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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : **C07D 233/96, 409/14, 417/14 C07D 401/14, 403/14, 413/14 A61K 31/415, 31/425**	**A1**	**(11) International Publication Number:** **WO 93/13077** **(43) International Publication Date:** 8 July 1993 (08.07.93)

(21) International Application Number: PCT/US92/10723

(22) International Filing Date: 9 December 1992 (09.12.92)

(30) Priority data:
811,184 20 December 1991 (20.12.91) US
978,650 19 November 1992 (19.11.92) US

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(81) Designated States: AU, CA, JP, NZ, PT, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: ANGIOTENSIN II RECEPTOR ANTAGONISTS

(57) Abstract

Substituted 1-benzylimidazole-5-methylidene hydantoins are disclosed as well as methods of preparing them, pharmaceutical compositions containing them, and methods of using them. 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, surgically induced vascular smooth muscle proliferation, and glaucoma.

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ANGIOTENSIN II RECEPTOR ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATION

This is a continuation-in-part of United States Serial Number 07/811,184, filed December 20, 1991.

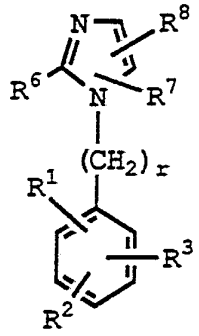
BACKGROUND OF THE INVENTION

The present invention relates to novel substituted derivatives of 1-benzylimidazole-5-methylidene hydantoins 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, 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. 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

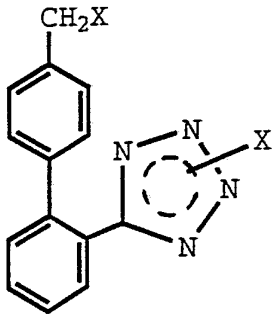
treatment of congestive heart failure, hyperaldosteronism, and glaucoma.

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

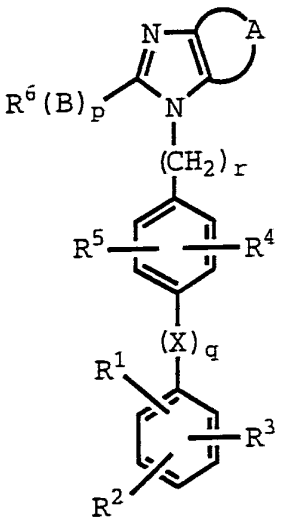


I

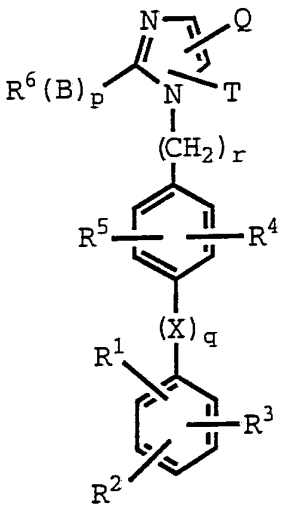
European Patent Application 0291969 discloses tetrazole intermediates to antihypertensive compounds



European Patent Application 401030 discloses substituted imidazo-fused 7-member ring heterocycles of Formula I and Ia



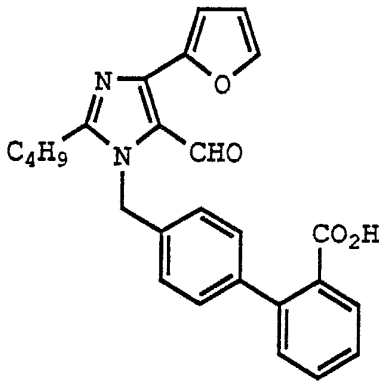
I



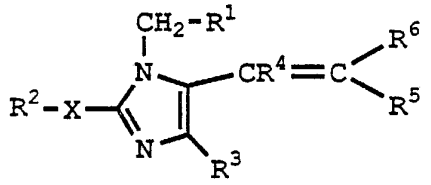
Ia

which are useful as angiotensin II antagonists.

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



European Patent Applications 403158 and 403159 disclose angiotensin II receptor antagonists of formula



in which:

R^1 is phenyl, biphenyl, naphthyl, or adamantylmethyl, which are unsubstituted or substituted by 1 to 3 substituents selected from Cl, Br, F, I, C_1-C_4-alkyl, nitro, CO_2R^7, tetrazol-5-yl, C_1-C_4-alkoxy, hydroxy, SC_1-C_4alkyl, SO_2NHR^7, SO_3H, $CONR^7R^7$, CN, SO_2C_1-C_4alkyl, or C_nF_{2n1}, wherein n is 1 to 3;

R^2 is C_2-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_3-C_6cycloalkyl, or $(CH_2)_{0-3}$phenyl unsubstituted or substituted by 1 to 3 substituents selected from C_1-C_4alkyl, nitro, Cl, Br, F, I, hydroxy, C_1-C_4alkoxy, or NR^7R^7;

X is a single bond, S, or O:

R^3 is hydrogen, Cl, Br, F, I, CHO, hydroxymethyl, $COOR^7$, $CONR^7R^7$, NO_2, or C_nF_{2n1}, wherein n is 1 to 3;

R^4 and R^5 are independently hydrogen, C_1-C_5alkyl, phenyl-Y-, naphthyl-Y-, or biphenyl-Y-, wherein the aryl groups are unsubstituted or substituted by 1 to 3 substituents selected from Cl, Br, F, I, C_1-C_4alkoxy, hydroxy, CO_2R^7, CN, NO_2, tetrazol-5-yl, SO_3H, CF_3, $CONR^7R^7$, SO_2NHR^7, C_1-C_4-alkyl, or NR^7R^7, or by methylenedioxy, phenoxy, or phenyl, except that R^4 and R^5 are not both selected from hydrogen or C_1-C_6alkyl;

Y is a single bond, O, S, or C_1-C_6alkyl which is straight or branched or optionally substituted by phenyl or benzyl, wherein each of the aryl groups is unsubstituted or substituted by halo, NO_2, CF_3, C_1-C_4alkyl, C_1-C_4alkoxy, CN, or CO_2R^7;

R^6 is -Z-$COOR^6$ or -Z-$CONR^7R^7$;

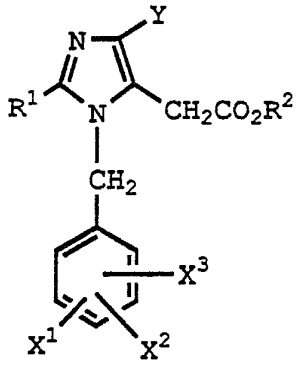
Z is a single bond, vinyl, CH_2-O-CH_2-, methylene optionally substituted by C_1-C_4alkyl, 1 or 2 benzyl groups, thienylmethyl, or furylmethyl, or -C(O)$NHCHR^9$-, wherein R^9 is H, C_1-C_4alkyl, phenyl, benzyl, thienylmethyl, or furylmethyl;

each R^7 independently is hydrogen, C_1-C_4alkyl, or $(CH_2)_m$phenyl, wherein m is 0 to 4; and

R^6 is hydrogen, C_1-C_6alkyl, or 2-di(C_1-C_4alkyl)amino-2-oxoethyl; or

R^5 and R^6 are both hydrogen, R^4 is -Z-$COOR^8$ and Z is other than a single bond; or a pharmaceutically acceptable salt thereof.

United States Patent 4,355,040 discloses imidazole-5-acetic acid derivatives of the formula

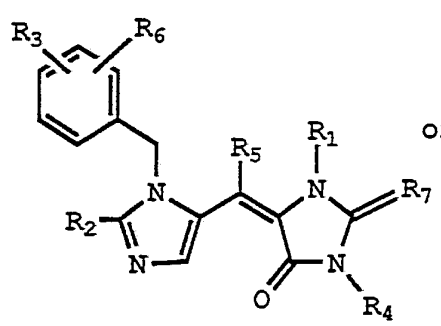


wherein R^1 is lower alkyl, cycloalkyl or, phenyl which may be substituted with 1 to 3 of halogen, nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkyl, lower alkoxyl, benzyloxyl and/or hydroxyl; X^1, X^2, and X^3 are each hydrogen, halogen, nitro, amino, lower alkyl, lower alkoxyl, benzyloxyl or hydroxyl; Y is halogen and R^2 is hydrogen or lower alkyl; provided that X^1 is halogen, lower alkyl, lower alkoxyl, benzyloxyl or hydroxyl when R^1 is unsubstituted or substituted phenyl only with 1 halogen, di(lower alkyl)amino, lower alkyl or lower alkoxyl, and its salts. The compounds are disclosed as having antihypertensive activity.

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.

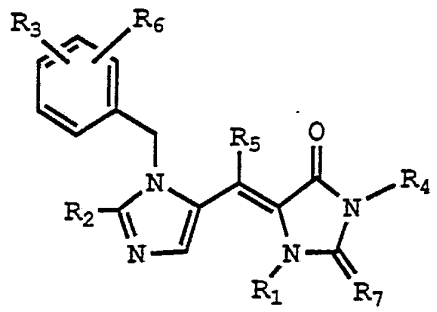
SUMMARY OF THE INVENTION

The present invention is a compound of Formula I or Ia



I

or



Ia

or a pharmaceutically acceptable salt thereof wherein R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are as defined below.

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

R_1 is

hydrogen,
methyl,
ethyl,
n-propyl,
i-propyl,
n-butyl,
i-butyl,
sec-butyl,
t-butyl,
n-amyl,
i-amyl,
n-hexyl,
aryl,
CH_2-aryl,
CH_2-heteroaryl, or
CH_2-cycloalkyl wherein aryl, heteroaryl, and cycloalkyl are as defined below in the detailed description of the invention;

R_2 is

methyl,
ethyl,
propyl,
i-propyl,
n-butyl,
n-pentyl,
2-propenyl,
2-butenyl,
3-butenyl, or
cyclopropyl,

R_3 is

$(CH_2)_nCO_2Y$ or $-C(CH_2)_m-CO_2Y$ wherein Y is hydrogen or lower alkyl, n is 0 or 1, m is 2 to 5;

R_4 is

hydrogen,
alkyl or branched alkyl of from 1 to 8 carbon atoms,
$-(CH_2)_m X(CH_2)_nH$ m = 1-6, n = 0-6, and X = O, N, S;

R_5 is hydrogen;

R_6 is

hydrogen,
chlorine,
fluorine,
methyl,
trifluoromethyl, or
methoxy; and

R_7 is oxygen.

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

R_1 is n-butyl, n-pentyl, n-propyl, benzyl, 2-thienylmethyl, 3-thienylmethyl, cyclopropylmethyl, cyclohexylmethyl, cyclopentylmethyl, 2-methyl-4-thiazolylmethyl, 2-amino-4-thiazolylmethyl, or 4-thiazolylmethyl;

R_2 is butyl and propyl;

R_3 is

$(CH_2)_nCO_2Y$ wherein n is 0, Y is hydrogen or methyl;

R_4 is hydrogen or alkyl of 3 to 6 carbons;

R_5 and R_6 are each hydrogen; and

R_7 is oxygen.

Still more preferred compounds of the instant invention are selected from

(E)-4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[2,5-dioxo-3-(3-methylbutyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[2,5-dioxo-3-(3-methylbutyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[(2,5-dioxo-3-methyl-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[(2,5-dioxo-3-methyl-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[(2,5-dioxo-3-(phenylmethyl)-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester

(Z)-4-[[2-Butyl-5-[(2,5-dioxo-3-(phenylmethyl)-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[(2,5-dioxo-3-phenyl-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[(2,5-dioxo-3-phenyl-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[2,5-dioxo-3-((2-thienyl)methyl)-4-imidazolidinylidene]-methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[2,5-dioxo-3-((2-thienyl)methyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[2,5-dioxo-3-(4-hydroxybutyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[2,5-dioxo-3-(4-hydroxybutyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[(3-butyl-1-methyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[(3-butyl-1-methyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[3-[(4-chlorophenyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[3-[(4-chlorophenyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-3-(cyclohexylmethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-3-(cyclohexylmethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-pentyl-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl] benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-pentyl-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl] benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[(1,3-dibutyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[(1,3-dibutyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[2,5-dioxo-1,3-bis(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[2,5-dioxo-1,3-bis(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(3-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(3-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-3-[(5-methyl-2-thienyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-3-[(5-methyl-2-thienyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(4-thiazolylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(4-thiazolylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[3-[(2-methyl-4-thiazoly)methyl]-2,5-dioxo-1-(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[3-[(2-methyl-4-thiazoly)methyl]-2,5-dioxo-1-(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-3-[(2-amino-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-3-[(2-amino-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]

methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(2-pyridinylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(2-pyridinylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(1H-tetrazol-5-ylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(1H-tetrazol-5-ylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-3-(1H-imidazol-5-ylmethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-3-(1H-imidazol-5-ylmethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-3-[(5-methyl-3-isoxazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-3-[(5-methyl-3-isoxazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-hexyl-2,5-dioxo-3-(3-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-hexyl-2,5-dioxo-3-(3-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[1-hexyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]

methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[1-hexyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-(cyclopropylmethyl)-2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-(cyclopropylmethyl)-2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-(methoxymethyl)-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-(methoxymethyl)-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-(hydroxymethyl)-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-(hydroxymethyl)-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]-3-chloro benzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]

methyl]-1H-imidazol-1-yl]methyl]-3-chloro benzoic acid and its methyl ester,

(Z)-N-[4-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]phenyl]-1,1,1-trifluoromethanesulfonamide,

(E)-N-[4-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]phenyl]-1,1,1-trifluoromethanesulfonamide,

(Z)-1-Butyl-5-[[2-butyl-3-[[4-(1H-tetrazol-5-yl)phenyl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione,

(E)-1-Butyl-5-[[2-butyl-3-[[4-(1H-tetrazol-5-yl)phenyl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione,

(Z)-4-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]-3-chlorobenzoic acid and its methyl ester,

(E)-4-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]-3-chlorobenzoic acid and its methyl ester,

(Z)-1-Butyl-5-[[2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione,

(E)-1-Butyl-5-[[2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione,

1-Butyl-5-[[2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methyl]-2,4-imidazolidinedione,

(Z)-5-[[2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]1-methyl-2,4-imidazolidinedione,

(E)-5-[[2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]1-methyl-2,4-imidazolidinedione,

(Z)-4'-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-

yl]methyl][1,1'-biphenyl]-2-carboxylic acid and its methyl ester,

(E)-4'-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid and its methyl ester,

(Z)-1-[4-[[2-butyl-5-[[2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]phenyl]cyclopentanecarboxylic acid and its methyl ester,

(E)-1-[4-[[2-butyl-5-[[2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]phenyl]cyclopentanecarboxylic acid and its methyl ester,

(Z)-1-[4-[[2-butyl-5-[[1-butyl-[3-(2-methyl-4-thiazoly)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]phenyl]cyclopentane-carboxylic acid and its methyl ester,

(E)-1-[4-[[2-butyl-5-[[1-butyl-[3-(2-methyl-4-thiazoly)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]phenyl]cyclopentane-carboxylic acid and its methyl ester,

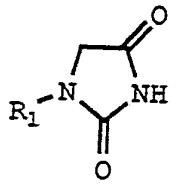
(Z)-4-[[2-Butyl-5-[[2,5-dioxo-1,3-bis(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[2,5-dioxo-1,3-bis(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

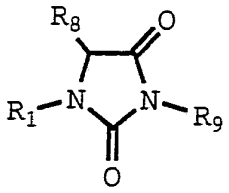
(Z)-4-[[2-butyl-5-[[3-butyl-1-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester, and

(E)-4-[[2-butyl-5-[[3-butyl-1-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester.

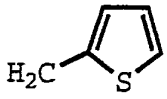
Preferred useful intermediates in the invention are



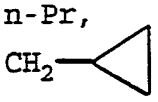
and



wherein R_1 is H,
Me,
n-Bu,
CH_2Ph; or



wherein R_8 is H, Br or $\overset{O}{\overset{\|}{P}}\text{-}(OEt)_2$; and
wherein R_9 is H,
Me,
n-Bu,
CH_2OMe,
n-Pr,



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 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, and

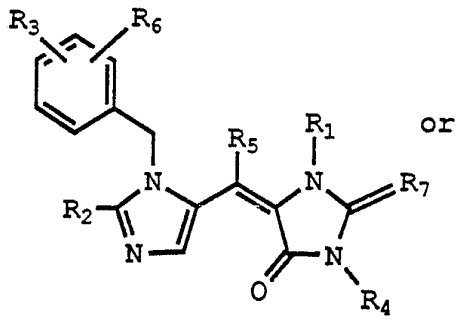
congestive heart failure in mammals. Compounds of the instant invention also have utility in prevention of vascular occlusion due to smooth muscle proliferation following vascular surgeries such as angioplasty, coronary bypass, transplantation, and the like. Additionally, antihypertensive agents as a class have been shown to be useful in lowering intraocular pressure. Thus, the other inventions are also useful in treating and/or preventing glaucoma.

The present invention is also a pharmaceutical composition for administering an effective amount of a compound of Formula I or Ia 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 or Ia and synthetic intermediates.

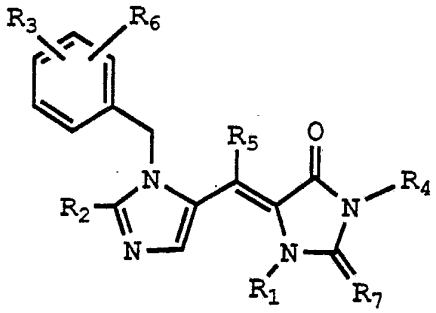
DETAILED DESCRIPTION

This invention is a compound of Formula I or Ia



I

or



Ia

or a pharmaceutically acceptable salt thereof wherein:

R_1 is

-hydrogen,

-straight or branched alkyl or alkenyl from 1 to 8 carbon atoms;

-alkyl as above with HO, NO_2, CN, NH_2, CO_2H, $CONH_2$, CO_2CH_3, $CO_2C_2H_5$, or $CONH_2$ substituents;

-$(CH_2)_n$aryl wherein n is an integer from 0 to 3 and aryl is Ph or Ph substituted with Cl, Br, I, F, CH_3, OCH_3, OH, NO_2, CN, $CONH_2$, CO_2H, NH_2, $NHCH_3$, or $N(CH_3)_2$ groups, methylenedioxy;

-$(CH_2)_n$heteroaryl wherein n is an integer from 0 to 3 and heteroaryl is 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 2-oxazolyl, 2-imidazolyl, 4-thiazolyl, 4-oxazolyl, 4-imidazolyl, 5-thiazolyl, 5-oxazolyl, 5-tetrazole, 3-isoxazole, 4-isoxazole, or 5-isoxazole;

-$(CH_2)_n$heteroaryl as above with Me, Et, Pr, Butyl, Cl, Br, I, F, OMe, OH, NO_2, NH_2, NHMe, NMe_2, CO_2R, SO_2NHR, SO_3H, $CONR_2$ substituents.

-$(CH_2)_n$cycloalkyl wherein n is an integer from 0 to 3 and cycloalkyl is a saturated or unsaturated ring of 3 to 7 carbon atoms;

-$(CH_2)_m$ $X(CH_2)_nH$ where X is O, S, N, and m and n are each independently integral from 1 to 6 carbon atoms;

R_2 is

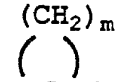
-$(CH_2)_n$ cycloalkyl, wherein n is an integer from 0 to 3, of from 3 to 6 carbon atoms;

alkyl of from 1 to 6 carbon atoms, or

alkenyl of from 2 to 6 carbon atoms,

OC_1-C_5 alkyl, and SC_1-C_5 alkyl;

R_3 is



$(CH_2)_nCO_2Y$ or wherein Y is hydrogen or lower alkyl, n is an integer of from 0 to 8, and m is an integer of from 2 to 7;

CH_2SO_2NHCOR,

$NHSO_2NHCOR$,

$NHCONHSO_2R$,

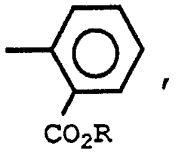
$PO(OR)_2$,

$CONHSO_2R$,

SO_3H,

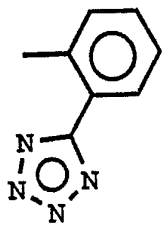
$B(OH)_2$

$-SO_2NHCOR$,

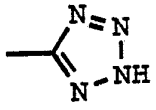


$-SO_2NHCONHR$,

$-NHSO_2CF_3$,



, or



$R_4 = R_1$

R_5 is hydrogen or alkyl of from 1 to 4 carbon atoms;

R_6 is hydrogen, chlorine, bromine, fluorine, methyl, trifluoromethyl, or methoxy; and

R_7 is oxygen or sulfur.

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 scope of the present invention.

Both E- and Z-isomers, for example, a compound of Formula I or Ia are included.

Certain compounds of the present invention possess 1 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 or Ia, the term "alkyl" means a straight or branched hydrocarbon radical having from 1 to 8 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, except where specifically stated otherwise.

The term "alkenyl" is an alkyl group as above bearing 1 double bond at any position with E- or Z-geometry.

The compounds of Formula I or Ia 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 or Ia 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 1977;66:1-19).

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," Journal of Pharmaceutical Science 1977;66:1-19).

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 or Ia and intermediates therefor may be prepared according to the syntheses outlined in Schemes I-VII below. Although these schemes often indicate exact structures, the methods apply widely to analogous compounds of Formula I or Ia and intermediates therefor, 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 or Ia involves oxidation of a 4-chloro-imidazol-5-methanol such as 1 (Scheme I) with manganese dioxide in an inert solvent such as tetrahydrofuran, dioxane, acetone, dichloromethane, and the like. The resulting aldehyde, 2, is then alkylated with a benzyl halide in the presence of a weak inorganic base such as Na_2CO_3, K_2CO_3, or Cs_2CO_3 in a polar, aprotic solvent like DMF, DMA, N-methyl pyrrolidone or DMSO. Preferred conditions for the benzylation employ 1 to 5 equivalents of Cs_2CO_3 in DMF at 0-35°C for 1 to 12 hours. Under the preferred conditions, the alkylated product, 3, is formed to a large excess over its imidazole-N-regioisomer and is easily purified by crystallization or chromatography methods standard to the art of organic chemistry. The 4-chloro group is reduced by catalytic hydrogenation to convert 3 to 4. Preferred conditions for this reduction employ 5% to 10% Pd on carbon, a polar protic solvent such as methanol or ethanol, and a weak base such as NaOAc, KOAc, or LiOAc. Saponification of 4 with strong aqueous base such as NaOH, KOH, or LiOH using a water miscible organic cosolvent such as methanol, ethanol, or tetrahydrofuran gives the intermediate imidazole aldehyde, 5.

Intermediate hydantoins (Scheme II), 7, are prepared in a two-step process, starting from the

appropriately N-substituted-glycine ester, 6. Treatment of 6 with a slight excess of dilute aqueous HCl and KNCO gives an intermediate urea that is cyclized to the hydantoin, 7, by treating with hot concentrated HCl. Furthermore compounds of the Type 6 may be treated with alkylisocyanates in methylene chloride at room temperature. The intermediate substituted ureas may then be cyclized in warm acid or base to afford hydantoins of the Type 1 bearing a R_4 substituent.

