Syntheses of 4-(Benzo[*b*]furan-2 or 3-yl)- and 4-(Benzo[*b*]-thiophen-3-yl)piperidines with 5-HT_2 Antagonist Activity

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The syntheses of 4-(benzo[*b*]furan-3-yl)piperidines, 4-(benzo[*b*]furan-2-yl)piperidines and 4-(benzo[*b*]thiophen-3-yl)piperidines with 5-HT_2 antagonist activity are described. Reaction of 1-acetyl-4-(2,4-difluorobenzoyl)piperidine **2** with methyl glycolate gave methyl 6-fluoro-3-(1-acetylpiperidin-4-yl)benzo[*b*]furan-2-carboxylate **3**, which was converted to 2-[2-[4-(benzo[*b*]furan-3-yl)piperidin-1-yl]ethyl-5,6,7,8-tetrahydro-1,2,4-triazolo-[4,3-*a*]pyridin-3(2*H*)-one hydrochloride **9**. Analogous benzo[*b*]furans **17a-d** and benzo[*b*]thiophenes **10a,b** and **18a** were prepared by a similar method. Cyclization of 4-fluoro-2-(4-pyridinylmethoxy)acetophenones **20a,b** afforded 4-(benzo[*b*]furan-2-yl)pyridines **21a,b**, which were converted to 2-[2-[4-(benzo[*b*]furan-2-yl)-piperidin-1-yl]ethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochlorides **24a,b**. Among them, benzo[*b*]furans **9** and **17a,d** and benzo[*b*]thiophenes **10** and **18a** showed potent 5-HT_2 antagonist activity *in vitro*.

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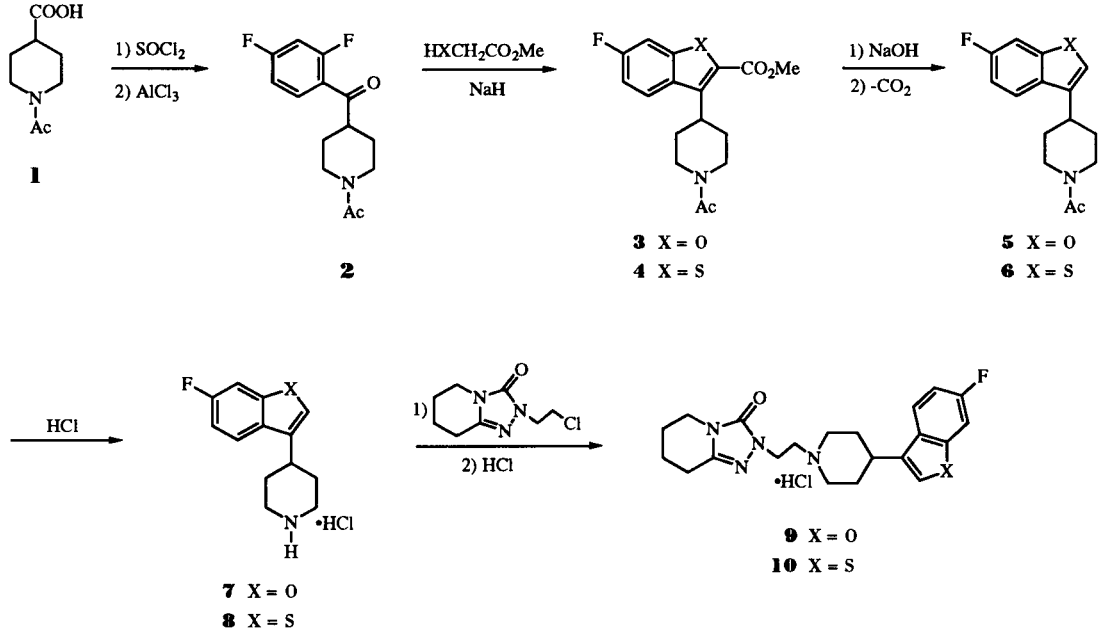
Introduction.

Serotonin S_2 (5-HT_2) receptors are present in brain tissue and in various smooth muscle cells and blood platelets. Although the physiological role of central 5-HT_2 receptors is not fully understood, it is known that many neuroleptics and antidepressants have 5-HT_2 antagonist activity [1]. On the other hand, peripheral 5-HT_2 receptors mediate vasoconstriction and platelet aggregation which appear to be relevant to some cardiovascular diseases [2]. A variety of the antagonists, therefore, have been prepared to develop CNS agents or cardiovascular drugs, most of which have a characteristic structure with a piperidine or piperazine moiety; *i.e.* 4-(indol-3-yl)piperidines [3], 4-benzoylpiperidines [4], 4-(biphenylmethylene)piperidines [5,6], 4-arylpiperidines [6], 4-arylpiperazines [6,7] or 4-(3-phenylindan-1-yl)piperazines [8]. In the present paper, we describe the syntheses of 4-(benzo[*b*]furan-3-yl)piperidines, 4-(benzo[*b*]furan-2-yl)piperidines and 4-(benzo[*b*]thiophen-3-yl)piperidines with 5-HT_2 antagonists.

We have previously reported that 2-[2-[4-[bis(4-fluorophenyl)methylene]piperidin-1-yl]ethyl]-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one is a potent 5-HT_2 antagonist and, thereby, demonstrated that the 2-ethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one group is an important moiety of 5-HT_2 antagonists [9]. We, therefore, introduced this structural component into the above piperidines to produce 5-HT_2 antagonists.

