Central Cholinergic Agents. IV.[1] Synthesis and Acetylcholinesterase Inhibitory Activities of ω-[*N*-Ethyl-*N*-(phenylmethyl)amino]-1-phenyl-1-alkanones and Their Analogues with Partial Conformational Restriction

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Inhibitors of acetylcholinesterase (AChE) have been designed based on a working hypothesis of the enzyme's active site. These compounds were tested for their inhibitory activities on AChE and ω-[*N*-ethyl-*N*-(phenylmethyl)amino]-1-phenyl-1-alkanones (3) were found to be potent inhibitors. Various analogues of 3 were prepared to study the effect on AChE inhibition of partial restriction of conformation. Compounds with potent AChE inhibition were further evaluated in terms of central selectivity: the ratio of central action (ameliorating effect on scopolamine-induced memory impairment using a T-maze alternation task) to peripheral action.

Keywords anticholinesterase; conformational restriction; structure–activity relationship; T-maze alternation task

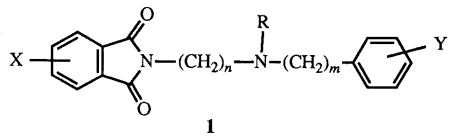
Inhibitors of acetylcholinesterase (AChE) have been targeted as one of the promising candidates for the treatment of senile dementia of the Alzheimer type (SDAT). In an attempt to find a new type of AChE inhibitor, we have proposed a new working hypothesis of the active site of the enzyme.[1a] This has been shown to be effective in the design of AChE inhibitors such as the phthalimide (**1**) and 3-phenylpropenamide derivatives (**2**) (Chart 1).[1a,b] The hypothesis, in essence, is based on an assumption that there exists a hydrophobic binding site (HBS-2) some distance removed from the conventional catalytic subsites: an anionic as well as an esteratic subsite and, closely adjacent to these, a hydrophobic binding site (HBS-1).[2] The existence of HBS-2 may have been confirmed by the detailed studies of the structure–activity relationships of **1** and **2**. Recently, Sussman *et al.* have reported the three-dimensional structure of AChE from *Torpedo californica*.[3] The X-ray analysis has revealed that the catalytic subsites are located near the bottom of a deep and narrow gorge of the enzyme and that 14 aromatic residues line its surface. The report has shown the existence of hydrophobic binding sites other than HBS-1. This, we believe, is in substantial support of our hypothesis, though it remains to be investigated which aromatic residue corresponds to HBS-2. This paper describes a continuing study based on the working hypothesis which can be used to search for novel AChE inhibitors.[4]

Design and Structural Alteration We have already described that the carbonyl groups of the phthalimide (**1**) and 3-phenylpropenamide derivatives (**2**) were important structural features for potent AChE inhibition, which presumably interacts with the enzyme by hydrogen bonding.[1a,b] We first prepared compounds **3a** and **4**—**7** to examine the replacement of imide (amide) linkages with other linkages (A in Chart 1). The design of these compounds is based on our preliminary structure–activity studies of **1**: potent inhibition is expected by the combination of $n=5$, $m=1$, R = Et, Y = 2-OMe, and X = 3,4-dimethoxy or 4-pyrrolidino.[5] Because **3a** showed the most potent inhibition, ω-[*N*-ethyl-*N*-(phenylmethyl)amino]-1-phenyl-1-alkanones (**3**) were chosen as key compounds for further structural alteration.

Although the acyclic key compounds (**3**) are very flexible, they must have taken on some specific conformations to interact better with the active site in a deep and narrow gorge. In order to shed some light onto this, we prepared the following analogues of **3** and studied the effect of restricting the flexibility (Chart 2):

a) the indanone derivatives (**8**),[6,7] b) the cyclohexyl phenyl ketone derivative (**9**), c) the piperidine derivatives (**10**),[8] and d) the tetrahydroisoquinoline derivative (**11**).

The effect of partial conformational restriction on central selectivity (see Biological Results and Discussion) was also



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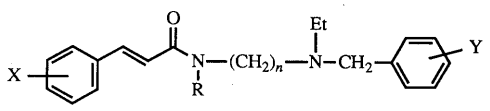

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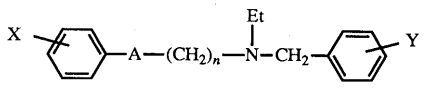


	A	*n*	X	Y
3a :	$COCH_2$	5	3,4-$(OMe)_2$	2-OMe
3b :	$COCH_2$	4	3,4-$(OMe)_2$	2-OMe
3c :	$COCH_2$	4	4-N⬠	2-OMe
3d :	$COCH_2$	4	4-N⬠	H
4 :	COO	5	3,4-$(OMe)_2$	2-OMe
5a :	CONH	5	3,4-$(OMe)_2$	2-OMe
5b :	CONAc	5	3,4-$(OMe)_2$	2-OMe
6 :	OCH_2	5	3,4-$(OMe)_2$	2-OMe
7 :	CH_2CH_2	5	3,4-$(OMe)_2$	2-OMe

