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# (54) Treating hypertension using a thromboxane $A_2$ receptor antagonist

(57) A method is provided for treating hypertension by administering a thromboxane $A_2$ receptor antagonist which preferably is a 7-oxabicycloheptane prostaglandin analog. In addition, new combinations are provided containing a thromboxane $A_2$ receptor antagonist and a beta blocker, an angiotensin converting enzyme inhibitor, a diuretic, an endopeptidase inhibitor or human ANF 99-126.

The antagonist may be administered in single or divided doses of from 0.5 to 2500 mg/one to four times daily.

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# METHOD OF TREATING HYPERTENSION

The present invention relates to a method for treating hypertension by administering a thromboxane $A_2$ receptor antagonist, which preferably is a 7-oxabicycloheptane prostaglandin analog, and to new combinations containing a thromboxane $A_2$ receptor antagonist.

In accordance with the present invention, a method is provided for treating hypertension wherein a therapeutically effective amount of a thromboxane $A_2$ receptor antagonist is systemically administered, such as orally or parenterally, to reduce blood pressure in mammals, including humans, during the period of treatment.

In addition, in accordance with the present invention, new combinations are provided, for treating hypertension, containing a thromboxane $A_2$ receptor antagonist and an angiotensin converting enzyme inhibitor, a beta blocker, a diuretic, an endopeptidase inhibitor and/or human ANF 99-126.

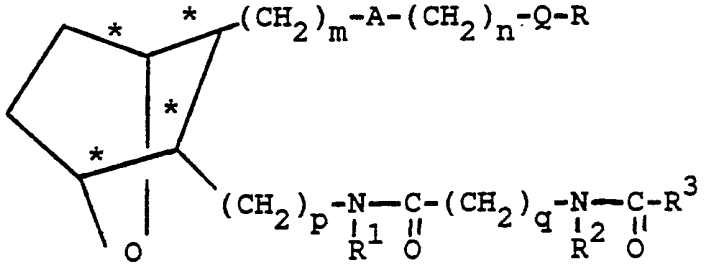
The term "thromboxane $A_2$ receptor antagonist" as employed herein includes compounds which are so-called thromboxane $A_2$ receptor antagonists, thromboxane $A_2$ antagonists,

thromboxane $A_2$/prostaglandin endoperoxide antagonists, TP-receptor antagonists, or thromboxane antagonists except insofar as the compound is solely an inhibitor of thromboxane synthesis.

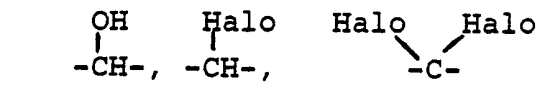
Thromboxane $A_2$ antagonists which may be employed herein are specific inhibitors of the actions of thromboxane $A_2$ and therefore produce the desired effect of thromboxane $A_2$ inhibition without causing other non-specific effects that may be undesirable.

The thromboxane $A_2$ receptor antagonist employed herein will preferably be a 7-oxabicycloheptane prostaglandin analog and will include 7-oxabicycloheptane substituted diamide prostaglandin analogs as disclosed in U.S. Patent No. 4,663,336, 7-oxabicycloheptane substituted amino prostaglandin analogs as disclosed in U.S. Patent No. 4,416,896 and 7-oxabicycloheptane prostaglandin analogs as disclosed in U.S. Patent No. 4,537,981. Other 7-oxabicycloheptane prostaglandin analogs may be included as will be apparent to one skilled in the art.

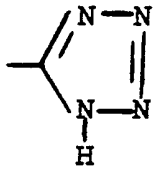
The 7-oxabicycloheptane substituted diamide prostaglandin analogs suitable for use herein, as disclosed in U.S. Patent No. 4,663,336, have the formula



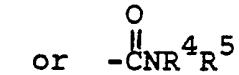
including all stereoisomers thereof, wherein m is 0 to 4; A is -CH=CH- or $-CH_2-CH_2-$; n is 1 to 5; Q is -CH=CH-, $-CH_2-$,



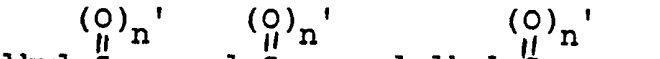
or a single bond; R is $CO_2H$, $CO_2$alkyl, $CO_2$ alkali metal, $CO_2$polyhydroxyamine salt, $-CH_2OH$,



