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(54) Title: ENDOTHELIN RECEPTOR ANTAGONISTS		
(57) Abstract		
Naphthoic derivatives and pharmaceutical compositions containing these compounds, and their use as endothelin receptor antagonists.		

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ENDOTHELIN RECEPTOR ANTAGONISTS
FIELD OF INVENTION

5 The present invention relates to novel compounds, pharmaceutical compositions containing these compounds and their use as endothelin receptor antagonists.

 Endothelin (ET) is a highly potent vasoconstrictor peptide synthesized and released by the vascular endothelium. Endothelin exists as three isoforms, ET-1, ET-2 and ET-3. [Unless otherwise stated "endothelin" shall mean
10 any or all of the isoforms of endothelin]. Endothelin has profound effects on the cardiovascular system, and in particular, the coronary, renal and cerebral circulation. Elevated or abnormal release of endothelin is associated with smooth muscle contraction which is involved in the pathogenesis of cardiovascular, cerebrovascular, respiratory and renal pathophysiology. Elevated levels of
15 endothelin have been reported in plasma from patients with essential hypertension, acute myocardial infarction, subarachnoid hemorrhage, atherosclerosis, and patients with uraemia undergoing dialysis.

In vivo, endothelin has pronounced effects on blood pressure and cardiac output. An intravenous bolus injection of ET (0.1 to 3 nmol/kg) in rats
20 causes a transient, dose-related depressor response (lasting 0.5 to 2 minutes) followed by a sustained, dose-dependent rise in arterial blood pressure which can remain elevated for 2 to 3 hours following dosing. Doses above 3 nmol/kg in a rat often prove fatal.

 Endothelin appears to produce a preferential effect in the renal
25 vascular bed. It produces a marked, long-lasting decrease in renal blood flow, accompanied by a significant decrease in GFR, urine volume, urinary sodium and potassium excretion. Endothelin produces a sustained antinatriuretic effect, despite significant elevations in atrial natriuretic peptide. Endothelin also stimulates plasma renin activity. These findings suggest that ET is involved in the regulation
30 of renal function and is involved in a variety of renal disorders including acute renal failure, cyclosporine nephrotoxicity and chronic renal failure.

 Studies have shown that in vivo, the cerebral vasculature is highly sensitive to both the vasodilator and vasoconstrictor effects of endothelin. Therefore, ET may be an important mediator of cerebral vasospasm, a frequent and
35 often fatal consequence of subarachnoid hemorrhage.

ET also exhibits direct central nervous system effects such as severe apnea and ischemic lesions which suggests that ET may contribute to the development of cerebral infarcts and neuronal death.

- ET has also been implicated in myocardial ischemia (Nichols *et al.*, Br. J. Pharm. 99: 597-601, 1989 and Clozel and Clozel, Circ. Res., 65: 1193-1200, 1989) coronary vasospasm (Fukuda *et al.*, Eur. J. Pharm. 165: 301-304, 1989 and Lüscher, Circ. 83: 701, 1991) heart failure, proliferation of vascular smooth muscle cells, (Takagi, Biochem & Biophys. Res. Commun.; 168: 537-543, 1990, Bobek *et al.*, Am. J. Physiol. 258:408-C415, 1990) and atherosclerosis, (Nakaki *et al.*, Biochem. & Biophys. Res. Commun. 158: 880-881, 1989, and Lerman *et al.*, New Eng. J. of Med. 325: 997-1001, 1991). Increased levels of endothelin have been shown after coronary balloon angioplasty (Kadel *et al.*, No. 2491 Circ. 82: 627, 1990).

- Further, endothelin has been found to be a potent constrictor of isolated mammalian airway tissue including human bronchus (Uchida *et al.*, Eur J. of Pharm. 154: 227-228 1988, LaGente, Clin. Exp. Allergy 20: 343-348, 1990; and Springall *et al.*, Lancet, 337: 697-701, 1991). Endothelin may play a role in the pathogenesis of interstitial pulmonary fibrosis and associated pulmonary hypertension, Glard *et al.*, Third International Conference on Endothelin, 1993, p. 34 and ARDS (Adult Respiratory Distress Syndrome), Sanai *et al.*, *Supra*, p. 112.

- Endothelin has been associated with the induction of hemorrhagic and necrotic damage in the gastric mucosa (Whittle *et al.*, Br. J. Pharm. 95: 1011-1013, 1988); Raynaud's phenomenon, Cinniniello *et al.*, Lancet 337: 114-115, 1991); Crohn's Disease and ulcerative colitis, Munch *et al.*, Lancet, Vol. 339, p. 381; Migraine (Edmeads, Headache, Feb. 1991 p 127); Sepsis (Weitzberg *et al.*, Circ. Shock 33: 222-227, 1991; Pittet *et al.*, Ann. Surg. 213: 262-264, 1991), Cyclosporin-induced renal failure or hypertension (Eur. J. Pharmacol., 180: 191-192, 1990, Kidney Int. 37: 1487-1491, 1990) and endotoxin shock and other endotoxin induced diseases (Biochem. Biophys. Res. Commun., 161: 1220-1227, 1989, Acta Physiol. Scand. 137: 317-318, 1989) and inflammatory skin diseases. (Clin Res. 41:451 and 484, 1993).

- Endothelin has also been implicated in preclampsia of pregnancy. Clark *et al.*, Am. J. Obstet. Gynecol. March 1992, p. 962-968; Kamor *et al.*, N. Eng. J. of Med., Nov 22, 1990, p. 1486-1487; Dekker *et al.*, Eur J. Ob. and Gyn. and Rep. Bio. 40 (1991) 215-220; Schiff *et al.*, Am. J. Ostet. Gynecol. Feb 1992, p.

624-628; diabetes mellitus, Takahashi *et al.*, Diabetologia (1990) 33:306-310; and acute vascular rejection following kidney transplant, Watschinger *et al.*, Transplantation Vol. 52, No. 4, pp. 743-746.

5 Endothelin stimulates both bone resorption and anabolism and may have a role in the coupling of bone remodeling. Tatrai *et al.*, Endocrinology, Vol. 131, p. 603-607.

 Endothelin has been reported to stimulate the transport of sperm in the uterine cavity, Casey *et al.*, J. Clin. Endo and Metabolism, Vol. 74, No. 1, p. 223-225, therefore endothelin antagonists may be useful as male contraceptives.
10 Endothelin modulates the ovarian/menstrual cycle, Kenegsberg, J. of Clin. Endo. and Met., Vol. 74, No. 1, p. 12, and may also play a role in the regulation of penile vascular tone in man, Lau *et al.*, Asia Pacific J. of Pharm., 1991, 6:287-292 and Tejada *et al.*, J. Amer. Physio. Soc. 1991, H1078-H1085.

