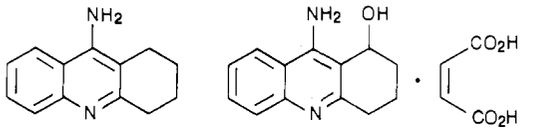
Communications to the Editor

(±)-9-Amino-1,2,3,4-tetrahydroacridin-1-ol. A Potential Alzheimer's Disease Therapeutic of Low Toxicity

Sir:

Alzheimer's disease (AD) has been recognized as one of the most disabling conditions affecting the aged and is the major cause of dementia among elderly people.[1] While numerous theories exist regarding the etiology of AD,[2] the hypothesis that a defect in the cholinergic system is involved has received the most attention in terms of a therapeutic strategy.[3]

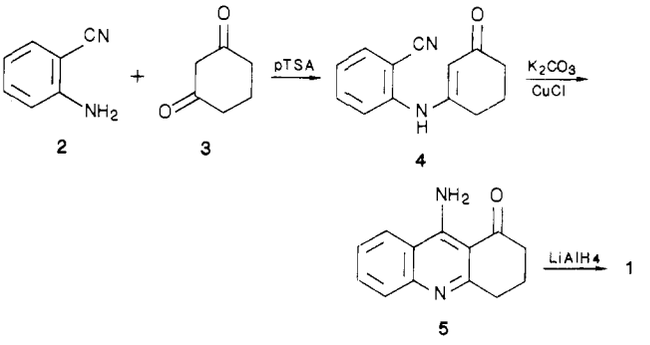
In support of this hypothesis, muscarinic agonists,[4] cholinergic releasing agents,[5] and cholinesterase inhibitors[6] have shown activity in AD patients in experimental situations. Furthermore, a recent clinical report on the efficacy of the cholinesterase inhibitor 1,2,3,4-tetrahydro-9-acridinamine (THA, tacrine)[7] created hope that a least a "first generation" of agents for the treatment of AD was at hand. The even more recent temporary suspension of THA from clinical trials in AD because of liver toxicity[8] prompts us to report on a new compound, (±)-9-amino-1,2,3,4-tetrahydroacridin-1-ol maleate (**1**, HP-029), which is currently in phase II clinical trials for AD.



THA 1

We became interested in tacrine-like compounds quite some time ago as part of our program in AD. This interest was prompted by the unique mechanism by which THA has been shown to inhibit cholinesterase;[9] it was, however, tempered by the known liver toxicity of THA.[10] We suspected that the lipophilic nature of THA would cause it to accumulate in tissues (including the liver), leading to its observed toxicity. Accordingly, compound **1** was designed with chemical functionality that should limit its toxicity. It was predicted that the 1-hydroxyl group of **1** (Scheme I), by providing a ready "handle" for glucuronide conjugation, might facilitate elimination and lessen toxicity without sacrificing the all-important abilities of the molecule to inhibit cholinesterase and cross the blood–brain barrier. Compound **1** exhibits a biochemical and pharmacological profile similar to THA and yet, in acute and subchronic toxicology studies, it is far less toxic than THA and is, until now, without measurable liver toxicity in humans.

Scheme I



2 3 4 5

The synthesis of **1** is shown in Scheme I. The condensation of anthranilonitrile (**2**) with cyclohexane-1,3-dione (**3**) under typical conditions for enamine formation (refluxing toluene, *p*-toluenesulfonic acid, H_2O separation) gave the enamino ketone (**4**), which was cyclized in refluxing THF in the presence of K_2CO_3 and CuCl to give 9-amino-3,4-dihydroacridin-1(2*H*)-one (**5**). Reduction of **5** with $LiAlH_4$ in THF afforded (±)-9-amino-1,2,3,4-tetrahydroacridin-1-ol, which was converted to its maleic acid salt (**1**) [mp 171–173 °C. Anal. ($C_{13}H_{14}N_2O \cdot C_4H_4O_4$) C, H, N,].

As stated above, certain types of impaired learning and memory (dementia) in humans (e.g. Alzheimer's disease) are thought to correspond to the development of a cholinergic deficit in the central nervous system. While the available animal models of AD are still imperfect,[11] it has been suggested that paradigms in which dementia is mimicked in animals by inducing a functional cholinergic lesion (through the use of antimuscarinic drugs) or by creating an actual lesion in an important cholinergic pathway (through the use of stereotaxically applied excitotoxins) may be valid models of demented states in humans. Two such models that we chose for our work are the impairment of 24-h memory in a passive dark-avoidance paradigm in mice, induced by scopolamine,[12] and the deficit in 72-h retention of a one-trial dark-avoidance task in rats, induced by ibotenic acid lesions in the nucleus basalis magnocellularis (NBM).[13] For brevity, only the results of these two key assays and an in vitro acetylcholinesterase (AChE) inhibition assay are presented here. Full biological results will appear elsewhere in the near future.

