Synthesis of 2-Phenylbenzofuran Derivatives as Testosterone 5α-Reductase Inhibitor

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Received September 11, 1998; accepted November 20, 1998

A series of 2-phenylbenzofuran derivatives with a carbamoyl, alkylamino, or alkyloxy group at the 5 or 6 position of the benzofuran ring were synthesized and evaluated for rat and human testosterone 5α-reductase inhibitory activities *in vitro*. Against rat enzyme, the carbamoyl derivatives had more potent inhibitory activities than the alkylamino or alkyloxy derivatives, and the 6-carbamoyl derivatives tended to be more potent than the 5-carbamoyl derivatives. Against human enzyme, the 6-substituted derivatives had more potent inhibitory activities than the 5-substituted derivatives. The 6-carbamoyl and 6-alkylamino derivatives tended to show stronger inhibitory activities against human type 1 enzyme than against type 2 enzyme, but they were not largely selective.

Key words 2-phenylbenzofuran; testosterone 5α-reductase inhibitor; benign prostatic hyperplasia

Testosterone is an androgenic hormone essential for maintaining the function of the male body. Testosterone is converted to an active androgen, dihydrotestosterone (DHT), which binds to an androgen receptor and forms a complex showing various hormonal actions. Testosterone 5α-reductase catalyzes the conversion of testosterone to DHT. Although DHT plays an important role in maintaining the prostate tissues, its excessive accumulation in the prostate causes hyperplastic growth of this organ. Benign prostatic hyperplasia (BPH) is a disease involving urinary dysfunction which is thought to be mediated by DHT.[1] The reduction of DHT concentration by inhibition of 5α-reductase can control the hyperplastic prostate growth and improve the pathology of BPH. Testosterone 5α-reductase inhibitors of potential use as medicines for the treatment of BPH have been investigated and reported. There are both steroidal inhibitors,[2] including MK 906 (Proscar®, Fig. 1), and non-steroidal ones.[3]

In recent research on a non-steroidal inhibitor, several potent inhibitors including ONO 3805[3f] and FK 143[3g] were found (Fig. 1). To avoid the undesired hormonal action potentially exhibited by steroidal compounds, it would be of great significance to develop a non-steroidal inhibitor which is clinically as effective as MK 906. We have already disclosed that the *N*-diphenylmethylcarbamoylandrostane-3-carboxylic acid compound **1a** (Fig. 1) shows potent inhibitory activity against rat and human 5α-reductase.[4] We planned to find a novel non-steroidal inhibitor by replacing the androstane structure with a non-steroidal one. We evaluated inhibitory activities against rat 5α-reductase in several simple carboxylic acids with a diphenylmethylcarbamoyl group and found that 4-carboxy-4′-(*N*-diphenylmethylcarbamoyl)-*trans*-stilbene **1b** (Fig. 1) showed inhibitory activity; inhibition (%) at 10^{-6} M was 29% and 84% against rat and human enzyme, respectively. In order to find a more potent inhibitor, we attempted to fix a conformation by converting the stilbene structure to a more rigid ring structure, 2-phenylbenzofuran. In our previous paper, we reported the synthesis and 5α-reductase inhibitory activities of 2-phenylbenzofuran derivatives with a diphenylmethylcarbamoyl group.[5] We herein describe the synthesis of a series of 2-phenylbenzofuran derivatives with a alkylcarbamoyl, alkylamino, or alkyloxy group and their inhibitory activities against rat and human 5α-reductase in detail. The activities against human type 1 and type 2 5α-reductase of several derivatives are also discussed.

Chemistry The synthetic route of the 2-phenyl-5-carbamoylbenzofuran derivatives with a carboxy or carboxy-

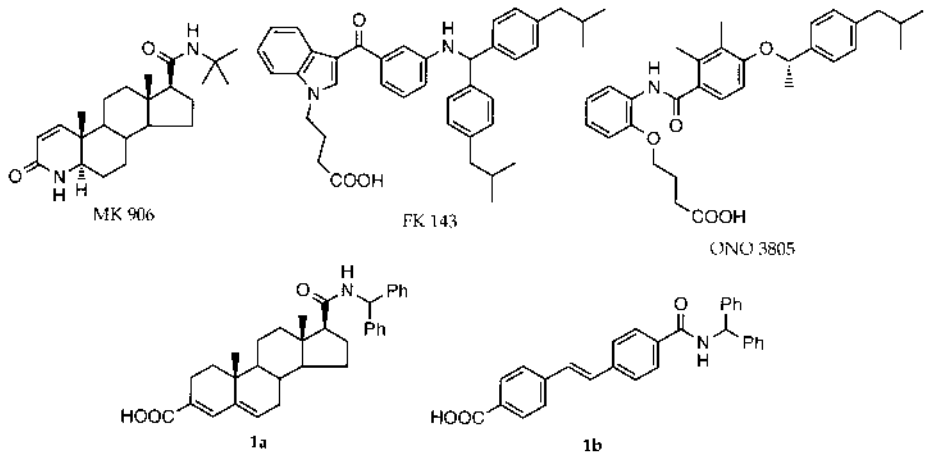

Fig. 1

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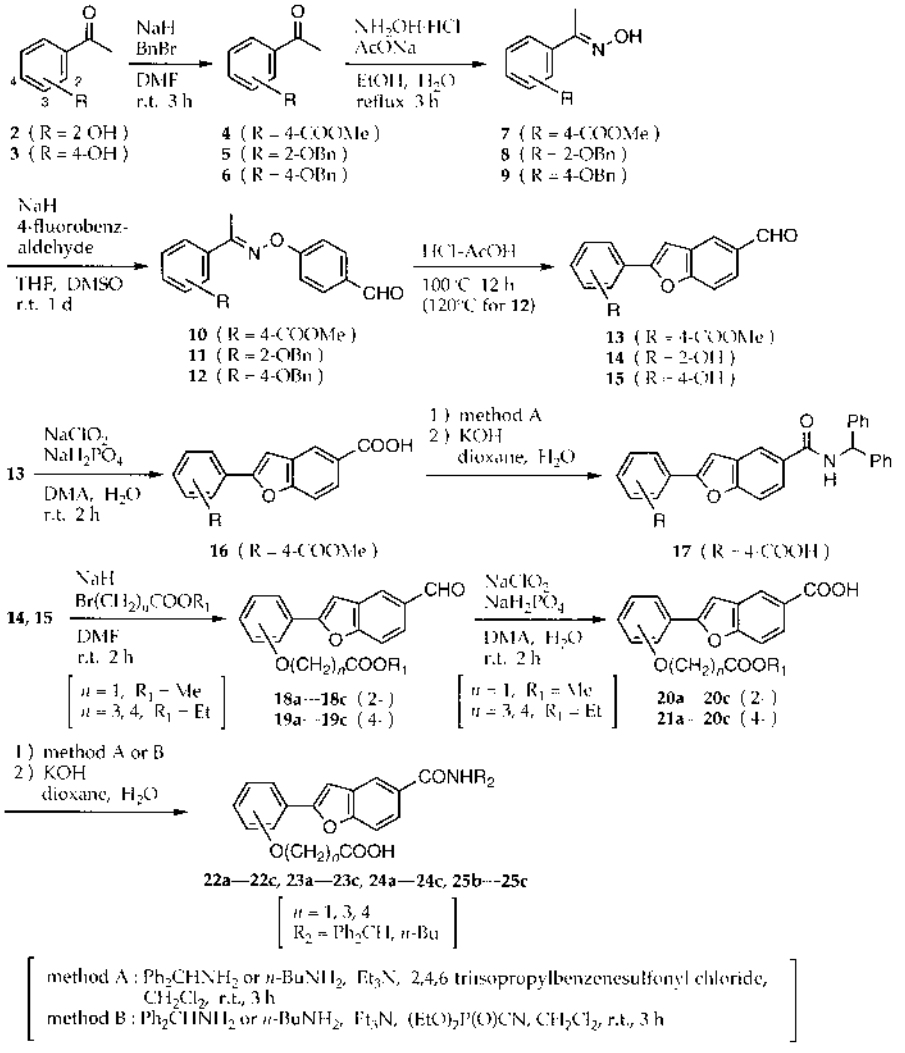


Chart 1

alkyloxy group at the 2- or 4-position of the phenyl moiety is shown in Chart 1. Hydroxyacetophenones (**2**, **3**) were alkylated with benzyl bromide in the presence of NaH in *N*,*N*-dimethylformamide (DMF) to give the benzyloxyacetophenone **5** and **6**, and then treatment of **5** and **6** with hydroxylamine yielded the oximes **8** (94% yield) and **9** (91%), respectively. Similarly, the oxime **7** was produced by reacting 4′-methoxycarbonylacetophenone (**4**) with hydroxylamine in 94% yield. The sodium salts of **7**, **8**, and **9** were reacted with 4-fluorobenzaldehyde in tetrahydrofuran (THF) and dimethylsulfoxide (DMSO) to give the *O*-phenyl oximes **10**, **11**, and **12** (47—55%). According to the method of Mooradian and Dupont,[6] heating a solution of the oximes **10**, **11**, and **12** in HCl-AcOH solution at 100—120 °C induced cyclization of the furan ring and yielded the 2-phenyl-5-formylbenzofuran compounds **13**, **14**, and **15** (5—54%). Compound **13** was oxidized with $NaClO_2$ to afford the carboxylic acid **16** (90%). Condensation reaction of **16** with diphenylmethylamine in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride[7] and triethylamine, followed by hydrolysis of the ester group with KOH in aqueous dioxane afforded 4-[5-(*N*-diphenylmethylcarbamoyl)benzofuran-2-yl]benzoic acid (**17**) (49%). Compounds **14** and **15** were alkylated with the ester of bromoalkylcarboxylic acid in the presence of NaH in DMF to give the 2-(2-alkyloxyphenyl)benzofuran compounds **18a**—**18c** (79—86% from **14**) and **19a**—**19c** (33—80% from **15**), respectively. The formyl groups of **18a**—**18c** and **19a**—**19c** were oxidized with $NaClO_2$ to yield the carboxylic acids **20a**—**20c** (88—99% from **18a**—**18c**) and **21a**—**21c** (64—93% from **19a**—**19c**), respectively. Condensation reaction of the carboxylic acids **20a**—**20c** and **21a**—**21c** with diphenylmethylamine or *n*-butylamine using 2,4,6-triisopropylbenzenesulfonyl chloride or diethyl cyanophosphonate (DEPC) gave the corresponding amides, and these amides were hydrolyzed with KOH in aqueous dioxane to yield the 2-phenyl-5-carbamoylbenzofuran derivatives **22a**—**22c** (60—89% from **20a**—**20c**), **23a**—**23c** (61—92% from **20a**—**20c**), **24a**—**24c** (47—88% from **21a**—**21c**), and **25b**—**25c** (58—65% from **21b**—**21c**) shown in Table 1.

The synthetic route of the 2-phenyl-5-carbamoylbenzofuran derivatives with a carboxyalkyloxy group at the 3-position of the phenyl moiety is shown in Chart 2. Benzyloxyacetophenone was produced by alkylating 3-hydroxyacetophenone (**26**) with benzyl bromide in the presence of NaH in DMF and it was then converted to the oxime. The reaction of the oxime with 4-fluorobenzaldehyde using NaH yielded the *O*-phenyl oxime **27** (58% from **26**). Cyclization induced by heating a solution of **27** in HCl-AcOH solution at 100 °C for

3 h gave 5-formylbenzofuran compound **28**[8] (43%), and oxidation of **28** with $NaClO_2$ yielded the carboxylic acid **29** (93%). Hydrogenolysis of the benzyloxy group of **29** followed by protection of the phenolic hydroxy group afforded the benzofurancarboxylic acid compound **30** (70%). Condensation of **30** with diphenylmethylamine or *n*-butylamine using DEPC followed by desilylation gave the amides **31** (21%) and **32** (37%), respectively. Treatment of **31** and **32** with the ester of bromoalkylcarboxylic acid in the presence of NaH in DMF yielded the 2-(3-alkyloxyphenyl)benzofuran compounds and hydrolysis of these compounds gave the 5-carbamoylbenzofuran derivatives **33a**—**33c** (39—69% from **31**) and **34a**—**34c** (41—49% from **32**) shown in Table 2.

The synthetic route of the 2-(3-carboxypropyloxy)phenyl-5-carbamoylbenzofuran derivatives is shown in Chart 3. The carboxylic acid **20b** was reacted with the corresponding amines in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride and triethylamine to give the amides and the ester group of the amides were hydrolyzed with KOH in aqueous dioxane to yield the 5-carbamoylbenzofuran derivatives **35a**—**35c** (86—92%) shown in Table 3.

The 6-carbamoylbenzofuran derivatives were synthesized

Table 1

Compound	Substitution	*n*	R_2	Method	Yield (%)
22a	2-	1	Ph_2CH	A	76
22b	2-	3	Ph_2CH	A	89
22c	2-	4	Ph_2CH	A	60
23a	2-	1	*n*-Bu	A	61
23b	2-	3	*n*-Bu	A	92
23c	2-	4	*n*-Bu	A	63
24a	4-	1	Ph_2CH	B	47
24b	4-	3	Ph_2CH	B	88
24c	4-	4	Ph_2CH	B	48
25b	4-	3	*n*-Bu	B	65
25c	4-	4	*n*-Bu	B	58

Table 2

Compound	*n*	R	Yield (%)
33a	1	Ph_2CH	69
33b	3	Ph_2CH	39
33c	4	Ph_2CH	57
34a	1	*n*-Bu	41
34b	3	*n*-Bu	41
34c	4	*n*-Bu	49

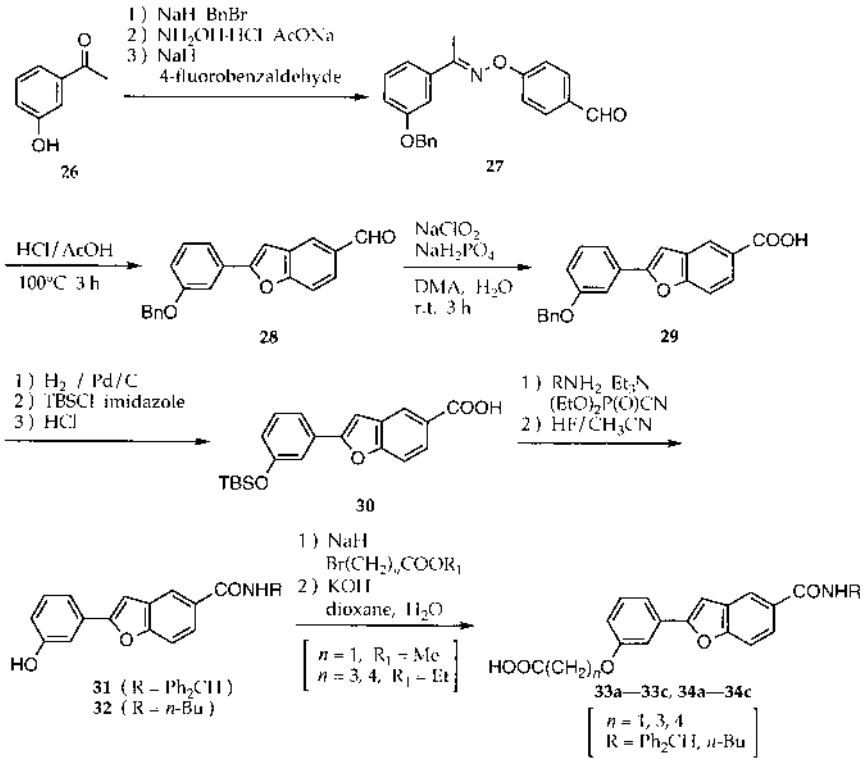


Chart 2

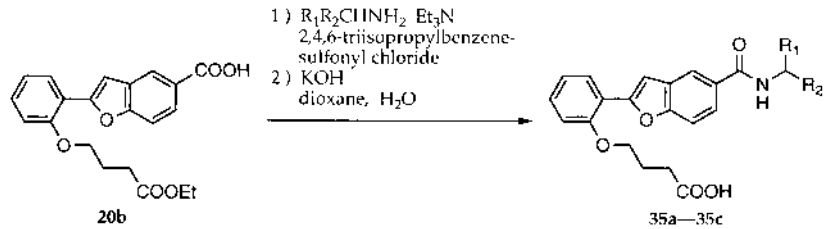


Chart 3

Table 3

Compound	R_1	R_2	Yield (%)
35a	4-F-Ph	4-F-Ph	90
35b	4-MeO-Ph	4-MeO-Ph	92
35c	Ph	$PhCH_2$	86