Condensation of imidazole-aldehyde intermediates 4 or 5 with hydantoin intermediates 7, as described in Scheme III, affords products of Formula I or Ia such as 10 and 11. The condensation is performed under strongly basic conditions in water or alcohol-water mixtures at 100-120°C. Suitable bases include NaOH, KOH, LiOH, $(Me)_4NOH$, and the like, with $(Me)_4NOH$ preferred. Regioisomeric products 10 and 11 are separated by crystallization or chromatography methods standard to the art of organic chemistry.

An alternative method of condensation to give esters 12 and 13 offers greater control of regiochemistry about the double bond as shown in Scheme IV. Intermediate imidazole-aldehyde, 4, is condensed with the phosphonate-hydantoin, 9, which is prepared according to the published method of Meanwell, et al, J.O.C., 56, 6879-6904 (1991) Depending upon the conditions used in the condensation, the ratio of Z to E isomers will vary. With alkoxides in alcoholic solvent a 1:1 ratio is observed. With 1,8-diazabicyclo[4.4.0]undec-7-ene (DBU), lithium chloride, and acetonitrile solvent, the Z isomer is formed in greater quantities than the E isomer with a Z:E ratio of ≥4:1. Compounds 12 and 13 are compounds of Formula I or Ia and may be converted to Compounds 10 and 11, as shown in Scheme III which are also compounds

of Formula I or Ia, by saponification of the ester group.

Furthermore Compounds 12 and 13 may be converted to compounds represented by Compound 16 by treatment with base in a suitable solvent and with an electrophile. Preferred conditions include treating Compound 12 with 5 equivalents of K_2CO_3 in DMF and an alkyl iodide.

In situations where the phosphonate 9 cannot be prepared an alternative procedure is available as outlined in Scheme V. The phosphonate 9a is prepared by treatment of diethyl 2,5-dioxo-4-imidazolidinone phosphonate with an electrophile and base in a suitable solvent. Preferred conditions include treating 9 with 5 equivalents K_2CO_3 in DMF and an alkyl iodide at room temperature and stirring for 4 to 16 hours. With less reactive electrophiles 9 can be treated with one equivalent of NaH in THF or DMF and the electrophile added at room temperature.

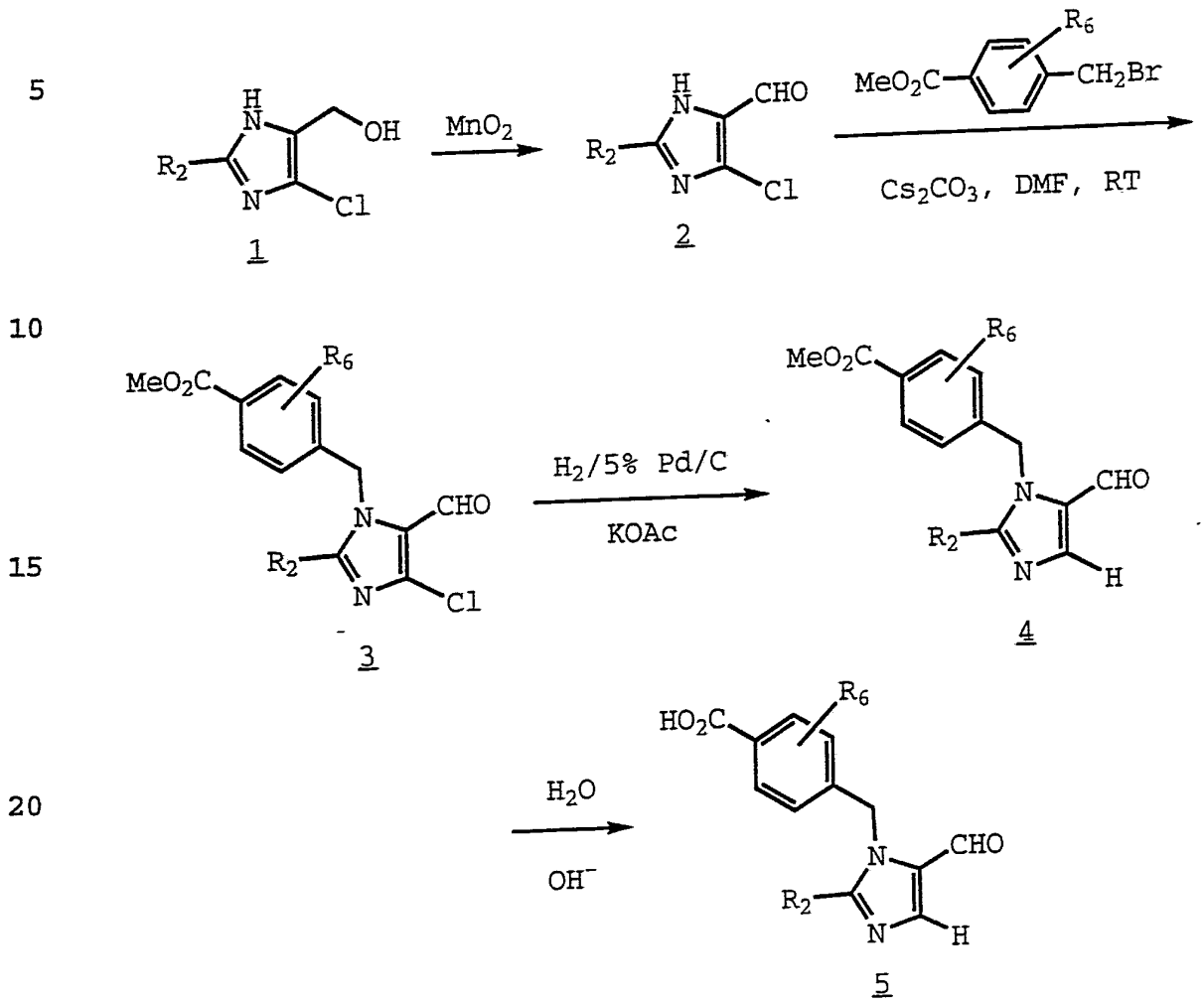
The phosphonate 9a is condensed with the intermediate aldehyde 4 (Scheme V) to give mixtures of the alkylidinene hydantoins 14 and 15. When DBU is used as a base in methylene chloride the Z isomer is formed predominantly. Compound 14 can be alkylated by treatment with base and a reactive electrophile. Typical condition include treating 14 with 5 equivalents of K_2CO_3, in DMF, and then adding the electrophile. Reactions proceed normally at room temperature. With less reactive electrophiles the reaction temperature may be elevated and additional quantities of electrophile added.

Ester saponification when R_4 and R_1 are not hydrogen is achieved by refluxing Compound 16 in acid; 2N HCl is preferable. Prolonged heating with concentrated HCl causes Z to E isomerisation. Alternatively the t-butyl ester, Compound 17, is hydrolysed by treatment with trifluoroacetic acid.

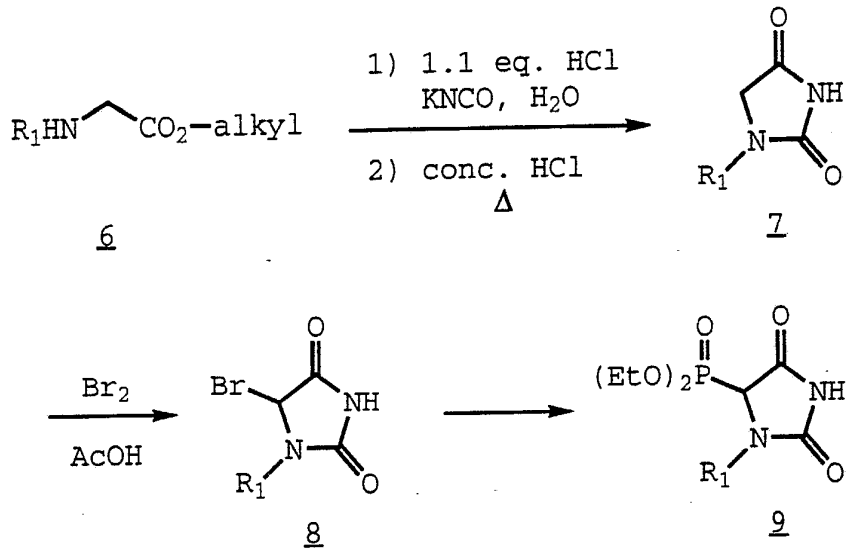
Scheme VI represents an alternative procedure for preparing compounds such as 16. In this case the imidazole aldehyde 21 is condensed with a phosphonate hydantoin, such as 9A to afford the adduct 23. Equally applicable would be a hydantoin phosphonate containing a combination of R_4 and R_1 substituents. Compound 23 is treated with a reactive electrophile and a base, such as butyl iodide and K_2CO_3 respectively, to afford Compound 24. This intermediate then upon treatment with a reactive electrophile affords 16 with good regioselectivity. More specifically the hydantoin 9A is condensed with 21 in CH_2Cl_2 using DBU as a base at room temperature. The Z-isomer is separated, alkylated at N-3, and treated with the trifluoromethanesulphonate derived from methyl 4-hydroxymethyl benzoate at -78°C in CH_2Cl_2. The reaction mixture is allowed to warm slowly to room temperature and the product 16 isolated upon removal of the protecting group.

A number of substituents are tolerated at position Y, as shown in Scheme VII. The condensation of a substituted phosphonate hydantoin with Compounds 24 through 28 is effected by the addition of base in an appropriate solvent. Typical conditions include the use of DBU in CH_2Cl_2 at room temperature as well as NaH in methanol. The reaction time is typically several hours with a greater portion of the Z isomer being formed when DBU is used as the base. Where the substrate contains an acidic hydrogen, as in Compound 29, a further equivalent of base is required for efficient conversion.

SCHEME I

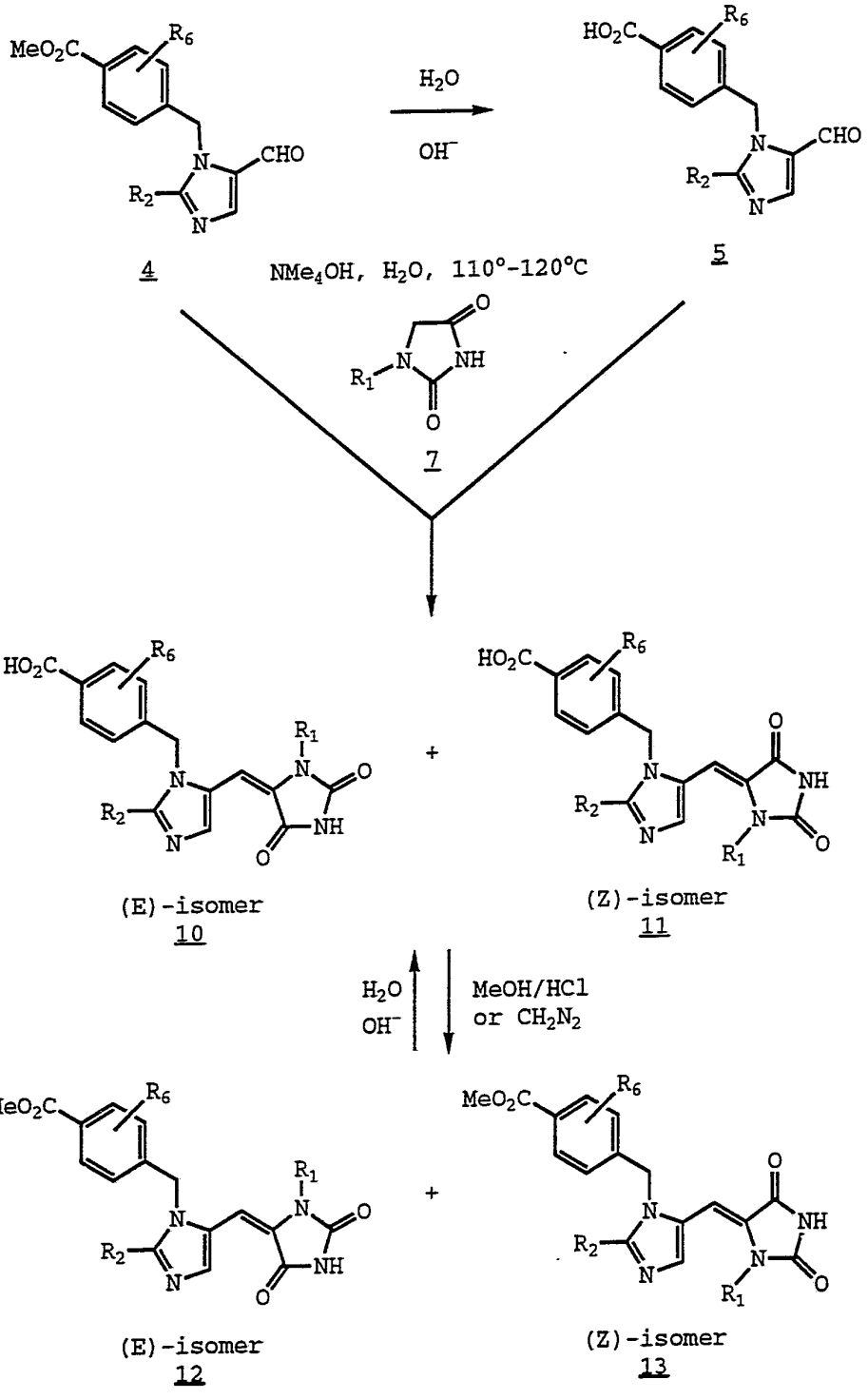


SCHEME II

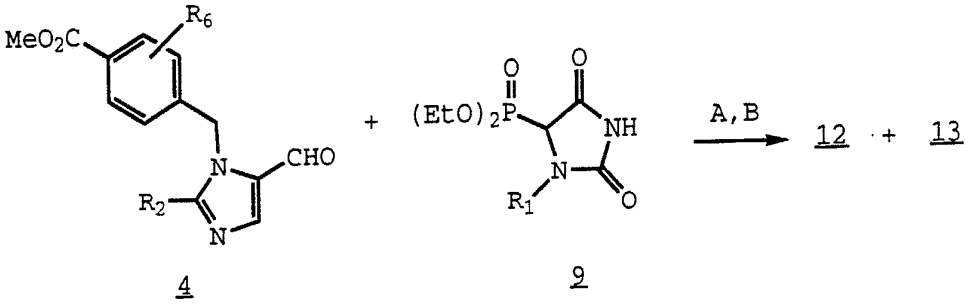


Meanwell, et al.
J.O.C. 56, 6897-6904 (1991).
(Report Compound where R_1 = H, CH_3)

SCHEME III

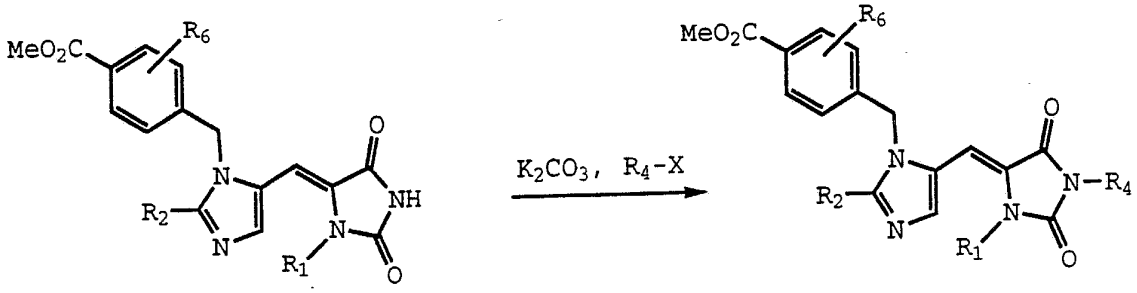

MeO2C
R6
CHO
N
R2
N
H2O
OH−
HO2C
R6
CHO
N
R2
N
4
5
NMe4OH, H2O, 110°-120°C
O
NH
R1
N
O
7
HO2C
R6
R1
N
R2
N
O
NH
O
(E)-isomer
10
+
HO2C
R6
O
NH
N
R2
N
R1
O
(Z)-isomer
11
H2O
OH−
MeOH/HCl
or CH2N2
MeO2C
R6
R1
N
R2
N
O
NH
O
(E)-isomer
12
+
MeO2C
R6
O
NH
N
R2
N
R1
O
(Z)-isomer
13

SCHEME IV

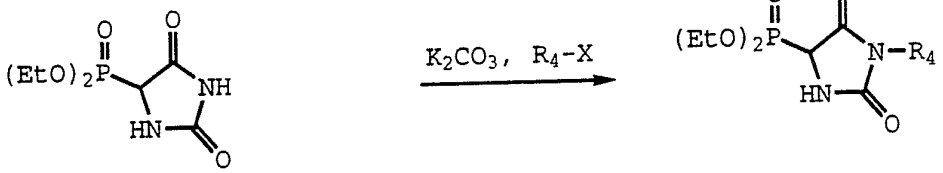


4 9

	12	13
Condition A: MeOH, NaH	30% Z,	23% E
Condition B: LiCl, DBu, MeCN	65% Z,	14% E

