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(54) **METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION**

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(58) **Field of Classification Search** 514/533, 514/381, 561, 563
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,610,816 A	9/1986	Berger	549/452
4,722,810 A	2/1988	Delaney et al.	260/402.5
4,740,499 A	4/1988	Olins	514/13
4,749,688 A	6/1988	Haslanger et al.	514/19
4,929,641 A	5/1990	Haslanger et al.	514/506
5,217,996 A	6/1993	Ksander	514/533
5,223,516 A	6/1993	Delaney et al.	514/339
5,273,990 A	12/1993	De Lombaert	514/381
5,294,632 A	3/1994	Erion et al.	514/381
5,399,578 A *	3/1995	Buhlmyer et al.	514/381
5,520,522 A	5/1996	Rathore et al.	417/322

FOREIGN PATENT DOCUMENTS

EP	0 342 850	11/1989
EP	0 343 911	11/1989
EP	0 361 365	4/1990
EP	0 443 983	8/1991
EP	0 498 361 A2	8/1992
EP	0 636 621	2/1995
EP	0 726 072 A2	8/1996
EP	0636621 B1	3/1997
GB	2 218 983	11/1989
WO	WO 90/09374	8/1990
WO	WO 92/14706	9/1992
WO	WO 93/09101	5/1993

WO	WO 01/74348 A2	10/2001
WO	WO 02/06253	1/2002
WO	WO 02/092622 A2	11/2002
WO	WO 03/066606	8/2003

OTHER PUBLICATIONS

Almeida et al., "Clearance Function of Type C Receptors of Atrial Natriuretic Factor in Rats", *Am J Physiol*, vol. 256, pp. R469-R475 (1989).

Bazil, Krulan and Webb, "Telemetric Monitoring of Cardiovascular Parameters in Conscious Spontaneously Hypertensive Rats", *J Cardiovasc Pharmacol*, vol. 22, pp. 897-905 (1993).

Consensus Trial Study Group, "Effects of Enalapril on Mortality in Severe Congestive Heart Failure", *N Eng J Med*, vol. 316, No. 23, pp. 1429-1435 (1987).

Stephenson et al., The hydrolysis of a-human atrial natriuretic peptide by pig kidney microvillar membranes is initiated by endopeptidase-24.11 *Biochem J*, vol. 243, pp. 183-187(1987).

Erdős, "Angiotensin I Converting Enzyme and the Changes in Our Concepts Through the Years"—Lewis K. Dahl Memorial Lecture, *Hypertension*, vol. 16, No. 4, pp. 363-370 (1990).

(Continued)

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(57) **ABSTRACT**

The invention relates a pharmaceutical composition comprising a combination of:

- (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof; and
- (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable carrier and to a method for the treatment or prevention of a condition or disease

selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's, glaucoma and stroke, comprising administering a therapeutically effective amount of the pharmaceutical composition to a mammal in need thereof.

OTHER PUBLICATIONS

Intengan, Park and Schiffrin, "Blood Pressure and Small Arteries in DOCA-Salt-Treated Genetically AVP-Deficient Rats", *Hypertension*, vol. 34, No. 4, Part 2, pp. 907-913 (1999).

Intengan, Thibault, Li and Schiffrin, "Resistance Artery Mechanics, Structure, and Extracellular Components in Spontaneously Hypertensive Rats", *Circulation*, vol. 100, No. 22, pp. 2267-2275 (1999).

Needleman et al., "Biochemical Pharmacology of Atrial Peptides", *Annu Rev Pharm Tox*, vol. 29, pp. 23-54 (1989).

Stephenson and Kenny, "Metabolism of Neuropeptides", *Biochem J*, vol. 241, pp. 237-247 (1987).

Sybertz et al., "SCH 39370, a Neutral Metalloendopeptidase Inhibitor, Potentiates Biological Responses to Atrial Natriuretic Factor and Lowers Blood Pressure in Desoxycorticosterone Acetate-Sodium Hypertensive Rats", *J Pharmacol Exp Ther*, vol. 250, No. 2, pp. 624-631 (1989).

Sybertz et al., "Atrial Natriuretic Factor-Potentiating and Antihypertensive Activity of SCH 34826", *Hypertension*, vol. 15, No. 2, pp. 152-161 (1990).

