Central Cholinergic Agents. II.[1] Synthesis and Acetylcholinesterase Inhibitory Activities of *N*-[ω-[*N*-Alkyl-*N*-(phenylmethyl)amino]alkyl]-3-arylpropenamides

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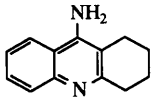
A series of *N*-[ω-[*N*-alkyl-*N*-(phenylmethyl)amino]alkyl]-3-arylpropenamides was prepared and tested for its inhibitory activities on acetylcholinesterase. Some in the series were found to be potent inhibitors. The structure–activity relationships were discussed in detail.

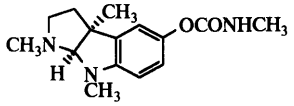
Keywords anticholinesterase; propenamide; structure–activity relationship; Hansch–Fujita analysis: hydrophobic binding site

The active site of acetylcholinesterase (AChE) is known to contain an anionic as well as an esteratic subsite and closely adjacent to these a hydrophobic binding site (HBS-1).[2] Inhibitors of AChE, such as physostigmine and tetrahydroaminoacridine (THA), bind to these sites, thus exerting their inhibitory effect on the enzyme (Chart 1).[2b,3] In a preceding paper,[1] we proposed that there may exist another hydrophobic binding site (HBS-2) some distance away from the anionic site. Investigation into compounds which interact with both hydrophobic binding sites as well as the anionic site was expected to reveal new types of AChE inhibitors. Based on this working hypothesis, 2-[ω-[*N*-alkyl-*N*-(ω-phenylalkyl)amino]alkyl]-1*H*-isoindole-1,3(2*H*)-diones (**1**) were designed and found to be potent AChE inhibitors. It was hoped to confirm the existence of HBS-2 by detailed study of the structure–activity relationships.

In order to find new inhibitors of AChE as well as to clarify the nature of HBS-2, we studied transformation of the phthalimide moiety of **1**, which is thought to interact with HBS-2 (Chart 2). The benzamide derivative (**2b**) was first prepared as a ring-opened analogue of **1a** which has 50%-inhibitory concentration (IC_{50}) of 151 nM. Replacement of the benzoyl group of **2b** with a cinnamoyl group led to **3b**, which showed stronger inhibitory activity than that of **2b** [IC_{50} = 1590 nM (**2b**), 539 nM (**3b**)]. *N*-[ω-[*N*-Alkyl-*N*-(phenylmethyl)amino]alkyl]-3-arylpropenamide derivatives (**3**) have two more positions for substitution than the benzamides (**2**). These prompted us to prepare a variety of 3-arylpropenamide derivatives (**3**) and examine their AChE inhibitory activities. This paper describes full details of the structure–activity relationships of the 3-arylpropenamide derivatives (**3**).



THA



physostigmine

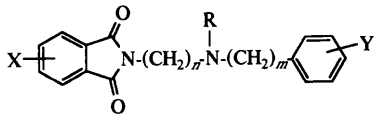


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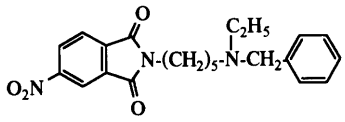
Chart 1

Chemistry Preparation of *N*-[ω-[*N*-alkyl-*N*-(phenylmethyl)amino]alkyl]-3-arylpropenamides (**3**) is illustrated in Chart 3. 2-[ω-[*N*-Alkyl-*N*-(phenylmethyl)amino]alkyl]-isoindole-1,3(2*H*)-diones (**1**)[1] were treated with hydrazine hydrate to give *N*-alkyl-*N*-(phenylmethyl)alkane-1,ω-diamines (**4**). Condensation of the 1,ω-diamines (**4**) with various 3-arylpropenoic acids (**5**) was carried out using diethyl phosphorocyanidate to yield the desired amides (**3**: R^3 = H). Reaction of the amide with acetic anhydride in the presence of *p*-toluenesulfonic acid gave *N*-acetyl derivatives (**3**: R^3 = Ac). Catalytic hydrogenation of the nitro group of **3a** over 10% Pd/C gave the amine (**3aa**), which was acylated to afford the acylamide (**3bb**).

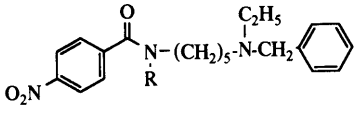
Butenamide (**6**) and 3-phenylpropionamide (**7**) were prepared in a similar manner to that described for **3** (R^3 = H). 1,5-Pentanediamine (**8**) was obtained by benzylation of **4c**.

Biological Results and Discussion

The measurement of AChE inhibitory activity was performed radiometrically according to the method of Klein-

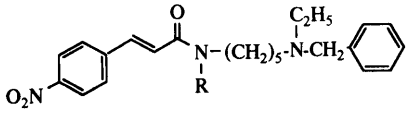


1a



2a : R=H

2b : R=Ac



3a : R=H

3b : R=Ac

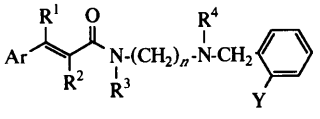


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Chart 2

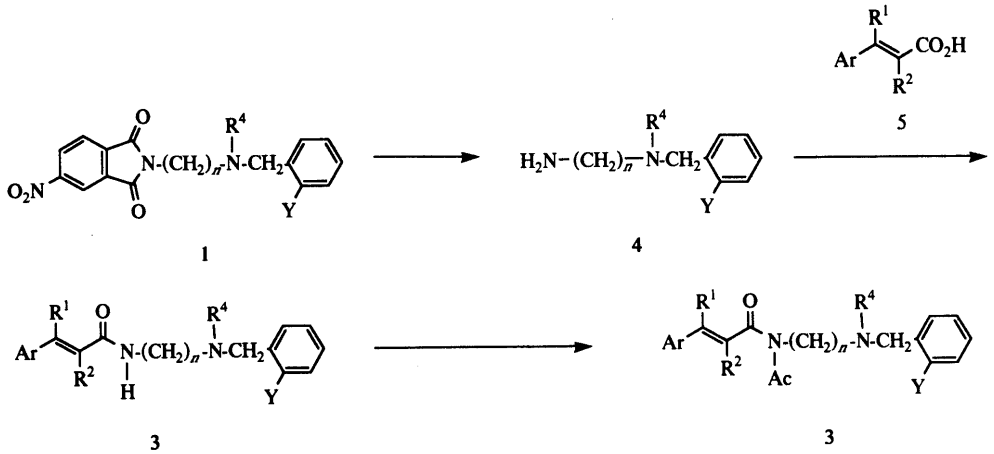
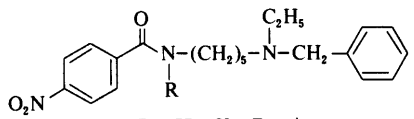
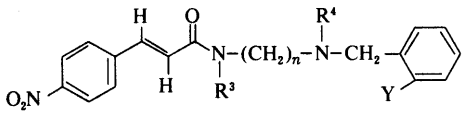


Chart 3

TABLE I. Physical and Biological Properties of *N*-[5-[*N*-Ethyl-*N*-(phenylmethyl)amino]pentyl]-4-nitrobenzamides (**2a**, **b**) and *N*-[ω-[*N*-Alkyl-*N*-(phenylmethyl)amino]alkyl]-3-arylpropenamides (**3a—l**)