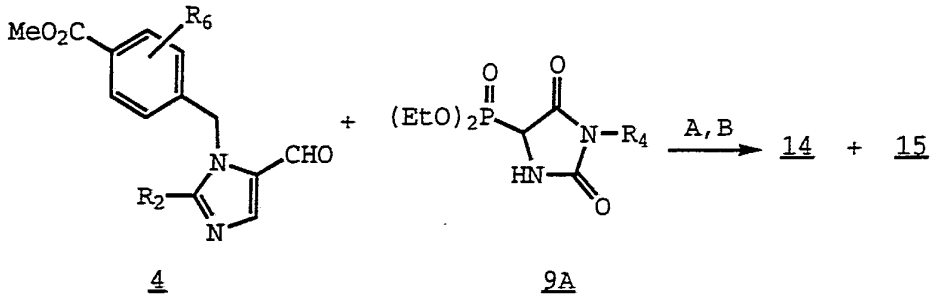


12 16



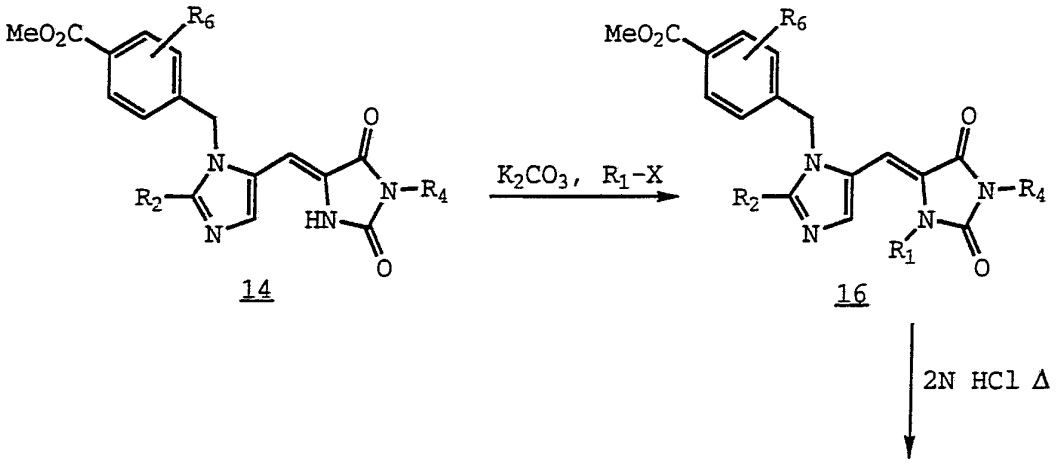
9 (R_1 = H) 9A

SCHEME V

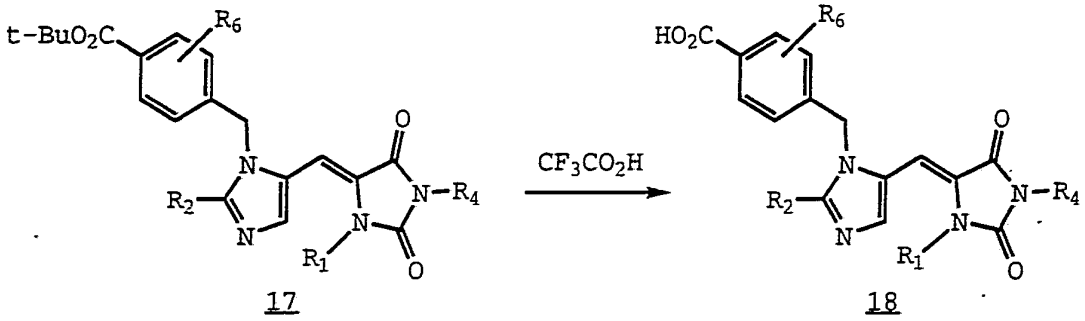


4 9A

Condition A: MeOH, NaH
Condition B: DBU, CH_2Cl_2

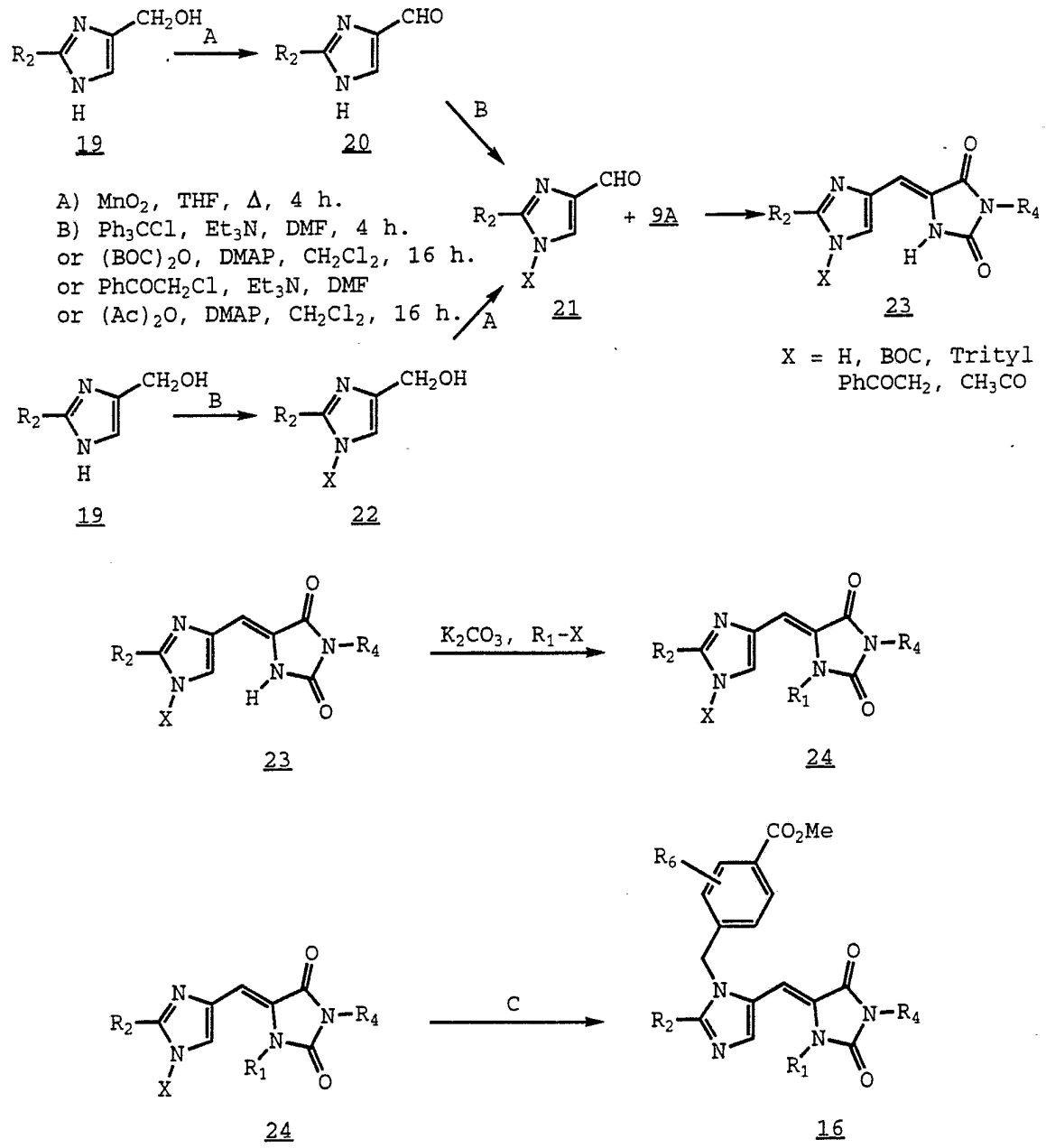


14 16

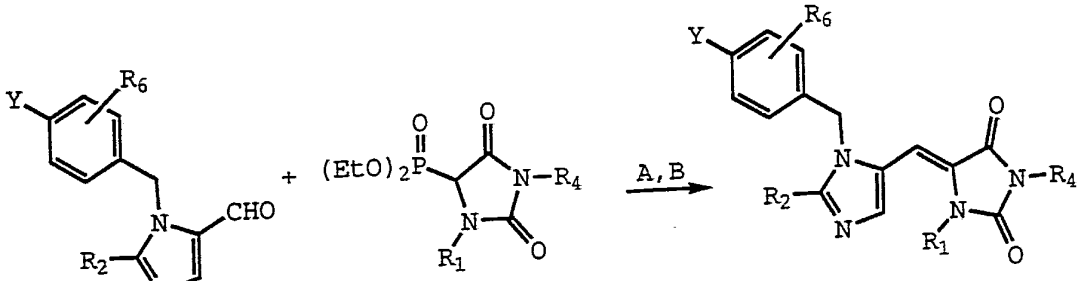


17 18

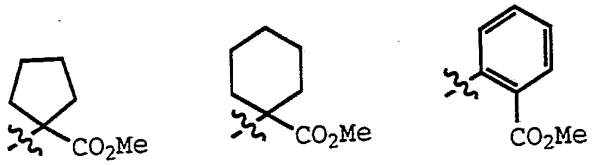
SCHEME VI


A
B
19
20
21
22
23
24
16
9A
A) MnO_2, THF, Δ, 4 h.
B) Ph_3CCl, Et_3N, DMF, 4 h.
or $(BOC)_2O$, DMAP, CH_2Cl_2, 16 h.
or $PhCOCH_2Cl$, Et_3N, DMF
or $(Ac)_2O$, DMAP, CH_2Cl_2, 16 h.
X = H, BOC, Trityl
$PhCOCH_2$, CH_3CO
K_2CO_3, R_1-X
C
C) i. (p-CO_2Me)$ArCH_2OH$, $(CF_3SO_2)_2O$, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, -78°C
ii. X=BOC, pH 7 buffer, 1 h.
X=Trityl, AcOH, MeOH, Δ, 1 h.
X=$PhCOCH_2$, Zn, AcOH.

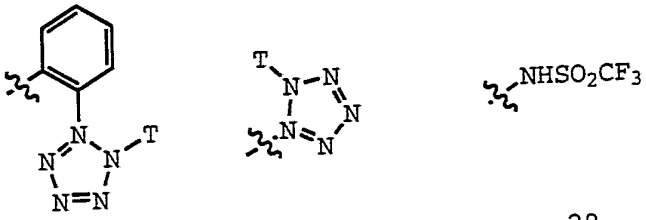
SCHEME VII



Y =



24 25 26



27 28 29

T= Triphenylmethyl

The compounds of Formula I or Ia are antagonists of angiotensin II. Dudley, D. T., et al, Molecular Pharmacology 1990;38:370-377 reported the existence of 2 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 or Ia 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 1990;38:370-7. Compounds of Formula I or Ia are active in the AT_1 test with IC_{50} values as in Table I below.

It is well established that compounds which antagonize the effect of angiotensin II at the AT_1 receptor have value for treatment of hypertension and heart failure.

TABLE I
(Page 1 of 3)

Example	AT_1 IC_{50} (nM)
1a	2.7
1b	2.82
2a	9.4
2b	8.8
3a	172
3b	83.8
4a	11.2
4b	4.17
5	643
6a	2.97
6b	1.43
15a	10.9
15b	10.3
16a	5.45
16b	6.92
17a	98.3
17b	49.5
18	21
20a	3.36
20b	2.47
21a	111
21b	89.3
22	1.67
23	3.39
24	10.3
25	6.39
26a	2.63
26b	2.22
29	>1000
32a	178
32b	1170
33	8.49
35	40.2
36	12.4
37	14.3
38	16.9
39	159
40	4.78
41	30.9
42	884
43	3.33
44	41.7

TABLE I
(Page 2 of 3)

Example	AT_1 IC_{50} (nM)
47	>1000
48	14.6
49	9.48
50	26.6
51	5.33
53	>1000
54	29.5
55	12.8
56	47.8
57	260
58	5.81
59	1.21
60	2.63
61	59.8
62	1.21
63	5.08
64	4.30
65	200
66	17.6
67	3.39
68	4.2
69	198
70	104
71a	3.21
71b	4.18
72	23.9
73	1.3
74	0.6
75	0.64
76a	3.36
76b	2.48
77	17.8
78	21.9
79	14.5
80	14.6
81	25.4
82	7.96
83	>1000
84	124
85	1.86
86	4.58

TABLE I
(Page 3 of 3)

Example	AT_1 IC_{50} (nM)
87a	10.0
87b	7.32
88a	276
88b	528
89	2.59
90	20.9
91	1.37
92	2.72
93	5.51
94	8.57
95	2.67
96a	15.9
96b	9.86
97a	700
97b	500
98	377
99	135
101	35.7
102	>1000
103	120
104	>1000
105	1.47
106	10.1
107	1450
108	8.47
109	11.1
110	2.47
111	70.0
112	6.44
113	18.3

Also, the compounds of Formula I or Ia 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 1990;38:370-7. The aforementioned test methods are incorporated herein by reference. Compounds of

Formula I or Ia are active in this in vitro functional assay with IC_{50} values ranging from 1×10^{-10} to 1×10^{-6} M.

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 1979;1:427-34 and in Clin. Soc. 1979;57:53-62.

Illustrative of the in vivo antihypertensive activity for compounds of Formula I or Ia is the data for Example 1a. This compound lowers blood pressure by ≥50 mm Hg and is efficacious for more than 24 hours with a single oral dose of 100 mg/kg in the renal hypertensive rat. Furthermore Example 73 lowers blood pressure by ≥30 mm Hg and is efficacious for more than 24 hours with a single oral dose of 30 mg/kg in the renal hypertensive rat.

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 Ia or a corresponding pharmaceutically acceptable salt of a compound of Formula I or Ia.

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 5% to 10% to about 70% 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 capsule, 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 as antihypertensive agents, 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 are illustrative of the final products of the instant invention as well as illustrative of intermediate compounds useful in preparing final compounds. They are not intended to limit the scope of the invention.

EXAMPLE 1a AND 1b

1a

(E)-4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoic acid

A solution of 3.44 g (0.012 mole) of 2-butyl-1-(4-carboxybenzyl)-5-formylimidazole, 2.40 g (0.016 mole) of 1-butylhydantoin, 25.92 g (0.071 mole) of 25% tetramethylammonium hydroxide-in-methanol and 12 mL of water is heated with stirring with an oil bath (bath temperature 135-150°C), allowing the methanol to distill over. After ca. 1/2 hour, the pot temperature is ca. 115-120°C. The temperature is maintained 115-120°C for 15 minutes. The reaction solution is cooled to 70°C and 5.04 g (0.084 mole) of glacial acetic acid and then ca. 100 mL of water are added to precipitate the mixed cis (Z) and trans (E) isomers. Separation of isomers is accomplished by heating the mixture with 200 mL of methanol, cooling, and filtering off the least soluble (E) isomer. Recrystallization of the (E) isomer is effected by dissolution in 50%

methanol-methylene chloride and concentration to remove methylene chloride. The separated pale yellow crystals are filtered; mp 287-289°C; tlc (2:10 MeOH-$CHCl_3$), 1 spot, Rf 0.4; nmr (DMSO-d_6), vinyl proton at δ 5.86 ppm; MS (CI) 425.1 (M^++1).

Analysis calculated for $C_{23}H_{28}N_4O_4 \cdot 0.25H_2O$:
C, 64.39; H, 6.70; N, 13.06.
Found: C, 64.36; H, 6.58; N, 12.87.

1b

(Z)-4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoic acid

The more soluble (Z) isomer is isolated from the methanol filtrate of Example 1a. The filtrate is concentrated. The residue is heated with 2-propanol to the boiling point. The insolubles are filtered. Isopropyl ether is added to the filtrate to precipitate some mixed isomers. After filtration and concentration the residue is recrystallized from ethyl acetate-isopropyl ether to give pure (Z) isomer; mp 163-165°C; nmr (DMSO-d_6), single vinyl proton at δ 6.25 ppm; MS (CI) 425 (M^++1).

Analysis calculated for $C_{23}H_{28}N_4O_4 \cdot 0.25H_2O$:
C, 64.39; H, 6.70; N, 13.06.
Found: C, 64.36; H, 6.58; N, 12.87.

EXAMPLE 2a AND 2b

2a

(E)-4-[[2-Butyl-5-[[2,5-dioxo-3-(3-methylbutyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid

This compound is prepared by a procedure similar to Example 1, starting from 1-isoamyl hydantoin. Pure (E) isomer is isolated as the least soluble isomer;

mp 288-290°C; nmr (DMSO-d_6), vinyl proton at 5.84 ppm; MS (CI) 439 (M^++1).

Analysis calculated for $C_{24}H_{30}N_4O_4$:

C, 65.73; H, 6.90; N, 12.78.

Found: C, 65.42; H, 6.88; N, 12.86.

2b

(Z)-4-[[2-Butyl-5-[[2,5-dioxo-3-(3-methylbutyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid

This isomer is isolated as the most soluble isomer in Example 2a. Its purity is 89.6% (Z) isomer and 8.2% (E) isomer as indicated by HPLC analysis and by integration of the vinyl proton of the major (Z) isomer at 6.25 ppm vs the minor (E) isomer at 5.84 ppm in the nmr (DMSO-d_6); mp 143-146°C.

Analysis calculated for $C_{24}H_{30}N_4O_{43} \cdot 0.75H_2O$:

C, 63.77; H, 7.03; N, 12.40.

Found: C, 63.79; H, 7.69; N, 12.76.

EXAMPLE 3a AND 3b

3a

(E)-4-[[2-Butyl-5-[(2,5-dioxo-3-methyl-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoic acid

This compound is prepared by a procedure similar to Example 1 except that the starting materials are the ester derivative, 2-butyl-1-(4-carbomethoxybenzyl)-5-formylimidazole, and 1-methylhydantoin. The crude mixed isomer products are purified and separated by silica gel column chromatography, eluting with 0.1:1.5:10 glacial acetic acid-methanol-chloroform. The "slow" moving material is the (E) isomer; tlc (0.1:2:10 acetic acid-methanol-chloroform system)

1 spot, Rf 0.5; mp 219-221°C; nmr (DMSO-d_6), vinyl proton at δ 5.96 ppm; MS (CI) 383 (M^++1).
Analysis calculated for $C_{20}H_{22}N_4O_4 \cdot 0.25H_2O$:
C, 62.08; H, 5.86; N, 14.48.
Found: C, 62.04; H, 5.96; N, 14.33.

3b

(Z)-4-[[2-Butyl-5-[(2,5-dioxo-3-methyl-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoic acid

The "fast" moving isomer isolated from chromatography in the above procedure, 3a, is identified as the pure (Z) isomer; tlc (0.1:2:10 acetic acid-methanol-chloroform system), 1 spot, Rf 0.7; mp 248-250°C; nmr (DMSO-d_6), vinyl proton at δ 6.19 ppm; MS (CI) 383 (M^++1).
Analysis calculated for $C_{20}H_{22}N_4O_4 \cdot 0.5H_2O$:
C, 61.37; H, 5.92; N, 14.32.
Found: C, 61.09; H, 5.98; N, 14.26.

EXAMPLE 4a AND 4b

4a

(E)-4-[[2-Butyl-5-[(2,5-dioxo-3-(phenylmethyl)-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid

This compound is prepared by a procedure similar to Example 3 starting with 1-benzylhydantoin. Pure (E) isomer is isolated as the compound that is least soluble in methanol; mp 297-298°C; nmr (DMSO-d_6) single vinyl proton at δ 5.90 ppm; MS (CI) 459 (M^++1).
Analysis calculated for $C_{26}H_{26}N_4O_4 \cdot 0.5H_2O$:
C, 66.79; H, 5.82; N, 11.99.
Found: C, 66.71; H, 5.94; N, 12.04.

4b

(Z)-4-[[2-Butyl-5-[(2,5-dioxo-3-(phenylmethyl)-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid

This isomer (Z) is isolated as the most soluble isomer in the above Example 4a. Its purity is estimated to be 85% (Z) and 15% (E) isomer as indicated by the ratio of the vinyl proton integrations in the nmr (DMSO-d_6); vinyl proton for (Z) isomer at δ 6.05 ppm; MS (CI) 459 (M^++1).

Analysis calculated for $C_{26}H_{26}N_4O_4 \cdot 0.75H_2O$:
C, 66.15; H, 5.88; N, 11.87.
Found: C, 65.96; H, 5.87; N, 11.79.

EXAMPLE 5

(E)-4-[[2-Butyl-5-[(2,5-dioxo-3-phenyl-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid

This compound is prepared by a procedure similar to Example 1. The compound least soluble in 2-propanol is identified as the pure (E)-isomer; mp 286-290°C; tlc (1:10 methanol-chloroform) 1 spot, Rf 0.2; nmr (DMSO-d_6) single vinyl proton at δ 5.89 ppm; MS (CI) 445 (M^++1).

Analysis calculated for $C_{25}H_{24}N_4O_4 \cdot H_2O$:
C, 64.92; H, 5.67; N, 12.11.
Found: C, 65.41; H, 5.47; N, 12.23.

EXAMPLE 6a AND 6b

6a

(E)-4-[[2-Butyl-5-[[2,5-dioxo-3-((2-thienyl)methyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid

This compound is prepared by a procedure similar to Example 3 starting with 1-(2-thienylmethyl)-hydantoin. Pure (E) isomer is isolated as the compound

that is least soluble in methanol; mp 297-299°C; tlc (0.1:5:20 acetic acid-methanol-chloroform), 1 spot, Rf 0.6; nmr (DMSO-d_6) single vinyl proton at δ 6.13 ppm; MS (CI) 465 (M^++1).

Analysis calculated for $C_{24}H_{24}N_4O_4S \cdot 0.25H_2O$:

C, 61.32; H, 5.47; N, 11.92.

Found: C, 61.30; H, 5.21; N, 11.95.

6b

(Z)-4-[[2-Butyl-5-[[2,5-dioxo-3-((2-thienyl)methyl)-4-imidazolidinylidene]-methyl]-1H-imidazole-1-yl]methyl]benzoic acid

This isomer (Z) is isolated as the most soluble isomer in the above Example 6a. It is recrystallized from ethylacetate to give pure (Z) isomer; mp 140-145°C; tlc (0.1:5:20 acetic acid-methanol-chloroform), 1 spot, Rf 0.8 nmr (DMSO-d_6), single vinyl proton at 6.16 ppm. MS (CI) 465 (M^++1).

Analysis calculated for $C_{24}H_{24}N_4O_4S \cdot 0.25\ C_4H_8O_2$:

C, 61.70; H, 5.39; N, 11.52.

Found: C, 61.43; H, 5.45; N, 11.69.

EXAMPLE 7

2-Butyl-1-(4-carboxybenzyl)-5-formylimidazole

A solution of 3.00 g (0.01 mole) of 2-butyl-1-(4-carbomethoxybenzyl)-5-formylimidazole in 100 mL of methanol and 15 mL (0.03 mole) of 2N sodium hydroxide is heated to the boiling point, allowing methanol to distill over. After 1 hour, the pot temperature is 85°C. Water (30 mL) and then 30 mL of 1N hydrochloric acid are added to precipitate a gum. This crystallized; wt 2.40 g. Recrystallization from ethyl acetate gives 1.30 g of product; mp 146-148°C; tlc (1:10 MeOH-$CHCl_3$), 1 spot, Rf 0.3; MS (CI) 287 (M^++1).

Analysis calculated for $C_{16}H_{18}N_2O_3$:

C, 67.12; H, 6.34; N, 9.78.

Found: C, 67.14; H, 6.28; N, 9.72.

EXAMPLE 8

2-Butyl-1-(4-carbomethoxybenzyl)-5-formylimidazole (J. Med. Chem. 1991;34:1514-17)

A solution of 1.00 g (0.003 mole) of 2-butyl-1-(4-carbomethoxybenzyl)-4-chloro-5-formylimidazole in 75 mL of methanol is reduced at low pressure with hydrogen and 0.30 g of 5% Pd/carbon in the presence of 0.30 g of potassium acetate to give product; mp 62-64°C; tlc (1:1 hexane-ethyl acetate) 1 spot, Rf 0.2; MS (CI) 301 (M^++1).

EXAMPLE 9

2-Butyl-1-(4-carbomethoxybenzyl)-4-chloro-5-formylimidazole (J. Med. Chem. 1991;34:1514-17).

A solution of 17.50 g (0.098 mole) of 2-butyl-4-chloro-5-formylimidazole (United States Patent 4,355,040) in 855 mL of DMF is treated with 91.65 g (0.28 mole) of cesium carbonate and the mixture is stirred at room temperature for 10 minutes. A solution of 22.56 g (0.099 mole) of methyl 4-(bromomethyl)benzoate in 270 mL of DMF is added and the mixture is stirred for 4 hours at room temperature. The cesium salts are filtered and the DMF filtrate is concentrated at reduced pressure. The crude product is purified by silica gel chromatography, eluting with methylene chloride, and then 1:7 ethyl acetate/methylene chloride, obtaining 23.16 g (74%) of pure product; mp 96-98°C; tlc (1:1 hexane-ethyl acetate), 1 spot, Rf 0.7; MS (CI), 335 (M^+).

EXAMPLE 10

1-Butyl hydantoin (Org. Mass. Spectrometry 1971;5:551-3).

A quantity of 24.4 g (0.30 mole) of potassium cyanate is added portionwise, at room temperature, to a stirred solution of 31.80 g (0.20 mole) of ethyl N-butylglycinate in 220 mL (0.22 mole) of 1N

hydrochloric acid. The solution is warmed to ca. 90°C (at ca. 50°C an oil separates). After 10 minutes at 90°C, concentrated hydrochloric acid (250 mL) is cautiously added over 2 minutes and the resulting solution is heated at 90-100°C for 1/2 hour. The solution is concentrated at reduced pressure to dryness. The last amounts of water are chased by addition and removal of 3 x 100 mL of absolute ethanol. The residue is extracted with 400 mL 50% ethanol-methylene chloride. The inorganics are filtered and the filtrate is concentrated to dryness. Trituration of the residue with 100 mL of water and filtration gives pure 1-butylhydantoin in 68% yield; mp 90-92°C; MS (EI) 156.1 (M^+).

Analysis calculated for $C_7H_{12}N_2O_2$:
C, 53.83; H, 7.69; N, 17.99.
Found: C, 53.88; H, 7.80; N, 17.85.

EXAMPLE 11

1-Isoamylhydantoin

This compound is prepared by the procedure outlined in Example 10; mp 84-85°C; MS (EI) 170 (M^+).
Analysis calculated for $C_8H_{14}N_2O_2$:
C, 56.45; H, 8.29; N, 16.46.
Found: C, 56.84; H, 8.38; N, 16.34.

EXAMPLE 12

1-Benzylhydantoin

This compound is prepared by the procedure outlined in Example 10; mp 139-140°C; MS (EI) 190 (M^+).
Analysis calculated for $C_{10}H_{10}N_2O_2 \cdot 0.1H_2O$:
C, 62.55; H, 5.35; N, 14.59.
Found: C, 62.48; H, 5.56; N, 14.36.

EXAMPLE 13

1-(2-Thienylmethyl)hydantoin

This compound is prepared by a procedure similar to that in Example 10; mp 140-142°C; MS (EI) 196 (M^+).
Analysis calculated for $C_8H_8N_2O_2S$:
C, 48.97; H, 4.11; N, 14.28.
Found: C, 49.00; H, 4.05; N, 14.19.

EXAMPLE 14

1-Phenylhydantoin

This compound is prepared by a procedure similar to that in Example 10; mp 193-194°C; MS (EI) 176 (M^+).
Analysis calculated for $C_9H_8N_2O_2$:
C, 61.36; H, 4.58; N, 15.90.
Found: C, 61.38; H, 4.52; N, 15.92.

EXAMPLE 15a AND 15b

15a (Condition A)

(E)-4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid, methyl ester

To a mixture of 1-butyl-2,4-dioxoimidazolidine-5-phosphonate (680 mg, 2.41 mmol) and 2-butyl-1-(4-carbomethoxybenzyl)-5-formylimidazole (490 mg, 1.67 mmol) in methanol (15 mL) is cautiously added sodium hydride 80% dispersion in oil. The mixture is stirred for 1 hour at room temperature. Acetic acid (0.30 mL, 5.24 mmol) is added dropwise which causes the yellow solution to lighten. The mixture is evaporated in vacuo. This mixture is extracted into dichloromethane, washed with water, and dried over sodium sulfate. NMR analysis of this reaction mixture indicates a 1:1 mixture of E- and Z-isomers. Chromatography on silica gel eluting with 97 $CHCl_3$ 3 MeOH affords pure Z-and then E-isomer. NMR on (E) isomer: ($CDCl_3$) single vinyl proton at δ 5.60 ppm.

E-isomer.

Analysis calculated for $C_{24}H_{30}N_4O_4$:

C, 65.73; H, 6.90; N, 12.78.

Found: C, 65.50; H, 6.87; N, 12.66.