Williford, Sharma, Korth and Sheu, "Spatial Heterogeneity of Intracellular Ca^{2+} Concentration in Nonbeating Guinea Pig Ventricular Myocytes", *Circ Res*, vol. 66, No. 1, pp. 241-249 (1990).

Zannad, "The Emerging Role of ACE Inhibitors in the Treatment of Cardiovascular Disease", *J Cardiovasc Pharmacol*, vol. 15, Suppl. 2, pp. S1, S5 (1990).

Caplus Abstract AN 1986:573042—Taub et al., f ZA8400670, Sep. 25, 1985.

Caplus Abstract AN 1995: 931230- Sugano et al., JP 07157459, Jun. 20, 1995.

Caplus Abstract AN 1995:412660—Yamada et al., JP 06234754, Aug. 23, 1994.

Matsumoto et al., "Blockade of renin-angiotensin system and enhancement of atrial natriuretic peptide with neutral endopeptidase inhibition cause natriuresis in congestive heart failure and renal dysfunction in conscious dogs", *JASN, Hemodynamics and Vascular Regulation*, p. 517, Sep. 1993).

* cited by examiner

METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

BACKGROUND OF THE INVENTION

The renin angiotensin system is a complex hormonal system comprised of a large molecular weight precursor, angiotensinogen, two processing enzymes, renin and angiotensin converting enzyme (ACE), and the vasoactive mediator angiotensin II (Ang II). See *J. Cardiovasc. Pharmacol.*, Vol. 15, Suppl. B, pp. S1-S5 (1990). The enzyme renin catalyzes the cleavage of angiotensinogen into the decapeptide angiotensin I, which has minimal biological activity on its own and is converted into the active octapeptide Ang II by ACE. Ang II has multiple biological actions on the cardiovascular system, including vasoconstriction, activation of the sympathetic nervous system, stimulation of aldosterone production, anti-natriuresis, stimulation of vascular growth and stimulation of cardiac growth. Ang II functions as a pressor hormone and is involved in the pathophysiology of several forms of hypertension.

The vasoconstrictive effects of angiotensin II are produced by its action on the non-striated smooth muscle cells, the stimulation of the formation of the adrenergic hormones epinephrine and norepinephrine, as well as the increase of the activity of the sympathetic nervous system as a result of the formation of norepinephrine. Ang II also has an influence on electrolyte balance, produces, e.g., anti-natriuretic and anti-diuretic effects in the kidney and thereby promotes the release of, on the one hand, the vasopressin peptide from the pituitary gland and, on the other hand, of aldosterone from the adrenal glomerulosa. All these influences play an important part in the regulation of blood pressure, in increasing both circulating volume and peripheral resistance. Ang II is also involved in cell growth and migration and in extracellular matrix formation.

Ang II interacts with specific receptors on the surface of the target cell. It has been possible to identify receptor subtypes that are termed, e.g., AT 1- and AT 2-receptors. In recent times great efforts have been made to identify substances that bind to the AT 1-receptor. Such active ingredients are often termed Ang II antagonists. Because of the inhibition of the AT 1-receptor such antagonists can be used, e.g., as anti-hypertensives or for the treatment of congestive heart failure, among other indications. Ang II antagonists are therefore understood to be those active ingredients which bind to the AT 1-receptor subtype.

Inhibitors of the renin angiotensin system are well-known drugs that lower blood pressure and exert beneficial actions in hypertension and in congestive heart failure as described. See, e.g. *N. Eng. J. Med.*, Vol. 316, No. 23, pp. 1429-1435 (1987). A large number of peptide and non-peptide inhibitors of the renin angiotensin system are known, the most widely studied being the ACE inhibitors, which includes the drugs captopril, enalapril, lisinopril, benazepril and spirapril. Although a major mode of action of ACE inhibitors involves prevention of formation of the vasoconstrictor peptide Ang II, it has been reported in *Hypertension*, Vol. 16, No. 4, pp. 363-370 (1990), that ACE cleaves a variety of peptide substrates, including the vasoactive peptides bradykinin and substance P. Prevention of the degradation of bradykinin by ACE inhibitors has been demonstrated, and the activity of the ACE inhibitors in some conditions has been reported in *Circ. Res.*, Vol. 66, No. 1, pp. 242-248 (1990), to be mediated by eleva-

effect of an ACE inhibitor is due solely to prevention of angiotensin formation and subsequent inhibition of the renin angiotensin system.

