Synthesis and SAR of 1-Alkyl-2-phenylethylamine Derivatives Designed from *N*,*N*-Dipropyl-4-methoxy-3-(2-phenylethoxy)phenylethylamine To Discover σ_1 Ligands

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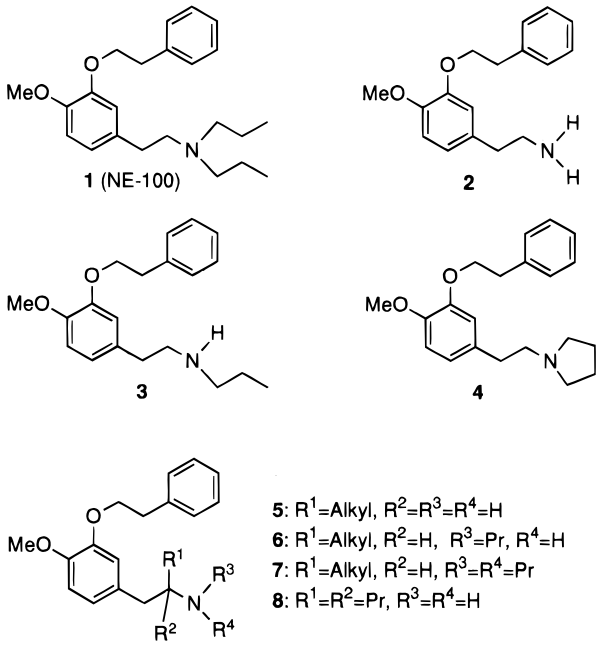
The synthesis and structure−activity relationships (SAR) of 1-alkyl-2-phenylethylamine derivatives **5**−**8** designed from *N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine hydrochloride (**1**, NE-100) are presented. The SAR between compound **1** and 1-alkyl-2-phenylethylamine derivatives suggested that the alkyl group on the 1-position carbon of 2-[4-methoxy-3-(2-phenylethyl)phenyl]ethylamine derivatives played the role of one of the propyl groups on the aminic nitrogen of compound **1**. (−)-*N*-Propyl-1-butyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine hydrochloride ((−)-**6d**, NE-537) and (−)-*N*-propyl-1-(3-methybutyl)-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine hydrochloride ((−)-**6i**, NE-535), typical compounds in this series, have potent and selective σ_1 affinity.

Introduction

Since Hellewell and Bowen[1] described σ_1 and σ_2 receptor subtypes, several σ_1 and σ_2 ligands have been presented.[2−7] Molecular cloning experiments[8,9] have suggested that σ binding protein did not seem to be related to cytochrome P-450 and neuropeptide Y receptor.[10,11] However, the molecular properties and signaling mechanisms mediated through σ receptors have not been fully elucidated. Among the several known σ_1 ligands, *N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)-phenyl]ethylamine hydrochloride (**1**) (Chart 1) has moderate selectivity at the σ_1 receptor over the σ_2 receptor[12] but is a useful ligand, since it is easily labeled by tritium[13] and can be used to study biochemical effects selectively mediated by the σ_1 receptor.[14,15] Selective and high-affinity σ_1 ligands containing a methoxy group to be labeled with tritium are more useful than compound **1** for determining the physiological and clinical significance of σ_1 ligands. Characterization of compound **1** and its derivatives **2**−**4**[16] yielded three suggestions for discovering σ ligands: (1) one propyl group of compound **1** might be required for formation of the fundamental conformation for interaction with σ receptors, since compound **3** has moderate σ affinity whereas compound **2** has none; (2) another propyl group of compound **1** might play an important role in interacting with the hydrophobic pocket of σ receptors, since compound **1** has about 30 times the σ affinity of compound **3**; (3) it might be best if the two propyl groups are located in different spaces to yield high σ affinity, since compound **4** containing a cyclic amine has moderate σ affinity (Chart 1).

In light of these suggestions, our interest focused on 1-alkyl-2-phenylethylamine derivatives **5**−**8**, since we anticipated that R^1 and/or R^2 of the derivatives **5**−**8** would play the role of the one or two propyl groups on the aminic nitrogen of compound **1** (Chart 1). In this paper, we present the synthesis and SAR of novel 1-alkyl-2-phenylethylamine derivatives **5**−**8**.

Chart 1



Chemistry

The processes for preparing 1-alkyl-2-phenylethylamine derivatives **5**−**8** (cf. Table 1) are depicted in generic Schemes 1 and 2.

Derivative **10** is prepared from benzaldehyde **9**[16] by standard synthetic procedures, modified Horner−Emmons condensation[17] of compound **9**, hydrogenation of

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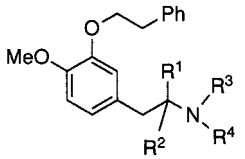
Table 1. 1-Alkyl-2-phenylethylamine Derivatives: Physical Data



