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(54) Titre : COMPOSITION PHARMACEUTIQUE COMPRENANT UN AGONISTE DES RECEPTEURS DE
L'IMIDAZOLINE I1 SELECTIF ET UN BLOQUEUR DES RECEPTEURS DE L'ANGIOTENSINE II
(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING A SELECTIVE I1 IMIDAZOLINE RECEPTOR AGONIST
AND AN ANGIOTENSIN II RECEPTOR BLOCKER

(57) **Abrégé/Abstract:**

The present invention relates to pharmaceutical compositions comprising selective imidazoline receptor agonists combined with angiotensin II receptor blockers. In particular, the present invention relates to pharmaceutical compositions comprising Moxonidine and Eprosartan mesylate. The invention also relates to the use of said compositions in the manufacture of a medicament for the treatment of hypertension, especially in hypertensive patients already suffering from type II diabetes or being susceptible to developing type II diabetes.

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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING A SELECTIVE I1 IMIDAZOLINE RECEPTOR AGONIST
AND AN ANGIOTENSIN II RECEPTOR BLOCKER

(57) Abstract: The present invention relates to pharmaceutical compositions comprising selective imidazoline receptor agonists combined with angiotensin II receptor blockers. In particular, the present invention relates to pharmaceutical compositions comprising Moxonidine and Eprosartan mesylate. The invention also relates to the use of said compositions in the manufacture of a medicament for the treatment of hypertension, especially in hypertensive patients already suffering from type II diabetes or being susceptible to developing type II diabetes.



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5 PHARMACEUTICAL COMPOSITION COMPRISING A SELECTIVE I1 IMIDAZOLINE
RECEPTOR AGONIST AND AN ANGIOTENSIN II RECEPTOR BLOCKER

Description

10 FIELD OF INVENTION

The present invention relates to pharmaceutical compositions comprising selective imidazoline receptor agonists combined with angiotensin II receptor (AT1) blockers (ARBs). In particular, the present invention relates to pharmaceutical compositions comprising Moxonidine and Eprosartan mesylate. The invention also relates to the use of said compositions in the manufacture of a medicament for the treatment of hypertension, especially in hypertensive patients already suffering from type II diabetes or being susceptible to developing type II diabetes.

20 BACKGROUND OF THE INVENTION

Recent studies such as the HOT (Hypertension Optimal Treatment) study have demonstrated the benefits of reducing blood pressure to below previously existing target levels [Hansson L. et al. (1998) Lancet 351(9118):1755-62]. As a result of the HOT and other trials the target blood pressure levels recommended by hypertension management guidelines have become increasingly stringent during recent years. In 2003, official hypertension guidelines recommend even more effective blood pressure lowering. The new ESC/ESH guidelines recommend to reduce blood pressure in all hypertensive patients to at least below 140/90 mm Hg, and below 130/80 mmHg in diabetics [European Society of Hypertension-European Society of Cardiology Guidelines Committee (2003) J Hypertens. 21(6):1011-53; and Chobanian AV et al. (2003) JAMA. 289(19):2560-72]. A trend towards even lower target levels can be expected in the future.

35 Although current hypertension management guidelines recommend increasingly stringent blood pressure targets, these targets are seldom achieved in clinical practice by one single drug.

In particular, systolic blood pressure is generally poorly controlled [Taylor Nelson Sofres Healthcare, Cardio Monitor® Study (1998)]. Even in patients with mild to moderate hypertension, mono-therapy is only effective in approximately 50 - 70 % of the patients and thus there is a clear need for combination therapy if stringent blood pressure targets are to be achieved.

5 Drugs used in combination therapy should satisfy a number of prerequisites, including complementary mechanism of action, enhanced efficacy in combination and maintained (or improved) tolerability [Trenkwalder P. (2002) J of Human Hypertension 16, Suppl 3: S17- S25].

The sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) are both contributors to the development and maintenance of hypertension [Rupp H & Jäger B. (2001) J Clin Basic Cardiol 4:47-51]. Activation of the SNS results in increased vasomotor tone and is thus causally related to the development and maintenance of high blood pressure. The RAAS on the other hand plays an important role in the physiological regulation of cardiovascular, renal and endocrine functions. Overactivation of this system contributes to the

10 development and persistence of various forms of hypertension.

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Within the TOPIC study, it was already demonstrated that the combined therapy with Moxonidine and the Angiotensin Converting Enzyme (ACE)-Inhibitor Enalapril shows a positive effect. The combination was effective in 27 % of those hypertensive patients being refractory to monotherapy with Moxonidine [Waters J. et al. (1999) J Clin Bas Cardiol. 2(2):219-24; Prichard et al. (2002) Blood Press 11(3):166-72].

20

A further review article by Vetter and Düsing suggests the combination of Moxonidine with ACE inhibitors as an example of useful combinations. Furthermore, the quadruple combination of a diuretic, a calcium channel blocker (CCB), Moxonidine and an ACE inhibitor or an angiotensin II receptor (AT1) blockers (ARB) is mentioned [Vetter H & Düsing R. (1997) Nieren- und Hochdruckkrankheiten 26(31):105-107].

25

In addition, within a further document it was suggested to combine Moxonidine with other antihypertensives, for example with ACE inhibitors and ARBs. A reduction of the central sympathetic tone through Imidazoline I1 receptor activation by Moxonidine in combination with the inhibition of the RAAS by an ARB may produce additive/synergistic antihypertensive effects [Farsang C. (2001) J Clin Basic Cardiol 4:197-200].

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Furthermore, Aranda et al. disclosed the synergistic antihypertensive effects of a combination therapy with Irbesartan and Moxonidine in patients with moderate essential hypertension who were unresponsive to monotherapy [Aranda P. et al. (1999) (Conference abstract: 13th Scientific Meeting of the Inter-American Society of Hypertension, USA) Hypertension. 33(4):1065]

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However, there is a clear need for novel and effective approaches in combination therapy in order to achieve a stringent control of the blood pressure levels, particularly with regard to the newly established target levels according to the recently proposed European and US guidelines [see above]. Especially patients with type II diabetes require two or more medications in order to reduce their blood pressure to the proposed low levels. [Zanchetti A & Ruilope LM (2002) J Hypertension; 20:2099-2110]. These target blood pressure levels are 130/80 mm Hg in diabetic subjects with proteinuria of up to 1 g/day and 125/75 mm Hg in those with proteinuria in excess of 1 g/day. Compliance issues surrounding the prescribing of several drug classes (coupled with spiraling costs for poly-pharmacy) will fuel the continued increase and acceptance of fixed dose combination products. Drugs used in combination therapy should satisfy a number of prerequisites, including complementary mechanism of action, enhanced efficacy in combination and maintained (or improved) tolerability.

SUMMARY OF THE INVENTION

Therefore, it is an object of the present invention to develop novel pharmaceutical compositions for the effective treatment of hypertension by the combination of drugs with different mechanisms of action in order to achieve a stringent control of blood pressure target levels, especially for the (pre)-diabetic hypertensive patient.

It now has been found, that the combined administration of the Imidazoline I1 receptor agonist Moxonidine and the angiotensin (AT1) receptor blocker (ARB) Eprosartan fulfills these criteria due to the complementary pharmacological properties of both drugs. The combined Moxonidine and Eprosartan therapy is well suited for the treatment of hypertension, particularly systolic hypertension and hypertension associated with metabolic and renal impairment and heart failure, because this drug combination inhibits the two main pressure systems SNS (sympathetic nervous system) and RAAS (renin-angiotensin-aldosterone system) and consequently inhibits neuro-hormonal activation.

The combination of two completely different modes of actions provides a powerful alternative to current Hydrochlorothiazide (HCTZ) combinations as well as offering the possibility of having greater protection for diabetic and renally impaired patients.

Accordingly, the present invention relates to a pharmaceutical composition comprising a selective I1 imidazoline receptor agonist or a pharmaceutically acceptable salt thereof and an angiotensin II receptor blocker (ARB) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In a preferred embodiment of the invention, the selective I1 imidazoline receptor agonist is selected from the group consisting of moxonidine, rilmenidine, LNP-509, S-23515, PMS-812, PMS-847 and BU-98008. In particular, the selective I1 imidazoline receptor agonist is moxonidine or a pharmaceutically acceptable salt thereof.

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In a preferred embodiment of the invention, the angiotensin II receptor blocker (ARB) is selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, prazosin, telmisartan and valsartan. In particular, the angiotensin II receptor blocker is eprosartan or a pharmaceutically acceptable salt thereof.

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In particular, the present invention relates to a pharmaceutical composition consisting of a fixed combination of moxonidine and eprosartan mesylate. In a further preferred embodiment of the invention, the pharmaceutical composition comprises 0.05 – 1 mg, preferably 0.2 – 0.6 mg, of Moxonidine, and 100 – 1000 mg, preferably 200 – 800 mg, more preferably 300 – 600 mg, of Eprosartan, corresponding to 122.6 – 1226.3 mg, preferably 245.2 mg – 980.8 mg, more preferably 367.9 – 735.8 mg, of Eprosartan mesylate. In particular, the present invention relates to a pharmaceutical composition, wherein the Moxonidine is present in a dose of 0.2 mg, 0.3 mg, 0.4 mg or 0.6 mg and the Eprosartan is present in a dose of 400 mg, 600 mg or 800 mg. Most preferred, the present invention relates to a pharmaceutical composition, wherein the Moxonidine is present in a dose of 0.2 mg or 0.4 mg and the Eprosartan is present in a dose of 600 mg.

The pharmaceutical composition according to the present invention can be in the form of a tablet consisting mainly of Eprosartan and further of Moxonidine homogeneously distributed within the Eprosartan. Alternatively, the pharmaceutical composition can be in the form of a coated tablet wherein a small Moxonidine containing core is coated with an Eprosartan containing blend. Additionally, the present invention relates to a pharmaceutical composition in the form of an Eprosartan containing tablet core coated with a thin layer comprising the Moxonidine. Furthermore, the pharmaceutical composition can be in the form of a bilayer tablet or in the form of a trilayer tablet. All mentioned types of tablets may be provided with an additional coating, e.g. in order to impart taste masking and / or a specific drug release profile.

In a further embodiment according to the present invention, the pharmaceutical composition additionally comprises a diuretic, in particular hydrochlorothiazide.

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Furthermore, the present invention relates to the novel use of a therapeutically effective amount of a selective I1 imidazoline receptor agonist and of a therapeutically effective amount of an angiotensin II receptor blocker for the manufacture of a medicament for the treatment of a subject suffering from or being susceptible to hypertension, in particular systolic hypertension.

In a preferred embodiment of the invention, a therapeutically effective amount of a selective I1 imidazoline receptor agonist and of a therapeutically effective amount of Eprosartan is used for the manufacture of a medicament for the treatment of a subject suffering from or being susceptible to hypertension, in particular systolic hypertension. Preferably, the Eprosartan is administered in a daily dosage range from 100 – 1000 mg, preferably 200 – 800 mg, most preferably 300 – 600 mg.

In a further preferred embodiment of the present invention, a therapeutically effective amount of Moxonidine and a therapeutically effective amount of an angiotensin II receptor blocker – especially Eprosartan – are used for the manufacture of a medicament for the treatment of a subject suffering from or being susceptible to hypertension, in particular systolic hypertension. Preferably, the Moxonidine is administered in a daily dosage range from 0.05 – 1 mg, preferably from 0.2 – 0.6 mg.

Additionally, it is an object of the present invention to use Eprosartan in a daily dosage of 400 mg, 600 mg or 800 mg and Moxonidine in a daily dosage of 0.2 mg, 0.3 mg, 0.4 mg or 0.6 mg for the manufacture of a medicament for the treatment of a subject suffering from or being susceptible to hypertension, in particular systolic hypertension. Preferably, it is an object of the present invention to use Eprosartan in a daily dosage of 600 mg and Moxonidine in a daily dosage of 0.2 or 0.4 mg for the manufacture of a medicament for the treatment of a subject suffering from or being susceptible to hypertension, in particular systolic hypertension.

A preferred embodiment of the present invention relates to the use of any of the above indicated combinations for the manufacture of a medicament for the treatment of a subject suffering from or being susceptible to hypertension, in particular systolic hypertension, associated with metabolic impairment. In particular, the metabolic impairment is characterized by insulin resistance, hyperglycemia, diabetes mellitus type II, and/or hyperlipidemia. Additionally, the subject can suffer from or be susceptible to hypertension, in particular systolic hypertension, associated with diabetes mellitus type II. Furthermore, the hypertension can be associated with renal impairment and/or heart failure.

Furthermore, the present invention relates to the novel use of a therapeutically effective amount of a selective I1 imidazoline receptor agonist, of a therapeutically effective amount of an angiotensin II receptor blocker and additionally of a therapeutically effective amount of a diuretic, in particular hydrochlorothiazide, for the manufacture of a medicament for the treatment of a subject suffering from or being susceptible to hypertension, in particular systolic hypertension, and related diseases as defined above.

DETAILED DESCRIPTION OF THE INVENTION

I. DEFINITIONS AND NOMENCLATURE

5 Before describing the present invention in detail, it is to be understood that this invention is not limited to specific dosage forms, carriers, or the like, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

10 It must be noted that as used in this specification and the appended claims, the singular forms "a," "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an active agent" or "a pharmacologically active agent" includes a single active agent as well as two or more different active agents in combination, reference to "a carrier" includes mixtures of two or more carriers as well as a single carrier, and the like.

15 In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

The terms "active agent," "pharmacologically active agent" and "drug" are used interchangeably herein to refer to a chemical compound that induces a desired pharmacological, physiological effect. The primary active agents herein are inhibitors of the renin-angiotensin system, in particular angiotensin II receptor antagonists, and selective imidazoline receptor agonists. The terms also encompass pharmaceutically acceptable, pharmacologically active derivatives of those active agents specifically mentioned herein, including, but not limited to, salts, esters, amides, prodrugs, active metabolites, analogs, and the like. When the terms "active agent," "pharmacologically active agent" and "drug" are used, then, or when an active agent such as an angiotensin II receptor antagonist or a selective imidazoline receptor agonist is specifically identified, it is to be understood that applicants intend to include the active agent per se as well as pharmaceutically acceptable, pharmacologically active salts, esters, amides, prodrugs, metabolites, analogs, etc.

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The term "selective imidazoline receptor agonist" as used herein refers to a pharmacologically active, pharmaceutically acceptable agent that binds selectively to the I1 subtype of imidazoline receptor (I1R). The selective imidazoline receptor agonists represent a new class of centrally acting antihypertensive agents that have been developed to control blood pressure effectively without the adverse effects of sedation and mental depression that usually are associated with centrally acting antihypertensive agents. This new generation of centrally acting antihypertensive agents is selective for the imidazoline receptor but has a low affinity for alpha(2)-adrenergic receptors.

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The term "inhibitor of the renin-angiotensin system" as used herein refers to a pharmacologically active, pharmaceutically acceptable agent that inhibits, directly or indirectly, the adverse effects of angiotensin, particularly angiotensin II. Included, without limitation, are agents that: inhibit angiotensin II synthesis; inhibit angiotensin II binding to the AT₁ receptor; or inhibit renin activity.

The terms "angiotensin II receptor antagonist" or "angiotensin II receptor blockers" as used herein refer to a pharmacologically active, pharmaceutically acceptable agent that block the angiotensin II Type 1 (AT(1)) receptor by inhibiting angiotensin II binding to the AT₁ receptor without effecting other hormone systems.

The term "diuretic" as used herein refers to a pharmacologically active, pharmaceutically acceptable agent that can be used in the treatment of hypertension and management of edema, such as with congestive heart failure.