The data comparing in vitro AChE inhibition and reversal of scopolamine-induced dementia in mice for **1** and

(1) For recent reviews on Alzheimer's disease, see: (a) Armstrong, W. *Recent Trends in Research on Alzheimer's Disease*; PJB Publications Ltd.: Surry, UK, 1986. (b) Katzman, R. *N. Engl. J. Med.* **1986**, *314*, 964.
(2) (a) Hershenson, F. W.; Moos, W. H. *J. Med. Chem.* **1986**, *29*, 1125. (b) Price, D. L. *Annu. Rev. Neurosci.* **1986**, *9*, 489.
(3) (a) Kopelman, M. D. *Q. J. Exp. Psychol.* **1986**, *38A*, 535. (b) Bartus, R. T.; Dean, R. L.; Beer, B.; Lippa, A. S. *Science (Washington, D.C.)* **1982**, *217*, 408.
(4) Harbaugh, R. E.; Roberts, D. W.; Coombs, D. W.; Saunders, R. L.; Reeder, T. M. *Neurosurgery* **1984**, *15*, 514.
(5) Wesseling, H.; Agoston, S.; Van Dam, G. B. P.; Pasma, J.; DeWit, D. J.; Havinga, H. *N. Engl. J. Med.* **1984**, *310*, 988.
(6) Mohs, R. C.; Davis, B. M.; Johns, C. A.; Mathe, A. A.; Greenwald, B. S.; Horvath, T. B.; Davis, K. L. *Am. J. Psychiatry* **1985**, *142*, 28.
(7) Summers, W. K.; Majovski, L. V.; Marsh, G. M.; Tachiki, K.; Kling, A. *N. Engl. J. Med.* **1986**, *315*, 1241.
(8) Marx, J. J. *Science (Washington, D.C.)* **1987**, *238*, 1041.
(9) Steinberg, G. M.; Mednick, M. L.; Maddox, J.; Rice, R.; Cramer, J. *J. Med. Chem.* **1975**, *18*, 1056.
(10) Summers, W. K.; Kaufman, K. R.; Altman, F., Jr.; Fischer, J. M. *Clin. Toxicol.* **1980**, *16*, 269.
(11) Hershenson, F. M.; Marriott, J. G.; Moos, W. H. *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic: New York, 1986; p 32.
(12) DeNoble, V. J.; Repetti, S. J.; Gelpke, L. W.; Wood, L. M.; Keim, K. L. *Pharmacol. Biochem. Behav.* **1986**, *24*, 1123.
(13) Haroutunian, V.; Kanof, P.; Davis, K. L. *Life Sci.* **1985**, *37*, 945.

0022-2623/88/1831-1278$01.50/0

Table I. Pharmacological Activity of 1

compound	acetylcholinesterase inhibition: IC_{50},[a] μM	reversal of scopolamine-induced memory impairment: %>CO (best dose, mg/kg sc)[b]	acute toxicity in mice: LD_{50},[c] mg/kg po
1	4.8 ± 1.0	33 (0.63)	136 (113–163)
THA	0.31 ± 0.08	40 (0.63)	39.8 (25.1–63.0)

[a] These values were obtained as described in ref 16, using a rat striatal preparation. They are reported as the mean ± SEM, with $N = 3$ for 1 and $N = 4$ for THA. [b] The procedures for this paradigm are essentially as described in ref 12. In our adaptation, groups of 15 CFW mice were used. A cutoff (CO) was defined for the scopolamine-vehicle group as the value for the animal with the second longest latency time, and results are reported as the percent of animals in the scopolamine-drug group that exhibited latencies greater than the cutoff time (ref 17). The reported dose is that at which the greatest effect was observed. [c] These values were obtained by a modification of the method of Bliss (ref 18). Groups of 10 mice were tested at four doses. The values in parentheses are 95% confidence limits.

