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(54) Titre : MEDICAMENT POUR TRAITER DES AFFECTIONS IMPLIQUANT UNE INHIBITION OU UNE BAISSE D'ACTIVITE DE PROTEINES TRANSPORTEUSES DE BICARBONATE REGULANT LE PH

(54) Title: MEDICAMENT FOR THE TREATMENT OF DISEASES REQUIRING INHIBITION OR A REDUCTION IN THE ACTIVITY OF PH VALUE-REGULATING BICARBONATE TRANSPORTER PROTEINS

(57) Abrégé/Abstract:
Disclosed is the use of selective imidazoline receptor agonists, particularly moxonidine, rilmenidine, LNP-509, S-23515, PMS-812, PMS-847, and BU-98008, and the physiologically acceptable salts thereof, for the production of pharmaceutical preparations used for treating and/or preventing functional disturbances and/or diseases in larger mammals or humans, which require inhibition or a reduction in the activity of proteins that regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters, particularly diseases which affect the bones as a result of an undesired bone resorption level, especially osteoporosis, diseases of the gastrointestinal tract, especially gastric ulcers, and neural and/or neuropsychiatric diseases that are related to a pathologically modified, preferably an increased, neural activity, preferably depression, Alzheimer's, eating disorders, and schizophrenia.

Abstract

The use of selective imidazoline receptor agonists, in particular of moxonidine, rilmenidine, LNP-509, S-23515, PMS-812, PMS-847 and BU-98008, and their physiologically compatible acid addition salts for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of functional disorders and/or diseases in larger mammals or humans which require inhibition or reduction of the activity of proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters, in particular of clinical pictures of bones which are caused by an undesirable amount of bone resorption, in particular osteoporosis, diseases of the gastrointestinal tract, in particular gastric ulcers, and neuronal and/or neuropsychiatric diseases connected with a pathologically altered, preferably increased, neuronal activity, preferably depression, Alzheimer's disease, eating disorders and schizophrenia, is described.

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MEDICAMENT FOR THE TREATMENT OF DISEASES REQUIRING INHIBITION OR A REDUCTION IN THE ACTIVITY OF PH VALUE-REGULATING BICARBONATE TRANSPORTER PROTEINS

Description

The present invention relates to the use of selective imidazoline receptor agonists and their physiologically compatible acid addition salts for the treatment and/or prophylaxis of functional disorders and/or diseases in larger mammals or humans which require inhibition or reduction of the activity of proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters, and to the preparation of medicaments suitable for this treatment and/or prophylaxis.

It is an object of the invention to develop novel pharmaceutical preparations which are suitable for the treatment of functional disorders and/or diseases which require inhibition or reduction of the activity of proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters. In particular, the object is to provide medicaments for the treatment and/or prophylaxis of diseases which are selected from the group consisting of clinical pictures of bones which are caused by an undesirable amount of bone resorption, in particular osteoporosis, diseases of the gastrointestinal tract, in particular gastric ulcers, and neuronal and/or neuropsychiatric diseases connected with a pathologically altered, preferably increased, neuronal activity, in particular depression, Alzheimer's disease, eating disorders and schizophrenia.

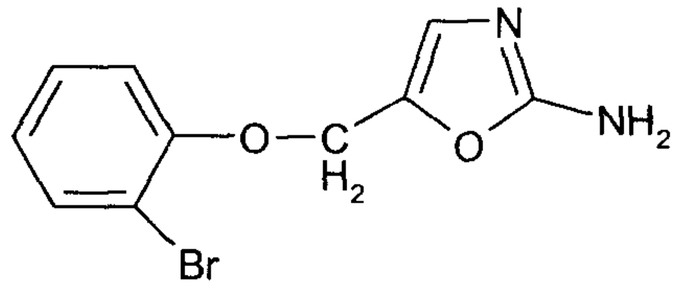
According to the invention, selective imidazoline receptor agonists and their physiologically compatible acid addition salts are used for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of functional disorders and/or diseases which require inhibition or reduction of the activity of proteins which

regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters, preferably for the treatment and/or prophylaxis of diseases selected from the group consisting of clinical pictures of bones which are caused by an undesirable amount of bone resorption, in particular osteoporosis, diseases of the gastrointestinal tract, in particular gastric ulcers, and neuronal and/or neuropsychiatric illnesses connected with a pathologically altered, preferably increased, neuronal activity, in particular depression, Alzheimer's disease, eating disorders and schizophrenia.

Suitable physiologically compatible acid addition salts of the selective imidazoline receptor agonists are salts with inorganic acids, for example hydrohalic acids, or with organic acids, for example lower aliphatic mono- or dicarboxylic acids such as acetic acid, fumaric acid or tartaric acid or aromatic carboxylic acids such as salicylic acid.

Compounds which represent selective imidazoline receptor agonists are already known, for example from European patent applications EP 0 710 658 and EP 0 846 688, and from PCT applications WO 01/41764 and WO 00/02878, without thereby restricting the group of selective imidazoline receptor agonists. The novel 5-(aryloxymethyl)-oxazoline derivatives described in European patent application EP 0 710 658 are distinguished by a selective affinity for the Type 1 imidazoline receptor. Novel imidazoline derivatives are described in European patent application EP 0 846 688 which possess an affinity for binding to imidazoline receptors, but hardly have any affinity to the adrenergic receptors. PCT application WO 01/41764 describes novel isoquinoline and quinoline derivatives which possess an affinity for imidazoline receptors. PCT application WO 00/02878 discloses novel β-carboline derivatives as potential ligands for imidazoline receptors. The aforementioned compounds may be prepared in known manner in accordance with the processes described in the aforementioned patent applications or analogously to these processes.

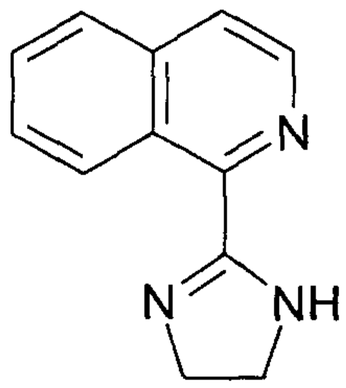
From the above patent applications, mention should be made in particular of the following compounds, which represent selective imidazoline receptor agonists. First of all, mention should be made of the compound 5-[(2-bromophenoxy)methyl]-4,5-dihydro-oxazol-2-ylamine (S-23515) of Formula I



I

which belongs to the 5-(aryloxymethyl)-oxazoline derivatives described in the above European patent application EP 0 710 658.

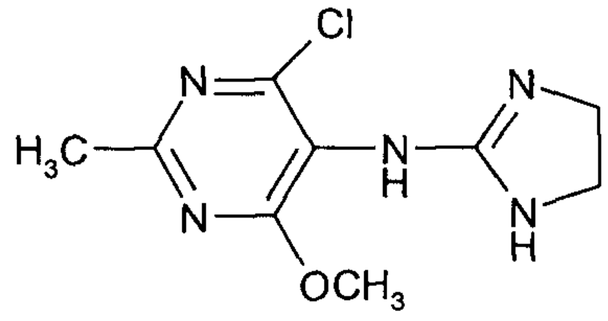
Furthermore, mention should be made of the compound 1-(4,5-dihydro-1H-imidazol-2-yl)-isoquinoline (BU98008) of Formula II



II.

which belongs to the isoquinoline and quinoline derivatives described in the above PCT application WO 01/41764. The aforementioned compounds may be prepared in known manner in accordance with the processes described in the aforementioned patent applications or analogously to these processes.