 Thus, endothelin receptor antagonists would offer a unique approach
15 toward the pharmacotherapy of hypertension, renal failure, cerebrovascular disease, myocardial ischemia, angina, heart failure, asthma, atherosclerosis, Raynaud's phenomenon, ulcers, sepsis, migraine, glaucoma, endotoxin shock, endotoxin induced multiple organ failure or disseminated intravascular coagulation, cyclosporin-induced renal failure and as an adjunct in angioplasty for prevention of
20 restenosis, diabetes, preclampsia of pregnancy, bone remodeling, kidney transplant, male contraceptives, infertility and priapism.

SUMMARY OF THE INVENTION

25 This invention comprises novel compounds represented by Formula (I) and pharmaceutical compositions containing these compounds, and their use as endothelin receptor antagonists which are useful in the treatment of a variety of cardiovascular and renal diseases including but not limited to: hypertension, acute and chronic renal failure, cyclosporine induced nephrotoxicity, stroke,
30 cerebrovascular vasospasm, myocardial ischemia, angina, heart failure, atherosclerosis, and as an adjunct in angioplasty for prevention of restenosis.

 This invention further constitutes a method for antagonizing endothelin receptors in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of
35 Formula (I).

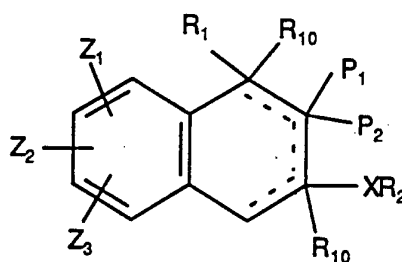
DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are represented by structural

Formula (I):

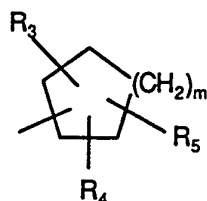
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1) A compound of Formula (I),



10 wherein:

R_1 is $-X(CH_2)_nAr$ or $-X(CH_2)_nR_8$ or



(c) ;

15

R_2 is hydrogen, Ar or (c);

P_1 is $-X(CH_2)_nR_8$;

P_2 is $-X(CH_2)_nR_8$, or $-XR_9Y$;

R_3 and R_5 are independently hydrogen, R_{11} , OH,

C_{1-8} alkoxy, $-S(O)_qR_{11}$, $-N(R_6)_2$, Br, F, I, Cl, CF_3 , $-NHCOR_6$, $-R_{11}CO_2R_7$,

20 $-R_{11}CO_2R_7$, $-XR_9Y$ or $-X(CH_2)_nR_8$ wherein each methylene group within $-X(CH_2)_nR_8$ may be unsubstituted or substituted by one or two $-(CH_2)_nAr$ groups;

R_4 is hydrogen, R_{11} , OH, C_{1-5} alkoxy, $-S(O)_qR_{11}$, $-N(R_6)_2$,

$-X(R_{11})$, Br, F, I, Cl or $-NHCOR_6$ wherein the C_{1-5} alkoxy may be unsubstituted or substituted by OH, methoxy or halogen;

25

R_6 is independently hydrogen or C_{1-4} alkyl;

R_7 is independently hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-8} alkynyl, all of which may be unsubstituted or substituted by one or more OH, $-N(R_6)_2$, $-CO_2R_{12}$, halogen or XC_{1-5} alkyl; or R_7 is $(CH_2)_nAr$;

R_8 is hydrogen, R_{11} , $-\text{CO}_2R_7$, $-\text{CO}_2\text{C}(R_7)_2\text{O}(\text{CO})\text{XR}_{11}$, $\text{PO}_3(R_7)_2$, $-\text{SO}_2\text{NR}_7R_{11}$, $-\text{CONR}_7\text{SO}_2R_{11}$, $-\text{SO}_3R_7$, $-\text{SO}_2R_7$, $-\text{P}(\text{O})(\text{OR}_7)R_7$, CN , $-\text{C}(\text{O})\text{N}(R_6)_2$, $-\text{NR}_7\text{SO}_2R_{11}$, tetrazole or OR_6 ;

R_9 is $(\text{CH}_2)_n$, C_{1-10} alkyl, C_{2-10} alkenyl or phenyl all of which may be unsubstituted or substituted by one or more OH , $\text{N}(R_6)_2$, COOH , halogen, >C=O or XC_{1-5} alkyl;

R_{10} is R_3 or R_4 ;

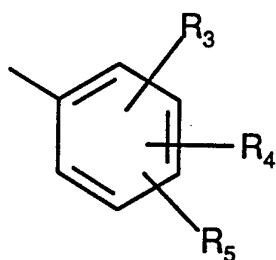
R_{11} is Ar , C_{3-8} cycloalkyl, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl all of which may be unsubstituted or substituted by one or more OH , CH_2OH , $\text{N}(R_6)_2$ or halogen;

R_{12} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-7} alkynyl;

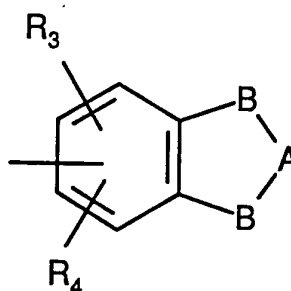
X is $(\text{CH}_2)_n$, O , NR_6 or $\text{S}(\text{O})_q$;

Y is CH_3 or $\text{X}(\text{CH}_2)_n\text{Ar}$;

Ar is:



(a)



(b)

naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted by one or more R_3 or R_4 groups;

A is C=O , or $[\text{C}(R_6)_2]_m$;

B is $-\text{CH}_2-$ or $-\text{O}-$;

Z_1 and Z_2 are independently hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, OH , C_{1-8} alkoxy, $\text{S}(\text{O})_q\text{C}_{1-8}$ alkyl, $\text{N}(R_6)_2$, Br , F , I , Cl , NHCOR_6 , $-\text{X}(\text{CH}_2)_nR_8$, phenyl, benzyl or C_{3-6} cycloalkyl wherein the C_{1-8} alkyl, C_{2-8} alkenyl or C_{2-8} alkynyl may be optionally substituted by COOH , OH , $\text{CO}(\text{CH}_2)_n\text{CH}_3$, $\text{CO}(\text{CH}_2)_n\text{CH}_2\text{N}(R_6)_2$, or halogen; or Z_1 and Z_2 together may be $-\text{O}-\text{A}-\text{O}-$ on contiguous carbons;

Z_3 is Z_1 or XR_9Y ;

q is zero, one or two;

n is an integer from 0 to six;

m is 1, 2 or 3; and the dotted line indicates the optional presence of

5 one or two double bonds; or a pharmaceutically acceptable salt thereof; provided that:

- R_2 is not hydrogen when X is $S(O)_q$;

- when an optional double bond is present there is only one R_{10} , and when the double bond is adjacent to P_1 and P_2 , there is no P_1 and P_2 is not

10 NR_6R_9Y ;

- when an optional double bond is present in Formula (I) and $X-R_2$ is attached to the double bond, X is not NR_6 ;

- when an optional double bond is present and R_1 is attached directly to the double bond, R_1 is not NR_6Ar ;

15 • when R_3 , R_5 , Z_1 , Z_2 , or Z_3 is $X(CH_2)_nR_8$ and n is 0, X is not oxygen or NR_6 when R_8 is OR_6 or CO_2H ;

- when R_8 is $CO(CR_{11})_2O(CO)XR_7$, X is not $S(O)_q$;

- when there are two double bonds present and R_1 and R_2 are phenyl, R_3 , R_4 and R_5 are not all hydrogen.