Chart 1

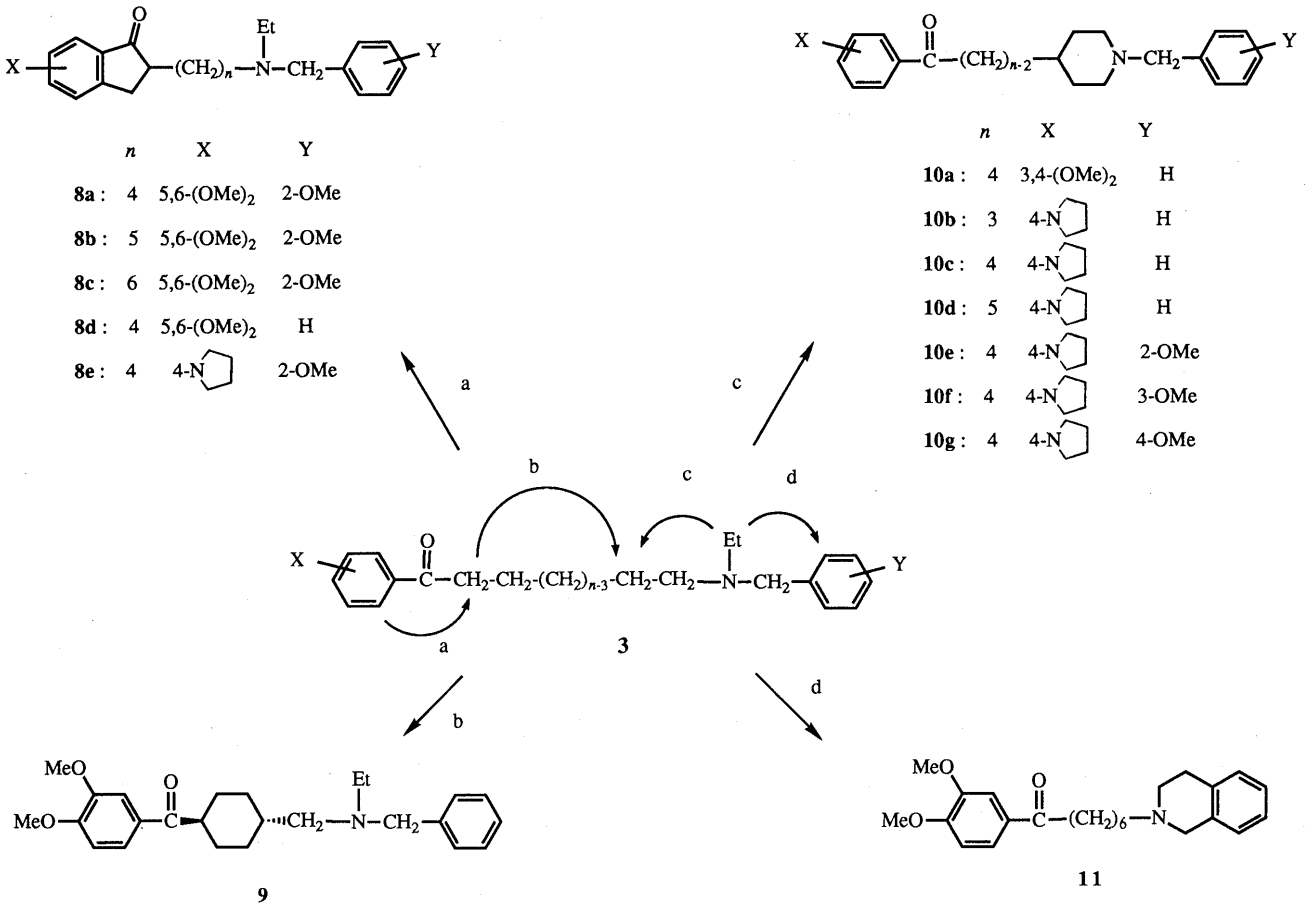


Chart 2

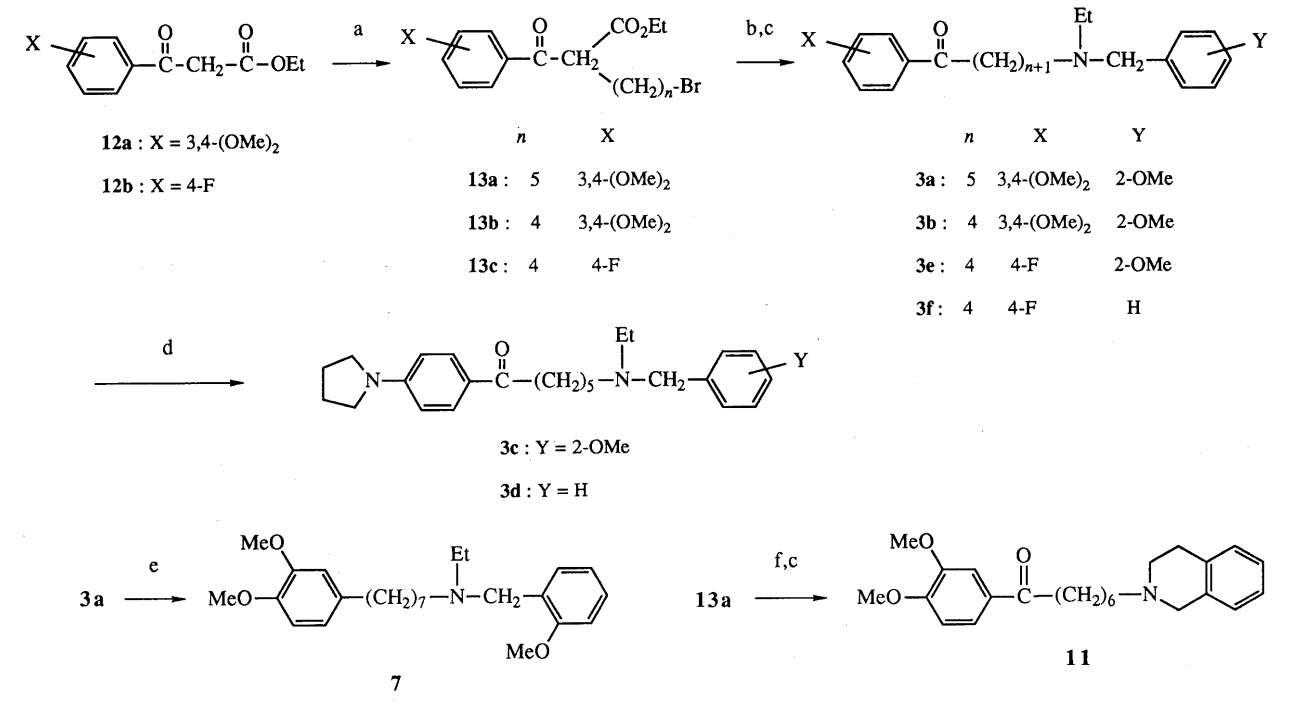
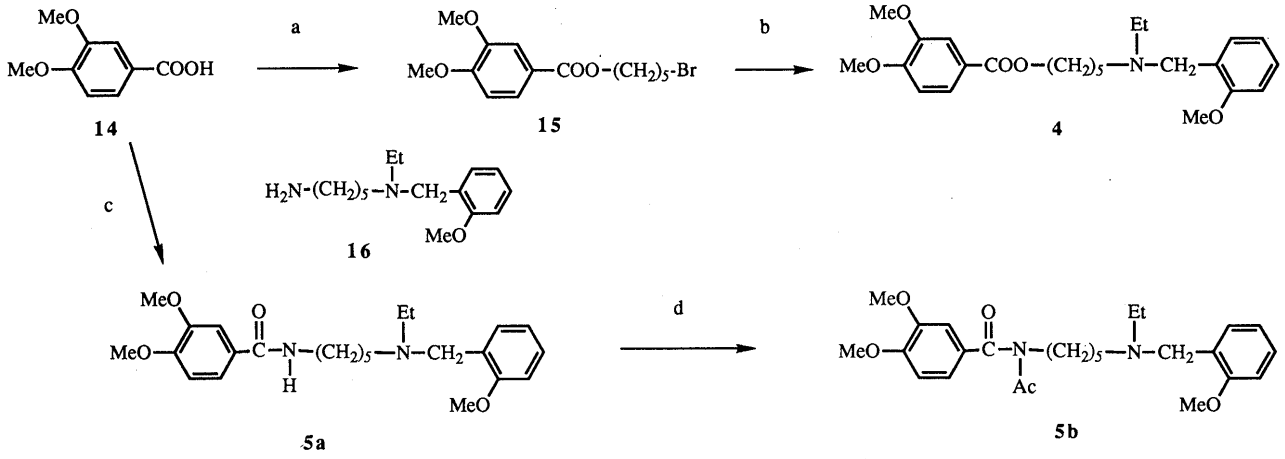
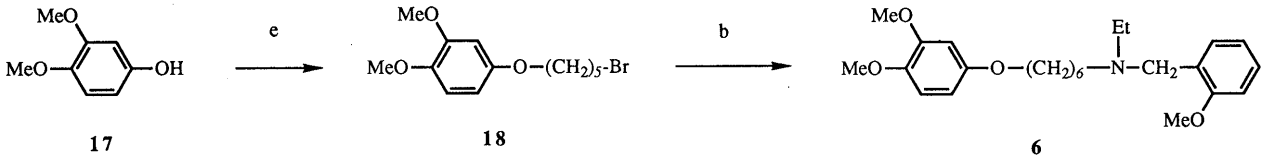


Chart 3





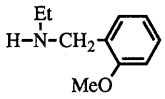
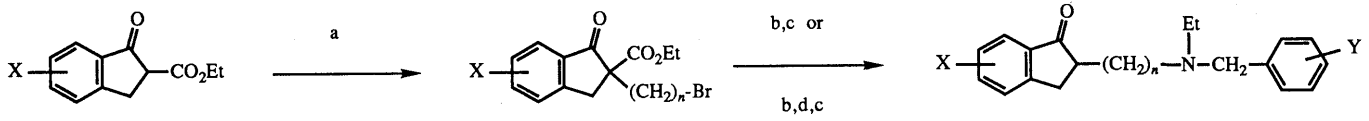
a : Br-$(CH_2)_5$-Br / K_2CO_3 b :  , K_2CO_3 c : **16**, diethylphosphoro cyanidate d: Ac_2O, *p*-toluenesulfonic acid e : 1) NaH, 2) Br-$(CH_2)_5$-Br

Chart 4

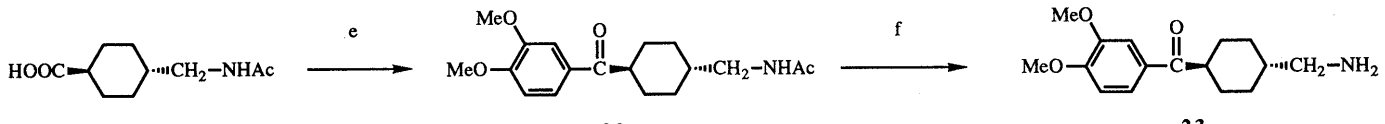


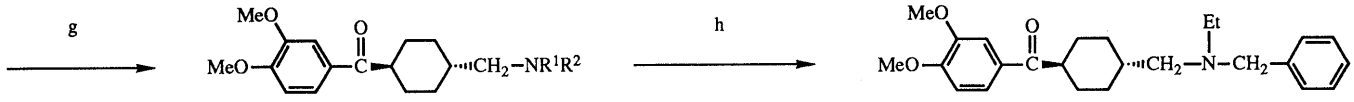
19a : X = 5,6-$(OMe)_2$

19b : X = 5-F

	n	X
20a :	4	5,6-$(OMe)_2$
20b :	5	5,6-$(OMe)_2$
20c :	4	5-F

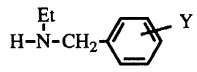
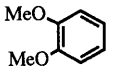
	n	X	Y
8a :	4	5,6-$(OMe)_2$	2-OMe
8b :	5	5,6-$(OMe)_2$	2-OMe
8c :	6	5,6-$(OMe)_2$	2-OMe
8d :	4	5,6-$(OMe)_2$	H
8e :	4	5-N 	2-OMe





24a : NR^1R^2 = $NHCH_2Ph$

24b : NR^1R^2 = $N(CH_2Ph)_2$

a : 1) NaH, 2) Br-$(CH_2)_n$-Br b :  c : KOH / H_2O-MeOH d: pyrrolidine e :  , $AlCl_3$ f : conc.HCl g : $PhCH_2Br$, K_2CO_3 h : EtI, K_2CO_3

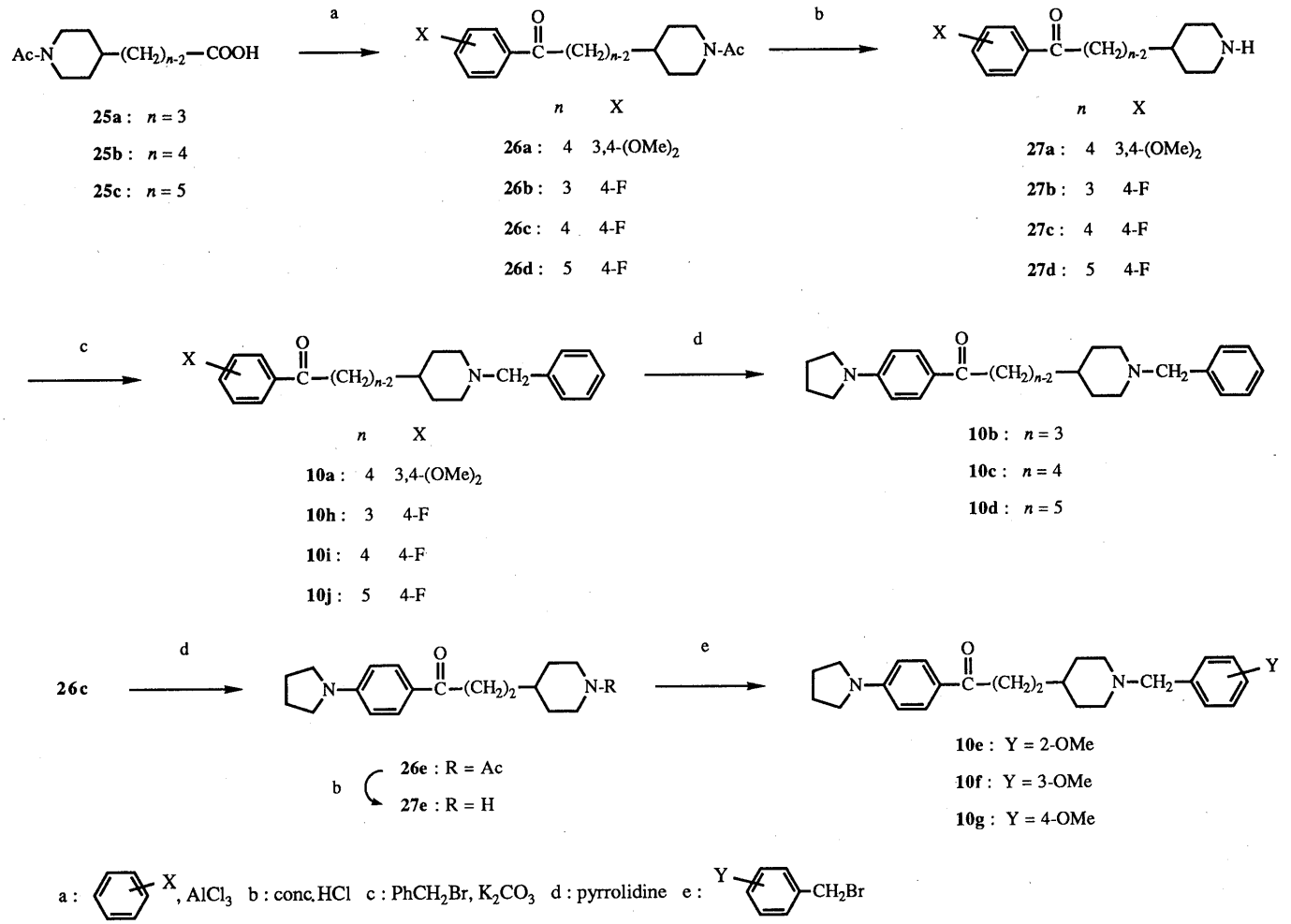


Chart 6

studied.

Synthesis Preparation of compounds **3**, **7** and **11** are outlined in Chart 3. Successive treatment of ethyl benzoylacetates (**12**) with sodium hydride followed by 2 eq of 1,ω-dibromoalkanes afforded the bromides (**13**). The bromides were allowed to react with benzylamines to give ω-[*N*-ethyl-*N*-(phenylmethyl)amino]-1-phenyl-1-alkanones (**3a, b, e, f**) after hydrolysis and subsequent decarboxylation. Similarly, the tetrahydroisoquinoline derivative (**11**) was prepared from **13a** using 1,2,3,4-tetrahydroisoquinoline as an amine. Substitution of the fluorine atom of **3e** and **3f** with pyrrolidine gave **3c** and **3d**, respectively. A $LiAlH_4$–$AlCl_3$ reduction of **3a** yielded the 7-phenylheptylamine (**7**).