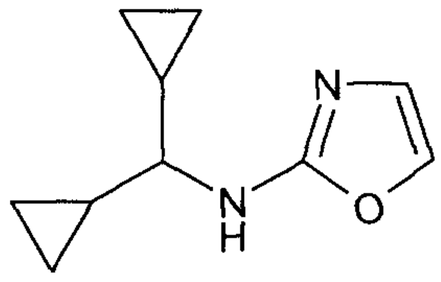
Furthermore, in particular the 5-[(2-imidazolin-2-yl)-amino]-pyrimidine derivatives described in German patent application No. 28 49 537, which possess hypotensive properties, fall within the group of selective imidazoline receptor agonists. Of these, mention should be made, in particular, of the compound 4-chloro-5-[(4,5-dihydro-1H-imidazol-2-yl)-amino]-6-methoxy-2-methylpyrimidine (= moxonidine) of Formula III



III

Moxonidine-containing pharmaceutical preparations are commercially available as antihypertensives under the trade name Physiotens® and used medicinally as antihypertensives. It is sufficiently known from the prior art that moxonidine is a selective ligand of the Type I imidazoline receptor (see also e.g. [Ernsberger (2000) Pharmacology of moxonidine: an I1-imidazoline receptor agonist. *J. Cardiovasc. Pharmacol.* 35: pp. 27-41]). The above compounds can be prepared in known manner according to the processes described in the aforementioned patent application or analogously to these processes.

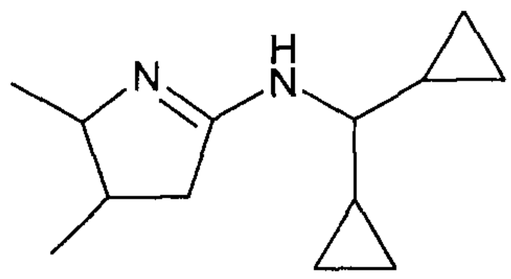
Furthermore, the cyclopropylmethylamines described in German patent application No. 23 62 754, which possess hypotensive properties, belong to the group of selective imidazoline receptor agonists. Of these, mention should be made in particular of the compound N-(dicyclopropylmethyl)-4,5-dihydro-2-oxazolamine (rilmenidine) of Formula IV



IV

That rilmenidine is a selective imidazoline receptor agonist is sufficiently known from the prior art (see e.g. [Bock et al. (1999) Analysis of the receptor involved in the central hypotensive effect of rilmenidine and moxonidine. *Naunyn Schmiedebergs Arch. Pharmacol.* 359: 262-71]). The above compounds can be prepared in known manner according to the processes described in the aforementioned patent application or analogously to these processes.

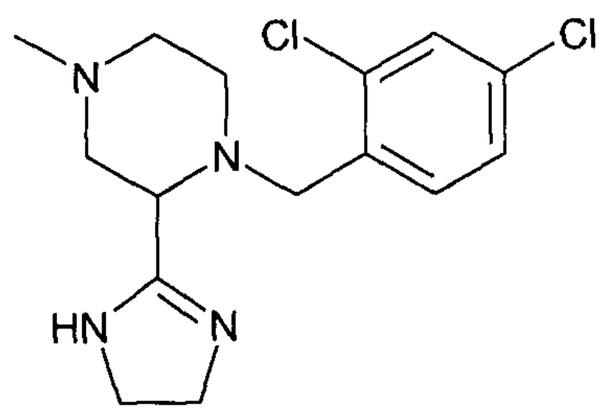
Furthermore, the novel aminopyrroline derivatives described in European patent application EP 1 101 756, which are suitable for the treatment of cardiovascular diseases, inter alia hypertension, belong to the group of selective imidazoline receptor agonists. Of these, mention should be made in particular of the compound cis-/trans-dicyclopropylmethyl-(4,5-dimethyl-4,5-dihydro-3H-pyrrol-2-yl)-amine (LNP-509) of Formula V



V

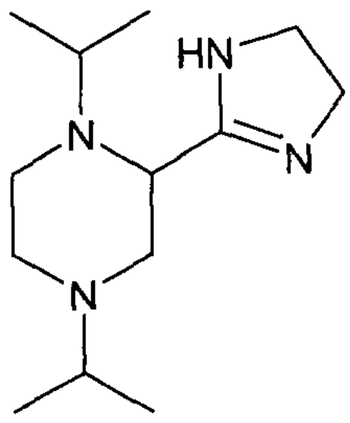
LNP-509 is a ligand which selects for the Type I1 imidazoline receptor and possesses hypotensive properties [Schann *et al.* (2001) Synthesis and biological evaluation of pyrrolinic isosteres of rilmenidine. Discovery of cis-/trans-dicyclopropylmethyl-(4,5-dimethyl-4,5-dihydro-3H-pyrrol-2-yl)-amine (LNP 509), an I1 imidazoline receptor selective ligand with hypotensive activity. *J. Med. Chem.* 44): 1588-93]. The above compounds can be prepared in known manner according to the processes described in the aforementioned patent application or analogously to these processes.

Also the novel substituted piperazine derivatives described in European patent application EP 0 638 568, which are suitable for the treatment of non-insulin-dependent diabetes, belong to the group of selective imidazoline receptor agonists. Of these, mention should be made in particular of the compound 1-(2,4-dichlorobenzyl)-2-(4,5-dihydro-1H-imidazol-2-yl)-4-methylpiperazine (PMS-812, also referred to as S-21663) of Formula VI



VI

or the compound 1-methyl-4-(2,4-dichlorobenzyl)-2-(4,5-dihydro-1H-imidazol-2-yl)-piperazine, and also the compound 1,2-diisopropyl-2-(4,5-dihydro-1H-imidazol-2-yl)-piperazine (PMS-847, also referred to as S-22068) of Formula VII



VII

PMS-812 (S-21663) and PMS-847 (S-22068) are imidazoline derivatives which bind to imidazoline receptors [Rondu *et al.* (1997) Design and synthesis of imidazoline

derivatives active on glucose homeostasis in a rat model of type II diabetes. 1. Synthesis and biological activities of N-benzyl-N'-(arylalkyl)-2-(4',5'-dihydro-1'H-imidazol-2'-yl)-piperazines. *J. Med. Chem.* 40: 3793-803; Le Bihan *et al.* (1999) Design and synthesis of imidazoline derivatives active on glucose homeostasis in a rat model of type II diabetes. 2. Syntheses and biological activities of 1,4-dialkyl-, 1,4-dibenzyl-, and 1-benzyl-4-alkyl-2-(4',5'-dihydro-1'H-imidazol-2'-yl)piperazines and isosteric analogues of imidazoline. *J. Med. Chem.* 42: 1587-603]. The above compounds can be prepared in known manner according to the processes described in the aforementioned patent application or analogously to these processes.

