• 系統編號	RN9607-1388
• 計畫中文名稱	四、六位取代 Coumarin 衍生物之合成及其抑制乙醯膽鹼酯 乙醯膽鹼酯 beta-amyloid 凝集活性之研究
• 計畫英文名稱	Synthesis of 4,6-Disubstituted Coumarin Derivativers and Inhibit Both Acetylcholinesterase and Acetylcholinesterase-Induced Beta-Amyloid Aggregration
• 主管機關	行政院國家科學委員會
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• 中文關鍵字	阿茲海默症; Pechmann 反應; β 類澱粉
• 英文關鍵字	Alzheimer's disease; Pechman reaction; Beta-amyloid; Bivalent ligand; Ochrocarpin B; Coumarin; Thioflavin; Acetylcholinesterase (AChE); Friedel-Craft acylation
• 中文摘要	阿茲海默症(Alzheimer's disease)已被認爲是一個主要的社會大眾健康問題，其臨床治療用藥的效力(potency) 及選擇性尚不佳。新化合物的合成及結構之修飾在 drug design 上有相當重要的地位。個人曾研究 Ochrocarpin B 之全合成，Ochrocarpin B 爲一具有抗癌活性之 coumarin 天然物(A2780 ovarian cancercell line; IC50 爲 3.8+- 0.3 .mu.g/mL) ，coumarin 天然物曾有報告指出具有乙醯膽鹼酯腖的抑制作用，因此，擬合成一系列含母核 coumarin 之四、六位取代衍生物 1-6 作爲新 bivalent ligands 並探討其抑制乙醯膽鹼酯腖及乙醯膽鹼酯腖誘導 A？瓠振鬲〝吽 C 標的物 1 之合成，以起始物 9 與 isovaleryl chloride (10) 進行 Friedel-Craftacylation，得到之化合物 11 再與 ethyl4-methylbenzoylacetate (12) 進行 Pechmann 反應，可得到 coumarin 13(Scheme 1)。coumarin 13 接著與 N-bromosuccinimide (NBS) 進行溴化反應，得到之溴化 coumarin 15 再與 N-benzylmethylamine(17)進行 SN2 反應製得標的物 1。因溴化反應無法進行而無法製得四、六位取代 coumarin 衍生物 1-6。去除六位醢基之四位取代 coumarin 衍生物 20 和 21，依上法順利合成之。合成之標的物四位取代 coumarin 衍生物 20 和 21，首先將依據 Elmann 等人所用之方法測試對乙醯膽鹼酯腖之選擇性， 再採 Inestrosa 等人所發表之 thioflavin-based fluorometry assay 做抑制乙醯膽鹼酯腖誘導 A？瓠振鬲〝妣桲蝖 A 以了解結構與活性之間的相關性。
• 英文摘要	Alzheimer's disease is a major health problem in mass society. In medicinal chemistry, new bivalent ligand is a successful approach

for improving drug potency and selectivity. The synthesis of new compounds and structure modification are important role in drug design. Our laboratory have been researched the total synthesis of Ochrocarpin B, the structure of Ochrocarpin B is composed of a core 4-phenylfranocoumarin moiety with 5-hydroxyl and 6-isovaryl substitution on the phenyl group of furanocoumarin. The inhibition of acetylcholinesterase (AChE) by coumarins has been reported recently, thus, we want to synthesis of 4, 2 6-substituted coumarin derivatives 1-6 as new bivalent ligands and evaluate their potential AChE inhibition and AChE-induced beta-amyloid aggregation. The synthesis of coumarin derivatives 1-6 is started from 9. 9 was Friedel-Craft acylation with isovaleryl chloride to obtain 11, and then 11 reacted with ethyl 4-methylbenzoylacetate (12) by Pechman reaction to give compouinds 13. Intermediate 13 reacted with N-bromosuccinimide (NBS) , then reacted with N-benzylmethylamine (17) to give 1. However, we didn't synthesize the target compounds 1-6, because the benzylic bromination couldn't work. Now we have synthesized 4-substituted coumarin derivatives 20 & 21. The coumarin derivatives 20 & 21 against recombinant human AChE and isolated serum BuChE were evaluated by studying the hydrolysis of acetylcholine (ATCh) following the method of Ellman. The ability of derivatives to inhibit the proaggregation action of AChE toward was assessed through a thioflavin T-based fluorometric assay reported by Inestrosa. From these activity results, we will understand the structure-activity relationships and further to modify the structure to obtain a good bivalent ligand.