MS (EI) 438.

15b (Conditions A)

(Z)-4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid, methyl ester

The Z-isomer is isolated as described in 15a; NMR ($CDCl_3$), single vinyl proton at δ 6.32 ppm.

Analysis calculated for $C_{24}H_{30}N_4O_4$:

C, 65.73; H, 6.90; N, 12.78.

Found: C, 65.54; H, 6.85; N, 12.53.

EXAMPLE 15a AND 15b

(Conditions B)

To diethyl 1-butyl-2,4-dioxoimidazolidine-5-phosphonate (590 mg, 2.1 mmol) in acetonitrile (5 mL) is added lithium chloride (79 mg, 1.86 mmol) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (277 μL, 1.85 mmol). A yellow solution forms within 5 minutes. 2-Butyl-1-(4-carbomethoxybenzyl)-5-formylimidazole (461 mg, 1.54 mmol) is added. After 10 minutes, lithium chloride (79 mg, 1.86 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (277 μL, 1.85 mmol) are again added. A precipitate develops. Upon stirring at room temperature for 16 hours, a wine-red solution remains. This mixture is concentrated in vacuo and applied directly to a silica gel column. Eluting with 95 $CHCl_3$ 5 MeOH affords, in order of increasing polarity, the Z-isomer (441 mg, 65%) and then the E-isomer (96 mg, 14%) which had identical spectral characteristics as the above compounds produced by Conditions A.

EXAMPLE 16a AND 16b

16a

(E)-4-[[2-Butyl-5-[[2,5-dioxo-3-((2-thienyl)methyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid, methyl ester

A mixture of the (E) carboxylic acid derivative from Example 6a and 30 mL of methanol is treated with a stream of hydrogen chloride gas, allowing the temperature to rise. The resulting solution is allowed to stand at room temperature overnight. The solution is concentrated to ca. 1/2 volume and excess saturated $NaHCO_3$ solution is added to precipitate pure crystalline product; mp 209-210°C; tlc (1:10 MeOH-$CHCl_3$) 1 spot, Rf 0.5; MS (CI) 479 (M^++1).

Analysis calculated for $C_{25}H_{26}N_4O_4S \cdot 0.1H_2O$:

C, 61.89; H, 5.44; N, 11.55.

Found: C, 62.20; H, 5.36; N, 11.43.

16b

(Z)-4-[[2-Butyl-5-[[2,5-dioxo-3-((2-thienyl)methyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid, methyl ester

This compound is prepared as in Example 16a from the (Z) carboxylic and derivative from Example 6b; mp 164-165°C; tlc (1:10 MeOH-$CHCl_3$) 1 spot, Rf 0.6; MS (CI) 479 (M^++1).

Analysis calculated for $C_{25}H_{26}N_4O_4S$:

C, 62.74; H, 5.48; N, 11.71.

Found: C, 63.00; H, 5.23; N, 11.47.

17a

(E)-4-[[2-Butyl-5-[[2,5-dioxo-3-(4-hydroxybutyl)-4-imidazolidinylidene]ethyl]-1H-imidazole-1-yl]methyl]benzoic acid, methyl ester

This compound is prepared as with the butyl hydantoin derivatives in Example 1a and then esterified with diazomethane. E-and Z-isomers are separated by flash chromatography on silica gel ($CHCl_3$-MeOH, 96:4); mp of (E) isomer 167-170°C; NMR ($CDCl_3$) single vinyl proton at δ 5.62; MS (CI) 455 (M^++1).

Analysis calculated for $C_{24}H_{30}N_4O_5$:

C, 63.42; H, 6.65; N, 12.33.

Found: C, 63.25; H, 6.67; N, 12.22.

17b

(Z)-4-[[2-Butyl-5-[[2,5-dioxo-3-(4-hydroxybutyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid, methyl ester

This compound is isolated from the chromatography in the above Example 17a; mp 76-86°C; MS (CI) 455 (M^++1).

Analysis calculated for $C_{24}H_{30}N_4O_5 \cdot 0.1CH_3OH$:

C, 63.24; H, 6.69; N, 12.24.

Found: C, 63.65; H, 6.91; N, 11.83.

EXAMPLE 18

(E)-4-[[2-Propyl-5-[(3-butyl-1-methyl-2,5-dioxo-4-imidazolidinylidene)-methyl]-1H-imidazole-1-yl]methyl]benzoic acid, methyl ester

A solution of 0.082 g (0.17 mmol) of the 2-propyl (E) isomer hydrochloride prepared similarly to Example 15a, and 0.024 g (0.17 mmol) of methyl iodide in 0.50 mL of DMF is cooled in an ice bath. With stirring, 0.50 g anhydrous potassium carbonate is added. The mixture is removed from the ice bath and stirred at room temperature for 1 hour. To complete the reaction, another 0.024 g of methyl iodide is added and the mixture is stirred for another 1 hour. Water (5 mL) is added to precipitate crude product. Recrystallization from ether gives pure N-methyl

derivative; mp 113-114°C; tlc (1:10 MeOH-$CHCl_3$) 1 spot,Rf 0.6; MS (CI) 439 (M^++1).

EXAMPLE 19

3-Butyl-2,5-dioxo-imidazolidene-4-phosphonic acid, diethyl ester

To a solution of 1-butylhydantoin (3.5 g, 0.022 moles) in glacial acetic acid (20 mL) at 90-100°C is added bromine (1.22 mL, 0.024 moles) in acetic acid (10 mL) batchwise; at such a rate that the initial orange-red color discharges to a yellowish solution. This addition rate takes about 5 minutes. The solution is stirred at 90-100°C for a further 60 minutes. 1H Analysis of the reaction mixture indicates incomplete conversion. A further amount of bromine (0.3 mL) is added and the solution is refluxed for 1 hour and then stirred for 16 hours at room temperature. Concentration in vacuo from toluene affords a viscous oil (5.5 g). This oil is dissolved in diethyl ether and treated with triethyl phosphite (3.7 mL, 0.022 moles). The solution is stirred for 16 hours at room temperature. The mixture is evaporated in vacuo and the required product isolated by chromatography on silica gel, eluting with 95 $CHCl_3$-5 MeOH. This viscous oil contains small amounts of an impurity but is sufficiently pure to be used in subsequent reactions; NMR (1H, $CDCl_3$) δ 8.86 (1H, br s), 4.30 (7H, m), 3.86 (1H, m), 3.38 (1H, m), 1.60 (2H, m), 1.35 (9H, m), 0.89 (3H, m); MS (CI) 293.

EXAMPLES 20a AND 20b

20a

E-4-[[2-butyl-5-[[3-[(4-chlorophenyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid

This compound is prepared by a procedure similar to example 1, starting from 1-[(4-chlorophenyl)methyl]-2,4-imidazolidinedione. Pure E isomer is isolated as the least soluble isomer in 2-propanol; mp 248-250°C; nmr (DMSO-d_6), vinyl proton at 5.89 ppm; MS (CI) 493 (m+).

Anal. Calcd. for $C_{26}H_{25}ClN_4O_4 \cdot 0.25\ H_2O$:
C, 62.77; H, 5.17; N, 11.26
Found: C, 62.84; H, 5.08; N, 11.12

20b

Z-4-[[2-butyl-5-[[3-[(4-chlorophenyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid

This compound is isolated as the most soluble isomer in Example 20a. It is purified by silica gel chromatography, eluting with 1:5:40 acetic acid-methanol-chloroform to give pure faster moving Z isomer; mp 225-227°C; nmr (DMSO-d_6), vinyl proton at 6.09 ppm; MS (CI) 493 (m^+).

Anal. Calcd. for $C_{26}H_{25}ClN_4O_4$:
C, 63.35; H, 5.11; N, 11.37
Found: C, 63.01; H, 5.09; N, 11.20

EXAMPLES 21a AND 21b

21a

E-4-[[2-butyl-5-[[3-[(3,4-dimethoxyphenyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid

This compound is prepared by a procedure similar to Example 1 starting from 1-[(3,4-dimethoxyphenyl) methyl]-2,4-imidazolidinedione. Pure E isomer is isolated as the least soluble isomer in methanol; mp 266-267°C;

NMR (DMSO-d_6), vinyl proton at 5.97 ppm; MS (CI), 519 (m^+ +1).

Anal. Calcd. for $C_{28}H_{30}N_4O_6$: C, 64.85; H, 5.83; N, 10.80

Found: C, 64.82; H, 6.03; N, 10.93

21b

Z-4-[[2-butyl-5-[[3-[(3,4-dimethoxyphenyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid

This compound is isolated as the most soluble isomer in Example 21a. It is purified by recrystallization from ethyl acetate; mp 225-226°C;

NMR (DMSO-d_6), vinyl proton at 6.14 ppm; MS (CI) 519 (m^+ +1).

Anal. Calcd. for $C_{28}H_{30}N_4O_6$: C, 64.85; H, 5.83; N, 10.80

Found: C, 64.62; H, 5.94 N, 10.73

EXAMPLE 22

Methyl Z-4-[[2-butyl-5-[(1,3-dibutyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

A mixture of 0.220 g (10.5 mmol) of the Z-isomer NH hydantoin from Example 15b, 0.50 mL of DMF, 0.20 g of powdered potassium carbonate and 0.101 g (0.5 mmol) of butyl iodide is stirred at 25°C for 2 hours. Crushed ice is added to precipitate the gummy product. The aqueous DMF is decantered and the gum is extracted into 15 mL of ether. The ether solution is washed with water, dried (K_2CO_3) and treated with hydrogen chloride to precipitate a gummy hydrochloride salt which crystallizes on inducement. Recrystallization from 2-propanol-ether gives pure product; mp 153-155°C; NMR (DMSO-d_6), vinyl proton at 6.26 ppm; MS (CI) 495.5 (m^+ +1).

Anal. Calcd. for $C_{28}H_{38}N_4O_4$ HCl: C, 63.32; H, 7.40; N, 10.55
Found: C, 63.51; H, 7.58; N, 10.36

EXAMPLE 23

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

This compound is prepared from the NH hydantoin derivative of Example 16b by an alkylation procedure similar to that in Example 22; mp of hydrochloride salt, 185-187°C;
NMR (DMSO-d_6), vinyl proton at 6.07 ppm; MS (CI) 535 (m^+ +1).
Anal. Calcd. for $C_{29}H_{34}N_4O_4S$ HCl: C, 60.99; H, 6.18; N, 9.81
Found: C, 60.69; H, 6.16; N, 9.69

EXAMPLE 24

Methyl E-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

This compound is prepared form the NH hydantoin derivative of Example 16a by an alkylation procedure similar to that in Example 22; mp 209-211°C;
NMR (DMSO-d_6), vinyl proton at 6.27 ppm; MS (CI) 535 (m^+ +1).
Anal. Calcd. for $C_{29}H_{34}N_4O_4$ HCl: C, 60.99; H, 6.18; N, 9.81
Found: C, 60.69 ; H, 6.14; N, 9.53

EXAMPLE 25

Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(2-thienyl)methyl]-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid

A solution of 0.174 g (0.30 mmol) of the ester from Example 23, 4 mL of methanol and 2 mL of

3N hydrochloric acid is maintained at reflux for 3 days. The volatiles are removed at reduced pressure and the crude product is chromatographed eluting with 5% methanol-chloroform. The product is isolated as a glassy foam; tlc (1:10 methanol chloroform) one spot, Rf 0.4;
NMR (DMSO-d_6), vinyl proton at 6.28 ppm; MS (CI) 521 (m^+ +1).
Anal. Calcd. for $C_{28}H_{32}N_4O_4S$: C, 64.59; H, 6.20; N, 10.76
Found: C, 64.60; H, 6.19; N, 10.33

EXAMPLES 26a AND 26b

26a

E-1-[4-[[2-butyl-5-[[2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]phenyl]cyclopentanecarboxylic acid

This compound is prepared by a procedure similar to that in Example 1. The product is isolated as the most soluble isomer in methanol in 70% purity nmr (DMSO-d_6) benzyl CH_2 at 5.36 ppm (major E isomer). The impurity is the minor Z isomer with benzyl CH_2 at 5.08 ppm; MS (CI) 533 (m^+ +1).
Anal. Calcd. for $C_{29}H_{32}N_4O_4S$: C, 65.39; H, 6.06; N, 10.52
Found: C, 65.01; H, 5.99; N, 10.41

26b

Z-1-[4-[[2-butyl-5-[[2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]phenyl]cyclopentanecarboxylic acid

This compound is isolated pure in Example 26a as the least soluble isomer in methanol; mp 261-263°C; NMR (DMSO-d_6) benzyl CH_2 at 5.08 ppm; MS (CI) 533 (m^+ +1).

Anal. Calcd. for $C_{29}H_{32}N_4O_4$ S: C, 65.39; H, 6.06; N, 10.52
Found: C, 65.14; H, 6.07; N, 10.35

EXAMPLE 27

1-[(3,4-Dimethoxyphenyl)methyl]-2,4-imidazolidinedione

This compound is prepared by a procedure similar to that in Example 10; mp 130-132°C C; MS (CI) 250 (M+)
Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19
Found: C, 57.46; H, 5.54; N, 11.19

EXAMPLE 28

1-[(4-Chlorophenyl)methyl]-2,4-imidazolidinedione

This compound is prepared by a procedure similar to that in Example 10; mp 169-171°C; MS (EI) 224 (M+)
Anal. Calcd. for $C_{10}H_9ClN_2O_2$: C, 53.47; H, 4.04; N, 12.47
Found: C, 53.50; H, 4.04; N, 12.48

EXAMPLE 29

Methyl 4-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinyl)hydroxymethyl]-1H-imidazol-1-yl]methyl]benzoate

To a suspension of 1-butyl-2,4-imidazolidinedione (0.600 g, 4.17 mmol) in THF (15 ml) at -78°C is added lithium diisopropylamide (2.1 equiv.). After stirring for 20 minutes a solution of methyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoate (1.250 g, 4.17 mmol) in THF (10 mL) is added dropwise over 10 minutes to form an orange solution. This solution is stirred for a further 20 minutes at -78°C and is then added to aqueous ammonium chloride. This mixture is evaporated in vacuo and then extracted into ethyl acetate. After washing with water and then brine the solution is dried over Na_2SO_4. Evaporation in vacuo and chromatography, eluant 5% methanol in chloroform,

affords the required product. Recrystallized from ethyl acetate containing traces of methanol.
Anal. Calcd. for $C_{24}H_{31}N_4O_5$: C, 63.14; H, 7.07; N, 12.27
Found: C, 62.89; H, 7.07; N, 12.56

EXAMPLE 30

Methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of diethyl 2,5-dioxo-4-imidazolylphosphonate (0.600 g, 2.53 mmol) in methanol (15 mL) is cautiously added sodium hydride (80% dispersion in oil) (0.152 g, 5.06 mmol) and stirred for 15 minutes to afford a pale yellow solution. To this is added methyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoate (0.730 g, 2.43 mmol). This mixture is stirred for 2 hours in which time a yellow precipitate develops. The reaction mixture is concentrated in vacuo and then diluted with water (10 mL). 1N HCl (5 mL) is added to afford a white precipitate. The precipitate is washed with water (20 mL) and then with ether (20 mL). This solid is the Z-isomer with the E-isomer evident in the filtrate.
Anal. Calcd. for $C_{20}H_{22}N_4O_4 \cdot HCl$: C, 57.34; H, 5.53; N, 13.38
Found: C, 57.11; H, 5.45; N, 12.93
MS (EI) 382

EXAMPLE 31

Diethyl 1-butyl-2,5-dioxo-4-imidazolylphosphonate

To a solution of diethyl 2,5-dioxo-4-imidazolylphosphonate (6.00 g, 0.025 moles) in DMF (15 mL), under N_2, is added K_2CO_3 (17.5 g, 0.127 moles) and 1-iodobutane (2.9 mL, 0.025 moles). This mixture is stirred at room temperature for 16 hours and then the mixture is filtered and the solid washed with ethyl

acetate. The filtrate is concentrated in vacuo, to afford a yellow oil which is redissolved in ethyl acetate and washed with water and brine and then dried over $MgSO_4$. Evaporation of solvents under high vacuum affords the required product as a viscous yellow oil which solidifies on standing.

Anal. Calcd. for $C_{11}H_{21N2}O_5P$: C, 45.21; H, 7.24; N, 9.58

Found: C, 44.83; H, 7.34; N, 9.84

MS (EI) 293

EXAMPLES 32a, 32b, 32c

32a

Methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of diethyl 1-butyl-2,5-dioxo-4-imidazolylphosphonate (1.47 g, 5.00 mmol) in methylene chloride (8 mL) at 0°C is added 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) (0.75 mL, 5.02 mmol). The yellow solution is stirred for 5 minutes and then a solution of methyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoate (1.25 g, 4.17 mmol) is added. This mixture is allowed to stir for 16 hours. The mixture is diluted with ethyl acetate containing 10% methylene chloride and washed with 1M aqueous HCl (15 mL), water and then brine. After drying over $MgSO_4$ the product is isolated as a yellow solid by concentration in vacuo and treatment with ether. Chromatography of the mother liquors after neutralizing with aqueous NaHCO3, eluting with 1% methanol in chloroform, affords a small amount of the corresponding E-isomer.

Data for Z-isomer as hydrochloride salt

Anal. Calcd. for $C_{24}H_{30}N_4O_4 \cdot HCl$: C, 60.69; H, 6.58; N, 11.80

Found: C, 60.25; H, 6.30; N, 11.48
mp 197-198°C; MS (EI) 438
Free base mp 172-173°C Recrystallized from ethyl acetate

32b

Methyl E-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate
Anal. Calcd. for $C_{24}H_{30}N_4O_4$. 0.33 H_2O: C, 64.84; H, 6.95; N, 12.60
Found: C, 64.55; H, 6.86; N, 12.46
MS (EI) 438 mp 172-174°C

32c Alternative procedure

Methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate

To a solution of diethyl 2,5-dioxo-4-imidazolylphosphonate (1.5 g, 6.33 mmol) in DMF (4 mL) is added K_2CO_3 and then 1-iodobutane (0.79 mL, 6.96 mmol). This mixture is stirred for 16 hours at room temperature. To this yellow mixture is added methyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoate (1.05 g, 3.5 mmol). After 2 hours methylene chloride (10 mL) was added to aid stirring. The mixture was stirred for 16 hours. After diluting the reaction mixture with water it was extracted with ethyl acetate. This extract was washed with water and brine. The extract was dried over $MgSO_4$, filtered and then concentrated until crystallization was apparent. The solid was collected and dried.

EXAMPLE 33

Methyl Z-4-[[2-butyl-5-[(1,3-dibutyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.475 g, 1.08 mmol) in DMF (6 mL) is added K_2CO_3 (0.750 g, 5.40 mmol). After stirring for 5 minutes 1-iodobutane (0.150 mL, 1.32 mmol) is added. The mixture is stirred for 16 hours, diluted with ethyl acetate and washed with water and brine and then dried over $MgSO_4$. A viscous oil is obtained by evaporation of the solvents in vacuo. This yellow oil is dissolved in ether and treated with ethereal HCl to precipitate a gummy solid. This gum is crystallized from 2-propanol/ether.

Anal. Calcd. for $C_{28}H_{38}N_4O_4$. HCl: C, 63.32; H, 7.40; N, 10.55

Found: C, 63.36; H, 7.56; N, 10.66

MS (EI) 494

EXAMPLE 34

Methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-3-pentyl-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.400 g, 0.92 mmol) in DMF (4 mL) is added K_2CO_3 (0.630 g, 4.57 mmol). After stirring for 5 minutes 1-iodopentane (0.155 mL, 1.19 mmol) is added. The mixture is stirred for 16 hours. After diluting with ethyl acetate and washing with water and brine the solution is dried over $MgSO_4$. A viscous oil is obtained by evaporation of the solvents in vacuo. This yellow oil is dissolved in ether and treated with ethereal HCl to precipitate a gummy solid. This gum is crystallized from 2-propanol/ether.

Anal. Calcd. for $C_{29}H_{40}N_4O_4$. HCl: C, 63.89; H, 7.58; N, 10.28
Found: C, 63.91; H, 7.26; N, 10.13
mp 128-130°C; MS (EI) 508

EXAMPLE 35

Methyl Z-4-[[2-butyl-5-[(1-butyl-3-hexyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl] benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate hydrochloride (0.450 g, 0.95 mmol) in DMF (4 mL) is added K_2CO_3 (0.800 g, 5.80 mmol). After stirring for 5 minutes 1-iodohexane (0.190 mL, 1.29 mmol) is added. The mixture is stirred for 16 hours, diluted with ethyl acetate, washed with water and brine, and then dried over $MgSO_4$. A viscous oil is obtained by evaporation of the solvents in vacuo. This yellow oil is dissolved in ether and treated with ethereal HCl to precipitate a gummy solid. This gum is triturated with pentane and ether to afford a pale yellow solid.
Anal. Calcd. for $C_{30}H_{42}N_4O_4$. HCl: C, 64.33; H, 7.92; N, 10.00
Found: C, 64.04; H, 7.61; N, 9.78
mp 134-135°C; MS (EI) 522

EXAMPLE 36

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(phenylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.509 g, 1.16 mmol) in DMF (6 mL) is added $K2CO_3$ (0.800 g, 5.80 mmol). After stirring for 5 minutes benzylbromide (0.150 mL, 1.26 mmol) is added. The mixture is stirred for

16 hours, diluted with ethyl acetate, washed with water and brine, and then dried over $MgSO_4$. A viscous oil is obtained upon chromatography on silica gel (eluant 1% methanol in chloroform) and evaporation of the solvents in vacuo. This yellow oil is dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo.

Anal. Calcd. for $C_{31}H_{36}N_4O_4$. HCl. 1.25 H_2O: C, 63.35; H, 6.78; N, 9.53

Found: C, 63.13; H, 6.83; N, 9.43

mp 110-113°C; MS (EI) 528

EXAMPLE 37

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-[[4-(methoxycarbonyl)phenyl]methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.500 g, 1.14 mmol) in DMF (4 mL) is added K_2CO_3 (0.800 g, 5.80 mmol). After stirring for 5 minutes methyl (4-bromomethyl)benzoate (0.275 g, 1.20 mmol) is added. The mixture is stirred for 16 hours, diluted with ethyl acetate, washed with water and brine, and then dried over $MgSO_4$. A viscous oil is obtained upon chromatography on silica gel (eluant 1% methanol in chloroform) and evaporation of the solvents in vacuo. This yellow oil is dissolved in ether and treated with ethereal HCl to precipitate a gummy solid. This gum is crystallized from 2-propanol/ ether.

Anal. Calcd. for $C_{33}H_{38}N_4O_6$. HCl: C, 64.13; H, 5.54; N, 9.06

Found: C, 63.44; H, 6.31; N, 8.79

mp 165-167°C; MS (EI) 528

EXAMPLE 38

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-[(4-nitrophenyl) methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate mono hydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.370 g, 0.84 mmol) in DMF (4 mL) is added K_2CO_3 (0.580 g, 4.20 mmol). After stirring for 5 minutes 4-nitrobenzylbromide (0.218 g, 1.01 mmol) is added. The mixture is stirred for 16 hours, diluted with ethyl acetate, washed with water and brine, and then dried over $MgSO_4$. A viscous oil is obtained upon chromatography on silica gel (eluant 1% methanol in chloroform) and evaporation of the solvents in vacuo. This yellow oil is dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo.

