₇-alkyl, in particular methyl or ethyl.

[0359] In this regard, 2-pyridyl, 3-pyridyl, 4-pyridyl or 2-pyrimidyl, in particular 2-pyridyl, 3-pyridyl or 4-pyridyl are especially preferred.

[0360] For the case 4.) both of the moieties R⁴ and R⁵ preferably together form one of the following rings:

[0361] In one embodiment, both of the moieties R⁴ and R⁵ together preferably form one of the following rings:

wherein R⁴, R₈ and R₉ are defined as under 2), including the preferred embodiments.

[0362] Most preferred, both substituents, R⁴ and R₅ are hydrogen, or one substituent is hydrogen and the other is a substituent other than hydrogen. In this regard, the other substituent is preferably methyl or O—C₃-C₇-alkyl. It is also preferred that both substituents are methyl or that one substituent is methyl and the other is halogen.

[0363] In one embodiment, R⁴ and R₅ together form a phenyl ring.

[0364] When both moieties R⁴ and R₅ together form one of the nitrogen-containing rings given above, then R⁴ is as defined under 2), preferably hydrogen, C(O)—C₃-C₇-alkyl, SO₂-aryl or C₃-C₇-alkylene-aryl, even more preferred hydrogen, C(O)—CH₂, SO₂-phenyl or benzyl. Both substituents R⁴ and R₅ on the nitrogen-containing ring are preferably hydrogen. For the case 5.), R⁴ and/or R₅ are preferably Adamantyl.

[0365] Preferably, one of both of the moieties R⁴ and R₅ is chosen from the group 1.), including the preferred embodiments thereof, and the other moiety is chosen from the group 1.), 2.) or 3.), including the respective preferred embodiments thereof. In this regard, the first moiety of R⁴ and R₅ is preferably methyl or hydrogen.

[0366] For the case 6.), R⁴, R₅ are preferably C₃-C₇-alkyl-NH₂, C₃-C₇-alkyl-NR₄⁻R₉⁻R₈⁻R₉⁻R₉⁻, CO—NR₉⁻R₉⁻R₉⁻⁸ or NR₉⁻R₉⁻R₉⁻⁸.

[0367] For the case C₃-C₇-alkyl-NR₄⁻R₉⁻R₉⁻ or C₃-C₇-alkyl-CO—NR₉⁻R₉⁻R₉⁻ are defined as under 2), including the preferred embodiments. Especially preferred, R₉⁻ is hydrogen and R₉⁻ is C(O)O—C₃-C₇-alkyl, C(O)-aryl, or SO₂—C₃-C₇-alkyl. Alternatively, both R₉⁻ and R₉⁻ can be C₃-C₇-alkyl. By these definitions, C₃-C₇-alkyl preferably means a methylene or ethylene moiety.

[0368] For the case CO—NR₉⁻R₉⁻ or R₉⁻ and R₉⁻ are defined as under 2), including the preferred embodiments. Especially preferred, R₉⁻ is hydrogen and R₉⁻ is C₃-C₇-alkyl, C₃-C₇-alkenyl, or C₃-C₇-alkylene aryl, even more preferred, isopropyl, propenyl or benzyl.

[0369] Especially preferred are the moieties CH₂NH₂, CH₂—NH—C(O)-O-tet-butyl, CH₂—NH—C(O)-methyl, CH₂—NH—C(O)-phenyl, CH₂—NH—SO₂—n-butyl, CH₂—N(Me)₃, C(O)—NH—CH(CH₃)₂, C(O)—NH—CH₂CH₂CH₃, C(O)—NH—CH₂-phenyl.
For the case 7), **R**^4, **R**^5 are preferably each optionally substituted azetidine-3-yl, pyrrolidine-2-yl, pyrrolidine-3-yl, piperidine-2-yl, piperidine-3-yl, piperidine-4-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, azepan-3-yl, azepan-2-yl, 1,4-diazepan-5-yl, 1,2,3,6-tetrahydropyridine-4-yl, 2,5-dihydro-1H-pyrrol-3-yl, especially preferred:

![Chemical structures](image)

Even more preferred are

![Chemical structures](image)

In this case, **R**^7 is defined as under 2), including the preferred embodiments. Especially preferred, **R**^7 is hydrogen, C^1-C^3-alkyl, C(O)—C^1—C^2-alkyl, C^1-C^2-alkylene-aryl, SO^2—aryl or SO^2—C^1-C^2-alkyl. Most preferred, **R**^7 is hydrogen, methyl, isopropyl, C(O)-Me, SO^2-phenyl, SO^2-Me or benzyl.

In a preferred embodiment, one of both of the moieties **R**^4 and **R**^5 is chosen from the group 1), including the preferred embodiments of group 1), and the other moiety of **R**^4 and **R**^5 is preferably methyl or hydrogen.

In a further preferred embodiment, one of both of the moieties **R**^4 and **R**^5 is chosen from the group 2), including the preferred embodiments of group 2), and the other moiety of **R**^4 and **R**^5 is preferably methyl or hydrogen.

In one preferred embodiment, one of both of the moieties **R**^4 and **R**^5 is chosen from the group 3), including the preferred embodiments of the group 3), and the other moiety of **R**^4 and **R**^5 is preferably methyl or hydrogen.

In a further preferred embodiment, one of both of the moieties **R**^4 and **R**^5 is chosen from the group 4), including the preferred embodiments of the group 4), and the other moiety of **R**^4 and **R**^5 is preferably methyl or hydrogen.

In a further preferred embodiment, one of both of the moieties **R**^4 and **R**^5 is preferably each optionally substituted azetidine-3-yl, pyrrolidine-2-yl, pyrrolidine-3-yl, piperidine-2-yl, piperidine-3-yl, piperidine-4-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, azepan-3-yl, azepan-2-yl, 1,4-diazepan-5-yl, 1,2,3,6-tetrahydropyridine-4-yl, 2,5-dihydro-1H-pyrrol-3-yl, especially preferred:

Even more preferred are

In this case, **R**^7 is defined as under 2), including the preferred embodiments. Especially preferred, **R**^7 is hydrogen, C^1-C^3-alkyl, C(O)—C^1—C^2-alkyl, C^1-C^2-alkylene-aryl, SO^2—aryl or SO^2—C^1-C^2-alkyl. Most preferred, **R**^7 is hydrogen, methyl, isopropyl, C(O)-Me, SO^2-phenyl, SO^2-Me or benzyl.

In a preferred embodiment, one of both of the moieties **R**^4 and **R**^5 is chosen from the group 1), including the preferred embodiments of group 1), and the other moiety of **R**^4 and **R**^5 is preferably methyl or hydrogen.

In a further preferred embodiment, one of both of the moieties **R**^4 and **R**^5 is chosen from the group 2), including the preferred embodiments of group 2), and the other moiety of **R**^4 and **R**^5 is preferably methyl or hydrogen.

In one preferred embodiment, one of both of the moieties **R**^4 and **R**^5 is chosen from the group 3), including the preferred embodiments of the group 3), and the other moiety of **R**^4 and **R**^5 is preferably methyl or hydrogen.

In a further preferred embodiment, one of both of the moieties **R**^4 and **R**^5 is chosen from the group 4), including the preferred embodiments of the group 4), and the other moiety of **R**^4 and **R**^5 is preferably methyl or hydrogen.

In a further preferred embodiment, one of both of the moieties **R**^4 and **R**^5 is preferably each optionally substituted azetidine-3-yl, pyrrolidine-2-yl, pyrrolidine-3-yl, piperidine-2-yl, piperidine-3-yl, piperidine-4-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, azepan-3-yl, azepan-2-yl, 1,4-diazepan-5-yl, 1,2,3,6-tetrahydropyridine-4-yl, 2,5-dihydro-1H-pyrrol-3-yl, especially preferred:
bonds, such as, for example, vinyl, 2-propenyl, 2-butenyl, 3-butenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-2-propenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-ethyl-2-butenyl, 2-ethyl-2-but enyl, 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl, 1-ethyl-1-methyl-2-propenyl und 1-ethyl-2-methyl-2-propenyl, in particular 2-propenyl, 2-butenyl, 3-methyl-2-butenyl or 3-methyl-2pentenyl.

[0388] Alkynyl is a branched or unbranched hydrocarbon chain containing at least one triple bond with 2 to 6, preferably 2 to 4 carbon atoms. Alkynyl preferably contains one or two triple bonds, most preferred one triple bond. Examples of the alkynyl groups are those as given for alkyl above, wherein these groups contain one or two triple bonds, such as, for example, ethynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-methyl-3-butylnyl, 2-methyl-3-butylnyl, 1-meth yl-2-butylnyl, 1,1-dimethyl-2-propynyl, 1-ethyl-2-propynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-methyl-1-propynyl, 1-methyl-2-propynyl, 1-methyl-3-propynyl, 1-methyl-4-propynyl, 2-methyl-3-propynyl, 2-methyl4-propynyl, 3-methyl-4-pentynyl, 4-methyl-2-pentynyl, 1,1dimethyl-2-butynyl, 1,2-dimethyl-3-butynyl, 1-ethyl-2-butynyl, 1-ethyl-3-butynyl, 2-ethyl-3-butynyl and 1-ethyl-1-methyl-2-propynyl, preferably ethynyl, 2-propynyl, 2-butynyl, 1-methyl-2-propynyl or 1-methyl-2-butynyl.

[0389] Heterocycloalkyl is a saturated alkyl ring or an alkyl ring on which a further saturated alkyl ring is anulated, with preferably 3 to 10 ring atoms in total, even more preferably 5 to 6 ring atoms, wherein this heterocycloalkyl contains at least one hetero atom, chosen from the group O, N, S or C, and contains 1 to 6, preferably 1 to 5 carbon atoms. Heterocycloalkyl preferably contains 1 or 2 heteroatoms, which are preferably from N and/or O. Examples of a heterocycloalkyl group contain, for example, N-pyrrolidinyl, N-piperidinyl, N-hexahydroaze pianyl, N-morpholinyl or N-piperazinyl, wherein in heterocycles containing amino groups such as, for example, N-pip erazinyl, these amino groups can be replaced by common moieties such as, for example, methyl, benzyl, benz (2- butoxy carbonyl), benzoyloxycarbonyl, tosyl (p-toluolsulfon yl), —SO₂—C₁₋₄-alkyl, —SO₂-phenyl or —SO₂-benzyl.

[0390] Aryl is an aromatic mono-, bi- or polycyclic moiety with preferably 6 to 20 carbon atoms, even more preferably 6 to 10 carbon atoms, and is preferably chosen from phenyl, biphenyl, naphthyl, tetrahydrophenanthrene, fluorenyl, indenyl and phenanthrenyl, even more preferably from phenyl and naphthyl, such as 1-naphthyl or 2-naphthyl. Most preferred is phenyl.

[0391] Alkylenearyl is an aryl bond via C₁₋₄, even more preferably C₁₋₃-alkylene, and in which the aryl moiety is optionally substituted, wherein alkylene and aryl are defined as given above. Alkylenearyl is especially in the aryl moiety the optionally substituted benzyl or phenethyl.

[0392] Aryloxy or —O-aryl is an aryl bond via oxygen, the aryl being defined as given above, in particular —O-phenyl.

[0393] Hetaryl is an aromatic ring containing at least one heteroatom, preferably 1 or 2 heteroatoms, chosen from the group O, N, or S and preferably 1 to 6, even more preferred 1 to 5 carbon atoms. The aromatic ring is preferably 5- or 6-membered. Hetaryl additionally includes the derivatives thereof anulated with aryl, namely an aromatic moiety with preferably 6 to 20 carbon atoms, even more preferred 6 to 10 carbon atoms, most preferred phenyl, which is anulated with this aromatic ring, containing at least one heteroatom. Hetaryl can also be chosen from an aromatic moiety with preferably 6 to 20, even more preferred 6 to 10 carbon atoms, most preferred phenyl, with a heterocycloalkyl group, which is anulated thereto. In this regard, the heterocycloalkyl group is as defined above. Hetaryl is preferably chosen from 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-thienyl, 3-thienyl, 2-pyrindyl, 3-pyrindyl, 4-pyrindyl, 2-thiazoyl, 4-thiazoyl, 5-thiazoyl, 2-oxazoyl, 4-oxazoyl, 5-oxazoyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 6-pyrimidyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 3-isothiazoly, 4-isothiaz oly, 5-isothiazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazol yl, 3-pyrazinyl, 4-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl.

[0394] Alkylenehetaryl is a hetaryl optionally substituted in the hetaryl moiety and bound via C₁₋₄, even more preferably C₁₋₃-alkylene, wherein alkylene and hetaryl are defined as given above. Alkylenehetaryl is preferably optionally substituted —CH₂-2-pyrindyl, —CH₃-2-pyrindyl, —CH₂-2-thienyl, —CH₃-2-thienyl, —CH₂-2-thiazoyl, —CH₃-2-thiazoyl, —CH₂-4-thiazoyl, —CH₃-5-thiazoyl, —CH₂-1-CH₁-2-pyrindyl, —CH₃-1-CH₁-2-pyrindyl, —CH₂-1-CH₂-3-pyrindyl, —CH₃-1-CH₂-3-pyrindyl, —CH₂-1-CH₃-2-thienyl, —CH₃-1-CH₃-2-thienyl, —CH₂-4-2-thiazoyl, —CH₂-4-3-thiazoyl or —CH₃-4-2-thiazoyl.

[0395] A bi- or tricyclic, saturated hydrocarbon moiety is a bicycloalkyl- or tricycloalkylmoiety and has 5 to 18 carbon atoms. In a bicycloalkyl moiety, the ring system preferably contains 5 to 12, even more preferably 6 to 10 carbon atoms. In a tricycloalkylmoiety the ring system preferably contains 6 to 16, even more preferably 6 to 12 carbon atoms. Examples of a bicycloalkyl moiety include indanyl, camphyl and norbornyl. Examples of a tricycloalkylmoiety include adamantyl.

[0396] Halogen is a halogen atom chosen from fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, even more preferably fluorine or chlorine.

[0397] Alkyl substituted with halogen refers to an alkyl moiety defined as given above, which is partially or completely substituted by fluorine, chlorine, bromine and/or iodine, for example CH₃F, CH₂F₂, CH₂Cl, 2-fluoroethyl, 2-chloroethyl, 2,2,2-trifluoroethyl.

[0398] If mentioned, the moieties and groups can preferably be singly or multiply, even more preferred singly, doubly or triply, most preferred singly or doubly substituted. The term “each optionally substituted” serves to make clear
that not only the moiety directly following, but all the indicated moieties in a respective group, can be substituted.

[0399] Examples of the substituents include: halogen, CN, CF₃, CHF₂, OCF₃, OCHF₂, NO₂, NH₂, OH, COOH, each branched or unbranched, optionally substituted C₁₋₈-alkyl, C₁₋₈-cycloalkyl, C₁₋₈-alkylene-O—C₁₋₈-alkyl or C₁₋₈-alkylene-thioalkyl, —O—C₁₋₈-alkyl, N(C₁₋₈-alkyl)₂, NH(C₁₋₈-alkyl), arylo, O-aryl, C₁₋₈-alkylene-O-aryl, NHCO—C₁₋₈-alkyl, NH—SO₂—C₁₋₈-alkyl, CO—C₁₋₈-alkyl, SO₂—C₁₋₈-alkyl, in which the alkyl moiety optionally substituted NHCO-aryl, NHCO-aryl, CONH₂, SO₂NH₂, SO₂-aryl, SO₃—C₁₋₈-alkyl, SO₂-aryl, N-pyridinyl, N-piperidinyl, and N-morpholiny. Preferred substituents are F, Cl, CF₃, OCF₃, NH₂, NO₂, OH, COOH, C₁₋₈-alkyl, methoxy, acetyl, NH-acetyl and SO₂NH₂.

Optical Isomers—Diastereomers—Geometric Isomers—Tautomers

[0400] The guanidine compounds of the formula I or IA or their salts, can have at least one asymmetric centre and can exist as enanomers and racemic mixtures, single enantionmers, diastereomeric mixtures and single diastereomers. The present invention includes all of these stereoisomeric forms of the guanidine compounds of formula I or IA.

[0401] The guanidine compounds of formula I or IA can be separated into their single stereoisomers by conventional methods, e.g., by fractional crystallization from a suitable solvent, e.g., methanol or ethyl acetate or from a mixture thereof or by chiral chromatography using an optically active stationary phase. The absolute stereochemistry can be determined by X-ray crystallography of the crystalline products or crystalline intermediates which, if necessary, can be derivatized with a reaction component which contains an asymmetric center of a known absolute configuration.

[0402] Alternatively, any stereoisomer of a guanidine of the formula I or IA can be obtained by stereospecific synthesis using optically pure starting materials or reaction components with known absolute configuration or by asymmetric synthesis methods.

[0403] The use of an enantiomerically- or diastereomerically pure compound is preferred. Particularly the guanidine compounds of the formula I or IA described herein can also exist as different tautomers of the guanidine group wherein, as is clear to a person of ordinary skill in the art, the kind of tautomerism depends on the nature of the moieties R₁, R₂ and R₃. Other tautomers, such as keto-enol tautomers, can also exist. All single possible tautomers, as well as mixtures thereof, are included in the guanidine compounds of formula I or IA.

Salts

[0404] The term “pharmacologically acceptable salts” refers to salts prepared from pharmaceutically acceptable, physiologically tolerated bases or acids, including inorganic or organic bases and inorganic or organic acids.

[0405] Salts derived from inorganic bases include aluminium, ammonium, calcium, copper, iron(II), iron(III), lithium, magnesium, manganese, potassium, sodium, zinc and the like. Especially preferred are the ammonium, calcium, lithium, magnesium, potassium and sodium salts. Salts which are derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines, including naturally existing substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzyldienediamine, diethylamine, 2-diethylaminomethanol, 2-dimethylaminooctanol, ethylendiamine, N-ethylmorpholine, N-ethylpiperidine, glu- camine, glucosamine, histidine, hydramine, isopropylamine, lysine, methylglucamine, morpholine, piperezine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripromy-, trimethamphetamine and the like.

[0406] When the guanidine of the present invention is basic, salts can be prepared from pharmaceutically acceptable physiologically tolerated acids, including inorganic and organic acids. Such acids include inter alia acetate acid, benzenesulfonic acid, benzoic acid, campher sulfonic acid, citric acid, ethane sulfonic acid, formic acid, fumaric acid, gluconic acid, glutamic acid, hydrobromic acid, hydrochloric acid, lactic acid, malic acid, maleic acid, mandelic acid, maleic acid, malonic acid, maleic acid, mandelic acid, maleic acid, nitric acid, pantethein acid, phosphoric acid, propionic acid, succinic acid, sulfuric acid, tartaric acid, p-toluene sulfonic acid, trifluoroacetic acid and the like. Especially preferred are citric acid, fumaric acid, hydrobromic acid, hydrochloric acid, maleic acid, phosphoric acid, sulfuric acid and tartaric acid.

[0407] When reference is made to the guanidine compounds of formula I or IA, this is to mean that the pharmaceutically acceptable salts thereof are also included.

Use, Fields of Application and Effects

[0408] The subject matter of the invention is also the use of guanidine compounds of the formula I or IA for the treatment of:

[0409] Depression and/or bipolar disorders such as, for example, dysthymic disorders, seasonally related disorders and/or psychotic disorders

[0410] Anxiety and/or stress-related disorders such as, for example, general stress disorders, panic disorders, compulsive disorders, posttraumatic disorders, acute stress disorders and/or social phobias

[0411] Memory disorders and/or Alzheimer disease

[0412] Schizophrenia, psychoses, psychotic disorders and/or psychotic-related disorders

[0413] Cerebrovascular disorders

[0414] Pain and/or pain-related disorders, addiction and drug-related disorders, including medication-related disorders

[0415] Amnesia

[0416] Alcohol- and/or drug abuse, including medication abuse

[0417] Disorders of the circadian rhythm and/or

[0418] Cushing Syndrome.

[0419] The term “disorder” in the sense according to the invention, refers to anomalies that are generally seen as disease states and which manifest themselves in the form of certain signs, symptoms and/or dysfunctions. The treatment can be directed to single disorders, in other words, anomalies or disease states, but multiple anomalies, which can possibly be causally connected to one another, can also occur together as patterns, in other words, syndromes, which can be treated according to the invention. This state can be temporary, progressive or permanent.

[0420] Compounds of the present invention can be used for the treatment or prevention of different diseases, in
which 5-HT5 receptors participate in the emergence and/or progression, i.e. diseases that are modulated by a 5-HT5 receptor activity, such as mental disorders. According to the “American Psychiatric Association DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th ed., 1994”, examples of such mental disorders are: attention disorders and socially disturbing behavior, learning disorders, delirium, dementia and amnestic and other cognitive disorders; disorders in connection with different substances, such as, for example, disorders in connection with alcohol consumption and alcohol induced disorders, withdrawal symptoms; schizophrenia and other psychotic disorders such as, for example schizophreniaform disorder, schizoaffective disorder and delusional disorder; substance-induced psychoses; paranoid disorders, disorders induced by neuroleptics; affective disorders such as, for example, depressive disorders (major depression, dysthymic disorder, seasonal-related disorder, unspecified depressive disorder), bipolar disorders (bipolar I disorder, bipolar II disorder, cyclothymic disorder, unspecified bipolar disorder, affective disorder induced by substances (amphetamine or amphetamine-like substances), unspecified affective disorder); disorders in connection with stress, such as, for example, acute stress disorder; anxiety disorders, such as, for example, panic disorders without agoraphobia, panic disorder with agoraphobia, agoraphobia without panic disorder in the pre-history, specific phobia, social phobia, compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, substance-induced anxiety disorder; somatoform disorders such as, for example, somatization disorder, unspecified somatoform disorder, conversion disorder, pain disorder, eating disorders, sleeping disorders such as, for example, primary sleeping disorders (dysomnia, parasomnia), sleeping disorders in connection with another mental disorder.

[0425] The subject matter of the invention is also, in particular, the use of guanidine compounds I and IA for the treatment of neuropathological, neuropsychiatric and neurodegenerative disorders.

[0426] By neuropathological disorders are, are understood disorders which are accompanied by neurological deficits, i.e. a condition characterized by symptoms of neurological loss.

[0427] According to the invention, the treatment of neurodegenerative and/or neuropsychiatric disorders is preferred. These disorders occur particularly in neuropathological disease patterns, which normally cause brain damage, for example, cerebral ischemia, stroke, epilepsy and seizures in general, chronic schizophrenia, other psychotic diseases, depression, states of anxiety, bipolar disorders, dementia, in particular Alzheimer dementia, demyelinating diseases, in particular multiple sclerosis, brain tumours and general inflammatory processes. A further neuropathological disorder is migraine as well as the signs, symptoms and dysfunctions associated therewith.

[0428] A treatment in the sense according to the invention includes not only the treatment of acute or chronic signs, symptoms and/or dysfunctions, but also a preventative treatment (prophylaxis), in particular as a relapse or phase prophylaxis. The treatment can be symptomatically oriented, for example as a suppression of symptoms. It can take place for a short time, be intermediately oriented, or can also be a long-term treatment, for example within the context of a maintenance therapy.
The term “binding partner for 5-HT5 receptors” describes substances which bind to 5-HT5 receptors and therefore may also be termed 5-HT5 receptor ligands. By binding, is understood every molecular interaction between the binding partner and the receptor, in particular under physiological conditions. These are normally classical interactions, to which electrostatic attraction, hydrogen-bonding, hydrophobic bonds, van-der-Waals forces or coordinative bindings of the sort seen with metal complexes belong. In addition to the reversible molecular interactions named above, irreversible interactions between binding partner and receptor such as e.g. covalent bindings, may also be considered.

Guanidine compounds according to the invention can competitively inhibit the binding of comparative binding partners such as 5-HT (5-hydroxytryptamine) or 5-CT (5-carboxamidotryptamine), to 5-HT5 receptors. The term competitive inhibition is understood such that the guanidine compounds according to the invention, compete with a comparative binding partner, in the present case e.g. 5-HT or 5-CT, for binding to the receptor.

According to a further embodiment, guanidine compounds according to the invention non-competitively inhibit the binding of comparative binding partners such as 5-HT (5-hydroxytryptamine) or 5-CT (5-carboxamidotryptamine), to 5-HT5 receptors. Non-competitive inhibition is understood such that guanidine compounds according to the invention modulate, in particular reduce the binding affinity of the binding of a comparative binding partner, in the present case e.g. 5-HT or 5-CT, to the receptor.

At least for the case of competitive inhibition, in other words in the case of reversible binding, the principle applies that the displacement of one binding partner by another increases with decreasing binding affinity of the one or increasing binding affinity of the other, with regard to the receptor. Guanidine compounds, according to the invention therefore expeditiously have a high binding affinity for 5-HT5 receptors. Such a binding affinity allows, on the one hand, an effective displacement of naturally occurring binding partners for 5-HT5 receptors, such as, for example, serotonin (5-hydroxytryptamine, 5-HT) itself, whereas the required concentration of guanidine compound according to the invention for a certain amount of this binding partner to bind to 5-HT5 receptors decreases with increasing binding affinity. With regard to the medical application, those guanidine compounds are therefore preferred whose binding affinity is so large that these compounds can be administered in justifiable amounts within the framework of an effective medical treatment.

One possibility to express the binding affinity is offered by the competition experiments mentioned above, with which one determines in-vitro the concentration of guanidine compound according to the invention which displaces another comparative binding partner from the receptor binding site by 50% (IC50-values). In this way one can also evaluate the competitive inhibition of the binding of 5-CT to 5-HT5 receptors, such that preferred guanidine compounds according to the invention have half-maximal inhibition constants IC50 of less than 10-5 M, preferably less than 10-6 M and in particular, less than 10-7 M. The binding affinity of guanidine compounds according to the invention can also be expressed via the inhibition constant Ki, which is generally also determined with in-vitro competition experiments. For the binding to 5-HT5 receptors guanidine compounds according to the invention preferably exhibit Ki-values of less than 10-6 M, preferably less than 10-7 M and particularly preferred less than 10-8 M.