Chart 4 illustrates the preparation of compounds **4**—**6**. The benzoic acid (**14**) was converted to the ω-bromoalkyl ester (**15**) by treatment with 1,ω-dibromoalkanes in the presence of K_2CO_3. The ω-bromoalkyl phenyl ether (**18**) was obtained in the same manner as described for **13**. Treatment of these bromides (**15**, **18**) with benzylamines gave the desired compounds (**4** and **6**). Condensation of benzoic acid (**14**) with *N*-ethyl-*N*-[(2-methoxyphenyl)-methyl]pentane-1,5-diamine (**16**)[1a] afforded the amide (**5a**), which was acylated to give the *N*-acetylamide (**5b**).

The indanone derivatives (**8**) were prepared from ethyl 1-indanone-2-carboxylate (**19**)[9] in the same manner as described for **3** (Chart 5). The cyclohexyl phenyl ketone derivative (**9**) was obtained by successive alkylation of the amine (**23**) with benzylbromide and ethylbromide. Preparation of **23** was done by hydrolysis of the amide (**22**), which in turn was prepared by the Friedel–Crafts reaction of 1,2-dimethoxybenzene with an acid chloride derived from *N*-acetyltranexamic acid (**21**).[10]

The Friedel–Crafts acylation of substituted benzenes with acid chlorides, prepared from the corresponding acids (**25**), gave *N*-acetylpiperidines (**26a**—**d**), which led to piperidine derivatives (**10a, h**—**j**) on hydrolysis and subsequent benzylation (Chart 6). The compounds (**10b**—**d**) were obtained by substitution of fluorine atom of **10h**—**j** with pyrrolidine. Similarly, treatment of **26c** with pyrrolidine gave **26e**, which led to **10e**—**g** on hydrolysis followed by reaction with (methoxyphenyl)methylbromides.

Biological Results and Discussion

The measurement of AChE inhibitory activity was carried out radiometrically according to the method described in the previous paper.[1a] The inhibitory activities of known compounds, physostigmine and tetrahydroaminoacridine (THA), were also measured: IC_{50} = 220 nM (physostigmine), 300 nM (THA).

Effect on AChE inhibition of variation of the linkage (A) was first examined and the results were shown in Table I. Inhibitory activity decreased in the order $-COCH_2-$ (**3a**) > $-COO-$ (**4**) > $-CONAc-$ (**5b**) > $-OCH_2-$ (**6**) >

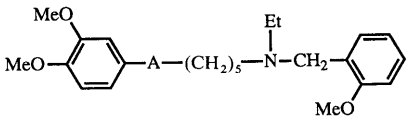
CH_2CH_2– (**7**) > –CONH– (**5a**). The keto carbonyl group exhibited the most potent inhibitory activity, which was 28 times greater than that shown by the imide carbonyl group (**3a** *vs.* **5b**). Because of the effectiveness of the keto carbonyl group at enhancing the potency, we chose ω-[*N*-ethyl-*N*-(phenylmethyl)amino]-1-phenyl-1-alkanones (**3**) as key compounds.[11]

Subsequently, we examined the effect of the ring closures shown by arrows a—d on AChE inhibition (Chart 2) and the results were shown in Table II. In general, the ring closures indicated by arrows a and c retained potency, whereas ring closures b and d resulted in a decrease in the activity. Thus, the indanone (**8a, b, d, e**) as well as the piperidine derivatives (**10a, c**) were equipotent with the key compounds (**3a—c**). The cyclohexyl phenyl ketone (**9**) and tetrahydroisoquinoline derivative (**11**) were very weak inhibitors of AChE, suggesting that they could not adopt a suitable conformation for interaction with the enzyme due to unfavorable ring closure. There is room for further investigation to obtain a clear explanation.

Closer examination of the structure–activity relationships of compounds **3**, **8** and **10** revealed that there were two differences between them. The first was the effects of substituents (Y): 2-methoxy substitution on both **3** and **8** enhanced the potency (**3c** *vs.* **3d**, **8a** *vs.* **8d**), whereas the activity of **10e** (Y = 2-OMe) was lower than that of **10c** (Y = H). The potency was also decreased by 3- or 4-methoxy substitution (**10f, g** *vs.* **10c**). The second is the effects of chain length (*n*). It was shown that **10c** (*n* = 4) was a more potent inhibitor than **10b** (*n* = 3) or **10d** (*n* = 5), however, **3a** and **8b** (*n* = 5) were more potent than **3b** and **8a** (*n* = 4), respectively. These results may suggest that the conformation which the piperidine derivatives (**10**) take for better interaction with the active site is slightly different from that taken by compounds bearing an *N*-ethylbenzylamino moiety (**3** and **8**).

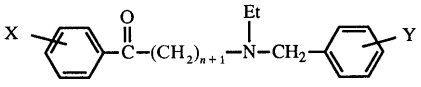
For AChE inhibitors to be possible therapeutic agents for SDAT, central selectivity might be required in addition to potent enzyme inhibition. In other words, AChE

TABLE I. Acetylcholinesterase Inhibitory Activities of Compounds (**3a**, **4**—**7**)



Compound	A	Inhibition of AChE (IC_{50}, nM)
3a	$COCH_2$	10.0
4	COO	190
5a	CONH	1490
5b	CONAc	280
6	OCH_2	920
7	CH_2CH_2	1070

TABLE II. Biological Activities of ω-[*N*-Ethyl-*N*-(phenylmethyl)amino]-1-phenyl-1-alkanones (**3**) and Their Analogues (**8**—**11**)[a]



3

Compound	*n*	X	Y	Inhibition of AChE (IC_{50}, nM)	Peripheral action[b] (MD,[c] mg/kg)	T-Maze alternation task[d] (MED,[e] mg/kg)
3a	5	3,4-$(OMe)_2$	2-OMe	10.0	50 (FAS)	>50
3b	4	3,4-$(OMe)_2$	2-OMe	24.3	50 (FAS)	>50
3c	4	4-N⟨ ⟩	2-OMe	50.0	50 (FAS)	>50
3d	4	4-N⟨ ⟩	H	305	NT[f]	NT[f]
8a	4	3,4-$(OMe)_2$	2-OMe	20.0	20 (FAS)	20
8b	5	3,4-$(OMe)_2$	2-OMe	6.01	20 (FAS)	>20
8c	6	3,4-$(OMe)_2$	2-OMe	100	NT[f]	NT[f]
8d	4	3,4-$(OMe)_2$	H	76.2	50 (FAS)	>50
8e	4	4-N⟨ ⟩	2-OMe	81.0	50 (FAS)	>50
9	—	—	—	38300	NT[f]	NT[f]
10a	4	3,4-$(OMe)_2$	H	52.0	20 (SAL)	10
10b	3	4-N⟨ ⟩	H	19000	NT[f]	NT[f]
10c	4	4-N⟨ ⟩	H	28.1	10 (FAS)	3
10d	5	4-N⟨ ⟩	H	220	NT[f]	NT[f]
10e	4	4-N⟨ ⟩	2-OMe	1900	NT[f]	NT[f]
10f	4	4-N⟨ ⟩	3-OMe	5320	NT[f]	NT[f]
10g	4	4-N⟨ ⟩	4-OMe	30200	NT[f]	NT[f]
11	—	—	—	18100	NT[f]	NT[f]
THA	—	—	—	300	30 (FAS)	10

a) See Chart 2 for the structure. *b*) FAS = fasciculation; SAL = salivation. *c*) MD = minimum dose (*p.o.*). *d*) Ameliorating effect on scopolamine-induced memory impairment by T-maze alternation task. *e*) MED = minimum effective dose (*p.o.*). *f*) NT = not tested.

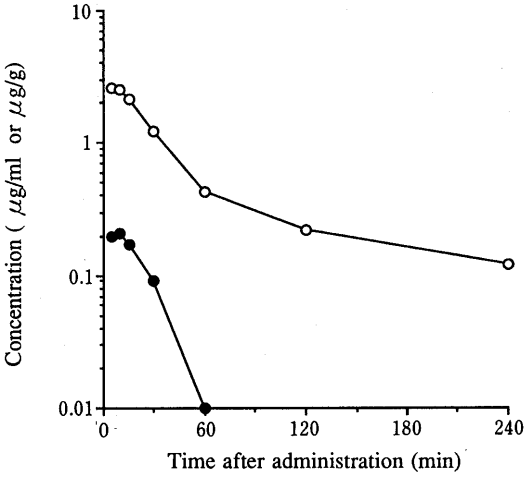


Fig. 1. Brain (○) and Plasma (●) Concentration of **10c** after Intravenous Administration to Rats at a Dose of 2 mg/kg

TABLE III. Concentration of **10c** in Brain and Plasma after Intravenous Administration to Rats at a Dose of 2 mg/kg

Time (min)	Concentration, means ± S.E.M., $n=3$		Brain/plasma ratio
	Brain (μg/g)	Plasma (μg/ml)	
5	2.56 ± 0.46	0.20 ± 0.01	12.8
10	2.54 ± 0.29	0.21 ± 0.02	12.1
15	2.11 ± 0.13	0.17 ± 0.01	12.4
30	1.23 ± 0.06	0.09 ± 0.01	13.7
60	0.43 ± 0.07	0.01 ± 0.01	43.0
120	0.22 ± 0.05	—[a]	—
240	0.12 ± 0.01	—[a]	—

a) Below the detection limit.

inhibitors might be expected to act selectively on the central nervous system, thus exerting ameliorating effects on cholinergic deficits without showing excessive peripheral effects. An estimate of central selectivity can be obtained from the ratio of central to peripheral action: minimum dose (peripheral action)/minimum effective dose (ameliorating effect on memory impairment). Therefore, compounds which showed potent AChE inhibition ($IC_{50} < 100$ nM) were first examined for their effects on peripheral behavioral changes such as salivation, lacrimation, diarrhea, and fasciculation (Table II). Most compounds (**3a—c**, **8a**, **b**, **d**, **e**, **10c** and THA) were found to show fasciculation at the minimum doses. Only treatment with **10a** induced salivation. Compounds were subsequently evaluated, at doses less than these minimum doses causing peripheral action, for their ameliorating effects on scopolamine-induced memory impairment by T-maze alternation task.[12] The piperidine (**10a**, **c**) and indanone derivatives (**8a**) as well as THA ameliorated memory impairment at doses ranging from 3 to 20 mg/kg (*p.o.*), whereas none of **3a—c** exhibited improvement at doses up to 50 mg/kg (*p.o.*). In terms of central selectivity, the compounds with partial conformational restriction (**8a** and **10a, c**) seem to have more preferable properties than the acyclic key compounds (**3**), though they all exhibited equipotent AChE inhibition. Especially **10c** showed the best ratio for central selectivity, which was better than THA: the actual ratios were calculated to be 3.3 (**10c**); 3.0 (THA); 2.0 (**10a**); 1.0 (**8a**); < 1.0 (**3a—c**, **8b**, **d**, **e**). The determination of the brain and plasma levels of **10c** may also suggest its good central selectivity. Table III and Fig. 1 show that **10c** exhibited rapid distribution to the brain, with brain concentrations exceeding plasma levels by 12 to 14-fold. This value seems to be comparable to, or slightly better than, that of THA.[13]

In summary, this study has arrived at the following conclusions: (1) it was revealed that the keto carbonyl group was more effective for potent inhibition than other groups and ω-[*N*-ethyl-*N*-(phenylmethyl)amino]-1-phenyl-1-alkanones (**3**) were potent AChE inhibitors; (2) the analogues with partial conformational restriction, such as the indanone (**8**) and piperidine (**10**) derivatives, retained the strong AChE inhibition of the acyclic compounds (**3**); (3) among the potent inhibitors (**3**, **8**, and **10**), the piperidine derivative (**10c**) displayed the most preferable central selectivity; and (4) **10c** also exhibited a 12 to 14-fold higher level in brain than in plasma.