Table 4. Cyclization Reaction of **40a**, **40b**

Condition	Substrate	Product	Yield (%)
a) LiCl DMPU 160 °C 15 h	**40b**	**41b**	21
b) Pyridinium chloride 200 °C 2 h	**40b**	**41a**	76
c) Pyridinium chloride 200 °C 2 h	**40a**	**41a**	45

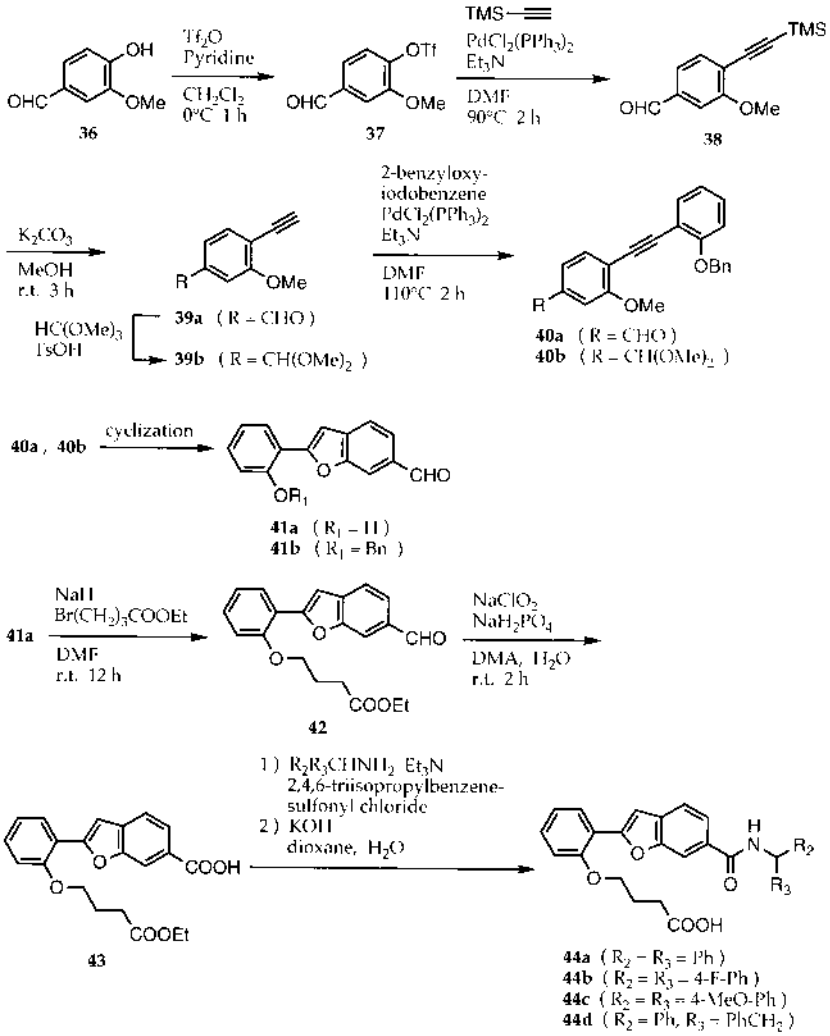


Chart 4

by the method shown in Chart 4. Vanillin (**36**) was treated with trifluoromethanesulfonic anhydride in the presence of pyridine to give the triflate **37** (97%), and **37** was reacted with trimethylsilylacetylene in the presence of a catalytic amount of $PdCl_2(Ph_3P)_2$ in DMF containing triethylamine at 90 °C to produce the coupling product **38** (74%). Desilylation of **38** using K_2CO_3 and MeOH gave the ethynyl compound **39a** (75%). The coupling reaction of **39a** and 2-benzyloxyiodobenzene using a catalytic amount of $PdCl_2(Ph_3P)_2$ in DMF at 110 °C gave the diphenylacetylene compound **40a** (34%). The same reaction of the dimethylacetal analogue **39b** synthesized from **39a** also yielded a coupling product **40b** (40%).

Next, cyclization of the furan ring was attempted. The results are shown in Table 4. According to the method of Hiroya *et al.*,[9] heating **40b** in the presence of LiCl at 160 °C in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) induced demethylation of the methoxy group and subsequent furan ring cyclization to produce the 2-phenyl-6-formylbenzofuran derivative **41b** (21%). We were able to obtain the desired benzofuran compound but this reaction was not efficient because the reaction time was long and the yield was low. Therefore, demethylation using some other dealkylating reagents was attempted. Among the reagents used, pyridinium chloride[10] was the most effective. By heating a mixture of **40b** and pyridinium chloride at 200 °C in the absence of solvent, demethylation and subsequent cyclization occurred and the benzofuran compound **41a** was given in

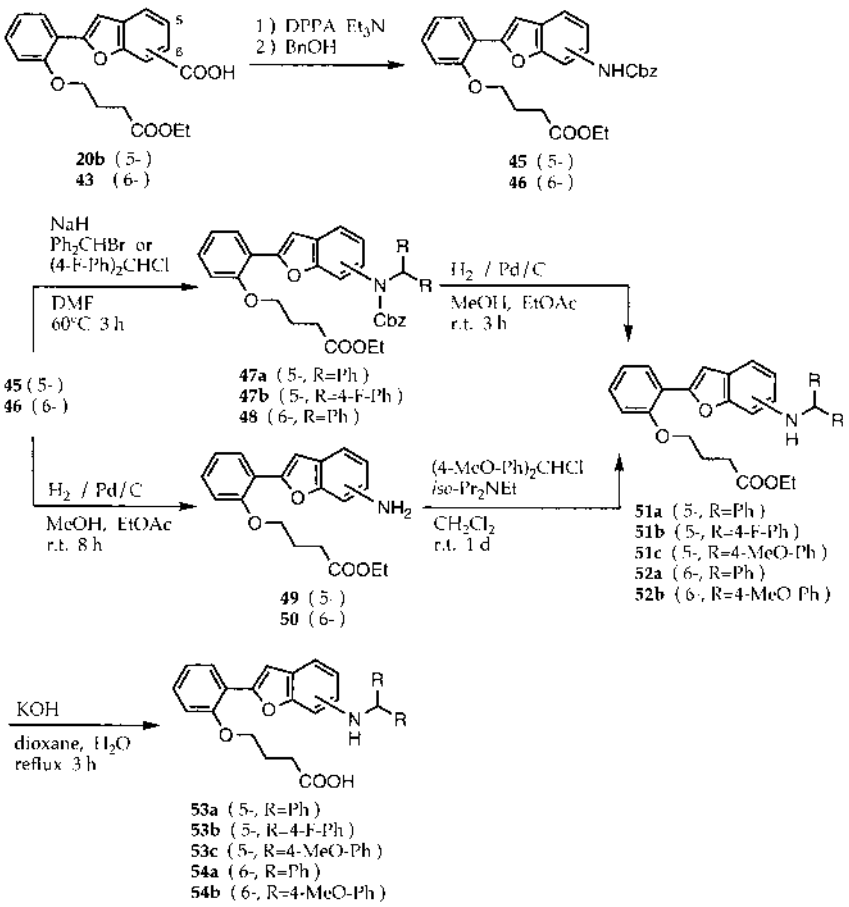


Chart 5

76% yield. In this reaction, debenzylation of the benzyloxy group occurred simultaneously. The formyl compound **40a** also afforded the cyclized product **41a** under the same reaction condition in 45% yield.

Finally, a butyric acid group was introduced. Alkylation of the sodium salt of **41a** with ethyl 4-bromobutyrate gave the *O*-alkyl compound **42** (75%) and **42** was oxidized to the carboxylic acid **43** (75%). Condensation reaction of **43** with several amines using 2,4,6-triisopropylbenzenesulfonyl chloride gave the amide compounds, and hydrolysis of the ester groups yielded the 2-phenyl-6-carbamoylbenzofuran derivatives **44a**—**44d** (69—89%).

The synthetic route of the 5- or 6-alkylaminobenzofuran derivatives is shown in Chart 5. The Curtius rearrangement of the carboxylic acids **20b** and **43** using diphenylphosphoryl azide (DPPA) and benzylalcohol gave the benzyloxycarbonylamino compounds **45** (74%) and **46** (53%). Treatment of **45** and **46** with diphenylmethyl bromide or 4,4′-difluorodiphenylmethyl chloride in the presence of NaH in DMF gave the *N*-alkyl compounds **47a** (80%), **47b** (91%), and **48** (76%), and hydrogenolysis of **47a**, **47b**, and **48** afforded the alkylamino compounds **51a** (58%), **51b** (81%), and **52a** (69%). Hydrolysis of the ester groups of **51a**, **51b**, and **52a** gave the 5- or 6-alkylaminobenzofuran derivatives **53a** (97%), **53b** (85%) and **54a** (59%). The 4,4′-dimethoxydiphenylmethylamino derivatives were synthesized by the following method. Hydrogenolysis of the benzyloxycarbonylamino compounds **45** and **46** gave the amino compounds **49** (85%) and **50** (80%). Treatment of **49** and **50** with 4,4′-dimethoxydiphenylmethyl chloride in the presence of *N*,*N*-diisopropylethylamine gave the *N*-alkyl compounds **51c** (45%) and **52b** (62%), and hydrolysis of **51c** and **52b** yielded the 5- or 6-(4,4′-dimethoxydiphenylmethylamino)benzofuran derivatives **53c** (94%) and **54b** (86%).

The synthetic route of the 5-diphenylmethyloxybenzofuran derivative is shown in Chart 6. The 5-aminobenzofuran compound **49** was treated with $NaNO_2$ and heated at 80 °C in diluted aqueous H_2SO_4 solution to give 5-hydroxybenzofuran derivative *via* diazonium salt. Under this reaction condition, the ester group was hydrolyzed simultaneously. The carboxylic acid group was converted to the methyl ester group to yield **55** (21%). Treatment of **55** with diphenylmethyl bromide in the presence of NaH gave the diphenylmethyloxy compound **56** (61%) and hydrolysis of **56** yielded the 5-diphenylmethyloxybenzofuran derivative **57** (98%).

Results and Discussion

The synthesized 2-phenylbenzofuran derivatives were evaluated for inhibitory activities against rat and human testosterone 5α-reductase *in vitro* using the standard method.[4b] The preparation of recombinant human type 1 and type 2 5α-reductase and the biological assay using human recombinant enzyme were carried out according to the protocol described in the experimental section. At first, we replaced the stilbene structure of the compound **1b** with the 2-phenylbenzofuran structure. Unexpectedly, the 4-(5-carbamoylbenzo[*b*]furan-2-yl)benzoic acid **17** showed no inhibitory activity against rat 5α-reductase. A molecular model inspection indi-

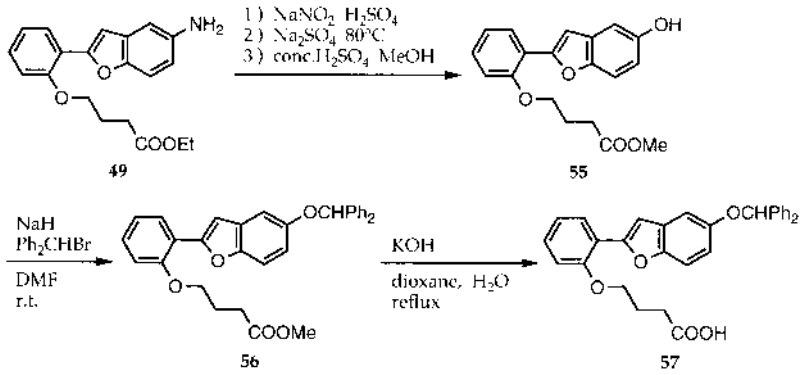
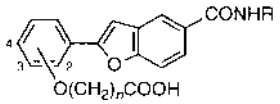


Chart 6

Table 5. Inhibitory Activities of the 5-Carbamoyl-2-phenylbenzofuran Derivatives against Rat 5α-Reductase (*in Vitro*)

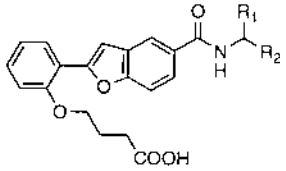


Substitution	n	Inhibition (%) at 10^{-6} M			
		Compound	[R=Ph_2CH]	Compound	[R=*n*-Bu]
4-COOH		**17**	0		
2-	1	**22a**	1	**23a**	1
2-	3	**22b**	51	**23b**	22
2-	4	**22c**	0	**23c**	10
3-	1	**33a**	32	**34a**	8
3-	3	**33b**	10	**34b**	6
3-	4	**33c**	7	**34c**	5
4-	1	**24a**	11		
4-	3	**24b**	2	**25b**	0
4-	4	**24c**	3	**25c**	1

cated that the spatial arrangement of the carboxyl group and the diphenylmethylcarbamoyl group of **17** was not completely in accordance with that of the two functional groups of **1b**. Therefore, we synthesized and evaluated 2-phenylbenzofuran compound with an alkyl carboxylic acid group at the 2-, 3-, or 4-position of the phenyl moiety.

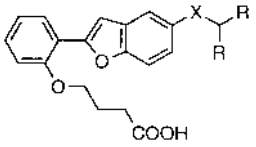
The inhibitory activities of the 5-carbamoylbenzofuran derivatives against rat 5α-reductase are shown in Table 5. Among the derivatives with a carboxymethyloxy, carboxypropyloxy, or carboxybutyloxy group at the 2-, 3-, or 4-position of the phenyl moiety, **22b**, which has a carboxypropyloxy group at the 2-position, showed the most potent inhibitory activity, and its activity against rat enzyme exceeded that of **1b**. The corresponding 5-[*N*-(1-butyl)carbamoyl]benzofuran derivative **23b** was less potent than **22b**. This result indicated that a diphenylmethyl group is effective in showing potent inhibitory activities in these benzofuran derivatives. Next, the 3-carboxypropyloxyphenyl group was fixed and the carbamoyl group was modified. The inhibitory activities of the 2-(3-carboxypropyloxy)phenyl-5-carbamoylbenzofuran derivatives are shown in Table 6. Although an introduction of a fluoro group on the phenyl groups of the carbamoyl moiety of **22b** reduced the inhibitory activity against rat enzyme (the compound **35a**), an introduction of a methoxy group increased the potency (the compound **35b**). The 1,2-diphenylethylcarbamoyl derivative **35c** had moderate inhibitory

Table 6. Inhibitory Activities of the 5-Carbamoyl-2-phenylbenzofuran Derivatives against Rat and Human 5α-Reductase (*in Vitro*)



Compound	R_1	R_2	Rat IC_{50} (nM)	Human Inhibition (%) at 10^{-6} M
22b	Ph	Ph	155	3
35a	4-F-Ph	4-F-Ph	279	2
35b	4-MeO-Ph	4-MeO-Ph	26.3	5
35c	Ph	$PhCH_2$	247	8

Table 7. Inhibitory Activities of the 5-Diphenylmethylamino or 5-Diphenylmethyloxy-2-phenylbenzofuran Derivatives against Rat and Human 5α-Reductase (*in Vitro*)



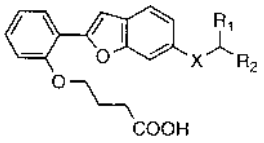
Compound	X	R	Rat IC_{50} (nM)	Human Inhibition (%) at 10^{-6} M
53a	NH	Ph	344	0
53b	NH	4-F-Ph	420	0
53c	NH	4-MeO-Ph	76	0
57	O	Ph	(45.4)[a]	0
22b	CONH	Ph	155	3

a) Inhibition (%) at 10^{-6} M

activity but was less potent than **22b**. On the other hand, these 5-carbamoyl derivatives showed little inhibitory activities against human enzyme.

