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IMIDAZOLYL-ALKENOIC ACIDS

The present invention relates to new imidazolyl-alkenoic acids which are angiotensin II receptor antagonists and are useful in regulating hypertension induced or exacerbated by angiotensin II, and in the treatment of congestive heart failure, renal failure, and glaucoma. This invention also relates to pharmaceutical compositions containing these compounds and methods for using these compounds as antagonists of angiotensin II, as antihypertensive agents and as agents for treating congestive heart failure, renal failure, and glaucoma.

BACKGROUND OF THE INVENTION

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The class of peptide pressor hormone known as angiotensin is responsible for a vasopressor action that is implicated in the etiology of hypertension in man. Inappropriate activity of the renin-angiotensin systems appears to be a key element in essential hypertension, congestive heart failure and in some forms of renal disease. In addition to a direct action on arteries and arterioles, angiotensin II (AII), being one of the most potent endogenous vasoconstrictors known, exerts stimulation on the release of aldosterone from the adrenal cortex. Therefore, the renin-angiotensin system, by virtue of its participation in the control of renal sodium handling, plays an important role in

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cardiovascular hemeostasis.

Interruption of the renin-angiotensin system with converting enzyme inhibitors, such as captopril, has proved to be clinically useful in the treatment of hypertension and congestive heart failure (Abrams, W.B., et al., (1984), Federation Proc., 43, 1314). The most direct approach towards inhibition of the renin-angiotensin system would block the action of AII at the receptor. Compelling evidence suggests that AII also contributes to renal vasoconstriction and sodium retention that is characteristic of a number of disorders such as heart failure, cirrhosis and complications of pregnancy (Hollenberg, N.K., (1984), J. Cardiovas. Pharmacol., 6, S176). In addition, recent animal studies suggest that inhibition of the renin-angiotensin system may be beneficial in halting or slowing the progression of chronic renal failure (Anderson, S., et al., (1985), J. Clin. Invest., 76, 612). Also, a recent patent application (South African Patent Application No. 87/01,653) claims that AII antagonists are useful as agents for reducing and controlling elevated intraocular pressure, especially glaucoma, in mammals.

The compounds of this invention inhibit, block and antagonize the action of the hormone AII, and are therefore useful in regulating and moderating angiotensin induced hypertension, congestive heart failure, renal failure and other disorders attributed to the actions of AII. When compounds of this invention are administered to mammals, the elevated blood pressure due to AII is reduced and other manifestations based on AII intercession are minimized and controlled. Compounds of this invention are also expected to exhibit diuretic activity.

Recognition of the importance of blocking and inhibiting the actions of AII has stimulated other efforts to synthesize antagonists of AII. The following references have disclosed imidazole derivatives which are

described as having AII blocking activity and useful as hypotensive agents.

Furukawa et al., U.S. Patent 4,340,598 discloses imidazol-5-yl-acetic acids and imidazol-5-yl-propanoic acids. Specifically, the discloser includes 1-benzyl-2-n-butyl-5-chloroimidazole-4-acetic acid and 1-benzyl-2-phenyl-5-chloroimidazole-4-propanoic acid.

Furukawa, et al., U.S. Patent 4,355,040 discloses substituted imidazole-5-acetic acid derivatives. A compound specifically disclosed is 1-(2-chlorobenzyl)-2-n-butyl-4-chloroimidazole-5-acetic acid.

Carini et al. in EP 253,310 disclose certain imidazolylpropenoic acids. Two intermediates described in this patent are ethyl 3-[1-(4-nitrobenzyl)-2-butyl-4-chloroimidazol-5-yl]propenoate and ethyl 3-[2-butyl-4-chloro-1-(4-aminobenzyl)imidazol-5-yl]propenoate.

Also, Wareing, in PCT/EP 86/00297, discloses as intermediates certain imidazolylpropenoate compounds. On page 62, Formula (CX) is ethyl 3-[1(-4-fluorophenyl)-4-isopropyl-2-phenyl-1H-imidazol-5-yl]-2-propenoate.

DESCRIPTION OF THE INVENTION

The compounds of the present invention that are blockers of angiotensin II receptors are:

(E)-3-[2-n-butyl-1-((4-carboxynaphth-1-yl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid and

(E)-3-[2-n-butyl-1-((4-carboxynaphth-1-yl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, ethyl ester;

or a pharmaceutically acceptable salt thereof, and

(E)-3-[2-n-butyl-1-((4-carboxypenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid methanesulfonate.

The invention also relates to pharmaceutical compositions comprising a pharmaceutical carrier and an

effective amount of a compound hereinabove named.

Also included in the present invention are methods for antagonizing angiotensin II receptors which comprises administering to a subject in need thereof an effective
5 amount of a compound hereinabove named. Methods of treating hypertension, congestive heart failure, glaucoma, and renal failure by administering these compounds are also included in this invention.

The compounds of this invention are prepared by
10 procedures described herein and illustrated by the examples. Reagents, protecting groups and functionality on the imidazole and other fragments of the molecule must be consistent with the proposed chemical transformations. Steps in the synthesis must be compatible with the
15 functional groups and the protecting groups on the imidazole and other parts of the molecule.

The starting material, 2-n-butylimidazole, is known to the art (J. Org. Chem. 45:4038, 1980) or is synthesized by known procedures. For example, imidazole
20 is converted to 2-n-butylimidazole by reacting imidazole with triethylorthoformate and p-toluenesulfonic acid to give 1-diethoxyorthoamide imidazole and then treating with n-butyl lithium to give the 2-lithium derivative of the orthoamide and alkylating with n-butyl iodide in a
25 suitable solvent, such as tetrahydrofuran (THF).

The 1-substituted naphthyl or benzyl group is incorporated onto the 2-n-butylimidazole by known procedures, for example, by reaction with substituted naphthyl or benzyl halide, mesylate or acetate, such as
30 2-chlorobenzyl bromide or 4-carbomethoxybenzyl bromide, in a suitable solvent, such as dimethylformamide (DMF), in the presence of a suitable acid acceptor, such as sodium alkylate, potassium or sodium carbonate, or a metal hydride, preferably sodium hydride at a reaction
35 temperature of about 25°C to about 100°C, preferably at about 50°C. The resulting 1-substituted-naphthyl or benzyl-2-n-butylimidazole is hydroxymethylated in the 5

-position, for example, by reacting with formaldehyde in the presence of sodium acetate in acetic acid to provide the 1-substituted-naphthyl or-benzyl-2-n-butyl-5-hydroxymethylimidazole intermediates.

