Synthesis and Evaluation of 5-Amino-5,6,7,8-tetrahydroquinolinones as Potential Agents for the Treatment of Alzheimer's Disease

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A series of 5-amino-5,6,7,8-tetrahydroquinolinones was designed and synthesized as acetylcholinesterase inhibitors. The compounds are related to hyperzine A, a naturally occurring cholinesterase inhibitor. They inhibit acetylcholinesterase *in vitro*, and many are active *in vivo* in reversing a scopolamine-induced impairment of 24 h memory in a passive avoidance paradigm. Although these compounds were designed as partial structures of huperzine A, it is unlikely that they bind to the enzyme in a similar fashion, since they lack the unsaturated three-carbon bridge of huperzine A and both the quinolinone nitrogen and the amino group must be substituted in order to obtain good enzyme affinity.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that is the major cause of dementia among the elderly. This disease affects about 2% of the population over the age of 65 and up to 50% of the population over the age of 85.[1] As general health care improves, and the proportion of elderly people in the population increases, the number of AD patients is anticipated to increase dramatically.

In the last 5 years significant progress has been made in identifying the processes underlying the deposition of the senile plaques and tangles which are characteristic of AD pathology. However, despite the efforts of many scientists from multiple disciplines, the etiology of AD remains unknown.[2] In addition, no unequivocal procedures for the diagnosis of AD are available.[1] In light of the above difficulties, much current work concentrates on the numerous biochemical deficits that have been documented to be associated with the neuropathology of the disease.[3] Thus, the severe loss of cholinergic neurons found in the autopsied brains of AD patients led to the formulation of the cholinergic hypothesis of age-related memory loss.[4] A number of approaches to cholinergic enhancement—muscarinic agonists, cholinergic releasing agents, and cholinesterase inhibitors—have been investigated as therapeutic agents for the palliative treatment of AD.[1a,3b] Although the aminoacridine cholinesterase inhibitor tacrine (Cognex) (Figure 1) was recently approved by the FDA, the aminoacridines suffer from dose-limiting side effects.[5] In addition, the cholinesterase inhibitors physostigmine, galanthamine, huperzine A, and the *N*-benzylpiperidine E-2020 are in clinical trials.[3b,6] While physostigmine has shown variable efficacy in the clinic, presumably due to its short half-life and narrow therapeutic index,[7] the other three drugs have produced encouraging preliminary results.[6,8] Although galanthamine, E-2020, and huperzine A are structurally diverse, there are common features relating them, including (a) each is a reversible cholinesterase inhibitor which does not acylate the enzyme and (b) each is selective for acetyl- versus butyrylcholinesterase. While the function of butyrylcholinesterase remains unknown,[9] clinical data with selective and nonselective acetylcholinesterase inhibitors suggest that butyrylcholinesterase inhibition may be associated with peripheral side effects.[10] However, this remains an unproven empirical observation.

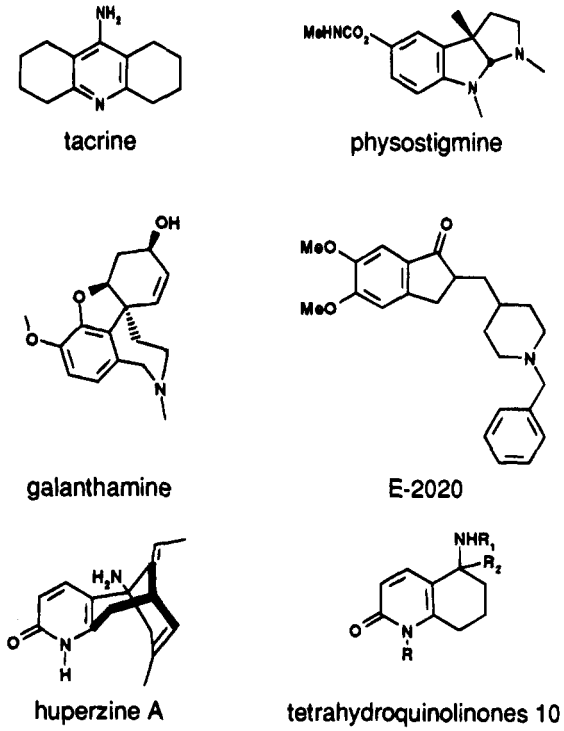

Figure 1.

The structure and anticholinesterase activity of huperzine A, a constituent of a Chinese herbal medicine, was reported in 1986.[11] Clinical trials in China indicate that huperzine A may be a safe and effective drug.[12] As part of our program to develop novel cholinesterase inhibitors for the treatment of AD, a series of 5-amino-5,6,7,8-tetrahydroquinolinones, based on the structure of huperzine A, was prepared. In designing these compounds, we postulated that the pyridinone and primary amine moieties are necessary for optimal enzyme inhibition. The synthesis and biological activity of these compounds are described in this paper.

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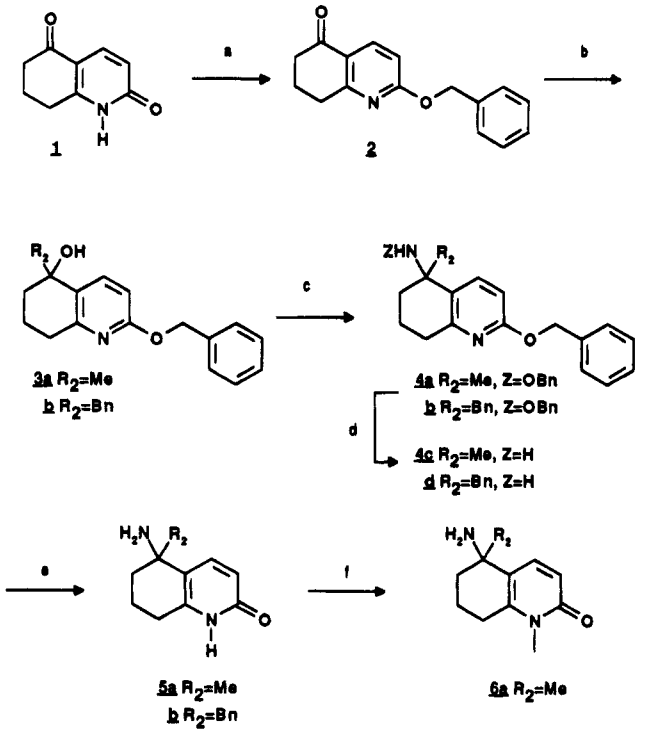
Scheme 1[a]



