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

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Abstract: The syntheses of 4-acylaminopyridine derivatives and their high affinity choline uptake improvement activities are described. N-propylcarbonyltetrahydroaminoacridine (**1**) was selected as a lead compound. Modification of its ring structure and acyl moiety led some active compounds. Among them, **9d** (MKC-231) showed the highest activity. This compound is expected to be a unique medicine for Alzheimer's disease.

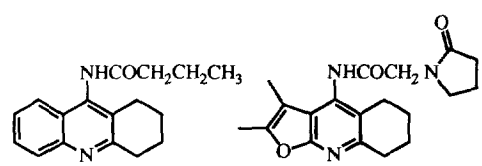
Introduction

In Alzheimer's disease (AD), it is widely accepted that the cholinergic function in the brain is defective, and there have been some reports that presynaptic choline uptake is deficient.[2)] High affinity choline uptake (HACU) is an important factor in the cholinergic nervous system and is demonstrated to be a regulatory step in acethylcholine (ACh) synthesis.[3)] So we considered that drugs improving the reduced HACU would be useful for the treatment of AD.

As reported in a previous paper,[4)] we designed and synthesized N-acyltetrahydroaminoacridine derivatives. These compounds were found to improve the reduced HACU in the hippocampal synaptosomes of AF64A-treated rats.

These results encouraged us to pursue further studies to determine more active compound(s). When we planned the new strategy, it was worth considering that the tetrahydroaminoacridine (THA) structure was contained in our compounds. THA is the first drug for AD treatment in the USA, but it is known to produce undesirable side effects, such as liver toxicities.[5)] So this partial structure might cause our compounds to become toxic. Therefore, we have tried to obtain a structural distinct compound with superior HACU improvement activity. We selected N-propylcarbonyltetrahydroaminoacridine (**1**) as the lead compound which was one of the most active derivatives as shown in the previous paper.[4)] Consequently we carried out transformation of the ring structure at first, and following modification of acyl moiety.

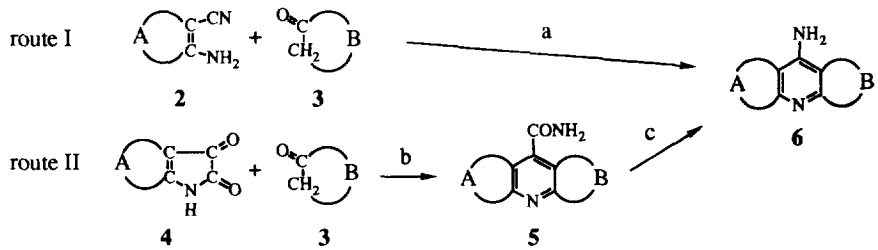
As a result, we obtained a new compound, 2-(2-oxopyrrolidin-1-yl)-N-(2,3-dimethyl-5,6,7,8-tetrahydrofuro[2,3-b]quinolin-4-yl)acetoamide **9d** (MKC-231), which is currently in clinical trials for AD. In this paper, we describe the syntheses and structure-activity relationship of the 4-acylaminopyridine derivatives, and an approach to a novel choline uptake enhancer, MKC-231.



1

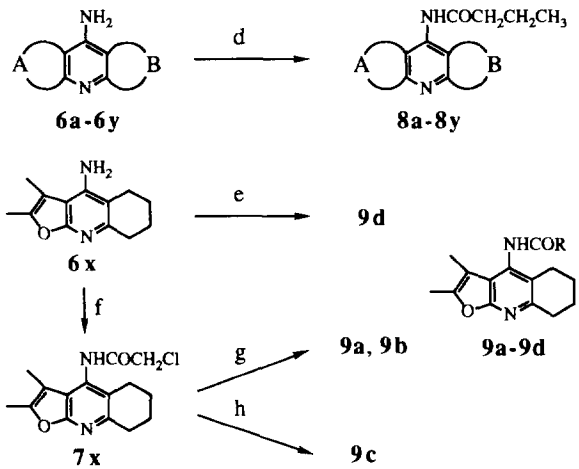
9d (MKC-231)

Scheme I



Reagents: (a) i) $ZnCl_2$, neat, xylene or nitrobenzene; ii) c.NH_4OH, MeOH; (b) $AcONH_4$, DMF; (c) Br_2, NaOH, H_2O