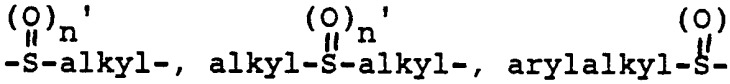
or



wherein $R^4$ and $R^5$ are the same or different and are H, lower alkyl, hydroxy, lower alkoxy or aryl at least one of $R^4$ and $R^5$ being other than hydroxy and lower alkoxy; p is 1 to 4; $R^1$ is H or lower alkyl; q is 1 to 12; $R^2$ is H or lower alkyl; and $R^3$ is H, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, lower alkoxy, arylalkyloxy, aryloxy, amino, alkylamino, arylalkylamino, arylamino,



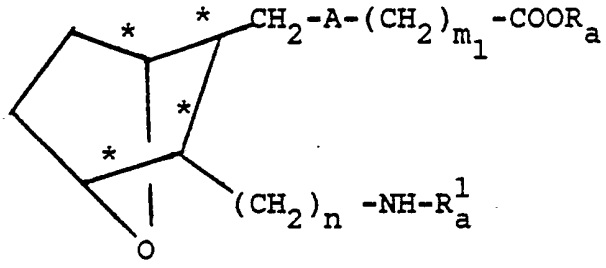
lower alkyl-S-, aryl-S-, arylalkyl-S-,



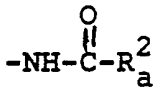
aryl-S-alkyl-, alkyl-S-alkyl-, arylalkyl-S-alkyl

(wherein n' is 0, 1 or 2), alkylaminoalkyl, arylaminoalkyl, arylalkylaminoalkyl, alkoxyalkyl, aryloxyalkyl or arylalkoxyalkyl.

The 7-oxabicycloheptane substituted amino prostaglandin analogs suitable for use herein, as disclosed in U.S. Patent No. 4,416,896, have the formula

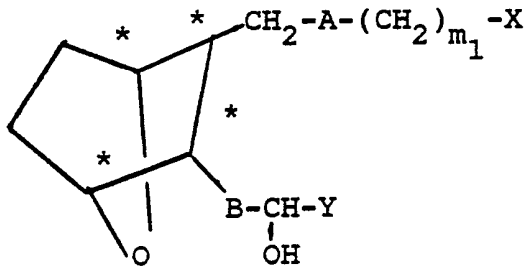


and including all stereoisomers thereof, wherein A is CH=CH or $(CH_2)_2$; $m_1$ is 1 to 8; $n_1$ is 0 to 5, $R_a$ is H or lower alkyl; and $R_a^1$ is lower alkyl, aryl, aralkyl, lower alkoxy, aralkoxy or



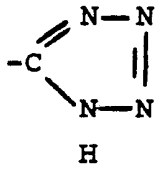
wherein $R_a^2$ is lower alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylamino, arylamino or aralkylamino.

The 7-oxabicycloheptane prostaglandin analogs suitable for use herein, as disclosed in U.S. Patent No. 4,537,981, have the formula



and including all stereoisomers thereof, wherein A and B may be the same or different and A is CH=CH or $(CH_2)_2$; B is CH=CH, C≡C or $(CH_2)_2$; $m_1$ is 1 to 8;

X is OH;



;

$CO_2R_a$ wherein $R_a$ is H or lower alkyl; or

wherein Z is H, lower alkyl, aryl, $SO_2$-$Q_1$ (with $Q_1$ being lower alkyl or aryl),

or $OR_b^2$ wherein $R_b^2$ is H, and Y is alkyl, substituted alkyl; aryl-lower alkyl; alkenyl; alkynyl, aryl; pyridyl; substituted pyridyl; pyridyl-lower alkyl; thienyl, substituted thienyl; thienyl-lower alkyl; cycloalkyl; cycloalkylalkyl; substituted cycloalkylalkyl; or phenoxymethyl.