2a: R=H **2b**: R=Ac



3a—k: Y=H **3l**: Y=OMe

Compd.[a] No.	*n*	R^3	R^4	Yield (%)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Inhibition of AChE (IC_{50}, nM)
2a	—	—	—	91	$C_{21}H_{27}N_3O_3 \cdot HCl$	62.14	6.95	10.35	61.92	7.07	10.21	5280
2b[b,c]	—	—	—	80	$C_{23}H_{29}N_3O_4$	—	—	—	—	—	—	1590
3a	5	H	Et	86	$C_{23}H_{29}N_3O_3 \cdot HCl$	63.95	7.00	9.73	63.81	6.91	9.63	3000
3b[b,d]	5	Ac	Et	83	$C_{25}H_{31}N_3O_4$	—	—	—	—	—	—	539
3c	3	H	Et	82	$C_{21}H_{25}N_3O_3$	68.64	6.86	11.44	68.51	6.79	11.34	11000
3d	4	H	Et	82	$C_{22}H_{27}N_3O_3 \cdot HCl$	63.23	6.75	10.05	63.14	6.59	10.03	7290
3e	6	H	Et	87	$C_{24}H_{31}N_3O_3 \cdot HCl$	64.64	7.23	9.42	64.63	7.17	9.40	4780
3f	7	H	Et	84	$C_{25}H_{33}N_3O_3 \cdot HCl$	65.28	7.45	9.14	65.03	7.19	9.06	9440
3g[b,e]	4	Ac	Et	77	$C_{24}H_{29}N_3O_4$	—	—	—	—	—	—	5520
3h[b,f]	6	Ac	Et	75	$C_{26}H_{33}N_3O_4$	—	—	—	—	—	—	2950
3i	5	H	Me	82	$C_{22}H_{27}N_3O_3 \cdot HCl$	63.23	6.75	10.05	63.17	6.71	9.98	16000
3j	5	H	iso-Pr	85	$C_{24}H_{31}N_3O_3 \cdot HCl$	64.64	7.23	9.42	64.47	7.11	9.31	7800
3k	5	H	Pr	87	$C_{24}H_{31}N_3O_3 \cdot HCl$	64.64	7.23	9.42	64.61	7.22	9.38	27000
3l	5	H	Et	90	$C_{24}H_{31}N_3O_4 \cdot HCl$	62.40	6.98	9.10	62.25	7.06	9.02	286

a) Amorphous powder unless otherwise noted. *b*) Oil. The structure was confirmed by IR, ^{1}H-NMR (see Experimental or Table VI), and MS spectra. *c*) MS *m/z*: 411 [M^+]. *d*) MS *m/z*: 437 [M^+]. *e*) MS *m/z*: 423 [M^+]. *f*) MS *m/z*: 451 [M^+].

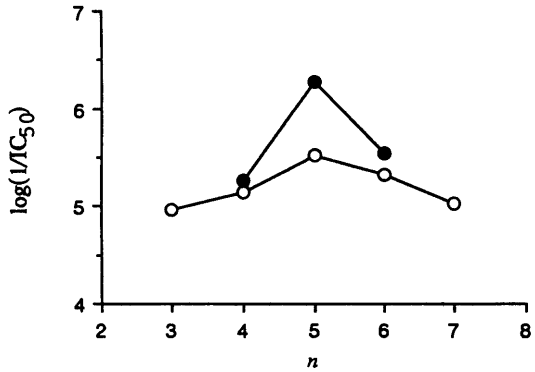


Fig. 1. Relationship between AChE Inhibition and Carbon Chain Length (*n*) of **3**

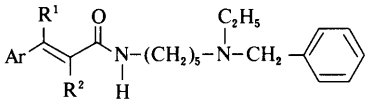
R^3=H (○); Ac (●).

berger and Yanai,[4] which is a slight modification of the method of Johnson and Russell.[5] The results were expressed as IC_{50} values. The IC_{50} values of physostigmine and THA were measured at 220 and 300 nM, respectively.

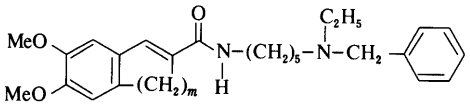
The effects of variation of the chain length (*n*) of **3** as well as the *N*-substituents (R^4) on AChE inhibition were examined first and the results are shown in Table I and Fig. 1. The figure clearly illustrates that optimum activities are associated with a chain length of 5 carbon atoms in both the *N*-H and *N*-Ac derivatives (**3a,c—f** and **3b,g,h**). The *N*-acetyl derivatives showed more potent activities than the *N*-H derivatives. Among the compounds bearing various *N*-alkyl substituents (**3a** and **3i—k**), **3a** (R^4=Et) was the most potent inhibitor. 2-Methoxy substitution on the phenyl ring of the benzylamino moiety, which we presume interacts with the anionic site as well as HBS-1,[1] increased the activity 10-fold (**3l** *vs.* **3a**). All these results are consistent with those obtained in the previous work,[1] thus supporting the existence of HBS-2.

The effects on AChE inhibition of variation of the aromatic ring (Ar) as well as substituents R^1 and R^2 were examined next and the results are shown in Table II. As an

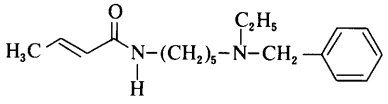
TABLE II. Physical and Biological Properties of *N*-[5-[*N*-Ethyl-*N*-(phenylmethyl)amino]pentyl]-3-arylpropenamides (**3m—w**) and Their Related Compounds (**6** and **7**)



3m—t



3u: $m=1$, **3v**: $m=2$, **3w**: $m=3$



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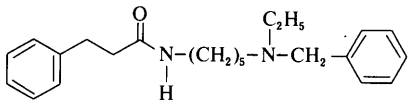

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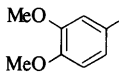
Compd.[a] No.	Ar	R^1	R^2	Yield (%)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Inhibition of AChE (IC_{50}, nM)
3m	Ph	H	H	87	$C_{23}H_{30}N_2O\cdot HCl$	71.39	8.07	7.24	71.33	8.00	7.17	11800
3n		H	H	81	$C_{22}H_{29}N_2O\cdot HCl$	68.11	7.79	10.83	68.05	7.68	10.71	4.210
3o[b]		H	H	86	$C_{21}H_{28}N_2O_2\cdot HCl$	66.92	7.76	7.43	66.54	7.55	7.40	19400
3p[c]		H	H	84	$C_{21}H_{28}N_2OS\cdot HCl$	64.18	7.44	7.13	63.74	7.25	7.06	15400
3q	Ph	H	Me	88	$C_{24}H_{32}N_2O\cdot HCl$	71.89	8.30	6.99	71.76	8.09	6.83	11600
3r[d]	Ph	H	Ph	86	$C_{29}H_{34}N_2O\cdot HCl$	75.22	7.62	6.05	74.87	7.43	5.89	7320
3s	Ph	Ph	H	87	$C_{29}H_{34}N_2O\cdot HCl$	75.22	7.62	6.05	75.11	7.47	5.97	5400
3t		H	H	87	$C_{25}H_{34}N_2O_3\cdot HCl$	67.17	7.89	6.27	67.08	7.76	6.05	5350
3u	—	—	—	86	$C_{26}H_{34}N_2O_3\cdot HCl$	68.03	7.69	6.10	67.89	7.54	5.96	1950
3v[e]	—	—	—	87	$C_{27}H_{36}N_2O_3\cdot HCl$	68.55	7.88	5.92	68.11	7.73	5.81	2520
3w	—	—	—	92	$C_{28}H_{38}N_2O_3\cdot HCl$	69.05	8.07	5.75	68.88	7.92	5.63	7950
6	—	—	—	90	$C_{18}H_{28}N_2O\cdot HCl$	66.54	9.00	8.62	66.35	8.98	8.52	52000
7	—	—	—	91	$C_{23}H_{32}N_2O\cdot HCl$	71.02	8.55	7.20	70.89	8.56	7.08	26000

a) Amorphous powder. *b*) MS *m/z*: 340 [M^+]. *c*) MS *m/z*: 356 [M^+]. *d*) MS *m/z*: 426 [M^+]. *e*) MS *m/z*: 436 [M^+].

