[2-(ω-Phenylalkyl)phenoxy]alkylamines: Synthesis and Dual Dopamine$_2$ (D_2) and 5-Hydroxytryptamine$_2$ (5-HT_2) Receptor Antagonistic Activities

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A series of [2-(ω-phenylalkyl)phenoxy]alkylamines was synthesized and their 5-hydroxytryptamine$_2$ (5-HT_2) and/or dopamine$_2$ (D_2) receptor antagonistic activities were examined *in vitro*. [2-(4-Phenylbutyl)phenoxy]alkylamines showed strong inhibition of both 5-HT_2 and D_2 receptors. In particular, [2-(4-phenylbutyl)phenoxy]-methylpiperidine derivatives, 10b, 10i and 10q, exhibited potent inhibition. The structure–activity relationships in this series of compounds are discussed.

Key words 5-hydroxytryptamine$_2$ (5-HT_2); dopamine$_2$ (D_2); dual antagonist; antagonistic activity; [2-(4-phenylbutyl)-phenoxy]alkylamine

Typical dopamine$_2$ (D_2) receptor antagonists, chlorpromazine, fluphenazine and haloperidol, have been used in the treatment of psychoses such as schizophrenia for the last four decades. However, they do not affect negative symptoms such as apathy and emotional withdrawal.[2)] Furthermore, pharmacological blockade of the D_2 receptor frequently induces extrapyramidal side effects (EPS) such as Parkinsonian syndrome.[3)] It has been suggested that central 5-hydroxytryptamine$_2$ (5-HT_2) receptor antagonists affect these negative symptoms and reduce EPS.[4)] Thus, the blockade of both 5-HT_2 and D_2 receptors is expected to be effective for the treatment of psychoses which have negative symptoms, and adverse reactions are expected to be reduced by blockade of the 5-HT_2 receptor. Recently, risperidone[5)] and perospirone (SM-9018)[6)] have been reported to be dual 5-HT_2 and D_2 receptor antagonists.

In recent years, the Mitsubishi Kasei group has developed a selective 5-HT_2 receptor antagonist, sarpogrelate (Fig. 1), which is a [2-(2-phenylethyl)phenoxy]-alkylamine derivative that acts as an antithrombotic.[7)] In the course of a study of [2-(ω-phenylalkyl)phenoxy]-alkylamine derivatives having five- or six-membered cyclic amino groups as the alkylamino moiety to determine the profiles of the compounds, we found that [2-(4-phenylbutyl)phenoxy]alkylamine derivatives function as dual 5-HT_2 and D_2 receptor antagonists (Fig. 2). Introduction of the cyclic amino moiety in this series of compounds was expected to diminish the flexibility of the basic part and to enhance the basicity of the amino moiety. In this paper, we describe the synthesis and structure–activity relationships (SAR) of these compounds.

Chemistry The synthetic routes to [2-(4-phenylbutyl)-phenoxy]alkylamino derivatives are illustrated in Chart 1.

Aldehydes **1** and phosphonium chloride **2** were subjected to Wittig reaction to give the corresponding olefins **3**, which were converted into phenol derivatives **4a—f** by catalytic hydrogenation. Alkylation of **4a—f** by epibromohydrin followed by treatment with dimethylamine provided amino alcohols **6a—m**. Compound **7** was prepared by alkylation of **4c** (R^1=H) with 3-dimethylaminopropyl chloride. Pyrrolidine derivatives **10c—g** were prepared by alkylation of **4c** with 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride (R^2=Cl) in the presence of *tert*-BuOK (method A), or by means of the Mitsunobu reaction[8)] between **4c** and 1-methyl-2-pyrrolidineethanol (R^2=OH) (method B). Piperidine (X=CH_2) and morpholine (X=O) derivatives **10a, b** and **10h—t** were synthesized as described below. Compounds **9**, prepared by alkylation of **4c** with tosylates (**8**: R^2=OTs) in the presence of *tert*-BuOK (method C), or by means of the Mitsunobu reaction[8)] between **4c** and the hydroxy derivative (**8**: R^2=OH) (method D), were reduced with lithium aluminum hydride to give *N*-methyl compounds, **10a, b, 10h—l** and **10r—t**. Compounds **10m—p** were prepared by the treatment of **9** with HCl. Conversion of the *N*-H group of **10n** to an *N*-ethyl group was performed by acetylation with Ac_2O, followed by the treatment of **11** with lithium aluminum hydride to give the *N*-ethyl compound **10q**.

Results and Discussion

Both 5-HT_2 and D_2 receptor antagonistic activities were examined *in vitro*. The *in vitro* activities were determined by a conventional ligand binding assay using ^{3}H-ligand and expressed as IC_{50} values.

First, we studied the influence of alkylene length in the phenylalkylphenoxy part of 3-dimethylamino-1-(ω-phenylalkylphenoxy)-2-propanol derivatives **6a—f** on D_2 receptor binding (Table 1). The tetramethylene compound

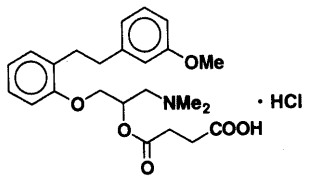

Fig. 1. Sarpogrelate

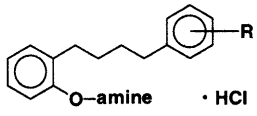

Fig. 2. [2-(4-Phenylbutyl)phenoxy]alkylamine Derivatives

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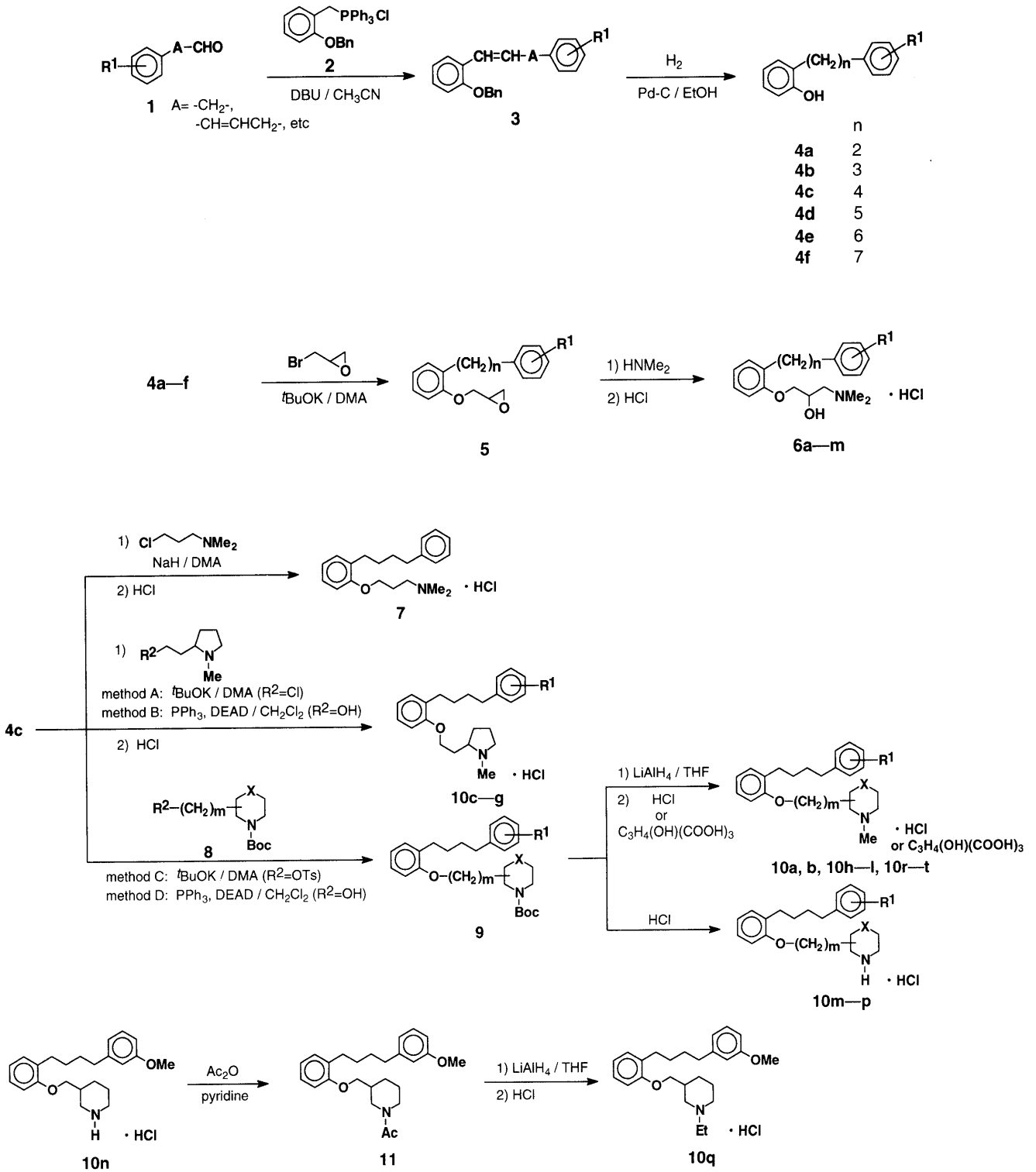
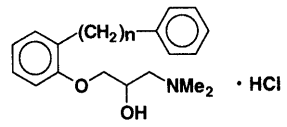