Anal. Calcd. for $C_{31}H_{35}N_5O_6$. HCl. H_2O: C, 59.27; H, 6.10; N, 11.15

Found: C, 59.03; H, 6.14; N, 10.89

MS (EI) 573

EXAMPLE 39

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-[[4-(trifluoromethyl)phenyl]methyl]-4-imidazolidinylidene] methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene) methyl]-1H-imidazol-1-yl]methyl]benzoate (0.450 g, 1.03 mmol) in DMF (4 mL) is added K_2CO_3 (0.800 g, 5.80 mmol). After stirring for 5 minutes 4-trifluoromethylbenzyl bromide (0.270 g, 1.13 mmol) is added. The mixture is stirred for 16 hours to generate a red colored mixture. After diluting with ethyl acetate and washing with water and brine the solution is dried over $MgSO_4$. A viscous oil is obtained upon chromatography on silica gel (eluant

1% methanol in chloroform) and evaporation of the solvents in vacuo. This orange oil is dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo. This solid is dissolved in methylene chloride and treated with pentane to afford a pale yellow solid.

Anal. Calcd. for $C_{33}H_{35}N_4O_4F_3$. HCl. 0.67 H_2O: C, 59.57; H, 5.83; N, 8.69

Found: C, 59.55; H, 5.65; N, 8.39

MS (EI) 596

EXAMPLE 40

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(3-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate mono hydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate hydrochloride (0.50 g, 1.05 mmol) in DMF (4 mL) is added K_2CO_3 (0.730 g, 5.29 mmol). After stirring for 5 minutes. 3-thienylmethyl bromide (0.250 g, 1.41 mmol) is added. The mixture is stirred for 16 hours to generate a viscous pale brown colored mixture. After diluting with ethyl acetate and washing with water and brine the solution is dried over $MgSO_4$. A viscous oil is obtained upon chromatography on silica gel (eluant 0.5% methanol in chloroform) and evaporation of the solvents in vacuo. This oil is dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo. This solid is crystallized from 2-propanol/ether.

Anal. Calcd. for $C_{33}H_{35}N_4O_4$. HCl. 0.67 H_2O: C, 60.99; H, 6.18; N, 9.81

Found: C, 60.83; H, 6.24; N, 9.61

mp 178-179°C; MS (EI) 534

EXAMPLE 41

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(2-phenylethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate mono hydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride (0.500 g, 1.05 mmol) in DMF (4 mL) is added K_2CO_3 (0.730 g, 5.29 mmol). After stirring for 5 minutes 2-phenylethyl bromide (0.215 mL, 1.57 mmol) is added. The mixture is stirred for 16 hours to generate a viscous yellow colored mixture. After diluting with ethyl acetate and ether and washing with water and brine the solution is dried over $MgSO_4$. A viscous oil is obtained upon chromatography on silica gel (eluant chloroform) and evaporation of the solvents in vacuo. This oil is dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo. This solid is crystallized from 2-propanol/ether.

Anal. Calcd. for $C_{33}H_{35}N_4O_4$. HCl: C, 65.50; H, 6.78; N, 9.22

Found: C, 65.68; H, 6.83; N, 9.58

mp 150-151°C; MS (CI) 543(M+1)

EXAMPLE 42

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(diphenylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate mono hydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene) methyl]-1H-imidazol-1-yl]methyl]benzoate hydrochloride (0.361 g, 0.76 mmol) in DMF (4 mL) is added K_2CO_3 (0.525 g, 3.80 mmol). After stirring for 5 minutes diphenylmethyl bromide (0.240 g, 0.97 mmol) is added. The mixture is stirred for 16 hours to generate a viscous yellow colored mixture. After diluting with ether and washing with water and brine the solution is dried over $MgSO_4$. This

oil was redissolved in DMF (4 mL) and $K2CO_3$ (0.525 g, 3.80 mmol) and bromodiphenyl methane (0.560 g, 2.27 mmol) is added. The mixture is stirred for 16 hours to generate a red colored mixture. After diluting with ether and washing with water and brine the solution is dried over $MgSO_4$. A viscous oil is obtained upon chromatography on silica gel (eluant chloroform) and evaporation of the solvents in vacuo. This oil is dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo. This solid is crystallized from 2-propanol/ether.

Anal. Calcd. for $C_{37}H_{40}N_4O_4$. HCl: C, 69.31; H, 6.45; N, 8.74

Found: C, 69.03; H, 6.09; N, 8.34

mp 184-185°C; MS (EI) 604

EXAMPLE 43

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-(cyclohexylmethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate mono hydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene) methyl]-1H-imidazol-1-yl]methyl]benzoate (0.250 g, 0.57 mmol) in DMF (4 mL) is added sodium hydride (80% dispersion in oil) (0.02 g, 0.67 mmol). After stirring for 5 minutes cyclohexylmethyl bromide (0.20 mL, 1.43 mmol) is added. The mixture is stirred for 16 hours and then a further amount of cyclohexylmethyl bromide is added (0.20 mL, 1.43 mmol) along with a catalytic amount of sodium iodide. The mixture is stirred for 16 hours, diluted with ether, washed with water and brine and dried over $MgSO_4$. A viscous oil is obtained upon chromatography on silica gel (eluant 1.0% methanol in chloroform) and evaporation of the solvents in vacuo. This oil is dissolved in ether and treated with ethereal HCl to

afford a foamy solid upon evaporation in vacuo. This solid is crystallized from 2-propanol/ether.
Anal. Calcd. for $C_{31}H_{42}N_4O_4$.HCl: C, 65.19; H, 7.59; N, 9.81
Found: C, 65.25; H, 7.64; N, 9.85
mp 157-158°C; MS (EI) 534

EXAMPLE 44

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(1H-tetrazol-5-ylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.300 g, 0.68 mmol) in DMF (5 mL) is added K_2CO_3 (0.500 g, 3.62 mmol). After stirring for 5 minutes 2-triphenylmethyl-1H-tetrazol-5-ylmethyl chloride (0.500 g, 1.39 mmol) is added. The mixture is stirred for 16 hours to generate a viscous orange colored mixture. After diluting with ethyl acetate and washing with water and brine the solution is dried over $MgSO_4$. A viscous oil is obtained upon chromatography on silica gel (eluant 0.5 % methanol in chloroform) and evaporation of the solvents in vacuo. This oil is dissolved in methanol (50 mL) and treated with acetic acid (0.04 mL, 0.70 mmol). After heating at 90°C (oil bath temp.) for 2 hours the solution is cooled and treated with water (10 mL) and hexanes (100 mL). The aqueous organic layer is separated and evaporated. This solid is redissolved in ethyl acetate/methylene chloride and washed with pH 7 buffer, dried over $MgSO_{44}$ and evaporated in vacuo. The hydrochloride salt is then prepared by dissolving this solid in methanol and treating with ethereal HCl. Evaporation in vacuo of this solution and crystallization (2-propanol/ether) affords the required compound.
Anal. Calcd. for $C_{26}H_{32}N_8O_4$.HCl: C, 56.38; H, 6.00; N, 19.73

Found: C, 56.06; H, 5.97; N, 20.12
mp 192-195°C; MS (CI) 521

EXAMPLE 45

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-(1H-imidazol-5-ylmethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene) methyl]-1H-imidazol-1-yl]methyl]benzoate hydrochloride (0.237 g, 0.50 mmol) in DMF (3 mL) is added K_2CO_3 (0.350 g, 2.54 mmol). After stirring for 5 minutes 4-(chloromethyl)-1-(triphenylmethyl)-1H-imidazole (0.250 g, 0.70 mmol) is added. The mixture is stirred for 16 hours, diluted with ethyl acetate, washed with water and brine and then dried over $MgSO_4$. A viscous oil is obtained upon chromatography on silica gel (eluant 0.5 % methanol in chloroform) and evaporation of the solvents in vacuo. This oil is dissolved in methanol (80 mL) and treated with acetic acid (30 mL). After heating at 90°C (oil bath temp.) for 4 hours the solution is cooled and treated with water (10 mL) and hexanes (100 mL). The aqueous organic layer is separated and evaporated. This solid is redissolved in ethyl acetate/methylene chloride and washed with pH 7 buffer, dried over $MgSO_{44}$ and evaporated in vacuo. The hydrochloride salt is then prepared by dissolving this solid in methanol and treating with ethereal HCl. Evaporation in vacuo of this solution and crystallization (2-propanol/ether) affords the required compound.

Anal. Calcd. for $C_{28}H_{34}N_6O_4 \cdot 2HCl \cdot H_2O$: C, 55.17; H, 6.28; N, 13.79
Found: C, 54.88; H, 6.13; N, 13.24
mp 202-205°C; MS (EI) 518

EXAMPLE 46

Diethyl 1-hexyl-2,5-dioxo-4-imidazolylphosphonate

To a solution of diethyl 2,5-dioxo-4-imidazolylphosphonate (6.00 g, 0.025 moles) in DMF (15 mL), under N_2, is added K_2CO_3 (17.5g, 0.127 moles) and 1-iodohexane (3.75 mL, 0.025 moles). This mixture is stirred at room temperature for 16 hours. The mixture is diluted with ether (300 mL) and washed with water and brine and then dried over $MgSO_4$. Evaporation of solvents under high vacuum affords the required product as a viscous yellow oil. (Mass spectrometry also revealed a small amount of diethyl 1,3-dihexyl-2,5-dioxo-4-imidazolylphosphonate).
MS (EI) 321

EXAMPLE 47

Methyl Z-4-[[2-butyl-5-[(1-hexyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate

To a solution of diethyl 1-hexyl-2,5-dioxo-4-imidazolylphosphonate (3.50 g, 0.011 moles) in methylene chloride (30 mL) at -40°C is added 1,8-diazabicyclo [5.4.0]undec-7-ene (1.64 mL, 0.011 moles). The yellow solution is stirred for 5 minutes and then a solution of methyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoate (3.25 g, 0.011 moles) is added. This mixture is allowed to stir for 16 hours with warming to room temperature. The mixture is diluted with ethyl acetate and washed with water and then brine. After adding methylene chloride (50 mL) and drying over $MgSO_{44}$ the product is isolated as a yellow solid by concentration in vacuo and treatment with ether.
Anal. Calcd. for $C_{26}H_{34}N_4O_4$. 0.3 H_2O: C, 66.16; H, 7.39; N, 11.87
Found: C, 65.96; H, 7.07; N, 11.70
mp 178-180°C; MS (EI) 466

EXAMPLE 48

Methyl Z-4-[[2-butyl-5-[(3-butyl-1-hexyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[[1-hexyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.50 g, 1.07 mmol) in DMF (4 mL) is added K_2CO_3 (0.740 g, 5.36 mmol). After stirring for 5 minutes 1-iodobutane (0.158 mL, 1.39 mmol) is added. The mixture is stirred for 16 hours. After diluting with ether (150 mL) and washing with water and brine the solution is dried over $MgSO_4$. A viscous oil is obtained by evaporation of the solvents in vacuo. This yellow oil is dissolved in ether and treated with ethereal HCl to precipitate a gummy solid. This gum is crystallized from 2-propanol/ether.

Anal. Calcd. for $C_{30}H_{43}N_4O_4.HCl.\ 0.3H_2O$: C, 63.64; H, 7.95; N, 9.89

Found: C, 63.65; H, 7.56; N, 9.43

mp 144-145°C; MS (EI) 522

EXAMPLE 49

Methyl Z-4-[[2-butyl-5-[[1-hexyl-2,5-dioxo-3-(3-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-hexyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.515 g, 1.11 mmol) in DMF (7 mL) is added K_2CO_3 (0.760 g, 5.51 mmol). After stirring for 5 minutes 3-thienylmethyl bromide (0.39 g, 2.20 mmol) is added. The mixture is stirred for 16 hours to generate a viscous pale brown colored mixture. After diluting with ether and washing with water and brine the solution is dried over $MgSO_4$. The solvents are evaporated in vacuo and this oil is dissolved in ether and treated with ethereal HCl to

afford a foamy solid upon evaporation in vacuo. This solid is crystallized from 2-propanol/ether.

Anal. Calcd. for $C_{31}H_{38}N_4O_4S$. HCl. H_2O: C, 60.32; H, 6.70; N, 9.08

Found: C, 59.95; H, 6.55; N, 8.68

MS (FAB) 564

EXAMPLE 50

Methyl Z-4-[[2-butyl-5-[[1-hexyl-2,5-dioxo-3-(phenylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-hexyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.516 g, 1.11 mmol) in DMF (7 mL) is added K_2CO_3 (0.760 g, 5.51 mmol). After stirring for 5 minutes benzylbromide (0.150 mL, 1.26 mmol) is added. The mixture is stirred for 16 hours. After diluting with ether and ethyl acetate and washing with water and brine the solution is dried over $MgSO_4$. A viscous oil is obtained upon evaporation of the solvents in vacuo. This yellow oil is dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo. This solid is crystallized from 2-propanol/ether.

Anal. Calcd. for $C_{33}H_{40}N_4O_4$. HCl: C, 64.68; H, 7.42; N, 10.06

Found: C, 64.76; H, 7.06; N, 10.53

mp 98-100°C; MS (CI) 557 (M+1)

EXAMPLE 51

Methyl Z-4-[[2-butyl-5-[1-hexyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate dihydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-hexyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.300 g, 0.643 mmol) in DMF (4 mL)

is added K_2CO_3 (0.440 g, 3.19 mmol). After stirring for 5 minutes 4-chloromethyl-2-methylthiazole hydrochloride (0.237 g, 1.29 mmol) is added. The mixture is stirred for 16 hours in which time a pale brown slurry forms. After diluting with ethyl acetate and washing with water and brine the solution is dried over $MgSO_4$. Chromatography eluting with 2% methanol in chloroform and evaporation in vacuo affords a viscous oil. This oil is dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo. This solid is crystallized from 2-propanol/ether.

Anal. Calcd. for $C_{31}H_{39}N_5O_4S$. 2HCl. H_2O: C, 55.67; H, 6.48; N, 10.47

Found: C, 55.57; H, 6.29; N, 10.15

mp 160-162°C; MS (EI) 577

EXAMPLE 52

Diethyl 1-(methoxymethyl)-2,5-dioxo-4-imidazolylphosphonate

To a solution of diethyl 2,5-dioxo-4-imidazolylphosphonate (3.61 g, 0.015 moles) in DMF (10 mL), under N_2, is added sodium hydride (80% dispersion in oil) (0.55 g, 0.018 moles) and stirred for 5 minutes. Chloromethyl methyl ether (tech. grade 85%) (1.9 mL, 0.021 moles) is added. This mixture is stirred at room temperature for 4 hours, diluted with ether and ethyl acetate (300 mL) and then washed with water and brine before drying over $MgSO_4$. The aqueous layer is back extracted with methylene chloride and combined with the previous organic fraction. Evaporation of solvents and chromatography (eluant 1% methanol in chloroform) and evaporation under high vacuum affords the required product.

MS (EI) 280

EXAMPLE 53

Methyl Z-4-[[2-butyl-5-[[(1-(methoxymethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl] benzoate

To a solution of diethyl 1-(methoxymethyl)-2,5-dioxo-4-imidazolylphosphonate (2.40 g, 8.57 mmol) in methylene chloride (10 mL) at 0°C is added 1,8-diazabicyclo [5.4.0]undec-7-ene (1.30 mL, 8.71 mmol). The yellow solution is stirred for 5 minutes and then a solution of methyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoate (2.0 g, 6.67 mmol) is added. This mixture is allowed to stir for 16 hours, diluted with ethyl acetate, and washed with water and then brine. After adding methylene chloride (50 mL) and drying over $MgSO_{44}$ the product is isolated as a yellow solid by partial concentration in vacuo and treatment with ether.

Anal. Calcd. for $C_{22}H_{26}N_4O_5$: C, 61.96; H, 6.15; N, 13.14

Found: C, 61.69; H, 6.17; N, 12.99

mp 185-186°C; MS (EI) 426

EXAMPLE 54

Methyl Z-4-[[2-butyl-5-[[3-butyl-1-(methoxymethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[[1-(methoxymethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.70 g, 1.07 mmol) in DMF (4 mL) is added K_2CO_3 (1.13 g, 8.19 mmol). After stirring for 5 minutes 1-iodobutane (0.24 mL, 2.11 mmol) is added. The mixture is stirred for 16 hours. After diluting with ether (150 mL) and washing with water and brine the solution is dried over $MgSO_4$. A viscous oil is obtained by evaporation of the solvents in vacuo. This yellow oil is dissolved in ether and treated with

ethereal HCl to precipitate a gummy solid. This gum is crystallized from 2-propanol/ether.

Anal. Calcd. for $C_{26}H_{34}N_4O_5$. HCl: C, 60.17; H, 6.80; N, 10.79

Found: C, 59.87; H, 6.88; N, 10.73

mp 133-134°C; MS (EI) 482

EXAMPLE 55

Methyl Z-4-[[2-butyl-5-[[1-(methoxymethyl)-2,5-dioxo-3-(phenylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[[1-methoxymethyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.34 g, 0.79 mmol) in DMF (4 mL) is added K_2CO_3 (0.55 g, 3.99 mmol). After stirring for 5 minutes benzylbromide (0.113 mL, 0.95 mmol) is added. The mixture is stirred for 16 hours, diluted with ether and washed with water and brine and then dried over $MgSO_4$. A viscous oil is obtained upon evaporation of the solvents in vacuo. This yellow oil is dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo. This solid is crystallized from 2-propanol/ether.

Anal. Calcd. for $C_{29}H_{32}N_4O_5$. HCl: C, 62.98; H, 6.01; N, 10.13

Found: C, 62.59; H, 5.97; N, 9.92

mp 137-138°C; MS (EI) 516

EXAMPLE 56

Methyl Z-4-[[2-butyl-5-[[1-(methoxymethyl)-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate dihydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[[1-(methoxymethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-

yl]methyl]benzoate (0.307 g, 0.721 mmol) in DMF (4 mL) is added K_2CO_3 (0.500 g, 3.62 mmol). After stirring for 5 minutes 4-chloromethyl-2-methylthiazole hydrochloride (0.265 g, 1.44 mmol) is added. The mixture is stirred for 48 hours. A pale brown slurry results which was diluted with ethyl acetate and washed with water and brine and then dried over $MgSO_4$. Chromatography eluting with 1% methanol in chloroform and evaporation in vacuo affords a viscous oil. This oil is dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo. This solid is crystallized from 2-propanol/ether.
Anal. Calcd. for $C_{27}H_{31}N_5O_5S$. 2HCl: C, 53.11; H, 5.45; N, 11.47
Found: C, 53.07; H, 5.46; N, 11.48
mp 205-209°C; MS (EI) 537

EXAMPLE 57

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-[(2-pyridinyl-N-oxide)methyl]-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.569 g, 1.2 mmol) in DMF (5 mL) is added K_2CO_3 (2.00 g, 15 mmol). After stirring for 5 minutes 2-chloromethylpyridine-N-oxide (0.230 g, 1.3 mmol) is added and the mixture is stirred for 16 hours. The dark brown mixture is filtered, concentrated in vacuo, and dissolved in 30% methylene chloride in ether (50 mL). This solution is washed with water and dried over K_2CO_3 and charcoal. A viscous oil is obtained by evaporation of the solvents in vacuo. This yellow oil is dissolved in hot ethyl acetate (5 mL) and upon brief standing crystallization occurs. The crystals are collected and washed with ether.

Anal. Calcd. for $C_{30}H_{35}N_5O_5$.: C, 66.04; H, 6.47; N, 12.84
Found: C, 66.34; H, 6.56; N, 12.88
mp 150-152°C; MS (CI) 546 (M+1)

EXAMPLE 58

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(2-pyridinylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate dihydrochloride

A solution of methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-[(2-pyridinyl-N-oxide)methyl]-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate in methylene chloride (2 mL) is added dropwise over 3 minutes to phosphorus trichloride (2.0 mL). After 15 minutes the mixture is concentrated under reduced pressure. The residue is dissolved in warm iso-propanol (3 mL) and saturated with HCl gas briefly. Ether is added and the crystals collected and washed with ether. A portion of this sample is recrystallized from 2-propanol/ether.
Anal. Calcd. for $C_{30}H_{35}N_5O_4$. 2HCl. $0.5H_2O$: C, 58.91; H, 6.26; N, 11.45
Found: C, 58.65; H, 6.04; N, 11.15
mp 195-197°C; MS (CI) 530 (M+1)

EXAMPLE 59

Z-4-[[2-butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidenel methyl]-1H-imidazol-1-yl]methyl]benzoic acid

A mixture of methyl Z-4-[[2-butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.428 g, 0.65 mmol) and 2N HCl (12 mL) is refluxed for 1 hour in which time all the solid dissolved. Solvents are removed in vacuo and the mixture is evaporated from ethanol (5 mL) three times. The solid that results is treated with 5% aqueuos

sodium acetate (10 mL) and water (10 mL) to precipitate a gummy solid which is dissolved in methylene chloride (30 mL). The organic layer is dried over Na_2SO_4 and then evaporated in vacuo. The residue is recrystallized from hot ethyl acetate/hexane.

Anal. Calcd. for $C_{28}H_{33}N_5O_4S$: C, 62.78.; H, 6.21; N, 13.07

Found: C, 63.01; H, 6.27; N, 13.05

mp 152-154°C; MS (CI) 536 (M+1)

EXAMPLE 60

Isomerisation of Z-4-[[2-butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid to E-4-[[2-butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-[(4-methyl-2-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid (0.25 g, 0.46 mmol) was dissolved in concentrated HCl (15 mL) and the mixture is refluxed for 4 hours. The mixture is concentrated in vacuo and aquous sodium acetate is added. The precipitate is collected and washed with water. This solid is dissolved in methanol (2 mL) and treated with charcoal and then filtered and concentrated in vacuo. The residue was recrystallized from hot ethyl acetate.

Anal. Calcd. for $C_{28}H_{33}N_5O_4S$. 0.25 H_2O: C, 62.26; H, 6.25; N, 12.97

Found: C, 62.28; H, 6.16; N, 12.62

mp 181-183°C; MS (CI) 536 (M+1)

EXAMPLE 61

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-[(2-chlorophenyl) methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene) methyl]-1H-imidazol-1-yl]methyl]benzoate (0.474 g, 1.0 mmol) in DMF (10 mL) is added K_2CO_3 (2.0 g, 15 mmol). After stirring for 5 minutes 1-chloro-2-chloromethylbenzene (0.177 g, 1.1 mmol) is added and the mixture is stirred for 16 hours. The mixture is filtered, concentrated in vacuo, and then dissolved in ether (50 mL). This solution is washed with water and dried over K_2CO_3. A viscous oil is obtained by evaporation of the solvents in vacuo which is purified via chromatography, eluant 1% methanol in chloroform. The appropriate fraction is dissolved in ether and treated with ethereal HCl and then evaporated in vacuo to afford a solid foam.