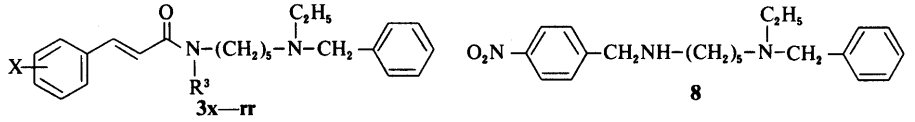
aromatic ring (Ar), the 3-pyridyl derivative (**3n**) was more potent than the phenyl derivative (**3m**), whereas the 2-furyl and 2-thienyl derivatives (**3o** and **3p**) were less potent inhibitors than **3m**. 2-Methyl-3-phenylpropenamide (**3q**) showed the same potency as **3m**. Both the 2,3-diphenylpropenamide (**3r**) and 3,3-diphenylpropenamides (**3s**) exerted more potency than **3m**. Ring-closed analogues of 3-(3,4-dimethoxyphenyl)propenamide (**3t**) were prepared in order to test the effect on enzyme inhibition of fixing the phenyl ring conformation. Among compounds (**3u—w**), both the indene and dihydronaphthalene derivatives (**3u** and **3v**) were found to be more potent inhibitors than **3t**, however, the dihydrobenzocycloheptene derivative (**3w**) was less potent than **3t**. This might be explained by their conformational differences: the benzene ring and the double bond of both indene and dihydronaphthalene have a coplanar conformation, whereas the olefinic group of the dihydrobenzocycloheptene ring is twisted (*ca.* 45°) out of plane.[7] Table II also demonstrates that replacement of the phenyl ring with a methyl group decreases the activity 4-fold (**6** *vs.* **3m**). Saturation of the double bond of **3m** resulted in a decrease of inhibitory potency (**7** *vs.* **3m**). From the above results the following conclusion may be drawn: (1) multiple hydrophobic interactions enhance the inhibitory activity; (2) the 3-phenyl ring and olefin portion should be linked together in a coplanar conformation in order to increase the potency. These suggested to us that there might be a similarity between HBS-2 and HBS-1, which has previously been described as a large area that is conformationally flexible and tends to assume a near planar form.[2b,6]

The effects of substituents (X) on the phenyl ring (Ar = Ph) were examined and analyzed quantitatively using the Hansch–Fujita method (Tables III and IV). Good correlation was obtained as shown in Eq. 1. The compounds used and their parameters are listed in Table IV. Correlations between the parameters used are insignificant, as shown in Table V.

$$\log(1/IC_{50}) = -0.174\pi + 0.611\sigma + 0.734I + 4.991 \quad (1)$$
$$(0.149)\ (0.249)\ (0.236)\ (0.137)$$
$$(r=0.919,\ n=25,\ s=0.245,\ F^3_{21}=37.93)$$

In Eq. 1, π represents a hydrophobic parameter and σ is used as an electronic parameter. It was found that an indicator variable term I, which takes the value of one for the *N*-Ac and zero for the *N*-H derivatives, is effective in the combined analysis of the *N*-H and *N*-Ac derivatives. Equation 1 shows that hydrophilic and electron-withdrawing groups enhance AChE inhibitory activity. This tendency was similar to that observed for substituent effects of the phthalimide derivatives (**1**).[1] In this quantitative study, satisfactory correlation was obtained without using steric parameters such as molecular refractivity (MR) and Es. Contribution of I to the activity seems to indicate that

TABLE III. Physical and Biological Properties of *N*-[5-[*N*-Ethyl-*N*-(phenylmethyl)amino]pentyl]-3-arylpropenamides (**3x—rr**) and Pentane-1,5-diamine (**8**)



3x—rr **8**

Compd. No.[a]	X	R^3	Yield (%)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Inhibition of AChE (IC_{50}, nM)
3x[b,c]	H	Ac	72	$C_{25}H_{32}N_2O_2$	—	—	—	—	—	—	2300
3y	3-NO_2	H	89	$C_{23}H_{29}N_3O_3 \cdot HCl$	63.95	7.00	9.73	63.77	6.83	9.62	2930
3z[b,d]	3-NO_2	Ac	78	$C_{25}H_{31}N_3O_4$	—	—	—	—	—	—	525
3aa[e]	4-NH_2	H	74	$C_{23}H_{31}N_3O \cdot 2HCl$	63.01	7.59	9.58	62.97	7.52	9.44	10200
3bb[f]	4-NHAc	H	68	$C_{25}H_{33}N_3O_2 \cdot HCl$	67.63	7.72	9.46	67.58	7.61	9.29	5670
3cc	4-Cl	H	91	$C_{23}H_{29}ClN_2O \cdot HCl$	65.56	7.18	6.65	65.29	7.01	6.45	15500
3dd[b,g]	4-Cl	Ac	76	$C_{25}H_{31}ClN_2O_2$	—	—	—	—	—	—	2140
3ee	4-Me	H	91	$C_{24}H_{32}N_2O \cdot HCl$	71.89	8.30	6.99	71.66	8.09	6.85	15800
3ff	4-CN	H	89	$C_{24}H_{29}N_3O \cdot HCl$	69.97	7.34	10.20	69.74	7.17	10.03	4950
3gg[b,h]	4-CN	Ac	76	$C_{26}H_{31}N_3O_2$	—	—	—	—	—	—	454
3hh	4-OH	H	91	$C_{23}H_{30}N_2O_2 \cdot HCl$	68.56	7.75	6.95	68.33	7.58	6.71	12600
3ii	4-OMe	H	92	$C_{24}H_{32}N_2O_2 \cdot HCl$	69.13	7.98	6.72	69.00	7.83	6.59	16300
3jj	3-OMe	H	94	$C_{24}H_{32}N_2O_2 \cdot HCl$	69.13	7.98	6.72	69.04	7.94	6.67	9310
3kk[b,i]	3-OMe	Ac	73	$C_{26}H_{34}N_2O_3$	—	—	—	—	—	—	5740
3ll	3,4,5-$(OMe)_3$	H	92	$C_{26}H_{36}N_2O_4 \cdot HCl$	65.46	7.82	5.87	65.33	7.99	5.78	4080
3mm	4-SMe	H	90	$C_{24}H_{32}N_2OS \cdot HCl$	66.57	7.68	6.47	66.47	7.81	6.39	21000
3nn	4-SOMe	H	89	$C_{24}H_{32}N_2O_2S \cdot HCl$	64.19	7.41	6.24	64.05	7.48	6.11	7500
3oo	4-SO_2Me	H	92	$C_{24}H_{32}N_2O_3S \cdot HCl$	61.99	7.15	6.02	61.85	7.03	5.97	3150
3pp[b,j]	4-SO_2Me	Ac	60	$C_{26}H_{34}N_2O_4S$	—	—	—	—	—	—	164
3qq	3-NO_2, 4-Cl	H	88	$C_{23}H_{28}ClN_3O_3 \cdot HCl$	59.23	6.27	9.01	59.00	6.05	8.93	1880
3rr[b,k]	3-NO_2, 4-Cl	Ac	69	$C_{25}H_{30}ClN_3O_4$	—	—	—	—	—	—	408
8[l]	—	—	38	$C_{21}H_{29}N_3O_2 \cdot 2HCl$	58.88	7.29	9.81	58.48	7.49	9.36	10700

a) Amorphous powder unless otherwise noted. *b*) Oil. The structure was confirmed by IR, ^{1}H-NMR (see Table VII), and MS spectra. *c*) MS *m/z*: 392 [M^+]. *d*) MS *m/z*: 437 [M^+]. *e*) MS *m/z*: 365 [M^+]. *f*) MS *m/z*: 407 [M^+]. *g*) MS *m/z*: 428 [M+2], 426 [M^+]. *h*) MS *m/z*: 417 [M^+]. *i*) MS *m/z*: 422 [M^+]. *j*) MS *m/z*: 470 [M^+]. *k*) MS *m/z*: 473 [M+2], 471 [M^+]. *l*) MS *m/z*: 355 [M^+].

