Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 14, pp. 1489-1494, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00238-3

DESIGN AND SYNTHESES OF 4-ACYLAMINOPYRIDINE DERIVATIVES: NOVEL HIGH AFFINITY CHOLINE UPTAKE ENHANCERS I [1)]

Haruyuki Chaki*, Haruko Yamabe, Mamoru Sugano, Shuji Morita, Tomoko Bessho, Reiko Tabata, Ken-Ichi Saito, Mitsuo Egawa#, Akihiro Tobe and Yasuhiro Morinaka

Yokohama Research Center, Mitsubishi Chemical Corporation
1000, Kamoshida-cho, Aoba-ku, Yokohama 227, Japan

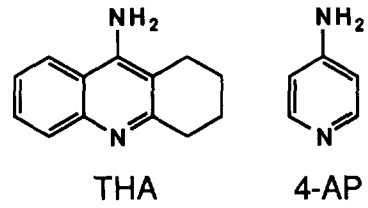
Abstract: 4-Acylaminopyridine derivatives were synthesized and found to have high affinity choline uptake improvement activity. Optimum activity was obtained when the n-propylcarbonyl group was introduced as the acyl moiety. A series of 2-oxo-1-pyrrolidineacetyl substituted derivatives also showed activity.

Introduction

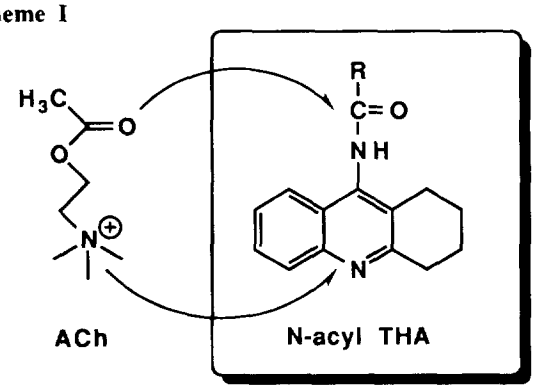
Alzheimer's disease (AD) is the most prevalent of the neurodegenerative diseases and main cause of dementia in elderly people. It is widely accepted that the cholinergic function in the brain of AD patients is defective,[2)] and it is recognized that there is a good correlation between the dysfunction of the cholinergic neuron and memory loss.[3)] Various therapeutic approaches have now been attempted to enhance the cholinergic neuron in the brain using agents such as acetylcholinesterase (AChE) inhibitors, muscarinic agonists, or acethylcholine (ACh) releasers. Particularly, clinical trials of many AChE inhibitors have been conducted. Among them, 9-amino-1,2,3,4- tetrahydroacridine (THA, tacrine) is already used in practice.

However, it has been reported that presynaptic choline uptake in AD patients is deficient.[4)] High affinity choline uptake (HACU) is an important factor in the cholinergic nervous system and is demonstrated to be a regulatory step in ACh synthesis.[5)] We considered that a better approach for the treatment of AD would be to activate the presynaptic cholinergic function, especially to improve the reduced HACU. Therefore, we have tried to find novel choline uptake enhancers which improve the reduced HACU in the hippocampal synaptosome of rats treated with AF64A, which is reported to decrease HACU.[6)]

When we started our study, 4-aminopyridine (4-AP) was already known to increase HACU.[7] But it is so toxic that it is unsuitable for clinical use.[8] We also realized that THA contained 4-AP as a partial structure and was used in clinical. However, THA had no action on the reduced HACU.[9] We assumed that there was some system that recognized ACh in order to regulate the choline uptake. We also assumed that the 1-nitrogen atom of 4-AP corresponded to the quaternary amine of ACh. Therefore, to introduce an acyl group to have more analogous structure to ACh, N-alkylcarbonyl THA derivatives were designed and synthesized (Scheme I). Furthermore, we investigated the 2-oxo-1-pyrrolidineacetyl group as an acyl moiety which was often contained in nootropic agents such as piracetam[10] and other acyl groups. As expected, the acylation of THA enhanced choline uptake, while AChE inhibitory activity was lost. Here we describe the syntheses and structure-activity relationship of 4-acylaminopyridine derivatives, novel choline uptake enhancers.