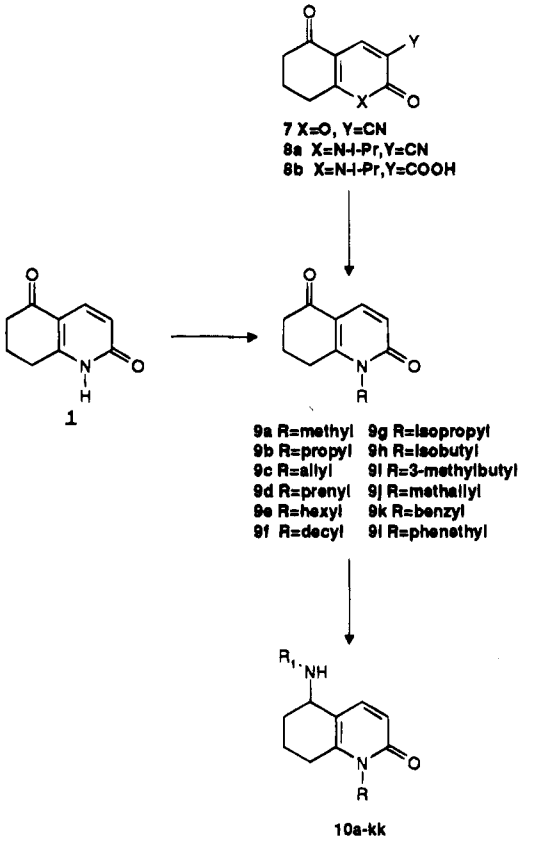
[a](a) Ag_2CO_3, benzyl bromide, toluene; (b) R_2MgBr, toluene; (c) $BnONH_2$, CF_3COOH, toluene; (d) BH_3–THF, THF; (e) 10% Pd on C, H_2, 55 psi, ethanol; (f) NaH, MeI, DMF.

Chemistry

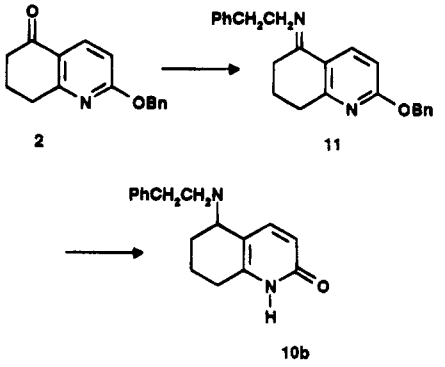
The synthesis of the target compounds is outlined in Schemes 1–3. The initial targets, compounds **5a,b** and **6**, were prepared from the tetrahydroquinolinone **1**[13] (Scheme 1). Protection of the amide by O-benzylation, followed by addition of methylmagnesium bromide to ketone **2**, provided tertiary alcohol **3a** in 72% yield. An acid-catalyzed substitution reaction with *O*-benzylhydroxylamine[14] followed by N–O bond cleavage with borane–THF,[15] and then debenzylation, gave the quinolinone **5a** in 29% yield for the three steps. N-Alkylation of **5a** with methyl iodide afforded amine **6a**. Preparation of **5b** was accomplished in a similar fashion in 11% yield from the ketone **2**.

The synthesis of the amines **10a–kk** is shown in Scheme 2. Alkylation of quinolinone **1** was effected through treatment with lithium hydride and an alkyl halide to provide the quinolinones **9a–f,h–k** (24–89% yield). The lower yields reflect increased amounts of O-alkylation that occurred with less reactive alkylating reagents (e.g., propyl iodide and phenethyl bromide).[16] Reactions employing sodium hydride gave more of the undesired O-alkylated product. The introduction of an isopropyl substituent on the tetrahydroquinolinone nitrogen necessitated an alternative synthesis, since all attempts to alkylate quinolinone **1** with an isopropyl halide provided the O-alkylated product exclusively. Treatment of the pyrone **7**[17] with isopropylamine, followed by acid hydrolysis, gave the carboxylic acid, which decarboxylated upon treatment with copper powder in quinoline to provide the ketone **9g** in 10% overall yield. Ketones **9a–l** were condensed with the appropriate amine in the presence of titanium(IV) isopropoxide[18] or *p*-toluenesulfonic acid to provide the corresponding imine. Reduction of the imines with sodium borohydride afforded the desired secondary amines **10a–kk**

Scheme 2



Scheme 3



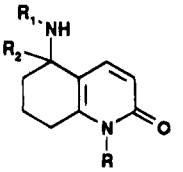
in 40–90% yield. Condensation of ketone **9d** with hydroxylamine followed by oxime reduction with Raney alloy under basic conditions gave the amine **10k** in 43% yield.

Compound **10b** required an alternate synthesis (Scheme 3), since the formation of an imine from the unsubstituted quinolinone **1** proved to be difficult. Condensation of the protected ketone **2** with phenethylamine in the presence of *p*-toluenesulfonic acid afforded imine **11**, which was reduced to the corresponding amine using sodium borohydride. Hydrogenolysis of the benzyl group provided quinolinone **10b** (47% overall yield). The properties of compounds **5a,b**, **6a**, and **10a–kk** are described in Table 1.

