Central Cholinergic Agents. 6. Synthesis and Evaluation of 3-[1-(Phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanones and Their Analogs as Central Selective Acetylcholinesterase Inhibitors

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Received March 14, 1994[⊗]

In an attempt to find central selective acetylcholinesterase (AChE) inhibitors, 3-[1-(phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanones **9** and their analogs were designed on the basis of our working hypothesis of the enzyme's active site. These compounds were prepared by regioselective Friedel–Crafts acylation of 2,3,4,5-tetrahydro-1*H*-1-benzazepines and related nitrogen heterocycles as a key step. Most compounds showed potent inhibitory activities with IC_{50}s in the 10–300 nM range. In order to estimate their central selectivities, we examined their effects on the apomorphine-induced circling behavior in rats with unilateral striatal lesions. Among compounds with potent AChE inhibition, 3-[1-(phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanone fumarate (**9a**, TAK-147) (IC_{50} of AChE inhibition = 97.7 nM) inhibited the circling behavior at 3 mg/kg po, in which it had no significant effect on peripheral cholinergic effects. This demonstrates that **9a** has favorable central selectivity. Furthermore, **9a** significantly ameliorated diazepam-induced passive avoidance deficit at 1 mg/kg po. The benzazepine derivative **9a** was selected as a candidate for clinical evaluation.

Senile dementia of the Alzheimer type (SDAT) has been shown to be closely associated with defects in the central cholinergic system.[1] Many clinical and animal studies suggest that cholinergic dysfunction may be one of the causes of disturbances in learning and memory in SDAT patients. Thus, pharmacological manipulation of the cholinergic system has been targeted as a viable approach for the treatment of SDAT.[2] Cholinergic enhancement can be achieved by the use of acetylcholine precursors, muscarinic agonists, or AChE inhibitors. Among them, much attention has been focused on AChE inhibitors after the report of clinical improvement with tetrahydroaminoacridine (THA).[3] THA has been approved by the FDA as the first agent for the treatment of SDAT, although it has disadvantages such as liver toxicity.

In an attempt to find a new type of AChE inhibitor, we have proposed a working hypothesis of the active site of the enzyme, without the knowledge of the enzyme structure.[4] This has been shown to be effective in the design of AChE inhibitors bearing an *N*-ethyl-*N*-(phenylmethyl)amino moiety such as 2-[ω-[*N*-ethyl-*N*-(phenylmethyl)amino]alkyl]-1*H*-isoindole-1,3(2*H*)-diones **1**[4a] and ω-[*N*-ethyl-*N*-(phenylmethyl)amino]-1-phenyl-1-alkanones **2** (Figure 1).[4c] 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).[5] Recently, the X-ray analysis of AChE from *Torpedo californica* has been reported by Sussman *et al.*[6] It was revealed that the catalytic subsites are located near the bottom of a deep and narrow gorge of the enzyme. It was also found that

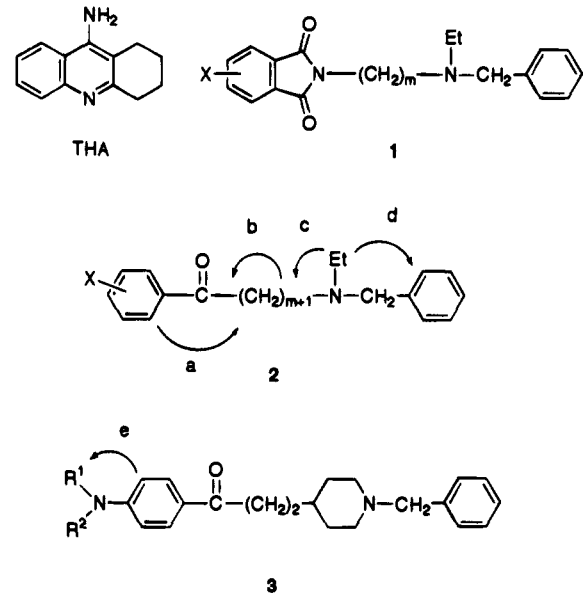


Figure 1.

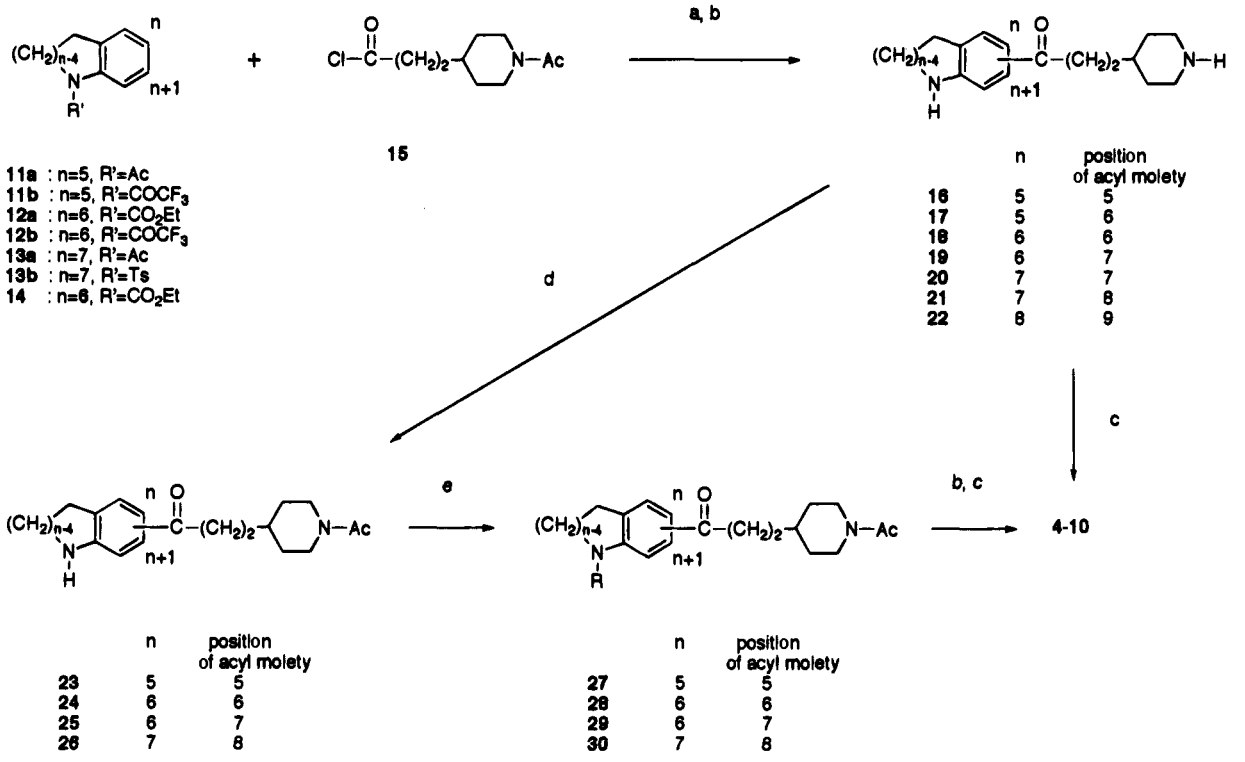
several aromatic residues exist some distance away from the catalytic subsites. By means of molecular modeling techniques, we are now investigating which aromatic residue corresponds to HBS-2 that has been assumed in our working hypothesis.

