Eur J Med Chem (1997) 32, 425–431

Benzofuran derivatives as ET_A-selective, non-peptide endothelin antagonists

JS Kaltenbronn[1]* J Quin III[1], BR Reisdorph[1], S Klutchko[1], EE Reynolds[2], KM Welch[2], MA Flynn[2], AM Doherty[1]

[1]*Department of Chemistry, Parke-Davis Pharmaceutical Research;*
[2]*Department of Pharmacology, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105, USA*

(Received 20 August 1996; accepted 31 October 1996)

Summary — The synthesis and SAR relationships of a series of 4-benzyloxy-3-methylbenzofuran-2-carboxylic acids are described. Compounds from this series show 2- to 16-fold selective binding to the ET_A receptor in the micromolar range, and two compounds from this series (**32** and **40**) were demonstrated to exhibit ET_A antagonist activity.

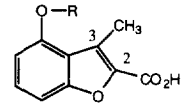
endothelin antagonist / benzofurancarboxylic acid

Introduction

The endothelins (ETs) are a family of vasoconstrictive peptides originally isolated from endothelial cells [1]. Two distinct receptor subtypes (ET_A and ET_B) have been cloned and expressed [2, 3]. A third subtype (ET_C) has been cloned from *Xenopus* dermal melanophores and heart [4, 5], although this subtype has not been described in mammalian tissues. Antagonism of the potent vasoconstrictor endothelin is a potential new approach to the treatment of a variety of human diseases including ischemia, hypertension, congestive heart failure, pulmonary hypertension, and subarachnoid hemorrhage [6].

A number of non-peptide endothelin antagonists have been reported. These include ET_A-selective compounds Shionogi 50-235 [7], PD-156707 [8] and BMS-182874 [9], and balanced ET_A/ET_B antagonists Bosentan [10], SB 209670 [11], CGS 27830 [12] and L-749329 [13]. A tripeptide antagonist (BQ-788) [14] has been reported to be selective for the ET_B receptor. What selectivity is desired for specific disease states is not clear at this time.

Screening of the Parke-Davis compound library identified two benzofurancarboxylic acid derivatives (**1** and **2**) that showed selectivity for the ET_A receptor.



	IC_{50} (μM)[a]		
	rET_A	hET_A	hET_B
1, R = CH_3	11	11	>25
2, R = CH_2Ph	3.7	3.8	>25

[a]*Receptor binding:* The rET_A test uses receptors derived from rabbit renal artery smooth muscle. The hET_A test uses cultured Ltk-cells expressing human cloned ET_A receptors, while the hET_B test uses CHO-K1 cells expressing human cloned ET_B receptors.

This paper describes the synthesis and SAR of a series of derivatives where R, the 3-methyl group, and the 2-carboxy function were varied sequentially.

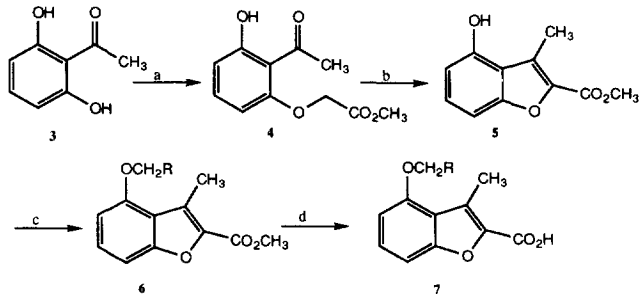
Chemistry

Variation of the benzyl moiety

Monoalkylation of **3** proceeded in 77% yield to give **4**. Cyclization with NaOMe in MeOH gave only moderate yields (54–59%) of **5** due to partial hydro-

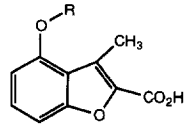
*Correspondence and reprints

lysis of the ester by the water liberated in this step (scheme 1). This intermediate **5** permitted easy access to the benzyl ethers described in table I. Both benzyl bromides and benzyl chlorides could be used as alkylating agents when used with KHMDS in DMF as the solvent, giving the intermediate ethers **6** in 45–65% yield. This observation was important because several of the oxygen-substituted benzyl bromides were unstable and could be prepared only with difficulty. The oxygen-substituted benzyl chlorides on the other hand, were quite stable. Basic hydrolysis of **6** gave **7** in yields of 40–95%.



Scheme 1. Variation of the benzyl moiety. a) $BrCH_2CO_2CH_3$, K_2CO_3, acetone. b) NaOMe, MeOH, reflux. c) $BrCH_2R$ or $ClCH_2R$, KHMDS, DMF. d) NaOH.

Table I. Endothelin binding affinity of compounds containing variations of the ether moiety.

