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Benzofuran Based PDE4 Inhibitors

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Abstract—Replacement of the 3,4-dialkoxyphenyl substructure common to a number of PDE4 inhibitors with a 2-alkyl-7-methoxybenzofuran unit is described. This substitution can result in either enhancement or substantial reductions in PDE4 inhibitory activity depending on the system to which it is applied. An in vitro SAR study of a potent series of 4-(2-heteroaryl-ethyl)-benzofurans **26** is also presented.

Introduction

Cyclic nucleotide phosphodiesterases (PDE1-7) are a family of enzymes that degrade the intracellular secondary messengers cAMP and cGMP[1] thereby limiting a host cell's response to extracellular signals mediated by these carriers. In a number of immunological cell types, elevation of cAMP levels by PDE4 inhibition[2] causes activation of negative feedback mechanisms resulting in suppression of the cell's inflammatory activities.[3] In particular, this type of manipulation brings about a marked reduction in the release of the proinflammatory cytokine TNF-α into the blood.[4] These observations have generated considerable interest in the use of PDE4 inhibitors for the treatment of various immunological disorders, including asthma and rheumatoid arthritis.[5,6] The discovery of the first PDE4 selective inhibitor, rolipram (**1**, Fig. 1) more than 2 decades ago,[7] provided a benchmark for the development of more potent and selective analogues. Initially, the majority of research in this area focused on replacement of the pyrrolidinone of **1** with a wide range of other functionality (represented by the general structure **2**).[8] In our laboratories, this approach led to the discovery of a clinical candidate RP 73401 (**3**).[9] More recently,[10] we reported a new series of PDE4 inhibitors (**4**) in which the 3,4-dialkoxyphenyl subunit of **3** was replaced by a benzimidazole ring system. In this paper, we report the synthesis and PDE4 inhibitory activity of the related benzofuran system **5**. We also describe the effect on PDE4 inhibition of pairing the 2-alkyl-7-methoxy-benzofuran scaffold with a selection of novel as well as established pyrrolidinone surrogates to generate the hybrid structures represented by **6**.[11]

Chemistry

The substituted benzofurans employed in this study were prepared by Pd (0)/Cu (I) catalyzed[12] coupling of an appropriate terminal acetylene with either aldehyde **7** or ester **8** (Scheme 1). This approach, although very direct, does require the use of excess alkyne to achieve useful conversion. Aldehyde **7** was a superior substrate for this reaction than ester **8**, (63% and 38% yields, respectively, with 1-hexyne) presumably as a result of decreased steric crowding around the C-Br bond of **7**. Simple carbonyl transformations of **9** and **10** provided the carboxylic acids **11** in good yield. Subsequent elaboration of these scaffolds (Scheme 2) into the corresponding *N*-(3,5-dichloropyridin-4-yl) amides (**5**),[10] tetrahydro-pyrimidin-2-one (**12**),[13] pyrrolidinone (**13**),[7b] pyrrolidine carbamate (**14**)[14] and pyrrolidine sulphonamide (**15**)[14] derivatives was carried out by adaptation of the published procedures for the synthesis of their respective 3,4-dialkoxyphenyl analogues. The 1-phenyl-2-pyridyl-ethane derivative **18**[15] was prepared from **9c** as shown in Scheme 3. Addition of phenylmagnesium bromide followed by oxidation of the resulting secondary alcohol gave ketone **16**. Subsequent addition of pyridin-4-yl-methyl lithium to **16**, followed by dehydration with TFA, then hydrogenation of the resulting olefin gave **18**

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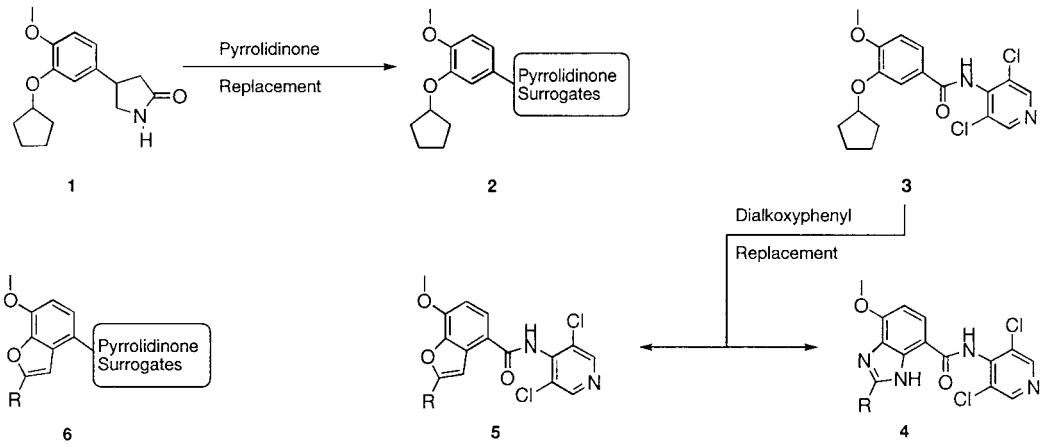
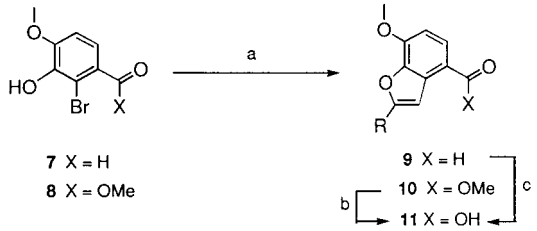
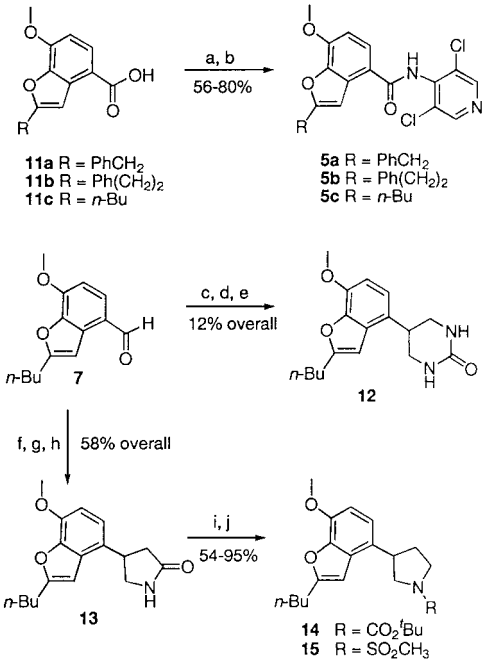


Figure 1. Evolution of the Rolipram family of PDEA inhibitors.

as a racemic mixture. The 2-(heteroaromatic)-substituted ethyl derivatives **26a–d, f** were prepared by treatment of **9c** with an appropriately protected[16] heteroaromatic-substituted-methyl lithium reagent, to give **19**, followed by dehydration (with concomitant deprotection) and olefin hydrogenation. *N*-oxide **26e** (Table 4) was derived from **26a** by *m*-CPBA oxidation. Compound **26g** (Scheme 4) was prepared by Wittig olefination of **9c**, to give **20**, followed by Heck coupling with 2-methoxy-5-bromo-pyridine to give **21**, reduction of the double bond and hydrolysis of the 2-methoxy-pyridine to the corresponding 2-pyridone. Compound **26h** was obtained by hydrogenation of **22**, followed by Claisen condensation with ethyl acetate and reaction of the resulting β-keto-ester with hydrazine.