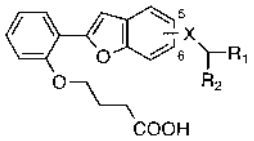
Inhibitory activities of the 5-alkylamino or 5-alkyloxy derivatives are shown in Table 7. Against rat enzyme, the diphenylmethylamino derivative **53a** and the fluoro-substituted derivative **53b** had moderate inhibitory activities and the methoxy-substituted derivative **53c** was the most potent. But all the 5-alkylamino derivatives were less potent than the corresponding 5-carbamoyl derivatives. These compounds also had no activities against human enzyme. The 5-diphenylmethyloxy derivative **57** had moderate inhibitory ac-

Table 8. Inhibitory Activities of the 6-Carbamoyl or 6-Diphenylmethylamino-2-phenylbenzofuran Derivatives against Rat and Human 5α-Reductase (*in Vitro*)



Compound	X	R_1	R_2	Rat IC_{50} (nM)	Human Inhibition (%) at 10^{-6} M
44a	CONH	Ph	Ph	29	73
44b	CONH	4-F-Ph	4-F-Ph	38	54
44c	CONH	4-MeO-Ph	4-MeO-Ph	36	44
44d	CONH	Ph	$PhCH_2$	87	87
54a	NH	Ph	Ph	1120	92
54b	NH	4-MeO-Ph	4-MeO-Ph	1260	36

Table 9. Inhibitory Activities of the 2-Phenylbenzofuran Derivatives against Human Type 1 and Type 2 5α-Reductase (*in Vitro*)



Compound	Substitution	X	R_1	R_2	IC_{50} (nM)	
					Type 1	Type 2
22b	5	CONH	Ph	Ph	310	$>10^5$
44a	6	CONH	Ph	Ph	62	270
44b	6	CONH	4-F-Ph	4-F-Ph	50	340
44c	6	CONH	4-MeO-Ph	4-MeO-Ph	130	930
44d	6	CONH	Ph	$PhCH_2$	53	72
54a	6	NH	Ph	Ph	32	30
54b	6	NH	4-MeO-Ph	4-MeO-Ph	42	480
FK143					3.0	11

tivity against rat enzyme and no activity against human enzyme.

Inhibitory activities of the 6-carbamoyl or 6-alkylamino derivatives are shown in Table 8. Against rat enzyme, the 6-diphenylmethylcarbamoyl derivative **44a**, the fluoro-substituted derivative **44b**, and the methoxy-substituted derivative **44c** showed highly potent inhibitory activities. The 6-(1,2-diphenylethyl)carbamoyl derivative **44d** was slightly less potent than **44a**. The 6-carbamoyl derivatives tended to be more potent than the corresponding 5-carbamoyl derivatives. The 6-alkylamino derivatives **54a** and **54b** had only weak activities. Against human enzyme, the 6-diphenylmethylcarbamoyl derivative **44a** and the 6-(1,2-diphenylethyl)carbamoyl derivative **44d** showed potent inhibitory activities. The introduction of a fluoro or methoxy group on the phenyl moiety of the diphenylmethyl group of **44a** slightly reduced the inhibitory activities (the compounds **44b** and **44c**). The 6-diphenylmethylamino derivative **54a** had highly potent activity comparable to that of **44a**, but the methoxy-substituted 6-diphenylmethylamino derivative **54b** had weak activity.

Against rat enzyme, the carbamoyl-substituted derivatives were more potent than the alkylamino and alkyloxy compounds and the 6-carbamoyl derivatives tended to be more active than the 5-carbamoyl derivatives. Against human enzyme, although the 5-substituted derivatives had no inhibitory activities, the 6-substituted derivatives showed potent activities. The derivatives with potent activities against human enzyme were evaluated for selectivity in the inhibition against human type 1 and type 2 5α-reductase. The results are shown in Table 9. The 5-diphenylmethylcarbamoyl derivative **22b** had moderate inhibitory activity against human type 1 enzyme and no activity against type 2 enzyme. The 6-carbamoyl derivatives **44a**, **44b**, and **44c** showed potent inhibitory activities against type 1 enzyme and moderate activities against type 2 enzyme. They were 4—7 times more potent against type 1 enzyme than against type 2 enzyme. The 6-(1,2-diphenylethyl)carbamoyl derivative **44d** and the 6-diphenylmethylamino derivative **54a** showed potent inhibitory activities against both type 1 and type 2 enzymes. Among the synthesized benzofuran derivatives, **54a** was the most potent against both enzymes. The methoxy-substituted 6-diphenylmethylamino derivative **54b** was as active against type 1 enzyme as **54a** but the activity of **54b** against type 2 enzyme was lower than that of **54a**.

The X-ray crystal structure of the methoxy-substituted 6-diphenylmethylcarbamoyl derivative **44c** is shown in Fig. 2.[11] The butyric acid group is on the opposite side against the furan oxygen. The stable conformations of the 6-diphenylmethylcarbamoyl derivative **44a** were calculated based on the X-ray structure of **44c**.[12] The stable conformations of **44a** are shown in Fig. 3. The locations of the diphenylmethyl group in the conformations shown in **44a-1**

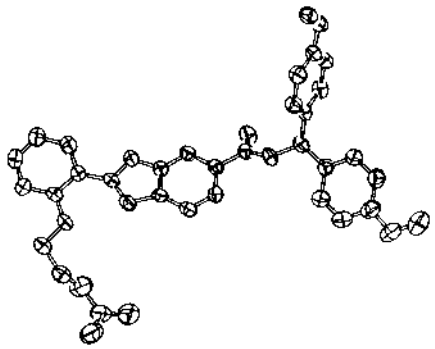


Fig. 2. Structure of **44c** Obtained by X-Ray Crystallographic Analysis

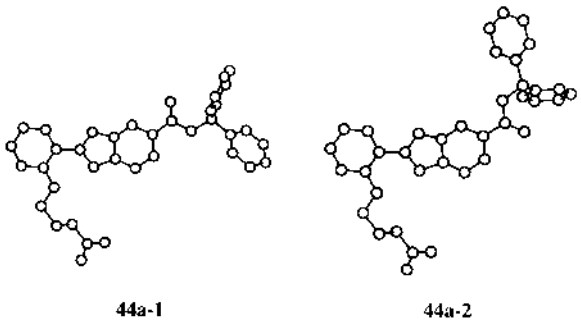


Fig. 3. Stable Conformations of **44a**

and **44a-2** are exceedingly different and there is little energy difference between these two conformations. This result indicates that the 6-carbamoyl group of **44a** can be located over a wide area in the region at the side of the oxygen of the benzofuran ring. The 5-carbamoyl derivatives, however, cannot place the 5-carbamoyl group at the side of the furan-oxygen. The distinct difference between the 5- and 6-carbamoyl derivatives in their inhibitory activities against human 5α-reductase is thought to derive from these structural differences.

In conclusion, a series of novel benzofuran derivatives with a carbamoyl, alkylamino, or alkyloxy group at the 5 or 6 position were synthesized, and their inhibitory activities against rat and human testosterone 5α-reductase were tested *in vitro*. Against rat enzyme, the 5- or 6-carbamoylbenzofuran derivatives showed potent inhibitory activities and the alkylamino and alkyloxy derivatives had moderate potency. Against human enzyme, the 6-substituted derivatives tended to be more potent than the 5-substituted derivatives. The derivatives had slight selectivity in the inhibition against human type 1 and type 2 5α-reductase and several compounds showed potent inhibitory activities against both types of enzymes.

Experimental

Melting points were taken on a micro melting point apparatus (Yanaco) and are uncorrected. ^{1}H-NMR spectra were obtained on a JEOL JNM-GX270 or JNM-EX270 spectrometer (270 MHz) using tetramethylsilane as an internal standard. Chemical shifts are given in δ values (ppm). IR spectra were recorded on a JASCO FT/IR8300 or JASCO FT/IR8900 spectrometer. Thin-layer chromatography was run on silica gel-coated plates (E. Merck, Silica gel 60F_{254} precoated) with a thickness of 0.25 mm. Silica gel 60 (E. Merck, 230—400 mesh) was used for column chromatography.

2′-Benzyloxyacetophenone (5) NaH (55%, 6.63 g, 152 mmol) was added to a solution of 2′-hydroxyacetophenone **2** (19.0 g, 140 mmol) in DMF (300 ml) under N_2 atmosphere and the mixture was stirred at room temperature for 15 min. Then, benzyl bromide (27.0 g, 158 mmol) was added to the mixture and the whole was stirred at room temperature for 3 h. The reaction mixture was poured into ice-cooled 0.5 N HCl and extracted with Et_2O. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–Et_2O (17 : 3—4 : 1) was concentrated under reduced pressure to give **5** (27.8 g, 97%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (3H, s), 5.17 (2H, s), 6.99—7.04 (2H, m), 7.35—7.47 (6H, m), 7.75 (1H, m). IR (film): 1674, 1597 cm^{-1}. EI-MS *m*/*z*: 226 (M^+).

2-Benzyloxy-1-(1-hydroxyiminoethyl)benzene (8) A solution of a mixture of **5** (32.2 g, 142 mmol), $NH_4OH \cdot HCl$ (15.3 g, 220 mmol), and AcONa (18.4 g, 224 mmol) in a mixture of EtOH (200 ml) and H_2O (100 ml) was stirred under reflux for 3 h. After removal of EtOH under reduced pressure, the mixture was poured into 0.5 N HCl and extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–EtOAc (7 : 3—3 : 2) was concentrated under reduced pressure to give **8** (33.1 g, 97%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 5.11 (2H, s), 6.94—6.99 (2H, m), 7.28—7.42 (7H, m), 8.48 (1H, br s). IR (KBr): 3237, 3110, 2934, 2874, 1597, 1578 cm^{-1}. EI-MS *m*/*z*: 241 (M^+).

4-Methoxycarbonyl-1-(1-hydroxyiminoethyl)benzene (**7**): By a similar method to that described for the preparation of **8**, 4-methoxycarbonylacetophenone (**4**) gave **7** (94%) as a white needle. mp 83—84 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.31 (3H, s), 3.93 (3H, s), 7.71 (2H, d, *J*=9 Hz), 8.01 (1H, br s), 8.05 (2H, d, *J*=9 Hz). IR (KBr): 3248, 3079, 2955, 1718, 1607 cm^{-1}. EI-MS *m*/*z*: 193 (M^+).

4-Benzyloxy-1-(1-hydroxyiminoethyl)benzene (**9**): **3** was successively treated with similar methods to those described for the preparation of **5** and **8** to afford **9** (91%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s), 5.10 (2H, s), 6.98 (2H, d, *J*=9 Hz), 7.30—7.50 (6H, m), 7.58 (2H, d, *J*=9 Hz).

2-Benzyloxy-1-[1-(4-formylphenyloxyimino)ethyl]benzene (11) NaH (55%, 6.63 g, 152 mmol) and was added to a solution of **8** (32.8 g, 136 mmol) in THF (300 ml) under N_2 atmosphere. Then, a solution of 4-fluorobenzaldehyde (18.6 g, 150 mmol) in DMSO (100 ml) was added in drops to the mixture and the whole was stirred at room temperature for 1 d. The reaction mixture was poured into ice-cooled 1 N HCl and extracted with Et_2O. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane-Et_2O (7 : 3—3 : 2) was concentrated under reduced pressure to give **11** (22.5 g, 48%) as a pale yellow solid. mp 70—72 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s), 5.14 (2H, s), 6.99—7.08 (3H, m), 7.17—7.47 (8H, m), 7.84 (2H, d, *J*=9 Hz), 9.90 (1H, s). IR (KBr): 3065, 3034, 1695, 1598, 1582 cm^{-1}. EI-MS *m*/*z*: 345 (M^+).

4-Methoxycarbonyl-1-[1-(4-formylphenyloxyimino)ethyl]benzene (**10**): By a similar method to that described for the preparation of **11**, **7** gave **10** (47%) as a pale yellow powder. mp 128—130 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.51 (3H, s), 3.96 (3H, s), 7.44 (2H, d, *J*=9 Hz), 7.87 (2H, d, *J*=9 Hz), 7.90 (2H, d, *J*=9 Hz), 8.11 (2H, d, *J*=9 Hz), 9.94 (1H, s). IR (KBr): 2957, 1717, 1678, 1596 cm^{-1}. EI-MS *m*/*z*: 297 (M^+).

4-Benzyloxy-1-[1-(4-formylphenyloxyimino)ethyl]benzene (**12**): By a similar method to that described for the preparation of **11**, **9** gave **12** (55%) as a pale yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 5.13 (2H, s), 7.03 (2H, d, *J*=9 Hz), 7.30—7.50 (7H, m), 7.75 (2H, d, *J*=9 Hz), 7.88 (2H, d, *J*=9 Hz), 9.92 (1H, s). IR (KBr): 2729, 1698, 1598 cm^{-1}. EI-MS *m*/*z*: 345 (M^+).

2-(2-Hydroxyphenyl)-5-formylbenzo[*b*]furan (14) A solution of **11** (20.5 g, 59.4 mmol) in 1 N HCl–AcOH solution (250 ml) was stirred at 100 °C for 12 h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–EtOAc (3 : 2—1 : 1) was concentrated under reduced pressure to give a residue, which was recrystallized from EtOAc–*n*-hexane to give **14** (4.55 g, 32%) as a pale yellow powder. mp 194—195 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.57 (1H, s), 6.99 (1H, d, *J*=8 Hz), 7.06 (1H, t, *J*=7 Hz), 7.28—7.34 (2H, m), 7.66 (1H, d, *J*=8 Hz), 7.83 (1H, dd, *J*=2, 8 Hz), 7.88 (1H, dd, *J*=2, 8 Hz), 8.16 (1H, d, *J*=2 Hz), 10.09 (1H, s). IR (KBr): 3276, 1672, 1609 cm^{-1}. EI-MS *m*/*z*: 238 (M^+).

2-(4-Methoxycarbonylphenyl)-5-formylbenzo[*b*]furan (**13**): By a similar method to that described for the preparation of **14**, **10** gave **13** (54%) as a pale yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 3.96 (3H, s), 7.26 (1H, d, *J*=2 Hz), 7.67 (1H, d, *J*=9 Hz), 7.91 (1H, dd, *J*=1, 9 Hz), 7.94—7.97 (2H, m),

8.13—8.17 (3H, m), 10.09 (1H, s).

2-(4-Hydroxyphenyl)-5-formylbenzo[*b*]furan (**15**): By a similar method to that described for the preparation of **14**, **12** gave **15** (5%) as a pale yellow powder. ^{1}H-NMR (DMSO-d_6) δ: 6.91 (2H, d, J=9 Hz), 7.36 (1H, s), 7.77—7.81 (2H, m), 7.84 (1H, dd, J=2, 8 Hz), 8.19 (1H, d, J=1 Hz), 9.97 (1H, s), 10.06 (1H, s). IR (KBr): 3298, 1673, 1615, 1602 cm^{-1}. EI-MS m/z: 238 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-5-formylbenzo[*b*]furan (18b) NaH (55%, 110 mg, 2.52 mmol) was added to a solution of **14** (500 mg, 2.10 mmol) in DMF (15 ml) under N_2 atmosphere and the mixture was stirred at room temperature for 15 min. Then, ethyl 4-bromobutyrate (540 mg, 2.77 mmol) was added to the mixture and the whole was stirred at room temperature for 2 h. The reaction mixture was poured into ice-cooled 1 N HCl and extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with CH_2Cl_2–EtOAc (1 : 0—9 : 1) was concentrated under reduced pressure to give a residue, which was triturated with Et_2O–*n*-hexane to afford **18b** (620 mg, 84%) as a pale yellow powder. mp 68—69 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz), 2.27—2.35 (2H, m), 2.61 (2H, t, J=7 Hz), 4.16 (2H, q, J=7 Hz), 4.24 (2H, t, J=6 Hz), 7.02 (1H, d, J=8 Hz), 7.10 (1H, t, J=8 Hz), 7.36 (1H, m), 7.41 (1H, s), 7.62 (1H, d, J=8 Hz), 7.85 (1H, d, J=1 Hz), 8.07 (1H, dd, J=2, 8 Hz), 8.15 (1H, d, J=1 Hz), 10.07 (1H, s). IR (KBr): 2973, 2964, 1729, 1688, 1605, 1586, 1568 cm^{-1}. EI-MS m/z: 352 (M^+).

2-(2-Methoxycarbonylmethyloxyphenyl)-5-formylbenzo[*b*]furan (**18a**): By a similar method to that described for the preparation of **18b**, **14** and methyl bromoacetate gave **18a** (86%) as a white powder. mp 152—153 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.90 (3H, s), 4.82 (2H, s), 6.91 (1H, d, J=8 Hz), 7.16 (1H, dd, J=7, 8 Hz), 7.36 (1H, m), 7.62 (1H, d, J=8 Hz), 7.82 (1H, s), 7.86 (1H, dd, J=2, 8 Hz), 8.12 (1H, dd, J=2, 8 Hz), 8.18 (1H, d, J=2 Hz), 10.07 (1H, s). IR (KBr): 1765, 1692, 1611, 1604, 1589 cm^{-1}. EI-MS m/z: 310 (M^+).