The above results, especially about the effect of partial conformational restriction on central selectivity, might be informative for searching for AChE inhibitors as possible therapeutic agents for SDAT.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi 260-10 spectrophotometer in a KBr disk for solids and liquid films for oils. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian GEMINI-200 (200 MHz) NMR spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

7-[*N*-Ethyl-*N*-[(2-methoxyphenyl)methyl]amino]-1-(3,4-dimethoxyphenyl)-1-heptanone Hydrochloride (3a) A mixture of ethyl 3,4-dimethoxy-β-oxobenzenepropionate (**12a**, 1.10 g, 4.36 mmol) and NaH (0.13 g, oil free, 5.42 mmol) in *N*,*N*-dimethylformamide (DMF, 10 ml) was stirred at room temperature for 30 min then 1,5-dibromopentane (1.80 g, 7.83 mmol) was added. The resulting mixture was stirred at room temperature for 16 h, poured into water, and extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, and the solvent and excess 1,5-dibromopentane were removed under reduced pressure to give crude ethyl α-(5-bromopentyl)-3,4-dimethoxy-β-oxobenzenepropionate (**13a**, 1.50 g, *ca.* 86%) as a pale yellow oil, which was used in the next step without further purification.

A mixture of **13a** (0.35 g, 0.87 mmol) and *N*-ethyl-*N*-[(2-methoxyphenyl)methyl]amine[14a] (0.29 g, 1.76 mmol) in toluene (15 ml) was refluxed for 12 h and the solvent was evaporated to afford a residue. A mixture of the residue and KOH (0.30 g) in ethanol–water (3 ml/0.5 ml) was refluxed for 6 h and the solvent was removed *in vacuo*. After extraction with CH_2Cl_2, the extracts were washed with water, dried over Na_2SO_4, concentrated to give an oily residue, which was chromatographed on silica gel eluting with ethyl acetate–methanol (20 : 1) to afford a colorless oil (0.27 g, 75%). IR (film): 2934, 2856, 1674, 1586 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, J = 7.1 Hz), 1.13—1.92 (8H, m), 2.32—2.67 (4H, m), 2.89 (2H, t, J = 7.0 Hz), 3.57 (2H, s), 3.78 (3H, s), 3.91 (6H, s), 6.74—7.03 (3H, m), 7.05—7.65 (4H, m).

Treatment of the oil with ethanolic HCl (1 eq) gave **3a** as an amorphous powder. *Anal.* Calcd for $C_{25}H_{35}NO_4 \cdot HCl$: C, 66.73; H, 8.06; N, 3.11. Found: C, 66.57; H, 8.08; N, 3.03.

The following compounds (**3b**, **11**) were prepared in the same manner as described for **3a**.

6-[*N*-Ethyl-*N*-[(2-methoxyphenyl)methyl]amino]-1-(3,4-dimethoxyphenyl)-1-hexanone Fumarate (**3b**): Colorless cubes, mp 111—113 °C. Yield: 68% (from **12a**). IR (film, free base): 2934, 2836, 1674, 1587 cm^{-1}. ^{1}H-NMR ($CDCl_3$, free base) δ: 1.03 (3H, t, J = 7.1 Hz), 1.18—1.90 (6H, m), 2.35—2.67 (4H, m), 2.88 (2H, t, J = 7.0 Hz), 3.57 (2H, s), 3.80 (3H, s), 3.94 (6H, s), 6.76—7.03 (3H, m), 7.07—7.67 (4H, m). *Anal.* Calcd for $C_{24}H_{33}NO_4 \cdot C_4H_4O_4$: C, 65.23; H, 7.23; N, 2.72. Found: C, 65.12; H, 7.33; N, 2.68.

1-(3,4-Dimethoxyphenyl)-6-(1,2,3,4-tetrahydroisoquinolin-2-yl)-1-heptanone Fumarate (**11**): Colorless cubes, mp 134—135 °C. Yield: 52% (from **12a**). IR (film, free base): 2932, 2854, 1733, 1674, 1587 cm^{-1}. ^{1}H-NMR ($CDCl_3$, free base) δ: 1.36—1.83 (8H, m), 2.50 (2H, t, J=7.4 Hz), 2.72 (2H, t, J=5.9 Hz), 2.83—2.97 (4H, m), 3.62 (2H, s), 3.94 (6H, s), 6.88 (1H, d, J=8.3 Hz), 6.96—7.14 (4H, m), 7.54 (1H, d, J=1.6 Hz), 7.59 (1H, dd, J=1.6, 8.3 Hz). *Anal.* Calcd for $C_{24}H_{31}NO_3 \cdot C_4H_4O_4$: C, 67.59; H, 7.09; N, 2.81. Found: C, 67.30; H, 7.24; N, 2.81.

6-[*N*-Ethyl-*N*-[(2-methoxyphenyl)methyl]amino]-1-[4-(pyrrolidin-1-yl)-phenyl]-1-hexanone Fumarate (3c) In the same manner as described for **3a**, crude 6-[*N*-ethyl-*N*-[(2-methoxyphenyl)methyl]amino]-1-(4-fluorophenyl)-1-hexanone (**3e**) was prepared from ethyl 4-fluoro-β-oxobenzenepropionate (**12b**) as a pale yellow oil in 78% yield. Crude **3e** was employed in the next step without further purification.

A mixture of **3e** (0.22 g, 0.62 mmol) and pyrrolidine (2 ml, 24.0 mmol) in a sealed tube was heated at 100 °C for 4 h. After removal of excess pyrrolidine *in vacuo* the residue was chromatographed on silica gel eluting with ethyl acetate to afford a colorless oil (0.17 g, 67%). IR (film): 2934, 2854, 1661, 1599 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.1 Hz), 1.30—1.83 (6H, m), 1.98—2.13 (4H, m), 2.40—2.60 (4H, m), 2.85 (2H, t, J=7.4 Hz), 3.30—3.43 (4H, m), 3.59 (2H, s), 3.81 (3H, s), 6.51 (2H, d, J=9.0 Hz), 6.80—6.97 (2H, m), 7.21 (1H, ddd, J=1.7, 7.4, 7.9 Hz), 7.41 (1H, dd, J=1.7, 7.4 Hz), 7.87 (2H, d, J=9.0 Hz).

The oil was treated with fumaric acid (1 eq) to give colorless cubes (0.20 g, 62% from **3e**), mp 139—140 °C. *Anal.* Calcd for $C_{26}H_{36}N_2O_2 \cdot C_4H_4O_4$: C, 68.68; H, 7.68; N, 5.34. Found: C, 68.49; H, 7.73; N, 5.21.

6-[*N*-Ethyl-*N*-(phenylmethyl)amino]-1-[4-(pyrrolidin-1-yl)phenyl]-1-hexanone Fumarate (3d) Compound **3d** was prepared from **12b** in the same manner as described for **3c** in 72% yield. Colorless cubes, mp 100—102 °C. IR (film, free base): 2930, 1686, 1596 cm^{-1}. ^{1}H-NMR ($CDCl_3$, free base) δ: 1.02 (3H, t, J=7.1 Hz), 1.20—1.78 (6H, m), 1.97—2.08 (4H, m), 2.37—2.56 (4H, m), 2.84 (2H, t, J=7.4 Hz), 3.30—3.42 (4H, m), 3.55 (2H, s), 6.51 (2H, d, J=9.0 Hz), 7.27—7.35 (5H, m), 7.86 (2H, d, J=9.0 Hz). *Anal.* Calcd for $C_{25}H_{34}N_2O \cdot C_4H_4O_4$: C, 70.42; H, 7.74; N, 5.66. Found: C, 70.38; H, 7.69; N, 5.61.

5-[*N*-Ethyl-*N*-[(2-methoxyphenyl)methyl]amino]pentyl 3,4-Dimethoxybenzoate (4) A mixture of 3,4-dimethoxybenzoic acid (**14**, 1.82 g, 10.0 mmol), 1,5-dibromopentane (6.90 g, 30.0 mmol), and K_2CO_3 (1.52 g, 11.0 mmol) in acetone (20 ml) was refluxed for 16 h, cooled to room temperature, and the precipitate was removed by filtration. The filtrate was concentrated and chromatographed on silica gel eluting with CH_2Cl_2 to afford 5-bromopentyl 3,4-dimethoxybenzoate (**15**, 3.05 g, 92%) as a colorless oil. IR (film): 2938, 1710, 1600, 1514 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.37—2.12 (6H, m), 3.42 (2H, t, J=6.0 Hz), 3.94 (6H, s), 4.31 (2H, t, J=6.0 Hz), 6.88 (1H, d, J=8.0 Hz), 7.54 (1H, s), 7.67 (1H, d, J=8.0 Hz).

The bromide (**15**) was allowed to react with *N*-ethyl-*N*-[(2-methoxyphenyl)methyl]amine in the same manner as described for **3a** to give **4** as a colorless oil in 65% yield. IR (film): 2936, 2836, 1710, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.1 Hz), 1.27—1.95 (6H, m), 2.36—2.70 (4H, m), 3.59 (2H, s), 3.80 (3H, s), 3.92 (6H, s), 4.29 (2H, t, J=7.0 Hz), 6.74—7.03 (3H, m), 7.07—7.77 (4H, m).

***N*-[5-[*N*-Ethyl-*N*-[(2-methoxyphenyl)methyl]amino]pentyl]-3,4-dimethoxybenzamide Hydrochloride (5a)** Diethyl phosphorocyanidate (0.70 g, 4.29 mmol) was added to a solution of 3,4-dimethoxybenzoic acid (**14**, 0.60 g, 3.29 mmol), *N*-ethyl-*N*-(2-methoxyphenyl)methyl-1,5-pentanediamine[1a] (**16**, 0.84 g, 3.35 mmol), and Et_3N (0.60 ml, 4.30 mmol) in DMF (6 ml) at 0—5 °C. The mixture was stirred at 0—5 °C for 20 min, warmed to room temperature, poured into water, and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4, and the solvent was removed *in vacuo* to afford a residue. Chromatographic purification of the residue on silica gel eluting with ethyl acetate–methanol (10 : 1) gave an oil (1.34 g). IR (film): 3314, 2936, 1632, 1583 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, J=7.1 Hz), 1.20—1.80 (6H, m), 2.35—2.70 (4H, m), 3.40 (2H, dt, J=6.0, 6.0 Hz), 3.58 (2H, s), 3.78 (3H, s), 3.89 (6H, s), 6.23 (1H, br t, J=6.0 Hz), 6.73—7.01 (3H, m), 7.07—7.50 (4H, m).