Neutral endopeptidase (EC 3.4.24.11; enkephalinase; atriopetidase; NEP) is a zinc-containing metalloprotease that cleaves a variety of peptide substrates on the amino terminal side of aromatic amino acids. See *Biochem. J.*, Vol. 241, pp. 237-247 (1987). Substrates for this enzyme include, but are not limited to, atrial natriuretic factors (ANFs), also known as ANPs, brain natriuretic peptide (BNP), met and leu enkephalin, bradykinin, neurokinin A and substance P.

ANPs are a family of vasodilator, diuretic and anti-hypertensive peptides which have been the subject of many recent reports in the literature. See, e.g., *Annu. Rev. Pharm. Tox.*, Vol. 29, pp. 23-54 (1989). One form, ANF 99-126, is a circulating peptide hormone which is released from the heart during conditions of cardiac distension. The function of ANF is to maintain salt and water homeostasis, as well as to regulate blood pressure. ANF is rapidly inactivated in the circulation by at least two processes: a receptor-mediated clearance reported in *Am. J. Physiol.*, Vol. 256, pp. R469-R475 (1989), and an enzymatic inactivation via NEP reported in *Biochem. J.*, Vol. 243, pp. 183-187 (1987). It has been previously demonstrated that inhibitors of NEP potentiate the hypotensive, diuretic, natriuretic and plasma ANF responses to pharmacological injection of ANF in experimental animals. The potentiation of ANF by two specific NEP inhibitors is reported by Sybertz et al., *J. Pharmacol. Exp. Ther.*, Vol. 250, No. 2, pp. 624-631 (1989), and in *Hypertension*, Vol. 15, No. 2, pp. 152-161 (1990), while the potentiation of ANF by NEP in general was disclosed in U.S. Pat. No. 4,749,688. In U.S. Pat. No. 4,740,499, Olins disclosed the use of thiorphan and kela-torphan to potentiate atrial peptides. Moreover, NEP inhibitors lower blood pressure and exert ANF-like effects, such as diuresis and increased cyclic guanosine 3',5'-monophosphate (cGMP) excretion in some forms of experimental hypertension. The anti-hypertensive action of NEP inhibitors is mediated through ANF because antibodies to ANF will neutralize the reduction in blood pressure.

Darrow et al. in European Patent Application No. 498361 disclose treating hypertension or congestive heart failure with a combination of certain Ang II antagonists or certain renin inhibitors with certain NEP inhibitors.

Powell et al. in European Patent Application No. 726072 disclose treating hypertension or congestive heart failure with a combination of the Ang II antagonist 2-butyl-6,7,8,9-tetrahydro-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4,4]nonan-4-one with a NEP inhibitor or a dual acting vasopeptidase inhibitor (single molecular entity with both ACE and NEP inhibitory activities). Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs, such as the heart and kidney. Sustained hypertension can lead as well to an increased occurrence of stroke. Therefore, there is a strong need to evaluate the efficacy of anti-hypertensive therapy, an examination of additional cardiovascular endpoints, beyond those of blood pressure lowering, to get further insight into the benefits of combined treatment.

The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different mode of action does not necessarily lead to combinations with advantageous effects. Accordingly, there is a need for more

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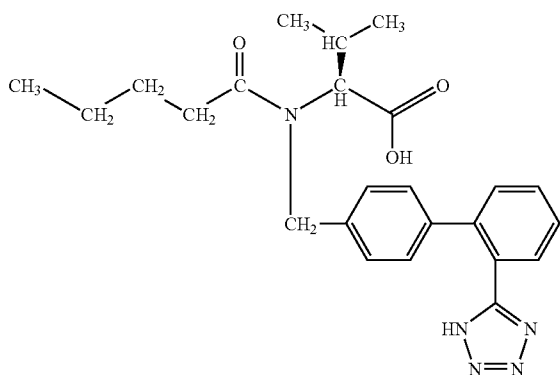
Other objects, features, advantages and aspects of the present invention will become apparent to those of skill from the following description. It should be understood, however, that the following description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following description and from reading the other parts of the present disclosure.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In one aspect, the present invention relates to pharmaceutical combinations comprising valsartan or pharmaceutically acceptable salts thereof and a NEP inhibitor or a pharmaceutically effective salts thereof, optionally in the presence of a pharmaceutically acceptable carrier and pharmaceutical compositions comprising them.