Useful binding partners can bind to 5-HT5 with a lower, a substantially identical, or a higher affinity than to a certain receptor different from 5-HT5. As such, binding partners for 5-HT5 receptors in the context of the use according to the invention include in particular those whose binding affinity to 5-HT5 receptors is so high as compared to the affinity for 5-HT receptors, that they are suitable in an advantageous manner for the use according to the invention. This does not necessarily require a comparatively more selective binding to 5-HT5 receptors, although selective binding partners for the 5-HT5 receptors are a special embodiment of the present invention.

For example, one can use binding partners of high affinity not only to 5-HT5, but also to other 5-HT receptors. In this context, high affinity means Ki-values normally in the range of 1-10-10 M to 1-10-6 M. According to a special embodiment, guanidine compounds in the high affinity range for 5-HT receptors have a binding profile which is characterized by a binding affinity to 5-HT5 which, in comparison to other binding affinities of this range, is substantially identical or only slightly less. Factors of 10 or less can be advantageous.

Guanidine compounds according to the invention have binding affinities for 5-HT5 receptors which are larger than for one or more 5-HT receptors different than 5-HT5, thus, in particular, the receptors classified in the 5-HT receptor classes 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT6 and 5-HT7 given above. If the binding affinity of a binding partner for 5-HT5 receptors is larger than that for a 5-HT receptor different than 5-HT5, one speaks of a selective binding of these binding partners to 5-HT5 receptors, relative to the 5-HT receptor different from 5-HT5. Special binding partners are those whose binding affinity for 5-HT5 receptors is larger than for at least one 5-HT receptor. Guanidine compounds whose binding affinity for 5-HT5 receptors is larger than for all of the 5-HT receptors different from 5-HT5, represent a further special class of guanidine compounds according to the invention.

The term “selectivity” is understood as the characteristic of a binding partner to preferably bind to 5-HT5 receptors. It is decisive for the selectivity described above that the binding affinities for, on the one hand, 5-HT5 receptors and, on the other hand, for one or more 5-HT receptors different from 5-HT5, are sufficiently different. Preferable are differences in affinity according to which binding affinity proportions of at least 2, more preferred of at least 5, especially preferred of at least 10, preferably at least 20, especially preferred of at least 50 and in particular of at least 100 exist.

According to a further embodiment, guanidine compounds according to the invention bind, with reference to one or more 5-HT receptors different from 5-HT5, selectively to 5-HT5 receptors with the advantageous binding affinities described above.

According to a further embodiment, guanidine compounds according to the invention bind, with reference to all 5-HT receptors different from 5-HT5, selectively to 5-HT5 receptors with the advantageous binding affinities described above.

Guanidine compounds which bind to 5-HT5 receptors with the affinities and selectivities described above, and
which are expressed in glia cells and in particular by astrocytes are especially preferred. According to the invention, the human receptor variant is a preferred target for guanidine compounds according to the invention.

[0442] The binding of guanidine compounds according to the invention to 5-HT5 receptors is coupled to an effector function. Binding partners can be agonistic or antagonistic as well as partially agonistic and/or partially antagonistic in function. According to the invention, compounds which completely or partially imitate the activity of 5-HT to 5-HT5 receptors, are termed agonists. According to the invention, guanidine compounds which can block the agonistic activity of 5-HT to 5-HT5 receptors are termed antagonists.

[0443] According to a special embodiment of the present invention, guanidine compounds are employed whose binding, at least to 5-HT5 receptors of HEK 293 or SHSY-5Y cells effects a change of the agonist-induced stimulation of the binding of GTP to membrane-bound G-proteins, a change in intracellular calcium levels, a change in the agonist-induced induction of phospholipase C activity and/or a change in the cAMP-production. Concerning the change in intracellular calcium levels, the use of guanidine compounds which effect an increase in intracellular calcium levels represents a special embodiment of the invention. This embodiment also includes guanidine compounds which are efficacious in known animal models for neurodegenerative and neuropsychiatric processes.

[0444] Preferred are guanidine compounds which, with reference to their effector function in the sense described above, are selective for 5-HT5 receptors.

Forms of Administration and Formulation

[0445] Due to their pharmacological characteristics, the guanidine compounds according to the invention are useful as active agents for therapeutic purposes. In this regard, the guanidine compounds according to the invention are preferably put into a suitable form for administration prior to administration.

[0446] Further subject matter of the present invention is therefore compositions, in particular pharmaceutical compositions which contain at least one guanidine compound according to the invention and a pharmaceutically acceptable carrier or diluent agent.

[0447] Carriers or adjuvants which are pharmaceutically acceptable are those which are known for use as such in the field of pharmacy and neighboring fields. In particular, those listed in relevant medicine books (for example: DAB (Deutsches Arzneimittelbuch), Ph. Eur. (Pharmacopoeia Europaea), BP (Baccalaureus Pharmaciae), NF (National Formulary), USP (United States Pharmacopoeia), as well as other carriers whose properties do not rule out a physiological application.

[0448] Suitable carriers and adjuvants can be the following: wetting agents; emulsifying and suspending agents; preservative agents; antioxidants; anti-irritation agents; chelate-forming agents; coating adjuvants; emulsion stabilizers; film-forming agents; gel-forming agents; scent-marking agents; taste correction agents; resins; hydrocolloids; solvents; solution mediators; neutralizing agents; permeation accelerators; pigments; quaternary ammonium compounds; fat replenishing agents and excess fat agents; ointment, cream or oil bases; silicon derivatives; spreading agents; stabilizers; sterilizing agents; suppository bases; tablet adjuvants such as binders, fillers, lubricants, degradation agents or coatings; propellants; desiccants; clouding agents; thickeners; waxes; softeners; white petrolatum oils. The form to be taken in this regard depends on the knowledge of the skilled person as, for example, illustrated in Fiedler, H. P., Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, 4th Edition, Aulendorf: ECV-Editor-Kantor-Verlag, 1996.

[0449] Examples of suitable carriers and diluent agents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, acacia gum, calcium phosphate, alginate, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methylcellulose, methyl- and propylhydroxybenzoates, talcum, magnesium stearate, and mineral oil.

[0450] The guanidine compounds according to the invention can be formulated so as to ensure an immediate or a delayed release of the active agent to the patient.

[0451] Examples of suitable pharmaceutical compositions are solid medication forms, such as meal, powder, granulate, tablets, in particular film tablets, pastilles, sachets, cachets, dragees, capsules, such as hard and soft gelatin capsules, suppositories or vaginal medication forms, semisolid medication forms such as ointments, creams, hydrogels, pastes or patches as well as liquid medication forms such as solutions emulsions, in particular oil-in-water emulsions, suspensions, for example, lotions, preparations for injection and infusion, eye and ear drops. Implanted delivery devices can also be used for the administration of the guanidine compounds according to the invention. Moreover, liposomes or microspheres can also be used.

[0452] The compositions according to the invention can, for example, be administered via a common route.

[0453] In the preparation of compounds according to the invention the active agents are normally mixed or diluted with a suitable adjuvant, in this case also termed excipient. Excipients can be solid, semisolid or liquid materials, which serve as the vehicle, carrier or medium for the active agent. The admixing of further adjuvants normally occurs in a common manner. Steps to confer a shape, optionally in connection with mixing processes, can be performed, for example, granulation, compression and the like.

[0454] The use according to the invention of the active agents according to the invention includes in the context of the treatment a method. In this regard, an efficaciously administered at least one guanidine compound of the Formula I or IA is administered to the individual to be treated, preferably a human, in particular a human and also livestock or a pet, normally formulated corresponding to pharmaceutical practice.

[0455] The invention also relates to the preparation of agents for the treatment of an individual, preferably a mammal, in particular a human, livestock or a pet.

[0456] The guanidine compound of Formula I or IA or a corresponding pharmaceutical composition can be administered orally, rectally, topically, parenterally, including subcutaneous, intravenously, and intramuscularly, ocularly, pulmonarily, or nasally. An oral administration is preferred.

[0457] Effective dosing of the active agent may depend on the type of guanidine compound, the type of administration, the sickness to be treated and the severity of the sickness to be treated. Such an effective dosing of the active agent can be determined by one of ordinary skill in the art in the field.

[0458] The dosing depends on the age, condition and weight of the patient as well as the type of application.
Normally the daily dose of active agent will be between about 0.5 and 100 mg/kg body weight for oral administration and between about 0.1 and 10 mg/kg body weight for parenteral administration.

Preparation of the Guanidine Compounds


Scheme 1:

Scheme 2:

[0460] Hetaryl amines II are commercially available or producible according to methods known in the literature (for example, Houben-Weyl, Methoden der organischen Chemie, Volume E8b and E8c, Stuttgart, 1994; M. B. Smith, J. March, March’s Advanced Organic Chemistry, New York, 2001). The amines IV used in the synthetic path shown in Scheme 1 are also commercially available or can be prepared according to known protocols (e.g., Houben-Weyl, Methoden der organischen Chemie, 4th Edition, Volume XI/1, Stuttgart, 1957).

For the case that the moiety Q is a substituted thiazole moiety, the guanidine compounds of the general Formula I according to the invention can be constructed in one of the last steps according to Scheme 2. For this, one uses α-haloketone V, which is commercially available or can be prepared according to the literature (e.g., Houben-Weyl, Methoden der organischen Chemie, 4th Edition, Volume VII/2c/, Stuttgart, 1977).

[0462] The use of the intermediate IVA for the preparation of the guanidines according to the invention proceeds according to methods known to one of ordinary skill in the art, as for example described in the literature cited above. [0463] The guanidine compounds according to the invention as well as the intermediates possibly obtained can be...
isolated in the conventional way as well as, if necessary, purified, for example, by recrystallization from common organic solvents, preferably a short chain alcohol such as ethanol, or by chromatographic techniques. [0464] Depending on the starting materials, the guanidine compounds according to the invention of the formula are obtained in free form or already as acid addition salts. The compounds in free form as well as salts of these compounds resulting according to the method can be transformed into desired acid addition salts or into the free form in a known manner. [0465] The following examples illustrate the invention without restricting it. It should be noted that the notation and the formulaic representation of salts with protonated nitrogen reflects only one of many included possibilities with regard to the distribution of charge. This also applies for tautomeric forms.

PREPARATION EXAMPLES

Example 1

N-(2-methoxybenzyl)-N'-1,3-thiazole-2-ylguanidine

[0466] 1.1. N-1,3-thiazole-2-yl-1H-imidazole-1-carbothioamide

[0467] 35 g (349.5 mmol) of 2-aminothiazole and 62.3 g (349.5 mmol) thiocarbonylthioimidazole were stirred in 1300 ml acetone for a total of four days at room temperature. Filtration of the precipitate formed and drying yielded 65.5 g of light yellow solid.

1.2. N-1,3-thiazole-2-yl-thiourea

[0468] A mixture of 65 g (309.1 mmol) N-1,3-thiazole-2-yl-1H-imidazole-1-carbothioamide and 260 g of ammonium acetate were heated to 80°C in 400 ml ethanol for 1.5 hours; after completion of reaction the solvent was distilled off and water was added to the obtained residue. After extraction with CH2Cl2 and drying of the organic phase with Na2SO4, 59.6 g of the target product were obtained.

1.3. N-(2-methoxybenzyl)-N'-1,3-thiazole-2-ylguanidine

[0469] 400 mg (2.51 mmol) N-1,3-thiazole-2-yl-thiourea were suspended in 20 ml of methanol and 392 mg (2.76 mmol) methyl iodide were added. The reaction mixture was stirred for 4 hours at reflux. Following removal of the solvent by vacuum distillation, the residue obtained was dissolved in 20 ml ethanol, 1.72 g (12.6 mmol) 2-methoxybenzylamine were added and the mixture was stirred for 20 hours at reflux. The solvent was removed on the rotovap. The residue was separated by preparative HPLC (RP-18 column, eluent water/acetonitrile/0.1% acetic acid) and 380 mg N-(2-methoxybenzyl)-N'-1,3-thiazole-2-ylguanidine were obtained.

[0470] ESI-MS [M+H]+=263.15

Example 2

N-(2,6-dimethoxybenzyl)-N'-4-(ethyl-1,3-thiazole-2-yl)guanidine

[0471] 2.1 N-[(4-phenyl-1,3-thiazole-2-yl)amino] carbonothioyl]benzamidine

[0472] 3.10 g 2-amino-4-phenylthiazole (176 mmol) and 3.00 g benzoylisothiocyanate were heated in 50 ml acetone for 2 hours at reflux, during which a yellow solid was formed. The reaction mixture was subsequently stirred for 30 minutes at 5°C, the solid was suction-isolated and washed multiple times with n-pentane. After drying, 4.20 g of the target structure was obtained as an amorphous yellow solid.

[0473] ESI-MS [M+H]+=340.05

2.2 N-(4-phenyl-1,3-thiazole-2-yl)thiourea

[0474] 4.20 g N-[(4-phenyl-1,3-thiazole-2-yl)amino] carbonothioyl]benzamidine (339 mmol) were suspended in 40 ml methanol, were dissolved in aqueous sodium hydroxide (550 mg NaOH dissolved in 3 ml H2O) and were heated for 3 hours at reflux. The reaction mixture was evaporation-concentrated, the residue obtained was stirred with water and the precipitated solid was suction-isolated. After drying, 2.90 g of a light yellow solid were obtained.

[0475] ESI-MS [M+H]+=236.05

2.3 Methyl N-(4-phenyl-1,3-thiazole-2-yl)imidothiocarbamate hydroiodide

[0476] 1.1 2.42 g methyl iodide were added to 2.54 g N-(4-phenyl-1,3-thiazole-2-yl)thiourea (235 mmol) in 50 ml methanol and stirred for 3 hours at reflux. The reaction mixture was subsequently concentrated, the residue obtained was mixed together with n-pentane and dried. 3.90 g of product were obtained as a yellow solid, which was further reacted without further purification.

[0477] ESI-MS [M+H]+=250.15

2.4 N-(2,6-dimethoxybenzyl)-N'-4-(phenyl-1,3-thiazole-2-yl)guanidine

[0478] 3.00 g methyl N-(4-phenyl-1,3-thiazole-2-yl)imidothiocarbamate hydroiodide (377 mmol) and 3.60 g 2,6-dimethoxybenzylamine (167 mmol) were dissolved in 30 ml n-propanol and heated for 2 hours at 95°C in the microwave (radiation: 300 watt). The mixture was subsequently concentrated, the residue was dissolved in CH2Cl2, was washed with H2O, 5% NaHCO3 — and saturated NaCl solution, was dried over MgSO4, was filtered and was evaporation-concentrated. Following chromatography on silica gel (eluent: CH2Cl2/methanol 96:4) the solid obtained was recrystallized from methanol and 1.25 g of a white amorphous solid was obtained.

[0479] ESI-MS [M+H]+=369.15

[0480] 1H-NMR (400 MHz, CDCl3), δ (ppm): 3.90 (s, 6H), 4.45 (d, 2H), 5.58 (d, 2H), 6.78 (s, 1H), 7.2-7.3 (m, 5H), 7.78 (m, 2H), 7.85 (m, 2H).

Example 3

N-(2,6-dimethoxybenzyl)-N'-4-(ethyl-1,3-thiazole-2-yl)guanidine

[0481] 3.1 N-[(2,6-dimethoxybenzyl]amino][imino]methyl]thiourea

[0482] 2.00 g (14.8 mmol) dithiobiuret were placed in 25 ml methanol and 2.10 g (14.8 mmol) methyliodide were added at room temperature. The mixture was heated for 3 hours at reflux, then the solution was concentrated, was diluted with 25 ml of ethanol and 2.47 g (14.8 mmol) 2,6-dimethoxybenzylamine were added. The mixture was subsequently stirred again for 2 hours at reflux and subsequently for 30 minutes at 5°C. Filtration of the precipitate formed yielded 970 mg N-[(2,6-dimethoxybenzyl]amino][imino]methyl]thiourea.

[0483] ESI-MS [M+H]+=268.3

3.2 N-(2,6-dimethoxy-benzyl)-N'-4-ethyl-thiazole-2-yl)guanidine

[0484] 200 mg (0.75 mmol) N-[(2,6-dimethoxybenzyl]amino][imino]methyl]thiourea, 130 mg (0.77 mmol)
1-bromo-2-butanone and 104 mg (0.80 mmol) diisopropyl ethyamine were suspended in 10 ml dioxane and were stirred for 2 hours at 100°C. Following concentration of the reaction mixture, the mixture was diluted with dichloromethane, was washed with aqueous sodium chloride solution and the organic phase was dried with magnesium sulfate. After removing the drying agent and solvent, an oily residue was obtained, which was then purified on silica gel with dichloromethane/methanol. 100 mg N-(2,6-dimethoxybenzyl)-N′-(4-ethyl-thiazole-2-yl)-guanidine were obtained as a white solid by mixing with n-pentane.

[0485] ESI-MS [M+H]+=269.05

The Preparation of the End Products of Formula I or IA

[0486] The compounds 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 17, 18, 20, 22, 23, 24, 26, 27, 28, 30, 92 and 93 were prepared by reaction of suitable starting materials of the Formulæ II and IV analogously to Examples 1 and 2, while the compounds 19, 21, 25, 31-104 were prepared by reaction of suitable starting materials of the Formulæ IV and V analogously to Example 3:

Example 4
N-(2,5-dimethylbenzyl)-N′-1,3-thiazole-2-ylguanidine hydrochloride

[0487] ESI-MS [M+H]+=261.25

Example 5
N-(2,6-dimethoxybenzyl)-N′-1,3-thiazole-2-ylguanidine

[0488] ESI-MS [M+H]+=293.25

Example 6
N-(2-chloro-6-methoxybenzyl)-N′-1,3-thiazole-2-ylguanidine hydrochloride

[0489] ESI-MS [M+H]+=297.05

Example 7
N-(2-chlorobenzyl)-N′-1,3-thiazole-2-ylguanidine hydrochloride

[0490] ESI-MS [M+H]+=267.05

Example 8
N-(2-ethoxybenzyl)-N′-1,3-thiazole-2-ylguanidine hydrochloride

[0491] ESI-MS [M+H]+=277.05

Example 9
N-(2-fluoro-6-methoxybenzyl)-N′-1,3-thiazole-2-ylguanidine

[0492] ESI-MS [M+H]+=281.05

Example 10
N-(2-hydroxybenzyl)-N′-1,3-thiazole-2-ylguanidine acetate

[0493] ESI-MS [M+H]+=249.1

Example 11
N-(2-methoxybenzyl)-N′-1,3-thiazole-2-ylguanidine hydrochloride

[0494] ESI-MS [M+H]+=277.05

Example 12
N-(3-chloro-6-methoxybenzyl)-N′-1,3-thiazole-2-ylguanidine hydrochloride

[0496] ESI-MS [M+H]+=267.0

Example 14
N-(3-methoxybenzyl)-N′-1,3-thiazole-2-ylguanidine hydrochloride

[0497] ESI-MS [M+H]+=263.1

Example 15
N-(4-methoxybenzyl)-N′-1,3-thiazole-2-ylguanidine

[0498] ESI-MS [M+H]+=263.05

Example 16
N-[2-(2-methoxyphenyl)ethyl]-N′-1,3-thiazole-2-ylguanidine hydrochloride

[0499] ESI-MS [M+H]+=277.1

Example 17
N-[2-(benzyloxy)benzyl]-N′-1,3-thiazole-2-ylguanidine

[0500] ESI-MS [M+H]+=339.05

Example 18
N-1,3-thiazole-2-yl-N′-[2-(trifluoromethyl)benzyl] guanidine

[0501] ESI-MS [M+H]+=301.0

Example 19
N-[4-[3,5-bis(trifluoromethyl)phenyl]-1,3-thiazole-2-yl]-N′-(2,6-dimethoxybenzyl)guanidine hydrobromide

[0502] ESI-MS [M+H]+=505.15
Example 20
N-[1-mino(1,3-thiazole-2-ylamino)methyl]-2-methoxybenzamide

[0503] ESI-MS [M+H*] = 277.05
Example 21
N-[4-(2,5-dichlorophenyl)-1,3-thiazole-2-yl]-N'-[2,6-dimethoxybenzyl]guanidine hydrobromide

[0504] ESI-MS [M+H*] = 437.15/439.15
Example 22
N-[3-(2-amino(1,3-thiazole-2-ylamino)methyl]propoxy)phenylacetamide

[0505] ESI-MS [M+H*] = 334.1
Example 23
N-[3-(3-acetylphenoxy)propyl]-N'-1,3-thiazole-2-ylguanidine (2E)-But-2-endoate

[0506] ESI-MS [M+H*] = 319.1
Example 24
N-(2-methoxybenzyl)-N'-methyl-N'-1,3-thiazole-2-ylguanidine (2E)-But-2-endoate

[0507] ESI-MS [M+H*] = 277.0
Example 25
N-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1,3-thiazole-2-yl]-N'-[2,6-dimethoxybenzyl]guanidine hydrobromide

[0508] ESI-MS [M+H*] = 427.15
Example 26
N-ethyl-N'-[2-methoxybenzyl]-N'-1,3-thiazole-2-ylguanidine (2E)-But-2-endoate

[0509] ESI-MS [M+H*] = 291.0
Example 27
N-1,3-benzothiazole-2-yl-N'-[2,6-dimethoxybenzyl]guanidine (2E)-But-2-endoate

[0510] ESI-MS [M+H*] = 343.1
Example 28
N-1,3-benzothiazole-2-yl-N'-[2-methoxybenzyl]guanidine (2E)-But-2-endoate

[0511] ESI-MS [M+H*] = 313.0
Example 29
N-[2-(4-chlorophenoxymethyl)]N'-1,3-thiazole-2-ylguanidine (2E)-But-2-endoate

[0512] ESI-MS [M+H*] = 297.0
Example 30
N-(2-methoxybenzyl)-N'-thiophene-3-yl-guanidine acetate

[0513] ESI-MS [M+H*] = 262.25
Example 31
N-(2-methoxybenzyl)-N'-[4-(phenyl-1,3-thiazole-2-yl)guanidine

[0514] ESI-MS [M+H*] = 339.05
Example 32
N-(2,6-dimethoxybenzyl)-N'(4-methyl-1,3-thiazole-2-yl)guanidine

[0515] ESI-MS [M+H*] = 307.25
Example 33
N-(2-methoxybenzyl)-N'-[4-(2-naphthyl)-1,3-thiazole-2-yl]guanidine

[0516] ESI-MS [M+H*] = 389.05
Example 34
N-(2,6-dimethoxybenzyl)-N'-[4-(2-naphthyl)-1,3-thiazole-2-yl]guanidine

[0517] ESI-MS [M+H*] = 419.15
Example 35
N-[4-(4-chlorophenyl)-1,3-thiazole-2-yl]-N'-[2-methoxybenzyl]guanidine

[0518] ESI-MS [M+H*] = 373.05
Example 36
N-(4-tert-butyl-1,3-thiazole-2-yl)-N'-[2,6-dimethoxybenzyl]guanidine

[0519] ESI-MS [M+H*] = 349.15
Example 37
N-(4-tert-butyl-1,3-thiazole-2-yl)-N'-[2-methoxybenzyl]guanidine (2E)-But-2-endoate

[0520] ESI-MS [M+H*] = 319.15
Example 38
N-[4-(4-chlorophenyl)-1,3-thiazole-2-yl]-N'-[2,6-dimethoxybenzyl]guanidine

[0521] ESI-MS [M+H*] = 403.25
Example 39
N-(2-methoxybenzyl)-N'-[4-methyl-1,3-thiazole-2-yl]guanidine (2E)-But-2-endoate

[0522] ESI-MS [M+H*] = 277.05
Example 40
N-(4,5-dimethyl-1,3-thiazole-2-yl)-N’-(2-methoxybenzyl)guanidine

[0523] ESI-MS [M+H+] = 291.15

Example 41
N-(2-methoxybenzyl)-N’-(4-pyridine-2-yl-1,3-thiazole-2-yl)guanidine

[0524] ESI-MS [M+H+] = 340.15

Example 42
N-(2,6-dimethoxybenzyl)-N’-(4-pyridine-2-yl-1,3-thiazole-2-yl)guanidine (2E)-But-2-endoiate

[0525] ESI-MS [M+H+] = 370.15

Example 43
N-[4-(2-chlorophenyl)-1,3-thiazole-2-yl]-N’-(2-methoxybenzyl)guanidine (2E)-But-2-endoiate

[0526] ESI-MS [M+H+] = 373.05

Example 44
N-[4-(2-chlorophenyl)-1,3-thiazole-2-yl]-N’-(2,6-dimethoxybenzyl)guanidine

[0527] ESI-MS [M+H+] = 403.05

Example 45
N-(2,6-dimethoxybenzyl)-N’-(4-pyridine-4-yl-1,3-thiazole-2-yl)guanidine

[0528] ESI-MS [M+H+] = 370.0

Example 46
N-(2-methoxybenzyl)-N’-(4-pyridine-4-yl-1,3-thiazole-2-yl)guanidine

[0529] 1H-NMR (400 MHz, CDCl3), δ (ppm): 3.85 (s, 3H), 4.40 (d, 2H), 6.95 (m, 1H), 7.15 (m, 1H), 7.25-7.80 (m, 6H). 8.55 (m, 2H).