Preferred examples of thromboxane $A_2$ receptor antagonists which may be employed herein include the 7-oxabicycloheptane compounds disclosed in U.S. Patent No. 4,537,981, especially, [1S-[1α,2α(5Z),3α(1E,3R,4S),4α]]-7-[3-(3-hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic acid; the 7-oxabicycloheptane substituted amino-prostaglandin analogs disclosed in U.S. Patent No. 4,416,896, especially, [1S-[1α,2α,(5Z),3α,4α]]-7-[3-[[2-(phenylamino)carbonyl] hydrazino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-

heptenoic acid; the 7-oxabicycloheptane substituted diamide prostaglandin analogs disclosed in U.S. Patent No. 4,663,336, especially, [1S-[1α,2α(5Z), 3α,4α]]-7-[3-[[[[(1-oxoheptyl)amino]acetyl]amino] methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid and the corresponding tetrazole, and [1S-[1α,2α(Z),3α,4α]]-7-[3-[[[[(4-cyclohexyl-1-oxobutyl)amino]acetyl]amino]methyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic acid.

Examples of other such thromboxane $A_2$ antagonists suitable for use herein include but are not limited to the phenoxyalkyl carboxylic acids disclosed in U. S. Patent No. 4,258,058 to Witte et al, especially 4-[2-(benzenesulfamido)ethyl]phenoxy-acetic acid, (BM 13,177 - Boehringer Mannheim), the sulphonamidophenyl carboxylic acids disclosed in U. S. Patent No. 4,443,477 to Witte et al, especially 4-[2-(4-chlorobenzenesulfonamido)-ethyl]phenylacetic acid, (BM 13,505, Boehringer Mannheim) the arylthioalkylphenyl carboxylic acids disclosed in U. S. Patent No. 4,752,676 especially 4-(3-((4-chlorophenyl)sulfonyl)propyl)benzeneacetic acid, (E)-5-[[[(pyridinyl)[3-(trifluoro-methyl)phenyl]methylene]amino]oxy]pentanoic acid also referred to as R68,070 - Janssen Research Laboratories, 3-[1-(4-chlorophenylmethyl)-5-fluoro-3-methylindol-2-yl]-2,2-dimethylpropanoic acid [(L-655240 Merck-Frosst) Eur. J. Pharmacol. 135(2):193, 17 Mar. 87], 5(Z)-7-([2,4,5-cis]-4-(2-hydroxyphenyl)-2-trifluoromethyl-1,3-dioxan-5-yl)heptenoic acid (ICI 185282, Brit. J. Pharmacol 90 (Proc. Suppl):228 P-Abs., Mar. 87), 5(Z)-7-[2,2-dimethyl-4-phenyl-1,3-dioxan-cis-5-yl]-

heptenoic acid (ICI 159995, Brit. J. Pharmacol. 86 (Proc. Suppl):808 P-Abs., Dec. 85), N,N'-bis[7-(3-chlorobenzeneaminosulfonyl)-1,2,3,4-tetrahydro-isoquinolyl]disulfonylimide (SKF 88046, Pharmacologist 25(3):116 Abs, 117 Abs, Aug. 83), [1α(Z)-2β,5α]-(+)-7-[5-[[(1,1'-biphenyl)-4-yl]-methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid (AH 23848 - Glaxo, Circulation 72(6):1208, Dec. 85, levallorphan allyl bromide (CM 32,191, Sanofi, Life Sci. 31 (20-21):2261, 15 Nov. 82), (Z,2-endo-3-oxo)-7-(3-acetyl-2-bicyclo-[2.2.1]heptyl-5-hepta-3Z-enoic acid, 4-phenylthiosemicarbazone (EP092 - Univ. Edinburgh, Brit, J. Pharmacol. 84(3):595, Mar. 85).

The disclosures of the above-mentioned patents are incorporated herein by reference.

In carrying out the method of the present invention, the thromboxane $A_2$ receptor antagonist may be administered systemically, such as orally or parenterally, to mammalian species, such as monkeys, dogs, cats, rats, humans, etc.

The thromboxane $A_2$ receptor antagonist may be incorporated in a conventional dosage form, such as a tablet, capsule, elixir or injectable. The above dosage forms will also include the necessary carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

With regard to such systemic formulations, single or divided doses of from about 0.5 to about

2500 mg, preferably from about 5 to 500 mg one to six times daily, may be administered in systemic dosage forms as described above for a prolonged period, that is, for as long as hypertension continues. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be employed.

The thromboxane antagonist can also be formulated with a diuretic for the treatment of hypertension. A combination product comprising thromboxane antagonist and a diuretic can be administered in an effective amount which comprises a totally daily dosage of about 30 to 600 mg, preferably about 30 to 330 mg of thromboxane antagonist, and about 15 to 300 mg preferably about 15 to 200 of the diuretic, to a mammalian species in need thereof. Exemplary of the diuretics contemplated for use in combination with a compound of this invention are the thiazide diuretics, e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylclothiazide, trichloromethiazide, polythiazide or benzthiazide as well as ethacrynic acid, tricrynafen, chlorothalidone, furosamide, musolimine, bumetanide, triamterene, amiloride and spironolactone and salts of such compounds.