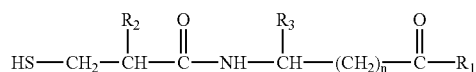
In another embodiment, the present invention relates to methods of treating cardiac and renal related conditions by administration of the pharmaceutical composition comprising valsartan plus a NEP inhibitor.

Valsartan is the AT 1-receptor antagonist (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2;(1H-tetrazol-5-yl)biphenyl-4-yl-methyl]amine of formula (I)



and is disclosed in EP 0443983 A and U.S. Pat. No. 5,399,578, the disclosures of which are incorporated herein in their entirety as if set forth herein.

A NEP inhibitor useful in said combination is a compound of the formula (II)



and pharmaceutically acceptable salts thereof,

wherein

R₂ is alkyl of 1 to 7 carbons, trifluoromethyl, phenyl, substituted phenyl, $-(\text{CH}_2)_1$ to 4-phenyl, or $-(\text{CH}_2)_1$ to 4-substituted phenyl;

R₃ is hydrogen, alkyl of 1 to 7 carbons, phenyl, substituted

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R₁ is hydroxy, alkoxy of 1 to 7 carbons, or NH₂;

n is an integer from 1 to 15; and

the term substituted phenyl refers to a substituent selected from lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, hydroxy, Cl, Br or F.

Preferred selective NEP inhibitors of formula (II) include compounds, wherein

R₂ is benzyl;

R₃ is hydrogen;

n is an integer from 1 to 9; and

R₁ is hydroxy.

Even more preferred selective NEP inhibitors of formula (II) are reported in the literature as SQ 28,603 which is the compound of formula (II), wherein

R₂ is benzyl;

R₃ is hydrogen;

n is one; and

R₁ is hydroxy.

The preparation of the selective NEP inhibitors of formula (II), wherein R₂ is other than trifluoromethyl are disclosed by Delaney et al. in U.S. Pat. No. 4,722,810. The preparation of the selective NEP inhibitors of formula (II), wherein R₂ is trifluoromethyl are disclosed by Delaney et al. in U.S. Pat. No. 5,223,516.

NEP inhibitors within the scope of the present invention include compounds disclosed in U.S. Pat. No. 4,610,816, herein incorporated by reference, including in particular N-[N-[1(S)-carboxyl-3-phenylpropyl]- (S)-phenylalanyl]- (S)-isoserine and N-[N-[(1S)-carboxy-2-phenylethyl]- (S)-phenylalanyl]-β-alanine; compounds disclosed in U.S. Pat. No. 4,929,641, in particular, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; SQ 28603 (N-[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]-β-alanine), disclosed in South African Patent Application No. 84/0670; UK 69578 (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid) and its active enantiomer(s); thiorphan and its enantiomers; retro-thiorphan; phosphoramidon; and SQ 29072 (7-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]-heptanoic acid). Also suitable for use are any pro-drug forms of the above-listed NEP inhibitors, e.g., compounds in which one or more carboxylic acid groups are esterified.

NEP inhibitors within the scope of the present invention also include the compounds disclosed in U.S. Pat. No. 5,217,996, particularly, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester; the compounds disclosed in EP 00342850, particularly (S)-cis-4-[1-[2-(5-indanyloxy)carbonyl]-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; the compounds disclosed in GB 02218983, particularly 3-(1-[6-endo-hydroxymethyl]bicyclo[2,2,1]heptane-2-exo-carbamoyl)cyclopentyl)-2-(2-methoxyethyl)propanoic acid; the compounds disclosed in WO 92/14706, particularly N-(1-(3-(N-t-butoxycarbonyl)-(S)-prolylamino)-2(S)-t-butoxy-carbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester; the compounds disclosed in EP 00343911; the compounds disclosed in JP 06234754; the compounds disclosed in EP 00361365, particularly 4-[[2-(Mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid; the compounds disclosed in WO 90/09374, particularly 3-[1-(Cis-4-carboxycarbonyl-cis-3-

