Design, Synthesis, Structure−Activity Relationships, and Biological Characterization of Novel Arylalkoxyphenylalkylamine σ Ligands as Potential Antipsychotic Drugs

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σ Receptor antagonists may be effective antipsychotic drugs that do not induce motor side effects caused by ingestion of classical drugs such as haloperidol. We obtained evidence that 1-(2-dipropylaminoethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran hydrochloride **2a** had selective affinity for σ receptor over dopamine D_2 receptor. This compound was designed to eliminate two bonds of apomorphine **1** to produce structural flexibility for the nitrogen atom and to bridge two benzene rings with a $-CH_2O-$ bond to maintain the planar structure. In light of the evidence, *N*,*N*-dipropyl-2-(4-methoxy-3-benzyloxylphenyl)ethylamine hydrochloride **10b** was designed. Since compound **10b** had eliminated a biphenyl bond of 6*H*-dibenzo[*b*,*d*]pyran derivative **2a**, it might be more released from the rigid structure of apomorphine **1** than compound **2a**. The chemical modification of compound **10b** led to the discovery that *N*,*N*-dipropyl-2- [4-methoxy-3-(2-phenylethoxyl)phenyl]ethylamine hydrochloride **10g** (NE- 100), the best compound among arylalkoxyphenylalkylamine derivatives **3**, had a high and selective affinity for σ receptor and had a potent activity in an animal model when the drug was given orally. We report here the design, synthesis, structure−activity relationships, and biological characterization of novel arylalkoxyphenylalkylamine derivatives **3**.

Introduction

Interest in σ receptors,[1] which were postulated by Martin et al.[2] to account for the actions of (±)-*N*-allylnormetazacine (SKF10,047), has continued to grow as they bind to typical and atypical antipsychotics.[3−5] The role of σ receptors can explain the antipsychotic-like effects of *cis*-9-[3-(3,5-dimethyl-1-piperazinyl)propyl] carbazole dihydrochloride (rimcazole),[6−13] (−)-(*S*)-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethylbenzamide (remoxipride),[14−19] α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazine-butanol HCl (BMY 14802),[20,21] 6-[6-(4-hydroxypiperidinyl)hexyloxy]-3-methylflavone HCl (NPC16377),[22] cinuperone,[23] 1-(cyclopropylmethyl)-4-[2′-(4″-fluorophenyl)-2′-oxoethyl]piperidine HBr (DuP734),[24] 1-cyclopropylmethyl-4-[2′-(4″-cyanophenyl)-2′-oxoethyl]piperidine HBr (XJ 448),[25,26] and *cis*-3-(hexahydroazepin-l-yl)-1-(3-chloro-4-cyclohexylphenyl)propene-1 HCl (SR 31742A),[27] which may not act primarily at the dopamine D_2 (D_2) receptor but do have a reasonable affinity for σ receptors.

σ Receptors are distributed in the cortex and the nucleus accumbens more so than in the striatum.[28] XJ 448,[25,26] which binds to σ receptor with high affinity and selectvity, modulated dopamine turn vein the rat frontal cortex and strongly blocked behavior induced by apomorphine in mice and by 2-(1-piperazinyl)quinoline (quipazine) in rats. XJ 448 did not cause catalepsy in the rat, but it did antagonize the catalepsy by haloperidol. These findings suggest that selective σ receptor antagonists may be effective antipsychotic drugs, compounds that do not induce the extrapyramidal symptoms and tardive dyskinesia caused by ingestion of classical D_2 receptor antagonists drugs such as haloperidol and chlorpromazine.

In contrast, there are several reports suggesting that σ receptor might not be involved in the etiology and/or pathology of schizophrenia. In a limited open-label study, BMY14802,[20,21] which has affinities for both σ and serotonin 5-HT_{1A} receptors,[51] has proven to have no significant improvement in psychiatric symptoms, as measured by the total brief psychiatric rating scale (BPRS) scores, and was dropped from the study. Rimcazole,[6−13] which has a weak but selective affinity for σ receptor, did not equal the efficacy of haloperidol or chlorpromazine, while rimcazole partially reduced schizophrenic symptoms in a majority of patients in open-label trials.

In addition to the relationship between σ receptor and schizophrenia, the molecular properties and signaling mechanisms mediated through σ receptor have not been fully elucidated, although a recent molecular cloning technique revealed[53,54] that the σ binding protein did not seem to be related to both cytochrome P-450 and neuropeptide Y receptor, which has been postulated to be the σ receptor for long time.[55,56]

These ambiguities might be ascribed to the lack of potent and selective ligands for σ receptor currently available. To address the physiological and clinical

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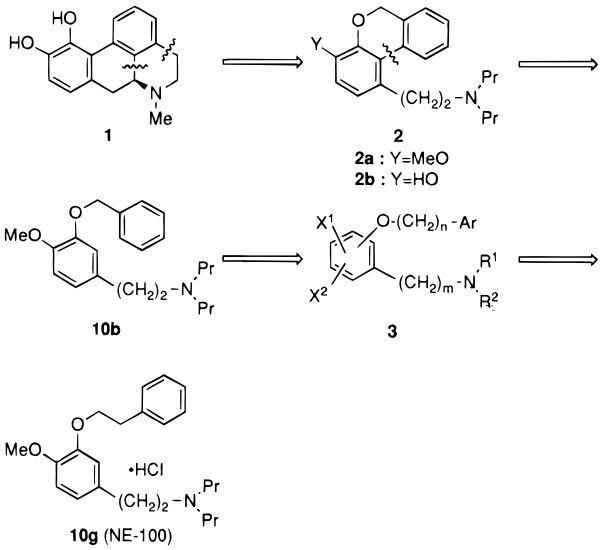
Scheme 1

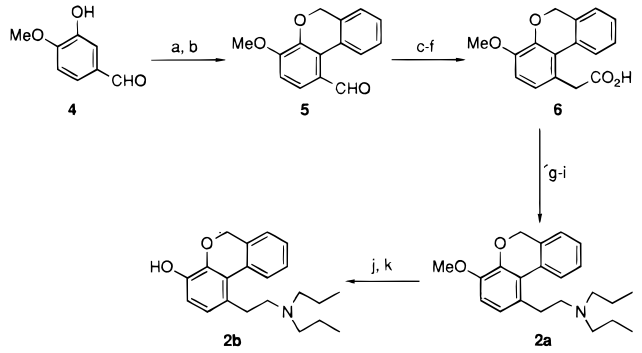


significance of σ ligands, discovery of potent and selective σ ligands is important.

In search of discovering σ ligands with high affinity and selectivity, miscellaneous structures[26,29−39] have been designed, synthesized, and evaluated to date. The σ ligands have a nitrogen atom and one or two benzene rings. The nitrogen and benzene ring(s) may be important for interaction with σ receptor. Furthermore, it would seem that the distance between nitrogen and benzene ring(s) of σ ligands is close to that of dopamine D_2 ligands. Actually, 4-[4-(*p*-chlorophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone (haloperidol) has high affinity for both σ and dopamine D_2 receptors. The structural estimate supports that apomorphine has affinity for dopamine D_2 and σ receptors. However, apomorphine does not have affinity for σ receptor.[40] We have been interested in the fact that apomorphine has a more rigid structure than haloperidol and presumed that σ affinity is influenced by the difference of structural flexibility between apomorphine and haloperidol. In light of the presumption, apomorphine has been modified to flexible compounds containing one nitrogen atom and two benzene rings: the novel 6*H*-dibenzo[*b*,*d*]-pyran derivatives **2**. The derivatives **2** have more interesting structures than the known compounds[41] modified from apomorphine since derivatives **2** have been designed to eliminate two bonds of apomorphine to produce structural flexibility for the nitrogen atom and to bridge two benzene rings with a $-CH_2O-$ bond to maintain the planar structure (Scheme 1). Derivatives **2a** and **2b** have been selective for σ receptor over D_2 receptor. Because of the elevated affinity of derivatives **2** (vs **1**) for σ receptor, our interest has focused on arylalkoxyphenylalkylamine derivatives of general formula **3**, since derivatives **3** are more released from the rigid structure of apomorphine than derivatives **2** (Scheme 1). This attempt has led to the discovery that compound **10g** (NE-100) has a high and selective affinity for σ receptor and has a potent activity in an animal model when the drug has been given orally.

We report here the design, synthesis, structure−activity relationships (SARs), and biological characterization of novel arylalkoxyphenylalkylamine derivatives **3**.

Scheme 2[a]



[a] Reagents and conditions: (a) 2-I-PhCH_2-Cl, K_2CO_3, KI, DMF rt; (b) Cu, DMF, heat; (c) $NaBH_4$, THF-MeOH; (d) $SOCl_2$, THF, DMF; (e) KCN, 18-crown-6, CH_3CN; (f) H_2SO_4, H_2O, AcOH, heat; (g) $SOCl_2$, PhH, heat; (h) $HNPr_2$, Et_3N, PhH, 0 °C to rt; (i) $LiAlH_4$, THF, heat; (j) HBr, AcOH, heat; (k) K_2CO_3, DMF, rt.

Chemistry

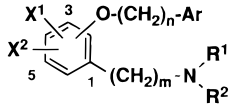
The synthetic work is described in two parts: (1) preparation of 6*H*- dibenzo[*b*,*d*]pyran derivatives **2** and (2) preparation of arylalkoxyphenylalkylamine derivatives **3**.

6*H*-Dibenzo[*b*,*d*]pyran Derivatives. The process of preparing 6*H*- dibenzo[*b*,*d*]pyran derivatives **2a** and **2b** is depicted in Scheme 2. Derivative **2a** was derived by reduction ($LiAlH_4$) of the corresponding amides prepared from carboxylic acid **6** via acyl chlorides. The carboxylic acid **6** was derived from aldehyde **5** in four generic steps, which were reduction ($LiAlH_4$), chloro replacement (SO_2Cl_2, hexamethylphosphoric triamide),[43] cyano substitution (18-crown-6, KCN), followed by hydrolysis (H_2SO_4). The aldehyde **5** was derived by Ullmann reaction of 2-bromo-3-(2-iodobenzyloxy)-4-methoxybenzaldehyde, a compound which was prepared by treatment of 2-bromo-3-hydroxy-4-methoxybenzaldehyde **4** with 2-iodobenzylbromide.

Derivative **2b** was prepared from **2a** by cleavage of two ether bonds followed by recyclization in the presence of K_2CO_3.

Arylalkoxyphenylalkylamine Derivatives. The process of preparing phenylalkylamine derivatives **10**, **16**, **19**, **21**, **22**, and **24**−**26** (cf. Tables 1 and 2) is depicted in the generic Schemes 3−7. Various phenylethylamine derivatives **10** were prepared via the corresponding phenylacetic acids **8** (Scheme 2). 4-Benzyloxy-3-hydroxybenzaldehyde **7aa** and 3-hydroxy-4-(2-phenylethoxy) benzaldehyde **7ab**, the required noncommercial starting materials for this sequence, were prepared from 3,4-dihydroxybenzaldehyde by treatment with corresponding phenylalkyl bromides in the presence of K_2CO_3 in *N*,*N*-dimethylformamide (DMF). On the other hand, esters **7a′** were provided from commercially available benzoic acids by acidic esterification (H_2SO_4/MeOH). Phenylacetic acids **5** were derived from aldehydes **7a** (method A) or esters **7a′** (method B) in the five generic steps of O-phenylalkylation, reduction, chloro replacement, cyano replacement,[43] and hydrolysis. In case of O-2-phenylethylation, 2-phenylethyl bromide required 4 equiv or more to complete etherification. Chloro replacement, by treatment with thionyl chloride in the presence of DMF, led to good results, as was the case in the presence of hexamethylphosphoric triamide.[43] Phenylethylamine derivatives **10** were derived by re-