Example 47
methyl-[2-[(iminomethyl)amino][2-methoxybenzyl]amino]-1,3-thiazole-4-yl]acetate

[0530] ESI-MS [M+H+] = 440.25

Example 48
N-(2-methoxybenzyl)-N’-(4-pyridine-3-yl-1,3-thiazole-2-yl)guanidine

[0531] ESI-MS [M+H+] = 340.15

Example 49
methyl-[2-[(2,6-dimethoxybenzyl)amino][iminomethyl]amino]-1,3-thiazole-4-yl]acetate

[0532] ESI-MS [M+H+] = 365.15

Example 50
N-(2,6-dimethoxybenzyl)-N’-(4-pyridine-3-yl-1,3-thiazole-2-yl)guanidine acetate

[0533] ESI-MS [M+H+] = 370.25

Example 51
2-(2cerr[[2,6-dimethoxybenzyl]amino][iminomethyl]amino)-1,3-thiazole-4-yl)-N’-(2-methoxybenzyl)acetamide (2E)-But-2-endoiate

[0534] ESI-MS [M+H+] = 440.25

Example 52
N-(2-methoxybenzyl)-N’-[4-(trifluoromethyl)-1,3-thiazole-2-yl]guanidine (2E)-But-2-endoiate

[0535] ESI-MS [M+H+] = 331.05

Example 53
N-(2,6-dimethoxybenzyl)-N’-[4-(trifluoromethyl)-1,3-thiazole-2-yl]guanidine

[0536] ESI-MS [M+H+] = 361.05

Example 54
N-(2-methoxybenzyl)-N’-(5-methyl-1,3-thiazole-2-yl)guanidine (2E)-But-2-endoiate

[0537] ESI-MS [M+H+] = 277.25

Example 55
N-(2,6-dimethoxybenzyl)-N’-(5-methyl-1,3-thiazole-2-yl)guanidine

[0538] ESI-MS [M+H+] = 307.25

Example 56
N-(2,6-dimethoxybenzyl)-N’-[4-(4-fluorophenyl)-1,3-thiazole-2-yl]guanidine

[0539] ESI-MS [M+H+] = 387.15

Example 57
N-(2,6-dimethoxybenzyl)-N’-[4-(4-methylphenyl)-1,3-thiazole-2-yl]guanidine

[0540] ESI-MS [M+H+] = 383.15

Example 58
N-(2,6-dimethoxybenzyl)-N’-[4-(4-methoxyphenyl)-1,3-thiazole-2-yl]guanidine

[0541] ESI-MS [M+H+] = 399.15

Example 59
N-(2-fluoro-6-methoxybenzyl)-N’-(4-phenyl-1,3-thiazole-2-yl)guanidine

[0542] ESI-MS [M+H+] = 357.05

Example 50
N-(2,6-dimethoxybenzyl)-N’-(4-pyridine-3-yl-1,3-thiazole-2-yl)guanidine acetate

[0533] ESI-MS [M+H+] = 370.25
Example 60
N-[4-(4-cyanophenyl)-1,3-thiazole-2-yl]-N'-(2,6-dimethoxybenzyl)guanidine

**[0544]** ESI-MS [M+H]+ = 394.05

Example 61
N-(2,6-dimethoxybenzyl)-N'-[4-(3-methoxyphenyl)-1,3-thiazole-2-yl]guanidine

**[0545]** ESI-MS [M+H]+ = 399.15

Example 62
N-[4-{4-(diethylamino)phenyl}-1,3-thiazole-2-yl]-N'-(2,6-dimethoxybenzyl)guanidine

**[0546]** ESI-MS [M+H]+ = 440.2

Example 63
N-(2,6-dimethoxybenzyl)-N'-[4-(4-pyrrolidine-1-ylphenyl)-1,3-thiazole-2-yl]guanidine hydrobromide

**[0547]** ESI-MS [M+H]+ = 438.3

Example 64
N-(2,6-dimethoxybenzyl)-N'-[4-[4-(trifluoromethoxy)phenyl]-1,3-thiazole-2-yl]guanidine hydrobromide

**[0548]** ESI-MS [M+H]+ = 453.05

Example 65
N-(2,6-dimethoxybenzyl)-N'-[4-(4-morpholine-4-ylphenyl)-1,3-thiazole-2-yl]guanidine hydrobromide

**[0549]** ESI-MS [M+H]+ = 454.15

Example 66
N-(2,6-dimethoxybenzyl)-N'-(5-phenyl-1,3-thiazole-2-yl)guanidine hydrobromide

**[0550]** ESI-MS [M+H]+ = 369.15

Example 67
N-[4-(1-benzofuran-2-yl)-1,3-thiazole-2-yl]-N'-(2,6-dimethoxybenzyl)guanidine hydrobromide

**[0551]** ESI-MS [M+H]+ = 409.05

Example 68
N-[4-(3,5-difluorophenyl)-1,3-thiazole-2-yl]-N'-(2,6-dimethoxybenzyl)guanidine hydrobromide

**[0552]** 1H-NMR (400 MHz, CDCl3), δ (ppm)=3.83 (s, 6H), 4.53 (d, 2H), 6.78 (d, 2H), 7.24 (m, 1H), 7.38-7.45 (m, 3H), 7.99 (s, 1H), 8.34 (s wide, 2H), 9.50 (s wide, 1H), 11.90 (s wide, 1H).

Example 69
N-[4-(1,3-benzodioxol-5-yl)-1,3-thiazole-2-yl]-N'-(2,6-dimethoxybenzyl)guanidine hydrobromide

**[0553]** ESI-MS [M+H]+ = 413.05

Example 70
N-(2,6-dimethoxybenzyl)-N'-[4-(2-fluorophenyl)-1,3-thiazole-2-yl]guanidine hydrobromide

**[0554]** ESI-MS [M+H]+ = 387.15

Example 71
N-[4-(2-[[2,6-dimethoxybenzyl]amino][imidino]methyl)amino]-1,3-thiazole-4-yl]phenyl)methanesulfonamide hydrobromide

**[0555]** ESI-MS [M+H]+ = 462.15

Example 72
N-(2,6-dimethoxybenzyl)-N'-[4-(3-thienyl)-1,3-thiazole-2-yl]guanidine acetate

**[0556]** ESI-MS [M+H]+ = 375.05

Example 73
N-(2,6-dimethoxybenzyl)-N'-[4-(3-fluorophenyl)-1,3-thiazole-2-yl]guanidine hydrobromide

**[0557]** ESI-MS [M+H]+ = 387.15

Example 74
N-(4-biphenyl-4-yl)-1,3-thiazole-2-yl-N'-(2,6-dimethoxybenzyl)guanidine hydrobromide

**[0558]** ESI-MS [M+H]+ = 445.15

Example 75
N-(2,6-dimethoxybenzyl)-N'-[4-(2-methoxyphenyl)-1,3-thiazole-2-yl]guanidine hydrobromide

**[0559]** ESI-MS [M+H]+ = 399.15

Example 76
N-(2,6-dimethoxybenzyl)-N'-(4-diphenylmethyl)-1,3-thiazole-2-yl]guanidine hydrobromide

**[0560]** ESI-MS [M+H]+ = 459.25

Example 77
N-[4-(5-chloro-2-thienyl)-1,3-thiazole-2-yl]-N'-(2,6-dimethoxybenzyl)guanidine hydrobromide

**[0561]** ESI-MS [M+H]+ = 409.05

Example 78
N-[4-(1-benzothiophene-2-yl)-1,3-thiazole-2-yl]-N'-(2,6-dimethoxybenzyl)guanidine hydrobromide

**[0562]** ESI-MS [M+H]+ = 425.05
Example 79
N-[4-{2-[[2-(6-dimethoxybenzyl)amino]amino]methyl-amino}-1,3-thiazole-4-yl]phenylacetamide acetate

[0563] ESI-MS [M+H]+=462.15

Example 80
N-(2,6-dimethoxybenzyl)-N'-8H-indeno[1,2-d][1,3]thiazole-2-ylguanidine hydrobromide

[0564] ESI-MS [M+H]+=381.15

Example 81
N-(2,6-dimethoxybenzyl)-N'-(5-methyl-4-phenyl-1,3-thiazole-2-yl)guanidine hydrobromide

[0565] ESI-MS [M+H]+=375.05

Example 82
N-(2,6-dimethoxybenzyl)-N'-[4-{4-(methylsulfonyl)phenyl}-1,3-thiazole-2-yl]guanidine hydrobromide

[0566] ESI-MS [M+H]+=447.05

Example 83
N-(2,6-dimethoxybenzyl)-N'-[4-(3-phenylisoxazole-5-yl)-1,3-thiazole-2-yl]guanidine hydrobromide

[0567] ESI-MS [M+H]+=436.15

Example 84
N-(2,6-dimethoxybenzyl)-N'-[4-{2-(trifluoromethyl)phenyl}-1,3-thiazole-2-yl]guanidine hydrobromide

[0568] ESI-MS [M+H]+=437.15

Example 85
N-[4-(1-adamantyl)-1,3-thiazole-2-yl]-N'-(2,6-dimethoxybenzyl)guanidine hydrobromide

[0569] ESI-MS [M+H]+=427.15

Example 86
N-(2-fluoro-6-methoxybenzyl)-N'-(4-methyl-1,3-thiazole-2-yl)guanidine

[0570] ESI-MS [M+H]+=295.05

Example 87
N-[4-{3,4-difluorophenyl}-1,3-thiazole-2-yl]-N'-(2,6-dimethoxybenzyl)guanidine hydrobromide

[0571] ESI-MS [M+H]+=405.15

Example 88
N-[4-(1,3-benzothiazole-2-yl)-1,3-thiazole-2-yl]-N'-(2,6-dimethoxybenzyl)guanidine hydrobromide

[0572] ESI-MS [M+H]+=426.05

Example 89
N-[4-(3-chlorophenyl)-1,3-thiazole-2-yl]-N'-(2,6-dimethoxybenzyl)guanidine hydrobromide

[0573] ESI-MS [M+H]+=403.05

Example 90
N-(2,6-dimethoxybenzyl)-N'-[4-(2-thienyl)-1,3-thiazole-2-yl]guanidine hydrobromide

[0574] ESI-MS [M+H]+=375.05

Example 91
N-[4-(2,4-difluorophenyl)-1,3-thiazole-2-yl]-N'-(2,6-dimethoxybenzyl)guanidine hydrobromide

[0575] ESI-MS [M+H]+=405.15

Example 92
N-(2-methoxybenzyl)-N'-(1-methyl-1H-benzimidazole-2-yl)guanidine

[0576] ESI-MS [M+H]+=310.15

Example 93
N-[1H-benzimidazole-2-yl]-N'-(2-methoxybenzyl)guanidine acetate

[0577] ESI-MS [M+H]+=296.15

Example 94
N-(2,6-dimethoxybenzyl)-N'-(4,5,6,7-tetrahydro-1,3-benzothiazole-2-yl)guanidine acetate

[0578] ESI-MS [M+H]+=347.15

Example 95
N-[2,6-dimethoxybenzyl]-N'-(4-(4-isopropylphenyl)-1,3-thiazole-2-yl)guanidine

[0579] ESI-MS [M+H]+=411.15

Example 96
N-(2,6-dimethoxybenzyl)-N'-(4-benzothiophene-3-yl)-1,3-thiazole-2-yl)guanidine hydrobromide

[0580] ESI-MS [M+H]+=425.05

Example 97
N-[4-cyclohexyl-1,3-thiazole-2-yl]-N'-(2,6-dimethoxybenzyl)guanidine

[0581] ESI-MS [M+H]+=375.15/376.15

Example 98
N-[4-(2-fluorophenyl)-1,3-thiazole-2-yl]-N'-(2-methoxybenzyl)guanidine

[0582] ESI-MS [M+H]+=357.05
Example 99

N-[4-(3-fluorophenyl)-1,3-thiazole-2-yl]-N'-[2-methoxybenzyl]guanidine

[0853] ESI-MS [M+H]+ = 357.05

Example 100

N-[2-methoxybenzyl]-N'-[4-[4-(trifluoromethoxy)phenyl]-1,3-thiazole-2-yl]guanidine

[0854] ESI-MS [M+H]+ = 423.05

Example 101

N-[4-(1,3-benzodioxol-5-yl)-1,3-thiazole-2-yl]-N'-[2-methoxybenzyl]guanidine

[0855] ESI-MS [M+H]+ = 383.05

Example 102

2-[(2,6-dimethoxybenzyl)amino][methylamino]-N,N,N4-trimethyl-1,3-thiazole-5-carboxamide

[0856] ESI-MS [M+H]+ = 378.15

Example 103

N-[2-methoxybenzyl]-N'-[4-[2-(trifluoromethyl)phenyl]-1,3-thiazole-2-yl]guanidine

[0857] ESI-MS [M+H]+ = 407.05

Example 104

N-[4-[2-[(methylamino)[2-methoxybenzyl]amino][methylamino]-1,3-thiazole-4-yl]phenyl]methanesulfonamide

[0858] ESI-MS [M+H]+ = 432.05

Example 105

N'-[2,6-dimethoxybenzyl]-N-(3-phenyl-1,2,4-thiadiazole-5-yl)guanidine (0.5 mmol) was prepared analogously to Example 1 with the following variations: the alkylation of N-(3-phenyl-1,2,4-thiadiazole-5-yl)thiourea with methyl iodide was performed in the presence of 1.5 equivalents triethylamine and the reaction of methyl N'-[2,6-dimethoxybenzyl]-1,3-thiazole-5-yl)midothiocarbamate proceeded with 2,6-dimethoxybenzyl amine at 140 °C. Following chromatographic purification, the product was converted to (2E)-but-2-enoic acid.

[0859] 1H-NMR (500 MHz, d6-DMSO), δ (ppm): 3.83 (s, 6H), 4.42 (d, 2H), 6.63 (s, 1H), 6.74 (d, 2H), 7.24 (sbr, 2H), 7.34 (t, 1H), 7.44 (m, 3H), 7.96 (sbr, 2H).

[0860] 13C-NMR (100.6 MHz, d6-DMSO), δ (ppm): 33.80 (t), 55.92 (q), 104.15 (2x), 112.67 (s), 127.13 (128.53 (2x), 129.73 (d), 133.14 (s), 134.00 (2x), 156.13 (s), 158.07 (s), 166.02 (2xs).

Example 106

N'-[2,6-dimethoxybenzyl]-N-(3-phenyl-1,2,4-thiadiazole-5-yl)guanidine (2E)-but-2-enoate; ESI-MS [M+H]+ = 340.05

[0852] The synthesis proceeded analogously to Example 105

Example 107

N'-[2,6-dimethoxybenzyl]-N'-[4-(trifluoromethyl)phenyl]-1,3-thiazole-2-yl]guanidine

[0853] Preparation took place analogously to Example 3 by reaction of 140 mg (0.52 mmol) N'-[(2,6-dimethoxybenzyl)amino][methylamino]phenyl]methyliothiourea with 140 mg (0.52 mmol) 4-(trifluoromethyl)phenacyl bromide. The emulsion was suspended in 3 ml dioxane, were added to 0.3 ml acetic acid and were heated for 40 minutes in the microwave (radiation 300 Watt). The mixture was subsequently concentrated and the crude product obtained was purified by chromatography on silica gel (dichloromethane/methanol 1:4%). Stirring of the yellow foam obtained with methyl tert.-butyl ether yielded 120 mg of a white amorphous solid.

[0854] ESI-MS [M+H]+ = 437.05.

[0855] The following were prepared analogously to Example 107:

Example 108

N'-[2,6-dimethoxybenzyl]-N'-[4-[3-(trifluoromethyl)phenyl]-1,3-thiazole-2-yl]guanidine

[0856] ESI-MS [M+H]+ = 437.05

Example 109

N-[4-[4-(difluoromethoxy)phenyl]-1,3-thiazole-2-yl]-N'-[2,6-dimethoxybenzyl]guanidine hydrobromide

[0857] ESI-MS [M+H]+ = 435.05

Example 110

N-[2,6-dimethoxybenzyl]-N'-[4-[4-(4-fluoro-2-methoxyphenyl)-1,3-thiazole-2-yl]guanidine hydrobromide

[0858] ESI-MS [M+H]+ = 412.15

Example 111

N-[2,6-dimethoxybenzyl]-N'-[4-[4-(5-fluoro-2-methoxyphenyl)-1,3-thiazole-2-yl]guanidine hydrobromide

[0859] ESI-MS [M+H]+ = 417.15

Example 112

N-[2,6-dimethoxybenzyl]-N'-[4-[4-(5-fluoro-2-methoxyphenyl)-1,3-thiazole-2-yl]guanidine hydrobromide
Example 113

N-(2,6-dimethoxybenzyl)-N’-[4-(2,6-dimethoxypyrene-1,3-thiazole-2-yl)]guanidine

[0601] ESI-MS [M+H+] = 429.15

Example 114

N-(2,6-dimethoxybenzyl)-N’-[4-(4-fluoro-1-naphthyl)-1,3-thiazole-2-yl]guanidine

[0602] ESI-MS [M+H+] = 437.25

Example 115

N-[4-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazole-2-yl]-N’-(2,6-dimethoxybenzyl)guanidine

[0603] ESI-MS [M+H+] = 411.15

Example 116

N-[4-(2-chloro-4-fluorophenyl)-1,3-thiazole-2-yl]-N’-(2,6-dimethoxybenzyl)guanidine

[0604] ESI-MS [M+H+] = 421.05

Example 117

N-(2,6-dimethoxybenzyl)-N’-[4-(2-furyl)-1,3-thiazole-2-yl]guanidine hydrobromide

[0605] ESI-MS [M+H+] = 359.15

Example 118

N-(2,6-dimethoxybenzyl)-N’-[4-(4-fluorophenyl)-5-methyl-1,3-thiazole-2-yl]guanidine

[0606] ESI-MS [M+H+] = 401.15

Example 119

N-[4-(2,6-dichlorophenyl)-1,3-thiazole-2-yl]-N’-(2,6-dimethoxybenzyl)guanidine

[0607] ESI-MS [M+H+] = 439.05

Example 120

tert-buty1 2-(2-[[[2,6-dimethoxypyrene] amino] (imino)methyl] amino]-1,3-thiazole-4-yl)pyrrolidine-1-carboxylate

[0608] ESI-MS [M+H+] = 462.25

Example 121

N-(2,6-dimethoxybenzyl)-N’-[4-(4-methyl-2-thienyl)-1,3-thiazole-2-yl]guanidine

[0609] ESI-MS [M+H+] = 289.05

Example 122

N-(2,6-dimethoxybenzyl)-N’-[4-pyrimidine-2-yl]-1,3-thiazole-2-yl]guanidine hydrobromide

[0610] ESI-MS [M+H+] = 370.85

Example 123

N-[4-(5-chloropyridine-2-yl)-1,3-thiazole-2-yl]-N’-(2,6-dimethoxybenzyl)guanidine acetate

[0611] ESI-MS [M+H+] = 404.25

Example 124

N-[4-(4-chloro-2-thienyl)-1,3-thiazole-2-yl]-N’-(2,6-dimethoxybenzyl)guanidine

[0612] ESI-MS [M+H+] = 409.05

Example 125
tert-butyl 2-(2-[[[2,6-dimethoxypyrene] amino] (imino)methyl] amino]-1,3-thiazole-4-yl)methyl] carbamate

[0613] ESI-MS [M+H+] = 422.15

Example 126

N-[4-(3,5-dichloropyridine-2-yl)-1,3-thiazole-2-yl]-N’-(2,6-dimethoxybenzyl)guanidine

[0614] ESI-MS [M+H+] = 440.05

Example 127

N-(4,5-dihydropyridinol[1,2-d][1,3]thiazole-2-yl)-N’-(2,6-dimethoxybenzyl)guanidine

[0615] ESI-MS [M+H+] = 395.15

Example 128

N-(2,6-dimethoxybenzyl)-N’-[5-(4-fluorophenyl)-1,3-thiazole-2-yl]guanidine

[0616] ESI-MS [M+H+] = 387.15

[0617] The following were prepared analogously to Example 2:

Example 129

N-(5-fluoro-2-methoxybenzyl)-N’-(4-phenyl-1,3-thiazole-2-yl)guanidine

[0618] ESI-MS [M+H+] = 357.05

Example 130

N-(5-fluoro-2-methoxybenzyl)-N’-(4-methyl-1,3-thiazole-2-yl)guanidine fumarate

[0619] ESI-MS [M+H+] = 295.05

Example 131

N-(2,6-dimethoxybenzyl)-N’-[4-isopropyl-1,3-thiazole-2-yl]guanidine

[0620] ESI-MS [M+H+] = 335.15
Example 132

N-(2-chloro-6-methoxybenzyl)-N'-(4-phenyl-1,3-thiazole-2-yl)guanidine

[0621] 132.1 2-chloro-6-methoxybenzylbromide

[0622] To 13.0 g (84.92 mmol) 3-chloro-2-methylanisole in 80 ml CCl₄ at reflux were added 0.4 g dibenzyl peroxide and then, subsequently and portion-wise, a mixture of 15.2 g N-bromosuccinimide and 0.4 g dibenzyl peroxide. After completion of reaction the mixture was evaporation-concentrated, the residue was dissolved in dichloromethane, was sequentially washed with water and saturated NaCl solution, was dried over MgSO₄, filtered and again evaporation-concentrated. 20.8 yellow oil.

132.2 2-chloro-6-methoxy-benzylamine hydrochloride

[0623] 13 g di-tert butylmethylcarbonate dissolved in 40 ml DMF were added drop-wise to a suspension of 24 g NaH (60% dispersion in mineral oil; de-oiled with n-pentane) in 20 ml DMF at 50 °C. After 1 hour 15 g 2-chloro-6-methoxy-benzylbromide (crude product 131.1) dissolved in DMF were added, a further 100 ml of DMF were added to the mixture and the mixture was stirred overnight at room temperature. For the workup, excess NaH was destroyed by addition of 20 ml DMF-water 1:1, the mixture was subsequently evaporation-concentrated until dry and the residue obtained was dissolved in dichloromethane, was sequentially washed with 0.1n HCl and saturated NaCl solution, was dried over MgSO₄, was filtered and evaporation-concentrated once again. Mixing of the thusly obtained oily residue with cyclohexane yielded 11.9 g of a beige solid, which were reacted further without being further purified.

[0624] For the Boc removal, 60 ml of 4n HCl in dioxane was added to 11.6 g of solid in 60 ml dichloromethane and was heated for 2 hours at 70°C: Evaporation concentration of the reaction mixture and treatment of the obtained oil with n-pentane yielded 6.0 g of 2-chloro-6-methoxy-benzylamine hydrochloride as an amorphous solid, ESI-MS [M+H]+ =172.05. For the further reactions the hydrochloride was transformed into the free base.

132.3 N-(2-chloro-6-methoxybenzyl)-N'-(4-phenyl-1,3-thiazole-2-yl)guanidine

[0625] Reaction of 0.35 g methyl-N'-(4-phenyl-1,3-thiazole-2-yl)imidodithiocarbamate hydroiodide (0.95 mmol) and 0.5 g 2-chloro-6-methoxy-benzylamine (2.91 mmol) analogously to Example 2, 2.4, yielded 220 mg N-(2-chloro-6-methoxy-benzyl)-N'-(4-phenyl-1,3-thiazole-2-yl)guanidine; ESI-MS [M+H]+ =373.05

[0626] The following were prepared analogously to Example 132:

Example 133

N-(2-chloro-6-methoxybenzyl)-N'-(4-pyridine-2-yl-1,3-thiazole-2-yl)guanidine

[0627] ESI-MS [M+H]+ =374.05

Example 134

N-(2-chloro-6-methoxybenzyl)-N'-(4-(5-chloropyrimidine-2-yl)-1,3-thiazole-2-yl)guanidine

[0628] ESI-MS [M+H]+ =410.05

Example 135

N-(2-chloro-6-methoxybenzyl)-N'-(4-pyridine-2-yl-1,3-thiazole-2-yl)guanidine

[0629] ESI-MS [M+H]+ =375.05

Example 136

N-(2-chloro-6-methoxybenzyl)-N'-(4-(4-fluorophenyl)-1,3-thiazole-2-yl)guanidine

[0630] ESI-MS [M+H]+ =391.05

Example 137

N-(4-(5-chloropyridine-2-yl)-1,3-thiazole-2-yl)-N'-(2-methylbenzyl)guanidine

[0631] 137.1 2-methoxy-6-methylbenzylamine hydrochloride

[0632] The preparation proceeded analogously to Example 2; 2.4, starting from 7.1 g (41.61 mmol) 2-methoxy-6-methylbenzylchloride. Removal of Boc yielded 1.2 g 2-methoxy-6-methylbenzylamine hydrochloride as a white solid; the hydrochloride was transformed into the free base for further reactions.

[0633] 1H-NMR (400 MHz, DMSO-d₆); δ (ppm)=2.38 (s, 3H), 3.29 (s, 3H), 3.98 (s, 2H), 6.86 (d, 1H), 6.92 (d, 1H), 7.29 (t, 1H), 7.45 (s, 1H).

137.2 N-(4-(5-chloropyridine-2-yl)-1,3-thiazole-2-yl)-N'-(2-methoxy-6-methylbenzyl)guanidine

[0634] The reaction proceeded analogouslyby to Example 2, 2.4, starting from 260 mg (0.63 mmol) methyl-N'-(4-(5-chloropyridine-2-yl)-1,3-thiazole-2-yl)imidodithiocarbamate hydroiodide with 260 mg (1.39 mmol) 2-methoxy-6-methylbenzylamine hydrochloride; after purification 64 mg of the target product were obtained as a white solid.

[0635] 1H-NMR (400 MHz, DMSO-d₆); δ (ppm)=2.48 (s, 3H), 3.85 (s, 3H), 4.75 (d, 2H), 6.89 (d, 1H), 6.99 (d, 1H), 7.29 (m, 1H), 7.40 (m, 1H), 7.73 (s, 1H), 7.91 (dd, 1H), 8.61 (d, 1H), 9.81 (s, 1H), 11.68 (s, 1H).