Results and Discussion

In vitro acetylcholinesterase inhibition (AChEI) was determined using the method of Ellman et al.,[19] and IC_{50} values are reported in Table 1. Although huperzine A is characterized by a primary amino group attached to

Table 1. Physical Data and Acetylcholinesterase Inhibition for 5-Amino-5,6,7,8-tetrahydroquilnolinones



compd	R	R_1	R_2	yield, %	recryst solvent[a]	mp, °C	molecular formula[b]	acetylcholinesterase inhibition IC_{50}, μM[k]
5a	H	H	Me	56	A	214–216	$C_{10}H_{14}N_2O$[c]	>100
5b	Me	H	Me	23	D	166–168	$C_{11}H_{16}N_2O$	>100
6a	H	H	Bn	28	G/A/D	235–238	$C_{16}H_{18}N_2O$[c]	>100
10a	Me	Bn	H	69[d]		159–161	$C_{17}H_{20}N_2O$[e]	>100
10b	H	$Ph(CH_2)_2$	H	42[d]	A/D	200–202	$C_{17}H_{20}N_2O$[c]	>100
10c	Me	$Ph(CH_2)_2$	H	24[d]	B/D	163–166	$C_{18}H_{22}N_2O$[f]	18.60 (12.50–27.50)
10d	*n*-Pr	$Ph(CH_2)_2$	H	71[d]	B	151–153	$C_{20}H_{26}N_2O$[e]	3.13 (2.36–4.15)
10e	Me	$Ph(CH_2)_3$	H	54[d]	B	171–173	$C_{19}H_{28}N_2O$[e]	48.44 (33.99–69.03)
10f	*n*-Pr	$(CH_3)_3C(CH_2)_2$	H	73[g]	A	183–184	$C_{18}H_{30}N_2O$[e]	15.59 (11.90–20.42)
10g	*n*-Pr	2-indanyl	H	75[g]	D/E	96–97	$C_{21}H_{26}N_2O$	3.91 (3.02–5.07)
10h	*n*-Pr	1-thienyl$(CH_2)_2$	H	87[g]	A/F	154–155	$C_{18}H_{24}N_2OS$[e,h]	5.97 (4.37–8.16)
10i	*n*-Pr	3-indolyl$(CH_2)_2$	H	69[g]	C/D	140–142	$C_{22}H_{27}N_3O$	3.16 (2.21–4.52)
10j	*n*-Pr	2-pyridyl$(CH_2)_2$	H	80[g]	A	148–149	$C_{19}H_{25}N_3O$[e]	4.34 (3.13–6.02)
10k	prenyl	H	H	43[g]	B/H	195–205	$C_{14}H_{20}N_2O$[c,i]	>100
10l	Me	4-Cl$Ph(CH_2)_2$	H	67[d]	D/E	110–112	$C_{18}H_{21}ClN_2O$	6.60 (4.91–8.87)
10m	Me	4-(MeO)$Ph(CH_2)_2$	H	55[d]	D/E	97–99	$C_{19}H_{24}N_2O_2$	9.61 (6.92–13.33)
10n	Me	4-Me$Ph(CH_2)_2$	H	56[d]	B/H	158–161	$C_{19}H_{24}N_2O$[e]	18.18 (8.65–38.20)
10o	Me	4-$(CF_3)Ph(CH_2)_2$	H	46[d]	D/E	104–106	$C_{19}H_{21}F_3N_2O$	12.89 (9.49–17.50)
10p	Me	3,4-$Cl_2Ph(CH_2)_2$	H	48[d]	B	172–173	$C_{18}H_{20}Cl_2N_2O$[e]	2.93 (1.98–4.33)
10q	*n*-Pr	3,4-$Cl_2Ph(CH_2)_2$	H	75[d]	D/E	105–107	$C_{20}H_{24}Cl_2N_2O$	1.05 (0.29–3.81)
10r	hexyl	3,4-$Cl_2Ph(CH_2)_2$	H	57[g]		160–162	$C_{23}H_{30}Cl_2N_2O$[e]	3.71 (2.89–4.78)
10s	decyl	3,4-$Cl_2Ph(CH_2)_2$	H	81[g]	A/F	120–121	$C_{27}H_{38}Cl_2N_2O$[j]	33.69 (26.39–43.01)
10t	*i*-Pr	3,4-$Cl_2Ph(CH_2)_2$	H	61[g]		174–175	$C_{20}H_{24}Cl_2N_2O$[c]	34.52 (14.86–80.21)
10u	*i*-Bu	3,4-$Cl_2Ph(CH_2)_2$	H	59[g]	A	182–183	$C_{21}H_{26}Cl_2N_2O$[e]	23.37 (18.38–29.73)
10v	3-Me-butyl	3,4-$Cl_2Ph(CH_2)_2$	H	54[g]	D/E	186–187	$C_{22}H_{28}Cl_2N_2O$[e]	2.34 (1.73–3.17)
10w	allyl	3,4-$Cl_2Ph(CH_2)_2$	H	73[d]	B	160–161	$C_{20}H_{22}Cl_2N_2O$[e]	9.21 (6.95–12.21)
10x	2-Me-2-propenyl	3,4-$Cl_2Ph(CH_2)_2$	H	80[g]	A/F	189–190	$C_{21}H_{24}Cl_2N_2O$[e]	5.32 (3.84–7.36)
10y	prenyl	3,4-$Cl_2Ph(CH_2)_2$	H	46[g]	B/D	179–181	$C_{22}H_{26}Cl_2N_2O$[c]	0.51 (0.15–1.73)
10z	Bn	3,4-$Cl_2Ph(CH_2)_2$	H	80[d]	B/D	176–178	$C_{24}H_{24}Cl_2N_2O$[e]	17.34 (13.6–22.11)
10aa	phenethyl	3,4-$Cl_2Ph(CH_2)_2$	H	52[g]	D/E	120–122	$C_{25}H_{26}Cl_2N_2O$	50.42 (25.94–98)
10bb	prenyl	2-Cl$Ph(CH_2)_2$	H	74[g]	A	176–177	$C_{24}H_{27}ClN_2O$[e]	0.52 (0.37–0.71)
10cc	prenyl	3-Cl$Ph(CH_2)_2$	H	87[g]	A/F	170–171	$C_{22}H_{27}ClN_2O$[e]	0.52 (0.39–0.70)
10dd	prenyl	2,5-$Cl_2Ph(CH_2)_2$	H	55[g]	A	183–184	$C_{22}H_{26}Cl_2N_2O$[e]	1.36 (0.62–3.00)
10ee	prenyl	3,5-$Cl_2Ph(CH_2)_2$	H	49[g]	A	183–184	$C_{22}H_{26}Cl_2N_2O$[e]	0.80 (0.32–2.02)
10ff	prenyl	2,4-$Cl_2Ph(CH_2)_2$	H	49[g]	B	165–166	$C_{22}H_{26}Cl_2N_2O$[e]	0.79 (0.24–2.59)
10gg	prenyl	3,4-$F_2Ph(CH_2)_2$	H	35[g]		166–167	$C_{22}H_{26}F_2N_2O$[e]	0.98 (0.37–2.56)
10hh	prenyl	3-(MeO)$Ph(CH_2)_2$	H	63[g]		152–154	$C_{23}H_{30}N_2O_2$[e]	1.10 (0.37–3.30)
10ii	prenyl	3,4-$(MeO)_2Ph(CH_2)_2$	H	55[g]	A	178–179	$C_{24}H_{32}N_2O_3$[e]	1.64 (1.05–2.57)
10jj	prenyl	3-(CF_3)-4-Cl$Ph(CH_2)_2$	H	70[g]		183–184	$C_{23}H_{26}ClF_3N_2O$[c]	0.79 (0.57–1.11)
10kk	prenyl	4-(HO)$Ph(CH_2)_2$	H	74[g]	C	160–161	$C_{22}H_{28}N_2O_2$	0.40 (0.30–0.55)
(±)-huperzine A[l]								0.08 (0.04–0.16)
galanthamine								0.63 (0.47–0.85)

