CONVENTION - COMPANY - PCT

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Section 29(1)
Regulation 3.1(2)

AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, WARNER-LAMBERT COMPANY of 2800 Plymouth Road, ANN ARBOR, MICHIGAN 48105, UNITED STATES OF AMERICA, being the applicant in respect of an Application for an invention entitled:-

4-(1H-PYRROL-1-YL)IMIDAZOLES WITH ANGIOTENSIN II ANTAGONIST ACTIVITY

state the following:-

1. The person nominated for the grant of the patent has entitlement from the actual inventor/s by assignment.

2. The person nominated for the grant of the patent has entitlement from the applicant/s of the application/s listed in the declaration under Article 8 of the PCT by assignment.

3. The basic application/s listed in the declaration under Article 8 of the PCT is/are the first application/s made in a Convention country in respect of the invention.

For and on behalf of
WARNER-LAMBERT COMPANY

Elizabeth M. Anderson
(Signature)

November 30, 1993
(Date)

Name: Elizabeth M. Anderson

Title: Assistant Secretary

File: .....

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GL25(o)

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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 656612

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4(1-(H)-PYRROL-1-YL)IMIDAZOLES WITH ANGIOTENSIN II ANTAGONIST ACTIVITY

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WARNER-LAMBERT COMPANY

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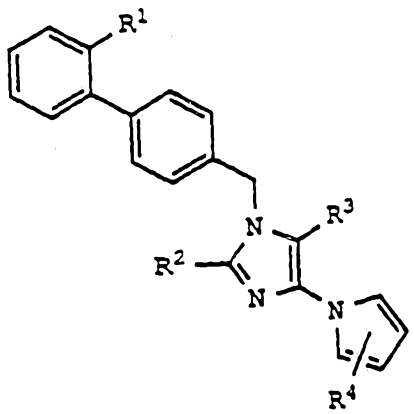
SHELSTON WATERS , 55 Clarence Street, SYDNEY NSW 2000

(57) Claim

1. A compound of formula

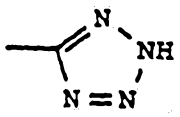


I

or a pharmaceutically acceptable salt thereof wherein

R^1 is

-COOH, or



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R^2 is

$-C_2H_5$,

$-{}_nC_3H_7$,

$-{}_nC_4H_9$,

$-CH_2CH=CH_2$,

$-CH_2CH=CHCH_3$, or

$-CH_2CH_2CH=CH_2$;

R^3 is

$-H$,

$-CN$,

$-CHO$,

$-CH_2OH$,

$-CO_2R^5$

$-CH_2O\overset{\overset{O}{\|}}{C}R^5$,

$-(CH_2)_nCN$,

$-(CH_2)_nCO_2R^5$,

$-(CH_2)_nCONH_2$,

$-(CH_2)_nCONHOH$,

$-CH=CHCO_2R^5$, or

$-CH=C(CH_3)CO_2R^5$

wherein R^5 is hydrogen or a straight or branched alkyl of from one to four carbon atoms and n is 1 or 2;

R^4 is absent or is one or two substituents selected from:

$2-CH_3$,

$2-CH_2CH_3$,

$2-CH_2CH_2CH_3$

$2-CF_3$,

$2-CO_2R^5$,

2-CHO,

$2-CH_2OH$,

$2-CH_2O\overset{\overset{O}{\|}}{C}R^5$,

$2-NO_2$,

2-Cl,

2-Br,

.../3

2-I,
2-$COCF_3$,
2-$COCCl_3$,
2-$CH(OH)CF_3$,
2-$CH(OH)CCl_3$,
2-$CONH_2$,
2-CONHOH,
3-CH_3,
3-CH_2CH_3,
3-CF_3,
3-CO_2R^5,
3-CHO,
3-CH_2OH,
3-CH_2OCR^5 (with $\|$ O),
3-NO_2,
3-$CONH_2$,
3-CONHOH,
2-CO_2R^5-4-NO_2,
2-$COCCl_3$-4-NO_2,
2-$COCF_3$-4-NO_2,
2-CO_2R^5-4-Cl,
2-$COCCl_3$-4-Cl,
2-$COCF_3$-4-Cl,
2-$COCF_3$-4-Cl,
2-CO_2R^5-4-Br,
2-$COCCl_3$-4-Br,
2-$COCF_3$-4-Br,
2-CO_2R^5-4-I,
2-$COCCl_3$-4-I,
2-$COCCF_3$-4-I,
2-NO_2-4-CO_2R_5,
2-Cl-4-CO_2R^5,
2-Br-4-CO_2R^5,
2-I-4, CO_2R^5,
2-CH_3-3-CO_2R^5,
2,5-$(CH_3)_2$,

2,5-$(CH_2CH_3)_2$,
2,5-$COCF_3$,
2-$CH_2CH_2CH_3$-5-CH_3,
2,5-$(Cl)_2$,
2,5-$(Br)_2$, and
2,5-$(I)_2$

wherein R^5 is hydrogen or a straight or branched alkyl of from one to four carbon atoms.

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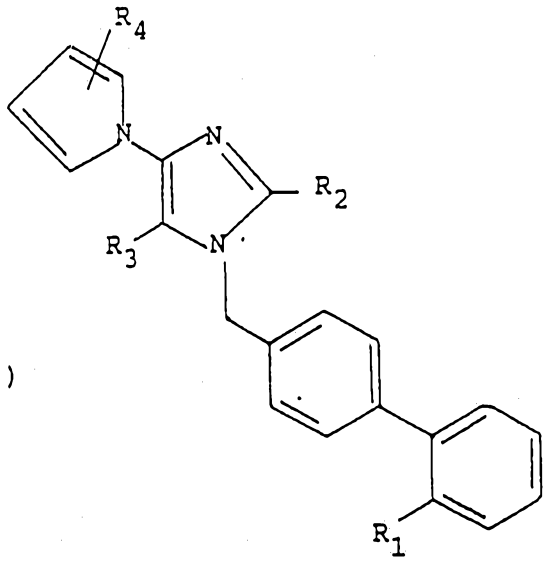
(54) Title: 4-(1-*H*-PYRROL-1-YL)IMIDAZOLES WITH ANGIOTENSIN II ANTAGONIST ACTIVITY



(I)

(57) Abstract

Substituted 4-(1-*H*-pyrrol-1-yl)imidazoles of formula (I) are disclosed as well as methods of preparing them, pharmaceutical compositions containing them, and methods of using them. Novel intermediates useful in the preparation of the compounds of the invention are also disclosed and synthetic methods for preparing the novel intermediates. The compounds are useful as antagonists of angiotensin II and thus are useful in the control of hypertension, hyperaldosteronism, congestive heart failure, glaucoma, vascular smooth muscle proliferation associated with atherosclerosis, and with postsurgical vascular restenosis.

4-(1-H-PYRROL-1-YL)IMIDAZOLES WITH ANGIOTENSIN II ANTAGONIST ACTIVITY

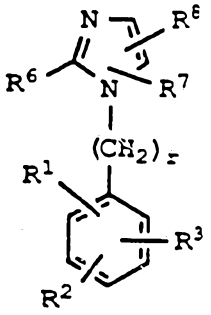
BACKGROUND OF THE INVENTION

The present invention relates to novel substituted derivatives of 4-(1H-pyrrol-1-yl)imidazoles which are useful as pharmaceutical agents, to methods for their preparation, to pharmaceutical compositions which include the compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment as well as the use of these agents as diagnostic tools. The novel compounds of the present invention are antagonists of angiotensin II (AII) useful in controlling hypertension, hyperaldosteronism, congestive heart failure, atherosclerosis, postsurgical vascular restenosis, renal failure, and glaucoma in mammals.

The enzyme renin acts on a blood plasma α_2-globulin, angiotensinogen, to produce angiotensin I, which is then converted by angiotensin-converting enzyme to AII. The latter substance is a powerful vasopressor agent which has been implicated as a causative agent for producing high blood pressure in various mammals, such as rats, dogs, and humans. Angiotensin II has also been found to stimulate vascular hyperplasia as reported by W. Osterrieder, et al (Hypertension 18[suppl II]:II60-II64, 1991); H. Azuma, et al (Jpn. J. Pharmacol. 52(4):541-552, 1990); and S. Laporte, et al (FASEB 5(4), Part I: A869, 1991). The compounds of this invention inhibit the action of AII at its receptors on target cells and thus prevent the increase in

blood pressure produced by this hormone-receptor interaction. By administering a compound of the instant invention to a species of mammal with hypertension due to AII, the blood pressure is reduced. The compounds of the invention are also useful for the treatment of congestive heart failure, hyperaldosteronism, atherosclerosis, postsurgical vascular restenosis, and glaucoma.

European Patent Application 0253310 discloses angiotensin II receptor blocking imidazoles of the formula



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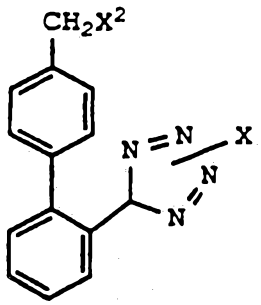
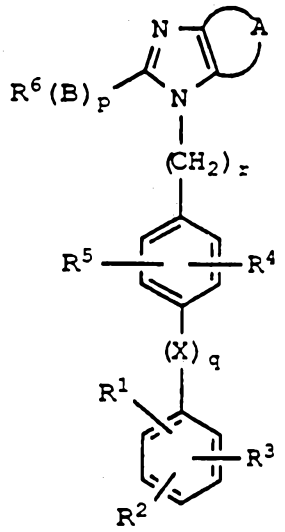
European Patent Application 0291969 disclose tetrazole intermediates to antihypertensive compounds



European Patent Application 401030 discloses substituted imidazo-fused seven-member ring heterocycles of Formulae I and Ia



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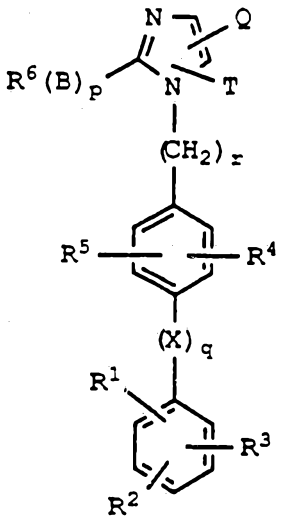
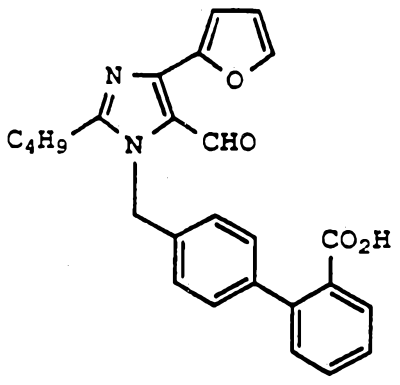


(Ia)

which are useful as angiotensin II antagonists.

WO 91/00277 discloses substituted imidazoles useful as angiotensin II blockers

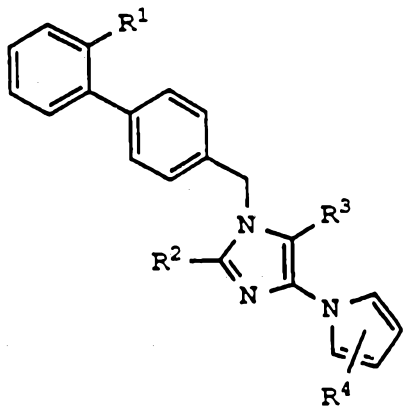


However, the compounds disclosed in the above references do not disclose or suggest the novel

combination of structural variations found in the compounds of the present invention described hereinafter.

SUMMARY OF THE INVENTION

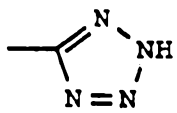
The present invention is a compound of Formula I



or a pharmaceutically acceptable salt thereof wherein R^1, R^2, R^3, and R^4 are as described below.

Preferred compounds of the instant invention are those of Formula I wherein

R^1 is -COOH or



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R^2 is

$-_nC_3H_7$ or

$-_nC_4H_9$;

R^3 is

-H,

$-COOR^5$

-CN,

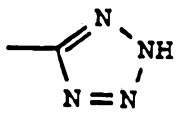
-CHO,

$-CH_2OH$,
$-(CH_2)_nCO_2R^5$,
$-CH=CHCO_2R^5$, or
$-CH=C(CH_3)CO_2R^5$

wherein R^5 is hydrogen or a straight or branched alkyl of from one to four carbon atoms and n is 1 or 2; R^4 is absent or is one or two substituents attached to the pyrrole ring selected from:

$2-CH_3$,
$2-CO_2R^5$,
$3-CO_2R^5$,
$2-CH_2OH$,
$3-CH_2OH$,
2-Cl,
2-Br,
2-CONHOH,
3-CONHOH,
$2-COCF_3$,
$2-COCCl_3$,
$2-CH(OH)CF_3$,
$2-CH(OH)CCl_3$,
$2,5-(Cl)_2$,
$2,5-(Br)_2$, and
$2,5-(CH_3)_2$.

More preferred compounds of the instant invention are those of Formula I wherein

R^1 is  ;

R^2 is

$-_nC_4H_9$ or
$-_nC_3H_7$;

R^3 is

-H,
-CN,
$-CO_2H$,
$-CO_2CH_3$,
$-CO_2C_2H_5$, or
$-CH_2OH$; and

R^4 is absent or is one or two substituents attached to the pyrrole ring selected from:
$2-CO_2CH_3$,
$2-COCF_3$,
$2-CO_2H$,
$2-CH(OH)CF_3$,
$2,5-(Cl)_2$, and
$2,5-(CH_3)_2$.

Yet still more preferred compounds of the instant invention are selected from the following list of compounds:

1) 2-butyl-5-cyano-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole,

2) 5-cyano-2-propyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole,

3) 2-butyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid,

4) 2-propyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid,

5) 2-butyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole,

6) ethyl 2-butyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate,

7) methyl 2-butyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate,

8) 2-butyl-5-(hydroxymethyl)-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole,

9) 5-cyano-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol- 1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)- methyl]-1H-imidazole,

10) 5-cyano-4-[2-(1-hydroxy-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole,

11) methyl 1-[5-cyano-2-propyl-1-[(2'-(1H-tetrazol-5-yl)-biphen-4-yl)methyl]-1H-imidazol-4-yl]-1H-pyrrole-2-carboxylate,

12) 1-[5-cyano-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazol-4-yl]-1H-pyrrole-2-carboxylic acid,

13) 5-cyano-4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole,

14) methyl 4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate,

15) 2-cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid,

16) methyl 2-cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate,

17) methyl 4-(2-propyl-5-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate,

18) 4-(2-propyl-5-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid,

19) 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxaldehyde,

20) methyl (E)-3-[4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)biphen-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate,

21) (E)-3-[4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)biphen-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoic acid,

22) 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid,

23) methyl 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate,

24) 4-(3-carboxy-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid,

25) ethyl (E)-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)biphen-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate,

26) (E)-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)biphen-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoic acid,

27) methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate,

28) 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid,

29) 2-propyl-4-(-1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxaldehyde,

30) 4-(2,5-dimethyl-1H-pyrrol-1-yl)-5-(hydroxymethyl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole,

31) 5-cyano-4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole,

32) methyl 4-(3-carboxymethyl-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate,

33) 4-(3-carboxymethyl-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid,

34) 4-(3-carboxy-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid,

35) 4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid,

36) 2-butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid,

37) methyl 4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)-biphen-4-yl)methyl]-1H-imidazole-5-carboxylate,

38) methyl 2-butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate,

39) 1-[5-carboxy-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazol-4-yl]-1H-pyrrole-2-carboxylic acid

40) ethyl (E)-2-methyl-3-[4-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)biphen-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate,

41) (E)-2-methyl-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)biphen-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoic acid, and

42) 4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid.