2-[2-(4-Ethoxycarbonyl-1-butyloxy)phenyl]-5-formylbenzo[*b*]furan (**18c**): By a similar method to that described for the preparation of **18b**, **14** and ethyl 5-bromovalerate gave **18c** (79%) as a white powder. mp 74—75 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz), 1.89—2.07 (4H, m), 2.46 (2H, t, J=7 Hz), 4.14—4.21 (4H, m), 7.01 (1H, d, J=8 Hz), 7.09 (1H, dd, J=7, 8 Hz), 7.35 (1H, m), 7.49 (1H, s), 7.62 (1H, d, J=8 Hz), 7.85 (1H, dd, J=2, 9 Hz), 8.07 (1H, dd, J=2, 8 Hz), 8.17 (1H, d, J=2 Hz), 10.07 (1H, s). IR (KBr): 2942, 2876, 1723, 1690, 1602, 1589, 1566 cm^{-1}. EI-MS m/z: 366 (M^+).

2-(4-Methoxycarbonylmethyloxyphenyl)-5-formylbenzo[*b*]furan (**19a**): By a similar method to that described for the preparation of **18b**, **15** and methyl bromoacetate gave **19a** (80%). ^{1}H-NMR (DMSO-d_6) δ: 3.73 (3H, s), 4.90 (2H, s), 7.11 (2H, d, J=9 Hz), 7.48 (1H, s), 7.81 (1H, d, J=9 Hz), 7.86 (1H, dd, J=1, 9 Hz), 7.90 (2H, d, J=9 Hz), 8.23 (1H, d, J=1 Hz), 10.07 (1H, s). IR (KBr): 2957, 1763, 1740, 1689, 1613, 1592 cm^{-1}. EI-MS m/z: 310 (M^+).

2-[4-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-5-formylbenzo[*b*]furan (**19b**): By a similar method to that described for the preparation of **18b**, **15** and ethyl 4-bromobutyrate gave **19b** (66%). ^{1}H-NMR (DMSO-d_6) δ: 1.19 (3H, t, J=7 Hz), 1.95—2.09 (2H, m), 2.48 (2H, t, J=7 Hz), 4.05—4.11 (4H, m), 7.08 (2H, d, J=9 Hz), 7.45 (1H, s), 7.80 (1H, d, J=9 Hz), 7.84—7.92 (3H, m), 8.22 (1H, d, J=1 Hz), 10.07 (1H, s). IR (KBr): 2944, 1737, 1698, 1615 cm^{-1}. EI-MS m/z: 352 (M^+).

2-[4-(4-Ethoxycarbonyl-1-butyloxy)phenyl]-5-formylbenzo[*b*]furan (**19c**): By a similar method to that described for the preparation of **18b**, **15** and ethyl 5-bromovalerate gave **19c** (33%). ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7 Hz), 1.65—1.80 (4H, m), 2.38 (2H, t, J=7 Hz), 4.02—4.10 (4H, m), 7.09 (2H, d, J=9 Hz), 7.45 (1H, s), 7.80 (1H, d, J=9 Hz), 7.83—7.92 (3H, m), 8.21 (1H, d, J=1 Hz), 10.07 (1H, s). IR (KBr): 2945, 2914, 2876, 1732, 1699, 1615, 1590 cm^{-1}. EI-MS m/z: 366 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]benzo[*b*]furan-5-carboxylic Acid (20b) A solution of a mixture of **18b** (500 mg, 1.42 mmol), $NaClO_2$ (1.50 g, 16.6 mmol), NaH_2PO_4 (1.50 g, 9.62 mmol), and 2-methyl-2-butene (1.0 ml) in a mixture of *N*,*N*-dimethylacetamide (DMA) (16 ml) and H_2O (8.0 ml) was stirred at room temperature for 2 h. The reaction mixture was acidified with 1 N HCl and extracted with CH_2Cl_2. The combined organic layer was washed with $Na_2S_2O_3$ aqueous solution, water, and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was triturated with Et_2O to give **20b** (460 mg, 88%) as a white powder. mp 167—168 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz), 2.27—2.35 (2H, m), 2.62 (2H, t, J=7 Hz), 4.17 (2H, q, J=7 Hz), 4.24 (2H, t, J=6 Hz), 7.02 (1H, d, J=8 Hz), 7.10 (1H, t, J=8 Hz), 7.35 (1H, m), 7.39 (1H, s), 7.57 (1H, d, J=9 Hz), 8.05—8.10 (2H, m), 8.42 (1H, d, J=2 Hz). IR (KBr): 2944, 2904, 2879, 2651, 2542, 1727, 1686, 1612, 1590 cm^{-1}. EI-MS m/z: 368 (M^+).

2-(4-Methoxycarbonylphenyl)benzo[*b*]furan-5-carboxylic Acid (**16**): By a similar method to that described for the preparation of **20b**, **13** gave **16** (90%) as a pale yellow powder. mp 293—295 °C. ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 3.96 (3H, s), 7.26 (1H, s), 7.59 (1H, d, J=9 Hz), 7.97 (2H, d, J=8 Hz), 8.07 (1H, dd, J=2, 9 Hz), 8.14 (2H, d, J=8 Hz), 8.38 (1H, d, J=2 Hz). IR (KBr): 2961, 1713, 1672, 1610, 1590 cm^{-1}. EI-MS m/z: 296 (M^+).

2-(2-Methoxycarbonylmethyloxyphenyl)benzo[*b*]furan-5-carboxylic Acid (**20a**): By a similar method to that described for the preparation of **20b**, **18a** gave **20a** (99%) as a white powder. mp 215—217 °C. ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 3.90 (3H, s), 4.83 (2H, s), 6.91 (1H, d, J=8 Hz), 7.15 (1H, t, J=7 Hz), 7.34 (1H, m), 7.54 (1H, d, J=9 Hz), 7.75 (1H, s), 8.03 (1H, dd, J=2, 9 Hz), 8.11 (1H, dd, J=2, 8 Hz), 8.40 (1H, d, J=2 Hz). IR (KBr): 3077, 2957, 2913, 2659, 2553, 1764, 1681, 1615 cm^{-1}. EI-MS m/z: 326 (M^+).

2-[2-(4-Ethoxycarbonyl-1-butyloxy)phenyl]benzo[*b*]furan-5-carboxylic Acid (**20c**): By a similar method to that described for the preparation of **20b**, **18c** gave **20c** (90%) as a white powder. mp 152—153 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz), 1.90—2.10 (4H, m), 2.46 (2H, t, J=7 Hz), 4.14—4.21 (4H, m), 7.01 (1H, d, J=8 Hz), 7.09 (1H, t, J=7 Hz), 7.34 (1H, m), 7.46 (1H, s), 7.56 (1H, d, J=9 Hz), 8.08 (1H, dd, J=1, 9 Hz), 8.44 (1H, d, J=1 Hz). IR (KBr): 3072, 2986, 2937, 2876, 2651, 2544, 1727, 1686, 1614, 1591, 1567 cm^{-1}. EI-MS m/z: 382 (M^+).

2-(4-Methoxycarbonylmethyloxyphenyl)benzo[*b*]furan-5-carboxylic Acid (**21a**): By a similar method to that described for the preparation of **20b**, **19a** gave **21a** (64%) as a white powder. ^{1}H-NMR (DMSO-d_6) δ: 3.73 (3H, s), 4.90 (2H, s), 7.11 (2H, d, J=9 Hz), 7.41 (1H, s), 7.69 (1H, d, J=9 Hz), 7.86 (1H, dd, J=1, 9 Hz), 7.90 (2H, d, J=9 Hz), 8.24 (1H, d, J=2 Hz), 12.86 (1H, br s).

2-[4-(3-Ethoxycarbonyl-1-propyloxy)phenyl]benzo[*b*]furan-5-carboxylic Acid (**21b**): By a similar method to that described for the preparation of **20b**, **19b** gave **21b** (93%) as a white powder. mp 175—177 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.19 (3H, t, J=7 Hz), 1.95—2.10 (2H, m), 2.48 (2H, t, J=7 Hz), 4.05—4.12 (4H, m), 7.08 (2H, d, J=9 Hz), 7.38 (1H, s), 7.68 (1H, d, J=8 Hz), 7.84—7.92 (3H, m), 8.23 (1H, d, J=2 Hz), 12.86 (1H, br s). IR (KBr): 2984, 2911, 2653, 1743, 1680, 1614, 1592 cm^{-1}. EI-MS m/z: 368 (M^+).

2-[4-(4-Ethoxycarbonyl-1-butyloxy)phenyl]benzo[*b*]furan-5-carboxylic Acid (**21c**): By a similar method to that described for the preparation of **20b**, **19c** gave **21c** (73%) as a white powder. mp 176—178 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7 Hz), 1.67—1.82 (4H, m), 2.38 (2H, t, J=7 Hz), 4.02—4.10 (4H, m), 7.08 (2H, d, J=9 Hz), 7.38 (1H, s), 7.68 (1H, d, J=9 Hz), 7.86 (2H, d, J=9 Hz), 7.89 (1H, dd, J=2, 9 Hz), 8.23 (1H, d, J=2 Hz), 12.87 (1H, br s). IR (KBr): 3067, 2950, 2872, 2651, 1731, 1685, 1616, 1592 cm^{-1}. EI-MS m/z: 382 (M^+).

4-[2-[5-(*N*-Diphenylmethylcarbamoyl)benzo[*b*]furan-2-yl]-phenyloxy]butyric Acid (22b) 2,4,6-Triisopropylbenzenesulfonyl chloride (497 mg, 1.64 mmol) was added in three portions every 30 min to a solution of a mixture of **20b** (400 mg, 1.09 mmol), diphenylmethylamine (300 mg, 1.64 mmol), Et_3N (221 mg, 2.18 mmol), and 4-dimethylaminopyridine (5.0 mg) in CH_2Cl_2 (8.0 ml) and the whole was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with CH_2Cl_2–EtOAc (24 : 1—23 : 2) was concentrated under reduced pressure to give a residue, which was recrystallized from acetone–Et_2O to afford *N*-diphenylmethyl-2-[2-(3-ethoxycarbonyl-1-propyloxy)phenyl]benzo[*b*]furan-5-carboxamide (550 mg, 95%) as a white powder. mp 174—176 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 2.25—2.33 (2H, m), 2.60 (2H, t, J=7 Hz), 4.15 (2H, q, J=7 Hz), 4.22 (2H, d, J=6 Hz), 6.50 (1H, d, J=8 Hz), 6.71 (1H, d, J=8 Hz), 7.01 (1H, d, J=8 Hz), 7.09 (1H, t, J=8 Hz), 7.26—7.43 (12H, m), 7.54 (1H, d, J=9 Hz), 7.79 (1H, dd, J=2, 8 Hz), 8.06 (1H, dd, J=2, 8 Hz), 8.08 (1H, d, J=2 Hz). IR (KBr): 3304, 3062, 3031, 2979, 1731, 1634, 1612, 1587 cm^{-1}. EI-MS m/z: 533 (M^+). *Anal*. Calcd for $C_{34}H_{31}NO_5$: C, 76.53; H, 5.86; N, 2.63. Found: C, 76.28; H, 5.84; N, 2.61.

A solution of the amide (500 mg, 0.937 mmol) in a mixture of 15% KOH aqueous solution (5 ml) and 1,4-dioxane (10 ml) was stirred under reflux under N_2 atmosphere for 2 h. The reaction mixture was acidified with 1 N HCl and extracted with $CHCl_3$ containing 3% MeOH. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was tritulated with Et_2O to give **22b** (428 mg, 90%) as a white powder. mp 256—258 °C. ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 2.26—2.33 (2H, m), 2.61 (2H, t, J=7 Hz),

4.19—4.28 (2H, m), 6.48 (1H, s), 7.05 (1H, d, J=8 Hz), 7.09 (1H, t, J=8 Hz), 7.27—7.44 (12H, m), 7.56 (1H, d, J=8 Hz), 7.81 (1H, dd, J=2, 8 Hz), 8.06 (1H, dd, J=2, 8 Hz), 8.13 (1H, d, J=2 Hz). IR (KBr): 3301, 3063, 3033, 2947, 1715, 1636, 1612, 1586 cm^{-1}. EI-MS m/z: 505 (M^+). *Anal*. Calcd for $C_{32}H_{27}NO_5 \cdot 4/5H_2O$: C, 73.92; H, 5.54; N, 2.69. Found: C, 73.75; H, 5.43; N, 2.68.

4-[5-(*N*-Diphenylmethylcarbamoyl)benzo[*b*]furan-2-yl]benzoic Acid (**17**): By a similar method to that described for the preparation of **22b**, **16** gave **17** (49%) as a white powder. mp 271—273 °C. ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 6.49 (1H, s), 7.25—7.45 (11H, m), 7.60 (1H, d, J=9 Hz), 7.85 (1H, dd, J=2, 9 Hz), 7.96 (2H, d, J=9 Hz), 8.14 (1H, d, J=8 Hz), 8.17 (1H, d, J=2 Hz). IR (KBr): 3305, 2924, 2874, 2676, 2550, 1687, 1633, 1611, 1591 cm^{-1}. EI-MS m/z: 447 (M^+). *Anal*. Calcd for $C_{29}H_{21}NO_4 \cdot 1/2H_2O$: C, 76.30; H, 4.86; N, 3.07. Found: C, 76.16; H, 4.79; N, 2.93.

2-[5-(*N*-Diphenylmethylcarbamoyl)benzo[*b*]furan-2-yl]phenyloxyacetic Acid (**22a**): By a similar method to that described for the preparation of **22b**, **20a** gave **22a** (76%) as a white powder. mp 218—220 °C. ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 4.78 (2H, s), 6.48 (1H, s), 6.95 (1H, d, J=8 Hz), 7.14 (1H, t, J=7 Hz), 7.27—7.40 (12H, m), 7.55 (1H, d, J=8 Hz), 7.79 (1H, dd, J=2, 9 Hz), 7.82 (1H, s), 8.10 (1H, dd, J=1, 8 Hz), 8.13 (1H, d, J=2 Hz). IR (KBr): 3424, 3332, 3059, 3030, 2928, 2586, 1744, 1637, 1611, 1586 cm^{-1}. EI-MS m/z: 477 (M^+). *Anal*. Calcd for $C_{30}H_{23}NO_5 \cdot 1/4H_2O$: C, 74.75; H, 4.91; N, 2.91. Found: C, 74.51; H, 4.72; N, 2.80.

5-[2-[5-(*N*-Diphenylmethylcarbamoyl)benzo[*b*]furan-2-yl]phenyloxy]valeric Acid (**22c**): By a similar method to that described for the preparation of **22b**, **20c** gave **22c** (60%) as a white powder. mp 249—252 °C. ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 1.91—2.08 (4H, m), 2.46 (2H, t, J=7 Hz), 4.18 (2H, t, J=6 Hz), 6.48 (1H, s), 7.00 (1H, d, J=8 Hz), 7.08 (1H, t, J=7 Hz), 7.22—7.40 (11H, m), 7.52—7.55 (2H, m), 7.73 (1H, dd, J=2, 9 Hz), 8.06 (1H, dd, J=2, 8 Hz), 8.15 (1H, d, J=2 Hz). IR (KBr): 3330, 3059, 3032, 2958, 2879, 1714, 1637, 1612, 1585 cm^{-1}. EI-MS m/z: 519 (M^+). *Anal*. Calcd for $C_{33}H_{29}NO_5 \cdot 1/10H_2O$: C, 76.02; H, 5.64; N, 2.69. Found: C, 75.92; H, 5.62; N, 2.57.

2-[5-[*N*-(1-Butyl)carbamoyl]benzo[*b*]furan-2-yl]phenyloxyacetic Acid (**23a**): By a similar method to that described for the preparation of **22b**, **20a** and 1-butylamine gave **23a** (61%) as a white powder. mp 198—200 °C. ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 0.98 (3H, t, J=7 Hz), 1.40—1.50 (2H, m), 1.60—1.68 (2H, m), 3.47 (2H, t, J=7 Hz), 4.78 (2H, s), 6.93 (1H, d, J=8 Hz), 7.14 (1H, t, J=8 Hz), 7.34 (1H, m), 7.53 (1H, d, J=8 Hz), 7.70 (1H, dd, J=2, 8 Hz), 7.82 (1H, s), 8.04 (1H, d, J=2 Hz), 8.10 (1H, dd, J=2, 8 Hz). IR (KBr): 3310, 2958, 2931, 2872, 2676, 2575, 1751, 1714, 1634, 1610 cm^{-1}. EI-MS m/z: 367 (M^+). *Anal*. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.63; H, 5.73; N, 3.72.