TABLE IV. Acetylcholinesterase Inhibitory Activity and Physicochemical Parameters of *N*-[5-[*N*-Ethyl-*N*-(phenylmethyl)amino]pentyl]-3-arylpropenamides (**3**)

Compd. No.	X	R^3	π[a]	σ[a]	I[b]	Inhibition of AChE log(1/IC_{50}) Obsd.	Calcd[c]	Δ[d]
3m	H	H	0.00	0.00	0	4.93	4.99	−0.06
3x	H	Ac	0.00	0.00	1	5.64	5.72	−0.08
3a	4-NO_2	H	−0.28	0.78	0	5.52	5.52	0.00
3b	4-NO_2	Ac	−0.28	0.78	1	6.27	6.25	0.02
3y	3-NO_2	H	−0.28	0.71	0	5.53	5.47	0.06
3z	3-NO_2	Ac	−0.28	0.71	1	6.28	6.21	0.07
3aa	4-NH_2	H	−1.23	−0.66	0	4.99	4.80	0.19
3bb	4-NHAc	H	−0.97	0.00	0	5.25	5.16	0.09
3cc	4-Cl	H	0.71	0.23	0	4.81	5.01	−0.20
3dd	4-Cl	Ac	0.71	0.23	1	5.67	5.74	−0.07
3ee	4-Me	H	0.56	−0.17	0	4.80	4.79	0.01
3ff	4-CN	H	−0.57	0.66	0	5.31	5.49	−0.18
3gg	4-CN	Ac	−0.57	0.66	1	6.34	6.23	0.11
3hh	4-OH	H	−0.67	−0.37	0	4.90	4.88	0.02
3ii	4-OMe	H	−0.02	−0.27	0	4.79	4.83	−0.04
3jj	3-OMe	H	−0.02	0.12	0	5.03	5.07	−0.04
3kk	3-OMe	Ac	−0.02	0.12	1	5.24	5.80	−0.56
3t	3,4-$(OMe)_2$	H	−0.04[e]	−0.15[e]	0	5.27	4.91	0.36
3ll	3,4,5-$(OMe)_3$	H	−0.06[e]	−0.03[e]	0	5.39	4.98	0.41
3mm	4-SMe	H	0.61	0.00	0	4.68	4.88	−0.20
3nn	4-SOMe	H	−1.58	0.49	0	5.12	5.57	−0.45
3oo	4-SO_2Me	H	−1.63	0.72	0	5.50	5.71	−0.21
3pp	4-SO_2Me	Ac	−1.63	0.72	1	6.79	6.45	0.34
3qq	3-NO_2, 4-Cl	H	0.43[e]	0.94[e]	0	5.73	5.49	0.24
3rr	3-NO_2, 4-Cl	Ac	0.43[e]	0.94[e]	1	6.39	6.22	0.17

a) Taken from the literature.[11] *b*) Indicator variable which takes the value of one for the NAc (R^3 = Ac) and zero for the NH (R^3 = H) derivatives. *c*) Calculated by Eq. 1. *d*) Δ, difference between observed and calcd values. *e*) Values summed for component substituents.

the interaction between the carbonyl group and the enzyme occurs in the case of the *N*-Ac derivatives. Furthermore, the importance of the carbonyl groups of both the amide portion and the *N*-acetyl group is shown by comparison of compounds **2a**, **b** and **8**: the *N*-acetyl derivative (**2b**) was more potent than the amide derivative (**2a**), which in turn was more potent than the 1,5-diamine (**8**). These results and the above quantitative study suggest that these carbonyl groups interact with the enzyme presumably by hydrogen bondings. In other words, there may exist at least one hydrogen bonding subsite in or near HBS-2.

In conclusion, some of the *N*-[ω-[*N*-alkyl-*N*-(phenylmethyl)amino]alkyl]-3-arylpropenamides (**3**) were found to be potent AChE inhibitors. The results of structure–activity relationships obtained in this study support the existence of HBS-2 and also allow speculation as to the nature of this site. Thus it appears that HBS-2 may contain at least one hydrogen bonding subsite in or close to the site. In order to confirm the hypothesis proposed in this and preceding papers as well as to search for new types of AChE inhibitors, further studies are now being undertaken.

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 KBr disks for solids and liquid films for oils. Mass spectra (MS) were measured on a JOEL JMS-01SC spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM-390 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. Chromatographic purifications were carried out on silica gel column (Kieselgel 60, 0.063—0.200 mm, Merck).

TABLE V. Simple Correlation Matrix for the Parameters of Eq. 1

	π	σ	I
π	1.000		
σ	0.089	1.000	
I	0.063	0.361	1.000

Preparation of *N*-Alkyl-*N*-(phenylmethyl)alkane-1,ω-diamines (4) 2-[ω-[*N*-Alkyl-*N*-(phenylmethyl)amino]alkyl]isoindole-1,3(2*H*)-diones (**1**) were treated with hydrazine hydrate to give **4** according to the method described earlier.[1] The yields and spectral data are listed in Table VI.

Preparation of 3-Arylpropenoic Acids (5) Commercially available 3-arylpropenoic acids (**5**) were used in condensation with **4** with the exception of certain acids, which were prepared in the following manner.

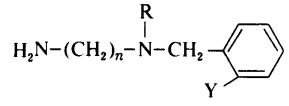
(*E*)-3-[4-(Methylthio)phenyl]propenoic Acid (5a) A mixture of 4-(methylthio)benzaldehyde (7.6 g) and ethoxycarbonylmethylidene triphenylphosphorane (20.9 g) in toluene (100 ml) was refluxed for 1 h and the solvent was removed *in vacuo*. Hexane was added to the residue and the resulting precipitate was removed by filtration. The filtrate was concentrated, diluted with CH_2Cl_2, passed through a plug of silica gel, and the solvent was evaporated off to give a residue. The residue was crystallized from hexane to afford ethyl (*E*)-3-[4-(methylthio)phenyl]propenoate (10.7 g, 96%) as colorless cubes, mp 47—48 °C. IR (KBr): 2978, 1706, 1628, 1590, 1492, 1437, 1365, 1307 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7 Hz), 2.43 (3H, s), 4.23 (2H, q, J=7 Hz), 6.33 (1H, d, J=16 Hz), 7.15 (2H, d, J=8 Hz), 7.38 (2H, d, J=8 Hz), 7.59 (1H, d, J=16 Hz).

A mixture of the ester (10.5 g) and K_2CO_3 (8.0 g) in methanol–water (200/40 ml) was refluxed for 1 h and the solvents were removed under reduced pressure to give a residue. An aqueous solution of the residue was made acidic (pH = 5—6) with 10% HCl. The resulting precipitate was collected by filtration, washed with water three times and dried *in vacuo* to give colorless cubes (9.1 g, 99%), mp 175—176 °C (lit.[8] 170—171 °C). IR (KBr): 2960, 2916, 2550, 1687, 1624, 1591 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide-d_6 (DMSO-d_6)) δ: 2.47 (3H, s), 6.45 (1H, d, J=16 Hz), 7.24 (2H, d, J=8 Hz), 7.51 (1H, d, J=16 Hz), 7.58 (2H, d, J=8 Hz), 8.00 (1H, br s).

(*E*)-3-[4-(Methylsulfinyl)phenyl]propenoic Acid (5b) A mixture of **5a** (2.0 g) and 30% H_2O_2 (0.7 ml) in acetic acid (8 ml) was heated at 50 °C for 1 h, cooled to room temperature and water was added to the mixture. The resulting precipitate was collected by filtration, washed with water three times and dried *in vacuo* to give colorless cubes (1.5 g, 69%), mp 217—218 °C. IR (KBr): 3422, 2914, 2566, 1692, 1639, 1016 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.73 (3H, s), 6.59 (1H, d, J=16 Hz), 7.62 (1H, d, J=16 Hz), 7.68 (2H, d, J=8 Hz), 7.87 (2H, d, J=8 Hz), 12.4 (1H, br s).

(*E*)-3-[4-(Methylsulfonyl)phenyl]propenoic Acid (5c) A mixture of **5a** (2.0 g) and 30% H_2O_2 (2 ml) in acetic acid (8 ml) was heated at 90—95 °C for 1 h, cooled to room temperature and water was added to the mixture.