Up to the present, most cholinergic agents under clinical trials are reported to show only mild to moderate ameliorating effects on memory deficits of SDAT patients.[7] One of the reasons is attributed to their adverse peripheral effects. This could be overcome by searching for central selective inhibitors of AChE. In other words, AChE inhibitors are expected to act selectively on the central nervous system, thus exhibiting ameliorating effects on cholinergic deficits without showing periph-

[⊗] Abstract published in *Advance ACS Abstracts*, June 15, 1994.

0022-2623/94/1837-2292$04.50/0

Scheme 1[a]



[a] (a) $AlCl_3$; (b) concentrated HCl; (c) $PhCH_2Br$, K_2CO_3; (d) Ac_2O; (e) RI, K_2CO_3.

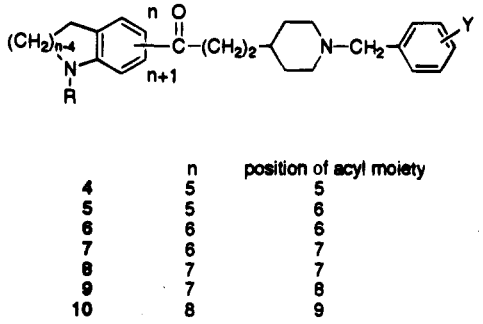


Figure 2.

eral effects. During our effort to find such inhibitors, we studied the effect of partial conformational restriction of **2**, which is shown by arrows a–d, on central selectivity (Figure 1)[4c] and found that 3-[1-(phenylmethyl)-4-piperidinyl]-1-[4-(1-pyrrolidinyl)phenyl]-1-propanone (**3**, NR^1R^2 = pyrrolidino) exhibited preferable selectivity.[8] This finding prompted us to prepare heterocyclic derivatives **4–10** (Figure 2), which are analogs of **3** with ring closure e. Here, we describe the synthesis and biological evaluation of 3-[1-(phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanones **9** and their analogs **4–8** and **10** as central selective AChE inhibitors.

Chemistry

The syntheses of compounds **4–10** are outlined in Scheme 1. The intermediates **16–22** were prepared by regioselective Friedel–Crafts acylation of 2,3,4,5-tetrahydro-1*H*-1-benzazepine **13** and related nitrogen heterocycles **11**, **12**, and **14** as a key reaction. All the reactions proceeded regioselectively except the formation of compound **17**.

According to our previous report,[10] acylation of appropriately NH-protected substrates **11–14** with an acid chloride, **15**, was carried out in the presence of 3.5 equiv of $AlCl_3$. After acid hydrolysis, regiochemically pure compounds **16**, **18**, **19**, **21**, and **22** were obtained in 35–63% yield from **11a** (R′ = Ac), **12a** (R′ = CO_2Et), **12b** (R′ = $COCF_3$), **13a** (R′ = Ac), and **14** (R′ = CO_2Et), respectively. Compound **17** was isolated by repeated recrystallization of a mixture of **16** and **17** (*ca.* 1:2), which in turn was prepared by acylation of **11b** (R′ = $COCF_3$). Acylation of **13b** (R′ = Ts) in the presence of 2 equiv of $AlCl_3$ followed by hydrolysis gave **20** in 8% yield with 79% recovery of **13b**.

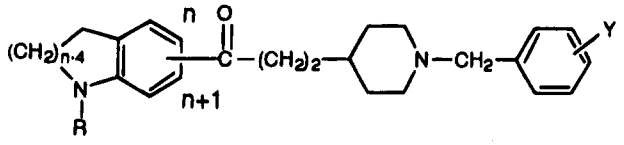
By two routes, these intermediates, **16–22**, were converted to **4–10**. In method A, **16–22** were allowed to react with 0.95 equiv of benzyl bromide to yield **4–10** (R = H). Treatment of **16–21** with 2 equiv of benzyl bromide gave **4–9** (R = CH_2Ph). In method B, reaction of compounds **16**, **18**, **19**, and **21** with Ac_2O afforded **23–26**, which were alkylated with various alkyl iodides to yield **27–30** (R = alkyl). Compounds **27–30** were then converted to **4**, **6**, **7**, and **9** (R = alkyl) by acid hydrolysis and subsequent benzylation.

Results and Discussion

AChE Inhibition. The measurement of AChE inhibitory activity was carried out radiometrically via the method of Kleinberger and Yanai.[11] The results are summarized in Table 1 as IC_{50} values (concentration required to inhibit control enzyme activity by 50%). The IC_{50} value of THA was measured to be 270.9 nM.

The effects on AChE inhibition of the size (*n*) of the heterocyclic ring as well as the substituents of the ring nitrogen (R) were examined. Among N-unsubstituted compounds **4a**, **5a**, **6a**, **7a**, **8**, **9a**, and **10**, an indoline derivative, **4a**, was the most potent inhibitor, *i.e.*, IC_{50} value of **4a** was 20 nM. Other compounds also exhibited potent activities with IC_{50}s in the 50–300 nM range.