Living cells are equipped with mechanisms to maintain the intracellular pH value. Firstly, cells are exposed to acidity resulting from their metabolism, and secondly the electric potential difference at the cell membrane represents a considerable driving force on the influx of H^+-ions into the cells. In particular, two mechanisms are responsible for keeping the intracellular pH value constant, metabolic buffering and transport of acids and bases through the cell membrane. Of particular interest here are those proteins which transport protons and bicarbonate ions across the cell membrane.

The protein superfamily of the bicarbonate transporters comprises both the Na^+-independent chloride-bicarbonate exchangers (abbreviated to AE, for “anion exchange”), various Na^+/bicarbonate cotransporters (abbreviated to NBC) and also Na^+-dependent anion exchangers (abbreviated to NDAE), such as the Na^+-dependent chloride-bicarbonate exchanger (abbreviated to N(D)CBE, from “Na^+-driven chloride/bicarbonate exchanger”). One characteristic of most bicarbonate transporters is that they are inhibited relatively effectively by the compound 4,4'-diisothiocyanostilbene-4,4'-disulphonate (DIDS) [Boron (2001) Sodium-coupled bicarbonate transporters. JOP 24 (Suppl.): 176-81].

The Na^+-independent chloride-bicarbonate (Cl^-/HCO_3^-) exchanger AE catalyses the release of the bicarbonate ion HCO_3^- from the cell in exchange for including a chloride ion Cl^- in the cell. This exchange is electrically neutral. This exchanger is known to play a part in particular in the regulation of the intracellular pH value, the cell volume and the intracellular chloride-ion concentration. This exchanger is generally activated by intracellular alkalosis. The gene family of the Na^+-independent chloride-bicarbonate (Cl^-/HCO_3^-) exchanger has hitherto comprised the three isoforms AE1, AE2 and AE3, which

at the amino acid level particularly in the carboxy-terminal region possess high homology and differ in their expression patterns.

Thus for example in ventricular myocytes the AE proteins are activated by extracellular acidosis or intracellular alkalosis. As a reaction to a drop in the extracellular pH value, the AE proteins begin to export bicarbonate ions; consequently, a drop in the intracellular pH value occurs. If the pH value inside the cell is increased, the intracellular pH value is normalised again by the activity of the AE proteins. During an ischaemia of the myocardium, inhibition of AE proteins in the ventricular myocytes is very useful, since the consequently reduced export of the intracellular bicarbonate ions prevents intracellular acidosis with its adverse consequences for the cells.

The Na+/bicarbonate cotransporters (NBC) catalyse the simultaneous transport of bicarbonate HCO_3^- and Na^+ ions across the cell membrane. The transport may take place dependent on the expressed NBC isoform with a stoichiometry of 3:1, 2:1 or, electrically neutrally, of 1:1. Furthermore, transport may be in an outward direction (out of the cell) as in the kidney or an inward direction (into the cell) as in the heart, the pancreas or the brain.

The Na^+-dependent anion exchangers (NDAE or N(D)CBE) catalyse the simultaneous transport of bicarbonate HCO_3^- and Na^+ ions across the cell membrane into the cell in exchange for releasing a chloride ion Cl^- from the cell. The NBCEs seem to be of greatest importance for pH regulation in neurons. The activity of the NDAEs can in contrast be detected in neurons, in the kidney and in fibroblasts [Romero et al. (2000) Cloning and characterization of a Na+-driven anion exchanger (NDAE1). A new bicarbonate transporter. *J. Biol. Chem.* 275: 24552-9].

It has now surprisingly been found that selective imidazoline receptor agonists and their physiologically compatible acid addition salts possess very advantageous pharmacological properties. In particular, it has been shown that selective imidazoline receptor agonists are inhibitors of the proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters and have an inhibiting action similar to that of the compound 4,4'-diisothiocyanostilbene-4,4'-disulphonate (DIDS), a standard inhibitor of bicarbonate transporter proteins. It follows from this that selective

imidazoline receptor agonists and their physiologically compatible acid addition salts not only, as indicated in the patent applications cited above, bind selectively to imidazoline receptors and are suitable for the treatment of pathological conditions associated with imidazoline receptors, such as for example cardiovascular diseases, in particular hypertension, or non-insulin-dependent diabetes, but also can be used for the treatment and/or prophylaxis of functional disorders and/or diseases in larger mammals or humans which require inhibition or reduction of the activity of proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters.

The functional disorders or diseases which can be treated by the compounds used according to the invention include in particular pathological conditions, the treatment of which requires inhibition or reduction of the activity of Na^+-independent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger proteins (AE). Furthermore, the functional disorders or diseases which can be treated by the compounds used according to the invention include in particular pathological conditions, the treatment of which requires inhibition or reduction of the activity of Na^+-/bicarbonate (Na^+ /HCO_3^-) cotransporter proteins (NBC). Furthermore, the functional disorders or diseases which can be treated by the compounds used according to the invention include in particular pathological conditions, the treatment of which requires inhibition or reduction of the activity of Na^+-dependent chloride/bicarbonate (Cl^- /HCO_3^-) exchanger proteins (NDAE and N(D)CBE).

Pharmacological evaluation of the compounds used according to the invention, which represent selective imidazoline receptor agonists, demonstrated in particular that selective imidazoline receptor agonists are suitable for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of functional disorders or clinical pictures of bones which are caused by an undesirable amount of bone resorption.

Human bones are subject to a continual dynamic remodelling process which involves bone resorption and bone build-up. These processes are controlled by specialised cell types: bone build-up is based on the deposition of bone matrix by osteoblasts, whereas bone resorption is based on the breakdown of bone matrix by osteoclasts. The majority of osteopathies are based on a disturbed equilibrium between bone formation and bone resorption. Thus the disease osteoporosis is characterised by a loss of bone matrix. Osteoclasts, the cells which are the most important participants in the bone resorption process, are polarised cells with a specialised region on the side facing

the bone surface, what is called the “ruffled border” in English, see Fig. 1. Between the “ruffled border” and the bone surface is the resorption lacuna. The osteoclasts transport protons through a vacuole-type H^+-ATPase across the “ruffled border” into the resorption lacuna, so that the liquid located therein is acidified. The acidic surroundings, also in combination with proteolytic enzymes additionally secreted into the resorption lacuna, causes the bone material to be dissolved and hence the bone to be broken down. In the osteoclast itself, the protons are provided by hydration of CO_2 and subsequent dissociation into protons and bicarbonate ions. The constant transport of protons out of the cell results in intracellular alkalisation, accompanied by an intracellular excess of bicarbonate ions. The bicarbonate ions are discharged via the AE protein located on the other side of the osteoclast by the simultaneous uptake of chloride ions. The electroneutrality is preserved by the transport of the Cl- ions on the bone side which takes place parallel to the proton transport. A reduction in the activity of the AE protein has been proved to reduce the process of bone resorption [Teti *et al.* (1989) Cytoplasmic pH regulation and chloride/bicarbonate exchange in avian osteoclasts. *J. Clin. Invest.* 83: 227-33; Hall et al. (1989) Optimal bone resorption by isolated rat osteoclasts requires chloride/bicarbonate exchange. *Calcif. Tissue Int.* 45: 378-80].

