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

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(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
$2, \mathbf{R} = \mathbf{C}\mathbf{H}_{2}\mathbf{P}\mathbf{h}$	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-

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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	$IC_{50}(\mu M)$			Formulaa	$Mp(^{\circ}C)$
		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	Н	>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 ₂ HPhCH 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 ₃ PhCH ₂	4.0	1.9	18	$C_{18}H_{13}O_4F_3$	235-237
33	4-NO ₂ PhCH 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 ₂ CH ₂ OPhCH ₂	4.9	4.8	>25	$C_{19}H_{16}O_6$	196–198
40	3,4-OCH ₂ OPhCH 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

^aAnalyses for C, H and N are within ±0.4% of the theoretical values.

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Variation at the 3-position

R²MgX or R²Li 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 CF₃Br are unstable, the recently described reagent CF₃SiMe₃ [15] was used to introduce the CF₃ group to give 9 ($R^2 = CF_3$) in 96% yield. Attempts to oxidize 9 ($R^2 = CF_3$) with Jones reagent or MnO₂ failed. However, the Dess-Martin reagent [16] cleanly gave the corresponding ketone 10 $(R^2 = CF_3)$ in 90% yield. Treatment of 10 $(R^2 = Ph \text{ or }$ 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.

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).



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) BBr₃, CH_2Cl_2 . d) BrCH₂CO₂CH₃, K₂CO₃, acetone. e) NaOMe, MeOH, reflux. f) BrCH₂Ph, KHMDS, DMF. g) NaOH.

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

Compound	R	<i>R</i> ²	<i>R</i> ³	IC ₅₀ (µМ)		Formula ^a	<i>Mp</i> (° <i>C</i>)		
				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°	>25	$C_{17}H_{14}N_4O_2 \cdot 0.2H_2O$	180–183		
21	PhCH ₂	CH ₃	CH ₂ CO ₂ H	>25	>25	$C_{18}H_{16}O_4$	135–137		
22	PhCH ₂	PhCH ₂ CH ₂	CO_2H	>25	>25	$C_{24}H_{20}O_4$	207–209		
23	$PhCH_2$	Ph	CO ₂ H	>25	>25	$C_{22}H_{16}O_4$	228-230		
24	CH ₃	CF_3	CO ₂ H	>25	>25	$C_{11}H_4O_4F_3$	212-214		

Table II. Endothelin binding affinity of compounds containing variations at R² and the acid functionality.

"Analyses for C, H and N are within $\pm 0.4\%$ of the theoretical values, except as noted; "calcd N, 5.18, found N, 4.70; "for hET_A the IC₅₀ = 4.3 μ M.



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 [¹²⁵I]-ET-1, while the ET_B assay used [¹²⁵I]-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-CO₂H 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-CF₃ analog (32).

Table II lists the $\dot{E}T_A$ 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 IC₅₀ of 16 μ M while **40** had an IC₅₀ of 3.9 μ M.

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 ¹H-NMR spectra were recorded on a Varian Unity 400 MHz spectrometer and were run in either CDCl₃ or DMSO- d_6 . Chemical ionization mass spectra were recorded on a Fisons VG Trio-2A mass spectrometer using 1% NH₃ in CH₄ 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 H₂O. Adjusting the pH to 3 with dilute HCl gave a solid which was collected and recrystallized from MeOH/H₂O to give 14.98 g (67.1% yield) of the product as a tan solid, mp 65–67 °C. ¹H-NMR (CDCl₃) 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/z225 (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 H₂O 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. ¹H-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 H₂O, sat NaHCO₃ and then sat NaCl. Drying over MgSO₄ and removal of the solvent under reduced pressure gave the crude product. Chromatography on silica gel, eluting with hexane/CHCl₃ (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)-3methylbenzofuran-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 H₂O and the resulting solution heated at reflux for 2 h. The solvent was removed under reduced pressure and the residue mixed with H₂O 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 H₂O, then dried over MgSO₄. Removal of the solvent under reduced pressure left the crude product. Recrystallization from MeOH/H₂O gave 180 mg (40.1% yield) of the product as a white solid, mp 204–205 °C, d. ¹H-NMR (DMSO-d₆) 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 I₂, 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 H₂O, sat NaHCO₃ and then sat NaCl. Drying over MgSO₄ and removal of the solvent under reduced pressure gave the crude product. Chromatography on silica gel, eluting with CH₂Cl₂ gave 6.4 g (78.9% yield) of the product as a pale-yellow oil. 'H-NMR (CDCl₃) 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 Cl₁H₂oO₃ (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/Et₃O, we obtained 6.13 g (84.2% yield) of

the product as a white solid. ¹H-NMR (CDCl₃) 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 C₁₅H₁₆O₃ (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 H₂O, sat NaHCO₃ and sat NaCl. Drying over MgSO₄ 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. ¹H-NMR (CDCl₃) 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⁺).