[0636] The following were prepared in an analogous manner:

Example 138

N-(4-(4-fluorophenyl)-1,3-thiazole-2-yl)-N'-(2-methoxy-6-methylbenzyl)guanidine

[0637] ESI-MS [M+H]+ =371.15

Example 139

N-(2-methoxy-6-methylbenzyl)-N'-(4-pyrimidine-2-yl-1,3-thiazole-2-yl)guanidine

[0638] ESI-MS [M+H]+ =355.05

Example 140

N-(2-methoxy-6-methylbenzyl)-N'-(4-(5-chloropyrimidine-2-yl)-1,3-thiazole-2-yl)guanidine

[0639] ESI-MS [M+H]+ =354.15
Example 141
N-(2-fluoro-6-methoxybenzyl)-N'-[4-(4-fluorophenyl)-1,3-thiazole-2-yl]guanidine

[0640] ESI-MS [M+H]+=375.15

Example 142
N-(2,6-dimethoxybenzyl)-N'-[4-(4-fluoro-2-hydroxyphenyl)-1,3-thiazole-2-yl]guanidine

[0641] 142.1 2-bromo-1-(4-fluoro-2-hydroxyphenyl)ethane

[0642] To 450 mg (2.92 mmol) 2-fluorohydroxyacetophenone in 5 ml diethylether were added 2.5 g CuBr₂ and were heated for 1 hour at 120° C. in the microwave. Filtration of the mixture over Celite and evaporation concentration yielded 870 mg of red oil, which was directly used further.

142.2 N-(2,6-dimethoxybenzyl)-N'-[4-(4-fluoro-2-hydroxyphenyl)-1,3-thiazole-2-yl]guanidine

[0643] Reaction analogously to Example 107 yielded the target product, 188 mg; ESI-MS [M+H]+=403.25.

Example 143
N-(2,6-dimethoxybenzyl)-N'-[4-(4-fluorobenzyl)-1,3-thiazole-2-yl]guanidine

[0644] Production analogously to Example 3, 3.2; the isolated crude product was purified by chromatography on RP-silica gel (Chromabond column, acetonitrile/water=40:1% glacial acetic acid; 0-100%). After lyophilization 1 mg of the target product was obtained as a white solid; ESI-MS [M+H]+=401.15.

Example 144
N-(2,6-dimethoxybenzyl)-N'-[4-(5-fluoropyridine-2-yl)-1,3-thiazole-2-yl]guanidine

[0645] 144.1 1-(5-fluoropyridine-2-yl)ethanone

[0646] 1 g (5.68 mmol) 2-bromo-5-fluoropyridine, 160 mg dichlorobis(triphenylphosphine) palladium and 170 mg CuI were suspended in baked flasks under protective gas in 30 ml acetonitrile, 6.09 g (16.87 mmol) (1-ethoxyvinyl)tributylstannane were added, the mixture was heated 8 hours at reflux, 200 ml 1.5n HCl were subsequently added and reflux was continued for an additional hour. For workup the mixture was neutralized with saturated NaHCO₃ solution, was extracted 3x with ethyl acetate, the combined organic phases were washed with saturated NaCl solution and were dried with MgSO₄. After filtration 30 ml saturated KF solution were added, the mixture was filtered over Celite and evaporation concentrated. Purification by chromatography on silica gel (dichloromethane/methanol 0-3%) yielded 120 mg 1-(5-fluoropyridine-2-yl)ethanone as an oil, which was directly reacted further.

[0647] ¹H-NMR (400 MHz, DMSO-d₆), δ (ppm)=2.65 (s, 3H), 7.92 (m, 1H), 8.18 (dd, 1H), 8.74 (d, 1H).

144.2 2-bromo-1-(5-fluoropyridine-2-yl)ethanone

[0648] 100 mg 1-(5-fluoropyridine-2-yl)ethanone, 500 mg polymer-bound tribromide (1 mmol Br₂/g, Aldrich) and 0.05 ml glacial acetic acid in 5 ml THF were shaken for approximately 24 hours at room temperature. Filtration and evaporation concentration yielded 150 mg of the desired bromide as a yellow oil, which was reacted further without further purification.

144.3 N-(2,6-dimethoxybenzyl)-N'-[4-(5-fluoropyridine-2-yl)-1,3-thiazole-2-yl]guanidine

[0649] The transformation proceeded analogously to Example 107; 83 mg of the target product were isolated; ESI-MS [M+H]+=388.15.

Example 145
N-[4-(3,5-difluoropyridine-2-yl)-1,3-thiazole-2-yl]-N'(2,6-dimethoxybenzyl)guanidine

[0650] 145.1 1-(3,5-difluoropyridine-2-yl)ethanone

[0651] Methylene magnesium bromide (10 ml of a 3N solution in diethyl ether) were added drop-wise with stirring to a solution of 15 g (10.71 mmol) 2-cyano-3,5-difluoropyridine in 100 ml THF at 0° C. and the mixture was subsequently stirred at room temperature until reaction was complete. For workup the mixture was acidified with 10% H₂SO₄ to pH 4, was subsequently made basic with 25% NH₄OH, was extracted 2x with dichloromethane, and the combined organic phases were dried with MgSO₄. Purification by chromatography on silica gel (dichloromethane/methanol 0-5%) yielded 500 mg of a light colored oil, which crystallized upon being left to stand.

[0652] ¹H-NMR (400 MHz, DMSO-d₆), δ (ppm)=2.62 (sm 3H), 8.11 (m, 1H), 8.86 (d, 1H).

145.2 2-bromo-1-(3,5-difluoropyridine-2-yl)ethanone

[0653] The bromination was performed analogously to Example 144.2, and the bromide obtained were reacted directly further.

145.3 N-[4-(3,5-difluoropyridine-2-yl)-1,3-thiazole-2-yl]-N'(2,6-dimethoxybenzyl)guanidine

[0654] The transformation proceeded analogously to Example 107; 90 mg of the target product was isolated as a light colored solid; ESI-MS [M+H]+=406.05.

Example 146
N-[2-(methoxy-1-methylphenyl)methyl]-N'[4-(4-phenyl)-1,3-thiazole-2-yl]guanidine

[0655] The preparation proceeded analogously to Example 2; ESI-MS [M+H]+=389.15.

Example 147
N-(2,6-dimethoxybenzyl)-N'[4-(p-toluidine)-1,3-thiazole-2-yl]guanidine hydrochloride

[0656] To 490 mg (1.06 mmol) tert-butyl 2-[[[2,6-dimethoxybenzyl]amino][4-[(4-fluorophenyl)-1,3-thiazole-4-yl]pyrrolidine-1-carboxylate from Example 120 in 20 ml dioxane were added 5 ml 4N HCl in dioxane at room temperature and the mixture was stirred for 3 hours. Chromatography on RP-silica gel of the crude product obtained following concentration (Chromabond column, acetonitrile/water+0.1% glacial acetic acid; 0-100%) yielded 240 mg of the target product as a light colored solid; ESI-MS [M+H]+=362.15.
Example 148
N-[4-(1-acetylpyrrolidine-2-yl)-1,3-thiazole-2-yl]-N'(2,6-dimethoxybenzyl)guanidine

[0657] A mixture of 100 mg (0.25 mmol) N-[2,6-dimethoxybenzyl]-N'-[4-(pyrrolidine-2-yl)-1,3-thiazole-2-yl] guanidine hydrochloride, Example 147, 0.021 ml acetyl chloride and 0.04 ml pyridine in 10 ml THF was stirred for 1 hour at 50 °C and then 4 hours at room temperature. Chromatography of the crude product on RP-silica gel (Chromabond column, acetonitrile/water+0.1% glacial acetic acid; 0-100%) yielded 33 mg of the desired product; ESI-MS [M+H]+ = 404.15.

Example 149
N-(2,6-dimethoxybenzyl)-N'-[4-(1-methylpyrrolidine-2-yl)-1,3-thiazole-2-yl]guanidine

[0658] To 72 mg (0.2 mmol) N-(2,6-dimethoxybenzyl)-N'-[4-(pyrrolidine-2-yl)-1,3-thiazole-2-yl]guanidine hydrochloride, Example 147, and 20 mg formaline (37% aqueous solution) were added 51 mg of sodium triacetate/borohydride at 10 °C, the mixture was then stirred for 30 minutes at 10 °C and 2 hours at room temperature. For workup, the mixture was evaporation-concentrated, the residue was dissolved in dichloromethane, was washed with water, was dried and was concentrated once again. Following chromatography of the crude product on RP-silica gel (Chromabond column, acetonitrile/water+0.1% glacial acetic acid; 0-100%), 22 mg of a white solid were obtained, ESI-MS [M+H]+ = 376.15.

Example 150
N-(2,6-dimethoxybenzyl)-N'-[4-[1-(phenylsulfonyl)pyrrolidine-2-yl]-1,3-thiazole-2-yl]guanidine

[0659] Reaction of 170 mg (0.38 mmol) N-(2,6-dimethoxybenzyl)-N'-[4-(pyrrolidine-2-yl)-1,3-thiazole-2-yl] guanidine hydrochloride, Example 147, with 68.85 mg phenylsulfonylic acid chloride and 0.12 ml triethylamine in 15 ml acetonitrile and purification of the crude product by chromatography on silica gel (dichloromethane/methanol 0-3%) yielded 70 mg of the desired product as a white solid; ESI-MS [M+H]+ = 502.45.

Example 151
N-[4-(1-benzylpyrrolidine-2-yl)-1,3-thiazole-2-yl]-N'(2,6-dimethoxybenzyl)guanidine

[0660] 177 mg N-(2,6-dimethoxybenzyl)-N'-[4-(pyrrolidine-2-yl)-1,3-thiazole-2-yl]guanidine, Example 147 free base, 100 mg of benzyl bromide and 870 mg polymer-bound triazabicyclodecene (1.3 mmol/g, Argonaut) were shaken in 20 ml acetonitrile overnight at room temperature. Chromatography on silica gel (dichloromethane/methanol 0.5%) of the residue obtained following evaporation concentration yielded 112 mg of a white solid; ESI-MS [M+H]+ = 452.15.

Example 152
N-(2-chloro-6-methoxybenzyl)-N'-[4-(3,5-difluoropyrrolidine-2-yl)-1,3-thiazole-2-yl]guanidine

[0661] Reaction of 130 mg (0.31 mmol) methyl-N'-[4-(3,5-difluoropyrrolidine-2-yl)-1,3-thiazole-2-yl]imidothiocar-
Example 156
N-(2,6-dimethoxybenzyl)-N'[4-[(1-isopropylpyrroli- 
dine-2-yl)-1,3-thiazole-2-yl]guanidine

[0668] Reductive amination of 100 mg (0.28 mmol) N-[4- 
(aminomethyl)-1,3-thiazole-2-yl]-N'(2,6-dimethoxybenzyl) 
guanidine hydrochloride, Example 154 free base, with 0.04 M acetonitrile and 120 mg sodium triacetoxyloroborohydrine in 
10 ml acetonitrile analogously to Example 149 yielded the 
target product as a white solid; 52 mg; ESI-MS [M+H+] = 404.15.

Example 157
N-[2-[[2-(6-dimethoxybenzyl)amino][imino] 
methyl][amino]-1,3-thiazole-4-yl]methyl]butane-1- 
sulfonamide

[0669] Reaction of 100 mg (0.33 mmol) N-[4-(aminom- 
eyl)-1,3-thiazole-2-yl]-N'(2,6-dimethoxybenzyl)guani- 
dine hydrochloride, Example 154 free base, with 60.4 mg 
butane sulfonic acid chloride in 5 ml THF with addition of 
480 mg polymer-bound NMM (1.7 mmol/g; Argonaut) and 
chromatography of the crude product on silica gel dichlo- 
romethane/methanol (99:1) yielded 46 mg; ESI-MS 
[M+H+] = 442.05.

Example 158
N-(2,6-Dimethoxybenzyl)-N'-[4-{[(dimethylamino) 
methyl]-1,3-thiazole-2-yl]guanidine acetate

[0670] Reductive amination of N-[4-(aminomethyl)-1,3- 
thiazole-2-yl]-N'-[2,6-dimethoxybenzyl]guanidine 
hydrochloride, Example 149 in 15 ml DMF using polymer-bound MP-triacectoxyborohydrine (2 mmol/g; Argonaut) yielded 24 mg of target 
product; ESI-MS [M+H+] = 350.15.

Example 159
Methyl[[2-[[2-(dimethoxybenzyl)amino][imino] 
methyl][amino]-1,3-thiazole-4-yl]methyl]carbamate

[0671] To 360 mg (1.12 mmol) N-[4-(aminomethyl)-1,3- 
thiazole-2-yl]-N'-[2,6-dimethoxybenzyl]guanidine hydro- 
chloride, Example 154 free base, in 13.5 ml THF were added 
0.2 ml NMM, and 0.1 ml chloroformic acid methyl ester in 
1.5 ml THF were added drop-wise with stirring. Following 
completion of the reaction, the mixture was concentrated, 
was diluted with dichloromethane, was washed with satu- 
rated NaCl solution, was dried and was concentrated. Chromatography of the crude product on silica gel (dichlo- 
romethane/methanol 0-1%) yielded 140 mg; ESI-MS 
[M+H+] = 380.05.

Example 160
methyl-2-[[2-(dimethoxybenzyl)amino][imino] 
methyl][amino]-4-(4-fluorophenyl)-1,3-thiazole-5- 
carboxylate

[0672] Bromination of 800 mg (4.08 mmol) methyl-4- 
fluorobenzoylacetate analogously to Example 144.2 and 
further reaction with thiazole analogously to Example 3 
yielded 27 mg.

[0673] 1H-NMR (400 MHz, DMSO-d6), δ (ppm)=3.68 (s, 
3H), 3.78 (s, 6H), 4.34 (m wide, 2H), 6.69 (d, 2H), 7.20 (m, 
2H), 7.32 (m, 1H), superimposed 6.95-7.40 (m, 2H), 7.63 (m 
wide, 2H).

Example 161
Tert-butyl 4-[[2-(6-dimethoxybenzyl)amino] 
(mimo)methyl]amino]-1,3-thiazole-4-yl)piperidine-1- 
carboxylate

[0674] ESI-MS [M+H+] = 476.15

Example 162
N-(2,6-dimethoxybenzyl)-N'-[4-(piperidin-4-yl)-1,3- 
thiazole-2-yl]guanidine hydrochloride

[0675] Removal of the Boc group starting from 490 mg 
(1.0 mmol) tert-butyl 4-[[2-(6-dimethoxybenzyl)amino] 
(mimo)methyl]amino]-1,3-thiazole-4-yl)piperidine-1-car- 
boxylate analogously to Example 147 yielded 380 mg of a 
solid; ESI-MS [M+H+] = 376.1

Example 163
N-(2,6-dimethoxybenzyl)-N'-[4-[1-(methylsulfonyl) 
piperidine-4-yl]-1,3-thiazole-2-yl]guanidine

[0676] ESI-MS [M+H+] = 454.05

Example 164
N-[4-(3-chloropyridine-2-yl)-1,3-thiazole-2-yl]-N'- 
(2,6-dimethoxybenzyl)guanidine

[0677] 164.1 1-(3-chloropyridine-2-yl)ethanone

[0678] Grignard reaction starting from 0.5 g (0.61 mmol) 
2-cyano-3-chloropyridine analogously to Example 145.1 
yielded 360 mg of the desired product as a light yellow oil.

[0679] 1H-NMR (400 MHz, DMSO-d6), δ (ppm)=2.65 (s, 
3H), 7.66 (m, 2H), 8.08 (m, 2H), 8.64 (m, 1H), 164.2 
N-[4-(3-chloropyridine-2-yl)-1,3-thiazole-2-yl]N'- 
(2,6-dimethoxybenzyl)guanidine

[0680] Bromination analogously to Example 144.2 and 
further reaction of the corresponding 2-bromo-1-(3-chloro- 
pyridine-2-yl)ethanone analogously to Example 3 yielded 
110 mg of target product as a light colored solid; ESI-MS 
[M+H+] = 404.25

Example 165
N-(2,6-dimethoxybenzyl)-N'-[4-(8-fluoroquinoline-
4-yl)-1,3-thiazole-2-yl]guanidine

[0681] 165.1 8-fluoroquinoline-4-yl triluromethane sul- 
fonate

[0682] 4.9 g triluromethane sulfonic acid anhydride dis- 
solved in 5 ml dichloromethane were added drop-wise to 1.9 
g (11.65 mmol) 8-fluoro-4-hydroxyquinoline and 4.7 ml 
triethylamine in 15 ml dichloromethane and the mixture was 
stirred for approximately 20 minutes at 5°C. For workup 
the mixture was diluted with 30 ml of water, was extracted 
with dichloromethane and the organic phase was washed with 
saturated NaCl solution. Purification by chromatography on 
silica gel (dichloromethane) of the crude product obtained 
after drying with MgSO4 yielded 2.3 g of the triflate as a 
light colored oil; ESI-MS [M+H+] = 295.5.
165.2 1-(8-fluorochinoline-4-yl)ethanone

[0683] 1.3 g (4.4 mmol) 8-fluorochinoline-4-yl trifluoromethane sulfonate, 153 mg tetrakis(triphenylphosphine)palladium and 600 mg LiCl were suspended in a baked flask under protective gas in 30 ml dioxane, 1.6 g (4.43 mmol) (1-ethoxyvinyl)-tributylstannane was added, the mixture was heated for 2 hours at reflux. The mixture was diluted with dichloromethane, was washed with water, was dried (MgSO₄) and was concentrated. The residue thus obtained was dissolved in 30 ml THF and, following addition 2 ml 1 M HCl, was stirred for 3 hours at room temperature. For workup, the mixture was adjusted with saturated NaHCO₃ solution to pH 11, was extracted with dichloromethane, the combined organic phases were washed with saturated NaCl solution and were dried with MgSO₄. Purification by chromatography on silica gel (dichloromethane) yielded 700 mg; ESI-MS [M+H]+=190.05.

165.3 2-bromo-1-(8-fluorochinoline-4-yl)ethanone

[0684] A total of 0.13 ml Br₂ were added portion-wise to 480 mg (2.54 mmol) 1-(8-fluorochinoline-4-yl)ethanone in 2 ml 48% HBr in water at 90° C. and were stirred for 30 minutes at 90° C. Following completion of the reaction, the water was diluted, was neutralized by addition of solid NaHCO₃ and was extracted with dichloromethane. Washing of the combined organic phases with saturated NaCl solution, drying and evaporation concentration yielded 600 mg of the desired bromide, which was directly reacted further. 165.4 N-[2,6-dimethoxybenzyl]-N’-[4-(8-fluorochinoline-4-yl)-1,3-thiazole-2-yl]guanidine

[0685] Reaction of 150 mg (0.56 mmol) 2-bromo-1-(8-fluorochinoline-4-yl)ethanone analogously to Example 3 yielded 110 mg of the target product as a white-yellow solid; ESI-MS [M+H]+=438.05.

Example 166

1-[2-[[imin0]2-methoxybenzyl]amino]-1,3-thiazole-4(5H)-yldene)piperidinum chloride

[0686] Reaction of 100 mg (0.38 mmol) N-(2-chloro-1-piperidin-1-ylthiophene-4-yl)methyl sulfonamide (preparation according to: Abdelalil, S.; Bauer, L. J. Het. Chem. 1988, 25 (6), 1849-1856) with 120 mg (0.38 mmol) N-[2-(methoxybenzyl)amino][mimo]-methyl[thiourea analogously to Example 3 yielded 12 mg of the desired product; ESI-MS [M+H+]=346.15. According to NMR, the compound exists as tautomeric mixture of 1-[2-[[imin0]2-methoxybenzyl]amino][mimo]-methyl[thiourea]-1,3-thiazole-4(5H)-yldene]piperidine and N-(2-methoxybenzothiazole)-N’-(4-piperidine-1-yl)-1,3-thiazole-2-yl]guanidine.

[0687] 13C-NMR (100.61 MHz, DMSO-d₆), δ (ppm): 23.61, 25.75, 36.23, 40.91, 49.94, 109.95, 120.28, 125.50, 128.30, 128.80, 157.09, 176.7677, 185.96.

Example 167

4-[2,6-dimethoxybenzyl]amino][imin0]methyl] amino]-1,3-thiazole-4(5H)-yldene)morpholine-4-ium chloride

[0688] 167.1 N-(2-chloro-1-morpholine-4-ylethylidene)-4-methylphenyl sulfonamide

[0689] To 1 g (5.02 mmol) 2-chloro-1-morpholine-4-ylethanminium chloride and 0.7 ml triethylamine in 25 ml acetonitrile were added 0.96 g p-toluene sulfonic acid chloride at 100° C. and the mixture was stirred for 2 hours at 5-10° C. For workup, the mixture was diluted with dichloromethane, was washed with water and saturated NaCl-solution, was dried with MgSO₄, was filtered and was evaporation-concentrated. Chromatography on silica gel (dichloromethane/methanol 0-3%) yielded 400 mg of the target products; ESI-MS [M+H+]=317.05.

167.2 4-[2,6-dimethoxybenzyl]amino][imin0]methyl] amino]-1,3-thiazole-4(5H)-yldene)morpholine-4-ium chloride

[0690] The mixture of 200 mg (0.75 mmol) N-[2,6-dimethoxybenzyl]amino][imin0]methyl]thiourea and 240 mg (0.75 mmol) N-(2-chloro-1-morpholine-4-ylethylidene)-4-methylphenyl sulfonamide in 20 ml 2-butanol was heated for 24 hours at reflux. Normal workup yielded 170 mg of a light-colored solid; ESI-MS [M+H+]=378.25.

According to NMR, the compound exists as a tautomeric mixture of 4-[2,6-dimethoxybenzyl]amino][imin0]methyl]amino]-1,3-thiazole-4(5H)-yldene)morpholine and N-(2,6-dimethoxybenzothiazole)-N’-(4-morpholine-4-yl)-1,3-thiazole-2-yl]guanidine.

[0691] 13C-NMR (100.61 MHz, DMSO-d₆), δ (ppm): 34.76, 36.36, 47.81, 55.95, 65.15, 104.1, 110.66, 130.19, 158.11, 160.00, 177.51, 180.89.

Example 168

N-(2-methoxybenzyl)-N’-(6-methyl-1,3-benzothiazole-2-yl)guanidine fumarate

[0692] 102 mg (0.62 mmol) 6-methyl-1,3-benzothiazole-2-amine and 200 mg (1.24 mmol) 1,1-di-H₁-imidazole-1-ylmethaneimine (Wu, Y.-Q.; Hamilton, S. K.; Wilkinson, D. E.; Hamilton, G. S. J. Org. Chem. 2002, 67, 7553) were provided in THF (1 ml) and were heated while stirring in a microwave at 300 W radiation for 40 minutes to 130° C. Following addition of 2-methoxybenzylamine (85 mg, 0.62 mmol) the reaction mixture was heated to 130° C. for 60 minutes (300 W, heating by cooling). The THF was distilled off under vacuum on a rotary evaporator, the residue was chromatographically purified (silica gel, dichloromethane, methanol). The solid thus obtained was washed with dichloromethane and tert-butylmethylether; 20 mg, ESI-MS [M+H+]=327.1

[0693] The following were prepared analogously to Example 168:

Example 169

N-(2,6-dimethoxybenzyl)-N’-(6-methyl-1,3-benzothiazole-2-yl)guanidine fumarate


Example 170

N-(6-ethoxy-1,3-benzothiazole-2-yl)-N’-(2-methoxybenzyl)guanidine fumarate


Example 171

N-(5-chloro-6-methyl-1,3-benzothiazole-2-yl)-N’-(2,6-dimethoxybenzyl)guanidine difumarate

[0696] ESI-MS [M+H+]=391.0.
Example 172
N-(2,6-dimethoxybenzyl)-N'-(5,6-dimethyl-1,3-benzothiazole-2-yl)guanidine fumarate


Example 181
N-(2,6-dimethoxybenzyl)-N'-(5-methyl-4H-1,2,4-triazole-3-yl)guanidine

[0698] The preparation of 2-(2,6-dimethoxybenzyl)-N'-(5-methyl-4H-1,2,4-triazole-3-yl)guanidine was performed analogously to Example 2, with the following variations: The saponification of N-[((5-methyl-4H-1,2,4-triazole-3-yl)amino]carbonothioyl]-benzamide in methanolic sodium hydroxide solution, could be performed even at room temperature. The N-(5-methyl-4H-1,2,4-triazole-3-yl)thiourea formed was alkylated with methyl iodide at room temperature and the resulting methyl N-(5-methyl-4H-1,2,4-triazole-3-yl)imidothiocarbamate was liberated by extraction of the organic phase with 1 N NaOH. Finally, the methyl N-(5-methyl-4H-1,2,4-triazole-3-yl)imidothiocarbamate was brought to reaction with 2,6-dimethoxybenzylamine in ethanol at 130° C. in the microwave (100 Watt) and the N-(2,6-dimethoxybenzyl)-N'-(5-methyl-4H-1,2,4-triazole-3-yl)guanidine was isolated following chromatographic purification on preparative HPLC (Merck: Chromolith RP-18E, 100-25; eluent water/acetonitrile/0.1 molar acetic acid).

[0700] ESI-MS [M+H]^+ = 291.15

Example 185
N-(2-methoxybenzyl)-N'-(5-methyl-4H-1,2,4-triazole-3-yl)guanidine acetate

[0701] The preparation was performed analogously to Example 183. Here the intermediately formed N-[methylthio)methyl]-5-methyl-4H-1,2,4-triazole-3-aminium iodide was reacted directly with 2-methoxybenzylamine in ethanol and a 1.5-fold excess of disopropylethylamine to yield the target product.