Chart 1

6c exhibited moderate inhibition of the D_2 receptor binding with an IC_{50} of 320 nM, while other compounds exhibited markedly less potent inhibition.

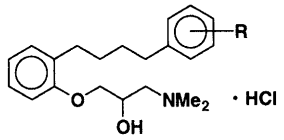
Next, the effect of the substituent R on the ω-phenyl group on 5-HT_2 and D_2 receptor binding was examined using tetramethylene compounds **6c** and **6g**—**m** (Table 2). Generally, these compounds showed potent inhibition with IC_{50}s of less than 50 nM in 5-HT_2 antagonism. Among them, 3-OMe (**6h**) and 3-OH (**6k**) compounds exhibited potent activity, and 3-Cl (**6l**) and 3,5-di-OMe (**6j**) compounds also exhibited potent inhibition with IC_{50}s of around 10—20 nM. However, 2-OMe (**6g**) and 4-OMe (**6i**) compounds exhibited *ca.* 10-fold lower activity than that of the 3-OMe compound (**6h**). This result suggests that, in the aminoalcohol series of OMe compounds **6g**—**j**, a regiospecific effect is involved. The D_2 receptor antagonistic activity of these compounds was moderate (220—530 nM). Sarpogrelate did not exhibit D_2 receptor antagonistic activity. In the case of amino alcohols, no improvement of D_2 receptor antagonistic activity was obtained

Table 1. D_2 Receptor Antagonistic Activity of 3-Dimethylamino-1-(ω-phenylalkylphenoxy)-2-propanol Derivatives



Compd.	*n*	D_2; IC_{50} (nM)
6a	2	>3000
6b	3	>3000
6c	4	320
6d	5	2680
6e	6	>3000
6f	7	>3000

Table 2. D_2 and 5-HT_2 Receptor Antagonistic Activities of 3-Dimethylamino-1-[2-(4-phenylbutyl)phenoxy]-2-propanol Derivatives



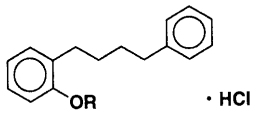
Compd.	R	5-HT_2; IC_{50} (nM)	D_2; IC_{50} (nM)
6c	H	24	320
6g	2-OMe	45	240
6h	3-OMe	4.3	220
6i	4-OMe	48	450
6j	3,5-di-OMe	14	500
6k	3-OH	6.1	530
6l	3-Cl	19	530
6m	3-Me	38	440
Sarpogrelate		150	>5000

by changing the substituent R on the ω-phenyl group.

On the other hand, the removal of the hydroxy group of **6c**, as in compound **7**, resulted in activities stronger than those of **6c** for both 5-HT_2 and D_2 antagonism (Table 3). The morpholine derivative **10a**, which is considered to be a cyclic analogue of **6c** in which the hydroxy and *N*-alkyl group are connected, also showed good activities in the inhibition of both the 5-HT_2 and D_2 receptors. The piperidine derivative **10b**, which has a methylene group that is more lipophilic than oxygen on the morpholine ring, had activities stronger than those of **10a** for both 5-HT_2 and D_2 antagonism. These results suggest that D_2 receptor antagonistic activity depends on the lipophilicity of the aminoalcohol moiety (estimated at 4.50 (**6c**), 5.21 (**7**), 5.55 (**10a**) and 6.26 (**10b**) by means of the CLOGP program).[9]

Next, the 5-HT_2 and D_2 receptor antagonistic activities of piperidine and pyrrolidine derivatives in the ω-phenylalkylphenoxy series and the effect of the alkoxy group on the ω-phenyl substituent were examined (Table 4). Generally, *N*-alkyl derivatives, having a methoxy group on the ω-phenyl substituent, showed potent 5-HT_2 inhibition with IC_{50}s of less than 10 nM. Among *N*-methylpyrrolidine derivatives (**10c**—**10g**), the 3-methoxyphenyl derivative **10e** was the most potent 5-HT_2 antagonist, but their D_2 receptor antagonistic activities were almost

Table 3. D_2 and 5-HT_2 Receptor Antagonistic Activities of [2-(4-Phenylbutyl)phenoxy]alkylamine Derivatives



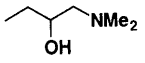
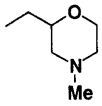
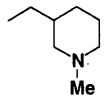
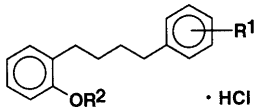
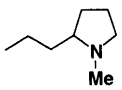
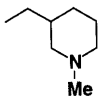
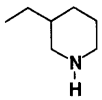
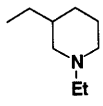
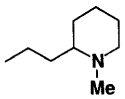
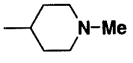
Compd.	R	5-HT_2; IC_{50} (nM)	D_2; IC_{50} (nM)
6c		24	320
7		12	18
10a		43	20
10b		5.9	1.4

Table 4. D_2 and 5-HT_2 Receptor Antagonistic Activities of Piperidine and Pyrrolidine Derivatives with a 2-(4-Phenylbutyl)phenoxy Group



Compd.	R^1	R^2	5-HT_2; IC_{50} (nM)	D_2; IC_{50} (nM)
10c	H		32	28
10d	2-OMe		22	40
10e	3-OMe		1.2	42
10f	4-OMe		5.7	55
10g	3,5-di-OMe		6.9	51
10b	H		5.9	1.4
10h	2-OMe		2.5	20
10i	3-OMe		2.2	9.2
10j	4-OMe		5.2	120
10k	3-OEt		11	58
10l	3-O^{i}Pr		94	120
10m	H		1.4	41
10n	3-OMe		4.4	44
10o	3-OEt		37	150
10p	3-O^{i}Pr		140	250
10q	3-OMe		5.5	3.4
10r	H		11	40
10s[a]	3-OMe		9.4	15
10t	3-OMe		2.6	120

a) Citrate.

the same. In contrast to the high 5-HT_2 receptor antagonistic activity of **10e**, the 3,5-dimethoxy compound **10g** showed reduced 5-HT_2 receptor antagonistic activity. The introduction of one more methoxy group at a sym-