compd	R^1	R^2	R^3	R^4	salt	method[a]	mp (°C)	analysis[b]
(±)-**10a**	Me	H	Boc	H		A	oil	$C_{23}H_{31}NO_4$
(±)-**10b**	Et	H	Boc	H		A	88.5−89.5[d]	$C_{24}H_{33}NO_4$
(±)-**10c**	*n*-Pr	H	Boc	H		A	89−90[d]	$C_{25}H_{35}NO_4$
(±)-**10d**	*n*-Bu	H	Boc	H		A	101.5−102[d]	$C_{26}H_{37}NO_4$
(±)-**10e**	*n*-Pen	H	Boc	H		A	91.5−92.5[d]	$C_{27}H_{39}NO_4$
(±)-**10f**	*n*-Hex	H	Boc	H		A	85−86[d]	$C_{28}H_{41}NO_4$
(±)-**10g**	*n*-Hep	H	Boc	H		A	82.5−83.5[d]	$C_{29}H_{43}NO_4$
(±)-**10h**	*n*-Oct	H	Boc	H		A	805−81[d]	$C_{30}H_{45}NO_4$
(±)-**10i**	*i*-Pen	H	Boc	H		A	103−104[d]	$C_{27}H_{39}NO_4$
(±)-**5a**	Me	H	H	H	HCl	B	88−90.5[e]	$C_{18}H_{23}NO_2 \cdot HCl \cdot 1/4TFA$
(±)-**5b**	Et	H	H	H	HCl	B	127.5−128.5[e]	$C_{19}H_{25}NO_2 \cdot HCl \cdot 1/20TFA$
(±)-**5c**	*n*-Pr	H	H	H	HCl	B	126.5−127.5[f]	$C_{20}H_{27}NO_2 \cdot HCl \cdot 1/2TFA$
(±)-**5d**	*n*-Bu	H	H	H		B	oil	$C_{21}H_{29}NO_2 \cdot 1/7CHCl_3$
(±)-**5e**	*n*-Pen	H	H	H	HCl	B	120.5−122[f]	$C_{22}H_{31}NO_2 \cdot HCl$
(±)-**5f**	*n*-Hex	H	H	H		B	oil	$C_{23}H_{33}NO_2 \cdot 1/20CHCl_3$
(±)-**5g**	*n*-Hep	H	H	H		B	oil	$C_{24}H_{35}NO_2 \cdot 1/15CHCl_3$
(±)-**5h**	*n*-Oct	H	H	H		B	oil	$C_{22}H_{31}NO_2 \cdot 1/20CHCl_3$
(±)-**5i**	*i*-Pen	H	H	H	HCl	B	91.5−92[g]	$C_{22}H_{31}NO_2 \cdot HCl$
(±)-**6a**	Me	H	*n*-Pr	H	HCl	C	79−80.5[h]	$C_{21}H_{29}NO_2 \cdot HCl$
(±)-**6b**	Et	H	*n*-Pr	H		C	oil	$C_{22}H_{31}NO_2 \cdot 1/4CHCl_3$
(±)-**6c**	*n*-Pr	H	*n*-Pr	H		C	oil	$C_{23}H_{33}NO_2 \cdot 1/20CHCl_3$
(±)-**6d**	*n*-Bu	H	*n*-Pr	H		C	oil	$C_{24}H_{35}NO_2 \cdot 1/10CHCl_3$
(+)-**6d**	*n*-Bu	H	*n*-Pr	H	HCl	D	82.5−83.5[h]	$C_{24}H_{35}NO_2 \cdot HCl$
(−)-**6d**	*n*-Bu	H	*n*-Pr	H	HCl	D	83−84[h]	$C_{24}H_{35}NO_2 \cdot HCl$
(±)-**6e**	*n*-Pen	H	*n*-Pr	H	HCl	C	93−94[h]	$C_{25}H_{37}NO_2 \cdot HCl$
(±)-**6f**	*n*-Hex	H	*n*-Pr	H		C	oil	$C_{26}H_{39}NO_2 \cdot 1/15CHCl_3$
(±)-**6g**	*n*-Hep	H	*n*-Pr	H		C	oil	$C_{27}H_{41}NO_2 \cdot 1/15CHCl_3$
(±)-**6h**	*n*-Oct	H	*n*-Pr	H		C	oil	$C_{28}H_{43}NO_2 \cdot 1/20CHCl_3$
(±)-**6i**	*i*-Pen	H	*n*-Pr	H	HCl	C	124−125[h]	$C_{25}H_{37}NO_2 \cdot HCl$
(+)-**6i**	*i*-Pen	H	*n*-Pr	H	HCl	D	98−99[h]	$C_{25}H_{37}NO_2 \cdot HCl$
(−)-**6i**	*i*-Pen	H	*n*-Pr	H	HCl	D	99−100[h]	$C_{25}H_{37}NO_2 \cdot HCl$
(±)-**7a**	Me	H	*n*-Pr	*n*-Pr		C	oil	$C_{24}H_{35}NO_2$
(±)-**7b**	Et	H	*n*-Pr	*n*-Pr		C	oil	$C_{25}H_{37}NO_2 \cdot 1/10CHCl_3$
(±)-**7c**	*n*-Pr	H	*n*-Pr	*n*-Pr		C	oil	$C_{26}H_{39}NO_2 \cdot 1/15CHCl_3$
(±)-**7d**	*n*-Bu	H	*n*-Pr	*n*-Pr		C	oil	$C_{27}H_{41}NO_2 \cdot 1/20CHCl_3$
(±)-**7e**	*n*-Pen	H	*n*-Pr	*n*-Pr	HCl	C	oil	$C_{28}H_{43}NO_2 \cdot HCl$
(±)-**7f**	*n*-Hex	H	*n*-Pr	*n*-Pr		C	oil	$C_{29}H_{45}NO_2 \cdot 1/15CHCl_3$
(±)-**7g**	*n*-Hep	H	*n*-Pr	*n*-Pr		C	oil	$C_{30}H_{47}NO_2 \cdot 1/20CHCl_3$
(±)-**7h**	*n*-Oct	H	*n*-Pr	*n*-Pr		C	oil	$C_{31}H_{49}NO_2 \cdot 1/20CHCl_3$
8	*n*-Pr	*n*-Pr	H	H	Fum[c]	E	167.5−168.5[i]	$C_{23}H_{33}NO_2 \cdot C_4H_4O_4$

[a] Methods A−E are described in the text. [b] Elemental analyses for all compounds were within ±0.4% of the theoretical values for the indicated formula. Analyses were performed for all elements except O. [c] Fumaric acid. [d−h] Recrystallization solvents are depicted: [d]hexane, [e]CH_2Cl_2−diisopropyl ether, [f]diisopropyl ether, [g]diisopropyl ether−hexane, [h]toluene−hexane. [i] Precipitation solvents are depicted: [i]acetone−diethyl ether.

the double bond over PtO_2, hydrolysis of the ester, and modified Curtius reaction of phenylpropionic acids using diphenyl phosphorazidate and *tert*-butyl alcohol[18] (method A). Deprotection of the *tert*-butoxycarbonyl group (Boc) of derivative **10** gives the primary amine **5** (method B). Treatment of compound **5** with 1.5−2.0 equiv of propyl bromide in *N*,*N*-dimethylformamide (DMF) containing potassium carbonate gives derivatives **6** and **7**, which can easily be separated by silica gel chromatography (method C). Optical derivative **6** is prepared by resolution of racemic derivative **5** using (+)- or (−)-mandelic acid followed by *N*-alkylation using 1.0−1.2 equiv of propyl bromide and potassium carbonate in DMF (method D) (Scheme 1).