TABLE VI. Spectral Data of *N*-Alkyl-*N*-(phenylmethyl)alkane-1,ω-diamines (4)



4

Compd.	n	R	Y	Yield (%)	IR (film) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ[a]
4a	3	Et	H	95	3354, 2966, 2934	1.05 (3H, t, J=7 Hz), 1.64 (2H, tt, J=7, 7 Hz), 2.38—2.88 (6H, m), 3.17 (2H, br s), 3.53 (2H, s), 7.32 (5H, s)
4b	4	Et	H	93	3362, 2934	1.01 (3H, t, J=7.5 Hz), 1.30—1.70 (4H, m), 2.13 (2H, br s), 2.30—2.88 (6H, m), 3.53 (2H, s), 7.27 (5H, s)
4c	5	Et	H	91	3350, 2932	1.04 (3H, t, J=7 Hz), 1.21—1.58 (6H, m), 1.88 (2H, br s), 2.44 (2H, t, J=7.5 Hz), 2.52 (2H, q, J=7 Hz), 2.68 (2H, t, J=7 Hz), 3.57 (2H, s), 7.26 (5H, s)
4d	6	Et	H	93	3310, 2930	1.00 (3H, t, J=7 Hz), 1.10—1.67 (8H, m), 1.82 (2H, br s), 2.27—2.82 (6H, m), 3.52 (2H, s), 7.27 (5H, s)
4e	7	Et	H	96	3350, 2930	0.90—1.77 (10H, m), 1.02 (3H, t, J=7 Hz), 2.28—2.87 (6H, m), 3.55 (2H, s), 3.92 (2H, br s), 7.27 (5H, s)
4f	5	Me	H	94	3354, 2940	1.08—1.80 (8H, m), 2.18 (3H, s), 2.38 (2H, t, J=7 Hz), 2.68 (2H, t, J=6.5 Hz), 3.48 (2H, s), 7.30 (5H, s)
4g	5	Pr	H	91	3350, 2932	0.83 (3H, t, J=7 Hz), 1.07—1.75 (8H, m), 2.13—2.87 (8H, m), 3.53 (2H, s), 7.30 (5H, s)
4h	5	iso-Pr	H	95	3350, 2930	0.99 (6H, d, J=7 Hz), 1.10—1.77 (8H, m), 2.10—2.55 (4H, m), 2.90 (1H, q of q, J=7, 7 Hz), 3.53 (2H, s), 7.25 (5H, s)
4i	5	Et	OMe	93	3358, 2932	1.03 (3H, t, J=7 Hz), 1.20—2.07 (8H, m), 2.32—2.80 (6H, m), 3.57 (2H, s), 3.80 (3H, s), 6.73—7.03 (2H, m), 7.18 (1H, dd, J=7, 7 Hz), 7.40 (1H, d, J=7 Hz)

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in parentheses.

TABLE VII. Spectral Data[a] of **2a**, **b**, **3c**—**z**, **cc**—**rr**,**6**, and **7**