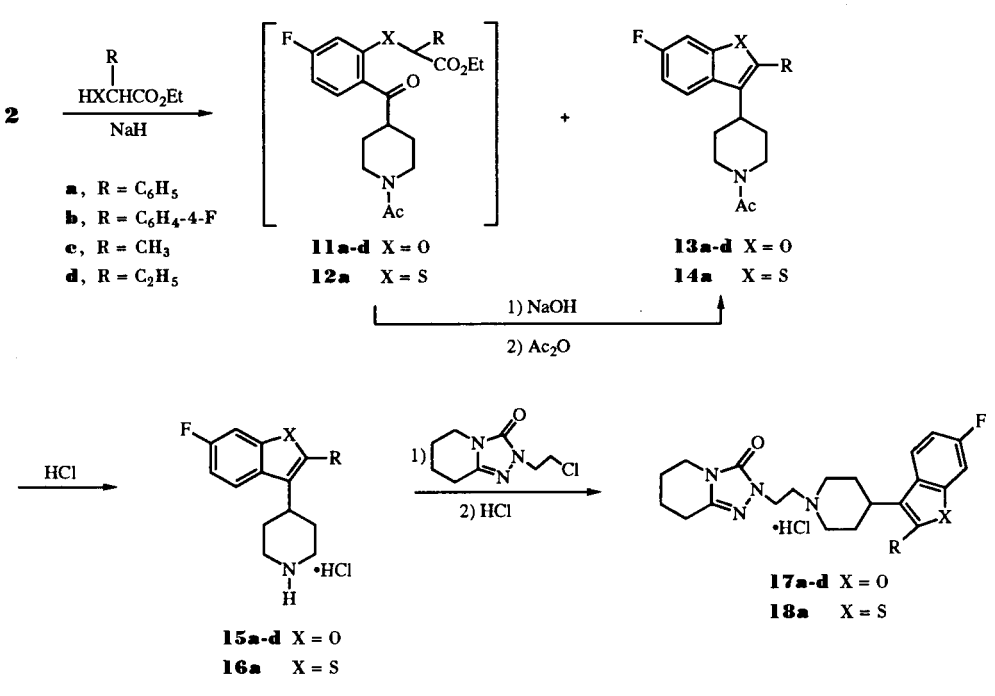
Scheme 1



Chemistry.

The synthetic pathways of 4-(benzo[*b*]furan-3-yl)piperidines and 4-(benzo[*b*]thiophen-3-yl)piperidines are shown in Schemes 1 and 2. A key compound, 1-acetyl-4-(2,4-difluorobenzoyl)piperidine **2**, was prepared by the method for the corresponding 1-formyl derivative described by Strupczewski *et al.* [10]. The reaction of **2** with methyl glycolate in the presence of sodium hydride gave benzo[*b*]-furan-2-carboxylate **3** in 35% yield. After hydrolysis of the ester group, the resulting carboxylic acid was heated in quinoline with copper powder to give decarboxylated compound **5**, which was treated with hydrochloric acid to afford deacetylated compound **7** in 59% yield from **3**. Similarly, the corresponding benzo[*b*]thiophene-2-carboxylate **4** was prepared in 38% yield, and the successive reactions gave **8** in 69% yield from **4**. The reaction of 2-(2-

Scheme 2



Scheme 3

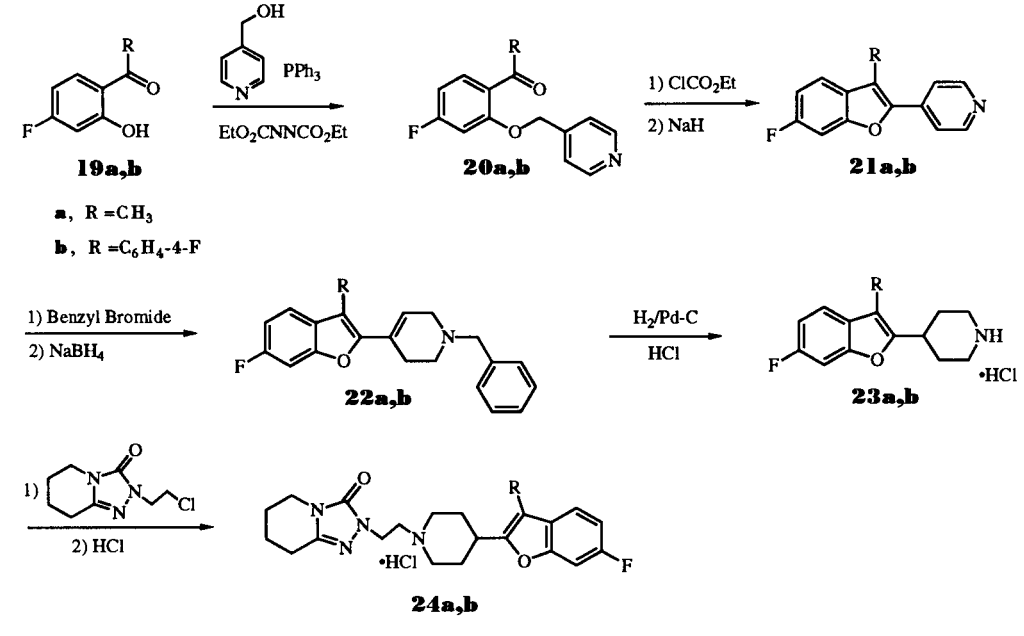
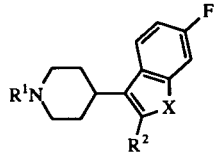