4-[2-[5-[*N*-(1-Butyl)carbamoyl]benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (**23b**): By a similar method to that described for the preparation of **22b**, **20b** and 1-butylamine gave **23b** (92%) as a white powder. mp 153—154 °C. ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 0.99 (3H, t, J=7 Hz), 1.42—1.50 (2H, m), 1.60—1.68 (2H, m), 2.26—2.34 (2H, m), 2.63 (2H, t, J=7 Hz), 3.45—3.50 (2H, m), 4.23 (2H, t, J=6 Hz), 7.02 (1H, d, J=8 Hz), 7.09 (1H, t, J=7 Hz), 7.34 (1H, m), 7.39 (1H, s), 7.53 (1H, d, J=8 Hz), 7.70 (1H, dd, J=2, 9 Hz), 8.04 (1H, d, J=2 Hz), 8.06 (1H, dd, J=2, 8 Hz). IR (KBr): 3301, 3063, 3033, 2947, 1715, 1636, 1612, 1586 cm^{-1}. EI-MS m/z: 395 (M^+). *Anal*. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.89; H, 6.36; N, 3.47.

5-[2-[5-[*N*-(1-Butyl)carbamoyl)benzo[*b*]furan-2-yl]phenyloxy]valeric Acid (**23c**): By a similar method to that described for the preparation of **22b**, **20c** and 1-butylamine gave **23c** (63%) as a white powder. mp 173—174 °C. ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 0.98 (3H, t, J=7 Hz), 1.40—1.50 (2H, m), 1.60—1.68 (2H, m), 1.93—2.08 (4H, m), 2.47 (2H, t, J=7 Hz), 3.47 (2H, t, J=7 Hz), 4.18 (2H, t, J=6 Hz), 7.00 (1H, d, J=8 Hz), 7.08 (1H, t, J=8 Hz), 7.34 (1H, m), 7.50—7.53 (2H, m), 7.66 (1H, dd, J=2, 8 Hz), 8.04—8.08 (2H, m). IR (KBr): 3374, 2955, 2931, 2870, 2612, 1700, 1618, 1607, 1584 cm^{-1}. EI-MS m/z: 409 (M^+). *Anal*. Calcd for $C_{24}H_{27}NO_5 \cdot 1/10H_2O$: C, 70.09; H, 6.67; N, 3.41. Found: C, 70.10; H, 6.46; N, 3.27.

4-[5-(*N*-Diphenylmethylcarbamoyl)benzo[*b*]furan-2-yl]phenyloxyacetic Acid (24a) A solution of a mixture of **21a** (60.0 mg, 0.183 mmol), diphenylmethylamine (41.0 mg, 0.224 mmol), Et_3N (39.0 μl, 0.287 mmol), and DEPC (34.0 μl, 0.223 mmol) in CH_2Cl_2 (5.0 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with CH_2Cl_2–EtOAc (24 : 1—23 : 2) was concentrated under reduced pressure to give *N*-diphenylmethyl-2-(4-methoxycarbonylmethyloxyphenyl)benzo[*b*]-furan-5-carboxamide (68.0 mg, 76%). ^{1}H-NMR (DMSO-d_6) δ: 3.72 (3H, s), 4.90 (2H, s), 6.45 (1H, d, J=9 Hz), 7.09 (2H, d, J=9 Hz), 7.24—7.30 (2H, m), 7.33—7.43 (9H, m), 7.67 (1H, d, J=9 Hz), 7.85—7.91 (3H, m), 8.25 (1H, d, J=2 Hz), 9.31 (1H, d, J=9 Hz). IR (KBr): 3280, 3061, 3030, 2935, 1764, 1631, 1614, 1592 cm^{-1}. EI-MS m/z: 491 (M^+).

A solution of the amide (64.0 mg, 0.130 mmol) in a mixture of 15% NaOH aqueous solution (1.0 ml) and 1,4-dioxane (2.0 ml) was stirred under reflux under N_2 atmosphere for 2 h. The reaction mixture was acidified with 1 N HCl and extracted with $CHCl_3$ containing 3% MeOH. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was washed with Et_2O to give **24a** (38.0 mg, 61%) as a white powder. mp 244—246 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.78 (2H, s), 6.45 (1H, d, J=9 Hz), 7.06 (2H, d, J=9 Hz), 7.25—7.43 (11H, m), 7.67 (1H, d, J=9 Hz), 7.85—7.92 (3H, m), 8.24 (1H, d, J=2 Hz), 9.31 (1H, d, J=9 Hz), 13.10 (1H, br s). IR (KBr): 3350, 3062, 3031, 2926, 1741, 1641, 1613 cm^{-1}. EI-MS m/z: 477 (M^+). *Anal*. Calcd for $C_{30}H_{23}NO_5 \cdot 1/4H_2O$: C, 74.75; H, 4.91; N, 2.91. Found: C, 74.79; H, 5.01; N, 2.91.

4-[4-[5-(*N*-Diphenylmethylcarbamoyl)benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (**24b**): By a similar method to that described for the preparation of **24a**, **21b** gave **24b** (88%) as a white powder. mp 222—223 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.93—2.03 (2H, m), 2.41 (2H, t, J=7 Hz), 4.06 (2H, t, J=6 Hz), 6.45 (1H, d, J=9 Hz), 7.08 (2H, d, J=9 Hz), 7.25—7.43 (11H, m), 7.66 (1H, d, J=9 Hz), 7.85—7.92 (3H, m), 8.24 (1H, d, J=2 Hz), 9.31 (1H, d, J=9 Hz), 12.17 (1H, br s). IR (KBr): 3312, 3061, 3031, 2941, 1709, 1634, 1614 cm^{-1}. FAB-MS m/z: 506 (($M+1)^+$). *Anal*. Calcd for $C_{32}H_{27}NO_5$: C, 76.02; H, 5.38; N, 2.77. Found: C, 76.04; H, 5.38; N, 2.69.

5-[4-[5-(*N*-Diphenylmethylcarbamoyl)benzo[*b*]furan-2-yl]phenyloxy]valeric Acid (**24c**): By a similar method to that described for the preparation of **24a**, **21c** gave **24c** (48%) as a white powder. mp 211—212 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.62—1.80 (4H, m), 2.30 (2H, t, J=7 Hz), 4.05 (2H, t, J=6 Hz), 6.45 (1H, d, J=9 Hz), 7.08 (2H, d, J=9 Hz), 7.25—7.43 (11H, m), 7.66 (1H, d, J=9 Hz), 7.85—7.91 (3H, m), 8.24 (1H, d, J=2 Hz), 9.31 (1H, d, J=9 Hz), 12.04 (1H, br s). IR (KBr): 3313, 3061, 3030, 2952, 1706, 1633, 1613, 1591 cm^{-1}. FAB-MS m/z: 520 (($M+1)^+$). *Anal*. Calcd for $C_{33}H_{29}NO_5 \cdot 1/2H_2O$: C, 74.98; H, 5.72; N, 2.65. Found: C, 75.02; H, 5.76; N, 2.55.

4-[4-[5-[*N*-(1-Butyl)carbamoyl]benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (**25b**): By a similar method to that described for the preparation of **24a**, **21b** and 1-butylamine gave **25b** (65%) as a white powder. mp 242—243 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, J=7 Hz), 1.30—1.42 (2H, m), 1.48—1.58 (2H, m), 1.93—2.03 (2H, m), 2.41 (2H, t, J=7 Hz), 3.25—3.40 (2H, m), 4.06 (2H, t, J=6 Hz), 7.08 (2H, d, J=9 Hz), 7.37 (1H, s), 7.64 (1H, d, J=9 Hz), 7.78 (1H, dd, J=2, 9 Hz), 7.87 (2H, d, J=9 Hz), 8.11 (1H, d, J=2 Hz), 8.46 (1H, t, J=6 Hz), 12.19 (1H, br s). IR (KBr): 3288, 2961, 2935, 2874, 1710, 1631, 1613, 1589 cm^{-1}. EI-MS m/z: 395 (M^+). *Anal*. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 70.08; H, 6.14; N, 3.49.

5-[2-[5-[*N*-(1-Butyl)carbamoyl]benzo[*b*]furan-2-yl]phenyloxy]valeric Acid (**25c**): By a similar method to that described for the preparation of **24a**, **21c** and 1-butylamine gave **25c** (58%) as a white powder. mp 218—220 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, J=7 Hz), 1.30—1.41 (2H, m), 1.49—1.58 (2H, m), 1.67—1.82 (4H, m), 2.30 (2H, t, J=7 Hz), 3.25—3.40 (2H, m), 4.05 (2H, t, J=6 Hz), 7.08 (2H, d, J=9 Hz), 7.36 (1H, s), 7.64 (1H, d, J=9 Hz), 7.78 (1H, dd, J=2, 9 Hz), 7.87 (2H, d, J=9 Hz), 8.11 (1H, d, J=2 Hz), 8.45 (1H, t, J=6 Hz), 12.05 (1H, br s). IR (KBr): 3300, 3077, 2960, 2935, 2871, 1709, 1626, 1611, 1588 cm^{-1}. FAB-MS m/z: 410 (($M+1)^+$). *Anal*. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.19; H, 6.74; N, 3.28.

3-Benzyloxy-1-[1-(4-formylphenyloxyimino)ethyl]benzene (27) 3′-Hydroxyacetophenone (**26**) was successively treated by similar methods to those described for the preparation of **5**, **8**, and **11** to afford **27** (58%) as a pale yellow powder. mp 68—70 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.47 (3H, s), 5.20 (2H, s), 7.15—7.53 (11H, m), 7.95 (2H, d, J=9 Hz), 9.93 (1H, s). IR (KBr): 2828, 2741, 1691, 1681, 1596, 1574 cm^{-1}. EI-MS m/z: 345 (M^+).

2-(3-Benzyloxyphenyl)-5-formylbenzo[*b*]furan (28) By a similar method to that described for the preparation of **14**, **27** gave **28** (43%) as a pale yellow powder. mp 154—156 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.16 (2H, s), 7.02 (1H, dd, J=2, 8 Hz), 7.11 (1H, s), 7.33—7.55 (8H, m), 7.64 (1H, d, J=9 Hz), 7.87 (1H, dd, J=1, 9 Hz), 8.13 (1H, d, J=2 Hz), 10.07 (1H, s). IR (KBr): 1692, 1594, 1567 cm^{-1}. EI-MS m/z: 328 (M^+).

2-(3-Benzyloxyphenyl)benzo[*b*]furan-5-carboxylic Acid (29) By a similar method to that described for the preparation of **20b**, **28** gave **29** (93%) as a white powder. ^{1}H-NMR (DMSO-d_6) δ: 5.22 (2H, s), 7.10 (1H, dd, J=2, 8 Hz), 7.32—7.62 (9H, m), 7.72 (1H, d, J=9 Hz), 7.94 (1H, dd, J=2, 9 Hz), 8.28 (1H, d, J=2 Hz), 12.89 (1H, br s). IR (KBr): 3035, 2870, 2653, 1686,

1605, 1593, 1569 cm^{-1}. EI-MS *m/z*: 344 (M^+).

2-[3-(*tert*-Butyldimethylsilyloxy)phenyl]benzo[*b*]furan-5-carboxylic Acid (30) A suspension of a mixture of **29** (4.80 g, 13.9 mmol) and 10% Pd–C (1.00 g) in MeOH (200 ml) was stirred at room temperature under H_2 atmosphere for 6 h. The palladium catalyst was filtered off and the filtrate was concentrated under reduced pressure to give a residue. A solution of a mixture of the residue, *tert*-butyldimethylsilyl chloride (4.61 g, 30.6 mmol), and imidazole (2.28 g, 33.5 mmol) in DMF (30 ml) was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layer was washed with water and brine. To the solution, conc.HCl (1.5 ml) was added and the whole was stirred at room temperature for 30 min. The solution was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give **30** (3.60 g, 70%) as a white powder. mp 177—179 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.26 (6H, s), 1.03 (9H, s), 6.87 (1H, dd, *J*=2, 8 Hz), 7.08 (1H, s), 7.30—7.37 (2H, m), 7.48 (1H, d, *J*=8 Hz), 7.59 (1H, d, *J*=9 Hz), 8.09 (1H, dd, *J*=2, 8 Hz), 8.40 (1H, d, *J*=2 Hz). IR (KBr): 3069, 2956, 2931, 2859, 2650, 1689, 1610, 1592, 1572 cm^{-1}. FAB-MS *m/z*: 369 ($(M+1)^+$).

5-(*N*-Diphenylmethylcarbamoyl)-2-(3-hydroxyphenyl)benzo[*b*]furan (31) A solution of a mixture of **30** (365 mg, 0.991 mmol), diphenylmethylamine (200 mg, 1.09 mmol), Et_3N (207 μl, 1.49 mmol), and DEPC (182 μl, 1.20 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a residue. A solution of the residue in a mixture of CH_3CN (10 ml) and 45% HF aqueous solution (1.0 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was recrystallized from EtOAc–*n*-hexane to give **31** (235 mg, 56%) as a white powder. ^{1}H-NMR (DMSO-d_6) δ: 6.46 (1H, d, *J*=8 Hz), 6.84 (1H, d, *J*=8 Hz), 7.23—7.45 (13H, m), 7.47 (1H, s), 7.69 (1H, d, *J*=9 Hz), 7.91 (1H, dd, *J*=1, 9 Hz), 8.28 (1H, d, *J*=1 Hz), 9.32 (1H, d, *J*=9 Hz), 9.73 (1H, s). IR (KBr): 3322, 3061, 3030, 1640, 1600, 1591 cm^{-1}. EI-MS *m/z*: 419 (M^+).

5-[*N*-(1-Butyl)carbamoyl]-2-(3-hydroxyphenyl)benzo[*b*]furan (**32**): By a similar method to that described for the preparation of **31**, **30** and 1-butylamine gave **32** (37%) as a white powder. mp 215—217 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, *J*=7 Hz), 1.30—1.42 (2H, m), 1.48—1.58 (2H, m), 3.25—3.35 (2H, m), 6.83 (1H, dd, *J*=2, 8 Hz), 7.28—7.35 (2H, m), 7.38 (1H, d, *J*=8 Hz), 7.46 (1H, s), 7.67 (1H, d, *J*=9 Hz), 7.82 (1H, dd, *J*=2, 9 Hz), 8.15 (1H, d, *J*=2 Hz), 8.47 (1H, t, *J*=6 Hz), 9.72 (1H, s). IR (KBr): 3380, 3227, 2958, 2934, 2876, 2864, 1622, 1600, 1582, 1544 cm^{-1}. EI-MS *m/z*: 309 (M^+).

3-[5-(*N*-Diphenylmethylcarbamoyl)benzo[*b*]furan-2-yl]phenyloxyacetic Acid (33a) NaH (55%, 8.0 mg, 0.183 mmol) was added to a solution of **31** (60.0 mg, 0.143 mmol) in DMF (3.0 ml) under N_2 atmosphere and the mixture was stirred at room temperature for 15 min. Then methyl bromoacetate (27.0 mg, 0.176 mmol) was added to the mixture and the whole was stirred at room temperature for 3 h. The reaction mixture was poured into ice-cooled 1 N HCl and extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with CH_2Cl_2–EtOAc (24 : 1—23 : 2) was concentrated under reduced pressure to give the ester. A solution of the ester in a mixture of 15% KOH aqueous solution (1.0 ml) and 1,4-dioxane (2.0 ml) was stirred under reflux under N_2 atmosphere for 2 h. The reaction mixture was acidified with 1 N HCl and extracted with $CHCl_3$ containing 3% MeOH. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was tritulated with Et_2O to give **33a** (47.0 mg, 69%) as a white powder. mp 231—233 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.80 (2H, s), 6.46 (1H, d, *J*=9 Hz), 7.00 (1H, dd, *J*=2, 8 Hz), 7.25—7.50 (12H, m), 7.56 (1H, d, *J*=8 Hz), 7.59 (1H, s), 7.71 (1H, d, *J*=9 Hz), 7.93 (1H, dd, *J*=2, 9 Hz), 8.29 (1H, d, *J*=2 Hz), 9.33 (1H, d, *J*=9 Hz), 13.02 (1H, br s). IR (KBr): 3290, 3062, 3031, 2926, 1754, 1635, 1611, 1571 cm^{-1}. EI-MS *m/z*: 477 (M^+). *Anal*. Calcd for $C_{30}H_{23}NO_5 \cdot 1/3H_2O$: C, 74.52; H, 4.93; N, 2.90. Found: C, 74.51; H, 5.05; N, 2.75.