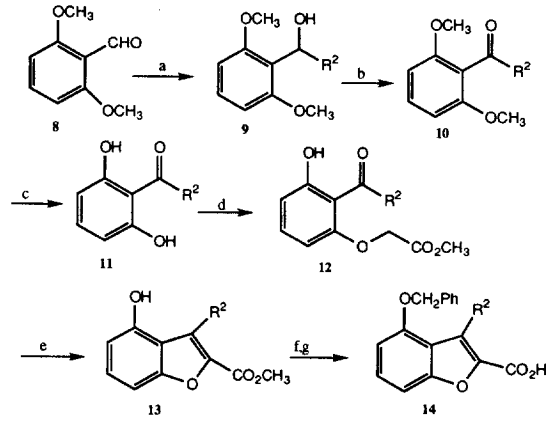


Compound	*R*	*IC_{50} (μM)*			*Formula*[a]	*Mp (°C)*
		rET_A	*hET_A*	*hET_B*		
1	CH_3	11	11	>25	$C_{11}H_{10}O_4$	237–239 d
2	$PhCH_2$	3.7	3.8	>25	$C_{17}H_{14}O_4$	183–185
25	H	>25	–	>25	$C_{10}H_8O_4$	273–274 d
26	4-$ClPhCH_2$	1.2	4.0	19	$C_{17}H_{13}O_4Cl \cdot 0.8H_2O$	230–233
27	3-$ClPhCH_2$	4.0	3.4	>25	$C_{17}H_{13}O_4Cl$	193–196
28	3,4-Di-$ClPhCH_2$	8.6	3.7	>25	$C_{17}H_{12}O_4Cl_2$	230–232
29	4-CO_2HPhCH_2	>25	–	>25	$C_{18}H_{14}O_6 \cdot 0.2H_2O$	288–289 d
30	4-$CNPhCH_2$	6.8	11	>25	$C_{18}H_{13}NO_4$	246–247
31	4-$FPhCH_2$	5.3	3.3	>25	$C_{17}H_{13}O_4F$	228–230
32	4-CF_3PhCH_2	4.0	1.9	18	$C_{18}H_{13}O_4F_3$	235–237
33	4-NO_2PhCH_2	11	–	>25	$C_{17}H_{13}NO_6 \cdot 0.2H_2O$	253–254
34	4-$MeOPhCH_2$	13	–	>25	$C_{18}H_{16}O_5$	204–205 d
35	3-$MeOPhCH_2$	8.7	8.7	>25	$C_{18}H_{16}O_5$	189–190
36	2-$MeOPhCH_2$	>25	–	>25	$C_{18}H_{16}O_5 \cdot 0.2H_2O$	230–232 d
37	3,4-Di-$MeOPhCH_2$	>25	–	>25	$C_{19}H_{18}O_6$	190–191
38	3,5-Di-$MePhCH_2$	>25	–	>25	$C_{19}H_{18}O_6$	195–197
39	3,4-$OCH_2CH_2OPhCH_2$	4.9	4.8	>25	$C_{19}H_{16}O_6$	196–198
40	3,4-OCH_2OPhCH_2	1.8	2.8	>25	$C_{18}H_{14}O_6$	212–213 d
41	CH_2=$CHCH_3$	8.0	7.0	>25	$C_{13}H_{12}O_4$	174–176

[a]Analyses for C, H and N are within ±0.4% of the theoretical values.

Variation at the 3-position

R^2MgX or R^2Li treatment of **8** gave **9** in 79–84% yield (scheme 2). Compound **9** could be oxidized to **10** with Jones reagent in 84% yield. Since Grignard reagents prepared from CF_3Br are unstable, the recently described reagent CF_3SiMe_3 [15] was used to introduce the CF_3 group to give **9** ($R^2 = CF_3$) in 96% yield. Attempts to oxidize **9** ($R^2 = CF_3$) with Jones reagent or MnO_2 failed. However, the Dess–Martin reagent [16] cleanly gave the corresponding ketone **10** ($R^2 = CF_3$) in 90% yield. Treatment of **10** (R^2 = Ph or CH_2CH_2Ph) with BBr_3 in CH_2Cl_2 gave over 95% yields of **11**. However, when **10** ($R^2 = CF_3$) was subjected to the same conditions, only a 40% yield of equal amounts of **11** and the corresponding monomethyl ether was obtained. The compounds were readily separated by silica-gel chromatography. The remainder of the synthesis was carried out as outlined in scheme 1. The compounds prepared according to this scheme are listed in table II.

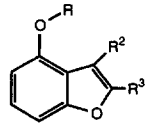


Scheme 2. Variation at the 3-position. a) R^2MgX or R^2Li in THF. When $R^2 = CF_3$, CF_3SiMe_3 was used. b) Jones reagent. When $R^2 = CF_3$, the Dess–Martin reagent was used. c) BBr_3, CH_2Cl_2. d) $BrCH_2CO_2CH_3$, K_2CO_3, acetone. e) NaOMe, MeOH, reflux. f) $BrCH_2Ph$, KHMDS, DMF. g) NaOH.