Table 1

Benzofurans and Benzothiophenes



Compound	X	R^1	R^2	Mp °C	Crystalization Solvent	Yield	Formula	Analysis C	H	N
3	O	Ac	CO_2Me	141-143	isopropyl ether	35	$C_{17}H_{18}FNO_4$	63.94	5.68	4.38
								63.82	5.71	4.42
4	S	Ac	CO_2Me	174-176	isopropyl ether	38	$C_{17}H_{18}FNO_3S$	60.88	5.41	4.17
								60.63	5.48	4.13
5	O	Ac	H	oil	–	69				
6	S	Ac	H	oil	–	88				
7 [a]	O	H	H	239-241	methanol-ether	95	$C_{13}H_{15}ClFNO$	61.06	5.91	5.47
								60.82	5.65	5.32
8 [a]	S	H	H	>285	methanol-ether	96	$C_{13}H_{15}ClFNS$	57.45	5.56	5.15
								57.44	5.72	5.04
9 [a]	O	Trz [e]	H	250-254	methanol-ether	87 [f]	$C_{21}H_{26}ClFN_4O_2$	59.92	6.23	13.31
								59.76	6.07	13.24
10 [a]	S	Trz [e]	H	248-250	methanol-ether	73 [f]	$C_{21}H_{26}ClFN_4OS$	57.72	6.00	12.82
								57.50	5.92	12.66
13a	O	Ac	Ph	oil	–	62				
13b	O	Ac	4-F-Ph	166-168	isopropyl ether	51	$C_{21}H_{19}F_2NO_2$	70.97	5.39	3.94
								70.93	5.54	4.07
13c	O	Ac	Me	128-129	isopropyl ether	31	$C_{16}H_{18}FNO_2$	69.80	6.59	5.08
								69.84	6.71	5.03
13d	O	Ac	Et	85-87	isopropyl ether	15	$C_{17}H_{20}FNO_2$	70.57	6.97	4.84
								70.39	7.13	4.78
14a	S	Ac	Et	oil	–	20				
15a [a]	O	H	Ph	>290	methanol-ether	73	$C_{19}H_{19}ClFNO$	68.78	5.77	4.22
								68.52	5.58	4.13
15b [a]	O	H	4-F-Ph	>290	methanol-ether	89	$C_{19}H_{18}ClF_2NO$	65.24	5.19	4.00
								68.95	5.15	3.84
15c [a]	O	H	Me	>290	methanol-ether	67	$C_{14}H_{17}ClFNO$	62.33	6.35	5.19
								62.56	6.59	5.43
15d [a]	O	H	Et	>290	methanol-ether	98	$C_{15}H_{19}ClFNO$	63.49	6.75	4.39
								63.48	6.71	4.86
16a [a]	S	H	Ph	>290	methanol-ether	64	$C_{19}H_{19}ClFNS$	65.60	5.50	4.02
								65.38	5.64	3.86
17a [a]	O	Trz [e]	Ph	260-265	methanol-ether	65 [f]	$C_{27}H_{30}ClFN_4O_2$	65.25	6.08	11.27
								65.08	5.94	11.25
17b [b]	O	Trz [e]	4-F-Ph	238-241	methanol-ether	58 [f]	$C_{27}H_{31}ClF_2N_4O_3$	60.84	5.86	10.51
								60.83	5.86	10.23
17c [c]	O	Trz [e]	Me	252-256	methanol-ether	74 [f]	$C_{22}H_{29}ClFN_4O_{2.5}$	59.52	6.58	12.62
								59.64	6.49	12.37
17d [c]	O	Trz [e]	Et	252-256	methanol-ether	77 [f]	$C_{23}H_{31}ClFN_4O_{2.5}$	60.34	6.82	12.23
								60.58	6.85	12.30
18a [d]	S	Trz [e]	Ph	211-213	chloroform-isopropyl ether	92 [f]	$C_{31}H_{34}FN_4O_{5.5}S$	61.88	5.69	9.31
								62.07	5.46	9.03

[a] Hydrochloride. [b] Hydrochloride Monohydrate. [c] Hydrochloride Hemihydrate. [d] Maleate Hemihydrate. [e] Trz: 2-Ethyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one. [f] Yield of the free base.