Table 5. Physicochemical Data for [2-(4-Phenylalkyl)phenoxy]alkylamines

Compd.[a]	Formula	Yield (%)[b]	mp (°C)	Analysis (%) Calcd (Found)			
				C	H	N	Cl
6b	$C_{20}H_{27}NO_2 \cdot HCl$	59	77—79	68.65 (68.64)	8.07 (7.82)	4.00 (4.06)	10.13 (10.41)
6c	$C_{21}H_{29}NO_2 \cdot HCl$	88	120—122	69.31 (69.09)	8.31 (8.40)	3.85 (3.87)	9.74 (9.83)
6d	$C_{22}H_{31}NO_2 \cdot HCl$	90	Oil	69.91 (69.87)	8.53 (8.60)	3.71 (3.75)	9.38 (9.19)
6e	$C_{23}H_{33}NO_2 \cdot HCl$	81	Oil	70.48 (70.32)	8.74 (8.76)	3.57 (3.60)	9.04 (9.22)
6f	$C_{24}H_{35}NO_2 \cdot HCl$	76	Oil	71.00 (71.03)	8.94 (9.21)	3.45 (3.54)	8.73 (8.54)
6g	$C_{22}H_{31}NO_3 \cdot HCl \cdot H_2O$	84	52—54	64.14 (64.27)	8.32 (8.14)	3.40 (3.45)	8.61 (8.79)
6h	$C_{22}H_{31}NO_3 \cdot HCl$	78	102—104	67.07 (66.76)	8.19 (8.21)	3.56 (3.49)	9.00 (8.90)
6i	$C_{22}H_{31}NO_3 \cdot HCl$	81	97—98	67.07 (67.14)	8.19 (8.38)	3.56 (3.52)	9.00 (8.75)
6j	$C_{23}H_{33}NO_4 \cdot HCl$	62	76—77	65.16 (64.76)	8.08 (8.01)	3.30 (3.36)	8.36 (8.35)
6k	$C_{21}H_{29}NO_3 \cdot HCl$	85	124—125	66.39 (66.14)	7.96 (8.04)	3.69 (3.66)	9.33 (9.28)
6l	$C_{21}H_{28}ClNO_2 \cdot HCl$	56	83—85	63.32 (63.38)	7.34 (7.37)	3.52 (3.54)	17.80 (18.13)
6m	$C_{22}H_{31}NO_2 \cdot HCl \cdot 1/9H_2O$	40	Oil	69.55 (69.28)	8.55 (8.49)	3.69 (3.57)	9.33 (9.51)
7	$C_{21}H_{29}NO \cdot HCl$	60	104—106	72.49 (72.33)	8.69 (8.84)	4.03 (4.11)	10.19 (9.89)
10a	$C_{22}H_{29}NO_2 \cdot HCl$	56	135—136	70.29 (70.01)	8.04 (8.05)	3.73 (3.72)	9.43 (9.39)
10b	$C_{23}H_{31}NO \cdot HCl$	69	162—164	73.87 (73.66)	8.63 (8.69)	3.75 (3.83)	9.48 (9.50)
10c	$C_{23}H_{31}NO \cdot HCl$	39	114—116	73.87 (73.56)	8.63 (8.49)	3.75 (3.86)	9.48 (9.42)
10d	$C_{24}H_{33}NO_2 \cdot HCl$	19	111—112	71.35 (71.29)	8.48 (8.52)	3.47 (3.40)	8.78 (8.72)
10e	$C_{24}H_{33}NO_2 \cdot HCl$	16	65—66	71.35 (70.92)	8.48 (8.44)	3.47 (3.47)	8.78 (8.73)
10f	$C_{24}H_{33}NO_2 \cdot HCl$	12	91—92	71.35 (70.96)	8.48 (8.55)	3.47 (3.48)	8.78 (8.65)
10g	$C_{25}H_{35}NO_3 \cdot HCl$	40	Oil	69.18 (69.00)	8.36 (8.29)	3.23 (3.24)	8.17 (8.17)
10h	$C_{24}H_{33}NO_2 \cdot HCl$	75	123—124	71.35 (71.31)	8.48 (8.57)	3.47 (3.36)	8.78 (8.77)
10i	$C_{24}H_{33}NO_2 \cdot HCl$	79	141—143	71.35 (71.08)	8.48 (8.51)	3.47 (3.37)	8.78 (8.95)
10j	$C_{24}H_{33}NO_2 \cdot HCl$	80	155—156	71.35 (71.18)	8.48 (8.57)	3.47 (3.47)	8.78 (8.98)
10k	$C_{25}H_{35}NO_2 \cdot HCl$	24	114—116	71.83 (71.87)	8.68 (8.62)	3.35 (3.34)	8.48 (8.36)
10l	$C_{26}H_{37}NO_2 \cdot HCl$	61	101—106	72.28 (72.10)	8.87 (8.96)	3.24 (3.26)	8.21 (8.22)
10m	$C_{22}H_{29}NO \cdot HCl$	85	182—184	73.41 (73.06)	8.40 (8.30)	3.89 (3.90)	9.85 (9.81)
10n	$C_{23}H_{31}NO_2 \cdot HCl$	89	136—137	70.84 (70.37)	8.27 (8.29)	3.59 (3.55)	9.09 (9.36)
10o	$C_{24}H_{33}NO_2 \cdot HCl$	86	81—83	71.35 (71.19)	8.48 (8.28)	3.47 (3.54)	8.78 (8.86)
10p	$C_{25}H_{35}NO_2 \cdot HCl$	84	119—121	71.83 (71.44)	8.68 (8.68)	3.35 (3.44)	8.48 (8.59)
10q	$C_{25}H_{35}NO_2 \cdot HCl$	79	136—137	71.83 (71.61)	8.68 (8.67)	3.35 (3.36)	8.48 (8.64)
10r	$C_{24}H_{33}NO \cdot HCl \cdot 1/4H_2O$	36	Oil	73.44 (73.14)	8.86 (8.77)	3.57 (3.55)	9.03 (8.93)
10s	$C_{25}H_{35}NO_2 \cdot C_3H_4(OH)(COOH)_3$	65	77—79	64.90 (64.83)	7.56 (7.69)	2.44 (2.38)	
10t	$C_{23}H_{31}NO_2 \cdot HCl$	36	122—123	70.84 (70.68)	8.27 (8.09)	3.59 (3.59)	9.09 (9.32)

a) **6a** was described in reference 5. *b*) Yield not optimized.