In treating hypertension, the thromboxane receptor antagonists may be administered in combination with an angiotensin-converting enzyme (ACE) inhibitor such as captopril, zofenopril, fosinopril, enalapril, lisinopril, (S)-1-[6-amino-

2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline (SQ 29,852) etc. employing the ACE inhibitor in an amount as indicated in the Physicians Desk Reference (PDR), for example, from about 5 to about 350 mg per day. Such combination would be at a weight ratio of thromboxane antagonist to ACE inhibitor of from about 1:10 to about 10:1.

The thromboxane receptor antagonists can also be administered in combination with a neutral endopeptidase inhibitor or with human ANF 99 - 126 in treating hypertension. Such combination would contain the thromboxane antagonist at from about 1 to about 500 mg per day and an endopeptidase inhibitor of from about 1 to about 100 mg per kg of body weight or the human ANF 99 - 126 at from about 0.001 to about 0.1 mg per kg of body weight.

In addition, in treating hypertension, the thromboxane receptor antagonists may be employed in combination with a beta blocker such as propranolol, nadolol, timolol maleate, metoprolol tartrate, labetalol hydrochloride and the like employing the beta blocker in amounts as indicated in the PDR such as in an amount of from about 5 to about 350 mg per day. Such a combination would be at a weight ratio of thromboxane antagonist to beta blocker of from about 1:10 to about 10:1.

The thromboxane receptor antagonist, in treating hypertension, may also be used in combination with a calcium channel blocker such as dihydropyridines such as nifedipine, nitrendipine, nimodipine, phenylalkylamines such as verapamil, benzothiazepines such as diltiazem and

benzazepines and the like employing the calcium channel blocker in amounts as indicated in the PDR such as in an amount of from about 1 to about 1000 mg per day. Such a combination would be at a weight ratio of thromboxane antagonist to calcium channel blocker of from about 1:10 to about 10:1.

The thromboxane receptor antagonist may also be employed in combination with direct vasodilators such as hydralazine or minoxidil.

The following Examples represent preferred embodiments of the present invention.

Example 1

An injectable solution of thromboxane $A_2$ receptor antagonist for intravenous use in treating hypertension is produced as follows:

| | |
|---|---|
| [1S-[1α,2α(5Z),3α,4α]]-7-[3-[[2-(phenylamino)carbonyl]hydrazino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (SQ 29,548) | 2500 mg |
| Methyl paraben | 5 mg |
| Propyl paraben | 1 mg |
| Sodium chloride | 25 g |
| Water for injection qs. | 5 l. |

The thromboxane $A_2$ receptor antagonist, preservatives and sodium chloride are dissolved in 3 liters of water for injection and then the volume is brought up to 5 liters. The solution is filtered through a sterile filter and aseptically filled into presterilized vials which are then closed with presterilized rubber closures. Each vial contains a concentration of 75 mg of active ingredient per 150 ml of solution.

Example 2

An injectable for use in treating hypertension is prepared as described in Example 1 except that the thromboxane $A_2$ receptor antagonist employed is [1S-[1α,2α(5Z),3α(1E,3R,4S),4α]]-7-[3-

(3-hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic acid (SQ 28,668).

Example 3

An injectable solution of thromboxane $A_2$ receptor antagonist for use in treating hypertension containing [1S-[1α,2α(5Z),3α,4α]]-7-[3-[[[[(1-oxoheptyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic acid (SQ 30,741) as the thromboxane $A_2$ receptor antagonist is prepared as described in Example 1.

Example 4

An injectable for use in treating hypertension is prepared as described in Example 1 except that the thromboxane $A_2$ receptor antagonist employed is [1S-[1α,2α(Z),3α,4α]]-7-[3-[[[[(4-cyclohexyl-1-oxobutyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid.

Example 5

A thromboxane $A_2$ antagonist formulation suitable for oral administration for use in treating hypertension is set out below.