Table 2

^{1}H NMR of Benzofurans and Benzothiophenes

3	(deuteriochloroform): 1.7-2.3 (m, 4H), 2.18 (*s*, 3H), 2.5-3.0 (m, 1H), 3.0-3.5 (m, 1H), 3.7-4.2 (m, 2H), 3.98 (*s*, 3H), 4.7-5.0 (m, 1H), 7.04 (dt, J = 3.4, 9.0 and 9.0 Hz, 1H), 7.25 (dd, J = 3.4 and 9.0 Hz, 1H), 7.72 (dd, J = 7.2 and 9.0 Hz, 1H)
4	(deuteriochloroform): 1.62-2.00 (m, 2H), 2.0-2.4 (m, 2H), 2.2 (*s*, 3H), 2.70 (t-like, 1H), 3.28 (t-like, 1H), 2.50-3.12 (m, 1H), 3.9 (*s*, 3H), 4.2-4.68 (m, 1H), 4.7-5.0 (m, 1H), 7.13 (dt, J = 3.4, 9.0 and 9.0 Hz, 1H), 7.5 (dd, J = 3.4 and 9.0 Hz, 1H), 7.99 (dd, J = 6.0 and 9.0 Hz, 1H)
5	(deuteriochloroform): 1.4-2.3 (m, 4H), 2.15 (*s*, 3H), 2.5-3.42 (m, 3H), 3.75-4.1 (d-like, 1H), 4.6-4.92 (d-like, 1H), 7.02 (dt, J = 2.5, 9.0 and 9.0 Hz, 1H), 7.20 (dd, J = 2.5 and 9.0 Hz, 1H), 7.39 (*s*, 1H), 7.48 (dd, J = 9.0 and 7.2 Hz, 1H)
6	(deuteriochloroform): 1.35-2.32 (m, 4H), 2.14 (*s*, 3H), 2.52-3.50 (m, 3H), 3.8-4.2 (m, 1H), 4.64-5.04 (m, 1H), 7.02 (*s*, 1H), 6.96-7.32 (m, 1H), 7.44-7.87 (m, 2H)
7 [a]	(dimethyl sulfoxide-d_6): 1.75-2.4 (m, 4H), 2.8-3.7 (m, 5H), 7.03-7.37 (m, 1H), 7.55 (dd, J = 3.0 and 9.0 Hz, 1H), 7.82 (m, 2H)
8 [a]	(dimethyl sulfoxide-d_6): 1.75-2.31 (m, 4H), 2.84-3.66 (m, 5H), 7.16 (m, 1H), 7.45 (*s*, 1H), 7.8-8.21 (m, 2H)
9 [b]	(deuteriochloroform): 1.6-2.43 (m, 8H), 2.24-2.94 (m, 6H), 2.96-3.28 (m, 3H), 3.45-3.77 (m, 2H), 3.93 (t, J = 7.2 Hz, 2H), 6.9-7.6 (m, 3H), 7.37, (*s*, 1H)
10 [b]	(deuteriochloroform): 1.65-2.08 (m, 7H), 2.10-2.47 (m, 3H), 2.52-3.0 (m, 5H), 3.0-3.30 (m, 2H), 3.62 (t-like, 2H), 3.93 (t, J = 7.2 Hz, 2H), 7.03 (*s*, 1H), 7.12 (m, 1H), 7.54 (dd, J = 3.0 and 9.0 Hz, 1H), 7.71 (dd, J = 7.2 and 9.0 Hz, 1H)
13a	(deuteriochloroform): 1.7-2.4 (m, 4H), 2.17 (*s*, 3H), 2.4-2.83 (m, 1H), 2.92-3.48 (m, 2H), 3.78-4.2 (d-like, 1H), 4.6-5.0 (d-like, 1H), 7.0 (dt, J = 3.0, 9.0 and 9.0 Hz, 1H), 7.21 (dd, J = 3.0 and 9.0 Hz, 1H), 7.39-7.75 (m, 6H)
13b	(deuteriochloroform): 1.7-2.4 (m, 4H), 2.2 (*s*, 3H), 2.4-2.82 (m, 1H), 2.93-3.5 (m, 2H), 3.8-4.2 (d-like, 1H), 4.62-5.03 (d-like, 1H), 6.92-7.4 (m, 4H), 7.52-7.8 (m, 3H)
13c	(deuteriochloroform): 1.65-2.35 (m, 4H), 2.17 (*s*, 3H), 2.41 (*s*, 3H), 2.35-3.40 (m, 3H), 3.8-4.2 (d-like, 1H), 4.62-5.03 (d-like, 1H), 6.92 (dt, J = 2.5, 9.0 and 9.0 Hz, 1H), 7.12 (dd, J = 2.5 and 9.0 Hz, 1H), 7.42 (dd, J = 9.0 and 9.0 Hz, 1H)
13d	(deuteriochloroform): 1.3 (t, J = 7.2 Hz, 3H), 1.50-2.3 (m, 4H), 2.19 (*s*, 3H), 2.35-3.23 (m, 3H), 2.75 (q, J = 7.2 Hz, 2H), 3.7-5.03 (br, 2H), 6.92 (dt, J = 2.5, 9.0 and 9.0 Hz, 1H), 7.12 (dd, J = 2.5 and 9.0 Hz, 1H), 7.43 (dd, J = 9.0 and 7.0 Hz, 1H)
14a	(deuteriochloroform): 1.6-2.7 (m, 5H), 2.17 (*s*, 3H), 2.8-3.4 (m, 2H), 3.7-4.0 (d-like, 1H), 4.6-4.95 (d-like, 1H), 7.10 (dt, J = 3.6, 9.0 and 9.0 Hz, 1H), 7.44 (*s*, 5H), 7.35-7.58 (m, 1H), 7.83 (dd, J = 7.0 and 9.0 Hz, 1H)
15a [a]	(dimethyl sulfoxide-d_6): 1.62-2.04 (m, 4H), 2.2-3.6 (m, 5H), 7.21 (dt, J = 3.6, 9.0 and 9.0 Hz, 1H), 7.46-7.87 (m, 6H), 8.26 (dd, J = 7.0 and 9.0 Hz, 1H)
15b [a]	(dimethyl sulfoxide-d_6): 1.7-2.1 (m, 2H), 2.2-3.7 (m, 7H), 7.05-7.95 (m, 6H), 8.0-8.35 (m, 1H)
15c [a]	(dimethyl sulfoxide-d_6): 1.58-1.94 (m, 2H), 2.42 (*s*, 3H), 2.05-3.5 (m, 7H), 7.12 (dt, J = 3.6, 9.0 and 9.0 Hz, 1H), 7.44 (dd, J = 3.6 and 9.0 Hz, 1H), 7.94 (dd, J = 7.0 and 9.0 Hz, 1H)
15d [a]	(dimethyl sulfoxide-d_6): 1.24 (t, J = 7.2 Hz, 3H), 1.4-1.9 (m, 2H), 1.95-3.5 (m, 7H), 2.79 (q, J = 7.2 Hz, 2H), 7.12 (dt, J = 3.6, 9.0 and 9.0 Hz, 1H), 7.44 (dd, J = 3.6 and 9.0 Hz, 1H), 7.94 (dd, J = 6.5 and 9.0 Hz, 1H)
16a [a]	(dimethyl sulfoxide-d_6): 1.50-1.85 (m, 1H), 1.85-2.9 (m, 5H), 2.9-3.4 (m, 3H), 7.32 (dt, J = 3.0, 9.0 and 9.0 Hz, 1H), 7.45 (*s*, 5H), 7.37-7.62 (m, 1H), 8.08 (dd, J = 6.5 and 9.0 Hz, 1H)
17a [b]	(deuteriochloroform): 1.66-2.08 (m, 6H), 2.08-2.48 (m, 4H), 2.48-2.92 (m, 4H), 2.92-3.25 (m, 3H), 3.45-3.75 (m, 2H), 3.93 (t, J = 7.2 Hz, 2H), 6.98 (dt, J = 10.0, 10.0 and 3.0 Hz, 1H), 7.19 (dd, J = 10.0 and 3.0 Hz, 1H), 7.35-7.9 (m, 6H)
17b [b]	(deuteriochloroform): 1.65--2.10 (m, 6H), 2.10-2.44 (m, 4H), 2.45-3.00 (m, 5H), 3.0-3.26 (m, 2H), 3.47-3.80 (t-like, 2H), 3.96 (t, J = 7.2 Hz, 2H), 6.85-7.40 (m, 4H), 7.48-7.90 (m, 3H)
17c [b]	(deuteriochloroform): 1.54-2.08 (m, 6H), 2.08-2.32 (m, 3H), 2.40 (*s*, 3H), 2.4-3.0 (m, 6H), 3.0-3.3 (m, 2H), 3.49-3.80 (m, 2H), 3.95 (t, J = 7.2 Hz, 2H), 6.77-7.20 (m, 2H), 7.54 (dd, J = 9.0 and 7.2 Hz, 1H)
17d [b]	(deuteriochloroform): 1.26 (t, J = 7.2 Hz, 3H), 1.50-2.08 (m, 6H), 2.08-2.40 (m, 3H), 2.42-3.0 (m, 8H), 3.0-3.24 (m, 2H), 3.50-3.75 (m, 2H), 3.95 (t, J = 7.2 Hz, 2H), 6.75-7.10 (m, 2H), 7.45-7.65 (m, dd, J = 7.2 and 9.0 Hz, 1H)
18a [b]	(deuteriochloroform): 1.52-2.0 (m, 7H), 2.0-2.40 (m, 4H), 2.51-2.82 (m, 2H), 2.98-3.23 (m, 2H), 3.91 (t, J = 7.2 Hz, 2H), 7.08 (dt, J = 3.0, 9.0 and 9.0 Hz, 1H), 7.28-7.60 (m, 6H), 8.05 (dd, J = 9.0 and 7.0 Hz, 1H)
21a	(deuteriochloroform): 2.50 (*s*, 3H), 6.87-7.32 (m, 2H), 7.38-7.60 (dd, J = 8.3 and 7.2 Hz, 1H), 7.64 (d-like, 2H), 8.69 (d-like, 2H)
21b	(deuteriochloroform): 6.9-7.65 (m, 9H), 8.55 (m, 2H)
22a	(deuteriochloroform): 2.30 (*s*, 3H), 2.50 (*s*, 4H), 3.25 (m, 2H), 3.64 (*s*, 2H), 6.22 (t, 1H), 6.8-7.50 (m, 8H)
22b	(deuteriochloroform): 2.12-2.40 (*s*, 2H), 2.57 (t-like, 2H), 3.08-3.24 (m, 2H), 3.58 (*s*, 2H), 6.35 (*s*, 1H), 6.78-7.53 (m, 12H)
23a [a]	(dimethyl sulfoxide-d_6): 1.6-2.4 (m, 4H), 2.20 (*s*, 3H), 2.8-3.64 (m, 5H), 7.16 (dt, J = 3.0, 10.0 and 10.0 Hz, 1H), 7.41-7.80 (m, 2H)
23b [a]	(dimethyl sulfoxide-d_6): 1.8-2.7 (m, 4H), 2.7-3.6 (m, 5H), 7.0-7.8 (m, 7H)
24a [b]	(deuteriochloroform): 1.6-2.7 (m, 8H), 2.1-2.4 (m, 5H), 2.15 (*s*, 3H), 2.58-3.0 (m, 5H), 3.0-3.3 (m, 2H), 3.52-3.88 (m, 2H), 3.92 (t, J = 7.2 Hz, 2H), 6.8-7.4 (m, 3H), 8.05 (dd, J = 9.0 and 7.0 Hz, 1H)
24b [a]	(dimethyl sulfoxide-d_6): 1.6-2.77 (m, 9H), 2.88-3.82 (m, 10H), 4.14 (t-like, 2H), 7.02-7.73 (m, 7H)