[0702] ESI-MS [M+H]^+ = 261.15

Example 192
N-(2-methoxybenzyl)-N'-(5-methyl-4H-1,2,4-triazole-3-yl)guanidine acetate

[0703] The compound 192 was prepared analogously to Example 107 by reacting suitable starting materials of the formulae IV and V:

Example 192
Ethyl 2-[(2,6-dimethoxybenzyl)amino](imino)methyl]amino]-1,3-thiazole-4-carboxylate acetate

[0704] The purification of the product proceeded by preparative HPLC (Merck: Chromolith RP-18E, 100-25; eluent water/acetonitrile/0.1 molar acetic acid).

[0705] ESI-MS [M+H]^+ = 365.05

Example 196
N-(2,6-dimethoxybenzyl)-N'-(5,6-dimethyl-1,3-thiazole-4-carboxylate bromide

[0707] 0.157 g (0.35 mmol) ethyl 2-[(2,6-dimethoxybenzyl)amino](imino)methyl]amino]-1,3-thiazole-4-carboxylate bromide were combined with 1.50 ml (17.28 mmol) disopropylamine and were heated in the microwave at 50 to 70° C. (150 Watt) for 2 hours. In this example, complete reaction was achieved only after further heating in the microwave at 70° C. (150 Watt) by “heating by cooling” after 4.5 hours. The reaction mixture was diluted with 20 ml dichloromethane and was washed with water (3×30 ml). After drying over MgSO₄, filtration and removal of the organic solvent under vacuum, the mixture was purified by preparative HPLC (Merck: Chromolith RP-18E, 100-25; eluent water/acetonitrile/0.1 molar acetic acid). 26 mg of 2-[(2,6-dimethoxybenzyl)amino](imino)methyl]amino]-N-isopropyl-1,3-thiazole-4-carboxamide were isolated.

[0708] ESI-MS [M+H]^+ = 378.15

Example 196
N-allyl-2-[(2,6-dimethoxybenzyl)amino](imino)methyl]amino]-1,3-thiazole-4-carboxamide

[0709] The following were prepared analogously to Example 196:

Example 193
N-allyl-2-[(2,6-dimethoxybenzyl)amino](imino)methyl]amino]-1,3-thiazole-4-carboxamide

[0710] ESI-MS [M+H]^+ = 376.15

Example 194
N-benzyl-2-[(2,6-dimethoxybenzyl)amino](imino)methyl]amino]-1,3-thiazole-4-carboxamide

[0711] ESI-MS [M+H]^+ = 426.15

Example 175
N-(2-methoxybenzyl)-N'-(5-phenyl-1,3,4-thiadiazole-2-yl)guanidine acetate

[0712] The compound 175 was prepared by reaction of suitable starting materials of the formulae II and IV as follows:

Example 175
N-(2-methoxybenzyl)-N'-(5-phenyl-1,3,4-thiadiazole-2-yl)guanidine acetate

[0713] 175.1. N-(5-phenyl-1,3,4-thiadiazole-2-yl)-1H-imidazole-1-carbothioamide

[0714] 1.80 g (6.56 mmol) 5-phenyl-[1,3,4]thiadiazole-2-yl-ammonium sulfate were provided in 10 ml DMF. After 2.0 g (7.29 mmol) N,N'-thiocarbonyldimidazole was added drop-wise in 10 ml acetonitrile and was stirred for 12 hours at room temperature. The solution was removed under vacuum, water was added to the residue and the solid formed was separated by filtration. After drying of the solid, 2.10 g N-(5-phenyl-1,3,4-thiadiazole-2-yl)-1H-imidazole-1-carbothioamide was isolated as a crude mixture, which was used without further separation.

[0715] 3H-NMR ([400 MHz, DMSO-d6]; δ (ppm) 7.33 (pt, 1H), 7.33-7.54 (m, 3H), 7.66 (m, 1H, J=1.1 Hz), 7.96 (dd, 2H, J=8.1 Hz, J=1.4 Hz), 8.16 (pt, 1H, J=1.3 Hz), 9.18 (s, 1H), 17.2 N-(5-phenyl-1,3,4-thiadiazole-2-yl)thiourea

[0716] 1.0 g of the crude mixture with N-(5-phenyl-1,3,4-thiadiazole-2-yl)-1H-imidazole-1-carbothioamide was
combined with 0.536 g (6.96 mmol) ammonium acetate in 4 ml ethanol. The reaction mixture was heated in the microwave (at 100 Watt) for 30 minutes at 90°C. After completion of the reaction, the solvent was distilled off under vacuum, and water was added to the residue formed. After extraction with CH₂Cl₂ and drying of the organic phase with magnesium sulfate, the product crystallized out of the organic solvent and, after filtration, was washed with diethyl ether. 0.52 g of the N-(5-phenyl-1,3,4-thiadiazole-2-yl)-thiourea was obtained.

[0717] ESI-MS [M+H⁺] = 237.05
175.3 Methyl N-(5-phenyl-1,3,4-thiadiazole-2-yl)imidothiocarbamate

[0718] 0.52 g (2.22 mmol) N-(5-phenyl-1,3,4-thiadiazole-2-yl)-thiourea were dissolved in 4 ml of methanol and 0.515 g (3.63 mmol) methyl iodide were added. The reaction mixture was stirred at 50°C for 2 hours and for another 12 hours at room temperature. For the liberation of the intermediate formed iodide salt, 0.427 g (3.30 mmol) disopropylethylamine were added to the mixture and were stirred for 2 hours at room temperature. The solvent was removed under vacuum and the residue was dissolved in dichloromethane. The liberation of the iodide salt can also alternatively proceed by extraction with 2 N sodium hydroxide solution. After extraction with water, (3×50 ml) the organic phase was dried over MgSO₄ and, following a removal of the solvent under vacuum, the 0.37 g of crude product were isolated, which were used in the following reaction without further purification.

[0719] ESI-MS [M+H⁺] = 251.10
175.4 N-(2-methoxybenzyl)-N'-(5-phenyl-1,3,4-thiadiazole-2-yl)guanidine acetate

[0720] 0.185 g (0.74 mmol) methyl N-(5-phenyl-1,3,4-thiadiazole-2-yl)imidothiocarbamate were dissolved together with 0.132 g (0.96 mmol) 2-methoxybenzylamine in 3 ml ethanol and were heated in the microwave (at 100 Watt) for 30 minutes at 90°C. In the cases in which the reaction did not go to completion, 2 ml of toluene were added and the mixture was again heated in the microwave (at 100 Watt) for 30 minutes at 100°C. After complete reaction, the solvent was removed under vacuum. The residue was separated by preparative HPLC (Merck: Chromolith RP-18E, 100-25; eluent water/acetonitrile/0.1 molar acetic acid) and 32 mg of the pure N-(2-methoxybenzyl)-N'-(5-phenyl-1,3,4-thiadiazole-2-yl)guanidine acetate were isolated.

[0721] ESI-MS [M+H⁺] = 340.15

[0722] The compounds 176-178, and 183 were prepared by reaction of suitable starting materials of the formulae II and IV analogously to Example 175:

Example 176
N-(2,6-dimethoxybenzyl)-N'-(5-phenyl-1,3,4-thiadiazole-2-yl)guanidine

[0723] ESI-MS [M+H⁺] = 370.15

Example 177
N-(2,6-dimethoxybenzyl)-N'-1H-imidazole-2-yl-guanidine acetate

[0724] ESI-MS [M+H⁺] = 276.15

Example 178
N-(2-methoxybenzyl)-N'-(5-methyl-1,3,4-thiadiazole-2-yl)guanidine

[0725] ESI-MS [M+H⁺] = 278.05

Example 183
N-1H-imidazole-2-yl-N'-(2-methoxybenzyl)guanidine acetate

[0726] ESI-MS [M+H⁺] = 246.05

[0727] The compounds 179 and 180 were prepared by reaction of suitable starting materials of the formulae II and IV analogously to Example 175, wherein the corresponding commercially available thiourea derivatives were treated with 1 N sodium hydroxide solution, as in 175.3, after the reaction with methyl iodide, to liberate the iodide salt. The addition of toluene, as in 175.4, was not necessary here:

Example 179
N-1H-indazole-3-yl-N'-(2-methoxybenzyl)guanidine acetate

[0728] ESI-MS [M+H⁺] = 296.15

Example 180
N-(2,6-dimethoxybenzyl)-N'-1H-imidazole-3-ylguanidine acetate

[0729] ESI-MS [M+H⁺] = 326.15

Example 182
N-1H-benzimidazole-2-yl-N'-(2,6-dimethoxybenzyl)guanidine diacetate

[0730] 182.1 N-1H-benzimidazole-2-ylthioiourea

[0731] 0.535 g (3.00 mmol) N,N'-thiocarbonyldimidazole was dissolved in 5 ml acetonitrile, and to this yellow solution was added drop-wise 0.40 g (3.00 mmol) 2-aminobenzimidazole, suspended in 5 ml acetonitrile, at room temperature. After 30 minutes, a precipitate formed, and the mixture was stirred another 12 hours. After 0.474 g (6.0 mmol) ammonium acetate in substance (German: “in Substanz”) was added to this mixture, the mixture was heated in the microwave (at 100 Watt) 30 minutes long at 90°C. The solvent was removed under vacuum, water was added to the residue and an extraction with dichloromethane (3×30 ml) followed. The combined organic phase was washed once again with water and, after drying over MgSO₄, the solvent was removed under vacuum. The product was purified by means of preparative HPLC (Merck: Chromolith RP-18E, 100-25; eluent wasser/acetonitrile/0.1 molar acetic acid). In this single pot procedure, 0.27 g of the N-1H-benzimidazole-2-ylthioiourea was directly recovered without isolation of the intermediate.

[0732] ESI-MS [M+H⁺] = 193.05

182.2 (1H-benzimidazole-2-ylamino)(methylthio)methanemineiodide

[0733] To 0.27 g (1.40 mmol) N-1H-benzimidazole-2-ylthioiourea were added 0.115 ml (1.83 mmol) methyl iodide dissolved in 4 ml of methanol. It was heated for 30 minutes at reflux. After completion of the reaction, the solvent was removed under vacuum and 0.47 g 1H-benzimidazole-2-
ylamino)(methylthio)methane iminium iodide was used without further purification for the following reaction.

[0734] ESI-MS [M+H⁺]=207.05

182.3 N-(1H-benimidazol-2-yl)-N'(2,6-dimethoxybenzyl) guanidine diacetate

[0735] 0.470 g (1.4 mmol) 1H-benimidazol-2-ylamino (methylthio)methane iminium iodide were dissolved in 4 ml ethanol and, after addition of 0.24 ml (1.4 mmol) disopropylethylamine and 0.282 g (1.69 mmol) 2,6-dimethoxybenzylamine, was heated together for 3 hours under reflux. Alternatively, the reaction can take place correspondingly in a microwave (at 100-200 Watt) for 30 minutes at 90-100°C. After complete reaction, the solvent was removed under vacuum. The residue was dissolved in water and the product in the organic phase was extracted with dichloromethane. The organic phase was washed 1 N NaOH (2x50 ml) to completely remove iodide from the product. After drying over MgSO₄ and filtration, the organic solvent was removed under vacuum. A voluminous precipitate formed after the residue was dissolved 4 ml acetonitrile/water (1:1) and 0.5 ml glacial acetic acid. The solid was filtered off and 30 mg of the desired product was obtained.

[0736] ESI-MS [M+H⁺]=326.25

[0737] The compounds 184 and 189 were prepared by reaction of suitable starting materials of the formulae II and IV analogously to Example 182:

Example 184

N-(2-methoxybenzyl)-N'-(4H-1,2,4-triazole-3-yl)guanidine acetate

[0738] ESI-MS [M+H⁺]=247.05

Example 189

N-(2,6-Dimethoxybenzyl)-N'-4H-1,2,4-triazole-3-ylguanidine acetate

[0739] ESI-MS [M+H⁺]=277.10

Example 187

N-(2,6-dimethoxybenzyl)-N'-(4-phenyl-1H-imidazole-2-yl)guanidine acetate

[0740] 187.1 N-(4-phenyl-1H-imidazole-2-yl)thiourea

[0741] 2.10 g (11.78 mmol) N,N'-thiocarbonyldiimidazole and 2.44 g (5.64 mmol) bis(4-phenyl-1H-imidazole-2-aminium) sulphate were combined and 50 ml of acetonitrile were added. The reaction mixture was warmed to 50°C. After 6 hours. Complete reaction, 2.26 g (29.29 mmol) ammonium acetate were added and the mixture was heated for one hour to 80°C. The batch was freed of solvent under vacuum. Water was added to the residue and this was extracted (3x150 ml) with dichloromethane. The combined organic phase was dried over MgSO₄, was filtered and was evaporation-concentrated; 1.78 g

[0742] ESI-MS [M+H⁺]=219.05

187.2 Methyl N-(4-phenyl-1H-imidazole-2-yl)imidothiocarbamate

[0743] The preparation proceeded analogously to 182.2. 1.89 g of product were isolated.

[0744] ESI-MS [M+H⁺]=233.95

187.3 N-(2,6-dimethoxybenzyl)-N'-(4-phenyl-1H-imidazole-2-yl)guanidine acetate

[0745] The preparation proceeded analogously to 182.3. Following purification, 180 mg of clean product were isolated.

[0746] ESI-MS [M+H⁺]=352.15

[0747] The compounds 186 and 188 were prepared by reacting suitable starting materials of the formulae II and IV analogously to Example 187:

Example 186

N-[4-(4-fluorophenyl)-1H-imidazole-2-yl]-N'-2(methoxybenzyl)guanidine

[0748] ESI-MS [M+H⁺]=340.15

Example 188

N-(2-methoxybenzyl)-N'-(4-phenyl-1H-imidazole-2-yl)guanidine acetate

[0749] ESI-MS [M+H⁺]=322.15

[0750] The compounds 191 and 195 were prepared by reaction of suitable starting materials of the formulae II and IV, as follows:

Example 191

N-(2,6-dimethoxybenzyl)-N'-(4-phenyl-1H-imidazole-2-yl)guanidine acetate

[0751] 191.1 N-(4-phenyl-1H-imidazole-2-yl)acetamide

[0752] 3.00 g (13.82 mmol) 2-bromo-4'-fluoroacetophene, 2.80 g (27.64 mmol) acetylguanidine and 15 ml acetonitrile were combined and were together brought to reaction in the microwave (at 100 Watt) for 60 minutes at 40°C by “heating by cooling”. After cooling, the solid formed was filtered off of the solvent. In addition, a total amount of 1.02 g N-[4-(4-fluorophenyl)-1H-imidazole-2-yl]acetamide were isolated by fractional crystallization with ethanol of the remainder of the mother liquor.

[0753] ESI-MS [M+H⁺]=220.05

[0754] 191.2 4-(4-fluorophenyl)-1H-imidazole-2-aminium chloride

[0755] 1.0 g (4.56 mmol) N-[4-(4-fluorophenyl)-1H-imidazole-2-yl]acetamide were suspended in 30 ml 2 N HCl and 30 ml ethanol and were stirred at 80°C for 2 hours. After removal of the solvent under vacuum, 0.97 g 4-(4-fluorophenyl)-1H-imidazole-2-aminium chloride were obtained, which was used in the following reaction without further purification.

[0756] ESI-MS [M+H⁺]=214.05

[0757] 191.3 N-[4-(4-fluorophenyl)-1H-imidazole-2-yl]thiourea

[0758] The preparation proceeded analogously to 187.1. After purification, 0.74 g of clean product were isolated.

[0759] ESI-MS [M+H⁺]=237.05

[0760] 191.4 Methyl N-[4-(4-fluorophenyl)-1H-imidazole-2-yl]imidothiocarbamate

[0761] The preparation proceeded analogously to 175.3, wherein the 4-(4-fluorophenyl)-N-[mimino(methylthio) methyl]-1H-imidazole-2-aminium iodide obtained as an intermediate, was treated with 2 N sodium hydroxide solution. Following purification, 0.75 g of clean product was isolated.
Example 195

N-(2,6-dimethoxybenzyl)-N'-[4-(4-fluorophenyl)-1H-imidazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 370.15

Example 196

N-(2-chlor-6-methoxybenzyl)-N'-[4-(4-fluorophenyl)-1H-imidazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 374.10/376.10

Example 190

N-(2,6-dimethoxybenzyl)-N'-[4-methyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 235.15

Example 197

N-(2,6-dimethoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 231.15

Example 198

N-(2,6-dimethoxybenzyl)-N'-[4-(4-fluorophenyl)-1,3-oxazole-2-yl]guanidine proceeded analogously to Example 197.

ESI-MS [M+H]^+ = 341.05

Example 199

N-(2,6-dimethoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine proceeded analogously to Example 197.

ESI-MS [M+H]^+ = 353.35

Example 200

N-(5-tert-butyl-1H-pyrazole-3-yl)-N-(2-methoxybenzyl)guanidine

ESI-MS [M+H]^+ = 321.15

Example 173

N-(4,5-dimethyl-1,3-oxazole-2-yl)-N'-[2-methoxybenzyl]guanidine

ESI-MS [M+H]^+ = 275.15

Example 174

N-(2,6-dimethoxybenzyl)-N'-[4,5-dimethyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 305.15

Example 177

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 178

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 179

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 180

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 181

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 182

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 183

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 184

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 185

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 186

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 187

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 188

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 189

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 190

N-(2,6-dimethoxybenzyl)-N'-[4-methyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 235.15

Example 191

N-(2,6-dimethoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 235.15

Example 192

N-(2,6-dimethoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 235.15

Example 193

N-(2,6-dimethoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 235.15

Example 194

N-(2,6-dimethoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 235.15

Example 195

N-(2,6-dimethoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 235.15

Example 196

N-(2,6-dimethoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 235.15

Example 197

N-(2,6-dimethoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 235.15

Example 198

N-(2,6-dimethoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 235.15

Example 199

N-(2,6-dimethoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 235.15

Example 200

N-(5-tert-butyl-1H-pyrazole-3-yl)-N-(2-methoxybenzyl)guanidine

ESI-MS [M+H]^+ = 291.15

Example 173

N-(4,5-dimethyl-1,3-oxazole-2-yl)-N'-[2-methoxybenzyl]guanidine

ESI-MS [M+H]^+ = 275.15

Example 174

N-(2,6-dimethoxybenzyl)-N'-[4,5-dimethyl-1,3-oxazole-2-yl]guanidine acetate

ESI-MS [M+H]^+ = 305.15

Example 177

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 178

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 179

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15

Example 180

N-(2-methoxybenzyl)-N'-[4-phenyl-1,3-oxazole-2-yl]guanidine

ESI-MS [M+H]^+ = 321.15
The reaction solution was concentrated and the colorless oil (0.29 g) was purified by chromatography on silica gel (Chromabond RP18; water/acetonitrile+0.1% acetic acid 0-80%), wherein 83 mg of light yellow foam were obtained. Stirring with diethylether yielded 53 mg of white solid.

Example 200

N-(2-methoxybenzyl)-N'-(5-phenyl-1H-pyrazole-3-yl)guanidine

Example 201

N-(2-methoxybenzyl)-N'-(5-phenyl-1H-pyrazole-3-yl)guanidine

Example 202

N-(2,6-dimethoxybenzyl)-N'-(5-phenyl-1H-pyrazole-3-yl)guanidine

Example 203

N-(2,6-dimethoxybenzyl)-N'-(1H-pyrazole-3-yl)guanidine

Example 204

N-(2,6-dimethoxybenzyl)-N'-(5-phenyl-1H-pyrazole-3-yl)guanidine

Example 205

N-(2-methoxybenzyl)-N'-(1H-pyrazole-3-yl)guanidine

Example 206

N-(2-methoxybenzyl)-N'-(5-(4-methylphenyl)-1H-pyrazole-3-yl)guanidine

Example 207

N-(2,6-dimethoxybenzyl)-N'-(5-(4-methylphenyl)-1H-pyrazole-3-yl)guanidine

Example 208

N-(2-methoxybenzyl)-N'-(5-(4-methoxyphenyl)-1H-pyrazole-3-yl)guanidine

Example 209

N-(2,6-dimethoxybenzyl)-N'-(5-(4-methoxyphenyl)-1H-pyrazole-3-yl)guanidine

Example 210

N-(2,6-dimethoxybenzyl)-N'-(2-fluoro-6-methoxybenzyl)guanidine

Example 211

N-(2,6-dimethoxybenzyl)-N'-(2-fluoro-6-methoxybenzyl)guanidine

Example 212

N-(5-(4-cloro-phenyl)-1H-pyrazole-3-yl)-N'-(2,6-dimethoxybenzyl)guanidine

Example 213

N-(5-(4-cloro-phenyl)-1H-pyrazole-3-yl)-N'-(2,6-dimethoxybenzyl)guanidine

Example 214

N-(5-(4-cloro-phenyl)-1H-pyrazole-3-yl)-N'-(2,6-dimethoxybenzyl)guanidine
Example 214
N-(2-methoxybenzyl)-N’-(1-methyl-1H-pyrazole-3-yl)guanidine

[0810] Starting from 160 mg 2-methyl-1-(1-methyl-1H-pyrazole-3-yl)-isourea hydroiodide; 34 mg target product.

[0811] ESI-MS [M+H]+=260

Example 215
N-(2,6-dimethoxybenzyl)-N’-(1-methyl-1H-pyrazole-3-yl)guanidine

[0812] Starting from 160 mg 2-methyl-1-(1-methyl-1H-pyrazole-3-yl)-isourea hydroiodide; 56 mg target product.

[0813] ESI-MS [M+H]+=290

Example 216
N-(5-tert-butyl-1H-pyrazole-3-yl)-N’-(2-methoxy-6-methylbenzyl)guanidine

[0814] Starting from 130 mg 1-(5-tert-butyl-1H-pyrazole-3-yl)-2-methyl-isourea hydroiodide; 47 mg target product.

[0815] ESI-MS [M+H]+=316

Example 217
N-(2-methoxybenzyl)-N’-(4-phenyl-1H-pyrazole-3-yl)guanidine

[0816] Starting from 150 mg 2-methyl-1-(4-phenyl-1H-pyrazole-3-yl)-isourea hydroiodide; 76 mg target product.

[0817] ESI-MS [M+H]+=322

Example 218
N-(2,6-dimethoxybenzyl)-N’-(4-phenyl-1H-pyrazole-3-yl)guanidine

[0818] Starting from 160 mg 2-methyl-1-(4-phenyl-1H-pyrazole-3-yl)-isourea hydroiodide; 83 mg target product.

[0819] ESI-MS [M+H]+=352

Example 219
N-(2,6-dimethoxybenzyl)-N’-(1-phenyl-1H-pyrazole-3-yl)guanidine

[0820] Starting from 160 mg 2-methyl-1-(1-phenyl-1H-pyrazole-3-yl)-isourea hydroiodide; 34 mg target product.

[0821] ESI-MS [M+H]+=352

Example 220
N-(2-methoxybenzyl)-N’-(1-phenyl-1H-pyrazole-3-yl)guanidine

[0822] Starting from 130 mg 2-methyl-1-(1-phenyl-1H-pyrazole-3-yl)-isourea hydroiodide; 47 mg target product.

[0823] ESI-MS [M+H]+=322

Example 221
N-[2-methoxy-5-(trifluoromethyl)benzyl]-N’-(4-phenyl-1,3-thiazole-2-yl)guanidine

[0824] The preparation of 2-methoxy-5-trifluoromethyl-benzylamine proceeded starting from 2-methoxy-5-
trifluoromethyl-benzonitrile by reduction with lithium aluminium hydride in tetrahydrofuran under standard
conditions.

Example 222
N-(2,6-dimethoxybenzyl)-N’-(4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridine-2-yl)guanidine

[0826] Reaction analogously to Example 107 starting from 210 mg 3-bromo-2,3-dihydro-4H-chromen-4-one
(0.92 mmol) yielded 80 mg of the desired product as a white solid; ESI-MS [M+H]+=399.1.

Example 223
N-(2,6-dimethoxybenzyl)-N’-(4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridine-2-yl)guanidine

[0827] 223.1 3-bromo-4-oxopiperidine-1-carboxylate
[0828] To 1 g N-benzyl-4-oxopiperidine-1-carboxylate (4.3 mmol) in 20 ml THF were added 0.5 ml glacial acetic acid
and 0.22 ml bromine at 10°C, and the mixture was stirred at room temperature for 1 hour. For workup, 20 ml of
water were added, the mixture was neutralized with NaHCO₃ and was subsequently extracted multiple times
with dichloromethane. The combined organic phases were then washed with saturated NaCl-solution, were
dried and were concentrated. In this way, 1.2 g of the desired bromide were obtained as a yellowish oil which was
used without further purification.

Example 224
N-(2,6-dimethoxybenzyl)-N’-(4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridine-2-yl)guanidine

[0830] 0.2 ml HBr (33% in glacial acetic acid) were added to 150 mg benzyl-2-[[2,6-dimethoxybenzyl]amino][mino]
 methyl[amino]-6,7-dihydro[1,3]thiazolo[5,4-c]pyridine-5(4H)-carboxylate

Example 225
N-(2,6-dimethoxybenzyl)-N’-(4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridine-2-yl)guanidine

[0831] Acetylation of 110 mg N-(2,6-dimethoxybenzyl)-N’-(4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridine-2-yl)
guanidine (0.26 mmol) Example 221.3 under standard conditions with acetylchloride and triethylamine in 15 ml
THF followed by purification, yielded 16 mg of the desired product as a white solid; ESI-MS [M+H]+=390.15.
Example 225

N-(2,6-dimethoxybenzyl)-N'-[5-(phenylsulfonyl)-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridine-2-yl] guanidine

Reaction of 30 mg N-(2,6-dimethoxybenzyl)-N'-\(\text{[5-(phenylsulfonyl)-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridine-2-yl]}\) guanidine (0.09 mmol, Example 221.3) with 18 mg phenylsulfonyl acid chloride and 40 mg polymer-bound DMAP (Argonaut; 1.06 mmol/g) in 5 ml dichloromethane followed by chromatographic purification (dichloromethane/methanol 2:4%) yielded 15 mg of the target product; ESI-MS \([M+H]^+\) = 488.15.