Novel intermediates useful in the preparation of compounds of the instant invention are:

1) 4-amino-2-butyl-5-cyanoimidazole,

2) 4-amino-5-cyano-2-propylimidazole,

3) 2-butyl-5-cyano-4-(1H-pyrrol-1-yl)imidazole,

4) 5-cyano-2-propyl-4-(1H-pyrrol-1-yl)imidazole,

5) ethyl 2-butyl-4-(1H-pyrrol-1-yl)imidazole-5-carboxylate,

6) methyl 2-butyl-4-(1H-pyrrol-1-yl)imidazole-5-carboxylate,

7) 2-butyl-5-(hydroxymethyl)-4-(1H-pyrrol-1-yl)-imidazole-5-carboxylate,

8) 5-cyano-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propylimidazole,

9) methyl 1-(5-cyano-2-propylimidazol-4-yl)-1H-pyrrole-2-carboxylate,

10) 5-cyano-4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propylimidazole,

11) methyl 4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propylimidazole-5-carboxylate,

12) methyl 2-butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]imidazole-5-carboxylate,

13) 5-cyano-4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propylimidazole,



14) methyl 2-cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)imidazole-5-carboxylate,

15) methyl 4-(2-propyl-5-methyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxylate,

16) 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxaldehyde,

17) methyl 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propyl-imidazole-5-carboxylate,

18) methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxylate,

19) 2-propyl-4-(1H-pyrrol-1-yl)-imidazole-5-carboxaldehyde,

20) 5-(hydroxymethyl)-2-propyl-4-(1H-pyrrol-1-yl)imidazole,

21) 2-butyl-5-(hydroxymethyl)-4-(1H-pyrrol-1-yl)imidazole,

22) 5-cyano-4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propylimidazole,

23) methyl 4-(2-methyl-3-carboxymethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxylate,

24) methyl 2-butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]imidazole-5-carboxylate,

25) methyl 2-propyl-4-(2,5-dichloro-1H-pyrrol-1-yl)-imidazole-5-carboxylate,

26) 5-(hydroxymethyl)-2-propyl-4-(1H-pyrrol-1-yl)-imidazole,

27) methyl 4-amino-2-cyclopropylimidazole-5-carboxylate,

28) 5-(hydroxymethyl)-2-propyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)imidazole,

29) methyl (E)-3-[4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propylimidazol-5-yl]-2-propenoic acid,

Angiotensin II mediates a variety of responses in various tissues, including contraction of vascular smooth muscle, excretions of salt and water from kidney, release of prolactin from pituitary, stimulation of aldosterone secretion from adrenal gland, and possible regulation of cell growth in both cardiac and vascular tissue. As antagonists of angiotensin II, the compounds of the instant invention are useful in controlling hypertension, hyperaldosteronism, congestive heart failure, and vascular smooth muscle proliferation associated with atherosclerosis and post-surgical vascular restenosis in mammals. Additionally, antihypertensive agents as a class have been shown to be useful in lowering intraocular pressure. Thus, the other inventions are also useful in treating and/or preventing glaucoma.

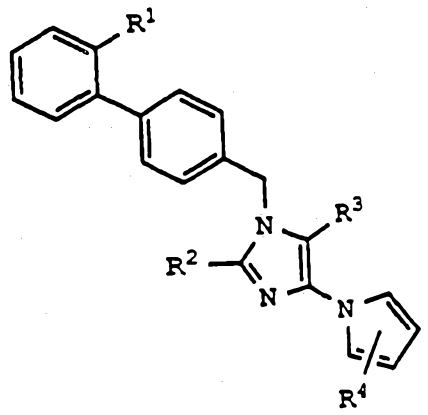
One method of particular interest is a method of treating hypertension comprising administering to a host suffering therefrom a therapeutically effective amount of 4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)-biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid, or the methyl ester thereof in unit dosage form.

The present invention is also a pharmaceutical composition for administering an effective amount of a compound of Formula I in unit dosage form in the treatment methods mentioned above.

Finally, the present invention is directed to methods for the preparation of a compound of Formula I and synthetic intermediates.

DETAILED DESCRIPTION OF THE INVENTION

The invention is of a compound of Formula

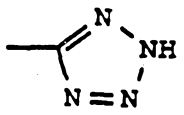


I

or a pharmaceutically acceptable salt thereof wherein

R^1 is

-COOH, or



;

R^2 is

$-C_2H_5$,

$-{}_nC_3H_7$,

$-{}_nC_4H_9$,

$-CH_2CH{=}CH_2$,

$-CH_2CH{=}CHCH_3$, or

$-CH_2CH_2CH{=}CH_2$;

R^3 is

-H,

-CN,

-CHO,

$-CH_2OH$,

$-COOR^5$

$-CH_2OC(=O)R^5$

$-(CH_2)_nCN$,

$-(CH_2)_nCO_2R^5$,

$-(CH_2)_nCONH_2$,

$-(CH_2)_nCONHOH$, or

$-CH{=}CHCO_2R^5$,

$-C{=}C(CH_3)CO_2R^5$

wherein R^5 is hydrogen or a straight or branched alkyl of from one to four carbon atoms and n is 1 or 2; and

R^4 is absent or is one or two substituents attached to the pyrrole ring selected from:

$2-CH_3$,

$2-CH_2CH_3$,

$2-CH_2CH_2CH_3$

$2-CF_3$,

$2-CO_2R^5$,

$2-CHO$,

$2-CH_2OH$,

$2-CH_2OC(=O)R^5$,

$2-NO_2$,

$2-Cl$,

$2-Br$,

$2-I$,

$2-COCF_3$,

$2-COCCl_3$,

$2-CH(OH)CF_3$,

$2-CH(OH)CCl_3$,

$2-CONH_2$,

$2-CONHOH$,

$3-CH_3$,

$3-CH_2CH_3$,

3-CF_3,
3-CO_2R^5,
3-CHO,
3-CH_2OH,
3-CH_2OCR^5, (‖ O)
3-NO_2,
3-$CONH_2$,
3-CONHOH,
2-CO_2R^5-4-NO_2,
2-$COCCl_3$-4-NO_2,
2-$COCF_3$-4-NO_2,
2-CO_2R^5-4-Cl,
2-$COCCl_3$-4-Cl,
2-$COCF_3$-4-Cl,
2-$COCF_3$-4-Cl,
2-CO_2R^5-4-Br,
2-$COCCl_3$-4-Br,
2-$COCF_3$-4-Br,
2-CO_2R^5-4-I,
2-$COCCl_3$-4-I,
2-$COCCF_3$-4-I,
2-NO_2-4-CO_2R_5,
2-Cl-4-CO_2R^5,
2-Br-4-CO_2R^5,
2-I-4-CO_2R^5,
2-CH_3-3-CO_2R^5,
2,5-$(CH_3)_2$,
2,5-$COCF_3$,
2,5-$(CH_2CH_3)_2$,
2-$CH_2CH_2CH_3$-5-CH_3,
2,5-$(Cl)_2$,
2,5-$(Br)_2$, and
2,5-$(I)_2$

wherein R^5 is hydrogen or a straight or branched alkyl of from one to four carbon atoms.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the cope of the present invention.

Certain compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

In the compounds of Formula I, the term "lower alkyl" means a straight or branched hydrocarbon radical having from one to six carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like.

Halogen is fluorine, chlorine, bromine, or iodine.

The compounds of Formula I are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compound of Formula I include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic

acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge, S. M., et al, "Pharmaceutical Salts," Journal of Pharmaceutical Science 66:1-19 (1977)).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of

suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge, S. M., et al., "Pharmaceutical Salts," Ibid.

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Compounds of Formula I may be prepared according to the syntheses outlined in Schemes I-VI. Although these schemes often indicate exact structures, the methods apply widely to analogous compounds of Formula I, given appropriate consideration to protection and deprotection of reactive functional groups by methods standard to the art of organic chemistry. The strategy for preparation of compounds of Formula I involves N(1) alkylation of a 4-(1H-pyrrol-1-yl)imidazole fragment with a biphenyl fragment. Schemes I, II, III, IV, and IVa deal with preparation of various 4-(1H-pyrrol-1-yl)imidazole fragments. Scheme V shows the synthesis of several biphenylmethyl halides and Scheme VI depicts the combination of the two fragments and subsequent manipulation to give compounds of Formula I. Additionally, many of the chemical modifications

which are described for the N-unsubstituted 4-(1H-pyrrol-1-yl)imidazole fragments are also possible, and often preferable, once the biphenyl fragment is attached at N(1).

Scheme I and II detail methods for the preparation of 2-alkyl-4-(1H-pyrrol-1-yl)imidazoles. The key intermediate in both schemes is **5** which can be prepared by three routes. In the first method (Scheme I), reaction of an alkyl orthoester (**1**) with an aminonitrile (**2**) in a polar solvent such as methanol or ethanol affords the imino ether (**3**) which is treated *in situ* with methanolic ammonia. A cyclization reaction occurs to give **5**. The second method (Scheme I) reacts an alkylimino ether (**4**) with an aminonitrile (**2**) in a polar solvent such as methanol or ethanol to give **5** in a single step. In those cases where the aminonitrile (**2**) and/or the alkylimino ether (**4**) are available as acid addition salts, it is necessary that at least one equivalent of a mild base such as potassium acetate, sodium acetate or the like be added for each equivalent of acid addition salt used in the reaction. The third method is detailed in Scheme II. In this route, an alkylimino ether (**4**) is reacted with an excess of aqueous cyanamide buffered (optimum pH 2.5-6.5) with dibasic sodium phosphate to afford the N-cyano-alkylimino ether (**7**). The N-cyano-alkylimino ether (**7**) is further reacted in a polar solvent such as methanol or ethanol with an acid addition salt of a glycine ester in the presence of a base such as triethylamine to produce the N-(N'-cyanoalkyl-imidoyl)-glycinate ester (**8**). Cyclization of (**8**) to the key intermediate (**5**) is effected by treatment with an alkoxide base such as sodium methoxide or

sodium ethoxide and the like in a polar solvent. Finally, treatment of **5** prepared via Scheme I or Scheme II with 2,5-dimethoxy-tetrahydrofuran derivatives in buffered acetic acid at reflux converts the free amino group to a substituted or unsubstituted pyrrole, affording **6**. Buffering of the acetic acid is best achieved by addition of 2-10 equivalents of either potassium or sodium acetate. This conversion of **5** to **6** is an example of the Paal-Knorr pyrrole synthesis which is well known to those skilled in the art of heterocyclic chemistry and has been reviewed in The Chemistry of Heterocyclic Compounds, E.C. Taylor, Editor, Pyrroles (Part 1), R. Alan Jones, Editor; John Wiley and Sons (1990), pp 206-294.

Selected examples of compound **6** wherein an ester group is located at the 5-position may be further modified to give additional 4-(1H-pyrrol-1-yl)imidazoles according to Scheme 3. Reduction of **6** with a hydride reducing agent such as lithium aluminum hydride, lithium borohydride, and the like affords the alcohol, **9**. Manganese dioxide oxidation of **7** gives the aldehyde **10**. Knoevenagel condensation of malonic acid with **10** in refluxing piperidine affords the free acid **11a**. Alteratively, **10** is converted to ester derivatives (**11b**) via the Wadsworth-Emmons reaction employing such reagents as, but not limited to, trimethylphosphonoacetate, triethylphosphoacetate, and tert-butyl diethylphosphonoacetate in polar solvents such as, tetrahydrofuran, acetonitrile, dimethylformamide, methanol and ethanol employing such bases as sodium hydride, sodium methoxide, potassium t-butoxide,

lithium diethylamide, and 1,8-diazabicyclo[5.4.0]non-5-ene to afford the appropriate ester of **11b**.

Electrophilic reactions of pyrrole derivatives are described in great detail in The Chemistry of Heterocyclic Compounds, E.C. Taylor, Editor, Pyrroles (Part 1), R. Alan Jones, Editor; John Wiley and Sons (1990), pp 329-497. Schemes IV and IVa show examples of such electrophilic substitutions pertinent to this invention. Treatment of a compound such as **6** (Scheme IV) with common electrophilic reagents including HNO_3/acetic anhydride, N-chlorosuccinimide, trichloroacetyl chloride, N-bromosuccinimide or trifluoroacetic anhydride gives compounds of formula **12** with predominantly 2-substitution of nitro, chloro, trichloroacetyl, bromo and trifluoroacetyl groups on the pyrrole ring. Nitration also gives some of the 3-nitro isomer. Use of two equivalents of N-chloro or N-bromosuccinimide gives the 2,5-dichloro and 2,5-dibromopyrrole groups at the 4-position of **12**.

Similarly, treatment of compounds of formula **6a** (Scheme IVa), wherein the pyrrole ring already has an electron withdrawing group at the 2-position, with common electrophilic reagents affords compounds of formula **12a** with a 2,4-substitution pattern on the pyrrole ring. Finally, treatment of compounds of formula **6b** (Scheme IV), wherein the pyrrole ring already has an electron withdrawing group at the 3-position, with common electrophilic reactions affords compounds of formula **12b** with a 2,4-substitution pattern complementary to the pattern seen on **12a**.

The synthesis of the biphenyl fragments (Scheme V) is based on methods of A. Suzuki, et al, Syn.

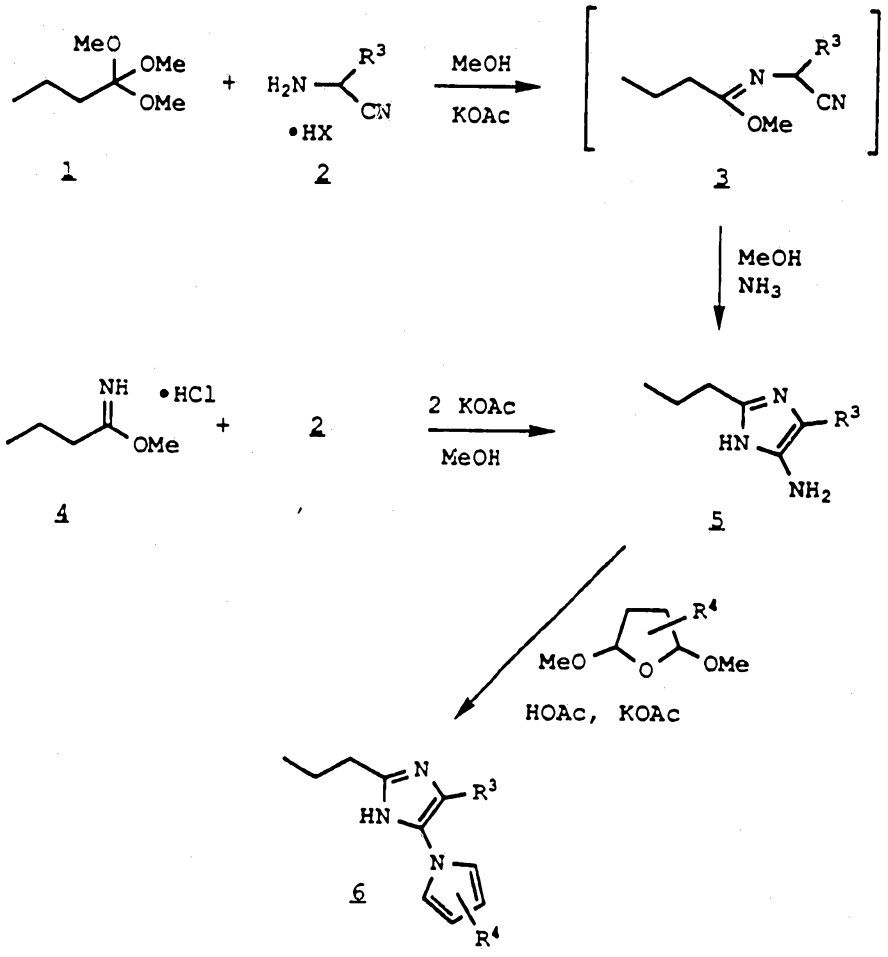
Commun. 11(7):513-519 (1981). The cross-coupling of o-bromobenzonitrile **13** or methyl o-bromobenzoate **13a** with p-tolylboronic acid **14** (F. R. Bean and J. R. Johnson, J. Amer. Chem. Soc. 54:4415-4424 (1934), European Patent 0470795) is effected by heating in dimethoxyethane or toluene in the presence of a palladium catalysts such as tetrakis(triphenylphosphine)-palladium(0) and two equivalents of an aqueous 2M solution of sodium carbonate to afford the unsymmetrical biphenyls, **15** and **15a**. The biphenylnitrile **15** is then converted to **16** by a two-step process. Thus, **15** is treated with trimethyltin azide in refluxing toluene solution to construct the tetrazole ring by a 1,3-dipolar cycloaddition. Subsequent replacement of the trimethyltin group on the newly constructed tetrazole ring is accomplished by treatment with triphenylmethyl chloride in pyridine solution, affording **16**. Both the trityl protected biphenyltetrazole **16** and the biphenylester **15a** are brominated at their respective benzylic positions by treatment with N-bromosuccinimide and a catalytic quantity of a radical initiator such as 2,2-azobis(2-methylpropionitrile) or benzoyl peroxide in refluxing carbon tetrachloride to afford the key intermediates **17** and **17a**, respectively.