[a] The ^{1}H nmr of the hydrochloride. [b] The ^{1}H nmr of the free base.

chloroethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one with **7** or **8** produced the desired product **9** or **10**, respectively.

Synthetic pathways of the corresponding 2-alkyl and 2-phenyl derivatives are a little complicated (Scheme 2). The reaction of **2** with ethyl mandelate gave 2-phenylbenzo[*b*]-furan **13a** in 30% yield together with a by-product, presumably 2-acetylphenoxyacetate **11a**, the structure of which could not be precisely determined because it could not be isolated in pure form. Compound **11a** could be converted to **13a** by hydrolysis and successive treatment with acetic anhydride according to the method described by Brady, *et al.* [11]. Thus, compound **13a** was obtained in 62% yield from **2**. Similarly, 2-(4-fluorophenyl)benzo[*b*]-furan **13b** and 2-phenylbenzo[*b*]thiophene **14a** were obtained in 51 and 27% yields, respectively. 2-Alkylbenzo[*b*]-furans **13c,d** could be obtained in 31 and 15% yields, respectively, by a similar method in which, however, the by-products **11c,d** were separated by extraction after hydrolysis with a sodium hydroxide solution. These benzo[*b*]-furans **13a-d** and benzo[*b*]thiophene **14a** were converted to the final compounds **17a-d** and **18a**, respectively, by a method similar to that described in the synthesis of **9**.

