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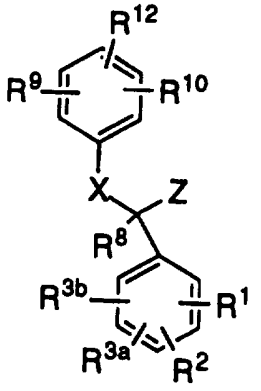
(54) Title: PHENOXYPHENYLACETIC ACID DERIVATIVES

(57) Abstract

Phenoxyphenylacetic acids and derivatives of general structural formula (I) have endothelin antagonist activity and are useful in treating cardiovascular disorders, such as hypertension, postischemic renal failure, vasospasm, cerebral and cardiac ischemia, myocardial infarction, endotoxic shock, benign prostatic hyperplasia, inflammatory diseases including Raynaud's disease and asthma.



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TITLE OF THE INVENTION

PHENOXYPHENYLACETIC ACID DERIVATIVES

RELATED APPLICATIONS

The present application is a continuation in part application of Case 18893IB, U.S. Serial Number 08/287,374 filed August 8, 1994, which is a continuation in part application of U.S. Serial Number 08/197,467 filed February 24, 1994, which is a continuation in part application of U.S. Serial Number 08/034,455 filed on March 19, 1993(abandoned).

SUMMARY OF THE INVENTION

This invention is concerned with non-peptidic endothelin receptor antagonists represented by the compound of Formula I, pharmaceutical compositions containing these compounds, as well as combination therapies which include a compound of the present invention. The compounds of the present invention are therapeutic agents particularly useful for the treatment of asthma, hypertension, pulmonary hypertension, arteriosclerosis, congestive heart failure, renal failure, particularly post-ischemic renal failure, cyclosporin nephrotoxicity, vasospasm, vascular restenosis, cerebral and cardiac ischemia and other ischemic states, myocardial infarction, Raynaud's disease, benign prostatic hyperplasia, inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, as well as other inflammatory diseases, or endotoxic shock caused by or associated with endothelin.

This invention further constitutes a method for antagonizing endothelin receptors in a mammal, including humans, which comprises administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

BACKGROUND OF THE INVENTION

Endothelin is a 21-amino acid peptide produced by endothelial cells. The peptide is secreted not only by endothelial cells but also by tracheal epithelial cells or from kidney cells. Endothelin (ET-1) has a potent vasoconstrictor effect. The vasoconstricting effect is caused by the binding of endothelin to its receptor on the vascular smooth muscle cells.[1-3]

Endothelin-1 (ET-1) is one of three recently identified potent vasoconstricting peptides which also includes endothelin-2 (ET-2) and endothelin-3 (ET-3) whose sequences differ from ET-1 by two and six amino acids, respectively.[4]

Increased levels of endothelin are found in the blood of patients with essential hypertension, acute myocardial infarction, pulmonary hypertension, Raynaud's disease or atherosclerosis or in the washing fluids of the respiratory tract of patients with asthma compared to normal levels.[5-8]

An experimental model of cerebral vasospasm and a second model of acute renal failure have led to the conclusion that endothelin is one of the mediators causing cerebral vasospasm following a subarachnoid hemorrhage, and renal failure.[9-10]

Endothelin was also found to control the release of many physiological substances such as renin, atrial natriuretic peptide, endothelium-derived relaxing factor (EDRF), thromboxane A_2,[14], prostacyclin, norepinephrine, angiotensin II and substance P.[11-16] Further, endothelin causes contraction of the smooth muscle of the gastrointestinal tract and the uterine smooth muscle.[17-19] Endothelin has also been shown to promote the growth of rat vascular smooth muscle cells which would suggest a possible relevance to arterial hypertrophy.[20]

Endothelin receptors are present in high concentration in the peripheral tissues and also in the central nervous system, and cerebral administration of endothelin has been shown to induce behavioral changes in animals, suggesting that endothelin may play an important role in controlling neural functions.[21]

Endotoxin has been shown to promote the release of endothelin. This finding has suggested that endothelin is an important mediator for endotoxin-induced diseases.[22-23]

A study has shown that cyclosporin added to a renal cell culture, increased endothelin secretion.[24] Another study has shown that administration of cyclosporin to rats, led to a decrease in the glomerular filtration rate and an increase in the blood pressure, in association with a remarkable increase in the circulating endothelin level. This cyclosporin-induced renal failure can be suppressed by the administration of anti-endothelin antibody.[25] These studies suggest that endothelin is significantly involved in the pathogenesis of cyclosporin-induced renal disease.

A recent study in patients with congestive heart failure demonstrated a good correlation between the elevated levels of endothelin in the plasma and the severity of the disease.[26]

Endothelin is an endogenous substance which directly or indirectly (through the controlled release of various other endogenous substances) induces sustained contraction of vascular or non-vascular smooth muscles. Its excess production or excess secretion is believed to be one of the factors responsible for hypertension, pulmonary hypertension, Raynaud's disease, bronchial asthma, acute renal failure, myocardial infarction, angina pectoris, arteriosclerosis, cerebral vasospasm and cerebral infarction. See A. M. Doherty, Endothelin: A New Challenge, J. Med. Chem., 35, 1493-1508 (1992).

Substances which specifically inhibit the binding of endothelin to its receptor are believed to block the physiological effects of endothelin and are useful in treating patients with endothelin related disorders.

The novel compounds of the present invention are useful as a non-peptidic endothelin antagonists, and have not been disclosed in any issued patents or published patent applications. Among the published patent applications disclosing linear and cyclic peptidic compounds as endothelin antagonists are the following: Fujisawa in European Patent Application EP-457,195 and Patent Cooperation Treaty (PCT)

International Application No. WO 93/10144, Banyu in EP-436,189 and 460,679, Immunopharmaceutics Inc. in WO 93/225580, Warner Lambert Co. WO 92/20706 and Takeda Chemical Ind. in EP-528,312, EP-543,425, EP-547,317 and WO 91/13089 .

Fujisawa has also disclosed two nonpeptidic endothelin antagonist compounds: anthraquinone derivatives produced by a fermentation process using Streptomyces sp. No. 89009 in EP-405,421 and U.S. Patent No. 5,187,195; and a 4-phenoxyphenol derivative produced by a fermentation process using Penicillium citreonigrum F-12880 in a UK Patent Application GB 2259450. Shionogi and Co. has also disclosed nonpeptidic endothelin antagonist triterpene compounds which were produced by a fermentation process using Myrica cerifera in WO 92/12991.

Among the non-peptidic endothelin antagonist compounds which are known in the patent literature are: 1) a series of substituted (1,4-quinolinoxy)methylbiphenylcarboxylic acids disclosed by Roussel-Uclaf in EP-498,723; 2) a series of of N-(4-pyrimidinyl)benzene-sulfonamides with different substitution patterns from Hoffmann-La Roche published in EP-510,526, EP-526,708 and EP-601,386; 3) a series of naphthalenesulfonamides and benzenesulfonamides disclosed by E.R. Squibb & Sons in EP-558,258 and EP-569,193, respectively; 4) a series of compounds represented by 3-(3-indolylmethyl)-1,4-diaza-2,5-dioxobicyclo[4.3.0]nonane-9-carboxylic acid from ImmunoPharmaceutics Inc. in WO 93/23404; 5) a series of fused [1,2,4]thiadiazoles substituted with an iminosulfonyl substituent from Takeda Chemical Ind. has been disclosed in EP-562,599; and 6) a series of indane and indene derivatives from SmithKline Beecham Corp. disclosed in WO 93/08779; and a series of related phenylalkyl derivatives from SmithKline Beecham disclosed in WO 94/02474.

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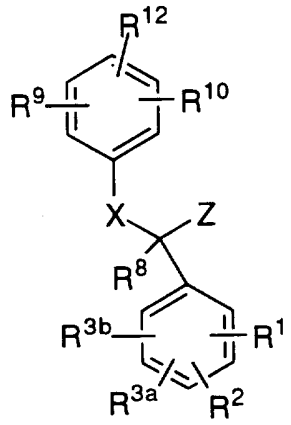
DETAILED DESCRIPTION OF THE INVENTION.

This invention is concerned with novel compounds of structural formula I:



I

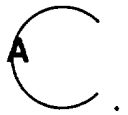
or a pharmaceutically acceptable salt thereof, wherein:

R^1, R^2, R^{3a} and R^{3b} are independently:

(a) H,
(b) F, Cl, Br, or I,
(c) $-NO_2$,
(d) $-NH_2$,
(e) $-NH(C_1-C_4)$-alkyl,
(f) $-N[(C_1-C_4)\text{-alkyl}]_2$,
(g) $-SO_2NHR^7$,
(h) $-CF_3$,
(i) (C_1-C_6)-alkyl,
(j) $-OR^7$,
(k) $-S(O)_n-(C_1-C_4)$-alkyl,
(l) $-NHCO-(C_1-C_4)$-alkyl,
(m) $-NHCO-O(C_1-C_4)$-alkyl,
(n) $-CH_2O-(C_1-C_4)$-alkyl,

(o) $-O-(CH_2)_m-OR^7$,
(p) $-CONR^7R^{11}$,
(q) $-COOR^7$, or
(r) -phenyl;

R^1 and R^2 on adjacent carbon atoms can be joined together to form a ring structure:



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A represents:

a) $-Y-C(R^4)=C(R^5)-$,
b) $-Y-C(R^4)=N-$,
c) $-Y-N=C(R^4)-$,
d) $-Y-[C(R^6)(R^6)]_s-Y-$,
e) $-Y-C(R^6)(R^6)-C(R^6)(R^6)-$,
f) $-C(R^4)=C(R^5)-Y-$,
g) $-N=C(R^4)-Y-$,
h) $-C(R^6)(R^6)-C(R^6)(R^6)-Y-$, or
i) $-C(R^4)=C(R^5)-C(R^4)=C(R^5)-$;

n is 0, 1 or 2;

m is 2, 3 or 4;

s is 1 or 2;

Y is -O-, $-S(O)_n-$ and NR^7;

R^4 and R^5 are independently:

(a) H,

(b) (C_1-C_6)-alkyl or (C_2-C_6)-alkenyl each of which is unsubstituted or substituted with one or two substituents selected from the group consisting of:

i) -OH,

ii) -O-(C_1-C_4)-alkyl,

iii) -S(O)$_n$-(C_1-C_4)-alkyl,

iv) -NR^7-(C_1-C_4)-alkyl,

v) -NHR^7,

vi) -$COOR^7$,

vii) -$CONHR^7$,

viii) -$OCOR^{11}$, or

ix) -$CONR^7R^{11}$,

(c) (C_3-C_7)-cycloalkyl,

(d) F, Cl, Br, I,

(e) CF_3,

(f) -$COOR^7$,

(g) -$CONR^7R^{11}$,

(h) -NR^7R^{11},

(i) -$NR^7CONR^7R^{11}$,

(j) -NR^7COOR^{11},

(k) -$SO_2NR^7R^{11}$,

(l) -O-(C_1-C_4)-alkyl,

(m) -S(O)$_n$-(C_1-C_4)-alkyl, or

(n) -$NHSO_2R^{11}$;

R^6 is:

(a) H,

(b) (C_1-C_4)-alkyl unsubstituted or substituted with one of the following substituents:

i) -OH,

ii) -NR^7R^{11},

iii) -$COOR^7$,

iv) $-CONHR^7$, or
v) $-CONR^7R^{11}$, or
(c) Cl, or F;

R^7 is:
(a) H,
(b) (C_1-C_6)-alkyl,
(c) phenyl,
(d) (C_1-C_6)-alkylphenyl, or
(e) (C_3-C_7)-cycloalkyl;

R^8 is:
(a) H,
(b) (C_1-C_6)-alkyl, unsubstituted or substituted with a substituent selected from the group consisting of:
(i) -phenyl,
(ii) $-(C_3-C_7)$-cycloalkyl,
(iii) $-NR^7R^{11}$,
(iv) -morpholin-4-yl,
(v) -OH,
(vi) $-CO_2R^7$, or
(vii) $-CON(R^7)_2$,
(c) phenyl, unsubstituted or substituted with a substituent selected from the group consisting of:
i) (C_1-C_4)-alkyl
ii) $-O-(C_1-C_4)$-alkyl
iii) $-CONR^7R^{11}$,
iv) F, Cl, Br or I, or
v) $-COOR^7$;

R^9 and R^{10} are independently:
(a) H,
(b) (C_1-C_6)-alkyl, unsubstituted or substituted with (C_3-C_7)-cycloalkyl or $-CO_2R^7$,

(c) (C_2-C_6)-alkenyl,
(d) (C_2-C_6)-alkynyl,
(e) Cl, Br, F, I,
(f) (C_1-C_6)-alkoxy,
(g) perfluoro-(C_1-C_6)-alkyl,
(h) (C_3-C_7)-cycloalkyl, unsubstituted or substituted with (C_1-C_6)-alkyl,
(i) phenyl,
(j) (C_1-C_6)-alkyl-$S(O)_n$-$(CH_2)_n$-,
(k) hydroxy-(C_1-C_6)-alkyl,
(l) $-CF_3$,
(m) $-CO_2R^7$,
(n) -OH,
(o) $-NR^7R^{11}$,
(p) $-[(C_1-C_6)\text{-alkyl}]NR^7R^{11}$,
(q) $-NO_2$,
(r) $-(CH_2)_n-SO_2-N(R^7)_2$,
(s) $-NR^7CO-(C_1-C_4)$-alkyl, or
(t) $-CON(R^7)_2$;

R^9 and R^{10} on adjacent carbons can join together to form a fused phenyl ring, unsubstituted or substituted with a substituent selected from the group consisting of: (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_3-C_7)-cycloalkyl and (C_1-C_6)-alkyl-(C_3-C_7)-cycloalkyl,

R^{11} is

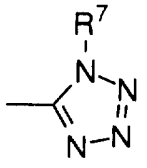
(a) (C_1-C_6)-alkyl, unsubstituted or substituted with a substituent selected from the group consisting of:
i) $-OR^7$,
ii) $-N[R^7]2$,
iii) $-NH_2$,
iv) $-COOR^7$,

v) -N[CH_2CH_2]$_2$Q,
vi) -CF_3, or
vii) -CON(R^7)$_2$;

(b) aryl, wherein aryl is defined as phenyl or naphthyl which is unsubstituted or substituted with one or two substituents selected from the group consisting of:
i) (C_1-C_4)-alkyl,
ii) -O-(C_1-C_4)-alkyl,
iii) -CO[NR^7]$_2$,
iv) F, Cl, Br or I,
v) -$COOR^7$,
vi) -NH_2,
vii) -NH[(C_1-C_4)-alkyl],
viii) -N[(C_1-C_4)-alkyl]$_2$, or
ix) -CON[CH_2CH_2]$_2$Q;

(c) -(C_1-C_4)-alkylaryl, wherein aryl is as defined above,

(d) (C_3-C_7)-cycloalkyl,

(e)  , or

(f) CF_3;

R^7 and R^{11} on the same nitrogen atom they can join together to form a ring selected from the group consisting of: morpholinyl, piperazinyl, or pyrrolyl, or

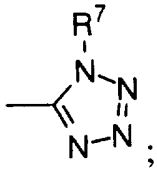
Q is O, S or -NR^7;

R^{12} is

(a) H

(b) $(C_1\text{-}C_6)$-alkyl, unsubstituted or substituted with one or two substituents selected from the group consisting of:

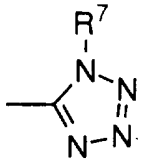
i) -OH,
ii) -O-$(C_1\text{-}C_4)$-alkyl,
iii) -O-$(C_1\text{-}C_4)$-cycloalkyl,
iv) -$S(O)_n$-$(C_1\text{-}C_4)$-alkyl,
v) -NR^7R^{11},
vi) -$COOR^7$,
vii) -$CONHR^7$,
viii) -$OCOR^{11}$,
ix) -$CONR^7R^{11}$,
x) -$NR^7CONR^7R^{11}$,
xi) -NR^7COOR^{11},
xii) -$C(R^6)(OH)$-$C(R^6)(R^7)(OH)$,
xiii) -$SO_2NR^7R^{11}$, or

xiv) 

;

(c) $(C_3\text{-}C_7)$-cycloalkyl,
(d) -OR^7,
(e) -$COOR^7$,
(f) -$CONH_2$,
(g) -$CONR^{16}OH$,
(h) -$CONR^7R^{11}$,
(i) -$CONR^7CO_2R^7$,
(j) -NH_2,
(k) -NR^7R^{11},
(l) -$NR^7CONR^7R^{11}$,
(m) -NR^7COOR^{11},
(n) -$C(R^6)(OH)$-$C(R^6)(R^7)(OH)$,
(o) -$SO_2NR^7R^{11}$,
(p) -$S(O)_2NR^7COR^{11}$,

(q) $-S(O)_2NR^7CO_2R^{11}$,
(r) $-S(O)_2NR^7CONR^7R^{11}$,
(s) $-NHSO_2R^{11}$,
(t) $-NR^7SO_2NR^7R^{11}$,
(u) $-CONHSO_2R^{11}$,
(v) -CO-amino acid, wherein amino acid is defined as an L-or D- amino acid selected from the group consisting of Ala, Ile, Phe, Asp, Pro and Val and which can be further substituted as a (C_1-C_6)-alkyl ester or an amide, or

(w)  ;

X is

(a) -O-,
(b) $-S(O)_n-$,
(c) $-NR^7-$,
(d) $-CH_2O-$,
(e) $-CH_2S(O)_n-$,
(f) $-CH_2NR^7-$,
(g) $-OCH_2-$,
(h) $-N(R^7)CH_2-$,
(i) $-S(O)_nCH_2-$, or
(j) -single bond;

Z is:

(a) $-CO_2H$,
(b) $-CO_2R^{13}$,
(c) -CONH-(tetrazol-5-yl),
(d) $-CONHSO_2OR^{11}$,
(e) $-CONHSO_2NR^7R^{11}$,

(f) -$CONHSO_2$-aryl, wherein aryl is defined as phenyl or naphthyl which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of:

i) (C_1-C4)-alkyl,
ii) -O-(C_1-C4)-alkyl,
iii) -$CONR^7R^{11}$,
iv) F, Cl, Br or I,
v) -$COOR^7$,
vi) -NH_2,
vii) -NH[(C_1-C4)-alkyl],
viii) -N[(C_1-C4)-alkyl]2,
ix) -phenyl,
x) -OH,
xi) -OCH_2CH_2OH,
xii) -CF_3;

(g) -$CONHSO_2$-(C_1-C_8)-alkyl, wherein the alkyl group is unsubstituted or substituted as defined in R^4(b),

(h) -$CONHSO_2$-(C_1-C4)-perfluoroalkyl,

(i) -tetrazol-5-yl,

(j) -$CONHSO_2$-heteroaryl, wherein heteroaryl is defined as carbazolyl, furyl, thienyl, pyrrolyl, isothiazolyl, imidazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrazolyl, pyrazinyl, pyridyl, pyrimidyl, purinyl or quinolinyl, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of:

i) (C_1-C4)-alkyl,
ii) -O-(C_1-C4)-alkyl,
iii) -$CONR^7R^{11}$,
iv) F, Cl, Br or I,
v) -$COOR^7$,
vi) -$NR^7CONR^7R^{11}$, and

vii) $-NR^7COOR^{11}$;

(k) $-SO_2NHCO$-aryl, wherein aryl is defined in Z(d) above,

(l) $-SO_2NHCO-(C_1-C_8)$-alkyl, wherein the alkyl group is unsubstituted or substituted as defined in R^4(b),

(m) $-SO_2NHCO-(C_1-C_4)$-perfluoroalkyl,

(n) $-SO_2NHCO$-heteroaryl, wherein heteroaryl is as defined in Z(g) above,

(o) $-SO_2NHCON(R^{11})_2$ wherein the R^{11} groups are the same or different,

(p) $-PO(OR^7)_2$, wherein the R^7groups are the same or different, or

(q) $-PO(R^{11})OR^7$;

R^{13} is:

(a) (C_1-C_4)-alkyl,

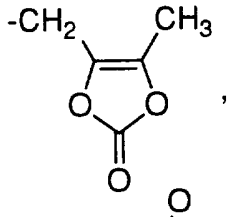
(b) $CHR^{14}-O-COR^{15}$,

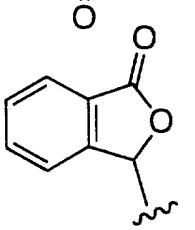
(c) $CH_2CH_2-N[(C_1-C_2)\text{-alkyl}]_2$,

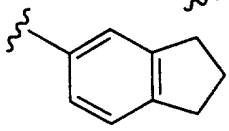
(d) $CH_2CH_2-N[CH_2CH_2]_2O$,

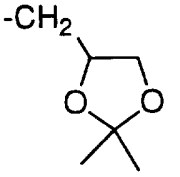
(e) $(CH_2CH_2O)_y-O-[(C_1-C_4)\text{-alkyl}]$, wherein y is 1 or 2,

(f) phenyl, naphthyl, CH_2-phenyl or CH_2-naphthyl, where phenyl or naphthyl is substituted or unsubstituted with $CO_2-(C_1-C_4)$-alkyl,

(g)  ,

(h)  ,

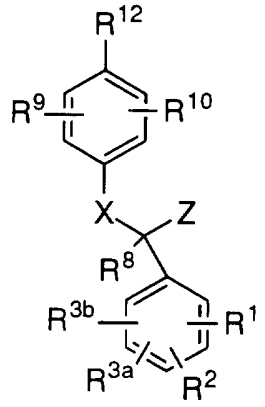
(i)  , or

(j)  ; and

R^{14} and R^{15} independently are $(C_1\text{-}C_6)$-alkyl or phenyl; and

R^{16} is H, $(C_1\text{-}C_6)$-alkyl or $(C_1\text{-}C_6)$-alkylphenyl.

An embodiment of the invention is the compound of structural formula II:



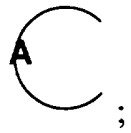
II

or a pharmaceutically acceptable salt thereof, wherein:

R^1, R^2, R^{3a} and R^{3b} are independently:

(a) H,
(b) F, Cl, Br, or I,
(c) $-NO_2$,
(d) $-NH_2$,
(e) $-NH(C_1-C_4)$-alkyl,
(f) $-N[(C_1-C_4)\text{-alkyl}]_2$,
(g) $-SO_2NHR^7$,
(h) $-CF_3$,
(i) (C_1-C_6)-alkyl,
(j) $-OR^7$,
(k) $-S(O)_n-(C_1-C_4)$-alkyl,
(l) $-NHCO-(C_1-C_4)$-alkyl,
(m) $-NHCO-O(C_1-C_4)$-alkyl,
(n) $-CH_2O-(C_1-C_4)$-alkyl,
(o) $-O-(CH_2)_m-OR^7$,
(p) $-CONR^7R^{11}$, or
(q) $-COOR^7$;

R^1 and R^2 on adjacent carbon atoms can be joined together to form a ring structure:



;

A represents:

a) $-Y-C(R^4)=C(R^5)-$,

b) $-Y-C(R^4)=N-$,

c) $-Y-N=C(R^4)-$,

d) $-Y-[C(R^6)(R^6)]_s-Y-$,

e) $-Y-C(R^6)(R^6)-C(R^6)(R^6)-$,

f) $-C(R^4)=C(R^5)-Y-$,

g) $-N=C(R^4)-Y-$,

h) $-C(R^6)(R^6)-C(R^6)(R^6)-Y-$, or

i) $-C(R^4)=C(R^5)-C(R^4)=C(R^5)-$;

m is 2, 3 or 4,

n is 0, 1 or 2,

s is 1 or 2,

Y is -O-, $-S(O)_n-$ and NR^7;

R^4 and R^5 are independently:

(a) H,

(b) (C_1-C_6)-alkyl or (C_2-C_6)-alkenyl each of which is unsubstituted or substituted with one or two substituents selected from the group consisting of:
  i) -OH,
  ii) -O-(C_1-C_4)-alkyl,
  iii) -S(O)$_n$-(C_1-C_4)-alkyl,
  iv) -NR^7-(C_1-C_4)-alkyl,
  v) -NHR^7,
  vi) -COOR^7,
  vii) -CONHR^7,
  viii) -OCOR^{11}, or
  ix) -CONR^{7}R^{11},
(c) (C_3-C_7)-cycloalkyl,
(d) F, Cl, Br, I,
(e) CF_3,
(f) -COOR^7,
(g) -CONR^{7}R^{11},
(h) -NR^{7}R^{11},
(i) -NR^{7}CONR^{7}R^{11},
(j) -NR^{7}COOR^{11},
(k) -SO$_2$NR^{7}R^{11},
(l) -O-(C_1-C_4)-alkyl,
(m) -S(O)$_n$-(C_1-C_4)-alkyl, or
(n) -NHSO$_2$R^{11};

R^6 is:

(a) H,
(b) (C_1-C_4)-alkyl unsubstituted or substituted with one or two substituents selected from the group consisting of:
  i) -OH,
  ii) -NR^{7}R^{11},
  iii) -COOR^7,
  iv) -CONHR^7, or

v) $-CONR^7R^{11}$, or

(c) Cl, or F;

R^7 is:

(a) H,
(b) (C_1-C_6)-alkyl,
(c) phenyl,
(d) (C_1-C_6)-alkylphenyl, or
(e) (C_3-C_7)-cycloalkyl;

R^8 is:

(a) H,
(b) (C_1-C_6)-alkyl, unsubstituted or substituted with one or two substituents selected from the group consisting of:
(i) -phenyl,
(ii) $-(C_3-C_7)$-cycloalkyl,
(iii) $-NR^7R^{11}$,
(iv) -morpholin-4-yl,
(v) -OH,
(vi) $-CO_2R^7$, or
(vii) $-CON(R^7)_2$, or
(c) phenyl;

R^9 and R^{10} are independently:

(a) H,
(b) (C_1-C_6)-alkyl, unsubstituted or substituted with (C_3-C_7)-cycloalkyl or $-CO_2R^7$,
(c) (C_2-C_6)-alkenyl,
(d) (C_2-C_6)-alkynyl,
(e) Cl, Br, F, I,
(f) (C_1-C_6)-alkoxy,
(g) perfluoro-(C_1-C_6)-alkyl,

(h) (C_3-C_7)-cycloalkyl, unsubstituted or substituted with (C_1-C_6)-alkyl,
(i) phenyl,
(j) (C_1-C_6)-alkyl-$S(O)_n$-$(CH_2)_n$-,
(k) hydroxy-(C_1-C_6)-alkyl,
(l) $-CF_3$,
(m) $-CO_2R^7$,
(n) -OH,
(o) $-NR^7R^{11}$,
(p) $-[(C_1-C_6)\text{-alkyl}]NR^7R^{11}$,
(q) $-NO_2$,
(r) $-(CH_2)_n-SO_2-N(R^7)_2$,
(s) $-NR^7CO-(C_1-C_4)$-alkyl, or
(t) $-CON(R^7)_2$;

R^9 and R^{10} on adjacent carbons can join together to form a fused phenyl ring, unsubstituted or substituted with a substituent selected from the group consisting of: (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_3-C_7)-cycloalkyl and (C_1-C_6)-alkyl-(C_3-C_7)-cycloalkyl,

R^{11} is

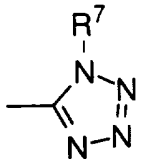
(a) (C_1-C_6)-alkyl, unsubstituted or substituted with a substituent selected from the group consisting of:
i) $-OR^7$,
ii) $-N[R^7]2$,
iii) $-NH_2$,
iv) $-COOR^7$,
v) $-N[CH_2CH_2]_2Q$,
vi) $-CF_3$, or
vii) $-CON(R^7)_2$;
(b) aryl, wherein aryl is defined as phenyl or naphthyl which is unsubstituted or substituted with

one or two substituents selected from the group consisting of:

i) $(C_1\text{-}C_4)$-alkyl,
ii) -O-$(C_1\text{-}C_4)$-alkyl,
iii) -CO[NR^7]2,
iv) F, Cl, Br or I,
v) -$COOR^7$,
vi) -NH_2,
vii) -NH[$(C_1\text{-}C_4)$-alkyl],
viii) -N[$(C_1\text{-}C_4)$-alkyl]2, or
ix) -CON[CH_2CH_2]2Q;

(c) -$(C_1\text{-}C_4)$-alkylaryl, wherein aryl is as defined above,

(d) $(C_3\text{-}C_7)$-cycloalkyl,

(e)  , or

(f) CF_3;

R^7 and R^{11} on the same nitrogen atom they can join together to form a ring selected from the group consisting of: morpholinyl, piperazinyl, or pyrrolyl, or

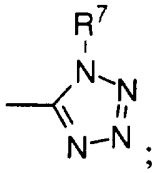
Q is O, S or -NR^7;

R^{12} is

(a) H

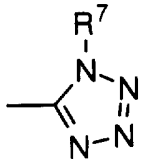
(b) $(C_1\text{-}C_6)$-alkyl, unsubstituted or substituted with one or two substituents selected from the group consisting of:

i) -OH,
ii) -O-$(C_1\text{-}C_4)$-alkyl,
iii) -O-$(C_1\text{-}C_4)$-cycloalkyl,
iv) -S(O)n-$(C_1\text{-}C_4)$-alkyl,

v) $-NR^7R^{11}$,
vi) $-COOR^7$,
vii) $-CONHR^7$,
viii) $-OCOR^{11}$,
ix) $-CONR^7R^{11}$,
x) $-NR^7CONR^7R^{11}$,
xi) $-NR^7COOR^{11}$,
xii) $-C(R^6)(OH)-C(R^6)(R^7)(OH)$,
xiii) $-SO_2NR^7R^{11}$, or
xiv)  ;

(c) (C_3-C_7)-cycloalkyl,
(d) $-OR^7$,
(e) $-COOR^7$,
(f) $-CONH_2$,
(g) $-CONR^{16}OH$,
(h) $-CONR^7R^{11}$,
(i) $-CONR^7CO_2R^7$,
(j) $-NH_2$,
(k) $-NR^7R^{11}$,
(l) $-NR^7CONR^7R^{11}$,
(m) $-NR^7COOR^{11}$,
(n) $-C(R^6)(OH)-C(R^6)(R^7)(OH)$,
(o) $-SO_2NR^7R^{11}$,
(p) $-S(O)_2NR^7COR^{11}$,
(q) $-S(O)_2NR^7CO_2R^{11}$,
(r) $-S(O)_2NR^7CONR^7R^{11}$,
(s) $-NHSO_2R^{11}$,
(t) $-NR^7SO_2NR^7R^{11}$,
(u) $-CONHSO_2R^{11}$,

(v) -CO-amino acid, wherein amino acid is defined as an L-or D- amino acid selected from the group consisting of Ala, Ile, Phe, Asp, Pro and Val and which can be further substituted as a (C_1-C_6)-alkyl ester or an amide, or

(w)  ;

X is

(a) -O-,
(b) -$S(O)_n$-,
(c) -NR^7-,
(d) -CH_2O-,
(e) -$CH_2S(O)_n$-,
(f) -CH_2NR^7-,
(g) -OCH_2-,
(h) -$N(R^7)CH_2$-,
(i) -$S(O)_nCH_2$-, or
(j) -single bond;

Z is:

(a) -CO_2H,
(b) -CO_2R^{13},
(c) -CONH-(tetrazol-5-yl),
(d) -$CONHSO_2OR^{11}$,
(e) -$CONHSO_2NR^7R^{11}$,
(f) -$CONHSO_2$-aryl, wherein aryl is defined as phenyl or naphthyl which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of:
i) (C_1-C_4)-alkyl,
ii) -O-(C_1-C_4)-alkyl,

iii) $-CONR^7R^{11}$,
iv) F, Cl, Br or I,
v) $-COOR^7$,
vi) $-NH_2$,
vii) $-NH[(C_1-C_4)\text{-alkyl}]$,
viii) $-N[(C_1-C_4)\text{-alkyl}]_2$,
ix) -phenyl,
x) -OH,
xi) $-OCH_2CH_2OH$,
xii) $-CF_3$;

(g) $-CONHSO_2-(C_1-C_8)$-alkyl, wherein the alkyl group is unsubstituted or substituted as defined in R^4(b),

(h) $-CONHSO_2-(C_1-C_4)$-perfluoroalkyl,

(i) -tetrazol-5-yl,

(j) $-CONHSO_2$-heteroaryl, wherein heteroaryl is defined as carbazolyl, furyl, thienyl, pyrrolyl, isothiazolyl, imidazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrazolyl, pyrazinyl, pyridyl, pyrimidyl, purinyl or quinolinyl, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of:
i) (C_1-C_4)-alkyl,
ii) $-O-(C_1-C_4)$-alkyl,
iii) $-CONR^7R^{11}$,
iv) F, Cl, Br or I,
v) $-COOR^7$,
vi) $-NR^7CONR^7R^{11}$, and
vii) $-NR^7COOR^{11}$;

(k) $-SO_2NHCO$-aryl, wherein aryl is defined in Z(d) above,

(l) $-SO_2NHCO-(C_1-C_8)$-alkyl, wherein the alkyl group is unsubstituted or substituted as defined in R^4(b),

(m) $-SO_2NHCO-(C_1-C_4)$-perfluoroalkyl,

(n) $-SO_2NHCO$-heteroaryl, wherein heteroaryl is as defined in Z(g) above,

(o) $-SO_2NHCON(R^{11})_2$ wherein the R^{11} groups are the same or different,

(p) $-PO(OR^7)_2$, wherein the R^7groups are the same or different, or

(q) $-PO(R^{11})OR^7$;

R^{13} is:

(a) (C_1-C_4)-alkyl,

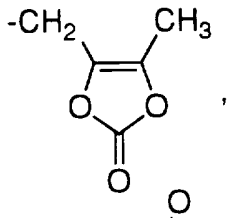
(b) $CHR^{14}-O-COR^{15}$,

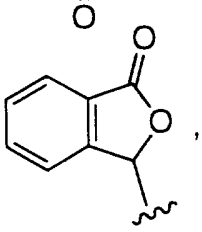
(c) $CH_2CH_2-N[(C_1-C_2)\text{-alkyl}]_2$,

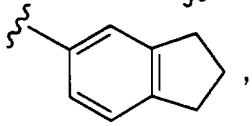
(d) $CH_2CH_2-N[CH_2CH_2]_2O$,

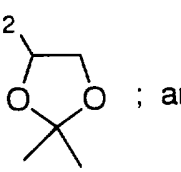
(e) $(CH_2CH_2O)_y-O-[(C_1-C_4)\text{-alkyl}]$, wherein y is 1 or 2,

(f) phenyl, naphthyl, CH_2-phenyl or CH_2-naphthyl, where phenyl or naphthyl is substituted or unsubstituted with $CO_2-(C_1-C_4)$-alkyl,

(g)  ,

(h)  ,

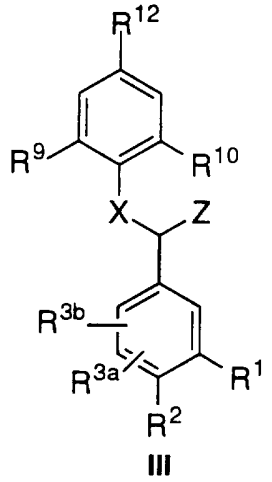
(i)  , or

(j)  ; and

R^{14} and R^{15} independently are (C_1-C_6)-alkyl or phenyl; and

R^{16} is H, (C_1-C_6)-alkyl, or (C_1-C_6)-alkylphenyl.

An embodiment of the compounds of Formula II are the compounds of Formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

R^1, R^2, R^{3a} and R^{3b} are independently:

(a) H,
(b) F, Cl, Br, or I,
(c) $-NO_2$,
(d) (C_1-C_6)-alkyl,
(e) $-OR^7$,
(f) $-NHCO-(C_1-C_4)$-alkyl,
(g) $-NHCO-O(C_1-C_4)$-alkyl,
(h) $-O-(CH_2)m-OR^7$,
(i) $-CONR^7R11$, or
(j) $-COOR^7$;

R^1 and R^2 on adjacent carbon atoms can be joined together to form a ring structure:

;

A represents:

a) -Y-C(R^4)=C(R^5)-,

b) -Y-C(R^4)=N-,

c) -Y-N=C(R^4)-,

d) -Y-[C(R^6)(R^6)]$_s$ -Y-,

e) -Y-C(R^6)(R^6)-C(R^6)(R^6)-,

f) -C(R^4)=C(R^5)-Y-,

g) -N=C(R^4)-Y-,

h) -C(R^6)(R^6)-C(R^6)(R^6) -Y-, or

i) -C(R^4)=C(R^5)-C(R^4)=C(R^5)-;

m is 2, 3 or 4,

n is 0, 1 or 2,

s is 1 or 2,

Y is -O-, -S- and NR^7

R^4 and R^5 are independently:

(a) H,

(b) (C_1-C_6)-alkyl,

(c) (C_3-C_7)-cycloalkyl,

(d) F, Cl, Br, I,

(e) -NR^7COOR^{11},

(f) -$SO_2NR^7R^{11}$,

(g) -O-(C_1-C_4)-alkyl,
(h) -S(O)$_n$-(C_1-C_4)-alkyl, or
(i) -NHSO$_2$R^{11};

R^6 is:
(a) H, or
(b) (C_1-C_4)-alkyl, or
(c) Cl, or F;

R^7 is:
(a) H,
(b) (C_1-C_6)-alkyl,
(c) phenyl, or
(d) benzyl;

R^8 is:
(a) H,
(b) (C_1-C_6)-alkyl, or
(c) phenyl;

R^9 and R^{10} are independently:
(a) H,
(b) (C_1-C_6)-alkyl, unsubstituted or substituted with (C_3 -C_7)-cycloalkyl,
(c) Cl, Br, F, I,
(d) (C_1-C_6)-alkoxy, or
(e) hydroxy-(C_1-C_6)-alkyl;

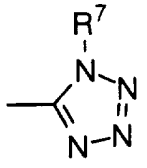
R^{11} is
(a) (C_1-C_6)-alkyl, unsubstituted or substituted with a substituent selected from the group consisting of:
i) -OR^7,
ii) -N[R^7]$_2$,
iii) -NH$_2$,

iv) $-COOR^7$,
v) $-N[CH_2CH_2]_2Q$,
vi) $-CF_3$, or
vii) $-CON(R^7)_2$;

(b) aryl, wherein aryl is defined as phenyl or naphthyl which is unsubstituted or substituted with one or two substituents selected from the group consisting of:
i) $(C_1\text{-}C_4)$-alkyl,
ii) $-O\text{-}(C_1\text{-}C_4)$-alkyl,
iii) $-CO[NR^7]_2$,
iv) F, Cl, Br or I,
v) $-COOR^7$,
vi) $-NH_2$,
vii) $-NH[(C_1\text{-}C_4)\text{-alkyl}]$,
viii) $-N[(C_1\text{-}C_4)\text{-alkyl}]_2$,
ix) $-CON[CH_2CH_2]_2Q$, or

(c) $-(C_1\text{-}C_4)$-alkylaryl, wherein aryl is as defined above,

(d) $(C_3\text{-}C_7)$-cycloalkyl,

(e)  , or

(f) CF_3;

R^7 and R^{11} on the same nitrogen atom they can join together to form a ring selected from the group consisting of: morpholinyl, piperazinyl, or pyrrolyl, or

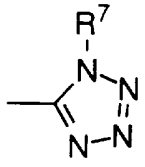
Q is O, S or $-NR^7$;

R^{12} is

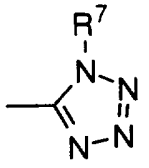
(a) H,

(b) (C_1-C_6)-alkyl, wherein alkyl is defined as unsubstituted or substituted with one or two substituents selected from the group consisting of:

i) -OH,
ii) -O-(C_1-C_4)-alkyl,
iii) -O-(C_1-C_4)-cycloalkyl,
iv) -$S(O)_n$-(C_1-C_4)-alkyl,
iv) -NR^7-(C_1-C_4)-alkyl,
v) -NR^7R^{11},
vi) -$COOR^7$,
vii) -$CONHR^7$,
viii) -$OCOR^{11}$,
ix) -$CONR^7R^{11}$,
x) -$NR^7CONR^7R^{11}$,
xi) -NR^7COOR^{11},
xii) -$C(R^6)(OH)$-$C(R^6)(R^7)(OH)$,
xiii) -$SO_2NR^7R^{11}$, or

xiv) 

(c) -$COOR^7$,
(d) -$CONH_2$,
(e) -$CONR^{16}OH$,
(f) -$CONR^7R^{11}$,
(g) -$CONR^7CO_2R^7$,
(h) -$C(R^6)(OH)$-$C(R^6)(R^7)(OH)$, or
(i) -$CONHSO_2R^{11}$,
(j) -$SO_2NR^7R^{11}$,
(k) -$NR^7SO_2NR^7R^{11}$,
(l) -CO-amino acid, wherein amino acid is defined as an L-or D- amino acid selected from the group consisting of Ala, Ile, Phe, Asp, Pro and Val and which can be further substituted as a (C_1-C_6)-alkyl ester or an amide, or

(m)  ;

X is

(a) -O-,
(b) $-NR^7-$, or
(c) -single bond;

Z is:

(a) $-CO_2H$,
(b) $-CO_2R^{13}$,
(c) -CONH(tetrazol-5-yl),
(d) $-CONHSO_2NR^7R^{11}$,
(e) $-CONHSO_2$-aryl, wherein aryl is defined as phenyl or naphthyl which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of:
  i) (C_1-C_4)-alkyl,
  ii) -O-(C_1-C_4)-alkyl,
  iii) $-CONR^7R^{11}$,
  iv) F, Cl, Br or I,
  v) $-COOR^7$,
  vi) $-NH_2$,
  vii) -NH[(C_1-C_4)-alkyl],
  viii) -N[(C_1-C_4)-alkyl]2,
  ix) -phenyl;
(f) $-CONHSO_2-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or substituted as defined in R^4(b),
(g) $-CONHSO_2$-heteroaryl, wherein heteroaryl is defined as carbazolyl, furyl, thienyl, pyrrolyl, isothiazolyl, imidazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrazolyl, pyrazinyl, pyridyl,

pyrimidyl, purinyl, or quinolinyl, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of:

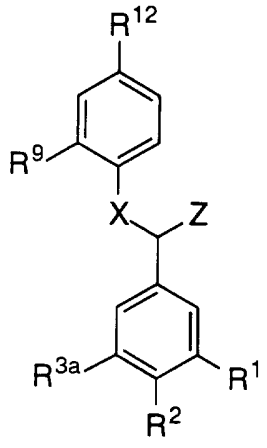
i) $(C_1$-$C4)$-alkyl,
ii) -O-$(C_1$-$C4)$-alkyl,
iii) $-CONR^7R^{11}$,
iv) F, Cl, Br or I,
v) $-COOR^7$,
vi) $-NR^7CONR^7R^{11}$, and
vii) $-NR^7COOR^{11}$;

(h) -tetrazol-5-yl;

R^{13} is: $(C_1$-$C_4)$-alkyl; and

R^{16} is H, $(C_1$-$C_6)$-alkyl, or $(C_1$-$C_6)$-alkylphenyl.