The oil was treated with ethanolic HCl (1 eq) to afford **5a** as a hygroscopic powder (1.30 g, 88%). *Anal.* Calcd for $C_{24}H_{34}N_2O_4 \cdot HCl$: C, 63.92; H, 7.82; N, 6.21. Found: C, 63.79; H, 7.96; N, 6.14.

***N*-Acetyl-*N*-[5-[*N*-ethyl-*N*-[(2-methoxyphenyl)methyl]amino]pentyl]-3,4-dimethoxybenzamide (5b)** A mixture of **5a** (0.90 g, 2.17 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) in acetic anhydride (10 ml, 106 mmol) was heated at 80 °C for 6 h and then cooled to room temperature. The mixture was diluted with water, made basic with 10% NaOH, and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4, and the solvent was removed *in vacuo* to give a residue which was chromatographed on silica gel eluting with ethyl acetate–methanol (20 : 1) to afford an oil (0.69 g, 70%). IR (film): 2936, 2838, 1692, 1655, 1597 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.80 (9H, m), 2.07 (3H, s), 2.43—2.81 (4H, m), 3.63—3.87 (7H, m), 3.91 (3H, s), 3.93 (3H, s), 6.78—7.06 (3H, m), 7.13—7.50 (4H, m).

***N*-Ethyl-6-(3,4-dimethoxyphenoxy)-*N*-[(2-methoxyphenyl)methyl]-1-hexylamine (6)** 3,4-Dimethoxyphenol (**17**) was treated successively with NaH and 1,6-dibromohexane in the same manner as described for **3a** to give crude 6-bromo-1-(3,4-dimethoxyphenoxy)hexane (**18**) as a pale yellow oil in 63% yield which was used in the next step without further purification.

Reaction of **18** with *N*-ethyl-*N*-[(2-methoxyphenyl)methyl]amine was done as described for **3a** to afford **6** as a colorless oil in 65% yield. IR (film): 2934, 2858, 1597, 1511 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, J=7.1 Hz), 1.16—1.95 (8H, m), 2.25—2.70 (4H, m), 3.57 (2H, s), 3.75—4.02 (11H, m), 6.26—6.56 (2H, m), 6.67—7.03 (3H, m), 7.06—7.51 (2H, m).

***N*-Ethyl-7-(3,4-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]-1-heptylamine (7)** A suspension of granular aluminum chloride (0.19 g, 1.42 mmol) in ether (2 ml) was added to a solution of $LiAlH_4$ (55 mg, 1.45 mmol) in ether (2 ml). The mixture was stirred at room temperature for 5 min. A solution of **3a** (0.30 g, 0.73 mmol) in ether (2 ml) was added dropwise to the mixture. The resulting mixture was refluxed for 1 h, poured into ice-water, and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4, and the solvent was evaporated to give a residue. Chromatographic purification of the residue on silica gel eluting with ethyl acetate–methanol (10 : 1) afforded **7** (0.26 g, 90%) as a colorless oil. IR (film): 3382, 2930, 2856, 1603, 1590, 1514, 1498 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.1 Hz), 1.16—1.72 (10H, m), 2.37—2.60 (6H, m), 3.59 (2H, s), 3.82 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 6.68—6.98 (5H, m), 7.22 (1H, t, J=8.0 Hz), 7.42 (1H, d, J=8.0 Hz).

Preparation of the Indanone Derivatives (8) Compounds **8a—d** were prepared from ethyl 5,6-dimethoxy-1-indanone-2-carboxylate (**19a**)[6] in the same manner as described for **3a**.

2-[4-[*N*-Ethyl-*N*-[(2-methoxyphenyl)methyl]amino]butyl]-5,6-dimethoxy-1-indanone Hydrochloride (**8a**): Hygroscopic powder. Yield: 77%. IR (film, free base): 2934, 2834, 1697, 1591 cm^{-1}. ^{1}H-NMR ($CDCl_3$, free base) δ: 1.03 (3H, t, J=7.1 Hz), 1.23—2.10 (6H, m), 2.32—2.84 (6H, m), 3.20 (1H, dd, J=8.3, 17.4 Hz), 3.57 (2H, s), 3.80 (2H, s), 3.90 (3H, s), 3.95 (3H, s), 6.72—7.00 (3H, m), 7.06—7.47 (3H, m). *Anal.* Calcd for $C_{25}H_{33}NO_4 \cdot HCl$: C, 67.03; H, 7.65; N, 3.13. Found: C, 66.89; H, 7.71; N, 3.09.

2-[5-[*N*-Ethyl-*N*-[(2-methoxyphenyl)methyl]amino]pentyl]-5,6-dimethoxy-1-indanone Hydrochloride (**8b**): Hygroscopic powder. Yield: 74%. IR (film, free base): 2932, 2854, 1698, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$, free base) δ: 1.03 (3H, t, J=7.1 Hz), 1.16—2.10 (8H, m), 2.27—2.80 (6H, m), 3.20 (1H, dd, J=8.3, 17.4 Hz), 3.56 (2H, s), 3.81 (3H, s), 3.90 (3H, s), 3.96 (3H, s), 6.71—7.03 (3H, m), 7.06—7.50 (3H, m). *Anal.* Calcd for $C_{26}H_{35}NO_4 \cdot HCl$: C, 67.59; H, 7.85; N, 3.03. Found: C, 67.44; H, 7.92; N, 2.98.

2-[6-[*N*-Ethyl-*N*-[(2-methoxyphenyl)methyl]amino]hexyl]-5,6-dimethoxy-1-indanone Hydrochloride (**8c**): Hygroscopic powder. Yield: 61%. IR (film, free base): 2930, 2854, 1697, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$, free base) δ: 1.03 (3H, t, J=7.1 Hz), 1.13—2.03 (10H, m), 2.30—2.83 (6H, m), 3.21 (1H, dd, J=8.3, 17.4 Hz), 3.57 (2H, s), 3.83 (3H, s), 3.92 (3H, s), 3.97 (3H, s), 6.75—7.03 (3H, m), 7.06—7.52 (3H, m). *Anal.* Calcd for $C_{27}H_{37}NO_4 \cdot HCl$: C, 68.12; H, 8.05; N, 2.94. Found: C, 68.06; H, 8.23; N, 2.85.

2-[4-[*N*-Ethyl-*N*-(phenylmethyl)amino]butyl]-5,6-dimethoxy-1-indanone Hydrochloride (**8d**): Hygroscopic powder. Yield: 77%. IR (film, free base): 2932, 1696, 1591 cm^{-1}. ^{1}H-NMR ($CDCl_3$, free base) δ: 1.00 (3H, t, J=7.1 Hz), 1.22—2.06 (6H, m), 2.30—2.82 (6H, m), 3.20 (1H, dd, J=8.0, 17.0 Hz), 3.52 (2H, s), 3.87 (3H, s), 3.93 (3H, s), 6.93 (1H, s), 7.14 (1H, s), 7.26 (5H, s). *Anal.* Calcd for $C_{24}H_{31}NO_3 \cdot HCl$: C, 68.97; H, 7.72; N, 3.35. Found: C, 68.76; H, 7.84; N, 3.09.

In the same manner as described for **3c**, 2-[4-[*N*-ethyl-*N*-[(2-methoxyphenyl)methyl]amino]butyl]-5-(pyrrolidin-4-yl)-1-indanone fumarate (**8e**) was prepared from ethyl 5-fluoro-1-indanone-2-carboxylate (**19b**), which in turn was obtained by the method described in the literature.[6]

8e: Colorless powder. Yield: 60% (from **19b**). IR (film, free base): 2932, 2848, 1686, 1596 cm^{-1}. ^{1}H-NMR ($CDCl_3$, free base) δ: 1.04 (3H, t, J=7.1 Hz), 1.28—1.65 (5H, m), 1.80—2.14 (5H, m), 2.40—2.73 (6H, m), 3.17 (1H, dd, J=8.3, 17.1 Hz), 3.30—3.45 (4H, m), 3.57 (2H, s), 3.80 (3H, s), 6.40 (1H, d, J=1.7 Hz), 6.52 (1H, dd, J=2.1, 8.6 Hz), 6.78—6.96 (2H, m), 7.19 (1H, ddd, J=1.7, 7.4, 8.0 Hz), 7.39 (1H, dd, J=1.7, 7.4 Hz), 7.60 (1H, d, J=8.6 Hz). *Anal.* Calcd for $C_{27}H_{36}N_2O_2 \cdot C_4H_4O_4$: C, 69.38; H,

7.51; N, 5.22. Found: C, 69.23; H, 7.67; N, 5.34.

19b: Pale yellow oil. Yield: 91%. IR (film): 2982, 1736, 1713 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.1 Hz), 3.35 (1H, dd, J=8.3, 17.4 Hz), 3.57 (1H, dd, J=4.0, 17.4 Hz), 3.74 (1H, dd, J=4.0, 8.3 Hz), 4.25 (2H, q, J=7.1 Hz), 7.04—7.22 (2H, m), 7.78 (1H, dd, J=5.0, 8.7 Hz).

Preparation of the Cyclohexyl Phenyl Ketone Derivative (9). *trans*-[4-(Acetylaminomethyl)cyclohexyl] 3,4-Dimethoxyphenyl Ketone (22) *trans*-4-(Acetylaminomethyl)cyclohexanecarboxylic acid[9] (**21**, 10.00 g, 50.2 mmol) was added portionwise to $SOCl_2$ (18.2 ml, 250 mmol) at 0—5 °C. After stirring for 10 min, excess $SOCl_2$ was evaporated to give a pale yellow powder which was washed with hexane and used in the next step without further purification.

Aluminum chloride (16.00 g, 120.0 mmol) was added portionwise to a mixture of the powder and 1,2-dimethoxybenzene (7.60 g, 55.0 mmol) in 1,2-dichloroethane (50 ml) at room temperature. The mixture was stirred at room temperature for 2 h, poured into ice-water, and extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, passed through a plug of silica gel, and the solvent was removed *in vacuo* to give colorless crystals. Recrystallization from CH_2Cl_2–ether afforded colorless scales (12.50 g, 78% from **21**), mp 149—151 °C. IR (KBr): 3446, 3328, 2924, 2852, 1666, 1649, 1594, 1584 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.01—1.28 (2H, m), 1.42—1.66 (3H, m), 1.83—2.03 (4H, m), 2.01 (3H, s), 3.13—3.30 (3H, m), 3.94 (3H, s), 3.96 (3H, s), 5.52 (1H, br), 6.90 (1H, d, J=8.3 Hz), 7.53 (1H, d, J=1.9 Hz), 7.58 (1H, dd, J=1.9, 8.3 Hz). *Anal.* Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.40; H, 7.28; N, 4.58.