Schenker *et al.* have prepared 4-(benzo[*b*]furan-2-yl)piperidines by catalytic hydrogenation of 2-(4-pyridinyl)-benzo[*b*]furans which were obtained by heating 2-(4-pyridinylmethoxy)benzaldehydes at 300° for 3 hours under a nitrogen atmosphere [12]. This method requires high temperatures and also seems to be unsuccessful when extended to the synthesis of 3-substituted-2-(4-pyridinyl)benzo[*b*]-furans because the corresponding intermediate ketones will be less reactive than the aldehydes. We, therefore, studied a new synthetic method shown in Scheme 3. Phenol derivative **19** was condensed with 4-pyridinemethanol to give **20** by the Mitsunobu reaction [13] in a moderate yield. Compound **20** was treated with ethyl chloroformate and sodium hydride to afford 2-(4-pyridinyl)benzo[*b*]-furan **21** in good yield. The reaction is considered to proceed *via* 1-ethyoxycarbonylpyridinium chloride which may activate the methylene group adjacent to the pyridine ring. Compound **21** could not be obtained by treatment with sodium hydride only. Quarternarization of **21** and the successive reduction gave 4-(benzo[*b*]furan-2-yl)piperidine **23**, which was converted to **24** by a method similar to that described in the synthesis of **9**.

Both 4-(benzo[*b*]furan-3-yl)piperidines **9** and **17a-d** and benzo[*b*]thiophenes **10** and **18a** showed potent 5-HT_2 antagonist activity *in vitro* (pA_2 values, 8.0-9.0). On the other hand, 4-(benzo[*b*]furan-2-yl)piperidines **24** had a low potency (pA_2 values, 7.0-7.2) [9].

EXPERIMENTAL

Melting points were determined by a Yanagimoto micro melting point apparatus and are uncorrected. The ^{1}H-nmr spectra were measured with a JEOL JNM-FX-90Q spectrometer using TMS as internal standard. For column chromatography, silica gel (Merck, Kieselgel 60, 0.05-0.2 mm) was used.

1-Acetyl-4-(2,4-difluorobenzoyl)piperidine (**2**).

A solution of thionyl chloride (40 ml, 550 mmoles) in dichloroethane (60 ml) was added dropwise to a stirred suspension of 1-acetylpiperidine-4-carboxylic acid (**1**) (73.0 g, 427 mmoles) in dichloroethane (240 ml) at 60°. After keeping at the same temperature for 20 minutes, the mixture was added portionwise to a stirred suspension of 2,4-difluorobenzene (68.0 g, 596 mmoles) and anhydrous aluminum chloride (133.3 g, 1000 mmoles) in dichloroethane (370 ml), and the resulting mixture was refluxed for 4 hours. The mixture was poured into a mixture of ice and concentrated hydrochloric acid and extracted with chloroform (300 ml). After concentration of the extract, the residue was crystallized with hexane to give **2** (61.0 g, 54%) as pale brown crystals, mp 94-98°; ^{1}H nmr (deuteriochloroform): 1.12-2.25 (m, 4H), 2.11 (s, 3H), 2.36-3.55 (m, 3H), 3.64-4.07 (m, 1H), 4.38-4.80 (m, 1H), 6.75-7.20 (m, 2H), 7.71-8.12 (m, 1H).

Anal. Calcd. for $C_{14}H_{15}F_2NO_2$: C, 62.91; H, 5.66; N, 5.24. Found: C, 63.16; H, 5.72; N, 5.08.

Methyl 6-Fluoro-3-(1-acetylpiperidin-4-yl)benzo[*b*]furan-2-carboxylate (**3**).

After addition of 60% sodium hydride (2.0 g, 50 mmoles) to a solution of **2** (10.2 g, 38.2 mmoles) and methyl glycolate (3.9 g, 43.3 mmoles) in tetrahydrofuran (100 ml), the mixture was refluxed for 3 hours. The solvent was evaporated, and the residue was extracted with chloroform (100 ml). After concentration of the extract, the residue was purified by column chromatography (eluent: 5% ethanol-chloroform) and crystallized from isopropyl ether to give **3** (4.0 g) as colorless crystals.

Compound **4** was similarly prepared from **2** and methyl thioglycolate as colorless crystals.

1-Acetyl-4-(6-fluorobenzo[*b*]furan-3-yl)piperidine (**5**).

Sodium hydroxide (0.8 g, 20 mmoles) was added to a solution of **3** (5.9 g, 18.5 mmoles) in a mixture of methanol (10 ml) and water (50 ml). The solution was stirred for 3 hours at room temperature. After the reaction mixture was acidified with concentrated hydrochloric acid, the precipitated material was collected by filtration to give 6-fluoro-3-(1-acetylpiperidin-4-yl)benzo[*b*]-furan-2-carboxylic acid (4.8 g, 85%), mp 240-242°. A mixture of the compound, copper powder (0.8 g) and quinoline (50 ml) was heated for 10 minutes at 200°. After removal of the insoluble material by filtration, the filtrate was dissolved in chloroform (100 ml) and washed with 10% hydrochloric acid (150 ml). After evaporation of the solvent, **5** (2.8 g) was obtained as an oil.