Scheme VI depicts the final assembly of biphenyl and 4-(1H-pyrrol-1-yl)imidazole fragments. Treatment of any of the 4-(1H-pyrrol-1-yl)imidazoles of structure type **6** with **17** in the presence of a suitable base such as Na_2CO_3, K_2CO_3, Cs_2CO_3, potassium t-butoxide, sodium methoxide, sodium hydride and the like in an inert solvent such as tetrahydrofuran or N,N-dimethylformamide gives rise to protected products such as **18**. The regiochemistry of this

alkylation process is highly selective for N(1) alkylation due to the steric hinderance to N(3) provided by the adjacent pyrrole ring. The preferred base for the transformation of **6** to **18** is Cs_2CO_3 in a solvent of N,N-dimethylformamide effected at ambient temperature. The trityl protecting group of compound **18** is removed by either refluxing with methanol overnight, by heating with methanol and a mild acid catalyst such as aqueous citric acid, or by brief treatment with warm acetic acid to afford **19** which is a compound of Formula I. Compounds of structure **19** where R^3 or R^4 or both R^3 and R^4 are esters further deprotection by saponification affords **20** which is also a compound of Formula I. In certain instances it is necessary to account for the reactivity of groups in R^3 and R^4 as depicted on compounds **18** and **19**, adjusting the synthetic strategy slightly in order to obtain additional desired compounds of Formula I. Such adjustments of Scheme VI are within the usual realm of expertise of a practitioner of the art of organic chemistry and include the use of additional protection and deprotection steps and the reordering of synthetic steps. The strategy for assembly of complex organic molecules is described in The Logic of Chemical Synthesis by E.J. Corey and Xue-Min Cheng, John Wiley and Sons (1989).

SCHEME I

4-(1H-Pyrrol-1-yl)imidazole Synthesis

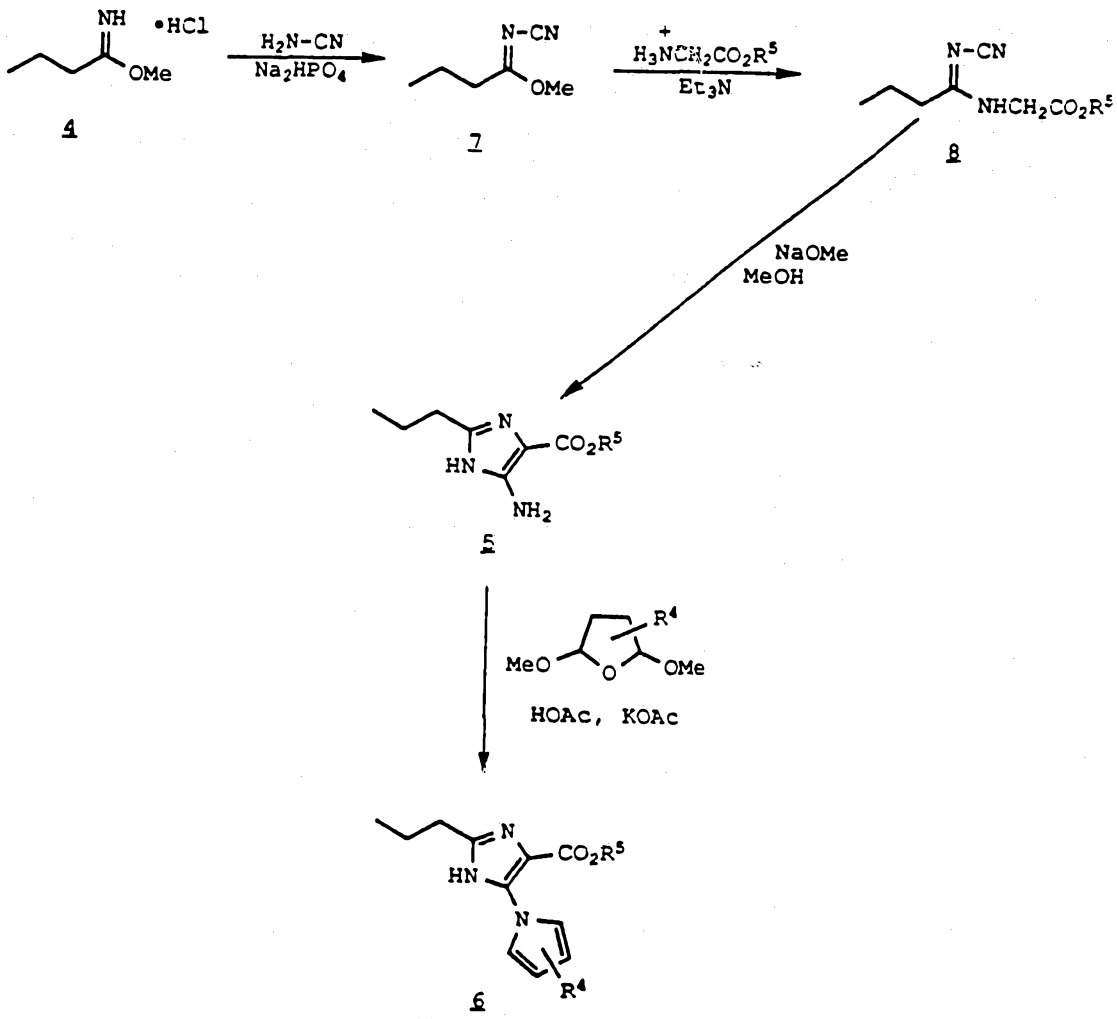


R^3 is CN, CO_2Et or CO_2Me

R^4 is H, 2-CH_3, 2-CH_2CH_3, 2,5-$(CH_3)_2$, 3-CH_3, 3-CH_2CH_3, 2-CO_2Me, 3-CO_2Et, 2-$CH_2CH_2CH_3$-5-CH_3 or 2-CH_3-3-CO_2Me

SCHEME II

Alternative 4-(1H-Pyrrol-1-yl)imidazole Synthesis

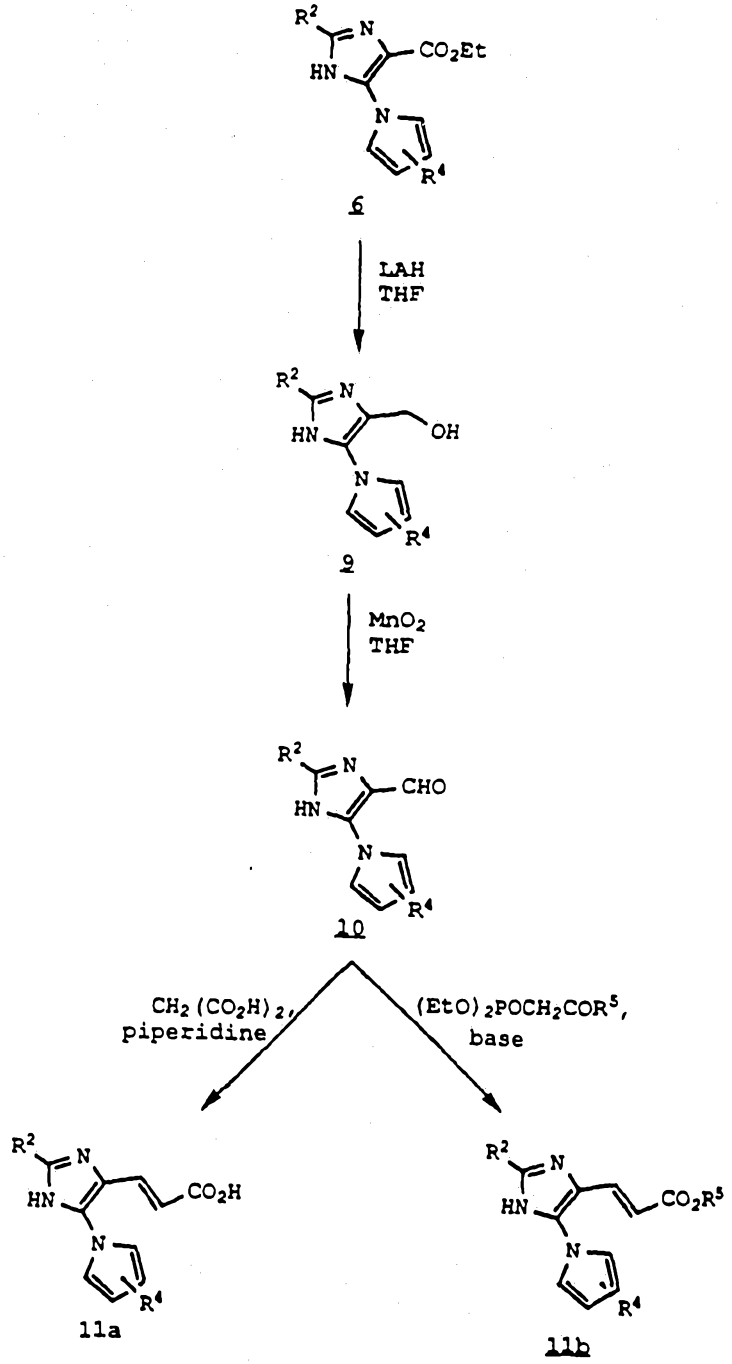


R^5 is $-CH_3$, $-C_2H_5$, $-C(CH_3)_3$

R^4 is H, 2-CH_3, 2-CH_2CH_3, 2,5-$(CH_3)_2$, 3-CH_3, 3-CH_2CH_3, 2-CO_2Me, 3-CO_2Et, 2-$CH_2CH_2CH_3$-5-CH_3 or 2-CH_3-3-CO_2Me

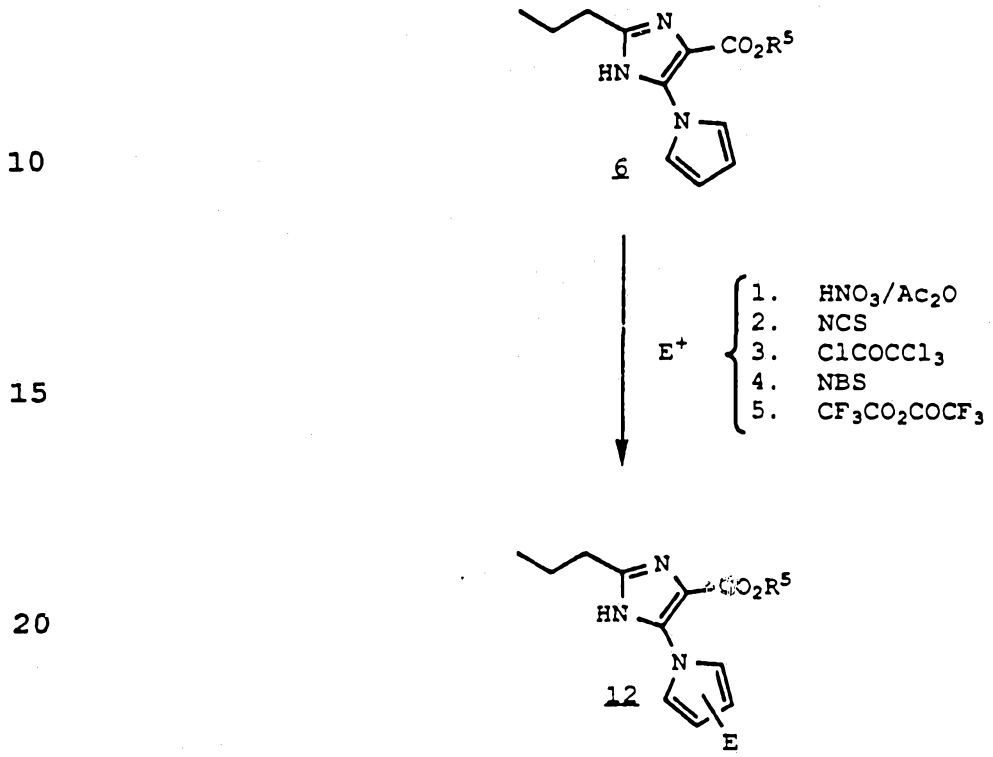
SCHEME III

Transformations of the Imidazole Ring



SCHEME IV

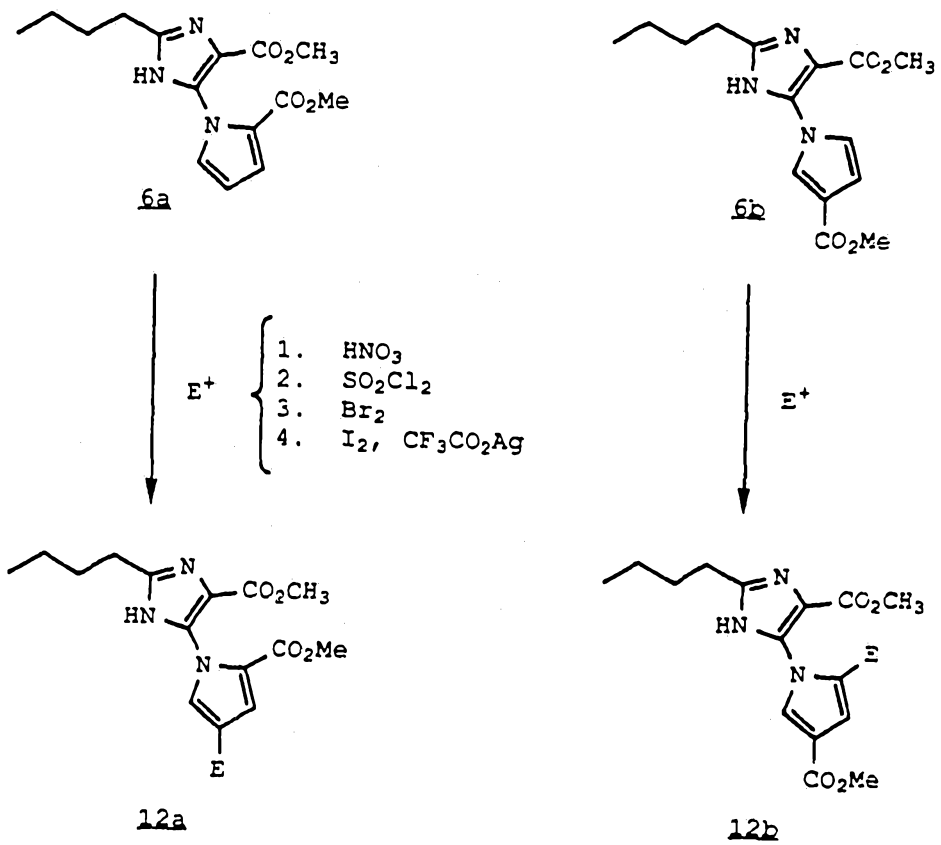
Electrophilic Substitution of Pyrrole Ring