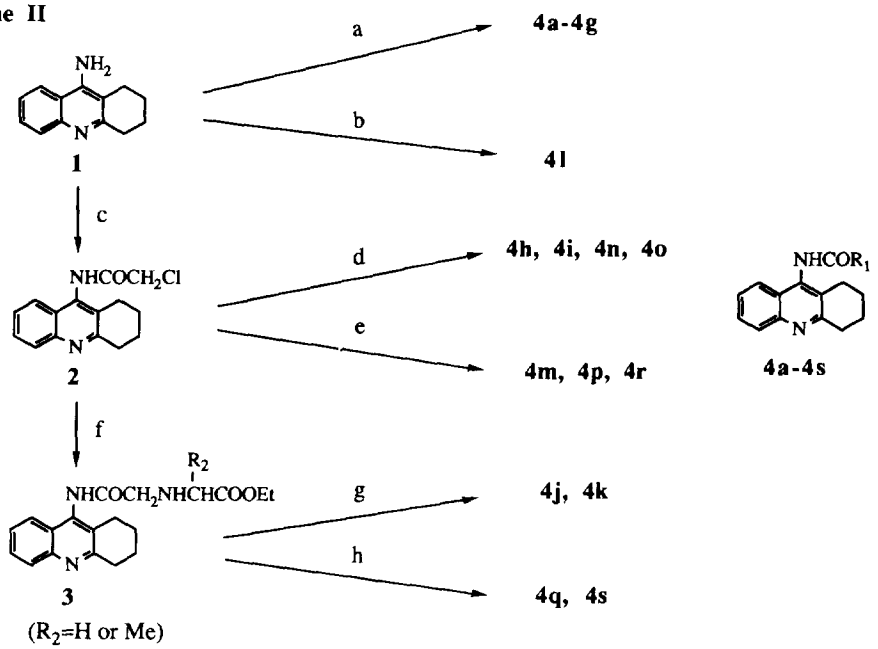
Scheme I



Chemistry

The synthesis of 4-acylaminopyridine derivatives **4a**-**4s** is shown in Scheme II. Compound **1** was synthesized according to the published procedure.[11] The acylation of **1** using acid anhydrides afforded a mixture of the monoacyl and diacyl derivatives, which was treated with ammonium hydroxide to give alkylcarbonyl derivatives **4a**-**4g**. The 2-oxo-1-pyrrolidineacetyl derivative **4l** was prepared by the direct acylation of **1** with methyl 2-oxo-1-pyrrolidineacetate. The acylation of **1** with chloroacetyl chloride followed by hydrolysis gave the chloroacetyl intermediate **2**. The substitution of **2** with amines afforded the corresponding aminoacetyl derivatives **4h**, **4i**, **4n** and **4o**.

Scheme II



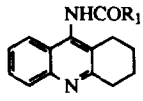
Reagents: (a) i) $(R_1CO)_2O$, C_5H_5N; ii) c.NH_4OH, MeOH; (b) methyl 2-oxo-1-pyrrolidineacetate, NaH, NMP; (c) i) $ClCH_2COCl$; ii) c.NH_4OH, MeOH; (d) methylamine, dimethylamine, pyrrolidine or imidazole; (e) 2-piperidone, 2-imidazolidone or hydantoin, NaH, DMF; (f) GlyOEt or AlaOEt; (g) NaOH, $EtOH/H_2O$; (h) urea, NMP

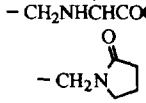
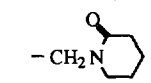
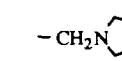
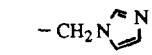
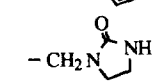
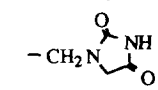
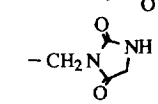
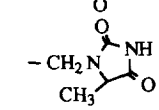
The 2-oxo-1-piperidineacetyl, 2-oxo-1-imidazolidineacetyl and 2,4-dioxo-3-imidazolidineacetyl derivatives (**4m**, **4p** and **4r**) were prepared from **2** with the metal salts of corresponding cyclic amides. The substitution of **2** with the amino acid ester gave the ester intermediate **3**, which was hydrolyzed to the carboxymethylaminoacetyl derivatives **4j** and **4k**. The 2,4-dioxo-1-imidazolidineacetyl derivatives **4q** and **4s** were prepared from **3** by heating with urea.

Biology

HACU was measured by the uptake amount of [^{3}H]choline in the hippocampal synaptosomes according to the method of Simon et al.[12] Intracerebroventricular administration of AF64A significantly decreased HACU to about 50% of the normal level.[13] To evaluate the effects of compounds, HACU improvement values were used. The value was calculated from the equation, [(B-A)/A]x100; A: HACU value measured in the hippocampal synaptosomes of AF64A-treated rats (control), B: HACU value when the compound was incubated with the synaptosomes of AF64A-treated rats. Compounds were evaluated at 10^{-5}, 10^{-6}, and 10^{-7}M. The potency of the active compound was estimated by the amount of increased HACU and the statistical significance.

Table I : HACU improvement activities of 4-acylaminopyridine derivatives



	R_1	HACU improvement (%) *1)		
		10^{-7}M	10^{-6}M	10^{-5}M
4a	$-CH_3$	-12	-10	-11
4b	$-CH_2CH_3$	3	1	3
4c	$-CH_2CH_2CH_3$	13	24 **	28 **
4d	$-CH_2CH_2CH_2CH_3$	-2	-1	18 *
4e	$-CH_2CH_2CH_2CH_2CH_3$	11	5	2
4f	$-CH(CH_3)_2$	12	9	15
4g	$-CH_2CH(CH_3)_2$	4	-22	0
4h	$-CH_2NHCH_3$	8	18	21 *
4i	$-CH_2N(CH_3)_2$	0	-13	-7
4j	$-CH_2NHCH_2COOH$	-4	-2	27
4k	$-CH_2NHCH(CH_3)COOH$	-7	6	13
4l		17 *	14	13
4m		-3	2	5
4n		1	-20	-71 **
4o		6	14	48 **
4p		6	1	25 *
4q		15 *	11	10
4r		-5	0	16
4s		4	2	11
	THA	8	8	-13

*1) (*)$p<0.05$, (**)$p<0.01$. vs. control.

