經由香豆素-3-活性氮丙啶之開環反應合成香豆素-3-甲醯胺衍生物及其生物活性評估

Effects of green tea , (+)-catechin and sodium salicylate on cisplatin induced nephrotoxicity in inbred mice

中文摘要

在有機化學領域，香豆素是一種重要結構，並且屬於苯並吡喃酮，香豆素廣泛地存在於植物而且具有許多不同的生物活性，包括抗凝血、雌性激素、皮膚光敏性、抗菌活性、抗氧化、血管擴張、鎭靜安眠、止痛、降溫等。

在化學合成和癌症化療中，氮丙啶是一種重要的化合物，有關 2-甲基-N-醯基氮丙啶的經由許多親核基開環現象已有多篇報導發表出來，正常的開環現象是指親核基攻擊氮丙啶環上 N-C 立體障礙小的地方並且斷裂，這是屬於 SN2 反應，而非正常的開環現象是指親核基攻擊氮丙啶環上 N-C 立體障礙大的地方並且斷裂，我們使用氮丙啶環的區域選擇性開環合成出一系列的香豆素-3-甲醯胺，在此研究經由活性 N-香豆素-3-羰基氮丙啶為起始物合成出四個系列的香豆素衍生物，第一個系列我們利用 N-香豆素-3-羰基氯 (20) 為起始物在 4N 氫氧化鈉催化下合成一系列的 N-香豆素-3-羰基氮丙啶 (21, 22)， 依樣 Stamm、 Mall、Falkenstein、Werry 和 Pen-Yuan Lin 等實驗室研究 N-醯基氮丙啶與自由基反應現象，第二個系列我們利用 N-香豆素-3-羰基氮丙啶 (21, 22) 為起始物在充滿自由基環境下合成一系列的香豆素-3-甲醯胺衍生物 (27-40)，第三個系列我們利用 N-香豆素-3-羰基氮丙啶 (21, 22) 和 4-羥基香豆素在鹼催化下合成出一系列的香豆素雙體 (41-48)， 第四個系列我們利用 N-香豆素-3-羰基氮丙啶 (21, 22) 和 7-羥基香豆素在鹼催化下合成出一系列的香豆素雙體 (49-52)，以上所有合成之化合物之物性與化學特性均以核磁共振儀測定其結構，質譜儀、高解析質譜儀測定其分子量，紅外線光譜儀測定部份官能基團並測定熔點。以上所有合成之化合物均測試 cancer cell lines (Colon 205, K-562, MCF7) 細胞毒性測試評估。

英文摘要

Coumarin is important structure of organic chemistry and belongs to the benzopyrones. Coumarins are widely distributed in plants and have a variety of bioactivities including anticoagulation, estrogenic, dermal photosensitizing, antimicrobial, antioxidation, vasodilation, antithelmintic, sedative and hypnotic, analgesic and hypothermic activities.

Aziridine is a class of compound important both in chemical synthesis and in chemotherapy of cancer. Ring opening of 2-methyl-N-acylaziridine by various nucleophiles has been reported. Nucleophilic attack at the unsubstituted carbon atom

of the aziridine ring is called ” normal“ ring cleavage (in the SN2). Nucleophilic attack at tertiary or secondary carbon atom of aziridine ring is called “Abnormal” ring cleavage. We used the regioselectivity of ring opening of aziridines to synthesize a series of Coumarin-3- carboxamides. Four series of coumarin derivatives were synthesized from N-(coumarin-3-carboxyl) aziridines in this study. First, we used coumarin-3-carboxyl chloride (20) and a series of azirides with 4N NaOH to synthesize a class of N-(coumarin-3-caboxyl) aziridines (21, 22). Reactions of N-acylazirides with the radical anion of naphthalene had previusly been studied by Stamm, Mall, Falkenstein, Werry and Pen-Yuan Lin. Second, we used N-(coumarin-3-carboxyl) aziridines (21, 22) and activated thiols with the radical anion of naphthalene to synthesize Coumarin-3- carboxamide derivatives (27-40). Third, we used N-(coumarin-3- carboxyl) aziridines and 4-hydroxycoumarins to synthesize coumarin dimmer (41-50). Fourth, we used N-(coumarin-3-carboxyl) aziridines and 7-hydroxycoumarins to synthesize coumarin dimmer (51-54). The physical and chemical characteristics of the synthesized compound 1-35 were measured by 1H-NMR, IR, HRMS, and melting point determination. The cytotoxicities of all synthesized compounds to cancer cell lines (Colon 205, K-562, MCF7) are also examined in this study.