E = 2-NO_2, 3-NO_2, 2-Cl, 2-5$(Cl)_2$, 2-$COCCl_3$, 2-Br, 2,5$(Br)_2$ or 2-$COCF_3$

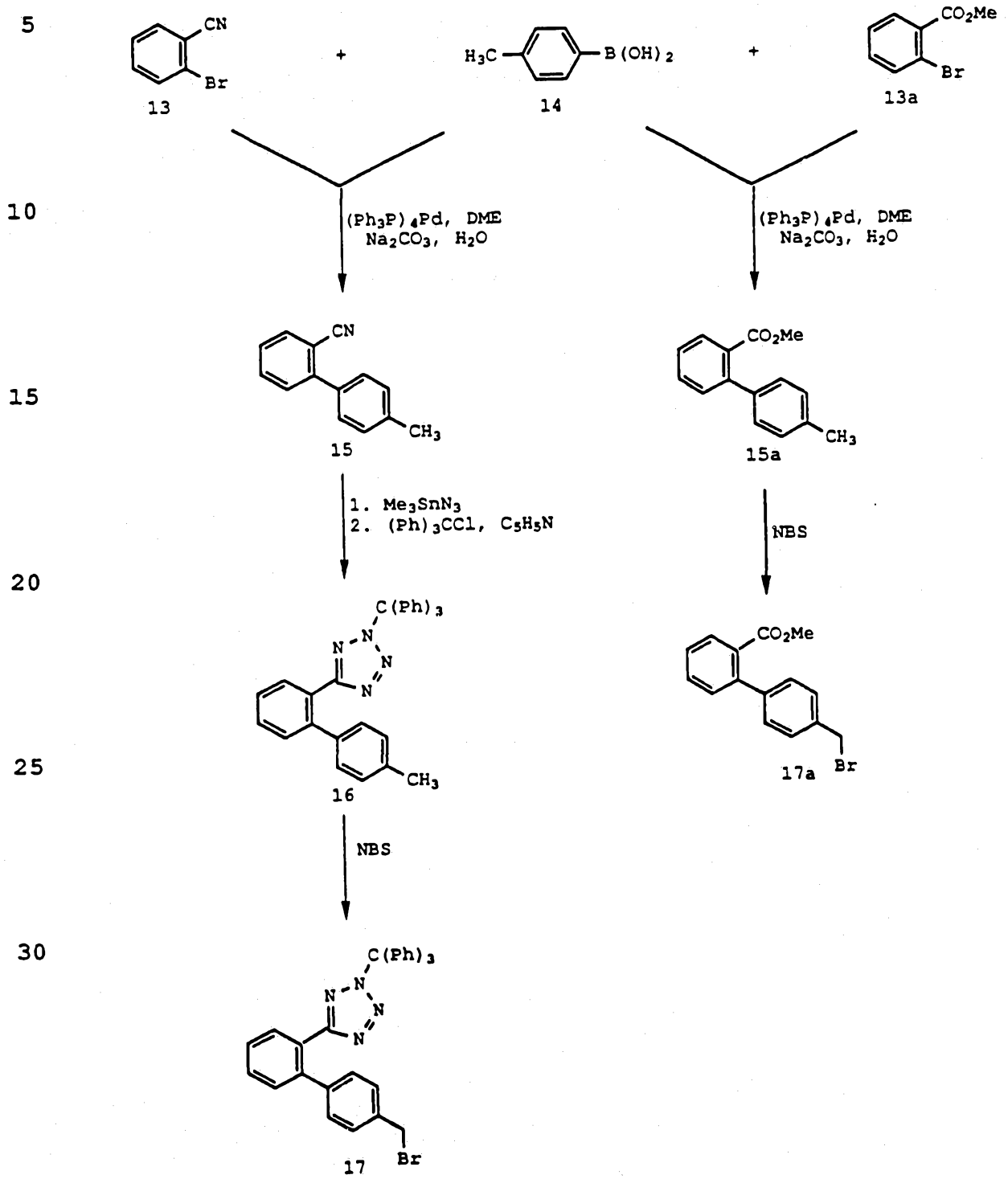
SCHEME IVa

Electrophilic Modification of Substituted Pyrroles



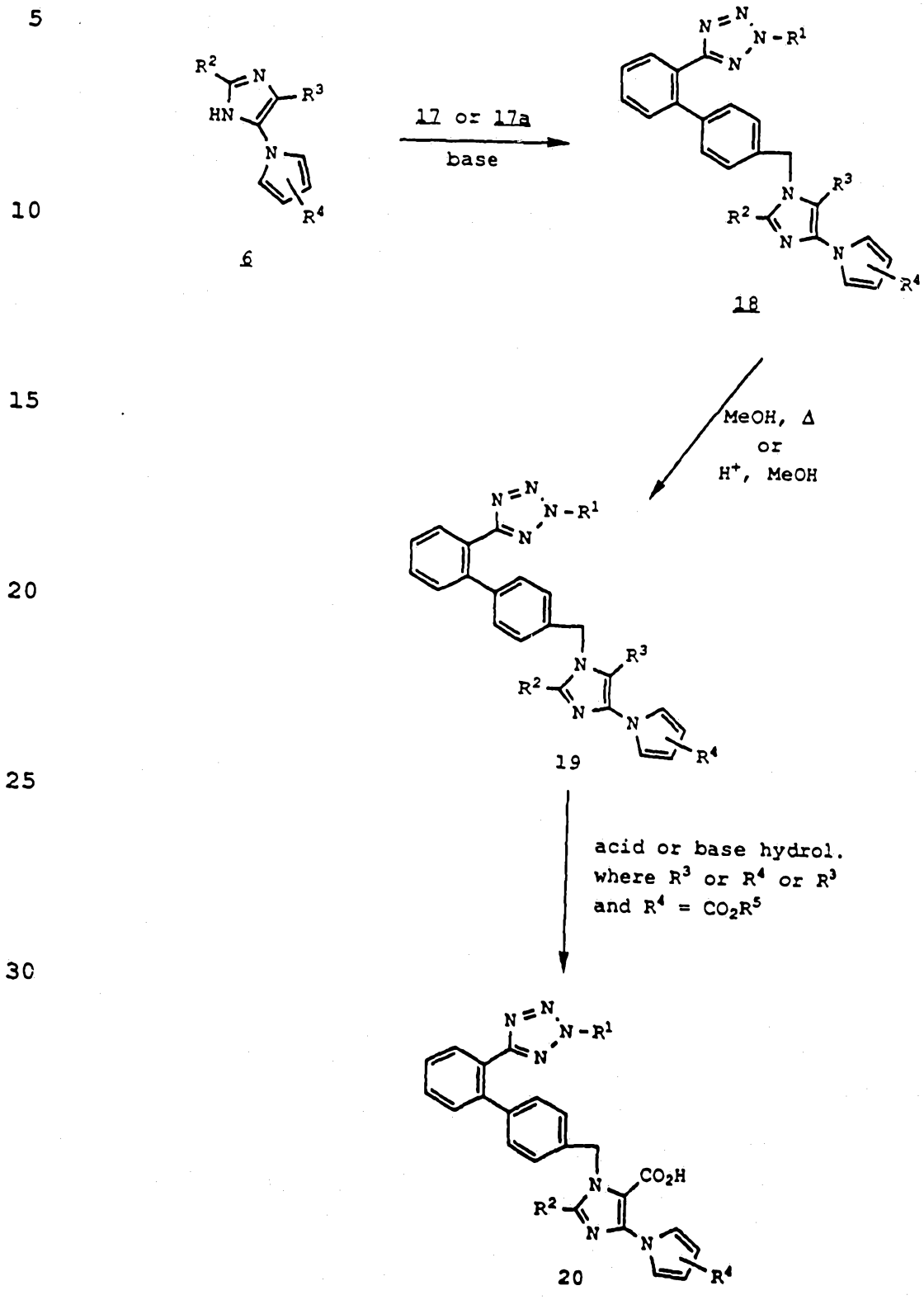
SCHEME V

Biphenyl Fragment Synthesis



SCHEME VI

Connection of Biphenyl and
4-(1H-Pyrrol-1-yl)imidazole Fragments



The compounds of Formula I are valuable antagonists of angiotensin II. Dudley, D.T., et al, Molecular Pharmacology 38:370-377 (1990) reported the existence of two subclasses of angiotensin II binding sites in rabbit adrenal gland and uterus and in the rat liver which differ in their tissue distribution and affinity for various peptide and nonpeptide ligands. Thus, the compounds of Formula I were tested for their ability to inhibit [^{3}H] angiotensin II binding to rat liver membranes (AT_1 test) according to the methods described by Dudley, D.T., et al, Molecular Pharmacology 38:370-377 (1990). Compounds of Formula I are active in the AT_1 test with IC_{50} values ranging from 0.1 nM to 1.0 μM.

Also, the compounds of Formula I were tested for functional activity in vitro. Thus, the compounds of the present invention were tested for their ability to antagonize angiotensin II induced contractions in rabbit aortic rings according to the method described by Dudley D.T., et al, Molecular Pharmacology 38:370-377 (1990). The aforementioned test methods are incorporated herein by reference. Compounds of Formula I are active in this in vitro functional assay with IC_{50} values ranging from 0.1 nM to 1.0 μM.

Finally, the compounds of Formula I were tested in vivo for blood pressure lowering effects in renal hypertensive rats (2-kidney, 1-clip Goldblatt model) according to the method described by S. Sen, et al, in Hypertension 1:427-434 (1979) and in Clin. Soc. 57:53-62, 1979.

Illustrative of the in vivo antihypertensive activity for compounds of Formula I is the data for 4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-

propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid (Example 14). This compound lowers blood pressure by ≥50 mm Hg and is efficacious for more than 24 hours with a single oral dose of 30 mg/kg in the above rodent model.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin,

dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg preferably 0.5 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.1 mg to about 50 mg per kilogram daily. A daily dose range of about 0.5 mg to about 30 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the

compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The following examples illustrate methods for preparing intermediate and final products of the invention. They are not intended to limit the scope of the invention.

EXAMPLE 1

Methyl propionimidate hydrochloride

Hydrogen chloride gas was bubbled through an ether (500 mL) solution of butyronitrile (275.4 g) and methanol (160 g) for a period of 3 hours. The temperature during the addition rose from -4 to 4°C and the reaction mixture stirred at -1°C for 1 hour, then stored at -25°C for 16 hours. The resulting suspension was stirred at -10°C and ether (1.8 L) added over a period of 40 minutes. The mixture was stirred for 1 hour at -6°C, then filtered under an atmosphere of N_2. The insoluble product was filtered, washed with ether, and dried to afford 280 g of methyl butyrimidate hydrochloride. The filtrate was cooled to -5°C for 30 minutes, filtered, and the insoluble product washed with ether to afford an additional 42 g of title product, mp 80-81°C. MS (DEI) 102 (M+1).

EXAMPLE 2

Methyl N-cyanobutyrimidate

The methyl butyrimidate salt from Example 1 (322 g, 2.34 mol) was dissolved in a 50% aqueous solution of cyanamide (236 g, 2.81 mol) and cooled in an ice-bath. Dibasic sodium phosphate (164 g, 1.15 mol) was added to the reaction mixture in portions over a period of 1 hour. The resulting suspension was stirred at room temperature for 2 hours and the liquid decanted from the reaction mixture. The remaining solid was diluted with water (2 L) and extracted with ether (3 x 600 mL). The combined organic layers were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue distilled under high vacuum to afford 258 g of methyl N-cyanobutyrimidate. MS (DEI) 127 (M+1).

EXAMPLE 3

Methyl N-(N'-cyanobutyrimidoyl)glycinate

Methyl N-cyanobutyrimidate (240 g, 1.90 mol) from Example 2 was dissolved in absolute methanol (1.5 L) and glycine methyl ester HCl (250 g, 1.99 mol) added to the reaction mixture. The suspension was cooled to -5°C and triethylamine (211 g, 2.09 mol) added over a period of 15 minutes. The resulting solution was stirred at 20°C for 17 hours, then concentrated under reduced pressure to an oily-solid residue (690 g). The residue was taken up in ethyl acetate and the insoluble salts removed by filtration. The filtrate was washed with water followed by 10% aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and evaporated to dryness under reduced

pressure. This product (370 g) was used in the next step without further purification.

EXAMPLE 4

Methyl 4-amino-2-propylimidazole-5-carboxylate

To stirred methanol at -2°C was added sodium methoxide (108 g, 2.0 mol) in portions over a period of 40 minutes. To this clear solution at -3°C was added a solution of methyl N-(N'-cyanobutyrimidoyl)-glycinate (Example 3, 344 g, 1.9 mol) in methanol (600 mL) over a period of 30 minutes. The resulting orange solution was allowed to warm to 13°C over a period of 1 hour, then refluxed for 1 hour. The dark solution was cooled to room temperature and evaporated to dryness under reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (4 x 1 L) and the combined organic layers washed with a saturated aqueous solution of sodium chloride. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated to dryness under reduced pressure. The residue was recrystallized from ethyl acetate at -10°C to afford 131 g (38% yield) of methyl 4-amino-2-propylimidazol-5-carboxylate, mp 133-136°C. MS (DEI) 184 (M+1).

EXAMPLE 5

Methyl 2-propyl-4-(1H-pyrrol-1-yl)imidazole-5-carboxylate

To stirred acetic acid (1.5 L) at 80°C was added over a 5-minute period a mixture of methyl 4-amino-2-propylimidazol-5-carboxylate (Example 4, 145 g, 0.798 mol) and sodium acetate (388 g, 4.73 mol). The

mixture was heated at reflux for 5 minutes and then 2,5-dimethoxy-tetrahydrofuran (117 g, 0.885 mol) added all at once. The resulting dark solution was refluxed for 20 minutes, then poured onto ice. The gummy mixture was extracted with dichloromethane, the combined organic layers washed with water and dried over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and the residue dissolved in dichloromethane (2 L). The dichloromethane solution was treated with silica gel (500 g) and the suspension filtered through a bed of silica gel (300 g) eluting with dichloromethane. The filtrate was evaporated to dryness under reduced pressure and the crude product recrystallized from ether/hexane (2:1) to provide 86 g (46% yield) methyl 2-propyl-4-(1H-pyrrol-1-yl)imidazol-5-carboxylate, mp 135-138°C. MS (DEI) 234 (M+1).