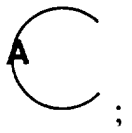
A subclass of the compounds of Formula III are the compounds of Formula IV:



IV

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 taken together form the ring structure:



;

A represents:

a) $-Y-[C(R^6)(R^6)]_s-Y-$, or

b) $-C(R^4)=C(R^5)-C(R^4)=C(R^5)-$;

s is 1 or 2;

Y is -O-;

R^{3a} is:

(a) H,
(b) F, Cl, Br, or I,
(c) (C_1-C_6)-alkyl,
(d) $-OR^7$,
(e) $-O-(CH_2)m-OR^7$,
(f) $-CONR^7R^{11}$, or
(g) $-COOR^7$;

m is 2, 3 or 4;

R^4 and R^5 are independently:

(a) H,
(b) (C_1-C_6)-alkyl,
(c) (C_3-C_7)-cycloalkyl,
(d) F, Cl, Br, I,
(e) $-NR^7COOR^{11}$,
(f) $-SO_2NR^7R^{11}$,
(g) $-O-(C_1-C_4)$-alkyl,
(h) $-S(O)_n-(C_1-C_4)$-alkyl, or
(i) $-NHSO_2R^{11}$;

n is 0, 1 or 2,

R^6 is:

(a) H, or
(b) (C_1-C_4)-alkyl, or
(c) Cl, or F;

R^7 is:

(a) H,
(b) (C_1-C_6)-alkyl,
(c) phenyl, or
(d) benzyl;

R^8 is:

(a) H,
(b) (C_1-C_6)-alkyl, or
(c) phenyl;

R^9 is:

(a) H,
(b) (C_1-C_6)-alkyl, unsubstituted or substituted with (C_3-C_7)-cycloalkyl,
(c) Cl, Br, F, I,
(d) (C_1-C_6)-alkoxy, or
(e) hydroxy-(C_1-C_6)-alkyl;

R^{11} is

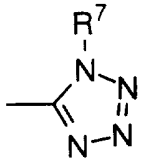
(a) (C_1-C_6)-alkyl, unsubstituted or substituted with a substituent selected from the group consisting of:
i) $-OR^7$,
ii) $-N[R^7]_2$,
iii) $-NH_2$,
iv) $-COOR^7$,
v) $-N[CH_2CH_2]_2Q$,

vi) $-CF_3$, or
vii) $-CON(R^7)_2$;

(b) aryl, wherein aryl is defined as phenyl or naphthyl which is unsubstituted or substituted with one or two substituents selected from the group consisting of:
i) $(C_1\text{-}C_4)$-alkyl,
ii) $-O\text{-}(C_1\text{-}C_4)$-alkyl,
iii) $-CO[NR^7]_2$,
iv) F, Cl, Br or I,
v) $-COOR^7$,
vi) $-NH_2$,
vii) $-NH[(C_1\text{-}C_4)\text{-alkyl}]$,
viii) $-N[(C_1\text{-}C_4)\text{-alkyl}]_2$, or
ix) $-CON[CH_2CH_2]_2Q$;

(c) $-(C_1\text{-}C_4)$-alkylaryl, wherein aryl is as defined above,

(d) $(C_3\text{-}C_7)$-cycloalkyl,

(e)  , or

(f) CF_3;

R^7 and R^{11} on the same nitrogen atom they can join together to form a ring selected from the group consisting of: morpholinyl, piperazinyl, or pyrrolyl, or

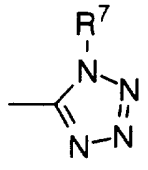
Q is O, S or $-NR^7$;

R^{12} is

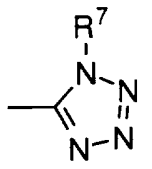
(a) H,

(b) $(C_1\text{-}C_6)$-alkyl, wherein alkyl is defined as unsubstituted or substituted with one or two substituents selected from the group consisting of:

i) -OH,
ii) -O-(C_1-C_4)-alkyl,
iii) -O-(C_1-C_4)-cycloalkyl,
iv) -$S(O)_n$-(C_1-C_4)-alkyl,
iv) -NR^7-(C_1-C_4)-alkyl,
v) -NR^7R^{11},
vi) -$COOR^7$,
vii) -$CONHR^7$,
viii) -$OCOR^{11}$,
ix) -$CONR^7R^{11}$,
x) -$NR^7CONR^7R^{11}$,
xi) -NR^7COOR^{11},
xii) -$C(R^6)(OH)$-$C(R^6)(R^7)(OH)$, or
xiii) -$SO_2NR^7R^{11}$,

xiv)  ,

(c) -$COOR^7$,
(d) -$CONH_2$,
(e) -$CONR^{16}OH$,
(f) -$CONR^7R^{11}$,
(g) -$CONR^7CO_2R^7$,
(h) -$C(R^6)(OH)$-$C(R^6)(R^7)(OH)$, or
(i) -$CONHSO_2R^{11}$,
(j) -$SO_2NR^7R^{11}$,
(k) -$NR^7SO_2NR^7R^{11}$,
(l) -CO-amino acid, wherein amino acid is defined as an L-or D- amino acid selected from the group consisting of Ala, Ile, Phe, Asp, Pro and Val and which can be further substituted as a (C_1-C_6)-alkyl ester or an amide, or

(m)  ;

X is

(a) -O-,
(b) -NR^7-, or
(c) -single bond;

Z is:

(a) -CO_2H,
(b) -CO_2R^{13},
(c) -CONH-(tetrazol-5-yl),
(d) -$CONHSO_2NR^7R^{11}$,
(e) -$CONHSO_2$-aryl, wherein aryl is defined as phenyl or naphthyl which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of:
  i) (C_1-C_4)-alkyl,
  ii) -O-(C_1-C_4)-alkyl,
  iii) -$CONR^7R^{11}$,
  iv) F, Cl, Br or I,
  v) -$COOR^7$,
  vi) -NH_2,
  vii) -NH[(C_1-C_4)-alkyl],
  viii) -N[(C_1-C_4)-alkyl]$_2$,
  ix) -phenyl;
(f) -$CONHSO_2$-(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or substituted as defined in R^4(b),
(g) -$CONHSO_2$-heteroaryl, wherein heteroaryl is defined as carbazolyl, furyl, thienyl, pyrrolyl, isothiazolyl, imidazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrazolyl, pyrazinyl, pyridyl,

pyrimidyl, purinyl, or quinolinyl, which is unsubstituted or substituted with one, two, or three substituents selected from the group consisting of:

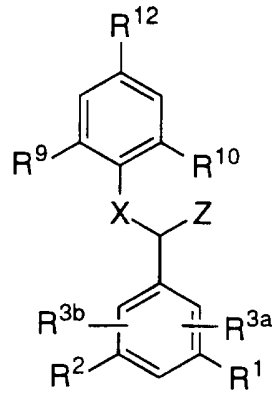
i) (C_1-C_4)-alkyl,
ii) -O-(C_1-C_4)-alkyl,
iii) $-CONR^7R^{11}$,
iv) F, Cl, Br or I,
v) $-COOR^7$,
vi) $-NR^7CONR^7R^{11}$, and
vii) $-NR^7COOR^{11}$;

(h) -tetrazol-5-yl;

R^{13} is: (C_1-C_4)-alkyl; and

R^{16} is H, (C_1-C_6)-alkyl, or (C_1-C_6)-alkylphenyl.

A second embodiment of the compounds of Formula II are the compounds of Formula V:



V

or a pharmaceutically acceptable salt thereof, wherein:

R^1, R^2, R^{3a} and R^{3b} are independently:

(a) H,

(b) F, Cl, Br, or I,
(c) $-NO_2$,
(d) (C_1-C_6)-alkyl,
(e) $-OR^7$,
(f) $-NHCO-(C_1-C_4)$-alkyl,
(g) $-NHCO-O(C_1-C_4)$-alkyl,
(h) $-O-(CH_2)_m-OR^7$,
(i) $-CONR^7R^{11}$, or
(j) $-COOR^7$;

m is 2, 3 or 4,

R^4 and R^5 are independently:

(a) H,
(b) (C_1-C_6)-alkyl,
(c) (C_3-C_7)-cycloalkyl,
(d) F, Cl, Br, I,
(e) $-NR^7COOR^{11}$,
(f) $-SO_2NR^7R^{11}$,
(g) $-O-(C_1-C_4)$-alkyl,
(h) $-S(O)_n-(C_1-C_4)$-alkyl, or
(i) $-NHSO_2R^{11}$;

n is 0, 1 or 2,

R^6 is:

(a) H,
(b) (C_1-C_4)-alkyl,or
(c) Cl or F;

R^7 is:

(a) H,
(b) (C_1-C_6)-alkyl,
(c) phenyl, or
(d) benzyl;

R^8 is:

(a) H,
(b) (C_1-C_6)-alkyl, or
(c) phenyl;

R^9 and R^{10} are independently:

(a) H,
(b) (C_1-C_6)-alkyl, unsubstituted or substituted with (C_3-C_7)-cycloalkyl,
(c) Cl, Br, F, I,
(d) (C_1-C_6)-alkoxy, or
(e) hydroxy-(C_1-C_6)-alkyl;

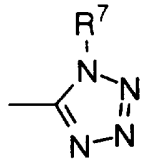
R^{11} is

(a) (C_1-C_6)-alkyl, unsubstituted or substituted with a substituent selected from the group consisting of:
i) $-OR^7$,
ii) $-N[R^7]_2$,
iii) $-NH_2$,
iv) $-COOR^7$,
v) $-N[CH_2CH_2]_2Q$,
vi) $-CF_3$, or
vii) $-CON(R^7)_2$;
(b) aryl, wherein aryl is defined as phenyl or naphthyl which is unsubstituted or substituted with one or two substituents selected from the group consisting of:
i) (C_1-C_4)-alkyl,

ii) -O-(C_1-C_4)-alkyl,
iii) -CO[NR^7]$_2$,
iv) F, Cl, Br or I,
v) -$COOR^7$,
vi) -NH_2,
vii) -NH[(C_1-C_4)-alkyl],
viii) -N[(C_1-C_4)-alkyl]$_2$, or
ix) -CON[CH_2CH_2]$_2$Q;

(c) -(C_1-C_4)-alkylaryl, wherein aryl is as defined above,

(d) (C_3-C_7)-cycloalkyl,

(e)  , or

(f) CF_3;

R^7 and R^{11} on the same nitrogen atom they can join together to form a ring selected from the group consisting of: morpholinyl, piperazinyl, or pyrrolyl, or

Q is O, S or -NR^7;

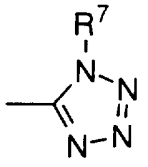
R^{12} is

(a) H,

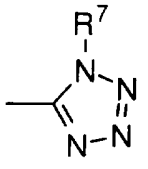
(b) (C_1-C_6)-alkyl, wherein alkyl is defined as unsubstituted or substituted with one or two substituents selected from the group consisting of:

i) -OH,
ii) -O-(C_1-C_4)-alkyl,
iii) -O-(C_1-C_4)-cycloalkyl,
iv) -S(O)$_n$-(C_1-C_4)-alkyl,
iv) -NR^7-(C_1-C_4)-alkyl,
v) -NR^7R^{11},
vi) -$COOR^7$,

vii) $-CONHR^7$,
viii) $-OCOR^{11}$,
ix) $-CONR^7R^{11}$,
x) $-NR^7CONR^7R^{11}$,
xi) $-NR^7COOR^{11}$,
xii) $-C(R^6)(OH)-C(R^6)(R^7)(OH)$, or
xiii) $-SO_2NR^7R^{11}$, or

xiv)  ;

(c) $-COOR^7$,
(d) $-CONH_2$,
(e) $-CONR^{16}OH$,
(f) $-CONR^7R^{11}$,
(g) $-CONR^7CO_2R^7$,
(h) $-C(R^6)(OH)-C(R^6)(R^7)(OH)$, or
(i) $-CONHSO_2R^{11}$,
(j) $-SO_2NR^7R^{11}$,
(k) $-NR^7SO_2NR^7R^{11}$,
(l) -CO-amino acid, wherein amino acid is defined as an L-or D- amino acid selected from the group consisting of Ala, Ile, Phe, Asp, Pro and Val and which can be further substituted as a (C_1-C_6)-alkyl ester or an amide, or

(m)  ;

X is

(a) -O-,
(b) $-NR^7-$, or
(c) -single bond;

Z is:

(a) $-CO_2H$,

(b) $-CO_2R^{13}$,

(c) -CONH-(tetrazol-5-yl),

(d) $-CONHSO_2NR^7R^{11}$,

(e) $-CONHSO_2$-aryl, wherein aryl is defined as phenyl or naphthyl which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of:

i) (C_1-C_4)-alkyl,

ii) -O-(C_1-C_4)-alkyl,

iii) $-CONR^7R^{11}$,

iv) F, Cl, Br or I,

v) $-COOR^7$,

vi) $-NH_2$,

vii) -NH[(C_1-C_4)-alkyl],

viii) -N[(C_1-C_4)-alkyl]$_2$,

ix) -phenyl;

(f) $-CONHSO_2-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or substituted as defined in R^4(b),

(g) $-CONHSO_2$-heteroaryl, wherein heteroaryl is defined as carbazolyl, furyl, thienyl, pyrrolyl, isothiazolyl, imidazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrazolyl, pyrazinyl, pyridyl, pyrimidyl, purinyl, or quinolinyl, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of:

i) (C_1-C_4)-alkyl,

ii) -O-(C_1-C_4)-alkyl,

iii) $-CONR^7R^{11}$,

iv) F, Cl, Br or I,

v) $-COOR^7$,

vi) $-NR^7CONR^7R^{11}$, and

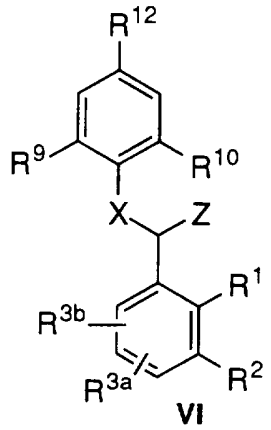
vii) $-NR^7COOR^{11}$;

(h) -tetrazol-5-yl;

R^{13} is: (C_1-C_4)-alkyl; and

R^{16} is H, (C_1-C_6)-alkyl, or (C_1-C_6)-alkylphenyl.

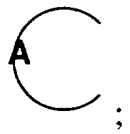
A third embodiment of compounds of Formula II are the compounds of Formula VI:



VI

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are represented by the following ring structure:



;

A represents:

a) $-Y-[C(R^6)(R^6)]_s-Y-$, or

b) $-C(R^4)=C(R^5)-C(R^4)=C(R^5)-$;

s is 1 or 2,

Y is -O-, -S- and NR^7;

R^{3a} and R^{3b} are independently:

(a) H,
(b) F, Cl, Br, or I,
(c) $-NO_2$,
(d) (C_1-C_6)-alkyl,
(e) $-OR^7$,
(f) $-NHCO-(C_1-C_4)$-alkyl,
(g) $-NHCO-O(C_1-C_4)$-alkyl,
(h) $-O-(CH_2)_m-OR^7$,
(i) $-CONR^7R^{11}$, or
(j) $-COOR^7$;

m is 2, 3 or 4,

R^4 and R^5 are independently:

(a) H,
(b) (C_1-C_6)-alkyl,
(c) (C_3-C_7)-cycloalkyl,
(d) F, Cl, Br, I,
(e) $-NR^7COOR^{11}$,
(f) $-SO_2NR^7R^{11}$,
(g) $-O-(C_1-C_4)$-alkyl,
(h) $-S(O)_n-(C_1-C_4)$-alkyl, or
(i) $-NHSO_2R^{11}$;

n is 0, 1 or 2,

R^6 is:

(a) H, or
(b) (C_1-C_4)-alkyl, or
(c) Cl or F;

R^7 is:

(a) H,
(b) (C_1-C_6)-alkyl,
(c) phenyl, or
(d) benzyl;

R^8 is:

(a) H,
(b) (C_1-C_6)-alkyl, or
(c) phenyl;

R^9 and R^{10} are independently:

(a) H,
(b) (C_1-C_6)-alkyl, unsubstituted or substituted with (C_3-C_7)-cycloalkyl,
(c) Cl, Br, F, I,
(d) (C_1-C_6)-alkoxy, or
(e) hydroxy-(C_1-C_6)-alkyl;

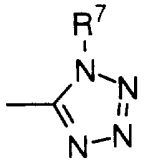
R^{11} is

(a) (C_1-C_6)-alkyl, unsubstituted or substituted with a substituent selected from the group consisting of:
i) $-OR^7$,
ii) $-N[R^7]_2$,
iii) $-NH_2$,
iv) $-COOR^7$,
v) $-N[CH_2CH_2]_2Q$,
vi) $-CF_3$, or
vii) $-CON(R^7)_2$;
(b) aryl, wherein aryl is defined as phenyl or naphthyl which is unsubstituted or substituted with one or two substituents selected from the group consisting of:
i) (C_1-C_4)-alkyl,

ii) -O-(C_1-C_4)-alkyl,
iii) -CO[NR^7]$_2$,
iv) F, Cl, Br or I,
v) -$COOR^7$,
vi) -NH_2,
vii) -NH[(C_1-C_4)-alkyl],
viii) -N[(C_1-C_4)-alkyl]$_2$, or
ix) -CON[CH_2CH_2]$_2$Q;

(c) -(C_1-C_4)-alkylaryl, wherein aryl is as defined above,

(d) (C_3-C_7)-cycloalkyl,

(e)  , or

(f) CF_3;

R^7 and R^{11} on the same nitrogen atom they can join together to form a ring selected from the group consisting of: morpholinyl, piperazinyl, or pyrrolyl, or

Q is O, S or -NR^7;

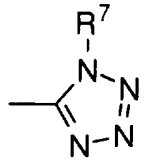
R^{12} is

(a) H,

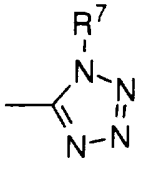
(b) (C_1-C_6)-alkyl, wherein alkyl is defined as unsubstituted or substituted with one or two substituents selected from the group consisting of:

i) -OH,
ii) -O-(C_1-C_4)-alkyl,
iii) -O-(C_1-C_4)-cycloalkyl,
iv) -S(O)$_n$-(C_1-C_4)-alkyl,
iv) -NR^7-(C_1-C_4)-alkyl,
v) -NR^7R^{11},
vi) -$COOR^7$,

vii) $-CONHR^7$,
viii) $-OCOR^{11}$,
ix) $-CONR^7R^{11}$,
x) $-NR^7CONR^7R^{11}$,
xi) $-NR^7COOR^{11}$,
xii) $-C(R^6)(OH)-C(R^6)(R^7)(OH)$,
xiii) $-SO_2NR^7R^{11}$, or

xiv)  ;

(c) $-COOR^7$,
(d) $-CONH_2$,
(e) $-CONR^{16}OH$,
(f) $-CONR^7R^{11}$,
(g) $-CONR^7CO_2R^7$,
(h) $-C(R^6)(OH)-C(R^6)(R^7)(OH)$, or
(i) $-CONHSO_2R^{11}$,
(j) $-SO_2NR^7R^{11}$,
(k) $-NR^7SO_2NR^7R^{11}$,
(l) -CO-amino acid, wherein amino acid is defined as an L-or D- amino acid selected from the group consisting of Ala, Ile, Phe, Asp, Pro and Val and which can be further substituted as a (C_1-C_6)-alkyl ester or an amide, or

(m)  ;

X is

(a) -O-,
(b) $-NR^7$-, or
(c) -single bond;

Z is:

(a) $-CO_2H$,

(b) $-CO_2R^{13}$,

(c) -CONH-(tetrazol-5-yl),

(d) $-CONHSO_2NR^7R^{11}$,

(e) $-CONHSO_2$-aryl, wherein aryl is defined as phenyl or naphthyl which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of:

i) (C_1-C_4)-alkyl,

ii) -O-(C_1-C_4)-alkyl,

iii) $-CONR^7R^{11}$,

iv) F, Cl, Br or I,

v) $-COOR^7$,

vi) $-NH_2$,

vii) -NH[(C_1-C_4)-alkyl],

viii) -N[(C_1-C_4)-alkyl]$_2$,

ix) -phenyl;

(f) $-CONHSO_2$-(C_1-C_8)-alkyl, wherein alkyl is unsubstituted or substituted as defined in R^4(b),

(g) $-CONHSO_2$-heteroaryl, wherein heteroaryl is defined as carbazolyl, furyl, thienyl, pyrrolyl, isothiazolyl, imidazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrazolyl, pyrazinyl, pyridyl, pyrimidyl, purinyl, or quinolinyl, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of:

i) (C_1-C_4)-alkyl,

ii) -O-(C_1-C_4)-alkyl,

iii) $-CONR^7R^{11}$,

iv) F, Cl, Br or I,

v) $-COOR^7$,

vi) $-NR^7CONR^7R^{11}$, and

vii) $-NR^7COOR^{11}$;

(h) -tetrazol-5-yl;

R^{13} is: (C_1-C_4)-alkyl; and

R^{16} is H, (C_1-C_6)-alkyl, or (C_1-C_6)-alkylphenyl.

An embodiment of the compounds of Formula I are:

2-[(2,6-dipropyl-4-hydroxymethyl)phenoxy]-2-(3-methylphenyl)acetic acid;

2-[(2,6-dipropyl-4-hydroxymethyl)phenoxy]-2-(4-phenoxyphenyl)-acetic acid;

2-[(2,6-dipropyl-4-hydroxymethyl)phenoxy]-2-(4-phenylphenyl)acetic acid;

2-[(2,6-dipropyl-4-hydroxymethyl)phenoxy]-2-(3-carboxyphenyl)acetic acid;

2-[(2,6-dipropyl-4-hydroxymethyl)phenoxy]-2-(3,4-ethylenedioxy-phenyl)acetic acid;

2-[(2,6-dipropyl-4-hydroxymethyl)phenoxy]-2-(3,4,5-trimethoxy-phenyl)acetic acid;

2-[(2,6-dipropyl-4-hydroxymethyl)phenoxy]-2-(3,4-methylenedioxy-phenyl)acetic acid;

2-[(2,6-dipropyl-4-hydroxymethyl)phenoxy]-2-(3,4-dimethoxy-phenyl)acetic acid;

2-[(2,6-dipropyl-4-hydroxymethyl)phenoxy]-2-(3,5-dimethoxy-phenyl)acetic acid;

2-((2,6-dipropyl-4-tetrazol-5-yl)phenoxy)-2-(3-bromophenyl)acetic acid

2-[(2,6-dipropyl-4-hydroxymethyl)phenoxy]-2-(3-bromophenyl)acetic acid;

2-[(2,6-dipropyl-4-hydroxymethyl)phenoxy]-2-(2-naphthyl)acetic acid;

2-[(2,6-dipropyl-4-(2-hydroxyethyl)phenoxy]-2-(2-naphthyl)acetic acid;

2-[(2,6-dipropyl-4-(2-hydroxyethyl)phenoxy]-2-(3,4-methylenedioxy-phenyl)acetic acid;

2-[(2,6-dipropyl-4-(2-hydroxyethyl)phenoxy]-2-(3-methoxyphenyl)-acetic acid;

2-[(2,6-dipropyl-4(1,2-dihydroxyethyl)phenoxy)]-2-(2-naphthyl)acetic acid;

2-[(2,6-dipropyl-4-(1-hydroxypentyl)phenoxy]-2-(2-naphthyl)acetic acid;

2-[(4-carboxy-2,6-dipropyl)phenoxy]-2-phenylacetic acid;

2-[(4-carboxy-2,6-dipropyl)phenoxy]-2-(3,4-dichlorophenyl)acetic acid;

2-[(4-carboxy-2,6-dipropyl)phenoxy]-2-(3-bromophenyl)acetic acid;

2-[(4-carboxy-2,6-dipropyl)phenoxy]-2-[3,4-methylenedioxyphenyl] acetic acid;

2-[(4-carboxy-2,6-dipropyl)phenoxy]-2-(3-methoxyphenyl)acetic acid;

(N-benzenesulfonyl)-2-[(4-(N-benzenesulfonyl)carboxamido-2,6-dipropylphenoxy]-2-(3-bromophenyl)acetamide;

(N-4-t-butylbenzenesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(benzenesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-phenylbenzenesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-chlorobenzenesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-methylbenzenesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(5-iso-butylthien-2-ylsulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-methoxybenzenesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-dimethylaminobenzenesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(2-methylbenzenesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(2-methoxycarbonylbenzenesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(2-chlorobenzenesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(3-chlorobenzenesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(phenylmethanesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(dansylsulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(8-quinolinesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenylacetamide;

N-(4-t-butylbenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(benzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-phenylbenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-chlorobenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-methylbenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(5-isobutylthien-2-ylsulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-methoxybenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-dimethylaminobenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-3,4-methylenedioxyphenyl)acetamide;

N-(2-methylbenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(2-methoxycarbonylbenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(2-chlorobenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(3-chlorobenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(phenylmethanesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(dansylsulfonyl)-2-(4-carboxy-2-propylphenoxy)-3,4-methylene-dioxyphenyl)acetamide;

N-(8-quinolinesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenylacetamide;

N-(8-quinolinesulfonyl)-2-(4-carboxamido-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

α-(4-carbomethoxy-2-*n*-propylphenoxy)-3,4-methylenedioxy-phenylacetic acid;

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-carbomethoxy-2-*n*-propyl-phenoxy)-3,4-methylenedioxyphenylacetamide;

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt;

α-(2-*iso*-butyl-4-carbomethoxyphenoxy)-3,4-methylenedioxyphenylacetic acid;

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*iso*-butyl-4-carbomethoxyphenoxy)-3,4-methylenedioxyphenylacetamide;

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*iso*-butyl-4-carboxyphenoxy)-3,4-methylenedioxyphenylacetamide;

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propyl-4-methoxycarbonylphenoxy)-α-methyl-3,4-methylenedioxyphenylacetamide;

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propyl-4-carboxyphenoxy)-α-methyl-3,4-methylenedioxyphenylacetamide dipotassium salt;

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propyl-4-carboxamidophenoxy)-3,4-methylenedioxyphenylacetamide;

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propyl-4-hydroxymethylphenoxy)-3,4-methylenedioxyphenylacetamide;

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-formyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide;

α-(4-acetyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetic acid;

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-acetyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide;

α-(2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetic acid

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide;

α-(3-methoxyphenoxy)-3,4-methylenedioxyphenylacetic acid;

α-(2-(2-hydroxyethyl)phenoxy)-3,4-methylenedioxyphenylacetic acid;

α-(2-(2-carbomethoxyethyl)phenoxy)-3,4-methylenedioxyphenylacetic acid;

α-(4-hydroxymethyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetic acid;

α-(4-(2-hydroxyethyl)-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetic acid;

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-(2-carbomethoxyethyl)phenoxy)-3,4-methylenedioxyphenylacetamide;

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-(2-carboxyethyl)phenoxy)-3,4-methylenedioxyphenylacetamide;

α-(2-(2-carboxyethyl)phenoxy)-3,4-methylenedioxyphenylacetic acid;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-carbomethoxy-2-*n*-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(4-*iso*-propylbenzenesulfonyl)carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-carboxamido-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-methylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-2-hydroxyethylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-morpholinylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-3-methylbutylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-carboxymethylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(L-Ala-OEt)carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-2-ethoxycarbonylethyl-carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxy-phenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(L-Ala)carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-2-carboxyethylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-3-hydroxypropyl-carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxy-phenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-tetrazol-5-ylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-3-(morpholin-4-yl)propyl-carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxy-phenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(D-Ala-OMe)carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(D-Ala)carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(3-carboxymethylpropyl)-carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxy-phenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(3-carboxypropyl)-carboxamido)-2-*n*-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxy-phenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-*iso*-propylcarbamoyl)amino-2-*n*-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

α-(2-*n*-propyl-4-methylaminosulfonylphenoxy)-3,4-methylenedioxy-phenylacetic acid;

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propyl-4-methylamino-sulfonylphenoxy)-3,4-methylenedioxyphenylacetamide potassium salt;

N-(4-*iso*-propylbenzenesulfonyl)-α-[4-(cyanomethyl)-2-*n*-propylphenoxy)]-3,4-methylenedioxyphenylacetamide;

N-(4-*iso*-propylbenzenesulfonyl)-α-[4-(tetrazol-5-ylmethyl)-2-*n*-propylphenoxy)]-3,4-methylenedioxyphenylacetamide;

N-(4-*iso*-propylbenzenesulfonyl)-α-[N-(4-carbomethoxyphenylamino)]-3,4-methylenedioxyphenylacetamide;

N-(4-*iso*-propylbenzenesulfonyl)-α-[N-(4-carboxyphenylamino)]-3,4-methylenedioxyphenylacetamide;

N-(3-pyridinesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(2-methyl-3-quinolinesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(3-quinolinesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-hydroxy-3-pyridinesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-ethoxybenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-carboxamidobenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-[4-(N,N-dimethylcarboxamido)benzenesulfonyl]-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-ethylthio-3-pyridinesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-ethoxy-3-pyridinesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-[(4-amino-2,5-dimethoxy)benzenesulfonyl]-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-[(2,5-dimethoxy)benzenesulfonyl]-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-[(3,4-dimethoxy)benzenesulfonyl]-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-[2-[5-(morpholin-4-yl)benzothiophene]sulfonyl]-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-[[2-(4-methoxy)benzothiophene]sulfonyl]-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-[4-[2-(benzyloxycarbonylamino)ethyl]benzenesulfonyl]-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-[[2,5-dimethoxy-4-((N-*iso*-propylcarbamoyl)amino)]benzene-sulfonyl]-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxy-phenyl)acetamide;

N-[(2,4-dimethoxy)benzenesulfonyl]-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-[(2,4,6-trimethoxy)benzenesulfonyl]-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(8-quinolinesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(3-quinolinesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(8-quinolinesulfonyl)-2-(4-carboxamido-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-*tert*-butylbenzenesulfonyl)-2-(4-carboxamido-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-(4-amino-2,5-dimethoxybenzenesulfonyl)-2-(4-carboxamido-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide;

N-[4-*iso*-propylbenzenesulfonyl]-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-[[4-[N-[2-(carbethoxy)ethyl]-carbamoyl]]-2-propylphenoxy]-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-[[4-[N-(2-carboxyethyl)carbamoyl]]-2-propylphenoxy]-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-[[4-[N-(2-carbamoylethyl)-carbamoyl]]-2-propylphenoxy]-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-*iso*-propylbenzenesulfonyl)-2-[4-[N-(2,2,2-trifluoroethyl)-carbamoyl]-2-propylphenoxy]-2-(3,4-methylenedioxyphenyl)acetamide;

A perferred embodiment of the compounds of this invention are:

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt;

N-(8-quinolinesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide;

N-(4-dimethylaminobenzenesulfonyl)-2-(4-carboxy-2-*n*-propyl-phenoxy)-2-(3,4-methylenedioxyphenyl)acetamide.

The alkyl substituents recited above denote straight and branched chain hydrocarbons of the length specified such as methyl, ethyl, isopropyl, isobutyl, neopentyl, isopentyl, etc.

The alkenyl-substituents denote alkyl groups as described above which are modified so that each contains a carbon to carbon double bond such as vinyl, allyl and 2-butenyl.

Cycloalkyl denotes rings composed of 3 to 8 methylene groups, each of which may be substituted or unsubstituted with other hydrocarbon substituents, and include for example cyclopropyl, cyclopentyl, cyclohexyl and 4-methylcyclohexyl.

The alkoxy substituent represents an alkyl group as described above attached through an oxygen bridge.

The heteroaryl is defined as carbazolyl, furyl, thienyl, pyrrolyl, isothiazolyl, imidazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrazolyl, pyrazinyl, pyridyl, pyrimidyl, purinyl or quinolinyl.

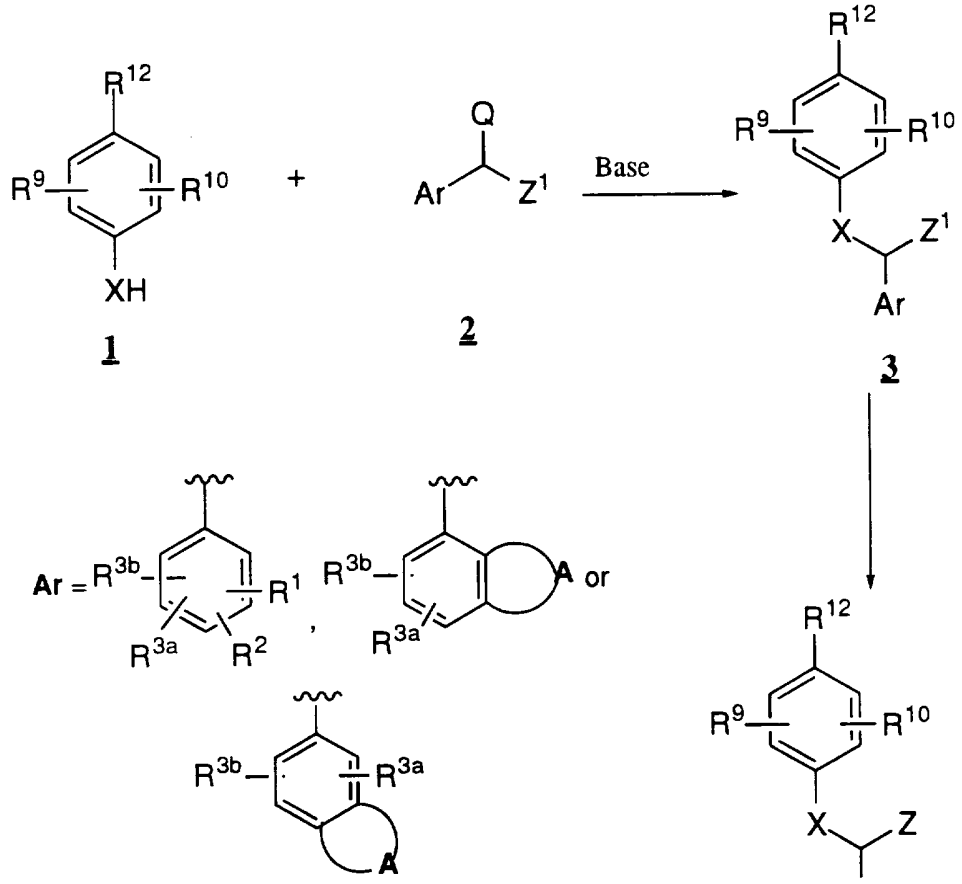
Although the reaction schemes described below are reasonably general, it will be understood by those skilled in the art of organic synthesis that one or more functional groups present in a given compound of Formula **I** may render the molecule incompatible with a particular synthetic sequence. In such a case an alternative synthetic route, an altered order of steps, or a strategy of protection and deprotection may be employed. In all cases the particular reaction conditions, including reagents, solvent, temperature and time, should be chosen so that they are consistent with the nature of the functionality present in the molecule.

The compounds of Formula **I** and specifically compounds of Formula **III** can be synthesized using the reactions and techniques described for the synthesis of the non-heterocyclic components in the patent application WO91/11999 (Merck & Co.; published on August 22,1991 under the Patent Cooperation Treaty), US Patent 5,177,095 (Merck & Co.; January 5, 1993), and also US Patent 5,240,938 (Merck & Co.; August 31, 1993).

The reaction schemes described below have been generalized for simplicity. It is further to be understood that in the

generalized schemes below, unless specified more narrowly in the text, the alkyl and aryl groups represent unfunctionalized or functionalized derivatives as described before. The leaving group Q present in the alkylating agents is either chloro, bromo, iodo, methanesulfonate, p-toluenesulfonate or triflate.

Scheme 1



Q = Cl, Br, I, OMs, OTs or OTf

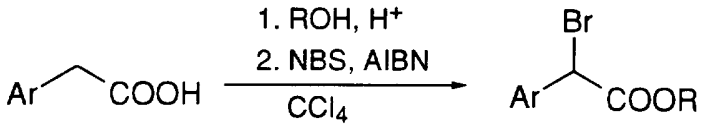
Z^1 = a precursor to Z

III, V or VI

More specifically, the compounds of Formula **III**, **V** or **VI** (where X is oxygen, sulphur or appropriately substituted nitrogen) can be synthesized as outlined in Scheme 1. The substituted compound **1** may be reacted with the alkylating agent **2** in an appropriate solvent such as alcohols (methanol, ethanol, isopropanol and like), dimethylformamide (DMF), dimethylsulfoxide (DMSO), tetrahydrofuran (THF) and acetone in the presence of an alkali metal salt such as alkoxides, carbonates, hydroxides and hydrides, or organic bases such as trialkylamines or alkyl lithiums to provide compound **3**. The Z^1 group present in compound **3** may then be further transformed to provide the appropriate compounds of Formula **III, V or VI.**

In general, the alkylating agent **2** can be prepared using methods and techniques outlined in US Patent 5,177,095. More specifically, compound **2** (where Z^1 is COOR and Q is Br) can be synthesized from the substituted arylacetic acids **4** as outlined in Scheme 2. The substituted arylacetic acid **4** is converted to the corresponding ester either by refluxing the acid in an appropriate alcohol in the presence of a catalytic amount of conc. sulfuric acid, or using other conventional methods of esterification. The resulting ester is then refluxed in carbon tetrachloride with N-bromosuccinimide and a catalytic amount of a radical initiator (e.g., AIBN or benzoylperoxide) to provide the 2-bromo-arylacetic acid ester **5**.

Scheme 2

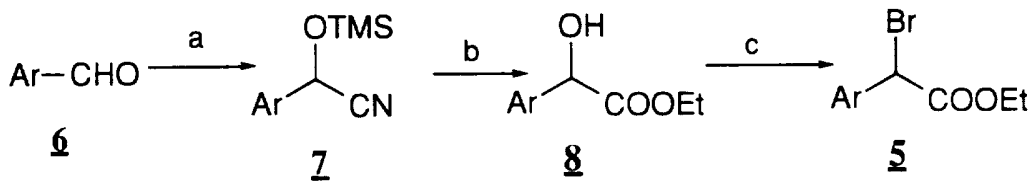


4 **5**

Alternatively, the ester **5** may also be prepared from appropriate aryl aldehydes (Scheme 3). The aldehyde **6** can be reacted with trimethylsilyl cyanide and catalytic amounts of KCN and 18-crown-6 to provide the corresponding trimethylsilyl cyanohydrin **7**,

which upon further treatment with the gaseous HCl and alcohol affords the 2-hydroxy ester **8**. The ester **8** is treated with triphenylphosphine and carbon tetrabromide in methylene chloride to give the 2-bromoarylacetate derivatives **5** .

Scheme 3



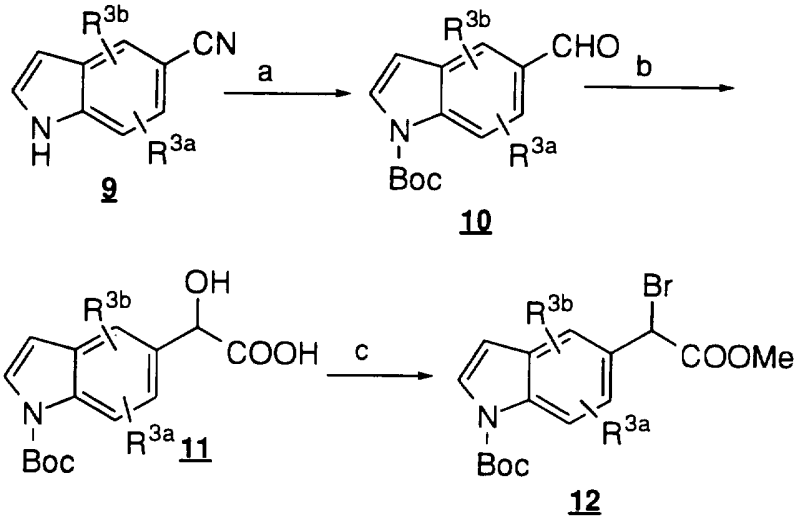
6 **7** **8** **5**

a. TMSCN, Cat. KCN, CH_2Cl_2, 18-Crown-6; b. HCl(g), EtOH;

c. CBr_4, Ph_3P, CH_2Cl_2

Scheme 4 illustrates a typical synthesis of an alkylating agent **12** (where Ar represents a heterocycle such as an indole). The appropriately substituted cyanoindole **9** (for a general synthesis of substituted indoles refer to, R. K. Brown, Indoles, Part One, Ed. W. J. Houlihan, Vol. 25, Chapter II, Wiley-Interscience, New York, 1972) is reduced with DIBAL-H to provide the corresponding aldehyde, which is then converted into the N-Boc derivative **10** . Reaction of **10** with the trichloromethide anion [generated from KOH and $CHCl_3$; J. M. Wyvratt et. al., J. Org. Chem., 52, 944-945 (1987)] followed by treatment with aqueous NaOH in DMF provides the alcohol **11**. Treatment of **11** with diazomethane followed by the reaction with CBr_4/Ph_3P yields the alkylating agent **12**.

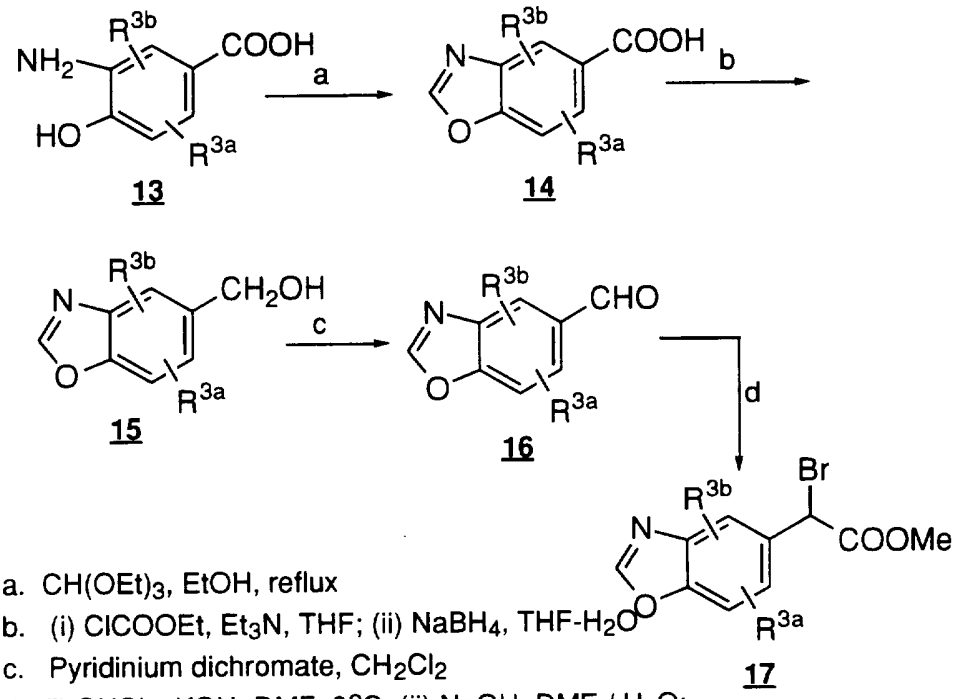
Scheme 4



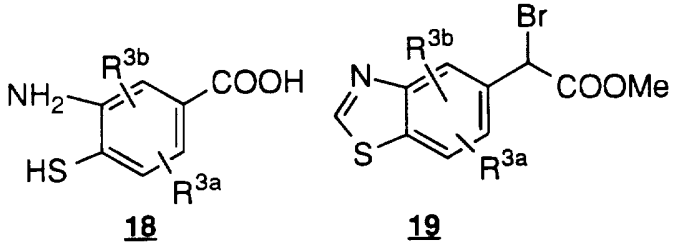
a. (i) DIBALH, Toluene; (ii) Boc_2O, DMAP, CH_2Cl_2
b. (i) $CHCl_3$, KOH, DMF, 0°C; (ii) NaOH, DME / H_2O
c. (i) CH_2N_2; (ii) CBr_4/Ph_3P, CH_2Cl_2

A typical synthesis of alkylating agents bearing a substituted benzoxazole or benzthiazole ring is outlined in Scheme 5. The substituted benzoxazole **14** is prepared from the corresponding o-aminophenol **13** by the reaction of an appropriate orthoester under refluxing conditions (for other methods of synthesis of benzoxazoles see, S. A. Lang and Y. Lin, Comprehensive Heterocyclic Chemistry, Vol. 6, 1-130, Ed. C. W. Rees; and references cited therein). Reduction of **14** with NaBH4 provides the alcohol **15** which is then subjected to pyridinium dichromate (PDC) oxidation to yield the corresponding aldehyde **16**. Further elaboration of **16** as outlined provides the key intermediate **17**. Similarly, the benzothiazole **19** can also be prepared form the appropriately substituted o-aminothiophenol **18**.

Scheme 5



a. $CH(OEt)_3$, EtOH, reflux
b. (i) ClCOOEt, Et_3N, THF; (ii) $NaBH_4$, THF-H_2O
c. Pyridinium dichromate, CH_2Cl_2
d. (i) $CHCl_3$, KOH, DMF, 0°C; (ii) NaOH, DME / H_2O;
(iii) HCl / MeOH; (iv) CBr_4/Ph_3P, CH_2Cl_2

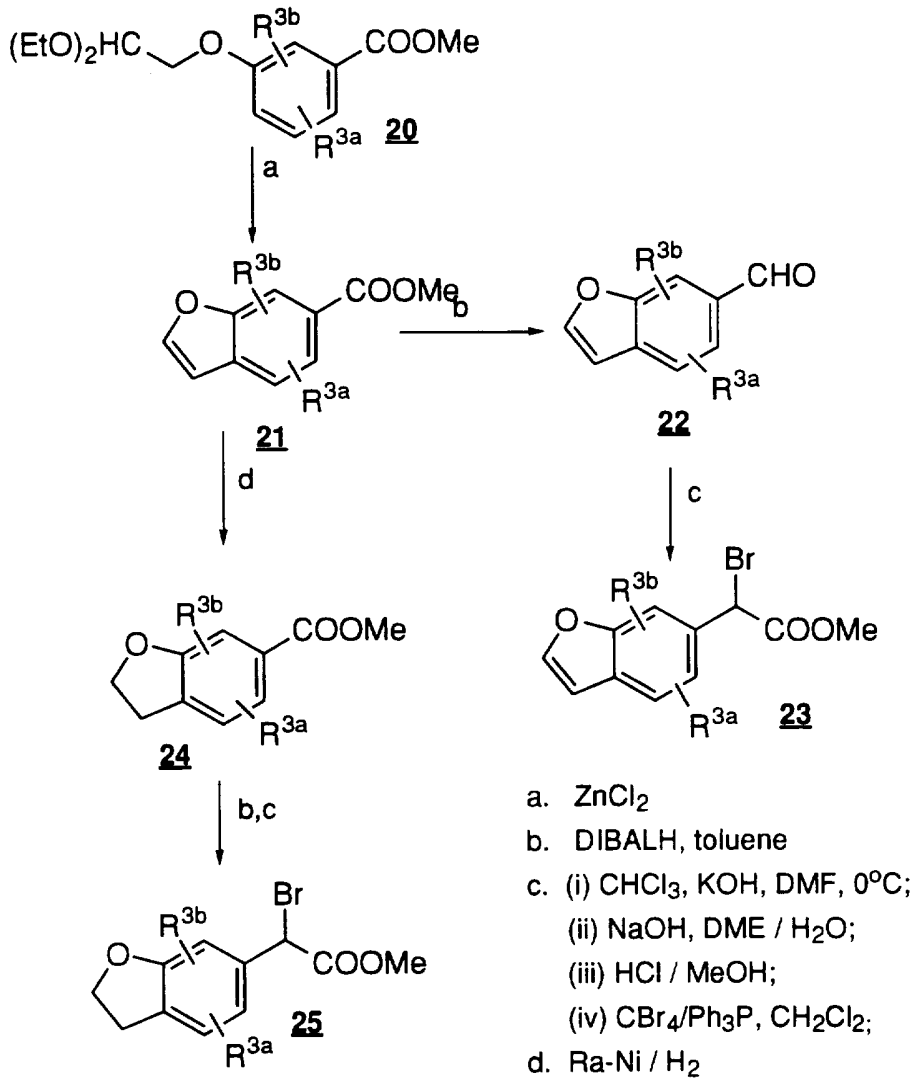


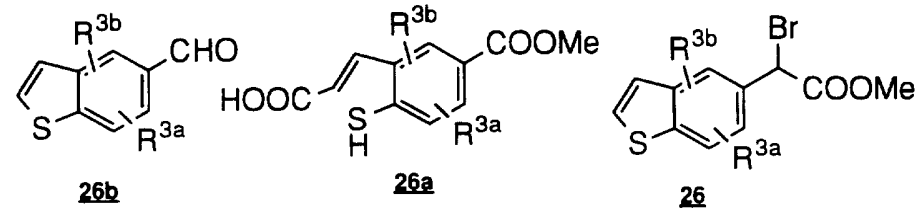
Scheme 6 illustrates the synthesis of benzofuran and dihydrobenzofuran alkylating agents **23** and **25**. The benzofuran **21** can be prepared from the α-phenoxy carbonyl compound **20** via a ring closure reaction [Stoermer and Wehln, Chem. Ber., 35, 3549 (1902)] (for general methods of synthesis of benzofurans and dihydrobenzofurans see, R. C. Elderfield and V. B. Meyer, Heterocyclic Compounds, Vol. 2, Chapter 1, Ed. R. C. Elderfield, Wiley; and references cited therein). The ester **21** is reduced to provide the aldehyde **22** which is then transformed into the corresponding alkylating agent **23**. The dihydrobenzofuran ester **24**, obtained by catalytic reduction of **21**, can also be transformed into the corresponding alkylating agent **25** using the sequence of reactions outlined in Scheme 6.