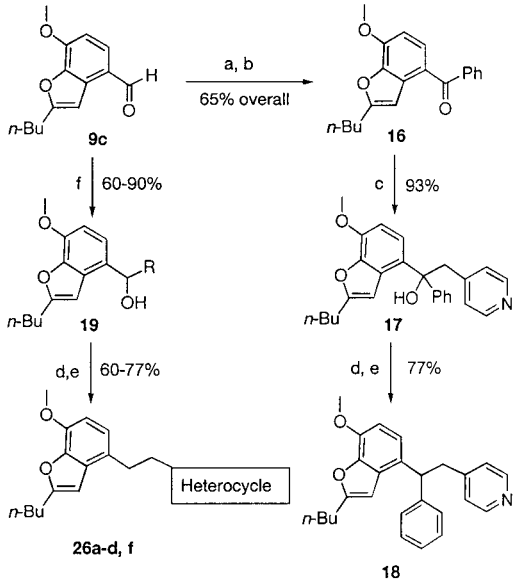
Scheme 1. *Reagents and conditions:* (a) $(Ph_3P)_2PdCl_2/CuI/Et_3N/RCCH/DMF/110\,^{\circ}C$. (b) NaOH/THF/MeOH/rt; (c) $NaClO_2/NaH_2PO_4/2$-methyl-2-butene, rt.



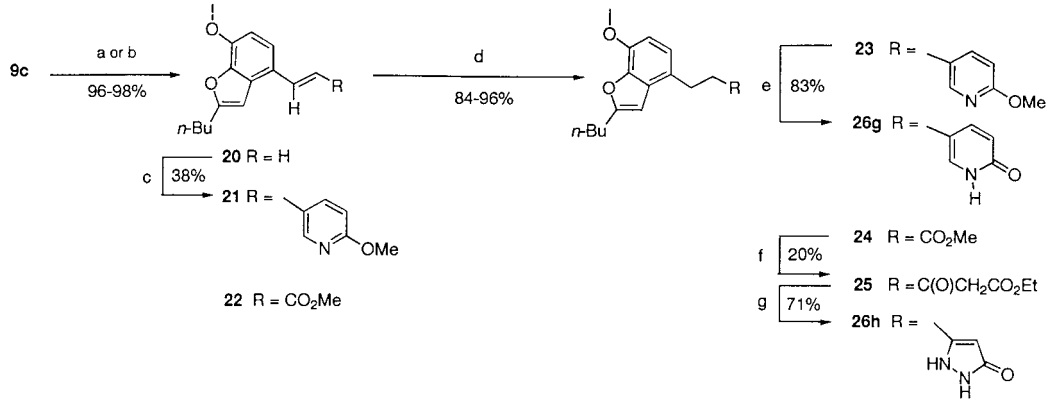
Scheme 2. *Reagents and conditions:* (a) $(COCl)_2/DMF$. (b) 4-Amino-3,5-dichloro-pyridine/$NaEt_2AlH_2$. (c) Cyanoacetic acid/piperidine. (d) H_2O_2/Na_2CO_3. (e) $Pb(OAc)_4$. (f) $Ph_3P{=}CHCO_2Me$. (g) $MeNO_2$/tetramethyl-guanidine. (h) Raney Ni. (i) LAH. (j) BOC_2O or RSO_2Cl/Et_3N.

Results and Discussion

Biological results are summarized in Tables 1–5. New compounds were evaluated by measuring their ability to inhibit guinea pig macrophage PDE4 (IC_{50}) using a previously published protocol.[17] Since there are a number of different PDE4 inhibitor assays in common use, comparisons between the activity of the benzofurans, which are the subject of this article, and certain of the

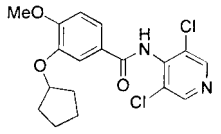
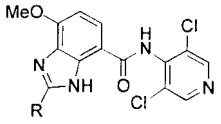
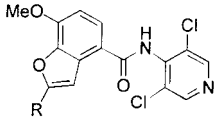


Scheme 3. *Reagents and conditions:* (a) PhMgBr. (b) PCC. (c) LDA/4-methyl-pyridine. (d) TFA. (e) $H_2/Pd/C$. (f) LDA/Me-(heterocycle).



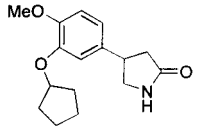
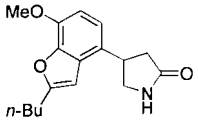
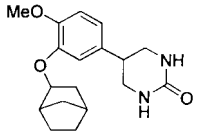
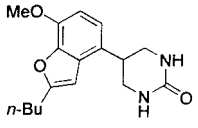
Scheme 4. *Reagents and conditions:* (a) $(Ph_3P)CH_3Br/Na(NSiMe_3)_2$. (b) $Ph_3P{=}CHCO_2Me$. (c) $(Ph_3P)_2PdCl_2$/5-bromo-2-methoxy-pyridine/Et_3N/DMF/100 °C. (d) H_2/Pd/C. (e) 1.5 M HCl/80 °C. (f) LDA/CH_3CO_2Et. (g) NH_2NH_2.

Table 1. Comparison between benzofuran benzimidazole and dialkoxy-phenyl scaffolds

Compound	Structure	IC_{50}(nM)[a]	IC_{50}(rolipram)/ IC_{50}(compound)[b]
3		1	300
			
4a	R = $PhCH_2$	24	12
4b	R = $Ph(CH_2)_2$	25	12
			
5a	R = $PhCH_2$	0.4	750
5b	R = $Ph(CH_2)_2$	0.7	430
5c	R = $CH_3(CH_2)_3$	2	150

[a]Partially purified PDE4 from guinea pig macrophage.
[b]Activity relative to rolipram was calculated by dividing the IC_{50} value obtained for a test compound into the IC_{50} value obtained for rolipram under the same assay conditions.