Table 6. Physicochemical Data for [2-(ω-Phenylalkyl)phenoxyl]alkylamines

Compd.[a]	Solvent[b]	^{1}H-NMR δ
6b	A	1.8—2.0 (2H, m), 2.55—2.75 (4H, m), 2.86 (6H, s), 3.1—3.3 (2H, m), 3.92 (1H, dd, J=7.8, 9.3 Hz), 4.14 (1H, dd, J=4.4, 9.3 Hz), 4.45—4.6 (1H, m), 6.82 (1H, d, J=7.8 Hz), 6.93 (1H, t, J=7.3 Hz), 7.1—7.35 (5H, m)
6c	B	1.5—1.8 (4H, m), 2.5—2.7 (4H, m), 2.89 (6H, s), 3.1—3.4 (2H, m), 3.8—4.2 (2H, m), 4.4—4.6 (1H, m), 6.83 (1H, d, J=8.3 Hz), 6.91 (1H, t, J=7.3 Hz), 7.1—7.3 (7H, m)
6d	A	1.3—1.5 (2H, m), 1.5—1.7 (4H, m), 2.5—2.65 (4H, m), 2.89 (6H, s), 3.15—3.4 (2H, m), 3.92 (1H, dd, J=7.9, 9.2 Hz), 4.16 (1H, dd, J=4.6, 9.2 Hz), 4.5—4.65 (1H, m), 6.82 (1H, d, J=7.9 Hz), 6.90 (1H, t, J=7.6 Hz), 7.1—7.4 (7H, m)
6e	B	1.3—1.7 (8H, m), 2.5—2.65 (4H, m), 2.90 (6H, s), 3.15—3.4 (2H, m), 3.94 (1H, dd, J=7.8, 9.3 Hz), 4.15 (1H, dd, J=4.4, 9.3 Hz), 4.5—4.65 (1H, m), 6.82 (1H, d, J=7.8 Hz), 6.90 (1H, t, J=7.3 Hz), 7.1—7.4 (7H, m)
6f	A	1.2—1.4 (6H, m), 1.45—1.7 (4H, m), 2.45—2.65 (4H, m), 2.93 (6H, s), 3.2—3.4 (2H, m), 3.93 (1H, dd, J=7.9, 9.2 Hz), 4.16 (1H, dd, J=4.0, 9.2 Hz), 4.45—4.7 (1H, m), 6.82 (1H, d, J=7.9 Hz), 6.91 (1H, t, J=7.6 Hz), 7.1—7.35 (7H, m)
6g	B	1.55—1.75 (4H, m), 2.55—2.7 (4H, m), 2.89 (6H, s), 3.15—3.4 (2H, m), 3.80 (3H, s), 3.93 (1H, dd, J=7.8, 9.8 Hz), 4.15 (1H, dd, J=4.4, 9.8 Hz), 4.5—4.6 (1H, m), 6.8—7.0 (4H, m), 7.1—7.25 (4H, m)
6h	A	1.55—1.75 (4H, m), 2.55—2.7 (4H, m), 2.87 (6H, s), 3.1—3.3 (2H, m), 3.89 (3H, s), 3.92 (1H, dd, J=7.6, 9.9 Hz), 4.14 (1H, dd, J=4.6, 9.9 Hz), 4.45—4.6 (1H, m), 6.7—7.0 (5H, m), 7.1—7.25 (3H, m)
6i	A	1.5—1.7 (4H, m), 2.5—2.65 (4H, m), 2.87 (6H, s), 3.1—3.35 (2H, m), 3.78 (3H, s), 3.93 (1H, dd, J=7.9, 9.2 Hz), 4.14 (1H, dd, J=4.6, 9.2 Hz), 4.5—4.6 (1H, m), 6.8—7.0 (4H, m), 7.05—7.2 (4H, m)
6j	A	1.55—1.7 (4H, m), 2.5—2.7 (4H, m), 2.88 (6H, s), 3.1—3.3 (2H, m), 3.77 (6H, s), 3.85—4.0 (1H, m), 4.1—4.2 (1H, m), 4.45—4.65 (1H, m), 6.30 (3H, s), 6.82 (1H, d, J=8.6 Hz), 6.91 (1H, t, J=7.6 Hz), 7.1—7.2 (2H, m)
6k	C	1.45—1.7 (4H, m), 2.4—2.65 (4H, m), 2.84 (6H, s), 3.1—3.3 (2H, m), 3.9—4.1 (2H, m), 4.2—4.4 (1H, m), 6.5—6.65 (3H, m), 6.8—7.2 (5H, m), 9.19 (1H, s)
6l	A	1.5—1.8 (4H, m), 2.12 (4H, t, J=6.6 Hz), 2.90 (6H, s), 3.15—3.35 (2H, m), 3.94 (1H, dd, J=7.9, 9.2 Hz), 4.15 (1H, dd, J=4.6, 9.2 Hz), 4.5—4.7 (1H, m), 6.84 (1H, d, J=7.9 Hz), 6.94 (1H, t, J=7.6 Hz), 7.04 (1H, d, J=6.6 Hz), 7.1—7.3 (5H, m)
6m	A	1.6—1.75 (4H, m), 2.32 (3H, s), 2.55—2.7 (4H, m), 2.85 (6H, s), 3.1—3.3 (2H, m), 3.92 (1H, dd, J=7.9, 9.2 Hz), 4.14 (1H, dd, J=4.6, 9.2 Hz), 4.5—4.65 (1H, m), 6.82 (1H, d, J=7.9 Hz), 6.85—7.04 (4H, m), 7.1—7.25 (3H, m)
7	A	1.55—1.8 (4H, m), 2.3—2.45 (2H, m), 2.55—2.8 (4H, m), 2.76 (6H, s), 3.1—3.2 (2H, m), 4.06 (2H, t, J=5.6 Hz), 6.80 (1H, d, J=7.8 Hz), 6.91 (1H, t, J=7.3 Hz), 7.1—7.3 (7H, m)
10a	A	1.55—1.8 (4H, m), 2.6—2.75 (4H, m), 2.76 (3H, s), 2.8—3.0 (2H, m), 3.3—3.55 (2H, m), 3.95—4.2 (3H, m), 4.36 (1H, t, J=12.2 Hz), 4.55 (1H, d, J=8.6 Hz), 6.82 (1H, d, J=8.6 Hz), 6.93 (1H, t, J=7.3 Hz), 7.1—7.35 (7H, m)
10b	A	1.35—1.8 (5H, m), 1.85—2.05 (2H, m), 2.25—2.95 (8H, m), 2.72 (3H, s), 3.35—3.6 (2H, m), 3.8—4.0 (2H, m), 6.77 (1H, d, J=8.0 Hz), 6.91 (1H, t, J=7.7 Hz), 7.1—7.35 (7H, m)
10c	B	1.55—1.8 (4H, m), 1.9—2.15 (2H, m), 2.15—2.35 (2H, m), 2.35—2.85 (7H, m), 2.75 (3H, s), 3.2—3.4 (1H, m), 3.8—4.3 (3H, m), 6.82 (1H, d, J=8.3 Hz), 6.91 (1H, t, J=7.3 Hz), 7.1—7.3 (7H, m)
10d	A	1.5—1.8 (4H, m), 1.9—2.15 (2H, m), 2.15—2.4 (2H, m), 2.4—2.9 (7H, m), 2.75 (3H, s), 3.25—3.5 (1H, m), 3.7—4.05 (2H, m), 3.80 (3H, s), 6.8—7.0 (4H, m), 7.05—7.25 (4H, m)
10e	A	1.5—1.8 (4H, m), 1.85—2.15 (2H, m), 2.15—2.35 (2H, m), 2.35—2.9 (7H, m), 2.74 (3H, s), 3.2—3.35 (1H, m), 3.7—4.1 (2H, m), 3.79 (3H, s), 6.65—6.8 (3H, m), 6.82 (1H, d, J=8.6 Hz), 6.91 (1H, t, J=7.6 Hz), 7.1—7.3 (3H, m)
10f	A	1.5—1.75 (4H, m), 1.9—2.15 (2H, m), 2.15—2.4 (2H, m), 2.4—2.7 (6H, m), 2.7—2.9 (1H, m), 2.73, 2.75 (together 3H, each singlet), 3.2—3.4 (1H, m), 3.76 (3H, s), 3.8—4.1 (2H, m), 4.15—4.3 (1H, m), 6.75—6.9 (3H, m), 6.91 (1H, t, J=7.6 Hz), 7.0—7.2 (4H, m)
10g	A	1.55—1.7 (4H, m), 1.85—2.9 (11H, m), 2.75, 2.77 (together 3H, each singlet), 3.2—3.4 (1H, m), 3.76 (6H, s), 3.8—4.1 (2H, m), 4.15—4.3 (1H, m), 6.30 (3H, s), 6.82 (1H, d, J=8.6 Hz), 6.91 (1H, t, J=7.9 Hz), 7.1—7.25 (2H, m)
10h	A	1.45—1.8 (5H, m), 1.85—2.05 (2H, m), 2.30—2.95 (8H, m), 2.72, 2.74 (together 3H, each singlet), 3.4—3.6 (2H, m), 3.80 (3H, s), 3.8—4.0 (2H, m), 6.7—7.0 (4H, m), 7.05—7.2 (4H, m)
10i	A	1.3—2.1 (7H, m), 2.2—3.0 (4.H, m), 2.62 (4H, t, J=6.6 Hz), 2.74 (3H, s), 3.35—3.6 (2H, m), 3.78 (3H, s), 3.8—4.0 (2H, m), 6.7—6.85 (4H, m), 6.91 (1H, t, J=6.9 Hz), 7.1—7.25 (3H, m)
10j	A	1.4—2.0 (7H, m), 2.3—3.0 (8H, m), 2.72, 2.74 (together 3H, each singlet), 3.4—3.6 (2H, m), 3.78 (3H, s), 3.8—4.0 (2H, m), 6.7—7.0 (4H, m), 7.05—7.2 (4H, m)
10k	A	1.40 (3H, t, J=6.9 Hz), 1.45—2.0 (7H, m), 2.25—2.95 (8H, m), 2.73 (3H, s), 3.35—3.6 (2H, m), 3.8—4.0 (2H, m), 4.00 (2H, q, J=6.9 Hz), 6.65—6.8 (4H, m), 6.91 (1H, t, J=7.8 Hz), 7.1—7.25 (3H, m)
10l	A	1.31 (6H, d, J=6.0 Hz), 1.35—1.75 (5H, m), 1.85—2.05 (2H, m), 2.25—2.9 (8H, m), 2.73 (3H, s), 3.35—3.6 (2H, m), 3.8—4.0 (2H, m), 4.45—4.6 (1H, m), 6.65—6.8 (4H, m), 6.91 (1H, t, J=7.5 Hz), 7.1—7.2 (3H, m)
10m	A	1.35—1.75 (5H, m), 1.85—2.15 (3H, m), 2.4—2.9 (7H, m), 3.4—3.6 (2H, m), 3.75—3.95 (2H, m), 6.75 (1H, d, J=7.9 Hz), 6.89 (1H, t, J=7.7 Hz), 7.1—7.3 (7H, m)
10n	A	1.3—2.2 (9H, m), 2.4—2.95 (6H, m), 3.4—3.6 (2H, m), 3.75—4.0 (2H, m), 3.78 (3H, s), 6.65—6.85 (4H, m), 6.89 (1H, d, J=7.3 Hz), 7.1—7.25 (3H, m)