By "pharmaceutically acceptable," such as in the recitation of a "pharmaceutically acceptable carrier," or a "pharmaceutically acceptable acid addition salt," is meant herein a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. "Pharmacologically active" (or simply "active"), as in a "pharmacologically active" derivative or metabolite, refers to a derivative or metabolite having the same type of pharmacological activity as the parent compound and approximately equivalent in degree. When the term "pharmaceutically acceptable" is used to refer to a derivative (e.g., a salt) of an active agent, it is to be understood that the compound is pharmacologically active as well, i.e., therapeutically effective to reduce elevated blood pressure.

"Carriers" or "vehicles" as used herein refer to conventional pharmaceutically acceptable excipient materials suitable for drug administration, and include any such materials known in the art that are nontoxic and do not interact with other components of a pharmaceutical composition or drug delivery system in a deleterious manner.

By an "effective" amount or a "therapeutically effective amount" of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect. In the combination therapy of the present invention, an "effective amount" of one component of the combination is the amount of that compound that is effective to provide the desired effect when used in combination with the other components of the combination. The amount that is "effective" will vary from subject to subject, depending on the age and general

condition of the individual, the particular active agent or agents, and the like. Thus, it is not always possible to specify an exact "effective amount." However, an appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

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The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, and improvement or remediation of damage. Thus, for example, "treating" a patient involves prevention of a particular disorder or adverse physiological event in a susceptible individual as well as treatment of a clinically symptomatic individual.

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II. THE ACTIVE AGENTS

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Selective I1 imidazoline receptor agonists

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The I1 subtype of imidazoline receptors (I1R) is a plasma membrane protein that is involved in diverse physiological functions. The I1-imidazoline receptor is a novel neurotransmitter receptor found mainly in the brainstem, adrenal medulla and kidney. The receptor functions at the cellular level works through arachidonic acid and phospholipid signaling cascades in neuronal cells with the net result of inhibiting sympathetic premotor neurons. The imidazoline receptors have been discovered to be involved in the central nervous system control of sympathetic outflow. A new class of centrally acting antihypertensive agents, the imidazoline receptor agonists have been developed to control blood pressure effectively without the adverse effects of sedation and mental depression that usually are associated with centrally acting antihypertensive agents. This new generation of centrally acting antihypertensive agents is highly selective for the imidazoline receptor but has a low affinity for alpha(2)-adrenergic receptors.

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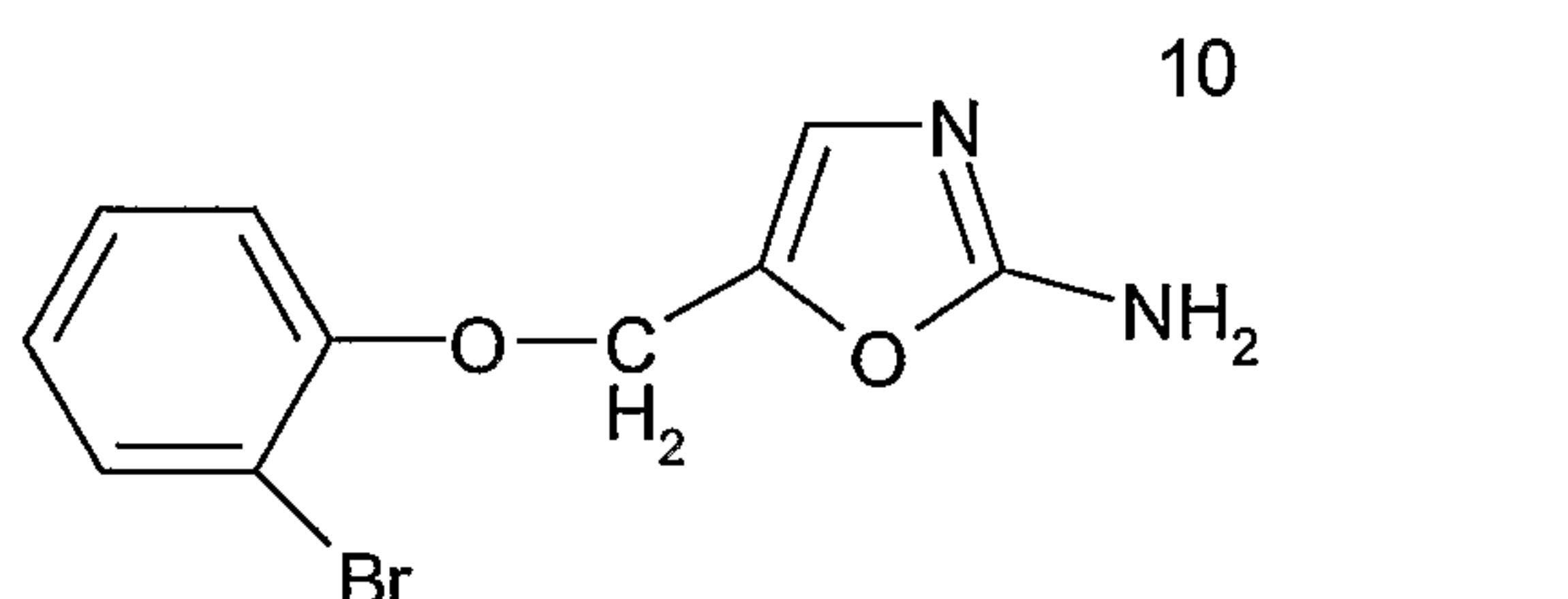
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Any orally active selective I1 imidazoline receptor agonist may be used in this invention. Some examples of selective I1 imidazoline receptor agonists suitable for use herein are described within European patent applications EP 0 710 658 and EP 0 846 688, as well as within the international applications WO 01/41764 und WO 00/02878, without limiting the group of selective I1 imidazoline receptor agonist. The novel 5-(Aryloxymethyl)-Oxazolin derivatives described within EP 0 710 658 are characterized by a selective affinity for the I1 imidazoline receptor. The document EP 0 846 688 describes novel imidazoline derivatives with high binding affinity towards the imidazolin receptor, but with low affinity towards adrenergic receptors. The PCT application WO 01/41764 discloses novel isochinoline and chinoline derivatives showing selective binding affinity towards imidazoline receptors. The PCT application WO 00/02878 relates to novel β -carboline derivatives as potential novel ligands for imidazoline receptors. Said com-

pounds can be prepared according to the well-known procedures described in the aforementioned patent applications or similarly to these procedures.

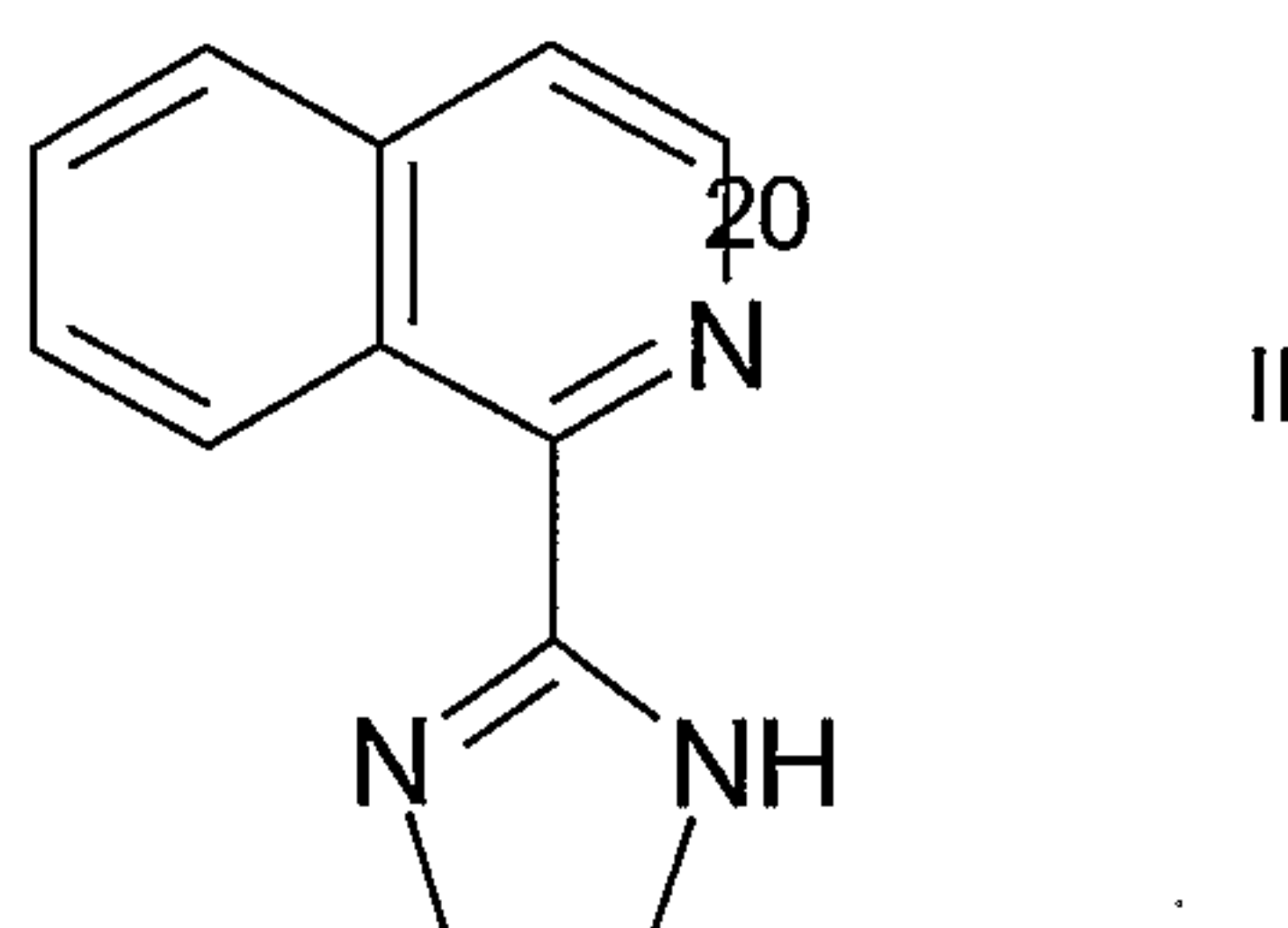
Preferred selective I1 imidazoline receptor agonists include moxonidine, rilmenidine, LNP-509, S-23515, PMS-812, PMS-847 and BU-98008, which are disclosed in more detail below. Particularly preferred is Moxonidine.

The compound 5-[(2-Bromophenoxy)methyl]-4,5-dihydro-oxazol-2-ylamine (S-23515) of the formula I



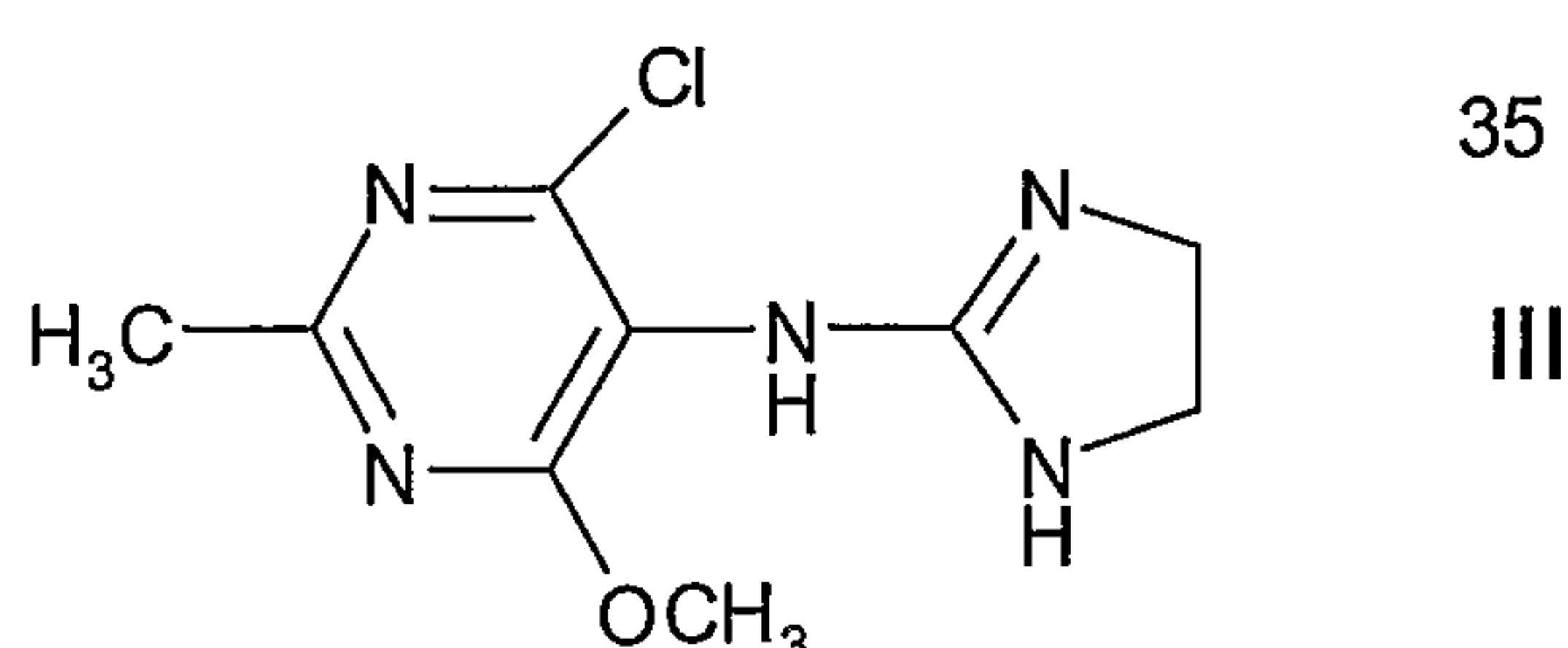
15 belongs to the 5-(Aryloxymethyl)-Oxazolin derivatives disclosed within EP 0 710 658.

Furthermore, the compound 1-(4,5-dihydro-1H-imidazol-2-yl)-isochinolin (BU98008) of the formula II



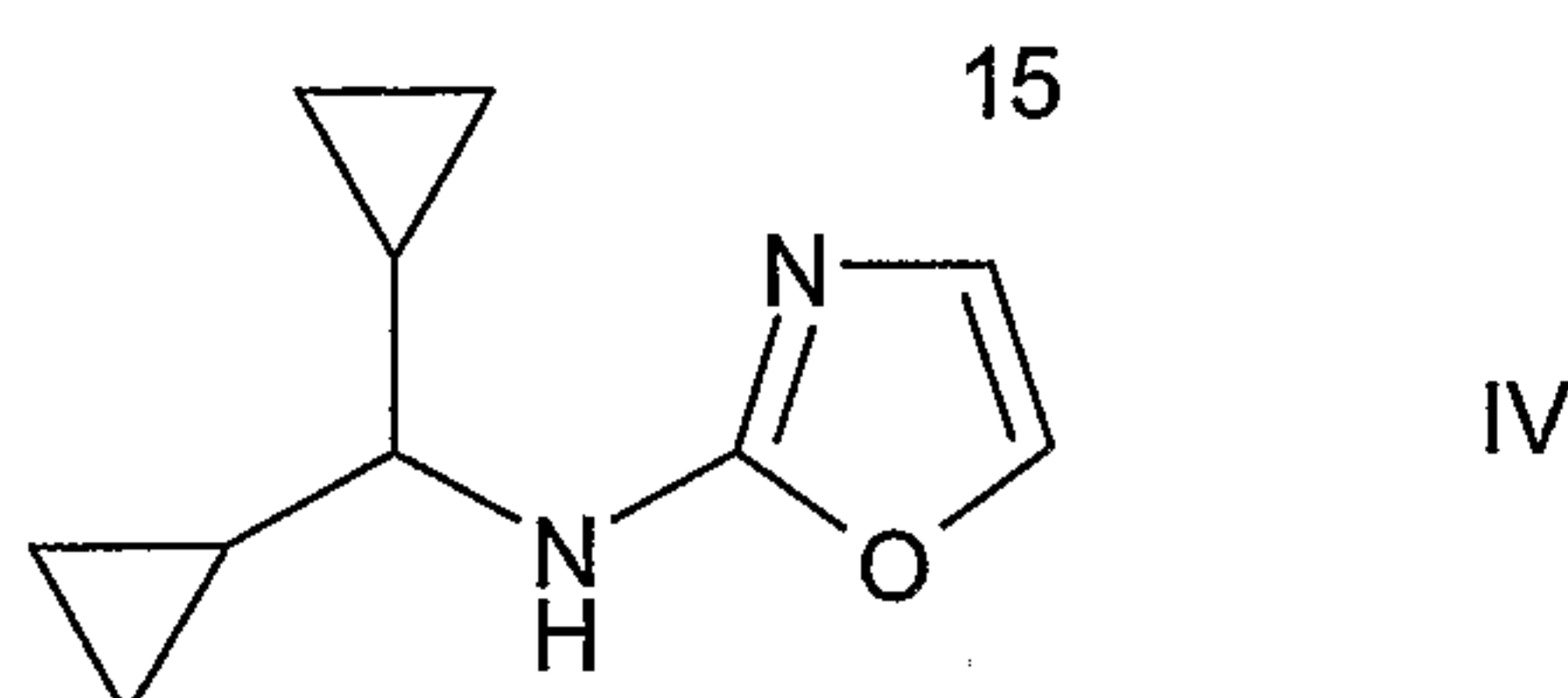
25 is presented as a particular selective I1 imidazoline receptor agonist, which belongs to the class of compounds disclosed within the aforementioned international patent application WO 01/41764.