Example 226

N-(5-benzyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridine-2-yl)-N'-(2,6-dimethoxybenzyl)guanidine

[0833] 226.1 1-benzyl-3-bromopiperidine-4-one hydrobromide

[0834] Bromination of 3 g N-benzyl-4-oxopiperidine (15.85 mmol) analogously to Example 221.1 yielded 5.2 g of the bromide as a light-yellow solid.

226.2 Liberation of the base from hydrobromide and reaction with 200 mg 1-benzyl-3-bromopiperidine-4-one (0.75 mmol) analogously to Example 107 yielded 93 mg of the desired product; ESI-MS \([M+H]^+\) = 438.3.

Biological Tests

[0835] 1. \(\text{[1]}\)H]5-CT Binding Assay h5-HT5A<sub>64</sub>

[0836] Membranes from HEK293-cells, which permanently express the h5-HT5A receptor gene, were incubated in 100 mM Tris-HCl-buffer (pH 7.7), containing 1 mM EDTA in the presence of 2.5 nM \([1\text{]}\)H]5-CT (600 µl total volume). The total binding is defined as the binding which is observed when the membranes are incubated alone in the presence of the radioligand. The inhibition induced by the compound is determined by incubation of cell membranes in the presence of the radioligand, and of different concentrations of the compound of interest. Unspecific binding is defined by the binding of \([1\text{]}\)H]5-CT, which is obtained by incubation of the membranes as for the total binding but in the presence of 10 µM methiothepine. Following an incubation of 75 minutes at 30°C the membrane suspension is filtered through GF/B-filters, wrapped in 0.03% PEI, wherein a Skatron® harvest system is used. The radioactivity retained in the filter is quantified by liquid scintillation counting.

2. Functional Assay for Human 5-HT5A Receptor Ligands-Serotonin-Induced Increase of GTP-Europium Binding

General Description:

[0837] Stimulation of G protein-coupled receptors by suitable agonists leads to the binding of GTP to the α-subunit of trimeric G-proteins, followed by the dissociation of the GTP-bound α-subunit from the γ-subunit and the activation of signal transduction. By using a Europium-labelled GTP-analog, GTP-Eu, the activation of a G-protein-coupled receptor by an agonist can be monitored as an increase in the binding of GTP-Eu to the receptor-G-protein-complex. After removal of unbound GTP-Eu, bound GTP-Eu can be quantified by measuring the time-resolved fluorescence emission in suitable detection apparatus.

[0838] Cell line: h5HT5A_18.2_SH-sy-5y, a human neuroblastoma cell line, which stably expresses the human 5-HT5A receptor.

[0839] Membrane preparation: Cell membranes are prepared according to a standard protocol in the presence of protease inhibitors and are partially purified by two sequential centrifugation steps at 40000×g. Aliquots are stored at −80°C.

Assay:

[0840] The assay is performed in filter plates with 96 wells (AcrorWell-96, Pall Corp.). The receptor membranes diluted in assay buffer (2.5 µM GDP, 100 mM NaCl, 3 mM MgCl₂, 50 mM HEPES pH 7.4) are added to the filter plate (5 pg receptor membrane/well). Test compounds are dissolved in 100% DMSO and serial dilutions are added to the receptor membranes (DMSO final concentration 0.5%). The reaction is started by addition of serotonin (final concentration 1 µM, total assay volume 100 µl). After a first incubation period of 30 min at 30°C, GTP-Eu (final concentration 10 nM) is added, followed by a second incubation period of 30 min at 30°C. The reaction is stopped by rapid vacuum filtration and the wells are washed twice with ice-cold assay buffer. Bound GTP-Eu is measured in a VICTOR multi-label counter (PerkinElmer Corp.) using the time-resolved Europium settings. The data are corrected with respect to the unspecific binding and IC50 values are calculated with PRISM 4.0 (GraphPad Inc.) using standard non-linear curve-fitting algorithms. Kb values are calculated from IC50 values using the Cheng-Prusoff approximation.

[0841] In both assays, different concentrations of the test substances are used, and the Ki or the IC50 values are determined. The affinity of selected compounds is shown in the following table:

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* means an affinity >500 nM
** means an affinity between 50 and 500 nM
*** means an affinity <50 nM

1. Guanidine compound of the general formula I

![Chemical structure of guanidine compound](image)

corresponding enantiomeric, diastereomeric and/or tautomeric forms thereof, as well as pharmaceutically acceptable salts thereof, wherein the given moieties have the following definitions:

W:

- a moiety of the general formula W1 or W2

![Chemical structure of W1](image)

![Chemical structure of W2](image)

wherein

A:

- NO₂, NH₂, OH, CN, CF₃, OCF₃, CHF₂, OCHF₂, COOH, O—CH₂—COOH, halogen, NH, or  
- each optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₆-C₆-alkynyl, C₆-C₆-cycloalkyl, C₆-C₆-alkylene-C₆-C₆-cycloalkyl, C₆-C₆-alkylene-heterocycloalkyl, ary1, hetaryl, heterocycloalkyl, C₆-C₆-alkylene-hetaryl or C₆-C₆-alkylene-ary1, or  

R₁⁻:

- each optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₆-C₆-alkynyl, C₆-C₆-cycloalkyl, C₆-C₆-alkylene-heterocycloalkyl, ary1, hetaryl, heterocycloalkyl, C₆-C₆-alkylene-hetaryl, C₆-C₆-alkylene-ary1, or C₆-C₆-alkylene-hetaryl;

R₂⁻:

- hydrogen, OH, CN, or  
- each optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₆-C₆-alkynyl, C₆-C₆-cycloalkyl, C₆-C₆-alkylene-heterocycloalkyl, ary1, hetaryl, heterocycloalkyl, C₆-C₆-alkylene-hetaryl, C₆-C₆-alkylene-ary1, or C₆-C₆-alkylene-hetaryl;
C<sub>a</sub>-alkylene-aryl, CO—O—hetaryl, CO—O—C<sub>b</sub>-alkyl
e-hetaryl, SO<sub>c</sub>—C<sub>a</sub>-alkyl, SO<sub>c</sub>-aryle, SO<sub>c</sub>-hetaryl, SO<sub>c</sub>—C<sub>a</sub>-alkylene-aryl or SO<sub>c</sub>—C<sub>a</sub>-alkylene-hetaryl;

or the the moieties R<sub>a</sub><sup>2</sup> and R<sub>a</sub><sup>4</sup> form, together with the nitrogen, a 3 to 7-membered, optionally substituted, saturated or aromatic heterocycle which can contain one, two or three different or same heteroatoms from the group O, N, S; wherein optionally two moieties substituted on this heterocycle can together form an anellated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or same heteroatoms O, N, S, and wherein the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

R<sub>a</sub><sup>4</sup>:
hydrogen or each optionally substituted C<sub>a</sub>-alkyl, C<sub>a</sub>-alkyl
e-O—C<sub>a</sub>-alkyl, C<sub>a</sub>-alkylene, C<sub>a</sub>-alkynyl, C<sub>a</sub>-alkyl
eyl, CO—C<sub>a</sub>-alkyl, CO—O—C<sub>a</sub>-alkyl, SO<sub>a</sub>—C<sub>a</sub>-alkyl, SO<sub>a</sub>-aryle, SO<sub>a</sub>-hetaryl, SO<sub>a</sub>—C<sub>a</sub>-alkylene-aryl or SO<sub>a</sub>—C<sub>a</sub>-alkylene-hetaryl;

B:
hydrogen or as moiety A is defined, or each independently of one another, two of the moieties A, B or R<sub>a</sub><sup>4</sup> form, together with a 3 to 7-membered, optionally substituted, saturated or unsaturated carbocycle or an optionally substituted, saturated or unsaturated or aromatic heterocycle which can contain one, two or three further different or same heteroatoms from the group O, N, S; wherein optionally two of the moieties substituted on this carbocycle or heterocycle can form an anellated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or same heteroatoms O, N, S, and wherein the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

R<sub>a</sub><sup>4</sup>:
hydrogen, OH, halogen, NO<sub>a</sub>, NH<sub>a</sub>, CN, CF<sub>a</sub>, CHF<sub>a</sub>, O—CF<sub>a</sub>, O—CHF<sub>a</sub>, or each optionally substituted C<sub>a</sub>-alkyl, C<sub>a</sub>-cycloalkyl, C<sub>a</sub>-alkyl
eyl-O—C<sub>a</sub>-alkyl, C<sub>a</sub>-alkylene, C<sub>a</sub>-alkynyl, C<sub>a</sub>-alkylene
eyl, pyrrolidinyl, piperidinyl, morpholiny, CO—C<sub>a</sub>-alkyl, SO<sub>a</sub>—C<sub>a</sub>-alkyl, CO—O—C<sub>a</sub>-alkyl, SO<sub>a</sub>—C<sub>a</sub>-alkylene-aryl, SO<sub>a</sub>—C<sub>a</sub>-alkylene-hetaryl, SO<sub>a</sub>-aryle, SO<sub>a</sub>-hetaryl, CO—N—C<sub>a</sub>-alkenyl, CONH<sub>a</sub>, CONH—C<sub>a</sub>-alkyl, SO<sub>a</sub>NH—C<sub>a</sub>-alkyl, CON—(C<sub>a</sub>-alkenyl)_, SO<sub>a</sub>N—(C<sub>a</sub>-alkenyl)_, NH—SO<sub>a</sub>—C<sub>a</sub>-alkenyl or NH—CO—C<sub>a</sub>-alkenyl;

D:
as moiety A is defined;

Z:
a moiety of the general formula Z1

with the indices
a=0-4
b=0, 1
c=0-4

wherein the sum of a, b and c is at least 1 and no more than 5;

R<sub>a</sub><sup>4</sup>, R<sub>a</sub><sup>2</sup>, R<sub>a</sub><sup>3</sup>, R<sub>a</sub><sup>4</sup> independently of one another:
hydrogen, halogen, OH, or each optionally substituted C<sub>a</sub>-alkyl, C<sub>a</sub>-alkyl
eyl, C<sub>a</sub>-alkylene, C<sub>a</sub>-alkynyl, C<sub>a</sub>-alkylene-C<sub>a</sub>-cyclo
cloalkyl, C<sub>a</sub>-cycloalkyl, aryl, C<sub>a</sub>-alkylene
eyl, C<sub>a</sub>-aryle, C<sub>a</sub>-hetaryl, or each independently of one another, two moieties R<sub>a</sub><sup>1</sup> and R<sub>a</sub><sup>2</sup> or R<sub>a</sub><sup>3</sup> and R<sub>a</sub><sup>4</sup> together form a 3 to 7-membered, optionally substituted, saturated or unsaturated carbocycle or heterocycle, wherein the heterocycle can contain up to three different or same heteroatoms from the group O, N or S;

V<sub>a</sub>:
—CO—, —CO—NR<sub>a</sub><sup>5</sup>—, —NR<sub>a</sub><sup>5</sup>—CO—, —O—,
—S—SO—, —SO—, —SO—NR<sub>a</sub><sup>5</sup>—,
—NR<sub>a</sub><sup>5</sup>—SO—, —CS—, —CS—NR<sub>a</sub><sup>5</sup>—,
—NR<sub>a</sub><sup>5</sup>—CS—, —CS—O—, —O—CS—
—O—CO—, —O—CN—,
—C(=CR<sub>a</sub>—R<sub>a</sub><sup>6</sup>—)—, —CR<sub>a</sub>—CR<sub>a</sub>—, —NR<sub>a</sub><sup>5</sup>—CR<sub>a</sub>—,
—CO—NR<sub>a</sub><sup>5</sup>—, —O—CO—NR<sub>a</sub><sup>5</sup>—,
—NR<sub>a</sub><sup>5</sup>—;

R<sub>a</sub><sup>4</sup>, R<sub>a</sub><sup>2</sup>, R<sub>a</sub><sup>3</sup> independently of one another:
hydrogen, OH or each optionally substituted C<sub>a</sub>-alkyl, C<sub>a</sub>-alkyl
eyl, C<sub>a</sub>-alkylene, C<sub>a</sub>-alkynyl, C<sub>a</sub>-alkylene-C<sub>a</sub>-cyclo
cloalkyl, C<sub>a</sub>-cycloalkyl, aryl, C<sub>a</sub>-alkylene
eyl, C<sub>a</sub>-aryle, C<sub>a</sub>-hetaryl, or each independently of one another, two moieties R<sub>a</sub><sup>1</sup> and R<sub>a</sub><sup>2</sup> or R<sub>a</sub><sup>3</sup> and R<sub>a</sub><sup>4</sup> together form a 3 to 7-membered, optionally substituted, saturated or unsaturated carbocycle or heterocycle, wherein the heterocycle can contain up to three different or same heteroatoms from the group O, N or S;

R<sub>a</sub><sup>4</sup>, R<sub>a</sub><sup>2</sup>, R<sub>a</sub><sup>3</sup>, R<sub>a</sub><sup>4</sup> independently of one another:
hydrogen, OH or each optionally substituted C<sub>a</sub>-alkyl, C<sub>a</sub>-alkyl
eyl, C<sub>a</sub>-alkylene, C<sub>a</sub>-alkynyl, C<sub>a</sub>-alkylene-C<sub>a</sub>-cyclo
cloalkyl, C<sub>a</sub>-cycloalkyl, aryl, C<sub>a</sub>-alkylene
eyl, C<sub>a</sub>-aryle, C<sub>a</sub>-hetaryl, or each independently of one another, two moieties R<sub>a</sub><sup>1</sup> and R<sub>a</sub><sup>2</sup> or R<sub>a</sub><sup>3</sup> and R<sub>a</sub><sup>4</sup> together form a 3 to 7-membered, optionally substituted, saturated or unsaturated carbocycle or heterocycle, wherein the heterocycle can contain up to three different or same heteroatoms from the group O, N or S;

R<sub>a</sub><sup>4</sup>, R<sub>a</sub><sup>2</sup>, R<sub>a</sub><sup>3</sup>, R<sub>a</sub><sup>4</sup> independently of one another:
hydrogen, OH or each optionally substituted C<sub>a</sub>-alkyl, C<sub>a</sub>-alkyl
eyl, C<sub>a</sub>-alkylene, C<sub>a</sub>-alkynyl, C<sub>a</sub>-alkylene-C<sub>a</sub>-cyclo
cloalkyl, C<sub>a</sub>-cycloalkyl, aryl, C<sub>a</sub>-alkylene
eyl, C<sub>a</sub>-aryle, C<sub>a</sub>-hetaryl, or each independently of one another, two moieties R<sub>a</sub><sup>1</sup> and R<sub>a</sub><sup>2</sup> or R<sub>a</sub><sup>3</sup> and R<sub>a</sub><sup>4</sup> together form a 3 to 7-membered, optionally substituted, saturated or unsaturated carbocycle or heterocycle, wherein the heterocycle can contain up to three different or same heteroatoms from the group O, N or S;
the group O, N, S, wherein optionally two moieties 
substituted on this carbo- or heterocycle together can 
form an annelated, saturated, unsaturated or aromatic 
carbocycle or heterocycle, wherein the heterocycle 
can contain up to three different or same heteroatoms 
O, N, S, and wherein the cycle formed can be 
optionally substituted or a further, optionally substituted 
cycle can be condensed onto this cycle;

Q: a doubly substituted 5-membered hetaryl moiety 
chosen from Q1 to Q7

R\(^1\), R\(^2\) each independently of one another a moiety 
chosen from the groups 1.), 2.), 3.), 4.), 5.), 6.) or 7.:

1.) hydrogen, halogen, CN, CF\(_3\), CHF\(_2\), or 
each optionally substituted C\(_1\)-C\(_10\)-alkyl, C\(_2\)-C\(_10\)- 
alkenyl, C\(_2\)-C\(_10\)-alkynyl, C\(_2\)-C\(_10\)-cycloalkyl, 
C\(_1\)-C\(_6\)-alkylene-C\(_3\)-C\(_8\)-cycloalkyl, C\(_1\)-C\(_6\)-alkyl 
ene-aryl, C\(_1\)-C\(_6\)-alkylene-hetaryl, C\(_1\)-C\(_6\)-alkylene-O—C\(_1\)-C\(_6\)-alkyl, C\(_1\)-C\(_6\)-alkylene-O-aryl, 
COO—C\(_1\)-C\(_6\)-alkyl or C\(_1\)-C\(_6\)-alkylene-COO—C\(_1\)-C\(_6\)- 
alkyl; 

2.) Phenyl or napthyl, which are each substituted with 
R\(^2\), R\(^3\) and R\(^4\), wherein 
R\(^2\), R\(^3\) and R\(^4\) each independently of one another 
represent a substituent from the following group: 
hydrogen, NO\(_2\), NH\(_2\), OH, CN, CF\(_3\), CHF\(_2\), OCF\(_3\), 
OCHF\(_2\), COOH, O—CH\(_2\)—COOH, SH, halogen, or 
each optionally substituted aryl, heterocycloalkyl, 
C\(_1\)-C\(_6\)-alkyl, C\(_2\)-C\(_6\)-alkenyl, C\(_2\)-C\(_6\)-alkynyl, 
C\(_2\)-C\(_6\)-cycloalkyl, 
C\(_1\)-C\(_6\)-alkylene-heterocycloalkyl, 
C\(_1\)-C\(_6\)-alkylene-aryl or C\(_1\)-C\(_6\)-alkylene-hetaryl, or 
O—R\(^5\), S—R\(^5\), NR\(^2\)R\(^3\), CO—OR\(^5\), NR\(^2\)R\(^3\), 
CO—O—R\(^5\), O—CH\(_2\)—COO—R\(^5\), NR\(^2\)R\(^3\), 
CO—R\(^5\), SO\(_2\)—R\(^5\), NR\(^2\)R\(^3\), SO\(_2\)—R\(^5\), 
SO\(_2\)NH\(_2\), CONH\(_2\), SO\(_2\)—NR\(^2\)R\(^3\), or 
CO—NR\(^2\)R\(^3\), or 
two of the moieties R\(^2\), R\(^3\) or R\(^4\) together form a 
3 to 7-membered, optionally substituted, satu 
rated, unsaturated or aromatic carbocycle or a 
an optionally substituted, saturated, unsaturated 
romatic heterocycle which can contain up to three 
different or same heteroatoms O, N, S and 
optionally two of the moieties substituted on this 
heterocycle can together form an annelated, satu 
rated, unsaturated or aromatic carbocycle or 
heterocycle, wherein the heterocycle can contain up to 
three different or same heteroatoms O, N, S and 
the cycle formed can be optionally substituted or 
a further, optionally substituted cycle can be con 
densed onto this cycle;

R\(^5\) each independently of one another a moiety 
chosen from the group consisting of halogen, 
NO\(_2\), NH\(_2\), OH, CN, CF\(_3\), CHF\(_2\), OCF\(_3\), OCHF\(_2\), 
NH—(C\(_1\)-C\(_6\)-alkyl) and N(C\(_1\)-C\(_6\)-alkyl); 
R\(^6\) each optionally substituted C\(_1\)-C\(_6\)-alkyl, C\(_2\)-C\(_6\)- 
alkenyl, C\(_2\)-C\(_6\)-alkynyl, C\(_2\)-C\(_6\)-cycloalkyl, C\(_2\)-C\(_6\)- 
alkylene-C\(_3\)-C\(_8\)-cycloalkyl, C\(_2\)-C\(_6\)-alkylene-hetero 
cycloalkyl, aryl, hetaryl, heterocycloalkyl or 
C\(_1\)-C\(_6\)-alkylene-O—C\(_1\)-C\(_6\)-alkyl;

R\(^7\) hydrogen, OH, CN, or 
each optionally substituted C\(_1\)-C\(_6\)-alkyl, C\(_2\)-C\(_6\)- 
alkenyl, C\(_2\)-C\(_6\)-alkynyl, C\(_2\)-C\(_6\)-cycloalkyl, 
C\(_1\)-C\(_6\)-alkylene-C\(_3\)-C\(_8\)-cycloalkyl, C\(_1\)-C\(_6\)-alkyl 
eene-heterocycloalkyl, aryl, hetaryl, heterocycloalkyl 
or C\(_1\)-C\(_6\)-alkylene-O—C\(_1\)-C\(_6\)-alkyl;
aryl, CO—O—C₆H₄-alkylene-aryl, CO—O-hetaryl, CO—O—C₆H₄-alkylene-hetaryl, 
SO₂—C₆H₄-alkylene, SO₂—aryl, SO₂-hetaryl, 
SO₂—C₆H₄-alkylene-aryl or SO₂—C₆H₄-alkylene-hetaryl;

R₉, R₁₀: hydrogen or 
each optionally substituted C₆H₅-alkyl, C₆H₅-alkenyl, C₆H₅-alkynyl, C₆H₅-alkoxylalkyl, 
C₆H₅-alkylene-C₆H₅-cycloalkyl, C₆H₅-alkylene-heterocycloalkyl, ary1, hetaryl, heterocycloalkyl, 
C₆H₅-alkylene-O—C₆H₄-alkyl, CO—C₆H₅-alkyl, CO—C₆H₅-hetaryl, 
CO—C₆H₅-alkylene-aryl, CO—C₆H₅-alkylene-hetaryl, 
CO—C₆H₅-alkylene-C₆H₄-alkylene-hetaryl, SO₂—C₆H₅-alkyl, SO₂—C₆H₅-hetaryl, 
SO₂—C₆H₅-alkylene-aryl or SO₂—C₆H₅-alkylene-hetaryl;

or the moieties R₉ and R₁₀, together with the nitrogen, 
form a 3 to 7-membered, optionally substituted, 
saturated or aromatic heterocycle, which can contain 
one, two or three further different or same heteroatoms 
O, N, S; and optionally two of the moieties 
substituted on this heterocycle can together form an 
anellated, saturated, unsaturated or aromatic 
carbo cycle or heterocycle, wherein the heterocycle 
can contain up to three different or identical heteroatoms 
O, N, S; and wherein the cycle formed can be 
optionally substituted or a further, optionally substituted 
cycle can be condensed onto this cycle;

5.) a C₆-C₁₈₅ bi- or tricyclic, saturated hydrocarbon moiety;

6.) each optionally substituted C₆H₅-alkyl-NH₂, 
C₆H₅-alkyl-NR₂, CO—NR₂, C₆H₅-alkyl-CO—NR₂, 
C₆H₅-alkyl-CO—NR₂, C₆H₅-alkyl-SO₂—NR₂, 
C₆H₅-alkyl-SO₂—NR₂, C₆H₅-alkyl-CONH₂, 
C₆H₅-alkyl-CONH₂, C₆H₅-alkyl-SO₂—NH₂, 
CO—NH₂, CO—NH₂, 
SO₂—NH₂, 
SO₂—NH₂, 
SO₂—NH₂, 
SO₂—NH₂, 
SO₂—NH₂, 

7.) a 4-7-membered mono- or bicyclic saturated or unsaturated heterocycle, which can contain up to two 
different or identical heteroatoms from the group O, 
N or S, wherein this cycle can also be multiply 
substituted. For the case that the heterocycle contains 
an N-atom, this can be substituted with a moiety 
R₉.