Table 6. (continued)

Compd.[a]	Solvent[b]	^{1}H-NMR δ
10o	A	1.39 (3H, t, J=7.1 Hz), 1.4—1.75 (5H, m), 1.85—2.15 (3H, m), 2.45—2.9 (7H, m), 3.4—3.55 (2H, m), 3.8—3.95 (2H, m), 4.01 (2H, q, J=7.0 Hz), 6.65—6.8 (4H, m), 6.88 (1H, t, J=7.1 Hz), 7.1—7.25 (3H, m)
10p	A	1.31 (6H, d, J=6.1 Hz), 1.35—1.75 (5H, m), 1.85—2.2 (3H, m), 2.4—2.9 (7H, m), 3.4—3.6 (2H, m), 3.8—3.95 (2H, m), 4.45—4.6 (1H, m), 6.65—6.8 (4H, m), 6.88 (1H, t, J=7.6 Hz), 7.05—7.25 (3H, m)
10q	A	1.39 (3H, t, J=7.1 Hz), 1.4—1.75 (5H, m), 1.85—2.15 (3H, m), 2.45—2.9 (7H, m), 3.4—3.55 (2H, m), 3.8—3.95 (2H, m), 4.01 (2H, q, J=7.0 Hz), 6.65—6.8 (4H, m), 6.88 (1H, t, J=7.1 Hz), 7.1—7.25 (3H, m)
10r	B	1.2—1.5 (1H, m), 1.55—2.45 (11H, m), 2.45—2.9 (5H, m), 2.76 (3H, s), 2.9—3.7 (2H, m), 3.95—4.2 (2H, m), 6.81 (1H, d, J=8.6 Hz), 6.91 (1H, t, J=6.9 Hz), 7.1—7.3 (7H, m)
10s	C	1.2—2.3 (12H, m), 2.5—3.7 (11H, m), 2.69 (3H, s), 3.71 (3H, s), 3.9—4.1 (2H, m), 6.7—6.8 (3H, m), 6.86 (1H, t, J=7.3 Hz), 6.92 (1H, d, J=7.9 Hz), 7.1—7.3 (3H, m)
10t	A	1.55—1.8 (4H, m), 2.05—2.2 (2H, m), 2.5—2.75 (6H, m), 2.65, 2.66 (together 3H, each singlet), 2.85—3.05 (2H, m), 3.2—3.35 (2H, m), 3.78 (3H, s), 4.63—4.75 (1H, m), 6.65—6.8 (4H, m), 6.92 (1H, t, J=6.9 Hz), 7.1—7.25 (3H, m)

a) **6a** was described in reference 5. *b*) A: $CDCl_3$, B: $CDCl_3+D_2O$, C: DMSO-d_6.

metric position on the ω-phenyl substituent did not improve the activity.

In the series of 3-piperidine derivatives (**10b**, **10h**—**10q**), the D_2 receptor antagonistic activity of *N*-Me compounds (**10b**, **10i**, **10k**, **10l**) was stronger than that of the corresponding *N*-H compounds (**10m**, **10n**, **10o**, **10p**, respectively). Among them, compounds having either a hydrogen or a methoxy group (**10b**, **10h**—**10j**, **10m**, **10n**, **10q**) as R^1 showed potent 5-HT_2 receptor antagonistic activity. In particular, *N*-alkyl-3-piperidine derivatives having either a hydrogen or a 3-methoxy group (**10b**, **10i**, **10q**) as R^1, showed potent inhibition with IC_{50}s of less than 10 nM for both 5-HT_2 and D_2 antagonism. Generally, the introduction of a 3-methoxy group on the ω-phenyl ring gave high 5-HT_2 receptor antagonistic activity in this series of compounds (**6h** shown in Table 2, **10e**, **10i**, **10n**, **10q**, **10s**, **10t** shown in Table 4). On the other hand, other alkoxy derivatives, having a bulkier alkoxy group, such as a 3-ethoxy or a 3-isopropoxy one (**10k**, **10l**, **10o**, **10p**) as R^1, were not effective, and exhibited less potent 5-HT_2 and D_2 antagonism. From the results for **10g** and the alkoxy substitutions (**10k**, **10l**, **10o**, **10p**), the size of the substituent on the ω-phenyl ring is an important factor for high 5-HT_2 and D_2 receptor antagonistic activities. Compound **10q**, which has an *N*-ethyl instead of an *N*-methyl group was prepared in an attempt to improve D_2 receptor antagonistic activity by increasing the lipophilicity of the amino moiety. Indeed, the *N*-Et compound **10q** was a more potent D_2 antagonist than the *N*-Me compound **10i**. Lipophilicity of the amino moiety of the compounds seems to be important, as indicated by the data in Table 3.

Other piperidine derivatives **10r**—**10t**, substituted at the 2 and 4 positions, which similarly have three carbon atoms between piperidine nitrogen and etheral oxygen, were synthesized for comparison with compound **10i** which is substituted at the 3 position of the piperidine ring. However, they were less active, especially in terms of D_2 receptor antagonistic activity.

Because of their potent activities *in vitro*, compounds **10b**, **10i** and **10q** were selected for further study *in vivo*. They were tested for the inhibition of apomorphine-induced climbing behavior, an index of antipsychotic activity in mice. These compounds were found to inhibit apomorphine-induced climbing behavior in a dose-dependent manner. The ED_{50} values of **10b**, **10i** and **10q** were 23.6, 42.7, and 17.8 mg/kg *p.o.*, respectively.

Also, in *in vitro* studies on vasoconstriction, the IC_{50} values of **10b**, **10i** and **10q** were 7.2, 6.5, and 12 nM, respectively. This result suggests that they are indeed 5-HT_2 receptor antagonists.