Variation of the acid functionality

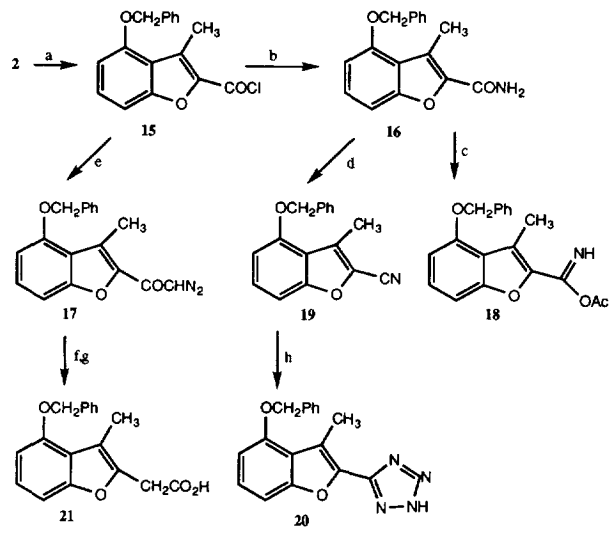
Thionyl chloride converted **2** to the acid chloride **15**, which when added as a suspension in dioxane to conc NH_4OH gave the amide **16** in 86% yield (scheme 3). When **16** was refluxed for 3 h in Ac_2O, an 80% yield of the imino acetate **18** was isolated. Treatment of **16** with CCl_3COCl at room temperature gave the nitrile **19** in 79% yield. Compound **19** was converted to the

Table II. Endothelin binding affinity of compounds containing variations at R^2 and the acid functionality.



Compound	*R*	*R^2*	*R^3*	*IC_{50} (μM)*		*Formula*[a]	*Mp (°C)*
				rET_A	*hET_B*		
16	$PhCH_2$	CH_3	$CONH_2$	>25	>25	$C_{17}H_{15}NO_3$	161–163
18	$PhCH_2$	CH_3	$C(=NH)OCH_3$	>25	>25	$C_{19}H_{17}NO_4$	170–171
19	$PhCH_2$	CH_3	CN	>25	>25	$C_{17}H_{13}NO_2 \cdot 0.4H_2O$[b]	85–87
20	$PhCH_2$	CH_3	2H-tetrazole	4.4[c]	>25	$C_{17}H_{14}N_4O_2 \cdot 0.2H_2O$	180–183
21	$PhCH_2$	CH_3	CH_2CO_2H	>25	>25	$C_{18}H_{16}O_4$	135–137
22	$PhCH_2$	$PhCH_2CH_2$	CO_2H	>25	>25	$C_{24}H_{20}O_4$	207–209
23	$PhCH_2$	Ph	CO_2H	>25	>25	$C_{22}H_{16}O_4$	228–230
24	CH_3	CF_3	CO_2H	>25	>25	$C_{11}H_4O_4F_3$	212–214

[a]Analyses for C, H and N are within ±0.4% of the theoretical values, except as noted; [b]calcd N, 5.18, found N, 4.70; [c]for hET_A the IC_{50} = 4.3 μM.



Scheme 3. Variation of the acid functionality; a) $SOCl_2$; b) NH_4OH; c) Ac_2O; d) Cl_3CCOCl; e) CH_2N_2; f) AgO, MeOH; g) NaOH; h) NaN_3, NH_4Cl.

tetrazole **20** in 60% yield. Arndt–Eistert homologation of **15** gave the acetic acid **21**. The compounds prepared according to this scheme are listed in table II.

Pharmacology

The endothelin binding assays have been described previously [17, 18]. In the rET_A assay, the receptor membranes were prepared from rabbit renal artery smooth muscle. For the human receptor binding assay (hET_A), cultured Ltk-cells expressing human-cloned ET_A receptors were used. For hET_B, CHO-K1 cells expressing human-cloned ET_B receptors were used. The ligand used for the ET_A assays was [^{125}I]-ET-1, while the ET_B assay used [^{125}I]-ET-3.

The functional assay measuring inhibition of ET-1 induced arachidonic acid release has also been described [19].