***trans*-[4-(Aminomethyl)cyclohexyl] 3,4-Dimethoxyphenyl Ketone (23)** A mixture of **22** (10.00 g, 31.3 mmol) and concentrated HCl (50 ml) was refluxed for 16 h and concentrated to give a residue. The residue was dissolved in water, washed twice with ethyl acetate, made basic with 10% NaOH, and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a pale brown oil (8.30 g, 96%), which was used in the next step without further purification. IR (film): 3372, 2930, 2854, 1663, 1584 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97—1.22 (2H, m), 1.27—1.67 (3H, m), 1.77—2.03 (6H, m), 2.60 (2H, d, J=5.9 Hz), 3.13—3.29 (1H, m), 3.94 (3H, s), 3.95 (3H, s), 6.89 (1H, d, J=8.3 Hz), 7.53 (1H, d, J=1.9 Hz), 7.58 (1H, dd, J=1.9, 8.3 Hz).

***trans*-(3,4-Dimethoxyphenyl) 4-[*N*-(Phenylmethyl)aminomethyl]cyclohexyl Ketone (24a) and *trans*-(3,4-Dimethoxyphenyl) 4-[*N*,*N*-Di(phenylmethyl)aminomethyl]cyclohexyl Ketone Hydrochloride (24b)** A solution of benzylbromide (1.20 g, 7.02 mmol) in ethanol (5 ml) was added dropwise to a mixture of **23** (2.00 g, 7.21 mmol) and K_2CO_3 (1.30 g, 9.41 mmol) in ethanol (30 ml) at 0—5 °C. The mixture was stirred at 0—5 °C for 2 h, and then at room temperature for 16 h. The solvent was removed *in vacuo* to afford a residue, which was chromatographed on silica gel eluting with ethyl acetate–methanol (20 : 1) to give **24a** (0.90 g, 34%) as colorless cubes and **24b** (free base, 1.00 g, 30%) as an oil which was treated with methanolic HCl (1 eq) to afford the hydrochloride.

24a: Colorless cubes, mp 90—93 °C. IR (KBr): 2930, 2846, 1667, 1594 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98—1.27 (2H, m), 1.45—1.71 (5H, m), 1.86—2.03 (3H, m), 2.53 (2H, d, J=6.5 Hz), 3.21 (1H, tt, J=3.2, 12.1 Hz), 3.80 (2H, s), 3.94 (3H, s), 3.95 (3H, s), 6.89 (1H, d, J=8.3 Hz), 7.22—7.38 (5H, m), 7.53 (1H, d, J=1.9 Hz), 7.58 (1H, dd, J=1.9, 8.3 Hz). *Anal.* Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.02; H, 7.94; N, 3.67.

24b: Colorless cubes, mp 179—183 °C. IR (KBr): 3432, 2932, 2844, 1730, 1661, 1593 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.72—0.96 (2H, m), 1.15—1.40 (2H, m), 1.53—1.86 (5H, m), 2.74 (2H, br), 3.16—3.55 (2H, m), 3.79 (3H, s), 3.83 (3H, s), 4.18—4.33 (2H, m), 4.48—4.62 (2H, m), 7.02 (1H, d, J=8.5 Hz), 7.39 (1H, d, J=1.9 Hz), 7.45—7.55 (6H, m), 7.59 (1H, dd, J=1.9, 8.5 Hz), 7.65—7.76 (4H, m). *Anal.* Calcd for $C_{30}H_{35}NO_3 \cdot HCl$: C, 72.93; H, 7.34; N, 2.83. Found: C, 72.79; H, 7.50; N, 2.61.

***trans*-[4-[*N*-Ethyl-*N*-(phenylmethyl)aminomethyl]cyclohexyl] 3,4-Dimethoxyphenyl Ketone Fumarate (9)** A mixture of **24a** (0.88 g, 2.39 mmol), ethylbromide (0.50 g, 4.59 mmol), and K_2CO_3 (0.43 g, 3.11 mmol) in ethanol (15 ml) was heated at 55—60 °C for 20 h. The solid was removed by filtration and the solvent was evaporated to give a residue. The residue was chromatographed on silica gel eluting with ethyl acetate to give a colorless oil (0.60 g, 63%). IR (film): 2934, 2844, 2796, 1670, 1596 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83—1.08 (5H, m), 1.42—1.68 (4H, m), 1.84—2.08 (3H, m), 2.25 (2H, d, J=6.9 Hz), 2.48 (2H, q, J=7.0 Hz), 3.09—3.27 (1H, m), 3.54 (2H, s), 3.94 (3H, s), 3.95 (3H, s), 6.88 (1H, d, J=8.3 Hz), 7.19—7.40 (5H, m), 7.53 (1H, d, J=1.9 Hz), 7.70 (1H, dd, J=1.9, 8.3 Hz).

The above oil was treated with fumaric acid (1 eq) to afford **9** as a colorless amorphous powder. *Anal.* Calcd for $C_{25}H_{33}NO_3 \cdot C_4H_4O_4$: C, 68.08; H, 7.29; N, 2.74. Found: C, 67.87; H, 7.31; N, 2.58.

Preparation of the Piperidine Derivatives (10). (1-Acetylpiperidin-4-yl)acetic Acid (25a) 4-Pyridine-acetic acid hydrochloride (25.00 g, 144 mmol) in acetic acid (400 ml) was hydrogenated over PtO_2 (1.00 g) at 40—45 °C under atmospheric pressure. After removal of the catalyst by filtration, the filtrate was concentrated to give a residue. A solution of the residue in acetic anhydride (200 ml) was refluxed for 1 h and concentrated to give a solid which was washed with ethanol to afford a colorless powder (23.30 g, 87%), mp 118—121 °C. IR (KBr): 3432, 2400—3200, 1707, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3+D_2O$) δ: 1.07—1.32 (2H, m), 1.73—2.18 (6H, m), 2.31 (2H, t, J=7.2 Hz), 2.58 (1H, ddd, J=2.5, 12.9, 12.9 Hz), 3.08 (1H, ddd, J=2.5, 12.9, 12.9 Hz), 3.74—3.88 (1H, m), 4.55—4.68 (1H, m). *Anal.* Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.10; H, 8.19; N, 7.49.

3-(1-Acetylpiperidin-4-yl)propionic Acid (25b) A mixture of ethoxycarbonylmethylenetriphenylphosphorane (89.40 g, 257 mmol) and 4-pyridinecarboxaldehyde (25.00 g, 233 mmol) in CH_2Cl_2 (100 ml) was stirred at room temperature for 10 min. The Wittig adduct was extracted with 5% HCl (150 ml) three times. The water layer was made basic with aq. KOH (30 g/100 ml) to take the pH to 9, and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4, and concentrated to give an oil. The oil was passed through a plug of silica gel and crystallized from hexane to give ethyl (*E*)-3-(4-pyridyl)propenoate (38.50 g, 93%) as colorless cubes, mp 64—66 °C. IR (KBr): 3430, 3050, 2970, 1710, 1640, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.1 Hz), 4.29 (2H, q, J=7.1 Hz), 6.60 (1H, d, J=16.2 Hz), 7.37 (2H, dd, J=1.8, 4.5 Hz), 7.60 (1H, d, J=16.2 Hz), 8.66 (2H, dd, J=1.8, 4.5 Hz). *Anal.* Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.74; H, 6.26; N, 7.80.

The above α, β-unsaturated ester was hydrogenated over PtO_2 and then acetylated with acetic anhydride in the same manner as described for **25a** to give ethyl 3-(1-acetylpiperidin-4-yl)propionate as an oil in 97% yield. IR (film): 2930, 1735, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00—1.32 (2H, m), 1.26 (3H, t, J=7.1 Hz), 1.40—1.80 (5H, m), 2.08 (3H, s), 2.34 (2H, t, J=7.5 Hz), 2.52 (1H, ddd, J=2.8, 12.9, 12.9 Hz), 3.02 (1H, ddd, J=2.8, 12.9, 12.9 Hz), 3.74—3.85 (1H, m), 4.14 (2H, q, J=7.1 Hz), 4.53—4.66 (1H, m).

An aq. KOH solution (90 g/150 mg) was added to a solution of the ester (16.00 g, 70.4 mmol) in methanol (30 ml). After stirring for 1 h at room temperature, the mixture was acidified to pH 4 with concentrated HCl. The resulting mixture was concentrated *in vacuo* to dryness, which was dissolved in acetone and the solid (KCl) was removed by filtration. The filtrate was concentrated and triturated in ether to give **25b** (13.00 g, 93%) as colorless cubes, mp 101—104 °C. IR (KBr): 3426, 2400—3200, 1728, 1599 cm^{-1}. ^{1}H-NMR ($CDCl_3+D_2O$) δ: 0.97—1.28 (2H, m), 1.43—1.85 (5H, m), 2.10 (3H, s), 2.39 (2H, t, J=7.0 Hz), 2.53 (1H, ddd, J=2.6, 12.9, 12.9 Hz), 3.03 (1H, ddd, J=2.6, 12.9, 12.9 Hz), 3.74—3.88 (1H, m), 4.53—4.68 (1H, m). *Anal.* Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.03; H, 8.72; N, 6.97.

4-(1-Acetylpiperidin-4-yl)butanoic Acid (25c) 4-(4-Pyridyl)butanoic acid hydrochloride[14] was hydrogenated over PtO_2 and then acetylated with acetic anhydride in the same manner as described for **24a** to give **24c** as a viscous oil in 85% yield. IR (film): 3412, 2400—3300, 1710, 1682 cm^{-1}. ^{1}H-NMR ($CDCl_3+D_2O$) δ: 0.75—1.17 (4H, m), 1.20—1.66 (5H, m), 1.82—2.01 (5H, m), 2.34 (1H, ddd, J=1.7, 12.8, 12.8 Hz), 2.86 (1H, ddd, J=1.7, 12.8, 12.8 Hz), 3.54—3.70 (1H, m), 4.30—4.44 (1H, m).

3-(1-Acetylpiperidin-4-yl)-1-(4-fluorophenyl)-1-propanone (26c) The acid **25b** (26.70 g, 134 mmol) was added portionwise to $SOCl_2$ (120 ml, 1.65 mol) at 0—5 °C. The mixture was stirred at 0—5 °C for 10 min and concentrated *in vacuo* to give an acid chloride as a pale yellow powder which was collected by filtration and washed with hexane. Aluminum chloride (46.00 g, 345 mmol) was added portionwise to a solution of the acid chloride in fluorobenzene (100 ml, *ca.* 1.07 mol). The mixture was stirred at room temperature for 2 h, poured into ice-water, and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel eluting with CH_2Cl_2–methanol (30 : 1) to give colorless cubes (23.40 g, 63%), mp 94—96 °C. IR (KBr): 3430,3050, 2930, 1695, 1635, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00—1.30 (2H, m), 1.44—1.95 (5H, m), 2.09 (3H, s), 2.53 (1H, ddd, J=2.6, 12.8, 12.8 Hz), 2.85—3.13 (3H, m), 3.74—3.90 (1H, m), 4.54—4.70 (1H, m), 7.15 (2H, dd, J=7.7, 8.4 Hz), 7.99 (2H, dd, J=5.5, 7.7 Hz). *Anal.* Calcd for $C_{16}H_{20}FNO_2$: C, 69.29; H, 7.27; N, 5.05. Found: C, 69.15; H, 7.29; N, 5.02.