Benzothiophene **26** may be synthesized from the corresponding aldehyde **26b** in a manner similar to that outlined in Scheme 6 for benzofuran **23**. Benzothiophene **26b** can be prepared by the oxidative cyclization (using an alkaline solution of potassium ferricyanide) of appropriately substituted o-mercaptocinnamic acid **26a** [C. Chmelewsky and P. Friedlander, Chem. Ber., 46, 1903 (1913)]. (For general methods of synthesis of benzothiophene, See, E. Champaigne in Comprehensive Heterocyclic Chemistry, vol. 4, Chapter 3-15; Eds. A. Katritzky and C.W. Rees.)

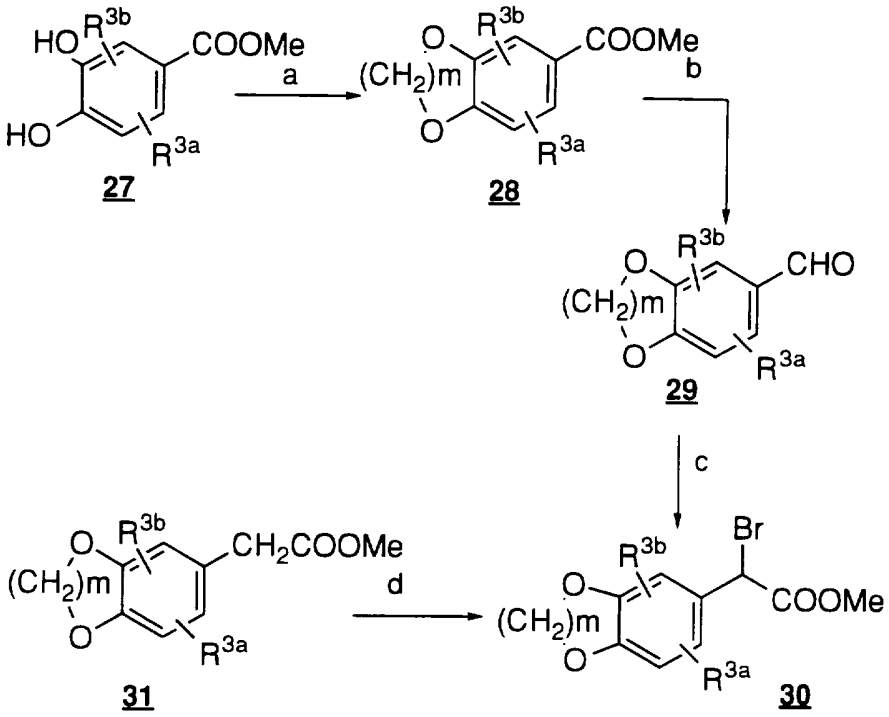
Scheme 7 outlines a typical synthesis of α-bromoaryl-acetates, **30** and **32**,bearing appropriately substituted methylenedioxy or 1,4-dioxane rings. The substituted catechol derivative **27** is treated with an appropriate dibromide (where m is 1 or 2) in the presence of cesium carbonate in dimethylformamide to provide **28**. Treatment of **28** with DIBALH yields the aldehyde **29** which is then transformed into the desired alkyl bromide as described.

Scheme 6


(EtO)2HC
O
R3b
COOMe
R3a
20
a
21
b
22
CHO
d
c
24
23
Br
b,c
25
a. ZnCl2
b. DIBALH, toluene
c. (i) CHCl3, KOH, DMF, 0°C;
(ii) NaOH, DME / H2O;
(iii) HCl / MeOH;
(iv) CBr4/Ph3P, CH2Cl2;
d. Ra-Ni / H2


R3b
CHO
S
R3a
26b
HOOC
COOMe
H
26a
Br
26

Scheme 7

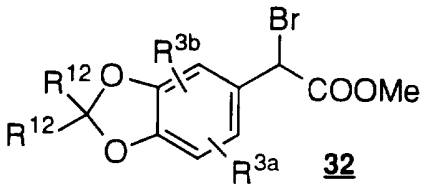


a. Br-$(CH_2)_m$-Br, Cs_2CO_3, DMF

b. DIBALH, toluene

c. (i) $CHCl_3$, KOH, DMF, 0°C; (ii) NaOH, DME / H_2O; (iii) HCl / MeOH; (iv) CBr_4/Ph_3P, CH_2Cl_2;

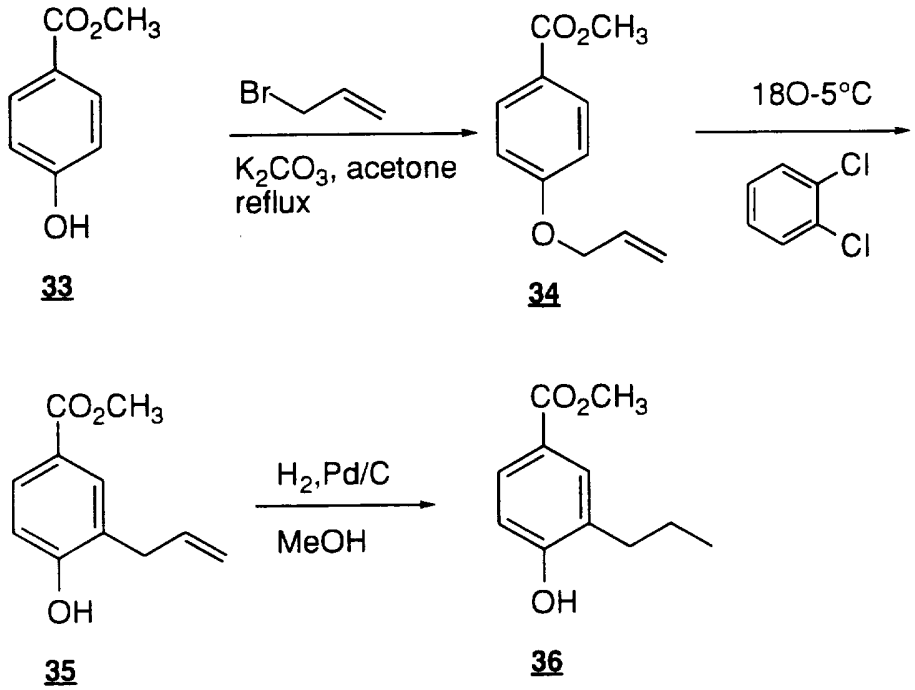
d. NBS, AIBN, CCl_4



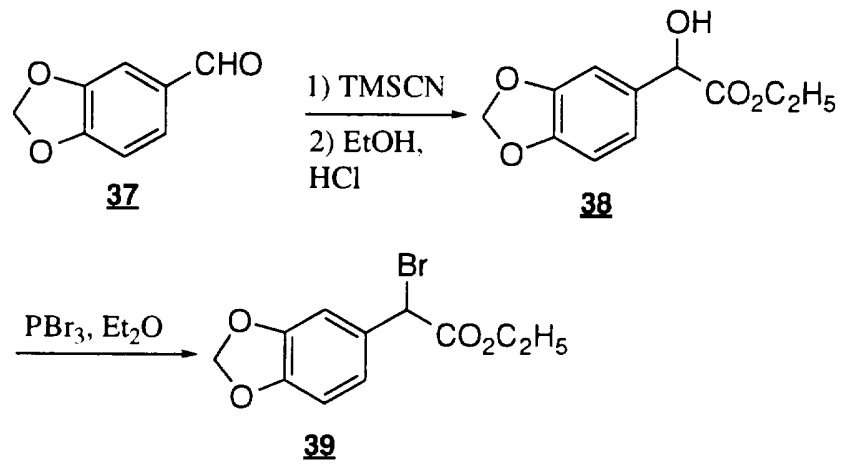
Following the synthetic route outlined in Scheme 8 below *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt, **45** is prepared.

Scheme 8

Methyl 4-hydroxy-3-propylbenzoate, **36**:

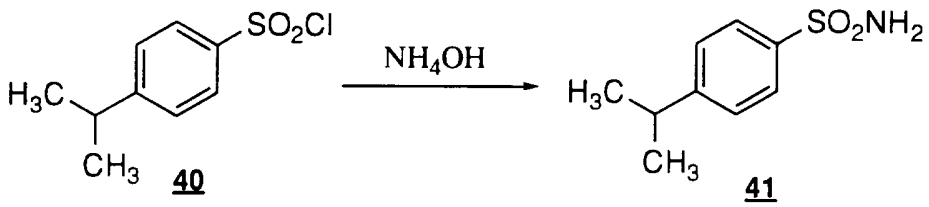


Ethyl α-bromo-3,4-methylenedioxyphenylacetate, **39**:



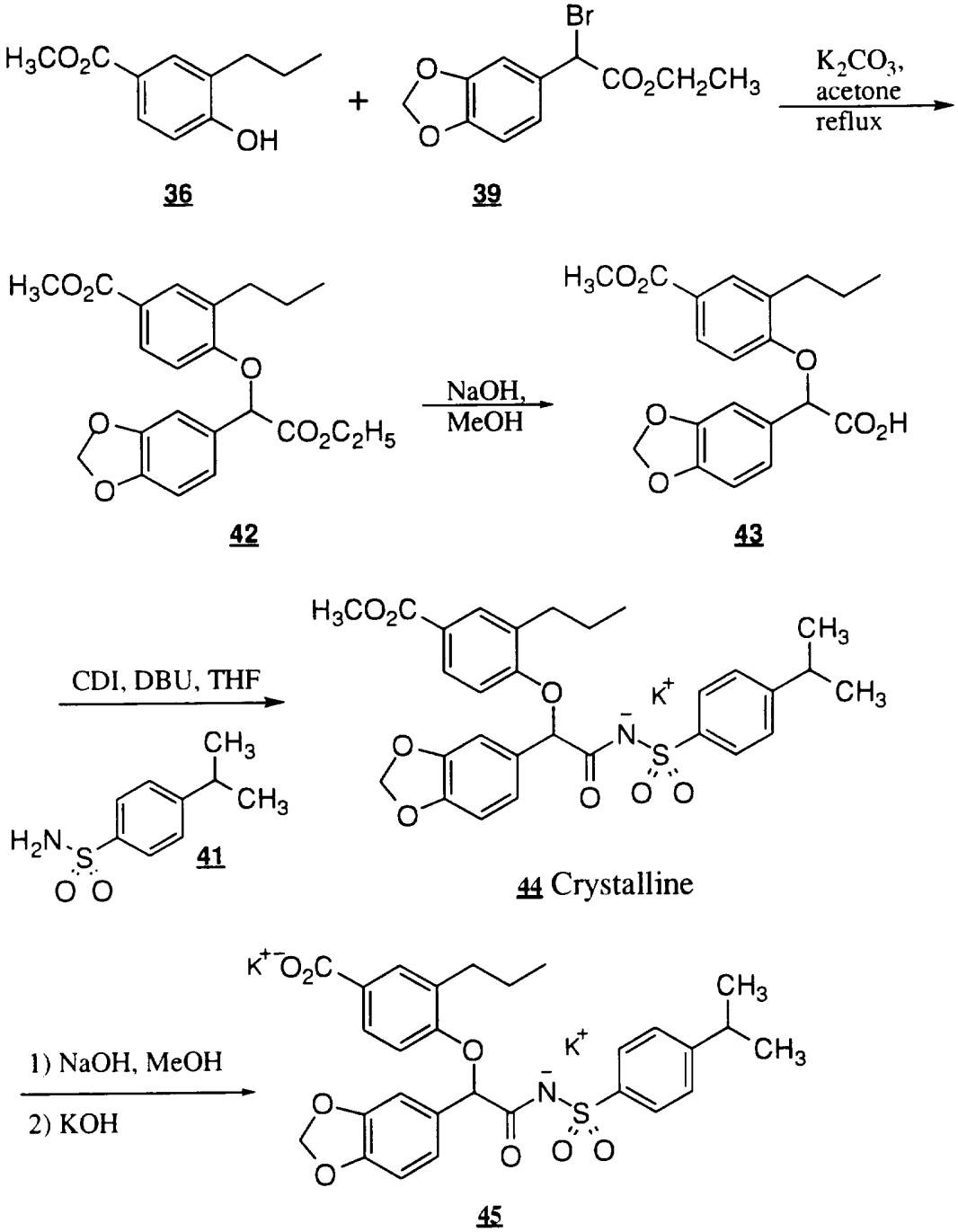
37 **38** **39**

4-*iso*-propylbenzenesulfonate, **41**:



40 **41**

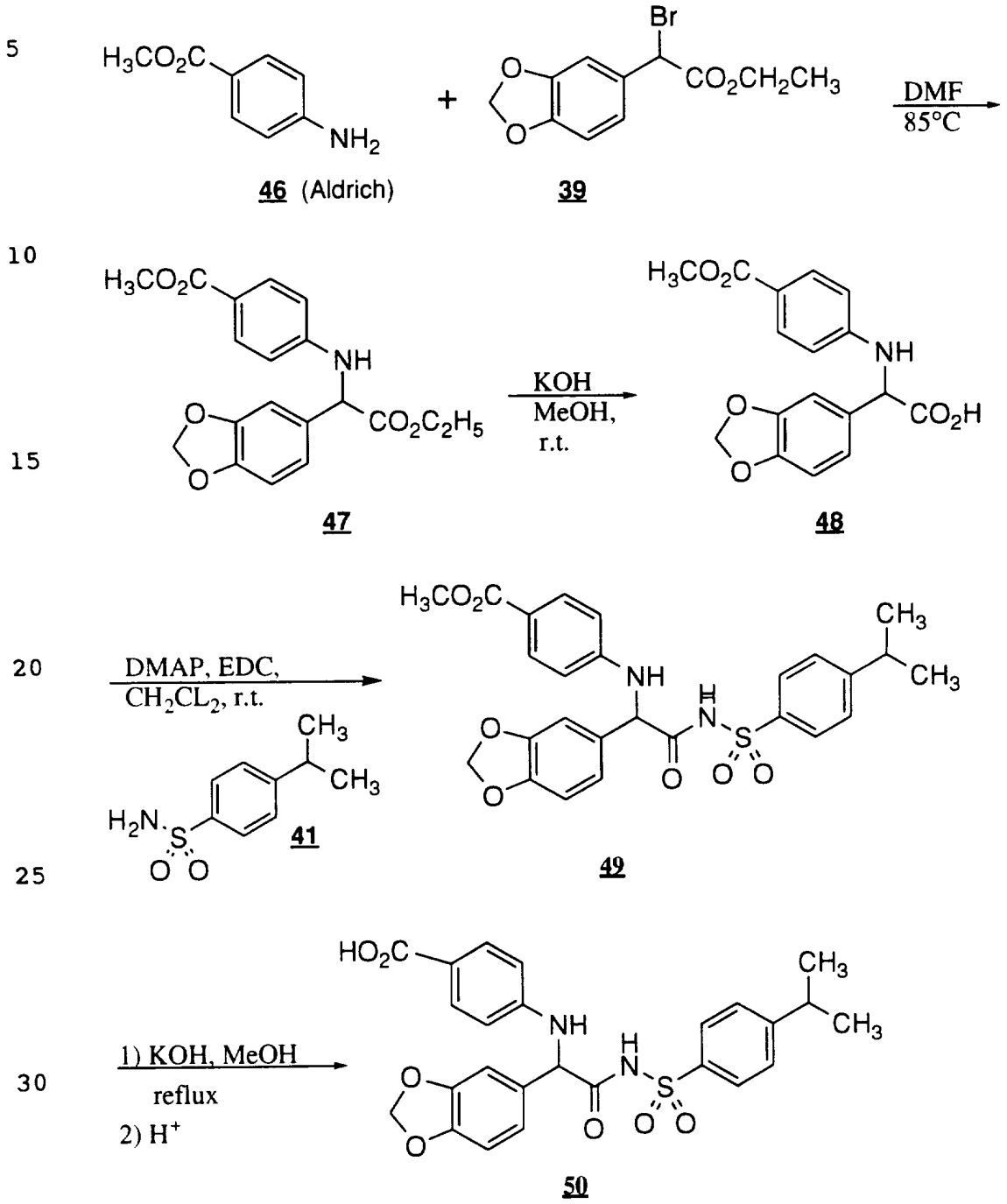
N-(4-iso-propylbenzenesulfonyl)-α-(4-carboxy-2-n-propyl-phenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt, **45**:

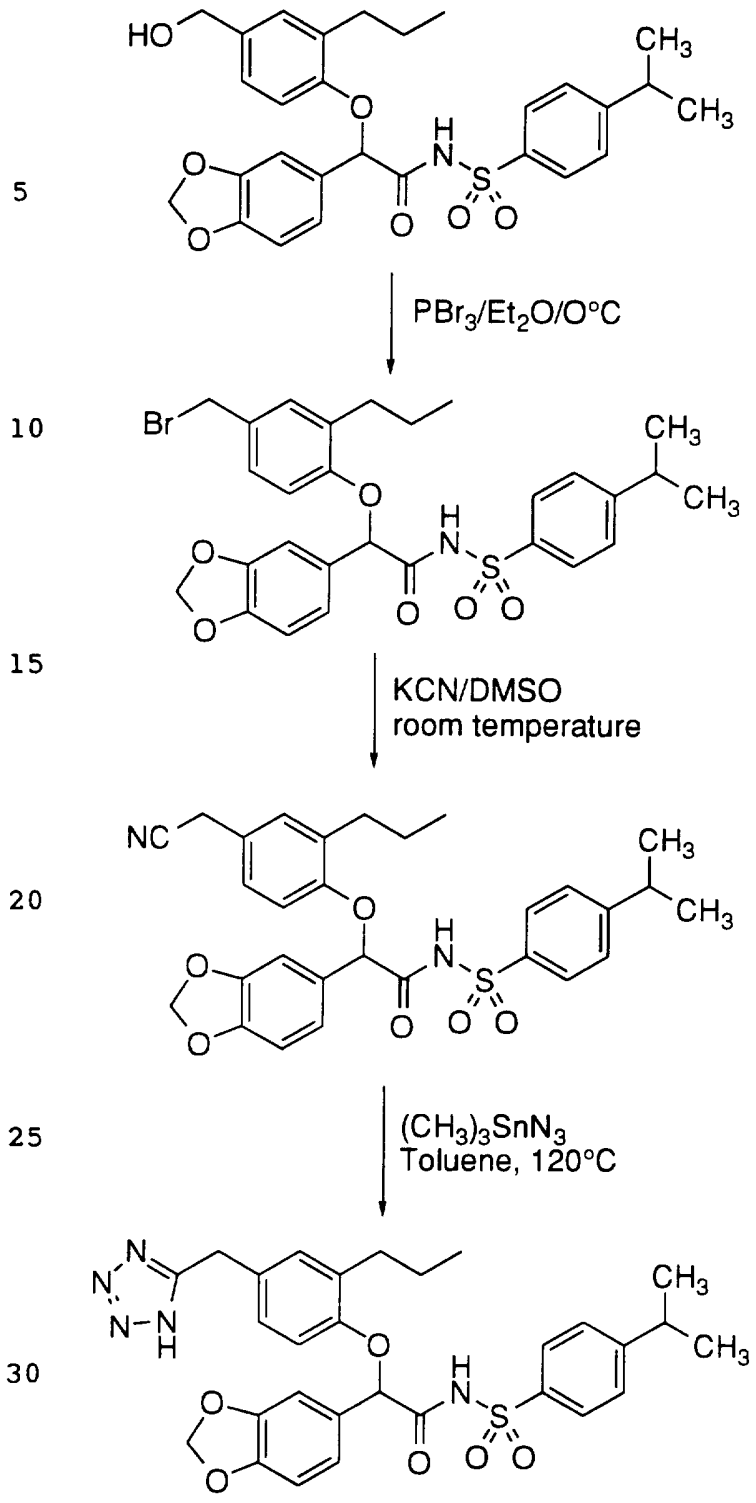


Crystalline, pK_{a1} = 5.4, pK_{a2} = 5.8; MW = 615.8, logP 2.7; Aqueous solubility > 50 mg/mL

Similarly, compounds of Formula IV wherein -A- is represented by $-OCH_2-$ and X is represented by -NH- can be prepared using the route described below

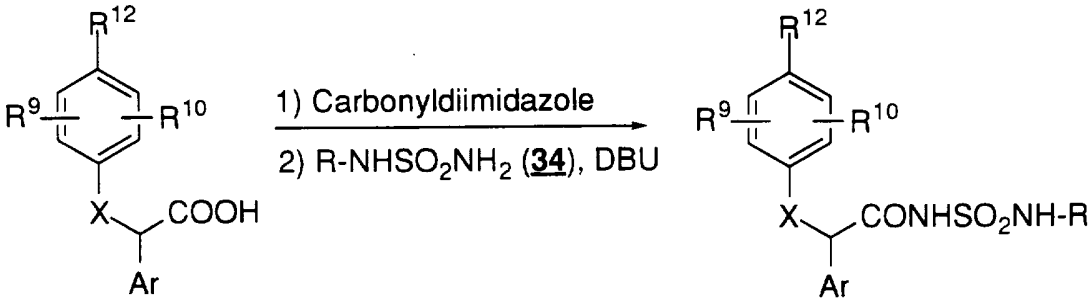
N-(4-iso-propylbenzenesulfonyl)-α-[N-(4-carboxyanilinyl)]-3,4-methylenedioxyphenylacetamide dipotassium salt, **50**:




HO
CH3
CH3
O
H
N
S
O
O
O
O
O
PBr3/Et2O/0°C
Br
KCN/DMSO
room temperature
NC
(CH3)3SnN3
Toluene, 120°C
N
N
N
H

Scheme 8 illustrates the synthetic route to compounds bearing N-acylsulfamides (**35**) (Z=-CONHSO2NH-R). The carboxylic acid **33** (Z_1=-COOH; Scheme 1) is reacted with 1,1'-carbonyldiimidazole (CDI) to provide the acylimidazole which is then reacted with an appropriate sulfamide (**34**) in the presence of DBU. The sulfamides (R-NHSO2NH2) can be prepared from appropriate primary amines using the literature procedures [W. L. Matier, W. T. Comer and D. Deitchman, J. Med. Chem., 15, 538-541(1972); J. D. Catt and W. L. Maiter, J. Org. Chem., 39, 566-568(1974)].

Scheme 8



33 **35**

The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the functionality present on the heterocycle and in the reactants being employed should be consistent with the chemical transformations being conducted. Depending upon the reactions and techniques employed, optimal yields may require changing the order of synthetic steps or use of protecting groups followed by deprotection.

The compounds useful in the novel method treatment of this invention form salts with various inorganic and organic acids and bases which are also within the scope of the invention. Such salts include ammonium salts, alkali metal salts like sodium and potassium salts, alkaline earth metal salts like the calcium and magnesium salts, salts with organic bases; e.g., dicyclohexylamine salts, N-methyl-D-glucamine salts, salts with amino acids like arginine, lysine, and the like. Also, salts with organic and inorganic acids may be prepared; e.g., HCl, HBr, H_2SO_4, H_3PO_4, methanesulfonic, toluenesulfonic, maleic, fumaric, camphorsulfonic.

The salts can be formed by conventional means, such as by reacting the free acid or free base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed *in vacuo* or by freeze-drying or by exchanging the cations of an existing salt for another cation on a suitable ion exchange resin.

It will be appreciated that the compounds of general Formula I in this invention may be derivatised at functional groups to provide prodrug derivatives which are capable of conversion back to the parent compounds *in vivo*. The concept of prodrug administration has been extensively reviewed (e.g. A.A. Sinkula in Annual Reports in Medicinal Chemistry, Vol 10, R.V. Heinzelman, Ed., Academic Press, New York London, 1975, Ch. 31, pp. 306-326, H. Ferres, Drugs of Today, Vol 19, 499-538 (1983) and J. Med. Chem., 18, 172 (1975)). Examples of such prodrugs include the physiologically acceptable and metabolically labile ester derivatives, such as lower alkyl (e.g. methyl

or ethyl esters), aryl (e.g. 5-indanyl esters), alkenyl (e.g. vinyl esters), alkoxyalkyl (e.g. methoxymethyl esters), alkylthioalkyl (e.g. methylthiomethyl esters), alkanoyloxyalkyl (e.g. pivaloyloxymethyl esters), and substituted or unsubstituted aminoethyl esters (e.g. 2-dimethylaminoethyl esters). Additionally, any physiologically acceptable equivalents of the compounds of general Formula I, similar to the metabolically labile esters, which are capable of producing the parent compounds of general Formula I *in vivo*, are within the scope of this invention.

It will be further appreciated that the majority of compounds of general Formula I claimed herein are asymmetric and are produced as racemic mixtures of enantiomers and that both the racemic compounds and the resolved individual enantiomers are considered to be within the scope of this invention. The racemic compounds of this invention may be resolved to provide individual enantiomers utilizing methods known to those skilled in the art of organic synthesis. For example, diastereoisomeric salts, esters or imides may be obtained from a racemic compound of general Formula I and a suitable optically active amine, amino acid, alcohol or the like. The diastereoisomeric salts, esters or imides are separated and purified, the optically active enantiomers are regenerated and the preferred enantiomer is the more potent isomer. The resolved enantiomers of the compounds of general Formula I, their pharmaceutically acceptable salts and their prodrug forms are also included within the scope of this invention.

Endothelin (ET-1), and two closely related bioactive peptides, ET-2 and ET-3, are widely distributed in mammalian tissues, and they can induce numerous biological responses in non-vascular as well as vascular tissues by binding to at least two distinct endothelin receptor subtypes. In addition to cardiovascular smooth muscle, neural and atrial sites, endothelin receptors may also be found in brain, gastrointestinal, kidney, lung, urogenital, uteral and placental tissues.

Endothelin is a potent vasoconstrictor peptide and thus plays a role in vivo in arterial pressure-volume homeostasis. Not only peripheral, but coronary vascular resistance as well, is increased by

endothelin; cardiac output is decreased, while plasma renin activity is increased. There is a reduction in renal blood flow and glomerular filtration rate, while levels of atrial natriuretic factor, vasopressin, and aldosterone become elevated.

It is also considered, in accordance with the present invention, that antagonists for the endothelin receptor may be useful in preventing or reducing restenosis subsequent to denudation following angioplasty. Such denudation results in myointimal thickening following angioplasty, due to increased endothelin release. Endothelin acts as a growth factor with respect to smooth muscle and fibroblastic cells, and possibly other types of cells, as well.

Endothelin is also a neuropeptide, acting on the posterior pituitary, where it modulates the release of the neurosecretory hormones vasopressin and oxytocin. Endothelin released from the posterior pituitary also acts as a circulating hormone, having a wide range of actions as discussed further above. This includes effects on the endocrine system, especially the adrenal glands. Endothelin increases plasma levels of epinephrine.

Consequently, the novel compounds of the present invention, which are receptor antagonists of endothelin, have therapeutic usefulness in preventing, decreasing or modulating the various physiological effects of endothelin discussed above, by wholly or partially blocking access of endothelin to its receptor.

Endothelin Receptor Binding Assays

The binding of the novel compounds of this invention to the endothelin receptor was determined in accordance with the assay described in detail immediately below. It is similar to the assay described in Ambar et al. (1989) Biochem. Biophys. Res. Commun. 158, 195-201; and Khoog et al. (1989) FEBS Letters, 253, 199-202.

The endothelins (ETs) have a number of potent effects on a variety of cells, and exert their action by interacting with specific receptors present on cell membranes. The compounds described in the present invention act as antagonists of ET at the receptors. In order to

identify ET antagonists and determine their efficacy *in vitro*, the following three ligand receptor assays were established.

Receptor binding assay using cow aorta membrane preparation:

Thoracic aortae were obtained from freshly slaughtered calves and brought to the lab on wet ice. The adventitia were removed, and the aorta was opened up lengthwise. The lumenal surface of the tissue was scrubbed with cheesecloth to remove the endothelial layer. The tissue was ground in a meat grinder, and suspended in ice-cold 0.25 *M* sucrose, 5 *mM* tris-HCl, pH 7.4, containing 0.5 mg/mL leupeptin and 7 mg/mL pepstatin A. Tissue was homogenized twice and then centrifuged for 10 minutes at 750 x *g* at 4°C. The supernatant was filtered through cheesecloth and centrifuged again for 30 minutes at 48,000 x *g* at 4°C. The pellet thus obtained was resuspended in the buffer solution described above (including the protease inhibitors), and aliquots were quick-frozen and stored at -70°C until use. Membranes were diluted into 50 *mM* potassium phosphate (KPi), 5 mM EDTA pH 7.5 containing 0.01% human serum albumin. Assays were done in triplicate. Test compounds and 100 *pM* [^{125}I]-endothelin-1 (2000-2200 Ci/mmole, obtained from New England Nuclear or Amersham) were placed in a tube containing this buffer, and the membranes prepared above were added last. The samples were incubated for 60 min at 37°C. At the end of this incubation, samples were filtered onto prewetted (with 2% BSA in water) glass fiber filter pads and washed with 150 *mM* NaCl, 0.1% BSA. The filters were assayed for ^{125}I radioactivity in a gamma counter. Nondisplaceable binding of [^{125}I]-endothelin-1 is measured in the presence of 100 nM unlabelled endothelin-1 [Endothelin-1 (ET-1) was purchased from Peptides International (Louisville, KY). ^{125}I-ET-1 (2000 Ci/mMol) was purchased from Amersham (Arlington Heights, IL)]. Specific binding is total binding minus nondisplaceable binding. The inhibitory concentration (IC_{50}) which gives 50% displacement of the total specifically bound [^{125}I]-endothelin-1 was presented as a measure of the efficacy of such compounds as ET antagonists.

Receptor binding assay using rat hippocampal membrane preparation:

Rat hippocampi were obtained from freshly sacrificed male Sprague-Dawley rats and placed in ice cold 0.25 *M* sucrose, 5 *mM* tris-HCl, pH 7.4 containing 0.5 mg/mL leupeptin, 7 mg/mL pepstatin A. Hippocampi were weighed and placed in a Dounce homogenizer with 25 volumes (wet weight to volume) ice-cold sucrose buffer in the presence of protease inhibitors. Hippocampi were homogenized using a Dounce (glass-glass) homogenizer with type A pestle, with homogenizer in ice. Tissue homogenate was centrifuged at 750 x *g* for 10 min at 4°C. Supernatant was filtered through dampened cheesecloth, and centrifuged again at 48,000 x *g* for 30 min at 4°C. Pellets were resuspended in sucrose buffer with protease inhibitors. Aliquots of this preparation were quick frozen and stored at -70°C until use. Membranes were diluted into 50 *mM* KPi, 5 *mM* EDTA pH 7.5 containing 0.01% human serum albumin. Assays were done in triplicate. Test compounds and 25 *pM* [^{125}I]-endothelin-1 (2000-2200 Ci/mmole, obtained from New England Nuclear or Amersham) were placed in a tube containing this buffer, and the membranes prepared above were added last. The samples were incubated for 60 min at 37°C. At the end of this incubation, samples were filtered onto prewetted (with 2% BSA in water) glass fiber filter pads and washed with 150 *mM* NaCl, 0.1% BSA. The filters were assayed for ^{125}I radioactivity in a gamma counter. Nondisplaceable binding of [^{125}I]-endothelin-1 is measured in the presence of 100 *nM* unlabelled endothelin-1 [Endothelin-1 (ET-1) was purchased from Peptides International (Louisville, KY). ^{125}I-ET-1 (2000 Ci/mMol) was purchased from Amersham (Arlington Heights, IL)]. Specific binding is total binding minus nondisplaceable binding. The inhibitory concentration (IC_{50}) which gives 50% displacement of the total specifically bound [^{125}I]-endothelin-1 was presented as a measure of the efficacy of such compounds as endothelin antagonists.

Receptor binding assay using cloned human ET receptors expressed in Chinese Hamster Ovary Cells:

Both endothelin receptor subtypes were cloned from a human cDNA library and were individually expressed in Chinese

Hamster Ovary cells. Cells were harvested by addition of 126 *mM* NaCl, 5 *mM* KCl, 2 *mM* EDTA, 1 *mM* NaH_2PO_4, 15 *mM* glucose, 10 *mM* tris/HEPES pH 7.4 Cells were centrifuged at 250 x *g* for 5 minutes. The supernatant was aspirated off, and the cells were resuspended in the 50 *mM* KPi, 5 *mM* EDTA pH 7.5 containing 0.01% human serum albumin. Assays were done in triplicate. Test compounds and 25-100 *pM* [^{125}I]-endothelin-1 (2000-2200 Ci/mmole, obtained from New England Nuclear or Amersham) were placed in a tube containing 50 *mM* KPi, 5 *mM* EDTA pH 7.5 containing 0.01% human serum albumin, and the cells prepared above were added last. The samples were incubated for 60 min at 37°C. At the end of this incubation, samples were filtered onto prewetted (with 2% BSA in water) glass fiber filter pads and washed with 150 *mM* NaCl, 0.1% BSA.

The filters were assayed for ^{125}I radioactivity in a gamma counter. Nondisplaceable binding of [^{125}I]-endothelin-1 is measured in the presence of 100 nM unlabelled endothelin-1 [Endothelin-1 (ET-1) was purchased from Peptides International (Louisville, KY). ^{125}I-ET-1 (2000 Ci/mMol) was purchased from Amersham (Arlington Heights, IL)]. Specific binding is total binding minus nondisplaceable binding. The inhibitory concentration (IC_{50}) which gives 50% displacement of the total specifically bound [^{125}I]-endothelin-1 was presented as a measure of the efficacy of such compounds as endothelin antagonists.

The binding assays described above were used to evaluate the potency of interaction of representative compounds of the invention with endothelin receptors. To determine whether these compounds were endothelin antagonists, assays which measure the ability of the compounds to inhibit endothelin-stimulated phosphatidylinositol hydrolysis were established. Rat uterus contains predominantly one of the known endothelin receptor subtypes (ET_A).

<u>Phosphatidylinositol hydrolysis assays using rat uterine slices:</u>

Diethylstilbestrol primed female Sprague-Dawley rats were sacrificed and their uteri were collected, dissected of fat and connective tissue and minced. Minced tissue was added to oxygenated (95% O_2,

5% CO_2) 127 *mM* NaCl, 25 *mM* $NaHCO_3$, 10 *mM* Glucose, 2.5 *mM* KCl, 1.2 *mM* KH_2PO_4, 1.2 *mM* $MgSO_4$, 1.8 *mM* $CaCl_2$. To the tissue mince, 1.2 *mM myo*-[^{3}H]-inositol (Amersham) was added. The mince was incubated 90 min at 37°C, with constant oxygenation. After incubation, the loaded tissue mince was washed five times with the same oxygenated buffer to remove excess radiolabelled inositol. The tissue mince was resuspended in the above buffer, containing 10 *mM* LiCl, aliquotted into tubes, and 3 *nM* endothelin-1 with and without test compounds was added to start the assay. Assays were done in quadruplicate. Samples were incubated at 37°C under blowing O_2 in a hooded water bath for 30 minutes. Reaction was stopped by addition of trichloroacetic acid to 6% concentration. Samples were sonicated for 10 min, centrifuged 20 min, then trichloroacetic acid was extracted with water-saturated ethyl ether. An aliquot of each sample was neutralized and diluted by addition of 50 *mM* tris-HCl pH 7.4. A 100 mL aliquot of this solution was assayed for radioactivity in a beta counter. The diluted neutralized sample was applied to Dowex 1 x 8-formate columns, washed with water, then washed with 60 *mM* ammonium formate, 5 *mM* sodium tetraborate. Samples were eluted with 200 *mM* ammonium formate, 5 *mM* sodium tetraborate. The radioactivity of each eluted sample was measured in a beta counter. Radioactivity was normalized by dividing radioactivity in post column sample by radioactivity in precolumn sample. Control values (100% stimulated) are values in the presence of endothelin minus the values in the absence of endothelin (basal). Test sample values are the values in the presence of endothelin and test sample minus basal. Inhibitory concentration (IC_{50}) is the concentration of test compound required to give a sample activity of 50% of control value.

Sarafotoxin S6c is a member of the endothelin family which binds preferentially to one of the known endothelin receptor subtypes (ET_B).

Phosphatidylinositol hydrolysis assays using rat lung slices:

Male Sprague-Dawley rats were sacrificed and their lungs were collected, dissected of fat and connective tissue and minced.

Minced tissue was added to oxygenated (95% O_2, 5% CO_2) 127 *mM* NaCl, 25 *mM* $NaHCO_3$, 10 *mM* glucose, 2.5 *mM* KCl, 1.2 *mM* KH_2PO_4, 1.2 *mM* $MgSO_4$, 1.8 *mM* $CaCl_2$. To the tissue mince, 1.2 *μM myo*-[^{3}H]-inositol was added. The mince was incubated 60 min at 37°C, with constant oxygenation. After incubation, loaded tissue mince was washed five times with the same oxygenated buffer to remove excess radiolabelled inositol. Tissue mince was resuspended in the above buffer, containing 10 *mM* LiCl, aliquotted into tubes, and 3 *nM* sarafotoxin S6c with and without test compounds was added to start the assay. Assays were done in quadruplicate. Samples were incubated at 37°C under blowing O_2 in a hooded water bath for 30 minutes. Reaction was stopped by addition of 0.5 mL 18% trichloroacetic acid to 6% concentration. Samples were sonicated for 10 min, centrifuged 20 min, then trichloroacetic acid was extracted with water-saturated ethyl ether. An aliquot of each sample was neutralized and diluted by addition of 50 *mM* tris-HCl pH 7.4. A 100 mL aliquot of this solution was assayed for radioactivity in a beta counter. The diluted neutralized sample was applied to Dowex 1 x 8-formate columns, washed with water, then washed with 60 *mM* ammonium formate, 5 *mM* sodium tetraborate. Samples were eluted with 200 *mM* ammonium formate, 5 *mM* sodium tetraborate. The radioactivity of each eluted sample was measured in a beta counter. Radioactivity was normalized by dividing radioactivity in post column sample by radioactivity in precolumn sample. Control values (100% stimulated) are values in the presence of sarafotoxin minus the values in the absence of sarafotoxin (basal). Test sample values are the values in the presence of sarafotoxin and test sample minus basal. Inhibitory concentration (IC_{50}) is the concentration of test compound required to give a sample activity of 50% of control value.

Phosphatidylinositol hydrolysis assays using cloned human endothelin receptors expressed in Chinese Hamster Ovary cells:

Endothelin receptors of both receptor subtypes were cloned from a human cDNA library and were individually expressed in

Chinese Hamster Ovary cells. Cells were loaded overnight by the addition of 1.2 μM *myo*-[^{3}H]-inositol to their growth medium. Cells were harvested by addition of 126 *mM* NaCl, 5 *mM* KCl, 2 *mM* EDTA, 1 *mM* NaH_2PO_4, 15 *mM* glucose, 10 *mM* tris/HEPES pH 7.4. Cells were washed five times by centrifugation at 250 x *g* for 5 minutes to remove excess radiolabelled inositol. The supernatant was aspirated off, and the cells were resuspended in the same oxygenated (95% O_2, 5% CO_2) buffer containing 10 *mM* LiCl, aliquotted into tubes, and 0.3 *nM* endothelin-1 with and without test compounds was added to start the assay. Assays were done in quadruplicate. Samples were incubated at 37°C under blowing O_2 in a hooded water bath for 30 minutes. Reaction was stopped by addition of 0.5 mL 18% trichloroacetic acid to 6% concentration. Samples were sonicated for 10 min, centrifuged 20 min, then trichloroacetic acid was extracted with water-saturated ethyl ether. An aliquot of each sample was neutralized and diluted by addition of 50 *mM* tris-HCl pH 7.4. A 100 mL aliquot of this solution was assayed for radioactivity in a beta counter. The diluted neutralized sample was applied to Dowex 1 x 8-formate columns, washed with water, then washed with 60 *mM* ammonium formate, 5 *mM* sodium tetraborate. Samples were eluted with 200 *mM* ammonium formate, 5 *mM* sodium tetraborate. The radioactivity of each eluted sample was measured in a beta counter. Radioactivity was normalized by dividing radioactivity in post column sample by radioactivity in precolumn sample. Control values (100% stimulated) are values in the presence of endothelin minus the values in the absence of endothelin (basal). Test sample values are the values in the presence of endothelin and test sample minus basal. Inhibitory concentration (IC_{50}) is the concentration of test compound required to give a sample activity of 50% of control value.

Using the methodology described above, representative compounds of the invention were evaluated and found to exhibit IC_{50} values of at least <50 μM thereby demonstrating and confirming the utility of the compounds of the invention as effective endothelin antagonists.

Intravenous Effect of Endothelin-1 Antagonist, *N*-(4-*iso*-propylbenzene-sulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide dipotassium salt [Example 58] on Endothelin 1-Induced Changes in Diastolic and Urethral Pressures in the Anesthetized Male Dog

Methodology for determining whether an ET-1 selective antagonist could inhibit the ET-1 mediated prostatic urethral contractions in a mongrel dog model:

On separate days, two fasted male mongrel dogs (HRP, Inc.) weighing 11.0 and 12.4 kg, were anesthetized with Sodium Pentobarbital (Steris Laboratories, Inc.) at 35 mg/kg (i.v.) to effect, followed by 4 mg/kg/hr (i.v.) infusion. A cuffed endotracheal tube was inserted and each animal was ventilated with room air using a positive displacement large animal ventilator (Harvard Apparatus) at a rate of 18 breaths/minute and an average tidal volume of 18 ml/kg body weight. Body temperature was maintained with a heating pad and heat lamp using a temperature controller (YSI) and esophageal probe. Two catheters (PE 260) were placed in the aorta via the femoral arteries (one in each artery) for administration of endothelin or phenylephrine and for continuous direct monitoring of blood pressure and heart rate using a Statham blood pressure transducer (Spectramed) and a computer system (Modular Instruments, Inc.). Two other catheters (PE 260) were placed in the vena cava via the femoral veins (one catheter in each vein) for administration of pentobarbital and *N*-(4-*iso*-propylbenzene-sulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide dipotassium salt [Example 58] . A supra-pubic incision approximately one-half inch lateral to the penis was made to expose the ureters, urinary bladder, prostate, and urethra. The dome of the bladder was retracted to facilitate dissection of the ureters. The ureters were cannulated with PE 90 and tied off to the bladder. Umbilical tape was passed beneath the urethra at the bladder neck and another piece of tape was placed approximately 1-2 cm. distal to the prostate. The

bladder dome was incised and a Micro-tip® catheter transducer (Millar Instruments, Inc.) was advanced into the urethra. The neck of the bladder was ligated with the umbilical tape to hold the transducer. The bladder incision was sutured with 3-0 silk (purse string suture). The transducer was withdrawn until it was positioned in the prostatic urethra. The position of the Micro-tip® catheter was verified by gently squeezing the prostate and noting the large change in urethral pressure prior to ligating the distal urethra.

Experimental Protocol:

Phenylephrine (PE) (10 μg/kg, intra-arterial) was administered and pressor effects on diastolic blood pressure (DBP) and intra-urethral pressure (IUP) were noted. When blood pressure returned to baseline, endothelin-1 (ET-1) (1 nmole/kg, intra-arterial) was administered. Changes in DBP and IUP were monitored for one hour and an ET-1 selective endothelin antagonist, such as the compound of Example 58, *N*-(4-*iso*-propylbenzene-sulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide dipotassium salt (30 mg/kg, intra-venous) was administered. Ten to fifteen minutes later when blood pressure had stabilized, ET-1 was administered again, and inhibition of ET-1 induced effects were noted. PE was administered at the end of the experiment to verify specificity for ET-1 blockade. The dogs were euthanized with an overdose of pentobarbital followed by saturated KCl.

The drugs utilized in the experiment described above were:

1) Phenylephrine, HCl (PE) (Sigma Chemical, Co.) was given at a volume of 0.05 mL/kg;

2) Endothelin-1 (ET-1) (Human, Porcine, Canine, Rat, Mouse, Bovine) (Peninsula Laboratories, Inc.) was given at a volume of 0.05 mL/kg;

3) ET-1 selective antagonist, such as the compound of Example 58, *N*-(4-*iso*-propylbenzene-sulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt, was given at a volume of 0.3 mL/kg.

All drugs were dissolved in isotonic saline solution.

Results:

ET-1 elicited an initial depressor effect followed by a longer pressor effect. In one dog, the pressor effect was biphasic. The decrease in DBP in both dogs averaged 13 mmHg, while the peak pressor effect averaged 26 mmHg. The average ET-1 induced increase in IUP was 15 mmHg. Ten to 14 minutes after administration of *N*-(4-*iso*-propylbenzene-sulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide dipotassium salt [Example 58], the dogs were challenged with ET-1 again and the depressor and pressor effects on DBP were inhibited 69% and 76%, respectively. The pressor effect on IUP was inhibited 93% (Table 1). Intra-arterial PE-induced increases in DBP and IUP did not change significantly after administration of *N*-(4-*iso*-propylbenzene-sulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide dipotassium salt [Example 58] in the one dog studied. Increases in DBP and IUP were inhibited 35 and 13%, respectively (Table 2).