Results and discussion

Table I shows the ET_A and ET_B binding activities of those compounds prepared according to scheme 1. The compounds exhibited a 2- to 16-fold selectivity for the ET_A receptor, but showed a rather flat SAR. The ether group in the 4-position was essential as shown by the absence of activity in **25**. Alkyl ethers (**1** and **41**) showed activity, but were somewhat less potent than the benzyl ethers. Among the benzyl ethers, substitution with either electron-donating or electron-withdrawing groups gave similar affinities (**34, 35** vs **32, 33**). However, a *p*-CO_2H substituent (**29**) was not tolerated. Disubstitution by methoxy groups (**37** and **38**) gave inactive compounds. However, when these groups were constrained in a 5- or 6-membered ring (**39** and **40**) activity was retained. The most potent compound against rET_A was the *p*-Cl derivative (**26**), while the most potent compound against hET_A was the *p*-CF_3 analog (**32**).

Table II lists the ET_A and ET_B activities of those compounds prepared according to schemes 2 and 3. The 3-methyl group was also essential for ET_A binding affinity, as all the derivatives prepared according to scheme 2 (**22–24**) were inactive. All modifications of the carboxyl group (scheme 3) led to inactive compounds, except for the tetrazole analog (**20**), where activity comparable to the carboxylic acid derivatives was obtained.

When tested in a functional assay demonstrating ET_A antagonist activity (inhibition of ET-1 induced arachidonic acid release) [19], **32** had an IC_{50} of 16 μM while **40** had an IC_{50} of 3.9 μM.

Experimental protocols

Biological assays

Detailed experimental protocols have been described previously [17–19].

Chemistry

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a Varian Unity 400 MHz spectrometer and were run in either $CDCl_3$ or DMSO-d_6. Chemical ionization mass spectra were recorded on a Fisons VG Trio-2A mass spectrometer using 1% NH_3 in CH_4 as the reagent gas. The microanalytical data were obtained by the Parke-Davis Analytical Chemistry Section.

Compounds **1** and **25** have been described in the literature [20, 21]. All other analogs are novel.

(2-Acetyl-3-hydroxy)phenoxyacetic acid, methyl ester ***4***

A solution of 15.2 g (0.1 mol) of 2,6-dihydroxyacetophenone in 200 mL of acetone was treated with 16.8 g (0.11 mol) of methyl bromoacetate and 22 g (0.16 mol) of K_2CO_3 and the mixture heated at reflux for 3 h. The mixture was filtered and the filtrate diluted with H_2O. Adjusting the pH to 3 with dilute HCl gave a solid which was collected and recrystallized from MeOH/H_2O to give 14.98 g (67.1% yield) of the product as a tan solid, mp 65–67 °C. ^{1}H-NMR ($CDCl_3$) δ 2.80 (s, 3 H), 3.83 (s, 3 H), 4.72 (s, 2 H), 6.24 (d, 1 H, J = 8.3 Hz), 6.63 (d, 1 H, J = 8.4 Hz), 7.32 (t, 1 H, J = 8.3 Hz), 13.2 (s, 1 H); MS, *m/z* 225 (M + H$^+$).

4-Hydroxy-3-methylbenzofuran-2-carboxylic acid, methyl ester **5**
To 200 mL MeOH was added in portions 3.1 g (0.133 g-atom) of Na pellets. When all had reacted, 14.98 g (0.067 mol) of **4** was added, and the solution heated at reflux for 4 h. The dark solution was poured into H_2O and the pH adjusted to 3 with dilute HCl. There was obtained 7.36 g (53.7% yield) of the product as a tan solid, mp 176–179 °C. ^{1}H-NMR (DMSO-d_6) δ 2.67 (s, 3 H), 3.86 (s, 3 H), 6.66 (d, 1 H, J = 7.7 Hz), 7.02 (d, 1 H, J = 8.2 Hz), 7.26 (t, 1 H, J = 8.2 Hz), 10.38 (s, 1 H); MS, m/z 201 (M + H$^+$).

Alkylation of the 4-hydroxy group to give **6**. *A general procedure illustrated with the preparation of 4-(4-methoxybenzyloxy)-3-methylbenzofuran-2-carboxylic acid, methyl ester*
A solution of 0.6 g (2.9 mmol) of **5** in 10 mL DMF was cooled to –80 °C and 7 mL (3.5 mmol) of a 0.5 M solution of potassium hexamethyldisilazide in toluene was added. After stirring for 15 min, the cooling was removed and 0.7 mL (4.6 mmol) of 4-methoxybenzyl chloride added. After stirring at room temperature for 2 h, the solution was diluted with EtOAc and washed twice with 1 N HCl, three times with H_2O, sat $NaHCO_3$ and then sat NaCl. Drying over $MgSO_4$ and removal of the solvent under reduced pressure gave the crude product. Chromatography on silica gel, eluting with hexane/$CHCl_3$ (50:50) gave 470 mg (49.5% yield) of the product as a white solid. MS, m/z 327 (M + H$^+$).