20 Also included in the invention are pharmaceutically acceptable salt complexes.

All alkyl, alkenyl, alkynyl and alkoxy groups may be straight or branched. The term "halogen" is used to mean iodo, fluoro, chloro or bromo.

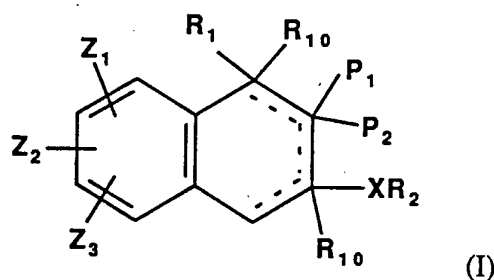
25 The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and diastereoisomers are contemplated to be within the scope of the present invention.

30 Preferred compounds are those wherein R_1 is $X(CH_2)_nAr$, (Ar is (a) or (b)), dihydrobenzofuranyl, benzodioxanyl, cyclohexyl, C_{1-4} alkyl; R_2 is (a), (b) C_{1-4} alkyl, indolyl or hydrogen; R_3 and R_5 are independently hydrogen, OH, C_{1-5} alkoxy, halogen, $-OC_{1-4}$ alkyl phenyl, $R_{11}CO_2R_7$, C_{1-4} alkyl, $N(R_6)_2$, $NH(CO)CH_3$, $-X(CH_2)_nR_8$, $-XR_9$ pyridyl, phenyl or $S(O)_pC_{1-5}$ alkyl; R_4 is hydrogen, OH, C_{1-5} alkoxy, halogen, C_{1-4} alkyl, $N(R_6)_2$, $NH(CO)CH_3$ or $S(O)_pC_{1-5}$ alkyl; Z_1 , Z_2 and Z_3 are independently XR_9Y , benzyl, hydrogen, OH,

C₁₋₅alkoxy, -N(R₆)₂, S(O)_qC₁₋₈alkyl, NHCOR₆, X(CH₂)_nR₈ or halogen, or Z₁ and Z₂ together may be -O-A-O on contiguous carbons; P₁ and P₂ are independently hydrogen, CO₂H or tetrazole; Ar is (a), (b), phenyl, or pyridyl; X is (CH₂)_n or oxygen.

- 5 More preferred are compounds wherein R₃ is hydrogen or -X(CH₂)_nR₈, R₁₁CO₂R₇; R₄ and R₅ are independently hydrogen, OH, C₁₋₅alkoxy, SC₁₋₅alkyl, F, Br, C₁₋₃alkyl or NH₂; Z₁ and Z₃ are hydrogen and Z₂ is hydrogen, OH, C₁₋₅alkoxy, halogen, X(CH₂)_nR₈, NH₂, benzyl, NH(CO)CH₃, or Z₁ and Z₂ together may be O-A-O.
- 10 Most preferred are compounds wherein R₁ is (a) or (b) and R₂ is (a) or (b); A is CH₂, B is -O-; there is no optional double bond; R₁ and XR₂ are trans to P₁; Z₂ is OH, C₁₋₅alkoxy, -OCH₂CHCH₂ or hydrogen, Z₁ and Z₃ are hydrogen; R₃ is XAr, hydrogen, X(CH₂)_qCOOH, X(CH₂)_qCONR₇SO₂R₁₁ or CH=CHCO₂H, R₄ is hydrogen, substituted phenyl, or C₁₋₂alkoxy; and R₅, R₁₀
- 15 and P₂ are hydrogen.

The present invention provides Compounds of Formula (I)



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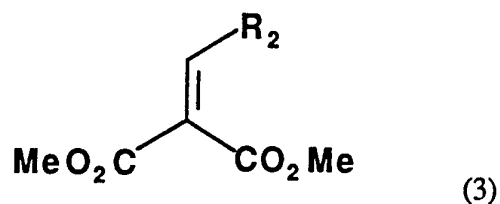
which for compounds wherein X is (CH₂)_n, n is 0 and R₁₀ is H, can be prepared by a process which comprises:

- a) reacting a substituted aldehyde of Formula (2)

25

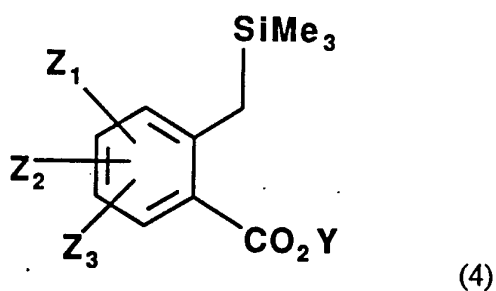


with dimethyl malonate in a suitable solvent such as benzene with a catalyst such as piperidinium acetate at reflux to provide a compound of Formula (3).



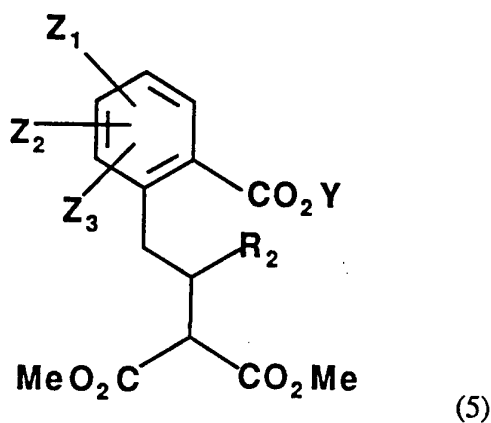
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Reaction of a compound of Formula (3) with a benzylsilane of structure (4) (wherein Y is C₁₋₅alkyl)



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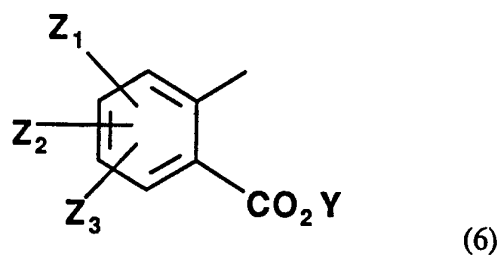
in the presence of anhydrous cesium fluoride in a solvent such as HMPA at 40-100°C affords compounds of structure (5).