Table 1. Effects of ET-1 Antagonist, *N*-(4-*iso*-propylbenzene-sulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide dipotassium salt [Example 58], on ET-1 Induced Changes in DBP and IUP in Anesthetized Male Dogs (n=2)

	CHANGE IN DBP (mmHg)		CHANGE IN IUP (mmHg)
DOG #	DEPRESSOR	PRESSOR	PRESSOR
	ET-1 (i.a.)		
HG FMJC	-10	19	18
HG FMHK	-15	33	11
MEAN	-13	26	15
SEM	3	7	4
	ET-1 + Example 58		
HG FMJC	-3	8	1
HG FMHK	-5	2	1
MEAN	-4	5	1
SEM	1	3	0
	% INHIBITION		
HG FMJC	70	58	94
HG FMHK	67	94	91
MEAN	69	76	93
SEM	2	18	2

Table 2. Effects of ET-1 Antagonist, *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt [Example 58], on PE-Induced Changes in DBP and IUP in Anesthetized Male Dog # HG FMJC

TREATMENT	INCREASE IN DBP (mmHg)	INCREASE IN IUP (mmHg)
Phenylephrine	17	31
Phenylephrine + Example 58	11	27
% Inhibition of Control	35	13

Conclusions:

ET-1 causes constriction of the prostatic urethra, as well as a complex hemodynamic response comprised of an initial depressor and subsequent pressor response in anesthetized dogs. The hemodynamic and prostatic urethral responses to ET-1 were specifically inhibited by *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt. The efficacy of the *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt in inhibiting the prostatic urethral pressor effect of ET-1 suggests that selective antagonists of ET-1 will be useful in the treatment of urinary obstruction in benign prostatic hyperplasia.

In Situ Rat Prostate:

Male Sprague-Dawley rats (Taconic Farms) weighing 300-400 grams were anesthetized with urethane (1.75 g/kg, ip), a tracheal cannula was inserted, and the femoral artery was cannulated. Core body temperature was maintained at 37 + 0.5 °C. A 4-5 cm midline abdominal incision was made to expose the bladder and prostate. The

prostate was separated from the bladder and surrounding capsule by blunt dissection with a forcep. A length of surgical silk was gently secured around the anterior tips of the prostate lobes. A second length of surgical silk attached to an atraumatic needle was passed through and tied to the base of the prostate approximately 10-12 mm posterior to the first tie. The posterior ligature was secured to an anchor post whereas the anterior ligature was connected to a Grass FT03 transducer (Grass Instruments, Quincy, MA) and maintained at a tension of 1 g. Signals from the transducer were amplified and recorded on a polygraph (Hewlett-Packard 8805B amplifiers and 7758A recorder, Palo Alto, CA). After equilibrating for approximately 15 min, the rats were administered pretreatment drugs (atropine 1 mg/kg, (+) propranolol 1 mg/kg) 10 min apart through the intra-arterial (IA) cannula. Thirty minutes later, ET-1 (0.3 nmoles/kg) was injected intra-arterial every thirty minutes for a total of three times. Five minutes before the third injection of ET-1, vehicle with or without an endothelin antagonist was injected IA. The response of the prostate to ET-1 was quantified by measuring the change (Δ) from baseline tension to the peak of the response during the 5-minute period after the third ET-1 injection.

The *in situ* rat postate protocol has been utilized to determine the antagonist activity and potency of compounds of this invention to block the direct contractile effects of ET-1 on the rat prostate in vivo. In this protocol, *N*-(4-*iso*-propylbenzene-sulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt was demonstrated to cause a specific inhibition of ET-1 to contract the prostate and will be useful in the treatment of urinary obstruction in benign prostatic hyperplasia.

Accordingly the novel compounds of the present invention are useful in human therapy for treating asthma, hypertension, renal failure particularly post-ischemic renal failure, cyclosporin nephrotoxicity, vasospasm, cerebral and cardiac ischemia, myocardial infarction, or endotoxin shock caused by or associated with endothelin,

by adminstration to a patient in need of such treatment of a therapeutically effective amount thereof.

In the management of hypertension and the clinical conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. Although the dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize, the dosage range will generally be about 0.5 mg to 1.0 g. per patient per day which can be administered in single or multiple doses. Perferably, the dosage range will be about 0.5 mg to 500 mg. per patient per day; more preferably about 0.5 mg to 200 mg. per patient per day.

The compounds of this invention can also be administered in combination with A_2-adrenosine receptor agonists, α-adrenergic antagonists, angiotensin II antagonists, angiotensin converting enzyme inhibitors, β-adrenergic antagonists, atriopeptidase inhibitors(alone or with ANP), calcium channel blockers, diuretics, potassium channel agonists, renin inhibitors, sertonin antagonists, sympatholytic agents, as well as other antihypertensive agents. For example, the compounds of this invention can be given in combination with such compounds as A-69729, FK 906, FK 744, UK-73900, CSG 22492C, amiloride, atenolol, atriopeptin, bendroflumethiazide, chlorothalidone, chlorothiazide, clonidine, cromakalin, cryptenamine acetates and cryptenamine tannates, deserpidine, diazoxide, doxazosin, guanabenz, guanethidine, guanethidine sulfate, hydralazine hydrochloride, hydrochlorothiazide, isradipine, ketanserin, losartan, metolazone, metoprolol, metoprolol tartate, methyclothiazide, methyldopa, methyldopate hydrochloride, minoxidil, nadolol, pargyline hydrochloride, pinacidil, pindolol,

polythiazide, prazosin, propranolol, rauwolfia serpentina, rescinnamine, reserpine, sodium nitroprusside, spironolactone, terazosin, timolol maleate, trichlormethiazide, trimethophan camsylate, verapamil, benzthiazide, quinethazone, ticrynafan, triamterene, acetazolamide, aminophylline, cyclothiazide, ethacrynic acid, furosemide, merethoxylline procaine, sodium ethacrynate, captopril, delapril hydrochloride, enalapril, enalaprilat, fosinopril sodium, lisinopril, pentopril, quinapril, quinapril hydrochloride, ramapril, teprotide, zofenopril, zofenopril calcium, diflusinal, diltiazem, felodipine, nicardipine, nifedipine, niludipine, nimodipine, nisoldipine, nitrendipine, and the like, as well as admixtures and combinations thereof. Combinations useful in the management of congestive heart failure include, in addition, compounds of this invention with cardiac stimulants such as dobutamine and xamoterol and phosphodiesterase inhibitors including amrinone and milrinone.

Typically, the individual daily dosages for these combinations can range from about one-fifth of the minimum recommended clinical dosages to the maximum recommended levels for those entities given singly. To illustrate these combinations, one of the endothelin antagonists of this invention effective clinically at a given daily dose range can be effectively combined, at levels which are less than that daily dose range, with the following compounds at the indicated per day dose range: hydrochlorothiazide (6-100 mg), chlorothiazide (125-500 mg), furosemide(5-80 mg), ethacrynic acid (5-200 mg), amiloride (5-20 mg), diltiazem(30-540 mg), felodipine(1-20 mg), nifedipine(5-120 mg), nitrendipine(5-60 mg), timolol maleate (1-20 mg), propanolol (10-480 mg), and methyldopa(125-2000 mg). In addition triple drug combinations of hydrochlorothiazide(6-100 mg) plus amiloride (5-20 mg) plus endothelin antagonists of this invention, or hydrochlorothiazide(6-100 mg) plus timolol maleate (1-20 mg) plus endothelin antagonists of this invention, or hydrochlorothiazide(6-100 mg) plus nifedipine (5-60 mg) plus endothelin antagonists of this invention are effective combinations to control blood pressure in hypertensive patients. Naturally, these dose ranges can be adjusted on a

unit basis as necessary to permit divided daily dosage and the dose will vary depending on the nature and severity of the disease, weight of the patient, special diets and other factors.

The present invention also relates to pharmaceutical compositions for treating asthma, hypertension, renal failure, particularly post-ischemic renal failure, cyclosporin nephrotoxicity, vasospasm, cerebral and cardiac ischemia, benign prostatic hyperplasia, myocardial infarction, or endotoxin shock caused by or associated with endothelin, comprising a therapeutically effective amount of the novel compound of this invention together with a pharmaceutically acceptable carrier therefor.

About 0.5 mg to 1.0 g. of compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which can be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unitform is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

The following examples illustrate the preparation of the compounds of Formula I and their incorporation into pharmaceutical compositions and as such are not to be considered as limiting the invention set forth in the claims appended hereto.

EXAMPLE 1

2-(2,6-Dipropyl-4-hydroxymethyl)phenoxyphenylacetic acids

Step A: Preparation of Alkyl 2-bromo-2-phenylacetates

Method A:

Substituted phenylacetic acid is convered to the corresponding methyl ester by refluxing the acid in methanol in the presence of a catalytic amount of conc. sulfuric acid. The ester thus obtained is then refluxed in carbon tetrachloride with N-bromosuccinimide (1.1 equiv) and AIBN (0.05-0.1 equiv). Upon completion of the reaction, the resulting product is purified by flash column chromatography using silica gel and ethyl acetate in hexane as eluent to provide the desired alkyl bromide.

Method B:

An arylaldehyde is reacted overnight with trimethylsilyl cyanide in the presence of catalytic amounts of KCN and 18-crown-6 in methylene chloride. The reaction mixture is quenched with water and extracted with CH_2Cl_2/ ethyl acetate/ether (1/2/2) mixture. The organic phase is washed with saturated aq. $NaHCO_3$ solution. After drying and concentration of the organic phase, the resulting trimethylsilyl cyanohydrin is hydrolyzed to give the corresponding hydroxy acid. Treatment with gaseous HCl in methanol or ethanol at

0°C for 0.5 h and then overnight at room temperature affords the crude 2-hydroxy ester. The ester is then treated with triphenylphosphine and carbon tetrabromide in methylene chloride at 0°C overnight. Methylene chloride is removed and flash column chromatography of the crude product using silica gel and ethyl acetate/hexane as eluent gives the desired 2-bromophenylacetates.

Step B: Alkylation of the phenol

(2,6-Dipropyl-4-hydroxymethyl)phenol (prepared as described in patent application WO 91/11999) is alkylated with 2-bromo-2-aryl esters in DMF using either cesium carbonate (Cs_2CO_3), or potassium carbonate (K_2CO_3), or sodium hydride (NaH). The alkylated product is purified by flash column chromatography using silica gel and ethyl acetate/hexane mixture as eluent to provide the desired substituted 2-phenoxy-2-phenylacetic acid esters.

Step C: General procedure for ester hydrolysis

The product of Step C is dissolved in methanol or ethanol and reacted with aqueous NaOH or LiOH, or KOH solution at room temperature for 1- 6 hours, neutralized to pH 7 with 1 N HCl and then concentrated in vacuo. The residue is purified on a silica gel flash chromatography column to afford the corresponding carboxylic acid.

The following phenoxyphenylacetic acid derivatives were prepared using the general procedures outlined in Example 1.

EXAMPLE 2

2-[(2,6-Dipropyl-4-hydroxymethyl)phenoxy]-2-(3-methylphenyl)acetic acid

^1H NMR (400 MHz, CD_3OD, ppm): δ 7.15 - 6.95 (m, 4H), 6.86 (s, 2H), 4.92 (br s, 1H), 4.5 (s, 2H), 2.3-2.1 (m, 4H), 2.2 (s, 3H), 1.5-1.35 (m, 2H), 1.32-1.18 (m, 2H), 0.7 (t, 6H).

EXAMPLE 3

2-[(2,6-Dipropyl-4-hydroxymethyl)phenoxy]-2-(4-phenoxyphenyl)-acetic acid

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.42 (d, 2H, J=8.4 Hz), 7.33 (dd, 2H, J=7.4 Hz, 8.5), 7.09 (t, 1H, J=7.4 Hz), 6.97-6.95 (m, 4H), 6.91 (d, 2H, J=8.4 Hz), 4.85 (s, 1H), 4.47 (s, 2H), 2.38 (t, 4H, J=8.0 Hz), 1.56 (sx, 2H, J=7.1 Hz), 1.42 (sx, 2H, J=7.1 Hz), 0.85 (t, 6H, J=7.3 Hz).

FAB-MS m/e = 435 (M+1)

EXAMPLE 4

2-[(2,6-Dipropyl-4-hydroxymethyl)phenoxy]-2-(4-phenylphenyl)acetic acid

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.62-7.60 (m, 4H), 7.51 (br, 2H), 7.44 (t, 2H, J=7.5 Hz), 7.34 (t, 1H, J=7.4 Hz), 6.99 (s, 2H), 4.83 (s, 1H), 2.40 (br, 4H), 1.53 (br, 2H), 1.42 (br, 2H), 0.82 (t, 6H, J=6.2 Hz).

FAB-MS m/e = 419 (M+1)

EXAMPLE 5

2-[(2,6-Dipropyl-4-hydroxymethyl)phenoxy]-2-(3-carboxyphenyl)-acetic acid

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 8.18 (s, 1H) 8.04 (d, 1H, J=7.5 Hz), 7.70 (d, 1H, J=7.4 Hz), 7.51 (d, 1H, J=7.6) Hz, 6.99 (s, 2H), 5.15 (s, 1H), 4.48 (s, 2H), 2.37 (m, 4H), 1.52 (m, 2H), 1.44 (m, 2H), 0.80 (t, 6H, J=7.3 Hz).

FAB-MS m/e = 387 (M+1)

EXAMPLE 6

2-[(2,6-Dipropyl-4-hydroxymethyl)phenoxy]-2-(3,4-ethylenedioxyphenyl)acetic acid

^{1}H NMR (200 MHz, CD_3OD, ppm): δ 6.95 (m, 3H), 6.85 (dd, 1H, J=8.3, 2.0 Hz), 6.72 (d, 1H, J=8.3 Hz), 4.76 (s, 1H), 4.46 (s, 2H), 4.20 (s, 4H), 2.37 (t, 4H, J=7.9 Hz), 1.44 (m, 4H), 0.83 (t, 6H, J=7.3 Hz).

FAB-MS m/e = 401 (M+1)

EXAMPLE 7

2-[(2,6-Dipropyl-4-hydroxymethyl)phenoxy]-2-(3,4,5-trimethoxyphenyl)acetic acid

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 6.97 (s, 2H), 6.80 (s, 2H), 4.88 (s, 1H), 4.48 (s, 2H), 3.81 (s, 6H), 3.75 (s, 3H), 2.39 (t, 3H, J=8.1 Hz), 1.55 (m, 2H), 1.41 (m, 2H), 0.82 (t, 6H, J=7.3 Hz).

FAB-MS m/e = 433 (M+1)

EXAMPLE 8

2-[2,6-Dipropyl-4-hydroxymethyl)phenoxy]-2-(3,4-methylenedioxyphenyl)acetic acid

^{1}H NMR (200 MHz, CD_3OD, ppm): δ 7.03 (s, 1H), 6.97 (s, 2H), 6.83 (d, 1H, J=7.7 Hz), 6.73 (d, 2H, J= 7.7 Hz), 5.94 (s, 2H), 4.84 (s, 1H), 4.48 (s, 2H), 2.38 (t, 4H, J=8.0 Hz), 1.46 (m, 4H), 0.85 (t, 6H, J=7.4 Hz).

FAB-MS m/e = 387 (M+1)

EXAMPLE 9

2-[(2,6-Dipropyl-4-hydroxymethyl)phenoxy]-2-(3,4-dimethoxy-phenyl)acetic acid

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.15 (d, 1H), 6.95 (d, 2H), 6.85 (dd, 2H), 4.8 (br s, 1H), 4.46 (br s, 2H), 3.84 (s, 3H), 3.8 (s, 3H), 2.35 (t, 4H), 1.62-1.47 (m, 2H), 1.45-1.3 (m, 2H), 0.85 (t, 6H).

EXAMPLE 10

2-[(2,6-Dipropyl-4-hydroxymethyl)phenoxy]-2-(3,5-dimethoxy-phenyl)acetic acid

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 6.954 (s, 2H), 6.66 (d, 2H), 6.39 (t, 1H), 4.747 (s, 1H), 4.47 (s, 2H), 3.74 (s, 6H), 2.39 (t, 4H), 1.60-1.51 (m, 2H), 1.437-1.35 (m, 2H), 0.82 (t, 6H).

EXAMPLE 11

2-((2,6-Dipropyl-4-tetrazol-5-yl)phenoxy)-2-(3-bromophenyl)acetic acid

1H NMR (400 MHz, CD_3OD, ppm): δ 7.73 (s, 2H), 7.67 (t, 1H, J=1.8 Hz), 7.57 (m, 1H), 7.46 (m, 1H), 7.33 (t, 1H, J=7.9 Hz), 5.89 (ddd, 1H, J=1.6, 10.1, 17.1 Hz), 5.41 (s, 1H), 5.08 (dd, 1H, J=10.1, 1.6 Hz), 5.01 (dd, 1H, J= 1.7, 17.1 Hz), 4.93 (s, 2H), 3.72 (s, 3H), 3.36-3.30 (m, 2H).

FAB-MS m/e = 470 (M+1)

EXAMPLE 12

2-[(2,6-Dipropyl-4-hydroxymethyl)phenoxy]-2-(3-bromophenyl)acetic acid

^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$,2/1, ppm): δ 7.667 (s, 1H), 7.496 (d, 1H), 7.3925 (d, 1H), 7.252 (t, 1H), 6.964 (s, 2H), 4.995 (s, 1H), 4.485 (s, 2H), 2.342 (t, 4H), 1.65-1.35 (m, 2H), 0.803 (t, 6H).

EXAMPLE 13

2-[(2,6-Dipropyl-4-hydroxymethyl)phenoxy]-2-(2-naphthyl)acetic acid

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 8.56-8.52 (m, 1H), 7.86-7.79 (m, 2H), 7.47-7.43 (m, 2H), 7.35-7.32 (m, 1 H), 6.91 (s, 2H), 5.36 (s, 1H), 4.44 (s, 1H), 1.46-1.41 (m, 2 H), 1.2-1.16 (m, 2H), 0.58 (t, J = 7.37, 6 H).

EXAMPLE 14

2-[(2,6-Dipropyl-4-(2-hydroxyethyl)phenoxy]-2-(2-naphthyl)acetic acid

STEP A: t-Butyldimethylsilyloxy-2,6-Dipropyl-4-formylbenzene

To a solution of 5.03 g (15.4 mmol)of t-butyl-dimethylsilyloxy-2,6-dipropyl-4-hydroxymethyl benzene in 30 mL of methylene chloride was added 8.7 g of pyridinium dichromate (PDC). The reaction mixture was stirred for 3 hours and then diluted with 300 mL of ethyl ether. The solution was then filtered through a pad of a 1:1 mixture of florisil and celite. Concentration of the filtrate gave 4.85 g of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.8 (s, 1H), 7.51 (s, 2H), 2.59-2.55 (m, 2H) 1.59-1.55 (m, 2H), 0.99 (s, 9H), 0.91 (t, J = 7.28 Hz, 3H), 0.20 (s, 6H).

STEP B: t-Butyldimethylsilyloxy-2,6-dipropyl-4-vinyl benzene

To a solution of 1.0 g (2.80 mmol) of methyl triphenylphosphonium bromide in 5.0 mL of ether at 0°C was added 1.12 mL (2.5M, 2.80 mmol) of butyllithium. The reaction mixture

was stirred for 30 minutes at 0°C and then 756 mg (2.33 mmol) of the title compound from Example 14 (Step A) was added. After stirring for 1h at room temperature, the reaction mixture was poured into ethyl acetate and washed with water and then saturated aqueous sodium chloride. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. Purification by flash chromotography (silica gel, hexane / ethyl acetate 97:3) gave 411 mg of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.02 (s, 2H), 6.6 (dd, J = 17.6, J = 10.7 Hz, 1H), 5.55 (d, J=17.6 Hz, 1H), 5.08 (d, J = 10.7 Hz, 1H), 2.53-2.50 (m, 4 H), 1.59-1.53 (m, 4H), 0.996 (s, 9 H), 0.90 (t, J = 7.33 Hz, 6 H), 0.16 (s, 6 H).

STEP C: t-Butyldimethylsilyloxy-2,6-dipropyl-4-(2-hydroxyethyl)-benzene

To a solution of 475 mg (1.48 mmol) of the product of Step B in 3 mL of THF at 0 °C was added 1.6 mL (1.62 mmol) of a 1N borane / THF solution. After 1 hour TLC indicated that the starting material had been consumed. The reaction mixture was quenched with 3 drops of methanol and then 0.70 mL (6.22 mmol) of 30 % sodium peroxide and 6.2 mL (6.2 mmol) of 1 N sodium hydroxide were added. After two hours the reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was then dried over sodium sulfate, filtered and concentrated. Flash chromatography (silica gel, hexane / ethyl acetate 4:1) gave 265 mg of the title compound as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.79 (s, 2 H), 3.79 (m, 2 H), 2.75 - 2.72 (m, 2 H), 2.51 - 2.48 (m, 4 H), 1.58 - 1.51 (m, 6 H), 0.99 (s, 9 H), 0.90 (t, J = 7.33, 6 H), 0.16 (s, 6 H).

STEP D: 2,6-Dipropyl-4-(2-hydroxyethyl)phenol

To a solution of 1.0 g (2.98 mmol) of the product of Step C in 3.0 mL of THF was added 3.57 mL (3.57 mmol) of 1.0 N

solution of tetrabutylammonium fluoride in THF. After 15 minutes TLC indicated that the reaction was complete. The reaction mixture was concentrated and then purified by flash chromatography (silica gel, hexane/ethyl acetate 3:1) to give 1.13 g of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.8 (s, 2 H) , 3.78 (t , J = 6.5 Hz, 2 H), 2.73 (t, J = 6.5 Hz, 2 H), 2.54 - 2.50 (m, 4H), 1.66 - 1.56 (m, 4 H), 0.96 (t , J = 7.3 Hz, 6 H).

STEP E: Methyl 2-[(2,6-dipropyl-4-(2-hydroxyethyl)phenoxy]-2-(2-naphthyl)acetate

The title compound was prepared from 2,6-dipropyl-4-(2-hydroxyethyl)phenol (Step D) by alkylating with methyl 2-bromo-2-(2-naphthyl)acetate using cesium carbonate or potassium carbonate in DMF. The reaction mixture was filtered through Celite and the filter cake was washed with methylene chloride. The filtrate was concentrated and the resultant material was purified by flash column chromatography to yield the titled ester.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.90 - 7.82 (m, 4 H) , 7.69 - 7.67 (m, 1 H) , 7.49 - 7.47 (m, 2H) , 6.8 (s, 2 H), 2.74 (t, J = 6.2 Hz, 2 H), 2.36-2.32 (m, 4 H), 1.49 - 1.41 (m, 4 H), 0.72 (t, J = 7.3, 6 H).

STEP F: 2-[(2,6-Dipropyl-4-(2-hydroxyethyl)phenoxy]-2-(2-naphthyl)acetic acid

The title compound was prepared from the product of Step E by saponification with 1N aqueous KOH in methanol as outlined in Step C of Example 1.

^{1}H NMR (400 MHz, CD_3OD, ppm) δ 7.84 - 7.7 (m, 4 H) , 7.73 (d, J = 6.8 Hz, 1 H) , 7.45-7.43 (m, 2 H), 6.79 (s, 2 H), 5.01 (s, 2 H), 3.66 (t, J = 7.2 Hz, 2 H), 2.68 (t, J = 7.2 Hz, 2 H), 2.33 - 2.29 (m, 4 H), 1.55 - 1.45 (m, 2H), 1.40- 1.28 (M, 2 H) , 0.69 (t, J = 7.3, 6 H). FAB- MS: m/e = 445 (M + K) , 429 (M + Na), 407 (M + 1).

The following phenoxyphenylacetic acid derivatives were prepared using the general procedures outlined in Example 14.

EXAMPLE 15

2-[(2,6-Dipropyl-4-(2-hydroxyethyl)phenoxy]-2-(3,4-methylenedioxyphenyl)acetic acid

^{1}H NMR (200 MHz, CD_3OD, ppm): δ 7.03 (s, 1H), 6.83 (m, 3H), 6.72 (d, 1H, J=7.8 Hz), 5.93 (s, 2H), 4.80 (s, 1H), 3.68 (t, 2H, J=7.1 Hz), 2.69 (t, 2H, J=7.1 Hz), 2.35 (t, 4H, J=7.9 Hz), 1.42 (m, 4H), 0.83 (t, 6H, J=7.3 Hz).

FAB-MS m/e = 401 (M+1)

EXAMPLE 16

2-[(2,6-Dipropyl-4-(2-hydroxyethyl)phenoxy]-2-(3-methoxyphenyl)-acetic acid

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.28 (t, 1H, J=7.9 Hz), 7.07 (m, 1H), 7.15 (m, 1H), 6.94 (m, 1H), 6.84 (s, 2H), 4.99 (s, 1H), 3.79 (s, 3H), 3.68 (t, 2H, J=7.1 Hz), 2.70 (t, 2H, J=7.1 Hz), 2.34 (t, 4H, J=8.0 Hz), 1.54-1.40 (m, 4H), 0.80 (t, 3H, J=7.3 Hz).

FAB-MS m/e = 387 (M+1)

EXAMPLE 17

2-[(2,6-Dipropyl-4(1,2-dihydroxyethyl)phenoxy)]-2-(2-naphthyl)acetic acid

STEP A: 2,6-dipropyl-4-vinylphenol

The title compound was prepared from t-butyldimethylsilyloxy-2,6-dipropyl-4-vinylbenzene (Step B, Example 14) by treatment with tetrabutylammonium fluoride in THF for a few hours. It was poured into ether/ethyl acetate mixture and washed with brine. After removal of the solvent the crude product was purified by flash column chromatography using ethyl acetate/hexane as eluent.

^{1}H NMR (400 MHz, $CDCL_3$, ppm): δ 7.01 (s, 2 H), 6.55 (dd, J = 17.6 , J = 11.0 Hz, 1H), 5.55 (d, J = 17.6 Hz, 1 H), 5.06 (d, J = 11.0 Hz, 1 H), 2.64 (t, J = 7.7 Hz, 4 H), 1.65 - 1.60 (m, 4 H), 0.96 (t, J = 7.2 Hz 6 H).

STEP B: Methyl 2-[(2,6-dipropyl-4-vinyl)phenoxy]-2-(2-naphthyl)-acetate

The title compound was prepared by alkylation of 2,6-dipropyl-4-vinyl phenol (Step A) with methyl 2-bromo-2-(2-naphthyl)acetate using the procedure for alkylation described in Step B of Example 1.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.9 - 7.8 (m, 4 H), 7.68 (d, J = 6.7 Hz, 1H), 7.50 - 7.48 (m, 2 H), 7.02 (s, 2 H), 6.57 (dd J = 18.4, 10.8 Hz, 1 H), 5.61 (d, J = 18.4, 1 H), 5.26 (s, 1 H), 5.14 (d, J = 10.8, 1 H), 3.73 (s, 1 H), 2.38 - 2.34 (m, 4 H), 1.54 - 1.43 (m, 4 H), 0.74 (t, J = 7.33 Hz, 6 H).

STEP C: Methyl 2-[(2,6-dipropyl-4-(1,2-dihydroxyethyl)phenoxy]-2-(2-naphthyl)acetate

To a solution of 6 mg (0.024 mmol) of OsO_4 and 31 mg (0.263 mmol) of N-methylmorpholine-N-oxide (NMO) in 3 mL of acetone and 2 drops of water was added 96 mg (0.239 mmol) of the product of Step B. After 90 minutes the reaction mixture was poured into a mixture of ether and water. The layers were separated and the aqueous layer was extracted twice with ether. The combined aqueous layers were washed with saturated sodium chloride, dried over

anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography (silica gel, hexane / ethyl acetate 1:1) gave 63 mg of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.89 - 7.80 (m, 4 H), 7.67 (d, J = 8.4 Hz, 1 H), 7.50 - 7.48 (m, 2 H), 6.9 (s, 2 H), 5.25 (s, 1 H), 4.75-4.68 (m, 1 H), 3.72 (s, 3 H), 3.75 - 3.61 (m, 2 H), 2.38 - 2.34 (m, 4 H), 1.53 - 1.46 (m, 4 H), 0.75 - 0.71 (m, 6 H).

STEP D: 2-[(2,6-Dipropyl-4-(1,2-dihydroxyethyl)phenoxy]-2-(2-naphthyl)acetic acid

The title compound was prepared from the product of Step C by saponification with 1N aqueous KOH solution as described above.

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.84 - 7.71 (m, 5 H), 7.46 - 7.42 (m, 2 H), 6.96 (s, 2 H), 5.03 (s, 1 H), 4.55 (t, J = 7.2 Hz, 1 H), 3.54 (d, J = 7.2 Hz, 2 H), 2.34 (t, J = 7.9 Hz, 4 H), 1.51-1.30 (m, 4 H), 0.70 (t, J = 7.3 Hz, 6 H).

EXAMPLE 18

2-[(2,6-Dipropyl-4-(1-hydroxypentyl)phenoxy]-2-(2-naphthyl)acetic acid

STEP A: Methyl 2-[(2,6-dipropyl-4-formyl)phenoxy]-2-(2-naphthyl)acetate

To a solution of 262 mg (0.645 mmol) of methyl 2-[(2,6-dipropyl-4-hydroxymethyl)phenoxy]-2-(2-naphthyl)acetate in 2 mL of methylene chloride was added 404 mg (0.968 mmol) of PDC. After 4 hours the reaction mixture was diluted with 20 mL of ether and filtered through a pad of florisil / celite and concentrated to give 235 mg of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.86 (s, H), 7.89-7.80 (m, 4 H), 7.65 (m, 1 H), 7.52 - 7.49 (m, 4 H), 5.35 (s, 1 H), 3.73 (s, 3 H), 2.47-2.43 (m, 4 H), 1.54-1.43 (m, 4 H), 0.77 (t, J = 7.3 Hz, 6 H).

STEP B: Methyl 2-[(2,6-dipropyl-4-(1-hydroxypentyl)phenoxy]-2-(2-naphthyl)acetate

To a solution of 56 mg (0.143 mmol) of the product of Step A in 1 mL of THF at -78 °C was added 0.075 mL (2.0 M in THF, 0.150 mmol) of n-butyl magnesium chloride. TLC analysis showed that the starting material remained unconsumed so 0.020 mL of n-butyl magnesium chloride was added. After 1 h the reaction mixture was diluted with saturated aqueous ammonium chloride solution and then extracted twice with ethyl acetate. The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. Purification by flash column chromatography (silica gel, hexane / ethyl acetate 6 : 1) gave 32 mg of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.89-7.82 (m, 4 H), 7.67 (m, 1 H), 7.49-7.47 (m, 2 H), 6.9 (s, 2 H), 5.26 (s, 1 H), 2.36 (t, J = 8.0 Hz, 4 H), 1.75-1.2 (m, 8 H), 0.86 (t, J = 7.2 Hz, 3 H), 0.72 (t , J = 7.3 Hz, 6 H).

STEP C: 2-[(2,6-Dipropyl-4-(1-hydroxypentyl)phenoxy)]-2-naphthylacetic acid

The title compound was prepared from the product of Step B by saponification with aqueous 1N KOH in methanol as described above.

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.84-7.72 (m , 5 H), 7.45 - 7.43 (m, 2 H), 6.91 (s, 2 H), 5.03 (s, 1 H), 4.45 (t, 1 H), 2.36 - 2.32 (m, 4 H), 1.75 -1.45 (m, 4 H), 1.35 -1.29 (m, 4 H), 0.87 (t, J = 7.2 Hz, 3 H), 0.70 (t, J = 7.2 Hz, 6 H).

FAB-MS : m/e = 487 (M+ K), 469 (M + Na).

EXAMPLE 19

2-[(4-Carboxy-2,6-dipropyl)phenoxy]-2-phenylacetic acid

STEP A: t-Butyl 2-[(4-carbomethoxy-2,6-dipropyl)phenoxy]-2-phenylacetate

Methyl 2,6-dipropyl-4-hydroxybenzoate (1.5 g, 6.383 mmol) was refluxed with K_2CO_3 (1.5 equiv) and t-butyl α-bromophenylacetate (2.4 g, 8.856 mmol) in acetone for 16 h. The reaction mixture was filtered through Celite, the filter cake was washed with acetone and the combined filtrate and washings were concentrated. The resulting crude oil was chromatographed (flash column) using silica gel and 10% ethyl acetate in hexane to give the titled compound (2.7 g).

^1H NMR (400 MHz, CD_3OD, ppm): δ 7.665 (s, 2H), 7.443 (dd, 2H), 7.345 (dd, 3H), 5.019 (s, 1H), 3.851 (s, 3H), 2.49-2.335 (m, 4H), 1.63-1.4 (m, 4H), 1.364 (s, 9H), 0.803 (t, 6H).

STEP B: t-Butyl 2-[(4-carboxy-2,6-dipropyl)phenoxy]-2-phenyl acetate

Saponification of the above t-butyl 2-[(4-carbomethoxy-2,6-dipropyl)phenoxy]-2-phenylacetate (200 mg, 0.47 mmol) with 1N aqueous solution of LiOH in methanol gave the titled compound (125 mg).

^1H NMR (400 MHz, CD_3OD, ppm): δ 7.66 (s, 2H), 7.5-7.4 (dd, 2H), 7.43-7.36 (dd, 3H) 4.88 (s, 1H), 2.5-2.35 (m, 4H), 1.63-1.33 (m, 4H), 1.38 (t, 9H), 0.83 (t, 6H).

STEP C: 2-[(4-Carbomethoxy-2,6-dipropyl)phenoxy]-2-phenylacetic acid

t-Butyl 2-[(4-carbomethoxy-2,6-dipropyl)phenoxy]-2-phenylacetate (Step A) (125 mg, 0.293 mmol) was treated with 3 mL

of trifluoroacetic acid (TFA) in methylene chloride for 2 h. The volatiles were removed to give the titled compound (90 mg).

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.67 (s, 2H), 7.463-7.44 (m, 2H), 7.387-7.362 (m, 3H), 5.177 (s, 1H), 3.856 (s, 3H), 2.377 (t, 4H), 1.6 -1.366 (m, 4H), 0.773 (t, 6H).

STEP D: 2-[(4-Carboxy-2,6-dipropyl)phenoxy]-2-phenylacetic acid

The product of Step C (70 mg, 0.19 mmol) was treated with 1N aqueous solution of LiOH in methanol. The reaction was monitored by TLC. When the starting material was completely consumed, the mixture was acidified at 0°C to pH 5 by addition of 1N HCl. The aqueous phase was extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated to yield the titled compound (25 mg).

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.68 (s, 2H), 7.52-7.45 (m, 2H), 7.43-7.365 (m, 3H), 5.175 (s, 1H), 2.43 (t, 4H), 1.64-1.4 (m, 4H), 0.83 (t, 6H).

EXAMPLE 20

2-[(4-Carboxy-2,6-dipropyl)phenoxy]-2-(3,4-dichlorophenyl)acetic acid

The titled compound was prepared using procedures similar to that described in Example 19.

^{1}H NMR (200 MHz, CD_3OD, ppm): δ 7.72 (d, 1H, J= 2.0 Hz) 7.69 (s, 2H), 7.56 (d, 1H, J=8.3 Hz), 7.43 (dd, 1H, J=8.3, 1.9 Hz), 5.18 (s, 1H), 2.45 (m, 4H), 1.58-1.43 (m, 4H), 0.84 (t, 6H, J=7.3 Hz).

FAB-MS m/e = 426 (M+1)

EXAMPLE 21

2-[(4-Carboxy-2,6-dipropyl)phenoxy]-2-(3-bromophenyl)acetic acid

The titled compound was prepared using procedures similar to that described in Example 19.

^{1}H NMR (200 MHz, CD_3OD, ppm): δ 7.73 (d, 1H, J=1.8 Hz), 7.69 (s, 2H), 7.56 (dd, 1H, J=7.8, 1.9 Hz), 7.46 (d, 1H, J=7.9 Hz), 7.32 (t, 1H, J=7.8 Hz), 5.19 (s, 1H), 2.44 (t, 4H, J=7.6 Hz), 1.70-1.34 (m, 4H), 0.84 (t, 6H, J=7.3 Hz).

FAB-MS m/e = 436 (M+1)

EXAMPLE 22

2-[(4-Carboxy-2,6-dipropyl)phenoxy]-2-[3,4-methylenedioxyphenyl] acetic acid

The titled compound was prepared using procedures similar to that described in Example 19.

^{1}H NMR (200 MHz, CD_3OD, ppm): δ 7.68 (s, 2H), 7.02 (d, 1H, J=1.6 Hz), 6.84 (m, 2H), 5.98 (s, 2H), 5.08 (s, 1H), 2.44 (t, 4H, J=7.9 Hz), 1.52 (m, 4H), 0.86 (t, 6H, J=7.3 Hz).

FAB-MS m/e = 401 (M+1)

EXAMPLE 23

2-[(4-Carboxy-2,6-dipropyl)phenoxy]-2-(3-methoxyphenyl)acetic acid

The titled compound was prepared using procedures similar to that described in Example 19.

^{1}H NMR (200 MHz, CD_3OD, ppm) δ 7.68 (s, 2H), 7.29 (t, 1H, J=7.9 Hz), 7.08 (d, 1H, J= 2.3 Hz), 7.03 (d, 1H, J=7.7 Hz), 6.95 (dd, 1H,

J=0.9, 8.3 Hz), 5.14 (s, 1H), 3.79 (s, 3H), 2.43 (t, 4H, J=7.9 Hz), 1.58-1.42 (m, 4H), 0.82 (t, 6H, J=7.3 Hz).

FAB-MS m/e = 387 (M+1)

EXAMPLE 24

(N-Benzenesulfonyl)-2-[(4-(N-benzenesulfonyl)carboxamido-2,6-dipropylphenoxy]-2-(3-bromophenyl)acetamide.

The titled compound was prepared using the procedure described for the synthesis of N-sulfonylcarboxamides in US Patent 5,177,095. The diacid 2-[(4-carboxy-2,6-dipropyl)phenoxy]-2-(3-bromophenyl)acetic acid (200 mg, 0.46 mmol; from Example 21) was refluxed with carbonyldiimidazole (1.5 equiv) in THF for 3-4 h. At room temperature, a mixture of 1.5 equiv of benzenesulfonamide and 1.5 equiv DBU in THF was added to the above reaction mixture, and the mixture was stirred overnight. The reaction mixture was diluted with ethyl acetate and washed with 5% aq. solution of citric acid. The solvent was removed and the crude product was purified by flash column chromatography to provide 238 mg of the titled compound.

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 8.07 (dd, 2H, J=1.4, 7.2 Hz), 7.91-7.88 (m, 2H), 7.67-7.49 (m,8H), 7.46 (s, 2H), 7.28-7.25 (m, 2H), 5.01 (s, 1H), 2.28-2.23 (m, 4H), 1.49-1.29 (m, 4H); 0.71 (t, 6H, J=7.4 Hz).

FAB-MS m/e = 713 (M+1).

EXAMPLE 25

N-(4-t-butylbenzenesulfonyl)-2-(4-methoxycarbonyl-2-propyl-phenoxy)-2-(3,4-methylenedioxyphenyl)acetamide

Step A: Preparation of 2-(4-carbomethoxy-2-propylphenoxy)-3,4-methylenedioxyphenylacetic acid

To ethyl 2-(4-carbomethoxy-2-propylphenoxy)-3,4-methylenedioxyphenylacetate (Step A of Example 56) (2.04 g, 5.10 mmol) in MeOH (40 mL) was added 5 N NaOH (8 mL). The rapid reaction was followed immediately by TLC to monitor mono deesterification. The reaction was quenched with 9 N HCl (4.5 mL) after loss of the ethyl ester and before methyl ester saponification. A saturated solution of $NaHCO_3$ was added to the reaction until it was basic and the MeOH was removed in vacuo. The residue was partitioned between Et_2O and water collecting the product in the aqueous phase and removing impurities with the organic phase. The aqueous phase was then acidified with 9 N HCl (pH = 1) and the product extracted into EtOAc. The solution was dried over $MgSO_4$, filtered and the solvent removed. yield = 1.78 g (4.78 mmol, 94%) rf = 0.16 (80:10:1/$CHCl_3$:MeOH:NH_4OH).

Step B: Preparation of the precursor sulfonamide

To a dichloromethane solution of the sulfonyl chloride (1eq) cooled to 0°C was added t-butylamine (3 eq). After 3-5 hrs the CH_2Cl_2 was removed and replaced with EtOAc. The reaction solution was washed with 1 N HCl, water, 1 N NaOH and brine. The resulting solution was dried over $MgSO_4$ and filtered. The solvent was removed. To the resulting solid was added a couple of drops of anisole and then TFA to remove the t-butyl group. After all of the sulfonamide had been deprotected, the TFA was removed in vacuo and the residue taken up in EtOAc/Et_2O. The solution was washed with saturated $NaHCO_3$ solution to remove any residual TFA, then with brine, dried over $MgSO_4$, filtered and the solvent removed.

The sulfonamide precursors used in the preparation of the compounds of Examples 28, 29, 31, 32, 37, 38, and 39 were prepared from the corresponding sulfonyl chlorides utilizing the procedure described above. The sulfonamide precursors used in the preparation

of the compounds of Examples 26 and 33-36 are commercially available.

The sulfonamide precursors used in Examples 27, 30 and 32, whose sulfonyl chlorides are not commercially available, were prepared using standard chemistry:

Preparation of precursor sulfonamide for Example 27

The t-butylsulfonamide of 4-bromobenzenesulfonyl chloride was prepared using the procedure described above. The t-butylsulfonamide was then coupled to phenylboronic acid in a palladium catalyzed cross-coupling reaction with NaOH, EtOH, toluene, and $Pd(PPh_3)_4$ at 100° C to afford the biphenylsulfonamide. Deprotection of the t-butylsulfonamide with TFA and anisole yielded the free sulfonamide.

Preparation of precursor sulfonamide for Example 30

The t-butylsulfonamide of 2-thiophenesulfonyl chloride was prepared using the procedure described above. Treatment of the t-butylsulfonamide with BuLi then isobutyl iodide afforded the 5-isobutyl-2-thiophene-t-butylsulfonamide which was then deprotected with TFA and anisole to yield the free sulfonamide.

Preparation of precursor sulfonamide for Example 32

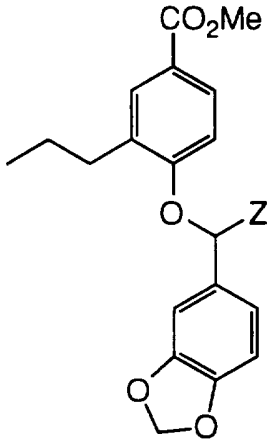
The t-butylsulfonamide of p-nitrobenzenesulfonyl chloride was prepared using the procedure described above. Reduction of the nitro group to the amine was accomplished with hydrogen in MeOH over Pd-C. Treatment of the free amine with LiBr and $(MeO)_3PO$ and then NaOH afforded the dimethylamine and the t-butylsulfonamide was deprotected with TFA and anisole to yield the free sulfonamide.

Step C: Preparation of N-(4-t-butylbenzenesulfonyl)-2-(4-carbomethoxy-2-propylphenoxy)-3,4-methylenedioxyphenylacetamide

To the product of Step A (57.2 mg, 0.154 mmol) in dry THF (0.75 mL) was added CDI (76.0 mg, 0.469 mmol) and the reaction heated to 50°C for 2.5 hr. To this solution was added a solution of p-t-butylphenyl-sulfonamide (131.7 mg, 0.618 mmol) and DBU (92.1 µL, 0.594 mmol) in dry THF (0.75 mL). The reaction continued to be stirred at 50°C monitoring by thin layer chromatography until all of the mono-acid was consumed (approx. 3 hr). The reaction was concentrated in vacuo and the residue was taken up in 50:50/Et_2O:EtOAc. The organic phase was washed with 10% citric acid (2x), water and brine then dried over $MgSO_4$, filtered and the solvent removed. Purification was accomplished by radial chromatography eluting with 3:2/Hex:EtOAc. yield = 74.3 mg (0.131 mmol, 85%) rf = 0.32 (80:10:1/$CHCl_3$:MeOH:NH_4OH) FAB mass spectrum, m/e 590.0 (M+Na calculated for $C_{30}H_{33}NSO_8$ 590). See Drummond, J.T.; Johnson, G. Tetrahedron Lett., **1988**, *29*, 1653.

EXAMPLES 26-39

Examples 26 through 39 were prepared following the procedures described above in Example 25.



Ex.#	Z	Mass Spectrum
26	$CONHSO_2Ph$	(M+1) 512.0
27	$CONHSO_2$-(p-phenyl)Ph	(M+Na) 610.0
28	$CONHSO_2$-(p-Cl)Ph	(M+) 546.0
29	$CONHSO_2$-(p-Me)Ph	
30	$CONHSO_2$-(5-iBu)thiophene	(M+Na) 596.4
31	$CONHSO_2$-(p-MeO)Ph	(M+1) 542.0
32	$CONHSO_2$-(p-NMe_2)Ph	(M+1) 555.1
33	$CONHSO_2$-(o-Me)Ph	(M+1) 526.1
34	$CONHSO_2$-(o-CO_2Me)Ph	(M+) 570.0
35	$CONHSO_2$-(o-Cl)Ph	(M+) 546.0
36	$CONHSO_2$-(m-Cl)Ph	(M+) 546.0
37	$CONHSO_2CH_2Ph$	(M+1) 526.1
38	CONH-dansyl	(M+1) 605.1
39	$CONHSO_2$-8-quinoline	(M+1) 563.4

The proton NMR data for Example 29 is given below:

EXAMPLE 29

N-(4-methylbenzenesulfonyl)-2-(4-methoxycarbonyl-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 0.89 (t, 3H), 1.59 (m, 2H), 2.34 (s, 3H), 2.63 (m, 2H), 3.85 (s, 3H), 5.49 (s, 1H), 5.97 (s, 2H), 6.55 (d, 1H), 6.79 (d, 1H), 6.91 (d, 1H), 6.96 (dd, 1H), 7.26 (d, 2H), 7.58 (dd, 1H), 7.70 (d, 2H), 7.74 (d, 1H).

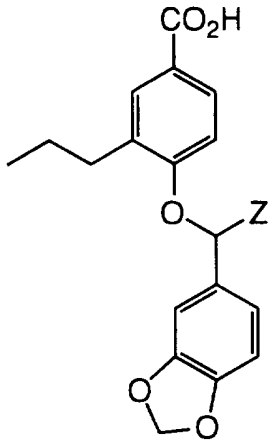
EXAMPLE 40

N-(4-t-butylbenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide

To the product of Example 25 (51.1 mg, 0.090 mmol) in MeOH (2 mL) was added 5 N NaOH (0.5 mL). The reaction was monitored by TLC. When the reaction was complete the MeOH was removed and the residue partitioned between water and Et_2O:EtOAc. The water layer was acidified with HCl solution and the product extracted into the organic phase. The organic phase was washed with brine then dried over $MgSO_4$, filtered and the solvent removed. Trituration with Et_2O/Hex provided a white solid. yield = 25.8 mg (0.047 mmol, 52%) FAB mass spectrum, m/e 554.2 (M+1 calculated for $C_{29}H_{31}NSO_8$ 554).