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in JP 07157459, particularly N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; the compounds disclosed in WO 94/15908 particularly N-(1-(N-hydroxycarbonylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine; the compounds disclosed in U.S. Pat. No. 5,273,990 particularly (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino methylphosphonic acid; the compounds disclosed in U.S. Pat. No. 5,294,632 particularly (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; the compounds disclosed in U.S. Pat. No. 5,250,522, particularly β -Alanine, 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl; the compounds disclosed in EP 00636621, particularly N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; the compounds disclosed in WO 93/09101, particularly 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; the compounds disclosed in EP 00590442 particularly ((L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)- β -alanine, N-[N-[(L)-[1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl]-2-phenylethyl]-L-phenylalanyl]-(*R*)-alanine, N-[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(*R*)-alanine, N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester, N-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(*S*)-isoserine, N-(*S*)-[3-mercapto-2-(2-methylphenyl)propionyl]-(*S*)-2-methoxy-(*R*)-alanine, N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(*S*)-isoserine, N-[1-[[1(S)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(*S*)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(*S*)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(*S*)-methionine, N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(*S*)-4-(methylmercapto)methionine, N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[1-(2-carboxy-4-phenylbutyl)-cyclopentane carbonyl]-(*S*)-isoserine, N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(*S*)-methionine ethyl ester, 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amino- ϵ -caprolactam; and the compounds disclosed in WO 93/10773 particularly N-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having at least one acid group, for example, COOH, can also form salts with bases. Corresponding internal salts may furthermore be formed, if a compound comprises, e.g., both a carboxy and an amino group.

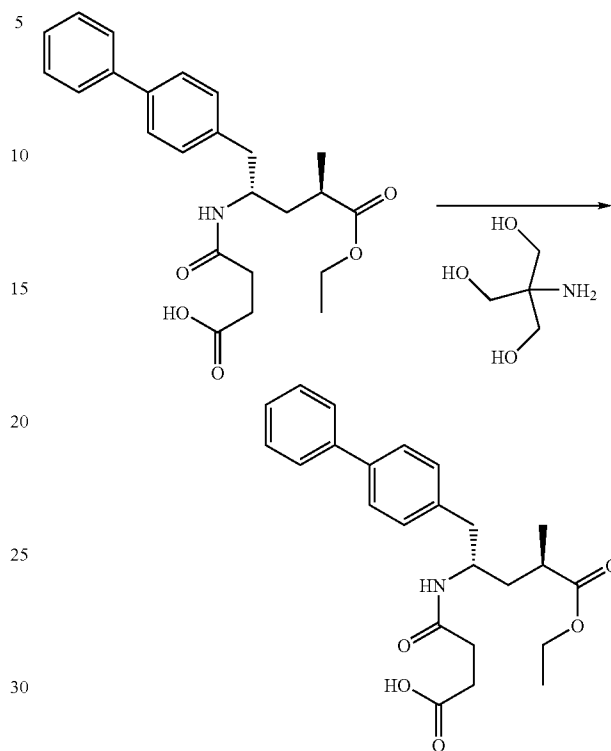
With respect to N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, preferred salts include the sodium salt disclosed in U.S. Pat. No. 5,217,996, the triethanolamine salt and the tris(hydroxymethyl)aminomethane salt. Preparation of the triethanolamine salt and the tris(hydroxymethyl)aminomethane salt may be carried out as follows:

Triethanolamine

To N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylm-

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mmol) of triethanolamine in 1 mL of ethyl acetate. The solid was collected and dried melting at 69-71 ° C.



Tris(hydroxymethyl)aminomethane

To N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester (3.2 g, 7.78 mmol) is added 32 ml of ethyl acetate and 940 mg (7.78 mmol) tris(hydroxymethyl)aminomethane. The suspension is diluted with 45 ml of ethyl acetate and refluxed overnight (~20 hours). The reaction is cooled to 0 ° C., filtered, solid washed with ethyl acetate and dried melting at 114-115 ° C.

It has surprisingly been found that, a combination of valsartan and a NEP inhibitor achieves greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone and promotes less angioedema than is seen with the administration of a vasopeptidase inhibitor alone. Greater efficacy can also be documented as a prolonged duration of action. The duration of action can be monitored as either the time to return to baseline prior to the next dose or as the area under the curve (AUC) and is expressed as the product of the change in blood pressure in millimeters of mercury (change in mmHg) and the duration of the effect (minutes, hours or days).

Further benefits are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used to diminish the incidence of side effects. The combined administration of valsartan or a pharmaceutically acceptable salt thereof and a NEP inhibitor or a pharmaceutically acceptable salt thereof results in a significant response in a greater percentage of treated patients, that is, a greater responder rate results, regardless of the underlying etiology

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