Accordingly, the selective imidazoline receptor agonists used according to the invention, since they reduce or inhibit bone resorption by the osteoclasts by the reduction in the activity of the AE protein of the osteoclasts, are suitable in particular for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of functional disorders or clinical pictures of bones which are caused by an undesirable amount of bone resorption. Osteopathies against which selective imidazoline receptor agonists can preferentially be used are in particular osteoporosis, hypercalcaemia, osteopenia, for example caused by metastases, dental diseases, hyperparathyroidism, periarticular erosions in rheumatoid arthritis and Paget’s disease. Furthermore, the selective imidazoline receptor antagonists used according to the invention may be used for alleviating, avoiding or therapy of osteopathies caused by glucocorticoid, steroid or corticosteroid therapy or by a deficiency of sex hormones. All these diseases are characterised by loss of bone substance based on the imbalance between bone build-up and bone breakdown.

Pharmacological evaluation of the compounds used according to the invention, which represent selective imidazoline receptor agonists, demonstrated in particular that

selective imidazoline receptor agonists are suitable for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of functional disorders or diseases of the gastrointestinal tract, e.g. gastric ulcers, duodenal ulcers, hypersecretion of gastric acid and motion sickness.

In fact, the parietal cells of the stomach possess a basolateral AE (isoform AE2), the activity of which is essential for maintaining secretion of gastric acid by apical H^+/K^+ ATPase [Muallem *et al.* (1988) Activation of the Na+/H+ and Cl-/HCO3- exchange by stimulation of acid secretion in the parietal cell. *J. Biol. Chem.* 263: 14703-11]. Inhibiting this AE protein results in reduced secretion of gastric acid. The epithelial cells of the large intestine possess an apical AE protein which is involved in the secretion of water and bicarbonate and represents the binding site of the cholera toxin.

Pharmacological evaluation of the compounds used according to the invention, which represent selective imidazoline receptor agonists, demonstrated in particular that selective imidazoline receptor agonists are suitable for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of neuronal and neuropsychiatric diseases connected with a pathologically changed, preferably increased, neuronal activity, such as for example depression, Alzheimer's disease, eating disorders (anorexia), schizophrenia, agitation (motor and affective restlessness), anxiety, sleep disturbance, epilepsy, and general illnesses based on altered dopamine release, illnesses resulting from ischaemic/hypoxic events and age-related degenerative illnesses.

Increased neuronal activity results in long-lasting intracellular acidification (increase in proton concentration), which makes the cell refractory to a new neuronal impulse. In this connection, intracellular protons function similarly to neuromodulatory factors, comparably with other types of intracellular messengers ("second messengers") [Takahashi & Copenhagen (1996) Modulation of neuronal function by intracellular pH. *Neurosci. Res.* 24: 109-16; Trapp *et al.* (1996) Acidosis of rat dorsal vagal neurons in situ during spontaneous and evoked activity. *J. Physiol.* 496: 695-710]. To overcome these refractory conditions, the intracellular acidification must be neutralised again, i.e. the lowered intracellular pH value must be raised to a physiologically neutral pH value. Anion exchanger proteins such as NDAE and N(D)CBE are responsible for this neutralisation, and also the presence of extracellular bicarbonate ions is essential for this [Canzoniero et

al. (1996) Recovery from NMDA-induced intracellular acidification is delayed and dependent on extracellular bicarbonate. Am. J. Physiol. 270: C593-9]. Inhibition of these exchangers results in the neutralisation of the intracellular pH value being slowed down, i.e. the intracellular proton concentration remains elevated for longer; as a consequence, the cells are refractory for longer against a new neuronal impulse [Bonnet *et al.* (2000) Alteration of intracellular pH and activity of CA3-pyramidal cells in guinea pig hippocampal slices by inhibition of transmembrane acid extrusion. *Brain Res.* 872: 116-24].

Where the invention relates to the treatment of disorders of the central nervous system which are associated with an altered intracellular pH value, the corresponding illnesses are preferably Alzheimer's disease, illnesses caused by the altered release of dopamine or other transmitters or illnesses due to ischaemic-hypoxic events.

In Alzheimer's disease, the increased proliferation of Alzheimer lymphoblasts is accompanied by intracellular alkalisation, which can be influenced by inhibiting of anion exchangers, e.g. those similar to the Na+/H+ exchanger [Urcelay E., Ibarreta D., Parrilla R., Ayuso M.S., Martin-Requero A. Enhanced proliferation of lymphoblasts from patients with Alzheimer dementia associated with calmodulin-dependent activation of the Na+/H+ exchanger; Neurobiol. Dis. 2001; 8: 289-98]. Furthermore, it has been reported that changes in the structure of anion exchangers on ageing and particularly in Alzheimer's disease can be influenced by an inhibitor of the anion exchanger [Bosman G.J., Renkawek K., Van Workum F.P., Bartholomeus I.G., Marini S., De Grip W.J.. Neuronal anion exchange proteins in Alzheimer's disease pathology. J. Neural. Transm. Suppl. 1998; 54: 248-57].

With regard to illnesses based on altered dopamine release, it should be recorded that the neuronal dopamine release is modulated by the intracellular pH value. The connections between the intracellular acidification and the increased dopamine release are discussed by Pothos [Regulation of dopamine quantal size in midbrain and hippocampal neurons. Behav. Brain. Res. 2002; 130: 203-7]. The inhibition of anion transporters which counteract acidification can therefore influence the dopamine release.

Illnesses resulting from ischaemic-hypoxic events are connected with the intracellular pH value as follows: since rapid re-establishment of the acidic intracellular pH value in conjunction with ischaemic-hypoxic events with the exchange of H+ for Na+ by

the Na+/H+ exchanger is associated with subsequent Ca2+ accumulation via the Na+/Ca2+ exchanger, the risk of cell damage is increased. The inhibition of anion transporters participating in the extracellular Na+ influx therefore exhibits a protective action. This accords with the increasing observation that inhibitors of the Na+/H+ exchanger have various protective effects after ischaemic-hypoxic events [Avkiran M., Marber M.S.. Na(+)/H(+) exchange inhibitors for cardioprotective therapy: progress, problems and prospects. J. Am. Coll. Cardiol. 2002 March 6; 39(5): 747-53].

The invention comprises the use of selective imidazoline receptor agonists for the preparation of pharmaceutical preparations for the treatment and prophylaxis of clinical pictures of bones which are caused by an undesirable amount of bone resorption, of diseases of the gastrointestinal tract, in particular gastric ulcers, of neuronal and neuropsychiatric diseases connected with a pathologically altered, preferably increased, neuronal activity, in particular depression, Alzheimer's disease, eating disorders and schizophrenia, and furthermore of diseases based on a disturbance in the acid-base balance (acidosis and alkalosis) or in the hydroelectrolytic balance. In particular, the invention comprises the use of selective imidazoline receptor agonists for the preparation of pharmaceutical preparations for the treatment and prophylaxis of osteoporosis.