5 Alternatively, the above prepared 5-hydroxymethyl-imidazole intermediates are prepared by reacting an imido ether, such as valeramidine methyl ether, with dihydroxyacetone in liquid ammonia under pressure to give 2-n-butyl-5-hydroxymethylimidazole. This intermediate is
10 reacted with acetic anhydride to give 1-acetyl-5-acetoxymethyl-2-n-butylimidazole. The diacetate intermediate is N-alkylated, for example, using 2-chlorobenzyl triflate or 4-carbomethoxybenzyl triflate, and the resulting 1-substituted-2-n-butyl-5-
15 acetoxymethyl-imidazole is treated with aqueous base, such as 10% sodium hydroxide solution, to give the 5-hydroxymethylimidazole intermediates described previously.

 The hydroxymethyl group of the hereinbefore prepared
20 intermediate is oxidized to an aldehyde by treatment with a suitable reagent, such as anhydrous chromic acid-silica gel in tetrahydrofuran or, preferably, with activated manganese dioxide, in a suitable solvent, such as benzene or toluene, or preferably methylene chloride, at a
25 temperature of about 25°C to about 140°C, preferably at about 25°C. The imidazol-5-carboxaldehydes are reacted with an appropriate phosphonate, such trimethyl-3-(2-thienyl)-2-phosphonopropionate. The phosphonates are prepared, for example, from trialkyl phosphonoacetates by
30 alkylation with an appropriate halide, mesylate or acetate in the presence of a suitable base, such as sodium hydride, in a suitable solvent, preferably glyme at a reaction temperature of about 25°C to about 110°C, preferably at about 55°C, to provide the appropriate
35 phosphonate. The reaction of the imidazol-5-carboxaldehydes with the phosphonates is performed in the presence of a suitable base, such as a metal alkoxide,

lithium hydride or preferably sodium hydride, in a suitable solvent, such as ethanol, methanol, ether, dioxane, tetrahydrofuran, or preferably glyme, at a reaction temperature of about 10°C to about 50°C, preferably at about 25°C, to provide a variable mixture of trans and cis, e.g., (E) and (Z), 1-substituted-2-n-butyl-5-CH=C[(2-thienyl)methyl]-(COOalkyl)-imidazoles. These isomers are readily separated by chromatography over silica gel in suitable solvent systems, preferably hexane in ethyl acetate mixtures. The esters are hydrolyzed to the corresponding acid compounds using base, such as potassium hydroxide, lithium hydroxide or sodium hydroxide, in a suitable solvent system, such as, for example, aqueous alcohols or diglyme.

Alternatively, the 1-substituted-2-n-butylimidazol-5-carboxaldehydes are prepared by the following procedure. Starting 2-n-butylimidazol-5-carboxaldehydes are reacted with an N-alkylating protecting reagent, such as chloromethyl pivalate (POM-Cl), in the presence of a base, such as potassium carbonate, in a suitable solvent, such as dimethylformamide, at a temperature of about 20°C to about 50°C, preferably at about 25°C, to give N-alkylation (e.g., POM-derivation) on the least hindered nitrogen atom of the imidazole nucleus. The 1-substituted-naphthyl or -benzyl group is incorporated onto the imidazole by N-alkylation of the above prepared aldehyde with a halomethylbenzene compounds, such as methyl 4-bromomethylbenzoate or methyl 4-bromomethylnaphthalene-1-carboxylate, at a temperature of about 80°C to about 125°C, preferably at about 100°C. The protecting group on the 3-nitrogen of the imidazole ring is removed by base hydrolysis, for example using a biphasic mixture of ethyl acetate and aqueous sodium carbonate, to give 1-substituted-n-butylimidazole-5-carboxaldehyde compounds. The compounds of this invention can be prepared from these 5-carboxaldehyde compounds by the methods described above.

Alternately, the 2-n-butylimidazole starting materials are reacted with trimethylsilylethoxymethyl(SEM) chloride to give 1-(trimethylsilyl)-ethoxymethyl-2-n-butylimidazole. The reaction is carried out, for example, in the presence of sodium hydride in a solvent such as dimethylformamide. The 5-tributyltin derivatives are prepared by lithiation with, for example, butyllithium in a suitable solvent, preferably diethyl ether, followed by treatment of the lithio imidazole derivative with a tributyltin halide, preferably tri-n-butyltin chloride, at about -10°C to about 35°C, preferably at about 25°C. The 1-SEM-2-n-butyl-5-tributyltinimidazole is coupled with an α,β -unsaturated acid ester having a leaving group on the β -position, such as a halide or trifluoromethanesulfonyloxy group, for example, $\text{BrCR}^4=\text{C}[(2\text{-thienyl)methyl}](\text{COOalkyl})$, in the presence of a phosphine ligand, such as bis(diphenylphosphino)propane, or triphenylphosphine and a palladium (II) compound, or preferably tetrakis(triphenylphosphine)palladium(0), with or without a base, such as tributylamine, at a temperature of about 50°C to about 150°C, preferably at about 120°C. Both the (E) and (Z) olefinic isomers are prepared by this procedure, and the isomeric esters are readily separated by chromatography over silica gel. The 1-SEM group from the (E) and (Z) isomers is hydrolyzed with acid, for example, aqueous hydrochloric, in a suitable alcoholic solvent, such as methanol or ethanol, and the 1-unsubstituted imidazole derivatives are converted to the 1-t-butoxycarbonyl (t-BOC) imidazoles with di-t-butyl dicarbonate (Hoppe-Seyler's Z. Physiol. Chem., (1976), 357, 1651). The t-BOC esters are alkylated and hydrolyzed with, for example, 2-chlorobenzyl triflate or 4-carbomethoxybenzyl triflate, in the presence of a suitable base, preferably diisopropylethylamine, in a suitable solvent, preferably methylene chloride, to afford the 1-substituted-imidazole derivatives (esters).

The (E) and (Z) isomers are hydrolyzed to the (E) and (Z) acids by the method described above.

The compounds of this invention are also prepared by the following procedure. The 1-substituted-2-n-butyl-
5 imidazole-5-carboxaldehydes, prepared as described above, are reacted with a substituted half-acid, half-ester derivative of a malonate, such as ethyl 2-carboxy-3-(2-thienyl)propionate, in the presence of a base, such as piperidine, in a suitable solvent, such as toluene, at a
10 temperature of about 80°C to about 110°C, preferably at about 100°C. The resulting 1-substituted-2-n-butyl-5-CH=C(R⁵)COOalkylimidazoles are hydrolyzed to the corresponding compounds of the present invention by alkaline hydrolysis as described above.