Table 2. Comparison between benzofuran and dialkoxy-phenyl scaffolds bearing pyrrolidinone and tetrahydropyrimidinone substituents

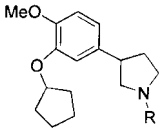
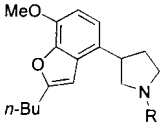
Compound	Structure	IC_{50}(nM)	IC_{50} (rolipram)/ IC_{50} (compound)[a]
1		300[b]	1
13		300[b]	1
27		200	1.5
12		48	6

[a]Activity relative to rolipram was calculated by dividing the IC_{50} value obtained for a test compound into the IC_{50} value obtained for rolipram under the same assay conditions.
[b]Test sample was a racemic mixture.

published inhibitor families cited in the following discussion (which were evaluated under different assay conditions) were made by referencing all activities relative to that of the widely used standard inhibitor rolipram.[18] Inhibitory activities against other PDE isozymes were not routinely measured.

Within the dichloropyridin-4-yl amide series (Table 1), the benzofuran scaffold appears to be more potent, in vitro, than the analogous benzimidazole system (**5a**,**b** versus **4a**,**b**),[19] imparting activity comparable to that of the parent 3,4-dialkoxyphenyl core structure **3**. The latter correlation holds reasonably well across the pyrrolidinone (Table 2, **1** versus **13**) and tetrahydropyrimidin-2-one families (**12** versus **27**) but breaks down for the case of the *N*-BOC-substituted pyrrolidine system (Table 3). In this instance, a 60 fold loss in potency was observed for the benzofuran scaffold relative to the dialkoxy-phenyl system (**28** versus **14**). It is not entirely clear why this loss occurs, particularly in view of the observation that the benzofuran and dialkoxyphenyl scaffolds impart similar potency in the related methylsulfonamide system (**29** versus **15**).

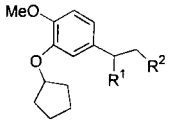
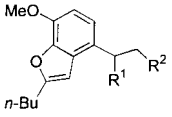
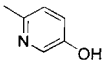
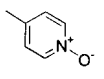
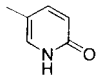
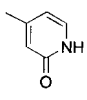
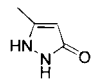
Table 3. Comparison between benzofuran and dialkoxy-phenyl scaffolds bearing an *N*-substituted pyrrolidine

Compound	Structure	IC_{50} (nM)	IC_{50} (rolipram)/ IC_{50} (compound)[a]
			
28	R = CO_2t-Bu		10[b]
29	R = SO_2Me		1[b]
			
14	R = CO_2t-Bu	1800[c]	0.16
15	R = SO_2Me	360[c]	1

[a]Activity relative to rolipram was calculated by dividing the IC_{50} value obtained for a test compound into the IC_{50}value obtained for rolipram under the same assay conditions.
[b]Calculated using data taken from reference 14.
[c]Test sample was a racemic mixture.

Differences in activity between the benzofuran and dialkoxyphenyl systems were also observed for the triarylethane series (Table 4). Comparison of **18** and **30** revealed a significant loss of activity in the benzofuran series. We speculated that increased steric interactions between the phenyl and benzofuranyl ring systems in **18** could well result in altered conformational preferences in this molecule (relative to **30**) which, in turn, may disfavor the bioactive conformer. This idea was subsequently supported by the observation that **26a** (in which the phenyl group of **18** has been removed) was highly active. In fact, **26a** was an order of magnitude more potent than its dialkoxyphenyl analogue **31**.[20] The level of activity observed for **26a** led us to examine some simple pyridine ring analogues of this system. The pyridazine **26b** was equipotent with **26a** suggesting that the key interactions in this part of the pharmacophore are not heavily dependent on pK_a. Introduction of a nitrogen adjacent to the ethylene linker (**26c**) was deleterious to activity, while replacement of the ring nitrogen with a phenolic hydroxyl (**26c** versus **26d**) or an *N*-oxide (**26a** versus **26e**) had little effect on potency. Surprisingly, the *N*-oxide **26e** was more than 20 times more potent than the isosteric pyridone **26f**, yet pyridone **26g** retained activity close to that of **26a**. Substitution of the six membered ring with a 5-membered heterocycle, as in **26h**, resulted in a further reduction in potency. While there are clear differences in activity among analogues **26a**–**h**, all of these compounds are, in an absolute sense, tight binding ligands for PDE4. In particular, **26a**, **b**, **e** and **g**, are approximately equipotent, despite the fact that they contain a variety of different Lewis base configurations. These results indicate a surprising level of tolerence to structural variation in this area of the rolipram pharmacophore and thus highlight a useful opportunity for the modification of physical–chemical

Table 4. Comparison between benzofuran and dialkoxy-phenyl scaffolds bearing (2-aryl)-ethyl substituents

Compound	Structure	IC_{50} (nM)	IC_{50} (rolipram)/ IC_{50}(compound)[a]
			
	R^1 R^2		
30	Ph[b] 	15	20
31	H 	11	27
			
	R^1 R^2		
18	Ph[b] 	2000	0.15
26a	H 	1	300
26b	H 	1	300
26c	H 	27	11
26d	H 	15	20
26e	H 	1	300
26f	H 	22	150
26g	H 	2	14
26h	H 	75	4

[a]Activity relative to rolipram was calculated by dividing the IC_{50} value obtained for a test compound into the IC_{50} value obtained for rolipram under the same assay conditions.
[b]Test sample was a racemic mixture.

Table 5. TNF-α inhibitory effects for a selection of benzofurans in a mouse endotoxemia model

Compound	ED_{50} (mg/Kg p.o.)
5a	30
5b	50
5c	20
15	> 50
26a	> 50
26b	> 50

properties of this class of compound without incurring a severe penalty in inhibitory potency.

Of the benzofurans in this paper tested (**5a**–**c**, **15**, **26a** and **26b**), **5c** was the most potent inhibitor of TNF-α release in vivo, as measured in a murine endotoxemia model (Table 5). In addition, a number of benzofurans of general formula **5** produced a pronounced emetic reaction in dogs when administered i.v. For example, **5a** caused emesis in 3/4 dogs at a dose of 0.3 mg/Kg. These results precluded further development of this series.