2. Guanidine compound of the general formula I

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{R}^1 & \quad \text{R}^2 \\
\text{Z} & \quad \text{W}
\end{align*}
\]

corresponding enantiomeric, diastereomeric and/or tautomeric forms thereof as well as pharmaceutically acceptable salts thereof, wherein the given moieties have the following definitions:

W:
- a moiety of the general formula W1 or W2

A:
- NO₂, NH₂, OH, CN, CF₃, OCF₃, CHF₂, O—CHF₂, C₆H₅-alkyl, O—C₆H₅-alkyl, NH—
  (C₆H₄-alkyl), NC(C₆H₄-alkyl), NHCO—C₆H₄-alkyl, 
  NHCO—C₆H₄-alkyl and SO₂—C₆H₄-alkyl;

4.) both moieties R₉ and R₁₀ together form a 4 to 
7-membered, optionally substituted, saturated or unsaturated 
or aromatic carbocycle or a 5- or 6-membered 
optionally substituted, saturated or unsaturated 
or aromatic heterocycle, which can contain up to 
three further different or identical heteroatoms O, N, S; and 
can be substituted with up to two further moieties, 
wherein optionally two moieties substituted 
this carbon or heterocycle can together form 
an anellated, saturated, unsaturated or aromatic 

- CO—O—C₆H₄-alkylene-aryl, CO—O-hetaryl, 
  CO—O—C₆H₄-alkylene-hetaryl, 
  SO₂—C₆H₄-alkylene, SO₂—aryl, SO₂-hetaryl, 
  SO₂—C₆H₄-alkylene-aryl or SO₂—C₆H₄-alkylene-hetaryl;

- or the moieties R₉ and R₁₀, together with the nitrogen, 
  form a 3 to 7-membered, optionally substituted, 
  saturated or aromatic heterocycle, which can contain 
one, two or three further different or same heteroatoms 
  O, N, S; and optionally two of the moieties 
  substituted on this heterocycle can together form an 
anellated, saturated, unsaturated or aromatic 
  carbocycle or heterocycle, wherein the heterocycle 
  can contain up to three different or identical heteroatoms 
  O, N, S; and wherein the cycle formed can be 
  optionally substituted or a further, optionally substituted 
  cycle can be condensed onto this cycle;

- a C₆-C₁₈₅ bi- or tricyclic, saturated hydrocarbon 
  moiety;

- each optionally substituted C₆H₅-alkyl-NH₂, 
  C₆H₅-alkyl-NR₂, CO—NR₂, C₆H₅-alkyl-CO—NR₂, 
  C₆H₅-alkyl-CO—NR₂, C₆H₅-alkyl-SO₂—NR₂, 
  C₆H₅-alkyl-SO₂—NR₂, C₆H₅-alkyl-CONH₂, 
  C₆H₅-alkyl-CONH₂, C₆H₅-alkyl-SO₂—NH₂, 
  CO—NH₂, CO—NH₂, 
  SO₂—NH₂, 
  SO₂—NH₂, 
  SO₂—NH₂, 
  SO₂—NH₂, 

- a 4-7-membered mono- or bicyclic saturated or unsaturated heterocycle, which can contain up to two 
different or identical heteroatoms from the group O, 
N or S, wherein this cycle can also be multiply 
substituted. For the case that the heterocycle contains 
an N-atom, this can be substituted with a moiety 
R₉.
R₁:
- each optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₂-C₆-cycloalkyl, C₂-C₆-alkylene-C₂-C₆-cycloalkyl, C₂-C₆-alkylidene-C₂-C₆-alkylene-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, C₆-C₁₆-alkylene-aryl, or C₆-C₁₆-alkylene-hetaryl; hydrogen, OH, CN, or each optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₂-C₆-alkylene-C₂-C₆-cycloalkyl, C₂-C₆-alkylidene-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, C₆-C₁₆-alkylene-aryl, or C₆-C₁₆-alkylene-hetaryl;

R₂:
- each optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₂-C₆-cycloalkyl, C₂-C₆-alkylene-C₂-C₆-cycloalkyl, C₂-C₆-alkylidene-C₂-C₆-alkylene-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, C₆-C₁₆-alkylene-aryl, or C₆-C₁₆-alkylene-hetaryl; hydrogen, OH, CN, or each optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₂-C₆-cycloalkyl, C₂-C₆-alkylene-C₂-C₆-cycloalkyl, C₂-C₆-alkylidene-C₂-C₆-alkylene-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, C₆-C₁₆-alkylene-aryl, or C₆-C₁₆-alkylene-hetaryl; or the moieties R₂ and R₃ form, together with the
- nitrogen, a 3 to 7-membered, optionally substituted, saturated or aromatic heterocycle, which can contain one, two or three further different or identical heteroatoms from the group O, N, S; wherein optionally two of the moieties substituted on this heterocycle can together form an annelated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S and wherein the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

R₃:
- hydrogen, OH, halogen, O₃N-₆., CN, CF₃, CHF₂, O-CF₃, O-CHE₂, or each optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₂-C₆-cycloalkyl, C₂-C₆-alkylene-C₂-C₆-cycloalkyl, C₂-C₆-alkylidene-C₂-C₆-alkylene-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, C₆-C₁₆-alkylene-aryl, or C₆-C₁₆-alkylene-hetaryl; or the moieties R₁, R₂, and R₃ independently of one another:
- hydrogen, or each optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₂-C₆-cycloalkyl, C₂-C₆-alkylene-C₂-C₆-cycloalkyl, aryl, heteroaryl, cycloalkyl, C₆-C₁₆-alkylene-aryl, or C₆-C₁₆-alkylene-hetaryl;

B:
- hydrogen or as moiety A is defined, or each independently of one another, two of the moieties A, B or R₃ together form a 3 to 7-membered, optionally substituted, saturated or unsaturated carbocycle or an optionally substituted, saturated or unsaturated or aromatic heterocycle which can contain one, two or three further different or identical heteroatoms from the group O, N, S; wherein optionally two moieties substituted on this}

Carbo- or heterocycle can together form an annelated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S and wherein the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;
SO₂-C₅-C₆-alkyl, C₅-C₆-cycloalkyl, aryl, C₅-C₆-alkylene-aryl, CO—O—C₅-C₆-alkylene-aryl, CO—O—C₅-C₆-cycloalkyl, aryl, C₅-C₆-cycloalkyl, C₅-C₆-alkylenearyl, C₅-C₆-alkylene-aryl, C₅-C₆-alkylene-hetaryl; R₄ and R₅ independently of one another;
hydrogen, OH or each optionally substituted C₅-C₆-alkyl, C₅-C₆-alkoxy, C₅-C₆-alkenyl, C₅-C₆-carboxylic, C₅-C₆-alkylcycloalkyl, aryl, C₅-C₆-cycloalkyl, aryl, C₅-C₆-alkylene-aryl, C₅-C₆-alkylene-hetaryl, or each independently of the third moiety, two moieties of R₄ and R₅ together form a 5 to 7-membered, optionally substituted, saturated or unsaturated carbocycle or an optionally substituted, saturated or unsaturated heterocycle which can contain one, two or three further different or identical heteroatoms from the group O, N, S, wherein optionally two of the moieties substituted on this carbocycle or heterocycle can together form an anellated, saturated, unsaturated or aromatic carbocycle or heterocycle wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S and wherein the cycle formed is optionally substituted or a further, optionally substituted cycle is condensed onto this cycle;
R₆: O, N, R₆₁ or S; R₆₁: hydrogen, or each optionally substituted C₅-C₆-alkyl, C₅-C₆-alkenyl, C₅-C₆-carboxylic, C₅-C₆-alkylcycloalkyl, aryl, C₅-C₆-cycloalkyl, aryl, C₅-C₆-alkylene-aryl, C₅-C₆-alkylene-hetaryl, or each independently of one another a moiety chosen from the groups 1), 2), 3), 4) or 5);
1.) hydrogen, halogen, CN, CF₃, CHF₂,
or each optionally substituted C₅-C₆-alkyl, C₅-C₆-alkenyl, C₅-C₆-alkylcycloalkyl, C₅-C₆-alkylene-C₅-C₆-cycloalkyl, C₅-C₆-alkylene-aryl, C₅-C₆-alkylene-hetaryl, or each optionally substituted aryl, hetaryl, heterocycloalkyl, C₅-C₆-alkenyl, C₅-C₆-cycloalkyl, C₅-C₆-alkylene-C₅-C₆-cycloalkyl, C₅-C₆-alkylene-hetaryl, C₅-C₆-cycloalkyl, aryl, C₅-C₆-alkenyl-aryl, C₅-C₆-alkylene-aryl, or two of the moieties R₆, R₆₁ or R₆₂ together form a 3 to 7-membered, optionally substituted, saturated, unsaturated or aromatic carbocycle or an optionally substituted, saturated or unsaturated aromatic heterocycle, which can contain up to three further different or identical heteroatoms O, N, S and optionally two moieties substituted on this heterocycle can together form an anellated,
saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S and the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

R<sup>5</sup> each optionally substituted C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkenyne, C<sub>2</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkyl, which is optionally substituted with a substituent from the group consisting of halogen, NO<sub>2</sub>, NH<sub>2</sub>, OH, CN, CF<sub>3</sub>, CHF<sub>2</sub>, OCFC<sub>3</sub>, OCH<sub>2</sub>F, NH—(C<sub>1</sub>-C<sub>6</sub>-alkyl) and N(C<sub>1</sub>-C<sub>6</sub>-alkyl);

R<sup>6</sup> each optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkenyne, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkyl, which is optionally substituted with a substituent from the group consisting of halogen, NO<sub>2</sub>, NH<sub>2</sub>, OH, CN, CF<sub>3</sub>, CHF<sub>2</sub>, OCFC<sub>3</sub>, OCH<sub>2</sub>F, NH—(C<sub>1</sub>-C<sub>6</sub>-alkyl) and N(C<sub>1</sub>-C<sub>6</sub>-alkyl);

R<sup>7</sup> and R<sup>8</sup> hydrogen, OH, CN, or each optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkenyne, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkyl, which is optionally substituted with a substituent from the group consisting of halogen, NO<sub>2</sub>, NH<sub>2</sub>, OH, CN, CF<sub>3</sub>, CHF<sub>2</sub>, OCFC<sub>3</sub>, OCH<sub>2</sub>F, NH—(C<sub>1</sub>-C<sub>6</sub>-alkyl) and N(C<sub>1</sub>-C<sub>6</sub>-alkyl);

R<sup>9</sup> each optionally substituted C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkenyne, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkyl, which is optionally substituted with a substituent from the group consisting of halogen, NO<sub>2</sub>, NH<sub>2</sub>, OH, CN, CF<sub>3</sub>, CHF<sub>2</sub>, OCFC<sub>3</sub>, OCH<sub>2</sub>F, NH—(C<sub>1</sub>-C<sub>6</sub>-alkyl) and N(C<sub>1</sub>-C<sub>6</sub>-alkyl);

5.) both moieties R<sup>4</sup> and R<sup>5</sup> together form a 4 to 7-membered, optionally substituted, saturated or unsaturated or aromatic carbocycle or a 5- or 6-membered optionally substituted, saturated or unsaturated or aromatic heterocycle, which can contain up to three further different or identical heteroatoms O, N, S and can be substituted with up to two further moieties, wherein optionally two moieties substituted on this carbocycle or heterocycle can be substituted with an anelated, saturated or unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S and wherein the cycle formed can be optionally substituted or a further, optionally substituted cycle can be condensed onto this cycle;

6.) a C<sub>2</sub>-C<sub>6</sub>-bi- or tricyclic, saturated hydrocarbon moiety.

3.) a 5- or 6-membered hetaryl moiety optionally substituted with one or two substituents from the group consisting of:

- 2-pyrryl, 3-pyrryl, 2-thiazoyl, 4-thiazoyl, 5-thiazoyl, 2-oxazoyl, 4-oxazoyl, 5-oxazoyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 6-pyrimidyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, thiazolyl, oxadiazolyl or triazinyl or their annelated derivatives indazolyl, benzothiophenyl, benzofuranyl, indolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, chinolinyl and isochinolinyl; or

- 2-thienyl or 3-thienyl optionally substituted with one or two substituents, wherein the substituents are chosen from the group consisting of halogen, NO<sub>2</sub>, NH<sub>2</sub>, OH, CN, CF<sub>3</sub>, CHF<sub>3</sub>, O—CHF<sub>2</sub>, C<sub>2</sub>-C<sub>6</sub>-alkyl, O—C<sub>2</sub>-C<sub>6</sub>-alkyl, NH—(C<sub>1</sub>-C<sub>6</sub>-alkyl), N(C<sub>1</sub>-C<sub>6</sub>-alkyl), NHCO—C<sub>1</sub>-C<sub>4</sub>-alkyl, N(HSO<sub>2</sub>—C<sub>2</sub>-C<sub>4</sub>-alkyl and SO<sub>2</sub>—C<sub>5</sub>-C<sub>6</sub>-alkyl.

W: W1:
A: halogen, OH, CN, CF<sub>3</sub>, CHF<sub>2</sub>, OCFC<sub>3</sub>, OCHF<sub>2</sub>, or each optionally substituted C<sub>2</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkenyne, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkyl, which is optionally substituted with a substituent from the group consisting of halogen, NO<sub>2</sub>, NH<sub>2</sub>, OH, CN, CF<sub>3</sub>, CHF<sub>2</sub>, OCFC<sub>3</sub>, OCHF<sub>2</sub>, NH—(C<sub>1</sub>-C<sub>6</sub>-alkyl) and N(C<sub>1</sub>-C<sub>6</sub>-alkyl);
R₂²: hydrogen, CH₃;
R₁, R₂, R₃ independently of one another:
hydrogen, OH, CN, C₁₋C₄-alkyl, C₆₋C₁₀-alkylene-O—C₁₋C₄-alkyl, substituted aryl, benzyl, CO—C₁₋C₄-alkyl, CO-aryl, CO—C₁₋C₄-alkylene-aryl, OCO—C₁₋C₄-alkyl, OCO-aryl or OOCO—C₁₋C₄-alkylene-aryl
Q is chosen from the group consisting of Q₁, Q₂ and Q₃;
R₂₂: hydrogen, optionally substituted C₁₋C₄-alkyl, in the aryl moiety optionally substituted benzyl, CO—C₁₋C₄-alkyl, optionally substituted benzozy, SO₂—C₁₋C₄-alkyl or in the aryl moiety optionally substituted SO₂-aryl.
4. Guanidine compound according to at least one of the claims 1 to 3, wherein the given moieties have the following definitions:
A: OH, F, Cl, CN, CF₃, optionally substituted C₁₋C₄-alkyl, O—C₁₋C₄-alkyl or S—C₁₋C₄-alkyl;
B: hydrogen, OH, F, Cl, CN, CF₃, OCF₃, OCH₂F₂, optionally substituted C₁₋C₄-alkyl, O—C₁₋C₄-alkyl or S—C₁₋C₄-alkyl;
R₁: hydrogen, F, Cl, CN, CF₃ or O—CF₃;
Z: each optionally substituted C₁₋C₄-alkyl or C₁₋C₄-alkylene-O—C₁₋C₄-alkyl;
R₂², R₃², R₄² each independently of one another:
hydrogen, F, CH₃;
R₁, R₂, R₃ independently of one another:
hydrogen, OH, CN, O-methyl, O-phenyl, acetyl, benzoyl, O-acetyl, O-benzyol;
Q is chosen from the group consisting of

R₂₁: hydrogen, CH₃, methanesulfonyl, phenylsulfonfyl or tosyl.
5. Guanidine compound according to at least one of the claims 1 to 4, wherein the given moieties have the following definitions:
A: OH, OCF₃, OCH₂, O-ethyl, O-propyl or O-i-propyl;
Z: —CH₂—, —CH₂—O—, —CH₂—CH₂— or —CH₂—;
two of the moieties R¹, R², or R³, are hydrogen, and the third moiety is hydrogen, OH, acetyl or benzoyl;
Q:

R₂₂: hydrogen, or each optionally substituted C₁₋C₄-alkyl, phenyl, benzyl, phenethyl, CO—C₁₋C₄-alkyl, CO-aryl, CO—O—C₁₋C₄-alkyl, SO₂—C₁₋C₄-alkyl, SO₂-aryl, SO₂-hetaryl or SO₂—C₁₋C₄-alkylene-aryl
R₂²: each optionally substituted C₁₋C₄-alkyl, ary, n-hetaryl, benzoyl, phenethyl or CH₂-hetaryl;
R₁, R₂, R₃ independently of one another:
hydrogen, OH, CN, O-methyl, O-phenyl, acetyl, benzoyl, O-acetyl, O-benzyol;
Q is chosen from the group consisting of

6. Guanidine compound according to at least one of the claims 1 to 5, wherein R² and/or R₃ each independently of one another represents a moiety chosen from the groups 1.), 2.), 3.), 4.) or 5.):
1.) hydrogen, F, Cl, CN, CF₃, or each optionally substituted C₁₋C₄-alkyl, C₆₋C₁₀-alkenyl, C₁₋C₄-alkylene-O—C₁₋C₄-alkyl or C₁₋C₄-cycloalkyl;
2.) R₂₁, R₂₂ and R₂₃ independently of one another:
hydrogen, CN, CF₃, CHF₂, OCF₃, OCH₂F₂, F, Cl, OH or each optionally substituted phenyl or hetaryl,
C₁₋C₄-alkyl, C₆₋C₁₀-cycloalkyl, O—R₃², NR₂²²⁺, CO—OR₂²⁺, NR₂—CO—O—R₂², O—CH₂—
COO—R₃², NR₂—CO—O—R₂², SO₂—R₂², NR₃—isolated from the group consisting of F, Cl, OH,
CN, CF₃, OCF₃, NH—(C₁₋C₄-alkyl) and N(C₁₋C₄-alkyl)₂;
R₂²: each optionally substituted C₁₋C₄-alkyl, ary, hetaryl or phenyl;
R₂²: hydrogen, each optionally substituted C₁₋C₄-alkyl, ary, hetaryl, benzoyl, phenethyl or CH₂-hetaryl;
R₃: each optionally substituted C₁₋C₄-alkyl, ary, hetaryl, benzoyl, phenethyl or CH₂-hetaryl;
or R₃ and/or R₃ form an optionally substituted 3- or 7-membered saturated or unsaturated ring which can contain up to two identical or different hetero atoms from the group O and N;
3.) benzoanthroyl, benzoantrayl, chinolinyl or isoquinolinyl;
4.) both moieties R² and R₃ together form one of the following rings:

wherein R₂² and R₃ are as defined under 2.);
5.) Adamantyl.
7. Guanidine compound according to claim 1 or 2, wherein the given moieties have the following definitions:
W: W₁;
A: halogen, OH, CN, CF₃, CHF₂, OCF₃, OCH₂F₂, or each optionally substituted C₁₋C₄-alkyl or C₆₋C₁₀-alkenyl,
O—CH₂—COO—R₃², O—R₃², S—R₃², NR₂²⁺, NR₂²⁺—CO—R₂², SO₂NH₂, NR₃—isolated from the group consisting of F, Cl, OH,
CN, CF₃, OCF₃, NH—(C₁₋C₄-alkyl) and N(C₁₋C₄-alkyl)₂;
R₂²: each optionally substituted C₁₋C₄-alkyl, C₆₋C₁₀-cycloalkyl, phenyl or benzyl;
R₂²: hydrogen, or each optionally substituted C₁₋C₄-alkyl, phenyl, benzyl, phenethyl, CO—C₁₋C₄-alkyl, CO-aryl, CO—O—C₁₋C₄-alkyl, SO₂—C₁₋C₄-alkyl, SO₂-aryl, SO₂-hetaryl or SO₂—C₁₋C₄-alkylene-aryl.
R₂²: each optionally substituted C₁₋C₄-alkyl, phenyl, benzyl, phenethyl, CO—C₁₋C₄-alkyl, CO-aryl,
CO—O—C₁₋₄-alkyl, SO₂—C₁₋₄-alkyl, SO₂-aryl, 
SO₂-hetaryl, or SO₂—C₁₋₄-alkylene-aryl; 
or the moieties R₄⁺ and R₅⁺ together form an optionally 
substituted 5- or 6-membered saturated or unsaturated 
ring, which can contain up to two identical or 
different heteroatoms from the group O and N;
R₄⁺: hydrogen or an optionally substituted C₁₋₄-alkyl 
moiety;
B: hydrogen or as moiety A is defined;
R₅⁺: hydrogen, F, Cl, CN, CF₃, O—CF₃, or 
each optionally substituted C₁₋₄-alkyl, aryl, C₁₋₄-O₈-
alkylamino or C₁₋₄-diakylamino;
in the formula Z₁ the sum of a, b and c is 1, 2 or 3;
R₆⁺, R₇⁺, R₈⁺ independently of one another: 
hydrogen, halogen, OH, optionally substituted C₁₋₄-
alkyl;
V₆⁺ —CO—, —CO—NR₅⁺⁻, —NR₅⁺—CO—, —O—,
—S—;
R₇⁺: hydrogen, CH₃;
R₈⁺, R₉⁺, R₁₀⁺ independently of one another: 
hydrogen, OH, CN, C₁₋₄-alkyl, C₁₋₄-alkylene-O—
C₁₋₄-alkyl, substituted aryl, benzyl, CO—C₁₋₄-O₈-
alkyl, CO-aryl, CO—C₁₋₄-alkylene-aryl, OCO—
C₁₋₄-alkyl, OCO-aryl or OCO—C₁₋₄-alkylene-
hetaryl;
Q is chosen from the group consisting of Q₁, Q₂, Q₃ and 
Q⁵;
R₉⁺: hydrogen, optionally substituted C₁₋₄-alkyl, in 
the aryl moiety optionally substituted benzyl, CO—C₁₋₄-
alkyl, optionally substituted benzoyl, SO₂—C₁₋₄-
alkyl or in the aryl moiety optionally substituted SO₂-
aryl.
8. Guanidine compound according to at least one of 
the claims 1, 2 or 7, wherein the given moieties have 
the following definitions:
A: OH, F, Cl, OCF₃, OCHF₂, optionally substituted 
C₁₋₄-alkyl, O—C₁₋₄-alkyl or S—C₁₋₄-alkyl;
B: hydrogen, OH, F, Cl, CF₃, OCF₃, OCHF₂, optionally 
substituted C₁₋₄-alkyl, O—C₁₋₄-alkyl or S—C₁₋₄-alkyl;
R₄⁺: hydrogen, F, Cl, CN, CF₃ or O—CF₃;
Z: each optionally substituted C₁₋₄-alkyl or C₁₋₄- 
alkylene—C₁₋₄-alkyl;
R₆⁺, R₇⁺, R₈⁺ each independently of one another: 
hydrogen, CH₃;
R₁⁺, R₂⁺, R₃⁺ independently of one another: 
hydrogen, OH, CN, O-methyl, O-phenyl, acetyl, ben-
zoyl, O-acetyl, O-benzoyl;
Q is chosen from the group consisting of 
R₉⁺: hydrogen, CH₃, phenyl, benzyl, methanesulfonyl, 
phenylsulfanyl or tosyl.
9. Guanidine compound according to at least one of 
the claims 1, 2, 7 or 8, wherein the given moieties have 
the following definitions:
A: OH, OCF₃, OCH₃, O-ethyl, O-propyl or O-i-propyl;
Z: CH₂—, CH₂—O—, CH₂—CH₂— or CH₂—
CH₃—O—;
two of the moieties R₁⁺, R₂⁺, or R₃⁺ are hydrogen, and 
the third moiety is hydrogen, OH, acetyl or benzoyl;
Q:

R₉⁺: hydrogen, CH₃, phenyl, benzyl, methanesulfonyl, 
phenylsulfanyl or tosyl.
10. Guanidine compound according to at least one of 
the claims 1, 2 or 7 to 9, wherein R₄⁺ and/or R₅⁺ each inde-
dependently from one another represent a moiety chosen from 
the groups 1.), 2.), 3.), 4.), 5.) or 7.):
1.) hydrogen, F, Cl, CN, CF₃, or 
each optionally substituted C₁₋₄-alkyl, C₁₋₄-alkyl-
eneyl, C₁₋₄-alkylene-O—C₁₋₄-alkyl or C₃₋₄-cy-
cloalkyl;
2.) R₆⁺, R₇⁺ and R₈⁺ independently of one another 
hydrogen, CN, CF₃, CHF₂, OCF₃, OCHF₂, F, Cl, OH 
or each optionally substituted phenyl or hetaryl, C₁₋₄-
alkyl, C₂₋₄-cycloalkyl, O—R₉⁺⁻, NR₉⁺⁻R₉⁺⁻, CO—
OR₉⁺⁻, NR₉⁺⁻O—R₉⁺⁻, O—CH₂—CO—R₉⁺⁻, 
NR₉⁺⁻CO—R₉⁺⁻, SO₂—R₉⁺⁻, NR₉⁺⁻SO₂—R₉⁺⁻, 
NR₉⁺⁻CO—O—R₉⁺⁻, SO₃H₂, CONH₂, SO₂—
NR₉⁺⁻R₉⁺⁻ or CO—NR₉⁺⁻R₉⁺⁻;
R₉⁺: C₁₋₄-alkyl, which is optionally substituted with 
a substituent from the group consisting of F, Cl, OH, 
CN, CF₃, OCF₃, NH—(C₁₋₄-alkyl) and N(C₁₋₄-
alkyl)₂;
R₉⁺: each optionally substituted C₁₋₄-alkyl, aryl, het-
aryl or phenyl;
R₉⁺: hydrogen, each optionally substituted C₁₋₄-
alkyl, alkyl, aryl, hetaryl, benzyl, phenethyl or CH₂-
hetaryl;
R₉⁺: hydrogen, each optionally substituted C₁₋₄-
alkyl, alkyl, aryl, hetaryl, benzyl, phenethyl or CH₂-
hetaryl;
or R₉⁺ and R₉⁺ form an optionally substituted 3- or 
7-membered saturated or unsaturated ring, which can 
contain up to two identical or different heteroatoms 
from the group O and N;
3.) benzothiophenyl, benzofuranyl, chinolinyl or isoqui-
nolinyl;
4.) both moieties \( R^4 \) and \( R^5 \) together form one of the following rings:

![Rings Diagram]

wherein \( R^2 \) and \( R^3 \) are defined as under 2.), or together can form an anellated 5-, or 6-membered ring;

5.) adamantyl;

7.) each optionally substituted azetidine-3-yl, pyrrolidine-2-yl, piperidine-3-yl, piperidine-3-yl, tetrahydrofuran-3-yl, azepan-4-yl, azepan-3-yl, azepan-2-yl, 1,4-diazepane-5-yl, 1,2,3,6-tetrahydropyridine-4-yl, 2,5-dihydro-1H-pyrrol-3-yl.

11. Guanidine compound according to at least one of the claims 1 to 10, wherein one moiety from \( R^4 \) and \( R^5 \) is chosen from group 1.), and the other moiety from \( R^2 \) and \( R^3 \) is chosen from the group 1.), 2.) or 3.).

12. Guanidine compound according to at least one of the claims 1 to 11 as a medicament.

13. Pharmaceutical composition, comprising at least one guanidine compound according to one of the claims 1 to 12, as well as a pharmaceutically acceptable carrier or dilution agent.