4-[3-[5-(*N*-Diphenylmethylcarbamoyl)benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (**33b**): By a similar method to that described for the preparation of **33a**, **31** and ethyl 4-bromobutyrate gave **33b** (39%) as a white powder. mp 195—197 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.92—2.10 (2H, m), 2.43 (2H, t, *J*=7 Hz), 4.09 (2H, t, *J*=6 Hz), 6.46 (1H, d, *J*=9 Hz), 7.01 (1H, dd, *J*=2, 8 Hz), 7.25—7.47 (11H, m), 7.48 (1H, s), 7.53 (1H, d, *J*=8 Hz), 7.59 (1H, s), 7.71 (1H, d, *J*=9 Hz), 7.92 (1H, dd, *J*=2, 9 Hz), 8.28 (1H, d, *J*=1 Hz), 9.33 (1H, d, *J*=9 Hz), 12.20 (1H, br s). IR (KBr): 3331, 3061, 3031, 2943, 1703, 1636, 1611, 1571 cm^{-1}. EI-MS *m/z*: 505 (M^+). *Anal*. Calcd for $C_{32}H_{27}NO_5 \cdot 7/5H_2O$: C, 72.41; H, 5.66; N, 2.64. Found: C, 72.49; H, 5.38; N, 2.55.

5-[3-[5-(*N*-Diphenylmethylcarbamoyl)benzo[*b*]furan-2-yl]phenyloxy]valeric Acid (**33c**): By a similar method to that described for the preparation of **33a**, **31** and ethyl 5-bromovalerate gave **33c** (57%) as a white powder. mp 216—218 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.65—1.80 (4H, m), 2.31 (2H, t, *J*=7 Hz), 4.08 (2H, t, *J*=6 Hz), 6.45 (1H, d, *J*=9 Hz), 7.01 (1H, dd, *J*=2, 8 Hz), 7.25—7.46 (11H, m), 7.48 (1H, s), 7.52 (1H, d, *J*=9 Hz), 7.58 (1H, s), 7.70 (1H, d, *J*=9 Hz), 7.92 (1H, dd, *J*=2, 9 Hz), 8.28 (1H, d, *J*=2 Hz), 9.32 (1H, d, *J*=9 Hz), 11.98 (1H, br s). IR (KBr): 3305, 3061, 2926, 1705, 1636, 1605, 1572 cm^{-1}. EI-MS *m/z*: 519 (M^+). HR-MS (EI) *m/z*: Calcd for $C_{33}H_{29}NO_5$ (M^+): 519.2045. Found: 519.2048.

3-[5-[*N*-(1-Butyl)carbamoyl]benzo[*b*]furan-2-yl]phenyloxyacetic Acid (**34a**): By a similar method to that described for the preparation of **33a**, **32** and methyl bromoacetate gave **34a** (41%) as a white powder. mp 180—181 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, *J*=7 Hz), 1.30—1.42 (2H, m), 1.48—1.58 (2H, m), 3.25—3.40 (2H, m), 4.80 (2H, s), 7.00 (1H, dd, *J*=2, 8 Hz), 7.41—7.49 (2H, m), 7.55 (1H, d, *J*=8 Hz), 7.58 (1H, s), 7.69 (1H, d, *J*=9 Hz), 7.83 (1H, dd, *J*=1, 9 Hz), 8.16 (1H, d, *J*=1 Hz), 8.48 (1H, t, *J*=6 Hz), 13.06 (1H, br s). IR (KBr): 3288, 2959, 2932, 2873, 1747, 1627, 1608, 1572 cm^{-1}. EI-MS *m/z*: 367 (M^+). *Anal*. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.91; H, 5.85; N, 3.79.

4-[3-[5-[*N*-(1-Butyl)methylcarbamoyl]benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (**34b**): By a similar method to that described for the preparation of **33a**, **32** and ethyl 4-bromobutyrate gave **34b** (41%) as a white powder. mp 157—158 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, *J*=7 Hz), 1.30—1.42 (2H, m), 1.50—1.58 (2H, m), 1.94—2.04 (2H, m), 2.43 (2H, t, *J*=7 Hz), 3.25—3.40 (2H, m), 4.09 (2H, t, *J*=6 Hz), 7.00 (1H, dd, *J*=2, 8 Hz), 7.43 (1H, t, *J*=8 Hz), 7.48 (1H, d, *J*=2 Hz), 7.53 (1H, d, *J*=8 Hz), 7.58 (1H, s), 7.68 (1H, d, *J*=9 Hz), 7.83 (1H, dd, *J*=2, 9 Hz), 8.15 (1H, d, *J*=2 Hz), 8.48 (1H, t, *J*=6 Hz), 12.17 (1H, br s). IR (KBr): 3339, 3113, 2959, 2931, 2874, 1747, 1712, 1619, 1600, 1573, 1544 cm^{-1}. EI-MS *m/z*: 395 (M^+). *Anal*. Calcd for $C_{23}H_{25}NO_5 \cdot 1/5H_2O$: C, 69.23; H, 6.42; N, 3.51. Found: C, 69.23; H, 6.20; N, 3.44.

5-[3-[5-[*N*-(1-Butyl)methylcarbamoyl]benzo[*b*]furan-2-yl]phenyloxy]valeric Acid (**34c**): By a similar method to that described for the preparation of **33a**, **32** and ethyl 5-bromovalerate gave **34c** (81%) as a white powder. mp 147—149 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, *J*=7 Hz), 1.30—1.42 (2H, m), 1.50—1.59 (2H, m), 1.65—1.73 (4H, m), 2.32 (2H, t, *J*=7 Hz), 3.25—3.40 (2H, m), 4.08 (2H, t, *J*=6 Hz), 7.00 (1H, dd, *J*=2, 8 Hz), 7.43 (1H, t, *J*=8 Hz), 7.48 (1H, d, *J*=2 Hz), 7.52 (1H, d, *J*=8 Hz), 7.58 (1H, s), 7.68 (1H, d, *J*=9 Hz), 7.83 (1H, dd, *J*=2, 9 Hz), 8.16 (1H, d, *J*=1 Hz), 8.49 (1H, t, *J*=6 Hz), 12.05 (1H, br s). IR (KBr): 3335, 3070, 2956, 2934, 2872, 1717, 1630, 1609, 1573, 1542 cm^{-1}. EI-MS *m/z*: 409 (M^+). *Anal*. Calcd for $C_{24}H_{27}NO_5 \cdot 1/4H_2O$: C, 69.63; H, 6.70; N, 3.38. Found: C, 69.74; H, 6.53; N, 3.33.

4-[2-[5-[*N*-(4,4′-Difluorodiphenylmethyl)carbamoyl]benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (35a) By a similar method to that described for the preparation of **22b**, **20b** and 4,4′-difluorodiphenylmethylamine gave **35a** (90%) as a white powder. mp 246—248 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.10—2.17 (2H, m), 2.50 (2H, t, *J*=7 Hz), 4.21 (2H, t, *J*=6 Hz), 6.46 (1H, d, *J*=9 Hz), 7.12 (1H, t, *J*=8 Hz), 7.18—7.22 (5H, m), 7.39—7.46 (6H, m), 7.69 (1H, d, *J*=9 Hz), 7.90 (1H, dd, *J*=2, 9 Hz), 7.98 (1H, dd, *J*=2, 8 Hz), 8.32 (1H, d, *J*=2 Hz), 9.29 (1H, d, *J*=9 Hz), 12.19 (1H, br s). IR (KBr): 3288, 3070, 3047, 2947, 2923, 1720, 1634, 1608, 1588 cm^{-1}. EI-MS *m/z*: 541 (M^+). *Anal*. Calcd for $C_{32}H_{25}F_2NO_5$: C, 70.97; H, 4.65; F, 7.02; N, 2.59. Found: C, 70.89; H, 4.75; F, 6.88; N, 2.63.

4-[2-[5-[*N*-(4,4′-Dimethoxydiphenylmethyl)carbamoyl]benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (35b) By a similar method to that described for the preparation of **22b**, **20b** and 4,4′-dimethoxydiphenylmethylamine gave **35b** (92%) as a white powder. mp 220—222 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.10—2.17 (2H, m), 2.50 (2H, t, *J*=8 Hz), 3.74 (6H, s), 4.21 (2H, t, *J*=6 Hz), 6.34 (1H, d, *J*=9 Hz), 6.91 (4H, d, *J*=9 Hz), 7.12 (1H, t, *J*=8 Hz), 7.21 (1H, d, *J*=8 Hz), 7.29 (4H, d, *J*=9 Hz), 7.41 (1H, m), 7.45 (1H, s), 7.67 (1H, d, *J*=9 Hz), 7.89 (1H, dd, *J*=2, 9 Hz), 7.97 (1H, dd, *J*=2, 8 Hz), 8.31 (1H, d, *J*=2 Hz), 9.15 (1H, d, *J*=9 Hz), 12.20 (1H, br s). IR (KBr): 3420, 2954, 2935, 2836, 1711, 1632, 1611, 1587 cm^{-1}. FAB-MS *m/z*: 565 (M^+). *Anal*. Calcd for $C_{34}H_{31}NO_7$: C, 72.20; H, 5.53; N, 2.48. Found: C, 72.00; H, 5.52; N, 2.47.

4-[2-[5-[*N*-(1,2-Diphenylethyl)carbamoyl]benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (35c) By a similar method to that described for the

preparation of **22b**, **20b** and 1,2-diphenylethylamine gave **35c** (86%) as a white powder. mp 244—246 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.11—2.18 (2H, m), 2.50 (2H, t, J=7 Hz), 3.09 (1H, dd, J=6, 14 Hz), 3.21 (1H, dd, J=10, 14 Hz), 4.22 (2H, t, J=6 Hz), 5.31 (1H, m), 7.10—7.28 (6H, m), 7.32—7.50 (8H, m), 7.65 (1H, d, J=9 Hz), 7.76 (1H, dd, J=2, 9 Hz), 7.97 (1H, dd, J=2, 8 Hz), 8.17 (1H, d, J=2 Hz), 8.91 (1H, d, J=9 Hz), 12.04 (1H, br s). IR (KBr): 3339, 3031, 2946, 2923, 2878, 1700, 1631, 1610, 1586 cm^{-1}. EI-MS m/z: 519 (M^+). HR-FAB-MS m/z: Calcd for ($C_{33}H_{29}NO_5$+H): 520.2124. Found: 520.2136.

3-Methoxy-4-trifluoromethanesulfonyloxybenzaldehyde (37) Trifluoromethanesulfonic anhydride (20.0 ml, 119 mmol) was added to a solution of a mixture of vanillin (**36**) (15.0 g, 98.6 mmol) and pyridine (27.0 ml, 335 mmol) in CH_2Cl_2 (200 ml) under N_2 atmosphere while the reaction temperature was kept under 5 °C. The reaction solution was stirred at 0 °C for 1 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 0.5 N HCl, water, and brine. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a residue which was chromatographed on silica gel. The eluate with *n*-hexane–EtOAc (17 : 3—3 : 1) was concentrated under reduced pressure to give **37** (27.1 g, 97%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 4.00 (3H, s), 7.42 (1H, d, J=8 Hz), 7.52 (1H, dd, J=2, 8 Hz), 7.57 (1H, d, J=2 Hz), 10.00 (1H, s). IR (film): 1708, 1606 cm^{-1}. EI-MS m/z: 284 (M^+).

3-Methoxy-4-trimethylsilylethynylbenzaldehyde (38) A solution of a mixture of **37** (700 mg, 2.46 mmol), trimethylsilylacetylene (2.10 ml, 15.0 mmol), Et_3N (1.55 ml, 11.2 mmol), and $(Ph_3P)_2PdCl_2$ (200 mg, 0.285 mmol) in DMF (5.0 ml) was stirred at 90 °C for 2 h. The reaction mixture was poured into water and extracted with Et_2O. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–Et_2O (17 : 3—4 : 1) was concentrated under reduced pressure to give **38** (380 mg, 66%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.28 (3H, s), 3.95 (3H, s), 7.37 (1H, d, J=1 Hz), 7.39 (1H, dd, J=1, 8 Hz), 7.59 (1H, d, J=8 Hz), 9.96 (1H, s). IR (film): 2961, 2845, 2732, 2157, 1701, 1597, 1567 cm^{-1}. EI-MS m/z: 232 (M^+).

4-Ethynyl-3-methoxybenzaldehyde (39a) A suspension of a mixture of **38** (370 mg, 1.59 mmol) and K_2CO_3 (420 mg, 3.04 mmol) in MeOH (15 ml) was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with Et_2O. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–Et_2O (23 : 2—4 : 1) was concentrated under reduced pressure to give a residue, which was recrystallized from Et_2O–*n*-hexane to afford **39a** (190 mg, 75%) as a pale orange needle. mp 78—79 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.51 (1H, s), 3.98 (3H, s), 7.40—7.44 (2H, m), 7.63 (1H, d, J=8 Hz), 9.99 (1H, s). IR (KBr): 3251, 3211, 2856, 1680, 1601, 1566 cm^{-1}. EI-MS m/z: 160 (M^+).

4-Ethynyl-3-methoxy-1-dimethoxymethylbenzene (39b) A solution of a mixture of **39a** (1.00 g, 6.24 mmol), trimethoxymethane (670 mg, 6.31 mmol), and *p*-toluenesulfonic acid (20 mg) in MeOH (15 ml) was stirred at 40 °C for 2 h. The reaction mixture was poured into $NaHCO_3$ aqueous solution and extracted with Et_2O. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–Et_2O (22 : 3—17 : 3) was concentrated under reduced pressure to give **39b** (1.24 g, 96%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 3.31 (1H, s), 3.33 (6H, s), 3.93 (3H, s), 5.37 (1H, s), 7.00 (1H, d, J=8 Hz), 7.02 (1H, s), 7.46 (1H, d, J=8 Hz). IR (film): 3283, 2939, 2909, 2832, 2107, 1609, 1571 cm^{-1}. EI-MS m/z: 206 (M^+).

4-(2-Benzyloxyphenyl)ethynyl-3-methoxybenzaldehyde (40a) A solution of a mixture of **39a** (12.5 g, 78.0 mmol), 2-benzyloxyiodobenzene (26.6 g, 85.8 mmol), Et_3N (32.4 ml, 234 mmol), and $(Ph_3P)_2PdCl_2$ (1.64 g, 2.34 mmol) in DMF (180 ml) was stirred at 110 °C for 2 h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–EtOAc (4 : 1—7 : 3) was concentrated under reduced pressure to give **40a** (9.04 g, 34%) as a yellow powder. mp 96—98 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.87 (3H, S), 5.21 (2H, s), 6.93—7.10 (2H, m), 7.24—7.80 (10H, m), 9.97 (1H, s). IR (KBr): 2214, 1689, 1598, 1566 cm^{-1}. EI-MS m/z: 342 (M^+).

4-(2-Benzyloxyphenyl)ethynyl-3-methoxy-1-dimethoxymethylbenzene (**40b**): By a similar method to that described for the preparation of **40a**, **39b** gave **40b** (40%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 3.34 (6H, s), 3.85 (3H, s), 5.21 (2H, s), 5.39 (1H, s), 6.93—7.02 (4H, m), 7.24—7.40 (4H, m), 7.48 (1H, d, J=8 Hz), 7.53—7.62 (3H, m). IR (KBr): 2983, 2956, 2937, 2900, 2833, 1608, 1595, 1574, 1567 cm^{-1}. EI-MS m/z: 388 (M^+).

2-(2-Hydroxyphenyl)-6-formylbenzo[*b*]furan (41a) A mixture of **40a** (6.27 g, 18.3 mmol) and pyridinium chloride (35.5 g, 307 mmol) was heated at 200 °C for 2 h. The reaction mixture was cooled to room temperature, and DMSO (15 ml) was added before it got solid. The whole was acidified with 1 N HCl and extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–EtOAc (7 : 3) was concentrated under reduced pressure to give **41a** (1.95 g, 45%) as a pale yellow powder. mp 189—191 °C. ^{1}H-NMR (DMSO-d_6) δ: 6.98—7.07 (2H, m), 7.31 (1H, m), 7.56 (1H, s), 7.81 (1H, d, J=8 Hz), 7.86 (1H, d, J=8 Hz), 7.94 (1H, dd, J=1, 8 Hz), 8.13 (1H, s), 10.06 (1H, s), 10.68 (1H, s). IR (KBr): 3246, 1663, 1612, 1573 cm^{-1}. EI-MS m/z: 238 (M^+).

By a similar method to that described for the preparation of **41a** from **40a**, **40b** also gave **41a** (76%) as a pale yellow powder.