Furthermore, the invention comprises in particular the use of a compound selected from the group consisting of moxonidine, rilmenidine, LNP-509, S-23515, PMS-812, PMS-847 and BU-98008 or their physiologically compatible acid addition salts for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of functional disorders and/or diseases in larger mammals or humans which require inhibition or reduction of the activity of proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters. In particular, the invention comprises the use of one of the above compounds or their physiologically compatible acid addition salts for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of functional disorders or diseases in larger mammals or humans which require inhibition or reduction of the activity of Na^+-independent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger (AE) proteins, of Na^+/bicarbonate (Na^+ /HCO_3^-) cotransporter (NBC) proteins or/and of Na^+-dependent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger (NDAE and N(D)CBE) proteins. In particular, the invention comprises the use of a compound selected from the group consisting of moxonidine, rilmenidine, LNP-509, S-23515, PMS-812, PMS-847 and BU-98008 or their physiologically compatible acid addition salts for the

preparation of pharmaceutical preparations for the treatment and/or prophylaxis of clinical pictures of bones which are caused by an undesirable amount of bone resorption, in particular osteoporosis, of diseases of the gastrointestinal tract, in particular gastric ulcers, or of neuronal and/or neuropsychiatric illnesses connected with a pathologically altered, preferably increased, neuronal activity, in particular depression, Alzheimer's disease, eating disorders and schizophrenia, in larger mammals or humans. Furthermore, the invention comprises in particular the use of one of the above compounds or their physiologically compatible acid addition salts for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of osteoporosis in larger mammals or humans.

Furthermore, the invention comprises the use of all the aforementioned compounds, in particular a compound selected from the group consisting of moxonidine, rilmenidine, LNP-509, S-23515, PMS-812, PMS-847 and BU-98008, or their physiologically compatible acid addition salts for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of one of the aforementioned functional disorders and/or diseases, in particular osteoporosis, in peri- or postmenopausal women.

It has now been found that moxonidine has an inhibitory effect on the proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters. In particular, it was discovered that moxonidine represents a selective inhibitor of the Na^+-independent chloride-bicarbonate exchanger (AE) proteins. The intracellular pH value is influenced by the reduction of the exchange or transport of bicarbonate ions across the cell membrane. The inhibitory action of moxonidine on bicarbonate transporter proteins is comparable to the action of 4,4'-diisothiocyanostilbene-4,4'-disulphonate (DIDS), a compound having an entirely different chemical structure. Owing to their inhibitory action on bicarbonate transporter proteins, moxonidine and its pharmacologically acceptable acid addition salts are therefore suitable in particular for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of functional disorders and/or diseases in larger mammals or humans which require inhibition or reduction of the activity of proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters. In particular, the invention comprises the use of moxonidine or its physiologically compatible acid addition salts for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of functional disorders or diseases which require inhibition or reduction of the activity of Na^+-

independent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger (AE) proteins, of Na^+/bicarbonate (Na^+ /HCO_3^-) cotransporter (NBC) proteins or/and of Na^+-dependent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger (NDAE and N(D)CBE) proteins, in particular for the treatment and/or prophylaxis of functional disorders or diseases in larger mammals and humans which are connected with clinical pictures of bones which are caused by an undesirable amount of bone resorption, with diseases of the gastrointestinal tract, or with neuronal and/or neuropsychiatric illnesses connected with a pathologically altered, preferably increased, neuronal activity. In particular, the invention comprises in particular the use of moxonidine or its physiologically compatible acid addition salts for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of osteoporosis in larger mammals or humans. Furthermore, the invention comprises the use of moxonidine or its physiologically compatible acid addition salts for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of one of the aforementioned functional disorders and/or diseases, in particular osteoporosis, in peri- or postmenopausal women.

In a further aspect, the invention comprises the use of moxonidine or its physiologically compatible acid addition salts for the preparation of pharmaceutical preparations for the simultaneous treatment and/or prophylaxis of osteoporosis and of hypertension in larger mammals or humans, in particular in peri- or postmenopausal women.

For the treatment according to the invention of functional disorders and/or diseases which require inhibition or reduction of the activity of proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters, in particular of Na^+-independent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger (AE) proteins, of Na^+/bicarbonate (Na^+ /HCO_3^-) cotransporter (NBC) proteins or/and of Na^+-independent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger (NDAE and N(D)CBE) proteins, in particular for the treatment and/or prophylaxis of clinical pictures of bones which are caused by an undesirable amount of bone resorption, in particular osteoporosis, of diseases of the gastrointestinal tract, in particular gastric ulcers, or of neuronal and/or neuropsychiatric illnesses connected with a pathologically altered, preferably increased, neuronal activity, in particular depression, Alzheimer's disease, eating disorders and schizophrenia, selective imidazoline receptor agonists, in particular compounds selected from the group consisting of moxonidine, rilmenidine, LNP-509, S-23515, PMS-812, PMS-847 and BU-

98008, and very particularly moxonidine, and their physiologically compatible acid addition salts may be administered in conventional pharmaceutical preparations orally, intravenously or alternatively transdermally.

Thus, selective imidazoline receptor agonists, in particular compounds selected from the group consisting of moxonidine, rilmenidine, LNP-509, S-23515, PMS-812, PMS-847 and BU-98008, and very particularly moxonidine, and their physiologically compatible acid addition salts may be contained, together with conventional pharmaceutical auxiliaries and/or excipients, in solid or liquid pharmaceutical preparations in an amount which is effective for the treatment of functional disorders and/or diseases which require inhibition or reduction of the activity of proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters, in particular of Na^+-independent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger (AE) proteins, of Na^+/bicarbonate (Na^+ /HCO_3^-) cotransporter (NBC) proteins or/and of Na^+-dependent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger (NDAE and N(D)CBE) proteins, in particular for the treatment and/or prophylaxis of clinical pictures of bones which are caused by an undesirable amount of bone resorption, in particular osteoporosis, of diseases of the gastrointestinal tract, in particular gastric ulcers, or of neuronal and/or neuropsychiatric diseases connected with a pathologically altered, preferably increased, neuronal activity, in particular depression, Alzheimer's disease, eating disorders and schizophrenia. Examples of solid preparations which can be formulated for direct or delayed active-substance release are preparations which can be administered orally, such as tablets, coated tablets, capsules, powders or granules, or alternatively suppositories and patches (transdermal therapeutic systems). These solid preparations may contain conventional pharmaceutical inorganic and/or organic excipients such as lactose, talcum or starch, in addition to conventional pharmaceutical auxiliaries, for example lubricants or tablet disintegrating agents. In the case of patches, the active substance is stored in an active-substance reservoir, in particular e.g. an active-substance matrix (e.g. a polymer matrix). Liquid preparations such as solutions, suspensions or emulsions of the active substances may contain the usual diluents such as water, oils and/or suspension agents such as polyethylene glycols and the like. Other auxiliaries may additionally be added, such as preservatives, taste correctives and the like.

The active substances may be mixed and formulated with the pharmaceutical auxiliaries and/or excipients in known manner. For the preparation of solid medicament forms, the active substances may for example be mixed with the auxiliaries and/or excipients in conventional manner and may be wet or dry granulated. The granules or powder may be poured directly into capsules or be pressed into tablet cores in conventional manner. These may be coated in known manner if desired. Patches or transdermal therapeutic systems may be constructed in conventional manner, e.g. from cover film, active-substance reservoir (self-adhesive or with additional adhesive layer) and backing film both as matrix-controlled and as membrane-controlled (i.e. equipped with an additional control membrane) systems.