[a] A = methanol, B = ethanol, C = 2-propanol, D = ethyl acetate, E = hexanes, F = ethyl ether, G = water, H = isopropyl ether. [b] Satisfactory elemental analyses (±0.4%) were obtained for all compounds. [c] HCl salt. [d] Prepared by method A: *p*-TsOH, $NaBH_4$. [e] Fumarate. [f] 2HCl monohydrate. [g] Prepared by method B: $Ti(O\text{-}i\text{-}Pr)_4$, $NaBH_4$. [h] C: calcd, 61.09; found, 60.63. [i] C: calcd, 62.56; found, 62.13. [j] Hemifumarate. [k] Values in parentheses are 95% confidence limits. [l] Racemic huperzine A was purchased from MindLabs Inc., Pittsburgh, PA.

a quaternary carbon, primary amines **5a,b**, **6a** (quaternary center present), and **10k** (no quaternary center), which were structurally closest to huperzine A, showed little enzyme affinity. As shown in the table, the addition of lipophilic groups to the quinolinone nucleus improved enzyme inhibition dramatically. Introduction of a phenethyl moiety on the amine nitrogen afforded an active lead (**10c**), but the activity was dependent on the presence of a substituent on the quinolinone nitrogen (**10b** versus **10c**). The phenethyl moiety conferred optimal activity when compared to the benzyl and phenylpropyl analogues (**10c** versus **10a,e**). Enzyme inhibition was further enhanced by variation of the quinolinone nitrogen substituent from methyl to propyl (**10c** versus **10d**). Replacement of the phenyl moiety of the phenethyl group with indan, indole, thiophene, or pyridine did not result in further enhancement of activity (**10d** versus **10g–j**). The compound bearing a *tert*-butyl group (**10f**) in place of the phenyl also exhibited good AChEI activity, although it was 5 times weaker than phenyl-substituted analogue **10d**.

The effect of substitution on the aromatic ring of the phenethyl moiety was investigated. In the *N*-methylquinolinone series, introduction of a 4-chloro substituent (**10l**) resulted in slight enhancement of enzyme affinity versus hydrogen (**10c**), methyl (**10n**), trifluoromethyl (**10o**) and possibly methoxy (**10m**). Enzyme affinity was further enhanced by increasing the number of aromatic halogen substituents (**10l** versus **10p**). Modification of the quinolinone nitrogen substituent (**10p-aa**) also affected enzyme inhibition. As mentioned above, binding to the enzyme was enhanced upon

Table 2. Butyrylcholinesterase Inhibition

compd	butyrylcholinesterase inhibition IC_{50}, μM[a]	compd	butyrylcholinesterase inhibition IC_{50}, μM[a]
10q	>100	**10gg**	>100
10y	2.50 (1.80–3.49)	**10hh**	>100
10bb	>100	**10jj**	>100
10cc	23.81 (13.17–43.05)	**10kk**	>100
10ff	89.52 (74.55–107.50)	(±)-huperzine A	>1000

[a] Values in parentheses are 95% confidence limits.

variation of the substituent from methyl to propyl. Further variation of this substituent indicated that small alkyl groups (up to approximately six carbons, **10p–r,v**) are tolerated by the enzyme. However, large groups (**10z,aa**) or branching of the aliphatic chain near the quinolinone nitrogen (**10t,u**) lowered the enzyme inhibition. Branching further along the aliphatic chain with introduction of a double bond led to the 3-methyl-2-butenyl (prenyl) analog **10y** which had good inhibitory activity. Addition of unsaturation to the side chain had an inconsistent effect. Thus, allyl (**10w**) was 8 times weaker than propyl (**10q**), while methallyl (**10x**) and prenyl (**10y**) were about 4 times more potent than the corresponding saturated analogues (**10u,v**). Interestingly, the prenyl series seemed relatively insensitive to the nature and number of aromatic substituents associated with the phenethyl moiety (**10bb–kk**).

The low enzyme affinity of analogues that bear a primary amino group or an unsubstituted quinolinone nitrogen (**5a,b**, **6a**, **10b,k**) but lack the two olefins in huperzine A supports studies by Kozikowski[20] that indicate the importance of the electrostatic field presented by the unsaturated three-carbon bridge of huperzine A to the enzyme. The observed activity of these compounds can be rationalized using the reported crystal structure of the enzyme as a guide.[21] The active site of the enzyme is located at the base of a deep, narrow cavity which is highly hydrophobic due to the 14 aromatic amino acid residues that line the gorge. The results with the unsubstituted (**10k**) amine and benzyl- (**10a**), phenethyl- (**10c**), 3-phenylpropyl- (**10e**), and 2-*tert*-butylethylamine (**10f**) substituents indicate a required interaction between a lipophilic group on the compound located two carbons from the benzylic amine and one of the aromatic residues surrounding the active site. The lack of activity of **10b**, a compound that has the required aromatic group but lacks a substituent on the quinolinone nitrogen, cannot be rationalized from the data presented here. One possible explanation stems from the hydrophilic nature of this compound, as the hydrophobic nature of the gorge may deny access to hydrophilic molecules such as **10b**.

A number of compounds were also tested for binding affinity to butyrylcholinesterase (Table 2). Of the compounds tested, most were very selective for acetylcholinesterase (by a factor > 45), with the only exception being compound **10y** which showed a selectivity factor of 5 for acetyl- versus butyrylcholinesterase inhibition.