Conclusion

The 7-methoxybenzofuran unit can function as a replacement for the dialkoxyphenyl moiety found in several classes of PDE4 inhibitor. This substitution is, however, not universally applicable and can result in enhancement or substantial reductions in potency depending on the pyrrolidine surrogate employed. An analysis of the failure of this replacement in the triaryl-ethane system **18** led to the synthesis of a particularly potent group of compounds represented by **26a**–**h**. These results further refine our understanding of the rolipram pharmacophore and provide an important caveat for researchers interested in generating new structural classes of PDE4 inhibitors by combining novel analogues of the dialkoxyphenyl scaffold with new or established pyrrolidine surrogates.

Experimental

^{1}H NMR spectra were recorded at a frequency of 300 M Hz. Unless otherwise specified, materials were obtained from commercial suppliers and were used without further purification. Melting points were determined using a Thomas–Hoover capillary melting point apparatus and are uncorrected. Anhydrous solvents were obtained from Aldrich. Column chromatography was performed on Merck silica gel (230–400 mesh).

2-Butyl-7-methoxy-benzofuran-4-yl carbaldehyde (9c). A solution containing **7** (6.96 g, 30 mmol), $(Ph_3P)_2PdCl_2$ (1.14 g, 1.6 mmol), CuI (144 mg, 0.75 mmol) in DMF (80 mL) was degassed, then flushed with argon. To this solution was added Et_3N (21 mL, 152 mmol) followed by 1-hexyne (12 mL, 105 mmol). The resulting solution was warmed to 110 °C and stirred at this temperature for 2 h. The mixture was then cooled to room temperature, diluted with ether, washed with water, then brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography, eluting with 15% ethyl acetate in hexanes, to give 4.4 g (63%) of **9c** as an oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7 Hz, 3H), 1.40 (m, 2H), 1.75 (m, 2H), 2.80 (t, J = 7 Hz, 2H), 4.09 (s, 3H), 6.80 (d, J = 8 Hz, 1H), 7.14 (s, 1H), 7.60 (d, J = 8 Hz, 1H), 10.0 (s, 1H); MS (EI) m/z 232 $(M)^+$. The following compounds were prepared using essentially the same procedure:

2-Benzyl-7-methoxy-benzofuran-4-yl carbaldehyde (9a). Obtained as a tan solid (78%) ^{1}H NMR ($CDCl_3$) δ 4.07 (s, 3H), 4.17 (s, 2H), 6.83 (d, J = 8 Hz, 1H), 7.12 (s, 1H), 7.31 (m, 5H), 7.62 (d, J = 8 Hz, 1H), 9.99 (s, 1H). MS (EI) m/z 266 $(M)^+$.

7-Methoxy-2-phenethyl-benzofuran-4-yl carbaldehyde (9b). Obtained as an oil (76%). ^{1}H NMR ($CDCl_3$) δ 3.10 (m, 4H), 4.08 (s, 3H), 6.83 (d, J = 8 Hz, 1H), 7.2–7.4 (m, 6H), 7.62 (d, J = 8 Hz, 1H), 10.0 (s, 1H). MS (EI) m/z 280 $(M)^+$.

2-Butyl-7-methoxy-benzofuran-4-carboxylic acid (11c). To a solution of **9c** (700 mg, 3 mmol) in *t*-butanol (30 mL) was added of 2-methyl-but-2-ene (3 mL) followed by a solution comprised of $NaClO_2$ (3.0 g technical grade, 27 mmol) and $NaH_2PO_4.H_2O$ (3.0 g, 22 mmol) in water (30 mL). The resulting mixture was stirred vigorously for 3.5 h, diluted with ethyl acetate, washed with water, then brine, dried over $MgSO_4$ and concentrated. The residue was triturated with ether and filtered to give 741 mg (99%) of **10c** as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.0 (t, J = 7 Hz, 3H), 1.46 (m, 2H), 1.80 (m, 2H), 2.86 (t, J = 7 Hz, 2H), 4.1 (s, 3H), 6.90 (d, J = 8 Hz, 1H), 7.10 (s, 1H), 8.0 (d, J = 8 Hz, 1H); MS (EI) m/z 249 $(M+H)^+$.

The following compounds were prepared using essentially the same procedure:

2-Benzyl-7-methoxy-benzofuran-4-yl carboxylic acid (11a). Obtained as a white solid (88%) ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 3H), 4.17 (s, 2H), 6.78 (d, J = 8 Hz, 1H), 7.04 (s, 1H), 7.2–7.4 (m, 5H), 7.98 (d, J = 8 Hz, 1H). MS (EI) m/z 282 $(M)^+$.

7-Methoxy-2-phenethyl-benzofuran-4-yl carboxylic acid (11b). Obtained as white solid (85%). ^{1}H NMR ($CDCl_3$) δ 3.13 (m, 4H), 4.08 (s, 3H), 6.81 (d, J = 8 Hz, 1H), 7.09 (s, 1H), 7.2–7.33 (m, 5H), 8.00 (d, J = 8 Hz, 1H). MS (EI) m/z 296 $(M)^+$.

2-Butyl-7-methoxy-benzofuran-4-carboxylic acid (3-5-dichloro-pyridin-4y-l)-amide (5c). To a suspension of **11c** (2.7 g, 10.8 mmol) in CH_2Cl_2 (20 mL) was added 1 drop of DMF followed by oxalyl chloride (10 mL, 2 M in CH_2Cl_2). The resulting mixture was stirred for 45 min (during which time the solid suspension gradually dissolved). This solution was then concentrated under vacuum and the crude product, 2-butyl-7-methoxy-benzofuran-4-carbonyl chloride, used without further purification. In a separate flask, 4-amino-3,5-dichloropyridine (3.6 g, 22 mmol) was dissolved in THF/toluene

(2/1, 60 mL). To this solution was added $NaEt_2AlH_2$ (5 mL, 2 M in toluene. CAUTION, pyrophoric reagent). The resulting mixture was warmed to 50 °C and stirred at this temperature for 1 h then cooled to room temperature. To this solution was added the crude acid chloride (prepared above) in THF (15 mL). The resulting mixture was warmed to 50 °C and stirred for 2 h. The reaction mixture was then cooled to room temperature and quenched with sat. sodium tartrate solution, diluted with ethyl acetate, washed with HCl (0.25 M), then brine, dried over $MgSO_4$ and concentrated. The residue was recrystallized from ethyl acetate to give 2.38 g (56%) of **5c** as a white solid. mp. 166–167 °C; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7 Hz, 3H), 1.41 (m, 2H), 1.75 (m, 2H), 2.80 (t, J = 7 Hz, 2H), 4.10 (s, 3H), 6.80 (d, J = 8 Hz, 1H), 6.97 (s, 1H), 7.65 (bs, 1H), 7.70 (d, J = 8 Hz, 1H), 8.56 (s, 2H); MS (EI) m/z 392 $(M)^+$. Combustion analysis $C_{19}H_{18}O_3N_2Cl_2$ requires C 58.0, H 4.6, N 7.1. Found C 58.0, H 4.6, N 6.9.