Hydrolysis of **6** *to give* **7**. *A general procedure illustrated with the preparation of 4-(4-methoxybenzyloxy)-3-methylbenzofuran-2-carboxylic acid*
A solution of 0.47 g (1.4 mmol) of 4-(4-methoxybenzyloxy)-3-methylbenzofuran-2-carboxylic acid, methyl ester in 5 mL MeOH and 10 mL dioxane was treated with a solution of 0.5 g (12.5 mmol) of NaOH in 5 mL H_2O and the resulting solution heated at reflux for 2 h. The solvent was removed under reduced pressure and the residue mixed with H_2O causing the Na salt to precipitate. The suspension was acidified to pH 3 with dilute HCl and extracted into EtOAc. The EtOAc was washed with H_2O, then dried over $MgSO_4$. Removal of the solvent under reduced pressure left the crude product. Recrystallization from MeOH/H_2O gave 180 mg (40.1% yield) of the product as a white solid, mp 204–205 °C, d. ^{1}H-NMR (DMSO-d_6) δ 2.63 (s, 3 H), 3.77 (s, 3 H), 5.16 (s, 2 H), 6.98 (m, 3 H), 7.18 (d, 1 H, J = 8.4 Hz), 7.41 (m, 3 H); MS, m/z 313 (M + H$^+$).

1-(2,6-Dimethoxyphenyl)-3-phenylpropan-1-ol **9a**, R^2 = CH_2CH_2Ph
A suspension of 1.09 g (0.045 g-atom) of Mg turnings in 10 mL THF was treated in portions with 8.27 g (44.7 mmol) of (2-bromoethyl)benzene in 40 mL THF. The reaction was initiated with a crystal of I_2, then refluxed for 1 h. 2,6-Dimethoxybenzaldehyde (5.0 g, 29.8 mmol) was then added dropwise and the solution stirred for 1 h at room temperature. The solution was treated with 1 N HCl and then diluted with EtOAc. The EtOAc solution was washed with H_2O, sat $NaHCO_3$ and then sat NaCl. Drying over $MgSO_4$ and removal of the solvent under reduced pressure gave the crude product. Chromatography on silica gel, eluting with CH_2Cl_2 gave 6.4 g (78.9% yield) of the product as a pale-yellow oil. ^{1}H-NMR ($CDCl_3$) δ 2.02 (m, 1 H), 2.22 (m, 1 H), 2.62 (m, 1 H), 2.88 (m, 1 H), 3.82 (s, 6 H), 5.19 (m, 1 H), 6.56 (d, 2 H, J = 8.4 Hz), 7.20 (m, 6H); MS, m/z 273 (M + H$^+$). Anal $C_{17}H_{20}O_3$ (C, H).

1-(2,6-Dimethoxyphenyl)benzyl alcohol **9b**, R^2 = *Ph*
In a manner similar to the above, but using a 1.8 M solution of PhLi in cyclohexane/Et_2O, we obtained 6.13 g (84.2% yield) of the product as a white solid. ^{1}H-NMR ($CDCl_3$) δ 3.78 (s, 6 H), 4.36 (d, 1 H, J = 11.8 Hz), 6.33 (d, 1 H, J = 10.8 Hz), 6.57 (d, 2 H, J = 8.4 Hz), 7.26 (m, 6 H); MS, m/z 245 (M + H$^+$). Anal $C_{15}H_{16}O_3$ (C, H).

1-(2,6-Dimethoxyphenyl)trifluoroethanol **9c**, R^2 = CF_3
A solution of 2.33 g (14 mmol) of 2,6-dimethoxybenzaldehyde in 35 mL THF was cooled in ice and 2.4 g (16.9 mmol) of trimethyl(trifluoromethyl)silane added followed by 0.1 mL of a 1 M solution of tetrabutylammonium fluoride in THF. The cooling was removed and the solution allowed to stir at room temperature for 1.5 h. The solution was then treated with 25 mL of 1 N HCl and allowed to stir for 2 h. The solution was extracted with EtOAc and the EtOAc washed with H_2O, sat $NaHCO_3$ and sat NaCl. Drying over $MgSO_4$ and removal of the solvent under reduced pressure left 3.18 g (96.4% yield) of the product as a pale-yellow solid, mp 67–69 °C. ^{1}H-NMR ($CDCl_3$) δ 3.88 (s, 3 H), 5.00 (d, 1 H), 5.58 (m, 1 H), 6.62 (d, 2 H), 7.30 (m, 1 H); MS, m/z 237 (M + H$^+$).