Finally, some of the compounds were assessed *in vivo* in a mouse passive avoidance assay for their ability to reverse scopolamine-induced memory impairment (Table 3).[22] Most of the compounds tested were found to be active in this assay. As has been pointed out, animal models of AD are, at best, imperfect.[23] For example, the scopolamine-induced dark avoidance model (SDDA) gives positive results not only with cholinergic enhancers, but also with analgesics, motor stimulants, and nootropic compounds. However, the combination of *in vitro* acetylcholinesterase inhibition combined with *in vivo* activity in SDDA is indicative of a centrally active cholinesterase inhibitor.[24]

Table 3. SDDA Activity

compd	active doses,[a] mg/kg, sc	compd	active doses,[a] mg/kg, sc
10c	1	**10y**	0.3 and 3
10g	1	**10cc**	NA
10h	1 and 10	**10ff**	1 and 3
10i	3	**10hh**	0.1, 0.3, and 1 (ip)
10j	NA	**10ii**	0.3, 1, 3, and 10
10l	0.3, 1, and 3	**10jj**	NA
10v	3	**10kk**	1
10x	3	galanthamine	0.63, 1.25, and 5

[a] A cutoff was defined for the scopolamine-vehicle group (see Experimental Section) as the value for the animal with the second longest latency time. The active doses are those which met the empirical positive activity criterion of 20% of the animals with latencies greater than the cutoff.

Conclusion

A series of novel acetylcholinesterase inhibitors was prepared. Although these compounds were designed as partial structures of huperzine A, it is unlikely that they bind to the enzyme in a similar fashion, since they lack the unsaturated three-carbon bridge of huperzine A, and both the quinolinone nitrogen and the amino group must be substituted in order to obtain good enzyme affinity. Some of the compounds are also active *in vivo* in the reversal of scopolamine-induced memory deficits in a passive avoidance model, and thus they may be of use for the palliative treatment of AD.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectra were determined by direct insertion with a Finnegan Model 4000 spectrophotometer with an INCOS data system. IR spectra were obtained with a Perkin-Elmer Model 1420 spectrophotometer. Nuclear magnetic resonance spectra were taken on a Varian XL-200 instrument. Chemical shifts are reported in parts per million relative to Me_4Si as an internal standard. Elemental analyses were performed by Oneida Research Services, Whitesboro, NY.

5,6,7,8-Tetrahydro-2-(phenylmethoxy)-5-oxoquinoline (2). A mixture of 5,6,7,8-tetrahydro-5-oxo-2(1*H*)-quinolinone (**1**) (30 g, 0.184 mol), benzyl bromide (37.8 g, 0.221 mol), and silver carbonate (30 g, 0.108 mol) in 350 mL of toluene was mechanically stirred in a Morton flask at room temperature for 68 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated *in vacuo* to leave an orange oil. Trituration with petroleum ether provided 37.3 g (80%) of a white solid. The petroleum ether was concentrated *in vacuo*, and the residue was again triturated with petroleum ether, to afford an additional 4.4 g (9%) of **2**: ^{1}H-NMR ($CDCl_3$) δ 8.18 (d, 1H, J = 8.7 Hz), 7.30–7.53 (m, 5H), 6.70 (d, 1H, J = 8.7 Hz), 5.45 (s, 1H), 3.03 (t, 3H, J = 6.7 Hz), 2.63 (t, 2H, J = 6.7 Hz), 2.17 (quin, 2H, J = 6.7 Hz); EIMS *m/e* (rel intensity) 253 (M^+, 100).

5,6,7,8-Tetrahydro-5-methyl-2-(phenylmethoxy)quinolin-5-ol (3). Methylmagnesium bromide (20.0 mL, 59.2 mmol, 3 M solution in diethyl ether) was added dropwise to a solution of **2** (15.0 g, 59.2 mmol) in 600 mL of toluene at room temperature. The exothermic reaction was controlled with an ice water bath. The resulting solution was stirred at room temperature for 0.5 h, and then it was quenched by the addition of saturated ammonium chloride solution. The layers were separated, and the aqueous phase was extracted with

ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to give 17.1 g of crude product. Purification by column chromatography on silica gel (elution with ethyl acetate–hexanes) provided 12.7 g (80%) of **3a** as a yellow liquid: ^{1}H-NMR ($CDCl_3$) δ 7.78 (d, 1H, J = 8.7 Hz), 7.25–7.53 (m, 5H), 6.68 (d, 1H, J = 8.7 Hz), 5.35 (s, 2H), 2.82 (br s, 2H), 1.67 (m, 4H), 1.51 (s, 3H); EIMS *m/e* (rel intensity) 269 (M^+, 59), 91 (100).

***N*-(5,6,7,8-Tetrahydro-5-methyl-2-(phenylmethoxy)quinolin-5-yl)-*O*-(phenylmethyl)hydroxylamine (4a).** Trifluoroacetic acid (13.3 g, 0.12 mol) was added to a solution of **3** (31.7 g, 0.12 mol) and *O*-benzylhydroxylamine (38 g, 0.32 mol) in 550 mL of toluene at room temperature. The resulting mixture was stirred for 24 h, and then it was poured over ice and basified with concentrated ammonium hydroxide solution. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over potassium carbonate, filtered, and concentrated to give 60 g of crude product. The product was deposited on silica gel and then filtered through a pad of silica gel (elution with 2 L of hexanes, followed by 5% ethyl acetate–hexanes) to leave 33 g of a pale yellow oil. Purification on a Waters Prep 500 (silica gel; elution with ethyl acetate–hexanes) provided 26.5 g (63%) of **4a** as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ 7.73 (d, 1H, J = 8.0 Hz), 7.24–7.50 (m, 10H), 6.60 (d, 1H, J = 8.0 Hz), 5.27–5.47 (br s, 1H), 5.33 (s, 2H), 4.64 (s, 2H), 2.70–2.87 (m, 2H), 2.13–2.30 (m, 1H), 1.73–2.00 (m, 2H), 1.53–1.73 (m, 1H), 1.37 (s, 3H); CIMS *m/e* (rel intensity) 375 (M^+ + 1, 96), 252 (100).