15 Alternately, the compounds of this invention are prepared as follows. The 1-substituted-2-n-butyl-imidazol-5-carboxaldehydes prepared hereinabove are treated with the lithium derivative of a substituted ethyl or methyl ester. These lithio derivatives are
20 prepared from the reaction of lithium diisopropylamide in a suitable solvent, preferably tetrahydrofuran, with an acid ester, such as ROOC-CH₂-CH₂-(2-thienyl), to generate the α-lithio derivatives at about -78°C to about -10°C, preferably at about -78°C, which are then treated with
25 the imidazol-carboxaldehyde. The intermediate β-hydroxy group of the imidazole ester is converted to a mesylate or an acetate and the mesylate, or preferably the acetate, is heated in a suitable solvent, such as toluene, with one to two equivalents of 1,8-diazo-
30 bicyclo[5.4.0]undec-7-ene, at about 50 to about 110°C, preferably at about 80°C, to afford 3-(imidazol-5-yl)-2-(2-thienyl)methyl-2-propenoic acid esters. The (E) isomer is the predominate olefinic isomer. The acids are prepared from the esters by the method described above.

35 Compounds of the present invention in which the substituent in the 1-position of the imidazole ring is substituted by carboxy are formed from the compounds in

which this group is substituted by $\text{CO}_2\text{C}_1\text{-C}_4$ alkyl using basic hydrolysis, such as aqueous sodium or potassium hydroxide in methanol or ethanol, or using acidic hydrolysis, such as aqueous hydrochloric acid.

5 Pharmaceutically acceptable acid addition salts of compounds of Formula (I) are formed with appropriate organic or inorganic acids by methods known in the art. For example, the base is reacted with a suitable inorganic or organic acid in an aqueous miscible solvent
10 such as ethanol with isolation of the salt by removing the solvent or in an aqueous immiscible solvent when the acid is soluble therein, such as ethyl ether or chloroform, with the desired salt separating directly or isolated by removing the solvent. Representative
15 examples of suitable acids are maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic,
20 benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

 Pharmaceutically acceptable base addition salts of compounds of Formula (I) in which R^8 is H are prepared by known methods from organic and inorganic bases, including
25 nontoxic alkali metal and alkaline earth bases, for example, calcium, lithium, sodium, and potassium hydroxide; ammonium hydroxide, and nontoxic organic bases, such as triethylamine, butylamine, piperazine, meglumine, choline, diethanolamine, and tromethamine.

30 Angiotensin II antagonist activity of the compounds of Formula (I) is assessed by in vitro and in vivo methods. In vitro antagonist activity is determined by the ability of the compounds to compete with ^{125}I -angiotensin II for binding to vascular angiotensin II
35 receptors and by their ability to antagonize the contractile response to angiotensin II in the isolated rabbit aorta. In vivo activity is evaluated by the

efficacy of the compounds to inhibit the pressor response to exogenous angiotensin II in conscious rats and to lower blood pressure in a rat model of renin dependent hypertension.

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Binding

The radioligand binding assay is a modification of a method previously described in detail (Gunther et al., Circ. Res. 47:278, 1980). A particular fraction from rat
10 mesenteric arteries is incubated in Tris buffer with 80 pM of ^{125}I -angiotensin II with or without angiotensin II antagonists for 1 hour at 25°C. The incubation is terminated by rapid filtration and receptor bound ^{125}I -angiotensin II trapped on the filter is quantitated with
15 a gamma counter. The potency of angiotensin II antagonists is expressed as the IC_{50} which is the concentration of antagonist needed to displace 50% of the total specifically bound angiotensin II. Exemplary of the IC_{50} of compounds of the invention (E isomers) is
20 about 0.1 nM to about 30nM.

Aorta

The ability of the compounds to antagonize angiotensin II induced vasoconstriction is examined in
25 the rabbit aorta. Ring segments are cut from the rabbit thoracic aorta and suspended in organ baths containing physiological salt solution. The ring segments are mounted over metal supports and attached to force displacement transducers which are connected to a
30 recorder. Cumulative concentration response curves to angiotensin II are performed in the absence of antagonist or following a 30-minute incubation with antagonist. Antagonist disassociation constants (K_B) are calculated by the dose ratio method using the mean effective
35 concentrations. Exemplary of the K_B of compounds of the invention (E isomers) is about 0.1 nM to about 0.50nM.

Inhibition of pressor response to
angiotensin II in conscious rats

Rats are prepared with indwelling femoral arterial and venous catheters and a stomach tube (Gellai et al.,
5 Kidney Int. 15:419, 1979). Two to three days following surgery the rats are placed in a restrainer and blood pressure is continuously monitored from the arterial catheter with a pressure transducer and recorded on a polygraph. The change in mean arterial pressure in
10 response to intravenous injections of 250 mg/kg angiotensin II is compared at various time points prior to and following the administration of the compounds intravenously or orally at doses of 0.1 to 300 mg/kg. The dose of compound needed to produce 50% inhibition of
15 the control response to angiotensin II (IC_{50}) is used to estimate the potency of the compounds.

Antihypertensive activity

The antihypertensive activity of the compounds is
20 measured by their ability to reduce mean arterial pressure in conscious rats made renin-dependent hypertensive by ligation of the left renal artery (Cangiano et al., J. Pharmacol. Exp. Ther. 208:310,
1979). Renal artery ligated rats are prepared with
25 indwelling catheters as described above. Seven to eight days following renal artery ligation, the time at which plasma renin levels are highest, the conscious rats are placed in restrainers and mean arterial pressure is continuously recorded prior to and following the
30 administration of the compounds intravenously or orally. The dose of compound needed to reduce mean arterial pressure by 30 mm Hg (IC_{30}) is used as an estimate of potency.

The intraocular pressure lowering effects employed
35 in this invention may be measured by the procedure described by Watkins, et al., J. Ocular Pharmacol., 1 (2):161-168 (1985).

The compounds of the instant invention are incorporated into convenient dosage forms, such as injectable preparations, or for orally active compounds, capsules or tablets. Solid or liquid pharmaceutical carriers are employed. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid, such as an ampoule, or an aqueous or nonaqueous liquid suspension.

For topical ophthalmologic administration, the pharmaceutical compositions adapted include solutions, suspensions, ointments, and solid inserts. Typical pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or vegetable oils, and water soluble ophthalmologically acceptable non-toxic polymers, for example, cellulose derivatives such as methyl cellulose. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting, and bodying agents, as for example, polyethylene glycols; antibacterial components, such as quarternary ammonium compounds; buffering ingredients, such as alkali metal chloride; antioxidants, such as sodium metabisulfite; and other conventional ingredients, such as sorbitan monolaurate.

Additionally, suitable ophthalmic vehicles may be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems.

The pharmaceutical preparation may also be in the form of a solid insert. For example, one may use a solid water soluble polymer as the carrier for the medicament. Solid water insoluble inserts, such as those prepared from ethylene vinyl acetate copolymer, may also be utilized.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral, parenteral, or topical products.