Scheme II



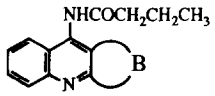
Reagents: (d) i) $(CH_3CH_2CH_2CO)_2O$, C_5H_5N; ii) c.NH_4OH, MeOH; (e) methyl 2-oxo-1-pyrrolidineacetate, NaH, NMP; (f) i) $ClCH_2COCl$, NMP; ii) c.NH_4OH, MeOH; (g) methylamine or imidazole, NaH, DMF; (h) i) GlyOMe, NMP; ii) urea, NMP

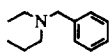
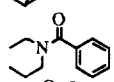
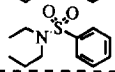
Chemistry

The synthetic routes of the compounds are shown in Schemes I and II. Preparation of the tricyclic amine intermediate **6** was done according to the published method[6)7)] with modified conditions (Scheme I). In route I, the condensation reaction of aminonitrile **2** with cyclic ketone **3** in the presence of excess anhydrous zinc chloride afforded the complex of **6** and zinc chloride, which was treated with ammonium hydroxide to give **6**. In route II, **6** was prepared by the Hofmann rearrangement of amide **5** which was the condensation product of isatin **4**, cyclic ketone **3** and ammonia.

The N-acyl derivatives **8a-8y** and **9a-9d** were prepared with the same manner as previously described[4)] (Scheme II). In these syntheses, compounds **8a-8y** were prepared by the acylation of **6a-6y**. Whereas, compounds **9a-9d** were directly obtained from tetrahydrofuroquinoline **6x** or via intermediate **7x**. The acylation of **6x** with methyl 2-oxo-1-pyrrolidineacetate gave **9d**. The other three derivatives, **9a**, **9b**, **9c** were obtained via the chloroacetyl intermediate **7x**.

Table I : HACU improvement activities of N-propylcarbonyl derivatives **8a-8n**



	B	HACU improvement (%) *1)*2) 10^{-7}M	10^{-6}M	10^{-5}M	Synthetic method of **8**
8a		10 *	17 **	16**	b, c, d
8b		14**	8	-7	a, d
8c		-6	-16	6	a, d
8d		-11	3	1	a, d
8e		3	19	12	a, d
8f		-1	-7	-6	a, d
8g		5	-6	-3	a, d
8h		14	14	14	a*3), d*4)
8i		13	16	10	*5)
8j		13	9	19**	b, c, d
8k		10	11	21**	b, c, d
8l		7	7	10	a, d
8m		7	0	-7	a*6), d
8n		26	10	5	a*7), d
1		13	24**	28**	

*1) HACU was measured by the uptake amount of [^{3}H]choline in the hippocampal synaptosomes. Each 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.[4]

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

*3) Amine was obtained as the ketal derivative by condensation of 2-aminobenzonitrile with 1,4-cyclohexanedione mono-ketal.

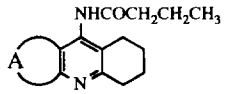
*4) **8h** was prepared by method (d) followed by hydrolysis of the ketal group.

*5) **8i** was prepared by reduction of **8h**.

*6) Amine intermediate was prepared by condensation of 2-aminobenzonitrile with 1-acetyl-4-piperidone followed by hydrolysis, then benzoylation.

*7) Amine intermediate was prepared with the same manner as *6), using sulfonylation instead of benzoylation.

Table II : HACU improvement activities of N-propylcarbonyl derivatives **8o-8y**



	A	HACU improvement (%) *1)*2) 10^{-7}M	10^{-6}M	10^{-5}M	Synthetic method of **8**
8o		9	2	3	a, d
8p		2	-5	7	b, c, d
8q		-1	3	-15	b, c, d
8r		-2	-4	10	a, d
8s		15	10	13	a, d
8t		1	1	12	a, d
8u		7	4	15	a, d
8v		7	3	1	a, d
8w		4	11	20*	a, d
8x		13	20*	38**	a, d
8y		4	2	18	a, d

*1),*2) See Table I

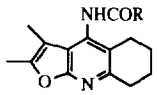
Results and discussion

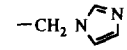
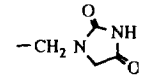
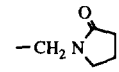
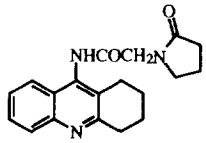
Compounds were evaluated *in vitro* by the same method outlined in the previous paper.[4] Compound **1** is cited for comparison purpose in Table I.