To obtain compound **8**, compound **11**[16] is treated with allylmagnesium bromide followed by hydrogenation of the two allyl groups to afford the desired compound. Direct reaction of propylmagnesium bromide with compound **11** did not yield compound **8** (Scheme 2).

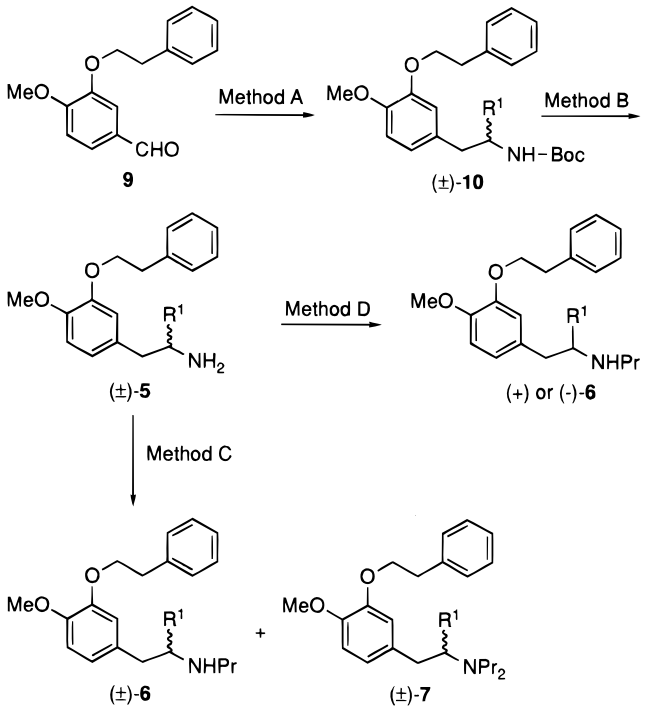
Results and Discussion

Binding data for compounds **5**−**8** are shown in Table 2, with the known data for compounds **1**−**4**.[16]

Compounds with substitution of alkyl groups of C4−C6 length (R^1), (±)-**5d**−(±)-**5f** and (±)-**5i**, exhibited higher σ affinity than compounds with substitution of shorter or longer alkyl groups, (±)-**5a**−(±)-**5c** or (±)-**5g** and (±)-**5h**. The potencies of compounds (±)-**5d**−(±)-**5f** and (±)-**5i** were in accord with that of *N*-propyl compound **3**. This suggests that the length of C4−C6 for R^1 best plays the role of one propyl group of **1**, enabling formation of the fundamental conformation for interaction with σ receptors or interaction with the hydrophobic pocket of σ receptors.

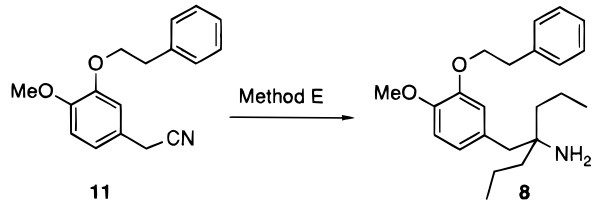
N-Propylated compounds (±)-**6a**−(±)-**6i** had much higher σ affinity than the compounds (±)-**5a**−(±)-**5i**, respectively. This finding suggests that the two alkyl groups, R^1 and *N*-propyl groups, are required for high

Scheme 1[a]



[a] Method A: (1) $R^1CH(CO_2Et)P(O)(OEt)_2$, NaH, THF; (2) H_2, 5% Pd/C, EtOH; (3) NaOH, H_2O, EtOH; (4) DPPA, Et_3N, PhH and then *t*-BuOH. Method B: (1) TFA−CH_2Cl_2. Method C: (1) PrBr (1.5−2.0 equiv), K_2CO_3, DMF. Method D: (1) resolution (salt with mandelic acid); (2) PrBr (1.0−1.2 equiv), K_2CO_3, DMF.

Scheme 2[a]

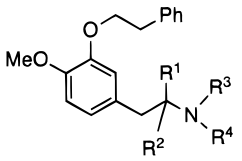


[a] Method E: (1) allyl-MgBr, Et_2O; (2) H_2, PtO_2, AcOEt.

σ affinity in 1-alkyl-2-phenylethyamine derivatives such as **1** and its derivatives. Among the *N*-propylated compounds, compounds (±)-**6d**, (±)-**6e**, and (±)-**6i** had particularly high σ affinities, and these potencies were approximately equal to that of compound **1**. Alkyl group of C4 or C5 length (R^1) might be preferred for playing the role of one propyl group of compound **1** and retaining high σ affinity of compound **1**. Furthermore, compounds (±)-**6d** and (±)-**6i** exhibited higher σ_1 selectivity than compound (±)-**6e**. We also studied the relationship between the optical isomers of compounds (±)-**6d** and (±)-**6i** and affinity. The (−)-isomers, (−)-**6d** and (−)-**6i**, had very high σ_1 affinity, while the (+)-isomers, (+)-**6d** and (+)-**6i**, exhibited approximately 50-fold reduction in σ_1 affinity. The σ_1 affinities of compounds (−)-**6d** and (−)-**6i** were about 300 and 400 times their respective σ_2 affinities.

N,*N*-Dipropylated compound **7** exhibited a more than 10-fold reduction in σ affinity compared to the *N*-propylated compound **6**, except for compounds (±)-**7a**−(±)-**7c**. Notably, however, compounds (±)-**7a**−(±)-**7c** were less potent than the corresponding compound **1**. This suggests that there may be steric restriction of binding at the space of the third alkyl group. The third alkyl group could hinder binding to σ receptors, since compound **1**, a compound nonsubstituted with the third alkyl group, exhibited the highest σ affinity among *N*,*N*-dipropylated compounds.