EXAMPLES 41-54

Examples 41 through 54 were prepared following the procedures described above in Example 40.



Ex. #	Z	Mass Spectrum
41	$CONHSO_2Ph$	(M+1) 498.0
42	$CONHSO_2$-(p-phenyl)Ph	(M+) 573.5
43	$CONHSO_2$-(p-Cl)Ph	(M+) 532.0
44	$CONHSO_2$-(p-Me)Ph	(M+K) 549.9
45	$CONHSO_2$-(5-iBu)thiophene	(M+Na) 582.0
46	$CONHSO_2$-(p-MeO)Ph	(M+1) 528.0
47	$CONHSO_2$-(p-NMe_2)Ph	(M+1) 541.1
48	$CONHSO_2$-(o-Me)Ph	(M+1) 512.0
49	$CONHSO_2$-(o-CO_2H)Ph	(M+1) 542.1
50	$CONHSO_2$-(o-Cl)Ph	(M+1) 532.2
51	$CONHSO_2$-(m-Cl)Ph	(M+1) 532.4
52	$CONHSO_2CH_2Ph$	(M+1) 512.1
53	CONH-dansyl	(M+1) 591.0
54	$CONHSO_2$-8-quinoline	(M+1) 549.2

The proton NMR data for several of the Examples is given below:

EXAMPLE 47

N-(4-dimethylaminobenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide

^{1}H NMR (300 MHz, CD_3OD, ppm): δ 0.89 (t, 3H), 1.59 (m, 2H), 2.62 (m, 2H), 3.03 (s, 6H), 5.48 (s, 1H), 5.96 (s, 2H), 6.43 (d, 1H), 6.64 (dd, 2H), 6.79 (d, 1H), 6.91 (m, 2H), 7.55 (dd, 1H), 7.64 (dd, 2H), 7.74 (d, 1H).

EXAMPLE 49

N-(2-carboxybenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 0.92 (t, 3H), 1.62 (m, 2H), 2.67 (m, 2H), 5.66 (s, 1H), 5.95 (s, 2H), 6.74 (d, 1H), 6.77 (d, 1H), 6.93 (d, 1H), 6.98 (dd, 1H), 7.60 (m, 2H), 7.69 (m, 1H), 7.75 (m, 2H), 8.09 (d, 1H).

EXAMPLE 53

N-(dansylsulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 0.83 (t, 3H), 1.51 (m, 2H), 2.57 (m, 2H), 2.88 (s, 6H), 5.40 (s, 1H), 5.95 (dd, 2H), 6.26 (d, 1H), 6.65 (d, 1H), 6.79 (d, 1H), 6.85 (dd, 1H), 7.19 (dd, 1H), 7.25 (d, 1H), 7.48 (t, 1H), 7.54 (t, 1H), 7.66 (d, 1H), 8.13 (d, 1H), 8.30 (dd, 1H), 8.53 (d, 1H).

EXAMPLE 54

N-(8-quinolinesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide

^{1}H NMR (300 MHz, CD_3OD, ppm): δ 0.85 (t, 3H), 1.54 (m, 2H), 2.59 (m, 2H), 5.57 (s, 1H), 5.94 (s, 2H), 6.47 (d, 1H), 6.66 (d, 1H), 6.71 (d, 1H), 6.87 (dd, 1H), 7.34 (dd, 1H), 7.58 (dd, 1H), 7.68 (m, 2H), 8.20 (dd, 1H), 8.39 (dd, 1H), 8.47 (dd, 1H), 8.83 (dd, 1H).

EXAMPLE 55

N-(8-quinolinesulfonyl)-2-(4-carboxamido-2-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide

To N-(8-quinolinesulfonyl)-2-(4-carboxy-2-propyl-phenoxy)-2-(3,4-methylenedioxyphenyl)acetamide, Example 54, (25.8 mg, 0.047 mmol) in dry DMF (0.5 mL) was added 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride, also referred to as EDC, (18.4 mg, 0.096 mmol), NH_4Cl (6.7 mg, 0.125 mmol), and TEA (17.5 mL, 0.125 mmol). Reaction was followed by thin layer chromatography (100:15:1.5/CH_2Cl_2:MeOH:HOAc). When the reaction was completed the DMF was removed in vacuo and the residue taken up in Et_2O/EtOAc. The solution was washed with 10% citric acid, water and brine then dried over $MgSO_4$, filtered and the solvent removed. The product was purified by chromatography eluting with 200:5:1.5/CH_2Cl_2:MeOH:HOAc. rf = 0.35 (100:5:1.5/CH_2Cl_2:MeOH:HOAc) FAB mass spectrum, m/e 548.0 (M+1 calculated for $C_{28}H_{25}N_3SO_7$ 548).

EXAMPLE 56

α-(4-carbomethoxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl)acetic acid

Step A: Preparation of ethyl α-(4-carbomethoxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetate

To a 2 L three necked 24/40 round bottom flask equipped with a mechanical stirrer, a nitrogen inlet and a dropping funnel was first added a solution of 36.0 g (0.185 mol) of methyl 4-hydroxy-3-*n*-propylbenzoate dissolved in 700 mL of anhydrous DMF followed by 66.4 g (0.204 mol) of cesium carbonate. The flask was purged with nitrogen and the reaction mixture was stirred at room temperature for 2 hours. A solution of 58.5 g (0.204 mol) of ethyl α-bromo-3,4-methylenedioxyphenylacetate dissolved in 100 mL of DMF was then added via an addition funnel over a 15 minute period. The reaction mixture was stirred an additional 1 hour at room temperature then quenched by addition to 5 L of a 5% aqueous citric acid solution. The organic product was extracted into diethylether (2 x 4 L), the organic layers were separated, washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and evaporated. The residue was applied to a silica gel (2 kg; 70-230 mesh) column equillibrated in 10% CH_2Cl_2-hexane. The column was then eluted successively with 12 L of 10% CH_2Cl_2-hexane, 12 L of 5% EtOAc-hexane, 4 L of 7.5% EtOAc-hexane, 12 L of 10% EtOAc-hexane, and finally 8 L of 20% EtOAc-hexane. Combination of the purified fractions and evaporation in vacuo afforded 76.3 g (74.2 theoretical) of the title compound as a pale yellow oil which was used without further purification in the next step.

Step B: Preparation of α-(4-carbomethoxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetic acid

A 1 L 3 necked 24/40 round bottom flask equipped with a mechanical stirrer, a dropping funnel, and a nitrogen inlet was charged with a solution of 76.3 g 0.185 mol) of the semi-purified product of

Step A dissolved in 500 mL of methanol. The flask was purged with nitrogen, the stirrer was started, and 37 mL of a 5.0 N aqueous solution of sodium hydroxide was added over a 30 minute period via an addition funnel. The reaction mixture was stirred at room temperature for an additional 30 minutes at which point TLC analysis (CH_2Cl_2-MeOH-NH_4OH 90:10:1) indicated that the starting material had been consumed. The reaction mixture was adjusted to pH=4 with 6 N HCl, and the bulk of the organic solvent was removed in vacuo. The precipitated organic product and the aqueous layer were next partitioned between CH_2Cl_2 (1 L) and water (1 L) which produced a copious emulsion. The reaction mixture was then aged overnight in a refridgerator which resulted in crystallization of the organic product. The crystalline solid was separated from the two phase mixture by filtration and washed with CH_2Cl_2. The solid was slurried again in diethylether, filtered, washed with hexane, and then dried in a vacuum to afford 65 g (94%) of the title compound as a white crystalline solid.
^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.93 (t, J=7.20 Hz, 3H), 1.62-1.75 (m, 2H), 2.63-2.70 (m, 1H), 2.77-2.81 (m, 1H), 3.84 (s, 3H), 5.54 (s, 1H), 5.94 (s, 2H), 6.81 (d, J=7.60 Hz, 1H), 6.89 (d, J=9.20 Hz, 1H), 7.08 (d, J=1.60 Hz, 1H), 7.11 (br s, 1H), 7.78-7.81 (m, 2H).

EXAMPLE 57

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-carbomethoxy-2-*n*-propyl-phenoxy)-3,4-methylenedioxyphenylacetamide

Step A: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carbomethoxy-2-*n*-propylphenoxy)-3,4-methylenedioxy-phenylacetamide

An oven dried three-necked 24/40 1 L round-bottom flask was equipped with a mechanical stirrer, a nitrogen inlet, and a septum. The flask was flushed with nitrogen, then charged with 20.06 g (53.9 mmol) of the product of Example 56, 400 mL of anhydrous THF, and 9.76 mL (70.0 mmol) of triethylamine. The flask and its contents were

stirred and cooled to -78°C with an external dry ice-acetone bath and then 7.30 mL (59.3 mmol) of trimethylacetyl chloride was added slowly via a syringe. After the addition was complete, the dry ice-acetone bath was replaced with an ice-water bath and the reaction was stirred at 0°C for 1 hour. A separate oven dried 3 necked 24/40 2 L round-bottom flask was equipped with a mechanical stirrer, a septum and a nitrogen inlet. The flask was flushed with nitrogen then charged with 16.102 g (80.8 mmol) of 4-*iso*-propylbenzenesulfonamide and 300 mL of anhydrous methyl sulfoxide. The stirrer was started and a 162 mL of a 1.0 M solution of lithium bis(trimethylsilylamide) in THF was slowly (mildly exothermic) added via a syringe through the septum. After the addition was complete, the reaction mixture was stirred at room temperature for an additional 30 minutes. The contents of the first reaction mixture including a fine white precipitate that was suspended in the reaction mixture were then slowly transfered to the stirred solution of the deprotonated sulfonamide in the second flask via a wide diameter cannula. The combined reaction mixture was then stirred for an additional 14 hours under a nitrogen atmosphere. The reaction was the quenched with 1.0 N HCl and the majority of the volatile solvents were removed in vacuo. The residue was partitioned between EtOAc and 1.0 N HCl, then organic layer was separated, washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was purified on a silica gel (3 kg; 70-230 mesh) chromatography column (15 cm x 150 cm) eluted with (90:10:1 CH_2Cl_2-MeOH-NH_4OH). Combination of the purified fractions and evaporation in vacuo afforded 18.367 g (62%) of the title compound.
^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.88 (t, *J*=7.60 Hz, 3H), 1.24 (d, *J*=7.00 Hz, 3H), 1.25 (t, *J*=7.00 Hz, 3H), 1.55-1.60 (m, 2H), 2.59-2.66 (m, 2H), 2.97 (sept, *J*=7.00 Hz, 1H), 3.83 (s, 3H), 5.52 (s, 1H), 5.97 (s, 2H), 6.50 (d, *J*=8.80 Hz, 1H), 6.80 (d, *J*=8.00 Hz, 1H), 6.89 (d, *J*=1.60 Hz, 1H), 6.94 (dd, *J*=2.00, 8.00 Hz, 1H), 7.14 (d, *J*=8.80 Hz, 2H), 7.59 (dd, *J*=2.20, 8.80 Hz, 1H), 7.75 (d, *J*=2.20, 1H), 7.79 (d, *J*=8.80 Hz, 2H).

EXAMPLE 58

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt

Step A: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt

To a solution of 18.367 g (33.2 mmol) of the product of Example 57 dissolved in 100 mL of methanol was added a solution of 6.56 g (116.9 mmol) of potassium hydroxide in 25 mL of water and the reaction mixture was stirred at 60°C under a nitrogen atmosphere. After 6 hours TLC analysis (80:15:1 $CHCl_3$-MeOH-NH_4OH) indicated that ester hydrolysis was complete. The reaction mixture was cooled to room temperature, diluted with 100 mL water, filtered through a 0.45 micron filter and then divided into two equal volume portions. The fractions were individually desalted and purified on a Waters Millipore Delta Prep 3000 liquid chromatograph equipped with an M1000 Prep-Pak module containing a 47 x 300 mm Delta-Pak C18 15μm 100A column cartridge. Two solvent resevoirs were employed: solvent system A (95-5 water-acetonitrile), and solvent system B (5-95 water-acetonitrile), and the column effluent was monitored simultaneously at 210 and 280 nm with a Waters model 490 UV-visible detector. Each fraction was pump-injected onto the column and desalted by elution (50 mL/min) with several column volumes of solvent system A. A gradient elution was then begun which had as initial conditions 100% solvent system A-0% solvent system B and reached after 30 minutes 50% solvent system A-50% solvent system B, and the fractions were collected with an ISCO Foxy 200 fraction collector. The purified fractions were combined in round bottom flasks, frozen in a -78°C dry ice-acetone bath, and lyophilized. Combination of the purified product afforded 18.719 g (92%) of the title compound as a white lyophilized powder.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.88 (t, *J*=7.20 Hz, 3H), 1.21 (d, *J*=7.00 Hz, 3H), 1.22 (d, *J*=7.00 Hz, 3H), 1.56-1.63 (m, 2H), 2.52-2.59 (m, 1H), 2.67-2.74 (m, 1H), 2.91 (sept, *J*=7.00 Hz, 1H), 5.33 (s, 1H), 5.92 (d, *J*=1.20 Hz, 1H), 5.93 (d, *J*=1.20 Hz, 1H), 6.72 (d, *J*=8.50 Hz, 1H), 6.76 (d, *J*=8.50 Hz, 1H), 7.04 (d, *J*=7.50 Hz, 1H), 7.05 (s, 1H), 7.21 (d, *J*=8.50 Hz, 2H), 7.64 (dd, J=2.00, 8.50 Hz, 1H), 7.67 (d, *J*=8.50 Hz, 2H), 7.73 (d, *J*=2.00 Hz, 1H).

Microanalysis for $C_{28}H_{27}NSO_8K_2 \cdot H_2O$.

Calc'd: C = 53.06; H = 4.61; N = 2.21; K = 12.34.

Found: C = 52.81; H = 4.56; N = 2.17; K = 12.02.

EXAMPLE 59

α-(2-*iso*-butyl-4-carbomethoxyphenoxy)-3,4-methylenedioxy-phenylacetic acid

Step A: Preparation of ethyl α-(2-*iso*-butyl-4-carbomethoxy-phenoxy)-3,4-methylenedioxyphenylacetate

To a solution of 1.008 g (4.84 mmol) of methyl 3-*iso*-butyl-4-hydroxybenzoate and 1.737 g (6.05 mmol) of ethyl α-bromo-3,4-methylenedioxyphenylacetate in 10 mL of acetone was added 1.338 g (10 mmol) of finely powdered potassium carbonate. The reaction mixture was magnetically stirred and refluxed for 4 hours, then cooled to room temperature, filtered and evaporated. The residue was purified on a silica gel flash chromatography column eluted with 10% EtOAc-hexane; combination of the purified fractions and drying in vacuo afforded 1.518 g (76%) of the title compound as an amorphous powder.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 0.90 (d, *J*=6.60 Hz, 3H), 0.94 (d, *J*=6.60 Hz, 3H), 1.17 (t, *J*=7.20 Hz, 3H), 2.02-2.08 (m, 1H), 2.55 (dd, *J*=7.20, 13.20 Hz, 1H), 2.64 (dd, *J*=7.20, 13.20 Hz, 1H), 3.85 (s, 3H), 4.11-4.19 (m, 2H), 5.56 (s, 1H), 5.96 (s, 2H), 6.70 (d, *J*=9.20 Hz, 1H), 6.68 (d, *J*=7.60 Hz, 1H), 7.02 (dd, *J*=1.60, 8.00 Hz, 1H), 7.05 (d, *J*=2.00 Hz, 1H), 7.78-7.81 (m, 2H).

Step B: Preparation of α-(2-*iso*-butyl-4-carbomethoxyphenoxy)-3,4-methylenedioxyphenylacetic acid

To a solution of 1.518 g (3.66 mmol) of the product of Step A dissolved in 8.0 mL of methanol was added 1.0 mL of a 5.0 M solution of aqueous sodium hydroxide. The reaction was stirred at room temperature and monitored by TLC (80:15:1 $CHCl_3$-MeOH-NH_4OH). After 1.5 hours the reaction was judged to be complete and the reaction mixture was adjusted to pH=5 with 1.0 N HCl. The reaction mixture was then partitioned between EtOAc and water, separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified on a silica gel flash chromatography column eluted with $CHCl_3$-MeOH-NH_4OH (80:15:1); evaporation of the purified fractions and drying in vacuo afforded the title compound as an amorphous foam. ^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.86 (d, *J*=6.80 Hz, 3H), 0.89 (d, *J*=6.80 Hz, 3H), 1.96-2.04 (m, 1H), 2.49 (dd, *J*=7.20, 12.80 Hz, 1H), 2.69 (dd, *J*=7.20, 12.80 Hz, 1H), 3.84 (s, 3H), 5.49 (s, 1H), 5.92 (d, *J*=1.20 Hz, 1H), 5.93 (d, *J*=1.20 Hz, 1H), 6.79 (d, *J*=8.00 Hz, 1H), 6.89 (d, *J*=8.80 Hz, 1H), 7.08 (dd, *J*=1.60, 8.00 Hz, 1H), 7.11 (d, *J*=1.60 Hz, 1H), 7.74 (d, *J*=2.40 Hz, 1H), 7.78 (dd, *J*=2.40, 8.80 Hz, 1H). CI-MS *m/e* = 386.2 (M^+).

EXAMPLE 60

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*iso*-butyl-4-carbomethoxyphenoxy)-3,4-methylenedioxyphenylacetamide

Step A: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(2-*iso*-butyl-4-carbomethoxyphenoxy)-3,4-methylenedioxyphenylacetamide

To a solution of 0.727 g (1.88 mmol) of the product of Step B in Example 58 dissolved in 4 mL of anhydrous THF was added 0.458 g (2.82 mmol) of 1,1' -carbonyldiimidazole and the mixture was magnetically stirred and refluxed for 2 hours. The reaction mixture was then cooled to room temperature, and 0.562 g (2.82 mmol) of 4-

iso-propylbenzenesulfonamide and 0.42 mL (2.82 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene were added. The reaction mixture was stirred an additional 3 hours at room temperature, then was evaporated in vacuo. The residue was partitioned between EtOAc and 1.0 N HCl and extracted. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated and the residue was purified on a silica gel flash chromatography column eluted with $CHCl_3$-MeOH-NH_4OH (80:15:1). Evaporation of the purified fractions and drying in vacuo afforded 0.666 g (63%) of the title compound.

^1H-NMR (400 MHz, CD_3OD, ppm): δ 0.81 (d, *J*=6.80 Hz, 3H), 0.84 (d, *J*=6.80 Hz, 3H), 1.23 (d, *J*=6.80 Hz, 3H), 1.24 (d, *J*=6.80 Hz, 3H), 1.88-1.94 (m, 1H), 2.45 (dd, *J*=7.00, 13.00 Hz, 1H), 2.58 (dd, *J*=7.00, 13.00 Hz, 1H), 2.95 (sept, *J*=6.80 Hz, 1H), 3.84 (s, 3H), 5.46 (s, 1H), 5.95 (d, *J*=1.20 Hz, 1H), 5.96 (d, *J*=1.20 Hz, 1H), 6.59 (d, *J*=8.60 Hz, 1H), 6.79 (d, *J*=8.00 Hz, 1H), 6.98 (br s, 1H), 6.99 (dd, *J*=1.60, 8.00 Hz, 1H), 7.30 (d, *J*=8.40 Hz, 2H), 7.60 (dd, J=2.00, 8.60 Hz, 1H), 7.70 (d, *J*=2.00 Hz, 1H), 7.72 (d, *J*=8.40 Hz, 2H).

EXAMPLE 61

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*iso*-butyl-4-carboxyphenoxy)-3,4-methylenedioxyphenylacetamide

Step A: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(2-*iso*-butyl-4-carboxyphenoxy)-3,4-methylenedioxyphenyl-acetamide

To a solution of 0.294 g (0.52 mmol) of the product of Example 60 dissolved in 3.0 mL of methanol was added 1.0 mL of a 5.0 N aqueous solution of sodium hydroxide. The reaction mixture was magnetically stirred at 60°C. After 3 hours TLC analysis ($CHCl_3$-MeOH-NH_4OH 80:15:1) indicated complete hydrolysis of the ester. The reaction was cooled to room temperature, adjusted to pH=5 with dropwise addition of 1.0 N HCl, then partitioned between EtOAc and water. The organic layer was separated, washed with saturated aqueous

NaCl, dried ($MgSO_4$), filtered and evaporated. The residue was dried in vacuo to afford 0.238 g (83%) of the title compound as an amorphous powder.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.82 (d, *J*=6.80 Hz, 3H), 0.85 (d, *J*=6.80 Hz, 3H), 1.24 (d, *J*=7.20 Hz, 3H), 1.25 (d, *J*=7.20 Hz, 3H), 1.91 (sept, *J*=6.80 Hz, 1H), 2.48 (dd, *J*=7.20, 13.20 Hz, 1H), 2.56 (dd, *J*=7.20, 13.20 Hz, 1H), 2.97 (sept, *J*=7.20 Hz, 1H), 5.51 (s, 1H), 5.97 (s, 1H), 6.50 (d, *J*=8.40 Hz, 1H), 6.81 (d, *J*=8.00 Hz, 1H), 6.91 (d, *J*=1.60 Hz, 1H), 6.95 (dd, *J*=1.60, 8.00 Hz, 1H), 7.36 (d, *J*=8.40 Hz, 2H), 7.62 (dd, *J*=2.20, 8.40 Hz, 1H), 7.72 (d, *J*=2.20 Hz, 1H), 7.79 (d, *J*=8.40 Hz, 2H).

FAB-MS *m/e* = 554 (M + 1).

EXAMPLE 62

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propyl-4-methoxycarbonyl-phenoxy)-α-methyl-3,4-methylenedioxyphenylacetamide

Step A: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propyl-4-methoxycarbonylphenoxy)-α-methyl-3,4-methylenedioxyphenylacetamide

To a solution of 0.516 g (0.93 mmol) of the product of Example 57 dissolved in 1.0 mL of anhydrous THF was added 2.80 mL (2.80 mmol) of a 1.0 M solution of lithium bis(trimethylsilylamide) in THF at -78°C under a nitrogen atmosphere. The reaction mixture was magnetically stirred at -78°C for 1 hour, then 174 μL (2.80 mmol) of iodomethane was added via syringe. The reaction was allowed to warm to room temperature and was stirred an additional 14 hours. The reaction was next quenched with excess 10% aqueous $NaHSO_4$ and partitioned between EtOAc and water. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated. The residue was purified on a silica gel flash chromatography column eluted with $CHCl_3$-MeOH-NH_4OH (90:10:1). Evaporation of the

purified fractions and drying in vacuo afforded 0.293 g (55%) of the title compound as an amorphous solid.
^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.99 (t, *J*=7.20 Hz, 3H), 1.31 (d, *J*=6.80 Hz, 6H), 1.64-1.72 (m, 2H), 1.66 (s, 3H), 2.64-2.73 (m, 1H), 2.81-2.88 (m, 1H), 3.02 (sept, *J*=6.80 Hz, 1H), 3.85 (s, 3H), 5.96 (s, 2H), 6.36 (d, *J*=8.40, 1H), 6.77 (d, *J*=8.40 Hz, 2H), 6.99 (m, 1H), 7.05 (br s, 1H), 7.37 (d, *J*=7.60 Hz, 1H), 7.43 (dd, *J*=2.40, 8.60 Hz, 1H), 7.76 (d, *J*=8.40 Hz, 2H), 7.81 (br s, 1H).
FAB-MS *m/e* = 568 (M + 1).

EXAMPLE 63

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propyl-4-carboxyphenoxy)-α-methyl-3,4-methylenedioxyphenylacetamide dipotassium salt

Step A: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propyl-4-carboxyphenoxy)-α-methyl-3,4-methylenedioxyphenylacetamide dipotassium salt

To a solution of 0.293 g (0.52 mmol) of the product of Example 62 dissolved in 2.0 mL of methanol was added a solution of 0.143 g (2.54 mmol) of potassium hydroxide dissolved in 1.0 mL of water. The reaction mixture was magnetically stirred at 60°C for 4 hours until TLC anlysis ($CHCl_3$-MeOH-NH_4OH 80:15:1) indicated complete hydrolysis of the starting material. The reaction mixture was then cooled to room temperature, diluted with 5.0 mL of water and filtered through a 0.45 micron filter. The filtrate was then purified on a Waters Millipore Delta Prep 3000 liquid chromatograph equipped with two DuPont Zorbax® 21.2 mm x 25 cm ODS reversed phase HPLC columns connected in series. Two solvent resevoirs were employed: solvent system A (95-5 water-acetonitrile), and solvent system B (5-95 water-acetonitrile), and the column effluent was monitored simultaneously at 210 and 280 nm with a Waters model 490 UV-visible detector. The reaction mixture was injected onto the column and desalted by elution (50 mL/min) with approximately 1L of solvent

system A. A gradient elution was then begun which had as initial conditions 100% solvent system A-0% solvent system B and reached after 30 minutes 50% solvent system A-50% solvent system B, and the fractions were collected with an ISCO Foxy 200 fraction collector. The purified fractions were combined in round bottom flasks, frozen in a -78°C dry ice acetone bath, and lyophilized. Combination of the purified product afforded 0.273 g (84%) of the title compound as a white lyophilized powder.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.96 (t, *J*=7.20 Hz, 3H), 1.25 (d, *J*=7.20 Hz, 3H), 1.26 (d, *J*=7.20 Hz, 3H), 1.64-1.71 (m, 2H), 1.67 (s, 3H), 2.58-2.65 (m, 1H), 2.74-2.82 (m, 1H), 2.96 (sept, *J*=7.20 Hz, 1H), 5.91 (d, *J*=1.20 Hz, 1H), 5.92 (d, *J*=1.20 Hz, 1H), 6.52 (d, *J*=8.40 Hz, 1H), 6.72 (d, *J*=8.00 Hz, 1H), 7.12 (dd, *J*=1.80, 8.00 Hz, 1H), 7.17 (d, *J*=2.00 Hz, 1H), 7.28 (d, *J*=8.80 Hz, 2H), 7.50 (dd, *J*=2.20, 8.40 Hz, 1H), 7.72 (d, *J*=8.80 Hz, 2H), 7.74 (d, *J*=2.00 Hz, 1H).

FAB-MS *m/e* = 591.6 ($M + K^+$).

EXAMPLE 64

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propyl-4-carboxamidophenoxy)-3,4-methylenedioxyphenylacetamide

Step A: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propyl-4-carboxamidophenoxy)-3,4-methylenedioxyphenylacetamide

To a solution of 0.162 g (0.30 mmol) of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide (free acidic form of the product of Example 58) dissolved in 1.5 mL of anhydrous THF was added 0.073 g (0.45 mmol) of 1,1'-carbonyldiimidazole and the resulting mixture was magnetically stirred and refluxed for 50 minutes. The reaction mixture was cooled to room temperature, and then added at 0°C to excess THF that had been previously saturated with anhydrous gaseous ammonia. The reaction mixture was sealed and then stirred at room temperature

for 14 hours. The reaction mixture was then poured into water (70 mL) and extracted with EtOAc (150 mL). The organic layer was separated, washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and evaporated in vacuo to afford the title compound as an amorphous solid.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.88 (t, *J*=7.60 Hz, 3H), 1.21 (d, *J*=6.80 Hz, 6H), 1.55-1.66 (m, 2H), 2.54-2.62 (m, 1H), 2.70-2.77 (m, 1H), 2.89 (sept, *J*=6.80 Hz, 1H), 5.36 (s, 1H), 5.93 (d, *J*=1.20 Hz, 1H), 5.94 (d, *J*=1.20 Hz, 1H), 6.75 (d, *J*=8.40 Hz, 1H), 6.78 (d, *J*=8.80 Hz, 1H), 7.02-7.04 (m, 2H), 7.06 (br s, 2H), 7.20 (d, *J*=8.40 Hz, 2H), 7.55 (dd, *J*=2.20, 8.60 Hz, 1H), 7.62-7.66 (m, 2H), 7.71 (s, 1H).

FAB-MS *m/e* = 539 (M + 1).

EXAMPLE 65

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propyl-4-hydroxymethyl-phenoxy)-3,4-methylenedioxyphenylacetamide

Step A: Preparation of methyl α-(4-hydroxymethyl-2-*n*-propyl-phenoxy)-3,4-methylenedioxyphenylacetate

To a solution of 3.84 g (23.13 mmol) of 4-hydroxy-3-*n*-propylbenzyl alcohol dissolved in 70 mL of anhydrous DMF was added 9.04 g (27.7 mmol) of cesium carbonate and the reaction mixture was magnetically stirred at room temperature for 15 minutes. Methyl α-bromo-3,4-methylenedioxyphenylacetate (7.58 g; 27.7 mmol) was added and the reaction mixture was then stirred for an additional 14 hours at room temperature under a nitrogen atmosphere. The reaction was then partitioned between 5% aqueous citric acid (700 mL) and EtOAc (100 mL) and extracted. The organic layer was separated, washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated. The residue was purified on a silica gel flash chromatography column eluted with 40% EtOAc-hexane. The purified fractions were combined,

evaporated, and dried in vacuo to afford 6.74 g (81%) of the title compound as a yellow oil.
^{1}H-NMR (200 MHz, $CDCl_3$, ppm): δ 0.97 (t, *J*=7.60 Hz, 3H), 2.55-2.75 (m, 2H), 2.71 (t, *J*=7.20 Hz, 2H), 3.71 (s, 3H), 4.59 (s, 2H), 5.55 (s, 1H), 5.97 (s, 2H), 6.69 (d, *J*=8.20 Hz, 1H), 6.82 (d, *J*=7.80 Hz, 1H), 7.02-7.28 (m, 4H).
FAB-MS *m/e* = 359 (M + 1).

Step B: Preparation of methyl α-(4-*tert*-butyldimethylsilyloxymethyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetate

To a solution of 2.50 g (6.98 mmol) of the product of Step A dissolved in 20 mL of dichloromethane was added 1.95 mL (14.0 mmol) of triethylamine, 1.26 g (8.38 mmol) of *tert*-butyldimethylchlorosilane, 85 mg (0.1 eq) of 4-dimethylaminopyridine and the reaction mixture was stirred at room temperature for 30 minutes under a nitrogen atmosphere. The reaction was then diluted with 100 mL EtOAc, washed with water, 1.0 N HCl, saturated aqueous $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered and evaporated in vacuo to afford 3.20 g (97%) of the title compound.
EI-MS *m/e* = 472 (M^+).

Step C: Preparation of α-(4-*tert*-butyldimethylsilyloxymethyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetic acid

To a solution of 3.20 g (6.78 mmol) of the product of Step B dissolved in 10 mL of methanol and 3 mL of dichloromethane was added 1.42 mL (7.12 mmol) of a 5.0 N aqueous solution of sodium hydroxide and the reaction mixture was magnetically stirred at room temperature. After 4 hours TLC analysis ($CHCl_3$-MeOH-NH_4OH 80:15:1) indicated complete hydrolysis and the reaction mixture was adjusted to pH=4 with 1.0 N HCl. The reaction mixture was then completely evaporated and dried in vacuo to afford the crude product which was used directly in the next step.
FAB-MS *m/e* = 481 (M + Na^+).

Step D: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-*tert*-butyldimethylsilyloxymethyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide

To a solution of 3.30 g (7.21 mmol) of the crude product from Step C dissolved in 40 mL of anhydrous THF was added 1.75 g (10.8 mmol) of 1,1'-carbonyldiimidazole and the reaction mixture was magnetically stirred and heated at reflux for 10 minutes. The reaction was then cooled to room temperature, 2.15 g (10.8 mmol) of 4-*iso*-propylbenzenesulfonamide and 1.61 mL (10.8 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene were added and the reaction was stirred for an additional 30 minutes at room temperature. The mixture was then diluted with EtOAc (80 mL), washed with 10% aqueous citric acid, saturated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated. The residue was partially purified on a silica gel flash chromatography column eluted with $CHCl_3$-MeOH-NH_4OH (92:8:0.5). The semi-purified material was combined and repurified on a second silica gel flash chromatography column eluted initially with 35% EtOAc-hexane, later with 50% EtOAc-hexane, and finally with 70% EtOAc-hexane. Combination of the purified fractions and evaporation afforded 3.20 g (69%) of the title compound as a yellow oil.
FAB-MS *m/e* = 678 ($M + K^+$).

Step E: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-hydroxymethyl-2-*n*-propylphenoxy)-3,4-methylenedioxy-phenylacetamide

To a solution of 3.20 g (5.01 mmol) of the product of Step D dissolved in 5.0 mL of anhydrous THF was added 5.06 mL (5.06 mmol) of a 1.0 M solution of tetrabutylammonium fluoride in THF and the reaction mixture was stirred at room temperature under a nitrogen atmosphere. After 2.5 hours 1.0 mL additional tetrabutylammonium fluoride in THF was added and the reaction mixture was stirred for an additional 14 hours. The reaction mixture was then concentrated in vacuo and applied to a silica gel flash chromatography column and

eluted with 60% EtOAc-hexane. Combination of the purified fractions and drying in vacuo afforded 0.691 g (26%) of the title compound as an amorphous powder.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.87 (t, *J*=7.60 Hz, 3H), 1.26 (d, *J*=6.80 Hz, 3H), 1.27 (d, *J*=6.80 Hz, 3H), 1.51-1.63 (m, 2H), 2.54-2.68 (m, 2H), 2.98 (sept, *J*=6.80 Hz, 1H), 4.46 (s, 2H), 5.37 (s, 1H), 5.95 (s, 1H), 6.51 (d, *J*=8.40 Hz, 1H), 6.77 (d, *J*=8.00 Hz, 1H), 6.88-6.95 (m, 3H), 7.10 (d, *J*=2.00 Hz, 1H), 7.36 (d, *J*=8.40 Hz, 2H), 7.77 (d, *J*=8.40 Hz, 2H).

FAB-MS *m/e* = 548 ($M + Na^+$).

EXAMPLE 66

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-formyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide

Step A: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-formyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide

To a solution of 0.573 g (1.09 mmol) of the product of Example 65 dissolved in 5.0 mL of dichloromethane was added 2.86 g (32.9 mmol) of manganese dioxide and 1.15 g of finely powdered 3A molecular sieves and the reaction mixture was magnetically stirred at room temperature for 14 hours. The reaction mixture was then filtered through a bed of celite and $MgSO_4$ and the filtrate was evaporated in vacuo. The residue was dissolved in dichloromethane and applied to a silica gel flash chromatography column and then eluted with 3% MeOH-CH_2Cl_2. Evaporation of the purified fractions and drying in vacuo afforded 0.149 g (26%) of the title compound.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.89 (t, *J*=7.60 Hz, 3H), 1.24 (d, *J*=7.20 Hz, 3H), 1.25 (d, *J*=7.20 Hz, 3H), 1.57-1.68 (m, 2H), 2.63-2.74 (m, 2H), 2.96 (sept, *J*=7.20 Hz, 1H), 5.56 (s, 1H), 5.97 (s, 2H), 6.70 (d, *J*=8.40 Hz, 1H), 6.80 (d, *J*=8.00 Hz, 1H), 6.91 (d, *J*=1.60 Hz, 1H), 6.96 (dd, *J*=1.60, 8.00 Hz, 1H), 7.34 (d, *J*=8.40 Hz, 2H), 7.53 (dd, *J*=2.00,

8.40 Hz, 1H), 7.66 (d, *J*=2.00 Hz, 1H), 7.76 (d, *J*=8.40 Hz, 2H), 9.77 (s, 1H).
FAB-MS *m/e* = 546 ($M + Na^+$).

EXAMPLE 67

α-(4-acetyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetic acid

Step A: Preparation of 4-hydroxy-2-*n*-propylacetophenone

A Parr hydrogenation apparatus flask was charged with a solution of 2.00 g (11.36 mmol) of 3-allyl-4-hydroxyacetophenone dissolved in 10 mL of ethanol and 200 mg of a 10% palladium on carbon catalyst. The flask was mounted in the Parr apparatus and shaken under a 46 psig hydrogen atmosphere for 15 minutes. At the end of this period TLC analysis (15% EtOAc-hexane) indicated that the starting material had been completely consumed, and the reaction mixture was filtered and evaporated. The residue was purified on a silica gel flash chromatography column eluted with 25% EtOAc-hexane. Evaporation of the purified fractions and drying in vacuo afforded 1.83 g (91%) of the title compound.
^{1}H-NMR (200 MHz, $CDCl_3$, ppm): δ 0.98 (t, *J*=7.40 Hz, 3H), 1.56-1.78 (m, 2H), 2.57 (s, 3H), 2.63 (t, *J*=7.20 Hz, 2H), 6.08 (br s, 1H), 6.84 (d, *J*=8.20 Hz, 1H), 7.74 (dd, *J*=2.20, 8.20 Hz, 1H), 7.79 (d, *J*=2.20 Hz, 1H).
FAB-MS *m/e* = 178 (M^+).

Step B: Preparation of methyl α-(4-acetyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetate

To a solution of 0.250 g (1.40 mmol) of the product of Step A dissolved in 3.0 mL of DMF was added 0.504 g (1.54 mmol) of cesium carbonate and the reaction mixture was magnetically stirred at room temperature under a nitrogen atmosphere for 15 minutes. Methyl α-bromo-3,4-methylenedioxyphenylacetate (0.422 g, 1.54 mmol) was then added and the resulting mixture was stirred at room temperature

for an additional 24 hours. The reaction mixture was then partitioned between 10% aqueous citric acid and EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated in vacuo to afford the title compound. ^1H-NMR (300 MHz, $CDCl_3$, ppm): δ 0.96 (t, *J*=7.50 Hz, 3H), 1.62-1.74 (m, 2H), 2.52 (s, 3H), 2.68-2.75 (m, 2H), 3.71 (s, 3H), 5.61 (s, 1H), 5.98 (s, 2H), 6.71 (d, *J*=8.60 Hz, 1H), 6.81 (d, *J*= 8.20 Hz, 1H), 7.02 (dd, *J*=1.80, 8.20 Hz, 1H), 7.04 (d, *J*=1.80 Hz, 1H), 7.73 (dd, *J*=2.20, 8.60 Hz, 1H), 7.79 (d, *J*=2.20 Hz, 1H).

FAB-MS *m/e* = 371 (M + 1).

Step C: Preparation of α-(4-acetyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetic acid

To a solution of 0.556 g (1.50 mmol) of the product of Step B dissolved in 4.0 mL of methanol was added 0.45 mL (2.25 mmol) of a 5.0 N aqueous solution of sodium hydroxide. The reaction mixture was stirred at room temperature and monitored by TLC ($CHCl_3$-MeOH-NH_4OH 80:15:1). After 4 hours the reaction was judged to be complete and the reaction mixture was adjusted to pH=7 with 6.0 N HCl. The mixture was then evaporated in vacuo and the residue was purified on a silica gel flash chromatography column eluted with $CHCl_3$-MeOH-NH_4OH (80:15:1). Evaporation of the purified fractions and drying in vacuo afforded 0.416 g (78%) of the title compound.

^1H-NMR (400 MHz, CD_3OD, ppm): δ 0.94 (t, *J*=7.60 Hz, 3H), 1.62-1.70 (m, 2H), 2.53 (s, 3H), 2.61-2.69 (m, 1H), 2.80-2.88 9m, 1H), 5.39 (s, 1H), 5.93 (d, *J*=1.20 Hz, 1H), 5.94 (d, *J*=1.20 Hz, 1H), 6.79 (d, *J*=8.00 Hz, 1H), 6.91 (d, *J*=8.80 Hz, 1H), 7.10 (dd, *J*=1.60, 8.00 Hz, 1H), 7.15 (d, *J*=1.60 Hz, 1H), 7.78 (d, *J*=2.40 Hz, 1H), 7.81 (dd, *J*=2.40, 8.80 Hz, 1H).

EXAMPLE 68

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-acetyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide

Step A: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-acetyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide

To a solution of 0.181 g (0.51 mmol) of the product of Example 67 dissolved in 2.5 mL of anhydrous DMF was added 0.248 g (1.53 mmol) of 1,1'-carbonyldiimidazole and the reaction mixture was magnetically stirred and heated at 80°C under a nitrogen atmosphere in an oil bath. After 20 minutes the reaction mixture was cooled to room temperature and 0.152 g (0.77 mmol) of 4-*iso*-propylbenzene-sulfonamide and 381 μL (2.55 mmol) was added. The reaction mixture was heated at 80°C for an additional 10 minutes then cooled again to room temperature and partitioned between EtOAc and 10% aqueous citric acid. The organic layer was separated, washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated. The residue was purified on a silica gel flash chromatography column eluted with $CHCl_3$-MeOH-NH_4OH (80:15:1); evaporation of the purified fractions and drying in vacuo afforded 0.128 g (47%) of the title compound as an amorphous solid.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.88 (t, *J*=7.60 Hz, 3H), 1.21 (d, *J*=6.80 Hz, 3H), 1.22 (d, *J*=6.80 Hz, 3H), 1.55-1.65 (m, 2H), 2.51 (s, 3H), 2.54-2.64 (m, 1H), 2.67-2.75 (m, 1H), 2.92 (sept, *J*=6.80 Hz, 1H), 5.43 (s, 1H), 5.94 (s, 2H), 6.75 (d, *J*=8.80 Hz, 1H), 6.77 (d, *J*=8.40 Hz, 1H), 7.01-7.03 (m, 2H), 7.23 (d, *J*=8.40 Hz, 2H), 7.66 (dd, *J*=2.40, 8.80 Hz, 1H), 7.67 (d, *J*=8.40 Hz, 2H), 7.73 (d, *J*=2.40 Hz, 1H).

FAB-MS *m/e* = 538 (M + 1).

EXAMPLE 69

α-(2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetic acid

FAB-MS for $C_{18}H_{18}O_5$: *m/e* = 337 ($M + Na^+$).

EXAMPLE 70

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide

FAB-MS for $C_{27}H_{29}NSO_6$: *m/e* = 534 ($M + K^+$).

EXAMPLE 71

α-(3-methoxyphenoxy)-3,4-methylenedioxyphenylacetic acid

EI-MS for $C_{16}H_{14}O_6$: *m/e* = 302 (M^+).

EXAMPLE 72

α-(2-(2-hydroxyethyl)phenoxy)-3,4-methylenedioxyphenylacetic acid

FAB-MS for $C_{17}H_{16}O_6$: *m/e* = 317 (M + 1).

EXAMPLE 73

α-(2-(2-carbomethoxyethyl)phenoxy)-3,4-methylenedioxyphenylacetic acid

CI-MS for $C_{19}H_{18}O_7$: *m/e* = 359 (M + 1).

EXAMPLE 74

α-(4-hydroxymethyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetic acid

CI-MS for $C_{19}H_{20}O_6$: *m/e* = 326 ($M^+ - H_2O$).

EXAMPLE 75

α-(4-(2-hydroxyethyl)-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetic acid

CI-MS for $C_{20}H_{22}O_6$: *m/e* = 359 (M + 1).

EXAMPLE 76

N-(4-iso-propylbenzenesulfonyl)-α-(2-(2-carbomethoxyethyl)phenoxy)-3,4-methylenedioxyphenylacetamide

ESI-MS for $C_{28}H_{29}NSO_8$: *m/e* = 540 (M + 1).

EXAMPLE 77

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-(2-carboxyethyl)phenoxy)-3,4-methylenedioxyphenylacetamide

CI-MS for $C_{27}H_{27}NSO_8$: *m/e* = 526 (M + 1).

EXAMPLE 78

α-(2-(2-carboxyethyl)phenoxy)-3,4-methylenedioxyphenylacetic acid

CI-MS for $C_{18}H_{16}O_7$: *m/e* = 345 (M + 1).

EXAMPLE 79

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-carbomethoxy-2-*n*-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

Step A: Ethyl 2-(4-carbomethoxy-2-*n*-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetate

To a mixutre of methyl 4-hydroxy-3-*n*-propylbenzoate (3.0 g, 15.46 mmol) and Cs_2CO_3 (5.1 g, 16 mmol) in dry dimethylformamide (50 mL) was added ethyl 2-bromo-2-(5-methoxy-3,4-methylenedioxy)phenylacetate (4.3 g, 15.56 mmol), and the resulting mixture was stirred at room temperature for 6 h. At the end of this period, the reaction mixture was diluted with ice water (300 mL) and extracted with ethyl acetate (3 x 60 mL). The combined organic phase was washed with water and brine, and then dried over anhydrous $MgSO_4$, filtered and solvent removed to give the crude product. Purification of the crude product by silica-gel flash column chromatography using ethyl acetate-hexane (1:9) afforded the titled product as an oil (5.1 g).

^1H NMR (200 MHz, $CDCl_3$, ppm) δ 7.82 (m, 2H); 6.75 (m, 3H); 6.61 (d, 1H, J = 1.5 Hz); 5.93 (s, 2H); 5.54 (s, 1H); 4.15 (m, 2H); 3.84 (s, 3H); 3.83 (s, 3H); 2.68 (m, 2H); 1.69 (m, 2H); 1.20 (t, 3H, J = 7.4 Hz); 0.90 (t, 3H, J = 7.4 Hz).

Step B: 2-(4-carbomethoxy-2-*n*-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetic acid

To a solution of the product of Step A (4.3 g, 12 mmol) in methanol (25 mL) was added aqueous 2N NaOH (10 mL) and the reaction mixture was stirred at room temperature. The rapid progress of mono-deesterification was monitored by TLC analysis using $CHCl_3$-MeOH-NH_4OH:(80:15:1). After 15 min, the reaction mixture was cooled to 0°C and neutralized with aqueous 2N HCl. Methanol was removed in vacuo and the resulting mixture was acidified with aqueous 2N HCl. The oily product which precipitated was extracted into methylene chloride (3 x 40 mL) and the combined organic phase was washed with water, brine and then dried over $MgSO_4$. Removal of the solvent in vacuo afforded the crude product which was then purified by flash-chromatography on silica gel using $CHCl_3$-MeOH-NH_4OH:(80:10:1) to give desired product as the ammonium salt. The

salt was treated with aqueous 1N HCl (20 mL) to provide the titled compound as a white solid (3.4 g).