1000 tablets each containing 400 mg of thromboxane $A_2$ receptor antagonist are produced from the following ingredients.

| | |
|---|---|
| [1S-[1α,2α(5Z),3α,4α]]-7-[3-[[[[(1-Oxoheptyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (SQ 30,741) | 400 g |
| Corn Starch | 50 g |
| Gelatin | 7.5 g |

| | |
|---|---|
| Avicel (microcrystalline cellulose) | 25 g |
| Magnesium stearate | 2.5 g |

The thromboxane $A_2$ receptor antagonist and corn starch are admixed with an aqueous solution of the gelatin. The mixture is dried and ground to a fine powder. The Avicel and then the magnesium stearate are admixed with the granulation. This is then compressed in a tablet to form 1000 tablets each containing 400 mg of active ingredient.

Example 6

A thromboxane $A_2$ antagonist tablet formulation for use in treating hypertension is prepared as described in Example 5 except that SQ 29,548 is employed as the thromboxane $A_2$ receptor antagonist in place of SQ 30,741.

Example 7

A thromboxane $A_2$ antagonist tablet formulation for use in treating hypertension is prepared as described in Example 5 except that SQ 28,668 is employed in place of SQ 30,741.

It will also be appreciated that the above thromboxane $A_2$ antagonist formulations may also include a beta blocker such as propranolol or atenolol, an ACE inhibitor such as enalapril, lisinopril, zofenopril, fosinopril or SQ 29,852, an endopeptidase inhibitor or human ANF 99-126, a diuretic or a vasodilator.

Example 8

A thromboxane receptor $A_2$ antagonist-calcium channel blocker formulation suitable for oral administration for treating hypertension is set out below.

1000 tablets each containing 400 mg of thromboxane $A_2$ antagonist and 100 mg diltiazem are produced from the following ingredients.

| | |
|---|---|
| [1S-[1α,2α(5Z),3α,4α]]-7-[3-[[[[(1-Oxoheptyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1] hept-2-yl]-5-heptenoic acid (SQ 30,741) | 400 g |
| Diltiazem | 100 g |
| Corn starch | 50 g |
| Gelatin | 7.5 g |
| Avicel (microcrystalline cellulose) | 25 g |
| Magnesium stearate | 2.5 g |

The thromboxane antagonist, diltiazem and corn starch are admixed with an aqueous solution of the gelatin. The mixture is dried and ground to a fine powder. The Avicel and then the magnesium stearate are admixed with the granulation. This is then compressed in a tablet to form 1000 tablets each containing 500 mg of active ingredients.

Example 9

An injectable solution for use in administering calcium channel blocker and thromboxane $A_2$ receptor antagonist is produced as follows:

| | |
|---|---|
| [1S-[1α,2α(5Z),3α,4α]]-7-[3-[[2-(phenylamino)carbonyl]hydrazino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (SQ 29,548) or SQ30,741 | 2500 mg |
| Nifedipine or diltiazem | 2500 mg |
| Methyl paraben | 5 mg |
| Propyl paraben | 1 mg |
| Sodium chloride | 25 g |
| Water for injection qs. | 5 l. |

The calcium channel blocker, thromboxane $A_2$ antagonist, preservatives and sodium chloride are dissolved in 3 liters of water for injection and then the volume is brought up to 5 liters. The solution is filtered through a sterile filter and aseptically filled into presterilized vials which are then closed with presterilized rubber closures. Each vial contains a concentration of 75 mg of active ingredient per 150 ml of solution.

Example 10

An injectable for use in treating hypertension is prepared as described in Example 9 except that the thromboxane $A_2$ antagonist employed is the phenoxyalkyl carboxylic acid 4-[2-(benzenesulfamido)ethyl]phenoxyacetic acid, disclosed in U. S. Patent No. 4,258,058.

Example 11

An injectable for use in treating hypertension is prepared as described in Example 9

except that the thromboxane $A_2$ antagonist employed is [1S-[1α,2β(Z),3β,4α]]-7-[3-[[[[(4-cyclohexyl-1-oxobutyl)amino]acetyl]amino]methyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic acid.