The following compounds were prepared using essentially the same procedure:

2-Benzyl-7-methoxy-benzofuran-4-carboxylic acid (3-5-dichloro-pyridin-4-yl)-amide (5a). (67%) mp 214–215 °C; ^{1}H NMR ($CDCl_3$) δ 4.08 (s, 3H), 4.16 (s, 2H), 6.82 (d, J = 8 Hz, 1H), 6.94 (s, 1H), 7.2–7.35 (m, 5H), 7.68 (bs, 1H), 7.72 (d, J = 8 Hz, 1H), 8.53 (s, 2H); MS (EI) m/z 426 $(M)^+$. Combustion analysis $C_{22}H_{16}O_3N_2Cl_2$ requires C 61.8, H 3.8, N 6.6. Found C 61.6, H 3.9, N 6.5.

7-Methoxy-2-phenethyl-benzofuran-4-carboxylic acid (3-5-dichloro-pyridin-4y-l)-amide(5b). (80%) ^{1}H NMR (DMSO) δ 3.04 (m, 2H), 3.11 (m, 2H), 3.34 (s, 3H), 7.0 (s, 1H), 7.04 (d, J = 8 Hz, 1H), 7.20 (m, 1H), 7.28 (m, 4H), 7.91 (d, J = 8 Hz, 1H), 8.73 (s, 2H), 10.4 (s, 1H); MS (EI) m/z 440 $(M)^+$.

5-(2-Butyl-7-methoxy-benzofuran-4-yl)-tetrahydro-pyrimidin-2-one (12). Prepared according to the procedure in reference 13 except starting with **9c** instead of 3-cyclopentoxy-4-methoxy-benzaldehyde. mp 222–223 °C; ^{1}H NMR (DMSO) δ 0.93 (t, J = 7 Hz, 3H), 1.37 (m, 2H), 1.67 (m, 2H), 2.75 (d, J = 7 Hz, 2H), 3.2–3.4 (m, 5H), 3.89 (s, 3H), 6.27 (bs, 2H), 6.78 (s, 1H), 6.79 (d, J = 8 Hz, 1H), 7.00 (d, J = 8 Hz, 1H); MS (EI) m/z 303 $(M+H)^+$. Combustion analysis $C_{17}H_{22}O_3N_2$ requires C 67.5, H 7.3, N 9.3. Found C 67.4, H 7.4, N 9.1.

(*R*,*S*)-4-(2-Butyl-7-methoxy-benzofuran-4-yl)-pyrrolidin-2-one (13). Prepared according to the procedure in reference 7b except starting with **9c** instead of 3-cyclopentoxy-4-methoxy-benzaldehyde. ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7 Hz, 3H), 1.42 (m, 2H), 1.75 (m, 2H), 2.63 (dd, J = 17, 8 Hz, 1H), 2.77 (dd, J = 17, 8 Hz, 1H), 2.80 (t, J = 7 Hz, 2H), 3.53 (t, J = 8 Hz, 1H), 3.81 (bt, J = 8 Hz, 1H), 3.90 (bt, J = 8 Hz, 1H), 4.0 (s, 3H), 6.40 (s, 1H), 6.5 (bs, 1H), 6.69 (d, J = 8 Hz, 1H), 6.99 (d, J = 8 Hz, 1H); MS (EI) m/z 287 $(M)^+$. Combustion analysis $C_{17}H_{21}O_3N$ requires C 71.0, H 7.4, N 4.9. Found C 70.9, H 7.4, N 4.8.

(*R*,*S*)-4-(2-Butyl-7-methoxy-benzofuran-4-yl)-1-(*t*-butyl-oxy-carbonyl)-pyrrolidine (14). Prepared according to the procedure in reference 14 except starting with **9c** instead of 3-cyclopentoxy-4-methoxy-benzaldehyde. ^{1}H NMR ($CDCl_3$ The product exists as two conformers in solution) δ 0.94 (t, J = 7 Hz, 3H), 1.43 (m, 2H), 1.50, 1.52 (two s, total 9H), 1.76 (bm, 2H), 2.11 (bm, 1H), 2.25 (bm, 1H), 2.79 (bt, J = 7 Hz, 2H), 3.33–3.72 (m, 4H), 3.76, 3.88 (two t, J = 8 Hz, total 1H), 4.00 (s, 3H), 6.45 (s, 1H), 6.69 (d, J = 8 Hz, 1H), 6.95 (d, J = 8 Hz, 1H); MS (EI) m/z 373 $(M)^+$. Combustion analysis $C_{22}H_{31}O_4N$ requires C 70.7, H 8.4, N 3.7. Found C 70.8, H 8.2, N 3.6. Using essentially the same procedure, except using methanesulphonyl chloride, the following was prepared

(*R*,*S*)-1-(methanesulphonyl)-4-(2-butyl-7-methoxy-benzofuran-4-yl)-pyrrolidine (15). ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7 Hz, 3H), 1.40 (m, 2H), 1.73 (m, 2H), 2.20 (m, 1H), 2.33 (m, 1H), 2.76 (t, J = 7 Hz, 2H), 2.85 (s, 3H), 3.36–3.50 (m, 2H), 3.60 (m, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 6.40 (s, 1H), 6.66 (d, J = 8 Hz, 1H), 6.94 (d, J = 8 Hz, 1H); MS (EI) m/z 351 $(M)^+$. Combustion analysis $C_{18}H_{25}O_4NS$ requires C 61.5, H 7.2, N 4.0. Found C 61.4, H 7.2, N 3.8.