Table 1. Physicochemical Data and AChE Inhibitory Activities of 4–10



compd	*n*	R	position of acyl moiety[a]	Y	synthetic method[b]	yield,[c] %	mp,[d] °C	formula[e]	inhibition of AChE,[f] IC_{50}, nM
4a	5	H	5	H	A	85	150–153	$C_{23}H_{28}N_2O{\cdot}C_4H_4O_4$	20
4b	5	Me	5	H	B	69	147–151 dec	$C_{24}H_{30}N_2O{\cdot}C_4H_4O_4$	10
4c	5	Et	5	H	B	77	155–157	$C_{25}H_{32}N_2O{\cdot}C_4H_4O_4$	11
4d	5	Pr	5	H	B	55	91–93	$C_{26}H_{34}N_2O{\cdot}C_4H_4O_4$	22
4e	5	Bu	5	H	B	69	127–129	$C_{27}H_{38}N_2O{\cdot}C_4H_4O_4$	29
4f	5	pentyl	5	H	B	75	140–142	$C_{28}H_{38}N_2O{\cdot}C_4H_4O_4$	47
4g	5	CH_2Ph	5	H	A	58	153–156 dec	$C_{30}H_{34}N_2O{\cdot}C_4H_4O_4$	68
4h	5	H	5	2-OMe	A	61	169–171 dec	$C_{24}H_{30}N_2O_2{\cdot}C_4H_4O_4$	812
4i	5	H	5	3-OMe	A	76	151–153 dec	$C_{24}H_{30}N_2O_2{\cdot}C_4H_4O_4$	2680
4j	5	H	5	4-OMe	A	62	101–103	$C_{24}H_{30}N_2O_2{\cdot}C_4H_4O_4$	13300
4k	5	H	5	2-F	A	51	144–147	$C_{23}H_{27}FN_2O{\cdot}C_4H_4O_4$	43
4l	5	H	5	3-F	A	74	163–165 dec	$C_{23}H_{27}FN_2O{\cdot}C_4H_4O_4$	16
4m	5	H	5	4-F	A	66	124–127	$C_{23}H_{27}FN_2O{\cdot}C_4H_4O_4$	89
4n	5	H	5	2-Cl	A	84	159–161	$C_{23}H_{27}ClN_2O{\cdot}C_4H_4O_4$	76
4o	5	H	5	3-Cl	A	82	157–159	$C_{23}H_{27}ClN_2O{\cdot}C_4H_4O_4$	59
4p	5	H	5	4-Cl	A	92	146–148	$C_{23}H_{27}ClN_2O{\cdot}C_4H_4O_4$	6360
4q	5	H	5	3-Me	A	77	160–163 dec	$C_{24}H_{30}N_2O{\cdot}C_4H_4O_4$	50
4r	5	H	5	3-NO_2	A	72	114–116[g]	$C_{23}H_{27}N_3O_3$	64
5a	5	H	6	H	A	62	157–158	$C_{23}H_{28}N_2O{\cdot}C_4H_4O_4$	113
5b	5	CH_2Ph	6	H	A	56	141–143 dec	$C_{30}H_{34}N_2O{\cdot}C_4H_4O_4{\cdot}0.5H_2O$	853
6a	6	H	6	H	A	82	138–142 dec	$C_{24}H_{30}N_2O{\cdot}C_4H_4O_4{\cdot}0.5H_2O$	54
6b	6	Me	6	H	B	79	170–172 dec	$C_{25}H_{32}N_2O{\cdot}C_4H_4O_4$	24
6c	6	CH_2Ph	6	H	A	55	178–181 dec	$C_{31}H_{36}N_2O{\cdot}C_4H_4O_4$	164
7a	6	H	7	H	A	77	175–177 dec	$C_{24}H_{30}N_2O{\cdot}C_4H_4O_4$	54
7b	6	Me	7	H	B	82	143–144 dec	$C_{25}H_{32}N_2O{\cdot}C_4H_4O_4$	36
7c	6	CH_2Ph	7	H	A	86	180–182 dec	$C_{31}H_{38}N_2O{\cdot}C_4H_4O_4$	1490
8	7	H	7	H	A	58	117–120	$C_{25}H_{32}N_2O{\cdot}C_4H_4O_4$	125
9a	7	H	8	H	A	63	176–178	$C_{25}H_{32}N_2O{\cdot}C_4H_4O_4$	97.7 ± 8.0[h]
9b	7	Me	8	H	B	81	100–102	$C_{26}H_{34}N_2O{\cdot}C_4H_4O_4$	81
9c	7	Et	8	H	B	83	84–87	$C_{27}H_{38}N_2O{\cdot}C_4H_4O_4$	376
9d	7	Pr	8	H	B	83	98–100	$C_{28}H_{38}N_2O{\cdot}C_4H_4O_4$	1330
9e	7	CH_2Ph	8	H	A	62	171–173	$C_{32}H_{38}N_2O{\cdot}C_4H_4O_4$	3140
9f	7	H	8	2-OMe	A	56	116–117	$C_{26}H_{34}N_2O_2{\cdot}C_4H_4O_4$	2620
9g	7	H	8	3-OMe	A	84	126–128	$C_{26}H_{34}N_2O_2{\cdot}C_4H_4O_4$	847
9h	7	H	8	4-OMe	A	55	168–170	$C_{26}H_{34}N_2O_2{\cdot}C_4H_4O_4$	55200
9i	7	H	8	2-F	A	81	165–170	$C_{25}H_{31}FN_2O{\cdot}C_4H_4O_4$	331
9j	7	H	8	3-F	A	86	156–160	$C_{25}H_{31}FN_2O{\cdot}C_4H_4O_4$	145
9k	7	H	8	4-F	A	61	158–163	$C_{25}H_{31}FN_2O{\cdot}C_4H_4O_4$	393
9l	7	H	8	3-Cl	A	81	138–144	$C_{25}H_{31}ClN_2O{\cdot}C_4H_4O_4$	333
9m	7	H	8	3-Me	A	84	152–158	$C_{26}H_{34}N_2O{\cdot}C_4H_4O_4$	224
9n	7	H	8	3-NO_2	A	58	161–163	$C_{25}H_{31}N_3O_3{\cdot}C_4H_4O_4$	390
10	8	H	9	H	A	69	165–166	$C_{26}H_{34}N_2O{\cdot}C_4H_4O_4$	127
THA									270.9 ± 19.2[h]

[a] Attachment position of 3-[1-(phenylmethyl)-4-piperidinyl]propionyl group. [b] Methods are described in the text. [c] Numbers represent the yield for the last step. Yields were not optimized. [d] Recrystallization from EtOH, unless otherwise noted. [e] All compounds are fumarates except for **4r** (free base). Elemental analyses for C, H, and N were within ±0.4% of the theoretical values. [f] The IC_{50} value is the concentration required to inhibit control enzyme activity by 50%. These values were derived from a single experiment done in triplicate, unless otherwise noted. All compounds were dissolved in DMSO. [g] Recrystallization from CH_2Cl_2–ether. [h] Mean ± SEM; $n = 5$.

The potency seemed to decrease gradually in accordance with increasing size (n) of the heterocyclic ring. Methyl substitution on the indoline nitrogen enhanced the activity (*cf.* **4a** vs **4b**), whereas substitution with the bulkier groups resulted in a gradual decrease of the potency (*e.g.*, **4b–g**). Similar tendencies were observed in the tetrahydroquinolines **6** and **7** and the tetrahydro-1-benzazepine derivatives **9**. Bulky substituent on the ring nitrogen (R) appeared to be tolerated in compounds bearing the acyl moiety at the para position to the ring nitrogen, *i.e.*, IC_{50} values of **4g** and **6c** were 68 and 164 nM, respectively. Compounds having the acyl moiety at the meta position, on the other hand, showed poor activities (*e.g.*, **5b**, **7c**, and **9e**). Using molecular modeling, we have investigated the interaction between compounds **4–10** and the enzyme. The study could rationally explain the above structure–activity relationships. The full details of the method, results, and discussion will be reported elsewhere.[9]

The effects of substitution on the benzylamino moiety were examined next. Among the substituents (Y) examined, a fluoro group at the meta position increased or retained the activity (*cf.* **4a** vs **4l** and **9a** vs **9j**). Meta substitution with other groups also seemed to be tolerated to some extent (*e.g.*, **4o,q,r** and **9m**). Substituents at the para position, however, resulted in a significant reduction of inhibitory potency (*e.g.*, **4j,p** and **9h**).

Evaluation of Compounds as Central Selective AChE Inhibitors. In the striatum, dopaminergic neurons inhibit firing of cholinergic neurons, and dopaminergic agonists such as apomorphine reduce the release and turnover of striatal acetylcholine.[12] Apomorphine produces circling behavior in rats with unilateral lesions of the striatum. Cholinergic agonists

inhibited circling behavior induced by apomorphine in rats and mice.[13] In the present study, we examined compounds that showed potent AChE inhibition (IC_{50} = 10–300 nM) for their effects on apomorphine-induced circling behavior in rats with unilateral striatal lesions caused by injection of excitatory amino acid.[14] Our aim here was to find compounds that inhibit the circling behavior at doses in which they do not cause any peripheral side effects. These compounds, central selective AChE inhibitors, could ameliorate learning and memory impairment without causing any adverse effects.