l-(2,6-Dimethoxyphenyl)-3-phenylpropan-l-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 CH₂Cl₂ 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. ¹H-NMR (CDCl₃) 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 C₁₇H₁₈O₃ (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. ¹H-NMR (CDCl₃) 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 C₁₅H₁₄O₃ (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 CH₂Cl₂. To this was added 2.32 g (9.8 mmol) of **9c** (R² = CF₃) and the mixture stirred at room temperature for 1 h. The mixture was diluted with 200 mL Et₂O 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, H₂O and then sat NaCl. Drying over MgSO₄ and removal of the solvent under reduced pressure left 2.08 g (90.4% yield) of the product as an oil. ¹H-NMR (CDCl₃) 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 BBr₃. The solution was stirred at 0 °C for 15 min, then at room temperature overnight. The solution was poured into 2 L H₂O and extracted with Et₂O. The Et₂O was extracted with 1 N NaOH, the NaOH brought to pH 1 with dilute HCl, and again extracted with Et₂O. The Et₂O was washed with sat NaCl, dried over MgSO₄, and the solvent removed under reduced pressure leaving 3.5 g (96.3% yield) of the product as a tan solid. ¹H-NMR (CDCl₃) 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 C₁₅H₁₄O₃ (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. ¹H-NMR (CDCl₃) 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 CH₂Cl₂ was cooled in ice and treated dropwise with 14.8 mL (0.156 mol) of BBr₃. After stirring for 15 min at 0 °C, the solution was allowed to stir at room temperature overnight. The solution was poured into H₂O and extracted with Et₂O. The Et₃O was extracted with 5% NaOH, the NaOH brought to pH 3 with dilute HCl, and then extracted with Et₂O. The Et₂O was washed with sat NaCl, dried over MgSO₄ 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 CHCl₃/MeOH (98:2) gave 420 mg of the monomethyl ether as a yellow oil. ¹H-NMR (CDCl₃) 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. ¹H-NMR (CDCl₃) 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 NH₄OH and the suspension stirred at room temperature for 2 h. The solid was collected and recrystallized from MeOH/H₂O to give 1.2 g (85.7% yield) of the amide as a white solid, mp 161–163 °C. 'H-NMR (DMSO- d_0) 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 Ac₂O was heated at reflux for 3 h. The solvent was removed under reduced pressure and the residue chromatographed on silica gel, eluting with CHCl₃. There was obtained 420 mg (40.8% yield) of the product as a white solid, mp 170–171 °C. ¹H-NMR (DMSO-d₆) 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 Et₃N. 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, H₂O, sat NaHCO₃ and sat NaCl. Drying over MgSO₄ and removal of the solvent under reduced pressure left the crude product. Recrystallization from MeOH/H₂O gave 372 mg (79% yield) of the product as a tan solid, mp 85–87 °C. ¹H-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 NaN₃ and 202 mg (3.8 mmol) of NH₄Cl and heated at 120 °C for 3 d. The mixture was poured into H₂O and the pH brought to 3 with dilute HCl. The mixture was extracted with EtOAc and the EtOAc washed with H₂O, then sat NaCl. Drying over MgSO₄ and removal of the solvent under reduced pressure left the crude product. Chromatography on silica gel, eluting with CHCl₃/MeOH (90:10) gave the product. Recrystallization from MeOH/H₂O gave 226 mg (59.5% yield) of the product as a tan solid, mp 180–183 °C. ¹H-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 Et₂O 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 Ag₂O 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/CHCl₃ (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 H₂O and warmed on a steam bath for 1 h. The solution was diluted with H₂O and washed with Et₂O. The aqueous phase was brought to pH 3 with dilute HCl and the solid collected. Recrystallization from MeOH/H₂O gave 90 mg (9.5% yield) of the product as a white solid, mp 135–137 °C. ¹H-NMR (CDCl₃) 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⁺).

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