Anal. Calcd. for $C_{31}H_{35}ClN_4O_4.HCl.\ 0.5\ H_2O$: C, 61.18; H, 6.13; N, 9.21

Found: C, 60.85; H, 6.18; N, 9.07

mp 120-130°C; MS (CI) 563 (M+1)

EXAMPLE 62

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-[(2-amino-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene] methyl]-1H-imidazol-1-yl]methyl]benzoate dihydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene) methyl]-1H-imidazol-1-yl]methyl]benzoate (0.569 g, 1.2 mmol) in DMF (5 mL) is added K_2CO_3 (2.0 g, 15 mmol). After stirring for 5 minutes 2-amino-4-chloromethylthiazole hydrochloride (0.222 g, 1.2 mmol) is added. The mixture is stirred for 48 hours and then filtered. The filtrate is concentrated in vacuo and dissolved in methylene chloride (30 mL). This solution is washed with water

and dried over K_2CO_3 and charcoal. A viscous oil is obtained by evaporation of the solvents in vacuo. This oil is dissolved in ether and treated with ethereal HCl to precipitate a gum which is collected by decantation. This gum is recrystallized from 2-propanol/ ether.

Anal. Calcd. for $C_{28}H_{34}N_6O_4S$. 2HCl. $2H_2O$: C, 50.90; H, 6.10; N, 12.87

Found: C, 51.23; H, 6.10; N, 12.67

mp 171-174°C; MS (CI) 551 (M+1)

EXAMPLE 63

Methyl Z-4-[[2-butyl-5-[2,5-dioxo-3-[(2-thienyl)methyl]-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate

HCl gas is passed through a mixture of the Z and E isomers of 4-[[2-butyl-5-[2,5-dioxo-3-[(2-thienyl)methyl]-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid (3.50 g, 7.5 mmol) in methanol (250 mL). The solid dissolved and the internal temperature rises to 50°C. The solution is allowed to stir for 16 hours at room temperature. The solution is concentrated to approximately 10 mL volume and saturated $NaHCO_3$ (150 mL) is added to adjust the pH to 7.5. The mixture is filtered and washed with water. The Z and E isomers are separated by chromatography (eluant 1-5% methanol in chloroform) and crytallized from warm ethyl acetate.

Anal. Calcd. for $C_{25}H_{26}N_4O_4S$. 0.1 H_2O: C, 61.89; H, 5.44; N, 11.55

Found: C, 62.07; H, 5.34; N, 11.31

mp 167-169°C; MS (CI) 479 (M+1)

EXAMPLE 64

Methyl Z-4-[[2-butyl-5-[[3-[(4-chlorophenyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

HCl gas is passed through a solution of methyl Z-4-[[2-butyl-5-[[3-[(4-chlorophenyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid (0.73 g, 1.5 mmol) in methanol (15 mL). The solution is allowed to stir for 16 hours at room temperature. The solution is concentrated to approximately 5 mL volume and then ether is added to induce crystallization. The mixture is filtered and washed with ether.

Anal. Calcd. for $C_{27}H_{27}N_4O_4Cl$. HCl: C, 59.67; H, 5.19; N, 10.31

Found: C, 59.45; H, 5.09; N, 9.99

mp 240-242°C; MS (CI) 507

EXAMPLE 65

4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinyl)methyl]-1H-imidazol-1-yl]methyl]benzoic acid

To a solution of E -4-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoic acid (0.84 g, 2.00 mmol) in 1N NaOH (2.04 mL, 2.04 mmol) and water (500 mL) is added PtO_2 (0.200 g) and then a hydrogen balloon is attached. The mixture is stirred for 3 hours. 1N HCl (2.04 mL, 2.04 mmol) is added and then the mixture is concentrated at reduced pressure. Ethanol (50 mL) is added and the mixture filtered. After evaporating in vacuo the residue is purified by crystallization and chromatography.

Anal. Calcd. for $C_{23}H_{30}N_4O_4S$. H_2O: C, 62.14; H, 7.26; N, 12.61

Found: C, 62.35; H, 7.08; N, 12.68

MS (CI) 427 (M+1)

EXAMPLE 66

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-[(4-chlorophenyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[[3-[(4-chlorophenyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.50 g, 0.92 mmol) in DMF (5 mL) is added K_2CO_3 (2.0 g, 15 mmol). After stirring for 5 minutes 1-iodobutane (0.184 g, 1.0 mmol) is added. The mixture is stirred for 4 hours. The mixture is filtered and the filtrate is concentrated in vacuo and treated with water (20 mL) to afford a gum upon decantation. This gum is dissolved in ether and washed with water and then dried over K_2CO_3. A viscous oil is obtained by evaporation of the solvents in vacuo. This oil is dissolved in ether and treated with ethereal HCl to precipitate a gum which is collected by decantation. This gum solidifies upon extended evaporation in vacuo. This solid foam contains 2-propanol as determined by 1H-NMR

Anal. Calcd. for $C_{31}H_{35}ClN_4O_4S \cdot HCl \cdot H_2O$. 0.15 i-PrOH:
Calcd. C, 60.26; H, 6.31; N, 8.95
Found: C, 60.50; H, 6.12; N, 8.86
MS (CI) 564 (M+1)

EXAMPLE 67

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[[2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.70 g, 1.46 mmol) in warm DMF (10 mL) is added K_2CO_3 (2.0 g, 15 mmol). After stirring for 5 minutes 1-iodobutane (0.312 g, 1.7 mmol) is added. The mixture is stirred for 2 hours. The mixture is filtered and the filtrate is concentrated in vacuo and treated with water (20 mL) to afford a gum upon decantation. This gum is dissolved in ether and washed with water and then dried over K_2CO_3. A viscous oil is obtained by evaporation

of the solvents in vacuo. This oil is dissolved in ether and treated with ethereal HCl to precipitate a gum which is collected by decantation. This gum is dissolved in warm ethanol and ether is added to induce crystallization. The crystals are collected and washed with ether.

Anal. Calcd. for $C_{29}H_{34}N_4O_4S \cdot HCl$: C, 60.99; H, 6.18; N, 9.81

Found: C, 60.69; H, 6.16; N, 9.69

mp 185-187°C; MS (CI) 535 (M+1)

EXAMPLE 68

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate dihydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate hydrochloride (0.474 g, 1.0 mmol) in DMF (5 mL) is added K_2CO_3 (2.0 g, 15 mmol). After stirring for 5 minutes 2-methyl-4-(chloromethyl)thiazole hydrochloride (0.184 g, 1.0 mmol) is added. An additional amount of DMF (10 mL) is added after stirring for 30 minutes. The mixture is stirred for 5 days and then filtered. The filtrate is concentrated in vacuo and dissolved in ether (50 mL). This solution is washed with water and dried over K_2CO_3 and charcoal. A viscous oil is obtained by evaporation of the solvents in vacuo which is dissolved in ether and treated with ethereal HCl and then evaporated in vacuo to afford a solid foam. Recrystallized from 2-propanol/ether.

Anal. Calcd. for $C_{29}H_{35}N_5O_4S \cdot 2\ HCl \cdot 0.5\ H_2O$: C, 55.14; H, 6.07; N, 11.08

Found: C, 55.00; H, 6.20; N, 11.09

mp 124-127°C; MS (CI) 550 (M+1)

EXAMPLE 69

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-[(3,5-dimethyl-4-isoxazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (1.00 g, 2.281 mmol) in DMF (10 mL) is added K_2CO_3 (1.580 g, 0.011 moles). After stirring for 15 minutes 4-chloromethyl-3,5-dimethylisoxazole (0.35 g, 2.39 mmol) is added. The mixture is stirred for 24 hours. The solvents were removed under high vacuum. After diluting with ethyl acetate and washing with water and brine the solution is dried over $MgSO_4$. Evaporation in vacuo affords a viscous oil. which is dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo. This solid is crystallized from ethyl acetate/hexane.
Anal. Calcd. for $C_{30}H_{37}N_5O_5$.HCl: C, 61.69; H, 6.56; N, 11.99
Found: C, 61.40; H, 6.58; N, 11.86
mp 146-148°C; MS (CI) 548 (M+1)

EXAMPLE 70

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-(2-naphthalenylmethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (1.00 g, 2.281 mmol) in DMF (10 mL) is added K_2CO_3 (1.580 g, 0.011 moles). After stirring for 15 minutes 1-bomomethylnaphthalene (0.53 g, 2.40 mmol) is added. The mixture is stirred for 24 hours then the solvents were removed under high vacuum. After diluting with ethyl acetate and washing with water and brine the solution is dried over $MgSO_4$. Evaporation in vacuo affords a viscous oil which is

dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo. This solid is crystallized from ethyl acetate/ether.
Anal. Calcd. for $C_{35}H_{38}N_4O_4.HCl.2H_2O$: C, 64.55; H, 6.66; N, 8.60
Found: C, 64.74; H, 6.51; N, 8.47
mp 93-95°C; MS (CI) 579 (M+1)

EXAMPLES 71a AND 71b

71a

Z-N-[4-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]phenyl]-1,1,1-trifluoromethanesulfonamide

To a solution of diethyl 3-butyl-2,5-dioxo-4-imidazolylphosphonate (1.48 g, 5.06 mmol) in ethanol (10 mL) was cautiously added sodium hydride batchwise (1.0 g, 25 mmol). The cloudy solution was stirred for 30 min. the aldehyde 1,1-dimethylethyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoate (0.68 g, 1.75 mmol) in ethanol (10 mL) was added over 30 min. This solution was heated at reflux for 2 hours. The reactin was cooled to room temperature and treated with glacial acetic acid (2 mL). Evaporation in vacuo affords a thick gel. Chromatography eluting with 0-4% methanol in chloroform affords the required Z-isomer
Anal. Calcd. for $C_{23}H_{28}N_5O_4.0.25H_2O$: C, 51.92; H, 5.40; N, 13.16
Found: C, 51.99; H, 5.62; N, 12.85
mp 171-5°C; MS (CI) 528 (M+1)

and then the more polar E-isomer

71b

E-N-[4-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]phenyl]-1,1,1-trifluoromethanesulfonamide

Anal. Calcd. for $C_{23}H_{28}N_5O_4.0.25H_2O.$: C, 51.92; H, 5.40; N, 13.16
Found: C, 51.92; H, 5.41; N, 13.50
mp 177-178°C; MS (CI) 528 (M+1)

EXAMPLE 72

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-[(3-methyl-2-thienyl)methyl]-2,5-dioxo-4-imidazolidinylidene] methyl]-1H-imidazol-1-yl]methyl]benzoate hydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (1.10 g, 2.876 mmol) in dry THF (20 mL) was carefully added sodium hydride (0.14 g, 4.67 mmol) and then the mixture was allowed to stir for 20 minutes. 2-Bromomethyl-3-methyl-thiophene (0.75 g, 3.925 mmol) in THF (10 mL) was added dropwise over 10 minutes. After stirring for 2 hours dilute aqueous HCl was added to the orange brown mixture until the pH was 7. This mixture was extracted with ethyl acetate and then dried over $MgSO_4$. The product was isolated by chromatography eluting with acetone in methylene chloride. The hydrochloride salt was prepared by the addition of HCl in isopropanol, and then crystallisation from THF/ether.
Anal. Calcd. for $C_{30}H_{36}N_4O_4S.1.14HCl$: C, 61.05; H, 6.34; N, 9.49
Found: C, 60.67; H, 6.05; N, 9.27
mp 160-162°C; MS (CI) 549 (M+1)

EXAMPLE 73

Z-4-[[2-butyl-5-[(1,3-dibutyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoic acid

1,1-dimethylethyl Z-4-[[2-butyl-5-[(1,3-dibutyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.88 g, 1.64 mmol) was disolved in methylene chloride (16 mL) and trifluoroacetic acid (16 mL). After stirring for 3 hours the reaction

mixture was evaporated in vacuo. Dilute $NaHCO_3$ was added to adjust the pH to 6 and extracted with ethyl acetate. This extract was dried over $MgSO_4$ and then evaporated in vacuo and purified via chromatography (eluant methanol in chloroform).

Anal. Calcd. for $C_{27}H_{36}N_4O_4$: C, 67.48; H, 7.55; N, 11.66

Found: C, 67.48; H, 7.76; N, 11.48

mp 182-184°C; MS (CI) 481 (M+1)

EXAMPLE 74

Z-4-[[2-butyl-5-[[1-butyl-3-[(5-methyl-2-thienyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid

1,1-dimethylethyl Z-4-[[2-butyl-5-[[1-butyl-3-[(5-methyl-2-thienyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.56 g, 0.948 mmol) was disolved in methylene chloride (10 mL) and trifluoroacetic acid (5 mL). After stirring for 16 hours the reaction mixture was evaporated in vacuo. pH 7 buffer was added and the mixture extracted with ethyl acetate. This extract was dried over $MgSO_4$ and then evaporated in vacuo and crystallized from THF/ether.

Anal. Calcd. for $C_{29}H_{34}N_4O_4S.0.3H_2O$: C, 65.15; H, 6.41; N, 10.48

Found: C, 64.46; H, 6.62; N, 10.39

mp 163-165°C; MS (CI) 535 (M+1)

EXAMPLE 75

Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid

1,1-dimethylethyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-[(2-thienyl)methyl]-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]-benzoate (1.28 g, 2.26 mmol) was disolved in methylene chloride (25 mL)

and trifluoroacetic acid (3.3 mL). After stirring for 16 hours an additional amount of trifluoroacetic acid (3 mL) was added. Stirred for a further 6 hours and then the reaction mixture was evaporated in vacuo. pH 7 buffer was added and the mixture extracted with ethyl acetate. This extract was dried over $MgSO_4$ and then evaporated in vacuo and crystallized from ethyl acetate/ether.

Anal. Calcd. for $C_{28}H_{32}N_4O_4S.0.5H_2O$: C, 63.50; H, 6.28; N, 10.58

Found: C, 63.58; H, 6.16; N, 10.44

mp 167-170°C; MS (CI) 521 (M+1)

EXAMPLES 76a AND 76b

76a

Z-1-Butyl-5-[[2-butyl-3-[[4-(1H-tetrazol-5-yl)phenyl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione

To a solution of diethyl 3-butyl-2,5-dioxo-4-imidazolylphosphonate (0.240 g, 0.86 mmol) in ethanol (10 mL) was added sodium hydride (0.072 g, 1.80 mmol) and the mixture stirred for 15 minutes. The aldehyde 2-butyl-1-[4-[1-(triphenylmethyl)tetrazol-5-yl]phenyl]methyl]-5-formylimidazole (0.400 g, 0.72 mmol) was added along with methylene chloride (5 mL). The mixture was stirred for 16 hours. The solvents were removed in vacuoo and the Z-isomer and E-isomer purified by chromatography eluting with 20% ethyl acetate in methylene chloride. The Z-isomer and the E-isomer were each separately dissolved in methanol (5 mL) containing a 10% aqueous solution of citric acid (0.5 mL). The reaction mixture was refluxed overnight. Water (20 mL) was added and extracted with hexane. The mixture was then extracted with ethyl acetate and washed with brine and dried over $MgSO_4$. After

evaporating in vacuo the residue was crytallized from a combination of hexane, ethyl acetate and methanol.
Anal. Calcd. for $C_{23}H_{28}N_8O_2S.0.9H_2O$: C, 59.40; H, 6.47; N, 24.09
Found: C, 59.79; H, 6.18; N, 23.57
mp 140-142°C; MS (CI) 449 (M+1)

76b

E-1-Butyl-5-[[2-butyl-3-[[4-(1H-tetrazol-5-yl)phenyl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione
Anal. Calcd. for $C_{23}H_{28}N_8O_2S.1.67H_2O$: C, 57.72; H, 6.60; N, 23.41
Found: C, 57.35; H, 5.94; N, 23.13
MS (CI) 449 (M+1)

EXAMPLE 77

Methyl Z-4-[[5-[[3-[(5-bromo-2-thienyl)methyl]-1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-2-butyl-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.750 g, 1.7 mmol) in DMF (10 mL) was added K_2CO_3 (1.17 g, 0.0085 moles). 2-bromomethyl-5-bromothiophene (0.46 g, 0.0018 moles) was added in one portion and the mixture stirred for 16 hours. The reaction mixture was filtered and evaporated in vacuo. The residue was extracted into ethyl acetate and then washed with water and brine. After drying over $MgSO_4$ and evaporation in vacuo the residue was purified by chromatography eluting with 10% ethyl acetate in methylene chloride. The required product was recrystallized as its hydrochloride salt.

Anal. Calcd. for $C_{29}H_{33}N_4O_4BrS.HCl.0.72H_2O$: C, 52.54; H, 5.39; N, 8.45
Found: C, 52.54; H, 5.51; N, 8.42
MS (CI) 613/615 (M+1)

EXAMPLE 78

Methyl Z-4-[[5-[[3-[(4-bromo-2-thienyl)methyl]-1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-2-butyl-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.750 g, 1.7 mmol) in DMF (10 mL) was added K_2CO_3 (1.17 g, 0.0085 moles). 2-bromomethyl-4-bromothiophene (0.46 g, 0.0018 moles) was added in one portion and the mixture stirred for 16 hours. The reaction mixture was filtered and evaporated in vacuo. The residue was extracted into ethyl acetate and then washed with water and brine. After drying over $MgSO_4$ and evaporation in vacuo the residue was dissolved in ether and treated with ethereal HCl to afford a white solid upon removal of solvents in vacuo.
Anal. Calcd. for $C_{29}H_{33}N_4O_4BrS.HCl.1.22H_2O$: C, 51.83; H, 5.47; N, 8.34
Found: C, 51.82; H, 5.32; N, 8.18
MS (CI) 613/615 (M+1)

EXAMPLE 79

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-[2-(2-thienyl)ethyl]-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.750 g, 1.7 mmol) in DMF (20 mL) was added K_2CO_3 (1.17 g, 0.0085 moles). 2-(2-thienyl)ethyl bromide (0.35 g, 0.0018 moles) was added in one portion and the mixture stirred for 16 hours. The reaction mixture was filtered and evaporated in

vacuo. The residue was extracted into ethyl acetate and then washed with water and brine. After drying over $MgSO_4$ and evaporation in vacuo the residue was purified by chromatography eluting with 50% ethyl acetate in methylene chloride. The required product was dissolved in ether and treated with ethereal HCl to afford a white solid upon removal of solvents in vacuo.

Anal. Calcd. for $C_{30}H_{37}N_4O_4S.HCl.1.15H_2O$: C, 59.47; H, 6.54; N, 9.25

Found: C, 59.48; H, 6.48; N, 9.01

MS (CI) 549 (M+1)

EXAMPLE 80

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-[2-(3-thienyl)ethyl]-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.750 g, 1.7 mmol) in DMF (20 mL) was added K_2CO_3 (1.17 g, 0.0085 moles). 2-(3-thienyl)ethyl bromide (0.35 g, 0.0018 moles) was added in one portion and the mixture stirred for 16 hours. A further amount of 2-(3-thienyl)ethyl bromide (0.35 g, 0.0018 moles) was added and the mixture stirred for 16 hours. The reaction mixture was filtered and evaporated in vacuo. The residue was extracted into ethyl acetate and then washed with water and brine. After drying over $MgSO_4$ and evaporation in vacuo the residue was purified by chromatography eluting with 20% ethyl acetate in methylene chloride. The required product was dissolved in ether and treated with ethereal HCl to afford a white solid upon removal of solvents in vacuo.

Anal. Calcd. for $C_{30}H_{37}N_4O_4S.HCl.0.87H_2O$: C, 59.97; H, 6.50; N, 9.32

Found: C, 59.99; H, 6.40; N, 9.27

MS (CI) 549 (M+1)

EXAMPLE 81

Methyl Z-4-[[5-[[3-[(5-bromo-3-thienyl)methyl]-1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-2-butyl-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.500 g, 1.1 mmol) in DMF (20 mL) was added K_2CO_3 (0.76 g, 0.0055 moles). 2-bromo-3-bromomethylthiophene (0.44 g, 0.0017 moles) was added in one portion and the mixture stirred for 16 hours. The reaction mixture was filtered and evaporated in vacuo. The residue was extracted into ethyl acetate and then washed with water and brine. After drying over $MgSO_4$ and evaporation in vacuo the residue was purified by chromatography eluting with 20% ethyl acetate in methylene chloride. The required product was dissolved in ether and treated with ethereal HCl to afford a white solid upon removal of solvents in vacuo. Anal. Calcd. for $C_{29}H_{34}N_4O_4SBrCl.HCl.1.56H_2O$: C, 51.32; H, 5.52; N, 8.26

Found: C, 51.32; H, 5.48; N, 8.15

MS (CI) 613/615 (M+1)

EXAMPLE 82

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(4-thiazolylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.750 g, 1.7 mmol) in DMF (20 mL) was added sodium hydride (60%) (0.17 g, 0.0043 moles). 4-chloromethylthiazole.hydrochloride (0.22 g, 0.0013 moles) was added in one portion and the mixture stirred for 64 hours. The reaction mixture was filtered and evaporated in vacuo. The residue was extracted into ethyl acetate and then washed with water and brine. After drying over $MgSO_4$ and evaporation in vacuo the

residue was purified by chromatography eluting with 20% ethyl acetate in methylene chloride. The required product was dissolved in ether and treated with ethereal HCl to afford a white solid upon removal of solvents in vacuo.

Anal. Calcd. for $C_{29}H_{34}N_4O_4SBrCl.HCl$: C, 58.62; H, 6.16; N, 12.22;
Found: C, 57.84; H, 6.09; N, 11.84;
MS (CI) 536 (M+1)

EXAMPLE 83

Methyl Z-1-[4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]phenyl] cyclopentanecarboxylate

Methyl Z-1-[4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]phenyl]cyclopentanecarboxylate was added to a solution of 3-butyl-2,5-dioxo-4-imidazolylphosphonate (2.42 g, 9.00 mmol) and DBU (1.31 g, 8.6 mmol) in methylene chloride (10 mL). This mixture was allowed to stand for 16 h at room temperature. This mixture was then purified by chromatography, eluant (1-10)% methanol in chloroform, and recrystallisation from hot ethyl acetate and ether. 1H-NMR indicated a small amount of the E-isomer was present in the purified Z-isomer fraction.