Initially, to set up a dose of the experiment for each compound, these compounds were examined for their effects on peripheral behavioral changes such as salivation, lacrimation, diarrhea, and fasciculation (Table 2). Most compounds exhibited fasciculation at doses of 3 or 10 mg/kg po. THA also caused fasciculation at 30 mg/kg po. Therefore, compounds were subsequently evaluated, at doses less than these doses causing fasciculation, for their inhibitory effects on the apomorphine-induced circling behavior. Among them, the benzazepine derivative **9a** significantly inhibited the circling behavior at 3 mg/kg po, in which it had no notable effect on peripheral cholinergic effects. Compounds **4b** and **6b** inhibited the circling at doses of 10 and 3 mg/kg po, respectively, although fasciculation was observed at these doses. THA also inhibited the circling behavior at 10 mg/kg po. Compounds **4g**,**n**, **6a**, **8**, and **10** only showed tendencies to inhibit the circling behavior. The selected compounds **4b**,**g**,**n**, **6a**,**b**, **8**, **9a**, and **10** and THA were further examined for their effects on diazepam-induced passive avoidance response. Compound **9a** and THA significantly ameliorated the memory impairment at doses of 1 and 10 mg/kg po, respectively (Table 3). None of the other compounds exhibited significant improvement *at doses that do not cause peripheral effects*. These results are in good accordance with those obtained by the circling tests. Among compounds **4**–**10** examined in this study, the benzazepine derivative **9a** was found to have the most preferable property in terms of central selectivity.

In order to compare **9a** and THA in more detail, their ED_{50} values of fasciculation and acute toxicities were examined. The ratio of ED_{50}(fasciculation)/MED(ameliorating effect on the memory impairment) given in Table 4 indicates that **9a** is about 7 times more central selective than THA. Table 4 also shows that **9a** has a 33 times wider therapeutic index than THA does. Furthermore, **9a** has been shown to produce, at doses of 0.3–3 mg/kg po, an apparent improvement of impaired learning and memory in other animal models such as scopolamine-induced impairment of delayed matching to sample task as well as impaired DRL (differential reinforcement at low rate) performance in AF64A-treated rats.[15a]

In conclusion, we have found that 3-[1-(phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanone fumarate (**9a**) is a central selective AChE inhibitor that does not cause any peripheral effects at doses that ameliorate learning and memory impairment. On the basis of these findings as well as further biological and neuropharmacological studies,[15] **9a** was chosen as a candidate for the treatment of senile dementia including SDAT. The benzazepine derivative **9a** is now under clinical investigation.

Table 2. Biological Data for Selected Compounds

	peripheral actions at the following doses,[a] mg/kg				inhibition of circling behavior[b]		
compd	1	3	10	30	dose[c]	no. of circlings[d]	% of control[e]
4a	NT	NS	F,L	F,L	control	51.3 ± 8.2	
					3	52.4 ± 7.0	102.2
4b	NT	NS	F,L	F,L,S	control	92.0 ± 10.0	
					3	68.7 ± 8.3	74.7
					10	51.9 ± 12.6	56.4*
4c	NT	NS	F	F,S	control	82.1 ± 6.8	
					3	89.7 ± 11.7	109.2
4d	NT	NT	NS	F	control	88.6 ± 6.9	
					10	81.0 ± 12.6	91.4
4e	NT	NS	F	F,D	control	78.1 ± 12.8	
					3	86.4 ± 10.3	110.6
4f	NT	NS	F,S	F,S	control	90.0 ± 18.4	
					3	79.0 ± 12.5	87.8
4g	NT	NS	F	F,L	control	80.7 ± 6.2	
					3	66.8 ± 14.6	82.8
4k	NT	NS	S	F,S	control	90.8 ± 7.8	
					10	86.7 ± 9.9	95.5
4l	NT	NS	F	F	control	87.3 ± 8.4	
					3	84.3 ± 8.6	96.7
4m	NT	NS	F,L	F,L	control	97.2 ± 27.2	
					3	107.4 ± 12.8	110.5
4n	NT	NT	NS	F	control	80.7 ± 6.2	
					10	67.5 ± 12.9	83.6
4o	NT	NT	NS	F	control	98.9 ± 15.0	
					10	94.9 ± 7.3	96.0
4q	NT	NS	F	F	control	80.0 ± 9.1	
					3	104.0 ± 14.7	130.0
4r	NT	NT	NS	F	control	80.7 ± 6.2	
					10	91.1 ± 16.0	112.9
5a	S	F,L,S	F,L,S	F,L	control	95.5 ± 6.1	
					1	107.9 ± 13.4	112.9
6a	NS	F	F	F,L	control	97.2 ± 27.2	
					1	70.1 ± 16.3	72.1
					control	94.0 ± 9.9	
					3	77.4 ± 9.4	81.4
6b	NS	F	F,L	F,L,S	control	94.0 ± 9.9	
					1	76.5 ± 9.5	82.3
					3	54.5 ± 8.7	58.0*
6c	NT	NT	NS	F	control	83.5 ± 9.8	
					10	88.0 ± 10.6	105.4
7a	NT	NS	F	F	control	51.3 ± 8.2	
					3	60.5 ± 21.5	118.0
7b	NT	NS	F	F,L	control	97.2 ± 27.2	
					3	105.6 ± 9.7	108.6
8	NT	NS	F	F,S	control	132.0 ± 18.4	
					3	94.7 ± 21.0	71.8
9a	NT	NS	F	F,L	control	107.4 ± 9.0	
					1	87.5 ± 10.4	81.4
					3	75.1 ± 9.3	69.9*
9b	NT	NS	F	F	control	115.6 ± 9.8	
					3	100.3 ± 18.3	86.7
9j	NS	S	F	F,L	control	95.5 ± 6.1	
					3	98.4 ± 8.4	103.0
9m	NT	NT	NS	L,S	control	64.1 ± 8.6	
					10	61.4 ± 10.6	95.8
10	NS	S	F,L	F,L	control	74.2 ± 10.3	
					1	60.7 ± 6.8	81.8
THA	NT	NT	NS	F	control	83.8 ± 7.2	
					3	73.6 ± 7.7	87.8
					10	55.9 ± 8.9	66.7*

[a] Compounds were administered orally. The following abbreviations are used, F = fasciculation, S = salivation, L = lacrimation, D = diarrhea, NS = no significant changes, and NT = not tested. [b] Effects on apomorphine-induced circling behavior in rats with unilateral striatal lesions. [c] Compounds were administered orally (mg/kg). Control groups were treated with saline. [d] Numbers of circlings were observed for 30 min; mean ± SEM (Student's *t*-test). [e] Asterisk (*) distinguishes statistically significant values ($p < 0.05$) using the Student's *t*-test.

Table 3. Ameliorating Effects of Compound **9a** and THA on Diazepam-Induced Memory Impairment of Passive Avoidance Response

compd (mg/kg po)	avoidance time (no. of rats)[a]
saline	300 ± 0 (7)
DZP[b] + saline	80.8 ± 26.0 (12)
9a (0.3) + DZP[b]	106.6 ± 51.5 (7)
9a (1) + DZP[b]	192.2 ± 42.5* (7)
9a (3) + DZP[b]	193.2 ± 41.5* (7)
saline	300 ± 0 (7)
DZP[b] + saline	18.4 ± 1.2 (12)
THA (1) + DZP[b]	98.3 ± 23.0 (7)
THA (3) + DZP[b]	112.7 ± 35.8 (7)
THA (10) + DZP[b]	127.1 ± 38.6* (7)
THA (30) + DZP[b]	138.1 ± 43.1* (7)

[a] The avoidance time (mean ± SEM) in seconds. Asterisk (*) distinguishes significant values ($p < 0.05$, compared with DZP control) using the Mann–Whitney *U*-test. [b] Diazepam (DZP, 5 mg/kg) was administered intraperitoneally.

