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• 計畫中文名稱	天然物乙醯膽鹼酯解脢抑制劑(-)Quinolactacin A2 的全合成
• 計畫英文名稱	An Enantio Total Synthesis of (-)Quinolactacin A2, an Acetylcholinesterase Inhibitor
• 主管機關	行政院國家科學委員會
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• 研究人員	黃聲東 Huang, Sheng-Tung
• 中文關鍵字	阿茲海默氏症; 乙醯膽鹼酯解脢抑制劑; 乙醯膽鹼酯解脢;
• 英文關鍵字	Alzheimer disease; Acetylcholinesterase inhibitor; Acetylcholinesterase (AChE); quinolactacin A2; Pictet-Spengler condensation
• 中文摘要	解脢抑制劑的藥物不只抑制乙醯膽鹼酯解脢也同時抑制 butylcholinesterase(BuChE) 而失智症是一種發生在中老年人的症候群，主要的特徵是認知及智力功能的衰退，包括記憶、思考、判斷力等。病患的日常生活及溝通能力會受到影響，需要他人長期照顧。而阿茲海默氏症（Alzheimer's disease）是造成失智症的主要原因。隨著醫療技術的進步，人類壽命的延長，Alzheimer's disease 成爲許多已開發國家日趨嚴重的問題。許多科學研究明確指出，阿茲海默氏症患者之所以會喪失記憶力的原因之一，就是腦部的神經傳導物質--也就是被稱爲乙醯膽鹼(acetylcholine)的腦部訊息物質大量減少。同時也發現乙醯膽鹼酯解脢（acetylcholinesterase）的酵素，參與部分的乙醯膽鹼分解。因此，下一步就是開發出可以抑制乙醯膽鹼酯解脢的藥物，藉以使得腦部有較多可使用的乙醯膽鹼。我們現在已有些被稱爲乙醯膽鹼酯解脢抑制劑的藥物，它可延緩乙醯膽鹼的分解。但現有的乙醯膽鹼酯導發可能肝毒性的副作用，使醫生在給藥時無法用到高劑量，而使其療效無法完全發揮。開發針對抑制乙醯膽鹼酯解脢的藥物而不抑制 butylcholinesterase(BuChE)將有助於對阿茲海默氏症患者使用乙醯膽鹼酯解脢抑制劑的療效完全發揮。從 fb90648 發酵槽中萃取出兩天然物 quinolactacin A1 (1)和 A2 (2)，這兩個天然物的化學結構是由不同的光譜分析鑑定而來。 quinolactacin A1 (1)和 A2 (2) 主要的化學結構是由一個 pyrrolo[3,4-b]quinolone 組合而成，天然物具有兩個 chiral centers 且之關係是非鏡像異構物 (diastereomer)。這兩個天然物雖然具有有效抑制乙醯膽鹼酯解脢的功效，且 quinolactacin A2 (2) 較對乙醯膽鹼酯解脢具有效力的抑制 (IC50= 19.8 μM)，而對 butylcholinesterase(BuChE)抑制較弱 (IC50 = 653 μM)。應 quinolactacin A2 (2)選擇性抑制乙醯膽鹼酯解脢所以利用這天然物和此天然物的衍生物來探討這酵素的結構將可以進一步了解這酵素的結構因而幫助未來研發更有效和減少導發可能肝毒性的副作用的乙醯膽鹼酯解脢抑制劑，此抑制劑將有助於對阿茲海默氏症患者使用乙醯膽鹼酯解脢抑制劑的療效完全發揮。此計畫爲 enantioselective 天然物 quinolactacin A2 (2)的合成。我們利用氨基酸

L-isoleucine 的的兩個 chiral centers 運用於建立天然物的兩個 chiral centers， pyrrolo[3,4-b]quinolone 的化學結構將由 Pictet-Spengler condensation 組合而成。此天然物之主要化學結構已於 3 合成步驟完成，且 Pictet-Spengler condensation 爲合成 pyrrolo[3,4-b]quinolone 的化學結構。經過許多測試，最後形成 lactame 環合成至今尚無研發出適當之合成方法，但尚有許多爲嘗試合成途徑等待嘗試。

- 英文摘要

Alzheimer disease (AD) is a neurodegenerative disorder that is the most common cause of dementia among elderly. This disease is mainly affect the central nervous system (CNS) characterized especially by premature senile mental deterioration. AD patients exhibit marked decline in cognitive ability and severe behavioral abnormalities such as irritability, anxiety, depression, disorientation, and restlessness. The precise mechanism causing the disease is still unknown; however, at the cellular level, there is a marked reduction in the levels of neurotransmitters such as acetylcholine (ACh), serotonin, noradrenaline, dopamine, glutamate and substance P; and the depletion of acetylcholine is the most important event. The major focus on the drug development in this area is symptomatic treatments aimed at repletion deficient neurotransmitters. One of an approach to enhance cholinergic deficit in AD patients is through cholinesterase inhibitors (ChEI), which block the ChE enzyme activity thereby invigorating cholinergic activity to enhance cognitive function. Inhibition acetylcholinesterase (AChE) activities in AD patients will boost endogenous level of acetylcholine (ACh) thereby invigorating cholinergic activity to enhance cognitive function. The AChE has been the target for drug development treatment for AD. The fungal metabolites, quinolactacin A1 (1) and A2 (2) were isolated from fermentation strain fb90648 are novel ChEIs. Both natural products 1 and 2 exhibited inhibitory activity against AChE with IC50 value of 280 and 19.8 .mu.M respectively. Quinolactacin A2 (2) is a weak BuChE inhibitors with IC50 values of 650 .mu.M. The natural products 1 and 2 are diastereomers. The architectural framework that is common in 1 and 2 is an unique pyrrolo[3,4-b]quinolone skeleton. The only difference between 1 and 2 are found in the stereo configuration of chiral center on C1`. The quinolactacin A1 (1) bears a R configuration on C1？？. On the other hand, compound 2 bears a S configuration on C1`. Since quinolactacin A2 exhibited 33 time more potent inhibitory effect toward AChE than BuChE, the selective inhibition property on AChE imposed on this chemical structure has attracted attention as lead structure for AChE inhibitors development. The progress of an efficient asymmetric synthesis of (-) quinolactacin A2 (2) was reported herein. We will utilize the stereo configuration in L-isoleucine as the chiral starting material for this asymmetric total synthesis. The core structural of this natural product was completed in 3 steps. The key step of this synthesis was a Pictet-Spengler condensation of the anhydride 3 and the ？] nitrile aniline 4 for construction of the quinolone ring skeleton. The final ring lactame ring closure was futile after various trials. Several other approaches toward the completion of the synthesis were in progress.