Table 2. 1-Alkyl-2-Phenylethylamine Derivatives: In Vitro Data



						IC_{50} (nM)[a]			
compd	R^1	R^2	R^3	R^4	salt	σ	σ_1	σ_2	D_2
1[b]	H	H	Pr	Pr	HCl	1.3	1.5	85	>1000
2[b]	H	H	H	H	HCl	>1000	NT	NT	>1000
3[b]	H	H	Pr	H	HCl	34	NT	NT	>1000
4[b]	H	H	$-(CH_2)_4-$		$(CO_2H)_2$	110	NT	NT	>1000
(±)-**5a**	Me	H	H	H	HCl	>1000	NT	NT	NT
(±)-**5b**	Et	H	H	H	HCl	>1000	NT	NT	NT
(±)-**5c**	*n*-Pr	H	H	H	HCl	330	NT	NT	NT
(±)-**5d**	*n*-Bu	H	H	H		160	NT	NT	NT
(±)-**5e**	*n*-Pen	H	H	H	HCl	110	NT	NT	NT
(±)-**5f**	*n*-Hex	H	H	H		170	NT	NT	NT
(±)-**5g**	*n*-Hep	H	H	H		420	NT	NT	NT
(±)-**5h**	*n*-Oct	H	H	H		>1000	NT	NT	NT
(±)-**5i**	*i*-Pen	H	H	H	HCl	130	NT	NT	NT
(±)-**6a**	Me	H	*n*-Pr	H	HCl	10	NT	NT	NT
(±)-**6b**	Et	H	*n*-Pr	H		8.0	7.8	330	>1000
(±)-**6c**	*n*-Pr	H	*n*-Pr	H		4.5	4.1	250	>1000
(±)-**6d**	*n*-Bu	H	*n*-Pr	H		2.1	1.9	320	>1000
(+)-**6d**	*n*-Bu	H	*n*-Pr	H	HCl	NT	34	210	NT
(−)-**6d**	*n*-Bu	H	*n*-Pr	H	HCl	NT	0.7	230	>1000
(±)-**6e**	*n*-Pen	H	*n*-Pr	H	HCl	1.5	2.2	110	>1000
(±)-**6f**	*n*-Hex	H	*n*-Pr	H		9.0	8.1	230	>1000
(±)-**6g**	*n*-Hep	H	*n*-Pr	H		13	NT	NT	NT
(±)-**6h**	*n*-Oct	H	*n*-Pr	H		170	NT	NT	NT
(±)-**6i**	*i*-Pen	H	*n*-Pr	H	HCl	1.8	1.6	210	>1000
(+)-**6i**	*i*-Pen	H	*n*-Pr	H	HCl	NT	22	190	NT
(−)-**6i**	*i*-Pen	H	*n*-Pr	H	HCl	NT	0.5	200	>1000
(±)-**7a**	Me	H	*n*-Pr	*n*-Pr		12	NT	NT	NT
(±)-**7b**	Et	H	*n*-Pr	*n*-Pr		5.7	5.6	390	>1000
(±)-**7c**	*n*-Pr	H	*n*-Pr	*n*-Pr		9.5	8.2	420	>1000
(±)-**7d**	*n*-Bu	H	*n*-Pr	*n*-Pr		29	NT	NT	NT
(±)-**7e**	*n*-Pen	H	*n*-Pr	*n*-Pr	HCl	30	NT	NT	NT
(±)-**7f**	*n*-Hex	H	*n*-Pr	*n*-Pr		150	NT	NT	NT
(±)-**7g**	*n*-Hep	H	*n*-Pr	*n*-Pr		230	NT	NT	NT
(±)-**7h**	*n*-Oct	H	*n*-Pr	*n*-Pr		>1000	NT	NT	NT
8	*n*-Pr	*n*-Pr	H	H	Fum[c]	>1000	NT	NT	NT

[a] IC_{50} values represent the means of 1−3 separate experiments obtained from 10 concentrations of each compound, run in duplicate. Variation between experiments was less than 15%. NT, not texted. [b] Binding data presented in ref 16. [c] Fumaric acid.

With these findings, we proceeded to examine the 1,1-dialkyl-2-phenylethylamine derivative **8** in the hope of discovering a high-affinity σ ligand. Contrary to expectation, compound **8** did not exhibit σ affinity, possibly due to steric hindrance of the tertiary alkyl group on the aminic nitrogen.

The above discussion about SAR of compounds **5**−**8** is based on van der Waals interaction between the alkyl group (R^1 and/or R^2) and the hydrophobic pocket of σ receptors. Notably, however, this discussion might not fully elucidate the SAR of compounds **5**−**8**, for example, high σ_1 selectivity of compounds (±)-**6d**, (−)-**6d**, (±)-**6i**, and (−)-**6i** and slight difference of σ affinity between compound **3** and (±)-**5d**−(±)-**5f** and (±)-**5i**. A difference of electron density (basicity) on the nitrogen atom among primary (**5**), secondary (**6**), and tertiary (**7**, **1**) amines could influence binding, since a hydrogen bond strongly promotes interaction between receptor and

ligand. The high σ_1 selectivity of compounds (±)-**6d**, (−)-**6d**, (±)-**6i**, and (−)-**6i** might be due to both the van der Waals and hydrogen bond interactions influenced by the length of alkyl group (R^1) and the electron density on the aminic nitrogen, respectively. The electron density on the nitrogen of the secondary amines might be more preferred than those of the primary and tertiary amines for σ or σ_1 affinity, since the secondary amines exhibited slightly higher σ or σ_1 affinity than the primary (**3** vs (±)-**5d**−(±)-**5f** and (±)-**5i**) and tertiary ((−),(±)-**6d** and (−),(±)-**6i** vs **1**) amines. On the other hand, compounds with high σ affinity (IC_{50} < 10 nM) did not exhibit affinity for dopamine D_2 receptors (IC_{50} > 1000 nM).