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken on a Jasco IR-810 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini-200 (200 MHz) NMR spectrometer. Chemical shifts are given in δ values (ppm) with tetramethylsilane as an internal standard, and coupling constants (J) are given in hertz. Where elemental analyses are given, results obtained were within ±0.4% of the theoretical values. Solutions in organic solvents were dried over anhydrous Na_2SO_4. Chromatographic purifications were carried out on silica gel columns (Kieselgel 60, 0.063–0.200 mm, Merck).

3-(4-Piperidinyl)-1-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanone (21). Freshly powdered $AlCl_3$ (23.7 g, 178 mmol) was added portionwise to a mixture of 3-(1-acetyl-4-piperidinyl)propionyl chloride (**15**) (11.0 g, 50.5 mmol)[6] and 1-acetyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine (**13a**) (9.6 g, 50.7 mmol)[16] in $ClCH_2CH_2Cl$ (50 mL) at room temperature. The mixture was stirred at 65–70 °C for 12 h, poured into ice–water, and extracted with CH_2Cl_2. The extracts were washed with water and dried. The solvents were removed in vacuo to afford a residue, which was chromatographed on silica gel eluting with EtOAc–MeOH (10:1) to give a crystal. Recrystallization from CH_2Cl_2–ether afforded 3-(1-acetyl-4-piperidinyl)-1-(1-acetyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanone (**21'**) (7.2 g, 38%) as colorless cubes: mp 133–134 °C; IR (KBr) 3442, 2930, 2854, 1686, 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02–1.31 (2 H, m), 1.32–2.12 (14 H, m), 2.32–2.67 (3 H, m), 2.74–2.85 (2 H, m), 2.92–3.13 (3 H, m), 3.72–3.88 (1 H, m), 4.53–4.78 (2 H, m), 7.37 (1 H, d, J = 7.8), 7.74 (1 H, d, J = 1.8), 7.83 (1 H, dd, J = 1.8, 7.8). Anal. ($C_{22}H_{30}N_2O_3$) C, H, N. A solution of **21'** (7.1 g, 19.2 mmol) in concentrated HCl (60 mL) was refluxed for 16 h and concentrated, and the remaining residue was dissolved in water. The solution was washed with EtOAc, made basic with 10% NaOH, and extracted with CH_2Cl_2. The extracts were washed with water, dried, and concentrated to give **21** (5.2 g, 95%) as a colorless powder after recrystallization from CH_2Cl_2–ether: mp 104–107 °C; IR (KBr) 3360, 2922, 2850, 1674, 1603, 1575 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04–1.28 (2 H, m), 1.33–1.52 (1 H, m), 1.52–2.07 (9 H, m), 2.58 (2 H, dt, J = 2.5, 12.1), 2.72–3.20 (8 H, m), 3.95 (1 H, br s), 7.17 (1 H, d, J = 7.7), 7.35 (1 H, d, J = 1.7), 7.40 (1 H, dd, J = 1.7, 7.7). Anal. ($C_{18}H_{26}N_2O$) C, H, N.

The following compounds, **16–19** and **22**, were prepared in the same manner and purified by recrystallization from CH_2Cl_2–ether.

1-(2,3-Dihydro-1*H*-indol-5-yl)-3-(4-piperidinyl)-1-propanone (16): yield 63% from 1-acetyl-2,3-dihydro-1*H*-indole (**11a**);[17] colorless cubes; mp 137–139 °C; IR (KBr) 3436, 3302, 2918, 2804, 1649, 1601 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03–1.28 (2 H, m), 1.30–1.80 (6 H, m), 2.58 (2 H, dt, J = 2.4, 12.1), 2.88 (2 H, t, J = 7.7), 3.00–3.14 (4 H, m), 3.68 (2 H, t, J = 8.4), 4.20 (1 H, br s), 6.55 (1 H, d, J = 8.1), 7.67–7.77 (2 H, m). Anal. ($C_{16}H_{22}N_2O$) C, H, N.

1-(2,3-Dihydro-1*H*-indol-6-yl)-3-(4-piperidinyl)-1-propanone (17): yield 7.3% from 1-(trifluoroacetyl)-2,3-dihydro-1*H*-indole (**11b**)[18] after repeated recrystallization; colorless powder; mp 146–148 °C; IR (KBr) 3432, 2948, 2834, 1681, 1621, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03–1.25 (2 H, m), 1.30–1.55 (1 H, m), 1.57–1.78 (4 H, m), *ca.* 1.95 (1 H, br), 2.58 (2 H, dt, J = 2.2, 12.0), 2.92 (2 H, t, J = 7.5), 2.97–3.13 (4 H, m), 3.60 (2 H, t, J = 8.4), *ca.* 3.85 (1 H, br), 7.11–7.18 (2 H, m), 7.30 (1 H, dd, J = 1.7, 8.1). Anal. ($C_{16}H_{22}N_2O$) C, H, N.

3-(4-Piperidinyl)-1-(1,2,3,4-tetrahydroquinolin-6-yl)-1-propanone (18): yield 43% from 1-(ethoxycarbonyl)-1,2,3,4-tetrahydroquinoline (**12a**);[19] pale yellow cubes; mp 121–123 °C; IR (KBr) 3286, 2924, 2844, 1658, 1607, 1587 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02–1.27 (2 H, m), 1.32–1.56 (1 H, m), 1.58–1.80 (5 H, m), 1.87–2.02 (2 H, m), 2.57 (2 H, dt, J = 2.5, 12.1), 2.73–2.92 (4 H, m), 3.00–3.13 (2 H, m), 3.32–3.42 (2 H, m), 4.40 (1 H, s), 6.40 (1 H, d, J = 9.1), 7.57–7.63 (2 H, m). Anal. ($C_{17}H_{24}N_2O$) C, H, N.

3-(4-Piperidinyl)-1-(1,2,3,4-tetrahydroquinolin-7-yl)-1-propanone (19): yield 34% from 1-(trifluoroacetyl)-1,2,3,4-tetrahydroquinoline (**12b**);[20] pale yellow cubes; mp 88–90 °C; IR (KBr) 3250, 2928, 2842, 1680, 1607, 1573 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02–1.28 (2 H, m), 1.30–1.57 (1 H, m), 1.59–1.80 (5 H, m), 1.87–2.02 (2 H, m), 2.57 (2 H, dt, J = 2.2, 12.1), 2.79 (2 H, t, J = 6.4), 2.90 (2 H, t, J = 7.7), 3.00–3.13 (2 H, m), 3.28–3.37 (2 H, m), 4.00 (1 H, s), 6.99 (1 H, d, J = 7.7), 7.05 (1 H, d, J = 1.8), 7.16 (1 H, dd, J = 1.8, 7.7). Anal. ($C_{17}H_{24}N_2O$) C, H, N.

1-(1,2,3,4,5,6-Hexahydrobenzazocin-9-yl)-3-(4-piperidinyl)-1-propanone (22): yield 35% from 1-(ethoxycarbonyl)-1,2,3,4,5,6-hexahydro-1-benzazocine (**14**);[10] colorless oil; IR (neat) 3400, 3324, 2922, 2848, 1675, 1602, 1571 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04–1.27 (2 H, m), 1.32–1.84 (11 H, m), 2.08 (1 H, br), 2.58 (2 H, dt, J = 2.3, 12.0), 2.80–3.15 (7 H, m), 3.28 (2 H, t, J = 5.2), 7.11 (1 H, d, J = 7.6), 7.28 (1 H, br s), 7.46 (1 H, dd, J = 1.8, 7.6).