Brief description of the drawing

Fig. 1: Schematic representation of an osteoclast

The drawing shows a schematic representation of an osteoclast with its "ruffled border". Between the "ruffled border" and the bone surface is the resorption lacuna, into which protons (H^+) are secreted. In the cell, hydrated CO_2 dissociates into protons (H^+) and bicarbonate ions (HCO_3^-). The bicarbonate ions are transported out of the osteoclast by the Na^+-independent chloride-bicarbonate (Cl^- /HCO_3^-) exchangers (AE). In return, chloride ions (Cl^-) pass into the cell.

The pharmacological effects of selective imidazoline receptor agonists and their pharmacologically acceptable acid addition salts were demonstrated in pharmacological standard tests using the example of the selective imidazoline receptor agonist moxonidine.

Measurement of the activity of bicarbonate transporter proteins in adult cardiac fibroblasts

The investigations were carried out on cardiac fibroblasts isolated from the left ventricle of the myocardium of 6-week-old Wistar rats. Myocardial tissue was placed in HBSS medium without Ca^{2+} and Mg^{2+} (GibcoBRL), cut into small pieces which were incubated with 1 mg/ml collagenase A (Roche) with continuous shaking for 10 min in HBSS medium. The first supernatant was discarded and the incubation operation was repeated three times, the supernatant being collected each time in a tube with 5 ml HBSS medium. After centrifuging at 160×g for 10 min, the pellet was re-suspended in a flask with DMEM (GibcoBRL), to which 10% foetal calf serum (FCS, from Sigma) was added. After 1 hour, all those cells which did not stick to the flask wall were separated off. The flasks were incubated in an air-humidified incubator with 5% CO_2 and at 37°C. Cardiac fibroblasts, which grew in a typical monolayer, were cultivated by means of standard cell culture techniques and at subconfluence were transferred into new flasks in a 1:3 ratio [Brilla et al. (1994) Collagen metabolism in cultured adult rat cardiac fibroblasts: response to agiotensin II and aldosterone. *J. Mol. Cell Cardiol.* 26: 809-820]. Immunohistochemical characterisation ruled out the possibility that the isolated cells were endothelial cells or vascular cells of the smooth musculature; rather, they were fibroblasts.

The intracellular pH value of an individual cell was measured using the fluorescent marker BCECF (2',7'-bis-(2-carboxymethyl)-5-[and -6]-carboxyfluorescein from Molecular Probes), the fluorescent intensity of which is pH-dependent. The cardiac fibroblasts were grown on glass microscope slides until at subconfluence, and were then laden with BCECF-acetoxymethyl ester. The fibroblasts thus pre-treated were washed with PBS and then preincubated with various test solutions and then rinsed. In so doing, the intracellular fluorescence of the BCECF was measured using an inverted microscope, to which a "PTI 710 Photon Counting Detection" system (Photon Technology International) with two monochromators was connected. The data were analysed using a fluorescence spectrometer. The measurement results – fluorescence signals – were converted into pH values using a calibration curve.

Composition of the bicarbonate solution: 118 mmol/l NaCl, 4.7 mmol/l KCl, 2.5 mmol/l CaCl2 x 2 H2O, 1.6 mmol/l MgCl2 x 7 H2O, 24.9 mmol/l NaHCO3, 1.2 mmol/l KH2PO4, 5.6 mmol/l glucose and either 0.4% or 10% FCS, equilibrated with 20% O2 and 5% CO2 for at least 30 min to ensure a pH value of 7.4.

The individual test solutions were based on the above bicarbonate solution and contained the following concentration of the compounds below:

- 10^{-6} mol/l guanabenz (Sigma)
- 10^{-6} mol/l to 10^{-9} mol/l moxonidine
- 10^{-3} mol/l H_2-DIDS (Molecular Probes)

Intracellular alkalisation of the cells was achieved by rinsing with a 5 mmol/l NH_4Cl-containing bicarbonate solution (NH_4Cl pulse).

Subsequent washing-out of the NH_4Cl by rinsing the cells with fresh bicarbonate solution results in intracellular acidification.

The measurement of the change in pH value following alkalisation shows the activity of the Na^+-independent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger (AE) protein, whereas the measurement of the change in pH value following acidification provides information about the activity of the Na^+/bicarbonate (Na^+ /HCO_3^-) cotransporter (NBC) protein or/and of the Na^+-dependent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger (NDAE and N(D)CBE) protein.

The effect of moxonidine, DIDS and guanabenz on the change in the intracellular pH value after alkalisation of the cells is determined by an NH_4Cl pulse. To this end, the BCECF-laden cardiac fibroblasts were preincubated for 30 min with a bicarbonate test solution containing one of the above compounds. Then the response of the intracellular pH value of the cells thus pre-treated to a 5 mmol/l NH_4Cl pulse was measured over time. Also the change in pH value which took place during the subsequent washing-out of the NH_4Cl (intracellular acidification) was further measured over time. The cells pre-treated with moxonidine or DIDS, compared with the cells pre-treated with guanabenz or the non-pre-treated cells (control), exhibited a considerably longer recovery after the intracellular alkalisation. To quantify the inhibitory effects, the percentage of the change in pH value still present relative to the maximum alkaline or maximum acidic pH value achieved was calculated. The proportion of the change in pH value still present after returning from the alkaline was determined 5 min and 8 min after the maximum alkaline pH value was achieved, whereas the corresponding value after recovery from the acidic was determined 1 min after the maximum acidic pH value was achieved.

Table 1 shows the effect of 10^{-6} mol/l moxonidine and 10^{-6} mol/l guanabenz on the change in the alkali loading of cardiac fibroblasts after intracellular alkalisation by an NH_4Cl pulse. What is given is the percentage of the change in pH value still present, relative to the maximum alkaline pH value reached after 5 and 8 min. The values are the mean value and standard deviation from 3 to 5 experiments.

Table 1:

	After 5 min	after 8 min
Control:	24.9 ± 14.8%	14.4 ± 10.8%
Moxonidine	58.8 ± 12.0%	41.9 ± 24.4%
Guanabenz	20.6 ± 5.2%	9.9 ± 2.7%

The dose-effect curve for the inhibitory effect of moxonidine on the recovery from the alkaline pH showed that moxonidine even in a concentration of 10^{-8} mol/l has a significantly inhibitory action.

Furthermore, the activity of the Na^+/bicarbonate (Na^+ /HCO_3^-) cotransporter (NBC) protein or/and of the Na^+-dependent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger (NDAE and N(D)CBE) protein can be determined by means of its activation owing to intracellular acidification according to the ammonium method [Boron & De Weer (1976) Intracellular pH transients in squid giant axons caused by CO2, NH3, and metabolic inhibitors. *J. Gen. Physiol*. 67: 91-112].

Pharmacological test relating to the effect of the compounds in pathological changes to bones

The inhibiting action of the test substances on the resorption of bone material was tested on a cell culture of chicken osteoclasts. Both the proton secretion into the extracellular space and the activity of the AE protein were measured in the presence and in the absence of the test substances. The activity of the AE protein was determined by measuring the cytosolic pH value in reaction to the change in the ionic composition of the extracellular medium and in reaction to the addition of the test substances or of control

substances with a known inhibiting or stimulating action [Teti *et al.* (1989) Cytoplasmic pH regulation and chloride/bicarbonate exchange in avian osteoclasts. *J. Clin. Invest.* 83: 227-33; Hall et al. (1989) Optimal bone resorption by isolated rat osteoclasts requires chloride/bicarbonate exchange. *Calcif. Tissue Int.* 45: 378-80].

