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(54) Composition for the treatment of hypertension and congestive heart failure, containing an angiotensin II antagonist and an endopeptidase inhibitor

(57) Hypertension and/or congestive heart failure are treated with the combination of the angiotensin 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 and a selective neutral endopeptidase inhibitor or a dual acting neutral endopeptidase inhibitor.

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Description

Darrow et al. in European Patent Application 498,361 disclose treating hypertension or congestive heart failure with a combination of an angiotensin II antagonist or a renin inhibitor with a neutral endopeptidase inhibitor.

Matsumoto et al., JASN, September 1993, disclose that the combined therapy of an angiotensin II blocker, DUP753, and a neutral endopeptidase inhibitor, candoxatril, may be useful in the treatment of congestive heart failure and renal failure.

Bernhart et al. in United States Patent 5,270,317 disclose a series of N-substituted heterocyclic derivatives which possess angiotensin II antagonist activity. Bernhart et al. disclose that such compounds can be used in the treatment of various cardiovascular complaints, especially hypertension, heart failure, and venous insufficiency, as well as in the treatment of glaucoma, diabetic retinopathy and various complaints of the central nervous system. It is also disclosed that such compound can be used in combination with other active agents such as tranquilizers, beta-blocking compounds, a calcium antagonist, or a diuretic.

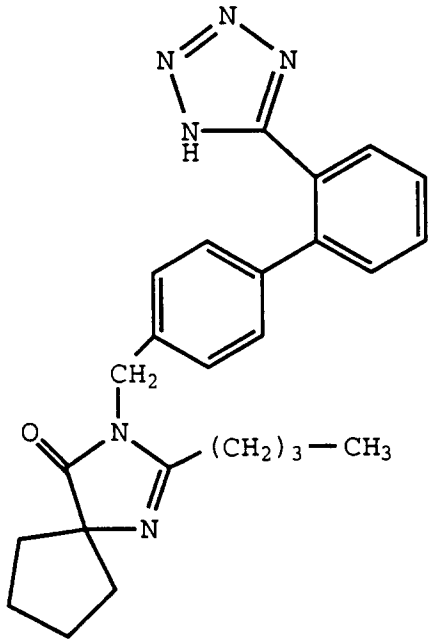
Selective neural endopeptidase inhibitors are taught by Delaney et al. in United States Patents 4,722,810 and 5,223,516 and the use of selective neutral endopeptidase inhibitors alone or in combination with angiotensin converting enzyme inhibitors to treat hypertension are disclosed by Delaney et al. U.K. Patent Application 2,207,351 and by Haslanger et al. in United States Patent 4,749,688. The treatment of congestive heart failure by administration of a combination of a selective neutral endopeptidase inhibitor and an angiotensin converting enzyme inhibitor is disclosed by Seymour in United States Patent 5,225,401.

Compounds possessing both neutral endopeptidase and angiotensin converting enzyme inhibition activity are disclosed by Flynn et al. in United States Patent 5,366,973, European Patent Application 481,522 and PCT Patent Applications WO 93/16103, and WO 94/10193, Warshawsky et al. European Patent Applications 534,363, 534,396 and 534,492, Fournie-Zaluski European Patent Application 524,553, Karanewsky et al. European Patent Application 599,444, Karanewsky European Patent Application 595,610, Robl et al., European Patent Application 629,627, Robl United States Patent 5,362,727 and European Patent Application 657,453.

This invention is directed to the discovery that the angiotensin 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 acts synergistically with a selective neutral endopeptidase inhibitor or a dual acting neutral endopeptidase inhibitor as defined below to reduce cardiac preload and afterload and enhance natriureses. The combination of this angiotensin II antagonist and the selective or dual acting neutral endopeptidase inhibitor produced significant reductions in left ventricular end diastolic pressure (LVEDP) and left ventricular systolic pressure (LVSP) that were greater than those produced by either treatment alone. Thus, the combination of this particular angiotensin II antagonist and the selective or dual acting neutral endopeptidase inhibitor is useful in treating hypertension and/or congestive heart failure.

The angiotensin II antagonist employed within this invention is the compound 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 having the structural formula

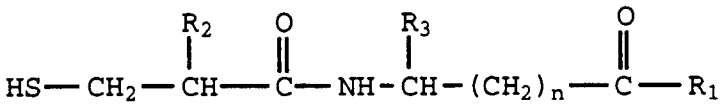
(I)



known in the literature as SR47436, BMS 186295, or irbesartan and pharmaceutically acceptable salts thereof such as the potassium and sodium salts. These angiotensin II antagonists and their method of preparation are disclosed by Bernhart et al. in United States Patent 5,270,317.

The selective neutral endopeptiadase inhibitor for use within this invention are those of the formula

(II)



and pharmaceutically acceptable salts thereof wherein:

R_2 is alkyl of 1 to 7 carbons, trifluoromethyl, phenyl, substituted phenyl, -$(CH_2)_{1\text{ to }4}$-phenyl, or -$(CH_2)_{1\text{ to }4}$-substituted phenyl;

R_3 is hydrogen, alkyl of 1 to 7 carbons, phenyl, substituted phenyl, -$(CH_2)_{1\text{ to }4}$-phenyl, or -$(CH_2)_{1\text{ to }4}$-substituted phenyl;

R_1 is hydroxy, alkoxy of 1 to 7 carbons, or NH_2;

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 are the selective neutral endopeptidase inhibitors of formula II wherein:

R_2 is benzyl;

R_3 is hydrogen;

n is an integer from 1 to 9; and

R_1 is hydroxy.