Conclusions

Our findings suggested that the 1-position alkyl group of 1-alkyl-2-phenylalkylamine derivatives played the role of one of the propyl groups on the aminic nitrogen of *N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]-ethylamine hydrochloride (**1**) and that there might be steric restriction for the third alkyl group at the 1-position (R^2). The 1-alkyl-2-phenylalkylamine derivatives containing one alkyl group on the 1-position carbon and one propyl group on the aminic nitrogen had high affinity for σ receptors. Among the derivatives, (−)-*N*-propyl-1-butyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine hydrochloride ((−)-**6d**) and (−)-*N*-propyl-1-(3-methybutyl)-2-[4-methoxy-3-(2-phenylethoxy)phenyl]-ethylamine hydrochloride ((−)-**6i**) may be useful for examining the physiological and clinical significance of the σ_1 receptor, since they are potent and selective σ_1 ligands, and the [*O-methyl*-^{3}H]-compound (−)-**6d** or (−)-**6i** could be produced by the same preparation procedure as that for [*O-methyl*-^{3}H]-compound **1**.

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 obtained on a Simazu/Kratos HV-300. Elemental analyses were performed by a Perkin-Elmer 240C (for carbon, hydrogen, and nitrogen) or Yokokawa-denki IC7000P (for halogen) and are within 0.4% of theory. Analytical thin-layer chromatography was conducted on precoated silica gel 60 F254 plates (Merck). Chromatography was performed on silica gel C-200, 100−200 mesh (Wako Pure Chemical) using the solvent systems (volume ratios) indicated below. Each of the experiments below illustrates one of the methods indicated in Table 1.

Method A: (±)-*N*-*tert*-Butoxycarbonyl-1-pentyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine ((±)-10e). A triethyl phosphonoacetate (4.75 g, 21.2 mmol) was added dropwise to a stirred suspension of 60% NaH in oil (0.86 g, 21.5 mmol) in 1,2-dimethoxyethane (25 mL) over 10 min. After stirring for 1 h at room temperature, to the reaction mixture was added *n*-pentyl bromide (3.23 g, 21.4 mL), and the resulting mixture was heated at reflux for 3 h. To the cooling mixture was added 60% NaH in oil (0.86 g, 21.5 mmol), and the resulting suspension was stirred for 0.5 h at room temperature. To the reaction mixture was added a solution of 4-methoxy-3-(2-phenylethoxy)benzaldehyde (**9**) (5.15 g, 20.1 mmol) in DME (10 mL), and the resulting mixture was allowed to heat at reflux for 2 h. The mixture was then partitioned between ethyl acetate and water. The separated organic phase was washed with water, saturated aqueous $NaHCO_3$, and saturated brine, dried ($MgSO_4$), and then concentrated in vacuo. The residue was chromatographed (hexanes/AcOEt 30:1) to obtain two isomers of ethyl 3-[4-methoxy-3-(2-phenylethoxy)phenyl]-2-pentylacrylate as a colorless oil (5.39 g, 68%).

***E*-Isomer:** 4.49 g (56%); ^{1}H NMR ($CDCl_3$) δ 0.84 (3 H, t, J = 7.0 Hz, CH_3 of Pen), 1.27−1.40 (4 H, m, 2 × CH_2), 1.33 (3 H, t, J = 7.1 Hz, CH_3 of Et), 1.45−1.65 (2 H, m, CH_2), 2.52 (2 H, br t, J = 7.9 Hz, C=CCH_2), 3.18 (2 H, t, J = 7.6 Hz, CH_2-Ph), 3.90 (3 H, s, CH_3O), 4.22 (2 H, t, J = 7.6 Hz, OCH_2Bn), 4.25 (2 H, q, J = 7.1 Hz, O_2CH_2), 6.89 (1 H, d, J = 8.2 Hz, ArH), 6.94 (1 H, d, J = 1.8 Hz, ArH), 7.00 (1 H, d d, J = 1.8, 8.2 Hz, ArH), 7.23−7.32 (5 H, m, ArH), 7.55 (1 H, br s, C=CH); MS (EI) *m*/*z* 396 (M^+), 105 (100%); IR (neat) 1703, 1625, 1600, 1580, 1516, 1455 cm^{-1}. Anal. ($C_{25}H_{32}O_4$) C, H.

***Z*-Isomer:** 0.44 g (6%); ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 6.6 Hz, CH_3 of Pen), 1.13 (3 H, t, J = 7.1 Hz, CH_3 of Et), 1.26−1.41 (4 H, m, 2 × CH_2), 1.43−1.53 (2 H, m, 2 × CH_2), 2.37 (2 H, br t, J = 7.1 Hz, C=CCH_2), 3.15 (2 H, t, J = 7.6 Hz, CH_2-Ph), 3.86 (3 H, s, CH_3O), 4.11 (2 H, q, J = 7.1 Hz, CO_2CH_2), 4.18 (2 H, t, J = 7.6 Hz, OCH_2Bn), 6.48 (1 H, br s, C=CH), 6.77−6.85 (3 H, m, ArH), 7.20−7.31 (5 H, m, ArH); MS (EI) *m*/*z* 396 (M^+), 105 (100%); IR (neat) 1714, 1603, 1582, 1515, 1455, 1443 cm^{-1}. Anal. ($C_{25}H_{32}O_4$) C, H.

Mixture of *E*- and *Z*-isomers: 0.44 g (6%).