The following compounds (**26a, b, d**) were prepared in the same manner as described for **26c**.

3-(1-Acetylpiperidin-4-yl)-1-(3,4-dimethoxyphenyl)-1-propanone (**26a**): Viscous oil. Yield: 68% (from **25b**). IR (film): 2932, 2848, 1672, 1638, 1560 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04—1.35 (3H, m), 1.47—1.88 (4H, m), 2.09 (3H, s), 2.55 (1H, ddd, J=2.8, 12.9, 12.9 Hz), 2.93—3.13 (3H, m), 3.76—3.90 (1H, m), 3.95 (3H, s), 3.96 (3H, s), 4.57—4.70 (1H, m), 6.90 (1H, d, J=8.4 Hz), 7.54 (1H, d, J=1.9 Hz), 7.59 (1H, dd, J=1.9, 8.4 Hz). *Anal.* Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.46; H, 7.92; N, 4.21.

2-(1-Acetylpiperidin-4-yl)-1-(4-fluorophenyl)-1-ethanone (**26b**): Colorless cubes, mp 63—65 °C. Yield: 85% (from **25a**). IR (KBr): 2910, 1726, 1678, 1638, 1592 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03—1.43 (2H, m), 1.53—1.97 (2H, m), 2.08 (3H, s), 2.10—3.27 (5H, m), 3.65—3.93 (1H, m), 4.47—4.78 (1H, m), 7.13 (2H, dd, J=8.5, 8.9 Hz), 7.99 (2H, dd, J=5.5, 8.9 Hz). *Anal.* Calcd for $C_{15}H_{18}FNO_2$: C, 68.42; H, 6.89; N, 5.32. Found: C, 68.36; H, 6.75; N, 5.28.

4-(1-Acetylpiperidin-4-yl)-1-(4-fluorophenyl)-1-butanone (**26d**): Colorless cubes, mp 77—78 °C. Yield: 66% (from **25c**). IR (KBr): 2928, 2856, 1690, 1640, 1596 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97—1.87 (9H, m), 2.08 (3H, s), 2.53 (1H, ddd, J=3.0, 12.8, 12.8 Hz), 2.89—3.12 (3H, m), 3.73—3.85 (1H, m), 4.52—4.66 (1H, m), 7.14 (2H, dd, J=8.5, 8.8 Hz), 7.99 (2H, dd, J=5.4, 8.8 Hz). *Anal.* Calcd for $C_{17}H_{22}FNO_2$: C, 70.08; H, 7.61; N, 4.81. Found: C, 69.76; H, 7.65; N, 4.81.

1-(4-Fluorophenyl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone (10i) A mixture of **26c** (11.50 g, 41.5 mmol) and concentrated HCl (60 ml) was refluxed for 15 h and concentrated to give crude crystals which were washed with ethanol and dried *in vacuo* to afford 1-(4-fluorophenyl)-3-(piperidin-4-yl)-1-propanone hydrochloride (**27c**, 11.20 g, *ca.* 99%) as a colorless powder, mp 190—192 °C. The powder was used for the next step without further purification.

A solution of **27c** (11.20 g, *ca.* 41.2 mmol) in water (30 ml) was made basic with aq. KOH (2.40 g/5 ml) and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and the solvent was evaporated to give a residue (9.12 g). A solution of benzylbromide (6.37 g, 37.2 mmol) in ethanol (10 ml) was added dropwise to a mixture of the residue and K_2CO_3 (7.50 g, 54.3 mmol) in ethanol (50 ml) at 0—5 °C. The mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was dissolved in water and extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, and the solvent was removed *in vacuo*. Chromatographic purification of the residue on silica gel eluting with ethyl acetate–methanol (30 : 1) afforded crude crystals, which were recrystallized from ether–hexane to give colorless cubes (12.10 g, 90%, from **26c**), mp 73—75 °C. IR (KBr): 2930, 1682, 1599 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.16—1.42 (3H, m), 1.53—1.77 (4H, m), 1.84—2.02 (2H, m), 2.83—3.00 (4H, m), 3.49 (2H, s), 7.13 (2H, dd, J=8.4, 9.0 Hz), 7.20—7.40 (5H, m), 7.98 (2H, dd, J=5.4, 9.0 Hz). *Anal.* Calcd for $C_{21}H_{24}FNO$: C, 77.51; H, 7.43; N, 4.30. Found: C, 77.44; H, 7.49; N, 4.31.

The following compounds (**10a, h, j**) were prepared in the same manner as described for **10i**.

1-(3,4-Dimethoxyphenyl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone (**10a**): Colorless needles, mp 67—69 °C. Yield: 69% (from **26a**). IR (KBr): 2932, 1679, 1584 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.44 (3H, m), 1.54—2.05 (6H, m), 2.82—3.00 (4H, m), 3.51 (2H, s), 3.94 (3H, s), 3.95 (3H, s), 6.88 (1H, d, J=8.4 Hz), 7.20—7.38 (5H, m), 7.51—7.62 (2H, m). *Anal.* Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.01; H, 7.96; N, 3.80.

1-(4-Fluorophenyl)-2-[1-(phenylmethyl)piperidin-4-yl]-1-ethanone (**10h**): Colorless cubes, mp 53—54 °C. Yield: 81% (from **26b**). IR (KBr): 2930, 1684, 1599 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25—1.47 (2H, m), 1.63—1.80 (2H, m), 1.86—2.10 (3H, m), 2.82—2.93 (4H, m), 3.49 (2H, s), 7.13 (2H, dd, J=8.4, 8.9 Hz), 7.22—7.35 (5H, m), 7.97 (2H, dd, J=5.4, 8.9 Hz). *Anal.* Calcd for $C_{20}H_{22}FNO$: C, 77.14; H, 7.12; N, 4.50. Found: C, 77.00; H, 6.98; N, 4.34.

1-(4-Fluorophenyl)-4-[1-(phenylmethyl)piperidin-4-yl]-1-butanone (**10j**): Colorless cubes, mp 53—55 °C. Yield: 81% (from **26d**). IR (KBr): 2926, 1686, 1597 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.37 (3H, m), 1.57—1.80 (6H, m), 1.80—1.98 (2H, m), 2.77—2.93 (4H, m), 3.46 (2H, s), 7.10 (2H, dd, J=8.4, 8.8 Hz), 7.15—7.31 (5H, m), 7.95 (2H, dd, J=5.4, 8.8 Hz). *Anal.* Calcd for $C_{22}H_{26}FNO$: C, 77.84; H, 7.72; N, 4.13. Found: C, 77.90; H, 7.76; N, 3.84.

Reaction of **10h** with pyrrolidine in the same manner as described for **3c** gave **10b**.

2-[1-(Phenylmethyl)piperidin-4-yl]-1-[4-(pyrrolidin-1-yl)phenyl]-1-ethanone (**10b**): Colorless cubes, mp 110—112 °C. Yield: 88%. IR (KBr): 2934, 1674, 1587 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24—1.46 (2H, m), 1.63—1.79 (2H, m), 1.85—2.10 (7H, m), 2.77 (2H, d, J=6.8 Hz), 2.79—2.92 (2H, m), 3.30—3.42 (4H, m), 3.48 (2H, s), 6.50 (2H, d, J=9.0 Hz), 7.18—7.34 (5H, m), 7.85 (2H, d, J=9.0 Hz). *Anal.* Calcd for $C_{24}H_{30}N_2O$: C, 79.52; H, 8.34; N, 7.73. Found: C, 79.55; H, 8.35; N, 7.77.

The following compounds (**10c, d** and **26e**) were similarly prepared from **10i, j** and **26c**, respectively.

3-[1-(Phenylmethyl)piperidin-4-yl]-1-[4-(pyrrolidin-1-yl)phenyl]-1-propanone Fumarate (**10c**): Colorless needles, mp 228—229 °C (dec.). Yield: 72%. IR (KBr): 3430, 2925, 2852, 2800, 2750, 1680, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$, free base) δ: 1.18—1.40 (3H, m), 1.45—1.76 (4H, m), 1.85—2.11 (6H, m), 2.80—2.95 (4H, m), 3.29—3.43 (4H, m), 3.48 (2H, s), 6.51 (2H, d, J=9.0 Hz), 7.20—7.38 (5H, m), 7.86 (2H, d, J=9.0 Hz). *Anal.* Calcd for $C_{25}H_{32}N_2O \cdot C_4H_4O_4$: C, 70.71; H, 7.37; N, 5.69. Found: C, 70.49; H, 7.35; N, 5.69.

4-[1-(Phenylmethyl)piperidin-4-yl]-1-[4-(pyrrolidin-1-yl)phenyl]-1-butanone Fumarate (**10d**): Colorless scales, mp 220—222 °C. Yield: 78%. IR (KBr): 3430, 2928, 2856, 1717, 1656, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$, free base) δ: 1.16—1.38 (5H, m), 1.60—2.16 (10H, m), 2.77—2.93 (4H, m), 3.30—3.43 (4H, m), 3.48 (2H, s), 6.51 (2H, d, J=9.0 Hz), 7.20—7.35 (5H, m), 7.86 (2H, d, J=9.0 Hz). *Anal.* Calcd for $C_{26}H_{34}N_2O \cdot C_4H_4O_4$: C, 71.12; H, 7.56; N, 5.53. Found: C, 71.19; H, 7.57; N, 5.53.

3-(1-Acetylpiperidin-4-yl)-1-[4-(pyrrolidin-1-yl)phenyl]-1-propanone (**26e**): Colorless cubes, mp 114—117 °C. Yield: 90%. IR (KBr): 3420, 2940, 2920, 2850, 1638, 1599 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83—1.93 (9H, m), 1.93—2.23 (5H, m), 2.33—3.05 (4H, m), 3.07—3.47 (4H, m), 3.63—3.93 (1H, m), 4.43—4.73 (1H, m), 6.50 (2H, d, J=9.0 Hz), 7.87 (2H, d, J=9.0 Hz). *Anal.* Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 72.99; H, 8.71; N, 8.46.

3-(Piperidin-4-yl)-1-[4-(pyrrolidin-1-yl)phenyl]-1-propanone (**27e**) was obtained by hydrolysis of **26e** in the same manner as described for **27c**.

27e: Colorless needles, mp 71—72 °C. Yield: 99%. IR (KBr): 3410, 2920, 2850, 1655, 1599 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.77—2.23 (12H, m), 2.40—3.50 (9H, m), 4.15 (1H, br s), 6.50 (2H, d, J=9.0 Hz), 7.87 (2H, d, J=9.0 Hz). *Anal.* Calcd for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15; N, 9.78. Found: C, 75.32; H, 9.13; N, 9.77.