1-(2,6-Dimethoxyphenyl)-3-phenylpropan-1-one **10a**, R^2 = CH_2CH_2Ph
A solution of 5.82 g (21.4 mmol) of **9a** (R^2 = CH_2CH_2Ph) in 300 mL acetone was cooled in ice and treated with 17.5 mL (140 mmol) of 8 N Jones reagent. The cooling was removed and the mixture stirred at room temperature for 1 h. Isopropanol (18 mL) was then added and the mixture stirred for 5 min. The mixture was filtered through Celite and the solvent removed under reduced pressure. The residue was taken up in CH_2Cl_2 and filtered through a plug of silica gel. Removal of the solvent under reduced pressure left 4.73 g (82% yield) of the product as a white solid. ^{1}H-NMR ($CDCl_3$) δ 3.04 (m, 4 H), 3.76 (s, 6 H), 6.53 (d, 2 H, J = 8.4 Hz), 7.22 (m, 6 H); MS, m/z 271 (M + H$^+$). Anal $C_{17}H_{18}O_3$ (C, H).

(2,6-Dimethoxyphenyl)phenylketone **10b**, R^2 = *Ph*
In a manner similar to the above, but using 6 g (24.6 mmol) of **9b** (R^2 = Ph), we obtained 4.99 g (83.9% yield) of the product as a light-orange solid. ^{1}H-NMR ($CDCl_3$) δ 3.70 (s, 6 H), 6.62 (d, 2 H, J = 8.4 Hz), 7.36 (m, 1 H), 7.42 (m, 2 H), 7.56 (m, 1 H), 7.84 (m, 2 H); MS, m/z 243 (M + H$^+$). Anal $C_{15}H_{14}O_3$ (C, H).

(2,6-Dimethoxyphenyl)trifluoromethylketone **10c**, R^2 = CF_3
A solution of 5.0 g (11.8 mmol) of the Dess-Martin reagent was suspended in 50 mL CH_2Cl_2. To this was added 2.32 g (9.8 mmol) of **9c** (R^2 = CF_3) and the mixture stirred at room temperature for 1 h. The mixture was diluted with 200 mL Et_2O and 120 mL of 1 N NaOH added and the mixture stirred for 10 min. The layers were separated and the organic phase washed with 1 N NaOH, H_2O and then sat NaCl. Drying over $MgSO_4$ and removal of the solvent under reduced pressure left 2.08 g (90.4% yield) of the product as an oil. ^{1}H-NMR ($CDCl_3$) δ 3.83 (s, 6 H), 6.59 (d, 2 H, J = 8.4 Hz), 7.40 (t, 1 H, J = 8.4 Hz); MS, m/z 235 (M + H$^+$).

(2,6-Dihydroxyphenyl)-3-phenylpropan-1-one **11a**, R^2 = CH_2CH_2Ph
A solution of 4.05 g (15 mmol) of **10a** (R^2 = CH_2CH_2Ph) in 285 mL CH_2Cl_2 was cooled in ice and treated dropwise with 40 mL (0.42 mol) of BBr_3. The solution was stirred at 0 °C for 15 min, then at room temperature overnight. The solution was poured into 2 L H_2O and extracted with Et_2O. The Et_2O was extracted with 1 N NaOH, the NaOH brought to pH 1 with dilute HCl, and again extracted with Et_2O. The Et_2O was washed with sat NaCl, dried over $MgSO_4$, and the solvent

removed under reduced pressure leaving 3.5 g (96.3% yield) of the product as a tan solid. ^{1}H-NMR ($CDCl_3$) δ 3.06 (t, 2 H), 3.50 (t, 2 H), 6.40 (d, 2 H), 7.26 (m, 6 H), 9.41 (s, 2 H); MS, *m/z* 243 (M + H$^+$). Anal $C_{15}H_{14}O_3$ (C, H).

*(2,6-Dihydroxyphenyl)phenylketone **11b**, R^2 = Ph*
In a manner similar to the above, but using 4.85 g (20 mmol) of **10b** (R^2 = Ph), we obtained 4.28 g (100% yield) of the product as an oil which crystallized on standing. ^{1}H-NMR ($CDCl_3$) δ 6.50 (d, 2 H), 7.32 (m, 1 H), 7.52 (m, 2 H), 7.62 (m, 1 H), 7.74 (m, 2H), 8.25 (s, 2 H); MS, *m/z* 215 (M + H$^+$).

*(2,6-Dihydroxyphenyl)trifluoromethylketone **11c**, $R^2 = CF_3$*
A solution of 2.56 g (10.9 mmol) of **10c** ($R^2 = CF_3$) in 100 mL CH_2Cl_2 was cooled in ice and treated dropwise with 14.8 mL (0.156 mol) of BBr_3. After stirring for 15 min at 0 °C, the solution was allowed to stir at room temperature overnight. The solution was poured into H_2O and extracted with Et_2O. The Et_2O was extracted with 5% NaOH, the NaOH brought to pH 3 with dilute HCl, and then extracted with Et_2O. The Et_2O was washed with sat NaCl, dried over $MgSO_4$ and the solvent removed under reduced pressure leaving the crude material as a mixture of the dihydroxy compound and the corresponding monomethyl ether. Chromatography on silica gel, eluting with $CHCl_3$/MeOH (98:2) gave 420 mg of the monomethyl ether as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ 3.90 (s, 3 H), 6.44 (d, 1 H, *J* = 8.2 Hz), 6.65 (d, 1 H, *J* = 8.4 Hz), 7.48 (t, 1 H, *J* = 8.4 Hz), 11.0 (s, 1 H); MS, *m/z* 221 (M + H$^+$).