In particular, the 5-[(2-Imidazolin-2-yl)-amino]-pyrimidine derivatives disclosed within German patent application DE 28 49 537, which possess blood pressure lowering properties, belong to the group of selective I1 imidazoline receptor agonists. In a preferred embodiment the present invention relates to the use of the compound 4-Chloro-5-[(4,5-dihydro-1H-imidazol-2-yl)-amino]-6-methoxy-2-methylpyrimidine (= Moxonidine) of the formula III



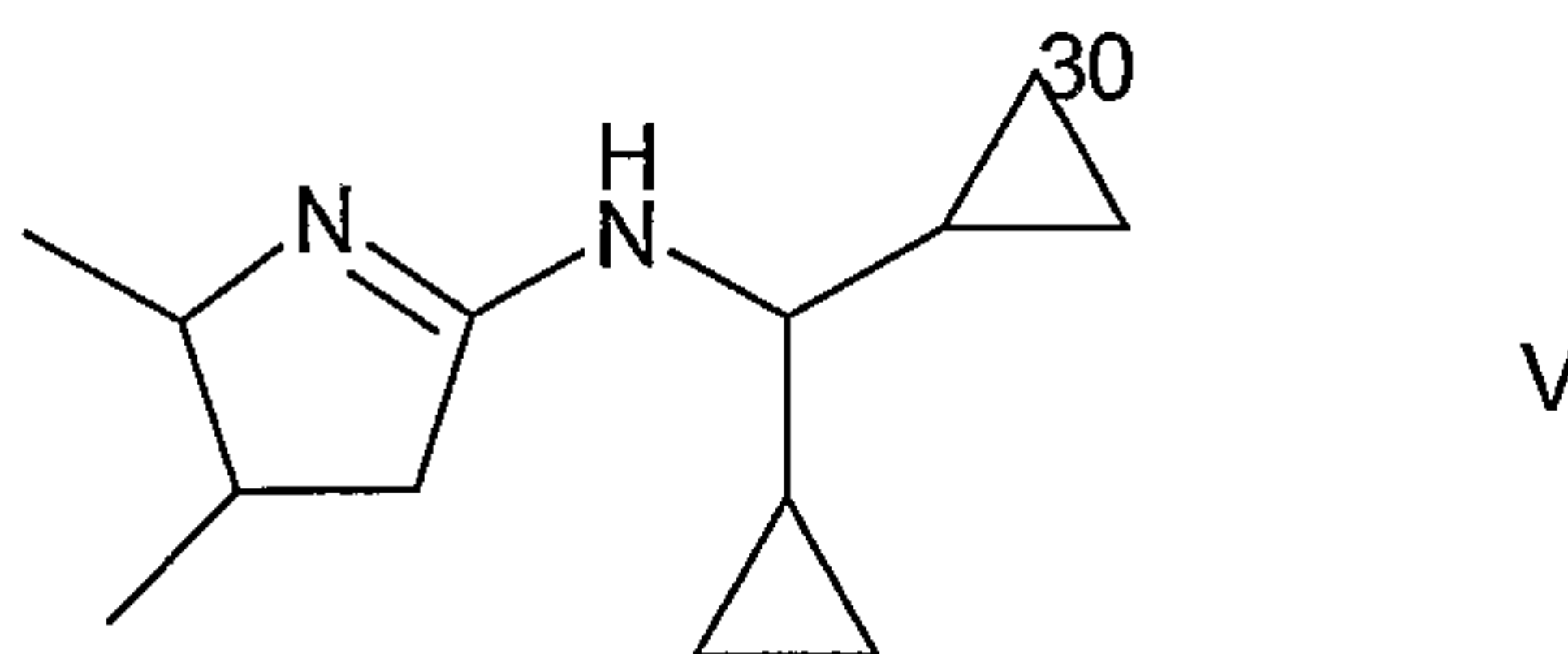
Pharmaceutical compositions comprising Moxonidine are e.g. available under the trade name Physiotens®, Cynt®, Moxon and are used as antihypertensives. It is well known in the state of the art, that moxonidine represents a selective ligand of the I1 subtype of imidazoline receptors (I1R) [Ernsberger (2000) J Cardiovasc Pharmacol. 35:S27-41]. Said compounds can
5 be prepared according to the well-known procedures described in the aforementioned patent applications or similarly to these procedures. The anti-hyperglycemic properties of Moxonidine are well known [EP 0689837]. Furthermore, Moxonidine is able to reduce plasma insulin already in patients with impaired glucose tolerance where fasting plasma glucose is not yet influenced.

10 Furthermore, the cyclopropylmethylamine derivatives disclosed within the German patent application DE 23 62 754 and possessing valuable blood pressure reducing properties belong to the group of selective I1 imidazoline receptor agonists. In particular, the present invention refers to the compound N-(dicyclopropylmethyl)-4,5-dihydro-2-oxazolamine (= Rilmenidine) of the formula IV



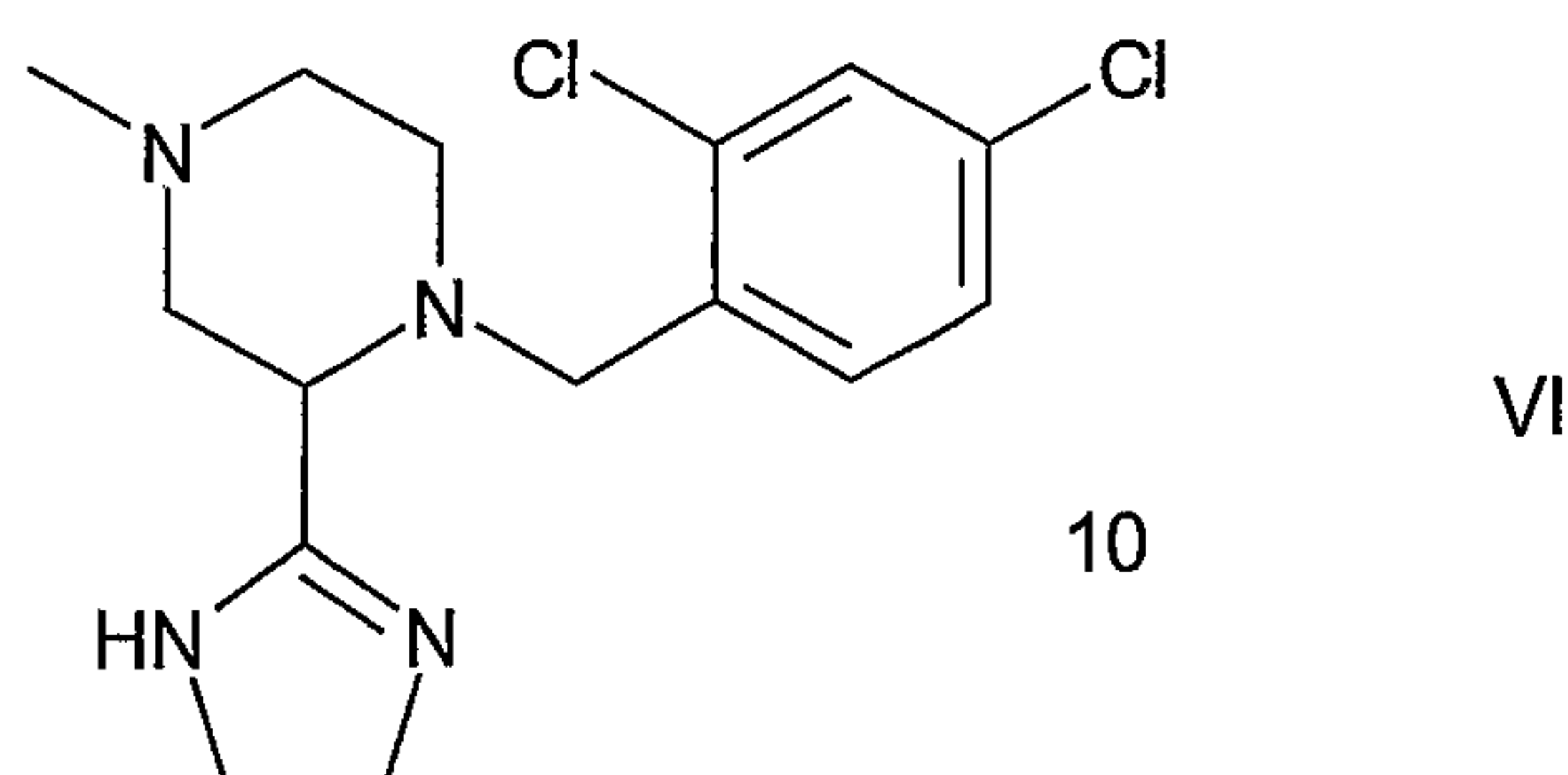
20 It is well known in the state of the art, that rilmenidine represents a selective ligand of the I1 subtype of imidazoline receptors (I1R) [Bock et al. (1999) Naunyn Schmiedebergs Arch Pharmacol. 359:262-71]). Said compounds can be prepared according to the well-known procedures described in the aforementioned patent applications or similarly to these procedures.

25 Furthermore, the novel aminopyrroline derivatives disclosed within the European patent application EP 1 101 756 which are suited for the treatment of cardiovascular disorders, such as hypertension, belong to the group of selective I1 imidazoline receptor agonists. In particular, the present invention relates to the use of the compound cis-/trans-dicyclopropylmethyl-(4,5-dimethyl-4,5-dihydro-3H-pyrrol-2-yl)-amine (= LNP-509) of the formula V

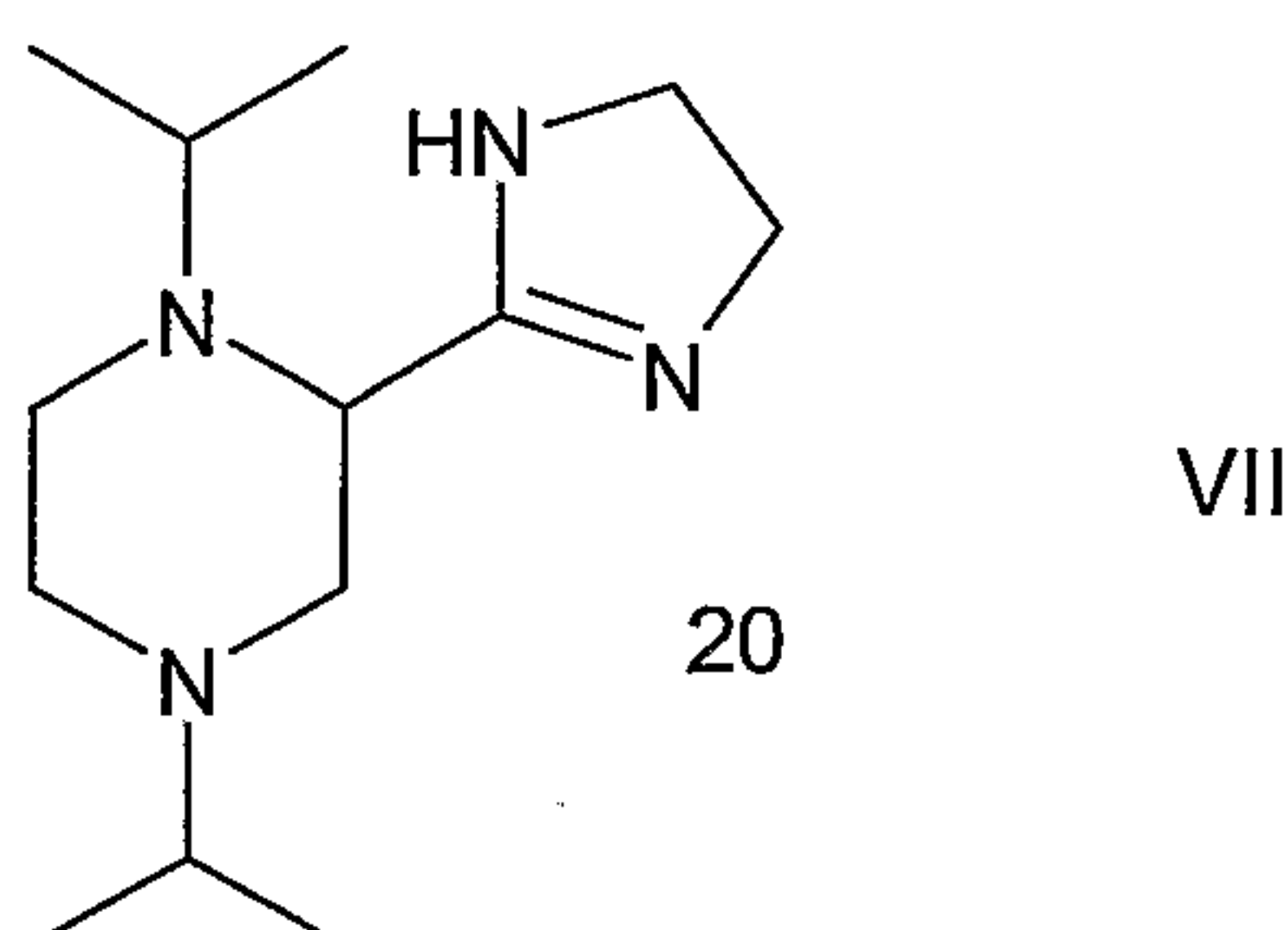


35 The compound LNP-509 is a selective ligand for the I1 subtype of imidazoline receptors and shows hypotensive characteristics [Schann et al. (2001) J Med Chem. 44:1588-93]. Said compounds can be prepared according to the well-known procedures described in the aforementioned patent applications or similarly to these procedures.