Compd.	IR (film) cm^{-1}	^1H-NMR ($CDCl_3$) δ[b]
2a	3304, 2934, 1647, 1600, 1526	1.05 (3H, t, J=7 Hz), 1.25—1.68 (6H, m), 2.42—2.61 (4H, m), 3.46 (2H, dt, J=6, 7 Hz), 3.58 (2H, s), 6.31 (1H, br s), 7.18—7.37 (5H, m), 7.91 (2H, d, J=8.5 Hz), 8.28 (2H, d, J=8.5 Hz)
2b	2936, 1690, 1664, 1526	1.01 (3H, t, J=7 Hz), 1.21—1.68 (6H, m), 2.28 (3H, s), 2.38 (2H, t, J=7.5 Hz), 2.48 (2H, q, J=7 Hz), 3.53 (2H, s), 3.71 (2H, t, J=7.5 Hz), 7.29 (5H, s), 7.68 (2H, d, J=9 Hz), 8.29 (2H, d, J=9 Hz)
3c[c]	3276, 2934, 1656, 1619, 1579	1.08 (3H, t, J=7 Hz), 1.33—1.90 (2H, m), 2.17—2.73 (4H, m), 3.43 (2H, dt, J=5, 6 Hz), 3.53 (2H, s), 6.21 (1H, d, J=15 Hz), 7.00—7.67 (9H, m), 8.20 (2H, d, J=9 Hz)
3d	3280, 2934, 1660, 1623, 1519	1.03 (3H, t, J=7 Hz), 1.47—1.83 (4H, m), 2.37—2.70 (4H, m), 3.36 (2H, dt, J=5, 6 Hz), 3.57 (2H, s), 6.37 (1H, d, J=15 Hz), 6.93 (1H, br t, J=5 Hz), 7.27 (5H, s), 7.48 (2H, d, J=8 Hz), 7.59 (1H, d, J=15 Hz), 8.15 (2H, d, J=8 Hz)
3e	3286, 2932, 1660, 1622, 1519	1.00 (3H, t, J=7 Hz), 1.10—1.77 (8H, m), 2.20—2.64 (4H, m), 3.35 (2H, dt, J=5, 6 Hz), 3.52 (2H, s), 5.97 (1H, br), 6.50 (1H, d, J=15 Hz), 7.25 (5H, s), 7.58 (2H, d, J=8 Hz), 7.63 (1H, d, J=15 Hz), 8.17 (2H, d, J=8 Hz)
3f	3290, 2930, 1661, 1622, 1520	1.00 (3H, t, J=7 Hz), 1.15—1.77 (10H, m), 2.27—2.65 (4H, m), 3.36 (2H, dt, J=5, 6 Hz), 3.53 (2H, s), 6.08 (1H, br), 6.53 (1H, d, J=15 Hz), 7.26 (5H, s), 7.60 (2H, d, J=9 Hz), 7.65 (1H, d, J=15 Hz), 8.18 (2H, d, J=9 Hz)
3g	2938, 1698, 1680, 1624, 1596, 1519	1.03 (3H, t, J=7.5 Hz), 1.36–1.83 (4H, m), 2.33—2.67 (4H, m), 2.40 (3H, s), 3.57 (2H, s), 3.71 (2H, t, J=7.5 Hz), 7.10—7.40 (6H, m), 7.65 (2H, d, J=9 Hz), 7.70 (1H, d, J=15 Hz), 8.21 (2H, d, J=9 Hz)
3h	2934, 1698, 1680, 1519	1.03 (3H, t, J=7 Hz), 1.16—1.83 (8H, m), 2.30—2.70 (4H, m), 2.40 (3H, s), 3.57 (2H, s), 3.73 (2H, t, J=7.5 Hz), 7.20 (1H, d, J=15 Hz), 7.27 (5H, s), 7.65 (2H, d, J=9 Hz), 7.70 (1H, d, J=15 Hz), 8.22 (2H, d, J=9 Hz)
3i	3286, 2932, 1660, 1622, 1519	1.13—2.03 (6H, m), 2.62 (3H, d, J=5 Hz), 2.83—3.35 (4H, m), 4.03—4.45 (2H, m), 6.85 (1H, d, J=15 Hz), 7.36—7.90 (8H, m), 8.16—8.47 (3H, m), 11.30 (br s)[d]
3j	3296, 2932, 1662, 1623, 1519	0.99 (6H, d, J=7 Hz), 1.10—1.77 (6H, m), 2.40 (2H, t, J=6 Hz), 2.73—3.13 (1H, m), 3.13—3.50 (2H, m), 3.53 (2H, s), 5.97 (1H, br), 6.48 (1H, d, J=15 Hz), 7.25 (5H, s), 7.58 (2H, d, J=9 Hz), 7.78 (1H, d, J=15 Hz), 8.17 (2H, d, J=9 Hz)
3k	3280, 2934, 1660, 1623, 1519	0.83 (3H, t, J=7 Hz), 1.10—1.75 (8H, m), 2.16—2.55 (4H, m), 3.33 (2H, dt, J=5, 6 Hz), 3.50 (2H, s), 6.03 (1H, br t , J=5 Hz), 6.49 (1H, d, J=15 Hz), 7.25 (5H, s), 7.57 (2H, d, J=8 Hz), 7.62 (1H, d, J=15 Hz), 8.17 (2H, d, J=8 Hz)
3l	3280, 2934, 1661, 1623, 1599, 1519	1.01 (3H, t, J=7 Hz), 1.16—1.76 (6H, m), 2.27—2.67 (4H, m), 3.34 (2H, dt, J=5, 6 Hz), 3.54 (2H, s), 3.80 (3H, s), 6.28 (1H, br), 6.44 (1H, d, J=16 Hz), 6.72—7.76 (7H, m), 8.18 (2H, d, J=8 Hz)
3m	3276, 2934, 1656, 1619, 1579	1.00 (3H, t, J=7.5 Hz), 1.15—1.70 (6H, m), 2.27—2.63 (4H, m), 3.33 (2H, dt, J=5, 6 Hz), 3.50 (2H, s), 5.88 (1H, br), 6.35 (1H, d, J=15 Hz), 7.10—7.60 (10H, m), 7.58 (1H, d, J=15 Hz)
3n	3442, 2922, 1669, 1630, 1562	1.07—1.95 (9H, m), 2.73—3.35 (6H, m), 4.27 (2H, d, J=5 Hz), 7.00 (1H, d, J=16 Hz), 7.33—7.80 (6H, m), 7.93 (1H, dd, J=5, 8 Hz), 8.40—8.65 (2H, m), 8.81 (1H, d, J=5 Hz), 9.05 (1H, s), 11.30 (1H, br s)[d]
3o	3278, 2934, 1658, 1620, 1566	1.00 (3H, t, J=7.5 Hz), 1.10—1.70 (6H, m), 2.23—2.63 (4H, m), 3.32 (2H, dt, J=5, 6 Hz), 3.53 (2H, s), 5.67 (1H, br), 6.26 (1H, d, J=15 Hz), 6.33—6.57 (2H, m), 7.05—7.52 (7H, m)
3p	3280, 2934, 1649, 1613, 1557	1.00 (3H, t, J=7.5 Hz), 1.22—1.74 (6H, m), 2.26—2.64 (4H, m), 3.31 (2H, dt, J=5, 6 Hz), 3.51 (2H, s), 5.73 (1H, br), 6.16 (1H, d, J=15 Hz), 6.90—7.37 (8H, m), 7.70 (1H, d, J=15 Hz)
3q	3326, 2934. 1650, 1616, 1533	1.01 (3H, t, J=7.5 Hz), 1.23—1.70 (6H, m), 2.07 (3H, s), 2.30—2.63 (4H, m), 3.32 (2H, dt, J=5, 6 Hz), 3.52 (2H, s), 5.83 (1H, br), 7.10—7.46 (11H, m)
3r	3326, 2934, 1665, 1616, 1509	1.00 (3H, t, J=7.5 Hz), 1.10—1.60 (6H, m), 2.26—2.60 (4H, m), 3.24 (2H, dt, J=5, 6 Hz), 3.50 (2H, s), 5.43 (1H, br t, J=6 Hz), 6.87—7.51 (15H, m), 7.86 (1H, s)
3s	3294, 2934, 1643, 1630, 1576	0.95—1.50 (6H, m), 1.00 (3H, t, J=7.5 Hz), 2.22—2.62 (4H, m), 3.04 (2H, dt, J=5, 6 Hz), 3.50 (2H, s), 5.12 (1H, br), 6.36 (1H, s), 7.26 (15H, m)
3t	3284, 2932, 1654, 1617, 1599, 1514	1.00 (3H, t, J=7 Hz), 1.20—1.70 (6H, m), 2.29—2.63 (4H, m), 3.32 (2H, dt, J=5, 6 Hz), 3.51 (2H, s), 3.87 (6H, s), 5.74 (1H, br t, J=5 Hz), 6.23 (1H, d, J=15 Hz), 6.80 (1H, d, J=9 Hz), 6.96—7.13 (2H, m), 7.28 (5H, s), 7.53 (1H, d, J=15 Hz)
3u	3314, 2934, 1627, 1561, 1532	1.01 (3H, t, J=7 Hz), 1.15—1.73 (6H, m), 2.29—2.66 (4H, m), 3.35 (2H, dt, J=5, 6 Hz), 3.52 (2H, s), 3.57 (2H, br s), 3.87 (6H, s), 5.95 (1H, br t, J=5 Hz), 6.93 (1H, s), 7.00 (1H, s), 7.26 (5H, s), 7.32 (1H, s)
3v	3334, 2932, 1643, 1606, 1518	1.00 (3H, t, J=7 Hz), 1.16—1.70 (6H, m), 2.28—2.97 (8H, m), 3.32 (2H, dt, J=5, 6 Hz), 3.52 (2H, s), 3.83 (3H, s), 3.86 (3H, s), 5.85 (1H, br t, J=5 Hz), 6.67 (2H, s), 7.08 (1H, s), 7.26 (5H, s)
3w	3326, 2930, 1645, 1604, 1519	1.01 (3H, t, J=7 Hz), 1.18—1.76 (6H, m), 1.84—2.20 (2H, m), 2.23—2.94 (8H, m), 3.31 (2H, dt, J=5, 6 Hz), 3.52 (2H, s), 3.83 (3H, s), 3.86 (3H, s), 5.89 (1H, br t, J=5 Hz), 6.63 (1H, s), 6.77 (1H, s), 7,22 (1H, s), 7.28 (5H, s)
3x	2934, 1685, 1619	1.00 (3H, t, J=7 Hz), 1.13—1.82 (6H, m), 2.27—2.63 (4H, m), 2.41 (3H, s), 3.52 (2H, s), 3.73 (2H, t, J=7 Hz), 6.99 (1H, d, J=15 Hz), 7.10—7.63 (10H, m), 7.74 (1H, d, J=15 Hz)
3y	3282, 2932, 1662, 1623, 1530	1.01 (3H, t, J=7 Hz), 1.13—1.73 (6H, m), 2.20—2.65 (4H, m), 3.36 (2H, dt, J=5, 6 Hz), 3.53 (2H, s), 5.98 (1H, br), 6.48 (1H, d, J=15 Hz), 7.26 (5H, s), 7.36—7.80 (3H, m), 8.15 (1H, d, J=8 Hz), 8.32 (1H, s)
3z	2936, 1683, 1625, 1531	1.03 (3H, t, J=7 Hz), 1.15—1.83 (6H, m), 2.33—2.70 (4H, m), 2.40 (3H, s), 3.57 (2H, s), 3.73 (2H, br t, J=7 Hz), 7.18 (1H, d, J=15 Hz), 7.26 (5H, s), 7.53 (1H, dd, J=8, 8 Hz), 7.70 (1H, d, J=15 Hz), 7.82 (1H, d, J=8 Hz), 8.20 (1H, d, J=8 Hz), 8.35 (1H, s)
3cc	3284, 2936, 1655, 1618, 1554	1.00 (3H, t, J=7 Hz), 1.18—1.73 (6H, m), 2.16—2.62 (4H, m), 3.31 (2H, dt, J=5, 6 Hz), 3.51 (2H, s), 6.03 (1H, br t, J=5 Hz), 6.35 (1H, d, J=15 Hz), 7.13—7.47 (9H, m), 7.54 (1H, d, J=15 Hz)
3dd	2936, 1686, 1620	1.00 (3H, t, J=7 Hz), 1.13—1.80 (6H, m), 2.30—2.63 (4H, m), 2.42 (3H, s), 3.52 (2H, s), 3.71 (2H, t, J=7 Hz), 7.02 (1H, d, J=15 Hz), 7.13—7.57 (9H, m), 7.68 (1H, d, J=15 Hz)
3ee	3280, 2932, 1655, 1618,	1.00 (3H, t, J=7 Hz), 1.15—1.76 (6H, m), 2.25—2.63 (4H, m), 2.33 (3H, s), 3.33 (2H, dt,

TABLE VII. (continued)