Example 11

1000 tablets each containing 200 mg of SQ 32,324 and 400 mg SQ 30,741 are produced from the following ingredients:

| | |
|---|---|
| (d-cis)-3-(acetyloxy)-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-1-[2-(methylamino)ethyl]-6-(trifluoro-methyl)-2H-1-benzazepin-2-one, monohydrochloride salt (SQ 32,324) | 200g |
| SQ 30,741 | 400g |
| Lactose | 100g |
| Avicel | 150g |
| Corn starch | 50g |
| Magnesium stearate | 5g |

SQ 32,324, SQ 30,741, lactose and Avicel are admixed, then blended with the corn starch. Magnesium stearate is added. The dry mixture is compressed in a tablet press to form 1000 505 mg tablets each containing 200 mg of active ingredient. The tablets are coated with a solution of Methocel E 15 (methyl cellulose) including as a color a lake containing yellow #6. The resulting tablets are useful in treating hypertension.

Example 12

Two piece #1 gelatin capsules each containing 50 mg of captopril and 250 mg of SQ 30,741 are filled with a mixture of the following ingredients:

| | |
|---|---|
| SQ 30,741 | 250 mg |
| Captopril | 50 mg |
| Magnesium stearate | 7 mg |
| USP lactose | 193 mg. |

The resulting capsules are useful in treating hypertension.

Example 13

An injectable solution for use in treating hypertension is produced as follows:

| | |
|---|---|
| (d-cis)-3-(acetyloxy)-1-[2-dimethyl-amino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-6-(trifluoromethyl)-2H-1-benzazepin-2-one, monohydrochloride (SQ 31,765) | 500 mg |
| SQ 30,741 | 250 mg |
| Methyl paraben | 5 mg |
| Propyl paraben | 1 mg. |
| Sodium chloride | 25 g |
| Water for injection qs. | 5 l. |

SQ 31,765, SQ 30,741, preservatives and sodium chloride are dissolved in 3 liters of water

for injection and then the volume is brought up to 5 liters. The solution is filtered through a sterile filter and aseptically filled into presterilized vials which are then closed with presterilized rubber closures. Each vial contains 5 ml of solution in a concentration of 100 mg of active ingredient per ml of solution for injection.

## Example 14

A thromboxane antagonist-beta blocker formulation suitable for oral administration for treating hypertension prepared as described in Example 1, is set out below.

1000 tablets each containing 400 mg of thromboxane antagonist and 40 mg nadolol are produced from the following ingredients.

| | |
|---|---|
| SQ 30,741 | 400 g |
| Nadolol | 40 g |
| Corn starch | 50 g |
| Gelatin | 7.5g |
| Avicel (microcrystalline cellulose) | 25 g |
| Magnesium stearate | 2.5 g |

## Example 15

The following experiment demonstrates that a thromboxane receptor antagonist decreases blood pressure.

A thromboxane receptor antagonist [1S-[1α,2α(5Z),3α,4α]]-7-[3-[[[[(1-oxoheptyl)-amino]acetyl]amino]methyl]-7-oxabicyclo-

[2.2.1]hept-2-yl]-5-heptenoic acid (SQ), or placebo (PLA) was given to 3 groups of 12 healthy human subjects (8 per group received SQ and 4 PLA). SQ was given as a single 50 mg IV bolus followed by an infusion of 3, 6 or 12 mg/hr for 48 hours. Mean pharmacodynamic (PD) parameters at 48 hours were:

| | Max. % Δ | % Increase Bleeding | % Decrease Platelet Aggregation | |
|---|---|---|---|---|
| Dose | Diastolic BP | Time | low | high |
| PLA | -14±3 | 22±15 | -9±11 | -7±6 |
| 3 | -20±3 | 156±55* | 98±4* | 89±17* |
| 6 | -18±3 | 111±19* | 100±0* | 76±7* |
| 12 | -28±8* | 122±34* | 100±0* | 88±16* |

(*$p<0.05$ vs. PLA)

SQ specifically inhibited $TXA_2$-mediated platelet aggregation ex vivo at low and high agonist (U46619) concentrations. Mean platelet $TXA_2$ receptor (R) affinity and density measured ex vivo were not changed. SQ increased template bleeding time when R occupancy was ≧99% but not when R occupancy was ≦70%.

From the above, it is seen that the thromboxane receptor antagonist reduced diastolic blood pressure.

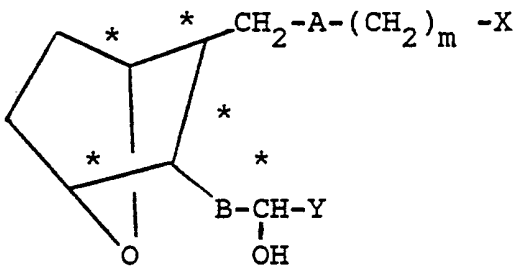
CLAIMS

1. Use of a thromboxane $A_2$ receptor antagonist for the manufacture of a medicament for treatment of hypertension in a mammalian species by administration of a blood pressure lowering amount of the medicament.