(2-Butyl-7-methoxy-benzofuran-4-yl)-phenyl-ketone (16). To a cooled (10 °C) solution of phenylmagnesium chloride in THF (6 mL, 0.66 M) was added a solution containing **9c** (580 mg, 2.5 mmol) in THF (2 mL). The resulting solution was warmed to room temperature over 10 min then the reaction was quenched by adding dilute hydrochloric acid (0.1 M). The mixture was diluted with ether, washed with water, then brine, dried over $MgSO_4$ and concentrated. The residue was taken up in CH_2Cl_2 (7 mL) and pyridinium chlorochromate (590 mg, 2.75 mmol) added. The resulting mixture was stirred for 1 h then diluted with CH_2Cl_2 and poured onto a column of silica gel. The product was eluted with 10% ethyl acetate in hexanes to give **15**, 500 mg (86%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7 Hz, 3H), 1.44 (m, 2H), 1.75 (m, 2H), 2.83 (t, J = 7 Hz, 2H), 4.09 (s, 3H), 6.72 (d, J = 8 Hz, 1H), 6.96 (s, 1H), 7.5 (m, 4H), 7.77 (m, 2H); MS (EI) m/z 308 $(M)^+$.

1-(2-Butyl-7-methoxy-benzofuran-4-yl)-1-phenyl-2-pyridin-4-yl-ethanol (17). A solution of diisopropylamine (345 μL, 2.5 mmol) in THF (6 mL) was cooled to −10 °C and a solution of *n*-butyl lithium (0.96 mL, 2.5 M in hexanes) added dropwise. The resulting solution was stirred for 15 min then cooled to −78 °C and 4-picoline (235 μL, 2.4 mmol) in THF (1 mL) added dropwise. This solution was stirred for 30 min then a solution of **16** (500 mg, 1.6 mmol) in THF (1 mL) added. The resulting solution was stirred for 15 min then a sat. solution of ammonium chloride added. The reaction mixture was diluted with ether, washed with water, then brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography, eluting with 60% ethyl acetate in hexanes, to give 605 mg of **17** as a white solid (93%). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H), 1.32 (m, 2H), 1.60 (m, 2H), 2.35 (bs, 1H), 2.65 (t, J = 7 Hz, 2H), 3.60 (d, J = 15 Hz, 1H), 3.66 (d, J = 15 Hz, 1H), 4.00

(s, 3H), 6.06 (s, 1H), 6.65 (d, $J=8$ Hz, 1H), 6.76 (d, $J=5$ Hz, 2H), 7.18 (d, $J=8$ Hz, 1H), 7.3 (m, 5H), 8.30 (d, $J=5$ Hz, 2H); MS (EI) m/z 401 $(M)^+$.

1-(2-Butyl-7-methoxy-benzofuran-4-yl)-1-phenyl-2-pyridin-4-yl-ethane (18). To a solution of **17** (375 mg, 0.93 mmol) in CH_2Cl_2 (8 mL) was added TFA (1.5 mL). The resulting dark red solution was stirred for 10 min then a further portion of TFA (1.5 mL) added. This solution was stirred for 20 min then diluted with ether, washed with sodium bicarbonate, then brine, dried over $MgSO_4$ and concentrated. The residue was taken up in a solution of THF/MeOH (6 mL, 1/1). This solution was added to 10% Pd/C (60 mg) and the resulting suspension placed under an atmosphere of hydrogen. The reaction mixture was then heated to 55 °C and stirred at this temperature for 2.5 h then cooled to room temperature and filtered through Celite. The catalyst was washed with CH_2Cl_2 and the combined filtrates concentrated. The residue was purified by flash chromatography eluting with 40% ethyl acetate in hexanes to give 276 mg of **18** (77%). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, $J=7$ Hz, 3H), 1.36 (m, 2H), 1.65 (m, 2H), 2.70 (t, $J=7$ Hz, 2H), 3.39 (m, 2H), 3.94 (s, 3H), 4.41 (t, $J=7$ Hz, 1H), 6.20 (s, 1H), 6.65 (d, $J=8$ Hz, 1H), 6.89 (bd, $J=5$ Hz, 2H), 7.00 (d, $J=8$ Hz, 1H), 7.2 (m, 5H), 8.37 (bs, 2H); MS (EI) m/z 385 $(M)^+$. Combustion analysis $C_{26}H_{27}O_2N$ requires C 81.0, H 7.0, N 3.6. Found C 81.0, H 6.9, N 3.5.

The following compounds were prepared using essentially the same procedures.

1-(2-Butyl-7-methoxy-benzofuran-4-yl)-2-pyridin-4-yl-ethane (26a). ^{1}H NMR ($CDCl_3$) δ 0.95 (t, $J=7$ Hz, 3H), 1.41 (m, 2H), 1.74 (m, 2H), 2.79 (t, $J=7$ Hz, 2H), 2.94 (m, 2H), 3.05 (m, 2H), 4.00 (s, 3H), 6.31 (s, 1H), 6.62 (d, $J=8$ Hz, 1H), 6.81 (d, $J=8$ Hz, 1H), 7.07 (d, $J=5$ Hz, 2H), 8.46 (bd, $J=5$ Hz, 2H); MS (EI) m/z 309 $(M)^+$. Combustion analysis $C_{20}H_{23}O_2N$ requires C 77.6, H 7.5 N 4.5. Found C 77.7, H 7.5, N 4.5.

1-(2-Butyl-7-methoxy-benzofuran-4-yl)-2-pyridazin-4-yl-ethane (26b). ^{1}H NMR ($CDCl_3$) δ 0.93 (t, $J=7$ Hz, 3H), 1.40 (m, 2H), 1.70 (m, 2H), 2.75 (t, $J=7$ Hz, 2H), 2.95 (m, 2H), 3.05 (m, 2H), 3.95 (s, 3H), 6.25 (s, 1H), 6.60 (d, $J=8$ Hz, 1H), 6.71 (d, $J=8$ Hz, 1H), 7.09 (m, 1H), 8.95 (m, 2H); MS (EI) m/z 310 $(M)^+$. Combustion analysis $C_{19}H_{22}O_2N_2$ requires C 73.5, H 7.1 N 9.0. Found C 73.5, H 7.4, N 8.8.

1-(2-Butyl-7-methoxy-benzofuran-4-yl)-2-pyrimidin-4-yl-ethane (26c). ^{1}H NMR ($CDCl_3$) δ 0.93 (t, $J=7$ Hz, 3H), 1.40 (m, 2H), 1.70 (m, 2H), 2.75 (t, $J=7$ Hz, 2H), 3.09 (m, 2H), 3.15 (m, 2H), 3.95 (s, 3H), 6.32 (s, 1H), 6.60 (d, $J=8$ Hz, 1H), 6.81 (d, $J=8$ Hz, 1H), 6.98 (dd, $J=5$,1 Hz, 1H), 8.50 (d, $J=5$ Hz, 1H), 9.12 (d, $J=1$ Hz, 1H); MS (EI) m/z 310 $(M)^+$. Combustion analysis $C_{19}H_{22}O_2N_2$ requires C 73.5, H 7.1, N 9.0. Found C 73.5, H 7.2, N 8.8.