Doses of the compounds of the present invention in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity selected from the range of .01 - 200 mg/kg of active compound, preferably 1 - 100 mg/kg. The selected dose is administered to a human patient in need of angiotensin II receptor antagonism from 1-6 times daily, orally, rectally, topically, by injection, or continuously by infusion. Oral dosage units for human administration preferably contain from 1 to 500 mg of active compound. Preferably, lower dosages are used for parenteral administration. Oral administration, at higher dosages, however, also can be used when safe and convenient for the patient. Topical formulations contain the active compound in an amount selected from 0.0001 to 0.1 (w/v%), preferably from 0.0001 to 0.01. As a topical dosage unit form, an amount of active compound from between 50 ng to 0.05 mg, preferably 50 ng to 5 mg, is applied to the human eye.

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

The method of this invention of antagonizing angiotensin II receptors in mammals, including humans, comprises administering to a subject in need of such antagonism an effective amount of a compound of the

instant invention. The method of this invention of producing antihypertensive activity and the method of treating congestive heart failure, glaucoma, and renal failure comprise administering a compound of the instant invention to a subject in need thereof an effective amount to produce said activity.

Contemplated equivalents of the present invention compounds are compounds otherwise corresponding thereto wherein substituents have been added to any of the unsubstituted positions of these compounds provided such compounds have the pharmaceutical utility of compounds of the instant invention.

The following examples illustrate preparation of compounds and pharmaceutical compositions of this invention. The examples are not intended to limit the scope of this invention as defined hereinabove and as claimed below.

Example 1

(E)-3-[2-n-Butyl-1-((2-chlorophenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

(i) 2-n-butyl-1-(2-chloro-phenyl)methyl-1H-imidazole

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Imidazole was converted to the 1-diethoxyorthoamide derivative by the method of Curtis and Brown, J. Org. Chem., (1980), 45, 20. Imidazole (12.8 g, 0.19 mol) and 118.4 g (0.8 mol) of triethylorthoformate were reacted in the presence of 1 g of p-toluenesulfonic acid to give 20.6 (61%), bp 65-70°C (0.1 mm) of 1-diethoxyorthoamide imidazole. This product (24.0 g, 0.14 mol) was dissolved in dry tetrahydrofuran (250 mL), cooled to -40°C and n-butyl lithium (0.14 mol, 56.4 mL of 2.5 M in hexane) was added at -40°C to -35°C. After 15 minutes n-butyl iodide (31.1 g, 0.169 mol) was added at -40°C, and the reaction was stirred overnight at ambient temperature. The

reaction was partitioned between ether and 0.3 N hydrochloric acid, and the organic layer was repeatedly extracted with dilute hydrochloric acid. The combined aqueous extracts were neutralized with sodium bicarbonate solution, extracted with methylene chloride, dried over magnesium sulfate and concentrated. A flash distillation on a Kugelrohr apparatus provided 14.8 g (85%) of 2-n-butylimidazole.

2-n-Butylimidazole (9.7 g, 0.078 mol) was dissolved in methanol (50 mL) and added dropwise to a solution of sodium methoxide (from sodium hydride (2.31 g, 0.0934 mol) in methanol (250 mL)). After one hour the solution was evaporated to dryness, and the sodium salt was taken up in dry dimethylformamide (150 mL) and 2-chlorobenzyl bromide (16.3 g, 0.079 mol) was added. The mixture was heated at 50°C for 17 hours under argon, poured onto ice water and the product was extracted into ethyl acetate. The extract was washed, dried, and concentrated to give 18.5 g of crude product which was chromatographed over silica gel with 2:1 ethyl acetate/hexane to provide 11.9 g (61%) of 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazole as an oil. Thin layer chromatography on silica gel with 4:1 ethyl acetate/hexane gave an R_f value of 0.59.

(ii) 2-n-butyl-1-(2-chlorophenyl)methyl-5-hydroxymethyl-1H-imidazole

Method 1

A mixture of 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazole (95.5 g, 0.384 mol), 37% formaldehyde (500 mL), sodium acetate (80 g) and acetic acid (60 mL) was heated to reflux for 40 hours under argon. The reaction was concentrated in vacuo, and the residue was stirred with 500 mL of 20% sodium hydroxide solution for 4 hours, diluted with water and extracted with methylene chloride. The extract was washed, dried, and concentrated. The

crude product (117 g) was flash chromatographed over 600 g of silica gel with a gradient of ethyl acetate to 10% of methanol in ethyl acetate to give 8.3 g of starting material, 24.5 g of a mixture of starting material and product, and 44 g (41%) of 2-n-butyl-1-(2-chlorophenyl)-methyl-5-hydroxymethyl-1H-imidazole; mp 86-88°C (from ethyl acetate). Further elution provided the bis (4,5-hydroxymethyl) derivative; mp 138-140°C (from ethyl acetate).

Method 2

A mixture of valeramidine methyl ether hydrochloride (250 g, 1.66 mol) and dihydroxyacetone (150 g, 0.83 mol) dissolved in liquid ammonia was allowed to stand overnight at room temperature in a pressure vessel, and then heated at 65°C for 4 hours at 375 psi. The ammonia was allowed to evaporate, and the residue was dissolved in methanol (3L). The resulting slurry was refluxed with added acetonitrile (1L). The solution was decanted from the solid ammonium chloride while hot. This procedure was repeated, and the combined acetonitrile extracts were treated with charcoal, filtered hot and the filtrate was concentrated in vacuum to give the dark oil, 2-n-butyl-5-hydroxymethylimidazole (253 g, 1.63 mol, 98%).

This crude alcohol (253 g) was treated with acetic anhydride (400 mL) at -15°C and then was allowed to warm to ambient temperature with stirring, and then stirred an additional 19 hours. The acetic anhydride was evaporated at reduced pressure, the residue taken up in methylene chloride, and the organic phase was washed with 5% sodium bicarbonate solution and water. The extract was dried over sodium sulfate and concentrated to give 323 g (83%) of 1-acetyl-4-acetoxymethyl-2-n-butylimidazole.

This diacetate was N-alkylated by the following procedure. To a solution of triflic anhydride (120 mL, 0.71 mol) in methylene chloride (200 mL) at -78°C under

argon was added a solution of diisopropyl ethylamine (128 mL, 0.73 mol) and 2-chlorobenzyl alcohol (104 g, 0.72 mol) in methylene chloride (350 mL) over a period of 20 minutes. After being stirred an additional 20 minutes at
5 -78°C, this solution was then treated with 1-acetyl-4-acetoxymethyl-2-n-butylimidazole (146 g, 0.61 mol) dissolved in methylene chloride (300 mL) over a 20-minute interval. The mixture was then stirred at ambient temperature for 18 hours and the solvents were
10 evaporated. The residual 2-n-butyl-5-acetoxymethyl-1-(2-chlorophenyl)methyl-1H-imidazole was used without purification for the hydrolysis of the acetate group.