2. The method as defined in Claim 1 wherein the thromboxane $A_2$ receptor antagonist is a 7-oxabicycloheptane prostaglandin analog.

3. The method as defined in Claim 2 wherein the 7-oxabicycloheptane prostaglandin analog is a 7-oxabicycloheptane substituted diamide prostaglandin analog or a 7-oxabicycloheptane substituted amino prostaglandin analog.

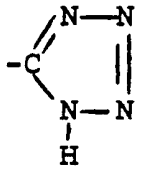
4. The method as defined in Claim 2 wherein the 7-oxabicycloheptane prostaglandin analog has the formula




and including all stereoisomers thereof, wherein

A and B may be the same or different and A is

CH=CH or $(CH_2)_2$; B is CH=CH, C≡C or $(CH_2)_2$; $m_1$ is 1 to 8; X is OH;



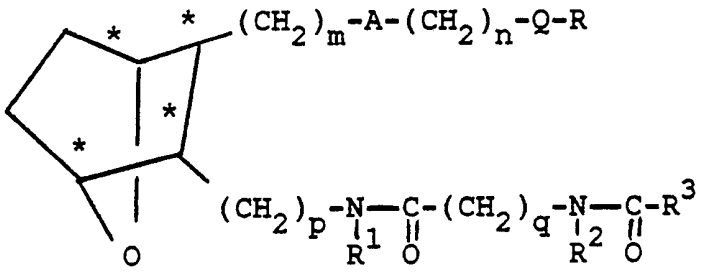
;

$CO_2R_a$ wherein $R_a$ is H or lower alkyl; or

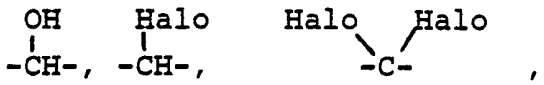
wherein Z is H, lower alkyl, aryl, $SO_2$-$Q_1$ (with $Q_1$ being lower alkyl or aryl),

or $OR_b^2$ wherein $R_b^2$ is H, and Y is alkyl; substituted alkyl; aryl-lower alkyl; alkenyl; alkynyl, aryl; pyridyl; substituted pyridyl; pyridyl-lower alkyl; thienyl, substituted thienyl; thienyl-lower alkyl; cycloalkyl; cycloalkylalkyl; substituted cycloalkylalkyl; or phenoxymethyl.

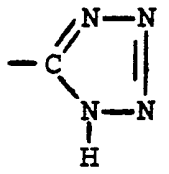
5. The method as defined in Claim 3 wherein the 7-oxabicycloheptane substituted diamide prostaglandin analog has the formula



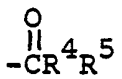
including all stereoisomers thereof, wherein m is 0 to 4; A is -CH=CH- or $-CH_2-CH_2-$; n is 1 to 5; Q is -CH=CH-, $-CH_2$,



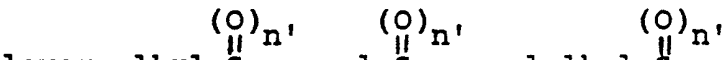
or a single bond; R is $CO_2H$, $CO_2$alkyl, $CO_2$ alkali metal, $CO_2$polyhydroxyamine salt, $-CH_2OH$,



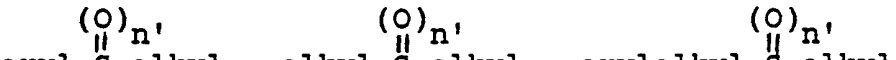
or



wherein $R^4$ and $R^5$ are the same or different and are H, lower alkyl, hydroxy, lower alkoxy or aryl at least one of $R^4$ and $R^5$ being other than hydroxy and lower alkoxy; p is 1 to 4; $R^1$ is H or lower alkyl; q is 1 to 12; $R^2$ is H or lower alkyl; and $R^3$ is H, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, lower alkoxy, arylalkyloxy, aryloxy, amino, alkylamino, arylalkylamino, arylamino,