2-(2-Benzyloxyphenyl)-6-formylbenzo[*b*]furan (41b) A solution of a mixture of **40b** (4.13 g, 10.6 mmol) and lithium chloride (1.36 g, 32.1 mmol) in DMPU (80 ml) was stirred at 160 °C for 5 h, while lithium chloride (1.36 g) was added every one hour. Then, the reaction solution was stirred for another 10 h. The reaction mixture was poured into ice-water and extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–EtOAc (47 : 3—23 : 2) was concentrated under reduced pressure to give a residue, which was recrystallized from acetone–Et_2O to yield **41b** (0.740 g, 21%) as a pale yellow powder. mp 126—128 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.28 (2H, s), 7.08—7.16 (2H, m), 7.35—7.47 (5H, m), 7.50—7.53 (2H, m), 7.63 (1H, d, J=8 Hz), 7.75 (1H, dd, J=1, 8 Hz), 8.00 (1H, s), 8.14 (1H, dd, J=2, 8 Hz), 10.06 (1H, s). IR (KBr): 1684, 1615, 1602, 1579, 1556 cm^{-1}. EI-MS m/z: 328 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-6-formylbenzo[*b*]furan (42) By a similar method to that described for the preparation of **18b**, **41a** and ethyl 4-bromobutyrate gave **42** (75%) as a pale yellow powder. mp 96—98 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz), 2.31 (2H, m), 2.61 (2H, t, J=7 Hz), 4.16 (2H, m), 4.23 (2H, t, J=6 Hz), 7.02 (1H, d, J=8 Hz), 7.09—7.13 (1H, m), 7.35—7.40 (2H, m), 7.71 (1H, d, J=8 Hz), 7.78 (1H, dd, J=1, 8 Hz), 8.01 (1H, s), 8.11 (1H, dd, J=2, 8 Hz), 10.07 (1H, s). IR (KBr): 2987, 1728, 1683, 1613 cm^{-1}. EI-MS m/z: 352 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]benzo[*b*]furan-6-carboxylic Acid (43) By a similar method to that described for the preparation of **20b**, **42** gave **43** (90%) as a white powder. mp 155—156 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz), 2.31 (2H, m), 2.61 (2H, t, J=7 Hz), 4.16 (2H, m), 4.23 (2H, t, J=6 Hz), 7.02 (1H, d, J=8 Hz), 7.11 (1H, m), 7.35—7.40 (2H, m), 7.71 (1H, d, J=8 Hz), 7.78 (1H, dd, J=1, 8 Hz), 8.01 (1H, s), 8.11 (1H, dd, J=2, 8 Hz), 10.07 (1H, s). IR (KBr): 2987, 1728, 1683, 1613 cm^{-1}. EI-MS m/z: 368 (M^+).

4-[2-[6-(*N*-Diphenylmethylcarbamoyl)benzo[*b*]furan-2-yl]-phenyloxy]butyric Acid (44a) 2,4,6-Triisopropylbenzenesulfonyl chloride (373 mg, 1.23 mmol) was added in three portions every 30 min to a solution of a mixture of **43** (300 mg, 0.814 mmol), diphenylmethylamine (226 mg, 1.23 mmol), Et_3N (283 μl, 2.04 mmol), and 4-dimethylaminopyridine (5.0 mg) in CH_2Cl_2 (6.0 ml) and the whole was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with CH_2Cl_2–EtOAc (24 : 1—23 : 2) was concentrated under reduced pressure to give a residue, which was recrystallized from acetone–*n*-hexane to afford *N*-diphenylmethyl-2-[2-(3-ethoxycarbonyl-1-propyloxy)phenyl]benzo[*b*]furan-6-carboxamide (390 mg, 90%) as a white powder. mp 168—170 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 2.26—2.34 (2H, m), 2.61 (2H, t, J=7 Hz), 4.15 (2H, q, J=7 Hz), 4.22 (2H, d, J=6 Hz), 6.50 (1H, d, J=8 Hz), 6.73 (1H, d, J=8 Hz), 7.01 (1H, d, J=9 Hz), 7.09 (1H, t, J=8 Hz), 7.27—7.40 (12H, m), 7.63 (1H, d, J=8 Hz), 7.70 (1H, dd, J=1, 8 Hz), 8.03 (1H, s), 8.07 (1H, dd, J=2, 8 Hz). IR (KBr): 3317, 3062, 3030, 2978, 2938, 1733, 1632, 1603, 1582 cm^{-1}. EI-MS m/z: 533 (M^+). *Anal*. Calcd for $C_{34}H_{31}NO_5$: C, 76.53; H, 5.86; N, 2.63. Found: C, 76.33; H, 5.88; N, 2.58.

A solution of the amide (380 mg, 0.712 mmol) in a mixture of 15% KOH aqueous solution (4.0 ml) and 1,4-dioxane (8.0 ml) was stirred under reflux under N_2 atmosphere for 2 h. The reaction mixture was acidified with 1 N HCl and extracted with $CHCl_3$ containing 3% MeOH. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent

was removed under reduced pressure and the residue was recrystallized from EtOAc–*n*-hexane to give **44a** (325 mg, 90%) as a white powder. mp 195—197 °C. ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 2.25—2.33 (2H, m), 2.62 (2H, t, J=7 Hz), 4.23 (2H, t, J=6 Hz), 6.49 (1H, m), 7.02 (1H, d, J=8 Hz), 7.09 (1H, t, J=8 Hz), 7.27—7.40 (13H, m), 7.64 (1H, d, J=8 Hz), 7.70 (1H, dd, J=1, 8 Hz), 8.02 (1H, s), 8.06 (1H, dd, J=2, 8 Hz). IR (KBr): 3327, 3062, 3030, 2931, 1709, 1630, 1602, 1582 cm^{-1}. EI-MS *m/z*: 505 (M^+). *Anal*. Calcd for $C_{32}H_{27}NO_5 \cdot 1/5H_2O$: C, 75.49; H, 5.42; N, 2.75. Found: C, 75.41; H, 5.32; N, 2.69.

4-[2-[6-[*N*-(4,4′-Difluorodiphenylmethyl)carbamoyl]benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (**44b**): By a similar method to that described for the preparation of **44a**, **43** and 4,4′-difluorodiphenylmethylamine gave **44b** (69%) as a white powder. mp 193—195 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.14 (2H, m), 2.49 (2H, t, J=6 Hz), 4.22 (2H, t, J=7 Hz), 6.47 (1H, d, J=9 Hz), 7.13 (1H, t, J=7 Hz), 7.17—7.23 (5H, m), 7.40—7.46 (6H, m), 7.76 (1H, d, J=8 Hz), 7.86 (1H, dd, J=1, 9 Hz), 7.99 (1H, dd, J=2, 8 Hz), 8.23 (1H, s), 9.29 (1H, d, J=8 Hz), 12.19 (1H, br s). IR (KBr): 3300, 1694, 1633, 1508 cm^{-1}. EI-MS *m/z*: 541 (M^+). *Anal*. Calcd for $C_{32}H_{25}F_2NO_5$: C, 70.97; H, 4.65; F, 7.02; N, 2.59. Found: C, 70.85; H, 4.78; F, 7.02; N, 2.69.

4-[2-[6-[*N*-(4,4′-Dimethoxydiphenylmethyl)carbamoyl]benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (**44c**): By a similar method to that described for the preparation of **44a**, **43** and 4,4′-dimethoxydiphenylmethylamine gave **44c** (73%) as a white powder. mp 207—209 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.14 (2H, m), 2.45 (2H, t, J=7 Hz), 3.74 (6H, s), 4.22 (2H, t, J=6 Hz), 6.34 (1H, d, J=9 Hz), 6.91 (4H, d, J=9 Hz), 7.13 (1H, t, J=8 Hz), 7.22 (1H, d, J=8 Hz), 7.29 (4H, d, J=9 Hz), 7.40—7.44 (2H, m), 7.75 (1H, d, J=8 Hz), 7.86 (1H, dd, J=1, 8 Hz), 7.99 (1H, dd, J=1, 8 Hz), 8.22 (1H, s), 9.17 (1H, d, J=9 Hz), 12.20 (1H, br s). IR (KBr): 3312, 1713, 1632, 1511 cm^{-1}. FAB-MS *m/z*: 565 (M^+). *Anal*. Calcd for $C_{34}H_{31}NO_7$: C, 72.20; H, 5.53; N, 2.48. Found: C, 71.91; H, 5.63; N, 2.60.

4-[2-[6-[*N*-(1,2-Diphenylethyl)carbamoyl]benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (**44d**): By a similar method to that described for the preparation of **44a**, **43** and 1,2-diphenylethylamine gave **44d** (82%) as a white powder. mp 177—179 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.14 (2H, m), 2.49 (2H, t, J=7 Hz), 3.07—3.25 (2H, m), 4.22 (2H, t, J=7 Hz), 5.31 (1H, m), 7.11—7.50 (14H, m), 7.73 (2H, s), 7.98 (1H, dd, J=2, 8 Hz), 8.08 (1H, s), 8.91 (1H, d, J=9 Hz), 12.18 (1H, br s). IR (KBr): 3306, 2958, 1712, 1631, 1530 cm^{-1}. FAB-MS *m/z*: 520 ((M+1)$^+$). *Anal*. Calcd for $C_{33}H_{29}NO_5 \cdot 1/2H_2O$: C, 74.98; H, 5.72; N, 2.65. Found: C, 74.89; H, 5.84; N, 2.48.

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-5-benzyloxycarbonylaminobenzo[*b*]furan (45) A solution of a mixture of **20b** (2.00 g, 5.43 mmol), DPPA (2.09 g, 7.59 mmol), and Et_3N (1.21 ml, 8.73 mmol) in toluene (20 ml) was stirred under reflux for 2 h. Then benzylalcohol (5.0 ml) was added to the reaction solution and the whole was stirred under reflux for 8 h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–EtOAc (4 : 1) was concentrated under reduced pressure to give a residue, which was recrystallized from Et_2O–*n*-hexane to afford **45** (1.91 g, 74%) as a white powder. mp 90—91 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz), 2.25—2.32 (2H, m), 2.61 (2H, t, J=7 Hz), 4.16 (2H, q, J=7 Hz), 4.21 (2H, t, J=6 Hz), 5.23 (2H, s), 6.68 (1H, br s), 6.99 (1H, d, J=8 Hz), 7.07 (1H, t, J=8 Hz), 7.15 (1H, dd, J=2, 9 Hz), 7.26—7.46 (8H, m), 7.74 (1H, br s), 8.04 (1H, dd, J=2, 8 Hz). IR (KBr): 3363, 1732, 1715, 1603, 1557 cm^{-1}. EI-MS *m/z*: 473 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-6-benzyloxycarbonylaminobenzo[*b*]furan (**46**): By a similar method to that described for the preparation of **45**, **43** gave **46** (53%) as a white powder. mp 96—98 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.16 (3H, t, J=7 Hz), 2.15 (2H, m), 2.55 (2H, t, J=7 Hz), 4.06 (2H, m), 4.20 (2H, t, J=6 Hz), 5.19 (2H, s), 7.26—7.47 (8H, m), 7.55 (1H, d, J=9 Hz), 7.87 (1H, s), 7.93 (1H, dd, J=2, 8 Hz), 9.96 (1H, s). IR (KBr): 3337, 1733, 1545 cm^{-1}. EI-MS *m/z*: 473 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-5-(*N*-benzyloxycarbonyl-*N*-diphenylmethylamino)benzo[*b*]furan (47a) NaH (55%, 24.0 mg, 0.550 mmol) was added to a solution of **45** (200 mg, 0.422 mmol) in DMF (3.0 ml) under N_2 atmosphere and the mixture was stirred at room temperature for 15 min. Then diphenylmethyl bromide (157 mg, 0.635 mmol) was added to the mixture and the whole was stirred at 60 °C for 3 h. The reaction mixture was poured into ice-cooled 1 N HCl and extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–EtOAc (4 : 1) was concentrated under reduced pressure to give **47a** (217 mg, 80%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 2.22—2.32 (2H, m), 2.58 (2H, t, J=7 Hz), 4.14 (2H, q, J=7 Hz), 4.19 (2H, t, J=6 Hz), 5.16 (2H, s), 6.69 (1H, s), 6.77 (1H, dd, J=1, 9 Hz), 6.98 (1H, d, J=8 Hz), 7.05 (1H, t, J=8 Hz), 7.12—7.35 (19H, m), 8.00 (1H, dd, J=2, 8 Hz). IR ($CHCl_3$): 2960, 2943, 1728, 1693, 1603, 1587 cm^{-1}. EI-MS *m/z*: 639 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-5-[*N*-benzyloxycarbonyl-*N*-(4,4′-difluorodiphenylmethyl)amino]benzo[*b*]furan (**47b**): By a similar method to that described for the preparation of **47a**, **45** and 4,4′-difluorodiphenylmethyl chloride gave **47b** (91%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 2.23—2.31 (2H, m), 2.58 (2H, t, J=7 Hz), 4.15 (2H, q, J=7 Hz), 4.19 (2H, t, J=6 Hz), 5.15 (2H, s), 6.62 (1H, s), 6.72 (1H, dd, J=2, 8 Hz), 6.90—7.35 (19H, m), 8.02 (1H, dd, J=2, 8 Hz). IR ($CHCl_3$): 2985, 2964, 2884, 1728, 1694, 1606 cm^{-1}. EI-MS *m/z*: 675 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-6-(*N*-benzyloxycarbonyl-*N*-diphenylmethylamino)benzo[*b*]furan (**48**): By a similar method to that described for the preparation of **47a**, **46** and diphenylmethyl bromide gave **48** (76%) as an amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, t, J=7 Hz), 2.12 (2H, m), 2.53 (2H, t, J=7 Hz), 4.04 (2H, m), 4.19 (2H, t, J=6 Hz), 5.08 (2H, s), 6.63 (1H, s), 6.90 (1H, dd, J=1, 8 Hz), 7.07 (1H, t, J=7 Hz), 7.12—7.39 (18H, m), 7.45 (1H, d, J=8 Hz), 7.88 (1H, dd, J=2, 8 Hz). IR ($CHCl_3$): 2985, 1727, 1694 cm^{-1}. EI-MS *m/z*: 639 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-5-aminobenzo[*b*]furan (49) A suspension of a mixture of **45** (820 mg, 1.73 mmol) and 10% Pd–C (82 mg) in MeOH (50 ml) was stirred at room temperature under H_2 atmosphere for 1 h. The palladium catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel. The eluate with CH_2Cl_2–EtOAc (23 : 2—9 : 1) was concentrated under reduced pressure and the residue was recrystallized from Et_2O–*n*-hexane to give **49** (470 mg, 85%) as a pale brown powder. mp 78—80 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz), 2.24—2.32 (2H, m), 2.60 (2H, t, J=7 Hz), 3.64 (2H, br s), 4.12—4.22 (4H, m), 6.67 (1H, dd, J=2, 8 Hz), 6.89 (1H, d, J=2 Hz), 6.98 (1H, d, J=9 Hz), 7.06 (1H, t, J=8 Hz), 7.17 (1H, s), 7.26—7.31 (2H, m), 8.02 (1H, dd, J=2, 8 Hz). IR (KBr): 3466, 3366, 2980, 2964, 2903, 2874, 1724, 1627, 1603, 1584 cm^{-1}. EI-MS *m/z*: 339 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-6-aminobenzo[*b*]furan (**50**): By a similar method to that described for the preparation of **49**, **46** gave **50** (80%) as a pale brown powder. mp 76—77 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz), 2.24—2.32 (2H, m), 2.61 (2H, t, J=7 Hz), 3.70 (2H, s), 4.16 (2H, q, J=7 Hz), 4.19 (2H, t, J=6 Hz), 6.63 (1H, dd, J=2, 8 Hz), 6.84 (1H, s), 6.96 (1H, d, J=8 Hz), 7.05 (1H, t, J=8 Hz), 7.19 (1H, s), 7.24 (1H, m), 7.36 (1H, d, J=8 Hz), 7.99 (1H, dd, J=2, 8 Hz). IR (KBr): 3391, 3296, 3202, 3064, 2982, 2964, 1724, 1625, 1597, 1583 cm^{-1}. EI-MS *m/z*: 339 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-5-(*N*-diphenylmethylamino)benzo[*b*]furan (51a) A suspension of a mixture of **47a** (197 mg, 0.308 mmol) and 10% Pd–C (20 mg) in a mixture of MeOH (3.0 ml) and EtOAc (1.0 ml) was stirred at room temperature under H_2 atmosphere for 12 h. The palladium catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel. The eluate with *n*-hexane–EtOAc (9 : 1) was concentrated under reduced pressure to give **51a** (90.0 mg, 58%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz), 2.17—2.28 (2H, m), 2.55 (2H, t, J=7 Hz), 4.11 (2H, q, J=7 Hz), 4.14 (2H, t, J=6 Hz), 5.53 (1H, s), 6.58 (1H, dd, J=2, 9 Hz), 6.65 (1H, d, J=2 Hz), 6.93 (1H, d, J=8 Hz), 7.02 (1H, t, J=7 Hz), 7.10 (1H, s), 7.21—7.42 (12H, m), 7.99 (1H, dd, J=2, 8 Hz). IR ($CHCl_3$): 3425, 2985, 2942, 2877, 1728, 1619, 1600, 1586 cm^{-1}. EI-MS *m/z*: 505 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-5-[*N*-(4,4′-difluorodiphenylmethyl)amino]benzo[*b*]furan (**51b**): By a similar method to that described for the preparation of **51a**, **47b** gave **51b** (81%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz), 2.21—2.29 (2H, m), 2.56 (2H, t, J=7 Hz), 4.07 (1H, s), 4.10—4.19 (4H, m), 5.50 (1H, s), 6.58 (1H, dd, J=2, 9 Hz), 6.61 (1H, d, J=2 Hz), 6.96 (1H, d, J=9 Hz), 6.99—7.07 (5H, m), 7.10 (1H, s), 7.24—7.37 (6H, m), 8.00 (1H, dd, J=2, 8 Hz). IR ($CHCl_3$): 2985, 2943, 1728, 1619, 1604 cm^{-1}. EI-MS *m/z*: 541 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-5-[*N*-(4,4′-dimethoxydiphenylmethyl)amino]benzo[*b*]furan (51c) A solution of a mixture of **49** (100 mg, 0.295 mmol), 4,4′-dimethoxydiphenylmethyl chloride (117 mg, 0.445 mmol), and *N*,*N*-diisopropylethylamine (102 mg, 0.885 mmol) in CH_2Cl_2 (3.0 ml) was stirred at room temperature for 1 d. The reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–EtOAc (17 : 3) was