The following compounds (**10e—g**) were prepared by treatment of **27e** with (methoxyphenyl)methylbromides as described for **10i**.

3-[1-[(2-Methoxyphenyl)methyl]piperidin-4-yl]-1-[4-(pyrrolidin-1-yl)-phenyl]-1-propanone (**10e**): Colorless cubes, mp 89—91 °C. Yield: 53%. IR (KBr): 2936, 1654, 1602 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.44 (2H, m), 1.54—1.82 (6H, m), 1.90—2.13 (5H, m), 2.82—3.00 (4H, m), 3.30—3.42 (4H, m), 3.54 (2H, s), 3.81 (3H, s), 6.51 (2H, d, J=8.9 Hz), 6.82—6.97 (2H, m), 7.17—7.28 (1H, m), 7.36 (1H, dd, J=1.7, 7.3 Hz), 7.86 (2H, d, J=8.9 Hz). *Anal.* Calcd for $C_{26}H_{34}N_2O_2$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.64; H, 8.48; N, 6.83.

3-[1-[(3-Methoxyphenyl)methyl]piperidin-4-yl]-1-[4-(pyrrolidin-1-yl)-phenyl]-1-propanone Fumarate (**10f**): Colorless cubes, mp 206—208 °C. Yield: 82%. IR (KBr): 3436, 2904, 2842, 1713, 1662, 1602 cm^{-1}. ^{1}H-NMR (DMSO-d_6 + D_2O) δ: 1.05—1.32 (3H, m), 1.43—1.58 (2H, m), 1.58—1.74 (2H, m), 1.85—2.08 (6H, m), 2.75—2.90 (4H, m), 3.23—3.37 (4H, m), 3.50 (2H, s), 3.73 (3H, s), 6.50—6.60 (4H, m), 6.78—6.92 (3H, m), 7.23 (1H, dd, J=8.0, 8.0 Hz), 7.79 (2H, d, J=8.9 Hz). *Anal.* Calcd for $C_{26}H_{34}N_2O_2 \cdot C_4H_4O_4$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.77; H, 7.42; N, 5.35.

3-[1-[(4-Methoxyphenyl)methyl]piperidin-4-yl]-1-[4-(pyrrolidin-1-yl)-phenyl]-1-propanone Fumarate (**10g**): Colorless cubes, mp 219—221 °C. Yield: 66%. IR (KBr): 3436, 2928, 2842, 1713, 1661, 1597 cm^{-1}. ^{1}H-NMR (DMSO-d_6 + D_2O) δ: 1.05—1.35 (3H, m), 1.43—1.58 (2H, m), 1.58—1.72 (2H, m), 1.88—2.10 (6H, m), 2.77—2.90 (4H, m), 3.23—3.37 (4H, m), 3.49 (2H, s), 3.74 (3H, s), 6.50—6.58 (4H, m), 6.88 (2H, d, J=8.7 Hz), 7.22 (2H, d, J=8.7 Hz), 7.79 (2H, d, J=8.9 Hz). *Anal.* Calcd for $C_{26}H_{34}N_2O_2 \cdot C_4H_4O_4$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.85; H, 7.49; N, 5.24.

Ameliorating Effects on Scopolamine-Induced Impairment of T-Maze Alternation Task[12] Male Wistar rats weighing 260—300 g, 9—10 weeks old, were maintained at 75—80% of their free feeding weights by daily feeding with measured rations. The T-maze apparatus consisted of a main alley 44 cm long by 12 cm wide to which was attached a start box (12 × 12 cm) and two arms 50 cm long by 12 cm wide. All rats received one session per day. Each session consisted of 11 trials. In the first trial, one 45 mg food pellet was available in either distal end of the arm. Subsequently, food was always baited only in the arm opposite the one that the rat chose on the preceding trial, regardless of whether the choice was correct or not. After training for 5 d, rats which reached a criterion of 80% or more correct responses were only used for a test session. Scopolamine hydrobromide (0.3 mg/kg, i.p.) administered 30 min before the test produced

memory impairment; the mean percent correct response was lowered to 55—65%, which was statistically significant at $p=0.01$. Ameliorating effects of test compounds on the impairment were studied. Saline and test compounds were given orally 30 min before administration of scopolamine hydrobromide (0.3 mg/kg, i.p.), 30 min later the test session consisting of 11 trials was performed. Eight to ten rats were used in each group and the intervals of each trial were 15 s. Mean percent correct responses of 10 trials from the second to eleventh trials were measured. For statistical analysis, Student's *t*-test was used. Minimum effective doses (MED), which were statistically significant at $p=0.05$, are shown in Table II.

Peripheral Action Effects of test compounds on peripheral action were studied using male Wistar rats, weighing 220—280 g, 8—9 weeks old. Four rats were used in each group. Rats were first placed in stainless steel cages (13 × 18 × 25 cm) for about 1 h for habituation. Test compounds were then administered orally, and behavioral changes such as salivation, lacrimation, diarrhea, and fasciculation were recorded. Minimum doses (MD) causing these peripheral changes are given in Table II.

Determination of 10c Concentration in Brain and Plasma Male Wistar rats weighing 260—300 g, 8 weeks old, were used. Three rats were used in each group. Test compound (**10c**, 2 mg/kg) was given to the rats intravenously and killed 5, 10, 15, 30, 60, 120, and 240 min after administration. Brain was homogenized with 4 volumes of saline. To brain and plasma samples (0.5 ml), 0.5 N NaOH (1.0 ml) and hexane (5.0 ml) was added, and vortexed for 20 min. The mixture was centrifuged at 2800 rpm for 5 min, and the supernatant (4.0 ml for brain and 3.0 ml for plasma samples) was evaporated to dryness *in vacuo* at 30 °C. The residue was dissolved in 250 μl of 0.05 M KH_2PO_4–methanol (1 : 2, v/v) and 100 μl of the solution was injected in high-performance lqiuid chromatography (HPLC).

Chromatography: A Hitachi 638-30 HPLC system was used. An analytical column of Merck Lichrospher RP—select B (250 × 4 mm) was used. The mobile phase was 0.05 M KH_2PO_4–methanol (1 : 2, v/v) with a flow-rate of 0.7 ml/min. The eluate was monitored by the spectrophotometric detector at 340 nm. The detection limit of **10c** in plasma and brain were 10 ng/ml or 50 ng/g, respectively.

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References and Notes

1) *a*) Part I: Y. Ishihara, K. Kato, and G. Goto, *Chem. Pharm. Bull.*, **39**, 3225 (1991); *b*) Part II: *idem*, *ibid.*, **39**, 3226 (1991); *c*) Part III: Y. Ishihara, H. Yukimasa, M. Miyamoto, and G. Goto, *ibid.*, **40**, 1177 (1992).
2) *a*) D. M. Quinn, *Chem. Rev.*, **87**, 955 (1987); *b*) A. G. Gilman, L. S. Goodman, T. W. Rall, and F. Murad (eds.), "GOODMAN and GILMAN's The Pharmacological Basis of Therapeutics," 7th ed., Macmillan Publishing Company, New York, 1985, p. 110.
3) After we submitted the first paper proposing the existence of HBS-2,[1a] Sussman *et al.* reported the X-ray analysis of AChE, see: J. L. Sussman, M. Harel, F. Frolow, C. Oefner, A. Goldman, L. Toker, and I. Silman, *Science*, **23**, 872 (1991).
4) *a*) G. Goto, H. Yukimasa, and T. Imamoto, EP-378207 [*Chem. Abstr.*, **114**, 61935*c* (1990)]; *b*) G. Goto, A. Nagaoka, and Y. Ishihara EP-383318 [*Chem. Abstr.*, **114**, 101369*e* (1990)]; *c*) G. Goto, A. Nagaoka, and Y. Ishihara, EP-401715 [*Chem. Abstr.*, **114**, 228533*j* (1990)].
5) As the substituents X, hydrophilic and electron-withdrawing groups such as nitro have been shown to enhance the potency.[1a,b] In this study, we have chosen 3,4-dimethoxy and 4-pyrrolidino groups as X, because preliminary *in vivo* study of **1** and **2** has suggested that these substituents might be effective in ameliorating the memory impairment.
6) Similar indanone derivatives bearing a phenethylamino moiety have been prepared as bradycardic agents by Psiorz *et al.*, see: M. Psiorz, J. Heider, A. Bomhard, N. Hauel, K. Noll, B. Narr, C. Lillie, W. Kobinger, and J. Daemmgen, DE 3630903 [*Chem. Abstr.*, **109**, 73164*k* (1988)].
7) Indanone derivatives bearing piperidine moiety have been prepared as AChE inhibitors, see: H. Sugimoto, Y. Iimura, Y. Yamaguchi, and K. Yamatsu, *Bioorg. Med. Chem. Lett.*, **2**, 871 (1992).
8) Using random screening, Sugimoto *et al.* have found similar piperidine derivatives as AChE inhibitors, see: H. Sugimoto, Y. Tsuchiya, H. Sugumi, K. Higurashi, N. Karibe, Y. Iimura, A. Sasaki, Y. Kawakami, T. Nakamura, S. Araki, Y. Yamanishi, and K. Yamatsu, *J. Med. Chem.*, **33**, 1880 (1990).
9) J. N. Chatterjea, R. Robinson, and M. L. Tomlinson, *Tetrahedron*, **30**, 507 (1974).
10) T. Naito, A. Okano, S. Kadoya, T. Miki, M. Inaoka, R. Moroi, and M. Shimizu, *Chem. Pharm. Bull.*, **16**, 728 (1968).
11) Investigation into the reason why the keto carbonyl group are effective in potent inhibition would give some information about hydrogen bonding subsite in or near HBS-2,[1b] which might be helpful in identifying the location of HBS-2. We should also note the other idea about the effect of the carbonyl group on AChE inhibition. Thus, Cardozo *et al.* suggested that there was a hydrogen bonding interaction between the esteratic site and the carbonyl oxygen of indanone derivatives which were similar to **8**, see: M. G. Cardozo, T. Kawai, Y. Iimura, H. Sugimoto, Y. Yamanishi, and A. J. Hopfinger, *J. Med. Chem.*, **35**, 590 (1992).
12) N. Yamazaki, A. Nagaoka, and Y. Nagawa, *Jpn. J. Psychopharmacol.*, **5**, 321 (1985).
13) *a*) J. A. Nielsen, E. E. Mena, I. H. Williams, M. R. Nocerini, and D. Liston, *Eur. J. Pharmacol.*, **173**, 53 (1989); *b*) M. C. Desai, P. F. Thadeio, C. A. Lipinski, D. R. Liston, R. W. Spencer, and I. H. Williams, *Bioorg. Med. Chem. Lett.*, **1**, 411 (1991).
14) E. E. Mikhlina and M. V. Rubtsov, *Zh. Obshch. Khim.*, **32**, 2177 (1962) [*Chem. Abstr.*, **58**, 9024 (1963)].