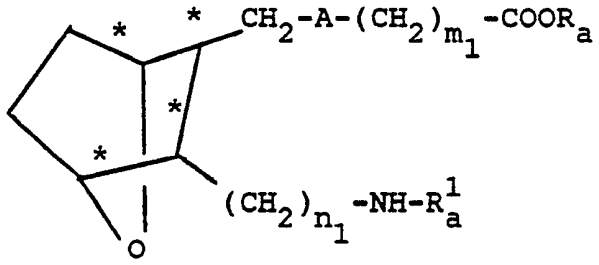
lower alkyl-S-, aryl-S-, arylalkyl-S-,



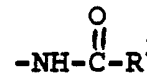
aryl-S-alkyl-, alkyl-S-alkyl-, arylalkyl-S-alkyl (wherein n' is 0, 1 or 2), alkylaminoalkyl,

arylaminoalkyl, arylalkylaminoalkyl, alkoxyalkyl, aryloxyalkyl or arylalkoxyalkyl.

6. The method as defined in Claim 3 wherein the 7-oxabicycloheptane substituted amino prostaglandin analog has the formula



and including all stereoisomers thereof, wherein A is CH=CH or $(CH_2)_2$; $m_1$ is 1 to 8; $n_1$ is 0 to 5, $R_a$ is H or lower alkyl; and $R_a^1$ is lower alkyl, aryl, aralkyl, lower alkoxy, aralkoxy or



wherein $R_a^2$ is lower alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylamino, arylamino or aralkylamino.

7. The method as defined in Claim 1 wherein the thromboxane $A_2$ receptor antagonist is [1S-[1α,2α(5Z),3α(1E,3R,4S),4α]]-7-[3-(3-hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid.

8. The method as defined in Claim 1 wherein the thromboxane $A_2$ receptor antagonist has the name [1S-[1α,2α(5Z),3α,4α]]-7-[3-[[[[(1-oxoheptyl) amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]

hept-2-yl]-5-heptenoic acid or the corresponding tetrazole.

9. The method as defined in Claim 1 wherein the thromboxane $A_2$ receptor antagonist has the name [1S-[1α,2α(Z),3α,4α]]-7-[3-[[[[(4-cyclohexyl-1-oxobutyl)amino]acetyl]amino]methyl]-7-oxabicyclo [2.2.1]hept-2-yl]-5-heptenoic acid.

10. The method as defined in Claim 1 wherein the thromboxane $A_2$ receptor antagonist has the name [1S-[1α,2α(5Z),3α,4α]]-7-[3-[[2-(phenylamino) carbonyl]hydrazino]methyl]-7-oxabicyclo[2.2.1] hept-2-yl]-5-heptenoic acid.

11. The method as defined in Claim 1 wherein the thromboxane $A_2$ receptor antagonist is administered orally or parenterally.

12. The method as defined in Claim 1 wherein the thromboxane receptor antagonist is administered in single or divided doses of from about 0.5 to about 2500 mg/one to four times daily.

13. The method as defined in Claim 1 wherein the thromboxane receptor antagonist is employed in combination with a diuretic.

14. The method as defined in Claim 1 wherein the thromboxane receptor antagonist is employed in combination with an angiotensin-converting enzyme inhibitor.

15. The method as defined in Claim 1 wherein the thromboxane receptor antagonist is employed in combination with a beta-blocker.

16. The method as defined in Claim 1 wherein the thromboxane receptor antagonist is employed in combination with a calcium channel blocker.

17. The method as defined in Claim 1 wherein the thromboxane receptor antagonist is employed in combination with a vasodilator.

18. A new pharmaceutical combination comprising a thromboxane receptor antagonist and a beta blocker.

19. The combination as defined in Claim 18 wherein the beta blocker is nadolol, propranolol, atenolol, timolol, metaprolol, acebutolol or labetalol.

20. A new pharmaceutical combination comprising a thromboxane $A_2$ receptor antagonist and an angiotensin converting enzyme inhibitor.

21. The combination as defined in Claim 20 wherein the angiotensin converting enzyme inhibitor is captopril, enalapril, lisinopril, fosinopril, SQ 29,852 or zofenopril.

22. A new pharmaceutical combination comprising a thromboxane $A_2$ receptor antagonist and an endopeptidase inhibitor or human ANF 99-126.

23. A new pharmaceutical combination comprising a thromboxane $A_2$ receptor antagonist and a diuretic or an endopeptidase inhibitor.