5,6,7,8-Tetrahydro-5-methyl-2-(phenylmethoxy)-5-quinolinamine (4c). Borane–tetrahydrofuran (144 mL, 0.14 mol, 1 M solution in tetrahydrofuran) was added dropwise to a 0 °C solution of **4a** (18 g, 48.1 mmol) in 70 mL of tetrahydrofuran. The mixture was then heated at reflux for 2 h. Subsequently the mixture was cooled to 0 °C, and 30 mL of water was carefully added. The tetrahydrofuran was removed *in vacuo*, 50 mL of 20% aqueous potassium hydroxide was added, and the resulting mixture was heated at reflux for 1.5 h. The mixture was allowed to cool to room temperature, and the product was extracted into dichloromethane. The solvent was removed *in vacuo*, and the residue was dissolved in 6 N HCl. The aqueous phase was washed with diethyl ether (to remove the benzyl alcohol formed in the reaction) and basified with 20% KOH solution, and the product was extracted into dichloromethane. The combined organic layers were washed with brine, dried over potassium carbonate, filtered, and concentrated to give 10.5 g of crude product. Purification on a Waters Prep 500 (silica gel, elution with 1% triethylamine–20% methanol–ethyl acetate) provided 8.82 g (68%) of **4c** as a pale yellow oil: ^{1}H-NMR (DMSO-d_6) δ 7.89 (d, 1H, J = 9.3 Hz), 7.23–7.45 (m, 5H), 6.65 (d, 1H, J = 9.3 Hz), 5.28 (s, 2H), 2.60–2.77 (m, 2H), 1.60–2.00 (m, 6H), 1.27 (s, 3H); CIMS *m/e* (rel intensity) 269 (M^+ + 1, 100).

5-Amino-5,6,7,8-tetrahydro-5-methyl-2(1*H*)-quinolinone Hydrochloride (5a). A mixture of **4c**·2HCl (9.5 g, 0.028 mol) and 730 mg of 10% palladium on carbon in 500 mL of absolute ethanol was shaken on a Parr hydrogenation apparatus, starting at 55 psi of hydrogen, until hydrogen uptake ceased. The catalyst was removed by filtration, and the filtrate was neutralized with 4-polyvinylpyridine. Concentration afforded 6.0 g of crude product, which was suspended in hot methanol, and the solid was collected. This material was combined with the sample which crystallized from the hot methanol, affording 4.01 g (67%) of **5a** as a white powder: mp 214–216 °C dec; ^{1}H-NMR (D_2O) δ 7.88 (d, 1H, J = 10.5 Hz), 6.58 (d, 1H, J = 10.5 Hz), 2.73 (t, 2H, J = 6.7 Hz), 1.90–2.20 (m, 4H), 1.73 (s, 3H); EIMS *m/e* (rel intensity) 178 (M^+, 4), 163 (100); IR 1660 cm^{-1}.

5-Amino-5,6,7,8-tetrahydro-1,5-dimethyl-2(1*H*)-quinolinone (6a). A mixture of sodium hydride (50% in oil, 2.9 g, 60.8 mmol) and the hydrochloride salt of **5a** (5.43 g, 25.4 mmol) in 370 mL of dimethylformamide was stirred at room temperature for 1.5 h. Methyl iodide (3.97 g, 27.9 mmol) was added to the resulting solution, and the mixture was kept at room temperature for 20 h. The solvent was removed *in vacuo*, and the residue was washed thoroughly with dichloromethane. The filtrate was concentrated, and the residue was dissolved in a mixture of ethyl acetate and methanol and treated with 0.5 equiv of fumaric acid. The precipitated solid (2.65 g) was combined with 1.9 g of material obtained in an earlier experiment and treated with 5% NaOH solution. Extraction of the product into dichloromethane and concentration *in vacuo* afforded 3.1 g of **6a** as the free base. Recrystallization from ethyl acetate gave 2.1 g (23%) of white crystals: mp 166–167.5 °C; ^{1}H-NMR (DMSO-d_6) δ 7.67 (d, 1H, J = 7.2 Hz), 6.28 (d, 1H, J = 7.2 Hz), 2.63 (t, 2H, J = 6.7 Hz), 1.50–1.93 (m, 4H), 1.20 (s, 3H); EIMS *m/e* (rel intensity) 192 (M^+, 10), 177 (100); IR 1660 cm^{-1}.

5,6,7,8-Tetrahydro-5-oxo-1-(3-methyl-2-butenyl)-2(1*H*)-quinolinone (9d). Lithium hydride (1.95 g, 0.25 mol) was added to a suspension of **1** (25 g, 0.15 mol) in 1 L of dimethylformamide, and the mixture was stirred at room temperature for 4 h. 3-Methyl-2-butenyl bromide (27.9 g, 0.17 mol) was added, and the mixture was stirred at ambient temperature for 18 h. Water was added to the mixture to quench any residual hydride, and then the mixture was concentrated *in vacuo*. The residue was partitioned between dichloromethane and water, and the layers were separated. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to give a brown oil. Trituration with hexanes and a small amount of ethyl acetate provided 24.8 g (70%) of **9d** as a tan solid: mp 93–94 °C; ^{1}H-NMR (DMSO-d_6) δ 7.84 (d, 1H, J = 9.3 Hz), 6.37 (d, 1H, J = 9.3 Hz), 5.00–5.13 (m, 1H), 4.70 (d, 2H, J = 5.5 Hz), 3.02 (t, 2H, J = 6.7 Hz), 2.45 (t, 2H, J = 6.7 Hz), 2.07 (quin, 2H, J = 6.7 Hz), 1.79 (s, 3H), 1.72 (s, 3H); EIMS *m/e* (rel intensity) 231 (M^+, 100); IR 1660 cm^{-1}.