A solution of crude 2-n-butyl-5-acetoxymethyl-1-(2-chlorophenyl)methyl-1H-imidazole (250 g) in methanol (200
15 mL) was treated with 10% sodium hydroxide solution (700 mL) and the mixture was heated on a steam bath for 4 hours. After cooling, methylene chloride was added, the organic phase was separated, washed with water, dried and concentrated. The residue was dissolved in ether,
20 cooled, and seeded to give the crude product. Recrystallization from ethyl acetate gave 176 g of 2-n-butyl-1-(2-chlorophenyl)methyl-5-hydroxymethyl-1H-imidazole; mp 86-88°C. This material was identical in all respects to the product prepared by Method 1.

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(iii) 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-carboxaldehyde

A solution of 2-n-butyl-1-(2-chlorophenyl)methyl-5-hydroxymethyl-1H-imidazole (5.4 g, 0.0194 mol) in toluene
30 (25 mL) was added to a suspension of activated manganese dioxide (27 g) in methylene chloride (325 mL). The suspension was stirred at room temperature for 17 hours. The solids were filtered and the filtrate concentrated
35 and flash chromatographed over silica gel with 6:4 hexane/ethyl acetate to afford 4.16 g (78%) of 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-carboxaldehyde, as

an oil. NMR and IR were consistent with the structure.

- (iv) (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid

Method A

(a) trimethyl 3-(2-thienyl)-2-phosphonopropionate

To a solution of 2-thiophenemethanol (2.28 g, 0.02 mol) in carbon tetrachloride (25 mL) was added triphenylphosphine (6.81 g, 0.026 mol), and the solution was refluxed for 3 hours. The cooled reaction mixture was diluted with hexane (60 mL), chilled and filtered. The concentrated filtrate (4.6 g) was flash chromatographed over silica gel with 7:3 hexane/ethyl acetate to provide 2-chloromethylthiophene (1.52 g, 57%) as an oil.

A suspension of sodium hydride (0.271 g, 11.3 mmol) in dry glyme (40 mL) under argon was treated dropwise with trimethyl phosphonoacetate (1.87 g, 10.3 mmol) in glyme (5 mL). The resulting mixture was stirred at room temperature for 1.5 hours. Then 2-chloromethyl-thiophene (1.5 g, 11.3 mmol) was added, and the mixture was stirred at 65°C for 18 hours. The reaction was partitioned between water and ethyl acetate, and the organic layer was washed with water and brine, dried with anhydrous magnesium sulfate and concentrated to 1.9 g of an oil. This was chromatographed over silica gel 4:1 ethylacetate/hexane to afford 800 mg (28%) of trimethyl 3-(2-thienyl)-2-phosphonopropionate.

- (b) methyl (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate

To a suspension of sodium hydride (69 mg, 2.87 mmol)

in glyme (5 mL) was added dropwise a solution of trimethyl 3-(2-thienyl)-2-phosphonopropionate in glyme (3 mL) under an atmosphere of argon. When the gas evolution had subsided, the mixture was heated to 50°C for 15 minutes. A solution of 2-n-butyl-1-(2-chlorophenyl)-methyl-1H-imidazol-5-carboxaldehyde (0.53 g, 1.92 mmol) in glyme (3 mL) was added, and the mixture was stirred at 60-65°C for 5 hours. The cooled reaction was partitioned between water and ethyl acetate, and the organic layer was washed with water, dried, concentrated and flash chromatographed over silica gel to give 336 mg (41%) of methyl (E)-3-[2-n-butyl-1-[(2-chlorophenyl)-methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate as an oil whose NMR was entirely consistent with the trans or E form of the olefin.

(c) (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid

20

A solution of methyl (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate (336 mg, 0.783 mmol) in ethanol (10 mL) was treated with 10% sodium hydroxide solution (4 mL), and the solution was stirred for 3 hours at 25°C. The pH was adjusted to 5 and a solid precipitated. The mixture was diluted with water, cooled and filtered to provide 309 mg of solid. A crystallization from ethyl acetate gave 195 mg (60%) of (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; mp 177-179°C.

30

Method B

(a) methyl 3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-3-hydroxy-2-(2-thienyl)methylpropanoate

35

To a solution of diisopropylamine (1.96 g, 0.0194 mol) in dry tetrahydrofuran (40 mL) held at -78°C under argon was added n-butyl lithium (7.3 mL, 0.0183 mol of 2.5 M in toluene), and the mixture was stirred for 10 minutes. Then, methyl 3-(2-thienyl)propanoate (2.83 g, 0.0166 mol) in tetrahydrofuran (2 mL) was added, and the mixture was stirred for 30 minutes at -78°C. A solution of 2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-carboxaldehyde (3 g, 0.0111 mol) in tetrahydrofuran (4 mL) was added, and the resulting mixture was stirred at -78°C for 30 minutes. The reaction was partitioned between saturated ammonium chloride solution and ether, the organic extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated to 6.67 g of crude product. This was flash chromatographed over 70 g of silica gel with 4:1 ethyl acetate/hexane to provide 4.03 g (81%) of methyl 3-[2-n-butyl-1-(2-chlorophenyl)-methyl-1H-imidazol-5-yl]-3-hydroxy-2-(2-thienyl)methylpropanoate.

(b) methyl 3-acetoxy-3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-2-(2-thienyl)methylpropanoate

A solution of methyl 3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-3-hydroxy-2-(2-thienyl)-methylpropanoate (4.03 g, 9.02 mmol) in methylene chloride (100 mL) was treated with 4-dimethylaminopyridine (0.386g, 3.16 mmol). Then acetic anhydride (8.5 mL, 9.02 mmol) was added dropwise to the stirred mixture. The mixture was stirred for 18 hours, water (35 mL) was added, the mixture was stirred for 1 hour and then diluted with ether and saturated sodium bicarbonate solution. The ether layer was washed with brine, dried with anhydrous magnesium sulfate and evaporated to give the title 3-acetoxy derivative as an oil (4.37 g, 99%).

(c) methyl (E)-3-[2-n-butyl-1-((2-chlorophenyl)-methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate

5 A mixture of methyl 3-acetoxy-3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-2-(2-thienyl)-methylpropanoate (4.36 g, 8.92 mmol) in dry toluene (80 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (3.2 mL, 21.4 mmol), and the resulting solution was
10 heated at 80°C under argon for 3 hours. The solvent was evaporated, the residue triturated with ether and activated charcoal was added. After filtration, the filtrate was concentrated to 6.29 g of an oil that was chromatographed over silica gel with 65:35 hexane/ethyl
15 acetate to give 2.89 g (76%) of methyl (E)-3-[2-n-butyl-1-((2-chlorophenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)-methyl-2-propenoate whose NMR and TLC (50% ethyl acetate in hexane on silica gel) were identical to the product prepared by Method A.