In conclusion, we found new [2-(4-phenylbutyl)phenoxy]alkylamino derivatives with potent dual 5-HT_2 and D_2 receptor antagonistic activities. The [2-(4-phenylbutyl)phenoxy]methylpiperidine derivatives, **10b**, **10i** and **10q**, exhibited particularly potent inhibition.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were obtained on a JEOL EX270 spectrometer and are reported as δ values relative to Me_4Si as the internal standard. Abbreviations of the ^{1}H-NMR peak patterns are as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. IR spectra were taken on a JASCO FT/IR-8900 spectrometer. Merck Silica gel 60 (230—400 mesh) was used for column chromatography. Tetrahydrofuran, *N*,*N*-dimethylacetamide, and dimethylsulfoxide are abbreviated as THF, DMA and DMSO, respectively. All compounds which have an asymmetric center are racemic.

2-(4-Phenylbutyl)phenol (4c: R^1=H) A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (6.09 g, 40.0 mmol) in CH_3CN was added dropwise to a hot solution of cinnamaldehyde (5.28 g, 40.0 mmol) and 2-benzyloxybenzyltriphenylphosphonium chloride[7] (19.8 g, 40.0 mmol) in CH_3CN (200 ml). The mixture was stirred for 3 h under reflux, then the solvent was removed. The residue was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and evaporated. The resulting residue was treated in EtOAc with a small amount of hexane to give crystals. The crystals were filtered off, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc = 9/1) to give 1-(2-benzyloxyphenyl)-4-phenylbutadiene (**3**: A = -$(CH_2)_2$-) (12.2 g, 98%) as a colorless oil. A solution of **3** (A = -$(CH_2)_2$-) (12.2 g) in EtOH (300 ml) was hydrogenated over 5% Pd–C (1.0 g) at 60 °C for 5 h with stirring. The catalyst was filtered off, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc = 8/1) to give 2-(4-phenylbutyl)phenol (**4c**: R^1=H) (8.34 g, 36.9 mmol, 92%) as a colorless solid. NMR ($CDCl_3$) δ: 1.55—1.8 (4H, m), 2.55—2.75 (4H, m), 4.66 (1H, s), 6.74 (1H, d, J=7.9 Hz), 6.85 (1H, t, J=7.3 Hz), 7.0—7.3 (7H, m).

2-[2-(4-Phenylbutyl)phenoxymethyl]oxirane (5: n=4, R^1=H) A so-

lution of 2-(4-phenylbutyl)phenol **4c** (R^1=H) (15.81 g, 69.9 mmol) in DMA (350 ml) was treated with *tert*-BuOK (7.84 g, 69.9 mmol) and the mixture was stirred at room temperature for 20 min. Then epibromohydrin (11.46 ml, 140 mmol) was added and the mixture was stirred overnight at room temperature. The resulting suspension was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=7/1) to give a colorless oil (19.68 g, 69.7 mmol, 100%). NMR ($CDCl_3$) δ: 1.5—1.8 (4H, m), 2.6—2.9 (6H, m), 3.2—3.4 (1H, m), 3.97 (1H, dd, J=5.3, 11.2 Hz), 4.19 (1H, dd, J=3.0, 10.9 Hz), 6.8—6.9 (2H, m), 7.1—7.35 (7H, m).

3-(*N*,*N*-Dimethylamino)-1-[2-(4-phenylbutyl)phenoxy]-2-propanol Hydrochloride (6c) A mixture of a solution of 2-[2-(4-phenylbutyl)phenoxymethyl]oxirane **5** (n=4, R^1=H) (19.68 g, 69.7 mmol) in THF (300 ml) and 50% by weight of aqueous dimethylamine (30 ml) was stirred overnight at room temperature. The solvent was removed, and the residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=10/1) to give 3-(*N*,*N*-dimethylamino)-1-[2-(4-phenylbutyl)phenoxy]-2-propanol (20.6 g, 62.9 mmol, 90%) as a colorless oil. This oil (20.5 g, 62.6 mmol) in dioxane (200 ml) was treated with 4 N HCl in dioxane (23.5 ml) and the mixture was stirred at room temperature for 10 min, then concentrated. The oily residue was dissolved in EtOAc (50 ml), and the solution was allowed to stand at room temperature. The precipitate was collected by filtration to give colorless crystals (22.1 g, 60.7 mmol, 97%).

Other 3-(*N*,*N*-dimethylamino)-1-[2-(ω-phenylalkyl)phenoxy]-2-propanol derivatives **6a—m** were prepared by alkylation of the phenol derivatives **4a—f**[10] with epibromohydrin, followed by treatment with dimethylamine as described for **6c**.

1-(*N*,*N*-Dimethyl)-3-[2-(4-phenylbutyl)phenoxy]propylamine Hydrochloride (7) A solution of 2-(4-phenylbutyl)phenol **4c** (R^1=H) (226 mg, 1.0 mmol) in DMA (10 ml) was treated with NaH (96 mg, 2.2 mmol, as a 55% w/w dispersion in mineral oil) under cooling and the mixture was stirred at room temperature for 30 min. 3-Dimethylaminopropylchloride hydrochloride (174 mg, 1.1 mmol) was added and the whole was stirred at 70 °C for 14 h, then poured into ice–water and extracted with EtOAc. The extract was washed with brine. The organic layer was dried and evaporated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=10/1) to give 1-(*N*,*N*-dimethyl)-3-[2-(4-phenylbutyl)phenoxy]propylamine (210 mg, 0.67 mmol, 67%) as a colorless oil. This oil (210 mg, 0.67 mmol) in EtOAc was treated with 4 N HCl in dioxane (0.18 ml, 0.72 mmol). The resulting solution was concentrated and allowed to stand at room temperature. The precipitate was collected by filtration to give colorless crystals (210 mg, 0.60 mmol, 89%).

2-[2-[2-[4-(3-Methoxyphenyl)butyl]phenoxy]ethyl]-1-methylpyrrolidine Hydrochloride (10e) (Method A) A solution of 2-[4-(3-methoxyphenyl)butyl]phenol **4c** (R^1=3-OMe) (1.35 g, 5.27 mmol) in DMA (20 ml) was treated with *tert*-BuOK (590 mg, 5.26 mmol) and the mixture was stirred at room temperature for 10 min. Then 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride (1.45 g, 7.88 mmol) and *tert*-BuOK (885 mg, 7.89 mmol) were added, and the mixture was stirred at 0 °C for 30 min and at 55 °C for 2 h. The resulting solution was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=10/1) to give 2-[2-[2-[4-(3-methoxyphenyl)butyl]phenoxy]ethyl]-1-methylpyrrolidine (920 mg, 2.50 mmol, 48%) as a colorless oil. This oil (920 mg, 2.50 mmol) in EtOAc (20 ml) was treated with 4 N HCl in dioxane (0.94 ml, 3.75 mmol). The resulting solution was concentrated. The oily residue was dissolved in EtOAc (15 ml), and the solution was allowed to stand at room temperature. The precipitate was collected by filtration to give colorless crystals (343 mg, 0.85 mmol, 34%).

Other pyrrolidine derivatives (**10d**, **10f**, **10g**) were similarly prepared except for **10c** which was prepared by method B.

1-Methyl-2-[2-[2-(4-phenylbutyl)phenoxy]ethyl]pyrrolidine Hydrochloride (10c) (Method B) Diethyl azodicarboxylate (DEAD) (0.46 ml, 3.0 mmol) was added to a solution of 2-(4-phenylbutyl)phenol **4c** (R^1=H) (226 mg, 1.0 mmol), 1-methyl-2-pyrrolidineethanol (390 mg, 3.0 mmol) and triphenylphosphine (790 mg, 3.0 mmol) in CH_2Cl_2 (40 ml) and the mixture was stirred overnight at room temperature. The resulting solution was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=10/1) to give 1-methyl-2-[2-[2-(4-phenylbutyl)phenoxy]ethyl]pyrrolidine (174 mg, 0.52 mmol, 52%) as a yellow oil. This oil (174 mg, 0.52 mmol) in EtOAc (5 ml) was treated with 4 N HCl in dioxane (0.20 ml, 0.80 mmol). The resulting solution was concentrated. The oily residue was dissolved in EtOAc (10 ml), and the solution was allowed to stand at room temperature. The precipitate was collected by filtration to give colorless crystals (144 mg, 0.39 mmol, 75%).