Additionally, the novel substituted piperazine derivatives disclosed within the European patent application EP 0 638 568 which are suited for the treatment of non-insulin dependent diabetes belong to the family of selective I1 imidazoline receptor agonists. In particular, the present invention relates to the compound 1-(2,4-dichlorobenzyl)-2-(4,5-dihydro-1H-imidazol-2-yl)-4-methylpiperazine (= PMS-812, also known as S-21663) of the formula VI



or to the compound 1-methyl-4-(2,4-dichlorobenzyl)-2-(4,5-dihydro-1H-imidazol-2-yl)-piperazine, as well as to the compound 1,2-Diisopropyl-2-(4,5-dihydro-1H-imidazol-2-yl)-piperazine (PMS-847, also known as S-22068) of the formula VII



PMS-812 (S-21663) as well as PMS-847 (S-22068) both represent imidazoline derivatives, which selectively bind to the imidazoline receptors [Rondou *et al.* (1997) J Med Chem. 40:3793-803; Le Bihan *et al.* (1999) J Med Chem. 42:1587-603]. Said compounds can be prepared according to the well-known procedures described in the aforementioned patent applications or similarly to these procedures.

Angiotensin receptor blockers

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Angiotensin II (AII) is a potent vasoconstrictor. Its generation in the renin-angiotensin cascade results from the enzymatic action of renin on a blood plasma α 2-globulin, angiotensinogen, to produce angiotensin I (AI). AI is then converted by angiotensin converting enzyme (ACE) to the octapeptide hormone AII. Angiotensin II binds to angiotensin subtype I (AT₁) and subtype 2 (AT₂) receptors, as well as to several other receptors. All the known physiological effects of angiotensin II are apparently due to its binding to, and activation of, the AT₁ receptor, which is abundantly expressed in the tissues affected by angiotensin II. Angiotensin II has been implicated as a causative agent in hypertension. Inhibiting the renin-angiotensin-aldosterone system (RAAS) through the use of angiotensin-converting enzyme (ACE) inhibitors which inhibit

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the production of Ang II via inhibition of the angiotensin converting enzyme has proven very useful in the treatment of hypertension, congestive heart failure (CHF) and progressive renal failure. More recently, agents that directly block the angiotensin II Type 1 (AT₁) receptor – so called “angiotensin II receptor antagonists or blockers” (AIIAs or ARBs) – have been developed.

5 Most of these nonpeptide angiotensin II receptor antagonists are directed at the AT₁ receptor. Angiotensin II receptor antagonists are generally highly specific, having very little effect on other hormone receptors as do the ACE inhibitors or on ion channels. Whether such specificity results in a different efficacy profile is still being determined. However, these drugs are extremely well-tolerated and very safe. ARBs are effective in the reduction of both systolic and diastolic blood
10 pressure and compare favorably to other classes of agents. ARBs are effective in slowing the progression of renal failure in patients with Type II diabetes and may be effective in other proteinuric conditions. Overall, ARBs represent an important addition to the armamentarium of cardiovascular therapies with an excellent safety record and an emerging profile of utility in multiple cardiovascular conditions [Shusterman N. (2002) Expert Opin Drug Saf. 1(2):137-52].

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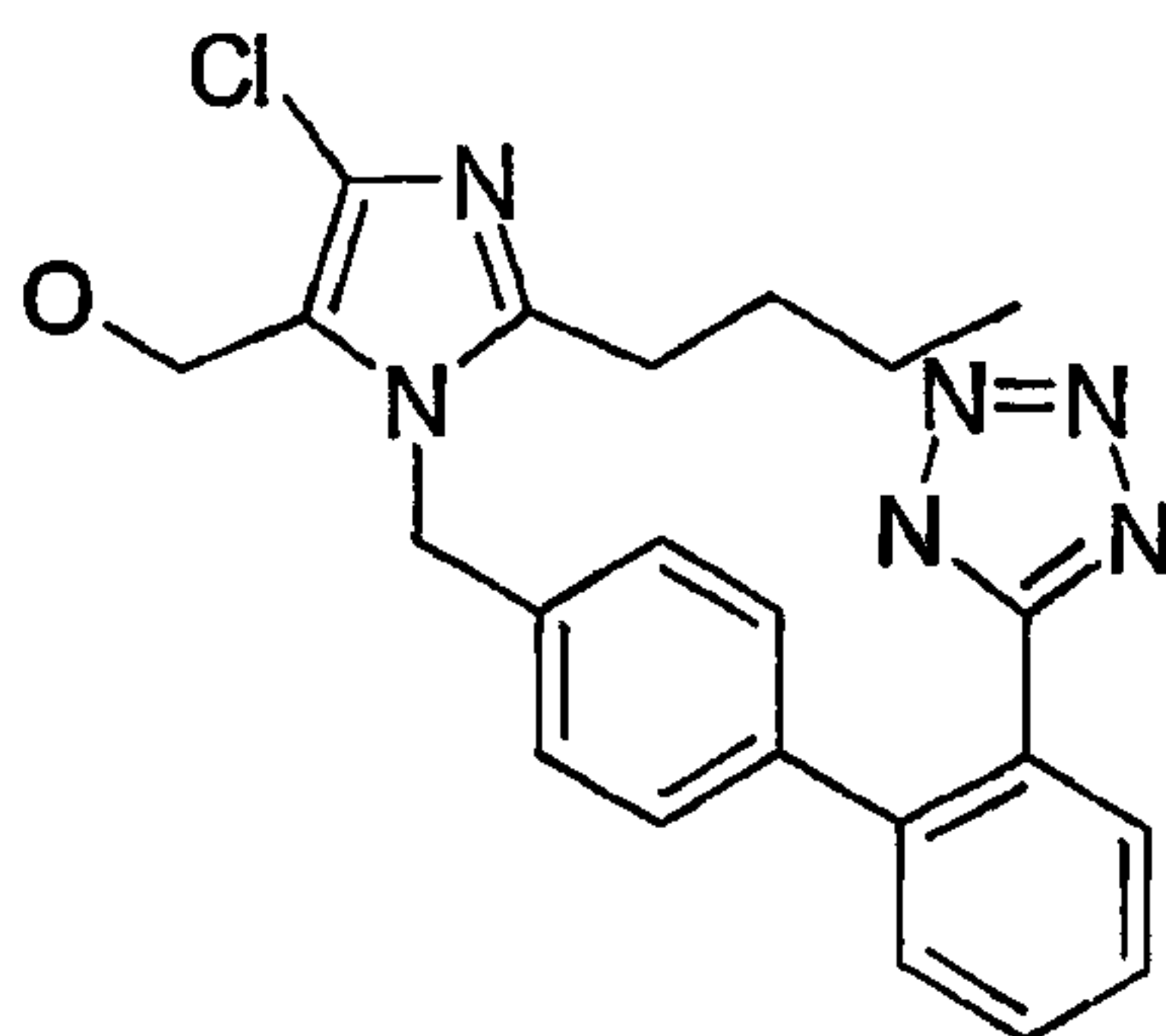
Any orally active antagonists of the AT₁ angiotensin II receptor may be used in this invention. Some examples of angiotensin II receptor antagonists suitable for use herein are saralasin (including saralasin acetate), candesartan (including candesartan cilexetil), CGP-63170, EMD-66397, KT3-671, LRB/081, valsartan, A-81282, BIBR-363, BIBS-222, BMS-184698, CV11194,
20 EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD150304, U-96849, U-97018, UP-275-22, WAY-126227, WK-1492.2K, YM-31472, losartan (including losartan potassium), E-4177, EMD-73495, eprosartan, HN-65021, irbesartan, L-159282, ME-3221, prazosartan, SL-91.0102, tasosartan, telmisartan, UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234, L-162441, L-163007, PD-123177, A81988, BMS-180560, CGP-38560A, CGP-48369,
25 DA-2079, DE-3489, DuP-167, EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739, HR-720, ICI D6888, ICI-D7155, ICI-D8731, isoteoline, KRI-1177, L-158809, L-158978, L-159874, LR B087, LY-285434, LY-302289, LY-315995, RG-13647, RWJ-38970, RWJ-46458, S-8307, S-8308, saprisartan, sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731, BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L163017, LY-301875, XH-148, XR-510, zolasartan, and PD-123319.
30

Preferred angiotensin II receptor antagonists include losartan (which is the prototype and best known angiotensin II receptor antagonist), irbesartan, eprosartan, candesartan, olmesartan, prazosartan, valsartan, telmisartan, which are disclosed in more detail below. Particularly
35 preferred is eprosartan.

Losartan potassium (losartan) represents the first antihypertensive in the class of Ang II receptor antagonists which is disclosed in a U.S. Pat. No. 5,138,069 and EP 0 253 310 A1.

Losartan, a compound of the formula VIII

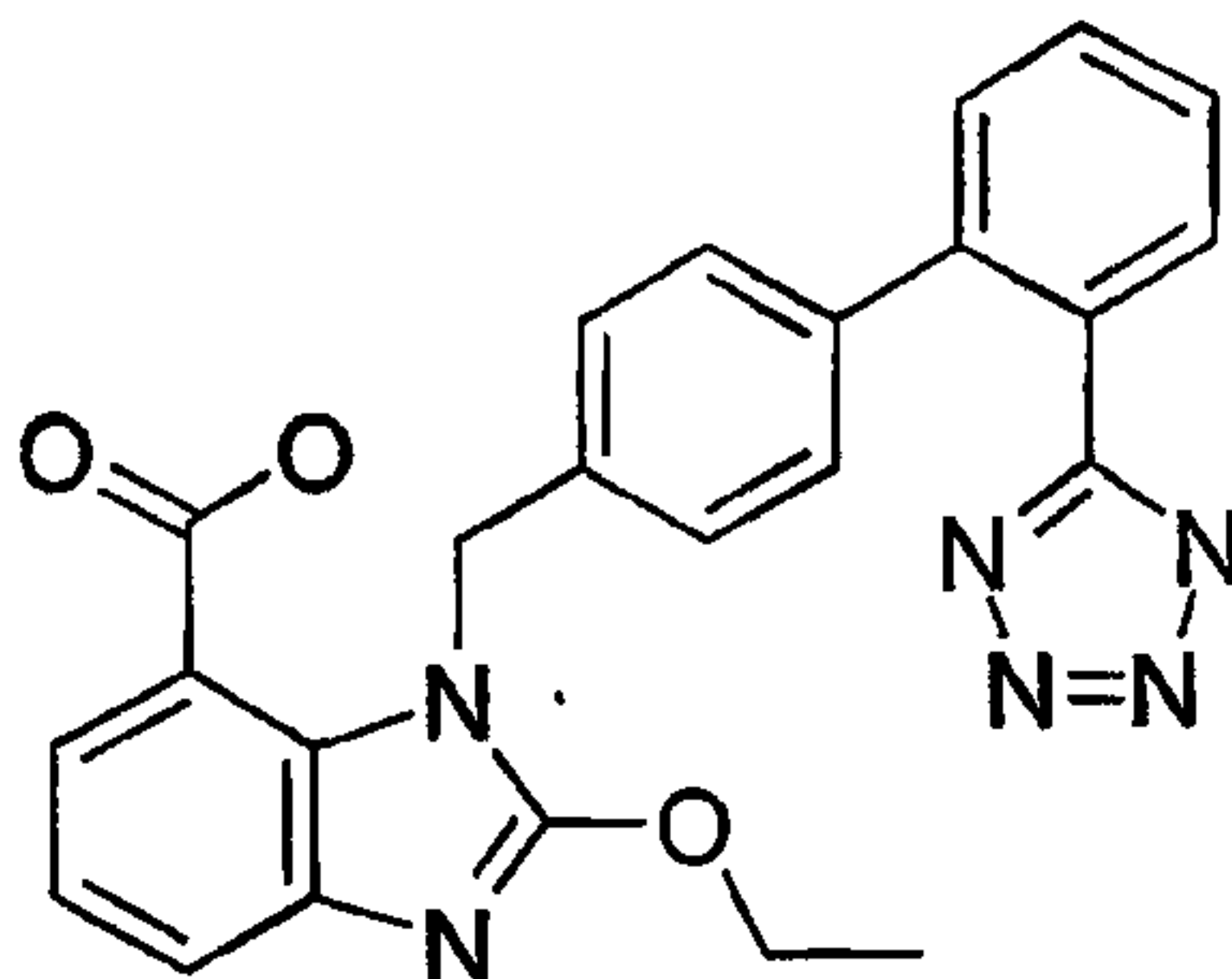
13



VIII

has been demonstrated to be a potent orally active AII antagonist and selectively binds the AT1 receptor subtype. Losartan is useful in the treatment of hypertension.

- 5 Candesartancilexetil (Candesartan, TCV-116) was disclosed in US Pat. No. 5,196,444 and European patent EP 0 459 136 B1, as a potent angiotensin II receptor antagonist with a long duration of action. Candesartan is a compound of the formula IX

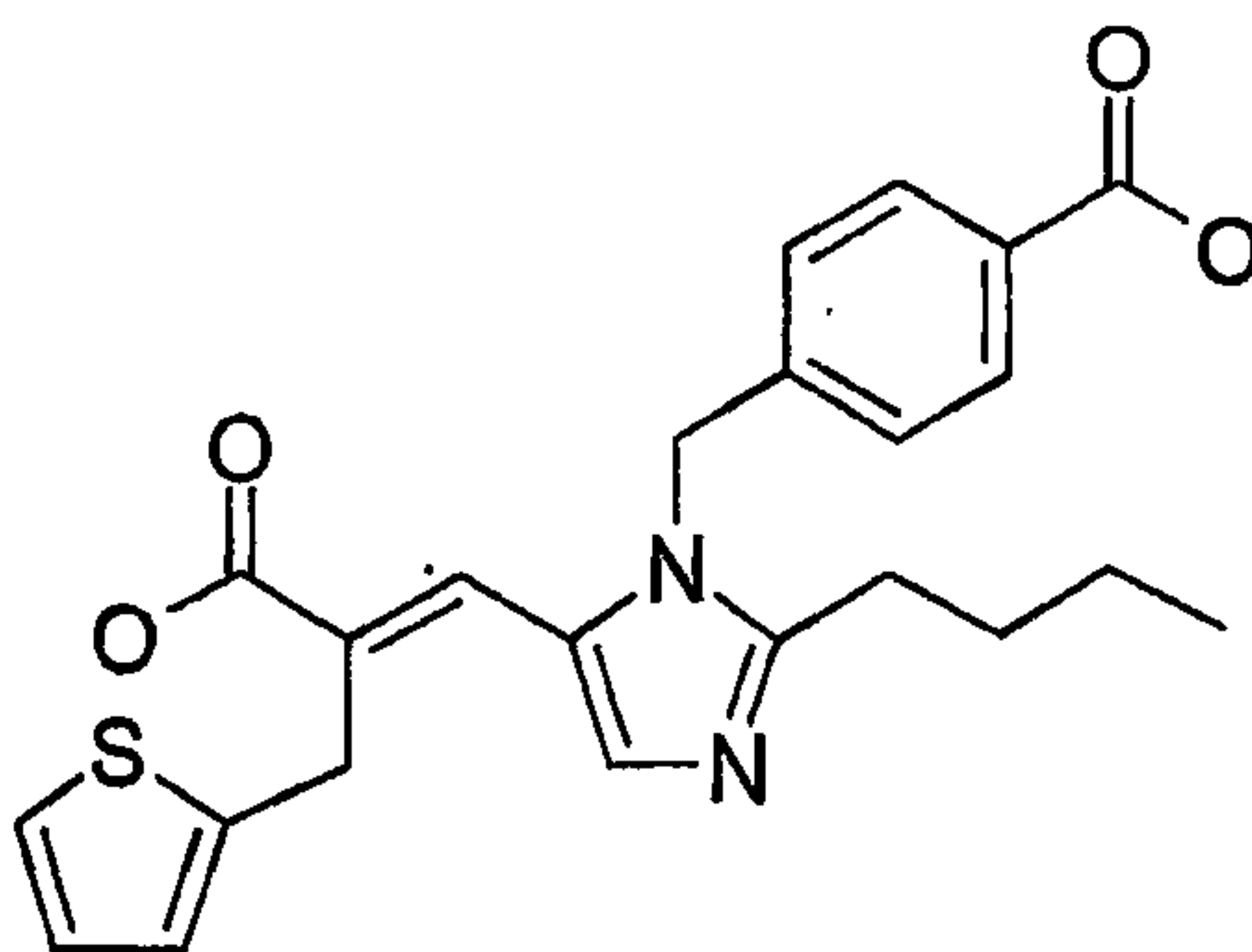


IX

- 10 and is useful for the treatment of hypertension.