20

(d) (E)-3-[2-n-butyl-1-((2-chlorophenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid

25 Basic hydrolysis of this ester (2.88 g, 6.71 mmol) according to Method A (iii) gave 2.59 g (93%) of (E)-3-[2-n-butyl-1-((2-chlorophenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; mp 175-177°C that was identical to the product from Method A.

30

Example 2

(E)-3-[2-n-Butyl-1-((4-carboxyphenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

35 (i) By the procedure of Example 1 [(ii) Method 2, (iii) and (iv) Method B] using 4-carbomethoxybenzyl alcohol in place of 2-chlorobenzyl alcohol, the title

compound was prepared; mp 250-253°C.

(ii) Preparation of Monomethanesulfonate

The title compound, 3600 g, was added to 2-propanol
5 (54 L) in a 20-gallon, glass-lined reactor. The stirred
suspension was cooled to approximately 8°C.
Methanesulfonic acid (2448 g) was added rapidly to the
vigorously stirred suspension. The starting material
dissolved quickly to give a clear solution within two
10 minutes. A slight exotherm to approximately 11°C was
observed. A fine, white solid began to precipitate from
the solution within an additional three minutes. The
suspension was stirred at a temperature of 3°C for 5.5
hours and the solid was collected by centrifugation.
15 After washing with 10 L of 2-propanol, the product was
dried under vacuum at 45°C to a constant weight of 4.21
kg (94% yield, uncorrected for assay).

The crude product (4.20 kg) was charged as a solid
to 12.6 L of stirred, glacial acetic acid in a 10-gallon,
20 glass-lined reactor. The slurry was heated to 80°C,
giving a homogeneous solution. The solution was filtered
warm through an in-line filter, and the reactor and
filter lines were washed with 4.2 L of additional acetic
acid. The combined acetic acid solutions were stirred
25 with slow cooling to 25°C in a separate 10-gallon, glass-
lined reactor. Precipitation of a solid began to occur
at about 45°C. After 2.5 hours the suspension was
diluted with 42 L of ethyl acetate, added in two equal
portions with a one hour interval between additions. The
30 suspension was stirred for an additional 18 hours to
allow complete precipitation. The solid product was
collected by centrifugation and washed with 10 L of ethyl
acetate. After drying to a constant weight under vacuum
at 40°C, a recovery of 3.80 kg of product; mp 251-252°C
35 (90.4%, uncorrected for assay) was obtained.

Example 3

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(4-pyridyl)methyl-2-propenoic Acid

- 5 (i) methyl 3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-3-hydroxy-2-(4-pyridyl)methylpropanoate

To a solution of diisopropylamine (3.58 mL, 25.6 mmol) in dry tetrahydrofuran (50 mL) held at -78°C under argon was added n-butyl lithium (10.2 mL, 25.6 mmol of 2.5 M in toluene), and the mixture was stirred for 10 minutes. Then, methyl 3-(4-pyridyl)propanoate (4.22 g, 25.6 mmol) (prepared by reaction of 4-pyridine carboxaldehyde with trimethyl phosphonoacetate in the presence of sodium hydride in ethylene glycol dimethyl ether, followed by catalytic hydrogenation of the double bond with 10% palladium on carbon at 3 atmosphere of hydrogen in an ethyl acetate solution (98%) to provide the saturated ester) was added in tetrahydrofuran (40 mL) and this mixture was stirred for 30 minutes at -78°C. A solution of 2-n-butyl-1-(2-chloro-phenyl)methyl-1H-imidazol-5-carboxaldehyde (5.9 g, 21.3 mmol) in tetrahydrofuran (10 mL) was added and stirring was continued for 30 minutes at -78°C. The reaction was partitioned between saturated ammonium chloride solution and ether, the organic extract was washed with brine, dried over magnesium sulfate, concentrated and flash chromatographed over silica gel with 5% methanol in ethyl acetate to provide 3.32 g (30%) of methyl 3-[2-n-butyl-1-(2-chlorophenyl)-methyl-1H-imidazol-5-yl]-3-hydroxy-2-(4-pyridyl)methyl-propanoate. TLC on silica gel with 5% methanol in ethyl acetate showed a homogenous product with an R_f of 0.79.

(ii) methyl 3-acetoxy-3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-2-(4-pyridyl)propanoate

5 A solution of methyl 3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-3-hydroxy-2-(4-pyridyl)methylpropanoate (3.32 g, 7.5 mmol) methylene chloride (50 mL), 4-dimethylaminopyridine (150 mg, 1.3 mmol) and acetic anhydride (7.1 mL, 75 mmol) was stirred
10 at ambient temperature for 18 hours. Water (5 mL) was added, the mixture was stirred for 2 hours and then diluted with methylene chloride and 5% sodium bicarbonate solution. The organic phase was washed with 5% sodium
15 bicarbonate solution and brine, dried and concentrated to give 4 g of the crude title compound. TLC on silica gel with 5% methanol ethyl acetate showed essentially one spot material with an R_f of 0.86. No starting material was detected. This material was not purified further.

20 (iii) methyl (E)-3-[2-n-butyl-1-((2-chlorophenyl)methyl)-1H-imidazol-5-yl]-2-(4-pyridyl)methyl-2-propenoate

25 A mixture of methyl 3-acetoxy-3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-2-(4-pyridyl)-propenoate (7.5 mmol), toluene (50 mL) and 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU) (3.4 mL, 22.5 mmol) was heated at 90°C for 18 hours under argon. The cooled
30 mixture was diluted with ether, and washed with brine, dried and concentrated to 3.1 g (97%) of the title compound. NMR showed that the trans or E isomer was the primary product.

35 (iv) (E)-3-[2-n-butyl-1-((2-chlorophenyl)methyl)-1H-imidazol-5-yl]-2-(4-pyridyl)-methyl-2-propenoic acid

A solution of methyl (E)-3-[2-n-butyl-1-((2-chlorophenyl)methyl)-1H-imidazol-5-yl]-2-(4-pyridyl)-methyl-2-propenoate (3.1 g, 7.3 mmol) in ethanol (16 mL) was treated with 10% sodium hydroxide solution and the mixture was stirred for 18 hours at 25°C. The solution was concentrated in vacuum, water was added, the pH was adjusted to 6.5 and the resulting solid was filtered, washed with water and crystallized from methanol/ether to afford 0.48 g of (E)-3-[2-n-butyl-1-((2-chlorophenyl)-methyl)-1H-imidazol-5-yl]-2-(4-pyridyl)methyl-2-propenoic acid; mp 178-182°C (d).