The inhibiting action of the test substances on resorption of bone material was investigated in an in vitro test. Osteoclasts isolated from newborn rats were brought into direct contact with discs of bone material from calves and were incubated together for at least 6 hours in the presence and in the absence of the test substances. Following the incubation, each bone disc was investigated using a microscope in order to determine the extent of bone resorption [Chambers *et al.* (1985) The effect of calcium-regulating hormones and prostaglandins on bone resorption by osteoclasts disaggregated from neonatal rabbit bones. *Endocrinology* 116: 234-9].

<u>Pharmacological test relating to the effect of the compounds on gastrointestinal ulcers</u>

The inhibiting effect of the test substances on the secretion of gastric acid was tested on a culture of parietal cells from rabbits. The activity of the AE protein and the associated acid secretion was measured in the presence and in the absence of the test substances both under basal conditions and after stimulation of acid production by the addition of known stimulating compounds [Muallem *et al.* (1988) Activation of the Na+/H+ and Cl-/HCO3- exchange by stimulation of acid secretion in the parietal cell. *J. Biol. Chem.* 263: 14703-11].

The inhibiting effect of the test substances on the occurrence of stress-induced gastrointestinal ulcers was tested on rats. In this model, rats were subjected to stress by immobilising them and partly submerging them in warm water at 22°C for 6 h. The occurrence of gastric lesions and their severity was compared in control rats and rats treated 30 min before being subjected to stress with a preventive dose of the test substances [Takagi & Okabe (1968) The effects of drugs on the production and recovery processes of the stress ulcer. *Jpn. J. Pharmacol.* 18: 9-18].

Pharmacological test relating to the effect of the compounds in neuronal or neuropsychiatric diseases connected with a pathologically altered, in particular increased, neuronal activity.

Increased neuronal activity results in long-lasting intracellular acidification (increase in proton concentration), which makes the cell refractory to a new neuronal impulse. Bicarbonate transporter proteins are responsible for the intracellular neutralisation which then follows. Inhibition of this exchanger results in slowing of the neutralisation of the intracellular pH value, and consequently the cells are refractory for longer to a new neuronal impulse. The inhibiting action of the test substances on the neuronal bicarbonate transporter proteins was investigated on hippocampal tissue sections from guinea pigs, by measuring both the intracellular pH value and the electric membrane potential of CA3-pyramidal cells in the presence and in the absence of the test substances and in comparison with control substances with known inhibiting or stimulating action [Bonnet *et al.* (2000) Alteration of intracellular pH and activity of CA3-pyramidal cells in guinea pig hippocampal slices by inhibition of transmembrane acid extrusion. *Brain Res.* 872: 116-24].

The test substance moxonidine, which is a selective imidazoline receptor agonist, completely surprisingly achieved an inhibiting effect on proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters. In particular, it was discovered that moxonidine represents a selective inhibitor both of the Na^+-independent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger (AE) proteins and of the Na^+/bicarbonate (Na^+ /HCO_3^-) cotransporter (NBC) proteins or/and of the Na^+-dependent chloride-bicarbonate (Cl^- /HCO_3^-) exchanger (NDAE and N(D)CBE) proteins. The inhibitory action of moxonidine on bicarbonate transporter proteins is comparable to the action of 4,4'-diisothiocyanostilbene-4,4'-disulphonate (DIDS), a compound having an entirely different chemical structure, the inhibitory action of which on bicarbonate transporters is sufficiently known from the prior art [Boron (2001) Sodium-coupled bicarbonate transporters. JOP 24 (Suppl.): 176-81]. That the observed action of moxonidine cannot be ascribed to its alpha-2 adrenergic properties is shown by the comparison with the compound guanabenz, a selective alpha-2 agonist established in the

prior art [Hieble & Ruffolo (1995) Possible structural and functional relationships between imidazoline receptors and alpha 2-adrenoceptors. *Ann. N. Y. Acad. Sci.* 763: 8-21].

The above test results therefore show that moxonidine and related compounds, such as other selective imidazoline receptor agonists, and their pharmacologically acceptable acid addition salts are capable of reducing the activity of bicarbonate transporter proteins and are therefore suitable for the treatment and/or prophylaxis of functional disorders and/or diseases in larger mammals or humans which require inhibition or reduction of the activity of proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters. The named compounds can therefore be used advantageously in particular for the treatment and/or prophylaxis of diseases of the gastrointestinal tract, in particular gastric ulcers, of clinical pictures of bones which are caused by an undesirable amount of bone resorption, in particular osteoporosis, or of [neuronal and/or neuropsychiatric illnesses] connected with a pathologically altered, in particular increased, neuronal activity.

The doses to be used may vary individually and will naturally vary according to the type of selective imidazoline receptor agonist used, the condition to be treated and the form of administration. Generally, the daily doses for treating the above functional disorders and/or diseases, in particular osteoporosis, in humans for oral administration are in the range of 0.01 to 1000 mg, for example approximately 0.1 to 100 mg, preferably approximately 0.2 to 10 mg. The above selective imidazoline receptor agonists, in particular a compound selected from the group consisting of moxonidine, rilmenidine, LNP-509, S-23515, PMS-812, PMS-847 and BU-98008, and very particularly moxonidine, or their pharmacologically acceptable acid addition salts may be administered in pharmaceutical preparations both for immediate and for delayed, regulated and/or controlled active-substance release. It goes without saying for the person skilled in the art that preparations with delayed, regulated and/or controlled active-substance release may contain larger amounts of active substance than preparations for immediate active-substance release.

The following example is intended to explain the preparation of a pharmaceutical preparation containing moxonidine – selected by way of example of a selective imidazoline receptor agonist – or its pharmaceutically acceptable salts in greater detail, but without limiting the scope of the invention.

Example: Moxonidine-containing film-coated tablets

Composition:

Tablet cores:		
Moxonidine	0.025	parts
Lactose	9.575	parts
Povidone USP	0.070	parts
Crospovidone USP	0.300	parts
Magnesium stearate	0.030	parts
(Water	0.750	parts)
Total solids	10.000	parts
Film coating:		
Hydroxypropylmethyl cellulose	0.156	parts
30%-strength aqueous ethylcellulose dispersion	0.480	parts
(= solid)	(0.144)	parts
Polyethylene glycol 6000	0.030	parts
Titanium dioxide	0.150	parts
Talc	0.1197	parts
Red iron oxide	0.0003	parts
(Water	3.864	parts)
Total solids	0.600	parts
Total amount of film coating suspension	4.800	parts

4.8 kg of the above film coating suspension was used for coating 10,000 tablet cores each weighing 100 mg.

Production of tablet cores:

The moxonidine and the lactose were mixed. The mixture was moistened thoroughly with a solution of the binder Povidone in water, thoroughly kneaded and the resulting product was spread on trays and dried at a temperature of approx. 50°C to a

moisture content of at most 0.5%. The dried product was passed through a 0.75 mm sieve (Frewitt machine). Once the resulting granules had been mixed with Crospovidone and magnesium stearate, tablet cores of a weight of 100 mg were pressed therefrom, so that each tablet core contained 0.25 mg active substance.