Table 1. Phenylalkylamine Derivatives: Physical Data

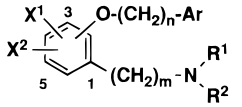


no.	X^1	X^2	$-O(CH_2)_n$-Ar	m	$-NR^1R^2$	salt[a]	method[b]	mp (°C)	analysis[c]
10a	3-MeO	H	2-OCH_2-Ph	2	N(*n*-Pr)$_2$	Oxa	A, C	124−126[n]	$C_{22}H_{31}NO_2 \cdot C_2H_2O_4$[d]
10b	4-MeO	H	3-OCH_2-Ph	2	N(*n*-Pr)$_2$	Oxa	A, C	126−127[n]	$C_{22}H_{31}NO_2 \cdot C_2H_2O_4$[d]
10c	5-Cl	H	2-OCH_2-Ph	2	N(*n*-Pr)$_2$	Oxa	A, E	161−163[n]	$C_{21}H_{28}ClNO \cdot C_2H_2O_4$[e]
10d	3-MeO	H	2-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	HCl	A, C	105−107[o]	$C_{23}H_{33}NO_2 \cdot HCl.0.33H_2O$[e]
10e	4-MeO	H	2-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	oxa	A, C	137−138[p]	$C_{23}H_{33}NO_2 \cdot C_2H_2O_4$[d]
10f	5-MeO	H	2-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	HCl	A, C	92−93[q]	$C_{23}H_{33}NO_2 \cdot HCl \cdot 0.1H_2O$[d]
10g	4-MeO	H	3-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	HCl	A, C	96−97[q]	$C_{23}H_{33}NO_2 \cdot HCl$[d]
10h	2-MeO	H	4-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	A, C	132−133[q]	$C_{23}H_{33}NO_2 \cdot C_2H_2O_4$[d]
10i	3-MeO	H	4-$(O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	A, C	108−110[p]	$C_{23}H_{33}NO_2 \cdot C_2H_2O_4$[d]
10j	3-F	H	2-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	A, D	137−138[n]	$C_{22}H_{30}FNO \cdot C_2H_2O_4$[d]
10k	5-F	H	2-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	HCl	B, D	85−86[r]	$C_{22}H_{30}FNO \cdot HCl \cdot 0.067C_6H_5CH_3$[d]
101	4-Cl	H	2-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	HCl	B, D	93−94[q]	$C_{22}H_{30}ClNO \cdot HCl$[d]
10m	5-Br	H	2-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	A, E	160−161[p]	$C_{22}H_{30}BrNO \cdot C_2H_2O_4$[e]
10n	3-Cl	5-Cl	2-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	B, D	152−153[n]	$C_{22}H_{29}Cl_2NO \cdot C_2H_2O_4$[d]
10o	3-Br	5-Br	2-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	A, C	137−138[p]	$C_{22}H_{29}Br_2NO \cdot C_2H_2O_4$[d]
10p	H	H	2-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	A, C	139−141[n]	$C_{22}H_{31}NO \cdot C_2H_2O_4$[d]
10q	5-Br	H	2-$O(CH_2)_3$-Ph	2	N(*n*-Pr)$_2$	Oxa	A, D	138−139[p]	$C_{23}H_{32}BrNO \cdot C_2H_2O_4$[e]
10r	5-Cl	H	2-$O(CH_2)_3$-Ph	2	N(*n*-Pr)$_2$	Oxa	A, D	140−141[p]	$C_{23}H_{32}ClNO \cdot C_2H_2O_4$[e]
10s	3-MeO	H	2-$O(CH_2)_2$-Ph	2	Pyrr[g]	Oxa	AC	126−128[q]	$C_{21}H_{27}NO_2C_2H_2O_4 \cdot 0.1H_2O$[d]
10t	4-MeO	H	3-$O(CH_2)_2$-Ph	2	Pyrr[g]	Oxa	A, C	140−142[p]	$C_{21}H_{27}NO_2 \cdot C_2H_2O_4 \cdot 0.1H_2O$[d]
10u	5-Cl	H	2-$O(CH_2)_2$-Ph	2	Pyrr[g]	Oxa	A, C	171−173[n]	$C_{20}H_{24}ClNO \cdot C_2H_2O_4$[e]
10v	3-MeO	H	2-$O(CH_2)_2$-Ph	2	Morp[h]	Oxa	A, C	163−165[n]	$C_{21}H_{27}NO_3 \cdot C_2H_2O_4 \cdot 0.1H_2O$[d]
10w	4-MeO	H	3-$O(CH_2)_2$-Ph	2	Morp[h]	Oxa	A, C	158−16[n]	$C_{21}H_{27}NO_3 \cdot C_2H_2O_4$[d]
10x	5-Cl	H	2-$O(CH_2)_2$-Ph	2	Morp[h]	Oxa	A, C	181−183[n]	$C_{20}H_{24}NO_2 \cdot C_2H_2O_4$[d]
10y	3-MeO	H	2-$O(CH_2)_2$-Ph	2	Pipe-Ph[i]	Oxa	A, C	198−200[n]	$C_{27}H_{32}N_2O_2 \cdot C_2H_2O_4$[d]
10z	4-MeO	H	3-$O(CH_2)_2$-Ph	2	Pipe-Ph[i]	Oxa	A, C	182−185[n]	$C_{27}H_{32}N_2O_2 \cdot C_2H_2O_4$[d]
10aa	3-MeO	H	2-$O(CH_2)_2$-Ph	2	Pipe-Pd-2[j]	Oxa	A, C	171−173[n]	$C_{26}H_{31}N_3O_2 \cdot C_2H_2O_4$[d]
10ab	4-MeO	H	3-$O(CH_2)_2$-Ph	2	Pipe-Pd-2[i]	Oxa	A, C	168−170[n]	$C_{26}H_{31}N_3O_2 \cdot C_2H_2O_4$[d]
10ac	5-Cl	H	2-$O(CH_2)_2$-Ph	2	Pipe-Pd-2[i]	Oxa	A, E	165−167[n]	$C_{25}H_{28}ClN_3O \cdot C_2H_2O_4 \cdot 0.1H_2O$[d]
10ad	5-Cl	H	2-$O(CH_2)_2$-Ph	2	Pipe-Pm-2[k]	Oxa	A, E	176−178[n]	$C_{24}H_{27}ClN_4O \cdot C_2H_2O_4$[d]
10ae	4-MeO	H	3-$O(CH_2)_2$-Ph	2	Pipe-Ph-OMe-2[l]	2HCl	A, C	172−173[s]	$C_{28}H_{34}N_2O_2 \cdot 2HCl$[e]
10af	5-Cl	H	2-$O(CH_2)_2$-Ph	2	Pipe-Ph-OMe-2[l]	2HCl	A, C	136−138[p]	$C_{27}H_{31}ClN_2O_2 \cdot 2HCl$[e]
10ag	4-$PhCH_2O$	H	3-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	HCl	A, C	96−98[q]	$C_{29}H_{37}NO_2 \cdot HCl$[e]
10ah	3-$PhCH_2O$	H	4-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	A,C	110−111[q]	$C_{29}H_{37}NO_2 \cdot HCl$[e]
16a	3-MeO	H	2-$O(CH_2)_2$-Ph	3	N(*n*-Pr)$_2$	Oxa	F, G, C	114−115[q]	$C_{24}H_{35}NO_2 \cdot C_2H_2O_4 \cdot 0.1H_2O$[d]
16b	4-MeO	H	3-$O(CH_2)_2$-Ph	3	N(*n*-Pr)$_2$	HCl	F, G, C	78−79[o]	$C_{24}H_{35}NO_2 \cdot HCl$[e]
16c	5-Cl	H	2-$O(CH_2)_2$-Ph	3	N(*n*-Pr)$_2$	Oxa	F, H	100−102[q]	$C_{23}H_{32}ClNO \cdot C_2H_2O_4$[d]
16d	5-Br	H	2-$O(CH_2)_2$-Ph	3	N(*n*-Pr)$_2$	Oxa	F,G,D	104−105[q]	$C_{23}H_{32}BrNO \cdot C_2H_2O_4 \cdot 0.2H_2O$[e]
16e	5-Cl	H	2-$O(CH_2)_2$-Ph	3	Pipe-Ph[i]	Oxa	F, H	163−165[n]	$C_{27}H_{31}ClN_2O \cdot C_2H_2O_4$[e]
16f	5-Cl	H	2-$O(CH_2)_2$-Ph	3	Pipe-Ph-OMe-2[l]	HCl	F, H	141−143[t]	$C_{28}H_{33}ClN_2O \cdot C_2H_2O_4$[e]
16g	5-Cl	H	2-$O(CH_2)_2$-Ph	3	Pipe-Pd-2[j]	Oza	F, H	150−152[n]	$C_{26}H_{30}ClN_3O \cdot C_2H_2O_4$[d]
16h	5-Cl	H	2-$O(CH_2)_2$-Ph	3	Pipe-Pd-2-Me-6[m]	Oxa	F, H	160−162[p]	$C_{27}H_{32}ClN_3O \cdot C_2H_2O_4$[d]
16i	5-Cl	H	2-$O(CH_2)_2$-Ph	3	Pipe-Pm-2[k]	Oxa	F, H	151−153[n]	$C_{25}H_{29}ClN_4O \cdot C_2H_2O_4$[d]
19	5-Cl	H	2-$O(CH_2)_2$-Ph	4	N(*n*-Pr)$_2$	Oxa	I	80−82[q]	$C_{27}H_{34}ClNO \cdot C_2H_2O_4$[d]
21a	4-HO	H	3-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	HCl	J	124−125[q]	$C_{22}H_{31}NO_2 \cdot HCl$[e]
21b	3-HO	H	4-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	HCl	J	123−124[q]	$C_{22}H_{31}NO_2 \cdot HCl$[e]
22a	5-Cl	H	2-$O(CH_2)_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	J, K	167−168[n]	$C_{22}H_{30}ClNO \cdot C_2H_2O_4$[e]
22b	4-MeO	H	3-$O(CH_2)_2$-Ph-F-4	2	N(*n*-Pr)$_2$	HCl	J, K	114−116[q]	$C_{23}H_{32}FNO_2HCl \cdot 0.33AcOEt$[e]
22c	4-MeO	H	3-$O(CH_2)_2$-Ph-Cl-3	2	N(*n*-Pr)$_2$	Oxa	J, K	79−80[u]	$C_{23}H_{32}ClNO_2 \cdot C_2H_2O_4$[d]
22d	4-MeO	H	3-$O(CH_2)_2$-Ph-OMe-4	2	N(*n*-Pr)$_2$	Oxa	J, K	110−111[q]	$C_{24}H_{35}NO_3 \cdot C_2H_2O_4 \cdot 0.429H_2O$[d]
22e	4-MeO	H	3-$O(CH_2)_2$-Ph-(OMe)2-3,4	2	N(*n*-Pr)$_2$	Oxa	J, K	132−134[p]	$C_{25}H_{37}NO_2 \cdot C_2H_2O_4 \cdot 0.1H_2O$[d]
22f	4-MeO	H	3-$O(CH_2)_2$-Thi-2[f]	2	N(*n*-Pr)$_2$	HCl	J, K	96−98[q]	$C_{21}H_{31}SNO_2 \cdot HCl \cdot 0.33H_2O$[d]
22g	3-MeO	H	2-$O(CH_2)_3$-Ph	2	N(*n*-Pr)$_2$	Oxa	J, K	113−114[q]	$C_{24}H_{35}NO_2 \cdot C_2H_2O_4$[d]
22h	4-MeO	H	3-$O(CH_2)_3$-Ph	2	N(*n*-Pr)$_2$	Oxa	J, K	82−83[p]	$C_{24}H_{35}NO_2 \cdot C_2H_2O_4$[d]
24	4-MeO	H	3-$O(CH_2)_2$-Ph	2	2- NH_2	HCl	L	114−115[p]	$C_{17}H_{21}NO_2 \cdot HCl$[e]
25	4-MeO	H	3-$O(CH_2)_2$-Ph	2	NH(*n*-Pr)$_2$	HCl	M	134−1 36[p]	$C_{20}H_{27}NO_2 \cdot HCl$[e]
26a	4-MeO	H	3-$O(CH_2)_2$-Ph	2	N(*n*-Pr)(iso-Amy)	HCl	M	134−136[p]	$C_{20}H_{37}NO_2 \cdot HCl \cdot 0.8H_2O$[e]
26b	4-MeO	H	3-$O(CH_2)_2$Ph	2	N(*n*-Pr)(*n*-Hex)	HCl	N	oil	$C_{25}H_{39}NO_2 \cdot HCl \cdot 0.8H_2O$[e]
26c	4-MeO	H	3-$O(CH_2)_2$Ph	2	N(*n*-Pr)($(CH_2)_3$-OH)	HCl	N	oil	$C_{26}H_{39}NO_2 \cdot HCl \cdot 0.2H_2O$[e]
2a						HCl		162−164[x]	$C_{22}H_{29}NO_2 \cdot HCl$[e]
2b						HCl		242−244[n]	$C_{21}H_{27}NO_2 \cdot HCl$[e]

[a] Oxa = oxalate. [b] Methods A−N are described in the text. [c] Elemental analyses for all compounds are within ±0.4% of the theoretical values for the indicated formula. [d] Analyses were performed for all elements except O. [e] Analyses were performed for C, H, N. [f] 2-Thienyl. [g] 1-Pyrrolidinyl. [h] 4-Morpholinyl. [i] 1-(4-Phenylpiperazinyl). [j] l-[4-(2-Pyridyl)piperazinyl]. [k] 1-[4-(2-Pyrimidinyl)piperazinyl]. [l] 1-[4-(2-Methoxyphenyl)piperazinyl]. [m] 1-[4-[2-(6-Methylpyridyl)]piperazinyl]. [n −x]Recrystallization solvents are depicted: [n]EtOH; [o]AcOEt-iso-Pr_2O; [p]iso-PrOH; [q]AcOEt; [r]toluene; [s]MeOH; [t]AcOEt-*n*-hexane; [u]iso-Pr_2O; [x]iso-PrOH-AcOEt.

duction (method C, $LiAlH_4$; method D, BH_3-THF) of the corresponding amides **9** via acyl chlorides. Derivatives **10** were also prepared from phenylethyl chlorides **11**, which were synthesized from acids **8** in two steps: by treatment with amines HNR^1R^2 with or without bases (K_2CO_3 or diisopropylethylamine) (method E).