Compound **6** was similarly prepared from **4** as an oil.

4-(6-Fluorobenzo[*b*]furan-3-yl)piperidine Hydrochloride (**7**).

A solution of **5** (2.8 g, 10.7 mmoles) in a mixture of ethanol (15 ml) and concentrated hydrochloric acid (50 ml) was refluxed for 20 hours. After concentration of the mixture, acetone (10 ml) was added to the residue and the insoluble material was collected by filtration to give colorless crystals **7** (2.6 g).

Compound **8** was similarly prepared from **6** as colorless crystals.

2-[2-[4-(6-Fluorobenzo[*b*]furan-3-yl)piperidin-1-yl]ethyl]-5,6,7,8-

tetrahydro-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one Hydrochloride (**9**).

A mixture of **7** (2.65 g, 10.4 mmoles), 2-(2-chloroethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one (2.52 g, 12.5 mmoles), sodium iodide (3.0 g, 20 mmoles) and anhydrous potassium carbonate (2.8 g, 20 mmoles) in *N*,*N*-dimethylformamide (100 ml) was heated at 100° for 15 hours. After evaporation of the solvent, the residue was extracted with chloroform (100 ml). The extract was concentrated to give an oil, which was purified with column chromatography (eluent: 5% ethanol-chloroform) to afford the free base of **9** (3.5 g) as colorless crystals, mp 139-140° (ether).

The free base of **9** was treated with hydrochloric acid in ethanol to give the hydrochloride **9**.

Compound **10** was similarly prepared from **8** as colorless crystals.

1-Acetyl-4-(6-fluoro-2-phenyl)benzo[*b*]furan-4-yl)piperidine (**13a**).

To a solution of **2** (5.4 g, 20 mmoles) and ethyl DL-mandelate (4.0 g, 22 mmoles) in tetrahydrofuran (100 ml), 60% sodium hydride (1.1 g, 28 mmoles) was added, and the resulting mixture was refluxed for 6 hours. After removal of the solvent, the residue was extracted with chloroform (100 ml). The extract was concentrated, and the residue was separated by column chromatography (eluent: chloroform) to give **13a** (2.0 g) as an oil.

Successive elution of the column (eluent: chloroform) gave crude **11a** (4.0 g) as an oil; ^{1}H nmr (deuteriochloroform): 1.09 (t, J = 7.2 Hz, 3H), 2.1 (s, 3H), 4.3 (q, J = 7.2 Hz, 2H), 6.5-7.0 (m, 2H), 7.0-7.75 (m, 5H), 7.76-7.97 (m, 1H). The product **11a** was dissolved in a solution of sodium hydroxide (0.9 g, 225 mmoles) in a mixture of ethanol (50 ml) and water (10 ml), and the resulting solution was stirred for 1 hour. After concentration of the mixture, the residue was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (100 ml). The extract was concentrated, and the residue dissolved in acetic anhydride (20 ml). After sodium acetate (3 g, 36.6 mmoles) was added to the solution and the mixture was refluxed for 2 hours. After concentration, the residue was dissolved in 10% sodium hydroxide solution (50 ml) and stirred for 1 hour at room temperature. The solution was extracted with chloroform (100 ml). After concentration of the extract, the residue was purified with column chromatography (eluent: chloroform) to give **13a** (2.2 g).

Compounds **13b** and **14a** were similarly prepared from **2** as colorless crystals.

1-Acetyl-4-(6-fluoro-2-methylbenzo[*b*]furan-4-yl)piperidine (**13c**).

To a solution of **2** (5.4 g, 20 mmoles) and ethyl DL-lactate (2.6 g, 22 mmoles) in tetrahydrofuran (100 ml), 60% sodium hydride (1.1 g, 28 mmoles) was added, and the mixture was refluxed for 6 hours. After removal of the solvent, the residue was acidified with 10% hydrochloric acid (50 ml), and extracted with ethyl acetate (100 ml). The extract was concentrated, and the residue was mixed with a solution of sodium hydroxide (0.8 g, 20 mmoles) in water (30 ml) and methanol (50 ml). The resulting mixture was refluxed for 1 hour. After concentration, the residue was extracted with chloroform (100 ml). The solvent was removed, and the residue was separated by column chromatography (eluent: chloroform) to give **13c** (1.7 g) as colorless crystals.

Compound **13d** was similarly prepared from **2** as colorless crystals.

Compounds **15a**, **15b**, **15c**, **15d** and **16a** were prepared from the corresponding 1-acetyl derivatives, **13a-d** and **14a**, by a method similar to that described in the synthesis of compound **7**.

Compounds **17a**, **17b**, **17c**, **17d** and **18a** were prepared from the corresponding 4-(benzo[*b*]furan-3-yl)piperidines **15a-d** and 4-(benzo[*b*]thiophen-3-yl)piperidine (**16a**), respectively, by a method similar to that described in the synthesis of compound **9**.

4-Fluoro-2-(4-pyridinylmethoxy)acetophenone (**20a**).

A solution of diethyl azodicarboxylate (9.3 g, 53 mmoles) in tetrahydrofuran (5 ml) was added dropwise to a solution of 4-fluoro-2-hydroxyacetophenone (**19a**) (8.2 g, 53 mmoles), 4-pyridinemethanol (5.9 g, 54 mmoles) and triphenylphosphine (13.9 g, 53 mmoles) in tetrahydrofuran (150 ml). The solution was stirred for 1 hour at room temperature. After evaporation of the solvent, the residue was partitioned between ethyl acetate (100 ml) and 10% hydrochloric acid (50 ml). The water layer was separated, basified with potassium carbonate and extracted with chloroform (100 ml). After concentration of the extract, the residue was purified with column chromatography (eluent: chloroform) to give **20a** (5.2 g, 38%) as colorless crystals, mp 59-60° (chloroform-isopropyl ether); ^{1}H nmr (deuteriochloroform): 2.63 (s, 3H), 5.19 (s, 2H), 6.55-7.0 (t-like, 2H), 7.05-7.60 (m, 2H), 7.84 (t, J = 7.4 Hz, 1H), 8.40-8.78 (m, 2H).