Eprosartan mesylate (Eprosartan) is a new imidazolyl-alkenoic acids disclosed within European patent EP 0 403 159 B1 and US Pat. No. 5,185,351.

Eprosartan, a compound of the formula X



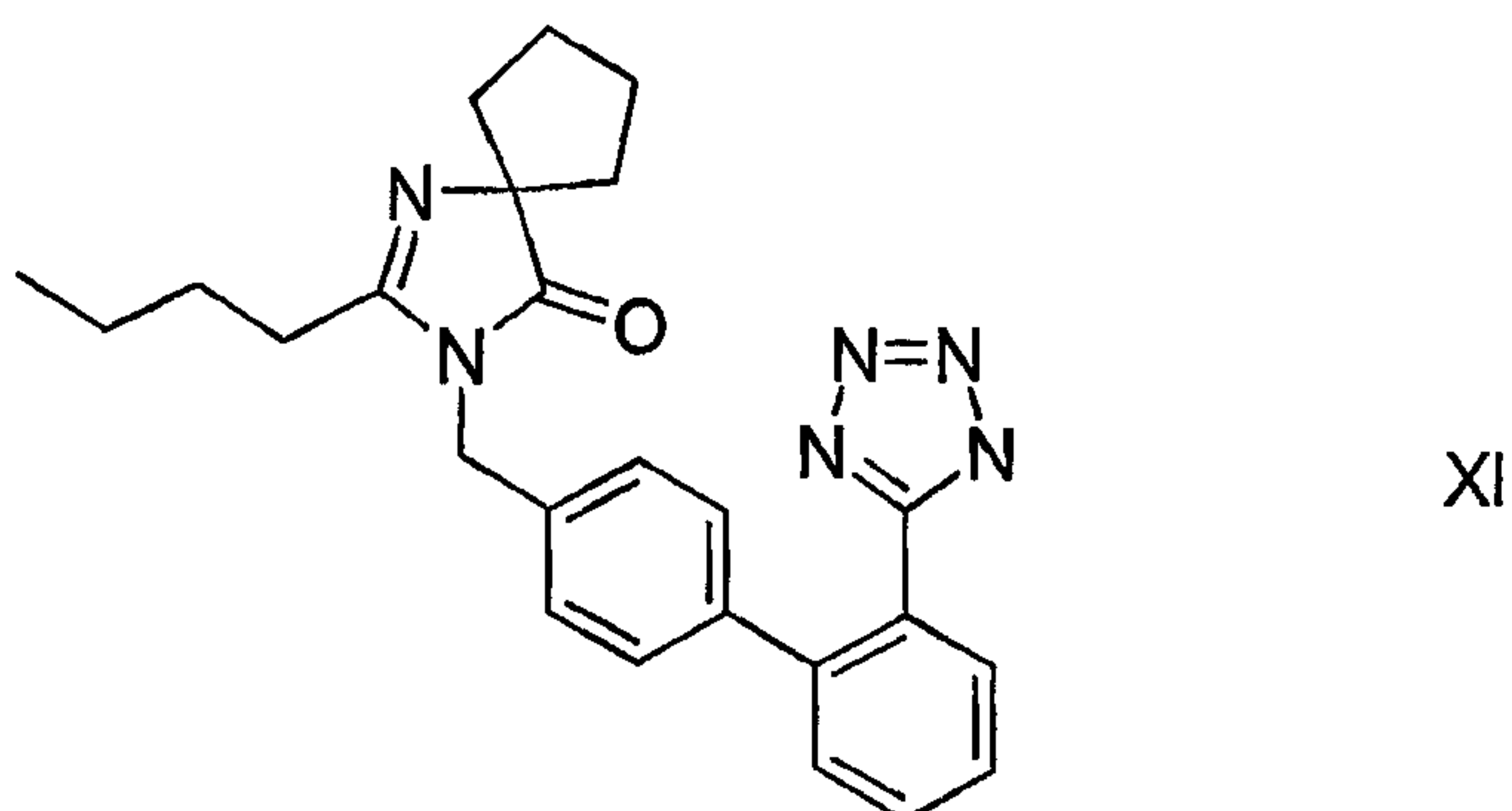
X

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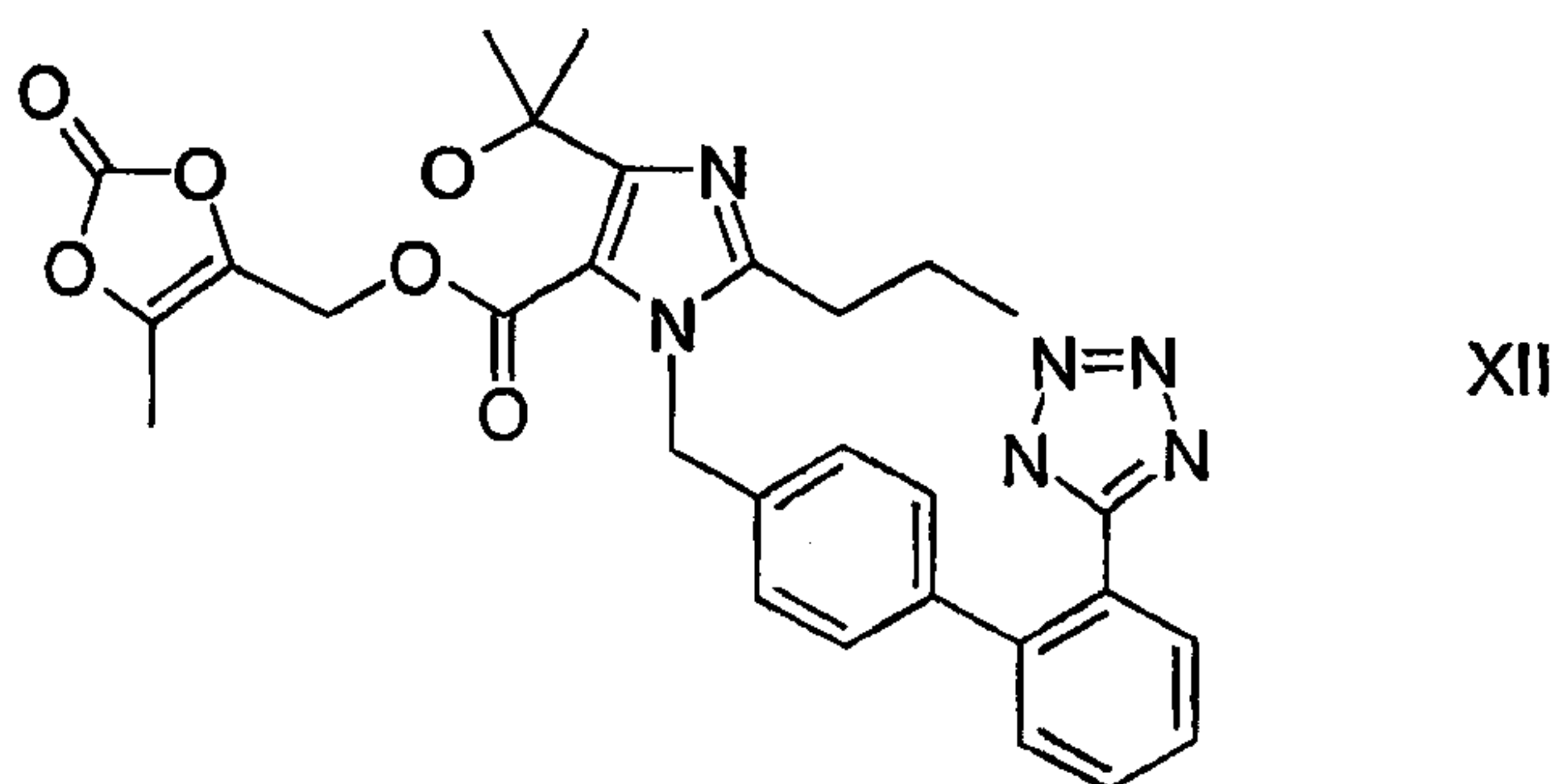
is a well known angiotension II receptor antagonist and is suited for the treatment of hypertension, congestive heart failure and renal failure.

Irbesartan (2-n-butyl-4-spirocyclopentane-1-[(2'-(tetrazol-5-yl)biphenyl-4-yl)-methyl]-2-imidazolin-5-one) belongs to a novel class of Imidazoline-based compounds, linked to a biphenyl moiety, with activity as angiotensin II (AT-II) antagonists disclosed within U.S. Pat. No. 5,270,317 and European patent EP 0 454 511 B1.

Irbesartan is a potent, long-acting angiotensin II receptor antagonist which is particularly useful in the treatment of cardiovascular ailments such as hypertension and heart failure, and possesses the following formula XI



Olmesartan (CS-866) belongs to a series of novel 1-(biphenylmethyl)imidazole compounds which are antagonists to angiotension II receptor. These compounds have valuable hypotensive activities, and which may, therefore, be used in the treatment and prophylaxis of hypertension, including diseases of the heart and circulatory system. Olmesartan is a compound of the following formula XII



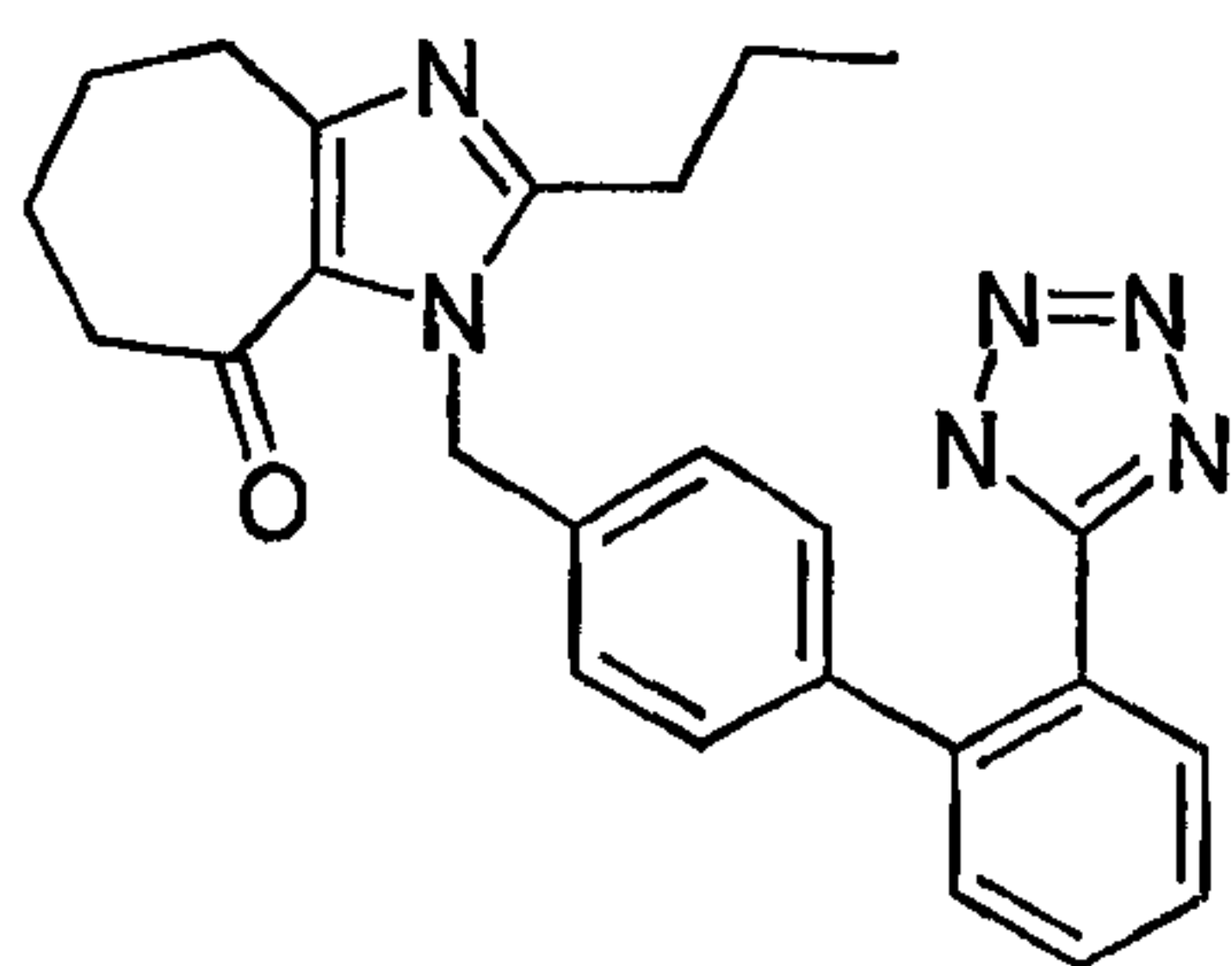
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and was disclosed within European patent No. 0 503 785 B1 and US Pat. No. 5,616,599.

Pratosartan belongs to a novel class of cycloheptolimidazole derivatives disclosed within U.S. Pat. No. 5,409,947.

Pratosartan, which has the following formula XIII

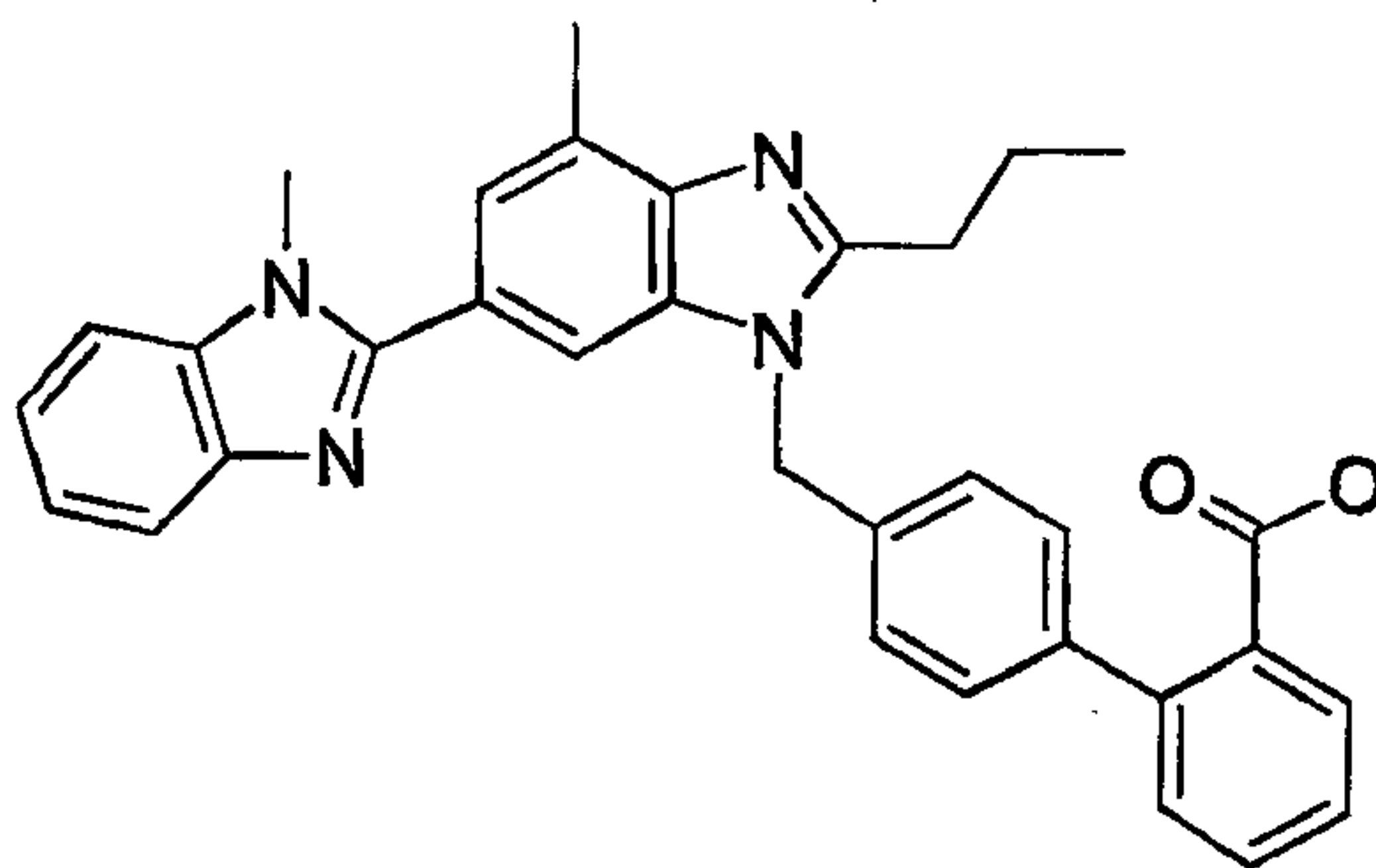
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XIII

is a known Angiotensin II receptor antagonist and is suited for the treatment of hypertension and congestive heart failure.