Table 2. Phenylalkylamine Derivatives: Biological Data



no.	X^1	X^2	$-O(CH_2)_n$-Ar	m	$-NR^1R^2$	salt[a]	σ IC_{50} (nM)[b]	D_2 IC_{50} (nM)[b]
10a	3-MeO	H	2-OCH_2-Ph	2	N(*n*-Pr)$_2$	Oxa	26	>1000
10b	4-MeO	H	3-OCH_2-Ph	2	N(*n*-Pr)$_2$	Oxa	28	>1000
10c	5-Cl	H	2-OCH_2-Ph	2	N(*n*-Pr)$_2$	Oxa	118	337
10d	3-MeO	H	2-O(CH_2)2-Ph	2	N(*n*-Pr)$_2$	HCl	2.7	>1000
10e	4-MeO	H	2-O(CH2)2-Ph	2	N(*n*-Pr)$_2$	Oxa	6.6	>1000
10f	5-MeO	H	2-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	HCl	7.1	791
10g	4-MeO	H	3-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	HCl	1.3	>1000
10h	2-MeO	H	4-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	6.8	>1000
10i	3-MeO	H	4-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	12	>1000
10j	3-F	H	2-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	22	>1000
10k	5-F	H	2-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	HCl	13	>1000
101	4-Cl	H	2-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	HCl	18	>1000
10m	5-Br	H	2-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	11	169
10n	3-Cl	5-Cl	2-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	281	>1000
10o	3-Br	5-Br	2-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	774	>1000
10p	H	H	2-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	15	436
10q	5-Br	H	2-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	44	685
10r	5-Cl	H	2-O(CH_2)$_3$-Ph	2	N(*n*-Pr)$_2$	Oxa	56	876
10s	3-MeO	H	2-O(CH_2)$_2$-Ph	2	Pyrr[a]	Oxa	28	>1000
10t	4-MeO	H	3-O(CH_2)$_2$-Ph	2	Pyrr[a]	Oxa	107	>1000
10u	5-Cl	H	2-O(CH_2)$_2$-Ph	2	Pyrr[a]	Oxa	36	69
10v	3-MeO	H	2-O(CH_2)$_2$-Ph	2	Morp[a]	Oxa	373	>1000
10w	4-MeO	H	3-O(CH_2)$_2$-Ph	2	Morp[a]	Oxa	>1000	>1000
10x	5-Cl	H	2-O(CH_2)$_2$-Ph	2	Morp[a]	Oxa	308	163
10y	3-MeO	H	2-O(CH_2)$_2$-Ph	2	Pipe-Ph[a]	Oxa	328	66
10z	4-MeO	H	3-O(CH_2)$_2$-Ph	2	Pipe-Ph[a]	Oxa	33	183
10aa	3-MeO	H	2-O(CH_2)$_2$-Ph	2	Pipe-Pd-2[a]	Oxa	>1000	137
10ab	4-MeO	H	3-O(CH_2)$_2$-Ph	2	Pipe-Pd-2[a]	Oxa	112	295
10ac	5-Cl	H	2-O(CH_2)$_2$-Ph	2	Pipe-Pd-2[a]	Oxa	>1000	51
10ad	5-Cl	H	2-O(CH_2)$_2$-Ph	2	Pipe-Pm-2[a]	Oxa	>1000	143
10ae	4-MeO	H	3-O(CH_2)$_2$-Ph	2	Pipe-Ph-OMe-2[a]	2HCl	25	11
10af	5-Cl	H	2-O(CH_2)$_2$-Ph	2	Pipe-Ph-OMe-2[a]	2HCl	640	88
16a	3-MeO	H	2-O(CH_2)$_2$-Ph	3	N(*n*-Pr)$_2$	Oxa	13	>1000
16b	4-MeO	H	3-O(CH_2)$_2$-Ph	3	N(*n*-Pr)$_2$	HCl	1.0	950
16d	5-Br	H	2-O(CH_2)$_2$-Ph	3	N(*n*-Pr)$_2$	Oxa	11	438
16e	5-Cl	H	2-O(CH_2)$_2$-Ph	3	Pipe-Ph	Oxa	142	180
16f	5-Cl	H	2-O(CH_2)$_2$-Ph	3	Pipe-Ph-OMe-2[a]	HCl	319	16
16g	5-Cl	H	2-O(CH_2)$_2$-Ph	3	Pipe-Pd-2[a]	Oxa	118	93
16h	5-Cl	H	2-O(CH_2)$_2$-Ph	3	Pipe-Pd-2-Me-6[a]	Oxa	415	293
16i	5-Cl	H	2-O(CH_2)$_2$-Ph	3	Pipe-Pm-2[a]	Oxa	169	115
19	5-Cl	H	2-O(CH_2)$_2$-Ph	4	N(*n*-Pr)$_2$	Oxa	26	>1000
21a	4-HO	H	3-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	HCl	3.1	>1000
21b	3-HO	H	4-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	HCl	25	>1000
22a	5-Cl	H	2-O(CH_2)$_2$-Ph	2	N(*n*-Pr)$_2$	Oxa	7.2	112
22b	4-MeO	H	3-O(CH_2)$_2$-Ph-F-4	2	N(*n*-Pr)$_2$	HCl	1.0	>1000
22c	4-MeO	H	3-O(CH_2)$_2$-Ph-Cl-3	2	N(*n*-Pr)$_2$	Oxa	1.5	>1000
22d	4-MeO	H	3-O(CH_2)$_2$-Ph-OMe-4	2	N(*n*-Pr)$_2$	Oxa	1.0	>1000
22e	4-MeO	H	3-O(CH_2)$_2$-Ph-(OMe)$_2$-3,4	2	N(*n*-Pr)$_2$	Oxa	67	NT[c]
22f	3-MeO	H	3-O(CH_2)$_2$-Thi-2[a]	2	N(*n*-Pr)$_2$	HCl	9.4	>1000
22g	3-MeO	H	3-O(CH_2)$_3$-Ph	2	N(*n*-Pr)$_2$	Oxa	1.7	>1000
22h	4-MeO	H	3-O(CH_2)$_3$-Ph	2	N(*n*-Pr)$_2$	Oxa	4.7	>1000
24	4-MeO	H	3-O(CH_2)$_2$-Ph	2	NH_2	HCl	>1000	>1000
25	4-MeO	H	3-O(CH_2)$_2$-Ph	2	N(*n*-Pr)	HCl	34	>1000
26a	4-MeO	H	3-O(CH_2)$_2$-Ph	2	N(*n*-Pr)(iso-Amy)	HCl	2.9	680
26b	4-MeO	H	3-O(CH_2)$_2$-Ph	2	N(*n*-Pr)(*n*-Hex)	HCl	1.8	619
26c	4-MeO	H	3-O(CH_2)$_2$-Ph	2	N(*n*-Pr)((CH_2)$_3$-OH)	HCl	19	>1000
2a							990	>1000
2b							558	>1000
apomorphine							>1000	5.1
BMY14802							158	>1000

[a] See Table 1. [b] IC_{50} values from duplicate determination. [c] Not tested.

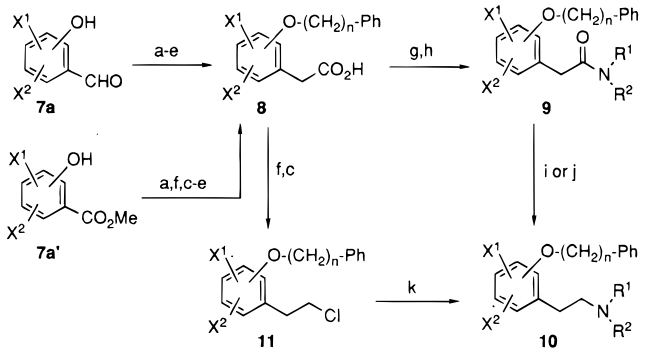
Various phenylpropylamine derivatives **16** were derived from the corresponding ethyl phenylpropionates **13** or phenylpropionic acids **14** with the procedure of method C, D, or H (Scheme 3). The propionates **13** were prepared by Horner−Emmons condensation,[44] followed by hydrogenation over PtO_2 (method F). The phenylpropionic acids **14** derived from the propionate **13** with generic hydrolysis (NaOH) (method G).

Phenylbutylamine **19** was prepared from phenylpropyl chloride **17a** in five steps, which were cyano replacement, hydrolysis, reduction, chloro substitution, and treatment with amines HNR^1R^2 (method I) (Scheme 4), as shown in Scheme 2.

Hydrogenation of benzyloxy compounds **20** with Pd-$(OH)_2$/C (method J) resulted in phenol derivatives **21**, which were treated with arylalkyl halides to afford derivatives **22** (method K) (Scheme 5).

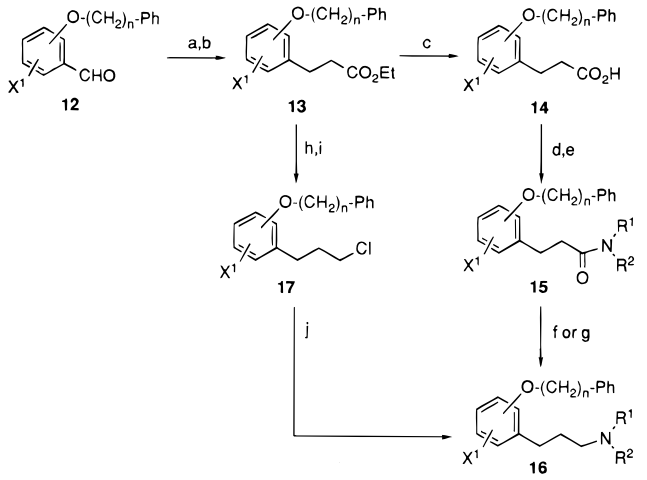
Scheme 6 depicts synthesis of primary, secondary, and tertiary amines. Primary amine **24** was provided by reduction of nitrile **23** with $NaBH_4$ and trifluoroacetic

Scheme 3[a]



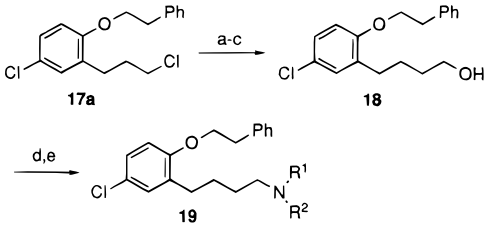
[a] Reagents and conditions: (a) K_2CO_3, $Ph(CH_2)_n$-X, DMF, 40−50 °C, (b) $NaBH_4$, NaOH, THF, H_2O, 0 °C to rt; (c) $SOCl_2$, THF, DMF; (d) KCN, 18-crown-6, CH_3CN; (e) KOH, H_2O, EtOH, heat; (f) $LiAlH_4$, THF, 0 °C to rt; (g) $SOCl_2$, $PhCH_3$, 75 °C; (h) HNR^1R^2, $PhCH_3$, 0 °C to rt; (i) $LiAlH_4$, THF, heat; (j) BH_3-THF, THF, heat; (k) HNR^1R^2. (Method A: a−e. Method B: a, f, c−e. Method C: g−i. Method D: g, h, j. Method E: f, c, k.)

Scheme 4[a]



[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, K_2CO_3, EtOH, H_2O, 0 °C to rt; (b) H_2, PtO_2, AcOEt; (c) NaOH, H_2O, MeOH; (d) $SOCl_2$, $PhCH_3$, 75 °C; (e) HNR^1R^2, $PhCH_3$, 0 °C to rt; (f) $LiAlH_4$, THF, heat; (g) BH_3·THF, THF, heat; (h) $LiAlH_4$, THF, 0 °C to rt; (i) $SOCl_2$, THF, DMF; (j) HNR^1R^2, heat. (Method C: d−f. Method D: d, e, g. Method F: a, b. Method G: c. Method H: h, i, j.)