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Benzylsilanes of Formula (4) may be prepared from the corresponding ortho-methyl benzoic acid esters (6) by treatment with a base such as lithium di-

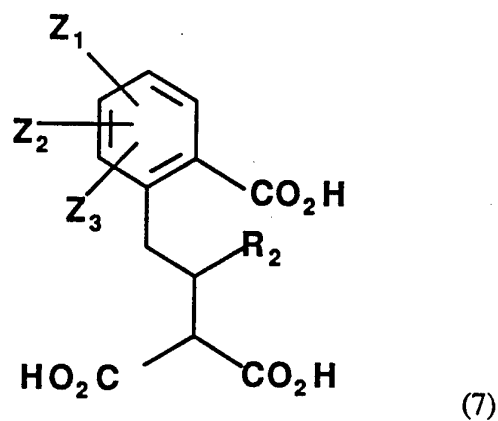
isopropylamide in the presence of chlorotrimethylsilane in a solvent such as anhydrous ether.



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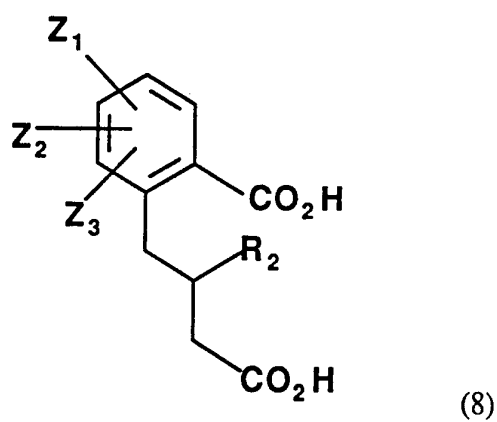
Saponification of a compound of Formula (5) using aqueous sodium or potassium hydroxide in a suitable solvent such as methanol or isopropanol followed by acidification with a dilute mineral acid such as hydrochloric affords a tri-acid of structure (7).

10

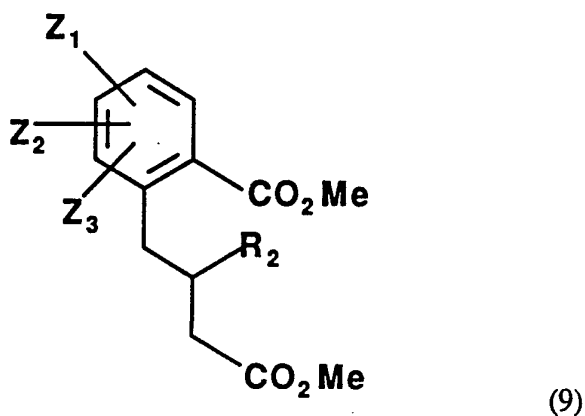


Thermolysis of a compound of Formula (7) at between 150-250°C affords a di-acid of Formula (8).

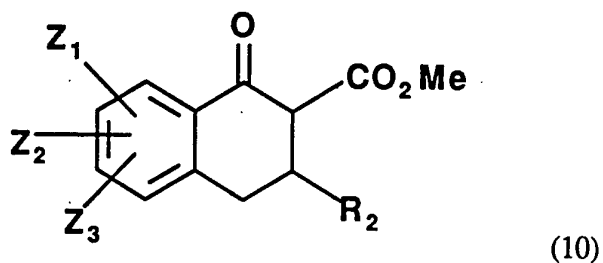
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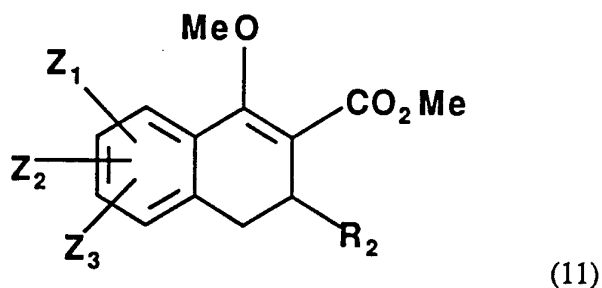
- Re-esterification of a compound of structure (8) with diazomethane in a solvent such as ether or alternatively treatment of (8) with a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene in a solvent such as acetonitrile followed by the addition of iodomethane affords diesters of Formula (9). As a further alternative,
- 5 compounds of structure (9) may be prepared from (8) by treatment with methanolic hydrogen chloride.



- 10 Dieckmann cyclization of a di-ester of formula (9) using sodium methoxide in methanol as a solvent affords, after acidic work-up, a β -keto-ester of Formula (10).



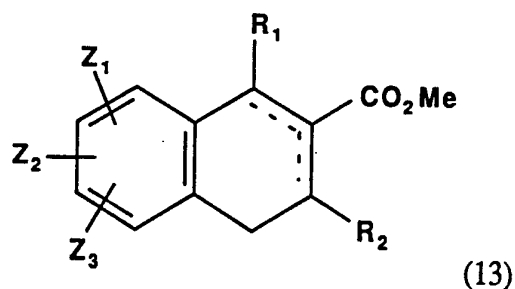
- 15 Treatment of a compound of Formula (10) with diazomethane in a solvent such as ether affords enol ethers of Formula (11).



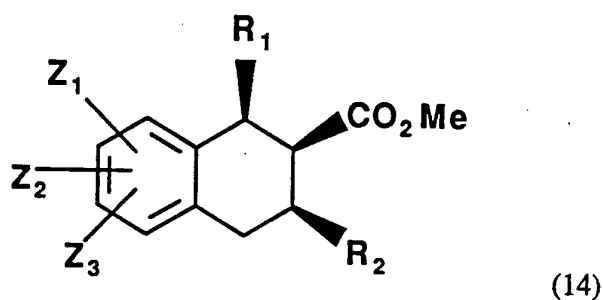
Reaction of a compound of Formula (11) with a Grignard reagent of Formula (12).



- 5 wherein R_1 is $X(CH_2)_nAr$, and X is $(CH_2)_n$ in a solvent such as ether or ether/tetrahydrofuran at approximately $0^\circ C$ affords compounds of Formula (13).

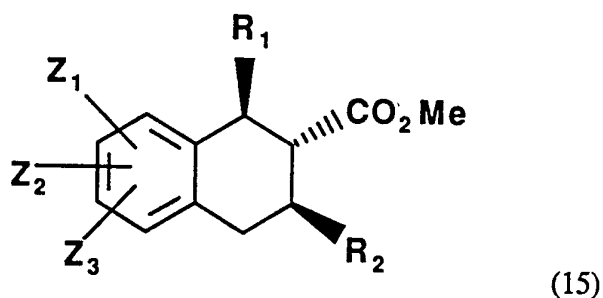


- 10 Hydrogenation of a compound of Formula (13) under hydrogen gas at approximately 50 p.s.i. in a suitable solvent such as ethyl acetate in the presence of a suitable catalyst such as 5-10% palladium on charcoal affords a racemic compound of Formula (14) with the predominant relative stereochemistry shown.