^{1}H NMR (200 MHz, CD_3OD, ppm) δ 7.78 (m, 2H), 6.77 (m, 3H), 6.61 (d, 1H, J = 1.5 Hz), 5.93 (s, 2H), 5.54 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.68 (m, 2H), 1.69 (m, 2H), 0.90 (t, 3H, J = 7.4 Hz).

Step C: N-(4-*iso*-Propylbenzenesulfonyl)-2-(4-carbomethoxy-2-n-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)-acetamide

To the product of Step B (0.12 g, 0.30 mmol) in dry THF (1.5 mL) was added 1,1'-carbonyldiimidazole (0.1 g, 0.61 mmol) and the reaction stirred at 50°C for 3 hr. To this solution was added a solution of 4-*iso*-propylbenezenesulfonamide (0.17 g, 0.9 mmol) and DBU (0.14 mL, 0.94 mmol) in dry THF (1.5 mL), and the reaction continued at 50°C for 4 hr. The reaction was diluted with ice water and acidified with aqueous 1N HCl. The precipitated material was taken up in EtOAc and the organic phase was washed with water, brine, and then dried over $MgSO_4$, filtered and the solvent removed. The product was purified by flash-chromatography on silica-gel using $CHCl_3$:MeOH:NH_4OH (80:10:1) as the eluting solvent to yield the titled product as the ammonium salt. Acidification of the ammonium salt afforded the titled product as a white solid (0.14 g).

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.78 (d, 2H, J = 8.4 Hz), 7.76 (d, 1H, J = 2.3 Hz), 7.62 (dd, 1H, J = 8.6, 2.2 Hz), 7.37 (d, 2H, J = 8.4 Hz), 6.70 (d, 1H, J = 1.4 Hz), 6.61 (d, 1H, J = 1.5 Hz), 5.97 (s, 2H), 5.49 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.98 (sept, 1H, J = 6.9 Hz), 2.65 (m, 2H), 1.59 (m, 2H), 1.25 (dd, 6H, J = 7.0, 2.5 Hz), 0.90 (t, 3H, J = 7.4 Hz).

$C_{30}H_{32}NO_9N$: Calc: C 59.50 H 5.33 N 2.31. Found: C 59.60 H 5.34 N 2.59

EXAMPLE 80

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

To the product of Example 79 (0.6 g, 1.02 mmol) in MeOH (15 mL) was added aqueous 2N NaOH (5 mL) and the reaction was stirred at 60°C for 3 h. When the reaction was complete the MeOH was removed in vacuo and the aqueous phase was acidified with 2N HCl. The product precipitated was extracted into methylene chloride (3 X 50 mL) and the combined organic phase was washed with brine then dried over $MgSO_4$, filtered and the solvent removed. The residue upon trituration with ether provided the titled product as a white solid (0.45 g).

^1H NMR (400 MHz, DMSO-d_6, ppm): δ 12.67 (br, 1H), 12.63 (br, 1H), 7.70 (d, 2H, J = 8.4 Hz), 7.66 (d, 1H, J = 2.1 Hz), 7.58 (dd, 1H, J = 8.5, 2.2 Hz), 7.40 (d, 2H, J = 8.4 Hz), 6.78 (d, 1H, J = 1.2 Hz), 6.66 (d, 1H, J = 1.2 Hz), 6.51 (d, 1H, J = 8.5 Hz), 6.02 (d, 2H, J = 3.1 Hz), 5.69 (s, 1H), 3.79 (s, 3H), 2.93 (sept, 1H, J = 6.9 Hz), 2.56 (m, 2H), 1.53 (m, 2H), 1.17 (d, 6H, J = 6.9 Hz), 0.83 (t, 3H, J = 7.4 Hz).
FAB mass spectrum : m/e 570 (M+1).
$C_{29}H_{31}NO_9S$: Calc: C 61.15 H 5.49 N 2.46 Found: C 60.86 H 5.64 N 2.71.

EXAMPLE 81

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(4-*iso*-propylbenzene-sulfonyl)carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylene-dioxyphenyl)acetamide

The titled compound was prepared from N-(4-*iso*-propylbenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-5-methoxy-

3,4-methylenedioxyphenyl)acetamide (Example 80) using a procedure similar to that described in Step C of Example 79.
FAB mass spectrum : m/e 751 (M+1).
$C_{38}H_{42}N_2O_{10}S_2 \cdot 0.5\ H_2O$: Calc.: C 60.06; H 5.70; N 3.69.
Found: C 60.15; H 5.73; N 3.58.

EXAMPLE 82

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-carboxamido-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

To N-(4-*iso*-propylbenzenesulfonyl)-2-(4-carboxy-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide (Example 80) (0.12 g, 0.21 mmol) in dry THF (1.5 mL) was added 1,1'-carbonyldiimidazole (0.1 g, 0.61 mmol) and the mixture was stirred at 50°C for 2h. The reaction was cooled to room temperature and was saturated with dry NH_3. The reaction mixture was stirred at room temperature for 1h and then acidified. The crude product isolated was purified by silica-gel flash column chromatography using $CHCl_3$-MeOH-NH_4OH: (40:10:1) to give the product as the ammonium salt. Acidification provided the desired titled product as a white solid (0.06 g).
^1H NMR (300 MHz, DMSO-d_6, ppm): δ 7.76 (br, 1H), 7.68 (d, 2H, J = 8.4 Hz), 7.64 (d, 1H, J = 2.1 Hz), 7.55 (dd, 1H, J = 8.6, 2.3 Hz), 7.40 (d, 2H, J = 8.4 Hz), 7.16 (br, 1H), 6.76 (s, 1H), 6.65 (d, 1H, J = 1.2 Hz), 6.53 (d, 1H, J = 8.7 Hz), 6.01 (d, 2H, J = 2.9 Hz), 5.67 (s, 1H), 3.78 (s, 3H), 2.93 (sept, 1H, J = 6.8 Hz), 2.55 (m, 2H), 1.54 (m, 2H), 1.17 (d, 6H, J = 6.9 Hz), 0.84 (t, 3H, J = 7.3 Hz).
FAB mass spectrum: m/e 569 (M+1).

EXAMPLE 83

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-methyl)carboxamido-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82.
^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.21 (q, 1H, J = 4.7 Hz), 7.68 (d, 2H, J = 8.4 Hz), 7.59 (d, 1H, J = 1.9 Hz), 7.49 (dd, 1H, J = 8.6, 2.1 Hz), 7.40 (d, 2H, J = 8.4 Hz), 6.77 (s, 1H), 6.65 (s, 1H), 6.53 (d, 1H, J = 8.7 Hz), 6.01 (d, 2H, J = 2.9 Hz), 5.67 (s, 1H), 3.78 (s, 3H), 2.93 (sept, 1H, J = 6.8 Hz), 2.73 (d, 3H, J = 4.4 Hz), 2.56 (m, 2H), 1.54 (m, 2H), 1.16 (d, 6H, J = 6.9 Hz), 0.84 (t, 3H, 7.3 Hz).
$C_{30}H_{34}N_2O_8S$: Calc: C 61.84; H 5.88; N 4.81.
Found: C 61.84; H 6.03; N 4.59.

EXAMPLE 84

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-2-hydroxyethylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82.
^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.77 (d, 2H, J = 8.4 Hz), 7.64 (d, 1H, J = 2.3 Hz), 7.51 (dd, 1H, J = 8.5, 2.4 Hz), 7.36 (d, 2H, J = 8.5 Hz), 6.68 (d, 1H, J = 1.4 Hz), 6.60 (m, 2H), 5.96 (s, 2H), 5.48 (s, 1H), 3.82 (s, 3H), 3.68 (t, 2H, J = 5.9 Hz), 3.46 (t, 2H, J = 5.9 Hz), 2.97 (sept, 1H, J = 6.9 Hz), 2.66 (m, 2H), 1.62 (m, 2H), 1.25 (dd, 6H, J = 6.9, 1.2 Hz), 0.90 (t, 3H, J = 7.4 Hz).
$C_{31}H_{36}N_2O_9S$: Calc: C 60.77; H 5.92; N 4.57.
Found: C 60.49; H 6.04; N 4.45

EXAMPLE 85

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-morpholinylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82.

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.77 (d, 2H, J = 8.5 Hz), 7.37 (d, 2H, J = 8.4 Hz), 7.22 (d, 1H, J = 2.1 Hz), 7.09 (dd, 1H, J = 8.4, 2.2 Hz), 6.66 (d, 1H, J = 1.5 Hz), 6.62 (d, 1H, J = 8.5 Hz), 6.57 (d, 1H, J = 1.5 Hz), 5.95 (s, 2H), 5.46 (s, 1H), 3.81 (s, 3H), 3.65 (m, 8H), 2.98 (m, 1H), 2.66 (m, 2H), 1.60 (m, 2H), 1.26 (d, 6H, J = 7.1 Hz), 0.90 (t, 3H, J = 7.4 Hz).

$C_{33}H_{38}N_2O_9S$: Calc: C 62.05; H 6.00; N 4.39.
Found: C 61.96; H 5.98; N 4.55.

EXAMPLE 86

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-3-methylbutylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82.

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.77 (d, 2H, J = 8.5 Hz), 7.60 (d, 1H, J = 2.3 Hz), 7.47 (dd, 1H, J = 2.3, 8.5 Hz), 7.36 (d, 2H, J = 8.5 Hz), 6.68 (d, 1H, J = 1.5 Hz), 6.59 (d, 1H, J = 1.4 Hz), 6.58 (d, 1H, J = 8.6 Hz), 5.96 (s, 2H), 5.48 (s, 1H), 3.82 (s, 3H), 3.36 (t, 2H, J = 7.5 Hz), 2.97 (m, 1H), 2.66 (m, 2H), 1.62 (m, 3H), 1.49 (q, 2H, J = 7.2 Hz), 1.25 (dd, 2H, J = 1.2, 6.9 Hz), 0.95 (d, 6H, J = 6.6 Hz), 0.90 (t, 3H, J = 7.4 Hz).

$C_{34}H_{42}N_2O_8S$: Calc: C 63.93; H 6.63; N 4.39.
Found: C 63.81; H 6.73; N 4.44.

EXAMPLE 87

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-carboxymethylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

Step A: N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-t-butoxy-carbonylmethylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82, where glycine-t-butyl ester was the amine starting material.

^{1}H NMR (300 MHz, $CDCl_3$ ppm): δ 7.70 (d, 2H, J = 8.2 Hz), 7.66 (d, 1H, J = 1.3 Hz), 7.56 (m, 1H), 7.41 (d, 2H, J = 8.2 Hz), 6.79 (s, 1H), 6.67 (s, 1H), 6.59 (d, 1H, J = 8.5 Hz), 6.03 (s, 2H), 5.71 (s, 1H), 3.88 (d, 2H, J = 5.5 Hz), 3.80 (s, 3H), 2.95 (sept, 1H, J = 6.9 Hz), 2.78 (m, 2H), 1.56 (m, 2H), 1.32 (s, 9H), 1.17 (d, 6H, J = 6.8 Hz), 0.86 (t, 3H, J = 7.3 Hz).

Step B: N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-carboxymethyl-carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

A solution of the product of Step A (0.069 g, 0.1 mmol) in anhydrous trifluoroacetic acid (1.5 mL) was stirred at room temperature for 4h. The excess reagent was evaporated in vacuo and the resulting residue was triturated with dry ether to give the titled product as white solid (0.6 g).

^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 7.70 (d, 2H, J = 8.2 Hz), 7.66 (d, 1H, J = 1.3 Hz), 7.56 (m, 1H), 7.41 (d, 2H, J = 8.2 Hz), 6.79 (s, 1H), 6.67 (s, 1H), 6.59 (d, 1H, J = 8.5 Hz), 6.03 (s, 2H), 5.71 (s, 1H), 3.88 (d, 2H, J = 5.5 Hz), 3.80 (s, 3H), 2.95 (sept, 1H, J = 6.9 Hz), 2.58 (m, 2H), 1.56 (m, 2H), 1.17 (d, 6H, J = 6.8 Hz), 0.86 (t, 3H, J = 7.3 Hz).

$C_{31}H_{34}N_2O_{10}S$ .0.4 H_2O: Calc.: C 58.74; H 5.53; N 4.42.
Found: C 58.79; H 5.83; N 4.37.

EXAMPLE 88

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(L-Ala-OEt)carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82, where L-alanine ethyl ester was the amine starting material.
^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.55 (d, 1H, J = 6.1 Hz), 7.69 (m, 3H), 7.57 (q, 1H, J = 9.2 Hz), 7.40 (m, 2H), 6.78 (d, 1H, J = 3.8 Hz), 6.63 (s, 1H), 6.55 (m, 1H), 6.02 (s, 2H), 5.70 (s, 1H), 4.39 (m, 1H), 4.08 (q, 2H, J = 6.8 Hz), 3.79 (d, 3H, J = 2.9 Hz), 2.93 (sept, 1H, J = 6.9 Hz), 2.57 (m, 2H), 1.55 (m, 2H), 1.37 (d, 3H, J = 5.5 Hz), 1.16 (m, 9H), 0.85 (t, 3H, J = 7.5 Hz).

EXAMPLE 89

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-2-ethoxycarbonylethyl-carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxy-phenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82, where β-alanine ethyl ester was the amine starting material.
^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.34 (t, 1H, J = 5.4 Hz), 7.68 (d, 2H, J = 8.3 Hz), 7.58 (d, 1H, J = 2.2 Hz), 7.49 (dd, 1H, J = 8.6, 2.3 Hz), 7.39 (d, 2H, J = 8.4 Hz), 6.77 (d, 1H, J = 1.4 Hz), 6.65 (d, 1H, J = 1.3 Hz), 6.53 (d, 1H, J = 8.8 Hz), 6.01 (s, 2H), 5.67 (s, 1H), 4.05 (q, 2H, J = 7.1 Hz), 3.78 (s, 3H), 3.44 (m, 2H), 2.92 (sept, 1H, J = 6.9 Hz), 2.53 (m, 2H), 1.54 (m, 2H), 1.16 (m, 9H), 0.84 (t, 3H, J = 7.4 Hz).

EXAMPLE 90

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(L-Ala)carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

The product from Example 88 was saponified to give the titled product.

^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.64 (br, 1H), 12.51 (br, 1H), 8.44 (dd, 1H, J = 7.1, 2.7 Hz), 7.69 (m, 3H), 7.56 (m, 1H), 7.40 (m, 2H), 6.77 (d, 1H, J = 1.6 Hz), 6.66 (d, 1H, J = 1.7 Hz), 6.55 (m, 1H), 6.01 (d, 2H, J = 2.6 Hz), 5.69 (s, 1H), 4.37 (pn, 1H, J = 7.4 Hz), 3.79 (d, 3H, J = 1.9 Hz), 2.93 (sept, 1H, J = 6.9 Hz), 2.57 (m, 2H), 1.54 (m, 2H), 1.36 (dd, 3H, J = 7.3, 2.7 Hz), 1.16 (d, 6H, J = 6.8 Hz), 0.85 (t, 3H, J = 7.2 Hz).

EXAMPLE 91

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-2-carboxyethylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

The product from Example 89 was saponified to give the titled product.

^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.64 (br, 1H), 12. 21 (br, 1H), 8.32 (t, 1H, J = 5.5 Hz), 7.68 (d, 2H, J = 8.4 Hz), 7.59 (d, 1H, J = 1.9 Hz), 7.49 (dd, 1H, J = 8.5, 2.1 Hz), 7.40 (d, 2H, J = 8.4 Hz), 6.77 (s, 1H), 6.65 (d, 1H, J = 1.2 Hz), 6.01 (d, 2H, J = 2.9 Hz), 5.68 (s, 1H), 3.79 (s, 3H), 3.39 (m, 2H), 2.93 (sept, 1H, J = 6.8 Hz), 2.55 (m, 2H), 1.54 (m, 2H), 1.16 (d, 6H, J = 6.9 Hz), 0.84 (t, 3H, J = 7.3 Hz).

$C_{32}H_{36}N_2O_{10}S$: Calc: C 59.99; H 5.66; N 4.37.

Found: C 59.72; H 5.77; N 4.49.

EXAMPLE 92

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-3-hydroxypropyl-carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxy-phenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82, where 3-aminopropanol was the amine starting material.

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 8.33 (m, 1H), 7.77 (d, 2H, J = 8.5 Hz), 7.60 (d, 1H, J = 2.3 Hz), 7.48 (dd, 1H, J = 8.5, 2.3 Hz), 7.36 (d, 2H, J = 8.4 Hz), 6.68 (d, 1H, J = 1.5 Hz), 6.60 (d, 1H, J = 1.4 Hz), 6.59 (d, 1H, J = 8.6 Hz), 5.96 (s, 2H), 5.48 (s, 1H), 3.82 (s, 3H), 3.63 (t, 2H, J = 6.3 Hz), 3.43 (t, 2H, J = 5.8 Hz), 2.97 (sept, 1H, J = 7.0 Hz), 2.66 (m, 2H), 1.80 (pn, 2H, J = 6.7 Hz), 1.61 (m, 2H), 1.25 (dd, 6H, J = 6.9, 1.3 Hz), 0.90 (t, 3H, J = 7.4 Hz).

$C_{32}H_{38}N_2O_9S$: Calc: C 61.33; H 6.11; N 4.47.
Found: C 61.07; H 6.09; N 4.48.

EXAMPLE 93

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-tetrazol-5-ylcarboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82, where 5-aminotetrazole was the amine starting material.

FAB-MS m/e = 640 (M+1)

EXAMPLE 94

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-3-(morpholin-4-yl)propyl-carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxy-phenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82, where 3-(N-morpholinyl)-aminopropane was the amine starting material.

^{1}H NMR (400 MHz, CD_3OD, ppm) δ 7.65 (d, 2H, J = 8.3 Hz), 7.65 (s, 1H), 7.58 (dd, 1H, J = 2.4, 8.6 Hz), 7.24 (d, 2H, J = 8.4 Hz), 6.81 (d, 1H, J = 8.6 Hz), 6.78 (d, 1H, J = 1.4 Hz), 6.69 (d, 1H, J = 1.4 Hz), 5.94 (s, 2H), 5.40 (s, 1H), 3.82 (s, 7H), 3.54 (m, 2H), 3.12 (m, 6 H), 2.92 (sept, 1H, J = 6.9 Hz), 2.66 (m, 2H), 1.62 (m, 2H), 1.22 (d, 6H, J = 6.9 Hz), 0.90 (t, 3H, J = 7.4 Hz).

$C_{35}H_{43}N_3O_9S$ .0.75 H_2O: Calc.: C 60.46; H 6.45; N 6.04.
Found: C 60.39; H 6.43; N 5.93.

EXAMPLE 95

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(D-Ala-OMe)carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82, where D-alanine methyl ester was the amine starting material.

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 8.54 (d, 1H, J = 6.8 Hz); 7.77 (d, 2H, J = 8.3 Hz), 7.66 (s, 1H), 7.53 (m, 1H), 7.36 (d, 2H, J = 8.3 Hz), 6.68 (s, 1H), 6.60 (m, 2H), 5.96 (s, 2H), 5.49 (s, 1H), 4.57 (m, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 2.97 (sept, 1H, J = 6.8 Hz), 2.67 (m, 2H), 1.62 (m, 2H),. 1.47 (d, 3H, J = 7.4 Hz), 1.24 (d, 6H, J = 7.0 Hz), 0.91 (t, 3H, J = 7.4 Hz).

EXAMPLE 96

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(D-Ala)carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

The product from Example 95 was saponified to give the titled product.

^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 12.64 (br, 1H), 12.48 (br, 1H), 8.44 (dd, 1H, J = 7.3, 2.6 Hz), 7.68 (m, 3H), 7.56 (m, 1H), 7.40 (dd, 2H, J = 4.0, 8.4 Hz), 6.77 (d, 1H, J = 2.3 Hz), 6.66 (m, 1H), 6.55 (dd, 1H, J = 21.0, 8.8 Hz), 6.01 (d, 2H, J = 3.6 Hz), 5.70 (d, 1H, J = 3.8 Hz), 4.37 (pn, 1H, J = 7.3 Hz), 3.78 (d, 3H, J = 1.8 Hz), 2.93 (sept, 1H, J = 7.0 Hz), 2.57 (m, 2H), 1.55 (m, 2H), 1.36 (dd, 3H, J = 7.3, 2.7 Hz), 1.16 (d, 6H, J = 6.9 Hz), 0.85 (t, 3H, J = 7.3 Hz).

EXAMPLE 97

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(3-carboxymethylpropyl)-carboxamido)-2-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxyphenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82, where methyl γ-aminobutyrate was the amine starting material.

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.77 (d, 2H, J = 8.5 Hz), 7.61 (d, 1H, J = 2.2 Hz), 7.48 (dd, 1H, J = 8.5, 2.3 Hz), 7.36 (d, 2H, J = 8.5 Hz), 6.68 (s, 1H), 6.59 (s, 1H), 6.59 (d, 1H, J = 8.3 Hz), 5.95 (s, 2H), 5.48 (s, 1H), 4.09 (q, 2H, J = 7.1 Hz), 3.82 (s, 3H), 3.37 (m, 2H), 2.97 (sept, 1H, J = 6.9 Hz), 2.66 (m, 2H), 2.38 (t, 2H, J = 7.4 Hz), 1.89 (pn, 2H, J = 7.1 Hz), 1.61 (m, 2H), 1.23 (d, 6H, J = 6.9 Hz), 0.90 (t, 3H, J = 7.3 Hz).

EXAMPLE 98

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-(3-carboxypropyl)-carboxamido)-2-*n*-propylphenoxy)-2-(5-methoxy-3,4-methylenedioxy-phenyl)acetamide

The product from Example 97 was saponified to give the titled product.

^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 12.63 (br, 1H), 12.06 (br, 1H), 8.27 (t, 1H, J = 5.5 Hz), 7.68 (d, 2H, J = 8.4 Hz), 7.60 (d, 1H, J = 2.2 Hz), 7.50 (dd, 1H, J = 8.5, 2.2 Hz), 7.40 (d, 2H, J = 8.4 Hz), 6.77 (d, 1H, J = 1.2 Hz), 6.66 (d, 1H, J = 1.3 Hz), 6.52 (d, 1H, J = 8.8 Hz), 6.01 (d, 2H, J = 2.9 Hz), 5.68 (s, 1H), 3.79 (s, 3H), 3.22 (q, 2H, J = 6.5 Hz), 2.92 (sept, 6.8 Hz), 2.54 (m, 2H), 2.25 (t, 2H, J = 7.4 Hz), 1.71 (pn, 7.1 Hz), 1.54 (m, 2H), 1.16 (d, 6H, J = 6.8 Hz), 0.84 (t, 3H, J = 7.3 Hz).
$C_{33}H_{38}N_2O_{10}S$: Calc: C 60.54; H 5.85; N 4.28.
Found: C 60.26; H 6.17; N 4.02.

EXAMPLE 99

N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-*iso*-propylcarbamoyl)amino-2-*n*-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetamide

Step A: 4-Nitro-2-(propen-3-yl)phenol

A mixture of 4-nitrophenoxyallyl ether (4.0 g, 22.35 mmol) and 1,2-dichlorobenzene (15 mL) was heated to reflux for 6h. The reaction mixture was cooled and purified by silica-gel flash column chromatography using hexanes and EtOAc-hexanes (1:6) as eluents, respectively. The pure product was obtained as an yellow oil (2.6 g).
^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 8.05 (d, 2H), 6.92 (d, 1H), 6.01 (m, 1H), 5.18 (m, 2H), 3.42 (d, 2H, J = 7.3 Hz).

Step B: Methyl 2-(4-nitro-2-(propen-3-yl)phenoxy)-2-(3,4-methylenedioxyphenyl)acetate

The titled compound was prepared using the procedures similar to that described in Step A of Example 79. Methyl 2-bromo-2-(3,4-methylenedioxyphenyl)acetate was used as the alkylating agent. Purification of the crude product was accomplished by silica-gel flash column chromatography using ethyl acetate-hexane (1:5). ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 8.05 (m, 2H), 7.02 (m, 2H), 6.78 (m, 2H), 5.96 (s, 2H), 5.6 (s, 1H), 5.15 (m, 2H), 4.15 (m, 2H), 3.75 (s, 3H), 3.47 (m, 2H).

Step C: 2-(4-(N-*iso*-propylcarbamoyl)amino-2-*n*-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetic acid

To a solution of the product of Step B (0.5 g) in methanol (6 mL) was added Pd-C(10%)(0.05g), and the reaction mixture was stirred at room temperature for 6h under an atmosphere of hydrogen gas. The catalyst was filtered off and the filtrate was concentrated in vacuo to give the desired methyl α-(4-amino-2-*n*-propylphenoxy)-2-(3,4-methylenedioxyphenyl)acetate (0.5 g) as a solid. This material without further purification was dissolved in dry THF (5 mL) and reacted with N-*iso*-propylisocyanate (0.1 mL) at room temperature for 12h. Purification of the crude product by flash chromatography using EtOAc-hexanes (1:2) gave the titled compound as white solid (0.36 g). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.1-6.77 (m, 6H), 6.61 (d, 1H, J = 1.5 Hz), 5.93 (s, 2H), 5.54 (s, 1H), 3.98 (m, 1H), 3.78 (s, 3H), 3.63 (m, 1H) 2.68 (m, 2H), 1.69 (m, 2H), 1.15 (dd, 6H, J = 7.0, 2.5 Hz), 0.90 (t, 3H, J = 7.4 Hz).

Step D: N-(4-*iso*-propylbenzenesulfonyl)-2-(4-(N-*iso*-propyl-carbamoyl)amino-2-*n*-propylphenoxy)-2-(3,4-methylene-dioxyphenyl)acetamide

The titled product was prepared from the product obtained in Step C using procedures similar to those described in Steps B and C of Example 79.

^{1}H NMR (300 MHz, CD_3OD, ppm): δ 7.78 (d, 2H, J = 8.4 Hz), 7.76 (m, 1H), 7.52 (m, 1H), 7.32 (d, 2H, J = 8.4 Hz), 7.07 (d, 1H,J = 1.4 Hz), 6.75-6.90 (m, 2H), 6.75 (d, 1H, J = 8.2 Hz), 6.42 (d, 1H, J = 8.2 Hz), 5.97 (s, 2H), 5.21 (s, 1H), 3.88 (m, 1H), 2.82 (m, 1H), 2.54 (m, 2H), 1.69 (m, 2H), 1.26 (dd, 6H, J = 7.0, 2.5 Hz), 1.15 (dd, 6H, J = 7.0, 2.5 Hz), 0.90 (t, 3H, J = 7.4 Hz).

FAB-MS: m/e 596 (M+1).

EXAMPLE 100

α-(2-*n*-propyl-4-methylaminosulfonylphenoxy)-3,4-methylenedioxy-phenylacetic acid

Step A: Preparation of 3-allyl-4-hydroxybenzenesulfonamide

To a solution of 5.00 g (28.9 mmol) of 4-hydroxybenzenesulfonamide dissolved in 30 mL of anhydrous DMF was added 10.36 g (31.8 mmol) of cesium carbonate and the reaction mixture was magnetically stirred at room temperature under a nitrogen atmosphere for 10 minutes. Allyl bromide (2.75 mL, 31.8 mmol) was added and the reaction mixture was then stirred for an additional 14 hours. The reaction mixture was then partitioned between EtOAc (60 mL) and 10% aqueous citric acid (200 mL) and extracted. The organic layer was separated, washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried ($MgSO_4$), filtered, evaporated and dried in vacuo to afford 5.40 g (88%) of a yellow solid. The crude *O*-allyl ether (5.36, 25.2 mmol) was then dissolved in 10 mL of 1,2-dichlorobenzene in a 50 mL round bottom flask and magnetically stirred at reflux under a nitrogen atmosphere for 15 hours. The reaction mixture was then cooled to room temperature and diluted with methanol. The 1,2-

dichlorobenzene was removed by extraction of the methanol layer with hexane, the methanol layer was separated, then evaporated. The residue was then purifed on a silica gel flash chromatography column eluted with 5% MeOH-CH_2Cl_2. Combination of the purified fractions, evaporation and drying in vacuo afforded 3.04 g (57%) of the title compound.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 3.38 (d, *J*=6.40 Hz, 2H), 5.02-5.10 (m, 2H), 5.94-6.04 (m, 1H), 6.84 (d, *J*=8.40 Hz, 1H), 7.58 (dd, *J*=2.40, 8.40 Hz, 1H), 7.61 (d, *J*=2.40 Hz, 1H).

CI-MS *m/e* = 213 (M^+).

Step B: Preparation of 4-hydroxy-3-*n*-propylbenzenesulfonamide

A Parr hydrogenation flask was charged with a solution of 3.04 g (14.30 mmol) of the product of Step A dissolved in 25 mL of ethanol and 0.300 g of a 10% palladium on carbon catalyst was added. The flask was mounted in the hydrogenation apparatus, freed of air, pressurized with hydrogen (40 psig) and shaken for 15 minutes. At the end of this period TLC analysis (3% MeOH-CH_2Cl_2, 2 elutions) indicated that the reaction was complete and the reaction mixture was filtered and evaporated. The product was dried in vacuo to afford 3.06 g (99%) of the title compound.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.94 (t, *J*=7.20 Hz, 3H), 1.58-1.68 (m, 2H), 2.01-2.62 (m, 2H), 6.82 (d, *J*=8.40 Hz, 1H), 7.55 (dd, J=2.40, 8.40 Hz, 1H), 7.60 (d, J=2.40 Hz, 1H).

FAB-MS *m/e* = 216 (M + 1).

Step C: Preparation of methyl α-(2-*n*-propyl-4-aminosulfonyl-phenoxy)-3,4-methylenedioxyphenylacetate

To a solution of 3.06 g (14.23 mmol) of the product of Step B dissolved in 25 mL of anhydrous DMF was added 4.87 g (15.0 mmol) of cesium carbonate and the reaction mixture was magnetically stirred under a nitrogen atmosphere at room temperature for 15 minutes. Methyl α-bromo-3,4-methylenedioxyphenylacetate (4.08g, 15.0 mmol) was then added and the reaction mixture was stirred for an additional 3 hours. The reaction mixture was then partitioned between

EtOAc (80 mL) and 10% aqueous citric acid (300 mL). The organic layer was separated, washed with saturated aqueous $NaHCO_3$, satuarated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated. The residue was dried in vacuo to afford 5.90 g (5.79 theoretical) of the title compound which was used in the next step without further purification.
^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.97 (t, *J*=7.20 Hz, 3H), 1.64-1.76 (m, 2H), 2.74 (t, *J*=7.20 Hz, 2H), 3.70 (s, 3H), 5.87 (s, 1H), 5.97 (s, 2H), 6.85 (d, *J*=8.00 Hz, 1H), 6.93 (d, *J*=8.40 Hz, 1H), 7.03 (d, *J*=1.60 Hz, 1H), 7.06 (dd, *J*=1.60, 8.00 Hz, 1H), 7.65 (dd, *J*=2.40, 8.40 Hz, 1H), 7.69 (d, *J*=2.40 Hz, 1H).
FAB-MS *m/e* = 408 (M + 1).

Step D: Preparation of methyl α-(2-*n*-propyl-4-methylamino-sulfonylphenoxy)-3,4-methylenedioxyphenylacetate

To a solution of 2.19 g (5.38 mmol) of the product of Step C dissolved in 20 mL of anhydrous THF was added 2.41 mL (16.1 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene and the reaction mixture was magnetically stirred under a nitrogen atmosphere for 25 minutes at room temperature. Iodomethane (1.00 mL; 16.1 mmol) was added and the reaction mixture was stirred an additional 15 hours at room temperature. The reaction mixture was diluted with EtOAc and a precipitate formed which was redissolved by addition of methanol. The mixture was further diluted with warm EtOAc (150 mL total), refridgerated overnight and a solid separated which was removed by filtration. The filtrate was evaporated in vacuo and the residue was purified on a silica gel flash chromatography column eluted with 5% EtOAc-$CHCl_3$. Combination of the purified fractions and evaporation in vacuo afforded 0.164 g of the title compound and a number of impure fractions which were reserved for repurification.
^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.97 (t, *J*=7.20 Hz, 3H), 1.65-1.77 (m, 2H), 2.48 (s, 3H), 2.74 (t, *J*=7.20 Hz, 2H), 3.71 (s, 3H), 5.87 (s, 1H), 5.98 (s, 2H), 6.85 (d, *J*=8.00 Hz, 1H), 6.96 (d, *J*=8.80 Hz, 1H), 7.04 (d, *J*=1.60 Hz, 1H), 7.07 (dd, J=1.60, 8.00 Hz, 1H), 7.58-7.61 (m, 2H).
ESI-MS *m/e* = 421 (M^+).

Step E: Preparation of α-(2-*n*-propyl-4-methylaminosulfonyl-phenoxy)-3,4-methylenedioxyphenylacetic acid

To a solution of 0.372 g (0.884 mmol) of the product of Step D dissolved in 3.0 mL of methanol was added 212 µL (1.06 mmol) of a 5.0 N aqueous sodium hydroxide solution which resulted in a cloudy suspension. The reaction was warmed to assist solution, methanol (1 mL) was added followed by dichloromethane (0.5 mL), however a clear solution was not obtained. Additional 5 N sodium hydroxide solution was added (212 µL), and finally 0.5 mL of THF was added which resulted in a clear solution. After stirring an additional 15 hours at room temperature, TLC analysis ($CHCl_3$-MeOH-NH_4OH 80:15:1) indicated complete hydrolysis of the starting material and the reaction was adjusted to pH=7 with 6 N HCl. The reaction mixture was then concentrated in vacuo and the residue was purified on a silica gel flash chromatography column eluted with $CHCl_3$-MeOH-HOAc (92:7:1). Combination of the purified fractions and drying in vacuo afforded 0.335 g (93%) of the title compound as an amorphous solid.
^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.96 (t, *J*=7.20 Hz, 3H), 1.66-1.78 (m, 2H), 2.48 (s, 3H), 2.73-2.77 (m, 2H), 5.74 (s, 1H), 5.97 (s, 2H), 6.85 (d, *J*=7.60 Hz, 1H), 6.98 (d, *J*=9.20 Hz, 1H), 7.07-7.10 (m, 2H), 7.59-7.62 (m, 2H).
ESI-MS *m/e* = 407 (M^+).

EXAMPLE 101

N-(4-*iso*-propylbenzenesulfonyl)-α-(2-*n*-propyl-4-methylamino-sulfonylphenoxy)-3,4-methylenedioxyphenylacetamide potassium salt

To a solution of 0.298 g (0.73 mmol) of the product of Example 100 dissolved in 4.0 mL of anhydrous THF was added 0.237 g (1.46 mmol) of 1,1'-carbonyldiimidazole and the reaction mixture was magnetically stirred and refluxed for 2 hours under a nitrogen atmosphere. The reaction mixture was then cooled to room temperature, 0.219 g (1.10 mmol) 4-*iso*-propylbenzenesulfonamide and 164 µL (1.10 mmol) 1,8-diazabicyclo[5.4.0]undec-7-ene were added and

the reaction was stirred and heated at reflux for an additional 10 minutes. The reaction mixture was then cooled to room temperature, partitioned between 10% aqueous citric acid and EtOAc and extracted. The organic layer which separated was washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated. The residue was redissolved in 1.0 mL of methanol and treated with 2.20 mL (3 eq) of a 1.1 M aqueous solution of potassium hydroxide. The mixture was then diluted with 5 mL of water and filtered through a 0.45 micron filter. The filtrate was desalted and purified on a Waters Millipore Delta Prep 3000 liquid chromatograph equipped with an M1000 Prep-Pak module containing a 47 x 300 mm Delta-Pak C18 15µm 100A column cartridge. Two solvent resevoirs were employed: solvent system A (95-5 water-acetonitrile), and solvent system B (5-95 water-acetonitrile), and the column effluent was monitored simultaneously at 210 and 280 nm with a Waters model 490 UV-visible detector. The column was preequillibrated with solvent system A and the filtrate was injected. The product was desalted by elution with 0.5 L of solvent system A (50 mL/min) then a gradient elution was begun which had as initial conditions 100% solvent system A-0% solvent system B and reached after 15 minutes 60% solvent system A-40% solvent system B, and the fractions were collected with an ISCO Foxy 200 fraction collector. The purified fractions were combined in round bottom flasks, frozen in a -78°C dry ice-acetone bath, and lyophilized. Combination of the purified product afforded 0.284 g (62%) of the title compound as a white lyophilized powder.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.89 (t, *J*=7.60 Hz, 3H), 1.21 (d, *J*=6.80 Hz, 3H), 1.22 (d, *J*=6.80 Hz, 3H), 1.57-1.64 (m, 2H), 2.45 (s, 3H), 2.56-2.63 (m, 1H), 2.70-2.76 (m, 1H), 5.37 (s, 1H), 5.93 (d, *J*=1.20 Hz, 1H), 5.94 (d, *J*=1.20 Hz, 1H), 6.76 (d, *J*=8.40 Hz, 1H), 6.85 (d, *J*=8.80 Hz, 1H), 7.02-7.04 (m, 2H), 7.21 (d, *J*=8.40 Hz, 2H), 7.47 (dd, *J*=2.40, 8.80 Hz, 1H), 7.52 (d, *J*=2.40 Hz, 1H), 7.65 (d, *J*=8.40 Hz, 2H).

ESI-MS *m/e* = 627 (M + 1).

EXAMPLE 102

N-(4-*iso*-propylbenzenesulfonyl)-α-[4-(cyanomethyl)-2-*n*-propylphenoxy)]-3,4-methylenedioxyphenylacetamide

Step A: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-bromomethyl-2-*n*-propylphenoxy)-3,4-methylenedioxy-phenylacetamide

To a solution of 0.200 g (.381 mmole) of the product of Example 65 dissolved in 1.5 mL of diethyl ether was added 0.837 mL (.837 mmole) of 1.0 M phosphorus tribromide in methylene chloride solution under nitrogen at 0°C. The reaction mixture was stirred at 0°C for 2 hours when TLC analysis (80:15:1 $CHCl_3$-MeOH-NH_4OH) indicated that the reaction was nearly complete. The reaction was quenched at 0°C with water and then partitioned with EtOAc. The aqueous portion was separated and the EtOAc portion was washed with brine (2 X 10 mL). The EtOAc portion was then dried over $MgSO_4$, filtered, evaporated to a residue, and then used in the next step of the reaction scheme.

Step B: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-cyanomethyl-2-*n*-propylphenoxy)-3,4-methylenedioxy-phenylacetamide

To a solution of the crude product of Step A dissolved in 1.5 mL of methyl sulfoxide was added 0.050 g (.762 mmole) of potassium cyanide at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 1 hour when TLC analysis (80:15:1 $CHCl_3$-MeOH-NH_4OH) indicated that the reaction had gone to completion. The reaction mixture was diluted with EtOAc and 10 % $NaHSO_4$ aqueous solution. The aqueous phase was separated and the EtOAc portion was washed with brine (2 X 10 mL). The EtOAc portion was then dried over $MgSO_4$, filtered, evaporated to a residue, and purified. Purification was done by reversed phase HPLC (Waters Millipore Delta Prep 4000 with Delta-Pak C18 15 μm 100 A column cartridge) with a solvent system of 30:70 water-acetonitrile and 0.1 % TFA buffer. The purified fractions collected were combined in a round

bottom flask, freeze in a -78°C dry ice-acetone bath, and lyophilized. The resulting lyophilized powder afforded 0.071 g (35 % 2-step yield).
^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.88 (t, J=7.37 Hz, 3H), 1.25 (d, J=6.92 Hz, 3H), 1.27 (d, J=6.97 Hz, 3H), 1.55 (m,2H), 2.60 (m, 2H), 2.99 (m, 1H), 3.75 (s, 2H), 5.40 (s, 1H), 5.96 (s, 2H), 6.53 (d, J=8.39 Hz, 1H), 6.78 (d, J=8.03 Hz, 1H), 6.86-6.96 (m, 3H), 7.10 (s, 1H), 7.37 (d, J=6.64 Hz, 2H), 7.78 (d, J=8.48 Hz, 2H).
MS (ESI): $C_{29}H_{30}N_2O_6S$ 534.63 Found: [535.1, M+1].

EXAMPLE 103

N-(4-*iso*-propylbenzenesulfonyl)-α-[4-(tetrazol-5-ylmethyl)-2-*n*-propylphenoxy)]-3,4-methylenedioxyphenylacetamide

A solution of 0.120 g (.224 mmole) of the product of Example 102 and 0.139 g (.673 mmole) of trimethyltin azide dissolved in 1.5 mL of toluene was heated in sealed pressure reaction tube and stirred for 5 hours at 120°C. Analytical HPLC analysis (30:70 water-acetonitrile with 0.1 % TFA) indicated that the reaction had gone to completion. The reaction mixture was cooled to room temperature when 2 M HCl solution was added. The reaction mixture was partitioned with EtOAc and the aqueous portion was separated. The EtOAc portion was washed with brine (2 X 10 mL), dried over $MgSO_4$, filtered, evaporated to a residue, and purified. Purification was done by reversed phase HPLC (Waters Millipore Delta Prep 4000 with Delta-Pak C18 15 μm 100 A column cartridge) with a solvent system of 30:70 water-acetonitrile and 0.1 % TFA buffer. The purified fractions collected were combined in a round bottom flask, freeze in a -78°C dry ice-acetone bath, and lyophilized. The resulting lyophilized powder afforded 0.0306 g (24 % yield).
^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.86 (t, J=7.47 Hz, 3H), 1.25 (d, J=6.82 Hz, 6H), 1.54 (m, 2H), 2.58 (m, 2H), 2.96 (m, 1H), 4.19 (s, 2H), 5.38 (s, 1H), 5.96 (s, 2H), 6.51 (d, J=8.30 Hz, 1H), 6.76 (d, J=8.53 Hz, 1H), 6.84-6.89 (m, 3H), 7.04 (s, 1H), 7.35 (d, J=8.30 Hz, 2H), 7.76 (d, J=8.35 Hz, 2H).

MS (ESI): C29H31N5O6S 577.66 Found: [578.2, M+1].

EXAMPLE 104

N-(4-iso-propylbenzenesulfonyl)-α-[N-(4-carbomethoxyphenylamino)]-3,4-methylenedioxyphenylacetamide

Step A: Preparation of ethyl α-[N-(4-carbomethoxyphenylamino)]-3,4-methylenedioxyphenylacetate

To a solution of 5.034 g (33.4 mmoles) of methyl 4-aminobenzoate dissolved in 50.0 mL of DMF was added 10.526 g (36.7 mmoles) of ethyl α-bromo-3,4-methylenedioxyphenylacetate. The reaction mixture was heated to 85°C and stirred in a sealed pressure reaction tube for 16 hours. TLC analysis (25% EtOAc:Hexanes) indicated that the reaction had gone to completion. The reaction mixture was transferred to a sep. funnel and partitioned between EtOAc and water. The aqueous portion was separated and the organic portion was washed with brine (2X25 mL), dried over MgSO4, filtered, and evaporated to a residue. Purification was done by flash chromatography eluting with 20% EtOAc:Hexanes. The purified fractions collected were combined and evaporated to afford 7.90 g of the titled product.
MS (ESI): C19H19NO6 357.36 Found: [357.9, M+1].

Step B: Preparation of α-[N-(4-carbomethoxyphenylamino)]-3,4-methylenedioxyphenylacetic acid

To a solution of 2.12 g (5.93 mmoles) of the product of Step A dissolved in 10 mL of methanol was added 6.52 mL (6.52 mmoles) of 1.0 N KOH solution in methanol. The reaction mixture was stirred at room temperature for 1 hour. TLC analysis (25% EtOAc:Hexanes) at that time indicated that there was no more starting material present in the reaction mixture. The reaction mixture was diluted with EtOAc and quenched with 10% NaHSO4 aqueous solution.

The aqueous phase was separated and the organic portion was washed with brine (2 X 15 mL), and evaporated to a residue. Purification was done by reversed phase HPLC (Waters Millipore Delta Prep 4000 with Delta-Pak C18 15 μm 100 A column cartridge) with a solvent system of 50:50 water-acetonitrile and 0.1 % TFA buffer. The purified fractions collected were combined in a round bottom flask, freeze in a -78°C dry ice-acetone bath, and lyophilized. The resulting lyophilized powder afforded 1.11 g (57% yield) of the titled product.
MS (CI): C17H15NO6 329.13 Found: [330.5, M+1].

Step C: Preparation of N-(4-iso-propylbenzenesulfonyl)-α-[N-(4-carbomethoxyphenylamino)]-3,4-methylenedioxyphenyl-acetamide

To a solution of 0.180 g (.547 mmole) of the product of Step B dissolved in 1.5 mL of methylene chloride was added 0.080 g (.656 mmole) of 4-dimethylaminopyridine, 0.147 g (.766 mmole) of 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride, and 0.120 g (.602 mmole) of the sulfonamide respectively. The reaction mixture was stirred at room temperature under nitrogen for 24 hours. TLC analysis (80:15:1 CHCl3-CH3OH-NH4OH) indicated that the reaction had gone to completion after 24 hours of stirring. The reaction mixture was diluted with EtOAc and transferred to a sep. funnel. The organic portion was washed with 2 N HCl (2X10 mL) and brine (1X10 mL), dried over MgSO4, filtered, and evaporated to a residue. Purification was done by reversed phase HPLC (Waters Millipore Delta Prep 4000 with Delta-Pak C18 15 μm 100 A column cartridge) with a solvent system of 40:60 water-acetonitrile and 0.1 % TFA buffer. The purified fractions collected were combined in a round bottom flask, freeze in a -78°C dry ice-acetone bath, and lyophilized. The resulting lyophilized powder afforded 0.060 g (21% yield) of titled product.
^{1}H-NMR (400 MHz, CD3OD, ppm): δ 1.25 (d, J=6.96 Hz, 3H), 1.26 (d, J=6.87 Hz, 3H), 2.97 (sept., J=7.06 Hz, 1H), 3.80 (s, 3H), 4.86 (s,

1H), 5.94(s, 2H), 6.45 (d, J=8.81 Hz, 2H), 6.87-6.75 (m, 3H), 7.36 (d, J=8.39 Hz, 2H), 7.65 (d, J=8.85 Hz, 2H), 7.78 (d, J=8.48 Hz, 2H).
MS (ESI): C26H26N2O7S 510.57 Found: [511.0, M+1].