Compd.	IR (film) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ[b]
	1544	J=5, 6 Hz), 3.51 (2H, s), 5.93 (1H, br t, J=5 Hz), 6.32 (1H, d, J=15 Hz), 7.00—7.45 (9H, m), 7.56 (1H, d, J=15 Hz)
3ff	3280, 2934, 2226, 1659, 1622, 1556	1.00 (3H, t, J=7 Hz), 1.20—1.73 (6H, m), 2.28—2.63 (4H, m), 3.33 (2H, dt, J=5, 6 Hz), 3.50 (2H, s), 6.25 (1H, br t, J=5 Hz), 6.48 (1H, d, J=15 Hz), 7.26 (5H, s), 7.41—7.70 (5H, m)
3gg	2936, 2228, 1698, 1623, 1531	1.01 (3H, t, J=7 Hz), 1.13—1.94 (6H, m), 2.27—2.65 (4H, m), 2.40 (3H, s), 3.53 (2H, s), 3.72 (2H, br t, J=7 Hz), 7.05—7.38 (6H, m), 7.49—7.77 (5H, m)
3hh	3295, 2935, 1661, 1622, 1520	1.00 (3H, t, J=7 Hz), 1.16—1.70 (6H, m), 2.28—2.63 (4H, m), 3.31 (2H, dt, J=5, 6 Hz), 3.52 (2H, s), 5.25 (1H, br), 6.04—6.43 (2H, m), 6.71 (2H, d, J=9 Hz), 7.05—7.67 (8H, m)
3ii	3284, 2932, 1655, 1604, 1551, 1512	1.01 (3H, t, J=7 Hz), 1.21—1.70 (6H, m), 2.28—2.63 (4H, m), 3.32 (2H, dt, J=5, 6 Hz), 3.53 (2H, s), 3.81 (3H, s), 5.85 (1H, br t, J=5 Hz), 6.25 (1H, d, J=15 Hz), 6.84 (2H, d, J=9 Hz), 7.30 (5H, s), 7.42 (2H, d, J=9 Hz), 7.57 (1H, d, J=15 Hz)
3jj	3280, 2934, 1656, 1620, 1579, 1554	1.00 (3H, t, J=7 Hz), 1.20—1.73 (6H, m), 2.27—2.64 (4H, m), 3.33 (2H, dt, J=5, 6 Hz), 3.52 (2H, s), 3.77 (3H, s), 6.02 (1H, br), 6.37 (1H, d, J=15 Hz), 6.74—7.40 (4H, m), 7.27 (5H, s), 7.55 (1H, d, J=15 Hz)
3kk	2936, 1691, 1619	1.09 (3H, t, J=7 Hz), 1.16—1.83 (6H, m), 2.33—2.80 (4H, m), 2.40 (3H, s), 3.73 (2H, t, J=7 Hz), 3.72 (2H, s), 3.80 (3H, s), 6.76—7.50 (10H, m), 7.69 (1H, d, J=15 Hz)
3ll	3284, 2936, 1656, 1619, 1583, 1545, 1505	1.00 (3H, t, J=7 Hz), 1.20—1.70 (6H, m), 2.28—2.63 (4H, m), 3.33 (2H, dt, J=5, 6 Hz), 3.52 (2H, s), 3.86 (9H, s), 5.90 (1H, br t, J=5 Hz), 6.30 (1H, d, J=15 Hz), 6.70 (2H, s), 7.28 (5H, s), 7.52 (1H, d, J=15 Hz)
3mm	3280, 2932, 1656, 1618, 1556	1.00 (3H, t, J=7 Hz), 1.13—1.77 (6H, m), 2.27—2.63 (4H, m), 2.43 (3H, s), 3.32 (2H, dt, J=5, 6 Hz), 3.50 (2H, s), 6.10 (1H, br t, J=5 Hz), 6.33 (1H, q, J=16 Hz), 7.04—7.43 (9H, m), 7.53 (1H, d, J=16 Hz)
3nn	3450, 3286, 2934, 1661, 1621, 1552, 1041	1.00 (3H, t, J=7 Hz), 1.20—1.76 (6H, m), 2.23—2.63 (4H, m), 2.71 (3H, s), 3.33 (2H, dt, J=5, 6 Hz), 3.52 (2H, s), 6.46 (1H, br t, J=5 Hz), 6.49 (1H, d, J=16 Hz), 7.28 (5H, s), 7.59 (1H, d, J=16 Hz), 7.60 (4H, s)
3oo	3288, 2932, 1661, 1623, 1547, 1306, 1149	1.00 (3H, t, J=7 Hz), 1.25—2.07 (6H, m), 2.29—2.63 (4H, m), 3.02 (3H, s), 3.34 (2H, dt, J=5, 6 Hz), 3.51 (2H, s), 6.17 (1H, br t, J=5 Hz), 6.48 (1H, d, J=16 Hz), 7.25 (5H, s), 7.55 (2H, d, J=8 Hz), 7.58 (1H, d, J=16 Hz), 7.86 (2H, d, J=8 Hz)
3pp	2932, 1687, 1623, 1308, 1149	1.07 (3H, t, J=7 Hz), 1.23—1.82 (6H, m), 2.35—2.76 (4H, m), 2.41 (3H, s), 3.04 (3H, s), 3.67 (2H, s), 3.73 (2H, t, J=7 Hz), 7.19 (1H, d, J=16 Hz), 7.30 (5H, s), 7.68 (2H, d, J=8 Hz), 7.69 (1H, d, J=16 Hz), 7.94 (2H, d, J=8 Hz)
3qq	3284, 2934, 1663, 1626, 1537	1.01 (3H, t, J=7 Hz), 1.16—1.73 (6H, m), 2.27—2.63 (4H, m), 3.34 (2H, dt, J=5, 6 Hz), 3.53 (2H, s), 6.28 (1H, br t, J=5 Hz), 6.47 (1H, d, J=16 Hz), 7.29 (5H, s), 7.53 (2H, s), 7.55 (1H, d, J=16 Hz), 7.95 (1H, s)
3rr	2936, 1685, 1626, 1537	1.03 (3H, t, J=7 Hz), 1.13—1.80 (6H, m), 2.32—2.68 (4H, m), 2.39 (3H, s), 3.56 (2H, s), 3.71 (2H, br t, J=7 Hz), 7.15 (1H, d, J=15 Hz), 7.27 (5H, s), 7.43—7.72 (3H, m), 7.98 (1H, s)
6	3284, 2934, 1671, 1629, 1551	1.01 (3H, t, J=7 Hz), 1.10—1.67 (6H, m), 1.82 (3H, dd, J=1.5, 7 Hz), 2.24—2.64 (4H, m), 3.25 (2H, dt, J=6, 6 Hz), 3.53 (2H, s), 5.60 (1H, br), 5.75 (1H, dq, J=1.5, 15 Hz), 6.81 (1H, dq, J=7, 15 Hz), 7.30 (5H, s)
7	3290, 2932, 1643, 1552	1.01 (3H, t, J=7.5 Hz), 1.05—1.62 (6H, m), 2.23—2.63 (6H, m), 2.82—3.28 (4H, m), 3.53 (2H, s), 5.36 (1H, br s), 7.23 (5H, s), 7.30 (5H, s)

a) Spectral data of free bases were measured. b) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in parentheses. c) mp 70—72 °C. d) HCl salt was measured in DMSO-d_6.

The resulting precipitate was collected by filtration, washed with water three times and dried *in vacuo* to give colorless cubes (1.8 g, 77%), mp 298—299 °C (lit.[8] 276—277 °C). IR (KBr): 3424, 2922, 2550, 1687, 1638, 1309, 1149 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.20 (3H, s), 6.66 (1H, d, J=16 Hz), 7.65 (1H, d, J=16 Hz), 7.93 (4H, s), 12.55 (1H, br s).

3,3-Diphenylpropenoic Acid (5d) Compound **5d** was prepared from 1,1-diphenylethylene and oxalyl chloride according to the method described in the literature.[9]

5,6-Dimethoxy-1*H*-indene-2-carboxylic Acid (5e), 3,4-Dihydro-6,7-dimethoxy-2-naphthalenecarboxylic Acid (5f), and 6,7-Dihydro-2,3-dimethoxy-5*H*-benzocycloheptene-8-carboxylic Acid (5g) Compound **5e—g** were prepared according to the method described in the literature.[10]

5e: Colorless cubes, mp 251—252 °C. Yield: 29% (from 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one). IR (KBr): 3600—2300, 1665, 1610, 1555 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.67 (2H, s), 3.93 (3H, s), 3.95 (3H, s), 7.07 (1H, s), 7.10 (1H, s), 7.81 (1H, s), 9.6 (1H, br s). *Anal.* Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.19; H, 5.52.

5f: Colorless cubes, mp 190—193 °C. Yield: 74% (from 6,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-one). IR (KBr): 3650—2400, 1660, 1604, 1568, 1518 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.59 (2H, t, J=8 Hz), 2.84 (2H, t, J=8 Hz), 3.88 (3H, s), 3.91 (3H, s), 6.73 (1H, s), 6.77 (1H, s), 7.57 (1H, s), 9.55 (br s). *Anal.* Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.54; H, 6.13.

5g: Colorless cubes, mp 158—159 °C. Yield: 64% (from 2,3-dimethoxy-5*H*-6,7,8,9-tetrahydrobenzocyclohepten-5-one). IR (KBr): 3600—2000, 1670, 1600, 1570, 1520 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.95 (6H, m), 3.87 (3H, s), 3.90 (3H, s), 6.68 (1H, s), 6.86 (1H, s), 7.80 (1H, s), 9.60 (1H, br s). *Anal.* Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.97; H, 6.55.