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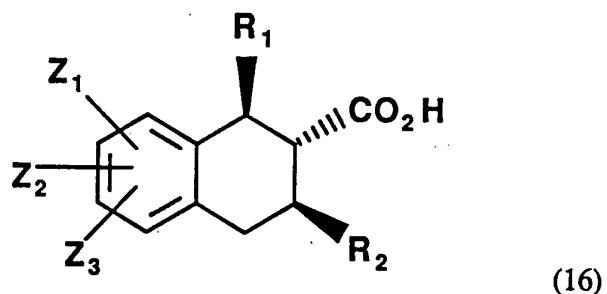
Epimerization using a base such as potassium t-butoxide in a solvent such as tertiary butanol affords a compound of Formula (15).



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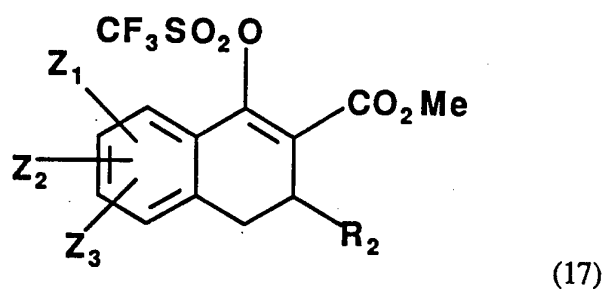
Saponification of an ester of Formula (15) using aqueous sodium or potassium hydroxide in a suitable solvent such as methanol or isopropanol affords, after acidification with a dilute mineral acid such as hydrochloric, an acid of Formula (16).

5



b) As an alternative, treatment of a β -keto-ester of Formula (10) with a base such as sodium hydride in a solvent such as tetrahydrofuran followed by the addition of N-phenyltrifluoromethanesulfonimide affords compounds of Formula (17).

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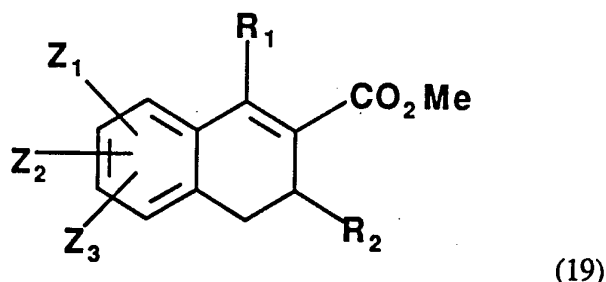


15 An enol triflate of Formula (17) may also be prepared from a compound of structure (10) by treatment with a base such as N,N-di-isopropylethylamine in a solvent such as dichloromethane followed by trifluoromethanesulfonic anhydride.

20 Treatment of an enol triflate of Formula (17) with an organostannane of Formula (18)



wherein R_1 is Ar in a solvent such as dioxane in the presence of a catalyst such as tetrakis(triphenylphosphine)palladium (0) affords compounds of Formula (19).



5

Hydrogenation of a compound of structure (19) as described above for compounds of Formula (13) affords tetrahydronaphthalenes of Formula (14).

c) As a further alternative treatment of a β -keto-ester of Formula (10) with an organocerium reagent of Formula (20)

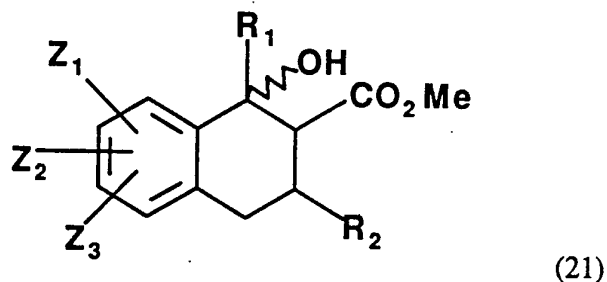
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in a solvent such as tetrahydrofuran at $-78^\circ C$ affords a product of Formula (21).

Organocerium compounds of Formula (20) may be prepared by treatment of the corresponding organolithium compound with anhydrous cerium III chloride at $-78^\circ C$ in a solvent such as tetrahydrofuran.

15



20 Hydrogenation of compounds of Formula (21) under hydrogen gas at approximately 50 p.s.i. in a suitable solvent such as ethyl acetate containing 5-20% acetic acid in the presence of a suitable catalyst such as 5-10% palladium on charcoal affords, after saponification as described for compounds of Formula (15), tetrahydronaphthalene carboxylic acids of Formula (16).

25

d) Saponification of esters of type (13) using aqueous sodium or potassium hydroxide in a suitable solvent such as methanol or isopropanol affords,

after acidification with a dilute mineral acid such as hydrochloric, acids of Formula (21), the double bond isomers of which may be separated chromatographically.

5 With appropriate manipulation and protection of any chemical functionalities, synthesis of the remaining compounds of the Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section.

10 In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

15 Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

20 Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

30 Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

35 Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

I. Binding Assay

A) Membrane Preparation

Rat cerebellum or kidney cortex were rapidly dissected and frozen immediately in liquid nitrogen or used fresh. The tissues, 1-2 g for cerebellum or 3-5 g for kidney cortex, were homogenized in 15 mls of buffer containing 20mM

Tris HCl and 5mM EDTA, pH 7.5 at 4°C using a motor-driven homogenizer. The homogenates were filtered through cheesecloth and centrifuged at 20,000 x g for 10 minutes at 4°C. The supernatant was removed and centrifuged at 40,000 xg for 30 minutes at 4°C. The resulting pellet was resuspended in a small volume of buffer
5 containing 50 mM Tris, 10 mM MgCl₂, pH 7.5; aliquotted with small vials and frozen in liquid nitrogen. The membranes were diluted to give 1 and 5 mg of protein for each tube for cerebellum and kidney cortex in the binding assay.

Freshly isolated rat mesenteric artery and collateral vascular bed were washed in ice cold saline (on ice) and lymph nodes were removed from along
10 the major vessel. Then, the tissue was homogenized using a polytron in buffer containing 20 mM Tris and 5mM EDTA, pH 7.5 at 4°C in 15 ml volume for ~6 gm of mesenteric artery bed. The homogenate was strained through cheesecloth and centrifuged at 2,000 xg for 10 min. at 4°C. The supernatant was removed and centrifuged at 40,000 xg for 30 min. at 4°C. The resulting pellet was resuspended
15 as explained above for cerebellum and kidney cortex. Approximately 10 mg of membrane protein was used for each tube in binding experiments.

B) [¹²⁵I]ET-1 Binding Protocol

[¹²⁵I]ET-1 binding to membranes from rat cerebellum (2-5 mg protein/assay tube) or kidney cortex (3-8 mg protein/assay tube) were measured
20 after 60 minutes incubation at 30°C in 50 mM Tris HCl, 10 mM MgCl₂, 0.05% BSA, pH 7.5 buffer in a total volume of 100 µl. Membrane protein was added to tubes containing either buffer or indicated concentration of compounds. [¹²⁵I]ET-1 (2200 Ci/mmol) was diluted in the same buffer containing BSA to give a final concentration of 0.2-0.5 nM ET-1. Total and nonspecific binding were measured in
25 the absence and presence of 100 nM unlabelled ET-1. After the incubation, the reactions were stopped with 3.0 ml cold buffer containing 50 mM Tris and 10 mM MgCl₂, pH 7.5. Membrane bound radioactivity was separated from free ligand by filtering through Whatman GF/C filter paper and washing the filters 5 times with 3 ml of cold buffer using a Brandel cell harvester. Filter papers were counted in a
30 gamma counter with an efficiency of 75%.