Scheme 5[a]



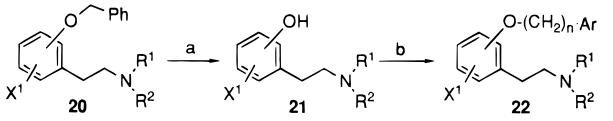
[a] Reagents and conditions: (a) KCN, 18-crown-6, CH_3CN; (b) KOH, H_2O, EtOH, heat; (c) $LiAlH_4$, THF, 0 °C to rt; (d) $SOCl_2$, THF, DMF, rt, (e) HNR^1R^1. (Method I: a−e.)

acid[45] (method L). Acylation of primary amine **24** resulted in amide, which was reduced to yield secondary amine **25** (method M). Furthermore, secondary amine **25** generated tertiary amines **26** by treatment with alkyl halides (method N).

Results and Discussion

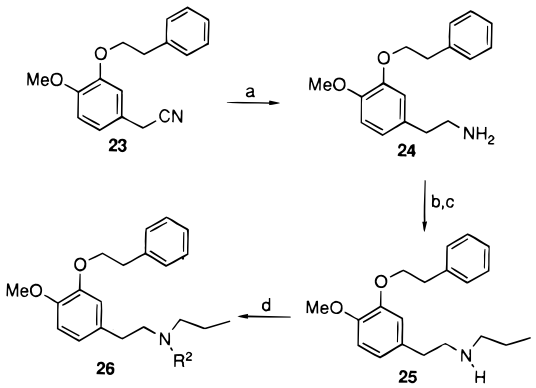
All compounds were examined for affinity at σ sites labeled with [^{3}H]-(+)-3-(3-hydroxyphenyl)-*N*-(1-propyl)-

Scheme 6[a]



[a] Reagents and conditions: (a) H_2, 5% $Pd(OH)_2$/C, MeOH; (b) K_2CO_3, $Ar(CH_2)_n$-X, DMF. (Method J: a. Method K: b.)

Scheme 7[a]



[a] Reagents and conditions: (a) $NaBH_4$, TFA, THF, rt to heat; (b) EtCOCl, Py, CH_2Cl_2, 0 °C to rt; (c) $LiAlH_4$, THF, heat; (d) R^2-X, K_2CO_3, DMF. (Method L: a. Method M: b, c. Method N: d.)

piperidine (3-PPP) and at D_2 receptors labeled with [^{3}H]-(−)sulpiride (Table 2), using the procedure described in the literature.[46]

Design of σ Ligands from Apomorphine via 6*H*-Dibenzo[*b*,*d*]pyran Derivatives 2. 6*H*-Dibenzo[*b*,*d*]-pyran derivatives **2** were designed to eliminate two bonds of apomorphine **1** to produce structural flexibility for the nitrogen atom and to bridge two benzene rings with a $-CH_2O-$ bond to maintain the planar structure of the two benzene rings. Compounds **2a** and **2b** bound with a weak affinity to σ receptor but did not have an affinity for dopamine D_2 receptor. Compound **10b** was designed from 6*H*-dibenzo[*b*,*d*]pyran derivative **2a** by elimination of its biphenyl bond to be more released from the rigid structure of apomorphine than derivative **2a**. Compound **10b** had a better affinity and selectivity for σ receptor than did 6*H*-dibenzo[*b*,*d*]pyran derivatives **2b** (20-fold). The dramatic change of σ affinity among apomorphine, **2b**, and **10b** might have been yielded by the difference of structural flexibility. It would seem that the free energy of the ligand is one of important factors in forming a stable receptor−ligand complex. However, at present, the power of computers might not be enough to analyze the quantitative relationship between free energy and the receptor−ligand complex. The design based on the qualitative difference of structural freedom among ligands may be useful as one of the drug designs.

SARs of Arylalkoxyphenylalkylamine Derivatives: σ Receptor Affinity and Selectivity. Compounds **10a** and **10c**, benzyloxy analogues similar to **10b**, also had good σ affinity. In light of these results, the focus of our study was set on the effect of changes of methylene length (n) on area B and that of substituted position on area C (Figure 1) in order to search for the best position of the benzene ring in arylalkoxyphenylalkylamine derivatives **3**.

Methylene (n = 1) of compound **10b** was prolonged to ethylene (n = 2) or propylene (n = 3). Corresponding compounds **10g** (NE-100) and **22h** had a greater in-

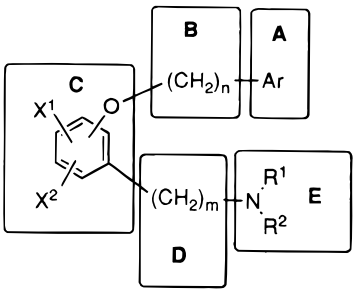


Figure 1.

crease in σ affinity (22- and 6-folds) than did benzyloxy compound **10b.** Compounds **10g** and **22h** also had great selectivity for σ binding sites over D_2 receptors. The difference in methylene length (n = 2 and 3) did not largely influence the affinity and selectivity for σ binding sites, but the ethylene moiety (n = 2) was slightly better than the propylene moiety (**10d**, **10g**, **22a**, **10m** vs **22g**, **22h**, **10r**, and **10q**). The 3-position on area C was slightly more desirable for the substituted position of the 2-phenylethoxy group than were the 2- and 4-positions (**10g** vs **10d** and **10i**). The 3-(2-phenylethoxy) group might control the whole conformation of the molecular-to-yield interaction with σ receptor and/or keep the benzene ring of 2-phenylethoxy group at a preferable position to yield a π−π interaction between the benzene ring and σ receptor.

The effects of several substituents (X^1 and X^2) and substituted positions on the central benzene ring (area C) were investigated next, with fixing of the dipropylaminoethyl group in areas D and E. The nonsubstituted derivative **7p** had a low affinity and selectivity for σ receptor (vs **10g**). The introduction of the methoxy group led to a good affinity and selectivity for σ binding sites on any substituted position **(10d**−**i**, **22g**, and **22h** vs **10p).** Hydroxy compounds **21a** and **21b** had a lower σ binding affinity than the corresponding methoxy compounds **10g** and **10i**. Halogen-substituted derivatives, especially hydrogen-disubsutituted derivatives, had a poor σ affinity and selectivity **(10j**−**10o**, **10q**, **10r**, and **22a** vs **10g**). In light of these results, high electron density on the central benzene ring may be important to produce high affinity and selectivity for σ receptor.

Prolongation of methylene length to propylene or butylene on area D did not appreciably affect affinity for σ binding sites and selectivity for σ sites over D_2 receptors **(10d**, **10g**, **22a**, **10m** vs **16a**−**16d** and **19**).

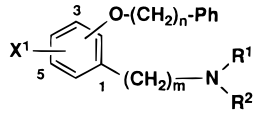
The greatest change of σ binding affinity and selectivity was recognized by variations of amino moiety on area E. Replacement of the dipropylamino group by cyclic amino groups decreased σ affinity (**10s**−**10af** and **16e**−**16i**) and increased D_2 binding affinity (**10u**, **10x**−**10af**, and **16e**−**16i**), a phenomenon notable in piperazine derivatives (**10y**−**10af** and **16f**−**16i**). On the basis of **10g,** substitution of hydrogen atoms or other alkyl groups for propyl groups on area E was productive. One propyl group was essential to yield σ affinity at least (**24** vs **25**). Both alkyl groups were necessary to retain the σ affinity of compound **10g** (**24** and **25** vs **10g**), and length was important for σ binding selectivity (**26a** and **26b** vs **10g**). Introduction of the hydrophilic function at the terminal position of the propyl group decreased σ affinity (**26c**). The results propose that two propyl groups of compound **10g** may not be localized, one propyl group might build the fundamental conformation to yield σ affinity, and the others elevate σ affinity.

Table 3. σ Selectivities of **10d**, **10g**, **16b**, and **22a**

	IC_{50} (nM)[a]						
no.	σ	D_2	D_1	PCP	α_1	$5HT_{1A}$	$5HT_2$
10d	2.7	>1000	>1000	>10000	11700	3580	8800
10g	1.3	>1000	>1000	>10000	10800	6460	>10000
16b	1.0	950	>1000	>10000	14100	373	>10000
22a	7.2	112	>1000	>10000	90	289	196

[a] IC_{50} values from duplicate determination.

Table 4. In Vivo Data: Effect for Behavior Induced by (+)-SKF10047 (in Mice)[a]



no.	X^1	O-$(CH_2)_n$-Ph	m	ED_{25} (μg/kg, po)
10a	3-MeO	2-OCH_2-Ph	2	64 ± 4%[b]
10b	4-MeO	3-OCH_2-Ph	2	>10000
10d	3-MeO	2-$O(CH_2)_2$Ph	2	79
10g (NE-100)	4-MeO	3-$O(CH_2)_2$Ph	2	6.5
16b	4-MeO	3-$O(CH_2)_2$Ph	3	44
22a	5-Cl	2-$O(CH_2)_2$Ph	2	235
BMY14802				7600

[a] SKF10047: 30 mg/kg ip. [b] Percent of control, **7a**: 10 mg/kg po.

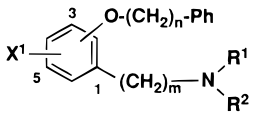
Some derivatives, which had a halogen or methoxy group on the terminal benzene ring (area A), indicated the same σ affinity and selectivity as **10g** (**22b**−**22d**), except for twice-substituted derivative **22e**. Thienyl replacement for the phenyl group decreased somewhat the affinity for σ binding sites (**22f** vs **10g**).

Detailed Study of σ Selectivity. Four compounds, **10d**, **10g**, **16b**, and **22a**, were further examined for affinity at five receptors (D_1: [^{3}H]-7-chloro-8-hydroxy-3-methyl-l-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH-23390), PCP: [^{3}H]-PCP, α_1: [^{3}H]-prazosin, $5\text{-}HT_{1A}$: [^{3}H]-hydroxy-2-(di-*n*-propylamino)tetralin, $5\text{-}HT_2$: [^{3}H]ketanserin) using the procedure described in the literature[46,47] to determine the exact nature of σ binding selectivity (Table 3). Compounds **10d** and **10g** had good selectivity for σ binding sites over D_1, D_2, PCP, α_1, $5\text{-}HT_{1A}$, and $5\text{-}HT_2$ receptors. Propylene analogue **16b** did not have a higher selectivity for σ binding sites over the $5HT_{1A}$ receptor. Chloro compound **22a** had a much poorer σ binding selectivity. The variation of electron density on the central benzene ring (area C) influences affinity for α_1, $5\text{-}HT_{1A}$, and $5\text{-}HT_2$ receptors in addition to D_2 receptor.

It has been presented that compound **10g** (NE-100) has potently inhibited [^{3}H]-(+)-*N*-isopentenylmetazocine (pentazocine) binding to σ_1, receptor (IC_{50} = 1.5 ± 0.3 nM) but weakly affected [^{3}H]-*N*,*N*′-di-(*o*-tolyl)guanidine (DTG) binding to σ_2 receptor (IC_{50} = 84.6 ± 32.9 nM).[48,57]

In Vivo Study. (+)-SKF10,047-induced stereotyped behavior in mice was evaluated for several derivatives using the procedure described in the literature[49,50] to confirm activity in the case of oral administration (Table 4). Compound **10b** did not have activity-concerning behavior, but compound **10a** slightly antagonized the

Table 5. In Vivo Data: Effect for MAP-Induced Hyperlocomotion (in Mice)[a]



no.	X^1	O-$(CH_2)_n$-Ph	*m*	% of control
10g (NE-100) (10 mg/kg, ip)	4-MeO	3-O$(CH_2)_2$Ph	2	119 ± 18
10d (10 mg/kg, ip)	3-MeO	2-O$(CH_2)_2$Ph	2	98 ± 10
16b (10 mg/kg, ip)	4-MeO	3-O$(CH_2)_2$Ph	3	99 ± 10
haloperidol (0.5 mg/kg, ip)				7.3 ± 3.0

[a] MAP = methamphetamine: 1 mg/kg, ip. $n = 6$.

effects of (+)-SKF10,047. Compound **10g** (NE-100), a compound in which the benzyl group of compound **10b** was replaced by a phenylethyl group, antagonized the stereotyped behavior induced by (+)-SKF10,047 (1,160-fold, vs BMY14802). Other compounds, namely **10d**, **16b**, and **22a**, had some oral activity, as compared to BMY14802. The order of potency of (+)-SKF 10,047-induced stereotyped behavior was **10g** (NE-100) > **16b** > **10d** > **22a** > BMY14802 > **10a** > **10b**. It seems that the remarkable effect of NE-100, compared with that of **10d**, **16b**, and **22a**, depends on the enteral absorption and/or metabolic stability.