concentrated under reduced pressure to give **51c** (75.0 mg, 45%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz), 2.21—2.29 (2H, m), 2.57 (2H, t, J=7 Hz), 3.79 (6H, s), 4.10—4.19 (4H, m), 5.45 (1H, s), 6.58 (1H, dd, J=2, 9 Hz), 6.64 (1H, d, J=2 Hz), 6.87 (4H, d, J=9 Hz), 6.96 (1H, d, J=8 Hz), 7.04 (1H, t, J=8 Hz), 7.10 (1H, s), 7.22—7.31 (2H, m), 7.29 (4H, d, J=9 Hz), 8.00 (1H, dd, J=2, 8 Hz). IR ($CHCl_3$): 2960, 2938, 2840, 1728, 1611, 1586 cm^{-1}. EI-MS m/z: 565 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-6-(*N*-diphenylmethylamino)benzo[*b*]furan (52a) By a similar method to that described for the preparation of **51a**, **48** gave **52a** (69%) as an oil. ^{1}H-NMR (DMSO-d_6) δ: 1.16 (3H, t, J=7 Hz), 2.12 (2H, m), 2.53 (2H, t, J=7 Hz), 4.06 (2H, m), 4.16 (2H, t, J=6 Hz), 5.73 (1H, d, J=6 Hz), 6.66—6.69 (2H, m), 6.79 (1H, dd, J=2, 8 Hz), 7.02 (1H, t, J=7 Hz), 7.06—7.14 (2H, m), 7.22—7.39 (8H, m), 7.44—7.46 (4H, m), 7.80 (1H, dd, J=2, 8 Hz). IR ($CHCl_3$): 3429, 2984, 1728, 1627 cm^{-1}. EI-MS m/z: 505 (M^+).

2-[2-(3-Ethoxycarbonyl-1-propyloxy)phenyl]-6-[*N*-(4,4′-dimethoxydiphenylmethyl)amino]benzo[*b*]furan (52b) By a similar method to that described for the preparation of **51c**, **50** gave **52b** (62%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 2.23—2.30 (2H, m), 2.59 (2H, t, J=7 Hz), 3.79 (6H, s), 4.12—4.19 (4H, m), 4.28 (1H, br s), 5.47 (1H, s), 6.56 (1H, dd, J=2, 9 Hz), 6.60 (1H, s), 6.87 (4H, d, J=9 Hz), 6.94 (1H, d, J=8 Hz), 7.01 (1H, t, J=7 Hz), 7.16 (1H, s), 7.19—7.34 (2H, m), 7.29 (4H, d, J=9 Hz), 7.93 (1H, dd, J=2, 8 Hz). IR ($CDCl_3$): 3399, 2956, 2935, 2836, 1731, 1626, 1610, 1585 cm^{-1}. EI-MS m/z: 565 (M^+).

4-[2-[5-(*N*-Diphenylmethylamino)benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (53a) A solution of **51a** (80.0 mg, 0.158 mmol) in a mixture of 15% KOH aqueous solution (1.5 ml) and 1,4-dioxane (3.0 ml) was stirred under reflux under N_2 atmosphere for 3 h. The reaction mixture was acidified with 1 N HCl and extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give **53a** (74.0 mg, 97%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 2.22—2.30 (2H, m), 2.63 (2H, t, J=7 Hz), 4.18 (2H, t, J=6 Hz), 5.54 (1H, s), 6.60 (1H, dd, J=2, 9 Hz), 6.65 (1H, d, J=2 Hz), 6.95 (1H, d, J=8 Hz), 7.04 (1H, t, J=8 Hz), 7.08 (1H, s), 7.22—7.44 (12H, m), 7.99 (1H, dd, J=2, 8 Hz). IR (KBr): 3416, 3061, 3028, 2930, 1709, 1619, 1599, 1585 cm^{-1}. EI-MS m/z: 477 (M^+).

4-[2-[5-[*N*-(4,4′-Difluorodiphenylmethyl)amino]benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (**53b**): By a similar method to that described for the preparation of **53a**, **51b** gave **53b** (85%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 2.22—2.30 (2H, m), 2.63 (2H, t, J=7 Hz), 4.18 (2H, t, J=6 Hz), 5.49 (1H, s), 6.57 (1H, dd, J=3, 9 Hz), 6.61 (1H, d, J=8 Hz), 6.96 (1H, d, J=8 Hz), 6.99—7.07 (5H, m), 7.08 (1H, s), 7.24—7.36 (6H, m), 7.99 (1H, dd, J=2, 8 Hz). IR (KBr): 3412, 3068, 2928, 1710, 1618, 1602 cm^{-1}. EI-MS m/z: 513 (M^+).

4-[2-[5-[*N*-(4,4′-Dimethoxydiphenylmethyl)amino]benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (**53c**): By a similar method to that described for the preparation of **53a**, **51c** gave **53c** (94%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 2.22—2.30 (2H, m), 2.63 (2H, t, J=7 Hz), 3.79 (6H, s), 4.17 (2H, t, J=6 Hz), 5.44 (1H, s), 6.58 (1H, dd, J=2, 9 Hz), 6.61 (1H, d, J=2 Hz), 6.87 (4H, d, J=9 Hz), 6.95 (1H, d, J=8 Hz), 7.04 (1H, t, J=8 Hz), 7.08 (1H, s), 7.22—7.35 (2H, m), 7.30 (4H, d, J=9 Hz), 7.99 (1H, dd, J=2, 8 Hz). IR (KBr): 3399, 2952, 2933, 2836, 1709, 1610, 1585 cm^{-1}. EI-MS m/z: 537 (M^+).

4-[2-[6-(*N*-Diphenylmethylamino)benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (**54a**): By a similar method to that described for the preparation of **53a**, **52a** gave **54a** (59%) as an amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 2.09 (2H, m), 2.47 (2H, t, J=7 Hz), 4.15 (2H, t, J=6 Hz), 5.73 (1H, d, J=6 Hz), 6.66—6.69 (2H, m), 6.89 (1H, dd, J=2, 9 Hz), 7.01 (1H, t, J=7 Hz), 7.11 (1H, d, J=8 Hz), 7.14 (1H, s), 7.21—7.36 (8H, m), 7.44—7.46 (4H, m), 7.80 (1H, dd, J=2, 8 Hz), 12.20 (1H, br s). IR (KBr): 3398, 3021, 2953, 2922, 1712, 1626, 1599, 1586 cm^{-1}. EI-MS m/z: 477 (M^+).

4-[2-[6-[*N*-(4,4′-Dimethoxydiphenylmethyl)amino]benzo[*b*]furan-2-yl]phenyloxy]butyric Acid (**54b**): By a similar method to that described for the preparation of **53a**, **52b** gave **54b** (86%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 2.24—2.31 (2H, m), 2.66 (2H, t, J=7 Hz), 3.79 (6H, s), 4.18 (2H, t, J=6 Hz), 5.47 (1H, s), 6.56 (1H, dd, J=2, 8 Hz), 6.59 (1H, s), 6.87 (4H, d, J=9 Hz), 6.94 (1H, d, J=9 Hz), 7.01 (1H, t, J=8 Hz), 7.14 (1H, s), 7.17—7.37 (2H, m), 7.28 (4H, d, J=9 Hz), 7.93 (1H, dd, J=2, 8 Hz). IR (KBr): 3414, 2954, 2934, 2836, 1709, 1626, 1610, 1585 cm^{-1}. FAB-MS m/z: 537 (M^+).

2-[2-(3-Methoxycarbonyl-1-propyloxy)phenyl]-5-hydroxybenzo[*b*]-furan (55) A solution of $NaNO_2$ (25.0 mg, 0.362 mmol) in H_2O (0.070 ml) was added to a solution of **49** (100 mg, 0.295 mmol) in a mixture of H_2O (0.30 ml) and conc.H_2SO_4 (0.053 ml) during 15 min while the reaction temperature was kept under 20 °C and the whole was stirred for 5 min. Then, ice (300 mg) and urea (2.2 mg, 0.0366 mmol) were added to the reaction solution. The whole was added to a solution of Na_2SO_4 (111 mg, 0.781 mmol) in a mixture of H_2O (0.074 ml) and H_2SO_4 (0.080 ml) at 80 °C and the reaction solution was stirred for 15 min. The reaction mixture was poured into brine and extracted with $CHCl_3$. The combined organic layer was dried and concentrated under reduced pressure to give a residue. A solution of the residue in MeOH (5.0 ml) and conc.H_2SO_4 (1 drop) was stirred under reflux for 30 min. The reaction mixture was poured into $NaHCO_3$ aqueous solution and extracted with $CHCl_3$. The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–EtOAc (49 : 1—19 : 1) was concentrated under reduced pressure to give a residue, which was triturated with Et_2O to give **55** (20.0 mg, 21%) as a pale orange powder. mp 152—154 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.24—2.34 (2H, m), 2.62 (2H, t, J=7 Hz), 3.70 (3H, s), 4.20 (2H, t, J=6 Hz), 4.67 (1H, s), 6.79 (1H, dd, J=3, 9 Hz), 6.97—7.10 (3H, m), 7.21 (1H, s), 7.27—7.37 (2H, m), 8.03 (1H, dd, J=2, 8 Hz). IR (KBr): 3382, 1717, 1601 cm^{-1}. EI-MS m/z: 326 (M^+).

2-[2-(3-Methoxycarbonyl-1-propyloxy)phenyl]-5-diphenylmethyloxybenzo[*b*]furan (56) NaH (55%, 6.0 mg, 0.138 mmol) was added to a solution of **55** (42.0 mg, 0.123 mmol) in DMF (3.0 ml) under N_2 atmosphere and the mixture was stirred at room temperature for 30 min. Then, diphenylmethyl bromide (37.0 mg, 0.150 mmol) was added to the mixture and the whole was stirred at room temperature for 3 h. The reaction mixture was poured into ice-cooled 1 N HCl and extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. The eluate with *n*-hexane–EtOAc (99 : 1—49 : 1) was concentrated under reduced pressure to give a residue, which was triturated with acetone–Et_2O to give **56** (38.0 mg, 61%) as a white powder. mp 133—135 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.22—2.32 (2H, m), 2.59 (2H, t, J=7 Hz), 3.67 (3H, s), 4.18 (2H, t, J=6 Hz), 6.24 (1H, s), 6.95—7.09 (4H, m), 7.16 (1H, s), 7.25—7.38 (8H, m), 7.46 (4H, d, J=7 Hz), 8.01 (1H, dd, J=2, 8 Hz). IR (KBr): 3028, 2953, 2942, 1730, 1614, 1597, 1583 cm^{-1}. EI-MS m/z: 492 (M^+).

4-[2-(5-Diphenylmethyloxybenzo[*b*]furan-2-yl)phenyloxy]butyric Acid (57) By a similar method to that described for the preparation of **53a**, **56** gave **57** (98%) as a white powder. mp 154—156 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.23—2.30 (2H, m), 2.64 (2H, t, J=7 Hz), 4.18 (2H, t, J=6 Hz), 6.24 (1H, s), 6.94—6.97 (2H, m), 7.03—7.09 (2H, m), 7.15 (1H, s), 7.24—7.36 (8H, m), 7.46 (4H, d, J=7 Hz), 8.00 (1H, dd, J=2, 8 Hz). IR (KBr): 3062, 3032, 2943, 1708, 1613, 1597, 1584 cm^{-1}. EI-MS m/z: 478 (M^+). *Anal*. Calcd for $C_{31}H_{26}O_5 \cdot 1/2H_2O$: C, 76.37; H, 5.58. Found: C, 76.24; H, 5.40.

Preparation of 5α-Reductase from Rat and Human Prostates and 5α-Reductase Assay Preparation of 5α-reductase from rat and human prostates and 5α-reductase assay were carried out by the procedure described in the previous report.[4b]

cDNA Cloning and Expression of Human Type 1 and Type 2 5α-Reductase in COS-1 Cells The cDNA of human 5α-reductase type 1 and type 2 were obtained by the polymerase chain reaction method from human cDNA libraries of liver and prostate (Clontech Laboratories, Inc.), respectively. They were ligated into pME18s expression vector. Transient transfections of COS-1 cells were carried out by the electroporation method (Gene Pulser™, Bio-Rad Laboratories, 960 μFD, 200 ohm, 300 V) with type 1 or type 2 expression vector. The cells were harvested for 48 h after transfection and were broken by freezing and thawing in 20 mM potassium phosphate buffer, pH 7.4, containing 10% glycerol, 0.33 M sucrose, 50 μM NADPH and 0.001% phenylmethylsulfonyl fluoride (PMSF). The broken cells were then homogenized by Polytron (Kinematica GmbH) and centrifuged at 10000×***g***. The pellet was resuspended in buffer and stored at −80 °C until assay. These crude membrane fractions were used as human type 1 and type 2 5α-reductase.

Biological Assay Using Human Type 1 and Type 2 5α-Reductase The reaction solution of type 1 was 40 mM potassium phosphate buffer, pH 7.5, containing 1 μM [^{14}C]testosterone, 1 mM dithiothreitol, and 0.5 mM NADPH, and that of type 2 was 100 mM Tris–citrate buffer, pH 5.5, containing 1 μM [^{14}C]testosterone, 1 mM dithiothreitol, and 1 mM NADPH. Test sample was added to 5 ml of DMSO and the control tube received the same volume of DMSO. The reaction was carried out for 15 min at 37 °C and then stopped with 2 ml of ethyl acetate containing testosterone, 5α-dihydrotestosterone, and androstenedione (10 μg each). After centrifugation at 1000×***g*** for 5 min, the ethyl acetate phase (upper) was transferred to a tube and then evaporated to dryness under nitrogen. The steroid was taken up in 30 μl of

ethyl acetate and the solution was applied to a Whatman LK5DF or LK6DF silica plate. The plate was developed in ethyl acetate–cyclohexane (1 : 1) at room temperature and air-dried, and the chromatography was then repeated. The radioactivity profile was determined with a bio-image analyzer (Fuji Film Co., Ltd.).

Acknowledgments The authors thank Mr. Yoji Furukawa for the X-ray crystal structure analysis and Ms. Tomoko Inaba for the biological assay. They are also grateful to Dr. Syuichi Miyamoto and Ms. Yoriko Iwata for calculation of the stable conformations.

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11) Crystal data of **44c**; $C_{34}H_{31}NO_7$, M.W.=565.6, T=298K, Cu$K\alpha$ radiation, λ=1.5418 Å, monoclinic, C2/c, a=34.838(5) Å, b=5.061(5) Å, c=34.808(5) Å, β=109.69(5)°, V=5788(5) Å^3, Z=8, R=0.067, R_w=0.066. Full X-ray crystallographic data has been deposited with the Cambridge Crystallographic Data Centre.
12) The stable conformations of **44a** were estimated using CHARMm/QUANTA. The structure in which the two methoxy groups were excluded from the X-ray structure of **44c** was used as an initial conformation.