A suspension of the mixture of *E*- and *Z*-isomers in ethyl 3-[4-methoxy-3-(2-phenylethoxy)phenyl]-2-pentylacrylate (5.16 g, 13.0 mmol) and 5% Pd/C (0.52 g) in ethanol (25 mL) was stirred under an atmosphere of hydrogen. After the theoretical amount of hydrogen was taken up, the suspension was filtered through Celite. To the filtrate was added a solution of KOH (3.17 g, 56.6 mmol) in water (5 mL), and the resulting solution was stirred overnight. The reaction mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and 1 N aqueous HCl. The separated organic phase was washed with saturated brine, dried ($MgSO_4$), and then concentrated in vacuo to obtain (±)-3-[4-methoxy-3-(2-phenylethoxy)phenyl]-2-pentylpropionic acid as a yellow oil (4.75 g, 99%), which was carried on to the next step: ^{1}H NMR ($CDCl_3$) δ 0.85 (3 H, t, J = 6.4 Hz, CH_3 of Pen), 1.16−1.42 (6 H, m, 3 × CH_2), 1.46−1.59 (2 H, m, CH_2), 2.55−2.69 (2 H, m, CH and one of CH_2 of propionic acid), 2.85 (1 H, d d, J = 4.9, 11.4 Hz, one of CH_2 of propionic acid), 3.14 (2 H, t, J = 7.6 Hz, CH_2Ph), 3.83 (3 H, s, CH_3O), 4.19 (2 H, t, J = 7.6 Hz, OCH_2-Bn), 6.69 (1 H, d, J = 1.8 Hz, ArH), 6.71 (1 H, dd, J = 1.8, 8.6 Hz, ArH), 6.79 (1 H, d, J = 8.6 Hz, ArH), 7.20−7.36 (5 H, m, ArH); MS (CI) *m*/*z* 370 (M^+), 105 (100%).

A solution of (±)-3-[4-methoxy-3-(2-phenylethoxy)phenyl]-2-pentylpropionic acid (4.01 g, 10.8 mmol), triethylamine (3.32 g, 11.7 mmol), and diphenyl phosphorazidate (3.32 g, 11.8 mmol) in benzene (40 mL) was heated at reflux for 2 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in *tert*-butyl alcohol (20 mL), and the resulting solution was heated at reflux for 20 h. The concentrated reaction mixture was dissolved in ethyl acetate, washed with 0.5 N aqueous sodium hydroxide, 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and saturated brine, dried ($MgSO_4$), and then concentrated in vacuo. The residue was chromatographed (hexanes/AcOEt, 25:1) and recrystallized from hexanes to obtain (±)-**10e** as a colorless crystal (3.08 g, 64%): mp 91.5−92.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (3 H, t, J = 6.5 Hz, CH_3 of Pen), 1.24−1.43 (8 H, m, 4 × CH_2), 1.38 (9 H, s, 3 × CH_3 of t-Bu), 2.65 (2 H, d, J = 6.6 Hz, CH_2 of ethylamine), 3.16 (2 H, t, J = 7.6 Hz, CH_2Ph), 3.65−3.89 (1 H, m, CH), 3.84 (3 H, s, CH_3O), 4.23 (1 H, br s, NH), 4.19 (2 H, t, J = 7.6 Hz, OCH_2Bn), 6.81−6.72 (2 H, m, ArH), 6.81 (1H, d, J = 8.7 Hz, ArH), 7.23−7.32 (5 H, m, ArH); MS (EI) *m*/*z* 441 (M^+), 100 (100%); IR (KBr) 3357, 1687, 1591, 1530, 1445, 1427 cm^{-1}. Anal. ($C_{27}H_{39}NO_4$) C, H, N.

Method B: (±)-1-Pentyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine Hydrochloride ((±)-5e). A solution of (±)-**10e** (2.89 g, 6.54 mmol) in a mixture of trifluoroacetic acid (10 mL) and dichloromethane (10 mL) was stirred at room temperature for 1.5 h. The reaction mixture was

concentrated in vacuo, and the residue was dissolved in dichloromethane (10 mL). To the resulting solution was added 4 N HCl in dioxane (10 mL, 40.0 mmol), concentrated, and recrystallized from diisopropyl ether to obtain (±)-**5e** as a yellow crystal (1.88 g, 76%): mp 120.5−122 °C; ^{1}H NMR ($CDCl_3$) δ 0.79 (3 H, t, J = 6.2 Hz, CH_3 of Pen), 1.10−1.70 (8 H, m, 4 × CH_2), 2.78 (1 H, d d, J = 9.5, 13.4 Hz, one of CH_2-Ar), 3.10−3.21 (3 H, m, CH_2Ph and one of CH_2Ar), 3.25−3.4 (1 H, m, CHN), 3.81 (3 H, s, CH_3O), 4.19 (2 H, t, J = 7.5 Hz, OCH_2Bn), 6.70−6.82 (3 H, m, ArH), 7.19−7.31 (5 H, m, ArH), 8.46 (3 H, br s, NH_3^+); MS (CI) m/z 342 (M^+ + 1, 100%), 325, 242, 105, 100; IR (KBr) 3436, 1603, 1517, 1467, 1455, 1428 cm^{-1}. Anal. ($C_{22}H_{31}NO_2$·HCl) C, H, N.

Method C: (±)-*N*-Propyl-1-pentyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine Hydrochloride ((±)-6e) and (±)-*N*,*N*-Dipropyl-1-pentyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine Hydrochloride ((±)-7e). A suspension of (±)-**5e** (1.46 g, 3.86 mmol), propyl bromide (0.72 g, 5.83 mmol), and K_2CO_3 (1.34 g, 9.68 mmol) in *N*,*N*-dimethylformamide (3.0 mL) was stirred at room temperature for 5 days. The reaction mixture was partitioned between ethyl acetate and water. The separated organic phase was washed with water and saturated brine, dried ($MgSO_4$), concentrated in vacuo, and then chromatographed ($CHCl_3$/EtOH, 200:1−50:1) to separate the two desired products. Each product was treated with 4 N HCl in dioxane in chloroform and gave (±)-**6e** (0.49 g, 30%, after recrystallization from toluene−hexanes) as a colorless crystal and (±)-**7e** (0.17 g, 10%) as a light yellow amorphous solid.