Anal. Calcd. for $C_{14}H_{12}FNO_2$: C, 68.56; H, 4.93; N, 5.71. Found: C, 68.27; H, 5.12; N, 5.65.

Compound **20b** was similarly prepared from **19b** in 54% yield as colorless crystals, mp 135-137° (isopropyl ether); ^{1}H nmr (deuteriochloroform): 5.02 (s, 2H), 6.64-7.37 (m, 6H), 7.36-7.65 (m, 1H), 7.72-8.05 (m, 2H), 8.4-8.6 (m, 2H).

Anal. Calcd. for $C_{19}H_{13}F_2NO_2$: C, 70.15; H, 4.03; N, 4.30. Found: C, 70.06; H, 4.30; N, 4.07.

6-Fluoro-3-methyl-2-(4-pyridinyl)benzo[*b*]furan (**21a**).

Ethyl chloroformate (1.6 g, 14.7 mmoles) was added dropwise to a solution of **20a** (3.4 g, 13.4 mmoles) in tetrahydrofuran (50 ml). After stirring for 0.5 hour at room temperature, 60% sodium hydride (0.6 g, 15 mmoles) was added to the mixture, which was stirred for 2 hours at the same temperature. The reaction mixture was concentrated to dryness *in vacuo*. The residue was dissolved in chloroform (50 ml), and washed with water (50 ml). After concentration of the solvent, the residue was purified with column chromatography (eluent: chloroform) to give **21a** (2.6 g, 87%) as colorless crystals, mp 109-111° (isopropyl ether).

Anal. Calcd. for $C_{14}H_{10}FNO$: C, 74.00; H, 4.44; N, 6.16. Found: C, 74.11; H, 4.72; N, 6.31.

Compound **21b** was similarly prepared from **20b** in 70% yield as colorless crystals, mp 128-130° (isopropyl ether).

Anal. Calcd. for $C_{19}H_{11}F_2NO$: C, 74.26; H, 3.61; N, 4.56. Found: C, 73.78; H, 4.63; N, 5.84.

6-Fluoro-3-methyl-2-(1-benzyl-1,2,5,6-tetrahydropyridin-4-yl)-benzo[*b*]furan (**22a**).

A solution of **21a** (2.85 g, 12.5 mmoles) and benzyl bromide (2.2 g, 12.9 mmoles) in toluene (50 ml) was refluxed for 10 hours. The precipitated material was collected to give 1-benzyl-4-(6-fluoro-3-methylbenzo[*b*]furan-2-yl)pyridinium bromide (5.0 g, 64%), mp 246-248°. The pyridinium salt was dissolved in ethanol (100 ml), and sodium borohydride (3.0 g, 78 mmoles) was added portionwise. After stirring for 2 hours, the mixture was concentrated to dryness *in vacuo*, and the residue was extracted with chloroform (100 ml). After concentration of the extract, the residue was puri-

fied with column chromatography (eluent: 5% ethanol-chloroform) to give **22a** (3.7 g, 92%) as an oil.

Compound **22b** was similarly prepared from **21b**. After treatment with hydrochloric acid, the hydrochloride of **22b** was obtained in 64% yield as colorless crystals, mp 240-243° (methanol-ether).

Anal. Calcd. for $C_{26}H_{22}ClF_2NO$: C, 71.32; H, 5.07; N, 3.20. Found: C, 71.18; H, 5.29; N, 3.17.

4-(6-Fluoro-3-methylbenzo[*b*]furan-2-yl)piperidine Hydrochloride (**23a**).

A mixture of **22a** (3.7 g, 12 mmoles) and 10% palladium charcoal (3 g) in ethanol (150 ml) and concentrated hydrochloric acid (5 ml) was shaken under a hydrogen atmosphere for 6 hours. After filtration of the insoluble material, the filtrate was concentrated to dryness *in vacuo*. The residue was crystallized with acetone to give **23a** (1.7 g, 55%), mp 276-278° (methanol-ether).

Anal. Calcd. for $C_{14}H_{17}ClFNO$: C, 62.33; H, 6.35; N, 5.19. Found: C, 62.01; H, 6.43; N, 5.23.

Compound **23b** was similarly prepared from **22b** in 82% yield as colorless crystals, mp >280° (methanol-ether).

Anal. Calcd. for $C_{19}H_{18}ClF_2NO$: C, 65.24; H, 5.19; N, 4.00. Found: C, 65.03; H, 5.10; N, 3.92.

Compound **24a** was prepared from **23a** in 61% yield by a method similar to that described in the synthesis of compound **9**; free base, an oil; hydrochloride, mp 247-250° (methanol-ether).

Anal. Calcd. for $C_{22}H_{28}ClFN_4O_2$: C, 60.75; H, 6.49; N, 12.88. Found: C, 60.80; H, 6.56; N, 12.90.

Compound **24b** was similarly prepared in 86% yield from **23b**; free base, an oil; hydrochloride, mp 253-255° (methanol-ether).

Anal. Calcd. for $C_{27}H_{29}ClF_2N_4O_2$: C, 62.97; H, 5.68; N, 10.88. Found: C, 63.23; H, 5.68; N, 10.90.

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