1-(2-Butyl-7-methoxy-benzofuran-4-yl)-2-[5-hydroxy-pyridin-2-yl]-ethane (26d). mp 127–128 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, $J=7$ Hz, 3H), 1.40 (m, 2H), 1.72 (m, 2H), 2.75 (t, $J=7$ Hz, 2H), 3.10 (bs, 4H), 3.95 (s, 3H), 6.46 (s, 1H), 6.60 (d, $J=8$ Hz, 1H), 6.85 (d, $J=8$ Hz, 1H), 7.02 (d, $J=8$ Hz, 1H), 7.21 (dd, $J=8$, 3 Hz, 1H), 8.26 (d, $J=3$ Hz, 1); MS (EI) m/z 325 $(M)^+$. Combustion analysis $C_{20}H_{23}O_3N$ requires C 73.8, H 7.1, N 4.3. Found C 73.5, H 7.0, N 4.2.

1-(2-Butyl-7-methoxy-benzofuran-4-yl)-2-[2-hydroxy-pyridin-4-yl]-ethane (26g). ^{1}H NMR ($CDCl_3$) δ 0.95 (t, $J=7$ Hz, 3H), 1.42 (m, 2H), 1.75 (m, 2H), 2.80 (m, 4H), 3.03 (t, $J=7$ Hz, 2H), 4.00 (s, 3H), 6.10 (d, $J=5$ Hz, 1H), 6.35 (s, 1H), 6.37 (s, 1H) 6.65 (d, $J=8$ Hz, 1H), 6.85 (d, $J=8$ Hz, 1H), 7.25 (d, $J=5$ Hz, 1H); MS (EI) m/z 325 $(M)^+$. Combustion analysis $C_{20}H_{23}O_3N$ requires C 73.8, H 7.1, N 4.3. Found C 73.9, H 7.1, N 4.3.

1-(2-Butyl-7-methoxy-benzofuran-4-yl)-2-pyridin-*N*-oxide-4-yl-ethane (26e). To a cooled (0 °C) solution of **26a** (788 mg, 2.5 mmol) in CH_2Cl_2 (12 mL) was added *m*-CPBA (615 mg, 75% technical grade). The resulting solution was stirred for 30 min then a further batch of *m*-CPBA (615 mg) added. This solution was stirred for 30 min then the reaction mixture poured onto a column of silica gel and the product eluted with 15% MeOH/25% CH_2Cl_2 in EtOAc to give 359 mg (44%) of **26e** as white solid. mp 73–75 °C; ^{1}H NMR (Acetone) δ 0.92 (t, $J=7$ Hz, 3H), 1.41 (m, 2H), 1.72 (m, 2H), 2.78 (t, $J=7$ Hz, 2H), 2.95 (m, 2H), 3.05 (m, 2H), 3.91 (s, 3H), 6.60 (s, 1H), 6.71 (d, $J=8$ Hz, 1H), 6.87 (d, $J=8$ Hz, 1H), 7.18 (bd, $J=5$ Hz, 2H), 8.00 (bd, $J=5$ Hz, 2H); MS (EI) m/z 325 $(M)^+$.

(2-Butyl-7-methoxy-benzofuran-4-yl)-ethene (20). To a cooled (0 °C) suspension of $(Ph_3P)CH_3Br$ (1.28 g, 3.6 mmol) THF (7 mL) was added $NaN(SiMe_3)_2$ (3.3 mL, 1 M in THF). The resulting yellow mixture was stirred for 25 min, then a solution of **9c** (690 mg, 3 mmol) in THF (3 mL) added in one portion. This suspension was stirred for 10 min then concentrated under vacuum. The residue was purified by flash chromatography, eluting with 20% ethyl acetate in hexanes to give 676 mg (98%) of **20** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.95 (t, $J=7$ Hz, 3H), 1.42 (m, 2H), 1.76 (m, 2H), 2.81 (t, $J=7$ Hz, 2H), 4.00 (s, 3H), 5.26 (d, $J=10$ Hz, 1H), 5.70 (d, $J=17$ Hz, 1H), 6.59 (s, 1H), 6.71 (d, $J=8$ Hz, 1H), 6.88 (dd, $J=17$, 10 Hz, 1H), 7.22 (d, $J=8$ Hz, 1H); MS (EI) m/z 230 $(M)^+$.

1-(2-Butyl-7-methoxy-benzofuran-4-yl)-2-(2-methoxy-pyridin-5-yl)-ethene (21). To a solution of **20** (676 mg, 2.94 mmol) in DMF (9 mL) was added 5-bromo-2-methoxy-pyridine (620 mg, 3.3 mmol), $(Ph_3P)PdCl_2$ (90 mg, 0.13 mmol) and Et_3N (1.5 mL, 11 mmol). The resulting solution was degassed, flushed with argon, then heated to 118 °C and stirred at this temperature for 4.5 h. The reaction mixture was then cooled to room temperature, diluted with ether, washed with water, then brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography, eluting with 10% ethyl acetate in hexanes, to give 369 mg (38%) of **21**. ^{1}H NMR ($CDCl_3$) δ 0.96 (t,

$J=7$ Hz, 3H), 1.43 (m, 2H), 1.77 (m, 2H), 2.83 (t, $J=7$ Hz, 2H), 3.97 (s, 3H), 4.03 (s, 3H), 6.65 (s, 1H), 6.78 (m, 2H), 7.00 (d, $J=16$ Hz, 1H), 7.15 (d, $J=16$ Hz, 1H), 7.30 (d, $J=8$ Hz, 1H), 7.83 (dd, $J=9$, 3 Hz, 1H), 8.23 (d, $J=3$ Hz, 1H); MS (EI) m/z 337 $(M)^+$.