Compounds **10g** (NE-100), **10d**, and **16a** had no effects on the hyperlocomotion induced by methamphetamine in mice (Table 5), in agreement with data of in vitro evaluation.

It has been presented that compound **10g** (NE-100) has been orally active in inhibiting the (+)-SKF10,047- or PCP-induced head-weaving behavior in rats,[51,57] PCP-induced ataxia or decreased attention in rhesus monkeys,[52,57] and PCP-induced ataxia or head-weaving behavior in dogs.[54,57] In light of this evidence, compound **10g** (NE-100) may have antipsychotic activity and may not have induced the extrapyramidal symptoms and tardive dyskineasia caused by ingestion of typical antipsychotics.

Conclusions

Arylalkoxyphenylalkylamine derivatives **3** have been designed from 6*H*-dibenzo[*b*,*d*]pyran derivatives **2**, based on the relationship of σ affinity and structural flexibility between apomorphine **1** and 6*H*-dibenzo[*b*,*d*]pyran derivatives **2**. It is proposed that the design based on the qualitative difference of structural freedom among ligands may be useful as one of drug designs.

N,*N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxyl)phenyl]-ethylamine hydrochloride **10g** (NE-100), the best compound among arylalkoxyphenylalkylamine derivatives **3**, is a potent and selective ligand of the central σ_1 binding sites. Compound **10g** might be useful to address the physiological and clinical significance of σ ligands. Phase II clinical studies with compound **10g** are in progress.

Experimental Section

Chemistry. Melting points were determined on a Yanaco MP-500D melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer 1760 spectrometer. Proton nuclear magnetic resonance (NMR) spectra were obtained using a Varian VXR-200 spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectra (MS) were taken on a Simazu/Kratos HV-300. Elemental analyses were performed using a Perkin-Elmer 240C (for carbon, hydrogen, and nitrogen) or Yokokawa-Denki IC7000P (for halogen and sulfur). Analytical thin-layer chromatography was conducted on precoated silica gel 60 F_{254} plates (Merck). Chromatography was performed on silica gel C-200, 100−200 mesh (Wako Pure Chemical), using the solvent systems (volume ratios) indicated below.

1-Formyl-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran (5). A mixture of 2-bromo-3-hydroxy-4-methoxybenzaldehyde (**4**) (106.3 g, 0.46 mol), 2-iodobenzyl chloride (117.6 g, 0.47 mol), K_2CO_3 (71.0 g, 0.51 mol), and KI (7.64 g, 46 mmol) in *N*,*N*-dimethylformamide (DMF) (800 mL) was stirred at room temperature for 22 h. After concentration in vacuo, the residue was partitioned between CH_2Cl_2 and water. The separated water layer was extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4), concentrated in vacuo, and recrystallized from MeOH to give 2-bromo-3-(2-iodobenzyloxy)-4-methoxybenzaldehyde (198.0 g, 96% yield).

A mixture of 2-bromo-3-(2-iodobenzyloxy)-4-methoxybenzaldehyde (197.6 g, 0.44 mol) and powdered copper (201.7 g, 3.17 atom) in DMF (600 mL) was stirred and heated under reflux for 4 h. To the cooled reaction mixture were added water and AcOEt followed by filtration through Celite. The separated organic layer was washed with 1 N HCl, water, and saturated brine, dried (Na_2SO_4), and concentrated in vacuo. The residual semisolid was recrystallized from AcOEt to give **5** (61.0 g, 57% yield): mp 113−114 °C; IR (KBr) 1672, 1592, 1567, 1301, 1283, 1255, 1220, 1099, 1013 cm^{-1}; MS *m*/*z* 240 (M^+); ^{1}H NMR ($CDCl_3$) δ 3.99 (3 H, s, CH_3O), 5.13 (2 H, s, CH_2O), 6.99 (1 H, d, $J = 8.6$ Hz, ArH), 7.30−7.48 (4 H, m, ArH), 7.73 (1 H, d, $J = 8.6$ Hz, ArH), 10.27 (1 H, s, CHO).

1-Hydroxycarbonylmethyl-4-methoxy-6*H*-dibenzo[*b*,*d*]-pyran (6). To a solution of 1-formyl-4-methoxy-6*H*-dibenzo-[*b*,*d*]pyran (**5**) (41.24 g, 171.6 mmol) in a mixture of tetrahydrofuran (THF) (400 mL) and MeOH (130 mL) was added $NaBH_4$ (1.79 g, 47.3 mmol) over 10 min followed by 1.5 h of stirring with ice-cooling. To the solution was added dropwise 1N HCl, followed by extraction with AcOEt. The extract was washed with saturated brine, dried ($MgSO_4$), and concentrated in vacuo to give crude 1-hydroxymethyl-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran, which was carried on to the next step.

To a solution of the crude 1-hydroxymethyl-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran in a mixture of THF (300 mL) and hexamethyl phosphoric amide (HMPA) (60 mL) was added thionyl chloride (18.8 mL, 30.7 g, 258 mmol) at room temperature, and the mixture was stirred for 1.5 h. The concentrated reaction mixture was partitioned between AcOEt and water. The separated organic layer was washed with saturated $NaHCO_3$ and saturated brine, dried ($MgSO_4$), and concentrated in vacuo to yield crude 1-chloromethyl-4-methoxy-6*H*-dibenzo-[*b*,*d*]pyran, which was carried on to the next step.

To a solution of the crude 1-chloromethyl-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran in CH_3CN (600 mL) was added 18-crown-6 (4.54 g, 17.2 mmol) and KCN (22.36 g, 343.4 mmol), and the mixture was stirred for 1 day at room temperature. The concentrated reaction mixture was partitioned between AcOEt and water. The separated organic layer was washed with saturated $NaHCO_3$ and saturated brine, dried ($MgSO_4$), concentrated in vacuo, and recrystallized from AcOEt to give 1-cyanomethyl-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran (32.05 g, 74% yield): mp 131−132 °C; IR (KBr) 2246, 1505, 1417, 1277, 1268, 1139, 1102, 1016 cm^{-1}; MS *m*/*z* 251 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.82 (3 H, s, CH_3O), 4.32 (2 H, s, CH_2CN), 4.96 (2 H, s, CH_2O), 7.06 (1 H, d, $J = 8.5$ Hz, ArH), 7.15 (1H, d, $J = 8.5$ Hz, ArH), 7.38−7.53 (3 H, m, ArH), 7.69 (1 H, br d, $J = 7.6$ Hz, ArH).

A solution of 1-cyanomethyl-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran (20.00 g) in a mixture of acetic acid (400 mL), sulfuric acid (40 mL), and water (120 mL) was heated at reflux for 20 h followed by concentrated in vacuo. The residue was poured onto ice. The resultant precipitate was collected by filtration and recrystallized from AcOEt to give **6** as a colorless crystal (18.28 g, 85% yield): mp 142−143 °C; IR (KBr) 1691, 1479,

1418, 1270, 1223, 1139, 1106, 1022 cm^{-1}; MS *m/z* 270 (M^+); ^1H NMR ($CDCl_3$) δ 3.91 (3 H, s, CH_3O), 4.00 (2 H, s, CH_2CN), 5.01 (2 H, s, CH_2O), 6.89 (1 H, d, $J = 8.5$ Hz, ArH), 7.02 (1 H, d, $J = 8.5$ Hz, ArH), 7.26−7.41 (3 H,m, ArH), 7.36 (1 H, m, ArH).

1-(2-Dipropylaminoethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]-pyran Hydrochloride (2a). A suspension of 1-hydroxycarbonylmethyl-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran (**6**) (780 mg, 2.87 mmol) and thionyl chloride (0.42 mL, 685 mg, 5.76 mmol) in benzene was heated at reflux for 30 min followed by concentrated in vacuo.

A solution of the above residue in benzene (10 mL) was added dropwise to a solution of Et_3N (321 mg, 3.17 mmol) and dipropylamine (321 mg, 3.17 mmol) while being stirred and cooled in an ice bath. After being stirred for 1.5 h at room temperature, the reaction mixture was washed with 1 N HCl, saturated $NaHCO_3$, and saturated brine, dried ($MgSO_4$), and concentrated in vacuo to give crude amide.

A mixture of the amide and $LiAlH_4$ (153 mg, 4.03 mmol) in THF (20 mL) was heated at reflux for 1 h. After the mixture was cooled in an ice bath, saturated Na_2SO_4 solution was added dropwise to the mixture, and the mixture was filtered through Celite, and concentrated in vacuo. The residue was chromatographed ($CHCl_3$/MeOH 50:1), treated with 4 N HCl in AcOEt, and recrystallized from 2-propanol/AcOEt to give **2a** as a colorless crystal (557 mg, 51% yield): mp 162−164 °C; IR (KBr) 3436, 2966, 2594, 2423, 1472, 1280, 1144, 1022 cm^{-1}; MS *m/z* 340 (M^+); ^1H NMR (DMSO-d_6) δ 0.89 (6 H, t, $J = 7.4$ Hz, CH_3C), 1.53−1.80 (4 H, m, CCH_2C), 2.93−3.13 (4 H, m, NCH_2), 3.16−3.34 (2 H, m, CH_2), 3.36−3.51 (2 H, m, CH_2), 3.79 (3 H, s, CH_3O), 4.92 (2 H, s, CH_2O), 6.99 (1 H, d, $J = 8.3$ Hz, ArH), 7.04 (1 H, d, $J = 8.3$ Hz, ArH), 7.33−7.53 (3 H, m, ArH), 7.79 (1 H, br d, $J = 7.1$ Hz, ArH), 10.65 (1 H, br s, exchangeable with D_2O, HCl). Anal. ($C_{22}H_{29}NO_2$·HCl) C, H, N.

1-(2-Dipropylaminoethyl)-4-hydroxy-6*H*-dibenzo[*b*,*d*]-pyran Hydrochloride (2b). A solution of 1-(2-dipropylaminoethyl)-4-methoxy-6*H*-dibenzo[*b*,*d*]pyran hydrochloride (**2a**) (1.00g, 2.66 mmol) in 37% HBr in acetic acid (15 mL) was heated at reflux for 8 h and concentrated in vacuo. A suspension of the above residue and K_2CO_3 (1.00g, 7.24 mmol) in DMF (10 mL) was stirred at room temperature for 1 day and filtered. The filtrate was concentrated in vacuo, chromatographed ($CHCl_3$/MeOH 50:1), treated with 4 N HCl in AcOEt, and recrystallized from EtOH to give **2b** as colorless crystals (g, 52% yield): mp 242−244 °C; IR (KBr) 3220, 3150, 2968, 2943, 2666, 1474, 1285, 1096, 1026 cm^{-1}; MS *m/z* 340 (M^+); ^1H NMR (CDMSO-d_6) δ 0.89 (6 H, t, $J = 7.0$ Hz, CH_3C), 1.53−1.78 (4 H, m, CCH_2C), 2.93−3.13 (4 H, m, NCH_2), 3.13−3.50 (4 H, m, CH_2), 4.90 (2 H, s, CH_2O), 6.81 (1 H, d, $J = 8.7$ Hz, ArH), 6.92 (1 H, d, $J = 8.7$ Hz, ArH), 7.30−7.51 (3 H, m, ArH), 7.78 (1 H, br d, $J = 8.4$ Hz, ArH), 9.18 (1 H, br s, exchangeable with D_2O, HO), 10.59 (1 H, br s, exchangeable with D_2O, HCl). Anal. ($C_{21}H_{27}NO_2$·HCl) C, H, N.