EXAMPLE 6

Methyl 2-propyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]imidazol-5-carboxylate

To a stirred solution of the methyl 2-propyl-4-(1H-pyrrol-1-yl)imidazol-5-carboxylate (Example 5, 26 g, 0.11 mol) in dichloromethane (500 mL) at room temperature was added trifluoroacetic anhydride (46.61 mL, 0.33 mol) in one portion. The resulting solution was stirred at room temperature for 18 hours, then cooled to 5°C in an ice-bath. A saturated aqueous solution of sodium bicarbonate (100 mL) was added slowly and the mixture stirred for 10 minutes. The organic layer was separated, washed with a saturated aqueous solution of sodium bicarbonate, then dried over anhydrous magnesium sulfate. The solvent was evaporated to dryness under

reduced pressure and the residue taken-up in ether. The crystallizing mixture was cooled to -10°C and the product collected by filtration to provide 23 g (62% yield) of the title compound, mp 158-159°C; MS (DEI) 329 (M^+).

EXAMPLE 7

4-Amino-2-butyl-5-cyanoimidazole

A solution of potassium acetate (2.94 g), anhydrous methanol (30 mL) and trimethyl orthovalerate (9.73 g) was treated with solid aminomalononitrile p-toluenesulfonate and the resulting suspension was stirred at room temperature for 18 hours under nitrogen atmosphere. Solids were removed by filtration and rinsed with anhydrous methanol (30 mL). The combined filtrate and washings were evaporated and the residue was treated with saturated, anhydrous methanolic ammonia (100 mL) at room temperature. The resulting solution was stirred for 18 hours then it was concentrated to about 50 mL. The concentrate was treated with activated charcoal and filtered. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate-hexane (70:30) to give pure product as a gum upon evaporation. This gum was redissolved in chloroform-ether (1:2) and concentrated at reduced pressure to afford a solid which was collected by filtration and rinsed with ether affording the desired product, mp 115-116°C. ^{1}H-NMR ($CDCl_3$) δ 9.0 (br, 1H), 4.2 (br, 2H), 2.6 (t, 2H), 1.6 (m, 2H), 1.3 (m, 2H), 0.9 (t, 3H).

EXAMPLE 8

2-Butyl-5-cyano-4-(1H-pyrrol-1-yl)imidazole

A solution of potassium acetate (5.0 g), acetic acid (22 mL) and 4-amino-2-butyl-5-cyanoimidazole (Example 7, 1.45 g) was heated to reflux and treated with 2,5-dimethoxy-tetrahydrofuran (1.25 mL). The reaction was held at reflux for 1 minute then cooled back to room temperature with an ice bath. The majority of the acetic acid was evaporated at reduced pressure then the residue was partitioned between ethyl acetate and 10% aqueous K_2CO_3 (120 mL) each. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography on silica gel, eluting with hexane-ethyl acetate (90:10 to 80:20). Evaporation of solvents gave a gum that was redissolved in dichloromethane and evaporated once again. The residual oil was held under a vacuum overnight to afford a waxy solid. ^{1}H-NMR ($CDCl_3$) δ 9.9 (br, 1H), 7.4 (s, 2H), 6.3 (s, 2H), 2.7 (t, 2H), 1.7 (m, 2H), 1.4 (m, 2H), 1.0 (t, 3H).

EXAMPLE 9

2-Cyano-4'-methylbiphenyl

Nitrogen was bubbled through a solution of 2-bromobenzonitrile (309.4 g, 1.70 mol) in dimethoxyethane (4.2 L) for 30 minutes then the following reagents added in succession: tetrakis(triphenylphosphine)palladium(0), (95 g, 0.082 mol); 2M aqueous sodium carbonate solution (1785 mL, 3.57 mol); and p-tolylboronic acid (239.1 g, 1.76 mol). The reaction mixture was heated under an atmosphere of nitrogen at 70° to 78°C for 19 hours. The two-phase mixture was cooled to room

temperature and the layers separated. The organic layer was evaporated to dryness under reduced pressure. The aqueous layer was extracted with ether (3 x 1.2 L) and the extracts added to the organic residue. The insoluble material was filtered off and washed with ether. The filtrate was dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The oily residue was filtered to remove the solids and the filtrate distilled under high vacuum (0.1-0.2 torr) collecting the fraction boiling between 135° to 140°C to afford 325 g of 2-cyano-4'-methylbiphenyl. MS (DEI) 193 (M+).

EXAMPLE 10

N-Trimethylstannyl-5-(4'-methylbiphenyl-2-yl)tetrazole

A solution of 2-cyano-4'-methylbiphenyl (1.93 g) in toluene (25 mL) was treated with trimethyltin azide (2.65 g) and heated at reflux for 24 hours. The resulting suspension was cooled to 70°C and filtered. The collected solid was dried at reduced pressure to give the title compound. ^{1}H-NMR ($CDCl_3$) δ 7.5 (m, 4H), 7.0 (q, 4H), 2.3 (s, 3H), 0.4 (s, 9H).

EXAMPLE 11

N-Triphenylmethyl-5-(4'-methylbiphenyl-2-yl)tetrazole

A mixture of N-trimethylstannyl-5-(4'-methyl-biphenyl-2-yl)tetrazole (Example 10, 0.4 g) and anhydrous pyridine (10 mL) was treated with triphenylmethyl chloride (0.3 g) and stirred at room temperature under a nitrogen atmosphere for 48 hours. The resulting solution was evaporated and the residue was partitioned between dichloromethane and saturated

aqueous $CuSO_4$. The organic layer was dried over $MgSO_4$ and evaporated. The residual solid was triturated with diisopropyl ether and collected by filtration to give the title compound, mp 163-165°C (decomp., gas evol.).

EXAMPLE 12

N-Triphenylmethyl-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole

A mixture of N-triphenylmethyl-5-(4'-methylbiphenyl-2-yl)tetrazole (Example 11, 12.7 g), N-bromosuccinimide (4.6 g), carbon tetrachloride (300 mL), and benzoyl peroxide (75 mg) was heated at reflux for 2.5 hours. The cooled suspension was filtered and the filtrate was evaporated to give the title compound as a crystalline solid. ^{1}H-NMR ($CDCl_3$) δ 8.2-6.7 (complex, 23H), 4.3 (s, 2H).

EXAMPLE 13

Methyl 4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate

Methyl 2-propyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]imidazole-5-carboxylate (15 g, 0.046 mol) from Example 6 was dissolved in DMF (500 mL) and Cs_2CO_3 (32.9 g, 0.1 mol) added. After 5 minutes, N-triphenylmethyl-5-[4'-(bromomethyl)-biphenyl-2-yl]tetrazole (Example 12, 26.9 g, 0.048 mol) was added and the reaction mixture stirred at room temperature for 6 hours. The reaction was filtered to remove insoluble salts and the DMF removed high vacuum. The residue was partitioned between ethyl acetate (150 mL) and water (50 mL). The organic layer was extracted with brine,

dried over anhydrous magnesium sulfate, and the solvent evaporated under reduced pressure. Chromatography of the residue on silica gel, eluting with a gradient of ethyl acetate/hexane (1:4) to ethyl acetate/hexane (1:1) afforded 25 g of the title compound in its triphenylmethyl-protected form. The triphenylmethyl protecting group was removed by refluxing in methanol (280 mL) containing 10% aqueous citric acid (28 mL) for 4 hours. The reaction mixture was diluted with water (100 mL) and the milky solution extracted with several times with hexane. The aqueous layer was extracted with ethyl acetate and the combined organic layers extracted with brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The residue was recrystallized using Hexane/ethyl acetate(1:1) to afford 13.4 g of the title compound. MS (FAB, thioglycerol) 564(M+1), mp 135-137°C.

EXAMPLE 14

4-[2-(1-Oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid

4-[2-(1-Oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate (2.5 g) from Example 13 was dissolved in DMF (45 mL). Water (0.4 mL) followed by potassium carbonate (3.1 g) were added and the reaction mixture stirred at room temperature for 48 hours. Tlc of the reaction mixture showed the reaction to be incomplete. Additional potassium carbonate (0.6 g) and water (0.2 mL) were added and the reaction mixture stirred

at room temperature for an another 18 hours. The insoluble materials were removed from the reaction mixture by filtration and washed with DMF. A 10% citric acid solution (100 mL) was added slowly to the filtrate and the resulting mixture extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure. The residue was recrystallized from hexane/ethyl acetate to afford 2.06 g (85% yield) of the title compound, mp 185-188°C, MS (FAB, thioglycerol) 550.3 (M+1).

EXAMPLE 15

2-Butyl-5-cyano-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole

A solution of 2-butyl-5-cyano-4-(1H-pyrrol-1-yl)imidazole (Example 8, 1.7 g) in anhydrous tetrahydrofuran (20 mL) was treated with a solution of potassium tert-butoxide (0.97 g) in anhydrous tetrahydrofuran (20 mL) at room temperature. The mixture was stirred for 5 minutes then a solution of N-triphenylmethyl-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole (Example 12, 6.0 g) in anhydrous tetrahydrofuran (20 mL) was added. The reaction was stirred at room temperature under nitrogen atmosphere for 18 hours. The resulting suspension was filtered and the filtrate was evaporated. The residue was purified by flash chromatography on silica gel, eluting with chloroform-hexane (90:10) to give the title compound in its triphenylmethyl-protected form. The triphenylmethyl protecting group was removed by refluxing in methanol for 24 hours. Evaporation gave a residue that was purified by chromatography on silica gel, eluting with a gradient of ethyl acetate-

hexane (50:50) to ethyl acetate. Evaporation of solvents gave a gum that was redissolved in dichloromethane and evaporated to give the title compound as a solid foam. MS (FAB, thioglycerol) 470 (m+Na-1), 448 (m).

EXAMPLE 16

2-Butyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid

A mixture of 2-butyl-5-cyano-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole (Example 15, 1.4 g) and 2N NaOH (75 mL) was heated at reflux for 24 hours. The cooled solution was acidified to pH 3.5 by portionwise addition of citric acid. The resulting precipitate was collected by filtration and rinsed well with water. The solid was then purified by C_{18}-reversed phase chromatography eluting with acetonitrile-water (40:60). The majority of the acetonitrile was evaporated from the pure fractions at reduced pressure, keeping the temperature below 30°C. The remaining aqueous portion was washed with ethyl acetate and the organic layer was dried over anhydrous magnesium sulfate and evaporated. The residue was dissolved in ether and evaporated once again to give the title compound as a colorless powder. MS (FAB, thioglycerol) 468 (m+1), 424 ($m-CO_2+1$).

EXAMPLE 17

2-Butyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole

A suspension of 2-butyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-

imidazole-5-carboxylic acid (Example 16, 50 mg) in toluene (10 mL) was heated at reflux for 1 hour. Evaporation gave a gummy solid that was redissolved in ether and evaporated again to give the title compound as a colorless powder. ^{1}H-NMR ($CDCl_3$) δ 7.9 (d, 1H), 7.6 (m, 2H), 7.4 (d, 2H), 7.1 (d, 2H), 6.9 (d, 2H), 6.8 (s, 2H), 6.5 (s, 1H), 6.1 (s, 2H), 5.0 (s, 2H), 2.4 (t, 2H), 1.6 (m, 2H), 1.3 (m, 2H), 0.9 (t, 3H).

EXAMPLE 18

4-Amino-5-cyano-2-propylimidazole

Using the method of Example 7, trimethyl orthobutyrate was substituted for trimethyl orthovalerate to afford the title compound. Recrystallization from tert-butyl methyl ether gave analytically pure material, mp 117-119°C. ^{1}H-NMR (DMSO-d_6) δ 5.9 (br, 2H), 5.7 (br, 1H), 2.4 (m, 2H), 1.6 (m, 2H), 0.9 (t, 3H).

EXAMPLE 19

5-Cyano-2-propyl-4-(1H-pyrrol-1-yl)imidazole

4-Amino-5-cyano-2-propylimidazole (Example 18) was treated as in Example 8 to afford the title compound as a crystalline solid upon evaporation of chromatography solvents, mp 75-78°C. ^{1}H-NMR ($CDCl_3$) δ 10.1 (br, 1H), 7.4 (s, 2H), 6.4 (s, 2H), 2.7 (t, 2H), 1.8 (m, 2H), 1.0 (t, 3H).

EXAMPLE 20

Ethyl 4-amino-2-butylimidazole-5-carboxylate

A mixture of methyl iminovalerate hydrochloride (4.8 g), ethyl 2-amino-2-cyanoacetate oxalate (4.0 g), anhydrous sodium acetate (9.1 g) and

absolute ethanol (75 mL) was stirred at room temperature for 18 hours. Solids were removed by filtration and the filtrate was evaporated. The residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated. Flash chromatography on silica gel, eluting with a gradient of dichloromethane-ethyl acetate (75:25) to ethyl acetate gives the title compound (2.7 g) as a pale yellow solid, mp 103-106°C. MS (DEI) 211 (m).

EXAMPLE 21

Ethyl 2-butyl-4-(1H-pyrrol-1-yl)imidazole-5-carboxylate

Ethyl 4-amino-2-butylimidazole-5-carboxylate (Example 20) was treated as in Example 8 to provide the title compound. Purification was achieved by flash chromatography on silica gel, eluting with dichloromethane-ethyl acetate (90:10), mp 74-77°C. MS (CI, CH_4) 262 (m+1).

EXAMPLE 22

5-Cyano-2-propyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole

Using the method described in Example 15, 5-cyano-2-propyl-4-(1H-pyrrol-1-yl)imidazole (Example 19, 2.0 g), potassium tert-butoxide (1.2 g) and N-triphenylmethyl-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole (Example 12, 7.0 g) were reacted to give the title product in its triphenylmethyl-protected form after purification by chromatography. This material was dissolved in methanol (200 mL), treated with aqueous 10% citric acid (10 mL) and heated at reflux for 2.5 hours. The resulting solution was

diluted with water (40 mL) and washed twice with hexanes. The methanol-water layer was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was dried over anhydrous magnesium sulfate and evaporated to a gum. This gum was dissolved in tert-butyl methyl ether and evaporated to a gum which was allowed to stand until seed crystals formed. Trituration with tert-butyl methyl ether gives the title compound as a crystalline solid, mp 179-181°C. MS (CI, CH_4+NH_3) 435 (m+1).

EXAMPLE 23

Methyl 2-butyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate

Using the method described in Example 15, ethyl 2-butyl-4-(1H-pyrrol-1-yl)imidazole-5-carboxylate (Example 21) and N-triphenylmethyl-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole (Example 12) are reacted and deprotected to give the title compound.

EXAMPLE 24

2-Propyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid

5-Cyano-2-propyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole (Example 22, 2.2 g) was treated with 2N KOH (75 mL) and heated at reflux for 12 hours. The resulting solution was cooled on an ice bath and treated dropwise with concentrated aqueous HCl (8 mL) followed by dropwise addition of aqueous 10% citric acid (50 mL). The resulting precipitate was collected by filtration and then it was partitioned between ethyl acetate and 10% citric acid. The

organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator, keeping the temperature below 25°C to give a foam. This foam was dissolved in ether-CH_2Cl_2 (1:1) and diluted to turbidity with hexanes. Evaporation of solvents as above gives the title compound as a colorless powder. MS (FAB, thioglycerol) 454 (m+1), 410 (m-CO_2+1).

EXAMPLE 25

2-Propyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole

Using the method described in Example 17, 2-propyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphenyl)methyl]imidazole-5-carboxylic acid (Example 24) is decarboxylated to give the title compound.