5,6,7,8-Tetrahydro-2,5-dioxo-2*H*-chromene-3-carbonitrile (7). A solution of sodium ethoxide (73 mL, 0.2 mol, 20% wt/wt sol in ethanol) was added to 1,3-cyclohexanedione (20 g, 0.18 mol) in 20 mL of ethanol, and the resulting mixture was heated at 60 °C for 1 h. (Ethoxymethylene)malononitrile (20.4 g, 0.17 mol) was added, and the mixture was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to room temperature, 500 mL of water was added, and the mixture was acidified with concentrated HCl solution to pH 2. The mixture was stirred at room temperature for 4.5 h, and the precipitated solid was collected by filtration and washed with diethyl ether to leave 10.1 g (31%) of **7** as an orange solid, which was used in the subsequent reaction without further purification: ^{1}H-NMR (DMSO-d_6) δ 8.60 (s, 1H), 2.95 (t, 2H, J = 6.7 Hz), 2.54 (t, 2H, J = 6.7 Hz), 2.08 (quin, 2H, J = 6.7 Hz).

5,6,7,8-Tetrahydro-5-oxo-1-(2-propyl)-2(1*H*)-quinoline-3-carboxylic Acid (8b). A solution of the pyrone **7** (19 g, 0.10 mmol) and isopropylamine (10.6 g, 0.18 mol) in 300 mL of methanol was heated at reflux for 2 h. The mixture was cooled, the solvent was removed *in vacuo*, and the residue was filtered through a pad of silica gel (elution with ethyl acetate) to give 6.2 g of product which was heated at reflux in 65 mL of concentrated HCl solution for 19 h. The mixture was cooled, and the precipitated solid was collected to provide 4.9 g (20%) of **8b** as white solid: ^{1}H-NMR (DMSO-d_6) δ 13.85 (br s, 1H), 8.63 (s, 1H), 4.88 (br s, 1H), 3.20 (t, 2H, J = 6.7 Hz), 2.4 (2H, obscured by DMSO), 2.08 (quin, 2H, J = 6.7 Hz), 1.58 (d, 6H, J = 6.7 Hz).

5,6,7,8-Tetrahydro-5-oxo-1-(2-propyl)-2(1*H*)-quinolinone (9g). The acid **8b** (6.4 g, 25.6 mmol) and Cu powder (0.44 g, 6.9 mmol) were heated in 30 mL of refluxing quinoline for 2 h. The resulting mixture was cooled to room temperature and partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane, and the combined organic phases were washed with 10% aqueous hydrochloric acid solution and brine, dried over magnesium sulfate, filtered, and concentrated to leave 3.8 g of a brown solid. Recrystallization from ethyl ether provided 3.0 g (58%) of **9g** as a tan solid: ^{1}H-NMR (DMSO-d_6) δ 7.80 (d, 1H, J = 10.0 Hz), 6.27 (d, 1H, J = 10.0 Hz), 4.57–4.87 (m, 1H), 3.05 (t, 2H, J = 6.7 Hz), 2.43 (t, 2H, J = 6.7 Hz), 2.04 (quin, 2H, J = 6.7 Hz), 1.51 (d, 6H, J = 7.7 Hz); EIMS *m/e* (rel intensity) 205 (M^+, 76), 135 (100); IR 1660 cm^{-1}.

General Procedures for the Reductive Amination of Quinolinones 9a-l. Procedure A: 5-[[2-(3,4-Dichlorophenyl)ethyl]amino]-5,6,7,8-tetrahydro-1-propyl-2(1*H*)-quinolinone (10q). A mixture of 2-(3,4-dichlorophenyl)ethylamine (4.2 g, 22 mmol), **9b** (3.5 g, 16.9 mmol), and a catalytic amount (257 mg) of *p*-toluenesulfonic acid was heated in 70 mL of refluxing toluene, with azeotropic removal of water for 3.5 d. An additional 1 g of the amine was added after 40 and 64 h. The resulting solution was cooled, the solvent was removed *in vacuo*, and the residue was reduced without purification.

Sodium borohydride (0.60 g, 16.9 mmol) was added to a solution of the crude imine in 70 mL of ethyl alcohol, and the resulting mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo*, the residue was carefully quenched with water, and then the product was extracted into dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to afford an orange oil. Purification on a Waters Prep 500 (silica gel, elution with methanol–ethyl acetate) afforded 4.8 g (75%) of **10q** as a tan solid. Recrystallization from ethyl acetate–hexanes provided 3.1 g of analytically pure material: mp 105–107 °C; ^{1}H-NMR (DMSO-d_6) δ 7.47–7.56 (m, 2H), 7.20–7.37 (m, 2H), 6.23 (d, 1H, J = 10.0 Hz), 3.73–3.93 (m, 2H), 2.47 (br s, 1H), 2.56–2.90 (m, 6H), 1.40–2.00 (m, 7H), 0.90 (t, 3H, J = 6.6 Hz); EIMS *m/e* (rel intensity) 383 ([M$^+$ + 4], 0.2), 381 ([M$^+$ + 2], 4), 379 (M$^+$, 8) 190 (100); IR 1655 cm^{-1}.

Procedure B: 5-[[2-(3,4-Dichlorophenyl)ethyl]amino]-5,6,7,8-tetrahydro-1-(2-propyl)-2(1*H*)-quinolinone Hydrochloride (10t). Titanium(IV) isopropoxide (8.9 g, 31.5 mmol) was added rapidly, dropwise, to a solution of **9g** (2.95 g, 14.3 mmol) and 2-(3,4-dichlorophenyl)ethylamine (5.5 g, 28.7 mmol) in 30 mL of acetonitrile. The resulting mixture was stirred at room temperature for 22 h, and then dichloromethane and water were added. The mixture was filtered, the layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered, and concentrated to leave a yellow oil which was reduced without further purification.

Sodium borohydride (0.54 g, 14.3 mmol) was added to a solution of the crude imine in 60 mL of ethanol, and the resulting mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo*, the residue was carefully quenched with water, and the product was extracted into dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to afford a yellow-brown oil. Purification on a Waters Prep 500 (silica gel, elution with methanol–dichloromethane) provided 3.3 g (61%) of an orange oil. The product was dissolved in hot ethanol and treated with 2-propanol saturated with anhydrous HCl. Ethyl acetate was added, and the salt was allowed to crystallize. Filtration provided 2.9 g (54%) of **10t** as a white powder: mp 174–175 °C; ^{1}H-NMR (DMSO-d_6) δ 9.43 (br s, 1H), 9.23 (br s, 1H), 7.57–7.68 (m, 3H), 7.23 (dd, 1H, J = 2.2, 8.6 Hz), 6.22 (d, 1H, J = 10.0 Hz), 4.23 (br s, 1H), 4.47–4.67 (m, 1H), 3.00–3.30 (m, 4H), 2.60–2.90 (m, 2H), 1.67–2.23 (m, 4H), 1.47 (d, 6H, J = 5.5 Hz); EIMS *m/e* (rel intensity) 383 ([M$^+$ + 4], 2), 381 ([M$^+$ + 2], 10), 379 (M$^+$, 12) 190 (100); IR 1657 cm^{-1}.