4-Benzyloxy-3-hyroxybenzaldehyde (7aa). A mixture of 3,4-dihydroxybenzaldehyde (27.63 g, 0.22 mol), benzyl bromide (35.93 g, 0.20 mol), and K_2CO_3 (30.41 g, 0.22 mol) in DMF (270 mL) was stirred at room temperature for 24 h. The concentrated reaction mixture in vacuo was dissolved in water, acidified with concentrated HCl, and extracted with AcOEt (200 mL × 2, and then 100 mL). The extract was washed with 0.5 N Na_2HPO_4 solution (400 mL × 3) to remove 3,4-dihydroxybenzaldehyde, and then the mixture was extracted with 1 N NaOH solution (400 mL × 2, and then 200 mL) to exclude 3,4-dibezyloxybenzaldehyde. To the stirred aqueous layer with cooling in an ice bath was added dropwise H_3PO_4 (49.0 g, 0.50 mol), followed by stirring with ice-cooling for 0.5 h. The resultant precipitate was collected by filtration, washed with several portions of water, dried in vacuo, and recrystallized from AcOEt to afford **7aa** as a pale yellow crystal (22.36 g, 49% yield): mp 115−117 °C; IR (KBr) 3203 (br), 1673, 1606, 1578, 1514 cm^{-1}; MS *m/z* 228 (M^+); ^1H NMR ($CDCl_3$) δ 5.21 (2 H, s, CH_2Ph), 5.80 (1 H, br s, exchangeable with D_2O, HO), 7.04 (1 H, d, $J = 8.3$ Hz, ArH), 7.38−7.47 (7 H, m, ArH), 9.34 (1 H, s, CHO).

3-Hydroxy-4-(2-phenylethoxy)benzaldehyde (7ab). A mixture of 3,4-dihydroxybenzaldehyde (11.65 g, 84.3 mmol), 2-phenylethyl bromide (46.83 g, 253 mmol), and K_2CO_3 (34.97 g 253 mmol) in DMF (55 mL) was stirred at room temperature for 48 h. After the inorganic powder was filtered off through Celite, the filtrate was concentrated in vacuo. To the residue was added water and concentrated HCl to acidify the mixture, followed by extraction with AcOEt (100 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of the residue (hexanes/AcOEt 3:1) gave **7ab** as a pale yellow oil (6.49 g, 32% yield): IR (neat) 3398 (br), 1682, 1616, 1586, 1510 cm^{-1}; MS *m/z* 242 (M^+); ^1H NMR ($CDCl_3$) δ 3.17 (2 H, t, $J = 6.8$ Hz, CH_2Ph), 4.36 (2 H, t, $J = 6.8$ Hz, CH_2O), 5.62 (1 H, br s, exchangeable with D_2O, HO), 6.96 (1 H, d, $J = 8.1$ Hz, ArH), 7.23−7.42 (7 H, m, ArH), 9.83 (1 H, s, CHO).

Method A: 4-Methoxy-3-(2-phenylethoxy)phenylacetic Acid (8a). A mixture of isovanillin (152.1 g, 1.00 mol), 2-phenylethyl bromide (615.0 mL, 836.3 g, 4.52 mol), and K_2CO_3 (656.5 g, 4.75 mol) in DMF (760 mL) was stirred and warmed at 40−50 °C for 5 h. The solvent was removed in vacuo, and then to the residue were added water (2.0 L) and hexanes (750 mL). After the resulting mixture (three phases) was vigorously stirred and cooled in an ice bath for 1.5 h, the precipitated crystal was collected by filtration, washed with several portions of water and cold hexanes, and then air-dried at room temperature to yield 4-methoxy-3-(2- phenylethoxy)-benzaldehyde as a colorless crystal (247.9 g, 97% yield): mp 46−47 °C; IR (KBr) 1688, 1587, 1511 cm^{-1}; MS *m/z* 256 (M^+); ^1H NMR ($CDCl_3$) δ 3.19 (2 H, t, $J = 7.5$ Hz, CH_2Ph), 3.96 (3 H, s, CH_3), 4.28 (2 H, t, $J = 7.5$ Hz, CH_2O), 6.98 (1 H, d, $J = 8.2$ Hz, ArH), 7.24−7.37 (5 H, m, ArH), 7.40 (1 H, d, $J = 1.8$ Hz, ArH), 7.46 (1 H, dd, $J = 1.8$, 8.2 Hz, ArH), 9.83 (1 H, s, CHO).

To the solution of the above aldehyde (247.8 g, 0.97 mol) in THF (760 mL) was added dropwise a solution of $NaBH_4$ (14.2 g, 0.38 mol) in 0.5 N NaOH solution (71 mL) in portions at a rate so as to maintain the temperature at 4−10 °C, while being stirred and cooled in an ice bath. After the mixture was stirred in the ice bath for 1 h and then at room temperature for 2.5 h, 0.5 N NaOH solution (71 mL) was added to the reaction mixture. The separated organic layer was washed with saturated brine (200 mL × 3), dried ($MgSO_4$), and filtered to afford a solution of 4-methoxy-3-(2-phenylethoxy)benzyl alcohol in THF. To the solution was added DMF (200 mL), and then thionyl chloride (95.0 mL, 155.0 g, 1.30 mol) was added dropwise at a rate to keep the temperature below 60 °C while being stirred. The mixture was stirred at ambient temperature for 1 h before being concentrated in vacuo. The oily residue was poured onto ice (500 g) and extracted with AcOEt (750 mL). The extract was washed with saturated brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to yield 4-methoxy-3-(2-phenylethoxy)benzyl chloride as a dark yellow oil (259.2 g), which was carried on to the next step.

A mixture of the above chloride, powdered KCN (97.7 g, 1.5 mol), and 18-crown-6 (13.22 g, 0.05 mol) in acetonitrile (750 mL) was vigorously stirred and heated under reflux for 7 h. After concentration in vacuo, the residue was partitioned between AcOEt (750 mL) and water (400 mL). The separated organic layer was washed with water (100 mL), saturated $NaHCO_3$ solution (100 mL × 2), and saturated brine (100 mL), dried ($MgSO_4$), and then concentrated in vacuo to yield 4-methoxy-3-(2-phenylethoxy)phenylacetonitrile as a light brown oil (247.3 g), which was carried on to the next step.

To the above nitrile was added a solution of KOH (224.4 g, 4.00 mol) in 90% aqueous EtOH, and the resulting solution was stirred and heated under reflux for 4 h. The solvent was removed in vacuo, and the residue was dissolved in water (450 mL). To the solution was added dropwise concentrated HCl (330 mL) while being stirred and cooled in an ice bath, then extracted with AcOEt (1.0 L). The organic layer was washed with saturated brine, dried ($MgSO_4$), filtered, concentrated in

vacuo, and recrystallized from a mixture of toluene (600 mL) and hexanes (400 mL) to yield **8a** as a colorless crystal (217.6 g, 76% yield based on isovanillin): mp 88−89 °C; IR (KBr) 3000 (br), 1723, 1519 cm^{-1}; MS *m/z* 286 (M^+); ^1H NMR ($CDCl_3$) δ 3.15 (2 H, t, J = 7.6 Hz, CH_2Ph), 3.54 (2 H, s, CH_2CO), 3.84 (3 H, s, CH_3), 4.19 (2 H, t, J = 7.6 Hz, CH_2O), 6.79−6.86 (3 H, m, ArH), 7.22−7.35 (5 H, m, ArH).

Method B: 4-Chloro-2-(2-phenylethoxy)phenylacetic Acid (8b). Methyl 4-chloro-2-hydroxybenzoate (10.42 g, 55.8 mmol), which was prepared from 4-chloro-2-hydroxybenzoic acid by treatment with H_2SO_4 in MeOH, was reacted with 2-phenylethyl bromide (30.50 mL, 41.34 g, 223 mmol) and K_2CO_3 (30.87 g, 223 mmol) in DMF (100 mL), using the procedure described in the first step of method A. The concentrated reaction mixture was partitioned between AcOEt and water. The separated organic layer was washed with water and saturated brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. A mixture of the above residue and $LiAlH_4$ (2.12 g, 55.9 mmol) in THF (100 mL) was stirred and cooled in an ice bath for 2 h. The reaction mixture was quenched with saturated Na_2SO_4 solution, filtered through $MgSO_4$ powder, concentrated in vacuo, and then column chromatographed (hexanes/AcOEt 10:1) to give an intermediate benzyl alcohol derivative as a colorless oil (12.70 g, 87% yield): IR (neat) 3368 (br), 1598, 1494 cm^{-1}; MS *m/z* 264 (M^+ + 2), 262 (M^+); ^1H NMR ($CDC1_3$) δ 2.03 (1 H, t, J = 7.0 Hz, exchangeable with D_2O, HO), 3.11 (2 H, t, J = 7.0 Hz, CH_2Ph), 4.21 (2 H, t, J = 7.0 Hz, CH_2O), 4.53 (2 H, d, J = 7.0 Hz, CH_2O), 6.83 (1 H, d, J = 1.5 Hz, ArH), 6.89 (1 H, dd, J = 1.5, 9.5 Hz, ArH), 7.15 (1 H, d, J = 9.5 Hz, ArH), 7.20−7.40 (5 H, m, ArH).

The benzyl alcohol derivative was chlorinated, cyanated, and hydrolyzed, using the procedure described in the third, fourth, and fifth steps of method A, before being recrystallized from toluene to afford **8b** as a colorless crystal (82% yield): mp 103.5−104.5 °C; IR (KBr) 2900 (br), 1714, 1703, 1599, 1495 cm^{-1}; MS *m/z* 292 (M^+ + 2), 290 (M^+); ^1H NMR ($CDCl_3$) δ 3.06 (2 H, J = 6.7 Hz, CH_2Ph), 3.58 (2 H, s, CH_2CO), 4.16 (2 H, t, J = 6.7 Hz, CH_2O), 6.84 (1 H, d, J = 2.0 Hz, ArH), 6.89 (1 H, dd, J = 2.0, 8.0 Hz, ArH), 7.09 (1 H, d, J = 8.0 Hz, ArH), 7.17−7.37 (5 H, m, ArH).

Method C: *N,N*-Dipropyl-2-[4-methoxy-3-(2-phenylethoxyl)phenyl]ethylamine Hydrochloride (10g, NE-100). A solution of 4-methoxy-3-(2-phenylethoxy)phenylacetic acid (**8a**) (84.0 g, 0.29 mol) and thionyl chloride (43.0 mL, 70.0 g, 0.59 mol) in toluene (420 mL) was stirred and heated at 80 °C for 2 h. After completely removing thionyl chloride in vacuo, the residue was again dissolved in toluene (120 mL). The solution was added dropwise to a solution of dipropylamine (120 mL, 88.6 g, 0.88 mol) in toluene (320 mL) over 1 h, while being stirred and cooled in an ice bath. After additional stirring for 18 h at room temperature, the reaction mixture was washed with water, (100 mL), 1 N HCl solution, saturated $NaHCO_3$ solution, and saturated brine, dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo to give an oily amide, which was used for the next step.

To a suspension of $LiAH_4$ (21.9 g, 0.58 mol) in THF (300 mL) was added dropwise over 0.5 h a solution of the above amide in THF (120 mL) while being stirred and cooled in an ice bath. After stirring at room temperature for 0.5 h, the reaction mixture was stirred and heated under reflux for 3 h. To the cooled and stirred reaction mixture was cautiously added saturated Na_2SO_4 solution to quench. Filtration through $MgSO_4$ powder, treatment with 4 N HCl in AcOEt (88 mL), concentration in vacuo, and recrystallization from AcOEt gave **10g** (NE-100) as a colorless crystal (89.5 g, 78% yield): mp 99−100 °C; IR (KBr) 2641, 2596, 2538, 1519 cm^{-1}; MS *m/z* 355 (M^+) ; ^1H NMR ($CDCl_3$) δ 1.00 (6 H, t, J = 7.3 Hz, CH_3), 1.70−2.02 (4 H, m, CH_2), 2.89−3.07 (4 H, m, CH_2N), 3.08−3.24 (6 H, m, CH_2Ph, CH_2CH_2Ar), 3.84 (3 H, s, CH_3O), 4.20 (2 H, t, J = 7.4 Hz, CH_2O), 6.72−6.84 (3 H, m, ArH), 7.22−7.37 (5 H, m, ArH), 12.38 (1 H, br s, exchangeable with D_2O, HCl). Anal. ($C_{23}H_{33}NO_2$·HCl) C, H, N, Cl.