EXAMPLE 26

5-Cyano-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propylimidazole

A solution of the 5-cyano-2-propyl-4-(1H-pyrrol-1-yl)imidazole (Example 19, 2.2 g) in toluene (65 mL) was treated with trifluoroacetic anhydride (4.8 mL) and heated at reflux for 2 hours. After cooling to room temperature, the resulting solution was diluted with ethyl acetate (100 mL) and stirred vigorously with 10% K_2CO_3 (100 mL) for 15 minutes. The organic layer was separated, dried over anhydrous magnesium sulfate and evaporated. The residual gum was purified by flash chromatography on silica gel, eluting with hexane-ethyl acetate (70:30) to afford an oil upon evaporation of solvents. This oil was dissolved in ether, and diluted gradually with

hexanes to induce crystallization, affording the title compound as a colorless solid, mp 104-105°C. ^{1}H-NMR ($CDCl_3$) δ 7.3 (m, 2H), 6.5 (t, 1H), 2.6 (t, 2H), 1.7 (m, 2H), 0.9 (t, 3H). IR ($CDCl_3$) cm^{-1} 2240 (CN), 1685 (CO).

EXAMPLE 27

5-Cyano-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole

N-triphenylmethyl-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole (Example 26, 2.1 g), 5-cyano-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-imidazole (Example ?, 0.89 g), N,N-dimethylformamide (10 mL), and anhydrous K_2CO_3 (0.5 g) were stirred at room temperature under nitrogen atmosphere for 24 hours. Ethyl acetate (50 mL) was added and inorganic solids were removed by filtration. The filtrate was evaporated at reduced pressure and the major product was isolated by flash chromatography on silica gel (toluene-acetonitrile 96:4) to afford the title compound in its triphenylmethyl-protected form (1.3 g). This material was dissolved in methanol (50 mL), treated with aqueous 10% citric acid (1.5 mL) and heated at reflux for 90 minutes. After cooling to room temperature, water (10 mL) and hexanes (100 mL) were added and the mixture was shaken vigorously. The methanol layer was separated, washed again with hexanes and evaporated. The residue was partitioned between ethyl acetate and water. The ethyl acetate layer was dried over anhydrous magnesium sulfate and evaporated. The resulting gum was dissolved in ether, concentrated and allowed to stand overnight to give some seed

crystals. The remaining gum was dissolved in tert-butyl methyl ether, seeded and diluted with diisopropyl ether. Crystallization gave the title product after filtration. MS (CI, CH_4+NH_3) 531 (m+1).

EXAMPLE 28

5-Cyano-4-[2-(1-hydroxy-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)-biphen-4-yl)methyl]-1H-imidazole

A solution of 5-cyano-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole (Example 27, 300 mg) in ethanol (5 mL) was chilled to 10°C and treated with $NaBH_4$ (30 mg). There was a period of rapid gas evolution then the reaction was stirred for 1 hour. Acetone (0.1 mL) was added and the reaction was stirred 10 minutes longer before partitioning between ethyl acetate and 10% citric acid (aq). The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$ and evaporated. Flash chromatography on silica gel, eluting with $CHCl_3$-CH_3OH-CH_3CN (90:5:5) gives the title compound as a foam upon evaporation of solvents. The foam was triturated with hexane-diisopropyl ether (3:1) to give a colorless powder. MS (FAB, thioglycerol) 533 (m+1).

EXAMPLE 29

2-Butyl-5-(hydroxymethyl)-4-(1H-pyrrol-1-yl)imidazole

A solution of ethyl 2-butyl-4-(1H-pyrrol-1-yl)imidazole-5-carboxylate (Example 21, 0.5 g) in tetrahydrofuran (15 mL) was treated with a 1M solution of $LiAlH_4$ in ether (2.1 mL). The reaction

was stirred overnight at room temperature then quenched by addition of saturated aqueous $(NH_4)_2SO_4$. The resulting suspension was extracted three times with ethyl acetate and the combined organic layers were dried over anhydrous magnesium sulfate and evaporated to afford the title compound as an off-white solid. MS (DEI) 205 (m).

EXAMPLE 30

5-Cyano-4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propylimidazole

A mixture of 5-cyano-2-propyl-4-(1H-pyrrol-1-yl)imidazole (Example 19, 200 mg), N-chloro-succinimide (270 mg) and tetrahydrofuran (4 mL) was stirred at room temperature for 24 hours. Evaporation of solvents, followed by flash chromatography on silica gel (hexane-ethyl acetate, 70:30) gives the title product. ^{1}H-NMR ($CDCl_3$) δ 6.1 (s, 2H), 2.7 (t, 2H), 1.8 (m, 2H), 0.9 (t, 3H).

EXAMPLE 31

1-[5-Carboxy-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazol-4-yl]-1H-pyrrole-2-carboxylic acid

Methyl 4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)-biphen-4-yl)methyl]-1H-imidazole-5-carboxylate (Example 13, 0.8 g) was dissolved in a solution sodium hydroxide (1.68 g) in water (14 mL) and the resulting solution refluxed overnight. After cooling in an ice-bath, conc HCl was added dropwise until the pH of the mixture was between 3-4. The insoluble product was collected by filtration, washed several times with water, and dried under reduced pressure

overnight at room temperature to afford 0.85 g of the title compound. ^{1}H-NMR (DMSO-d_6) δ 7.8-7.5 (m, 4H), 7.3-7.0 (m, 5H), 6.9 (m, H), 6.3 (m, 1H), 5.7 (s, 2H), 2.6 (t, 2H), 1.7-1.4 (m, 2H), 0.9 (t, 3H).

EXAMPLE 32

2-Butyl-5-(hydroxymethyl)-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole

Using the method described in Example 13, 2-butyl-5-(hydroxymethyl)-4-(1H-pyrrol-1-yl)-imidazole-5-carboxylate (Example 29) and N-triphenylmethyl-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole (Example 12) are reacted and deprotected to give the title compound.

EXAMPLE 33

5-Cyano-4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole

Using the procedure from Example 13, 5-cyano-4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propylimidazole (Example 30) and N-triphenylmethyl-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole (Example 12) are reacted and deprotected to give the title compound.

EXAMPLE 34

Methyl 1-(5-cyano-2-propylimidazol-4-yl)-1H-pyrrole-2-carboxylate

Using the method of Example 5, 4-amino-5-cyano-2-propylimidazole (Example 7) was reacted with methyl 2,5-dimethoxy-tetrahydrofuran-2-carboxylate to afford the title compound. ^{1}H-NMR 9.4 (br, 2H), 7.3 (m, 1H), 7.2 (m, 1 H), 6.4 (t, 1H), 3.8 (s, 3H), 2.7 (t, 2H), 1.8 (m, 2H), 1.0 (t, 3H).

EXAMPLE 35

Methyl 1-[5-cyano-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazol-4-yl]-1H-pyrrole-2-carboxylate

Using the procedure from Example 13, methyl 1-(5-cyano-2-propylimidazol-4-yl)-1H-pyrrole-2-carboxylate (Example 34) and N-triphenylmethyl-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole (Example 12) were reacted and deprotected to give the title compound. MS (CI, CH_4+NH_3) 507 ($M+CH_3$).

EXAMPLE 36

1-[5-Cyano-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazol-4-yl]-1H-pyrrole-2-carboxylic acid

A solution of methyl 1-[5-cyano-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazol-4-yl]-1H-pyrrole-2-carboxylate (Example 35) in tetrahydrofuran-methanol (2:1) was treated with two equivalents of 1N NaOH at 0°C. The reaction mixture was stirred at reflux for 20 hours then treated with two equivalents of 1N HCl. The reaction mixture was then partitioned between ethyl acetate and brine and the organic layer is dried over $MgSO_4$ and evaporated to afford the title compound. MS (FAB, thioglycerol) 479 (M+1).

EXAMPLE 37

Methyl cylcopropylformimidate hydrochloride

Using an analogous procedure to that described in Example 1, but starting from cyclopropyl cyanide was obtained the title compound methyl cyclopropylimidate hydrochloride. ^{1}H-NMR ($CDCl_3$)

12.42 (br s, 1H), 11.28 (br. s, 1H), 4.21 (s, 3H), 2.42 (m, 1H), 1.23 (m, 4H).

EXAMPLE 38

Methyl N-cyanocyclopropylformimidate

Using an analogous procedure to that described in Example 2, but starting from methyl cyclopropylformimidate hydrochloride (Example 37) afforded the title compound methyl N-cyano-cyclopropylformimidate. ^{1}H-NMR ($CDCl_3$) 3.80 (s, 3H), 2.27 (m, 1H), 1.19 (m, 4H).

EXAMPLE 39

Methyl N-(N'-cyano-cylcopropylformimidoyl)glycinate

Using an analogous procedure to that described in Example 3, but starting from methyl N-cyano-cyclopropylformimidate (Example 38) was obtained the title compound methyl N-(N'-cyanocyclopropyl-formimidoyl)glycinate. ^{1}H-NMR ($CDCl_3$) 6.10 (br s, 1H), 4.04 (d, 2H), 3.79 (s, 3H), 2.18 (m, 1H), 1.12 (m, 4H).

EXAMPLE 40

Methyl 4-amino-2-cyclopropylimidazole-5-carboxylate

Using an analogous procedure to that described in Example 4, but starting from methyl N-(N'-cyano-cylcopropylformimidoyl)glycinate (Example 39) was obtained the title compound methyl 4-amino-2-cyclopropylimidazole-5-carboxylate in 78% yield. MS (DEI) 181(M^+) and 182(M+1).

EXAMPLE 41

Methyl 2-cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)-imidazole-5-carboxylate

A suspension of methyl 4-amino-2-cyclopropyl-imidazole-5-carboxylate (Example 40, 5.72 g, 0.032 mol) in ethanol (40 mL) was treated with acetic acid (25 mL) and the mixture refluxed to effect solution. To the hot solution was added acetonylacetone (5.41 g, 0.047 mol) and the whole stirred and refluxed for 18 hours. The solvent was removed under reduced pressure and the residue purified by flash chromatography eluting with a gradient of CH_2Cl_2 to 20% EtOAc in CH_2Cl_2 to afford 7.93 g of the title compound methyl 2-cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)imidazole-5-carboxylate. ^{1}H-NMR ($CDCl_3$) 5.85 (s, 2H), 3.68 (s, 3H), 2.0 (s, 6H), 1.80-2.0 (m, 1H), 1.0-1.18 (m, 4H).

EXAMPLE 42

Methyl 2-cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate

Using an analogous procedure to that described in Example 13, but starting from methyl 2-cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)imidazole-5-carboxylate (Example 41) was obtained the title compound methyl 2-cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate. MS (CI, CH_4+NH_3) 494 (M^+).

EXAMPLE 43

2-Cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid

To a solution of methyl 2-cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)-biphen-4-yl)methyl]-1H-imidazole-5-carboxylate (Example 42, 1.91 g) in anhydrous THF was added potassium trimethylsilanolate (1.57 g) and the mixture stirred at ambient temperature for 20 hours. The solvent was removed under reduced pressure and the residue taken-up in water (25 mL). The aqueous solution was filtered and extracted with ethyl acetate. The aqueous layer was acidified to pH 4.5 with 1N HCl and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate and evaporated to give the title compound 2-cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid. MS (CI, CH_4+NH_3) 480 (M^+).

EXAMPLE 44

Methyl 4-(2-methyl-5-propyl-1H-pyrrol-1-yl)-2-propyl-imidazole-5-carboxylate

Using an analogous procedure to that described in Example 41, but starting from 2,5-octanedione was obtained the title compound methyl 4-(2-methyl-5-propyl-1H-pyrrol-1-yl)-2-propyl-imidazole-5-carboxylate. ^{1}H-NMR ($CDCl_3$) 5.90 (s, 2H), 3.70 (s, 3H), 2.75 (t, 2H), 2.30 (t, 2H), 2.0 (s, 3H), 1.90-1.70 (m, 2H), 1.58-1.35 (m, 2H), .98(t, 3H), .8 (t, 3H).

EXAMPLE 45

Methyl 4-(2-methyl-5-propyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate

Using an analogous procedure to that described in Example 13, but starting from methyl 4-(2-methyl-5-propyl-1H-pyrrol-1-yl)-2-propyl-imidazole-5-carboxylate (Example 44) was obtained the title compound methyl 4-(2-methyl-5-propyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate, mp 95-101°C. MS (DEI) 523(M^+) 524(M+1).

EXAMPLE 46

4-(2-Methyl-5-propyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid

Using an analogous procedure to that described in Example 43, but starting from methyl 4-(2-methyl-5-propyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate (Example 45) was obtained the title compound 4-(2-methyl-5-propyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)-methyl]-1H-imidazole-5-carboxylic acid. MS (DEI) 523(M^+) 524(M+1).

EXAMPLE 47

Methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-imidazole-5-carboxylate

Using an analogous procedure to that described in Example 41, but starting from methyl 4-amino-2-propylimidazol-5-carboxylate (Example 4) provided the

title compound methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-imidazole-5-carboxylate, mp 175-176°C.

EXAMPLE 48

5-(Hydroxymethyl)-2-propyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)imidazole

Using an analogous procedure to that described in Example 29, but starting from methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-imidazole-5-carboxylate (Example 47) was obtained the title compound 5-(hydroxy-methyl)-2-propyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)imidazole. MS (DEI) 233(M^+) 234(M+1).

EXAMPLE 49

4-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxaldehyde

To a solution of 5-(hydroxy-methyl)-2-propyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)imidazole (Example 48, 6.0 g, 0.026 mol) in dry THF (125 mL) was added MnO_2 (11.2 g, 0.13 mol) and the reaction mixture refluxed for 4 hours under an atmosphere of nitrogen. The reaction mixture was cooled, filtered through celite, and the resulting filtrate evaporated under reduced pressure. Purification by flash chromatography (silica; 2:1 hexane ethyl acetate) gave the title compound 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxaldehyde (4.5 g, 75%), mp 119-121°C.

EXAMPLE 50

4-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(N-triphenylmethyl-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxaldehyde

A mixture of N-(triphenylmethyl)-5-[4'-(bromomethyl)-biphenyl-2-yl]tetrazole (Example 12, 9.66 g, 17.34 mmol), 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1H-imidazole-5-carboxaldehyde (Example 49, 4.0 g, 17.4 mmol), and cesium carbonate (13 g, 40 mmol) in DMF (30 mL) was stirred under an atmosphere of dry nitrogen at room temperature overnight. The reaction mixture was poured over water (750 mL) and the resulting precipitate was collected by filtration. The solid was taken up in ethyl acetate and extracted with water, adjusting the pH of the aqueous layer to pH 8-9 by the addition of sodium bicarbonate. The organic layer was dried over $MgSO_4$ and evaporated to give the crude product as a mixture of regioisomers which were separated by flash chromatography (silica; 3:1 hexane/EtOAc).

High Rf regioisomer:

4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(N-triphenylmethyl-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxaldehyde. ^{1}H-NMR (DMSO-d_6) 5.62 (s, 2H, benzylic CH_2)

Analysis for $C_{46}H_{41}N_7O$:

Calc.: C, 78.05; H, 5.84; N, 13.85.

Found: C, 77.64; H, 5.65; N, 13.65.

EXAMPLE 51

Methyl (E)-3-[4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-2-(triphenylmethyl)-2H-tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate

A solution of 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(N-tri-phenylmethyl-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxaldehyde (Example 50, 5 g) and (carbomethoxy-methylene)triphenylphosphorane (13 g) in toluene (50 mL) was heated at reflux for 30 minutes. The reaction mixture was cooled and filtered and the filtrate was concentrated on the rotovap. Purification of the residue by flash chromatography (silica; 2:1 hexane/EtOAc) gave the pure (E)-isomer (2.7 g) as an oil.