Example 4

(E)-3-[2-n-Butyl-1-((4-carboxynaphth-1-yl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

(i) 2-n-butyl-5-hydroxymethyl-4-iodoimidazole

N-Iodosuccinimide (148.75 g, 0.661 mol) was added to a stirred solution of 2-n-butyl-4-hydroxymethylimidazole (100.78 g, 0.652 mol) in 500 mL of absolute ethanol. After 20 minutes the solution was heated to 40-45°C for 45 minutes, diluted with 2.5 liters of water, and chilled. The crystalline product was collected by filtration, washed with water, and dried to give 174.5 g (95%) of crystals; mp 166-166.5°C.

(ii) 2-n-butyl-4-iodoimidazol-5-carboxaldehyde

A stirred mixture of 174.1 g (0.62 mol) of 2-n-butyl-5-hydroxymethyl-4-iodoimidazole and 360 g (4.14 mol) of manganese dioxide in 3 liters of methylene chloride was refluxed for 24 hours using a trap to remove water. The hot reaction mixture was filtered through Celite® which was then washed with 4.5 liters of boiling methylene chloride. The combined filtrates were concentrated to dryness, the residue was dissolved twice.

in 150 mL of methanol and the solution was concentrated to dryness. The residue was dissolved in 130 mL of methanol and chilled. After crystallization had occurred, 700 mL of water was added slowly. The mixture
5 was chilled, the solid was collected by filtration, and washed with water to give 145.2 g (84%) of product; mp 104-105°C.

10 (iii) methyl 4-[(2-n-butyl-5-formyl-4-iodo-1H-imidazol-1-yl)methyl]naphthalene-1-carboxylate

A suspension of 29.53 g (0.214 mol) of powdered potassium carbonate, 60.00 g (0.214 mol) of 2-n-butyl-4-
15 iodoimidazole-5-carboxaldehyde and 65.68 g (0.235 mol) of methyl 4-bromomethylnaphthalene-1-carboxylate (E.A. Dixon, A. Fischer, and F.P. Robinson, Can. J. Chem. 59, 2629 (1981)) in 600 mL of dimethylformamide was stirred for 5 hours under argon at 70°C. An additional 6.56 g
20 (0.0235 mol) of the bromomethyl ester was added and the suspension was stirred an additional 15 hours at 70°C. The reaction mixture was poured into water and the resulting solid was collected by filtration, washed with water, and triturated several times with 250 mL of
25 boiling methanol to give 86.8 g (85%) of a solid; mp 177.5-179°C.

30 (iv) methyl 4-[(2-n-butyl-5-formyl-1H-imidazol-1-yl)methyl]naphthalene-1-carboxylate

A suspension of 40.0 g (83.9 mmol) of methyl 4-[(2-n-butyl-5-formyl-4-iodo-1H-imidazol-1-yl)methyl]-naphthalene-1-carboxylate, 9.07 g (92.4 mmol) of potassium acetate, and 6.0 g of 10% palladium on carbon in 1.2 liters of ethyl acetate was hydrogenated for 2 hours. The solids were removed by filtration and an additional 8.0 g of 10% palladium on carbon and 9.01 g (92.4 mmol) of potassium acetate was added. After hydrogenating the reaction mixture an additional 2 hours, the solids were removed by filtration and the solution was concentrated to about 1/3 volume. The ethyl acetate solution was washed with aqueous sodium carbonate solution, dried over magnesium sulfate, and concentrated under vacuum to give an oil which crystallized. Recrystallization from methylene chloride-hexane gave 25.77 g (87.6%) of colorless crystals; mp 95.5-97°C.

(v) methyl (E)-3-[2-n-butyl-1-[(4-carbomethoxynaphth-1-yl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate

The title compound was prepared from 25.0 g of methyl 4-[(2-Butyl-5-formyl-1H-imidazol-1-yl)methyl]naphthalene-1-carboxylate following the procedure of Example 3 to give 22.12 g (56%) of product as the hydrochloride salt; mp 217-218°C.

(vi) (E)-3-[[2-n-butyl-1-[(4-carboxynaphth-1-yl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl]propenoic acid

A slurry containing 14.46 g (26.14 mmol) of methyl (E)-3-[2-n-butyl-1-[(4-carbomethoxynaphth-1-yl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoate, 8.38 g (2.09 mmol) of potassium hydroxide in a mixture of 165 mL of ethanol and 85 mL of water was stirred at ambient temperature for 18 hours.

Concentration under vacuum and dilution with water gave 400 mL of a clear solution. Adjustment of the pH to 4.03 with hydrochloric acid gave crystals which when recrystallized from methanol gave 9.89 g (80%) of
5 colorless crystals; mp 218-219°C as a partial hydrate.

Example 5

(E)-3-[2-n-Butyl-1-[(4-carboxynaphth-1-yl)methyl]-1H-
10 imidazole-5-yl]-2-[(2-thienyl)methyl]-2-propenoic Acid,
Ethyl Ester

A solution of 5.0 g (14.27 mol) of methyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]naphthalene-1-
15 carboxylate in 60 ml of ethanol was treated with a solution of 2.0 g (50 mmol) of sodium hydroxide in 30 ml of water. After stirring at 25°C for 18 h the reaction mixture was concentrated under vacuum, diluted to 50 ml with water, and the pH was brought to 3.15 with 12N
20 hydrochloric acid. Filtration of the chilled mixture gave 4.71 g of white crystals; mp 183-184°C. Recrystallization from ethyl acetate gave a different crystal form; mp 134-135°C.

25 To a solution of 27.2 g (0.119 mol) of ethyl 2-carboxy-3-(2-thienyl) propionate in 250 ml of benzene was added 4.71 g (14 mmol) of the above aldehyde-acid, 3.58 g (42 mmol) of piperidine, and 10 ml of pyridine and the solution refluxed for 18 h using a trap to remove water.
30 The volatiles were then removed under vacuum, toluene was added, and the volatiles were again removed. The residue was treated with 2.5% sodium bicarbonate solution and hexane, which caused separation of an oil. Addition of ethyl acetate gave two phases. The aqueous phase was
35 filtered, taken to pH 3.86 with 12N, hydrochloric acid and extracted with ethyl acetate. This ethyl acetate solution was dried over magnesium sulfate and concentrated under vacuum to give a gum which was

dissolved in ether and then acidified with ethereal HCl. Trituration of the resulting gum with ether gave 5.32 g of finely divided white crystals; mp 180-181.5°C, soften at 176°C (hydrochloride salt).