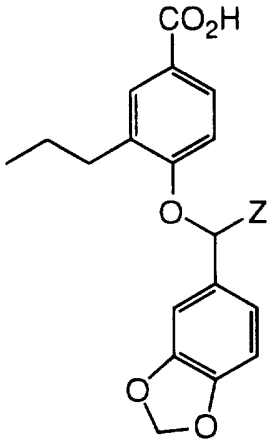
EXAMPLE 105

N-(4-iso-propylbenzenesulfonyl)-α-[N-(4-carboxyphenylamino)]-3,4-methylenedioxyphenylacetamide

Following the hydrolysis procedure described in Example 58 the titled compound is prepared from N-(4-iso-propylbenzene-sulfonyl)-α-[N-(4-carbomethoxyphenylamino)]-3,4-methylenedioxy-phenylacetamide.

EXAMPLES 106-121

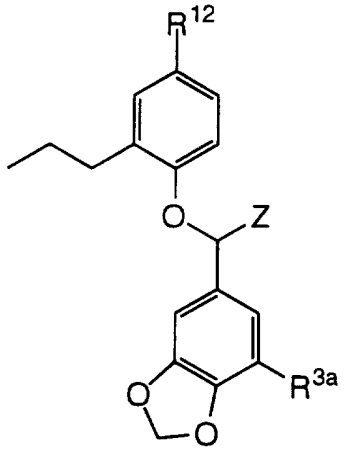
Examples 106 through 121 were prepared following the procedures described in Example 40.



Ex. #	Z	Mass Spectrum (M+1)
106	$CONHSO_2$-3-pyridyl	(M+1) 513
107	$CONHSO_2$-(2-Me)-3-quininolinyl	(M+1) 563
108	$CONHSO_2$-3-quininolinyl	(M+1) 549
109	$CONHSO_2$-(4-OH)-3-pyridyl	(M+1) 529
110	$CONHSO_2$-(4-OEt)Ph	($M+NH_4^+$) 559
111	$CONHSO_2$-(4-$CONH_2$)Ph	(M+1) 542
112	$CONHSO_2$-[4-$CO(N(Me)_2)$]Ph	(M+1) 569
113	$CONHSO_2$-(4-SEt)-3-pyridyl	(M+1) 559
114	$CONHSO_2$-(4-OEt)-3-pyridyl	(M+1) 543
115	$CONHSO_2$-(4-amine, 2,5-di-OMe)Ph	(M+1) 573
116	$CONHSO_2$-(2,5-di-OMe)Ph	(M+1) 558
117	$CONHSO_2$-(3,4-di-OMe)Ph	(M+1) 558
118	$CONHSO_2$-[5-(4-morpholinyl)]-2-benzothiophene	(M+1) 639
119	$CONHSO_2$-(4-OMe)-2-benzothiophene	(M+1) 585
120	$CONHSO_2$-[4-($(CH_2)_2NHCBz$))]Ph	(M+1) 675

121	$CONHSO_2$-(2,5-di-OMe,4-NHCONHiPr)Ph	(M+1) 658
122	$CONHSO_2$-(2,4-di-OMe)Ph	-
123	$CONHSO_2$-(2,4,6-tri-OMe)Ph	-

EXAMPLES 124-129



Ex #	R^{12}	R^{3a}	Z	Mass Spectrum (M+1)
124	CO_2H	H	$CONHSO_2$-8-quininolinyl	579
125	CO_2H	H	$CONHSO_2$-3-quininolinyl	579
126	$CONH_2$	OMe	$CONHSO_2$-8-quininolinyl	578
127	$CONH_2$	OMe	$CONHSO_2$-(4-t-butyl)Ph	553
128	$CONH_2$	OMe	$CONHSO_2$-(4-amine,2,5-di-OMe)Ph	572
129	CO_2H	H	$CONHSO_2NH$-(4-iPr)Ph	555

EXAMPLE 130

N-[N'-(4-*iso*-propylbenzene)aminosulfonyl]-α-[(4-carboxy-2-n-propyl)phenoxy]-3,4-methylenedioxyphenylacetamide

Step A: Preparation of N-(4-isopropylbenzene)-N'-tert-butyl-sulfamide

To a solution of p-isopropylaniline (1.69 g, 11.77 mmol) in CH_2Cl_2 (0.5 ml) was added N,N-diisopropylethylamine (2 ml) followed by the dropwise addition of a solution of N-t-butylsulfamoyl chloride (1.01 g, 5.88 mmol) [prepared according to the procedure described by W.L. Matier and W.T. Comer, J. Med. Chem., 15:5, 538 (1972)] in CH_2Cl_2 (0.4 ml) via a syringe at 0°C. The reaction mixture was then magnetically stirred at room temperature for 18 hrs. The reaction was diluted with CH_2Cl_2 and quenched with aqueous1N HCl. The organic phase was separated, washed with water, saturated aqueous NaCl, dried ($MgSO_4$), filtered, evaporated and dried in vacuo to yield an impure solid. The residue was purified by triturating with Hex:EtOAc (4:1) to yield 930 mg (58%) of the titled product as a white solid.

^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 1.1-1.3 (m, 15H), 2.7-2.9 (m, 1H), 6.9-7.2 (m, 4H).

ESI-MS *m/e* = 271 (M + 1).

Step B: Preparation of *N* -4-isopropylbenzenesulfamide

A solution of 0.9 g (3.32 mmol) of the product of Step A in trifluoroacetic acid (15 ml) was magnetically stirred at room temperature until TLC indicated the reaction was complete. The solvent was removed in vacuo, washed with cold Et_2O, and filtered to yield 553 mg (78 %) of the titled product as a white solid.

^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 1.1-1.3 (d, 6H), 1.7-1.9 (m, 1H), 7.1 (s, 4H).

CI-MS, *m/e* = 232 (M + NH_4^+).

Step C: Preparation of N-[N'-(4-*iso*-propylbenzene)aminosulfonyl]-α-[(4-carbomethoxy-2-n-propyl)phenoxy]-3,4-methylene-dioxyphenylacetamide

The compound from Step B was reacted with the carboxylic acid, obtained in Step B of Example 56, according to the procedure described in Step C of Example 25 to provide the titlted compound.

^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 0.8-0.9 (t, 3H), 1.1-1.3 (d, 6H), 1.4-1.7 (m, 2H), 2.5-2.9 (m, 2H), 2.7-2.9 (m, 1H), 3.8 (s, 3H), 5.3 (s, 1H), 5.9 (s, 2H), 6.5-6.7 (dd, 2H), 6.8-7.1 (m, 6H), 7.5-7.6 (dd, 1H), 7.7 (s, 1H).

ESI-MS, *m/e* = 659 (M+1).

Step D: Preparation of N-[N'-(4-*iso*-propylbenzene)aminosulfonyl]-α-[(4-carboxy-2-n-propyl)phenoxy]-3,4-methylenedioxy-phenylacetamide

The titled compound was prepared following the procedure described in Example 40.

^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 0.8-0.9 (t, 3H), 1.1-1.3 (d, 6H), 1.4-1.7 (m, 2H), 2.5-2.9 (m, 2H), 2.7-2.9 (m, 1H), 5.3 (s, 1H), 5.9 (s, 2H), 6.5-6.7 (dd, 2H), 6.8-7.1 (m, 6H), 7.5-7.6 (dd, 1H), 7.7 (s, 1H).

EXAMPLE 131

N-(4-*iso*-propylbenzenesulfonyl)-α-[4-methanesulfonylamino-2-n-propylphenoxy]-3,4-methylenedioxyphenylacetamide

α-(4-Amino-2-n-propylphenoxy)-3,4-methylenedioxy-phenylacetate (Product of Step C Example 99) was reacted with methanesulfonyl chloride in a mixture of pyridine and methylene chloride to provide α-[4-(N-methanesulfonyl)amino-2-n-propyl-phenoxy]-3,4-methylenedioxy- phenylacetate, which upon further

elaboration following the procedures described in Example 99 provided the titled compound.
^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 0.8-0.9 (t, 3H), 1.1-1.3 (d, 6H), 1.4-1.7 (m, 2H), 2.4-2.69 (m, 2H), 2.72 (s, 3H), 2.75-2.9 (m, 1H), 5.3 (s, 1H), 5.85 (s, 2H), 6.6-6.7 (dd, 2H), 6.8-7.1 (m, 6H), 7.6-7.75 (dd, 1H), 7.9 (s, 1H).

EXAMPLE 132

N-(4-*iso*-propylbenzenesulfonyl)-α-[(4-(N,N-dimethylcarbamoyl)-amino-2-n-propylphenoxy]-3,4-methylenedioxy-phenylacetamide

The title compound was prepared by reacting the amine from Example 99 (Step C) with N,N-dimethylcarbamoyl chloride.
^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 0.95 (t, 3H), 1.1-1.3 (d, 6H), 1.45-1.8 (m, 2H), 2.5-2.7 (m, 2H), 2.75-2.9 (m, 1H), 3.0 (s, 6H), 5.3 (s, 1H), 5.85 (s, 2H), 6.6-6.7 (dd, 2H), 6.8-7.1 (m, 6H), 7.6-7.75 (dd, 1H), 7.9 (d, 2H).

EXAMPLE 133

N-(4-*iso*-propylbenzenesulfonyl)-α-[4-methoxycarbonylamino-2-n-propylphenoxy]-3,4-methylenedioxy-phenylacetamide

The title compound was prepared by reacting the amine from Example 99 (Step C) with ethylchloroformate.
^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 0.9 (t, 3H), 1.1-1.3 (m, 9H), 1.45-1.7 (m, 2H), 2.45-2.7 (m, 2H), 2.8-3.0 (m, 1H), 4.1-4.25 (q, 2H), 5.3 (s, 1H), 5.9 (s, 2H), 6.5-6.75 (m, 2H), 6.8-7.0 (m, 6H), 7.6-7.75 (dd, 1H), 7.8 (d, 2H).

EXAMPLE 134

Methyl 3-allyl-4-hydroxybenzoate

Step A: Preparation of methyl 4-allyloxybenzoate

To a nitrogen flushed 5 L three neck round bottom flask fitted with a mechanical stirrer, condenser, and a nitrogen inlet was charged 608 g (4 mol) of methyl 4-hydoxybenzoate, 520 ml (727 g, 6.00 mol, 1.5 eq) of allyl bromide, 663 g (9.6 mol of anhydrous potassium carbonate, and 2.3 L of acetone. The mixture was refluxed with vigorous stirring for 90 min. Additional potassium carbonate, (50 g) was added, and 25 g added again after an additional 50 min. After 20 min (total reaction time of 160 min), the suspension was allowed to cool to ambient temperature and stirred overnight. The mixture was filtered and the cake washed with 3 L of acetone. The solution was concentrated to obtain 788.6 g (theoretical yield 768.9 g) of a pale yellow, almost colorless oil which was used without purification in the next step. The product was a single spot on TLC (silica-1:1 EtOAc/Hex) and the MNR was consistent with methyl 4-allyloxybenzoate.

Step B: Preparation of methyl 3-allyl-4-hydroxybenzoate

To a nitrogen flushed magnetically stirred 3 L single neck round bottom flask fitted with a condenser, and a nitrogen inlet was charged the methyl 4-allyloxybenzoate, 400 mL of 1,2-dichlorobenzene, and 10 g of BHT. The solution was heated and distillate collected untill the head temperature reached that of 1,2-dichlorobenzene (180°C). The solution was then refluxed for 6.5 hr, then cooled to 140°C and aged overnight. The hot solution was then poured into 2.5 L of hexanes and the resulting suspension aged overnight with stirring. The suspension was filtered, and the cake washed with hexanes. The solid was air dried affording 747.7g (97.3% yield) as a white solid having a faint odor of o-dichlorobenzene.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 3.42 (dt *J*=6.4,1.4 Hz, 2H), 3.87 (s, 3H), 5.11-5.18 (m, 2H), 5.87 (bs, 1H), 5.93-6.06 (m,1H), 6.83 (d, *J*=7.9 Hz, 1H), 7.79-7.85 (m, 2H).

EXAMPLE 135

Methyl 4-hydoxy-3-n-propylbenzoate

Step A: Preparation of methyl 4-hydoxy-3-n-propylbenzoate

A solution of 363 g of methyl 3-allyl-4-hydoxybenzoate in 1.5 L of methanol was hydrogenated for 1 hr in a Parr^R type shaker at 40 psi and ambient temperature using 1.5 g of 10% palladium on carbon as the catalyst. The reaction was filterd through Sulka-Floc^R and the cake washed with 1 L of methanol. The combined filtrate was concentrated and the oil flushed with ether. Hexanes (1.5 L) were added and the resulting suspension cooled to 0°C. The product was collected by filtration, washed with hexanes and dried affording 176.6 g of methyl 4-hydoxy-3-n-propylbenzoate. A second crop of 166.4 g was obtained by concentrating the filtrate, diluting with hexanes and filtering, bringing the total to 343 g (94.3% yield).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 0.94 (t *J*=7.4 Hz, 3H), 1.63 (m, 2H), 2.59 (t *J*=7.7 Hz, 2H), 3.86 (s, 3H), 5.87 (s, 1H), 6.84 (d *J*=8.4 Hz, 1H), 7.76 (dd *J*=8.4, 2.2 Hz, 1H), 7.81 (d *J*=2.2 Hz, 1H).

EXAMPLE 136

Ethyl 3,4-methylenedioxy-d,l-mandelate

Step A: α-Trimethylsilyloxy-3,4-methylenedioxyphenylacetonitrile

To a nitrogen flushed magnetically stirred 3 L single neck round bottom flask fitted with a nitrogen inlet was charged 285g (1.9 mol) of piperonal, 200g (2.0 mol) of trimethylsilylycyanide, 0.2 g of potassium cyanide, 0.2 g of 18-crown-6 and 500 mL of methylene chloride. The mixture was stirred at ambient temperature for 75 min,

during which time the reaction exothermed to 35°C. A second charge of 5 g of piperonal was added and the reaction stirred an additional 75 min. The reaction mixture was diluted with ether and 250 mL of saturated sodiuim bicarbonate solution was added. The mixture was stirred for 20 min before partitioning. The organic layer was washed with another 250 mL portion of saturated sodiuim bicarbonate, twice with brine (300 mL), dried with sodium sulfate, filtered and concentrated leaving 489.6 g (481.4 g theoretical yield) of the title compound as a pale yellow oil. This was used as is without purification in the next step.

Step B: Preparation of ethyl 3,4-methylenedioxy-d,l-mandelate

To a nitrogen flushed magnetically stirred 3 L single neck round bottom flask fitted with a gas inlet was charged the product obtained from the previous step and 1 L of absolute ethanol. The solution was cooled to 0°C and HCl gas gently bubbled through the solution for 1 hr. After a few minutes the reaction solidified to a white mass which was aged at room temperature overnight. 1 L of methylene chloride, and 1 L of water were added. The mixture was shaken for ca 5 min dissolving some of the white solid. The mixture was decanted and the procedure repeated several more times until all of the solid had been dissolved. The layers were separated and the aqueous layer back extracted once with methylene chloride. The combined organic layer was washed with brine, dried with magnesium sulfate and filtered through a pad of silica . The solution was concentrated, flushed with ether and diluted with hexanes. The white slurry was cooled to 0°C then filtered. The cake was washed with 1:2 ether/hexanes followed by hexanes. The product was dried affording 347.2 g of the title compound as a white solid. A second crop of 24 g was obtained by concentrating the mother liquors, bringing the total to 371.4 g (85.8% yield).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.22 (t, *J*=7.2 Hz, 3H), 3.41.(d, *J*=5.6 Hz, 1H), 4.10-4.31 (m, 2H), 5.03 (d, *J*=5.6 Hz, 1H), 5.94 (s, 2H), 6.77 (d, *J*=8.5 Hz, 1H), 6.85-6.90 (m, 2H).

EXAMPLE 137

Ethyl α-bromo-3,4-methylenedioxyphenylacetate

Step A Preparation of ethyl α-bromo-3,4-methylenedioxyphenylacetate

To a nitrogen flushed 5 L three neck round bottom flask fitted with a mechanical stirrer, a dropping funnel and a nitrogen inlet was charged 433.8g (1.93 mol) of ethyl 3,4-methylenedioxy-d,l-mandelate and 3.5 L of ether. The suspension was cooled to 0-5°C and a solution of 179g (0.66 mol) of PBr_3 in 500 mL of ether was added over a period of 30 min. The reaction was aged for 2.5 hr at 0-5°C during which time, an additional 24.2 g (0.09 mol) of PBr_3 was added. The solid initially present slowly dissolved leaving a clear yellow solution. The reaction was quenched by careful addition of 800 mL of saturated sodiuim bicarbonate solution and 200 mL of water. The layers were separated and the aqueous layer extracted once with ether. The combined organic phase was washed once with saturated sodiuim bicarbonate solution, 10% sodium bisulfite solution, brine, dried with magnesium sulfate, and filtered through a pad of silica. The solution was concentrated to 507.6 g (91.4%) of a pale yellow oil. Essentially a single spot on TLC (silica-1:1 Et_2O/Hex), NMR indicates a small amount of ether is present. This was used as is without purification in the next step.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 1.27 (t, *J*=7.2 Hz, 3H), 4.10-4.35 (m, 2H), 5.26 (s, 1H), 5.96 (s, 2H), 6.72 (d, *J*=8. Hz, 1H), 6.94 (dd, *J*=8.0, 1.8 Hz, 1H), 7.11 (d, *J*=1.8 Hz, 1H).

EXAMPLE 138

α-(4-Carbomethoxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl)acetic acid sodium salt

Step A: Preparation of ethyl α-(4-carbomethoxy-2-*n*-propyl-phenoxy)-3,4-methylenedioxyphenylacetate

To a 2 L three necked 24/40 round bottom flask equipped with a mechanical stirrer, a nitrogen inlet and a dropping funnel was first added a solution of 36.0 g (0.185 mol) of methyl 4-hydroxy-3-*n*-propylbenzoate dissolved in 700 mL of anhydrous DMF followed by 66.4 g (0.204 mol) of cesium carbonate. The flask was purged with nitrogen and the reaction mixture was stirred at room temperature for 2 hours. A solution of 58.5 g (0.204 mol) of ethyl α-bromo-3,4-methylenedioxyphenylacetate dissolved in 100 mL of DMF was then added via an addition funnel over a 15 minute period. The reaction mixture was stirred an additional 1 hour at room temperature then quenched by addition to 5 L of a 5% aqueous citric acid solution. The organic product was extracted into diethylether (2 x 4 L), the organic layers were separated, washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and evaporated. The residue was applied to a silica gel (2 kg; 70-230 mesh) column equillibrated in 10% CH_2Cl_2-hexane. The column was then eluted successively with 12 L of 10% CH_2Cl_2-hexane, 12 L of 5% EtOAc-hexane, 4 L of 7.5% EtOAc-hexane, 12 L of 10% EtOAc-hexane, and finally 8 L of 20% EtOAc-hexane. Combination of the purified fractions and evaporation in vacuo afforded 76.3 g (74.2 theoretical) of the title compound as a pale yellow oil which was used without further purification in the next step.

Step B: Preparation of α-(4-carbomethoxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetic acid sodium salt

A 1 L 3 necked 24/40 round bottom flask equipped with a mechanical stirrer, a dropping funnel, and a nitrogen inlet was charged with a solution of 76.3 g 0.185 mol) of the semi-purified product of Step A dissolved in 500 mL of methanol. The flask was purged with nitrogen, the stirrer was started, and 37 mL of a 5.0 N aqueous solution of sodium hydroxide was added over a 30 minute period via an addition funnel. The reaction mixture was stirred at room temperature for an additional 30 minutes at which point TLC analysis (CH_2Cl_2-MeOH-

NH_4OH 90:10:1) indicated that the starting material had been consumed. The reaction mixture was adjusted to pH=4 with 6 N HCl, and the bulk of the organic solvent was removed in vacuo. The precipitated organic product and the aqueous layer were next partitioned between CH_2Cl_2 (1 L) and water (1 L) which produced a copious emulsion. The reaction mixture was then aged overnight in a refridgerator which resulted in crystallization of the organic product. The crystalline solid was separated from the two phase mixture by filtration and washed with CH_2Cl_2. The solid was slurried again in diethylether, filtered, washed with hexane, and then dried in a vacuum to afford 65 g (85.3%) of the title compound as a white crystalline solid.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.93 (t, *J*=7.2 Hz, 3H), 1.62-1.75 (m, 2H), 2.63-2.70 (m, 1H), 2.77-2.81 (m, 1H), 3.84 (s, 3H), 5.54 (s, 1H), 5.94 (s, 2H), 6.81 (d, *J*=7.6 Hz, 1H), 6.89 (d, *J*=9.2 Hz, 1H), 7.08 (d, *J*=1.6 Hz, 1H), 7.11 (br s, 1H), 7.78-7.81 (m, 2H).

Microanalysis for $C_{20}H_{20}O_7Na_{0.75}\cdot 1.25\ H_2O$.

Calc'd: C = 58.29; H = 5.50; Na = 4.18

Found: C = 58.19; H = 5.17; Na = 3.93

EXAMPLE 139

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-carbomethoxy-2-*n*-propyl-phenoxy)-3,4-methylenedioxyphenylacetamide

Step A: Preparation of ethyl α-(4-carbomethoxy-2-*n*-propyl-phenoxy)-3,4-methylenedioxyphenylacetate

To a nitrogen flushed 5 L three neck round bottom flask fitted with a mechanical stirrer, condenser, and a nitrogen inlet was charged 326g (1.68 mol) of methyl 4-hydoxy-3-n-propylbenzoate, 507.6 g (1.73 mol) of ethyl α–bromo-3,4-methylenedioxyphenylacetate from above, 235g (1.70 mol) of anhydrous potassium carbonate, and 1.7 L of acetone. The mixture was refluxed with vigorous stirring for 9 hr. The suspension was allowed to cool to ambient temperature and stirred overnight. The mixture diluted with 2 L of ether, cooled to 0°C

and filtered through Super-Cel^{R}. The cake washed with ether and the combined filtrate concentrated. The residue was redissolved in ether and the organic layer washed with once with 1 N HCl, saturated sodiuim bicarbonate solution, 10% sodium bisulfite solution, brine, dried with magnesium sulfate, treated with charcoal and filtered through a plug of silica. The pale yellow solution was concentrated to 697.3 g (theoretical 678 g) of a thick yellow oil which was used without purification in the next step. NMR was consistent with the title compound.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ 0.95 (t, J=7.3 Hz, 3H), 1.17 (t, J=7.1 Hz, 3H), 1.61-1.81 (m, 2H), 2.63-2.80 (m, 2H), 3.85 (s, 3H), 4.07-4.23 (m, 2H), 5.58 (s, 1H), 5.96 (s, 2H), 6.71 (d, J=8.5 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 7.02 (d,d, J=8.0,1.7 Hz, 1H), 7.05 (d, J=1.7 Hz, 1H), 7.79 (d,d, J=8.5, 2.2 Hz, 1H), 7.84 (d, J=2.2 Hz, 1H).

Step B: Preparation of α-(4-carbomethoxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetic acid

To a nitrogen flushed 5 L 3 neck round bottom flask equipped with a mechanical stirrer, a dropping funnel, and a nitrogen inlet was charged with 697.3 g (1.68 mol) of the crude product of Step A and 2 L of methanol. 500 mL of 5.0 N (1.5 eq) aqueous sodium hydroxide was added over a 20 minute period via an addition funnel. The reaction mixture was stirred at room temperature for an additional 1 hr at which point TLC analysis (CH_2Cl_2-MeOH-NH_4OH 90:10:1) indicated that the starting material had been consumed. The reaction mixture neutralized with 420 mL of 6 N HCl, and the bulk of the organic solvent was removed in vacuo. The residue was dissolved in ether and extracted with a combination of aqueous NaOH and $NaHCO_3$. The aqueous layer was extracted with ether and the combined organic layer was washed with aqueous $NaHCO_3$. The aqueous layer was acidified with HCl and extracted with ether. The ether solution was dried with magnesium sulfate, filtered, and concentrated to afford 708.9g (theoretical 625 g) of the title compound as a viscous orange oil.

NMR indicated that it was ca 85% product by weight (15% ether) thus providing a corrected yield of 602.6 g (96.4% yield)
^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 0.93 (t, *J*=7.4 Hz, 3H), 1.56-1.77 (m, 2H), 2.68 (t, 2H), 3.84 (s, 3H), 5.57 (s, 1H), 5.95 (s, 2H), 6.42 (bs, 1H), 6.71 (d, *J*=8.5 Hz, 1H), 6.79 (d, *J*=7.9 Hz, 1H), 6.99-7.05 (m, 2H), 7.78 (d,d, *J*= 8.5, 2.2 Hz, 1H), 7.82 (d, *J*=2.2, 1H).

Step C: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carbomethoxy-2-*n*-propylphenoxy)-3,4-methylenedioxy-phenylacetamide potassium salt.

To a nitrogen flushed 5 L 3 neck round bottom flask equiped with a mechanical stirrer, a dropping funnel, a condenser and a nitrogen inlet was charged 1 L of THF and 350 g (2.16 mol, 1.42 eq) of carbonyl diimidazole (CDI). The mixture was heated to reflux and a solution of 663.6 g (1.52 mol) of acid from Step B and 1 L of THF was added dropwise over a period of 30 min. The reaction was monitored for coversion of the acid to the acyl imidazolide by NMR. An additional 85 g of CDI was added over 45 min. The solution was cooled and 291 g (1.48 mol) 4-*iso*-propylbenzenesulfonamide was added as a solid in one portion and the solution aged 20 min. DBU 230 mL (234g, 1.54 mol) was added dropwise over 10 min resulting in an exotherm to 45°C. The reaction was aged at room temperatyure for 3 hr then concentrated in vacuo. The residue was partitioned between 2.75 L of 2.5 N HCl and 3 L of ether. The aqueous layer was extracted with 1 L of ether, and the combined organic layer washed with 2 N HCl and saturated potassium bicarbonate solution. The etherial layer was transferred to a 5 L 3 neck round bottom flask equipped with a mechanical stirrer. 1 L of aqueous potassium bicarbonate solution was added and the mixture stirred overnight at room temperature. The resulting thick suspension was filtered and the cake washed with 500 mL of water followed by 1 L of ether. The product was then slurried in the funnel with additional ether and sucked dry yielding 741g of a tan solid The solid was recharged to a 5 L 3 neck round bottom flask equipped with a mechanical stirrer to which was added 1 L of ethyl acetate and

500 mL of saturated potassium bicarbonate solution. The slurry was stirred at room temperature for 1 hr, diluted with 3 L of ether, and the slurried stirred at room temperature overnight. The product was filtered, washed with 500 mL of water and 1 L of ether and dried in vacuo. The yield was 592 g of the title compound as a white crystalline solid. A second crop of 47.6 g was obtained from the mother liqours bringing the total to 639.6 g (74% of theory)
^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 0.88 (t, *J*=7.4 Hz, 3H), 1.21 (d, *J*=6.9 Hz, 6H), 1.52-1.66 (m, 2H), 2.50-2.76 (m, 2H), 2.90 (sept, *J*=6.9 Hz, 1H), 3.84 (s, 3H), 5.35 (s, 1H), 5.94 (s, 2H), 6.69 (d, *J*=8.6 Hz, 1H), 6.76 (d, *J*=8.5 Hz, 1H), 7.04 (m, 2H), 7.20 (d, *J*=, 8.4 Hz, 2H), 7.61 (dd, *J*=8.5, 2.20, Hz, 1H), 7.67 (d, *J*=8.4, 2H), 7.71 (d, *J*=2.1 Hz, 1H).

EXAMPLE140

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt

Method A:

Step A : Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide dipotassium salt

A mixture of 204 g (0.345 mol) of the product of Example 139, 420 mL of 1.0 N KOH in methanol and 500 mL of water was stirred at 60°C under a nitrogen atmosphere. After 3 hours TLC analysis (90:10:1 CH_2Cl_2-MeOH-NH_4OH) indicated that ester hydrolysis was complete. The reaction mixture was cool slightly, then concentrated on a rotary evaporator to a weight of 500 g. 2.5 L of isopropanol was added and the solution reconcentrated to an oil. The residue was flushed with an additional 2-3 L of isopropanol untill crystallization began. The slurry was concentrated to ca 1.5 L and cooled to 30°C, filtered and washed with 300 mL of IPA and 500 mL of ether. The product was dried affording 185 g of semi-pure title compound as a white crystalline solid. A second crop of 17 g was

obtained from the filtrate after cooling. The material was recrystallized as follows: 168 g was dissolved in 3 L of absolute ethanol at reflux, filtered hot, and the flask and funnel rinsed with an additional 500 mL of ethanol. 70 mL of water was added and the solution cooled to 0°C over 2 hr then aged at 0°C for 6 hr. The product was collected by filtration, washed with ethanol, then air. The yield was 160.8 g of the title compound as a white crystalline solid.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.88 (t, *J*=7.2 Hz, 3H), 1.21 (d, *J*=7.0 Hz, 3H), 1.22 (d, *J*=7.0 Hz, 3H), 1.56-1.63 (m, 2H), 2.52-2.59 (m, 1H), 2.67-2.74 (m, 1H), 2.91 (sept, *J*=7.0 Hz, 1H), 5.33 (s, 1H), 5.92 (d, *J*=1.2 Hz, 1H), 5.93 (d, *J*=1.2 Hz, 1H), 6.72 (d, *J*=8.5 Hz, 1H), 6.76 (d, *J*=8.5 Hz, 1H), 7.04 (d, *J*=7.5 Hz, 1H), 7.05 (s, 1H), 7.21 (d, *J*=8.5 Hz, 2H), 7.64 (dd, J=2.0, 8.5 Hz, 1H), 7.67 (d, *J*=8.5 Hz, 2H), 7.73 (d, *J*=2.0 Hz, 1H).

Microanalysis for $C_{28}H_{27}NSO_8K_2 \cdot 3.4\ H_2O$.

KF = 9.00 (calc for 3.4 H_2O = 9.04)

Calc'd: C = 49.67; H = 5.03; N = 2.07; K = 11.55; S = 4.74.

Found: C = 49.30; H = 4.95; N = 2.06; K = 11.85; S = 4.82

Method B:

Step A Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide

A mixture of 205 g (0.345 mol) of the product of Example 139, 425 mL of 1.0 N KOH in methanol and 500 mL of water was stirred at 60°C under a nitrogen atmosphere. After 1.75 hours TLC analysis (90:10:1 CH_2Cl_2-MeOH-NH_4OH) indicated that ester hydrolysis was complete. The reaction mixture was cooled slightly, then concentrated on a rotary evaporator. The concentrate was acidified with 400 mL of 2 N HCl and extracted first with 6 L of ether-EtOAc-CH_2Cl_2 4:1:1, then with 3 L of 1 :2 EtOAc-CH_2Cl_2. The organic layers were washed with 250 mL of 2N HCl, then with 3 X 500 mL of water, dried with magnesium sulfate, filtered, and concentrated, during which, the product began to crystallize. The solution was

concentrated to a white sluury of ca 750 mL, diluted with 1 L of hexanes, cooled to 0°C, aged 1 hr then filtered. The product was air dried affording 170.0 g (91% yield) of the title compound as a white crystalline solid.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.88 (t, *J*=7.2 Hz, 3H), 1.21 (d, *J*=7.00Hz, 3H), 1.22 (d, *J*=7.0 Hz, 3H), 1.56-1.63 (m, 2H), 2.52-2.59 (m, 1H), 2.67-2.74 (m, 1H), 2.91 (sept, *J*=7.0 Hz, 1H), 5.33 (s, 1H), 5.92 (d, *J*=1.2 Hz, 1H), 5.93 (d, *J*=1.2 Hz, 1H), 6.72 (d, *J*=8.5 Hz, 1H), 6.76 (d, *J*=8.5 Hz, 1H), 7.04 (d, *J*=7.5 Hz, 1H), 7.05 (s, 1H), 7.21 (d, *J*=8.5 Hz, 2H), 7.64 (dd, J=2.0, 8.5 Hz, 1H), 7.67 (d, *J*=8.5 Hz, 2H), 7.73 (d, *J*=2.0 Hz, 1H).

Microanalysis for $C_{28}H_{29}NO_8S$

Calc'd: C = 62.33; H = 5.42; N = 2.60; S = 5.94.

Found: C = 62.15; H = 5.48; N = 2.54; S = 5.99

Step B: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide dipotassium salt

159.7 g (0.296 mol) of acid from Step A was suspended in 3 L of absolute ethanol. To this was added 590 mL of 1.0 N KOH in methanol over 20 min while simultaneously warming the mixture to 50°C. The clear and colorless solution was cooled to 0°C during which it was seeded with 20 mg of the title compound. The suspension was stirred for 2 hr at 0°C, 1 L of ether was added and the suspension filtered. The solid was dried affording 168.4g of the title compound as a white crystalline solid. A second crop of 22.3 g of comparable quality material was obtained by concentrating the ML to ca. 1 L, diluting with 1 L of ether, filtering, and recrystallizing the solid (27 g) so obtained from 200 mL of 98% ethanol. Thus affording after drying a total of 190.7 g (96.8% yield corr'd for water content) of the title compound.

Microanalysis for $C_{28}H_{27}K_2NO_8S \cdot 2.75\ H_2O$.

KF = 7.45 (calc for 2.75 H_2O = 7.44)

Calc'd: C = 50.55; H = 4.92; N = 2.11; K = 11.75;

Found: C = 50.69; H = 4.56; N = 2.05; K = 11.20; S = 4.71

EXAMPLE 143

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt

Step A : Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide di-S-(-)-α–methylbenzylamine salt

32.4 g of the acid from Example 139 was dissolved in 500 mL of isopropanol, and 15.5 mL of S -(-)-α-methylbenzyl amine was added. The solution was allowed to stand at room temperature overnight. The mixture was filtered and the cake washed with a small amount of isopropanol. The solid was recryastallized 4 more times from isopropanol affording 4.5 of the title compound.

Step B: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide dipotassium salt

The α–methylbenzylamine salt from step A was partitioned between ethyl acetate and $NaHSO_4$, dried with $MgSO_4$, filtered and concentrated. The residue was dissolved in methanol-water at room temperature, and basicified with ca. 12 mL of 1 N NaOH in methanol, diluted with water and filtered through a 0.45 micron. The solution was desalted and purified on a Waters Millipore Delta Prep 3000 liquid chromatograph equipped with an M1000 Prep-Pak module containing a 47 x 300 mm Delta-Pak C18 15μm 100A column cartridge. Two solvent resevoirs were employed: solvent system A (95-5 water-acetonitrile), and solvent system B (5-95 water-acetonitrile), and the column effluent was monitored simultaneously at 210 and 280 nm with a Waters model 490 UV-visible detector. Each fraction was pump-injected onto the column and desalted by elution (50 mL/min) with several column volumes of solvent system A. A gradient elution was then begun which had as initial conditions 100% solvent system A-0%

solvent system B and reached after 30 minutes 50% solvent system A-50% solvent system B, and the fractions were collected with an ISCO Foxy 200 fraction collector. The purified fractions were combined in round bottom flasks, frozen in a -78°C dry ice-acetone bath, and lyophilized. Combination of the purified product afforded __ of the title compound as a white lyophilized powder.

^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.88 (t, *J*=7.2 Hz, 3H), 1.21 (d, *J*=7.0 Hz, 3H), 1.22 (d, *J*=7.0 Hz, 3H), 1.56-1.63 (m, 2H), 2.52-2.59 (m, 1H), 2.67-2.74 (m, 1H), 2.91 (sept, *J*=7. Hz, 1H), 5.33 (s, 1H), 5.92 (d, *J*=1.2 Hz, 1H), 5.93 (d, *J*=1.2 Hz, 1H), 6.72 (d, *J*=8.50Hz, 1H), 6.76 (d, *J*=8.5 Hz, 1H), 7.04 (d, *J*=7.5 Hz, 1H), 7.05 (s, 1H), 7.21 (d, *J*=8.5 Hz, 2H), 7.64 (dd, J=2.0, 8.5 Hz, 1H), 7.67 (d, *J*=8.5 Hz, 2H), 7.73 (d, *J*=2.0 Hz, 1H).

Microanalysis for $C_{28}H_{27}NSO_8K_2 \cdot H_2O$.

Calc'd: C = 53.06; H = 4.61; N = 2.21; K = 12.34.

Found: C = 52.81; H = 4.56; N = 2.17; K = 12.02.

EXAMPLE 142

N-(4-*iso*-propylbenzenesulfonyl)-2-[[4-[N-[2-(carbethoxy)ethyl]-carbamoyl]]-2-propylphenoxy]-2-(3,4-methylenedioxyphenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82 except that β-alanine ethyl ester (liberated from the corresponding hydrochloride in situ) was the amine starting material. The crude product was flash chromatographed over silica gel (gradient elution, 1-5% $MeOH/CH_2Cl_2$) to give the desired product as a white foam in 78% yield; homogeneous by TLC (10/90 $MeOH/CH_2Cl_2$); mp 167-168°C; MS (ESI) 639 $(M+H)^+$.

Analysis ($C_{33}H_{38}N_2O_9S \cdot 0.75H_2O$):

Calcd:	C, 60.78;	H, 6.10;	N, 4.30
Found:	C, 60.69	H, 5.88	N, 4.30

^{1}H NMR (400 MHz, CD_3OD, ppm): δ 8.36 (t, 1H, J = 5 Hz), 7.72 (d, 2H, J = 8.4 Hz), 7.58 (d, 1H, J = 2.3 Hz), 7.46 (dd, 1H, J = 8.5, 2.3 Hz),

7.30 (d, 2H J = 8.4 Hz), 6.93-6.98 (m, 2H), 6.77 (d, 1H, J = 7.9 Hz), 6.65 (d, 1H, J = 8.7 Hz), 5.95 (s, 2H), 5.47 (s, 1H), 4.13 (q, 2H, J = 7.1 Hz), 3.57-3.63 (m, 2H), 2.93-2.98 (m, 1H), 2.68 (m, 2H), 2.62 (t, 2H, J = 6.9 Hz), 1.60 (m, 2H), 1.21-1.25 (m, 6H), 0.88 (t, 3H, J = 7.4 Hz).

EXAMPLE 143

N-(4-*iso*-propylbenzenesulfonyl)-2-[[4-[N-(2-carboxyethyl)carbamoyl]]-2-propylphenoxy]-2-(3,4-methylenedioxyphenyl)acetamide

The product from Example 142 was saponified (excess NaOH in MeOH, 60°C, 4 h) to give the titled product as a white solid in quantitative yield; mp 199-201°C; MS (ESI) 611 $(M+H)^+$.

Analysis ($C_{31}H_{34}N_2O_9S \cdot 0.4H_2O$):

Calcd:	C, 60.25;	H, 5.67;	N, 4.55
Found:	C, 60.49	H, 5.48	N, 4.18

^1H NMR (400 MHz, CD_3OD, ppm): δ 7.76 (dd, 2H, J = 1.8, 8.5 Hz), 7.58 (d, 1H, J = 2.3 Hz), 7.46 (dd, 1H, J = 2.4, 8.6 Hz), 7.35 (d, 2H J = 8.4 Hz), 6.92 (dd, 1H, J = 1.7, 8.0 Hz), 6.87 (d, 1H, J = 1.6 Hz), 6.78 (d, 1H, J = 8.0 Hz), 6.56 (d, 1H, J = 8.7 Hz), 5.96 (s, 2H), 5.51 (s, 1H), 3.58 (m, 2H), 2.95 (m, 1H), 2.68 (m, 2H), 2.61 (t, 2H, J = 7.2 Hz), 1.58 (m, 2H), 1.21-1.25 (m, 6H), 0.88 (t, 3H, J = 7.4 Hz).

EXAMPLE 144

N-(4-*iso*-propylbenzenesulfonyl)-2-[[4-[N-(2-carbamoylethyl)-carbamoyl]]-2-propylphenoxy]-2-(3,4-methylenedioxyphenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82. The crude product was flash chromatographed over silica gel (gradient elution, 2-10% MeOH/CH_2Cl_2) to yield the desired product as a white foam in 42%

yield; homogeneous by TLC (10/90 MeOH/CH_2Cl_2), mp 110-112°C; MS (ESI) 610 $(M+H)^+$.

Analysis ($C_{31}H_{35}N_3O_8S \cdot 0.75H_2O$):

Calcd:	C, 59.73;	H, 5.90;	N, 6.76
Found:	C, 59.74	H, 5.61	N, 6.62

^1H NMR (400 MHz, CD_3OD, ppm): δ 7.77 (d, 2H, J = 8.3 Hz), 7.59 (d, 1H, J = 2.3 Hz), 7.46 (dd, 1H, J = 2.4, 8.6 Hz), 7.36 (d, 2H J = 8.7 Hz), 6.92 (dd, 1H, J = 1.5, 8.0 Hz), 6.87 (d, 1H, J = 1.6 Hz), 6.78 (d, 1H, J = 8.1 Hz), 6.58 (d, 1H, J = 8.6 Hz), 5.97 (s, 2H), 5.50 (s, 1H), 3.59 (t, 2H, J = 7.0 Hz), 2.98 (m, 1H), 2.68 (m, 2H), 2.51 (t, 2H, J = 6.9 Hz), 1.60 (m, 2H), 1.21-1.28 (m, 6H), 0.89 (t, 3H, J = 7.4 Hz).

EXAMPLE 145

N-(4-*iso*-propylbenzenesulfonyl)-2-[4-[N-(2,2,2-trifluoroethyl)-carbamoyl]-2-propylphenoxy]-2-(3,4-methylenedioxyphenyl)acetamide

The titled compound was prepared using procedures similar to those described in Example 82 except that trifluoroethylamine was used as the amine starting material. The crude product was flash chromatographed over silica gel (gradient elution, 1-4% MeOH/CH_2Cl_2) to give the desired product as a white foam in 79% yield; homogeneous by TLC (5/95 MeOH/CH_2Cl_2), mp 110-112°C; MS (ESI) 621 $(M+H)^+$.

Analysis ($C_{30}H_{31}F_3N_2O_7S \cdot 0.5H_2O$):

Calcd:	C, 57.22;	H, 5.12;	N, 4.46
Found:	C, 57.33	H, 4.87	N, 4.52

^1H NMR (400 MHz, CD_3OD, ppm): δ 7.71 (d, 2H, J = 8.3 Hz), 7.63 (d, 1H, J = 2.4 Hz), 7.52 (dd, 1H, J = 2.2, 8.4 Hz), 7.29 (d, 2H J = 8.3 Hz), 6.97 (m, 2H), 6.77 (d, 1H, J = 7.9 Hz), 6.68 (d, 1H, J = 8.7 Hz), 5.96 (s, 2H), 5.47 (s, 1H), 4.05 (dq, 2H, J = 3.0, 9.2 Hz), 2.92 (m, 1H), 2.68 (m, 2H), 1.61 (m, 2H), 1.19-1.30 (m, 6H), 0.89 (t, 3H, J = 7.3 Hz).

EXAMPLE 146

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-*N*-*t*-butyloxycarbonyl-aminosulfonyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide

Step A: Preparation of methyl α-(4-*N*-*t*-butyloxycarbonylamino-sulfonyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetate

To a stirred solution of 76 mg (0.187 mmol) of methyl α-(2-*n*-propyl-4-aminosulfonylphenoxy)-3,4-methylenedioxyphenylacetate (the product of Example 100 Step C), 29 uL (0.206 mmol) of triethylamine and 2.3 mg (0.0187 mmol) of DMAP hydrochloride in1 mL of methylene chloride was added 47 mg (0.215 mmol) of di-*tert*-butyl-dicarbonate. After 1.5 hours, TLC analysis (5% methanol / methylene chloride) indicated that the coupling was complete and the reaction mixture was diluted with ethyl acetate, partitioned with water, washed another time with water, and washed with brine. The organic layer was then dried over magnesium sulfate, filtered, and the filtrate concentrated *in vacuo* and dried on vacuum to afford 95 mg (100%) of the title compound as an amorphous solid.
^{1}H-NMR (400 MHz, $CDCl_3$,ppm) δ 0.97 (t,*J*=7.40 Hz,3H), 1.35 (s,9H), 1.62-1.75 (m,2H), 2.66-2.79 (m,2H), 3.71 (s,3H), 5.60 (s,1H), 5.98 (s,2H), 6.75 (d,*J*=9.2 Hz,1H), 6.81 (d,*J*=8.0 Hz,1H), 6.99-7.04 (m,2H), 7.74-7.76 (m,2H).

Step B: Preparation of methyl α-(4-*N*-*t*-butyloxycarbonylamino-sulfonyl-2-*n*-propylphenoxy)-3,4-methylenedioxy-phenylacetic acid

To a stirred solution of 95 mg (0.187 mmol) of the product of Step A in 0.75 mL of methylene chloride and 0.75 mL of methanol was added 45 uL (0.225 mmol) of 5N sodium hydroxide. After 5 hours, TLC analysis (5% methanol / methylene chloride) indicated slow ester hydrolysis and an additional 45 uL (0.225 mmol) of 5N sodium

hydroxide was added. The reaction mixture stirred 2 days, at which time TLC analysis (5% methanol / methylene chloride) indicated the ester hydrolysis was complete. The reaction was extracted with ethyl following acidification to pH4-5 with 10% citric acid and dilution with water. The extract was washed with brine, dried over magnesium sulfate, filtered and the filtrate was evaporated *in vacuo* and dried to afford 75 mg (82%) of the title compound as an amorphous solid.
^{1}H-NMR (400 MHz, CD_3OD,ppm) δ 0.96 (t,*J*=7.40 Hz,3H), 1.34 (s,9H), 1.62-1.75 (m,2H), 2.75 (t,*J*=7.40 Hz,2H), 5.78 (s,1H), 5.97 (s,2H), 6.84 (d,*J*=8.00 Hz,1H), 6.99 (d,*J*=9.20 Hz,1H), 7.06-7.10 (m,2H), 7.72-7.74 (m,2H).
APCI-MS *m/e* = 511 (M+NH_4).