Analysis for $C_{49}H_{45}N_7O_2$:

Calc.: C, 77.04; H, 5.94; N, 12.83.

Found: C, 77.02; H, 5.76; N, 12.70.

EXAMPLE 52

Methyl (E)-3-[4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate

A solution of methyl (E)-3-[4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-2-(tri-phenylmethyl)-2H-tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate (Example 51, 1.0 g) in 100 mL methanol was treated with 10% aqueous citric acid (20 mL) and the resulting mixture was heated at reflux for 30 minutes. The reaction mixture was cooled, diluted with 20 mL water and extracted with hexane. The methanol layer was collected and concentrated to 50 mL on the rotovap. It was diluted

with water and the resulting precipitate was collected by filtration. Recrystallization from isopropyl ether gave pure deprotected tetrazole (490 mg), mp 212-213°C.

Analysis for $C_{30}H_{31}N_7O_2$:
Calc.: C, 69.08; H, 5.99; N, 18.80.
Found: C, 69.24; H, 6.15; N, 18.59.

EXAMPLE 53

(E)-3-[4-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoic acid

A solution of methyl (E)-3-[4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate (Example 52, 1.55 g, 3 mmol), and potassium trimethylsilanolate (0.96 g, 7.5 mmol) in dry THF (80 mL) was stirred at room temperature for 3 hours under an atmosphere of dry nitrogen. The resulting precipitate was collected by filtration, air dried, and then dissolved in water (50 mL). The free acid was precipitated out by the addition of 1N HCl and collected by filtration giving (E)-3-[4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoic acid (1.3 g, 83%) as a partial hydrate, mp 144-150°C.

Analysis for $C_{29}H_{29}N_7O_2 \cdot 0.7H_2O$:
Calc.: C, 66.84; H, 5.90; N, 18.81.
Found: C, 66.94; H, 5.82; N, 18.72.

EXAMPLE 54

5-(Hydroxymethyl)-2-propyl-4-(1H-pyrrol-1-yl)imidazole

Using an analogous procedure to that described in Example 29, but starting from methyl 2-propyl-4-(1H-pyrrol-1-yl)imidazol-5-carboxylate (Example 5) the title compound 5-(hydroxymethyl)-2-propyl-4-(1H-pyrrol-1-yl)imidazole was obtained, mp 155-158°C.

EXAMPLE 55

2-Propyl-4-(1H-pyrrol-1-yl)-imidazole-5-carboxaldehyde

Using an analogous procedure to that described in Example 49, but starting from 5-(hydroxymethyl)-2-propyl-4-(1H-pyrrol-1-yl)imidazole (Example 54) was obtained the title compound 2-propyl-4-(1H-pyrrol-1-yl)-imidazole-5-carboxaldehyde, mp 118.5-120°C.

EXAMPLE 56

4-(1H-Pyrrol-1-yl)-2-propyl-1-[[2'-(N-triphenyl-methyl-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxaldehyde

Using an analogous procedure to that described in Example 50, but starting from 2-propyl-4-(1H-pyrrol-1-yl)-imidazole-5-carboxaldehyde (Example 55) was obtained the title compound 4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(N-tri-phenylmethyl-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxaldehyde which was used in the next step without further purification.

EXAMPLE 57

Ethyl (E)-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-2-(triphenylmethyl)-2H-tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate

Using an analogous procedure to that described in Example 51, but starting from 4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(N-tri-phenylmethyl-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxaldehyde (Example 56) and (carbethoxy-methylene)triphenylphosphorane was obtained the title compound ethyl (E)-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-2-(triphenylmethyl)-2H-tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate which was used directly in the next step.

EXAMPLE 58

Ethyl (E)-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate

Using an analogous procedure to that described in Example 52, but starting from ethyl (E)-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-2-(triphenylmethyl)-2H-tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate (Example 57) afforded the title compound ethyl (E)-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate which was hydrolyzed to the directly to the acid in the next step.

EXAMPLE 59

(E)-3-[4-(1H-Pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoic acid

Using an analogous procedure to that described in Example 53, but starting from ethyl (E)-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate (Example 53) was obtained the title compound (E) 3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoic acid. MS (FAB, thioglycerol) 480 (M+1) 588 (M+thioglycerol).

EXAMPLE 60

Ethyl (E)-2-methyl-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-2-(triphenylmethyl)-2H-tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate

Using an analogous procedure to that described in Example 51, but starting from 4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(N-tri-phenylmethyl-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxaldehyde (Example 56) and (carbethoxy-ethylidene)triphenylphosphorane was obtained the title compound ethyl (E)-2-methyl-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-2-(triphenylmethyl)-2H-tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate. MS (FAB, thioglycerol) 764(M+1).

EXAMPLE 61

Ethyl (E)-2-methyl-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate

Using an analogous procedure to that described in Example 52, but starting from ethyl (E)-2-methyl-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-2-(triphenylmethyl)-2H-tetrazol-5-yl]-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate (Example 60) afforded the title compound ethyl (E)-2-methyl-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate. MS (CI, CH_4 + NH_3) 522(M+1).

EXAMPLE 62

(E)-2-Methyl-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoic acid

Using an analogous procedure to that described in Example 53, but starting from ethyl (E)-2-methyl-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate (Example 61) was obtained the title compound (E)-2-methyl-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoic acid. MS (CI, CH_4 + NH_3) 494 (M+1).

EXAMPLE 63

4-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxaldehyde

Prepared from 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(N-triphenylmethyl-tetrazol-5-yl)-1,1'-

biphenyl-4-yl]methyl]-1H-imidazole-5-carboxaldehyde according to the procedure of Example 52. MS (EI, CH_4 + NH_3) 465 (M^+).

EXAMPLE 64

Methyl 4-(2-methyl-3-carboxymethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxylate

Using an analogous procedure to that described in Example 5, but starting from methyl 4-amino-2-propylimidazol-5-carboxylate (Example 4) and methyl 5-acetoxy-2-methyl-4,5-dihydrofuran-3-carboxylate (Synthetic Communications 20(13):1923-1929 (1990)) afforded the title compound methyl 4-(2-methyl-3-carboxymethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxylate, mp 161-162°C.

Anal for $C_{15}H_{19}N_3O_4$:

Calc.: C, 59.01; H, 6.27; N, 13.76.

Found: C, 58.85; H, 6.44; N, 13.59.

MS (CI, CH_4 + NH_3) 305 (M^+).

EXAMPLE 65

Methyl 4-(3-carboxymethyl-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate

Using an analogous procedure to that described in Example 50, but starting from methyl 4-(2-methyl-3-carboxymethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxylate (Example 64) afforded the title compound methyl 4-(3-carboxymethyl-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate.

MS (FAB, thioglycerol) 782 (M^+).

EXAMPLE 66

Methyl 4-(3-carboxymethyl-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate

Using an analogous procedure to that described in Example 52, but starting from methyl 4-(3-carboxymethyl-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate (Example 65) afforded the title compound methyl 4-(3-carboxymethyl-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)-biphen-4-yl)methyl]-1H-imidazole-5-carboxylate. MS (CI, CH_4 + NH_3) 540 (M^+).

EXAMPLE 67

4-(3-Carboxymethyl-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid and 4-(3-carboxy-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid

To a solution of methyl 4-(3-carboxymethyl-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate (Example 66, 1.98 g) in methanol (10 mL) was added 2N KOH (4.5 mL) and the reaction mixture heated under reflux for 4 hours. The solvent was diluted with water and acidified with 1N HCl and the crude mixture of products collected by filtration. Purification by chromatography over silica gel eluting with CH_2Cl_2/MeOH/AcOH (9/1/0.1) afforded two products in order of elution:

A) 4-(3-carboxymethyl-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-

1H-imidazole-5-carboxylic acid (0.5 g). MS (CI, CH_4 + NH_3) 482 (m-CO_2).

B) 4-(3-carboxy-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid (1.05 g). MS (FAB, thioglycerol) 512 (M^+).

EXAMPLE 68

Methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-imidazole-5-carboxylate

Using an analogous procedure to that described in Example 41, but starting from methyl 4-amino-2-propylimidazol-5-carboxylate (Example 4) was obtained the title compound methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxylate.

Anal for $C_{14}H_{19}N_3O_2$:

Calc.: C, 64.35; H, 7.33; N, 16.08.

Found: C, 64.64; H, 7.52; N, 16.08.

MS (CI, CH_4 + NH_3) 261 (M^+).

EXAMPLE 69

Methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate

Using an analogous procedure to that described in Example 50, but starting from methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxylate (Example 68) afforded the title compound methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(2-triphenyl-methyl-2H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate. MS (FAB, thioglycerol) 738 (M^+).

EXAMPLE 70

Methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate

Using an analogous procedure to that described in Example 50, but starting from methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate (Example 69) was obtained the title compound methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate.

Anal for $C_{28}H_{29}N_7O_2 \cdot CH_3OH$:

Calc.: C, 66.02; H, 6.30; N, 18.58.

Found: C, 65.93; H, 5.92; N, 18.25.

MS (FAB, thioglycerol) 496 (M^+).

EXAMPLE 71

4-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid

A mixture of methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate 9 (Example 70) in methanol (5 mL) containing 5 mL of 2.5N NaOH was heated under reflux for 3 hours. The reaction mixture was cooled, acidified with 10% citric acid to pH 4, and extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The acid was further purified by flash chromatography on silica gel eluting with 5% methanol in ethyl acetate to furnish 0.2 g for the title compound 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-

tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid. MS (FAB, thioglycerol) 482 (M^+).

EXAMPLE 72

Methyl 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propyl-imidazole-5-carboxylate

Using an analogous procedure to that described in Example 5, but starting from methyl 4-amino-2-propylimidazol-5-carboxylate (Example 4) and 3-carboethoxy-2,5-dimethoxytetrahydrofuran (prepared by the method of Niels Clauson-Kaas, Acta Chem. Scand. 6:556-559 (1952)) afforded the title compound methyl 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxylate. MS (CI, CH_4 + NH_3) 305 (M^+) 306 (M+1).

EXAMPLE 73

Methyl 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate

Using an analogous procedure to that described in Example 13, but starting from 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxylate (Example 72) afforded the title compound methyl 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate.

Anal for $C_{29}H_{29}N_7O_2$:

Calc.: C, 64.55; H, 5.42; N, 18.17.

Found: C, 64.68; H, 5.35; N, 18.56.

MS (CI, CH_4 + NH_3) 539 (M^+).

EXAMPLE 74

4-(3-Carboxyethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid

A solution of methyl 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)-biphen-4-yl)methyl]-1H-imidazole-5-carboxylate (Example 73, 0.2 g) in ethanol (2.5 mL) and water (1.25 mL) was treated with lithium hydroxide (0.17 g) ant the reaction mixture stirred a room temperature for 3 days. The reaction mixture was diluted with water, extracted with ether, and the aqueous layer acidified to pH 2 with 1N HCl. The cloudy solution was extracted with ether and the combined organic layers dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue taken-up in ethyl acetate. Petroleum ether was added dropwise to precipitate the product which was collected by filtration to yield 0.11 g of the title compound 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid. MS (CI, CH_4 + NH_4) 410 (M-CO_2H, -CO_2Et).

EXAMPLE 75

4-(3-Carboxy-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid

Using an analogous procedure to that described in Example 71, but starting from methyl 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate (Example 73) afforded the title compound 4-(3-carboxy-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-

tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid. MS (CI, CH_4 + NH_4) 410 (M- $2CO_2H$).

EXAMPLE 76

4-(2,5-Dimethyl-1H-pyrrol-1-yl)-5-(hydroxymethyl)-2-propyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole

To a solution of methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(2-triphenyl-methyl-2H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate (Example 69, 1.0 g) in THF (12 mL) was added dropwise 1.5 mL of a 1M solution of LAH in ether. The reaction mixture was stirred overnight then quenched with aqueous ammonium sulfate. The resulting suspension was filtered and the insoluble material washed with hot ethyl acetate. The filtrate was separated and the organic layer extracted with brine. The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude product was purified by flash chromatography eluting with 5% acetone in CH_2Cl_2 to afford title compound 4-(2,5-dimethyl-1H-pyrrol-1-yl)-5-(hydroxymethyl)-2-propyl-1-[(2'-(2-triphenyl-methyl-2H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole, mp 185-186°C.

EXAMPLE 77

4-(2,5-Dimethyl-1H-pyrrol-1-yl)-5-(hydroxymethyl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole

Using an analogous procedure to that described in Example 52, but starting from 4-(2,5-dimethyl-1H-pyrrol-1-yl)-5-(hydroxymethyl)-2-propyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphen-4-yl)methyl]-

1H-imidazole (Example 76) was obtained the title compound 4-(2,5-dimethyl-1H-pyrrol-1-yl)-5-(hydroxymethyl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole.

EXAMPLE 78

Methyl 2-propyl-4-(2,5-dichloro-1H-pyrrol-1-yl)imidazole-5-carboxylate

Using an analogous procedure to that described in Example 30, but starting from methyl 2-propyl-4-(1H-pyrrol-1-yl)imidazole-5-carboxylate (Example 5) was obtained the title compound methyl 2-propyl-4-(2,5-dichloro-1H-pyrrol-1-yl)imidazole-5-carboxylate.

EXAMPLE 79

Methyl 4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate

Using an analogous procedure to that described in Example 13, but starting from methyl 2-propyl-4-(2,6-dichloro-1H-pyrrol-1-yl)imidazole-5-carboxylate (Example 77) was obtained the title compound methyl 4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate.

EXAMPLE 80

4-(2,5-Dichloro-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid

Using an analogous procedure to that described in Example 14, but starting from methyl 4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-

carboxylate (Example 79) was obtained the title compound 4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid.

EXAMPLE 81

Methyl 2-butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate

Using an analogous procedure to that described in Example 13, but starting from methyl 2-butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]imidazol-5-carboxylate was obtained the title compound methyl 2-butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate, mp 91-96°C. MS (CI, CH_4 + NH_3) 592 (M + CH_3).

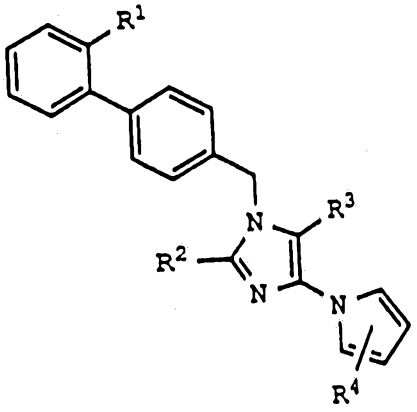
EXAMPLE 82

2-Butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid

Using an analogous procedure to that described in Example 14, but starting from methyl 2-butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate (Example 81) was obtained the title compound 2-butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid, mp 160-173°C. MS (FAB, thioglycerol) 564(M+1).