3-(4-Piperidinyl)-1-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-7-yl)-1-propanone (20). Freshly powdered $AlCl_3$ (8.6 g, 64.5 mmol) was added portionwise to a mixture of **15** (7.0 g, 32.2 mmol), CS_2 (20 mL), and $ClCH_2CH_2Cl$ (20 mL) at room temperature. After the mixture was stirred for 30 min, 1-(*p*-tolylsulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (**13b**) (6.6 g, 21.9 mmol)[10] was added to the mixture. The resulting mixture was stirred at room temperature for 3 days, poured into ice–water, and extracted with CH_2Cl_2. The extracts were washed with water and dried. The solvents were removed in vacuo to afford a residue. Chromatographic purification of the residue on silica gel eluting with EtOAc–MeOH (10:1) gave 3-(1-acetyl-4-piperidinyl)-1-[1-(*p*-tolylsulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-7-yl]-1-propanone as an oil. Starting material **13b** (5.2 g, 79%) was also recovered. A solution of the oil in concentrated HCl (5 mL) was refluxed for 12 h and concentrated, and the residue was dissolved in water. The solution was washed with EtOAc, made basic with 10% NaOH, and extracted with CH_2Cl_2. The extracts were washed with water and dried, and the solvent was evaporated to give **20** (0.5 g, 8%) as colorless cubes after recrystallization from CH_2Cl_2–ether: mp 122–124 °C; IR (KBr) 3290, 3234, 3162, 2922, 2846, 1670, 1591 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03–1.57 (3 H, m), 1.59–1.96 (9 H, m), 2.58 (2 H, dt, J = 2.5, 12.1), 2.77–3.20 (8 H, m), 4.16 (1 H, br s), 6.67 (1 H, d, J = 8.2), 7.65 (1 H, dd, J = 2.1, 8.2), 7.72 (1 H, d, J = 2.1). Anal. ($C_{18}H_{26}N_2O \cdot 0.2H_2O$) C, H, N.

3-[1-(Phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanone Fumarate (9a). A solution of benzyl bromide (2.95 g, 17.2 mmol) in EtOH (10 mL) was added dropwise to a mixture of **21** (5.2 g, 18.2 mmol) and K_2CO_3 (3.3 g, 23.9 mmol) in EtOH (100 mL) at 0–5 °C. The mixture was stirred at room temperature for 3 h and concentrated to give a residue. The residue was dissolved in 5% HCl, washed with EtOAc, made basic with 10% NaOH, and extracted with CH_2Cl_2. The extracts were washed with water, dried, and concentrated to afford a residue. Chromatographic purification of the residue on silica gel eluting with

Table 4. Compound **9a** and THA: Comparative Data

compd	fasciculation,[a] ED_{50}, mg/kg po	acute toxicity in rat,[a] LD_{50}, mg/kg po	diazepam,[b] MED, mg/kg po	central selectivity[c]	therapeutic index[d]
9a	10.2 (4.9–16.8)	333.7 (224.9–493.2)	1	10.2	334
THA	14.9 (8.0–27.6)	102.2 (48.6–168.0)	10	1.5	10.2

[a] 95% confidence limits determined by probit analysis are in parentheses. [b] Ameliorating effects on diazepam-induced memory impairment of passive avoidance response. See Table 3. [c] ED_{50}(fasciculation)/MED(ameliorating effect on diazepam-induced memory impairment). [d] LD_{50}/MED(ameliorating effect on diazepam-induced memory impairment).

EtOAc–MeOH (20:1) gave colorless cubes (free base of **9a**, 5.75 g), mp 120–121 °C. To a solution of the crystals (5.74 g, 15.2 mmol) in CH_2Cl_2 (20 mL) was added a solution of fumaric acid (1.77 g, 15.2 mmol) in hot MeOH (20 mL). After evaporation of solvents, EtOH (20 mL) was added to the remaining residue and the mixture allowed to stand at room temperature. The resulting precipitate was collected by filtration and washed with cold EtOH to yield **9a** (6.83 g, 76%) as colorless needles: mp 176–178 °C; IR (KBr) 3432, 2930, 1677 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.15–1.34 (3 H, m), 1.46–1.77 (8 H, m), 1.93–2.10 (2 H, m), 2.66–2.75 (2 H, m), 2.78–2.97 (6 H, m), *ca.* 3.4 (2 H, br s), 3.53 (2 H, s), *ca.* 5.5 (1 H, br s), 6.60 (2 H, s), 7.13 (1 H, d, J = 7.8), 7.24–7.38 (6 H, m), 7.41 (1 H, d, J = 1.6). Anal. ($C_{25}H_{32}N_2O{\cdot}C_4H_4O_4$) C, H, N.

The compounds **4a,h–r**, **5a**, **6a**, **7a**, **8**, **9f–n**, and **10** listed in Table 1 were similarly prepared. In the preparation of compounds **4g**, **5b**, **6c**, **7c**, and **9e** listed in Table **1**, 2 equiv of benzyl bromide was used.

3-(1-Acetyl-4-piperidinyl)-1-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanone (26). A solution of Ac_2O (0.79 g, 7.7 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of **21** (2.20 g, 7.7 mmol) in CH_2Cl_2 (20 mL) at 0–5 °C. The mixture was stirred at room temperature for 10 min, washed with 10% NaOH, dried, and concentrated to give colorless cubes (2.15 g, 85%): mp 86–88 °C; IR (KBr) 3436, 3318, 3004, 2920, 1678, 1621 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02–1.27 (2 H, m), 1.46–1.88 (10 H, m), 2.08 (3 H, s), 2.52 (1 H, dt, J = 2.6, 12.9), 2.78–2.87 (2 H, m), 2.90–3.12 (5 H, m), 3.73–3.87 (1 H, m), 4.54–4.68 (1 H, m), 7.17 (1 H, d, J = 7.7), 7.34 (1 H, d, J = 1.7), 7.38 (1 H, dd, J = 1.7, 7.7). Anal. ($C_{20}H_{28}N_2O_2$) C, H, N.

3-(1-Acetyl-4-piperidinyl)-1-(2,3-dihydro-1*H*-indol-5-yl)-1-propanone (23). Compound **23** was prepared from **16** as described for **26**: yield 89%; colorless cubes; mp 145–146 °C; IR (KBr) 3434, 3246, 2932, 1659, 1620, 1604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02–1.27 (2 H, m), 1.46–1.86 (5 H, m), 2.08 (3 H, s), 2.52 (1 H, dt, J = 2.4, 13.0), 2.85–3.15 (5 H, m), 3.68 (2 H, t, J = 8.4), 3.72–3.87 (1 H, m), 4.20 (1 H, br s), 4.54–4.68 (1 H, m), 6.55 (1 H, d, J = 8.4), 7.67–7.77 (2 H, m). Anal. ($C_{18}H_{24}N_2O_2$) C, H, N.