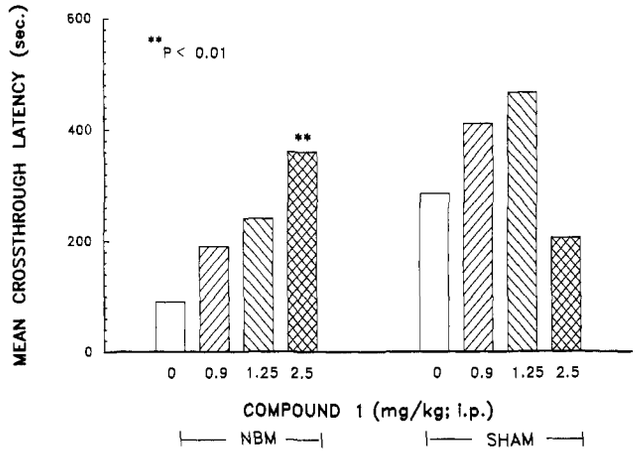


Figure 1. Effect of 1 on the 72-h retention of passive avoidance in NBM lesioned rats. The procedures for this test are described in ref 13. Groups of 10 rats were used per dose; the zero mg/kg dose corresponds to an injection of pure saline. There was a significant impairment of retention test performance in the saline-injected NBM lesioned rats (ANOVA $F = 8.56$, $P < 0.01$, Newman–Keuls test, $P < 0.05$). There was a statistically significant (ANOVA $F = 3.3$, $P < 0.025$) enhancement of retention by HP 029 in both lesioned and sham-operated rats. In the lesioned rats, HP 029 exerted its greatest effect at the 2.5 mg/kg dose (Newman–Keuls test, $P < 0.01$).

THA are summarized in Table I. As an AChE inhibitor, 1 is somewhat less active in vitro than THA and yet is active in the same dose range as THA in reversing scopolamine-induced memory impairment (Table I);[14] it is also active in the NBM model, reversing the retention deficit in the lesioned animals and enhancing learning in the sham-operated animals. At the 2.5 mg/kg dose, the deficit in the lesioned animals was not only reversed but performance was actually improved above the level of normal sham-operated controls (Figure 1).

Compound 1 was further evaluated for acute toxicity in mice (Table I). It can be seen that 1 is significantly less toxic than THA while, as indicated above, 1 and THA are essentially equipotent in reversing scopolamine-induced dementia; this toxicity differential was also observed in longer term studies. Thus, even though 1 is less potent than THA as an AChE inhibitor, it is considerably less toxic and, at the same time, equally effective in an assay that may be predictive of activity in Alzheimer's disease.

In view of these and other results, clinical trials were initiated with 1. In light of the recently reported results with THA, we feel it timely to report that upon completion of phase I with 1, an acceptable dose range for outpatient evaluation has been defined. Neither laboratory nor clinical evidence of drug-induced hepatotoxicity has been reported in 1396 subject days of exposure (normal young and elderly volunteers as well as in AD patients).[15] Further studies to establish the safety and efficacy of 1 in AD are under way.

Registry No. 1, 112964-99-5; 1 (free base), 112964-98-4; 2, 1885-29-6; 3, 504-02-9; 4, 104675-23-2; 5, 104675-26-5; AChE, 9000-81-1.

(14) These data suggest that, in addition to cholinesterase inhibition, there may be other components to the mechanism of action of 1. Further studies aimed at elucidating the mechanism of action are 1 are under way and will be reported at a later date.

(15) (a) Lassman, H. B.; Puri, S. K., unpublished results. (b) Murphy, M. F., unpublished results. Further details of the clinical aspects of this work will be published shortly.

(16) Ellman, G. L.; Courtney, K. D.; Andres, V., Jr.; Featherstone, R. M. *Biochem. Pharmacol.* **1961**, *7*, 88.

(17) 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 (see: Bammer, G. *Neurosci. Biobehav. Rev.* **1982**, *6*, 274). To control for this fact, individual cutoff (CO) values were determined for each test, compensating 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 CO 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 empirical positive activity criterion of 3/15 mice with latencies over CO.

(18) Bliss, C. I. *Q. J. Pharm. Pharmacol.* **1938**, *11*, 192.

Gregory M. Shutske,* Frank A. Pierrat
Michael L. Cornfeldt, Mark R. Szewczak
Francis P. Huger, Gina M. Bores
Departments of Chemical Research and Biological Research
Hoechst-Roussel Pharmaceuticals, Inc.
Somerville, New Jersey 08876

Vahram Haroutunian, Kenneth L. Davis
Department of Psychiatry
Bronx Veterans Administration Medical Center
Bronx, New York 10468
Received January 13, 1988

Methyl Mercapturate Episulfonium Ion: A Model Reactive Metabolite of Dihaloethanes

Sir:

Dihaloethanes (DHEs), commonly used as soil fumigants, gasoline additives, solvents, and synthetic intermediates,[1] have been found to be carcinogenic in animals.[2] This activity is dependent on both glutathione (GSH) and

(1) Fishbein, L. *J. Toxicol. Environ. Health* **1980**, *6*, 1133.
(2) Storer, R. D.; Conolly, R. B. *Carcinogenesis* **1983**, *4*, 1491.

0022-2623/88/1831-1279$01.50/0