Method D: *N,N*-Dipropyl-2-[4-chloro-2-(2-phenylethoxyl)phenyl]ethylamine Hydrochloride (10l). A 1.0 M solution of borane THF complex in THF (16 mL, 16 mmol) was added dropwise to a solution of *N,N*-dipropyl-[4-chloro-2-(2-phenylethoxy)phenyl]acetamide, which was derived from 4-chloro-2-(2-phenylethoxy)phenyl]acetic acid (**8b**) (1.51 g, 5.20 mmol) using the procedure described in the first and second steps of method C, in THF (15 mL). The mixture was stirred and heated under reflux for 2 h. MeOH was added to the stirred and cooled reaction mixture, and the resulting solution was concentrated in vacuo. After the residue had been heated under reflux for 0.5 h with concentrated HCl (15 mL), the solution was made basic with 40% NaOH solution and then extracted with AcOEt. The organic layer was washed with saturated brine, dried ($MgSO_4$), filtered, chromatographed (hexanes/AcOEt 5:1), treated with 4 N HCl in AcOEt, concentrated in vacuo, and then recrystallized from AcOEt to afford **10l** as a colorless crystal (1.23 g, 59% yield): mp 93−94 °C; IR (KBr) 2597, 2531, 2475, 1599, 1496 cm^{-1}; MS *m/z* 361 (M^+ + 2), 359 (M^+); ^1H NMR ($CDCl_3$) δ 0.95 (6 H, t, J = 7.3 Hz, CH_3), 1.75 (4 H, m, CH_2), 2.74−3.10 (8 H, m, CH_2N, CH_2Ar), 3.14 (2 H, t, J = 6.6 Hz, CH_2Ph), 4.28 (2 H, t, J = 6.6 Hz, CH_2O), 6.88 (1 H, d, J = 2.2 Hz, ArH), 6.90 (1 H, dd, J = 2.2, 7.9 Hz, ArH), 7.18 (1 H, d, J = 7.9 Hz, ArH), 7.22−7.38 (5 H, m, ArH), 12.15 (1 H, br s, exchangeable with D_2O, HCl). Anal. ($C_{22}H_{30}ClNO$·HCl) C, H, N, Cl.

Method E: 1-[2-[5-Chloro-2-(2-phenylethoxyl)phenyl]-ethyl-4-(2-pyridyl)piperazine Oxalate (10ac). To a solution of 5-chloro-2-(2-phenylethoxy)phenylacetic acid (**8b**) (23.23 g, 79.9 mmol) in THF (120 mL) was added $LiAlH_4$ (4.34 g, 114.4 mmol) in small amounts while being stirred and cooled in an ice bath. After additional stirring for 2 h in an ice bath, the reaction mixture was quenched with saturated Na_2SO_4 solution and then filtered through $MgSO_4$ powder to yield the solution of alcohol in THF. The solution was treated with thionyl chloride and DMF in THF, using the procedure described in the third step of method A, before being column chromatographed (hexanes/AcOEt 5:1) to yield 2-[5-chloro-2-(2-phenylethoxyl)phenyl]ethyl chlorides (**11a**) as a colorless oil (18.52 g, 79% yield): IR (neat) 1494 cm^{-1}; MS *m/z* 298 (M^+ + 4), 296 (M^+ + 2), 294 (M^+); ^1H NMR ($CDCl_3$) δ 2.96 (2 H, t, J = 7.4 Hz, CH_2), 3.09 (2 H, t, J = 6.6 Hz, CH_2), 3.52 (2 H, t, J = 6.6 Hz, CH_2), 4.15 (2 H, t, J = 7.4 Hz, CH_2), 6.73 (1 H, d, J = 8.4 Hz, ArH), 7.09−7.38 (7 H, m, ArH).

A solution of **11a** (1.50 g, 5.08 mmol) and 1-(2-pyridyl)-piperazine (2.32 mL, 2.49 g, 15.3 mmol) in diisopropylethylamine (10 mL) was stirred and heated under reflux for 10 h. The reaction mixture was concentrated in vacuo, and column chromatographed (hexanes/AcOEt 5:1) to give the desired free amine (0.57 g). Treatment of the free amine with oxalic acid (122 mg, 1.35 mmol) in EtOH and recrystallization from EtOH gave **10ac** as colorless crystal (0.49 g, 19% yield): mp 165−167 °C; IR (KBr) 2585 (br), 1720, 1595, 1493 cm^{-1}; MS *m/z* 423 (M^+ + 2), 421 (M^+); ^1H NMR (DMSO-d_6) δ 2.75−2.91 (4 H, m, CH_2), 2.91−3.03 (4 H, m, CH_2), 3.08 (2 H, t, J = 7.0 Hz, CH_2Ph), 3.60−3.80 (4 H, m, CH_2), 4.25 (2 H, t, J = 7.0 Hz, CH_2O), 6.73 (1 H, dd, J = 5.0, 8.0 Hz, ArH), 6.94 (1 H, d, J = 8.0 Hz, ArH), 7.04 (1 H, d, J = 8.0 Hz, ArH), 7.13−7.40 (7 H, m, ArH), 7.61 (1 H, m, ArH), 8.18 (1 H, dd, J = 2.5, 5.0 Hz, ArH). Anal. ($C_{25}H_{28}ClN_3O$·$C_2H_2O_4$·0.1H_2O) C, H, N, Cl.

Method F: Ethyl 3-[5-chloro-2-(2-phenyl)ethoxyphenyl]propionate (13a). A mixture of 5-chloro-2-(2-phenylethoxy) benzaldehyde (32.0 g, 0.12 mol), triethyl phosphonoacetate (55.0 g, 0.24 mol) and 6 M K_2CO_3 solution (40 mL, 0.24 mol) in EtOH (100 mL) was stirred in an ice bath for 2 h. The mixture was stirred at room temperature for 15 h followed by filtration. The obtained light yellow solid was washed with water and cold diisopropyl ether and carried on to the next step without further purification.

A suspended solution of the above solid and PtO_2 (2.45 g) in AcOEt (200 mL) was stirred under a hydrogen atmosphere with a reaction check on TLC (hexanes/AcOEt 19:1) to avoid a yield of ethyl 3-[5-chloro-2-(2-cyclohexyl)ethoxyphenyl]propionate as a byproduct. Filtration through Celite, concentration in vacuo, and then column chromatography (hexanes/AcOEt 30:1) yielded **13a** as a colorless oil (30.49 g, 75%

yield): IR (neat) 1734, 1494 cm^{-1}; MS *m/z* 334 ($M^+ + 2$), 332 (M^+); ^1H NMR ($CDCl_3$) δ 1.26 (3 H, t, $J = 7.1$ Hz, CH_3), 2.47 (2 H, t, $J = 7.7$ Hz, CH_2), 2.85 (2 H, t, $J = 7.7$ Hz, CH_2), 3.10 (2 H, t, $J = 6.7$ Hz, CH_2Ph), 4.13 (2 H, q, $J = 7.1$ Hz, CH_2O), 4.15 (2 H, t, $J = 6.7$ Hz, CH_2CO_2), 6.72 (1 H, d, $J = 9.4$ Hz, ArH), 7.09 (1 H, d, $J = 2.6$ Hz, ArH), 7.10 (1 H, dd, $J = 2.6$, 9.4 Hz, ArH), 7.19−7.36 (5 H, m, ArH).

Method G: 3-[5-Chloro-2-(2-phenyl)ethoxyphenyl]propionic Acid (14a). A mixture of **13a** (16.64 g, 50.0 mmol) and 5 N NaOH solution (20 mL, 100 mmol) in EtOH (100 mL) was stirred at room temperature for 24 h. After concentration, the residue was dissolved in H_2O and washed with Et_2O. To the water layer was added concentrated HCl for acidification, and then the mixture was extracted with CH_2Cl_2. The extract was washed with saturated brine, dried ($MgSO_4$), filtered and concentrated in vacuo to give **14a** as a colorless oil (14.93 g, 98% yield), which was carried on to the next step: IR (neat) 3300 (br), 1708, 1494 cm^{-1}; MS *m/z* 306 ($M^+ + 2$), 304 (M^+); ^1H NMR ($CDCl_3$) δ 2.52 (2 H, t, $J = 7.6$ Hz, CH_2), 2.85 (2 H, t, $J = 7.6$ Hz, CH_2), 3.10 (2 H, t, $J = 6.7$ Hz, CH_2Ph), 4.16 (2 H, q, $J = 6.7$ Hz, CH_2O), 6.73 (1 H, d, $J = 9.5$ Hz, ArH), 7.11 (1 H, d, $J = 2.5$ Hz, ArH), 7.12 (1 H, dd, $J = 2.5$, 9.5 Hz, ArH), 7.22−7.35 (5 H, m, ArH).

Method H: *N,N*-Dipropyl-3-[5-chloro-2-(2-phenylethoxy)phenyl]propylamine oxalate (16c). Treatment of **13a** (10.76 g, 32.3 mmol) with $LiAlH_4$ (1.84 g, 48.5 mmol) in THF (100 mL), using the procedure described for the second step of method B, yielded alcohol as a colorless oil (8.55 g, 91% yield): IR (neat) 3369 (br), 1596, 1493 cm^{-1}; MS *m/z* 292 ($M^+ + 2$), 290 (M^+); ^1H NMR ($CDCl_3$) δ 1.59−1.82 (2 H, m, CH_2), 1.67 (1H, br s, exchangeable with D_2O, HO), 2.60 (2 H, t, $J = 7.5$ Hz, CH_2), 3.09 (2 H,t, $J = 6.5$ Hz, CH_2Ph), 3.55 (2 H, t, $J = 6.0$ Hz, CH_2), 4.17 (2 H, t, $J = 6.5$ Hz, CH_2Ar), 6.74 (1 H, d, $J = 10.0$ Hz, ArH), 7.02−7.15 (2 H, m, ArH), 7.20−7.40 (5 H, m, ArH).

Treatment of the above alcohol (3.24 g, 11.1 mmol) with thionyl chloride (1.22 mL, 1.99 g, 16.7 mmol) in a mixture of THF (25 mL) and DMF (5 mL) using the procedure described in the third step of method A yielded crude **17a** (3.21 g) as a colorless oil. The crude product was carried on to the next step. The crude **17a** (604 mg) was heated at 80 °C in dipropylamine (5 mL) for 39 h, and then concentrated in vacuo. Column chromatography (hexanes/AcOEt 5:1), treatment with oxalic acid, and then recrystallization from AcOEt gave **16c** as a colorless crystal (380 mg, 52% yield based on the alcohol): mp 100−102 °C; IR (KBr) 2585 (br), 1719, 1632, 1493 cm^{-1}; MS *m/z* 375 ($M^+ + 2$), 373 (M^+); ^1H NMR ($CDCl_3$) δ 0.93 (6 H, t, $J = 7.4$ Hz; CH_3), 1.50−1.69 (4 H, m, CH_2), 1.78−1.93 (2 H, m, CH_2), 2.57 (2 H, t, $J = 7.2$ Hz, CH_2Ar), 2.78−2.96 (6 H, m, CH_2N), 3.09 (2 H, t, $J = 6.6$ Hz, CH_2Ph), 4.18 (2 H, t, $J = 6.6$ Hz, CH_2O), 6.76 (1 H, d, $J = 8.7$ Hz, ArH), 7.04 (1 H, d, $J = 2.5$ Hz, ArH), 7.14 (1 H, dd, $J = 2.5$, 8.7 Hz, ArH), 7.21−7.37 (5 H, m, ArH), 11.84 (1 H, br s, exchangeable with D_2O, CO_2H). Anal. ($C_{23}H_{32}ClNO{\cdot}C_2H_2O_4$) C, H, N, Cl.

Method I: *N,N*-Dipropyl-4-[5-chloro-2-(2-phenylethoxy)phenyl]butylamine Oxalate (19). Oily 4-[5-chloro-2-(2-phenylethoxy)phenyl]butanol (**18**) was derived from the crude **17a** by cyano replacement, hydrolysis, and reduction described in method A (4th and 5th steps) and method E (first step) in 66% yield: IR (neat) 3350 (br), 1596, 1494 cm^{-1}; MS *m/z* 306 ($M^+ + 2$), 304 (M^+); ^1H NMR ($CDCl_3$) δ 1.40 (1 H, s, exchangeable with D_2O, HO), 1.47−1.68 (4 H, m, CH_2), 2.54 (2 H, m, CH_2), 3.10 (2 H, t, $J = 6.5$ Hz, CH_2Ph), 3.59 (2 H, m, CH_2), 4.15 (2 H, t, $J = 6.5$ Hz, CH_2O), 6.71 (1 H, dd, $J = 4.0$, 6.5 Hz, ArH), 7.01−7.40 (7 H, m, ArH).