Continued elution from the column gave 486 mg of the dihydroxy compound. ^{1}H-NMR ($CDCl_3$) δ 6.46 (d, 2 H, *J* = 8.2 Hz), 7.38 (t, 1 H, *J* = 8.2 Hz), 8.71 (s, 2 H); MS, *m/z* 207 (M + H$^+$).

*4-Benzyloxy-3-methylbenzofuran-2-carbonyl chloride **15***
To 20 mL $SOCl_2$ was added in portions 3.0 g (10.6 mmol) of **2**. The mixture was warmed to effect solution and then stirred at room temperature overnight. The $SOCl_2$ was removed under reduced pressure, Et_2O was added, and the solvent removed again. The residue was triturated with hexane to give 2.34 g (73.4% yield) of the acid chloride, mp 110–112 °C.

*4-Benzyloxy-3-methylbenzofuran-2-carboxamide **16***
A suspension of 1.5 g (5.0 mmol) of **15** in 20 mL dioxane was added in portions to 50 mL of conc NH_4OH and the suspension stirred at room temperature for 2 h. The solid was collected and recrystallized from MeOH/H_2O to give 1.2 g (85.7% yield) of the amide as a white solid, mp 161–163 °C. ^{1}H-NMR (DMSO-d_6) δ 2.66 (s, 3 H), 5.25 (s, 2 H), 6.92 (d, 1 H, *J* = 8.1 Hz), 7.13 (d, 1 H, *J* = 8.2 Hz), 7.42 (m, 7 H), 7.83 (s, 1 H); MS, *m/z* 282 (M + H$^+$).

*3-Methyl-4-(phenylmethoxy)-2-benzofurancarboximidic acid acetate **18***
A solution of 1.1 g (3.9 mmol) of **16** in 25 mL Ac_2O was heated at reflux for 3 h. The solvent was removed under reduced pressure and the residue chromatographed on silica gel, eluting with $CHCl_3$. There was obtained 420 mg (40.8% yield) of the product as a white solid, mp 170–171 °C. ^{1}H-NMR (DMSO-d_6) δ 2.34 (s, 3 H), 2.68 (s, 3 H), 5.27 (s, 2 H), 6.96 (d, 1 H, *J* = 8.2 Hz), 7.20 (d, 1 H, *J* = 8.2 Hz), 7.38 (m, 1 H), 7.44 (m, 3 H), 7.52 (m, 2 H), 10.66 (s, 1 H); MS, *m/z* 324 (M + H$^+$).

*4-Benzyloxy-3-methylbenzofuran-2-carbonitrile **19***
A suspension of 504 mg (1.8 mmol) of **16** in 10 mL CH_2Cl_2 was warmed to effect solution and then treated with 0.5 mL (3.6 mmol) of Et_3N. After cooling in ice, the solution was treated with 0.3 mL (2.2 mmol) of trichloroacetyl chloride. The cooling was removed and the solution stirred at room temperature for 3 h. The mixture was diluted with EtOAc and washed with 1 N HCl, H_2O, sat $NaHCO_3$ and sat NaCl. Drying over $MgSO_4$ and removal of the solvent under reduced pressure left the crude product. Recrystallization from MeOH/H_2O gave 372 mg (79% yield) of the product as a tan solid, mp 85–87 °C. ^{1}H-NMR (DMSO-d_6) δ 2.50 (s, 3 H), 5.28 (s, 2 H), 7.01 (d, 1 H, *J* = 8.0 Hz), 7.25 (d, 1 H, *J* = 8.4 Hz), 7.42 (m, 6 H); MS, *m/z* 264 (M + H$^+$).

*5-(4-Benzyloxy-3-methylbenzofuran-2-yl)-2H-tetrazole **20***
A solution of 0.33 g (1.3 mmol) of **19** in 7 mL DMF was treated with 246 mg (3.8 mmol) of NaN_3 and 202 mg (3.8 mmol) of NH_4Cl and heated at 120 °C for 3 d. The mixture was poured into H_2O and the pH brought to 3 with dilute HCl. The mixture was extracted with EtOAc and the EtOAc washed with H_2O, then sat NaCl. Drying over $MgSO_4$ and removal of the solvent under reduced pressure left the crude product. Chromatography on silica gel, eluting with $CHCl_3$/MeOH (90:10) gave the product. Recrystallization from MeOH/H_2O gave 226 mg (59.5% yield) of the product as a tan solid, mp 180–183 °C. ^{1}H-NMR (DMSO-d_6) δ 2.77 (s, 3 H), 5.29 (s, 2 H), 6.98 (d, 1 H, *J* = 8.0 Hz), 7.26 (d, 1 H, *J* = 8.2 Hz), 7.34–7.56 (m, 6 H); MS, *m/z* 307 (M + H$^+$).