Preparation of the film coating suspension:

The hydroxypropylmethyl cellulose and the polyethylene glycol 6000 were dissolved in part of the water. A suspension of talc, titanium dioxide and iron oxide in the remaining water was added to this solution with stirring. The resulting suspension was diluted with gentle stirring with the 30%-strength aqueous ethylcellulose dispersion.

Film-coating of the tablet cores:

The film coating suspension was sprayed on to the tablet cores in a film-coating apparatus, while warm air at approx. 70°C warmed the tablet cores to a temperature of approx. 45°C. Then the film-coated tablets were dried for 16 hours at a temperature of approx. 45°C.

Claims

1. The use of selective imidazoline receptor agonists or their physiologically compatible acid addition salts for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of functional disorders and/or diseases in larger mammals or humans which require inhibition or reduction of the activity of proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters.

2. The use according to Claim 1, characterised in that the proteins regulating the intracellular pH value are Na+-independent chloride-bicarbonate exchanger proteins.

3. The use according to Claim 1, characterised in that the proteins regulating the intracellular pH value are Na+/bicarbonate cotransporter proteins.

4. The use according to Claim 1, characterised in that the proteins regulating the intracellular pH value are Na+-dependent chloride-bicarbonate exchanger proteins.

5. The use according to Claim 1, characterised in that the functional disturbance and/or disease is selected from the group consisting of clinical pictures of bones which are caused by an undesirable amount of bone resorption, diseases of the gastrointestinal tract, or of neuronal and/or neuropsychiatric illnesses connected with a pathologically altered, in particular increased, neuronal activity.

6. The use according to one of the preceding Claims 1, 2 or 5, characterised in that the functional disorder and/or disease is a clinical picture of bones which is caused by an undesirable amount of bone resorption, selected from the group comprising osteoporosis, hypercalcaemia, osteopenia, dental diseases, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease and osteopathies caused by glucocorticoid, steroid or corticosteroid therapy or by a deficiency of sex hormone(s).

7. The use according to Claim 6, characterised in that the functional disorder and/or disease is osteoporosis.

8. The use according to one of the preceding claims, characterised in that the selective imidazoline receptor agonists are a compound selected from the group moxonidine, rilmenidine, LNP-509, S-23515, PMS-812, PMS-847 and BU-98008.

9. The use according to Claim 8, characterised in that the selective imidazoline receptor agonist is moxonidine.

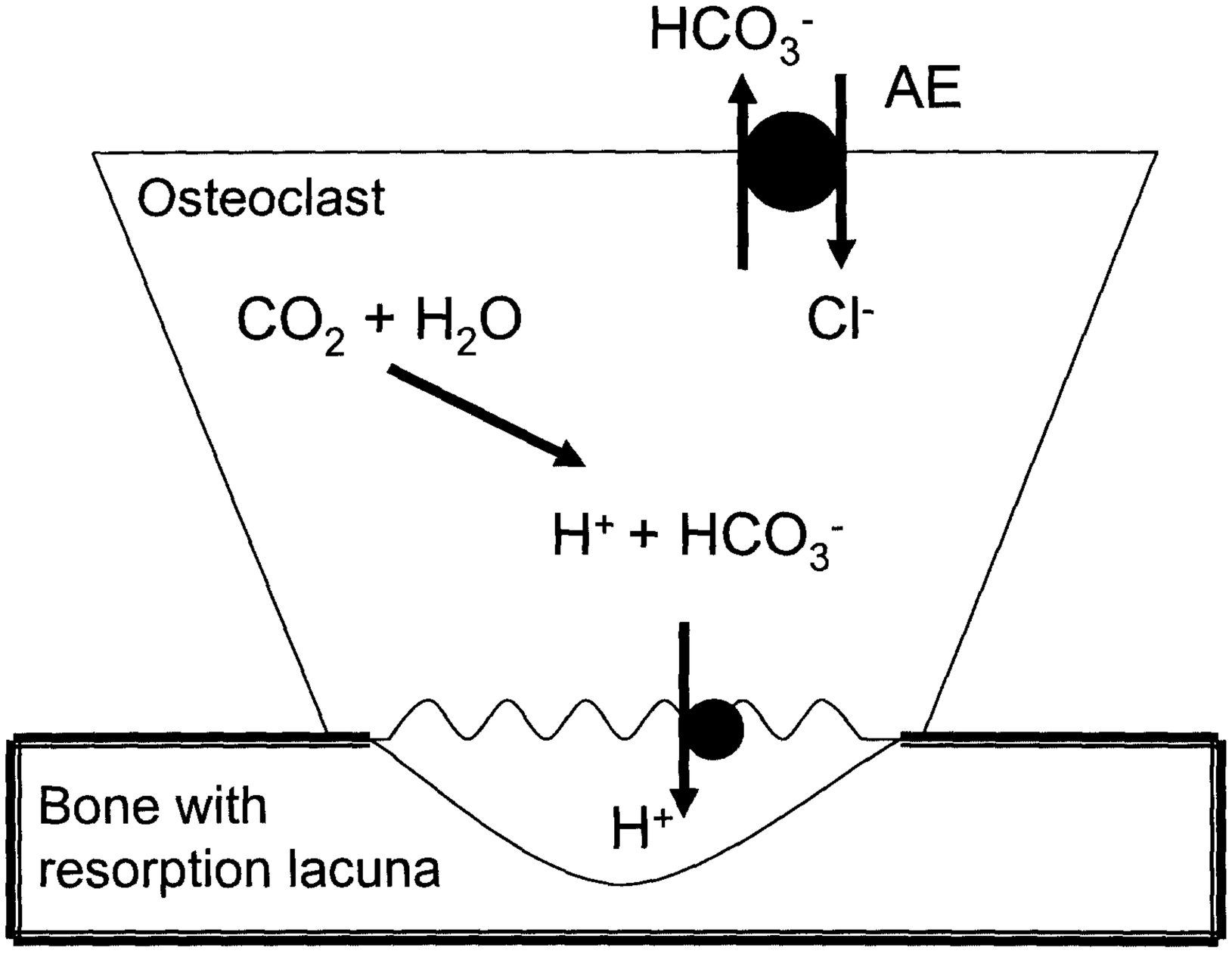
10. The use according to one of the preceding claims, characterised in that the humans are peri- or postmenopausal women.

11. The use of moxonidine or its physiologically compatible acid addition salts for the preparation of pharmaceutical preparations for the simultaneous treatment and/or prophylaxis of osteoporosis and of hypertension in larger mammals or humans.

12. The use according to Claim 11, characterised in that the humans are peri- or postmenopausal women.

13. A process for the preparation of pharmaceutical preparations for the treatment and/or prophylaxis of functional disorders and/or diseases in larger mammals or humans which require inhibition or reduction of the activity of proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters, characterised in that an amount which is effective for the treatment and/or prophylaxis of functional disorders and/or diseases which require inhibition or reduction of the activity of proteins which regulate the intracellular pH value and belong to the superfamily of bicarbonate transporters, of a selective imidazoline receptor agonist or its physiologically compatible acid addition salts together with conventional pharmaceutical auxiliaries is converted into a suitable medicament form.

Fig. 1


HCO_3^-
AE
Osteoclast
$CO_2 + H_2O$
Cl^-
$H^+ + HCO_3^-$
H^+
Bone with
resorption lacuna