- 5 Telmisartan (4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid) is an angiotensin-II-antagonist, which is useful for treating hypertension and cardiac insufficiency and for treating other cardiovascular disorders including ischaemic peripheral circulation disorders, myocardial ischaemia (angina). Telmisartan showing the following formula XIV



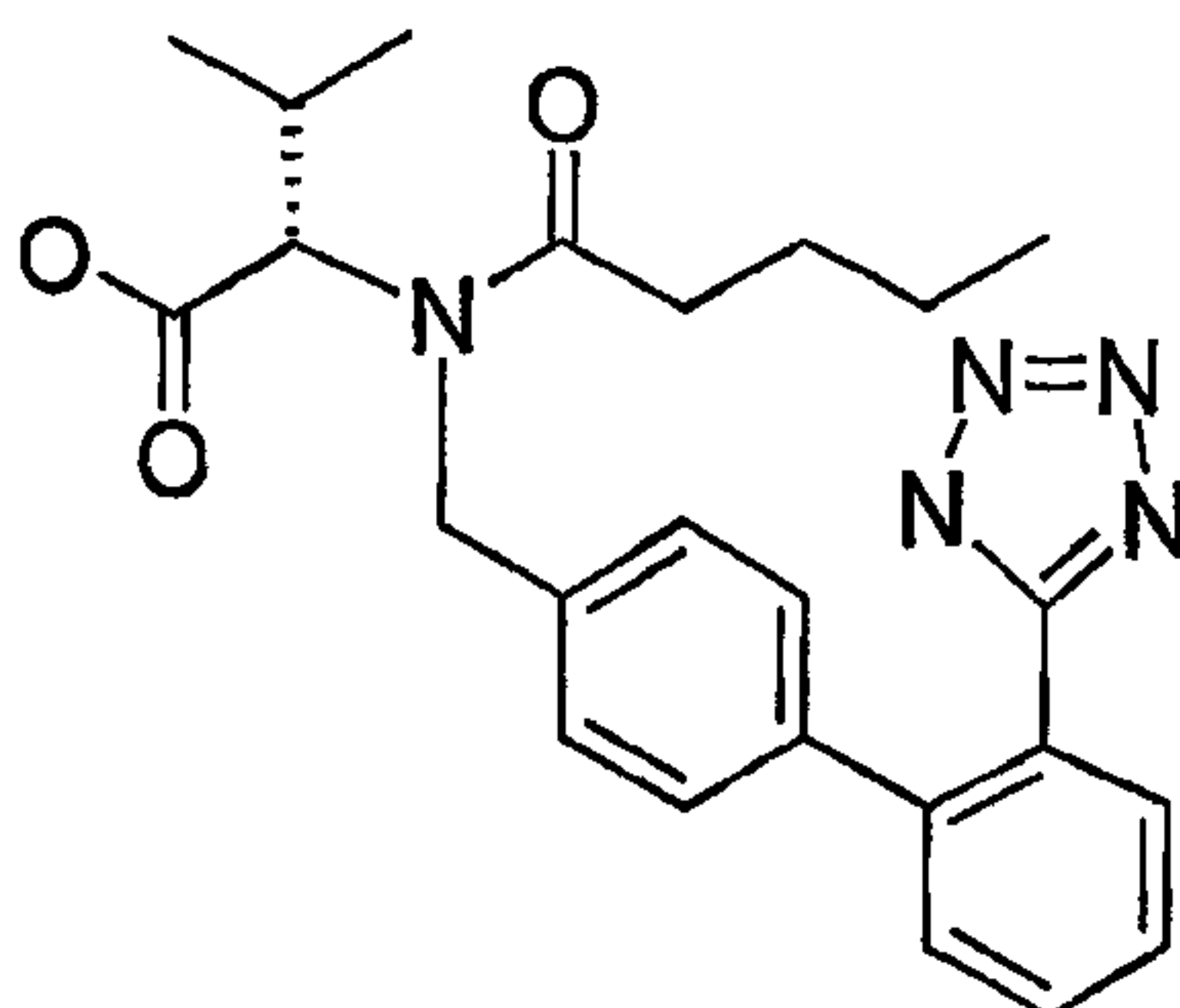
XIV

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belongs to a class of novel benzimidazole compounds having angiotensin II antagonist activity which were disclosed within European patent No. 0 502 314 B1 and US Pat. No. 5,591,762.

- 15 Valsartan ((S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-yl-methyl]amine) belongs to novel acyl derivatives which exhibit potent angiotensin II antagonistic activity and are potentially useful as antihypertensive agents. These compounds are disclosed within European patent EP 0 443 983 B1 and US Pat. No. 5,399,578.

Valsartan has the following formula XV



XV

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Diuretics

The "diuretic" employed in a composition of the present invention may be any suitable diuretic, or combination of two or more diuretics, such as acetazolamide, amiloride, azosemide, bendroflumethiazide, benzothiazide, bumetanide, chlorothiazide, chlorthalidone, clopamide, cyclopenthiazide, cyclothiazide, dichlorphenamide, dorzolamide, ethacrynate sodium, ethacrynic acid, ethoxzolamide, furosemide, hydrochlorothiazide, hydroflumethiazide, indapamide, mefruside, methazolamide, methylclothiazide, metolazone, metozalone, muzolimide, piretanide, polythiazide, quinethazone, spironolactone, trichlormethiazide, torsemide, triamterene, trichlormethiazide, tripamide, xipamide. Preferably, the diuretic is hydrochlorothiazide (6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide).

Derivatives

Any of the active agents may be administered in the form of a salt, ester, amide, prodrug, active metabolite, analog, or the like, provided that the salt, ester, amide, prodrug, active metabolite, or analog is pharmaceutically acceptable and pharmacologically active in the present context. Salts, esters, amides, prodrugs, metabolites, analogs, and other derivatives of the active agents may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 4th Edition (New York: Wiley-Interscience, 1992).

For example, acid addition salts are prepared from a drug in the form of a free base using conventional methodology involving reaction of the free base with an acid. Suitable acids for preparing acid addition salts include both organic acids, e.g., acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. An acid addition salt may be reconverted to the free base by treatment with a suitable base. Conversely, preparation of basic salts of acid moieties that may be present on an active agent may be carried out in a similar manner using a pharmaceutically acceptable base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, trimethylamine, or the like. Preparation of esters involves transformation of a carboxylic acid group via a conventional esterification reaction involving nucleophilic attack of an RO⁻ moiety at the carbonyl carbon. Esterification may also be carried out by reaction of a hydroxyl group with an esterification reagent such as an acid chloride. Esters can be reconverted to the free acids, if desired, by using conventional hydrogenolysis or hydrolysis procedures. Amides may be prepared from esters, using suitable amine reactants, or they may be prepared from an anhydride or an acid

chloride by reaction with ammonia or a lower alkyl amine. Prodrugs and active metabolites may also be prepared using techniques known to those skilled in the art or described in the pertinent literature. Prodrugs are typically prepared by covalent attachment of a moiety that results in a compound that is therapeutically inactive until modified by an individual's metabolic system.

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Other derivatives and analogs of the active agents may be prepared using standard techniques known to those skilled in the art of synthetic organic chemistry, or may be deduced by reference to the pertinent literature. In addition, chiral active agents may be in isomerically pure form, or they may be administered as a racemic mixture of isomers

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III. PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS

Oral dosage forms are used to administer the combination of active agents, and include tablets, capsules, caplets, solutions, suspensions, and/or syrups, and may also comprise a plurality of granules, beads, powders, or pellets that may or may not be encapsulated. Such dosage forms are prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts, e.g., in Gennaro, A. R. (ed.), Remington: The Science and Practice of Pharmacy, 20th Edition (Lippincott, Williams and Wilkins, 2000). Tablets and capsules represent the most convenient oral dosage forms, in which cases solid pharmaceutical carriers are employed.

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Tablets may be manufactured using standard tablet processing procedures and equipment. One method for forming tablets is by direct compression of a powdered, crystalline, or granular composition containing the active agent(s), alone or in combination with one or more carriers, additives, or the like. As an alternative to direct compression, tablets can be prepared using wet-granulation or dry-granulation processes. Tablets may also be molded rather than compressed, starting with a moist or otherwise tractable material; however, compression and granulation techniques are preferred.

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In addition to the active agent(s), then, tablets prepared for oral administration using the method of the invention will generally contain other materials such as binders, diluents, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, and the like. Binders are used to impart cohesive qualities to a tablet, and thus ensure that the tablet remains intact after compression. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, waxes, and natural and synthetic gums, e.g., acacia sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, and the like), and Veegum. Diluents are typically necessary to increase bulk so that a practical size tablet is ulti-

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mately provided. Suitable diluents include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Lubricants are used to facilitate tablet manufacture; examples of suitable lubricants include, for example, magnesium stearate, calcium stearate, and stearic acid. Disintegrants are used to facilitate disintegration of the tablet, and are generally starches, clays, celluloses, algins, gums, or crosslinked polymers. Fillers include, for example, materials such as silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose, and microcrystalline cellulose, as well as soluble materials such as mannitol, urea, sucrose, lactose, dextrose, sodium chloride, and sorbitol. Stabilizers are used to inhibit or retard drug decomposition reactions that include, by way of example, oxidative reactions. Surfactants may be anionic, cationic, amphoteric, or nonionic surface active agents.

The dosage form may also be a capsule, in which case the active agent-containing composition may be encapsulated in the form of a liquid or solid (including particulates such as granules, beads, powders, or pellets). Suitable capsules may be either hard or soft, and are generally made of gelatin, starch, or a cellulosic material, with gelatin capsules preferred. Two-piece hard gelatin capsules are preferably sealed, such as with gelatin bands or the like. See, for example, Remington: The Science and Practice of Pharmacy, cited supra, which describes materials and methods for preparing encapsulated pharmaceuticals. If the active agent-containing composition is present within the capsule in liquid form, a liquid carrier is necessary to dissolve the active agent(s). The carrier must be compatible with the capsule material and all components of the pharmaceutical composition, and must be suitable for ingestion.

When two or more active agents are combined in a single pharmaceutical dosage form, possible interactions among the active agents, and among the active agents and the excipients, must be considered. Such consideration is well within the purview of those skilled in the art of pharmaceutical formulation. For example, eprosartan mesylate is acidic and may react with basic compounds or alkali esters in such a way as to cause hydrolysis and/or degradation of other compounds, e.g. moxonidine. The present composition thus encompasses pharmaceutical compositions wherein two or more of the active agents are separated from each other within the pharmaceutical dosage form, by, for example, separating potentially interacting compounds from each other within the pharmaceutical dosage form, as in separate flat layers of a tablet (e.g., a bilayer or trilayer tablet), concentric or other coat-type layers, coated beads or granules (which may be incorporated into a compressed tablet or into a capsule), and/or by using buffers (see, for example, U.S. Pat. No. 6,235,311). It will also be appreciated by those in the art that such dosage forms, wherein two or more active agents are physically separated from the other active agents, can be manufactured so that different active agents will have different release profiles, e.g., if one active agent is formulated with an enteric coating, another active agent is formulated in a sustained release matrix, and the like. Alternatively, non-reactive pharmaceutically active derivatives of one or more of the potentially interacting compounds may be used.

Solid dosage forms, whether tablets, capsules, caplets, or particulates, may, if desired, be coated so as to provide for taste masking and / or delayed release. Dosage forms with delayed release coatings may be manufactured using standard coating procedures and equipment.

5 Such procedures are known to those skilled in the art and described in the pertinent texts, e.g., in Remington, *supra*. Generally, after preparation of the solid dosage form, a delayed release coating composition is applied using a coating pan, an airless spray technique, fluidized bed coating equipment, or the like. Delayed release coating compositions comprise a polymeric material, e.g., cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose propionate

10 phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypopyl methylcellulose succinate, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose acetate succinate, polymers and copolymers formed from acrylic acid, methacrylic acid, and/or esters thereof.

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Sustained release dosage forms provide for drug release over an extended time period, and may or may not be delayed release. Generally, as will be appreciated by those of ordinary skill in the art, sustained release dosage forms are formulated by dispersing a drug within a matrix of a gradually bioerodible (hydrolyzable) material such as an insoluble plastic, a hydro-

20 philic polymer, or a fatty compound, or by coating a solid, drug-containing dosage form with such a material. Insoluble plastic matrices may be comprised of, for example, polyvinyl chloride or polyethylene. Hydrophilic polymers useful for providing a sustained release coating or matrix cellulosic polymers include, without limitation: cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose,

25 cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethyl cellulose phthalate, hydroxypropylcellulose phthalate, cellulose hexahydrophthalate, cellulose acetate hexahydrophthalate, and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, acrylic acid alkyl esters, methacrylic acid alkyl esters, and the like, e.g. copolymers of acrylic acid, methacrylic acid,

30 methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate, with a terpolymer of ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride (sold under the tradename Eudragit RS) preferred; vinyl polymers and copolymers such as polyvinyl pyrrolidone, polyvinyl acetate, polyvinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymers; zein; and shellac, ammoniated shellac, shellac-acetyl

35 alcohol, and shellac n-butyl stearate. Fatty compounds for use as a sustained release matrix material include, but are not limited to, waxes generally (e.g., carnauba wax) and glyceryl tristearate.

IV. UTILITY AND ADMINISTRATION

The methods and compositions of this invention are directed at individuals who are suffering from or being susceptible to hypertension, in particular systolic hypertension, or hypertension associated with metabolic impairment (insulin resistance, hyperglycemia, diabetes mellitus type II, and/or hyperlipidemia) and/or renal impairment and/or heart failure. In particular, the methods and compositions of this invention are directed at individuals who are suffering from hypertension associated diabetes mellitus type and/or at (pre)-diabetic hypertensive patients which need a stringent control of their blood pressure levels.

10

On average, diabetic individuals are twice as likely to have hypertension as non-diabetics. Recent recommendations point towards a tight blood pressure control in hypertensive diabetics, following the UK Prospective Diabetes Study (UKPDS). Tight control of blood pressure in type 2 diabetic patients results in a clinically important reduction in the risk of deaths related to diabetes, complications related to diabetes, progression of diabetic retinopathy and deterioration in visual activity. Type 2 Diabetes most often occurs in overweight or obese adults after the age of 30 and is often preceded by insulin resistance and/or hyperglycemia, which is also related to coronary heart disease. Factors that contribute to insulin resistance and type 2 Diabetes include genetics, obesity, physical inactivity and advancing age, all of which are also major predisposing risks for hypertension and cardiovascular disease. The relationship, therefore, between diabetes, hypertension and microvascular and macrovascular complications is complex.