1-*tert*-Butoxycarbonyl-3-(*p*-toluenesulfonyloxymethyl)piperidine (8: m=1, X=CH_2, R^2=OTs) *p*-Toluenesulfonyl chloride (20.97 g, 110 mmol) was added to a solution of 1-*tert*-butoxycarbonyl-3-(hydroxymethyl)piperidine (19.73 g, 91.6 mmol) in pyridine (200 ml) at room temperature. The resulting solution was stirred overnight at room temperature. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with brine, dried and evaporated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=13/7) to give 1-*tert*-butoxycarbonyl-3-(*p*-toluenesulfonyloxymethyl)piperidine (32.69 g, 88.48 mmol, 97%) as a colorless solid. NMR ($CDCl_3$) δ: 1.15—1.35 (1H, m), 1.44 (9H, s), 1.5—1.95 (4H, m), 2.46 (3H, s), 2.5—2.95 (2H, m), 3.75—4.0 (2H, m), 3.89 (2H, d, J=6.3 Hz), 7.35 (2H, d, J=8.2 Hz), 7.79 (2H, d, J=8.4 Hz).

1-*tert*-Butoxycarbonyl-3-[2-(4-phenylbutyl)phenoxymethyl]piperidine (9: m=1, X=CH_2) (Method C) A solution of 2-(4-phenylbutyl)phenol **4c** (R^1=H) (1.20 g, 5.30 mmol) in DMA (350 ml) was treated with *tert*-BuOK (714 mg, 6.36 mmol) and the mixture was stirred at 0 °C for 10 min. Then 1-*tert*-butoxycarbonyl-3-(*p*-toluenesulfonyloxymethyl)piperidine **8** (m=1, X=CH_2, R^2=OTs) (2.35 g, 6.36 mmol) was added and the whole was stirred overnight at room temperature. The resulting suspension was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=4/1) to give 1-*tert*-butoxycarbonyl-3-[2-(4-phenylbutyl)phenoxymethyl]piperidine (2.13 g, 5.04 mmol, 95%) as a colorless oil. NMR ($CDCl_3$) δ: 1.25—2.1 (9H, m), 1.45 (9H, s), 2.55—2.9 (6H, m), 3.7—4.2 (4H, m), 6.79 (1H, d, J=8.0 Hz), 6.86 (1H, t, J=7.7 Hz), 7.05—7.2 (5H, m), 7.25—7.35 (2H, m).

1-Methyl-3-[2-(4-phenylbutyl)phenoxymethyl]piperidine Hydrochloride (10b) A solution of 1-*tert*-butoxycarbonyl-3-[2-(4-phenylbutyl)phenoxymethyl]piperidine **9** (m=1, X=CH_2) (718 mg, 1.70 mmol) in THF (5 ml) was added to a suspension of $LiAlH_4$ (193 mg, 5.09 mmol) in THF (15 ml) at room temperature. The mixture was refluxed for 30 min, then cooled, and Na_2SO_4 decahydrate was added slowly. The whole was stirred for 1 h, insoluble material was filtered off, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=4/1) to give 1-methyl-3-[2-(4-phenylbutyl)-phenoxymethyl]piperidine (496 mg, 1.47 mmol, 87%) as a colorless oil. This oil (480 mg, 1.42 mmol) in EtOAc (5 ml) was treated with 4 N HCl in dioxane (0.53 ml, 2.13 mmol) and the mixture was stirred at room temperature for 10 min, then concentrated. The oily residue was dissolved in EtOAc/CH_2Cl_2=9/1, and the solution was allowed to stand at room temperature. The precipitate was collected by filtration to give colorless crystals (423 mg, 1.13 mmol, 80%).

3-[2-(4-Phenylbutyl)phenoxymethyl]piperidine Hydrochloride (10m) A solution of 1-*tert*-butoxycarbonyl-3-[2-(4-phenylbutyl)phenoxymethyl]piperidine **9** (m=1, X=CH_2) (1.678 g, 3.96 mmol) in dioxane (10 ml) was treated with 4 N HCl in dioxane (10 ml) and the mixture was stirred at room temperature for 5 h, then concentrated. The oily residue was dissolved in EtOAc/CH_2Cl_2=1/1, and the solution was allowed to stand at room temperature. The precipitate was collected by filtration to give colorless crystals (1.21 g, 3.35 mmol, 85%).

The morpholine derivative **10a** and other piperidine derivatives **10h—l**, **10n—t**, but not **10q** and **10t**, were similarly prepared by method C.

1-*tert*-Butoxycarbonyl-4-[2-[4-(3-methoxyphenyl)butyl]phenoxy]-piperidine (9: m=0, X=CH_2) (Method D) DEAD (1.12 ml, 7.12 mmol) was added to a solution of 2-[4-(3-methoxyphenyl)butyl]phenol **4c** (R^1=3-OMe) (1.65 g, 6.44 mmol), 1-*tert*-butoxycarbonyl-4-hydroxypiperidine (1.30 g, 6.46 mmol) and triphenylphosphine (1.86 g, 7.09 mmol) in CH_2Cl_2 (30 ml) and the mixture was stirred at room temperature for 3.5 h. Then 1-*tert*-butoxycarbonyl-4-hydroxypiperidine (648 mg, 3.22 mmol), triphenylphosphine (844 mg, 3.22 mmol) and DEAD (0.51 ml, 3.22 mmol) were added, and the mixture was stirred at room temperature for 1 h. The resulting solution was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=5/1) to give a colorless oil (2.30 g, 5.23 mmol, 82%). NMR ($CDCl_3$) δ: 1.48 (9H, s), 1.5—1.95 (8H, m), 2.55—2.7 (4H, m),

3.35—3.65 (4H, m), 3.79 (3H, s), 4.55—4.65 (1H, m), 6.7—6.9 (5H, m), 7.1—7.25 (3H, m).

4-[2-[4-(3-Methoxyphenyl)butyl]phenoxy]-1-methylpiperidine Hydrochloride (10t) A solution of 1-*tert*-butoxycarbonyl-4-[2-[4-(3-methoxyphenyl)butyl]phenoxy]piperidine **9** ($m=0$, $X=CH_2$) (1.30 g, 2.96 mmol) in THF (15 ml) was treated with a suspension of $LiAlH_4$ (227 mg, 5.98 mmol) in THF (15 ml) and the mixture was stirred at room temperature for 30 min and under reflux for 2 h, then cooled. To the resulting suspension, Na_2SO_4 decahydrate was slowly added. The whole was stirred for 1 h, insoluble material was filtered off, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH = 20/1) to give 4-[2-[4-(3-methoxyphenyl)butyl]phenoxy]-1-methylpiperidine (900 mg, 2.55 mmol, 86%) as a light yellow oil. This oil (900 mg, 2.55 mmol) in EtOAc (10 ml) was treated with 4 N HCl in dioxane (0.95 ml, 3.82 mmol). The resulting solution was concentrated. The oily residue was dissolved in EtOAc, and the solution was allowed to stand at room temperature. The precipitate was collected by filtration to give colorless crystals (410 mg, 1.05 mmol, 42%).

1-Acetyl-3-[2-[4-(3-methoxyphenyl)butyl]phenoxymethyl]piperidine (11) A solution of 3-[2-[4-(3-methoxyphenyl)butyl]phenoxymethyl]-piperidine hydrochloride **10n** (1.34 g, 3.44 mmol) in pyridine (10 ml) was treated with Ac_2O (2.4 ml, 21.7 mmol) and the mixture was stirred at room temperature for 30 min, diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (EtOAc) to give a colorless oil (1.30 g, 3.29 mmol, 96%). NMR ($CDCl_3$) δ: 1.25—2.1 (9H, m), 2.07, 2.11 (together 3H, each singlet), 2.5—3.1 (6H, m), 3.78 (3H, s), 3.7—4.0 (3H, m), 4.25—4.65 (1H, m), 6.65—6.95 (5H, m), 7.05—7.25 (3H, m).

