• 系統編號	RC8901-0467
• 計畫中文名稱	具抗癌潛能之非傳統性抗葉酸類緣物之合成研究
• 計畫英文名稱	Synthesis of Non-Classical Antifolates as Potential Anticancer Agents
• 主管機關	行政院國家科學委員會 • 計畫編號 NSC88-2314-B038-111
• 執行機構	台北醫學院藥學系
• 本期期間	8708 ~ 8807
• 報告頁數	0 頁 • 使用語言 英文
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• 中文關鍵字	非傳統性抗葉酸類藥物；抗癌藥物；脂溶性；葉酸；二氫葉酸還原？
• 英文關鍵字	Non-classical antifolate；Anticancer drug；Lipophilicity；Folic acid；Dihydrofolate reductase
• 中文摘要	在本計畫中,我們擬合成兩系列的非傳統性葉酸拮抗劑:第一類爲 5-[1-methyl-3-(phenylamino)propan-1-yl]pyrimidine 衍生物(Class I)以及第二類的 5-[N-(phenyl)-pyrrolidin-3-yl]pyrimidine 衍生物(Class II,Fig.1),以便進行抗癌藥效之測試。我們利用 Methyl vinyl ketone(1)與接有各種取代基的 Aniline 衍生物(2,如 2-,3-,and 4-methoxyaniline,or other halogen substituted anilines)反應,得到了 N-(acetoethyl)aniline 衍生物(3),再經甲基化得到 N-methyl-N-acetoethyl anilines(4)。由於化合物 4 在各種條件下,都會經由.beta.-elimination 轉變成 N-methylaniline 衍生物,無法如預期的與 Malononitrile 反應,因此無法製備第一類化合物。所以目前我們計畫的重點擺在第二類化合物的製備。利用 1,4-dibromo-2-butanol(5)與化合物 2 反應,得到 N-phenyl substituted pyrrolidin-3-ols(6a-g),進一步將其氧化成 Pyrrolidin-3-ones(7),再分別與 Malononitrile 或 Ethyl cyanoacetate 反應,就可以得到 3-(2-dicyanomethylene)-pyrrolidines (8) and 3-(2-cyano-2-ethoxycarbonylmethylene)-pyrrolidines(11)。化合物 8 或 11 加以氫化後分別得到化合物 9 和 12,再與 Guanidine carbonate 作用,便可如預期的得到第二類標的物 10 和 13。目前我們已製備了第二類標的物如 10a,b 和 13a,b,此外化合物 10c-g 和 13c-g 的合成正被進行著,而這些化合物將在近期內測試其體外抗癌活性。
• 英文摘要	In this grant proposal, we plan to synthesize two series of non-classical antifolates, namely, 5-[1-methyl-3-(phenylamino) propan-1-yl]-pyrimidine derivatives (Class I) and 5-[N-(phenyl) -pyrrolidin-3-yl]pyrimidine derivatives (Class II, Fig. 1), as potential anticancer agents. Condensation of commercially available methyl vinyl ketone (1) with various substituted anilines (2, such as 2-,3-, and 4-methoxyaniline, or other halogen substituted anilines) gave N-(acetoethyl)-aniline derivatives (3), which were further

methylated to afford the corresponding N-methyl-N-acetoethyl anilines (4) in low yield. Attempts to react compounds 4 with malononitrile failed, since compounds 4 were converted into undesired N-methylaniline derivatives under various conditions via .beta.-elimination. We are unable to prepare compounds of Class I. Therefore, we focused our research on the preparation of Class II targeted compounds. We have already synthesized several Class II compounds by the condensation of 1,4-dibromo-2-butanol (5) with various substituted anilines (2) to give N-phenyl-pyrrolidin-3-ols (6). Compounds 6 were further oxidized, and the products, pyrrolidin-3-ones (7), were then reacted with malononitrile or ethyl cyanoacetate to afford 3-(2-dicyanomethylene)pyrrolidines (8) and 3-(2-cyano-2-ethoxycarbonylmethylene)-pyrrolidines (11), respectively. The double-bond of compounds 8 and 11 were reduced, and the products, 9 and 12, were treated with guanidine carbonate to yield the desired targeted compounds 10 and 13, respectively. So far, we have prepared several compounds of Class II, such as 10a,b and 13a,b. The synthesis of other target compounds 10c-g and 13c-g are in progress. The in vitro antitumor effect of the target compounds will be studied in near future.