a) Modification of the right part (ring B) of tricyclic structure

Table I shows the HACU improvement activity of **8a-8n**. In this series of compounds, the left part of the tricyclic structure was fixed to the phenyl ring. Of these, the 4-methyl substituted derivative (**8a**) was the most active, but it was as potent as the unsubstituted compound **1**. While the 3,4-dehydro compound (**8b**) and 2-aza compounds (**8j** and **8k**) showed decreased activity, the other transformed compounds did not show any activity.

Table III : HACU improvement activities of N-acyl derivatives of **6y**



	R	HACU improvement (%) *1)*2) 10^{-8}M	10^{-7}M	10^{-6}M
9a	$-CH_2NHCH_3$	14	10	3
9b		5	4	3
9c		5	12	16
9d (MKC-231)		55**	72*	64**
10		15	17*	14

*1),*2) See Table I

b) Modification of the left part (ring A) of tricyclic structure

Table II shows the HACU improvement activity of **8o-8y**. In this series of compounds, the right part of the tricyclic structure was fixed to the cyclohexane ring. Of these, the introduction of fluoro atom or methyl group to the phenyl ring caused a loss in potency (**8o-8r**). The pyridine derivative (**8s**) also gave the same results. However, in the case of the thiophene ring, the unsubstituted (**8t** and **8u**) or 3-methyl (**8v**) derivatives did not show any activity, while the introduction of a second methyl group led to the active compound (**8w**). Consequently, the 2,3-dimethylfurane derivative (**8x**) was prepared and was proved to have high HACU improvement activity.

c) Optimization of N-acyl group of 8x.

Table III shows the HACU improvement activity of **9a-9d**. In this series of compounds, the optimization of the acyl moiety was carried out. Here, we introduced the acyl groups which brought the successful result in the previous study.[4] Unexpectedly, the methylaminoacetyl (**9a**), imidazolylacetyl (**9b**), and 2,4-dioxo-1-imidazolidineacethyl (**9c**) derivatives did not show any activity. In contrast with these compounds, the 2-oxo-1-pyrrolidineacetyl derivative **9d** gave promising results. Although the corresponding THA derivative **10**[4] had only slight activity, **9d** showed strong potency even at low concentrations.

In conclusion, the optimization of N-propylcarbonyltetrahydroaminoacridine (**1**) toward more potent compound(s) possessing the HACU improvement activity was performed. In this study, the transformation of two rings fused to 4-aminopyridine followed by modification of the acyl moiety were carried out. As a result, we chose to use the novel choline uptake enhancer, 2-(2-oxopyrrolidin-1-yl)-N-(2,3-dimethyl-5,6,7,8-tetrahydrofuro[2,3-b]quinolin-4-yl)acetoamide **9d** (MKC-231). This compound was already found to have *in vivo* activity[8] and it showed low acute toxicity in rats.[9] It is currently in clinical trials and is expected to be a unique and useful medicine for AD.

References and Notes

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1) This paper is dedicated to the late Kunihiro Ninomiya for his great contribution to the progress of this project.
2) Rylett, R. J.; Ball, M. J.; Calhoun, E. H., *Brain Res.* **1983**, *289*, 169.
3) (a) Kuhar, M. J.; Murrin, L. C., *J. Neurochem.* **1978**, *30*, 15.
   (b) Tucek, S., *J. Neurochem.* **1985**, *44*, 11.
4) See our previous paper.
5) (a) Summers, W. K.; Kaufman, K. R.; Altman, F. Jr.; Fischer, J. M.,*Clin. Toxicol.* **1980**, *16*, 269.
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7) Bielavsky, J., *Collection Czechoslov. Chem. Commun.* **1977**, *42*, 2802.
8) Bessho, T.; Takashina, K.; Ooshima, C.; Egawa, M.; Tobe, A., *Neurobiol. Aging* **1994**, *15*, suppl.1, S103.
9) **9d**: ALD (Approximate Lethal Dose) >2000mg/kg p.o. (rats)
   This data is owed to Mr. Kazuo Toshida.

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