3-(1-Acetyl-4-piperidinyl)-1-(1,2,3,4-tetrahydroquinolin-6-yl)-1-propanone (24). Compound **24** was prepared from **18** as described for **26**: yield 92%; colorless cubes; mp 129–130 °C; IR (KBr) 3324, 2934, 2856, 1649, 1631, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.26 (2 H, m), 1.44–1.85 (5 H, m), 1.87–2.00 (2 H, m), 2.08 (3 H, s), 2.52 (1 H, dt, J = 2.6, 12.6), 2.74–2.92 (4 H, m), 3.02 (1 H, dt, J = 2.6, 12.6), 3.38 (2 H, t, J = 5.3), 3.72–3.85 (1 H, m), 4.42 (1 H, s), 4.53–4.66 (1 H, m), 6.40 (1 H, d, J = 9.0), 7.56–7.65 (2 H, m). Anal. ($C_{19}H_{26}N_2O_2$) C, H, N.

3-(1-Acetyl-4-piperidinyl)-1-(1,2,3,4-tetrahydroquinolin-7-yl)-1-propanone (25). Compound **25** was prepared from **19** as described for **26**: yield 87%; pale yellow cubes; mp 89–90 °C; IR (KBr) 3324, 2942, 2852, 1674, 1625, 1604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.26 (2 H, m), 1.42–1.83 (5 H, m), 1.87–2.02 (2 H, m), 2.08 (3 H, s), 2.52 (1 H, dt, J = 2.3, 12.6), 2.80 (2 H, t, J = 6.2), 2.84–3.10 (3 H, m), 3.33 (2 H, t, J = 5.5), 3.73–3.85 (1 H, m), 4.00 (1 H, s), 4.55–4.67 (1 H, m), 7.00 (1 H, d, J = 7.7), 7.04 (1 H, d, J = 1.8), 7.15 (1 H, dd, J = 1.8, 7.7). Anal. ($C_{19}H_{26}N_2O_2$) C, H, N.

3-(1-Acetyl-4-piperidinyl)-1-(1-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanone (30a). A mixture of **26** (0.75 g, 2.28 mmol), MeI (3.24 g, 22.8 mmol), and K_2CO_3 (0.41 g, 2.97 mmol) in MeOH (10 mL) was heated at 40 °C for 48 h, and the solvent was removed in vacuo to give a residue. The residue was dissolved in water and extracted with CH_2Cl_2. The extracts were washed with water and dried, and the solvent was removed in vacuo to afford an oily residue, which was passed through a plug of silica gel eluting with EtOAc to give an oil (0.69 g, 88%): IR (neat) 2924, 2852, 1677, 1644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02–1.28 (2 H, m), 1.47–1.88 (9 H, m), 2.09 (3 H, s), 2.53 (1 H, dt, J = 2.5, 12.8), 2.77–3.10 (7 H, m), 2.94 (3 H, s), 3.73–3.86 (1 H, m), 4.54–4.67 (1 H, m), 7.17 (1 H, d, J = 7.7), 7.44 (1 H, dd, J = 1.7, 7.7), 7.52 (1 H, d, J = 1.7).

The following compounds, **27a–e**, **28**, **29**, and **30b,c**, were prepared in the same manner as that described for **30a**.

3-(1-Acetyl-4-piperidinyl)-1-(1-methyl-2,3-dihydro-1*H*-indol-5-yl)-1-propanone (27a): yield 80%; colorless oil; IR (neat) 3512, 2926, 2852, 1641, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02–1.27 (2 H, m), 1.45–1.86 (8 H, m), 2.52 (1 H, dt, J = 2.6, 12.7), 2.83–3.11 (5 H, m), 2.86 (3 H, s), 3.50 (2 H, t, J = 8.4), 3.73–3.86 (1 H, m), 4.53–4.67 (1 H, m), 6.35 (1 H, d, J = 8.4), 7.68 (1 H, d, J = 1.8), 7.76 (1 H, dd, J = 1.8, 8.4 Hz).

3-(1-Acetyl-4-piperidinyl)-1-(1-ethyl-2,3-dihydro-1*H*-indol-5-yl)-1-propanone (27b): yield 97%; pale yellow oil; IR (neat) 2926, 2850, 1645, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03–1.30 (5 H, m), 1.47–1.96 (5 H, m), 2.08 (3 H, s), 2.52 (1 H, dt, J = 2.2, 12.7), 2.84–3.12 (5 H, m), 3.26 (2 H, q, J = 7.2), 3.54 (2 H, t, J = 8.6), 3.73–3.87 (1 H, m), 4.54–4.67 (1 H, m), 6.35 (1 H, d, J = 8.3), 7.67 (1 H, d, J = 1.8), 7.74 (1 H, dd, J = 1.8, 8.3).

3-(1-Acetyl-4-piperidinyl)-1-(1-propyl-2,3-dihydro-1*H*-indol-5-yl)-1-propanone (27c): yield 88%; pale yellow oil; IR (neat) 2928, 2856, 1639, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (3 H, t, J = 7.4), 1.04–1.28 (2 H, m), 1.46–1.86 (7 H, m), 2.08 (3 H, s), 2.52 (1 H, dt, J = 2.2, 12.7), 2.83–3.18 (7 H, m), 3.56 (2 H, t, J = 8.6), 3.72–3.86 (1 H, m), 4.53–4.67 (1 H, m), 6.33 (1 H, d, J = 8.4), 7.61 (1 H, d, J = 1.8), 7.73 (1 H, dd, J = 1.8, 8.4).

3-(1-Acetyl-4-piperidinyl)-1-(1-butyl-2,3-dihydro-1*H*-indol-5-yl)-1-propanone (27d): yield 95%; pale yellow oil; IR (neat) 2928, 2856, 1642, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (3 H, t, J = 7.3), 1.02–1.85 (11 H, m), 2.08 (3 H, s), 2.50 (1 H, dt, J = 2.6, 12.8), 2.82–3.10 (5 H, m), 3.18 (2 H, t, J = 7.2), 3.55 (2 H, t, J = 8.5), 3.72–3.86 (1 H, m), 4.53–4.67 (1 H, m), 6.32 (1 H, d, J = 8.3), 7.66 (1 H, d, J = 1.7), 7.73 (1 H, dd, J = 1.7, 8.3).

3-(1-Acetyl-4-piperidinyl)-1-(1-pentyl-2,3-dihydro-1*H*-indol-5-yl)-1-propanone (27e): yield 91%; pale yellow oil; IR (neat) 2928, 2856, 1646, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (3 H, t, J = 6.7), 1.03–1.45 (6 H, m), 1.47–1.85 (7 H, m), 2.08 (3 H, s), 2.52 (1 H, dt, J = 2.3, 12.7), 2.82–3.10 (5 H, m), 3.17 (2 H, t, J = 7.3), 3.53 (2 H, t, J = 8.6), 3.73–3.85 (1 H, m), 4.53–4.66 (1 H, m), 6.32 (1 H, d, J = 8.4), 7.66 (1 H, d, J = 1.4), 7.73 (1 H, dd, J = 1.4, 8.4).

3-(1-Acetyl-4-piperidinyl)-1-(1-methyl-1,2,3,4-tetrahydroquinolin-6-yl)-1-propanone (28): yield 69%; colorless oil; IR (neat) 2925, 2854, 1643, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.27 (2 H, m), 1.46–1.85 (5 H, m), 1.89–2.10 (5 H, m), 2.52 (1 H, dt, J = 2.6, 13.0), 2.73–3.08 (8 H, m), 3.35 (2 H, t, J = 5.5), 3.72–3.86 (1 H, m), 4.52–4.65 (1 H, m), 6.50 (1 H, d, J = 8.7), 7.59 (1 H, d, J = 2.2), 7.71 (1 H, dd, J = 2.2, 8.7).