(±)-6e: mp 93−94 °C; ^{1}H NMR ($CDCl_3$) δ 0.80 (3 H, t, J = 6.5 Hz, CH_3 of Pen), 0.91 (3 H, t, J = 7.4 Hz, CH_3 of Pr), 1.10−2.00 (10 H, m, 5 × CH_2), 2.65−2.90 (2 H, m, CH_2N), 2.90 (1 H, dd, J = 8.4, 13.2 Hz, one of CH_2Ar), 3.15 (2 H, t, J = 7.5 Hz, CH_2Ph), 3.10−3.30 (1 H, m, CHN), 3.34 (1 H, dd, J = 5.0, 13.2 Hz, one of CH_2Ar), 3.84 (3 H, s, CH_3O), 4.20 (2 H, t, J = 7.5 Hz, OCH_2Bn), 6.75−6.84 (3 H, m, ArH), 7.20−7.35 (5 H, m, ArH), 9.44 (2 H, br s, NH_2^+); MS (CI) m/z 384 (M^+ + 1, 100%), 142; IR (KBr) 3436, 2955, 2857, 2796, 2741, 2515, 2428, 1605, 1589, 1519, 1498, 1455 cm^{-1}. Anal. ($C_{25}H_{37}NO_2$·HCl) C, H, N.

(±)-7e: ^{1}H NMR ($CDCl_3$) δ 0.78 (3 H, t, J = 6.3 Hz, CH_3 of Pen), 0.92 (3 H, t, J = 7.3 Hz, CH_3 of Pr), 0.98 (3 H, t, J = 7.3 Hz, CH_3 of Pr), 1.05−2.15 (12 H, m, 6 × CH_2), 2.65−3.05 (5 H, m, 2 × CH_2N and CHN), 3.16 (2 H, t, J = 7.4 Hz, CH_2Ph), 3.40−3.55 (2 H, m, CH_2Ar), 3.84 (3 H, s, CH_3O), 4.22 (2 H, t, J = 7.4 Hz, OCH_2Bn), 6.80−6.90 (3 H, m, ArH), 7.20−7.40 (5 H, m, ArH), 11.83 (1 H, br s, NH^+); MS (CI) m/z 426 (M^+ + 1), 184 (100%); IR (KBr) 3401, 2934, 2874, 2607, 2471, 1661, 1605, 1591, 1516, 1455 cm^{-1}. Anal. ($C_{28}H_{43}NO_2$·HCl) C, H, N.

Method D: (−)-*N*-Propyl-1-(3-methylbutyl)-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine Hydrochloride ((−)-6i) and (+)-*N*-Propyl-1-(3-methylbutyl)-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine Hydrochloride ((+)-6i). After reaction of (±)-*N*-*tert*-butoxycarbonyl-1-(3-methylbutyl)-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine ((±)-**10i**) (89.69 g, 203 mmol) in a mixture of trifluoroacetic acid (156 mL) and dichloromethane (156 mL) (method B), to the concentrated residue was added saturated aqueous $NaHCO_3$, followed by extraction with CH_2Cl_2. The extract was dried ($MgSO_4$), concentrated in vacuo, and chromatographed ($CHCl_3$/MeOH, 30:1−20:1) to obtain (±)-1-(3-methylbutyl)-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine (free amine of (±)-**5i**) (59.65 g, 86%).

A mixture of the free amine of (±)-**5i** (59.65 g, 175 mmol) and (*R*)-(−)-mandelic acid (26.58 g, 175 mmol) in 2-propanol (257 mL) was heated at reflux to dissolve and left to stand overnight. The precipitated crystal was collected by filtration, and the recrystallization of the crystal from 2-propanol was repeated four times to obtain mandelate (30.27 g). The resulting crystal was partitioned between diethyl ether and 1 N aqueous NaOH. The separated organic phase was washed with 1 N aqueous NaOH and saturated brine, dried ($MgSO_4$), and concentrated in vacuo to obtain optical **5i** (21.22 g, 36%).

A mixture of the optical amine (19.53 g, 57.2 mmol), propyl bromide (7.74 g, 62.9 mM), and K_2CO_3 (9.49 g, 68.7 mmol) was treated by method C, and the resulting HCl salt was recrystallized from toluene−hexanes to obtain (−)-**6i** (16.20 g, 67%): mp 99−100 °C; $[\alpha]_D$ = −21.7 (c = 0.580, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80 (3 H, t, J = 6.1 Hz, CH_3 of iso-Pen), 0.83 (3 H, t, J = 6.1 Hz, CH_3 of iso-Pen), 0.91 (3 H, t, J = 7.4 Hz, CH_3 of Pr), 1.05−2.05 (7 H, m, 3 × CH_2 and $CHMe_2$), 2.60−2.95 (2 H, m, CH_2N), 2.91 (1 H, d d, J = 8.2, 13.3 Hz, one of CH_2Ar), 3.16 (2 H, t, J = 7.4 Hz, CH_2Ph), 3.10−3.35 (1 H, m, CHN), 3.34 (1 H, d d, J = 5.4, 13.3 Hz, one of CH_2Ar), 3.84 (3 H, s, CH_3O), 4.20 (2 H, t, J = 7.4 Hz, OCH_2Bn), 6.70−6.90 (3 H, m, ArH), 7.15−7.45 (5 H, m, ArH), 9.43 (2 H, br s, NH_2^+); MS (CI) m/z 384 (M^+ + 1), 142 (100%); IR (KBr) 3447, 2956, 2793, 2511, 2428, 1592, 1520, 1497, 1454 cm^{-1}. Anal. ($C_{25}H_{37}NO_2$·HCl) C, H, N.