5-Amino-5,6,7,8-tetrahydro-1-(3-methyl-2-butenyl)-2(1*H*)-quinolinone Hydrochloride (10k). A mixture of **9d** (4.5 g, 19.5 mmol), hydroxylamine hydrochloride (2.7 g, 39.0 mmol), and sodium acetate (3.2 g, 39.0 mmol) in 40 mL of a 1:1 mixture of ethanol and water was heated at reflux for 4 h, and then the solution was allowed to cool to room temperature. The precipitated oxime (4.4 g, 98%) was collected and reduced without further purification.

The oxime and nickel–aluminum alloy (Raney type, 5.4 g) were suspended in 70 mL of ethanol, and 52 mL of 10% sodium hydroxide solution was added rapidly. The exothermic reaction was then heated at reflux for 3 h, and then it was cooled and filtered. The filter cake was washed with dichloromethane and water. The organic layer was separated, and the aqueous layer was washed with dichloromethane. The combined organic layers were washed with brine, dried over K_2CO_3, filtered, and concentrated to provide 3.1 g of an oily solid. A solution of the product in hot ethanol was treated with 2-propanol saturated with anhydrous HCl. The solvent was removed *in vacuo*, and the salt was recrystallized from ethanol–isopropyl ether, providing 1.7 g (43%) of **10k** as a white powder: mp 195–205 °C dec. ^{1}H-NMR (DMSO-d_6) δ 8.53 (br s, 3H), 7.63 (d, 1H, J = 8.6 Hz), 6.37 (d, 1H, J = 8.6 Hz), 4.97–5.03 (m, 1H), 4.45–4.78 (m, 2H), 4.21 (br s, 1H), 2.71 (br s, 2H), 1.72–2.00 (m, 4H), 1.75 (s, 3H), 1.68 (s, 3H); EIMS *m/e* (rel intensity) 232 (M$^+$, 34), 41 (100); IR 1660 cm^{-1}.

Biological Methods

Measurement of Acetylcholinesterase and Butyrylcholinesterase Inhibition. Acetylcholinesterase activity was based on the method of Ellman.[19] Rat striatal homogenates (1:20 w/v in 0.05 M NaH_2PO_4 and 0.05 M Na_2HPO_4, adjusted to pH 7.2) were incubated at 37 °C for 10 min with drug in 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB), and a separate solution of acetylthiocholine was prepared in an identical buffer. Aliquots of drug solution and acetylthiocholine solution were added to cuvettes yielding final concentrations of 0.25 mM DTNB and 5 mM acetylthiocholine. Absorbance changes were monitored with a Beckman DU-50 spectrophotometer and slope values determined with the Kindata/program. Values for percent inhibition were calculated relative to a control sample, and the IC_{50} values were calculated by log-probit analysis.

Inhibition of butyrylcholinesterase inhibition was measured as described above for acetylcholinesterase by substituting BuChE (Sigma Chemical Co.; from human serum) and butyrylthiocholine for enzyme and substrate, respectively.

Reversal of Scopolamine Dementia (SDDA). Three groups of 15 male CFW mice were used: a vehicle/vehicle control group, a scopolamine/vehicle group, and a scopolamine/drug group. Thirty minutes prior to training, the vehicle/vehicle control group received normal saline sc, and the scopolamine/vehicle and scopolamine/drug groups received scopolamine sc (3.0 mg/kg, administered as scopolamine hydrobromide). Five minutes prior to training, the vehicle/vehicle control and scopolamine/vehicle groups received distilled water and the scopolamine/drug group received the test compound in distilled water. The training/testing apparatus consisted of a plexiglass box approximately 48 cm long and 30 cm high and tapering from 26 cm wide at the top to 3 cm wide at the bottom. The interior of the box was divided equally by a vertical barrier into a light compartment (illuminated by a 25-W reflector lamp suspended 30 cm from the floor) and a dark compartment (covered). There was a hole at the bottom of the barrier 2.5 cm wide and 6 cm tall and a trap door which could be dropped to prevent an animal from passing between the two compartments. A Coulbourn Instruments small animal shocker was attached to two metal plates which ran the entire length of the apparatus, and a photocell was placed in the dark compartment 7.5 cm from the vertical barrier and 2 cm off the floor. The behavioral session was controlled by a PDP 11/34 minicomputer. At the end of the pretreatment interval, an animal was placed in the light chamber directly under the light fixture and facing away from the door to the dark chamber. The apparatus was then covered and the system activated. If the mouse passed through the barrier to the dark compartment and broke the photocell beam within 180 s, the trap door dropped to block escape to the light compartment and an electric shock was administered at an intensity of 0.4 mA for 3 s. The animal was then immediately removed from the dark compartment and placed in its home cage. If the animal failed to break the photocell beam within 180 s, it was discarded. The latency in seconds for each mouse was recorded. Twenty-four hours later, the animals were again tested in the same apparatus except that no injections were made and the mice did not receive a shock. The test day latency in seconds for each animal was recorded.

The high degree of variability (due to season of the year, housing conditions, and handling) found in one-trial passive avoidance paradigms is well-known.[25] To control for this fact, individual cutoff values were determined for each test, com-

pensating for intertest variability. Additionally, it was found that 5–7% of the mice in the scopolamine/vehicle control groups were insensitive to scopolamine at 3 mg/kg, sc. Thus, the cutoff value was defined as the second highest latency time in the control group to more accurately reflect the 1/15 expected control responders in each test group. Experiments with a variety of standards repeated under a number of environmental conditions led to the development of the following empirical criteria: for a valid test, the cutoff value had to be less than 120 s and the vehicle/vehicle control group had to have at least 5/15 animals with latencies greater than cutoff. For a compound to be considered active the scopolamine/compound group had to have at least 3/15 mice with latencies greater than cutoff.

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