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• 計畫中文名稱	細胞中電子傳遞鏈 complex I (NADH:ubiquinone oxidoreductase)酵素活抑制劑 Pterulone 其最佳衍生物的合 成
• 計畫英文名稱	Optimization of Antagonistic Effect of Pterulone on NADH:Ubiquinone Oxidoreducatse (Complex I)
• 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	粒線體; 電子傳遞鏈抑制劑
• 英文關鍵字	Mitochondria; Complex I inhibitor; NADH:Ubiquinone oxidoreducatse
• 中文摘要	在粒線體電子傳遞鏈已知爲細胞中產能的最重要過程，在傳 遞過程中主要包括了四個複合體(Complexs I, II, III, IV)，其中 Complex I (NADH:Ubiquinone oxidoreductase)爲高能分子 NADH 進入電子傳遞鏈的入口。而細胞中可以轉換出 ATP 的高能分子除了 NADH 外另一個則是 FADH2，而 Complex II 則是 FADH2 高能 分子的入口處，在細胞中 NADH 扮演了主要提供能量的角色，而 FADH2 則較爲少量且次要。Pterulon 爲真菌 Pterula sp82618 所代謝出來具有抗其他真菌的代謝物質，根據研究發現此化合物具有抑制 complex I 酵素活性，部分屬於 complex I 抑制劑的化合物已被應用於農業上作爲殺蟲劑方面的用途。近年來在一些報告中發現這類抑制劑對正常細胞的細胞毒性相當得低(IC50=36 iM)但卻可以有效的抑制癌細胞的生長，雖然完整的機制尚未清楚瞭解但已知主要的途徑是藉由抑制促進癌細胞生長的酵素 ODC (orthine decarboxylase，是癌細胞中特有的酵素)的活性而達到抑制癌細胞生長的目的。因此本研究擬利用經全合成的天然物 Pterulone 及其衍生物對純化出來的細胞粒線體電子傳遞鏈中 Complex I 酵素活性的抑制效果進行探討。本研究結果中發現目前所合成的這些化合物其抑制酵素活性的效果仍未達理想，即抑制酵素活性 IC50 仍是太高介於 4~55 mM 之間接近於 Pterulone 的抑制活性與 Rotenone 的 0.5 nM 相差甚遠，因此還需進行結構式的修改及酵素活性的測試。
• 英文摘要	Complex I is the first of three large enzyme complexes located in the innermitochondrial membrane. This enzyme forms the electron transport chain that carries electron from NADH to molecular oxygen during oxidative phosphorylation. There are a wide variety of natural and synthetic inhibitors of complex I which have found multiple applications. Recently, it has been shown that inhibition of complex I cause concomitant reduction in the activity of orthine decarboxylase (ODC). Orthine decarboxylase (ODC) is responsible for the biosynthesis of polyamine growth factors required for cellular proliferation, and induction of ODC activity has been associated with tumor promotion. Since the over expression of ODC in tumor cell contributes to aberrant proliferation, the

ability of complex I inhibitors to reduce ODC activity makes them promising candidates as next generation antitumor agents. The fungal metabolites pterulone (1) and its analogue 2 were isolated from fermentations of a Pterula sp 82168 species, and Mycena galopus, respectively. Pterulone (1) exhibited significant antifungal activity, and it is a highly potent inhibitor of complex I with an IC50 value of 36 mM. Although the pharmacological profile of 2 has not yet been reported, compound 2 is structurally related to 1; therefore, it is believed that 2 will exhibit similar biological activity as pterulone (1). The goal of this study is to identify novel lead complex I inhibitors through structure-activity relationship (SAR) study based on compound 2. These lead compounds synthesized through this SAR study would be more amenable to further synthetic modification as required for optimization of physical and pharmacological properties. So far, seven compounds synthesized in this project, they exhibit the IC50 between 4 mM to 55 mM; they are much less potent as compared with rotenone (IC50 = 0.5 nM). The antagonistic effects of the analogues herein were only with little improvement as compared with pterulone (IC50=36 mM). From these preliminary SAR study, the data suggest that the binding environment for these inhibitors are composed with hydrophobic amino acid, and the dimension of binding site are large enough to tolerated large halogen group. Detail on studying the binding domain by variation on the inhibitors is currently under way.