Most preferred for use in this invention is the selective neutral endopeptidase inhibitor of formula II reported in the literature as SQ 28,603 which is the compound of formula II wherein:

R_2 is benzyl;

R_3 is hydrogen;

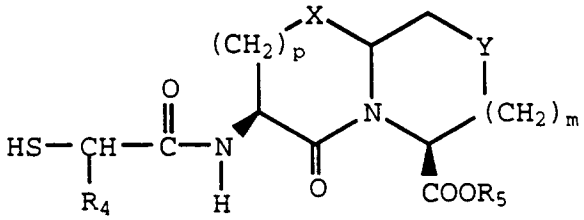
n is one; and

R_1 is hydroxy.

The preparation of the selective neutral endopeptidase inhibitors of formula II wherein R_2 is other than trifluoromethyl are disclosed by Delaney et al. in United States Patent 4,722,810. The preparation of the selective neutral endopeptidase inhibitors of formula II wherein R_2 is trifluoromethyl are disclosed by Delaney et al in United States Patent 5,223,516.

Dual acting neutral endopeptidase inhibitors suitable for use within this invention are compounds which possess both neutral endopeptidase inhibiting activity and angiotensin converting enzyme inhibiting activity. Particularly useful are the dual acting inhibitors of the formula

(III)



and pharmaceutically acceptable salts thereof wherein:

p is one or two;

X is O or S;

m is zero or one;

Y is CH_2, S or O provided that Y is S or O only when m is one;

R_4 is hydrogen, alkyl of 1 to 7 carbons, phenyl, substituted phenyl, -$(CH_2)_{1\text{ to }4}$-phenyl, -$(CH_2)_{1\text{ to }4}$-substituted phenyl, cycloalkyl of 3 to 7 carbons, -$(CH_2)_{1\text{ to }4}$-cycloalkyl of 3 to 7 carbons, heteroaryl, and -$(CH_2)_{1\text{ to }4}$-heteroaryl;

R_5 is hydrogen, alkyl of 1 to 7 carbons, -$(CH_2)_{1\text{ to }4}$-phenyl and -$(CH_2)_{1\text{ to }4}$-substituted phenyl;

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; and

the term heteroaryl refers to monocyclic rings of 5 or 6 atoms containing one or two O and S atoms and/or one to four N atoms provided that the total number of heteroatoms in the ring is 4 or less and bicyclic rings wherein the 5 or 6 membered heteroaryl ring as defined above is fused to a benzene or pyridyl ring.

Preferred are the dual acting neutral endopeptidase inhibitors of formula III wherein:

R_4 is benzyl, cyclopropylmethyl, or straight or branched chain alkyl of 3 to 5 carbons;
p is one or two;
X is O or S;
m is zero or one;
Y is CH_2, S, or O provided that Y is S or O when m is one; and
R_5 is hydrogen.

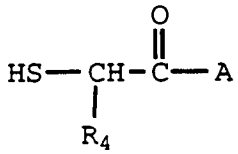
Most preferred for use in this invention is the dual acting neutral endopeptidase inhibitor of formula III wherein:

R_4 is benzyl;
p is two;
Y is S;
m is one;
Y is CH_2 ; and
R_5 is hydrogen.

The dual acting neutral endopeptidase inhibitors of formula III are disclosed in European Patent Application 629,627 of Robl et al.

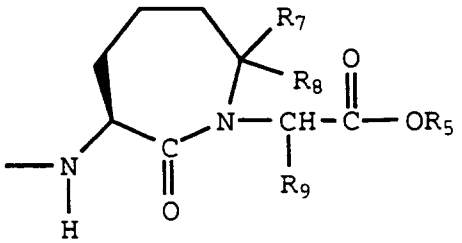
Also useful as neutral endopeptidase inhibitors for use within this invention are the dual acting inhibitors of the formula

(IV)



and pharmaceutically acceptable salts thereof wherein:

A is



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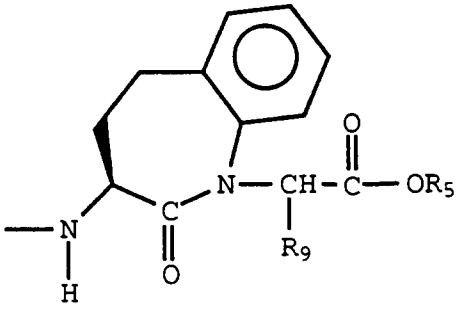

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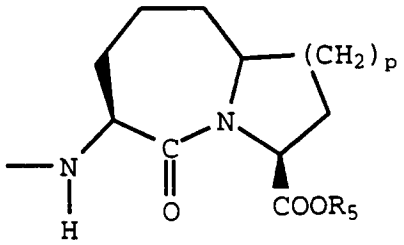

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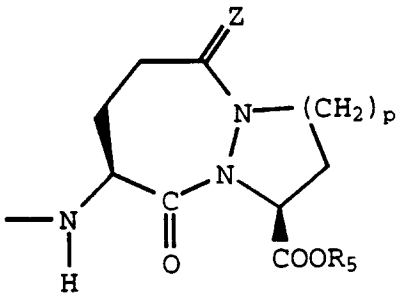

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R_4, R_5, and p are as defined above;

R_7 and R_8 are both hydrogen, or both alkyl of 1 to 7 carbons, or R_7 is hydrogen and R_8 is alkyl of 1 to 7 carbons, phenyl, -$(CH_2)_{1\ to\ 4}$-phenyl and -$(CH_2)_{1\ to\ 4}$-substituted phenyl, or R_7 and R_8 taken together with the carbon to which they are attached complete a cycloalkyl of 3 to 5 carbons.

R_9 is hydrogen or alkyl of 1 to 7 carbons.

Z is oxo or two hydrogens.

Preferred are the dual acting neutral endopeptidase inhibitors of formula IV wherein:

R_4 is benzyl;

R_7 and R_8 are both methyl;

R_9 is hydrogen or methyl, especially hydrogen;

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