強效抗癌劑 1-Aroylindole 及 1-Aroylindoline 類緣物之研究

Synthesis of 1-Aroylindoles and 1-Aroylindolines as Potent Anticancer Agents

中文摘要

基於生物等效性的概念，我們利用 combretastatin A-4 (CA-4)為模版來合成兩類強效抗癌劑 1-aroylindoles 及 1-aroylindolines，並且討論結構與活性的關係以及進行生物活性的評估。1-Aroylindoles 是由不同取代的 indoles 與 3,4,5-trimethoxybenzoic anhydride 或 3,4,5-trimethoxybenzoyl chloride 反應得到，而 1-aroylindolines 則是先將具有取代的 indoles 還原成 indolines，再與 3,4,5-trimethoxybenzoyl chloride 或 3,4,5-trimethoxy-2-nitrobenzoic acid 反應得到。2-23 的結構屬於 1-aroylindoles，而 25-30 則屬於 1-aroylindolines。

從抑制口腔上皮細胞癌 KB 細胞株生長的活性評估中得知，2、4、7、11、13、14、24 及 26 的 IC50 濃度範圍在 210-652 nM 間，表現出中等抗癌活性，9、12 及 25 的 IC50 分別為 20 nM、8 nM 以及 87 nM，表現出強效抗癌活性，22 的 IC50 為 1.1 nM，比 CA-4 (IC50 為 1.65 nM)的活性稍微增加，而最強效化合物 23 的 IC50 為 0.16 nM，比 CA-4 強 10 倍。

結構與活性的關係資料顯示將 C-5 位置的 methoxy 以推電子基團如 methyl (4)、5,6-methylenedioxy (7)、amino (11)或 N,N-dimethylamino (12)來取代仍然保持強效抗癌活性。在 1-aroylindole 的 C-2 位置有 methyl 基團取代可增加活性。而在 C-3 位置有取代基則失去活性。藉由仿照 AVE-8063 及 combretastatin A-4 分別導入 amino 和 hydroxyl 官能基於 1-aroylindole 的 C-4 位置，架構出 22 和 23，可得到最佳的抗癌活性。

英文摘要

Two classes of 1-aroylindoles and 1-aroylindolines were synthesized as potent anticancer agents based on the bioisosterism concept utilizing combretastatin A-4 (CA-4) as a template. 1-Aroylindoles were prepared by reacting substituted indoles with 3,4,5-trimethoxybenzoic anhydride or 3,4,5-trimethoxybenzoyl chloride. 1-Aroylindolines were prepared by reducing substituted indoles to indolines and then reacting with 3,4,5-trimethoxybenzoyl chloride or 3,4,5-trimethoxy-2-nitrobenzoic acid. 2-23 belong to 1-aroylindoles and 25-30 belong to 1-aroylindolines. Structure-activity relationship study was also discussed.

2, 4, 7, 11, 13, 14, 24 and 26 showed moderate cytotoxicities with IC50 values of 210-652 nM in inhibiting oral epidermoid carcinoma KB cell growth in vitro. 9, 12 and 25 exhibited potent cytotoxicities with IC50 values of 20 nM, 8 nM, and 87 nM,

respectively. 22 showed a slight increase in activity with IC50 values of 1.1 nM as compared to CA-4 (IC50 values of 1.65 nM). The most potent compound 23 showed strong antiproliferative activity against KB cell line with IC50 values of 0.16 nM, 10-fold more potent than CA-4.

The structure-activity relationship study of these compounds revealed that the methoxy group at the C-5 position could be replaced with an electron-donating group such as methyl (4), 5,6-methylenedioxy (7), amino (11) or N,N-dimethylamino (12) while retaining strong cytotoxicity. Addition of a methyl group at the C-2 position in 1-aroylindole increased the cytotoxic potency. Substitution at the C-3 position led to a substantial loss of potency. The introduction of 4-amino and 4-hydroxy substitution in the 1-aroylindole gave 22 and 23, which contribute to significant extent for maximal activity by mimicking AVE-8063 and combretastatin A-4 respectively.