Step C: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-*N*-*t*-butyloxycarbonyl-aminosulfonyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide

A solution of 68 mg (0.138 mmol) of the product of Step B and 34 mg (0.207 mmol) of carbonyldiimidazole in 0.8 mL of dry tetrahydrofuran was refluxed using a heated oil bath. After 2 hours, TLC analysis (20% methanol / methylene chloride) indicated the desired intermediate had formed. The reaction mixture was then cooled to room temperature and 41 mg (0.207 mmol) of dry 4-*iso*-propylbenzenesulfonamide and 31 uL (0.207 mmol) of DBU were added. The reaction mixture was refluxed again for 25 minutes, allowed to cool, after which TLC analysis (20% methanol / methylene chloride) indicated the desired product had been formed. The reaction mixture was poured into 10% citric acid and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was purified by silica-gel flash chromatography eluting first with 3% methanol / methylene chloride and then with 5% methanol / methylene chloride. The mixed fractions containing both the title compound and the des-*t*-butyloxycarbonyl version of the title compound were combined, evaporated and used in Example 147. The purified fractions were

combined and evaporated to afford 11 mg (12%) of the title compound as an amorphous solid.
^{1}H-NMR (400 MHz, CD_3OD,ppm) δ 0.88 (t,*J*=7.40 Hz,3H), 1.24 (d,*J*=7.20 Hz,3H), 1.25 (d,*J*=7.20 Hz,3H), 1.35 (s,9H), 1.56-1.68 (m,2H), 2.60-2.69 (m,1H), 2.70-2.77 (m,1H), 2.95 (sept., *J*=7.20 Hz,1H), 5.46 (s,1H), 5.95 (s,2H), 6.77 (d,*J*=8.40 Hz,1H), 6.81 (d,*J*=8.40 Hz,1H), 7.00-7.03 (m,2H), 7.27 (d,*J*=8.00 Hz,2H), 7.60 (dd,*J*=2.40, 8.40 Hz,1H), 7.64 (d,*J*=8.00 Hz,2H), 7.68 (d,*J*=2.4 Hz,1H).
ESI-MS *m/e* = 697 (M+Na).

EXAMPLE 147

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-*N*-*t*-butyloxycarbonylamino-sulfonyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide

A solution of 18 mg (0.0267 mmol) of mixed fractions from Step C of Example 146 in 0.8 mL of dimethylsulfoxide was heated to reflux for 3 minutes and cooled to room temperature. After the heating, TLC analysis (20% methanol / methylene chloride) indicated thermal deprotection was complete. The reaction was diluted with 6 mL of water and filtered through a 0.45 mm filter disc. The filtrate was purified using a Waters 600E HPLC system with a 9.4 x 250 mm 5 mm Zorbax-RX C8 at 40°C eluting at 5.0 mL/min first using 100% B (95-5 water-acetonitrile) with 0.1% TFA for 12 minutes and then switching 65% A (95-5 acetonitrile-water) 35% B (95-5 water-acetonitrile) each with 0.1% TFA where the column effluent was monitored simultaneously at 210 and 277 nM with a Waters model 490 UV-visible detector. The purified fractions were combined in a round bottom flask, frozen in a -78°C dry ice-acetone bath and lyophylized to afford 10.7 mg (71%) of the title compound as a white lyophilized powder.
^{1}H-NMR (400 MHz, CD_3OD,ppm) δ 0.90 (t,*J*=7.20 Hz,3H), 1.26 (d,*J*=6.80 Hz,3H), 1.27 (d,*J*=6.80 Hz,3H), 1.54-1.68 (m,2H), 2.60-2.72

(m,2H), 3.00 (sept., *J*=6.80 Hz,1H), 5.54 (s,1H), 5.97 (s,2H), 6.65 (d,*J*=8.40 Hz,1H), 6.78 (d,*J*=8.00 Hz,1H), 6.84 (d,*J*=1.60 Hz,1H), 6.91 (dd,*J*=1.60, 8.00 Hz,1H), 7.37 (d,*J*=8.40 Hz,2H), 7.53 (dd,*J*=2.40, 8.40 Hz,1H), 7.66 (d,*J*=2.4 Hz,1H), 7.76 (d,*J*=8.40 Hz,2H).
ESI-MS *m/e* = 575 (M+H).

EXAMPLE 148

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-(*N*-methylacetamido aminosulfonyl)-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide

Step A: Preparation of methyl a-(4-(*N* -methylacetamido-aminosulfonyl)-2-*n*-propylphenoxy)-3,4-methylene-dioxyphenylacetate

To a stirred solution of 500 mg (1.23 mmol) of methyl α-(4-aminosulfonyl-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetate (the product of Example 100, Step C) in dry dimethylformamide (2 mL) was added 80uL (1.35 mmol) of methyl isocyanate followed by 6 mg (0.06 mmol) of cuprous chloride. The reaction mixture was stirred overnight, after which TLC analysis (5 % methanol / methylene chloride) indicated the reaction had not proceeded to completion. Subsequently, an additional 80 uL (1.35 mmol) of methyl isocyanate, 6 mg (0.06 mmol) of cuprous chloride as well as 342 uL (2.46 mmol) of triethylamine was added and the reaction mixture was again stirred overnight. TLC analysis (5 % methanol / methylene chloride) indicated the reaction had proceeded to completion. The reaction mixture was poured into1N HCl and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, filtered and the filtrate concentrated *in vacuo* and dried to afford 570 mg (100%) of the title compound as an amorphous solid.

^{1}H-NMR (400 MHz, CD_3OD,ppm) δ 0.96 (t,*J*=7.20 Hz,3H), 1.64-1.77 (m,2H), 2.65 (s,3H), 2.74 (t,*J*=7.00 Hz,2H), 3.71 (s,3H), 5.88 (s,1H), 5.98 (s,2H), 6.85 (d,*J*=8.00 Hz,1H), 6.95 (d,*J*=8.40 Hz,1H), 7.04 (dd,*J*=1.60, 8.40 Hz,1H), 7.07 (d,*J*=1.60 Hz,1H), 7.72-7.76 (m,2H).
ESI-MS *m/e* = 464 (M+1).

Step B: Preparation of α-(4-(*N* -methylacetamidoaminosulfonyl)-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetic acid

To a stirred solution of 570 mg (1.23 mmol) of the product of Step A in 6 mL of methanol was added 540 uL (2.71 mmol) of 5N sodium hydroxide. The reaction mixture was allowed to stir overnight after which TLC analysis (90:10:1 chloroform / methanol / acetic acid) indicated the saponification had proceeded to completion. The reaction mixture was acidified to pH=2 using 6 N HCl, poured into water, and extracted with ethyl acetate. The extract was dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product. Purification of the crude product by silica-gel flash chromatography using (92:7:1 chloroform / methanol / acetic acid) afforded 384 mg (70%) of the title compound as an amorphous solid.
^{1}H-NMR (400 MHz, CD_3OD,ppm) δ 0.96 (t,*J*=7.40 Hz,3H), 1.62-1.77 (m,2H), 2.65 (s,3H), 2.74 (t,*J*=7.60 Hz,2H), 5.76 (s,1H), 5.98 (s,2H), 6.85 (d,*J*=8.00 Hz,1H), 6.95 (d,*J*=8.40 Hz,1H), 7.06 (d,*J*=1.60 Hz,1H), 7.08 (dd,*J*=1.60, 8.00 Hz,1H), 7.72-7.75 (m,2H).
CI-MS *m/e* = 538 (M+1).

Step C: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-(*N*-methylacetamido-aminosulfonyl)-2-n-propylphenoxy)-3,4-methylenedioxyphenylacetamide

A solution of 384 mg (0.853 mmol) of the product of Step B and 208 mg (1.28 mmol) of carbonyldiimidazole in 2 mL of dry tetrahydrofuran was refluxed 2 minutes by placing the reaction mixture into a preheated oil bath. After brief refluxing and gas evolution, TLC analysis (90:10:1 chloroform / methanol / acetic acid) indicated that the desired intermediate had formed. The reaction mixture was then cooled

to room temperature and 255 mg (1.28 mmol) of dry 4-*iso*-propylbenzenesulfonamide, 10 mg (0.085 mmol) of DMAP followed by 191 uL (1.28 mmol) of DBU was added. The reaction mixture was refluxed for 3 minutes, allowed to cool and stir at room temperature 1 hour after which TLC analysis (96:3:1 chloroform / methanol / acetic acid) indicated the desired product had been formed. The reaction mixture was poured into 10% citric acid and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was partially purified by silica-gel flash chromatography eluting first with ethyl acetate and then with (92:7:1 chloroform / methanol / acetic acid). The purified fractions were combined to afford 48 mg (9%) of the title compound. Upon standing, material precipitated from the ethyl acetate fractions to afford an addition 55 mg (10%) of the title compound. The remainder of semi-purified material was combined and purified using a Waters Delta Prep 3000 HPLC by applying the residue in 6 ml total volume (4.5 mL methanol and 1.5 mL water) to an M1000 Prep-Pak module containing a 47 x 300 mm 15 uM DeltaPak C18 column and eluting isocratically at 50 mL/min using 60% A (95-5 acetonitile-water) and 40% B (95-5 water-acetonitrile) each with 0.1% TFA. The column effluent was monitored simultaneously at 210 and 277 nM with a Waters model 490 UV-visible detector and the purified fractions were combined in a round bottom flask, frozen in a -78°C dry ice-acetone bath and lyophylized. The HPLC purified lyophylizate155 mg (29%), the silica gel purified amorphous solid 48 mg (9%) and the precipitated amorphous solid 55 mg (10%) were combined to afford 258 mg (48%) of the title compound.

^{1}H-NMR (400 MHz, CD_3OD,ppm) δ 0.89 (t,*J*=7.40 Hz,3H), 1.26 (d,*J*=6.80 Hz, 3H), 1.27 (d,*J*=6.80 Hz, 3H), 1.55-1.65 (m,2H), 2.63-2.70 (m,5H), 3.00 (sept.,*J*=6.80 Hz, 1H), 5.56 (s,1H), 5.97 (s,2h), 6.67 (d,*J*=8.40 Hz, 1H), 6.79 (d,*J*=7.60 Hz, 1H), 6.84 (d,*J*=1.60 Hz, 1H), 6.91 (dd,*J*=1.60, 7.60 Hz, 1H), 7.38 (d,*J*=8.40 Hz, 2H), 7.62 (dd,*J*=2.40, 8.40 Hz, 1H), 7.71 (d,*J*=2.40 Hz, 1H), 7.77 (d,*J*=8.40 Hz, 2H).

CI-MS *m/e* = 632 (M+1).

Step D: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-(*N*-methylacetamido-aminosulfonyl)-2-n-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt

To a solution of 250 mg (0.396 mmol) of the product of Step C in 3 mL of methanol was added 1.58 mL (1.58 mmol) of a 1N potassium hydroxide in methanol solution. The reaction mixture was stirred 15 minutes at RT, diluted with 7 mL of water and filtered through a 0.45 uM filter disc. The filtrate was purified using a Waters Delta Prep 3000 HPLC by applying the compound in a 15 ml total volume (8 mL methanol and 7 mL water) to an M1000 Prep-Pak module containing a 47 x 300 mm 15 uM DeltaPak C18 column and eluting at 50 mL/min first using 100% B (95-5 water-acetonitrile) for 10 minutes and then a 30 minute linear gradient to 60% A (95-5 acetonitile-water) and 40% B (95-5 water-acetonitrile). The column effluent was monitored simultaneously at 210 and 277 nM with a Waters model 490 UV-visible detector and the purified fractions were combined in a round bottom flask, frozen in a -78°C dry ice-acetone bath and lyophylized to afford 221 mg (79%) of the title compound as a white lyophilized powder.

^{1}H-NMR (400 MHz, CD_3OD,ppm) δ 0.89 (t,*J*=7.40 Hz, 3H), 1.22 (d,*J*=6.80 Hz, 3H), 1.23 (d,*J*=6.80 Hz, 3H), 1.53-1.68 (m,2H), 2.54-2.62 (m,4H), 2.67-2.74 (m,1H), 2.91 (sept., *J*=6.80 Hz, 1H), 5.34 (s,1H), 5.92 (s,2H), 6.73-6.79 (m,2H), 7.00-7.02 (m,2H), 7.20 (d,*J* =8.00 Hz, 2H), 7.57 (dd,*J*=1.80, 8.60 Hz, 1H), 7.61-7.64 (m,3H).

ESI-MS *m/e* = 701 (M+1).

EXAMPLE 149

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-(methylsulfonylamino-*N'*-oxomethyl)-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt

Step A: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-a-(4-(methylsulfonylamino-*N*'-1-oxomethyl)-2-*n*-propyl-phenoxy)-3,4-methylenedioxyphenylacetamide

A solution of 146 mg (0.271 mmol) of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide (free acidic form of the product of Example 58) and 66 mg (0.406 mmol) of carbonyldiimidazole in 1 mL of dry tetrahydrofuran was refluxed for 1.5 hours. The reaction mixture was cooled to room temperature and 39 mg (0.406 mmol) of methanesulfonamide and 101 uL (0.667 mmol) of DBU were added and the mixture was refluxed again. The reaction progress was monitored by analytical HPLC analysis using a Waters 600E HPLC system with a 4.6 x 250 mm 5um Zorbax-RX C18 at 40°C and eluting isocratically 1.5 mL/min using 60% A (95-5 acetonitrile-water) 40% B (95-5 water-acetonitrile) each with 0.1% TFA where the column effluent was monitored simultaneously at 210 and 277 nM with a Waters model 490 UV-visible detector. After 1.0 hour of additional refluxing, analytical HPLC analysis indicated that the coupling was complete. The reaction mixture poured into 1N HCl and extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered, and the filtrate evaporated *in vacuo* to afford 160 mg (96%) of the title compound as an amorphous solid.

^{1}H-NMR (400 MHz, CD_3OD,ppm) δ 0.90 (t,*J*=7.40 Hz, 3H), 1.25 (d,*J*=6.80 Hz, 3H), 1.26 (d,*J*=6.80 Hz, 3H), 1.53-1.66 (m,2H), 2.58-2.63 (m,2H), 3.00 (sept., *J*=6.80 Hz, 1H), 3.33 (s,3H), 5.54 (s,1H), 5.97 (s,2H), 6.61 (d,*J*=8.80 Hz, 1H), 6.79 (d,*J*=8.00 Hz, 1H), 6.87 (d,*J*=1.60 Hz, 1H), 6.93 (dd,*J*=1.60, 8.80 Hz, 1H), 7.36 (d,*J*=8.40 Hz, 2H), 7.56 (d,*J*=2.40, 8.80 Hz, 1H), 7.70 (d,*J* =2.40 Hz, 1H), 7.77 (d,*J*=8.40 Hz, 2H).

CI-MS *m/e* = 634 (M+NH4).

Step B: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-(methylsulfonylamino-*N*'-1-oxomethyl)-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt

To a solution of 160 mg (0.260 mmol) of the product of Step B in 1 mL of methanol was added 1.04 mL (1.04 mmol) of a 1N potassium hydroxide in methanol solution. The reaction mixture was stirred 15 minutes at RT, diluted with 4 mL of water and filtered through a 0.45 uM filter disc. The filtrate was purified using a Waters Delta Prep 3000 HPLC by applying the compound in a 10 ml total volume (6 mL methanol and 4 mL water) to an M1000 Prep-Pak module containing a 47 x 300 mm 15 mM DeltaPak C18 column and eluting at 50 mL/min first using 100% B (95-5 water-acetonitrile) for 10 minutes and then a 30 minute linear gradient to 60% A (95-5 acetonitile-water) and 40% B (95-5 water-acetonitrile). The column effluent was monitored simultaneously at 210 and 277 nM with a Waters model 490 UV-visible detector and the purified fractions were combined in a round bottom flask, frozen in a -78°C dry ice-acetone bath and lyophylized to afford 138 mg (77%) of the title compound as a white lyophilized powder.

^{1}H-NMR (400 MHz, CD_3OD,ppm) δ 0.87 (t,*J*=7.40 Hz, 3H), 1.21 (d,*J*=6.80 Hz, 6H),1.52-1.67 (m,2H), 2.51-2.58 (m,1H), 2.67-2.74 (m,1H), 2.91 (sept.,*J*=6.80 Hz, 1H), 3.07 (s,3H), 5.33 (s,1H), 5.92 (s,2H), 6.70 (d,*J*=8.80 Hz, 1H), 6.74 (dd,*J*=2.20, 6.20 Hz, 1H),7.02-7.04 (m,2H), 7.21 (d,*J*=8.40 Hz,2H), 7.65 (d,*J*=8.40 Hz,2H), 7.70 (dd,*J* =2.20, 8.40 Hz, 1H), 7.78 (d,*J*=2.00 Hz, 1H).

ESI-MS *m/e* = 693 (M+1).

EXAMPLE 150

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-(aminosulfonylamino-*N*'-oxomethyl)-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt

Step A: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-(aminosulfonylamino-*N*'-1-oxomethyl)-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide

A solution of 158 mg (0.293 mmol) of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide (free acidic form of the product of Example 58) and 71 mg (0.440 mmol) of carbonyldiimidazole in 1 mL of dry tetrahydrofuran was refluxed for 3.5 hours. The reaction mixture was cooled to room temperature and 141 mg (1.47 mmol) of sulfamide and 110 uL (0.733 mmol) of DBU were added and the mixture was refluxed again. The reaction progress was monitored by analytical HPLC analysis using a Waters 600E HPLC system with a 4.6 x 250 mm 5um Zorbax-RX C8 at 40°C and eluting isocratically 1.5 mL/min using 60% A (95-5 acetonitrile-water) 40% B (95-5 water-acetonitrile) each with 0.1% TFA where the column effluent was monitored at 254 nM with a Waters model 490 UV-visible detector. After 2.0 hour of additional refluxing, analytical HPLC analysis indicated that the coupling was complete. The reaction mixture was diluted with 2.5 mL of methanol and 2 mL of water, filtered and the filtrate partially purified was purified using a Varian 5500 HPLC by applying the compound in a 4.5 ml total volume (2.5 mL methanol and 2 mL water) onto two in series 21.2 x 250 mm 7mm Zorbax ODS columns and eluting at 15 mL/min with 60% acetonitrile and 40% water both with 0.1% TFA. The column effluent was monitored 254 nM with a Kratos Spectroflow 783 UV detector. Combination and evaporation of the purified fractions afforded 50 mg (28%) of the title compound. The mixed fractions were combined and subjected to a second preparative HPLC chromatography using a linear gradient over 35 minutes from 65% water and 35% acetonitrile both with 0.1%TFA to 65% acetonitrile and 35% water both with 0.1%TFA, holding all other conditions from the previous chromatography. The purified fractions were combined and concentrated to afford 57 mg (31%) of the title compound, which was combined with the previously purified material

to provide a total of 107 mg (59%) of the title compound as an amorphous solid.
^{1}H-NMR (400 MHz, CD_3OD,ppm) δ 0.89 (t,*J*=7.40 Hz, 3H), 1.25 (d,*J*=6.80 Hz, 3H), 1.26 (d,*J*=6.80 Hz, 3H), 1.53-1.66 (m,2H), 2.58-2.73 (m,2H), 2.98 (sept., *J*=6.80 Hz, 1H), 5.54 (s,1H), 5.97 (s,2H), 6.62 (d,*J*=8.80 Hz, 1H), 6.79 (d,*J*=8.00 Hz, 1H), 6.86 (d,*J*=1.60 Hz, 1H), 6.92 (dd,*J*=1.60, 8.00 Hz, 1H), 7.36 (d,*J*=8.50 Hz, 2H), 7.56 (d,*J*=2.40, 8.80 Hz, 1H), 7.69 (d,*J* =2.40 Hz, 1H), 7.77 (d,*J*=8.50 Hz, 2H).
ESI-MS *m/e* = 618 (M+1).

Step B: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-(aminosulfonylamino-*N*'-1-oxomethyl)-2-*n*-propyl-phenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt

To a solution of 107 mg (0.173 mmol) of the product of Step B in 1.5 mL of methanol was added 0.691 mL (0.691 mmol) of a 1N potassium hydroxide in methanol solution. The reaction mixture was stirred 15 minutes at RT, diluted with 1 mL of water and filtered through a 0.45 uM filter disc. The filtrate was purified using a Varian 5500 HPLC by applying the compound in a 4.0 ml total volume (3 mL methanol and 1 mL water) onto two in series 21.2 x 250 mm 7mm Zorbax ODS columns and eluting at 15 mL/min first using 95% water and 5% acetonitrile for 10 minutes and then a 30 minute linear gradient to 60% acetonitrile and 40% water. The column effluent was monitored 254 nM with a Kratos Spectroflow 783 UV detector and the purified fractions were combined in a round bottom flask, frozen in a -78°C dry ice-acetone bath and lyophylized to afford 84 mg (73%) of the title compound as a white lyophilized powder.
^{1}H-NMR (400 MHz, CD_3OD,ppm) δ 0.87 (t,*J*=7.40 Hz, 3H), 1.20 (d,*J*=6.80 Hz, 3H), 1.21 (d,*J*=6.80 Hz, 3H), 1.53-1.66 (m,2H), 2.51-2.59 (m,1H), 2.67-2.74 (m,1H), 2.91 (sept.,*J*=6.80 Hz, 1H), 3.07 (s,3H), 5.33 (s,1H), 5.92 (s,2H), 6.71-6.75 (m,2H), 7.01-7.04 (m,2H), 7.19-7.22 (m,2H), 7.64-7.70 (m,3H), 7.77 (d,*J*=2.4 Hz, 1H).
ESI-MS *m/e* = 694 (M+1).

EXAMPLE 151

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-cyano-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide potassium salt

Step A: Preparation of 3-allyl-4-hydroxybenzonitrile

To a stirred solution of 25.00 g (210.1 mmol) of 4-cyanophenol (Aldrich) in 100 mL of acetone was added 30.49 g (220.6 mmol) of powdered potassium carbonate followed by 19.09 mL (220.6 mmol) of allyl bromide and the reaction mixture refluxed overnight. TLC analysis (15% ethyl acetate / hexane) indicated that the alkylation was complete and the reaction mixture was filtered, the filtrated evaporated *in vacuo* to afford 33.20 g (99%) of a light yellow oil. The 33.20 (209 mmol) of crude *O*-allyl ether was dissolved in 100 ml of 1,2-dichlorobenzene and stirred at reflux for 56 hours until TLC analysis (15% ethyl acetate / hexane) indicated essentially no starting *O*-allyl ether remained. The reaction mixture was poured into 300 mL of hexane, cooled in a freezer overnight, and the precipitate was filtered on and dried on vacuum to provide 29.76 g (90%) of the title compound as a light tan amorphous solid. ^{1}H-NMR (300 MHz, $CDCl_3$,ppm) d 3.36 (D,*J*=6.30 Hz,2H), 5.09-5.19 (m,2H), 5.79 (bs,1H), 5.86-6.00 (m,1H), 6.82 (dd,*J*=1.80, 7.20 Hz,1H), 7.38-7.41 (m,2H).
EI-MS *m/e* = 159 (M^+)

Step B: Preparation of 4-hydroxy-3-*n*-propylbenzonitrile

A Parr hydrogenation shaker was charged with a solution of 29.76 g (187 mmol) of the product of Step A in 100 mL of ethanol and 3.00 g of a 10% palladium on carbon catalyst was added. The flask was mounted in the hydrogenation appartus, freed of air, pressurized with hydrogen (40 psig) and shaken 80 minutes. At the end of this preiod, TLC analysis (15% ethyl acetate / hexane) indicated that the reaction was complete and the reaction mixture was filtered and

evaporated. The product was dried *in vacuo* to afford 30.01 g (99%) of the title compound as a yellow oil.
^{1}H-NMR (300 MHz, $CDCl_3$,ppm) δ 0.92 (t,*J*=7.40 Hz,3H), 1.53-1.65 (m,2H), 2.54 (t,*J*=7.60 Hz,2H), 6.77 (d,*J*=8.10 Hz,1H), 7.32-7.37 (m,2H).
EI-MS *m/e* = 161 (M^+)

Step C: Preparation of methyl α-(2-*n*-propyl-4-cyanophenoxy)-3,4-methylenedioxyphenylacetate

To a stirred solution of 4.50 g (27.95 mmol) of the product of Step B in 30 mL of acetone was added 4.64 g (33.54 mmol) of powdered potassium carbonate and the reaction mixture was stirred for 10 minutes. Methyl a-bromo-3,4-methylenedioxyphenylacetate (8.01 g; 29.35 mmol) was then added and the reaction mixture refluxed overnight. The reaction mixture was cooled, filtered, and the filtrate evaporated *in vacuo*, dried on vacuum to afford 10.30 g (9.87g theoretical) of the title compound which was used without purification in the next step.
^{1}H-NMR (300 MHz, $CDCl_3$,ppm) δ 0.92 (t,*J*=7.40 Hz,3H), 1.58-1.68 (m,2H), 2.60-2.71 (m,2H), 5.53 (s,1H), 5.95 (s,2H), 6.68 (d,*J*=8.10 Hz,1H), 6.78 (d,*J*=7.80 Hz,1H), 6.95-6.98 (m,2H), 7.35-7.39 (m,2H).
EI-MS *m/e* = 353 (M^+)

Step D: Preparation of methyl α-(2-*n*-propyl-4-cyanophenoxy)-3,4-methylenedioxyphenylacetic acid

To a solution of 3.5 g (8.64 mmol) of the product of Step C in 30 mL of methanol was added 2.07 mL (10.37 mmol) of 5.0 N aqueous sodium hydroxide solution. After stirring overnight, TLC analysis (80:15:1 chloroform / methanol / ammonium hydroxide) indicated that the saponification was complete. The reaction mixture was acidified to pH 3 with 6 N aqueous HCl and concentrated *in vacuo*. With heating and sonnication, the residue was redissolved in ethyl acetate, washed with brine, dried over magnesium sulfate, filtered, and the filtrate evaporated *in vacuo* to afford 2.92 g (99%) of the title

compound as an amorphous solid which was used without further purification in the next step.
^{1}H-NMR (300 MHz, CD_3OD,ppm) δ 0.90 (t,*J*=7.40 Hz,3H), 1.58-1.68 (m,2H), 2.66 (t,*J*=7.60 Hz,2H), 5.72 (s,1H), 5.92 (s,2H), 6.60 (d,*J*=8.10 Hz,1H), 6.90-6.93 (m,1H), 7.00-7.04 (m,2H), 7.45-7.47 (m,2H).
EI-MS *m/e* = 339 (M^+)

Step E: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-cyano-2-*n*-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide

To a stirred solution of 2.92 g (8.61 mmol) of the the product of Step D in 40 mL of methylene chloride was added 2.31 g (12.05 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1.26 g (10.33 mmol) of 4-dimethylaminopyridine, and 1.89 g ((9.47 mmol) of 4-*iso*-propylbenzenesulfonamide. The reaction mixture was stirred overnight and after TLC analysis (80:15:1 chloroform / methanol / ammonium hydroxide) was poured into 1 N HCl and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, filtered, and evaporated *invacuo*. The residue was partially purified with silica gel flash chromatography eluting first with 40% ethyl acetate-hexane and then with 3% methanol-methylene chloride to flush the column. All of the product product fractions were tainted with a contaminant and combined and concentrated for a subsequent chromatography. The 3.86 g of semi-purified material was dissolved in 15 mL of acetonitrile and 15 mL of water and filtered through a 0.45 uM filter disc. The compound was purified using a Waters Delta Prep 3000 HPLC by applying the filtered solution to an M1000 Prep-Pak module containing a 47 x 300 mm 15 mM DeltaPak C18 column and eluting at 50 mL/min first using 50% A (95-5 acetonitile-water) and 50% B (95-5 water-acetonitrile) with 0.1% TFA for 15 minutes and then 70% A (95-5 acetonitile-water) and 30% B (95-5 water-acetonitrile) both with 0.1% TFA. The column effluent was monitored simultaneously at 210 and 277 nM with a Waters model

490 UV-visible detector and the purified fractions were combined in a round bottom flask and concentated *in vacuo* to afford 1.45 g (38%) of the title compound as an amorphous solid.
^{1}H-NMR (500 MHz, CD_3OD,ppm) δ 0.89 (t,*J*=7.50 Hz,3H), 1.26 (d,*J*=7.00 Hz,3H), 1.27 (d,*J*=7.00 Hz,3H), 1.53-1.61 (m,2H), 2.59-2.66 (m,2H), 3.00 (sept.,*J*=7.00 Hz,1H), 5.55 (s,1H), 5.97 (s,2H), 6.60 (d,*J*=7.50 Hz,1H), 6.79 (d,*J*=8.00 Hz,1H), 6.85 (d,*J*=2.50 Hz,1H), 6.92 (dd,*J*=2.00, 8.20 Hz,1H), 7.31 (dd,*J*=2.50, 8.00 Hz,1H), 7.38 (d,*J*=8.50 Hz,2H), 7.45 (d,*J*=2.00 Hz,1H), 7.78 (d,*J*=8.50 Hz,2H).

Step F: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-cyano-2-*n*-propylphenoxy)-3,4-methylenedioxy-phenylacetamide potassium salt

To a stirred solution of 393 mg (0.756 mmol) of the the product of Step E in 1 ml of methanol was added 2.26 mL (2.27 mmol) of a 1 N potassium hydroxide solution in methanol. The reaction mixture was stirred 15 minutes, diluted with water and filtered through a 0.45 mm filter disc. The filtrate was purified using a Varian 5500 HPLC by applying the compound in a 4.0 ml total volume (3 mL methanol and 1 mL water) onto two in series 21.2 x 250 mm 7mm Zorbax ODS columns and eluting at 15 mL/min first using 85% water and 15% acetonitrile for 10 minutes and then a 30 minute linear gradient to 50% acetonitrile and 50% water. The column effluent was monitored 254 nM with a Kratos Spectroflow 783 UV detector and the purified fractions were combined in a round bottom flask, frozen in a -78°C dry ice-acetone bath and lyophylized to afford 177 mg (42%) of the title compound as a white lyophilized powder.
^{1}H-NMR (500 MHz, CD_3OD,ppm) δ 0.88 (t,*J*=7.50 Hz,3H), 1.23 (s,3H), 1.24 (s,3H), 1.55-1.62 (m,2H), 2.53-2.59 (m,1H), 2.67-2.73 (m,1H), 3.90-2.94 (m,1H), 5.37 (s,1H), 5.94 (s,2H), 6.76-6.78 (m,2H), 7.02-7.04 (m,2H), 7.21 (d,*J*=8.50 Hz,2H0, 7.27 (dd,*J*=2.00, 8.50 Hz,1H), 7.38 (d,*J*=2.00 Hz,1H), 7.66 (d,*J*=8.50 Hz,2H).
ESI-MS *m/e* = 559 (M+1).

EXAMPLE 152

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-tetrazo-5-yl-2-*n*-propyl-phenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt

Step A: Preparation of N-(4-iso-propylbenzenesulfonyl)-α-(4-tetrazo-5-yl-2-n-propylphenoxy)-3,4-methylenedioxy-phenylacetamide

A stirred solution of 600 mg (1.15 mmol) of the product of Example 151, Step F and 284 mg (1.38 mmol) of trimethyltinazide in 2 mL of toluene was heated with an oil bath at reflux overnight. The reaction was evaporated *in vacuo*, purified by silica gel flash chromatography eluting with methylene chloride / methanol / acetic acid 100:3:1, and the purified fractions concentrated *in vacuo* to afford 244 mg (38%) of the title compound as an amorphous solid.
^{1}H-NMR (500 MHz, CD_3OD,ppm) δ 0.90-0.94 (m,2H), 1.16-1.19 (m,6H), 1.60-1.68 (m,2H), 2.64-2.75 (m,2H), 2.89-2.95 (m,1H), 5.56 (s,1H), 5.96 (s,2H), 6.73 (d,*J*=8.50 Hz,1H), 6.79 (d,*J*=8.00 Hz,1H), 6.89 (d,*J*= 2.00 Hz,1H), 6.94 (dd,*J*=2.00, 8.00 Hz,1H), 7.34 (dd,*J*=1.50, 8.50 Hz,2H), 7.64 (dd,*J*=2.00, 8.50 Hz,1H), 7.76 (d,*J*=2.00 Hz,1H), (dd,*J*=2.00, 8.50 Hz,2H).
ESI-MS *m/e* = 564 (M+1).

Step B: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-tetrazo-5-yl-2-*n*-propylphenoxy)-3,4-methylenedioxy-phenylacetamide dipotassium salt

To a stirred solution of 240 mg (0.426 mmol) of the product of Step A in 3 ml of methanol was added 2.41 mL (2.41 mmol) of a 1 N potassium hydroxide solution in methanol. The reaction mixture was stirred 15 minutes, diluted with 4 mL of water and filtered

through a 0.45 mm filter disc. The filtrate was purified using a Varian 5500 HPLC by applying the compound in a 8.0 ml total volume (4 mL methanol and 4 mL water) onto two in series 21.2 x 250 mm 7mm Zorbax ODS columns and eluting at 15 mL/min first using 90% water and 10% acetonitrile for 5 minutes and then a 30 minute linear gradient to 40% acetonitrile and 60% water. The column effluent was monitored 254 nM with a Kratos Spectroflow 783 UV detector and the purified fractions were combined in a round bottom flask, frozen in a -78°C dry ice-acetone bath and lyophylized to afford 196 mg (72%) of the title compound as a white lyophilized powder.
^{1}H-NMR (500 MHz, CD_3OD,ppm) δ 0.91 (t,*J*=7.20 Hz,3H), 1.15 (d,*J*=7.0 Hz,3H), 1.16 (d,*J*=7.0 Hz,3H), 1.62-1.68 (m,2H), 2.58-2.64 (m,1H), 2.74-2.80 (m,1H), 2.86 (sept.,*J*=7.00 Hz,1H), 5.36 (s,1H), 5.93 (d,*J*=1.20 Hz,1H), 5.94 (d,*J*=1.20 Hz,1H), 6.76 (d,*J*=7.50 Hz,1H), 6.82 (d,*J*=8.50 Hz,1H), 7.04-7.07 (m,2H), 7.20 (d,*J*=8.50 Hz,2H), 7.65-7.69 (m,3H), 7.78(d,*J*=2.00 Hz,1H).
ESI-MS *m/e* = 640 (M+1).

EXAMPLE 153

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-*N*-methyl-*N*-methoxy-carboxamido-2-*n*-propylphenoxy)-3,4-methylenedioxyphenylacetamide

Step A: *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-*N*-methyl-*N*-methoxycarboxamido-2-n-propylphenoxy)-3,4-methylenedioxyphenylacetamide

To a 0° C suspension of 2.00 g (3.25 mmol) of the product of Example 58 and 951 mg (9.75 mmol) N,O- dimethylhydroxylamine hydrochloride in 15 mL of methylene chloride and 1.36 mL (9.75 mmol) of triethylamine was added 1.49 g (9.75 mmol) of 1-hydroxybenzotriazole hydrate and 1.87 g (9.75 mmol) of 1-(-3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The reaction mixture was stirred 16 hour and allowed to warm to room temperature after which TLC analysis (10% methanol/methylene

chloride) indicated that the coupling reaction was complete. The reaction was diluted with ethyl acetate (30 mL) and partitioned with water (150 mL). The organic layer was washed with 1 N HCl (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, evaporated and dried in vacuo affording 1.64 g (87%) of the title compound as an amorphous powder.

^{1}H-NMR(400 MHz, d_6-DMSO,ppm): δ 0.82 (t,*J*=7.20 Hz,3H), 1.17 (d,*J*=7.20 Hz,6H), 1.43-1.58 (m,2H), 2.48-2.60 (m,2H), 2.93 (sept, *J*=7.20 Hz,1H), 3.19 (s,1H), 3.51 (s,3H), 5.66 (s,1H), 6.03 (d,*J*=1.20 Hz,1H), 6.04 (d,*J*=1.20 Hz,1H), 6.47 (d,*J* =8.40 Hz,1H), 6.91-6.98 (m,3H), 7.25 (dd,*J*= 2.00, 8.40 Hz, 1H), 7.38 (d,*J*= 2.00 Hz, 1H), 7.41 (d,*J*= 8.40 Hz,2H), 7.69 (d,*J*= 8.40 Hz,2H).

ESI-MS *m/e* = 583 (M+1).

EXAMPLE154

N-(4-*iso*-propylbenzenesulfonyl)-α-(4-(1-oxoethyl)-2-*n*-propyl-phenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt

Step A: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-(1-oxoethyl)-2-n-propylphenoxy)-3,4-methylenedioxy-phenylacetamide

To a 0° C stirred suspension of 594 mg (1.02 mmol) of the product of Example 153 in 8 mL of dry tetrahydrofuran was added 1.19 mL (3.57 mmol) of methylmagnesium chloride as a 3.0 M solution in tetrahydrofuran. Following the grignard addition, a homogenous reaction mixture was achieved and then allowed to warm to room temperature. After stirring 3 hours, TLC analysis (10% methanol / methylene chloride) indicated that the coupling reaction was complete. The reaction mixture was poured into 5% 6N HCl / ethanol (20 mL) and then partitioned between brine (60 mL) and ethyl acetate (30 mL). The extract was dried over magnesium sulfate, filtered and the filtrate

concentrated *in vacuo* affording 373 mg (68%) of the title compound as an amorphous powder.
^{1}H-NMR (400 MHz, CD_3OD,ppm) δ 0.88 (t,*J*=7.20 Hz,3H), 1.21 (d,*J*=6.80 Hz,6H), 1.54-1.66 (m,2H), 2.51 (s,3H), 2.55-2.63(m,1H), 2.67-2.75 (m,1H), 2.91 (sept.,*J*=6.80 Hz,1H), 5.43 (s,1H), 5.94 (d,*J*=1.20 Hz,2H), 6.74-6.77 (m,2H), 7.01-7.03 (m,2H), 7.23 (d,*J*=8.40 Hz,2H), 7.65-7.69 (m,3H), 7.73 (d,*J*=2.40 Hz,1H).
CI-MS *m/e* = 538 (M+1).

Step B: Preparation of *N*-(4-*iso*-propylbenzenesulfonyl)-α-(4-(1-oxoethyl)-2-n-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide potassium salt

The titled compound is prepared using the product of Step A according to the procedure described in Example 152, Step B.

WHAT IS CLAIMED IS:

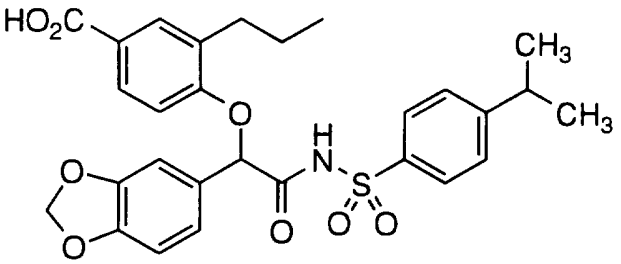
1. A compound which is: *N*-(4-*iso*-propylbenzene-sulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxy-phenylacetamide or a pharmaceutically acceptable salt thereof.

2. A compound which is: *N*-(4-*iso*-propylbenzene-sulfonyl)-α-(4-carboxy-2-*n*-propylphenoxy)-3,4-methylenedioxy-phenylacetamide dipotassium salt.

3. A method of treating renal failure by administering to a mammal in need of such treatment with a therapeutically effective amount of the compound recited in Claim 1.

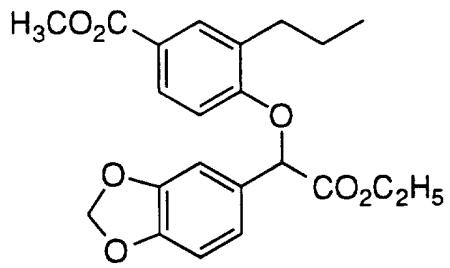
4. A pharmaceutical composition which comprises a pharmaceutically effective amount of the compound recited in Claim 1 and a pharmaceutically acceptable carrier.

5. A process for the preparation of a compound of structural formula:



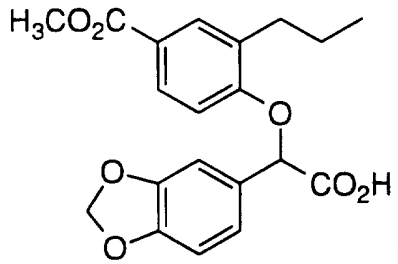
as a dipotassium salt, comprising the steps of:

(a) refluxing methyl 4-hydroxy-3-propylbenzoate with ethyl α-bromo-3,4-methylenedioxyphenylacetate, in potassium carbonate and acetone to form a diester,



;

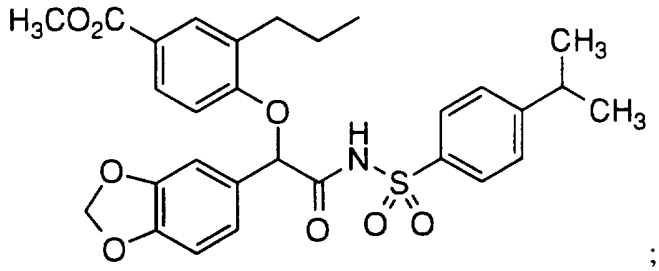
(b) hydrolyzing the diester using sodium hydroxide and methanol to form a monoester-monoacid,



;

(c) heating the monoester-monoacid with carbonyldiimidazole in tetrahydrofuran to form the imidazolide;

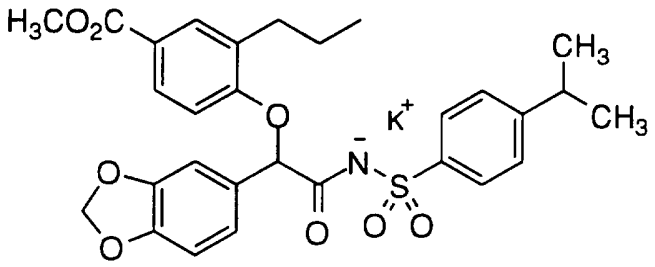
(d) reacting the imidazolide with 4-iso-propylbenzenesulfonate, and diazabicycloundecene to form N-(4-iso-propylbenzene-sulfonyl)-α-(4-carboxy-2-n-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide,



;

(e) treating N-(4-iso-propylbenzenesulfonyl)-α-(4-carbomethoxy-2-n-propylphenoxy)-3,4-methylenedioxyphenylacetamide with potassium

bicarbonate and ether to form N-(4-iso-propylbenzenesulfonyl)-α-(4-carbomethoxy-2-n-propylphenoxy)-3,4-methylenedioxyphenyl-acetamide potassium salt,



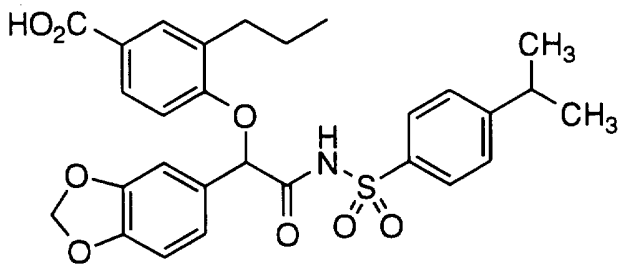
;

(f) crystallizing N-(4-iso-propylbenzenesulfonyl)-α-(4-carbomethoxy- 2-n-propylphenoxy)-3,4-methylenedioxyphenylacetamide potassium salt using ethyl acetate;

(g) hydrolyzing N-(4-iso-propylbenzenesulfonyl)-α-(4-carbomethoxy-2-n-propylphenoxy)-3,4-methylenedioxyphenylacetamide potassium salt with potassium hydroxide and methanol to form the compound of formula I, N-(4-iso-propylbenzenesulfonyl)-α-(4-carboxy-2-n-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt; and

(h) crystallizing N-(4-iso-propylbenzenesulfonyl)-α-(4-carboxy- 2-n-propylphenoxy)-3,4-methylenedioxyphenylacetamide dipotassium salt with ethanol to form the compound of formula I as the dipotassium salt.

6. A process for the resolution of the compound of structural Formula I:



as the dipotassium salt, comprising the steps of:

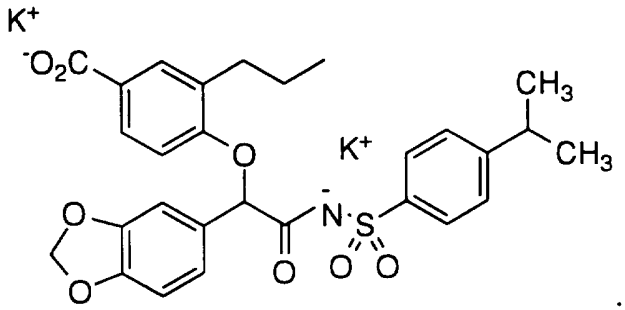
(a) reacting the diacid with R-(+)-α-methylbenzyl amine in isopropanol at room temperature overnight to form the diamine salt;

(b) recrystallizing the diamine salt from isopropanol to isolate an enantiomerically pure diamine salt;

(c) neutralizing the enantiomerically pure diamine salt using a solution of ethyl acetate and aqueous $NaHSO_4$ to form the the free acid;

(d) reacting the free acid with potassium hydroxide to form the enantiomerically pure dipotassium salt; and

(e) purifying the enantiomerically pure dipotassium salt to isolate enantiomerically pure dipotassium salt,



7. The process as recited in Claim 6, comprising purifying enantiomerically pure dipotassium salt by high pressure liquid chromatography.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/09967

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/335; C07D 317/54,317/56,317/58
US CL :514/456, 464, 465, 466 ; 549/221, 366, 434, 441, 447
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/456, 464, 465, 466 ; 549/221, 366, 434, 441, 447

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

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

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A, 5,334,598(BAGLEY ET AL) 02 AUGUST 1994, column 23-30, schemes 1-7.	5-7
A	HETEROCYCLES, Volume 30, No. 2, issued 1990, Jung et al., "Preparation of N-...Lycorine", see compound No. 14, page 84.	1-4

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

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

Date of the actual completion of the international search 03 NOVEMBER 1995	Date of mailing of the international search report 28 NOV 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Y.N. GUPTA Telephone No. (703) 308-1235

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