15

There is a clear need for novel and effective approaches in combination therapy in order to achieve a stringent control of the blood pressure levels to below previously existing target levels. Especially patients with type II diabetes require two or more medications in order to reduce their blood pressure to the proposed low levels. These target blood pressure levels are 130/80 mm Hg in diabetic subjects with proteinuria of up to 1 g/day and 125/75 mm Hg in those with proteinuria in excess of 1 g/day. Many (pre-)diabetic hypertensive individuals who are in a clear need of a stringent control of their blood pressure are not optimally treated for this condition, commonly due to the lack of an effective, safe, and convenient therapy. As therapy would be chronic for (pre)-diabetic hypertensive patients, probably for the life of the patient, it should be simple and convenient for the patient. A high compliance rate for chronic therapy is found when a drug is administered orally once per day.

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In a preferred embodiment of the present invention, the combination of a selective imidazoline receptor agonist and an angiotensin II receptor blocker and optionally the diuretic is comprised within a single unit-dose tablet or capsule for once-daily dosing. The present invention thus addresses a major medical need by providing an effective, safe, simple, and convenient

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way to lower the blood pressure level in hypertensive patients, especially in (pre-) diabetic patients, which has a high probability for patient compliance.

It is strongly preferred that the active agents be administered in a single dosage form, as emphasized above. However, in some cases, a patient may be given each active agent in its own separate dosage form, or a combination of individual "combination" dosage forms containing two or more of the present active agents. When separate dosage forms are used, the selective imidazoline receptor agonist and the angiotensin II receptor blocker and optionally the diuretic can be administered at essentially the same time (concurrently), or at separately staggered times (sequentially). Optimum beneficial effects are achieved when the active blood level concentrations of each active agent are maintained at substantially the same time, meaning that simultaneous drug administration is generally preferred. A single oral dosage form comprising all the active agents is, however, much preferred. Such a dosage form provides convenience and simplicity for the patient, thus increasing the chances for patient compliance, especially in patients who already take multiple medications due to existing heart disease or other diseases.

Since two or even three active agents are being used together in a combination therapy, the potency of each of the agents and the interactive effects achieved by combining them together must also be taken into account. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactically effective dosage amounts.

Preferred oral dosage forms contain a therapeutically effective unit dose of each active agent, wherein the unit dose is suitable for once-daily oral administration. The therapeutically effective unit dose of any particular active agent will depend, of course, on the active agent, the needs of the patient, and on other factors known to the prescribing physician. Those of ordinary skill in the art of pharmaceutical formulation can readily deduce suitable unit doses for various active agents. In general, however, the therapeutically effective unit dosages for each of the active agents are as follows:

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Angiotensin II receptor blocker: approximately 1 mg to approximately 1000 mg of an angiotensin II receptor blocker selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, prazosin, telmisartan and valsartan. Preferably, 100 – 1000 mg, more preferably 200 – 800 mg, most preferably 300 – 600 mg of Eprosartan.

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Selective imidazoline receptor agonist: approximately 0.05 mg to approximately 20 mg of an selective imidazoline receptor agonist selected from the group consisting of moxonidine, rilmenidine, LNP-509, S-23515, PMS-812, PMS-847 and BU-98008. Preferably, 0.1 – 0.6 mg, more preferably 0.2 – 0.4 mg of Moxonidine.

Diuretic: optionally, approximately 1 mg to approximately 500 mg of the diuretic, preferably 5 – 50 mg of hydrochlorothiazide.

5 In a particularly preferred embodiment, the active ingredients are as follows:

600 mg of Eprosartan

0.2 mg of Moxonidine

In a particularly preferred embodiment, the active ingredients are as follows:

10 600 mg of Eprosartan

0.3 mg of Moxonidine

In a particularly preferred embodiment, the active ingredients are as follows:

600 mg of Eprosartan

15 0.4 mg of Moxonidine

In a particularly preferred embodiment, the active ingredients are as follows:

400 mg of Eprosartan

0.2 mg of Moxonidine

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In a particularly preferred embodiment, the active ingredients are as follows:

400 mg of Eprosartan

0.3 mg of Moxonidine

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In a particularly preferred embodiment, the active ingredients are as follows:

400 mg of Eprosartan

0.4 mg of Moxonidine

In a particularly preferred embodiment, the active ingredients are as follows:

30 600 mg of Eprosartan

0.4 mg of Moxonidine

12.5 mg of Hydrochlorothiazide

In a particularly preferred embodiment, the active ingredients are as follows:

35 600 mg of Eprosartan

0.4 mg of Moxonidine

25 mg of Hydrochlorothiazide

The formulations of the invention will be administered for as long as the patient suffers from or is susceptible to hypertension, in particular systolic hypertension, or hypertension associated with metabolic impairment (insulin resistance, hyperglycemia, diabetes mellitus type II, and/or hyperlipidemia) and/or renal impairment and/or heart failure; very likely, this will be for a prolonged period and possibly for the life of the patient. Administration for at least one to two weeks is required for minimal benefit to be achieved. In addition to the preferred formulations designed for daily dosing, sustained release forms of such formulations may be employed, which may provide for dosing biweekly, weekly, monthly, or the like.

V. PACKAGED KITS

In another embodiment, a packaged kit is provided that contains a plurality of oral dosage forms for self administration; a container means, preferably sealed, for housing the dosage forms during storage and prior to use; and instructions for a patient to carry out drug administration. The instructions will typically be written instructions on a package insert, a label, and/or on other components of the kit, and the oral dosage forms are as described herein. Each dosage form may be individually housed, as in a sheet of a metal foil-plastic laminate with each dosage form isolated from the others in individual cells or bubbles, or the dosage forms may be housed in a single container, as in a plastic bottle. The present kits will also typically include means for packaging the individual kit components, i.e., the dosage forms, the container means, and the written instructions for use. Such packaging means may take the form of a cardboard or paper box, a plastic or foil pouch, etc.

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the foregoing description as well as the examples that follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages, and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

FIGURES

Figure 1: Effect of oral treatment with moxonidine (Mox, 1 mg/kg), eprosartan (Epro, 3 mg/kg) or their combination on the systolic blood pressure of renal hypertensive rats 6 weeks after narrowing of the right renal artery.

Figure 2: Effect of oral treatment with moxonidine (Mox, 1 mg/kg), eprosartan (Epro, 3 mg/kg) or their combination on the diastolic blood pressure of renal hypertensive rats 6 weeks after narrowing of the right renal artery.

5

EXPERIMENTAL

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of pharmaceutical formulation and the like, which are within the skill of the art.

10 Such techniques are fully explained in the literature. In the following examples, efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.) but some experimental error and deviation should be accounted for. Unless otherwise indicated, temperature is in degrees Celsius and pressure is at or near atmospheric pressure at sea level. All reagents were obtained commercially unless otherwise indicated.

15

EXAMPLE 1

A tablet formulation was produced by a high shear Fielder granulation. The purified water
20 is added during granulation to form the dihydrate of the Eprosartan salt. The film coat is applied to a level of approximately 2.5 – 4 % of core weight.

	Ingredients	Amounts (& w/w)
25	<u>Intragranular</u>	
	Eprosartan mesylate (400 mg as zwitterion)	61.32
	Lactose, Monohydrate (Impalpable) NF	3.59
	Microcrystalline Cellulose (Avicel PH102) NF	3.59
30	Pregelatinized starch (Starch 1551) USP	3.59
	Purified water USP	4.36
	<u>Extragranular</u>	
	Croscarmellose sodium (Ac-Di-Sol)	4.00
35	Microcrystalline cellulose (Avicel PH102) NF	18.74
	Moxonidine (0.4 mg)	0.06
	Magnesium stearate	0.75
40	Tablet core weight	100
	Film coating: Opadry Blue OY-S-20900	

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EXAMPLE 2 – PHARMACOLOGICAL ASSAY FOR HYPERTENSION

1. Introduction

5 The effect of a combined administration of moxonidine, as an example for an selective imidazoline I₁-receptor agonist, and eprosartan, as an example for an angiotensin II AT₁ receptor antagonist, was analysed by measuring their influence on the blood pressure and heart rate of 2K1C (two-kidney one-clip) hypertensive rats. The “two-kidney one-clip” technique results in renal ischemia and in the development of hypertension. In the rat, this technique produces
10 chronic changes, similar to those in human beings with unilateral renal artery stenosis. 2K1C rats represent a pressure overload model of hypertension, characterized by the activation of the renin-angiotensin aldosterone system (RAAS) and peripheral vasoconstriction. This model is widely used as a high renin model of hypertension for the evaluation of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists (ARBs).

15

2. Methods

Animals: Male Sprague-Dawley CFY rats were used. Animals were fed commercial laboratory rat food pellet and allowed to drink tap water ad libitum throughout the experiments.

20

Two-kidney one-clip hypertension: Under ether anesthesia an incision was made on the right side of the dorsolvertebrocostal angle. After light exterioration of the right kidney a silver clip was placed on the renal artery, close to its origin from the aorta. The left kidney was not disturbed.

25

Measurement of blood pressure and heart rate: Blood pressure and heart rate were measured by the tail cuff method (Model 229, IITC Inc., CA, USA) from the 1st week after clipping the renal artery, once a week for 6 weeks. At the time of blood pressure measurements the animals were minimally warmed to an ambient temperature of 29 °C using a thermostated
30 warming chamber.

Experimental protocol: Animals developing stable hypertension during the 6-week-study period were used for the drug treatments. 12 animals with established hypertension were used for each treatment group as follows:

35

- Vehicle
- Moxonidine 1 mg/kg
- Eprosartan 3 mg/kg
- Moxonidine 1 mg/kg + Eprosartan 3 mg/kg

The animals were treated orally and the blood pressure was measured 30 min, 1 h, 2 h and 4 hours there after. Different treatments were applied randomly during the day.

Statistical analysis: Parameters were expressed as mean $\pm$ standard error of the mean (SE) and after analysis of variance were compared by means of the modified 't'-statistical method of Wallenstein et al. [Wallenstein S et al. (1980) Circ. Res. 47:1-9].

3. Results

The effects of moxonidine (1 mg/kg), eprosartan (3 mg/kg) and their combination on the blood pressure are demonstrated in Table 1 and Figures 1 and 2.

Moxonidine treatment caused a significant decrease in blood pressure of renal hypertensive rats, showing a maximal effect 2 hours after the administration of the drug (Table 1; 16 % and 19 % decrease in the systolic and diastolic blood pressure, respectively). There was a moderate recovery of blood pressure 4 hours after treatment.

Administration of eprosartan also significantly decreased the blood pressure (Table 1), with maximal effects of 19 % and 21 % (systolic and diastolic blood pressure, respectively) 2 hours after the treatment.

Administration of the two drugs together resulted in a significantly stronger decrease in both the systolic and diastolic blood pressure compared to the blood pressure effects of Moxonidine and Eprosartan alone (Table 1, Figures 1 and 2), reaching maximum values 4 hours after administration (26 % and 33 % decrease in systolic and diastolic blood pressure, respectively).

Heart rate did not change significantly during the experiment in the vehicle treated animals. None of the treatments induced significant alterations in the heart rate during the investigations (Table 2).

Table 1:

Effect of oral treatment with moxonidine (Mox), eprosartan (Epro) or their combination on the blood pressure of renal hypertensive rats 6 weeks after narrowing of the right renal artery ('two kidney - one clip hypertension').

5

Group	BW (g)	Blood Pressure	Before surgery	After surgery				
				6 th week	After drug administration			
					30 min	1 h	2 h	4 h
Control	351±8.6	SBP	121±4.0	145±2.7	142±5.4	143±4.2	140±4.5	143±4.7
		MBP	97±1.4	133±2.4	126±5.2	129±3.3	123±3.9	130±4.9
		DBP	84±1.0	127±2.5	118±5.0	122±2.9	114±4.2	123±5.1
Mox 1 mg/kg	346±4.4	SBP	121±3.7	145±1.8	136±3.6	130±2.1 *	122±3.5 *	129±3.1
		MBP	96±1.0	130±1.3	124±3.2	117±2.6 *	107±4.2 *	116±3.5
		DBP	84±1.2	124±1.6	118±3.1	110±3.3*	100±4.8	109±3.8
Epro 3 mg/kg	347±8.6	SBP	125±3.3	147±1.9	131±2.8	131±3.1 *	119±4.5 *	125±6.1 *
		MBP	98±1.0	131±1.6	117±2.8	116±2.5 *	105±4.6 *	112±6.6 *
		DBP	84±1.0	124±2.0	111±2.8	109±2.3 *	98±4.8 *	106±6.6 *
Mox 1 mg/kg + Epro 3 mg/kg	345±5.3	SBP	124±3.6	146±2.1	130±3.8	122±3.5 *	110±3.1 *	108±4.7 *§#
		MBP	97±1.3	134±1.9	116±3.8	106±2.8 *§#	98±3.6 *	94±4.8 *§#
		DBP	84±0.9	129±2.0	109±3.9	98±3.1 *§#	92±4.4 *	87±4.9 *§#

BW = body weight of the animals; SBP = systolic blood pressure (mmHg); MBP = mean blood pressure (mmHg); DBP = diastolic blood pressure (mmHg).

Results are mean ± SE of 12 animals.

- 10 Asterisks denote statistically significant difference ($P < 0.05$) compared to the * control (vehicle treated), § moxonidine or # eprosartan treated animals.

Table 2:

- 15 Effect of oral treatment with moxonidine (Mox), eprosartan (Epro) or their combination on the heart rate (beats/min) of renal hypertensive rats 6 weeks after narrowing of the right renal artery ('two kidney - one clip hypertension'). (For details see table 1)

Group	n	Before surgery	After surgery				
			6 th week	After drug administration			
				30 min	1 h	2 h	4 h
Control	12	378±6.2	358±7.1	361±5.3	361±6.8	367±5.4	374±4.7
Mox 1mg/kg	12	386±8.1	371±7.6	383±5.3	376±6.7	368±5.9	384±6.0
Epro 3mg/kg	12	385±7.7	373±6.4	370±6.9	375±7.4	378±4.3	376±5.2
Mox 1mg/kg + Epro 3mg/kg	12	368±7.0	361±7.4	374±5.3	363±12.4	374±4.6	377±6.3

4. Conclusion

Both moxonidine and eprosartan significantly decreased the blood pressure of renal hypertensive (2K1C) rats. The combination of the two drugs shows significant synergistic effects.

5 The combination produces surprisingly strong blood pressure lowering effects compared to the single compounds. The marked antihypertensive effect of the combination does suggest that it is reasonable to use smaller doses of the individual compounds to achieve the same antihypertensive effect with less adverse side effects.

10 These results were confirmed by an independently later published clinical study on 10 human patients suffering from hypertensive chronic renal failure [Neumann J et al. (2003) "Eprosartan combined with moxonidine normalizes sympathetic hyperactivity in hypertensive chronic renal failure patients" J Am Soc Nephrol; 14:20A]. It was shown that the combined treatment of Eprosartan with Moxonidine reduced sympathetic activity to normal levels.

15

EXAMPLE 3 – PHARMACOLOGICAL ASSAY FOR GLUCOSE TOLERANCE

1. Introduction

20

The effect of a combined administration of Moxonidine as an example for a selective Imidazoline I1 receptor agonist and Eprosartan as an example for an Angiotensin II At1 receptor antagonist was analyzed by measuring their influence on plasma glucose level in "Zucker rats". The "Zucker rat" is a model of impaired glucose tolerance and is widely used to analyze compound effects on glucose tolerance.