II. In Vitro Vascular Smooth Muscle Activity

Rat aorta are cleaned of connective tissue and adherent fat, and cut into ring segments approximately 3 to 4 mm in length. Vascular rings are
35 suspended in organ bath chambers (10 ml) containing Krebs-bicarbonate solution of the following composition (millimolar): NaCl, 112.0; KCl, 4.7; KH₂PO₄, 1.2; MgSO₄, 1.2; CaCl₂, 2.5; NaHCO₃, 25.0; and dextrose, 11.0. Tissue bath solutions

are maintained at 37°C and aerated continuously with 95% O₂/5% CO₂. Resting tensions of aorta are maintained at 1 g and allowed to equilibrate for 2 hrs., during which time the bathing solution is changed every 15 to 20 min. Isometric tensions are recorded on Beckman R-611 dynographs with Grass FT03 force-displacement transducer. Cumulative concentration-response curves to ET-1 or other contractile agonists are constructed by the method of step-wise addition of the agonist. ET-1 concentrations are increased only after the previous concentration produces a steady-state contractile response. Only one concentration-response curve to ET-1 is generated in each tissue. ET receptor antagonists are added to paired tissues 30 min prior to the initiation of the concentration-response to contractile agonists.

ET-1 induced vascular contractions are expressed as a percentage of the response elicited by 60 mM KCl for each individual tissue which is determined at the beginning of each experiment. Data are expressed as the mean $\pm$ S.E.M. Dissociation constants (K_b) of competitive antagonists were determined by the standard method of Arunlakshana and Schild.

The following examples are illustrative and are not limiting of the compounds of this invention.

EXAMPLE 1

(1RS, 2SR, 3SR)-1,3-Bis(3,4-methylene-dioxyphenyl)-1,2,3,4-tetrahydro-2-naphthoic acid

a) Benzyl-methyl-2-[1-(3,4-methylenedioxyphenyl)-2-(2-methylcarboxyphenyl)ethyl] malonate.

To a solution of benzyl, methyl-2-(3,4-methylenedioxybenzyliden)-malonate (2.16 g, 6.35 mmol) and methyl o-trimethylsilylmethyl benzoate (2.12 g, 9.53 mmol) in HMPA (6 mL) at room temperature was added CsF (1.93 g, 12.70 mmol) in one portion. The mixture was heated to 60 °C for 3 h under argon and then quenched with water, and extracted with 1:1 EtOAc/Hexane. The organic layer was separated and washed with brine and dried (NaSO₄). After removing the solvent, chromatography of the residue with 4:1 Hexane/EtOAc gave 1.87 g (60%) of an inseparable 1:1 mixture of title compounds as colorless oil: R_f 0.31 (silica gel, 2:1 *n*-hexane/EtOAc).

- b) Methyl-3-(3,4-methylenedioxyphenyl)-4-(2-methylcarboxyphenyl)butanoate.

To a solution of triester (a) (3.30 g, 6.73 mmol) in 10 mL of ether acetate was added 330 mg of 10% Pd/C and the mixture was stirred under H₂ atmosphere at room temperature for 7 h. Filtration and concentration gave 2.70 g of the crude acids which were directly used in the following reaction without further purification.

The neat crude acids (2.70 g) were heated to 150 °C for 1 h and flash chromatography of the residue with 4:1 *n*-hexane/ethyl acetate gave 2.30 g (96% over two steps) of (b) as a colorless oil: *R_f* 0.46 (silica gel, 2:1 *n*-hexane/EtOAc).

- c) (±)-Phenethyl--(3SR)-1-methoxy-3-(3,4-methylenedioxyphenyl)-3,4-dihydro-2-naphthoate.

To a solution of diester (800 mg, 2.24 mmol) in 10 mL of THF was added 3 mL of a solution of 25% wt NaOMe/MeOH and the mixture was heated to reflux for 1 h. After cooling to room temperature, the mixture was poured into 1N HCl and extracted twice with 1:1 hexane/EtOAc. The combined organic extract was washed with brine and dried (Na₂SO₄). Removal of the solvent gave the crude b-keto ester, which was used in the next reaction without further purification.

To a solution of the crude b-keto ester in 10 mL of toluene was added phenethyl alcohol (0.41 mL, 3.36 mmol) and DMAP (10 mg) and the mixture was refluxed for 28 h. After cooling to room temperature, the mixture was poured into water and extracted twice with 1:1 hexane/EtOAc. The combined organic extract was washed with brine and dried (Na₂SO₄). Removal of the solvent gave the crude b-keto ester, which was used in the next reaction without further purification.

To a solution of the crude ester in 10 mL of ethanol at room temperature was added 20 mL of diazomethane solution (13 mmol) and the mixture was stirred under argon at room temperature for 17 h. The reaction was quenched with AcOH and the solution was then concentrated. Flash chromatography of the residue with 4:1 hexane/EtOAc gave 647 mg (67% over 3 steps) of a 1:1 mixture of inseparable diastereomeric methyl enoethers (c) as colorless oil.

- d) ($\pm$)-Phenethyl--(3SR)-1,3-bis(3,4-methylenedioxyphenyl)-3,4-dihydro-2-naphthoate.

To a mixture of 1-bromo-3,4-methylenedioxybenzene (423 mg, 2.10 mmol) and Mg (68 mg, 2.80 mmol) in 3 mL of THF was added 2 μ L of MeI and the mixture was irradiated by ultrasound for 30 min. (Mg disappeared). To a solution of methyl enol ether 7 (300 mg, 0.70 mmol) in 4 mL of THF at 0°C under argon was dropwise added the Grignard reagent methylenedioxyphenyl MgBr in THF. After 15 minutes, the reaction was quenched with aq. HCl and the mixture was extracted with 1:1 hexane/EtOAc. The organic extract was washed with brine and dried (Na₂SO₄). After removing the solvent, flash chromatography of the residue with 4:1 hexane/EtOAc gave 250 mg (69%) of 1:1 mixture of inseparable diastereomers (d) as colorless oil: *R_f* 0.45 (silica gel, 3:1 *n*-hexane/EtOAc); MS *m/e* (MH⁺) 519; Anal. Calcd. for C₃₃H₂₆O₆: C, 76.43; H, 5.05. Found: C, 76.70; H, 5.14.

- e) (1RS, 2SR, 3SR)-Methyl-1,3-bis(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydro-2-naphthoate.