Compound **19** was generated from **18** using the procedure described in the second and third steps of method H in a 31% yield as a colorless crystal: mp 80−82 °C (recrystallized from AcOEt); IR (KBr) 2602 (br), 1720, 1703, 1626, 1490 cm^{-1}; MS *m/z* 398 ($M^+ + 2$), 387 (M^+); ^1H NMR ($CDCl_3$) δ 0.97 (6 H, t, $J = 7.3$ Hz, CH_3), 1.47−1.74 (8 H, m, CH_2), 2.54 (2 H, t, $J = 7.1$ Hz, CH_2), 2.91−2.95 (6 H, m, CH_2N), 3.10 (2 H, t, $J = 6.7$ Hz, CH_2Ph), 4.18 (2 H, t, $J = 6.7$ Hz, CH_2O), 6.75 (1 H, d, $J = 8.6$ Hz, ArH), 7.03 (1 H, d, $J = 2.5$ Hz, ArH), 7.11 (1 H, dd, $J = 2.5$, 8.6 Hz, ArH), 7.23−7.36 (5 H, m, ArH), 11.82 (1 H, br s, exchangeable with D_2O, CO_2H). Anal. ($C_{24}H_{34}ClNO\ C_2H_2O_4$) C, H, N, Cl.

Method J: *N,N*-Dipropyl-2-[4-hydroxy-3-(2-phenylethoxy)phenyl]ethylamine Hydrochloride (21a). A suspended solution of free amine, obtained by treatment of **10ag** (6.5 g, 13.9 mmol) with 1 N NaOH solution, and 5% $Pd(OH)_2/C$ (0.65 g) in MeOH (60 mL) was stirred under an atmosphere of hydrogen. After the theoretical amount of hydrogen had been taken up, the suspension was filtered through Celite. To the filtrate was added dropwise 4 N HCl in AcOEt (5.2 mL, 20.8 mmol) while being stirred and cooling in ice bath. Concentration in vacuo and recrystallization from AcOEt yielded **21a** as a colorless crystal (4.77 g, 91% yield): mp 124−125 °C; IR (KBr) 3401, 2728, 2655, 2536, 2481, 1599, 1520 cm^{-1}; MS *m/z* 342 ($M^+ + 1$); ^1H NMR ($CDCl_3$) δ 1.00 (6 H, t, $J = 7.4$ Hz, CH_3), 1.77−1.96 (4 H, m, CH_2), 2.90−3.07 (4 H, m, CH_2), 3.08−3.20 (6H, m, CH_2), 4.26 (2 H, t, $J = 6.7$ Hz, CH_2O), 5.50 (1 H, br s, exchangeable with D_2O, HO), 6.66 (1 H, dd, $J = 2.0$, 8.1 Hz, ArH), 6.79 (1 H, d, $J = 2.0$ Hz, ArH), 6.83 (1 H, d, $J = 8.1$ Hz, ArH), 7.21−7.40 (5 H, m, ArH), 12.31 (1H, br s, exchangeable with D_2O, HCl). Anal. ($C_{22}H_{31}NO_2{\cdot}HCl$) C, H, N.

Method K: *N,N*-Dipropyl-2-[3-[2-(4-fluorophenyl)-ethoxy]-4-methoxyphenyl]ethylamine Hydrochloride (22b). *N,N*-Dipropyl-2-[3-hydroxy-4-methoxyphenyl]ethylamine hydrochloride (527 mg, 1.83 mmol), which was derived **10b** by hydrogenation using the procedure described in Method J, was reacted with 2-(4-fluorophenyl)ethyl chloride (3.49 g, 22.0 mmol), K_2CO_3 (3.77 g, 27.3 mmol), and KI (28 mg, 0.17 mmol) in DMF (10 mL) at 60 °C for 54 h. The concentrated reaction mixture was partitioned between AcOEt and water. The separated organic layer was washed with 0.5 N NaOH solution and saturated brine, dried ($MgSO_4$), filtered, chromatographed ($CHCl_3$/EtOH 20:1), treated with 4 N HCl in AcOEt, and recrystallized from AcOEt to yield **22b** as a colorless crystal (205 mg, 27% yield): mp 114−116 °C; IR (KBr) 2606, 2530, 2475, 1515 cm^{-1}; MS *m/z* 374 ($M^+ + 1$); ^1H NMR ($CDCl_3$) δ 1.00 (6 H, t, $J = 7.3$ Hz, CH_3), 1.77−1.98 (4 H, m, CH_2), 2.93−3.04 (4 H, m, CH_2), 3.08−3.15 (6 H, m, CH_2), 3.83 (3 H, s, CH_3O), 4.18 (2 H, t, $J = 7.1$ Hz, CH_2O), 6.73−6.84 (3H, m, ArH), 6.94−7.06 (2 H, m, ArH), 7.22−7.32 (2 H, m, ArH), 12.34 (1 H, br s, exchangeable with D_2O, HCl). Anal. ($C_{23}H_{32}ClFNO_2{\cdot}$ HCl$\cdot$ 0.33AcOEt) C, H, N, Cl, F.

Method L: 2-[4-Methoxy-3-(2-phenylethoxy)phenyl]-ethylamine Hydrochloride (24). TFA (204.0 mL, 301.9 g, 2.65 mol) was added dropwise at such a rate so as to maintain the gentle reflux to a mixture of $NaBH_4$ (100.0 g, 2.64 mol) and 4-methoxy-3-(2-phenylethoxy)phenylacetonitrile, which was derived from isovanillin (201.1 g, 1.32 mol) in four steps using the procedure described in Method A, in THF (1.0 L) while being stirred. After the addition was complete, the reaction mixture was allowed to heat under reflux for 2 h before cooling in an ice bath. To the cooled mixture was added dropwise water (100 mL) and concentrated HCl (400 mL), over 1 h, and then warmed at 50 °C for 0.5 h until evolution of hydrogen was complete. After treatment with 10 N NaOH solution to basify, the organic layer was separated, washed with 1 N NaOH solution (100 mL × 2) and saturated brine (100 mL), dried (Na_2SO_4), and filtered. To the filtrate was added concentrated HCl (165 mL) and then concentrated. The residual solid was recrystallized from 2-propanol (IPA) to give **24** as a colorless crystal (261.5g, 64% yield based on isovanillin): mp 114−115 °C; IR (KBr) 2958 (br), 1604, 1520 cm^{-1}; MS *m/z* 272 ($M^+ + 1$); ^1H NMR ($CDCl_3$) δ 2.92−3.03 (2 H, m, CH_2), 3.03−3.25 (4 H, m, CH_2), 3.79 (3 H, s, CH_3O), 4.19 (2 H, t, $J = 7.4$ Hz, CH_2O), 6.73−6.82 (3H, m, ArH), 7.15−7.34 (5 H, m, ArH), 8.31 (3 H, br s, exchangeable with D_2O, NH_2, HCl). Anal. ($C_{17}H_{21}NO_2{\cdot}HCl$) C, H, N.

Method M: *N*-Propyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine Hydrochloride (25). Propionyl chloride (17.67 g, 135.8 mmol) was added dropwise over 20 min to a solution of **24** (38.00 g, 123.4 mmol) and triethylamine (27.48 g, 271.6 mmol) in CH_2Cl_2 (190 mL) while being stirred

and cooled in an ice bath. After stirring for 12 h at room temperature, the reaction mixture was concentrated in vacuo and then partitioned between AcOEt and water. The separated organic layer was washed with 1 N HCl solution, saturated $NaHCO_3$ solution, and saturated brine, dried (Na_2SO_4), filtered, and then concentrated in vacuo to give amide, which was used for the next step.

Reduction of the above amide with $LiAlH_4$ (10.54 g, 277.7 mmol) in THF (380 mL), treatment with 4 N HCl in AcOEt (46 mL, 184 mmol), and recrystallization from IPA using the procedure described in the third step of method C, yielded **25** as a colorless crystal (34.97 g, 81% yield): mp 134−136 °C; IR (KBr) 2769 (br), 1519 cm^{-1}; MS *m/z* 314 ($M^+ + 1$); ^1H NMR ($CDCl_3$) δ 0.99 (3 H, t, $J = 7.4$ Hz, CH_3), 1.87−1.99 (2 H, m, CH_2), 2.80−3.02 (2 H, m, CH_2), 3.02−3.28 (6 H, m, CH_2), 3.82 (3 H, s, CH_3O), 4.17 (2 H, t, $J = 7.4$ Hz, CH_2O), 6.73−6.81 (3 H, m, ArH), 7.18−7.36 (5 H, m, ArH), 9.73 (2 H, br s, exchangeable with D_2O, NH, HCl). Anal. ($C_{20}H_{27}NO_2$·HCl) C, H, N.

Method N: *N*-Hexyl-*N*-propyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine Hydrochloride (26b). A mixture of **25** (432 mg, 1.23 mmol), 1-iodohexane (0.92 mL, 1.32 g, 6.23 mmol), and K_2CO_3 (379 mg, 2.74 mmol) in DMF (4.5 mL) was stirred at room temperature for 24 h. The reaction mixture was poured into water, extracted with AcOEt, washed with 1 N NaOH solution and saturated brine, dried ($MgSO_4$), filtered, concentrated, column chromatographed (hexanes/AcOEt 1:1), and then treated with 4 N HCl in AcOEt to yield **26b** as a colorless oil (354 mg, 66% yield): IR (neat) 2439 (br), 1516 cm^{-1}; MS *m/e* 398 ($M^+ + 1$); ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, $J = 6.5$ Hz, CH_3), 1.00 (3 H, t, $J = 7.4$ Hz, CH), 1.24−1.37 (6 H, m, CH_2), 1.68−1.93 (4 H, m, CH_2), 2.92−3.08 (4 H, m, CH_2), 3.09−3.20 (6 H, m, CH_2), 3.84 (3 H, s, CH_3O), 4.20 (2 H, t, $J = 7.5$ Hz, CH_2O), 6.72−6.84 (3 H, m, ArH), 7.21−7.38 (5 H, m, ArH), 12.34 (1 H, br s, exchangeable with D_2O, HCl). Anal. ($C_{26}H_{39}NO_2$·HCl·0.2H_2O) C, H, N.

Radioligand Binding Study. Male Wistar rats (200−250 g, Japan SLC, Japan) were decapitated, and the brains were rapidly removed. The entire brain or striatum (D_2 receptor binding) was homogenized in 20 volumes of 50 mM Tris/HCl (pH 7.7) buffer (Tris buffer), using a Physcotoron homogenizer. The homogenate was centrifuged at 50000*g* for 10 min, and the pellet was rehomogenized with Tris buffer and recentrifuged; this procedure was repeated twice. The final pellet was resuspended with Tris buffer and was used for radioligand binding assay.

σ (2 nM [^3H]-(+)-3-PPP), D_1 (1 nM [^3H]-SCH23390), D_2 (15 nM [^3H]-sulpiride), PCP (5 nM [^3H]-PCP), α_1 (0.2 nM [^3H]-prazosin), 5-HT_{1A} (0.2 nM [^3H]-8-OH-DPAT), and 5-HT_2 (5 nM [^3H]-ketanserin) receptor sites were determined according to the methods of Tanaka et al.[46] and Billard et al.[47] Briefly, 1 mL of membrane suspension and radiolabeled ligand was incubated with various concentrations (at least five) of unlabeled drugs. Incubations were terminated by rapid filtration through a Whatman GF/B glass fiber filter that had been soaked for at least 4 h in a solution of 0.5% polyethylenimine and then washed with Tris buffer. The filter-bound radioactivity was measured using a liquid scintillation spectrometer. IC_{50} values from competitive inhibition experiments were determined using the Marquardt−Levenberg nonlinear curve fitting procedure of the RS/1 program (BBN Research System) running on a VAX/VMS system.

Effects on (+) SKF10,047-Induced Stereotyped Behavior in Mice.[49,50] Male ICR mice (Japan SLC, Japan), 25−30 g, were placed individually into clear acrylic cages (24 m × 17.5 m × 12 cm) and allowed a minimum of 1 h to acclimatize to the new environment (10 mice in each group). Then, 30 min after administration of the vehicle, (+) BMY14802 (po), phenylalkylamine derivatives (po), and (+) SKF10,047 (30 mg/kg, ip) were administered. Behavioral rating was begun at 10 min after (+) SKF10,047 injection and studied 5 min thereafter for 40 min. The rating scale for stereotyped behavior is (0) control behavior, (1) sniffing, grooming, and rearing, (2) nondirectional movements, reciprocal forepaw treading, and sniffing greater than that in rating 1, (3) turning, circling, or backpedaling behavior, (4) continuous circling, weaving, or backpedaling behavior, (5) dyskinetic extension and flexion of limbs, head, and neck. Ten mice for vehicle and each of three different doses of drugs were used to observe dose−response reactions. The total score of the control groups was defined as 100%, and the percent of control of each treatment group was calculated and ED_{25} values determined.

Effects on Methamphetamine (MAP)-Induced Hyperlocomotion in Mice. Male ICR mice (20−30 g, Charles River, Japan) were used. We have described the handling procedures in detail.[51]

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