25

2. Methods

Animals: Male Zucker rats (HsdOla fa/fa) from Harlan were used in the experiments. The animals were fed commercial lab chow and had unlimited access to tap water throughout the experiment.

30

Experimental protocol: Animals were treated for 3 weeks with either vehicle or the active compounds. Moxonidine was applied via the drinking water. Eprosartan was administered daily into the stomach via a cannula. Ten animals were used in each of the following treatment groups:

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- Vehicle
- Moxonidine 1 mg/kg

- Moxonidine 1 mg/kg + Eprosartan 3 mg/kg
- Moxonidine 1 mg/kg + Eprosartan 30 mg/kg
- Moxonidine 1 mg/kg + Eprosartan 100 mg/kg

5 At the end of the drug treatment period the animals were subjected to an oral glucose tolerance test. Animals were given a solution containing 2 g glucose via a cannula into the stomach. Blood samples were drawn before and at 30, 60, 90, and 120 minutes after the glucose load by tail vein cannulation and analyzed for plasma glucose levels.

10 Statistical analysis: Parameters were expressed as mean $\pm$ standard error of the mean (SE) and after analysis of variance were compared by means of T-Test.

3. Results

15 The effects of Moxonidine (1 mg/kg) alone and in combination with increasing doses (3 mg/kg; 30 mg/kg; 100 mg/kg) of Eprosartan are presented in Table 3.

Moxonidine treatment resulted in a significant reduction in plasma glucose levels at 60 and 90 minutes after the oral glucose challenge.

20

Combined administration of Moxonidine (1 mg/kg) and Eprosartan caused a further dose-dependent reduction in plasma glucose level. This further reduction was significant at 90 and 120 minutes in the group dosed with 30 mg Eprosartan and at 30, 90, and 120 minutes in the group receiving 100 mg/kg Eprosartan in addition to Moxonidine.

25

4. Conclusion

30 The above presented experiments showed that even in view of the well-known anti-hyperglycemic effects of Moxonidine, the combination of Moxonidine with Eprosartan showed further dose-dependent reduction of the plasma glucose levels, thereby showing synergistic effects. The drug combination has surprisingly strong plasma glucose lowering effects in a model for impaired glucose tolerance compared to the single compounds. This additional characteristic next to the marked antihypertensive effect of the drug combination makes it ideally suited for the treatment of hypertensive patients suffering from metabolic impairment, i.e. insulin
35 resistance, hyperglycemia, and/or diabetes mellitus.

Table 3:

Effect of oral treatment with moxonidine (Mox) or the combined treatment with moxonidine (Mox) and eprosartan (Epro) on the plasma glucose levels of Zucker rats after 30, 60, 90 or 120 min after glucose challenge.

5

Group	N	Minutes after glucose challenge					AUC (mg/dl*min)
		0	30	60	90	120	
Control	10	93 ± 4	269 ± 8	260 ± 17	288 ± 26	283 ± 26	30161±1712
1 mg/kg Mox	10	97 ± 6	240 ± 15	211 ± 15 *	221 ± 11 *	224 ± 14	24960±1268 *
1 mg/kg Mox + 3 mg/kg Epro	10	75 ± 3 * §	226 ± 25	192 ± 17 *	224 ± 21	222 ± 17	23729±2097 *
1 mg/kg Mox + 30 mg/kg Epro	10	90 ± 12	225 ± 9 *	205 ± 13 *	182 ± 11 * §	181 ± 12 * §	22415±911 *
1 mg/kg Mox + 100 mg/kg Epro	10	87 ± 3	159 ± 12 * §	177 ± 10 *	181 ± 14 * §	156 ± 10 * §	19172±1160 * §

Glucose levels are given in mg/dl. The data represent means ± SE of 10 animals.

AUC = "area under the curve"

10 Arterisks denote statistically significant differences (p<0.05) compared to control * vehicle-treated or § Moxonidine-treated animals (T-test).

From the aforementioned pharmacological tests it becomes clear, that the combination of a selective imidazoline receptor agonist such as Moxonidine together with an angiotensin II
15 receptor blocker such as Eprosartan provides a potential novel treatment method for hypertensive patients in need of a stringent control of their blood pressure levels to below previously existing target levels.

Furthermore, there is evidence that the use of ARBs may prevent the occurrence of dia-
20 betes in hypertensive individuals and will reduce cardiovascular events in diabetics. ARBs have been shown to slow the progression of renal disease in diabetic patients and prevent the occurrence of end-stage renal disease when compared to treatment regimens that do not include an ARB. On the other hand, Moxonidine is known to beneficially influence metabolism in diabetic patients. Moxonidine is able to reduce plasma insulin already in patients with impaired glucose
25 tolerance where fasting plasma glucose is not yet influenced.

Furthermore, a complementary pharmacological activity of the combination Moxonidine/Eprosartan is expected particularly in low renin hypertension and in systolic hyper-
tension. The low response rate of Eprosartan in spontaneously hypertensive rats (SHR), a
30 model for low renin hypertension, will be increased by the combination with Moxonidine which shows excellent activity in SHR.

ARBs are described to inhibit catecholamine outflow from sympathetic nerve terminals by blockade of presynaptic AT1 receptors. This effect was especially described for Eprosartan [Ohlstein EH et al. (1997) Pharmacology 55:244-251]. This pronounced peripheral sympatholytic activity of Eprosartan coupled with the central sympatholytic properties of Moxonidine
5 appears to reveal additive and/or synergistic effects particularly in systolic hypertension and heart failure.

Furthermore, hypertension is often associated with metabolic impairment (insulin resistance, hyperglycemia, diabetes mellitus type II, and/or hyperlipidemia) and both are linked by
10 excessive activity of the sympathetic nervous system. Thus, in a further aspect of the present invention, the dual peripheral/central sympatholytic effects of the combination Moxonidine/Eprosartan represent an ideal drug combination for the treatment of hypertension associated with insulin resistance, hyperglycemia and/or diabetes mellitus. This was proven by the combined administration of Moxonidine with Eprosartan which showed an additional synergistic effect on the plasma glucose levels.
15

Stimulation of both, the SNS and RAAS reveals neurohormonal activation (increase of catecholamines, renin, angiotensin II and aldosterone plasma levels) and consequently promotes structural remodelling of vascular, cardiac and renal tissue as seen in chronic heart failure and renal disease. Therefore optimal drug treatment for end organ disease would attenuate
20 both the SNS and RAAS. Moxonidine, through activation of Imidazoline I1 receptors in both the brain stem and the kidneys, at sub-antihypertensive doses attenuates sympathetic over-activity and consequently ameliorates glomerulosclerosis, proteinuria and renal remodelling in rats whereas Angiotensin receptor blockers like Eprosartan are known to reduce cardiac, renal and
25 vascular structural and functional damage due to blockade of the AT1 receptor.

In conclusion, the present invention provides with the combined administration of Moxonidine and Eprosartan within one pharmaceutical preparation a novel highly effective treatment method of hypertension, particularly systolic hypertension and hypertension associated with metabolic and renal impairment and heart failure, because this combination inhibits
30 the two main pressure systems SNS and RAAS and consequently neurohormonal activation. This profile of action fulfills the requirements set up for an ideal combination therapy, i.e. complementary mechanism of action and enhanced efficacy. The excellent tolerability of both Moxonidine and Eprosartan is expected to be maintained given that both drugs possess excellent safety profiles.
35

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WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising moxonidine or a pharmaceutically acceptable salt thereof as a selective I1 imidazoline receptor agonist and eprosartan or a pharmaceutically acceptable salt thereof as an angiotensin II receptor blocker and a pharmaceutically acceptable carrier.
2. The pharmaceutical composition according to claim 1 wherein the composition consists of a fixed combination of moxonidine or a pharmaceutically acceptable salt thereof and eprosartan mesylate and a pharmaceutically acceptable carrier.
3. The pharmaceutical composition according to claim 2, wherein the moxonidine is present in a dose of 0.05-1 mg.
4. The pharmaceutical composition according to claim 3 wherein the moxonidine is present in a dose of 0.2-0.6 mg.
5. The pharmaceutical composition according to any one of claims 2 - 4, wherein the eprosartan is present in a dose of 100-1000 mg.
6. The pharmaceutical composition of claim 5 wherein the eprosartan is present in a dose of 300-600 mg.
7. The pharmaceutical composition according to any one of claims 2 to 6, wherein the moxonidine is present in a dose of 0.2 mg and the eprosartan is present in a dose of 600 mg.
8. The pharmaceutical composition according to any one of claims 2 to 6, wherein the moxonidine is present in a dose of 0.4 mg and the eprosartan is present in a dose of 600 mg.
9. The pharmaceutical composition according to any one of claims 2 to 8, wherein the pharmaceutical composition is in the form of a tablet consisting mainly of eprosartan and further of moxonidine homogeneously distributed within the eprosartan.
10. The pharmaceutical composition according to any one of claims 2 to 8, wherein the pharmaceutical composition is in the form of a coated tablet wherein a small moxonidine containing core is coated with an eprosartan containing blend.
11. The pharmaceutical composition according to any one of claims 2 to 8, wherein the pharmaceutical composition is in the form of an eprosartan containing tablet core coated with a thin layer comprising the moxonidine.
12. The pharmaceutical composition according to any one of claims 2 to 8,

wherein the pharmaceutical composition is in the form of a bilayer tablet.

13. The pharmaceutical composition according to any one of claims 2 to 8, wherein the pharmaceutical composition is in the form of a trilayer tablet.

14. The pharmaceutical composition according to any one of claims 1 - 13 wherein the composition additionally comprises a diuretic.

15. The pharmaceutical composition according to claim 14 wherein the diuretic is hydrochlorothiazide.

16. Use of a therapeutically effective amount of a moxonidine as a selective I1 imidazoline receptor agonist and of a therapeutically effective amount of eprosartan as an angiotensin II receptor blocker for the manufacture of a medicament for the treatment of a subject suffering from or being susceptible to hypertension.

17. Use according to claim 16 wherein the hypertension is systolic hypertension.

18. Use according to any one of claims 16 and 17, wherein the eprosartan is present in an amount in a daily dosage range from 100-1000 mg.

19. Use according to claim 18 wherein the eprosartan is present in an amount in a daily dosage range from 300-600 mg.

20. Use according to claim 16 or 17, wherein the moxonidine is present in an amount in a daily dosage range from 0.05-1 mg.

21. Use according to claim 20 wherein the moxonidine is present in an amount in a daily dosage range from 0.2-0.6 mg.

22. Use according to claim 16 or 17, wherein the eprosartan is present in an amount in a daily dosage of 600 mg, and the moxonidine is present in an amount in a daily dosage of 0.2 or 0.4 mg.

23. Use according to any one of claims 16 and 18 to 22, wherein the subject suffers from or is susceptible to hypertension associated with metabolic impairment.

24. Use according to claim 23 wherein the hypertension is systolic hypertension.

25. Use according to claim 23 or 24, wherein the metabolic impairment is characterized by insulin resistance, hyperglycemia and/or hyperlipidemia.

26. Use according to any one of claims 16, 18 to 23 and 25, wherein the subject

is suffering from or being susceptible to hypertension associated with diabetes mellitus type II.

27. Use according to claim 26 wherein the hypertension is systolic hypertension.

28. Use according to any one of the claims 16, 18 – 23, 25 and 26, wherein the hypertension is further associated with renal impairment.

29. Use according to claim 28 wherein the hypertension is systolic hypertension.

30. Use according to any one of claims 16, 18 – 23, 25, 26, and 28, wherein the hypertension is further associated with heart failure.

31. Use according to claim 30 wherein the hypertension is systolic hypertension.

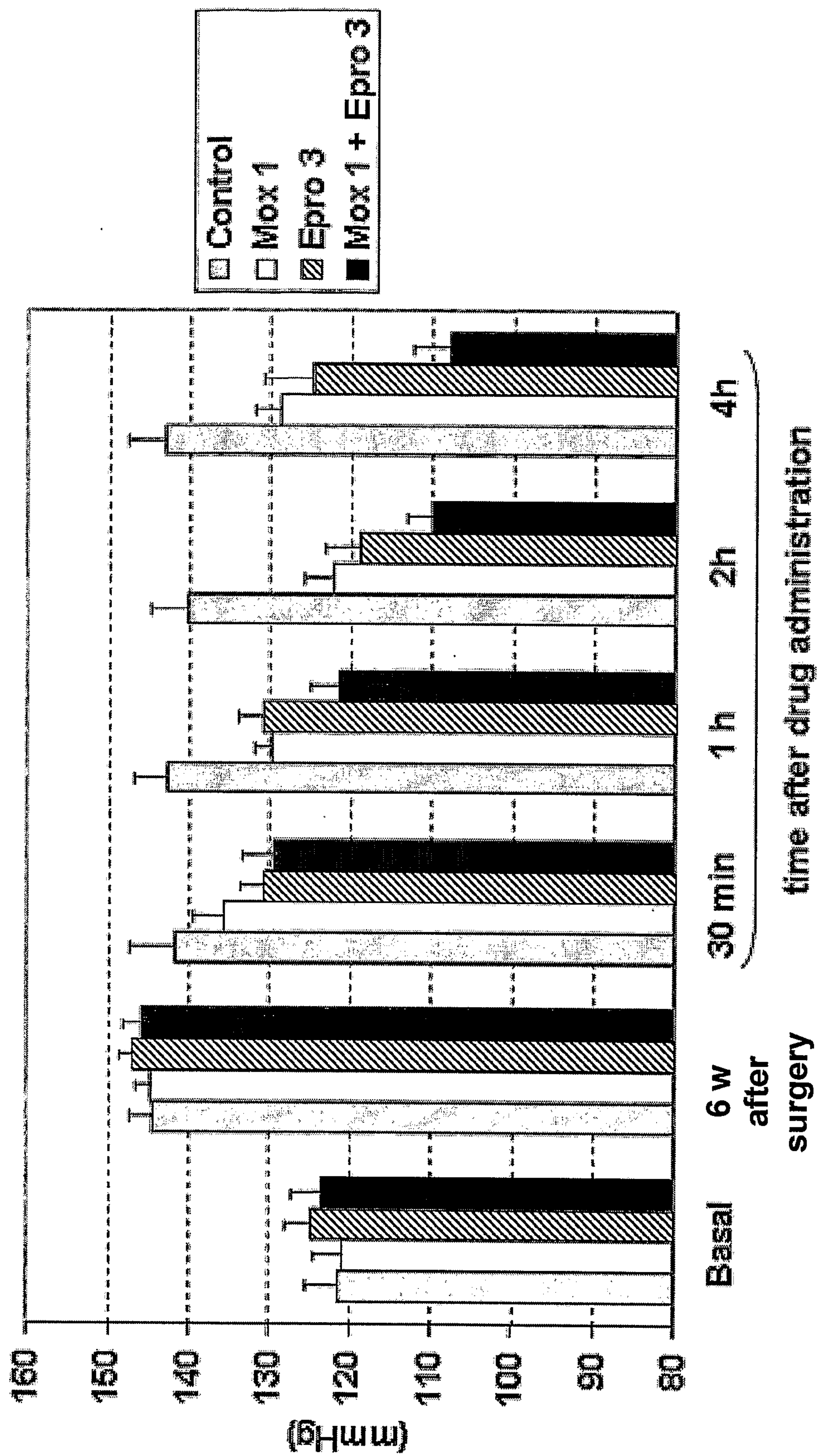
32. Use according to any one of claims 16 to 31, wherein the medicament further comprises a therapeutically effective amount of a diuretic.

33. Use according to claim 32 wherein the diuretic is hydrochlorothiazide.

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Fig. 1

Systolic blood pressure



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Fig. 2 **Diastolic blood pressure**