To a solution of phenethyl ester (d) (454 mg, 0.876 mmol) in 4 mL of EtOAc was added 60 mg of 10% Pd/C and shaken under H₂ (55 Psi) at room temperature for 24 h. After filtration and concentration, the residue was dissolved in ether and added excess of diazomethane solution in ether. The reaction was quenched with acetic acid and washed with water, brine and dried (Na₂SO₄). After removing the solvent, flash chromatography of the residue with 4:1 Hexane/EtOAc gave 160 mg (43%) of methyl ester (e) as a colorless oil: *R_f* 0.52 (silica gel, 3:1 *n*-hexane/EtOAc).

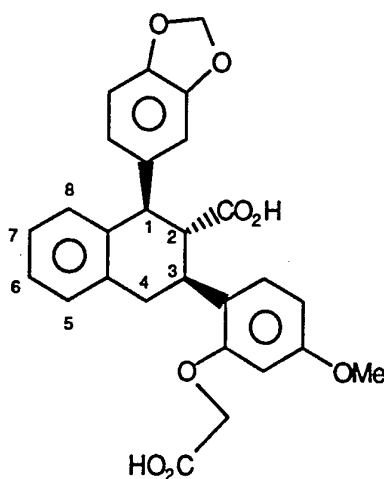
- f) (1RS, 2RS, 3SR)-Methyl-1,3-bis(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydro-2-naphthoate.

To solution of methyl ester (e) (160 mg, 0.373 mmol) in 3 mL of THF was added 0.7 mL of 25% NaOMe/MeOH and stirred at room temperature under argon for 18 h. The mixture was poured into 1N HCl and extracted with 1:1 Hexane/EtOAc. The organic extract was washed with brine and dried (Na₂SO₄). After removing the solvent, flash chromatography of the residue with 4:1 *n*-hexane/EtOAc gave 130 mg (81%) of (f) as a white solid: *R_f* 0.52 (silica gel, 3:1 *n*-hexane/EtOAc).

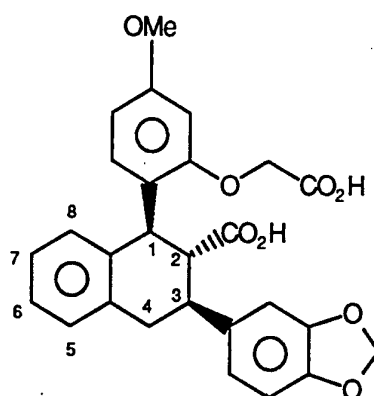
g) (1RS, 2SR, 3SR)-1,3-Bis(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydro-2-naphthoic acid.

To a solution of methyl ester (f) (110 mg, 0.257 mmol) in 6 mL of 1:1 MeOH/THF was added 2 mL of 10% NaOH and heated to 70 °C for 7 h. The mixture was poured into water and washed with 1:1 Hexane/EtOAc. The aqueous solution was acidified with 6N HCl to pH 5 and extracted with EtOAc. The organic extract was washed with brine and dried (Na₂SO₄). Removal of the solvent gave 100 mg (94%) of the title acid as a white solid: *R_f* 0.07 (silica gel, 2:1 *n*-hexane/EtOAc); ¹H NMR (CDCl₃) δ 3.00-3.25 (m, 3H), 4.38 (d, *J*=10.8 Hz, 1H), 5.94 (s, 4H), 6.55-7.18 (m, 10H); MS *m/e* 416 (M⁺); FAB HRMS Calcd. for C₂₅H₁₉O₆Na₂:461.0977. Found: 461.0954. Anal. Calcd. for C₂₅H₁₉O₆·H₂O: C, 69.12; H, 5.10. Found: C, 68.89 H, 5.41

EXAMPLE 2



(1RS, 2RS, 3SR)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydro-2-naphthoic acid.

EXAMPLE 3

5 (1R, 2SR, 3RS)-1-(2-Carboxymethoxy-4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydro-2-naphthoic acid.

EXAMPLE 4

10 Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Inhalant Formulation

15 A compound of Formula (I) (1 g) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

Tablets/IngredientsPer Tablet

20	1. Active ingredient (Cpd of Form. (I))	40 mg
	2. Corn Starch	20 mg
	3. Alginic acid	20 mg
25	4. Sodium Alginate	20 mg
	5. Mg stearate	<u>1.3 mg</u> 2.3 mg

30

Procedure for tablets:

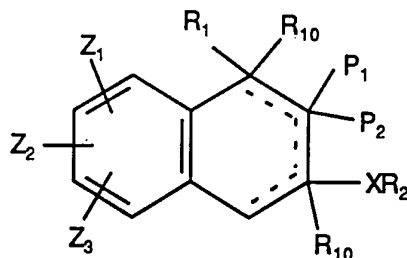
- Step 1 Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.
- 5 Step 2 Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.
- 10 Step 3 The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.
- Step 4 The wet granules are then dried in an oven at 140°F (60°C) until dry.
- 15 Step 5 The dry granules are lubricated with ingredient No. 5.
- Step 6 The lubricated granules are compressed on a suitable tablet press.

Parenteral Formulation

- 20 A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of Formula (I) in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

CLAIMS:

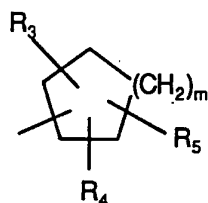
1) A compound of Formula (I),



5

wherein:

R_1 is $-X(CH_2)_nAr$ or $-X(CH_2)_nR_8$ or



10

(c) ;

R_2 is hydrogen, Ar or (c);

P_1 is $-X(CH_2)_nR_8$;

P_2 is $-X(CH_2)_nR_8$, or $-XR_9Y$;

15

R_3 and R_5 are independently hydrogen, R_{11} , OH,

C_{1-8} alkoxy, $-S(O)_qR_{11}$, $N(R_6)_2$, Br, F, I, Cl, CF_3 , $-NHCOR_6$, $-R_{11}CO_2R_7$, $-R_{11}CO_2R_7$, $-XR_9Y$ or $-X(CH_2)_nR_8$ wherein each methylene group within $-X(CH_2)_nR_8$ may be unsubstituted or substituted by one or two $-(CH_2)_nAr$ groups;

R_4 is hydrogen, R_{11} , OH, C_{1-5} alkoxy, $-S(O)_qR_{11}$, $-N(R_6)_2$, $-X(R_{11})$, Br, F, I, Cl or $-NHCOR_6$ wherein the C_{1-5} alkoxy may be unsubstituted or substituted by OH, methoxy or halogen;

20

R_6 is independently hydrogen or C_{1-4} alkyl;

R_7 is independently hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-8} alkynyl, all of which may be unsubstituted or substituted by one or more OH,

$-N(R_6)_2$, $-CO_2R_{12}$, halogen or XC_{1-5} alkyl; or R_7 is $(CH_2)_nAr$;