Results and discussion

There were several compounds which showed HACU improvement activity as shown in Table I. In the alkylcarbonyl series, optimum activity was obtained with the n-propylcarbonyl derivative (**4c**). Increasing or decreasing the carbon chain reduced their activity. Branching of the carbon chain also gave the same results (**4f** and **4g**). Azasubstitution of the corresponding alkylcarbonyl derivatives produced undesirable results (**4h** vs. **4c**).

Similarly the carboxymethylaminoacetyl derivatives did not show any activity (**4j** and **4k**). In the cyclic series **4l-4s**, the carbonyl group(s) or double bond(s) were necessary to improve the potency (**4l**, **4o**, **4p** and **4q**). The 2-oxo-1-pyrrolidineacetyl derivative showed activity at 10^{-7}M (**4l**). Ring expansion or decarbonylation showed unsatisfied results (**4m**, **4n** vs. **4l**). Azasubstitution at the C_3 position of the ring maintained the activity (**4p** vs. **4l**). The introduction of the second carbonyl group to the ring brought different results (**4q** vs. **4r**). Methyl substitution at the C_5 position of the ring was accompanied with reduced activity compared to that of the unsubstituted derivative (**4s** vs. **4q**). These results suggest that the moderate bulkiness of the N-acyl substituent should be necessary to show HACU improvement activities. The introduction of heteroatoms decreased its activity in the acyclic series **4a-4k**. In the cyclic series, the proper position of carbonyl group(s) or double bond(s) should be important to show activity.

In conclusion, we have demonstrated that the acylated derivatives of THA, which contain 4-AP, have HACU improvement activity. Among these compounds, their activities might be dependent on the carbon chain length or proper functional group(s) of the N-acyl substituent. In the acyclic series, the unbranched C_3 alkyl chain length produced the highest activity, while in the cyclic series, the introduction of carbonyl group(s) or double bond(s) to the five-membered ring was preferable. Studies on these compounds could be helpful to elucidate the importance of the function of cholinergic mechanisms in AD. Further syntheses and assays of related compounds are described in the following publications.

References and Notes

Present address: Research and Development Department, Mitsubishi Chemical Corporation, Tennoz Central Tower, 2-24, Higashishinagawa 2-chome, Shinagawa-ku, Tokyo 140, Japan

1) This paper is dedicated to the late Kunihiro Ninomiya for his great contribution to the progress of this project.

2) (a) Davies, P., *Brain Res.* **1979**, *171*, 319.
(b) Perry, E. K.; Tomlinson, B. E.; Blessed, G.; Bergmann, K.; Gibson, P. H.; Perry, R. H., *Br. Med. J.* **1978**, *2*, 1457.
(c) Davies, P.; Maloney, A. J. R., *Lancet* **1976**, *2*, 1403.
(d) Whitehouse, P. J.; Price, D. L.; Struble, R. G.; Clark, A. W.; Coyle, J. T.; DeLong, M. R., *Science* **1982**, *215*, 1237.

3) Perry, E. K.; Tomlinson, B. E.; Blessed, G.; Bergmann, K.; Gibson, P. H.; Perry, R. H., *Br. Med. J.* **1978**, 2, 1457.

4) Rylett, R. J.; Ball, M. J.; Calhoun, E. H., *Brain Res.* **1983**, *289*, 169.

5) (a) Kuhar, M. J.; Murrin, L. C., *J. Neurochem.* **1978**, *30*, 15.
(b) Tucek, S., *J. Neurochem.* **1985**, *44*, 11.

6) Rylett, R. J.; Calhoun, E. H., *J. Neurochem.* **1980**, *34*, 713.

7) Levent Buyukuysal, R.; Wurtman, R.J., *Brain Res.* **1989**,*482*, 371.

8) Schafer, E. W. JR.; Brunton, R. B.; Cunningham, D. J., *Toxicol. Appl. Pharmcol.* **1974**, *26*, 532.

9) In house data, see Table I.

10) Giurgea, C., *Curr. Dev. Psychopharmacol.* **1976**, *3*, 223.

11) Moore, J. A.; Kornreich, L. D., *Tetrahedron Lett.* **1963**, 1277.

12) Simon, J. R.; Kuhar, M. J., *Nature* **1975**, *255*, 162.

13) Bessho, T.; Takashina, K.; Ooshima, C.; Egawa, M.; Tobe, A., *Neurobiol. Aging* **1994**, *15*, suppl.1, S103.

(*Received in Japan* 10 *April* 1995; *accepted* 1 *June* 1995)