Anal. Calcd. for $C_{29}H_{38}N_4O_4$: C, 68.75; H, 7.56; N, 11.06
Found: C, 68.63; H, 7.55; N, 10.98
MS (CI) 507 (M+1)

EXAMPLE 84

Methyl Z-1-[4-[[2-butyl-5-[[1-butyl-[3-(2-methyl-4-thiazoly)methyl]-2,5-dioxo-4-imidazolidinylidene] methyl]-1H-imidazol-1-yl]methyl]phenyl]cyclopentane-carboxylate monohydrochloride

Methyl Z-1-[4-[[2-butyl-5-[[1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-

yl]methyl]phenyl]cyclopentanecarboxylate (1.00 g, 1.97 mmol) and 4-chloromethyl-2-methylthiazole monohydrochloride (0.363 g, 1.97 mmol) were dissolved in DMF (10 mL). K_2CO_3 (3.0 g, 21.7 mmol) was added and the mixture stirred for 16 hours. The mixture was filtered and evaporated. The residue was added to water and the gum that formed was dissolved in ether. After washing the ethereal fraction with water and drying over K_2CO_3 the product was purified by chromatography, eluant (0.5-3)% methanol in chloroform. The appropriate fraction was dissolved in ether and treated with ethereal HCl. The solid foam that resulted upon extended evaporation in vacuo was collected and shown by 1H NMR to contain the required product as well as the corresponding E-isomer (10%).

Anal. Calcd. for $C_{34}H_{43}N_5O_4S.HCl.H_2O$: C, 60.74; H, 6.90; N, 10.42

Found: C, 61.09; H, 6.78; N, 10.48

MS (CI) 618 (M+1)

EXAMPLE 85

Z-1-[4-[[2-butyl-5-[[1-butyl-[3-(2-methyl-4-thiazoly)methyl]-2,5-dioxo-4-imidazolidinyli-dene]methyl]-1H-imidazol-1-yl]methyl]phenyl] cyclopentanecarboxylic acid

Methyl Z-1-[4-[[2-butyl-5-[[1-butyl-2,5-dioxo-[3-(2-methyl-4-thiazoly)methyl]-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]phenyl]cyclopentanecarboxylate monohydrochloride (0.340 g, 0.5 mmol) and 2N HCl (15 mL) were heated at reflux for 2 hours. After evaporation in vacuo the residue was dissolved in methanol and treated with saturated aqueous NaOAc to precipitate a gum. This gum crystallized from ethyl acetate and was then recrystallized from methanol.

Anal. Calcd. for $C_{33}H_{41}N_5O_4S$: C, 65.65; H, 6.84; N, 11.60

Found: C, 65.43; H, 6.74; N, 11.22
MS (CI) 604 (M+1)

EXAMPLE 86

Methyl E-4-[[2-butyl-5-[[3-butyl-1-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate dihydrochloride

To a solution of methyl E-4-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.66 g, 1.5 mmol) in DMF (10 mL) is added K_2CO_3 (3.0 g, 15 mmol). After stirring for 5 minutes 2-methyl-4-chloromethylthiazole hydrochloride (0.28 g, 1.5 mmol) is added. The mixture is stirred for 16 hours and then filtered. The filtrate is concentrated in vacuo and dissolved in ether (50 mL). This solution is washed with water and dried over K_2CO_3 and charcoal. The mixture is filtered and allowed to stand in which time the product crystallizes. Petroleum ether is added to complete crystallization.
Anal. Calcd. for $C_{29}H_{35}N_5O_4S$: C, 63.37; H, 6.42; N, 12.74
Found: C, 63.46; H, 6.38; N, 12.72
mp 109-111°C; MS (CI) 550 (M+1)

EXAMPLES 87a AND 87b

87a

Methyl Z-4-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]-3-chlorobenzoate

To a solution of diethyl 3-butyl-2,5-dioxo-4-imidazolylphosphonate (0.49 g, 1.72 mmol) in acetonitrile (5 mL) was added lithium chloride (0.15 g, 3.47 mmol) and then DBU (0.52 mL, 3.47 mmol). This mixture was stirred for 5 minutes under N_2.

Methyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]-3-chlorobenzoate (0.48 g, 1.43 mmol) in acetonitrile (5 mL) was added and the mixture stirred for 4 days. The solvent was removed in vacuo and the isomers separated by chromatography eluting with (1-5)% methanol in chloroform.

Anal. Calcd. for $C_{24}H_{29}N_4O_4Cl$: C, 60.95; H, 6.18; N, 11.85

Found: C, 60.50; H, 6.11; N, 11.30

MS (CI) 473 (M+1)

87b

Methyl E-4-[[2-butyl-5-[[3-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]-3-chlorobenzoate

Anal. Calcd. for $C_{24}H_{29}N_4O_4Cl$: C, 60.95; H, 6.18; N, 11.85

Found: C, 60.47; H, 6.06; N, 11.23

mp 186-187°C; MS (CI) 473 (M+1)

EXAMPLES 88a AND 88b

88a

Methyl Z-1-[4-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]phenyl]cyclohexanecarboxylate

Methyl Z-1-[4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]phenyl]cyclohexanecarboxylate was added to a solution of 3-butyl-2,5-dioxo-4-imidazolylphosphonate (0.16 g, 0.58 mmol) and sodium hydride (80% in oil) (0.032 g, 1.16 mmol) in methanol (3 mL). This mixture was allowed to stir for 16 hours at room temperature. This mixture was then purified by chromatography, eluant (1-10)% methanol in chloroform. The Z-isomer was separated from the E-isomer.

Anal. Calcd. for $C_{30}H_{40}N_4O_4$: C, 69.20; H, 7.74; N, 10.76
Found: C, 68.85; H, 7.67; N, 10.46
mp 139-140°C; MS (CI) 521 (M+1)

88b

Methyl E-1-[4-[[2-butyl-5-[[3-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl] phenyl]cyclohexanecarboxylate

Anal. Calcd. for $C_{30}H_{40}N_4O_4$: C, 69.20; H, 7.74; N, 10.76
Found: C, 68.90; H, 7.80; N, 10.55
mp 189-190°C; MS (CI) 521 (M+1)

EXAMPLE 89

Methyl Z-4-[[2-butyl-5-[[1-(cyclopropylmethyl)-2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene] methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-cyclopropylmethyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.39 g, 0.89 mmol) in DMF (5 mL) is added K_2CO_3 (0.67 g, 4.47 mmol). After stirring for 5 minutes 3-bromomethylthiophene (1.20 mmol) is added. The mixture is stirred for 16 hours. The mixture is diluted with ethyl acetate and washed with water and dried over $MgSO_4$. After purification by chromatography, eluting with (0-40)% ethyl acetate in methylene chloride, the hydrochloride is prepared by the addition of ethereal HCl. The product is crystallized from ethyl acetate.
Anal. Calcd. for $C_{29}H_{32}N_4O_4S$: C, 61.20; H, 5.84; N, 9.84
Found: C, 61.07; H, 5.82; N, 9.50
mp 184-190°C; MS (CI) 533 (M+1)

EXAMPLE 90

Methyl E-4-[[5-[(3-butyl-1-methyl-2,5-dioxo-4-imidazolidinylidene)methyl]-2-propyl-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl E-4-[[5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-2-propyl-1H-imidazol-1-yl]methyl]benzoate (0.082 g, 0.07 mmol) in DMF (0.5 mL) is added K_2CO_3 (0.50 g, 3.62 mmol) and then methyliodide (0.024 g, 0.17 mmol). After stirring for 1 hour a further amount of 1-iodomethane is added (0.024 g, 0.17 mmol). The mixture is stirred for an additional 1 hour. The mixture is diluted with water and the gum that precipitates is collected by decantation. This gum is dissolved in methylene chloride and treated with charcoal and K_2CO_3. This mixture is filtered, concentrated and crystallized from ether.

Anal. Calcd. for $C_{24}H_{30}N_4O_4$ $0.3H_2O$: C, 65.20; H, 6.93; N, 12.67

Found: C, 65.16; H, 6.88; N, 12.60

mp 113-114°C; MS (CI) 439 (M+1)

EXAMPLE 91

Z-1-Butyl-5-[[2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione

To Z-1-butyl-5-[[2-butyl-3-[[2'-(N-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione (0.800 g, 1.04 mmol) was added methanol (100 mL) and 5% aqueous citric acid (5 mL). This white heterogenous mixture was refluxed for 3 hour in which time a solution formed. The solution was cooled to room temperature and diluted with water (10 mL) and hexanes (100 mL). The aquous methanol fraction was evaporated in vacuo and then dissolved in a mixture of ethyl acetate and water. After drying the

organic fraction over Na_2SO_4 the product was precipitated by the addition of ether to a methylene chloride solution.
HPLC eluant 55%(0.1%TFA in H_2O) 45% MeCN, RT 2.98 [99%]
MS (CI) 525 (M+1)

EXAMPLE 92

E-1-Butyl-5-[[2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione

To E-1-butyl-5-[[2-butyl-3-[[2'-(N-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione (0.100 g, 0.13 mmol) was added methanol (50 mL) and 5% aqueous citric acid (5 mL). This white heterogenous mixture was refluxed for 3 hour in which time a solution formed. The solution was cooled to room temperature and diluted with water (10 mL) and hexanes (100 mL). The aquous methanol fraction was evaporated in vacuo and then dissolved in a mixture of ethyl acetate and water. After drying the organic fraction over Na_2SO_4 the solvents were removed in vacuo and the residue triturated with hexanes.
HPLC eluant 45%(0.1%TFA in H_2O) 55% MeCN, RT 2.25 [95%]
MS (CI) 525 (M+1)

EXAMPLE 93

Z-5-[[2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]1-methyl-2,4-imidazolidinedione

To Z-5-[[2-butyl-3-[[2'-(N-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]-1-methyl-2,4-imidazolidinedione (0.300 g, 0.414 mmol) was added methanol (50 mL) and glacial acetic acid (0.2 mL). This white heterogenous mixture was refluxed for 4 hours in which time a solution formed. The solution was cooled to room

temperature and diluted with water (5 mL) and hexanes (50 mL). The aqueous methanol fraction was evaporated in vacuo and then dissolved in a minimal amount of methanol. Ether was added to precipitate a white solid.

Anal. Calcd. for $C_{26}H_{26}N_8O_2$ $0.67H_2O$: C, 63.16; H, 5.57; N, 22.66

Found: C, 63.43; H, 5.66; N, 22.33

HPLC eluant 67%(0.1%TFA in H_2O) 33% MeCN, RT 4.4 [92%]

MS (CI) 483 (M+1)

EXAMPLE 94

E-5-[[2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]1-methyl-2,4-imidazolidinedione

To a mixture of the E and Z-isomers of 5-[[2-butyl-3-[[2'-(N-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]-1-methyl-2,4-imidazolidinedione (0.400 g, 0.552 mmol) was added methanol (50 mL) and glacial acetic acid (0.2 mL). This white heterogenous mixture was refluxed for 3 hour in which time a solution formed. The solution was cooled to room temperature and diluted with water (5 mL) and hexanes (50 mL). The aqueous methanol fraction was evaporated in vacuo and then triturated with ethyl acetate. The insoluble residue was collected and determined to be the E-isomer.

HPLC eluant 45%(0.1%TFA in H_2O) 55% MeCN, RT 1.9 [95%]

MS (CI) 483 (M+1)

EXAMPLE 95

1-Butyl-5-[[2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methyl]-2,4-imidazolidinedione

To a solution of 1-butyl-5-[[2-butyl-3-[[2'-(N-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methyl]-2,4-

imidazolidinedione (0.080 g, 0.10 mmol) in methanol (30 mL) was added glacial acetic acid (0.06 mL). This mixture was refluxed for 5 hours. The solution was cooled to room temperature and diluted with water (10 mL) and hexanes (50 mL). The aquous methanol fraction was evaporated in vacuo and then redissolved in a minimum volume of methanol. Ether was added and the solid that precipitated collected.

HPLC eluant 67%(0.1%TFA in H_2O) 33% MeCN, RT 5.4 [98%]

MS (CI) 527 (M+1)

Anal. Calcd. for $C_{29}H_{34}N_8O_2.H_2O$: C, 63.95; H, 6.66; N, 20.57

Found: C, 64.15; H, 6.66; N, 20.07

EXAMPLES 96a AND 96b

96a

Methyl Z-4'-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylate

To a solution of diethyl 3-butyl-2,5-dioxo-4-imidazolylphosphonate (0.540 g, 1.91 mmol) in methanol (15 mL) is added NaH (80% in oil, 0.115 g, 3.83 mmol). The solution is stirrred for 5 minutes and then 2-butyl-1-[(2'-carbomethoxy-1,1'-biphen-4-yl)methyl]-1H-imidazole-5-carboxaldehyde (0.515 g, 1.37 mmol) is added. The yellow solution is stirred for 16 hours at room temperature and then diluted with ethyl acetate and saturated ammonium chloride. The organic fraction is washed with brine and then dried over Na_2SO_4. Chromatography separates the Z and E-isomers, eluant (0-2)% methanol in chloroform.

Z-isomer

Anal. Calcd. for $C_{30}H_{34}N_4O_4$: C, 70.02; H, 6.66; N, 10.89

Found: C, 69.58; H, 6.58; N, 10.55

MS (CI) 515 (M+1)

96b

Methyl E 4'-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylate

Anal. Calcd. for $C_{30}H_{34}N_4O_4$: C, 70.02; H, 6.66; N, 10.89

Found: C, 69.63; H, 6.54; N, 10.65

MS (CI) 515 (M+1)

EXAMPLE 97a AND 97b

97a

Methyl Z-4'-[[4-bromo-2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylate

To a solution of diethyl 3-butyl-2,5-dioxo-4-imidazolylphosphonate (0.105 g, 0.372 mmol) in methanol (10 mL) is added sodium hydride (80% in oil, 0.022 g, 0.733 mmol). The solution is stirrred for 5 minutes and then 4-bromo-2-butyl-1-[(2'-carbomethoxy-1,1'-biphen-4-yl)methyl]-1H-imidazole-5-carboxaldehyde (0.130 g, 0.286 mmol) is added. The yellow solution is stirred for 16 hours at room temperature and then diluted with ethyl acetate and saturated ammonium chloride. The organic fraction is washed with brine and then dried over Na_2SO_4. Chromatography separates the Z and E-isomers, eluant (30-50)% ethyl acetate in hexane.

Anal. Calcd. for $C_{30}H_{33}N_4O_4Br$: C, 60.71; H, 5.60; N, 9.44

Found: C, 60.59; H, 5.71; N, 9.06

MS (CI) 593/595

97b

Methyl E-4'-[[4-bromo-2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylate

Anal. Calcd. for: $C_{30}H_{33}N_4O_4Br$: C, 60.71; H, 5.60; N, 9.44

Found: C, 60.45; H, 5.48; N, 9.42

MS (CI) 593/595

EXAMPLE 98

Methyl Z-4-[[2-butyl-5[2-[butyl[[(methoxymethyl)amino]carbonyl]amino]-2-carboxyethenyl]-1H-imidazol-yl]methyl]benzoate

To a solution of methyl Z-4-[[2-butyl-5-[[3-butyl-1-(methoxymethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride. (0.100 g, 0.193 mmol) in THF was added 1N NaOH (0.22 mL, 0.22 mmol) and then methanol (2 mL). The yellow solution was stirred for1.5 hours and then 1N HCl (0.22 mL, 0.22 mmol) was added. The reaction mixture was evaporated in vacuo to a white solid. This solid was dissolved in ethyl acetate and water. The organic layer was dried briefly over $MgSO_4$ and then concentrated to 1/6 original volume. An equal volume of hexane was added and the solid collected.

Anal. Calcd. for: $C_{26}H_{36}N_4O_6$: C, 62.38; H, 7.25; N, 11.19

Found: C, 61.97; H, 7.17; N,11.15

mp 155°C; MS (FAB) 501

EXAMPLE 99

Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-[1-(phenyl-methyl)-1H-imidazol-2-yl]methyl-4-imidazolidinylidenel methyl]-1H-imidazol-1-yl]methyl]benzoate

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene) methyl]-1H-imidazol-1-yl]methyl]benzoate hydrochloride (0.190 g, 0.400 mmol) in DMF (1 mL) is added K_2CO_3 (0.300 g, 2.17 mmol). After stirring for 5 minutes 1-(phenylmethyl)-2-chloromethyl-1H-imidazole monohydrochloride (0.130 g, 0.53 mmol) is added. The mixture is stirred for 16 hours to generate a brown colored mixture. After diluting with ethyl acetate and washing with water and brine the solution is dried over $MgSO_4$. A viscous oil is obtained upon chromatography on silica gel (eluant 0.5% methanol in chloroform) and evaporation of the solvents in vacuo. This oil is dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo. This solid is crystallized from 2-propanol/methanol/ ether.

Anal. Calcd. for $C_{35}H_{40}N_6O_4$. 2HCl. 0.67H2O: C, 61.67; H, 6.21; N, 12.33

Found: C, 61.06; H, 6.14; N, 11.98

mp 247-248°C; MS (EI) 608

EXAMPLE 100

Methyl Z-4-[[2-butyl-5-[[2,5-dioxo-1-[[2-(trimethylsilyl)ethoxy]methyl]-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate

To a solution of methyl Z-4-[[2-butyl-5-[(2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.200 g, 0.524 mmol) in DMF (2 mL) is added sodium hydride (80% in oil, 0.02 g, 0.67 mmol) and the mixture stirred for 5 minutes. (Trimethylsilyl)ethoxymethyl chloride SEM-Cl (0.100 mL, 0.536 mmol) is added and the mixture allowed to stir for 16 hours. The solvents are removed in vacuo and the residue dissolved in ethyl acetate and water. After drying thr organic fraction over $MgSO_4$ the required product is isolated by chromatography, eluting

with 0.5% methanol in chloroform. Crystallized from ether.

Anal. Calcd. for $C_{26}H_{36}N_4O_5Si$: C, 60.90; H, 7.08; N, 10.93

Found: C, 60.81; H, 7.09; N, 10.73

mp 146-148°C; MS (CI) 513

EXAMPLE 101

Methyl Z-4-[[2-butyl-5-[[1-(hydroxymethyl)-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate dihydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[[2,5-dioxo-1-[[2-(trimethylsilyl)ethoxy]methyl]-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.390 g, 0.760 mmol) in DMF (5 mL) is added K_2CO_3 (0.525 g, 3.80 mmol). After stirring for 5 minutes 4-chloromethyl-2-methylthiazole hydrochloride (0.275 g, 1.49 mmol) is added. The mixture is stirred for 16 hours. Water is added and the gum that precipitates is separated. This gum is dissolved in ethyl acetate, washed with water and brine, and then dried over $MgSO_4$. Chromatography eluting with 0.5% methanol in chloroform and evaporation in vacuo affords a viscous oil. This oil is dissolved in methylene chloride (5 mL) and treated with trifluoroacetic acid (5 mL). After stirring for 90 minutes the mixture is concentrated in vacuo and then extracted into methylene chloride from pH 7 buffer. The organic phase is dried over $MgSO_{44}$ and then evaporated in vacuo to afford an oil. This oil is disssolved in 2-propanol and treated with ethereal HCl (1M, 2mL). The white gummy solid that results is crystallized from methanol/ 2-propanol/ ether.

Anal. Calcd. for $C_{26}H_{29}N_5O_5S$. 2HCl: C, 52.35; H, 5.24; N, 11.74

Found: C, 52.25; H, 5.32; N, 11.55

mp 208-211°C; MS (CI) 522

EXAMPLE 102

Methyl Z-4-[[5-[[3-[(1,1'-biphenyl)-4-ylmethyl]-1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-2-butyl-1H-imidazol-1-yl]methyl]benzoate

To a solution of methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.438 g, 1.00 mmol) in DMF (10 mL) is added K_2CO_3 (0.42 g, 3.00 mmol). After stirring for 5 minutes biphenylmethyl chloride (0.210 g, 1.00 mmol) is added. The mixture is stirred for 16 hours, filtered, and evaporated in vacuo. The gum is dissolved in ethyl acetate and washed with water, brine and dried over $MgSO_4$. Chromatography eluting with (50-100)% ethyl acetate in hexane, evaporation in vacuo affords a foam.

Anal. Calcd. for $C_{37}H_{40}N_4O_4 \cdot 0.3H_2O$: C, 72.84; H, 6.71; N, 9.18

Found: C, 72.73; H, 6.75; N, 9.12

MS (CI) 604

EXAMPLE 103

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-[2-oxo-2-(2-thienyl)ethyl]-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate (0.660 g, 1.50 mmol) in DMF (10 mL) is added sodium hydride (60% in oil, 0.08 g, 2.0 mmol). After stirring for 5 minutes 2-(bromoacetyl)thiophene (0.500 g, 2.44 mmol) is added. The mixture is stirred for 16 hours, filtered and evaporated in vacuo. The gum is dissolved in ethyl acetate and washed with water, brine and dried over $MgSO_4$. Chromatography eluting with (0-5)% methanol in dichloromethane and evaporation

in vacuo affords a foam. The hydrochloride salt is prepared.

Anal. Calcd. for $C_{30}H_{34}N_4O_4S$. HCl. H_2O: C, 58.38; H, 6.04; N, 9.08

Found: C, 58.21; H, 5.99; N, 8.74

MS (CI) 563

EXAMPLE 104

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(2-oxo-2-phenylethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.660 g, 1.50 mmol) in DMF (10 mL) is added K_2CO_3 (0.62 g, 4.5 mmol). After stirring for 5 minutes (bromoacetyl)benzene (0.320 g, 1.6 mmol) is added. The mixture is stirred for 16 hours, filtered, and evaporated in vacuo. The gum is dissolved in ethyl acetate and washed with water, brine and dried over $MgSO_4$. Chromatography eluting with (50-100)% ethyl acetate in hexane and evaporation in vacuo affords a foam. The hydrochloride salt is prepared.

Anal. Calcd. for $C_{32}H_{36}N_4O_5S$. HCl. H_2O: C, 62.89; H, 6.43; N, 9.17

Found: C, 62.74; H, 6.43; N, 9.03

MS (CI) 557

EXAMPLE 105

Z-4-[[2-Butyl-5-[[2,5-dioxo-1,3-bis(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid

To a solution of 1,1-dimethylethyl Z-4-[[2-butyl-5-[(2,5-dioxo-4-imidazolidinylidene)methyl]benzoate (0.660 g, 1.55 mmol) in DMF (5 mL) and THF (5 mL) is added NaH (0.13 g, 3.25 mmol). After stirring for 5 minutes 2-thienylmethyl bromide (0.58 g, 3.28 mmol) is added. The mixture is stirred for 16 hours,

filtered and evaporated in vacuo. The gum is dissolved in ethyl acetate and washed with water, brine and dried over $MgSO_4$. Chromatography eluting with (50-100)% ethyl acetate in hexane and evaporation in vacuo affords a foam. This foam is dissolved in methylene chloride (15 mL) and trifluoroacetic acid (4 mL) is added. The mixture is evaporated in vacuo and then dissolved in ethyl acetate. After washing with pH 4 buffer and drying over $MgSO_{44}$ the product is isolated by chromatography, eluant (2-5)% methanol in chloroform. Crystallized from THF/ Ether

Anal. Calcd. for $C_{29}H_{28}N_4O_4S_2.H_2O$: C, 62.12; H, 5.03; N, 9.99

Found: C, 62.24; H, 5.05; N, 9.90

mp 204-205°C; MS (CI) 561

EXAMPLE 106

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-(5-isoxazolyl-methyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.420 g, 0.96 mmol) in DMF (20 mL) is added K_2CO_3 (0.40 g, 4.5 mmol). After stirring for 5 minutes 5-bromomethylisoxazole (0.160 g, 1.00 mmol) is added. The mixture is stirred for 16 hours, filtered and evaporated in vacuo. The gum is dissolved in ethyl acetate and washed with water and, brine, and dried over $MgSO_4$. Chromatography eluting with (0-5)% methanol in methylene chloride and evaporation in vacuo affords a foam. The hydrochloride salt was prepared.