14. Use of compounds of the general formula IVA for the preparation of 5HT5A receptor ligands:

\[
\begin{align*}
W & \rightarrow Z \rightarrow NH_2
\end{align*}
\]

IV A

15. Use according to claim 14 for the preparation of the guanidine compounds according to one of the claims 1 to 12.

16. Use of a guanidine compound of the general formula IVA

\[
\begin{align*}
W_1 & \rightarrow Z \rightarrow NH_2
\end{align*}
\]

of the corresponding enantiomeric, diastereomeric and/or tautomeric forms thereof as well as pharmaceutically acceptable salts thereof

wherein the given moieties have the following definitions:

- \( W_1 \): a moiety of the general formula W1 or W2

\[
\begin{align*}
A & \rightarrow B \rightarrow C \rightarrow D \rightarrow E
\end{align*}
\]

- \( A \): NO, NH, OH, CN, CF, OCF, CHF, OCHF, COOH, 0—CH=—COOH, halogen, SH, or each optionally substituted \( C_{1-6} \)-alkyl, \( C_{1-6} \)-alkenyl, \( C_{1-6} \)-alkynyl, \( C_{1-6} \)-cycloalkyl, \( C_{1-6} \)-alkylene-\( C_{1-6} \)-cycloalkyl or \( C_{1-6} \)-alkylene-heterocycloalkyl, aryld, hetaryl, heterocycloalkyl, \( C_{1-6} \)-alkylene-hetaryl or \( C_{1-6} \)-alkylene-arylation, or \( O—R^4 \), \( CO—R^4 \), \( S—R^4 \), \( SO—R^4 \), \( CO—O—R^4 \), \( NR^4—CO—O—R^4 \), \( O—CH_2—COO—R^4 \), \( NR^4—CO—R^4 \), \( CONH—R^4 \), \( NO_2—R^4 \), \( NR^4—SO—R^4 \), \( SO_2—NR^4—R^4 \) or \( CO—NR^4—R^4 \);

- \( R^1 \): each optionally substituted \( C_{1-6} \)-alkyl, \( C_{1-6} \)-alkenyl, \( C_{1-6} \)-alkynyl, \( C_{1-6} \)-cycloalkyl, \( C_{1-6} \)-alkylene-heterocycloalkyl, aryld, hetaryl, heterocycloalkyl, \( C_{1-6} \)-alkylene-hetaryl, or \( C_{1-6} \)-alkylene-arylation, \( C_{1-6} \)-alkylene-hetaryl, \( SO_2—C_{1-6} \)-alkyl, \( SO_2—C_{1-6} \)-alkylene-arylation or \( SO_2—C_{1-6} \)-alkylene-hetaryl;

- \( R^2 \): hydrogen, OH, CN, or each optionally substituted \( C_{1-6} \)-alkyl, \( C_{2-6} \)-alkenyl, \( C_{2-6} \)-alkynyl, \( C_{2-6} \)-cycloalkyl, \( C_{2-6} \)-alkylene-heterocycloalkyl, aryld, hetaryl, heterocycloalkyl, \( C_{2-6} \)-alkylene-hetaryl, \( C_{2-6} \)-alkylene-arylation, or \( C_{2-6} \)-alkylene-hetaryl, \( CO—C_{2-6} \)-alkylene-arylation, \( CO—C_{2-6} \)-alkylene-hetaryl, \( CO—O—C_{2-6} \)-alkyl, \( CO—O—C_{2-6} \)-alkylene-arylation, \( CO—O—C_{2-6} \)-alkylene-hetaryl, \( SO_2—C_{2-6} \)-alkyl, \( SO_2—C_{2-6} \)-alkylene-arylation or \( SO_2—C_{2-6} \)-alkylene-hetaryl;

- \( R^3 \): each optionally substituted \( C_{1-6} \)-alkyl, \( C_{2-6} \)-alkenyl, \( C_{2-6} \)-alkynyl, \( C_{2-6} \)-cycloalkyl, \( C_{2-6} \)-alkylene-heterocycloalkyl, aryld, hetaryl, heterocycloalkyl, \( C_{2-6} \)-alkylene-hetaryl, \( C_{2-6} \)-alkylene-arylation, or \( C_{2-6} \)-alkylene-hetaryl, \( CO—C_{2-6} \)-alkylene-arylation, \( CO—C_{2-6} \)-alkylene-hetaryl, \( CO—O—C_{2-6} \)-alkyl, \( CO—O—C_{2-6} \)-alkylene-arylation, \( CO—O—C_{2-6} \)-alkylene-hetaryl, \( SO_2—C_{2-6} \)-alkyl, \( SO_2—C_{2-6} \)-alkylene-arylation or \( SO_2—C_{2-6} \)-alkylene-hetaryl; or the moieties \( R^2 \) and \( R^3 \) form, together with the nitrogen, a 3 to 7-membered, optionally substituted, saturated or aromatic heterocycle, which can contain one, two or three further different or identical heteroatoms from the group O, N, S; wherein optionally two moieties substituted on this heterocycle can together form an anellated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms, O, N, S and wherein the so-formed
cycle can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

\[ R^1_2^3 = \] hydrogen, or each optionally substituted C-C_{alkyl}, C_C_{alkenyl}, C_C_{alkenyl}-O-C_C_{alkyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C_{alkenyl}, C_C}_{
E: O, N — R^1 _O, or S;
R^1 _O:
hydrogen, or
each optionally substituted C_1-C_10-alkyl, CO—C_1-C_4-alkyl, SO_2—C_1-C_4-alkyl, CO—O—C_1-C_4-alkyl, aryl, C_1-C_4-alkylene-aryl, CO-aryl, CO-hetaryl, SO_2-aryl, SO_2-hetaryl, CO—O-aryl, CO—C_1-C_4-alkylene-aryl, SO_2—C_1-C_4-alkylene-aryl or CO—O—C_1-C_4-alkylene-aryl;
R^1 _O, R^2 _O each independently of one another, a moiety chosen from the groups 1), 2), 3), 4), 5), 6) or 7):
1.) hydrogen, halogen, CN, CF_3, CFH_2, or
each optionally substituted C_1-C_10-alkyl, C_2-C_10-alkenyl, C_2-C_10-alkynyl, C_2-C_10-cycloalkyl, C_2-C_10-alkylene-C_2-C_10-cycloalkyl, C_2-C_10-alkylene-aryl, C_2-C_10-alkylene-hetaryl, C_1-C_9-alkylene-O—C_1-C_9-alkyl, C_1-C_9-alkylene-O-aryl, COO—C_1-C_4-alkyl or C_1-C_4-alkylene-COO—C_1-C_4-alkyl;
3.) phenyl or naphthyl, which are substituted with R^1 _O, R^2 _O and R^3 _O, wherein
R^1 _O, R^2 _O and R^3 _O each independently of one another represent a substituent from the following group:
hydrogen, NO_2, NH_2, OH, CN, CF_3, CHF_2, OCF_3, OCHF_2, COOH, O—CH_2—COOH, SH, halogen, or
each optionally substituted ary1, hetaryl, heterocycloalkyl, C_1-C_9-alkyl, C_1-C_9-alkenyl, C_1-C_9-alkynyl, C_1-C_9-cycloalkyl, C_1-C_9-alkylene-C_2-C_9-cycloalkyl, C_1-C_9-alkylene-hetaryl, C_1-C_9-cycloalkylene-aroyl or C_1-C_9-alkylene-hetaryl, or
O—R^1 _O, S—R^1 _O, N(R^3 _O)_2, CO—OR^3 _O, CO—O—R^3 _O, O—CH_2—COO—R^3 _O, SO_2—N(R^3 _O)_2, SO_2—R^3 _O, SO_2—NH_2, CONH_2, SO_2—NR^3 _O—R^3 _O, or
CO—NR^3 _O—R^3 _O, or
two of the moieties R^1 _O, R^2 _O or R^3 _O together form a 3 to 7-membered, optionally substituted, saturated, unsaturated carbocycle or an optionally substituted, saturated, unsaturated aromatic heterocycle which can contain up to three further different or identical heteroatoms O, N, S, and optionally two moieties substituted on this heterocycle can form an anelated, saturated, or unsaturated aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three further different or identical heteroatoms O, N, S, and the cycle formed may optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle:
R^2 _O each optionally substituted C_1-C_9-alkyl, C_2-C_9-alkenyl, C_2-C_9-alkynyl, C_2-C_9-cycloalkyl, C_2-C_9-alkylene-C_2-C_9-cycloalkyl, C_2-C_9-alkylene-hetaryl, heterocycloalkyl, aryl or hetaryl;
R^3 _O each optionally substituted C_1-C_9-alkyl, C_2-C_9-alkenyl, C_2-C_9-alkynyl, C_2-C_9-cycloalkyl, C_2-C_9-alkylene-C_2-C_9-cycloalkyl, C_2-C_9-alkylene-hetaryl, heterocycloalkyl, aryl or hetaryl;
R^4 _O, R^5 _O each independently of one another, a moiety chosen from the groups 1), 2), 3), 4), 5), 6) or 7):
1.) hydrogen, halogen, CN, CF_3, CFH_2, or
each optionally substituted C_1-C_10-alkyl, C_2-C_10-alkenyl, C_2-C_10-alkynyl, C_2-C_10-cycloalkyl, C_2-C_10-alkylene-C_2-C_10-cycloalkyl, C_2-C_10-alkylene-aryl, C_2-C_10-alkylene-hetaryl, C_1-C_9-alkylene-O—C_1-C_9-alkyl, C_1-C_9-alkylene-O-aryl, COO—C_1-C_4-alkyl or C_1-C_4-alkylene-COO—C_1-C_4-alkyl;

or both moieties R₂ and R₅ form, together with the nitrogen, a 3 to 7-membered, optionally substituted, saturated or aromatic heterocycle, which can contain one, two or three different or identical heteroatoms O, N, S; and optionally two moieties substituted on this heterocycle can together form an annelated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S, and the cycle formed can be optionally substituted or a further, optionally substituted cycle can be condensed onto this cycle;

3.) a 5- or 6-membered, hetaryl moiety, optionally substituted with 1 or 2 substituents from the group consisting of: 2-furyl, 3-furyl, 2-pyryrol, 3-pyryrol, 2-thienyl, 3-thienyl, 2-pyrindyl, 3-pyrindyl, 2-thiazolyl, 3-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 6-pyrimidyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 3-isothiazolyl, 5-isothiazolyl, 5-isoxazolyl, 4-isooxazolyl, 5-isoxazolyl, 3-imidazolyl, 4-imidazolyl, 3-pyridazinyl, 4-pyridazinyl, 5-oxazolyl, 6-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, thiazolyl, oxadiazolyl or triazinyl or their annelated derivatives indazolyl, indolyl, benzoindolyl, benzofuranyl, indoliny, benzimidazolyl, benzthiazolyl, benzoxazolyl, chinoliny and isoquinoliny;

4.) both moieties R₂ and R₅ together form a 4 to 7-membered, optionally substituted, saturated or unsaturated or aromatic carbocycle or a 5- or 6-membered optionally substituted, saturated or unsaturated or aromatic heterocycle, which can contain up to three further different or identical heteroatoms O, N, S, and which can be substituted with up to two further moieties, wherein optionally two moieties substituted on this carbocycle or heterocycle together form an annelated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three further different or identical heteroatoms O, N, S and wherein the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

5.) a C₇-C₁₀ bi- or tricyclic, saturated hydrocarbon moiety;


7.) a 4-7-membered mono- or bicyclic saturated or unsaturated heterocycle, which can contain up to two different or identical heteroatoms from the group O, N or S, wherein this cycle can also be multiply substituted. For the case that the heterocycle contains an N-atom, this can be substituted with an R₂/O-moiety.

for the preparation of a medicament for the treatment of diseases modulated by a 5-HT₅ receptor activity.

17. Use of a guanidine compound of the general formula IA

\[ \text{IA} \]

of the corresponding enantiomeric, diastereomeric and/or tautomeric forms thereof as well as pharmaceutically acceptable salts thereof, wherein the given moieties have the following definitions:

W:

a moiety of the general formula W₁ or W₂

\[ \text{W₁} \]

\[ \text{W₂} \]

A: NO₂, NH₂, OH, CN, CF₃, OCCF₃, CHF₂, OCHF₂, COOH, O—CH₂—COOH, halogen, SH, or each optionally substituted C₁-C₆-alkyl, C₁-C₆-alkynyl, C₁-C₆-cycloalkyl, C₁-C₆-cycloalkenyl, C₁-C₆-cycloalkynyl, or C₁-C₆-cycloalkene-heterocycloalkyl, aryl, hetaryl, heterocycloalkyl, C₁-C₆-alkylene-hetaryl or C₁-C₆-alkylene-aryle, or


R¹₄:

each optionally substituted C₁-C₆-alkyl, C₁-C₆-alkynyl, C₁-C₆-cycloalkyl, C₁-C₆-cycloalkenyl, C₁-C₆-cycloalkynyl, C₁-C₆-cycloalkene-heterocycloalkyl, aryl, hetaryl, heterocycloalkyl, C₁-C₆-alkylene-aryle, C₁-C₆-alkylene-hetaryl, C₁-C₆-alkylene-aryle, or C₁-C₆-alkylene-hetaryl;

R²:

hydrogen, OH, CN, or each optionally substituted C₁-C₆-alkyl, C₁-C₆-alkynyl, C₁-C₆-cycloalkyl, C₁-C₆-cycloalkenyl, C₁-C₆-cycloalkynyl, C₁-C₆-cycloalkene-heterocycloalkyl, aryl, hetaryl, heterocycloalkyl, C₁-C₆-alkylene-aryle, C₁-C₆-alkylene-hetaryl, C₁-C₆-alkylene-hetaryl, C₁-C₆-alkylene-O—C₁-C₆-alkyl,
CO—C1-C6-alkyl, CO-aryl, CO-hetaryl, CO—C1-C6-alkylene-aryl, CO—C1-C6-alkylene-hetaryl, CO—O—C1-C6-alkyl, CO—O—aryl, CO—O—C1-C6-alkylene-aryl, CO—O—hetaryl, CO—O—C1-C6-alkylene-hetaryl, SO2—C1-C6-alkylene-aryl or SO2—C1-C6-alkylene-hetaryl;

R2:
each optionally substituted C1-C6-alkyl, C1-C6-alkylene-aryl, C1-C6-alkylamino, C1-C6-dialkylamino, pyrrolidinyl, piperidinyl, morpholinyl, CO—C1-C6-alkyl, SO2—C1-C6-alkyl, CO-aryl, SO2-aryl, CO—C1-C6-alkylene-aryl, SO2—C1-C6-alkylene-aryl, SO2-aryl, SO2-hetaryl, CONH2, CON—C1-C6-alkyl, SO2-N(C1-C6-alkyl), NH—SO2—C1-C6-alkyl or NH—CO—C1-C6-alkyl;

D: as moiety A is defined;

Z: a moiety of the general formula Z1

\[
\begin{align*}
V2: & \quad \text{with the indices} \\
|a| &= 0-4, \quad |b| = 0, \quad |c| = 0-4 \\
R_{21}, R_{22}, R_{23}, R_{24} & \text{ independently of one another:} \\
\text{hydrogen, halogen, OH, or} \\
\text{each optionally substituted C1-C6-alkyl, C1-C6-alkylene-aryl, C1-C6-alkylamino, C1-C6-dialkylamino, pyrrolidinyl, piperidinyl, morpholinyl, CO—C1-C6-alkyl, SO2—C1-C6-alkyl, CO-aryl, SO2-aryl, CO—C1-C6-alkylene-aryl, SO2—C1-C6-alkylene-aryl, SO2-aryl, SO2-hetaryl, CONH2, CON—C1-C6-alkyl, SO2-N(C1-C6-alkyl), NH—SO2—C1-C6-alkyl or NH—CO—C1-C6-alkyl;}
\end{align*}
\]

R2:
hydrogen, or

each optionally substituted C1-C6-alkyl, C1-C6-alkylene-aryl, C1-C6-alkylamino, C1-C6-dialkylamino, pyrrolidinyl, piperidinyl, morpholinyl, CO—C1-C6-alkyl, SO2—C1-C6-alkyl, CO-aryl, SO2-aryl, CO—C1-C6-alkylene-aryl, SO2—C1-C6-alkylene-aryl, SO2-aryl, SO2-hetaryl, CONH2, CON—C1-C6-alkyl, SO2-N(C1-C6-alkyl), NH—SO2—C1-C6-alkyl or NH—CO—C1-C6-alkyl;

B: 
hydrogen or as moiety A is defined,
or each independently from another, two of the moieties A, B or R2 together form a 3 to 7-membered, optionally substituted, saturated or unsaturated carbocycle or a heterocycle, which can contain one, two or three further different or identical heteroatoms from the group O, N, S; wherein optionally two moieties substituted on this heterocycle together can form an annelated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S, and wherein the so-formed cycle can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

R3:
hydrogen, OH, halogen, NO2, NH2, CN, CF3, O—CF3, O—CHF2, O—CF2O, or each optionally substituted C1-C6-alkyl, C1-C6-alkylene-aryl, C1-C6-alkylamino, C1-C6-dialkylamino, pyrrolidinyl, piperidinyl, morpholinyl, CO—C1-C6-alkyl, SO2—C1-C6-alkyl, CO-aryl, SO2-aryl, CO—C1-C6-alkylene-aryl, SO2—C1-C6-alkylene-aryl, SO2-aryl, SO2-hetaryl, CONH2, CON—C1-C6-alkyl, SO2-N(C1-C6-alkyl), NH—SO2—C1-C6-alkyl or NH—CO—C1-C6-alkyl;
Q: each independently of the third moiety, two moieties of 
R¹, R² or R³ together form a 5 to 7-membered, optionally substituted, saturated or unsaturated carbo
cycle, or an optionally substituted, saturated or unsaturated, which can contain one, two or three 
different or identical heteroatoms from the group O, 
N, S, wherein optionally two moieties substituted on this carbo-
or heterocycle can together form an anellated, saturated or unsaturated aromatic 
cycle or heterocycle, wherein the heterocycle may 
contain up to three different or identical heteroatoms 
O, N, S and wherein the cycle formed can optionally 
be substituted or a further, optionally substituted 
cycle can be condensed onto this cycle;

Q: a doubly substituted 5-membered hetaryl moiety, 
chosen from Q1 to Q6

E: O, N—R₂⁻¹ or S;
R₂⁻¹:
hydrogen, or
each optionally substituted C₁₋₃-alkyl, CO—C₁₋₃- 
alkyl, SO₂—C₁₋₃-alkyl, CO—O—C₁₋₃-alkyl, CO—het
aryl, CO—O-hetaryl, CO—O—C₁₋₃-alkylene-hetaryl,
SOC₁₋₃-alkylene-hetaryl, OCO—C₁₋₃-alkyl,
OCO-hetaryl, OCO—C₁₋₃-alkylene-
hetaryl, OCO—C₁₋₃-alkylene-hetaryl, SO₂—C₁₋₃- 
alkyl, SO₂-aryl, SO₂-hetaryl or SO₂—C₁₋₃-alkyl,

Q6

R², R³ each independently of one another a moiety chosen from the groups 1), 2), 3), 4) or 5):
1.) hydrogen, halogen, CN, CF₃, CHF₂, or 
each optionally substituted C₁₋₃-alkyl, C₂₋₅- 
alkenyl, C₂₋₅-cycloalkyl, 
C₁₋₃-alkyl-alkynyl, C₁₋₃-alkyl-
ene-aryl, C₁₋₃-alkyl-hetaryl, C₁₋₃-alkyllene-
ene-O—C₁₋₃-alkyl, C₁₋₃-alkylene-O-aryl, 
COO—C₁₋₃-alkyl or C₁₋₃-alkylene-COO— 
C₁₋₃-alkyl;
4.) Phenyl or naphthyl, which are each substituted with 
R₅⁻², R₅⁻³ and R₅⁻⁴, wherein 
R₅⁻², R₅⁻³ and R₅⁻⁴ each independently from one 
other represent a substituent from the following 
group:
hydrogen, NO₂, NH₂, OH, CN, CF₃, CHF₂, OCF₃,
OCHF₂, COOH, O—CH₂—COOH, SH, halogen, or 
each optionally substituted aryl, hetaryl, heterocy
cloalkyl, C₁₋₃-alkyl, C₂₋₅-alkenyl, C₂₋₅-alkynyl, C₂₋₅-cycloalkyl, C₁₋₃-alkylene-C₁₋₃-cycloalkyl,

Q5

C₁₋₃-alkyl-alkynyl, or C₁₋₃-alkylene-aryl or C₁₋₃-alkylene-hetaryl, or 

Q4

O—R₅⁻², S—R₅⁻², NR₅⁻², CO—OR₅⁻², NR₅⁻², CO—O—R₅⁻², 
O—CH₂—COO—R₅⁻², NR₅⁻², CO—R₅⁻², 
SO₂—R₅⁻², NR₅⁻², CO—O—R₅⁻², 
SO₂—R₅⁻², CONH₂, SO₂—NR₂⁻⁴, 

Q3

R₅⁻², R₅⁻³ or R₅⁻⁴ together form a 
3 to 7-membered, optionally substituted, saturated, unsaturated aromatic het
erocycle, which can contain up to three further 
different or identical heteroatoms O, N, S, and 
only two moieties substituted on this hetero
cycle together can form an anellated, saturated, unsaturated or aromatic heterocycle or heterocycle, 
wherein the heterocycle can contain up to three 
different or identical heteroatoms O, N, S, and 
The cycle formed can optionally be substituted or a further, optionally substituted cycle can be con
densed onto this cycle;

R₅⁻² each optionally substituted C₁₋₃-alkyl, C₂₋₅- 
alkenyl, C₂₋₅-cycloalkyl, C₁₋₃-alkylene-heterocycloalkyl, het
erocycloalkyl, aryl or hetaryl;

R₈⁻ each optionally substituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, C₃-C₆-alkylene-C₃-C₆-cycloalkyl, C₃-C₆-alkylene-heterocycloalkyl, aryl, hetaryl, heterocycloalkyl, CO—C₆-C₆-alkyl, C₆-C₆-alkylenearyl, C₆-C₆-alkylene-hetaryl, CO—O—C₆-C₆-alkyl, CO—O—C₆-C₆-alkylenearyl, CO—O—C₆-C₆-alkylene-hetaryl, C₆-C₆-alkyl, C₆-C₆-alkylenearyl, C₆-C₆-alkylene-hetaryl, CO—O—C₆-C₆-alkyl, CO—O—C₆-C₆-alkylenearyl, CO—O—C₆-C₆-alkylene-hetaryl, C₆-C₆-alkyl, C₆-C₆-alkylenearyl, C₆-C₆-alkylene-hetaryl, C₆-C₆-alkyl, C₆-C₆-alkylenearyl, C₆-C₆-alkylene-hetaryl, or both moieties R₈⁺ and R₈⁻ form, together with the nitrogen, a 3 to 7-membered, optionally substituted, saturated or aromatic heterocycle, which can contain one, two or three further different or identical heteroatoms O, N, S; and optionally two moieties substituted on this heterocycle can together form an anellated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or same heteroatoms O, N, S and the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

3.) a 5- or 6-membered, hetaryl moiety, optionally substituted with one or two substituents from the group consisting of:
2-furyl, 3-furyl, 2-pyrylol, 3-pyrylol, 2-thiényl, 3-thiényl, 2-pyridyl, 3-pyridyl, 4-pyrydyl, 2-thiazollyl, 4-thiazollyl, 5-thiazollyl, 2-oxazollyl, 4-oxazollyl, 5-oxazollyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 6-pyrimidyl, 3-pyrazollyl, 4-pyrazollyl, 5-pyrazollyl, 3-isothiazollyl, 4-isothiazollyl, 5-isothiazollyl, 2-imidazolly, 4-imidazolly, 5-imidazolly, 3-pyridazolly, 4-pyridazolly, 5-pyridazolly, 6-pyridazolly, 3-isoxazollyl, 4-isoxazollyl, 5-isoxazollyl, thiadiazollyl, oxadiazollyl or triazinyl or their anelated derivatives indazollyl, indoly, benzothiophenyl, benzofuranyl, indolinyl, benzimidazollyl, benzthiazollyl, benzoazollyl,chinolinyl and isochnolinyl;

4.) both moieties R¹⁴ and R¹⁵ together form a 4 to 7-membered, optionally substituted, saturated or unsaturated or aromatic carbocycle or a 5- or 6-membered optionally substituted, saturated or unsaturated or aromatic heterocycle, which can contain up to three further different or identical heteroatoms O, N, S, and can be substituted with up to two further moieties, wherein optionally two moieties substituted on this carb- or heterocycle can together form an anellated, saturated, unsaturated or aromatic carbocycle or heterocycle, wherein the heterocycle can contain up to three different or identical heteroatoms O, N, S and wherein the cycle formed can optionally be substituted or a further, optionally substituted cycle can be condensed onto this cycle;

5.) a C₆-C₁₀- bi- or tricyclic, saturated hydrocarbon moiety;

for the manufacture of a medicament for the treatment of diseases which are modulated by a 5-HT₅ receptor activity.

18. Use according to claim 16, wherein R¹⁴ and/or R¹⁵ have the following meanings:
2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiényl, 3-thiényl, benzothiophenyl, benzofuranyl, chinolinyl or isochnolinyl, which may optionally be substituted with 1 or 2 moieties.

19. Use according to claim 16 or 17 for the treatment of neuropathological, neuropsychiatric and neurodegenerative disorders, symptoms and dysfunctions.

20. Use according to at least one of the claims 16 to 18 for the treatment of migraine and brain damage.

21. Use according to claim 18 for the treatment of neuropathological, neuropsychiatric and neurodegenerative diseases, selected from the group consisting of cerebral ischemia, stroke, epilepsy and seizures in general, psychoses, schizophrenia, autism, OCD-syndrome, cognitive diseases, attention disorders, depressions, bipolar and/or unipolar depressions, states of anxiety, dementia, senile dementia, Alzheimer dementia, demyelinizing diseases, multiple sclerosis and brain tumors.

22. Use according to claim 16 or 17 for the treatment of diseases chosen from the group consisting of cerebral vascular disorders, pain, disorders due to pain, addiction, disorders due to drugs, amnesia, alcohol abuse, drug abuse, disorders of the circadian rhythm and Cushing syndrome.

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