1-Ethyl-3-[2-[4-(3-methoxyphenyl)butyl]phenoxymethyl]piperidine Hydrochloride (10q) A solution of 1-acetyl-3-[2-[4-(3-methoxyphenyl)butyl]phenoxymethyl]piperidine **11** (1.30 g, 3.29 mmol) in THF (10 ml) was treated with a suspension of $LiAlH_4$ (121 mg, 3.19 mmol) in THF (5 ml) and the mixture was stirred at room temperature for 1 h. To the resulting suspension, Na_2SO_4 decahydrate was slowly added. The mixture was stirred for 1 h, insoluble material was filtered off, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH = 4/1) to give 1-ethyl-3-[2-[4-(3-methoxyphenyl)butyl]phenoxymethyl]piperidine (1.20 g, 3.14 mmol, 96%) as a colorless oil. This oil (1.20 g, 3.14 mmol) in EtOAc (10 ml) was treated with 4 N HCl in dioxane (1.18 ml, 4.72 mmol). The resulting solution was concentrated. The oily residue was dissolved in EtOAc, and the solution was allowed to stand at room temperature. The precipitate was collected by filtration to give colorless crystals (1.05 g, 2.51 mmol, 80%).

In Vitro* Studies. 5-HT$_2$ Receptor Binding Assay** The 5-HT$_2$ receptor binding assay of Leysen *et al.* [11] was employed with some modifications. Male Wistar rats, each weighing between 280 and 320 g, were decapitated, and the brains were immediately removed from the skulls. The cortex and the striatum were separated, frozen, and stored at -80 °C until needed. The cortex was placed in 50 mM Tris–HCl buffer solution (pH 7.7) and homogenized in a Polytron PT-20, and the homogenate was centrifuged at 49000 × ***g for 10 min. The pellet was again suspended in the same Tris buffer solution and centrifugation was repeated. Finally, the resulting pellet was again suspended in the same Tris buffer solution, the protein content was adjusted to 0.57 mg of protein per ml, and the suspension was stored at -80 °C.

The receptor binding assay was started by adding 440 μl of the membrane suspension to a tube containing 50 μl of [^{3}H]ketanserin and 10 μl of the test compound (dissolved in DMSO). The mixture was incubated for 1 h at 30 °C, and then the reaction was stopped by filtration under vacuum through a Whatman GF/B glass filter. The filter was rinsed twice, each time with 4 ml of ice-cold Tris buffer solution placed in the scintillation vial. Then, ACS-II was added and the radioactivity on the filter was measured using a liquid scintillation counter. Non-specific binding was assayed in the presence of an additional 20 μM atropine. The inhibition of binding by the test compound was analyzed to estimate the IC_{50} (the concentration of the test compound causing 50% inhibition of binding) using the least-squares method.

***In Vitro* Studies. Vasoconstriction Experiment** Contractions of the rat caudal arteries were investigated by the method of Van Nueten *et al.* [12] Male Sprague-Dawley rats, each weighing approximately 500 g, were killed by rapid exsanguination. The caudal arteries were dissected free from connective tissue and cut into spiral strips (2 × 20 mm). The resulting preparations were mounted in organ baths, each containing 10 ml of Tyrode solution maintained at 37 °C, and then gassed with a mixture of 95% (by volume) O_2 and 5% CO_2. The preparations were allowed to equilibrate for 1 h before being used in the experiment.

An initial optimum resting tension of 0.5 g was applied to the preparations, and isometric contractions were recorded with force-displacement transducers. The relaxant effects of the test compounds were determined on preparations which had been precontracted with 5-HT (5-hydroxytryptamine) (3×10^{-6} M), which is an agonist of the 5-HT$_2$ receptor. After the contractile response to 5-HT had reached a steady state, the test compound was added cumulatively to the bathing medium. At the end of the experiments, papaverine (10^{-4} M) was added to produce the maximum relaxation. The relaxation induced by each test compound was calculated as a percentage of the maximum relaxation induced by 10^{-4} M papaverine. The concentrations causing one half of the maximum relaxation (IC_{50}) were calculated by the least-squares method.

D$_2$ Receptor Binding Assay The D$_2$ receptor binding assay of Köhler *et al.* [13] was employed with modifications. It was performed in a similar manner to the 5-HT$_2$ receptor binding assay, except for the use of the D$_2$ antagonist [^{3}H]raclopride as the ^{3}H-ligand and the striatum instead of the cortex.

***In Vivo* Studies. Apomorphine-Induced Climbing in Mice** The method is a modification of that of Protais *et al.* [14] Male ddY mice (21—26 g) were individually placed in wire-mesh cylindrical cages (12 cm diameter, 14 cm high) and were left for 2 h without food. Then mice (six mice per group) were orally given a test compound or the vehicle (30% polyethylene glycol), and 35 min thereafter injected with 1.0 mg/kg s.c. of apomorphine. After 10 min the climbing behavior of the mice was observed for 1 min. ED_{50} values were calculated by linear regression analysis.

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References and Notes

1) Present address: *Patent Department, Sankyo Co., Ltd.*
2) *a*) Lader M., *J. Int. Med. Res.*, **17**, 1—16 (1989); *b*) Hollister L. E., *Drug Dev. Res.*, **9**, 9—21 (1986).
3) Remington G., *Can. J. Psychiatry.*, **34**, 211—220 (1989).
4) *a*) Bersani G., Grispini A., Marini S., Pasini A., Valducci M., Ciani N., *Curr. Ther. Res.*, **40**, 492—500 (1986); *b*) Reyntjens A., Gelders Y. G., Hoppenbrouwers M.-L. J. A., Vanden Bussche G., *Drug Dev. Res.*, **8**, 205—211 (1986); *c*) Meltzer H. Y., Nash J. F., *Pharmacol. Rev.*, **43**, 587—604 (1991).
5) Janssen P. A. J., Niemegeers C. J. E., Awouters F., Schellekens K. H. L., Megens A. A. H. P., Meert T. F., *J. Pharmacol. Exp. Ther.*, **244**, 685—693 (1988).
6) Hirose A., Kato T., Ohno Y., Shimizu H., Tanaka H., Nakamura M., Katsube J., *Jpn. J. Pharmacol.*, **53**, 321—329 (1990).
7) Kikumoto R., Hara H., Ninomiya K., Osakabe M., Sugano M., Fukami H., Tamao Y., *J. Med. Chem.*, **33**, 1818—1823 (1990).
8) Mitsunobu O., *Synthesis*, **1981**, 1—28.
9) Leo A., Weininger D., "CLOGP3 Reference Manual, Daylight Software 4.34," Daylight Chemical Information Systems, Inc., Irvine.
10) Fujimoto K., Tanaka N., Asai F., Ito T., Koike H., Eur. Pat. EP600717 (1994) [*Chem. Abstr.*, **123**, 169510*k* (1995)].
11) Leysen J. E., Niemegeers C. J. E., Van Nueten J. M., Laduron P. M., *Mol. Pharmacology.*, **21**, 301—314 (1982).
12) Van Nueten J. M., Janssen P. A. J., Van Beek J., Xhonneux R., Verbeuren T. J., Vanhoutte P. M., *J. Pharmacol. Exp. Ther.*, **218**, 217—230 (1981).
13) Köhler C., Hall H., Ögren S., Gawell L., *Biochem. Pharmacol.*, **34**, 2251—2259 (1985).
14) Protais P., Costentin J., Schwartz J. C., *Psychopharmacology.*, **50**, 1—6 (1976).
15) *Neuroscience Research Laboratories, Sankyo Co., Ltd.*