Anal. Calcd. for $C_{28}H_{33}N_5O_5$. HCl. $1.6H_2O$: C, 57.50; H, 6.41; N,11.97

Found: C, 57.19; H, 6.41; N,11.70

MS (CI) 520

EXAMPLE 107

Methyl Z-4-[[2-butyl-5-[[2,5-dioxo-4,4,4-(trifluoro-butyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate

To a solution of diethyl 2,5-dioxo-1-[4,4,4-(trifluorobutyl)]-4-imidazolylphosphonate (2.43 g, 7.01 mmol) in methylene chloride (15 mL) was added 1,8-diazabicyclo [5.4.0]undec-7-ene (1.07 g, 7.02 mmol). The yellow solution is stirred for 10 minutes and then a solution of methyl 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoate (2.11 g, 7.01 mmol) was added. This mixture is allowed to stir for 16 hours. The mixture is diluted with ethyl acetate and washed with water and then brine. After drying over $MgSO_4$ the product is isolated as a yellow solid by concentration in vacuo and treatment with ether. Crystallized from ethyl acetate.

Anal. Calcd. for $C_{24}H_{27}N_4O_4F_3$: C, 58.53; H, 5.53; N, 11.38

Found: C, 58.93; H, 5.51; N, 11.28

mp 188-189°C; MS (CI) 493

EXAMPLE 108

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-[(5-methyl-3-isoxazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate

To a solution of methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (0.700 g, 1.60 mmol) in DMF (14 mL) is added K_2CO_3 (1.10 g, 7.98 mmol). After stirring for 5 minutes 3-chloromethy-5-methyllisoxazole [approx. 90% pure] (0.42 g, 1.00 mmol) is added. The mixture is stirred for 16 hours, filtered, and evaporated in vacuo. The gum is dissolved in ethyl acetate and washed with water, brine and dried over $MgSO_4$. Chromatography eluting with (2-5)% methanol in methylene chloride and evaporation in vacuo affords a solid gum.

Anal. Calcd. for $C_{29}H_{35}N_5O_5$: C, 65.27; H, 6.61; N, 13.12
Found: C, 65.31; H, 6.66; N, 12.81
MS (CI) 534

EXAMPLE 109

Methyl Z-4-[[2-butyl-5-[[1-ethyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate dihydrochloride

To a solution of Methyl Z-4-[[2-Butyl-5-[[1-ethyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate (1.28 g, 3.23 mmol) in DMF (15 mL) is added K_2CO_3 (2.68 g, 19.42 mmol). After stirring for 5 minutes 4-chloromethyl-2-methylthiazole hydrochloride (0.624 g, 3.39 mmol) is added. The mixture is stirred for 3 days. A further amount of 4-chloromethyl-2-methylthiazole hydrochloride (1.248 g, 6.78 mmol) was added as well as an additional amount of K_2CO_3 (1.34 g, 9.7 mmol). The thick mixture was stirred for 2 days. The mixture was filtered and evaporated in vacuo. The gum was dissolved in ethyl acetate and washed with water, brine and dried over $MgSO_4$. Chromatography eluting with (40-100)% ethyl acetate in hexane. The hydrochloride salt was prepared by the addition of ethereal HCl to the product in ethyl acetate. The salt was recrystallized from i-propanol/ether.

Anal. Calcd. for $C_{27}H_{31}N_5O_4S.2HCl$: C, 54.54; H, 5.59; N, 11.78
Found: C, 54.18; H, 5.54; N, 11.45
MS (CI) 522

EXAMPLE 110

Methyl Z-4-[[2-butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene] methyl]-1H-imidazol-1-yl]methyl]-3-chloro benzoate monohydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]-3-chloro benzoate (0.700 g, 1.48 mmol) in DMF (10 mL) is added K_2CO_3 (1.02 g, 7.40 mmol). After stirring for 5 minutes 4-chloromethyl-2-methylthiazole hydrochloride (0.54 g, 2.96 mmol) is added. The mixture is stirred for 16 hours. The mixture was filtered and evaporated in vacuo. The gum was dissolved in ethyl acetate and washed with water, brine and dried over $MgSO_4$. Chromatography eluting with 50% ethyl acetate in methylene chloride. The hydrochloride salt was prepared by the addition of ethereal HCl to the product in ether. The salt was recrystallized from i-propanol/ether.

Anal. Calcd. for $C_{29}H_{34}N_5O_4SCl$ 1.13HCl 1.26 H_2O:
C, 53.95; H, 5.86; N, 10.84
Found: C, 53.75; H, 5.67; N, 10.45
MS (CI) 584

EXAMPLE 111

Methyl Z-4-[[2-Butyl-5-[[3-[(2-methyl-4-thiazoly) methyl]-2,5-dioxo-1-(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl] benzoate dihydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[[2,5-dioxo-1-(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate. (1.00 g, 2.03 mmol) in DMF (15 mL) is added K_2CO_3 (1.92 g, 14.20 mmol). After stirring for 5 minutes 4-chloromethyl-2-methylthiazole hydrochloride (0.56 g, 3.05 mmol) is added. The mixture is stirred for 18 hours. The mixture was

filtered and evaporated in vacuo. The gum was dissolved in ethyl acetate and washed with water and then brine. Dried over $MgSO_4$. The hydrochloride salt was prepared by the addition of ethereal HCl to the product in ether. The salt was recrystallized from i-propanol/ ether.

Anal. Calcd. for $C_{29}H_{33}N_5O_4SF_3$ 2HCl 1.5 H_2O: C, 49.50; H, 5.30; N, 9.95

Found: C, 49.90; H, 5.31; N, 9.89

MS (CI) 604; mp 132-134°C

EXAMPLE 112

Methyl Z-4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate dihydrochloride

To a solution of methyl Z-4-[[2-butyl-5-[1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate. (0.70 g, 1.59 mmol) in DMF (15 mL) is added K_2CO_3 (1.10 g, 7.98 mmol). After stirring for 5 minutes 4,4,4-trifluoromethyl-1-iodobutane (0.38 g, 1.59 mmol) is added and the mixture stirred for 18 hours. The mixture was filtered and evaporated in vacuo. The gum was dissolved in ethyl acetate and washed with water, brine and dried over $MgSO_4$. The hydrochloride salt was prepared by the addition of ethereal HCl to the product in ether. The salt was recrystallized from i-propanol/ ether.

Anal. Calcd. for $C_{28}H_{35}N_4O_4F_3$. 1HCl: C, 57.40; H, 6.20; N, 9.58

Found: C, 57.38; H, 6.11; N, 9.44

MS (CI) 549; mp 161-162°C

EXAMPLE 113

Methyl Z-4-[[2-butyl-5-[[2,5-dioxo-1,3-bis(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of methyl Z-4-[[2-Butyl-5-[1-(4,4,4-trifluorobutyl)-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate. (0.98 g, 2.80 mmol) in DMF (10 mL) is added K_2CO_3 (1.95 g, 14.15 mmol). After stirring for 5 minutes 4,4,4-trifluoromethyl-1-iodobutane (0.74 g, 3.10 mmol) is added and the mixture stirred for 18 hours. The mixture was filtered and evaporated in vacuo. The gum was dissolved in ethyl acetate and washed with water, brine and dried over $MgSO_4$. The hydrochloride salt was prepared by the addition of ethereal HCl to the product in ether. The salt was recrystallized from i-propanol/ ether.

Anal. Calcd. for $C_{28}H_{32}N_4O_4F_6$. 1HCl: C, 52.63; H, 5.21; N, 8.77

Found: C, 52.78; H, 5.18; N, 8.62

MS (CI) 603; mp 141-142°C

EXAMPLE 114

Z-1-Butyl-5-[[2-butyl-3-(triphenylmethyl)-3H-imidazol-5-yl]methylene]-2,4-imidazolidinedione

To a solution of diethyl 1-butyl-2,5-dioxo-4-imidazolidinylphosphonate (2.94 g, 10 mmol) in methylene chloride (10 mL) was added DBU (1.5 mL, 10 mmol) and the mixture stirred for 5 minutes. 2-butyl-1-(triphenylmethyl)-1H-imidazol-4-carboxaldehyde (2.20 g, 5.58 mmol) was added and the yellow solution stirred for 16 hours. The mixture was evaporated in vacuo, redissolved in ethyl acetate, and washed with water and then brine. After drying over $MgSO_4$ the product was isolated by chromatography on silica eluting with chloroform.

MS (CI) 533

EXAMPLE 115

Z-1,3-Dibutyl-5-[[2-butyl-3-(triphenylmethyl)-3H-imidazol-5-yl]methylene]-2,4-imidazolidinedione

To a solution of Z-1-butyl-5-[[2-butyl-3-(triphenylmethyl)-3H-imidazol-5-yl]methylene]-2,4-imidazolidinedione (1.20 g, 2.26 mmol) in DMF (5 mL) was added K_2CO_3 (1.56 g, 11.3 mmol) and then 1-iodobutane (0.344 mL, 3.02 mmol). The mixture was stirred for 16 hours and then diluted with ether and washed with water and brine. After drying over $MgSO_4$ the product was isolated by chromatography on silica eluting with 80 % petroleum ether 20 % ethyl acetate. MS (CI) 588

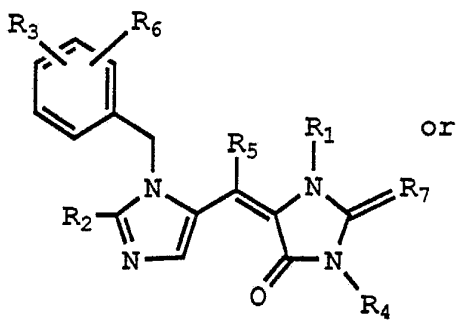
EXAMPLE 116

Methyl Z-4-[[2-butyl-5-[(1,3-dibutyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoate monohydrochloride

To a solution of trifluoromethanesulfonic anhydride (0.094 mL, 0.56 mmol) in methylene chloride (10 mL) at -78°C was added a solution of methyl 4-(hydroxymethyl)benzoate (0.093 g, 0.56 mmol) and N,N-diisopropylethylamine (0.098 mL, 0.56 mmol) in methylene chloride (10 mL) dropwise over 5 minutes. This solution was stirred for 15 minutes and then a solution of Z-1,3-dibutyl-5-[[2-butyl-3-(triphenylmethyl)-3H-imidazol-5-yl]methylene]-2,4-imidazolidinedione (0.330 g, 0.56 mmol) in methylene chloride (5 mL) was added dropwise. The mixture was allowed to slowly warm to room temperature within the cooling bath overnight. Glacial acetic acid (10 mL) and water (2 mL) were added and the mixture boiled for 1 hour on a steam bath. After evaporation in vacuo the residue was dissolved in ethyl acetate, washed with saturated $NaHCO_3$ and brine, and then dried over $MgSO_4$. Chromatography eluting with $CHCl_3$ afforded the required product with spectral characteristics identical with the product formed in Example 33

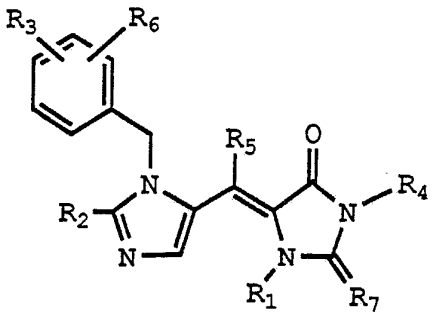
CLAIMS

1. A compound of formula



I

or



Ia

or a pharmaceutically salt thereof wherein:

R_1 is

-hydrogen,

-straight or branched alkyl or alkenyl from 1 to 8 carbon atoms;

-alkyl as above with HO, NO_2, CN, NH_2, CO_2CH_3, $CO_2C_2H_5$, or $CONH_2$ substituents;

-$(CH_2)_n$aryl wherein n is an integer from 0 to 4 and aryl is Ph or Ph substituted with Cl, Br, I, F, CH_3, OCH_3, OH, NO_2, CF_3, CN, $CONH_2$, CO_2H, NH_2, $NHCH_3$, or $N(CH_3)_2$ groups, methylenedioxy;

-$(CH_2)_n$heteroaryl wherein n is an integer from 0 to 3 and heteroaryl is 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 2-oxazolyl, 2-imidazolyl, 4-thiazolyl, 4-oxazolyl, 4-imidazolyl, 5-thiazolyl, 5-oxazolyl, 5-tetrazole, 3-isoxazole, 4-isoxazole, or 5-isoxazole;

-$(CH_2)_n$heteroaryl as above with Me, Et, Pr, Butyl, Cl, Br, I, F, OMe, OH, NO_2, NH_2, NHMe, NMe_2, CO_2R, CO_2H, SO_2NHR, SO_3H, $CONR_2$, CN, CF_3 substituents.

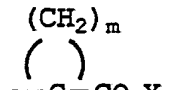
$-(CH_2)_m X(CH_2)_n H$ wherein X is O, S, or N and m and n are each independently integral from 1 to 6 carbon atoms;

$-(CH_2)_n$cycloalkyl wherein n is an integer from 0 to 3 and cycloalkyl is a saturated or unsaturated ring of 3 to 7 carbon atoms;

R_2 is

cycloalkyl of from 3 to 6 carbon atoms;
alkyl of from 1 to 6 carbon atoms,
alkenyl of from 2 to 6 carbon atoms, OC_1-C_5 alkyl, and SC_1-C_5 alkyl;

R_3 is

$(CH_2)_n CO_2Y$ or  wherein Y is hydrogen or lower alkyl, n is an integer of from 0 to 3, and m is an integer of from 2 to 7;

wherein R = C_1-C_8 alkyl,

CH_2SO_2NHCOR,

$NHSO_2NHCOR$,

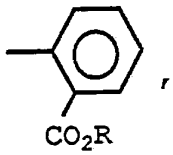
$NHCONHSO_2R$,

$PO(OR)_2$,

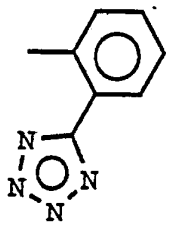
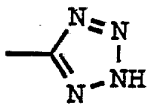
$CONHSO_2R$,

SO_3H,

$B(OH)_2$,

$-SO_2NHCOR$, ,

$-SO_2NHCONHR$,

$-NHSO_2CF_3$, , or 

$R_4 = R_1$

R_5 is hydrogen or alkyl of from 1 to 4 carbon atoms;

R_6 is hydrogen, chlorine, bromine, fluorine, methyl, trifluoromethyl, or methoxy; and

R_7 is oxygen or sulfur.

2. A compound according to Claim 1 wherein:

R_1 is

hydrogen,
methyl,
ethyl,
n-propyl,
i-propyl,
n-butyl,
i-butyl,
sec-butyl,
t-butyl,
n-amyl,
i-amyl,
n-hexyl,
aryl,
CH_2-aryl,
CH_2-heteroaryl, with H, Me, Cl, OMe, NH_2, NMe_2, substituents, or
CH_2-cycloalkyl wherein aryl, heteroaryl, and cycloalkyl are as defined in Claim 1;

R_2 is

propyl,
i-propyl,
n-butyl,
n-pentyl, or
cyclopropylmethyl,

R_3 is

$(CH_2)_nCO_2Y$ or $-C(-(CH_2)_m-)-CO_2Y$ wherein Y is hydrogen or lower alkyl, n is 0 or 1, m is 2 to 5;

R_4 is
hydrogen,
alkyl or branched alkyl of from 1 to 8 carbon atoms,
$-(CH_2)_m X(CH_2)_nH$ m = 1-6, n = 1-6, and X = O, N, S;
R_5 is hydrogen;
R_6 is
hydrogen,
chlorine,
fluorine,
methyl,
trifluoromethyl, or
methoxy; and
R_7 is oxygen.

3. A compound according to Claim 1 wherein:
R_1 is n-butyl, n-pentyl, n-propyl, benzyl, 2-thienylmethyl, 3-thienylmethyl, cyclopropylmethyl, cyclohexylmethyl, cyclopentylmethyl, 2-methyl-4-thiazolylmethyl, 2-amino-4-thiazolylmethyl, or 4-thiazolylmethyl, 2-amino-4-thienylmethyl, 2-methyl-4-thienylmethyl;
R_2 is butyl and propyl;
R_3 is
$(CH_2)_nCO_2Y$ wherein n is 0, Y is hydrogen or methyl;
R_4 is hydrogen or alkyl of 3 to 6 carbons;
R_5 and R_6 are each hydrogen; and
R_7 is oxygen.

4. A compound according to Claim 1 selected from:
(E)-4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[2,5-dioxo-3-(3-methylbutyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[2,5-dioxo-3-(3-methylbutyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[(2,5-dioxo-3-methyl-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[(2,5-dioxo-3-methyl-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[(2,5-dioxo-3-(phenylmethyl)-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[(2,5-dioxo-3-(phenylmethyl)-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[(2,5-dioxo-3-phenyl-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[(2,5-dioxo-3-phenyl-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[2,5-dioxo-3-((2-thienyl)methyl)-4-imidazolidinylidene]-methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[2,5-dioxo-3-((2-thienyl)methyl)-4-imidazolidinylidene]methyl]-1H-

imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[2,5-dioxo-3-(4-hydroxybutyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[2,5-dioxo-3-(4-hydroxybutyl)-4-imidazolidinylidene]methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Propyl-5-[(3-butyl-1-methyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Propyl-5-[(3-butyl-1-methyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazole-1-yl]methyl]benzoic acid and its methyl ester.

(Z)-4-[[2-Butyl-5-[[3-[(4-chlorophenyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[3-[(4-chlorophenyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-3-(cyclohexylmethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-3-(cyclohexylmethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-pentyl-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-pentyl-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[(1,3-dibutyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[(1,3-dibutyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[2,5-dioxo-1,3-bis(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[2,5-dioxo-1,3-bis(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-(3-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-(3-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-3-[(5-methyl-2-thienyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-3-[(5-methyl-2-thienyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-(4-thiazolylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-(4-thiazolylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[3-[(2-methyl-4-thiazoly)methyl]-2,5-dioxo-1-(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[3-[(2-methyl-4-thiazoly)methyl]-2,5-dioxo-1-(4,4,4-trifluorobutyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-3-[(2-amino-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-3-[(2-amino-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-(2-pyridinylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-(2-pyridinylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-(1H-tetrazol-5-ylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-(1H-tetrazol-5-ylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-3-(1H-imidazol-5-ylmethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-3-(1H-imidazol-5-ylmethyl)-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-3-[(5-methyl-3-isoxazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-3-[(5-methyl-3-isoxazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-hexyl-2,5-dioxo-3-(3-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-hexyl-2,5-dioxo-3-(3-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[1-hexyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[1-hexyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-(cyclopropylmethyl)-2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-(cyclopropylmethyl)-2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-(methoxymethyl)-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-(methoxymethyl)-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-(hydroxymethyl)-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-(hydroxymethyl)-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]-3-chloro benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]-3-chloro benzoic acid and its methyl ester,

(Z)-N-[4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]phenyl]-1,1,1-trifluoromethanesulfonamide,

(E)-N-[4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]phenyl]-1,1,1-trifluoromethanesulfonamide,

(Z)-1-Butyl-5-[[2-butyl-3-[[4-(1H-tetrazol-5-yl)phenyl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione,

(E)-1-Butyl-5-[[2-butyl-3-[[4-(1H-tetrazol-5-yl)phenyl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione,

(Z)-4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl]-3-chlorobenzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-

yl]methyl]-3-chlorobenzoic acid and its methyl ester,

(Z)-1-Butyl-5-[[2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione,

(E)-1-Butyl-5-[[2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]-2,4-imidazolidinedione,

1-Butyl-5-[[2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methyl]-2,4-imidazolidinedione,

(Z)-5-[[2-Butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]1-methyl-2,4-imidazolidinedione,

(E)-5-[[2-Butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3H-imidazol-4-yl]methylene]1-methyl-2,4-imidazolidinedione,

(Z)-4'-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid and its methyl ester,

(E)-4'-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1H-imidazol-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid and its methyl ester,

(Z)-1-[4-[[2-Butyl-5-[[2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]phenyl]cyclopentanecarboxylic acid and its methyl ester,

(E)-1-[4-[[2-Butyl-5-[[2,5-dioxo-3-(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]phenyl]cyclopentanecarboxylic acid and its methyl ester,

(Z)-1-[4-[[2-Butyl-5-[[1-butyl-[3-(2-methyl-4-thiazoly)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-

yl]methyl]phenyl]cyclopentanecarboxylic acid and its methyl ester,

(E)-1-[4-[[2-Butyl-5-[[1-butyl-[3-(2-methyl-4-thiazoly)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]phenyl]cyclopentanecarboxylic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[2,5-dioxo-1,3-bis(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(E)-4-[[2-Butyl-5-[[2,5-dioxo-1,3-bis(2-thienylmethyl)-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester,

(Z)-4-[[2-Butyl-5-[[3-butyl-1-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester, and

(E)-4-[[2-Butyl-5-[[3-butyl-1-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1H-imidazol-1-yl]methyl]benzoic acid and its methyl ester.

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

6. 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.

7. 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.

8. 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.

9. 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.

10. 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.

11. 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.

12. A method of preventing surgically induced vascular smooth muscle proliferation.

13. 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.

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

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

16. A method of preventing restenosis after angioplasty or bypass surgery comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

17. A method of inhibiting progression or inducing regression of atheroma comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

18. A method of treating diabetic retinopathy in mammals comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

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

20. A method of treating left ventricular hypertrophy regression comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

21. A method of prevention of infarction comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

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

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/10723

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 C07D233/96; C07D409/14; C07D417/14; C07D401/14
C07D403/14; C07D413/14; A61K31/415; A61K31/425

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]
Y	EP,A,0 403 159 (SMITHKLINE BEECHAM) 19 December 1990 cited in the application *see whole document, particularly definitions of R5 and R6*	1-5,7,9, 11
Y	WO,A,9 100 277 (E.I.DU PONT DE NEMOURS AND COMPANY) 10 January 1991 cited in the application *see whole document, especially definitions of R7 and R8 and examples 182-186 and examples 22?-241*	1-5,7,9, 11
Y	EP,A,0 425 211 (SMITHKLINE BEECHAM CORPORATION) 2 May 1991 *see definitions of R5 and R6*	1-5,7,9, 11

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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
10 MARCH 1993	23. 03. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCRUTON-EVANS I.

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	EP,A,0 401 030 (MERCK AND CO INC) 5 December 1990 cited in the application	1-5,7,9, 11
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