*Preparation of **17***
A solution of 1.17 g (3.9 mmol) of **15** in 20 mL benzene was added dropwise over 0.5 h to an Et_2O solution of diazomethane kept at 0 °C. After stirring at 0 °C for 1 h, the solution was allowed to warm to room temperature overnight. A few drops of HOAc was added and the solvent removed under reduced pressure. Trituration with hexane gave 995 mg (83.6% yield) of the product as a yellow solid. The material was used directly in the following step.

*4-Benzyloxy-3-methylbenzofuran-2-acetic acid **21***
A suspension of 995 mg (3.2 mmol) of **17** in 20 mL MeOH was warmed to effect solution. This was then treated with 0.6 g Ag_2O and heated at reflux for 2 h. The mixture was filtered and the solvent removed under reduced pressure. Chromatography on silica gel, eluting with hexane/$CHCl_3$ (50:50) gave 160 mg of the intermediate ester as an oil.

A solution of the oil in 5 mL MeOH was treated with a solution of 0.2 g (5.0 mmol) of NaOH in 1 mL H_2O and warmed on a steam bath for 1 h. The solution was diluted with H_2O and washed with Et_2O. The aqueous phase was brought to pH 3 with dilute HCl and the solid collected. Recrystallization from MeOH/H_2O gave 90 mg (9.5% yield) of the product as a white solid, mp 135–137 °C. ^{1}H-NMR ($CDCl_3$) δ 2.35 (s, 3 H), 3.78 (s, 2 H), 5.15 (s, 2 H), 6.67 (d, 1 H, *J* = 7.7 Hz), 7.01–7.48 (m, 8H); MS, *m/z* 297 (M + H$^+$).

References

1 Yanigasawa M, Kurihara H, Kimura H et al (1988) *Nature (Lond)* 332, 411–415
2 Arai H, Hori S, Aramori I, Ohkubo H, Nakanishi S (1990) *Nature (Lond)* 348, 730–732
3 Sakurai T, Yanigasawa M, Takuwa Y et al (1990) *Nature (Lond)* 348, 732–735
4 Karne S, Jayawickreme CK, Lerner MR (1993) *J Biol Chem* 268, 19126–19133

5 Kumar C, Mwang V, Nuthulaganti P et al (1994) *J Biol Chem* 269, 13414–13420
6 Doherty AM (1992) *J Med Chem* 35, 1493–1508
7 Mihara S, Sakurai K, Nakaura M, Konoike T, Fujimoto M (1993) *Eur J Pharmacol Mol Pharmacol Sect* 247, 219–221
8 Doherty AM, Patt WC, Edmunds JJ et al (1995) *J Med Chem* 38, 1259–1263
9 Stein P, Hunt J, Floyd D et al (1994) *J Med Chem* 37, 329–331
10 Roux S, Clozel M, Sprecher U, Gray G, Clozel JP (1993) *Circulation* 88, 1–170
11 Elliott JD, Lago MA, Cousins RD et al (1994) *J Med Chem* 37, 1553–1557
12 Mugrage B, Moliterni J, Robinson L et al (1993) *Biorg Med Chem Lett* 3, 2099–2104
13 Walsh T, Fitch K, Chakravarty P et al (1994) *Abstracts, 208th National ACS Meeting*, ACS, Washington, DC MEDI-145
14 Ishikawa K, Ihara M, Noguchi K et al (1994) *Proc Natl Acad Sci USA* 91, 4892–4896
15 Surya Prakash GK, Krishnamurti R, Olah GA (1989) *J Am Chem Soc* 111, 393–395
16 Dess DB, Martin JC (1983) *J Org Chem* 48, 4155–4156
17 Cody WL, Doherty AM, He JX et al (1993) *Med Chem Res* 3, 154–162
18 Reynolds EE, Keiser JA, Haleen SJ et al (1995) *J Pharmacol Exp Ther* 273, 1410–1417
19 Doherty AM, Cody WL, DePue PL et al (1993) *J Med Chem* 36, 2585–2594
20 Salvi VS, Sentha S (1968) *J Indian Chem Soc* 45, 439–445
21 Atkinson JG, Guindon Y, Lau CK (1983) *Chem Abstr* 103, 215151