CLAIMS

1. A compound of formula

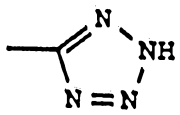


I

or a pharmaceutically acceptable salt thereof wherein

R^1 is

-COOH, or



;

R^2 is

$-C_2H_5$,

$-{}_nC_3H_7$,

$-{}_nC_4H_9$,

$-CH_2CH=CH_2$,

$-CH_2CH=CHCH_3$, or

$-CH_2CH_2CH=CH_2$;

R^3 is

-H,

-CN,
-CHO,
$-CH_2OH$,
$-CO_2R^5$
$-CH_2O\overset{\overset{O}{\|}}{C}R^5$,
$-(CH_2)_nCN$,
$-(CH_2)_nCO_2R^5$,
$-(CH_2)_n$ [illegible]$_2$,
$-(CH_2)_n$ [illegible]OH,
$-CH=CHCO_2R^5$, or
$-CH=C(CH_3)CO_2R^5$

wherein R^5 is hydrogen or a straight or branched alkyl of from one to four carbon atoms and n is 1 or 2;

R^4 is absent or is one or two substituents selected from:

$2-CH_3$,
$2-CH_2CH_3$,
$2-CH_2CH_2CH_3$
$2-CF_3$,
$2-CO_2R^5$,
2-CHO,
$2-CH_2OH$,
$2-CH_2O\overset{\overset{O}{\|}}{C}R^5$,
$2-NO_2$,
2-Cl,
2-Br,
2-I,
$2-COCF_3$,
$2-COCCl_3$,
$2-CH(OH)CF_3$,
$2-CH(OH)CCl_3$,

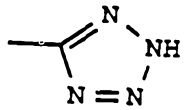
2-$CONH_2$,
2-CONHOH,
3-CH_3,
3-CH_2CH_3,
3-CF_3,
3-CO_2R^5,
3-CHO,
3-CH_2OH,
3-CH_2OCR^5 (‖ O),
3-NO_2,
3-$CONH_2$,
3-CONHOH,
2-CO_2R^5-4-NO_2,
2-$COCCl_3$-4-NO_2,
2-$COCF_3$-4-NO_2,
2-CO_2R^5-4-Cl,
2-$COCCl_3$-4-Cl,
2-$COCF_3$-4-Cl,
2-$COCF_3$-4-Cl,
2-CO_2R^5-4-Br,
2-$COCCl_3$-4-Br,
2-$COCF_3$-4-Br,
2-CO_2R^5-4-I,
2-$COCCl_3$-4-I,
2-$COCCF_3$-4-I,
2-NO_2-4-CO_2R_5,
2-Cl-4-CO_2R^5,
2-Br-4-CO_2R^5,
2-I-4, CO_2R^5,
2-CH_3-3-CO_2R^5,
2,5-$(CH_3)_2$,
2,5-$(CH_2CH_3)_2$,
2,5-$COCF_3$,

2-$CH_2CH_2CH_3$-5-CH_3,
2,5-$(Cl)_2$,
2,5-$(Br)_2$, and
2,5-$(I)_2$

wherein R^5 is hydrogen or a straight or branched alkyl of from one to four carbon atoms.

2. A compound according to Claim 1 wherein

R^1 is -COOH or



;

R^2 is

$-_nC_3H_7$ or
$-_nC_4H_9$;

R^3 is

-H,
$-CO_2R^5$
-CN,
-CHO,
$-CH_2OH$,
$-(CH_2)_nCO_2R^5$ or
$-CH=CHCO_2R^5$

wherein R^5 is hydrogen or a straight or branched alkyl of from one to four carbon atoms and n is 1 or 2;

R^4 is absent or is one or two substituents selected from:

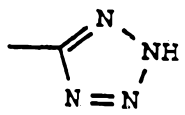
2-CH_3,
2-CO_2R^5,
3-CO_2R^5,
2-CH_2OH,
3-CH_2OH,
2-Cl,

2-Br,
2-CONHOH,
3-CONHOH,
2-$COCF_3$,
2-$COCCl_3$,
2-$CH(OH)CF_3$,
2-$CH(OH)CCl_3$,
2,5-$(Cl)_2$,
2,5-$(Br)_2$, and
2,5-$(CH_3)_2$

wherein R^5 is hydrogen or a straight or branched alkyl of from one to four carbon atoms.

3. A compound according to Claim 1 wherein

R^1 is -COOH or



;

R^2 is

-nC_3H_7 or
-nC_4H_9;

R^3 is

-H,
-CN,
-CO_2H,
-CO_2CH_3,
-$CO_2CH_2CH_3$, or
-CH_2OH; and

R^4 is absent or is one or two substituents selected from:

2-CO_2CH_3,
2-$COCF_3$,
2-CO_2H,

2-$CH(OH)CF_3$,
2,5-$(Cl)_2$, and
2,5-$(CH_3)_2$.

4. A compound according to Claim 1 selected from 2-butyl-5-cyano-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole and 5-cyano-2-propyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole.

5. A compound according to Claim 1 selected from 2-butyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid and 2-propyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid.

6. A compound according to Claim 1 selected from 2-butyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole and 2-propyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole.

7. A compound according to Claim 1 selected from ethyl 2-butyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate and methyl 2-butyl-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)-methyl]-1H-imidazole-5-carboxylate.

8. A compound according to Claim 1 named 2-butyl-5-(hydroxymethyl)-4-(1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole.

9. A compound according to Claim 1 selected from 5-cyano-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole and 5-cyano-4-[2-(1-hydroxy-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole.

10. A compound according to Claim 1 selected from methyl 1-[5-cyano-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazol-4-yl]-1H-pyrrole-2-carboxylate and 1-[5-cyano-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazol-4-yl]-1H-pyrrole-2-carboxylic acid and 1-[5-carboxy-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazol-4-yl]-1H-pyrrole-2-carboxylic acid.

11. A compound according to Claim 1 selected from 5-cyano-4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)-methyl]-1H-imidazole and methyl 4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate and 4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)-methyl]-1H-imidazole-5-carboxylic acid.

12. A compound according to Claim 1 selected from 2-butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid, and methyl 2-butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-1-[(2'-(1H-

tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate.

13. A compound according to Claim 1 selected from 4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid, and methyl 4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)-biphen-4-yl)methyl]-1H- imidazole-5-carboxylate.

14. A compound according to Claim 1 selected from methyl 2-cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate and 2-cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)-methyl]-1H-imidazole-5-carboxylic acid.

15. A compound according to Claim 1 selected from methyl 4-(2-propyl-5-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'- (1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate and 4-(2-propyl-5-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)-methyl]-1H-imidazole-5-carboxylic acid.

16. A compound according to Claim 1 selected from methyl (E)-3-[4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate and (E)-3-[4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoic acid.

17. A compound according to Claim 1 selected from ethyl (E)-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate and (E)-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoic acid.

18. A compound according to Claim 1 selected from ethyl (E)-2-methyl-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoate and (E)-2-methyl-3-[4-(1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazol-5-yl]-2-propenoic acid.

19. A compound according to Claim 1 selected from 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxaldehyde and 4-(2,5-dimethyl-1H-pyrrol-1-yl)-5- (hydroxymethyl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole.

20. A compound according to Claim 1 selected from methyl 4-(3-carboxymethyl-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate, 4-(3-carboxymethyl-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid and 4-(3-carboxy-2-methyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid.

21. A compound according to Claim 1 selected from methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate and 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)-biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid.

22. A compound according to Claim 1 selected from methyl 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)-methyl]-1H-imidazole-5-carboxylate, 4-(3-carboxy-ethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid and 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)-methyl]-1H-imidazole-5-carboxylic acid.

23. A compound selected from
4-amino-2-butyl-5-cyanoimidazole,
4-amino-5-cyano-2-propylimidazole,
2-butyl-5-cyano-4-(1H-pyrrol-1-yl)imidazole,
5-cyano-2-propyl-4-(1H-pyrrol-1-yl)imidazole,
ethyl 2-butyl-4-(1H-pyrrol-1-yl)imidazole-5-carboxylate,
methyl 2-butyl-4-(1H-pyrrol-1-yl)imidazole-5-carboxylate,
2-butyl-5-(hydroxymethyl)-4-(1H-pyrrol-1-yl)-imidazole-5-carboxylate,
5-cyano-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propylimidazole,



methyl 1-(5-cyano-2-propylimidazol-4-yl)-1H-pyrrole-2-carboxylate,

5-cyano-4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propylimidazole,

methyl 4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propylimidazole-5-carboxylate,

methyl 2-butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H- pyrrol-1-yl]imidazole-5-carboxylate,

5-cyano-4-(2,5-dichloro-1H-pyrrol-1-yl)-2-propylimidazole,

methyl 2-cyclopropyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)-imidazole-5-carboxylate,

methyl 4-(2-methyl-5-propyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxylate,

4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxaldehyde,

methyl 4-(3-carboxyethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxylate,

methyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propylimidazole-5-carboxylate,

2-propyl-4-(1H-pyrrol-1-yl)-imidazole-5-carboxaldehyde,

5-(hydroxymethyl)-2-propyl-4-(1H-pyrrol-1-yl)imidazole,

2-butyl-5-(hydroxymethyl)-4-(1H-pyrrol-1-yl)imidazole,

5-cyano-4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propylimidazole,

methyl 4-(2-methyl-3-carboxymethyl-1H-pyrrol-1-yl)-2- propylimidazole-5-carboxylate,

methyl 2-butyl-4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]imidazole-5-carboxylate,

methyl 2-propyl-4-(2,5-dichloro-1H-pyrrol-1-yl)imidazole-5-carboxylate,

5-(hydroxymethyl)-2-propyl-4-(1H-pyrrol-1-yl)imidazole,

methyl 4-amino-2-cyclopropylimidazole-5-carboxylate,

5-(hydroxymethyl)-2-propyl-4-(2,5-dimethyl-1H-pyrrol-1-yl)imidazole, and

methyl (E)-3-[4-(2,5-dimethyl-1H-pyrrol-1-yl)-2-propylimidazol-5-yl]-2-propenoic acid.

24. A pharmaceutical composition adapted for administration as an antihypertensive agent comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

25. A method of treating hypertension comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

26. A method of treating hypertension comprising administering to a host suffering therefrom a therapeutically effective amount of 4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(1H-tetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylic acid, or the methyl ester thereof in unit dosage form.

27. A pharmaceutical composition adapted for administration as an agent for treating hyperaldosteronism comprising a therapeutically effective amount of a compound according to

Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

28. A method of treating hyperaldosteronism comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

29. A pharmaceutical composition adapted for administration as an agent for treating congestive heart failure comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

30. A method of treating congestive heart failure comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

31. A pharmaceutical composition adapted for administration as an agent for treating glaucoma comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

32. A method of treating glaucoma comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

33. A pharmaceutical composition adapted for administration as an agent for treating restenosis related to vascular surgery comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

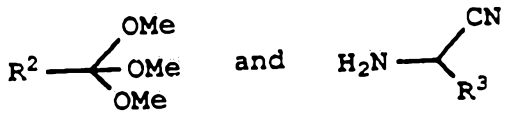
34. A method of treating postsurgical restenosis comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

35. A pharmaceutical composition adapted for administration as an agent for treating atherosclerosis comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

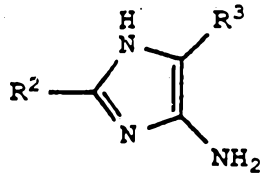
36. A method of treating atherosclerosis comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

37. A process for the preparation of a compound according to Claim 1 comprising

1) reacting



and NH_3 to produce a 4-amino-2,5-disubstituted imidazole derivative



;

2) treating the imidazole derivative from Step 1 with a 2,5-dimethoxytetrahydrofuran derivative under acidic conditions to produce a 4-(1H-pyrrol-1-yl)imidazole derivative;

3) reacting the product of Step 2 with an electrophilic reagent producing substituents on the pyrrole ring;

4) alkylating the product of Step 3 with a substituted (biphen-4-yl)methyl reagent in the presence of a base to produce a substituted 1-(biphen-4-yl)methyl-4-(1H-pyrrol-1-yl)imidazole derivative; and

5) treating the product of Step 4 to remove common protecting groups to produce a compound of Formula I.

38. A process according to Claim 37 wherein in Step 1 an acid addition salt of amino-malononitrile is treated with an ortho ester in the presence of a mild base to form an iminoether which is then treated with ammonia.

39. A process according to Claim 37 wherein in Step 2 a 4-amino-2,5-disubstituted imidazole is heated with a 2,5-dimethoxytetrahydrofuran

derivative in buffered acetic acid to produce a substituted 4-(1H-pyrrol-1-yl)imidazole.

40. A process according to Claim 37 wherein methyl 4-amino-2-propylimidazole-5-carboxylate is heated with 2,5-dimethoxytetrahydrofuran in buffered acetic acid to produce methyl 2-propyl-4-(1H-pyrrol-1-yl)imidazole-5-carboxylate.

41. A process according to Claim 37, Step 2 which comprises treating a 4-(1H-pyrrol-1-yl)imidazole from Step 1 with an electrophilic reagent selected from sulfuryl chloride, nitric acid, N-chlorosuccinimide, chlorine, N-bromosuccinamide, bromine, iodine, trichloroacetylchloride, and trifluoroacetic anhydride.

42. A process according to Claim 37, for the preparation of methyl 2-propyl-4[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]imidazole-5-carboxylate which comprises treating methyl 2-propyl-4-(1H-pyrrol-1-yl)imidazole)-5-carboxylate with trifluoroacetic anhydride in an aprotic solvent.

43. A process according to Claim 37 which comprises alkylation of a 4-(1H-pyrrol-1-yl)imidazole derivative with a (biphen-4-yl)methyl reagent in the presence of a base to produce a substituted 1-(biphen-4-yl)methyl-4-(1H-pyrrol-1-yl)imidazole derivative that is subsequently treated to remove common protecting groups to produce a compound of Formula I.

44. A process according to Claim 37, step 4 which comprises reacting methyl 2-propyl-4[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]imidazole-5-carboxylate with N-triphenylmethyl-5-[4'-(bromoethyl)biphen-2-yl]tetrazole and cesium carbonate in N,N-dimethylformamide solution to produce methyl 4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[(2'-(N-triphenylmethyltetrazol-5-yl)biphen-4-yl)methyl]-1H-imidazole-5-carboxylate, which is subsequently deprotected by treating first with acid and then with base and water to give 4-[2-(1-oxo-2,2,2-trifluoroethyl)-1H-pyrrol-1-yl]-2-propyl-1-[2'-(1H-tetrazol-5-yl)-biphen-4-yl)methyl-1H-imidazole-5-carboxylic acid.

45. A compound according to Claim 1, substantially as herein described with reference to any one of the Examples.

46. A process for the preparation of a compound according to Claim 1 which process is substantially as herein described with reference to any one of the Examples.

47. The product whenever prepared by the process of any one of claims 37 to 44 or 46.

DATED this 28th day of November, 1994
Attorney: IAN T. ERNST
Fellow Institute of Patent Attorneys of Australia
of SHELSTON WATERS



INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/04633

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D403/04; A61K31/415; C07D403/14; C07D233/90
A61K31/40; A61K31/41

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	EP,A,0 401 030 (MERCK & CO. INC.) 5 December 1990 cited in the application see page 6, line 5 see page 6, line 15 see page 6, line 18 see page 6, line 45 - line 47 see page 8, line 35 see page 10, line 47 see page 9, line 43 see page 20, line 34 - line 42 see page 21; figures FORM.7	23
A	WO,A,9 100 281 (E.I.DU PONT DE NEMOURS AND COMPANY) 10 January 1991	

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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)

"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

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"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.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
26 AUGUST 1992	05. 10. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	DE BUYSER I.A.F.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	WO,A,9 100 277 (E.I.DU PONT DE NEMOURS AND COMPANY) 10 January 1991 cited in the application	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9204633 SA 61186

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		CA-A-	2018103	01-12-90
		JP-A-	3074369	28-03-91
WO-A-9100281	10-01-91	AU-A-	6057290	17-01-91
		EP-A-	0479892	15-04-92
WO-A-9100277	10-01-91	AU-A-	5957990	17-01-91
		EP-A-	0479903	15-04-92