(*E*)-*N*-[5-[*N*-Ethyl-*N*-(phenylmethyl)amino]pentyl]-3-(4-nitrophenyl)-2-propenamide Hydrochloride (3a) Diethyl phosphorocyanidate (1.1 ml) and Et_3N (0.76 ml) were added successively to a suspension of 4-nitrocinnamic acid (0.88 g) and *N*-ethyl-*N*-(phenylmethyl)pentane-1,5-diamine (**4c**, 1.0 g) in *N*,*N*-dimethylformamide (DMF, 10 ml) at 0—5 °C. The mixture was stirred at 0—5 °C for 20 min, warmed to room temperature, diluted with water, 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 as a main fraction. IR (film): 3288, 2936, 1736, 1661, 1624, 1599, 1520 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7 Hz), 1.10—2.04 (6H, m), 2.20—2.66 (4H, m), 3.36 (2H, dt, J=5, 6 Hz), 3.53 (2H, s), 6.13 (1H, br), 6.50 (1H, d, J=15 Hz), 7.27 (5H, s), 7.62 (1H, d, J=15 Hz), 7.58 (2H, d, J=9 Hz), 8.18 (2H, d, J=9 Hz).

The oil was treated with ethanolic HCl (1 eq) and the resulting solid was triturated in ether, collected by filtration, and dried *in vacuo* to give a hygroscopic amorphous powder (1.7 g). The yield and analytical data of **3a** are shown in Table I.

The following compounds (**2a**, **3c—f**, **i—w**, **y**, **aa—cc**, **ee**, **ff**, **hh—jj**, **ll—oo**, **qq**, **6**, and **7**) listed in Tables I, II, III and VII were prepared in the same manner as described for **3a**.

(*E*)-*N*-Acetyl-*N*-[5-[*N*-ethyl-*N*-(phenylmethyl)amino]pentyl]-3-(4-nitrophenyl)-2-propenamide (3b) A mixture of **3a** (0.34 g) and a catalytic amount (30 mg) of *p*-toluenesulfonic acid in acetic anhydride (5 ml) was heated at 80 °C for 6 h and 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 evaporated to afford an oil, which was chromatographed on silica gel eluting with ethyl acetate–methanol (20 : 1) to give an oil (0.29 g). IR (film): 2936, 1697, 1682, 1624, 1597, 1520 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7 Hz), 1.20—1.82 (6H, m), 2.27—2.67 (4H, m), 2.42 (3H, s), 3.54 (2H, s), 3.73 (2H, br t, J=6 Hz), 7.18 (1H, d, J=15 Hz), 7.31 (5H,

s), 7.67 (2H, d, $J=9$ Hz), 7.71 (1H, d, $J=15$ Hz), 8.23 (2H, d, $J=9$ Hz). The yield and mass spectrum of this sample are shown in Table I.

The following compounds (**2b**, **3g**, **h**, **x**, **z**, **dd**, **gg**, **kk**, **pp**, **rr**) listed in Tables I, III and VII were prepared in the same manner as described for **3b**.

(*E*)-3-(4-Aminophenyl)-*N*-[5-[*N*-ethyl-*N*-(phenylmethyl)amino]-pentyl]-2-propenamide Dihydrochloride (3aa) A suspension of **3a** (0.70 g) and concentrated HCl (0.4 ml) in ethanol (30 ml) was hydrogenated over 10% Pd/C (50 mg) under an atmospheric pressure at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated to give a residue. The residue was dissolved in 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. Chromatographic purification of the residue on silica gel eluting with ethyl acetate–methanol (20 : 1) gave an oil. IR (film): 3462, 3370, 2934, 1687, 1618 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, $J=7$ Hz), 1.13—1.83 (6H, m), 2.24—2.65 (4H, m), 3.43—3.83 (4H, m), 3.51 (2H, s), 6.04—7.37 (6H, m), 7.27 (5H, s), 7.65 (1H, d, $J=15$ Hz).

The oil was treated with ethanolic HCl (2 eq) and the resulting solid was triturated in ether, collected by filtration, and dried *in vacuo* to afford a hygroscopic amorphous powder (0.55 g). The yield, mass spectrum, and analytical data are given in Table III.

(*E*)-3-(4-Acetylaminophenyl)-*N*-[5-[*N*-ethyl-*N*-(phenylmethyl)amino]-pentyl]-2-propenamide Hydrochloride (3bb) A mixture of **3aa** (0.13 g) and acetyl chloride (53 mg) in pyridine (3 ml) was stirred at room temperature for 1 h, diluted with water, and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure to afford a residue. The residue was chromatographed on silica gel eluting with ethyl acetate–methanol (10 : 1) to give an oil (0.11 g). IR (film): 3318, 2936, 1678, 1618, 1589, 1552 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, $J=7$ Hz), 1.20—1.83 (6H, m), 2.13 (3H, s), 2.30—3.43 (6H, m), 3.52 (2H, s), 5.73 (1H, t, $J=6$ Hz), 6.28 (1H, d, $J=15$ Hz), 7.13—7.80 (11H, m).

The oil was treated with ethanolic HCl (1 eq) to afford a hygroscopic amorphous powder (0.09 g). The yield, mass spectrum, and analytical data of **3bb** are given in Table III.

***N*-(Ethyl-*N'*-[(4-nitrophenyl)methyl]-*N*-(phenylmethyl)pentane-1,5-diamine Dihydrochloride (8)** 4-Nitrobenzylbromide (0.5 g) was added portionwise to a mixture of *N*-ethyl-*N*-(phenylmethyl)pentane-1,5-diamine (**4c**, 1.0 g) and K_2CO_3 (0.45 g) in ethanol (20 ml) at room temperature. The resulting mixture was stirred for 16 h, and the solvent was removed *in vacuo* to give a residue. Water (100 ml) was added to the residue and the mixture was extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and the solvent was evaporated to give an oil, which was chromatographed on silica gel eluting with ethyl acetate–methanol (5 : 1) to afford a pale yellow oil (0.37 g). IR (film): 3306, 2932, 2858, 2802, 1669, 1602, 1518 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, $J=7$ Hz), 1.22—1.60 (6H, m), 2.20 (1H, br s), 2.39—2.65 (6H, m), 3.58 (2H, s), 3.88 (2H, s), 7.18—7.37 (5H, m), 7.49 (2H, d, $J=8.5$ Hz), 8.17 (2H, d, $J=8.5$ Hz).

The oil was treated with ethanolic HCl (2 eq) and the resulting solid was triturated in ether, collected by filtration, and dried *in vacuo* to give a hygroscopic amorphous powder (0.38 g). IR (KBr): 3418, 2948, 2774, 1635, 1607, 1523 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.43 (5H, m), 1.63—1.86 (4H, m), 2.82—3.14 (6H, m), 4.22—4.40 (4H, m), 7.37—7.53 (3H, m), 7.60—7.78 (2H, m), 7.93 (2H, d, $J=8.7$ Hz), 8.28 (2H, d, $J=8.7$ Hz), 9.82 (2H, br s), 11.0 (1H, br s). The yield and analytical data of this sample are given in Table III.

Biological Method and Materials The cerebral cortex of male Wistar rats was homogenized with 20 volumes of ice-coold 0.32 M sucrose, and centrifuged at $1000 \times g$ for 10 min. The supernatant (Sl) was preincubated in a scintillation vial with a test compound for 15 min at room temperature, then [acetyl-^{3}H]-acetylcholine (final 200 μM) was added and the incubation was continued for 30 min. The reaction was terminated by adding a 1 M solution of chloroacetic acid, followed by a toluene-based scintillant, and the vials were capped and shaken to transfer the produced [^{3}H]-acetic acid to the toluene phase. Radioactivity in the toluene phase was then counted by liquid scintillation spectrometry (Aloka LSC-903 or LSC-1000). The inhibitory activities were expressed as the 50%-inhibitory concentration (IC_{50}), which was calculated by probit analysis. The inhibitory activities of physostigmine and THA were measured using the same technique.

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