The combined filtrates when resoluted were concentrated and partitioned between diethyl ether and 1 N aqueous NaOH. The separated organic phase was washed with 1 N aqueous NaOH and saturated brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was treated with (*S*)-(+)-mandelic acid (37% yield), and the resulting optical amine was reacted with propyl bromide (73% yield), by the same procedure as for the preparation of compound (−)-**6i**, to obtain (+)-**6i**: mp 98−99 °C; $[\alpha]_D$ = +21.9 (c = 0.456, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80 (3 H, t, J = 6.1 Hz, CH_3 of iso-Pen), 0.83 (3 H, t, J = 6.1 Hz, CH_3 of iso-Pen), 0.91 (3 H, t, J = 7.4 Hz, CH_3 of Pr), 1.05−2.05 (7 H, m, 3 × CH_2 and $CHMe_2$), 2.60−2.95 (2 H, m, CH_2N), 2.91 (1 H, dd, J = 8.2, 13.3 Hz, one of CH_2Ar), 3.16 (2 H, t, J = 7.4 Hz, CH_2Ph), 3.10−3.35 (1 H, m, CHN), 3.34 (1 H, dd, J = 5.4, 13.3 Hz, one of CH_2Ar), 3.84 (3 H, s, CH_3O), 4.20 (2 H, t, J = 7.4 Hz, OCH_2Bn), 6.70−6.90 (3 H, m, ArH), 7.15−7.45 (5 H, m, ArH), 9.43 (2 H, br s, NH_2^+); MS (CI) m/z 384 (M^+ + 1), 142 (100%); IR (KBr) 3523, 2955, 2795, 2511, 2427, 1592, 1520, 1498, 1454 cm^{-1}. Anal. ($C_{25}H_{37}NO_2$·HCl) C, H, N.

Method E: 1,1-Dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine Fumarate (8). A solution of 4-methoxy-3-(2-phenylethoxy)phenylacetonitrile (**11**) (10.00 g, 37.4 mmol) in dried diethyl ether (50 mL) was added dropwise over 0.5 h to a refluxed solution of allylmagnesium bromide in dried diethyl ether which was prepared by treatment of allyl bromide (9.29 g, 76.8 mmol) and magnesium (1.93 g, 79.4 mmol) in dried diethyl ether (100 mL). After heating for 8 h, the resulting mixture was quenched with saturated aqueous NH_4Cl and then extracted with ethyl acetate. The extract was washed with saturated aqueous NH_4Cl and saturated brine, dried ($MgSO_4$), concentrated in vacuo, and then chromatographed ($CHCl_3$/EtOH, 100:1), followed by treatment with fumaric acid in a mixture of acetone and diethyl ether to obtain 1,1-diallyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine fumarate (2.03 g, 11%): mp 127−128.5 °C; ^{1}H NMR (DMSO-d_6) δ 2.10−2.30 (4 H, m, 2 × CCH_2C of allyl), 2.69 (2 H, s, CH_2Ar), 3.03 (2 H, t, J = 7.1 Hz, CH_2Ph), 3.73 (3 H, s, CH_3O), 4.13 (2 H, t, J = 7.1 Hz, OCH_2Bn), 5.11 (2 H, dd, J = 5.11, 8.9 Hz, 2 × one of CH_2=C), 5.18 (2 H, s, 2 × one of CH_2=C), 5.80−6.05 (2 H, m, CH=C), 6.48 (2 H, s, CH=CH of fumaric acid), 6.76 (1H, dd, J = 1.5, 8.3 Hz, ArH at 6), 6.90 (1 H, d, J = 8.3 Hz, ArH at 5), 6.92 (1 H, d, J = 1.5 Hz, ArH at 2), 7.15−7.40 (5 H, m, ArH of Ph); MS (CI) m/z 352 (M^+ + 1), 110 (100%); IR (KBr) 3078, 2910, 1694, 1642, 1566, 1520, 1442, 1368, 1264 cm^{-1}. Anal. ($C_{23}H_{29}NO_2$·$C_4H_4O_4$) C, H, N.

The fumarate (1.64 g, mmol) was treated with 2 N aqueous NaOH in ethyl acetate to obtain the free amine. The free amine was stirred with PtO_2 (25 mg) in ethyl acetate (15 mL) under an atmosphere of hydrogen. After the theoretical amount of hydrogen was taken up, the suspension was filtered through Celite. The filtrate was concentrated in vacuo and the chromatographed ($CHCl_3$/EtOH, 15:1), followed by treatment with fumaric acid in a mixture of acetone and diethyl ether to give **8** (1.35 g, 82%): mp 167.5−168.5 °C; ^{1}H NMR (DMSO-d_6) δ 0.85 (6 H, t, J = 6.1 Hz, 2 × CH_3 of Pr), 1.10−1.55 (8 H, m, CH_2CH_2 of Pr), 2.75 (2 H, s, CH_2Ar), 3.03 (2 H, t, J = 7.0 Hz, CH_2Ph), 3.73 (3 H, s, CH_3O), 4.14 (2 H, t, J = 7.0 Hz, OCH_2-Bn), 6.44 (2 H, s, CH=CH of fumaric acid), 6.73 (1 H, dd, J = 1.6, 8.1 Hz, ArH), 6.91 (1 H, d, J = 8.1 Hz, ArH), 6.92 (1 H, d, J = 1.6 Hz, ArH), 7.15−7.40 (5 H, m, ArH); MS (CI) m/z 356

($M^+ + 1$), 114 (100%); IR (KBr) 2962, 2870, 1692, 1650, 1520, 1454, 1444, 1380, 1264 cm^{-1}. Anal. ($C_{23}H_{33}NO_2 \cdot C_4H_4O_4$) C, H, N.

***σ*, *σ*$_1$, *σ*$_2$, and Dopamine D$_2$ Binding Assays.** Compounds **5**−**8** were examined for affinity at *σ* sites labeled with [^{3}H]-(+)-3-(3-hydroxphenyl)-*N*-(1-propyl)piperidine (3-PPP) using guinea pig brain membranes, at σ_1 sites labeled with [^{3}H]-(+)-*N*-isopetenylnormetazocine (pentazocine) using guinea pig brain membranes, at σ_2 sites labeled with [^{3}H]-1,3-di-*o*-tolylguanidine (DTG) in the presence of 100 nM (+)-pentazocine using guinea pig brain membranes, and at dopamine D_2 receptors labeled with [^{3}H]-(−)-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-3,5-dichloro-2-hydroxy-6-methoxybenzamide[19] (raclopride) using rat striatal membranes (Table 2), using the procedures described in the literature.[12,19]

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