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Synthetic Conversion of ACAT Inhibitor to Acetylcholinesterase Inhibitor

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Abstract—Natural product acyl-CoA:cholesterol acyltransferase (ACAT) inhibitor pyripyropene A was synthetically converted to acetylcholinesterase (AChE) inhibitor via heterolitic cleavage of the 2-pyrone ring, followed by γ-acylation/cyclization with several aroyl chlorides. The 4-pyridyl analogue selectively showed AChE inhibitory activity (IC_{50} = 7.9 μM) and no ACAT inhibitory activity IC_{50} = >1000 μM. © 2000 Elsevier Science Ltd. All rights reserved.

Acetylcholinesterase (AChE) inhibitors such as tacrine[1] and E2020[2] have been proposed as therapeutic agents for Alzheimer's disease. Recently, we found the arisugacins A (**1**) and B (**2**),[3] strongly inhibit AChE with IC_{50} values of 1 and 26 nM, respectively (Fig. 1). Structurally related territrem B (**3**),[4] found by Ling et al., is also a potent AChE inhibitor. Interestingly, arisugacins have similar structures to pyripyropene A (**4**), Scheme 1[5] which was reported as acyl-CoA:cholesterol acyltransferase (ACAT) inhibitor. However, **4** does not show any AChE inhibitory activity and **1** does not inhibit ACAT, and vice versa.

Since **4** is available in the gram scale, the pyridine moiety of **4** was synthetically converted to 3,4-*di*-*O*-methoxy-substituted benzene ring as **1** to confirm the possibility for development of new AChE inhibitor from **4**. The advantage of this procedure is that absolute stereochemistry of analogues is identified as **4**. The 2-pyrone ring of **4** was cleaved by our method,[6] following γ-acylation/cyclization[7] with production of **6a**. Three hydroxyl groups of **6a** were acetylated (**6b**), and the carbonyl moiety was reduced (**6c**) (Scheme 1).

The AChE (from human erythrocytes) inhibitory activity was determined by our method.[3] Similar to starting material **4**, **6b** and **6c** did not show AChE inhibitory activity at 100 μM; however, **6a** showed marginal inhibition (Table 1). Furthermore, several analogues (**7a**–**13a**)[7] were not showing ACAT inhibitory activity at >1000 μM, but among them, 4-pyridyl analogue **13a** inhibited AChE with an IC_{50} value of 7.9 μM.

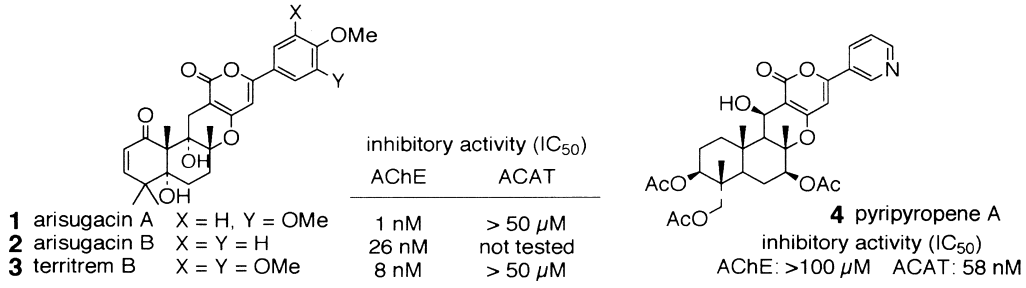

Figure 1.

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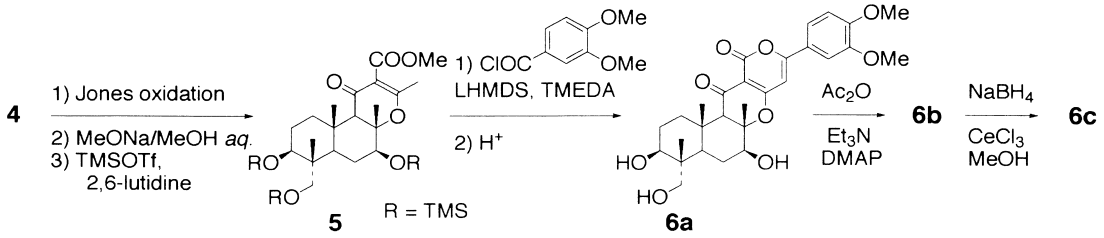
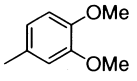
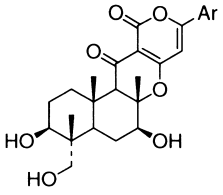
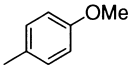
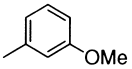
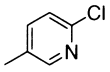


Scheme 1.

Table 1.

		Ar	AChE inhibitory activity (IC_{50}, μM)		Ar	AChE inhibitory activity (IC_{50}, μM)
	6a		58	**10a**		101
	**7a**		70	**11a**		35
	8a		>93	**12a**		80
	9a		99	**13a**		7.9

We simulated the three-dimensional view of **1** docking with AChE[8] in the collaboration with Dr. Itai. As a result, **1** is properly buried along the long and narrow cavity of the enzyme.[9] Supposing that **6a**–**13a** can fill a similar position of the AChE active site as **1**, the 3-*O*-methoxy group of the benzene ring of **1** does not covalently bind to AChE, but the aromatic ring may interact with the hydrophobic gorge. From these results, **4** is able to be converted to develop a new selective AChE inhibitor.

Acknowledgements

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