1-(2-Butyl-7-methoxy-benzofuran-4-yl)-2-(2-hydroxy-pyridin-5-yl)-ethane (26f). To a solution of **21** (369 mg, 1.1 mmol) in THF/MeOH (4 mL, 1/1) was added 10% Pd/C (60 mg). The resulting suspension was stirred under an atmosphere of hydrogen for 4 h then filtered through Celite. The catalyst was washed with CH_2Cl_2 and the combined filtrates concentrated under vacuum. The residue was purified by flash chromatography, eluting with 10% ethyl acetate in hexanes, to give 309 mg of **23** (83%). ^{1}H NMR ($CDCl_3$) δ 0.95 (t, $J=7$ Hz, 3H), 1.42 (m, 2H), 1.74 (m, 2H), 2.77 (t, $J=7$ Hz, 2H), 2.87 (m, 2H), 3.00 (m, 2H), 3.90 (s, 3H), 4.00 (s, 3H), 6.30 (s, 1H), 6.64 (d, $J=8$ Hz, 1H), 6.64 (d, $J=8$ Hz, 1H), 6.82 (d, $J=8$ Hz, 1H), 7.3 (dd, $J=8$, 3 Hz, 1H), 7.93 (d, $J=3$ Hz, 1H); MS (EI) m/z 339 $(M)^+$). This material was then suspended in aqueous HCl (3 mL, 1.5 M) and the mixture heated to 80 °C and stirred at this temperature for 5.5 h. The resulting mixture was cooled to room temperature, diluted with ethyl acetate, washed with water, then brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography, eluting with ethyl acetate to give 248 mg (70% based on **20**) of **26g** as an oil. ^{1}H NMR ($CDCl_3$) δ 0.95 (t, $J=7$ Hz, 3H), 1.42 (m, 2H), 1.74 (m, 2H), 2.68–2.81 (m, 4H), 2.92 (t, $J=7$ Hz, 2H), 4.00 (s, 3H), 6.30 (s, 1H), 6.50 (d, $J=9$ Hz, 1H), 6.61 (d, $J=8$ Hz, 1H), 6.77 (d, $J=8$ Hz, 1H), 7.04 (d, $J=2$ Hz, 1H), 7.28 (dd, $J=9$, 2 Hz, 1H); MS (EI) m/z 325 $(M)^+$. Combustion analysis $C_{20}H_{23}O_3N$ requires C 73.8, H 7.1, N 4.3. Found C 74.0, H 7.2, N 4.2.

3-(2-Butyl-7-methoxy-benzofuran-4-yl)-propionic acid methyl ester (24). A solution of **22** (2.4 g, 8.3 mmol) in THF/MeOH (20 mL, 1/1) was added to 10% Pd/C (350 mg) and the resulting suspension stirred under a hydrogen atmosphere for 3 h then filtered through Celite. The catalyst was washed with CH_2Cl_2 and the combined filtrates concentrated under vacuum. The residue was purified by flash chromatography, eluting with 10% ethyl acetate in hexanes to give 2.31 g of **24** (96%). ^{1}H NMR ($CDCl_3$) δ 0.92 (t, $J=7$ Hz, 3H), 1.40 (m, 2H), 1.73 (m, 2H), 2.65 (t, $J=7$ Hz, 2H), 2.77 (t, $J=7$ Hz, 2H), 3.05 (t, $J=7$ Hz, 2H), 3.65 (s, 3H), 3.98 (s, 3H), 6.39 (s, 1H), 6.64 (d, $J=8$ Hz, 1H), 6.90 (d, $J=8$ Hz, 1H); MS (EI) m/z 290 $(M)^+$.

5-(2-Butyl-7-methoxy-benzofuran-4-yl)-3-oxo-pentanoic acid ethyl ester (25). To a cooled (−78 °C) solution of LDA (5.8 mL, 1.5 M in cyclohexane) in THF (15 mL) was added, dropwise, a solution of ethyl acetate (0.85 mL, 8.7 mmol) in THF (5 mL). The resulting solution was stirred for 20 min then a solution of **23** (2.26 g, 7.8 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 15 min then the cold bath removed and stirring continued until the reaction mixture reached ambient temperature. Water was then added and the mixture diluted with ether, washed with water, then brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography, eluting with 20% ether in hexanes, to give 527 mg of **25** ^{1}H NMR ($CDCl_3$) δ 0.92 (t, $J=7$ Hz, 3H), 1.25 (t, $J=7$ Hz, 3H) 1.44 (m, 2H), 1.76 (m, 2H), 2.80 (t, $J=7$ Hz, 2H), 2.90 (m, 2H), 3.03 (m, 2H), 3.45 (s, 2H), 4.00 (s, 3H), 4.17 (q, $J=7$ Hz, 2H), 6.40 (s, 1H), 6.63 (d, $J=8$ Hz, 1H), 6.88 (d, $J=8$ Hz, 1H); MS (EI) m/z 346 $(M)^+$.

5-[2-(2-butyl-7-methoxy-benzofuran-4-yl)-ethyl]-1,2-dihydro-pyrazol-3-one (26h). To a solution of **25** (440 mg, 1.27 mmol) in $MeOH/H_2O$ (5.5 mL 10/1) was added hydrazine hydrate (89 μL, 2.54 mmol). The resulting mixture was stirred for 15 min, then neutralized with 1 M HCl. This mixture was diluted with water and filtered to give 283 mg (71%) of **26h** as a solid. mp 222 223 °C; ^{1}H NMR (DMSO) δ 0.93 (t, $J=7$ Hz, 3H), 1.37 (m, 2H), 1.69 (m, 2H), 2.75 (m, 4H), 2.95 (m, 2H), 3.34 (s, 1H), 3.89 (s, 3H), 5.27 (s, 1H), 6.67 (s, 1H), 6.74 (d, $J=8$ Hz, 1H), 6.90 (d, $J=8$ Hz, 1H); MS (EI) m/z 314 $(M)^+$. Combustion analysis $C_{18}H_{22}O_3N_2$ requires C 68.8, H 7.0, N 8.9. Found C 68.5, H 7.0, N 8.8.

Biological assays

Inhibition of guinea pig PDE4 in vitro was measured according to the published procedure.[17]

Murine endotoxemia model. Compounds were administered orally in a vehicle of 0.5% methylcellulose/0.2% Tween-80 in water to male, Balb/c mice (20–25 g, Taconic Labs.) 4 h prior to challenge with LPS (*E. coli* 055:B5, Sigma Chemical Co., St. Louis, MO, 30 μg/mouse by intraperitoneal injection). Ninety minutes following LPS challenge, mice were anesthetized with Isoflurane and blood was collected by cardiac puncture. The whole blood was allowed to clot on ice and serum was prepared by centrifugation at $200\times g$ for 10 min. Serum was assayed for TNF-α by ELISA (Genzyme Corp., Cambridge, MA). Dose response curves were generated in duplicate from $n=4$–6 mice per dose.

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References and Notes

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20. This compound was prepared in the same way as **26a**, except using 3-cyclopentoxy-4-methoxy-benzaldehyde as starting material instead of **9c**.