5

Example 6

An oral dosage form for administering orally active Formula (I) compounds is produced by screening, mixing and filling into hard gelatin capsules the ingredients in proportions, for example, as shown below.

10

<u>Ingredients</u>	<u>Amounts</u>
(E)-3-[2-n-butyl-1-[(4-carboxy-phenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid methanesulfonate	100 mg
magnesium stearate	10 mg
lactose	100 mg

Example 7

The sucrose calcium sulfate dihydrate and orally active Formula (I) compounds are mixed and granulated with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

20

<u>Ingredients</u>	<u>Amounts</u>
(E)-3-[2-n-butyl-1-[(4-carboxy-naphth-1-yl)-methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid	75 mg
calcium sulfate dihydrate	100 mg
sucrose	15 mg
starch	8 mg

talc	4 mg
stearic acid	2 mg

Example 8

(E)-3-[2-n-Butyl-1-((4-carboxynaphth-1-yl)methyl)-
5 1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,
ethylester, 50 mg, is dispersed in 25 mL of normal saline
to prepare an injectable preparation.

Example 9

10

A topical opthamological solution for administering
Formula (I) compounds is produced by mixing under sterile
conditions the ingredients in proportions, for example,
as shown below.

15

<u>Ingredients</u>	<u>Amounts</u> (mg/mL)
(E)-3-[2-n-butyl-1-((4-carboxyphenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid methanesulfonate	1.0
dibasic sodium phosphate	10.4
monobasic sodium phosphate	2.4
chlorobutanol	5.0
hydroxypropanol methylcellulose	5.0
sterile water	q.s.ad 1.0mL
1.0 N sodium hydroxide	q.s.ad pH 7.4

It is to be understood that the invention is not
limited to the embodiments illustrated hereabove and the
right to the illustrated embodiments and all
20 modifications coming within the scope of the following
claims is reserved.



What is claimed is:

1. A compound which is (E)-3-[2-n-butyl-1-((4-carboxynaphth-1-yl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid or a pharmaceutically acceptable salt thereof.
5
2. A compound which is (E)-3-[2-n-butyl-1-((4-carboxynaphth-1-yl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, ethyl ester or a pharmaceutically acceptable salt thereof.
10
3. A compound which is (E)-3-[2-n-butyl-1-((4-carboxypenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid methanesulfonate.
15
4. A pharmaceutical composition comprising a pharmaceutical carrier and the compound of claim 1.
- 20 5. A pharmaceutical composition comprising a pharmaceutical carrier and the compound of claim 2.
6. A pharmaceutical composition comprising a pharmaceutical carrier and the compound of claim 3.
25
7. A method of treating hypertension which comprises administering to a subject in need thereof an effective amount of the compound of claim 1.
- 30 8. A method of treating hypertension which comprises administering to a subject in need thereof an effective amount of the compound of claim 2.
9. A method of treating hypertension which
35 comprises administering to a subject in need thereof an effective amount of the compound of claim 3.



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10. A method of treating congestive heart failure which comprises administering to a subject in need thereof an effective amount of the compound of claim 1.

5 11. A method of treating congestive heart failure which comprises administering to a subject in need thereof an effective amount of the compound of claim 2.

10 12. A method of treating congestive heart failure which comprises administering to a subject in need thereof an effective amount of the compound of claim 3.

15 13. A method of treating renal failure which comprises administering to a subject in need thereof an effective amount of the compound of claim 1.

20 14. A method of treating renal failure which comprises administering to a subject in need thereof an effective amount of the compound of claim 2.

15. A method of treating renal failure which comprises administering to a subject in need thereof an effective amount of the compound of claim 3.

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ABSTRACT

IMIDAZOLYL-ALKENOIC ACIDS

Angiotensin II receptor antagonists that are imidazolyl-alkenoic acids are useful in regulating hypertension and in the treatment of congestive heart failure, renal failure, and glaucoma, pharmaceutical compositions including these antagonists, and methods of using these compounds to produce angiotensin II receptor antagonism in mammals.

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What is claimed is:

1. A compound which is (E)-3-[2-n-butyl-1-((4carboxynaphth-1-yl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid or a pharmaceutically acceptable salt thereof.
2. A compound which is (E)-3-[2-n-butyl-1-((4carboxynaphth-1-yl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, ethyl ester or a pharmaceutically acceptable salt thereof.
3. A compound which is (E)-3-[2-n-butyl-1-((4carboxypenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid methanesulfonate.
4. A pharmaceutical composition comprising a pharmaceutical carrier and the compound of claim 1.
5. A pharmaceutical composition comprising a pharmaceutical carrier and the compound of claim 2.
6. A pharmaceutical composition comprising a pharmaceutical carrier and the compound of claim 3.
7. The use of a pharmaceutical composition in the treatment of hypertension which comprises administering to a subject in need thereof an effective amount of the compound of claim 1.
8. The use of a pharmaceutical composition in the treatment of hypertension which comprises administering to a subject in need thereof an effective amount of the compound of claim 2.



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9. The use of a pharmaceutical composition in the treatment of hypertension which comprises administering to a subject in need thereof an effective amount of the compound of claim 3.

10. The use of a pharmaceutical composition in the treatment of congestive heart failure which comprises administering to a subject in need thereof an effective amount of the compound of claim 1.

11. The use of a pharmaceutical composition in the treatment of congestive heart failure which comprises administering to a subject in need thereof an effective amount of the compound of claim 2.

12. The use of a pharmaceutical composition in the treatment of congestive heart failure which comprises administering to a subject in need thereof an effective amount of the compound of claim 3.

13. The use of a pharmaceutical composition in the treatment of renal failure which comprises administering to a subject in need thereof an effective amount of the compound of claim 1.

14. The use of a pharmaceutical composition in the treatment of renal failure which comprises administering to a subject in need thereof an effective amount of the compound of claim 2.

15. The use of a pharmaceutical composition in the treatment of renal failure which comprises administering to a subject in need thereof an effective amount of the compound of claim 3.

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13 OCT 1998

What is claimed is:

1. A compound which is (E)-3-[2-n-butyl-1-((4carboxynaphth-1-yl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid or a pharmaceutically acceptable salt thereof.
2. A compound which is (E)-3-[2-n-butyl-1-((4carboxynaphth-1-yl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, ethyl ester or a pharmaceutically acceptable salt thereof.
3. A compound which is (E)-3-[2-n-butyl-1-((4carboxypenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid methanesulfonate.
4. A pharmaceutical composition comprising a pharmaceutical carrier and the compound of claim 1.
5. A pharmaceutical composition comprising a pharmaceutical carrier and the compound of claim 2.
6. A pharmaceutical composition comprising a pharmaceutical carrier and the compound of claim 3.