25

R_8 is hydrogen, R_{11} , $-CO_2R_7$, $-CO_2C(R_7)_2O(CO)XR_{11}$, $PO_3(R_7)_2$, $-SO_2NR_7R_{11}$, $-CONR_7SO_2R_{11}$, $-SO_3R_7$, $-SO_2R_7$, $-P(O)(OR_7)R_7$, CN, $-C(O)N(R_6)_2$, $-NR_7SO_2R_{11}$, tetrazole or OR_6 ;

R_9 is $(CH_2)_n$, C_{1-10} alkyl, C_{2-10} alkenyl or phenyl all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, COOH, halogen, $>C=O$ or XC_{1-5} alkyl;

R_{10} is R_3 or R_4 ;

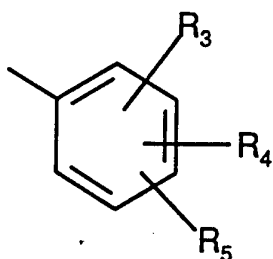
5 R_{11} is Ar, C_{3-8} cycloalkyl, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl all of which may be unsubstituted or substituted by one or more OH, CH_2OH , $N(R_6)_2$ or halogen;

R_{12} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-7} alkynyl;

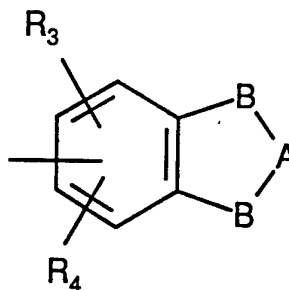
X is $(CH_2)_n$, O, NR_6 or $S(O)_q$;

10 Y is CH_3 or $X(CH_2)_nAr$;

Ar is:



(a)



(b)

15

naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholynyl, piperidinyl, piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted
20 by one or more R_3 or R_4 groups;

A is $C=O$, or $[C(R_6)_2]_m$;

B is $-CH_2-$ or $-O-$;

Z_1 and Z_2 are independently hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, OH, C_{1-8} alkoxy, $S(O)_qC_{1-8}$ alkyl, $N(R_6)_2$, Br, F, I, Cl, $NHCOR_6$,
25 $-X(CH_2)_nR_8$, phenyl, benzyl or C_{3-6} cycloalkyl wherein the C_{1-8} alkyl, C_{2-8} alkenyl or C_{2-8} alkynyl may be optionally substituted by COOH, OH, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R_6)_2$, or halogen; or Z_1 and Z_2 together may be $-O-A-O-$ on contiguous carbons;

Z_3 is Z_1 or XR_9Y ;

30 q is zero, one or two;

n is an integer from 0 to six;

m is 1, 2 or 3; and the dotted line indicates the optional presence of one or two double bonds; or a pharmaceutically acceptable salt thereof; provided that

- R₂ is not hydrogen when X is S(O)_q;
- 5 • when an optional double bond is present there is only one R₁₀ and when adjacent to P₁ and P₂, there is no P₁ and P₂ is not NR₆R₉Y;
- when an optional double bond is present in Formula (I) and X-R₂ is attached to the double bond, X is not NR₆;
- when an optional double bond is present and R₁ is attached directly to
10 the double bond, R₁ is not NR₆Ar;
- when R₃, R₅, Z₁, Z₂, or Z₃ is X(CH₂)_nR₈ and n is 0, X is not oxygen or NR₆ when R₈ is OR₆ or CO₂H; and
- when R₈ is CO(CR₁₁)₂O(CO)XR₇, X is not S(O)_q; and
- when there are two double bonds present and R₁ and R₂ are phenyl; R₃,
15 R₄ and R₅ are not all hydrogen.

2. A compound of claim 1 wherein R₁ is X(CH₂)_nAr, (Ar is (a) or (b)), dihydrobenzofuranyl, benzodioxanyl, cyclohexyl, or C₁₋₄alkyl; R₂ is (a), (b), C₁₋₄alkyl, indolyl or hydrogen; R₃ and R₅ are independently hydrogen, OH,
20 C₁₋₅alkoxy, halogen, -OC₁₋₄alkyl phenyl, R₁₁CO₂R₇, C₁₋₄alkyl, N(R₆)₂, NH(CO)CH₃, -X(CH₂)_nR₈, -XR₉ pyridyl, phenyl or S(O)_pC₁₋₅alkyl; R₄ is hydrogen, OH, C₁₋₅alkoxy, halogen, C₁₋₄alkyl, N(R₆)₂, NH(CO)CH₃ or S(O)_pC₁₋₅alkyl; Z₁, Z₂ and Z₃ are independently XR₉Y, benzyl, hydrogen, OH, C₁₋₅alkoxy, -N(R₆)₂, S(O)_qC₁₋₈alkyl, NHCOR₆, X(CH₂)_nR₈ or halogen, or Z₁
25 and Z₂ together may be -O-A-O on contiguous carbons; P₁ and P₂ are independently hydrogen, CO₂H or tetrazole; Ar is (a), (b), phenyl, or pyridyl; X is (CH₂)_n or oxygen.

3. A compound of claim 2 wherein R₃ is hydrogen or -X(CH₂)_nR₈, R₁₁CO₂R₇; R₄ and R₅ are independently hydrogen, OH, C₁₋₅alkoxy, SC₁₋₅alkyl, F, Br, C₁₋₃alkyl or NH₂; Z₁ and Z₃ are hydrogen and Z₂ is hydrogen, OH, C₁₋₅alkoxy, halogen, X(CH₂)_nR₈, NH₂, benzyl, NH(CO)CH₃, or Z₁ and Z₂
30 together may be O-A-O.

4. A compound of claim 3 wherein R₁ is (a) or (b); R₂ is (a) or (b); A is CH₂, B is -O-; there is no optional double bond; R₁ and XR₂ are trans to P₁; Z₂ is OH, C₁₋₅alkoxy, -OCH₂CHCH₂ or hydrogen, Z₁ and Z₃ are hydrogen; R₃ is XAr,
35

hydrogen, $X(\text{CH}_2)_q\text{COOH}$, $X(\text{CH}_2)_q\text{CONR}_7\text{SO}_2\text{R}_{11}$ or $\text{CH}=\text{CHCO}_2\text{H}$, R_4 is hydrogen, substituted phenyl, or C_{1-2} alkoxy; and R_5 , R_{10} and P_2 are hydrogen.

5 5. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

10 6. A method of antagonizing endothelin receptors which comprises administering to a subject in need thereof, an effective amount to antagonize endothelin receptors or a compound of claim 1.

7. A method of treating hypertension, renal failure or cerebrovascular disease which comprises administering to a subject in need thereof, an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/08917

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/245; C07D 317/46

US CL : 549/214, 434, 436, 444, 445; 560/40, 250; 562/446

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 549/214, 434, 436, 444, 445; 560/40, 250; 562/446

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US, A, 4,401,676 (PATCHETT ET AL) 30 AUGUST 1983, COLUMN 1 LINES 30 + .	1-7 --- 1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

14 NOVEMBER 1994

Date of mailing of the international search report

05 DEC 1994

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