3-(1-Acetyl-4-piperidinyl)-1-(1-methyl-1,2,3,4-tetrahydroquinolin-7-yl)-1-propanone (29): yield 75%; colorless oil; IR (neat) 2925, 2854, 1675, 1641, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.27 (2 H, m), 1.46–1.85 (5 H, m), 1.89–2.10 (5 H, m), 2.52 (1 H, dt, J = 2.6, 13.0), 2.73–3.08 (8 H, m), 3.26 (2 H, t, J = 5.5), 3.72–3.86 (1 H, m), 4.52–4.65 (1 H, m), 7.00 (1 H, d, J = 8.3), 7.13–7.20 (2 H, m).

3-(1-Acetyl-4-piperidinyl)-1-(1-ethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanone (30b): yield 96%; col-

orless oil; IR (neat) 2926, 2852, 1677, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02–1.28 (5 H, m), 1.48–1.86 (9 H, m), 2.08 (3 H, s), 2.52 (1 H, dt, J = 1.7, 12.3), 2.77–3.12 (7 H, m), 3.23 (2 H, q, J = 6.9), 3.74–3.88 (1 H, m), 4.55–4.68 (1 H, m), 7.16 (1 H, d, J = 7.7), 7.41 (1 H, d, J = 7.7), 7.51 (1 H, s).

3-(1-Acetyl-4-piperidinyl)-1-(1-propyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanone (30c): yield 80%; colorless oil; IR (neat) 2928, 2850, 1679, 1646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (3 H, t, J = 7.3), 1.02–1.27 (2 H, m), 1.48–1.86 (11 H, m), 2.08 (3 H, s), 2.53 (1 H, dt, J = 2.8, 12.8), 2.77–3.20 (9 H, m), 3.74–3.87 (1 H, m), 4.54–4.68 (1 H, m), 7.16 (1 H, d, J = 7.7), 7.41 (1 H, d, J = 7.7), 7.51 (1 H, s).

1-(1-Methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone Fumarate (9b). Compound **30a** was hydrolyzed with concentrated HCl as described for **21** to afford a pale yellow oil. Treatment of the oil with benzyl bromide, in the same manner as described for **9a**, gave **9b** as colorless cubes from EtOH: yield 81% from **30a**; mp 100–102 °C; IR (KBr) 3438, 2924, 1678 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.14–1.30 (3 H, m), 1.46–1.88 (8 H, m), 1.94–2.10 (2 H, m), 2.72–3.02 (11 H, m), *ca.* 3.35 (2 H, br s), 3.53 (2 H, s), 6.60 (2 H, s), 7.19 (1 H, d, J = 7.5), 7.30 (5 H, s), 7.40 (1 H, s), 7.43 (1 H, d, J = 7.5). Anal. ($C_{26}H_{34}N_2O \cdot C_4H_4O_4$) C, H, N.

Compounds **4b–f**, **6b**, **7b**, and **9c,d** listed in Table 1 were similarly prepared.

Biological Methods. AChE Inhibition Assay. AChE inhibitory activity was determined as described previously.[4a] The cerebral cortex of male Wistar rats was homogenized with 20 volumes of ice-cooled 0.32 M sucrose and centrifuged at 1000*g* for 10 min. The supernatant (S1) fraction was preincubated in a scintillation vial with 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.[21] These values were derived from a single experiment done in triplicate. All test compounds were dissolved in DMSO.

Peripheral Action and Acute Toxicity. Effects of test compounds on peripheral cholinergic effects were studied using male Wistar rats weighing 220–280 g, 8–9 weeks old. Three rats were used in each group. Rats were first placed in stainless steel cages (13 × 18 × 25 cm^3) for about 1 h for habituation. Each test compound was then administered orally, and behavioral changes such as salivation, lacrimation, diarrhea, and fasciculation were recorded 15 min to 4 h after dosing. Tests were performed at doses of 1, 3, 10, and 30 mg/kg. Doses causing even slight peripheral changes are given in Table 2.

Six rats were used to determine the ED_{50} value of fasciculation. ED_{50} was calculated by the incidence at 1 h after dosing. The LD_{50} value was determined using six rats from the survival rate at 3 days after a single administration. These values were calculated by Finney's probit analysis,[21] and the results are shown in Table 4.

Effects on Circling Behavior in Rats with Unilateral Striatal Lesions. After anesthesia with pentobarbital, male Jcl:Wistar rats weighing 260–300 g, 10 weeks old, were positioned in a David Kopf small animal stereotaxic apparatus, and an injection needle (0.13 mm i.d. and 0.31 mm o.d.) was inserted into the right striatum through a burr hole in the calvarium (coordinates: 8.2 mm A; 2.8 mm L; 4.3 mm from dura, according to the rat brain atlas of Pellegrino and Cushman).[22] Quinolinic acid (150 nmol) was dissolved in 0.5 μL of phosphate-buffered saline (pH 7.2) and infused over a period of 5 min as previously described.[14] One week later, apomorphine (0.5 mg/kg) was injected subcutaneously, and the number of circlings was measured for 30 min after administration automatically by a rotometer.[23] Only rats showing stable ipsilateral circling behavior were used for the test. Apomorphine (0.5 mg/kg sc) was administered 30 min before the test. Each test compound was given orally 30 min before the administration of apomorphine. Eight to 10 rats were used in each group, and the number of circlings was similarly measured for 30 min. Student's t-test was used for statistical analysis.

Effects on Diazepam-Induced Memory Impairment of Passive Avoidance Task in Rats.[24] Male Wistar rats weighing 220–270 g, 8–9 weeks old, were used. Seven to 12 rats were used in each group. A two-compartment step through passive avoidance apparatus was used.[25] A front illuminated chamber (25 × 10 × 25 cm^3) was connected to a rear dark chamber (30 × 30 × 30 cm^3) equipped with a grid floor; the two compartments were separated by a guillotine door. Each rat was subjected to a single pretraining trial about 1 h before the acquisition trial: when the rat placed in the front chamber entered the rear chamber on all four paws, the door was closed and the rat was allowed to remain in the chamber for 10 s. In the acquisition trial, the rat was placed in the front chamber and the time taken from opening the door until the rat entered the dark chamber was recorded. As soon as the rat entered the dark chamber, an AC 2 mA foot shock was applied to the grid floor. At the retention test 24 h later, the rat was again placed in the front chamber and the door was opened 30 s later; the time from opening the door until the rat entered the dark chamber was recorded as the avoidance time. Diazepam (5 mg/kg) was administered intraperitoneally 30 min before the acquisition trial. Each test compound was given orally 30 min before the administration of diazepam. When the avoidance times of a test compound were significantly different ($p < 0.05$) from those of a control group treated with saline by the Mann–Whitney U-test, the compound was evaluated as active. Compound **9a** was tested at 0.3, 1, and 3 mg/kg. THA was tested at 1, 3, 10, and 30 mg/kg. These data are given in Table 3. Minimum effective dose required to improve the impairment of the passive avoidance task (MED) is shown in Table 4.

Acknowledgment. We thank Dr. A. Nagaoka for his encouragement and helpful discussion throughout this work and acknowledge the able technical assistance of Mr. M. Sasaki and Ms. M. Okura.

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