四羥基香豆素衍生物之合成及抗菌

Synthesis and antibacterial activity evaluation

中文摘要

香豆素(coumarin)在有機化合物裡是一個很重要的結構，被發現具有抑制細菌、抗發炎、抗凝血和抗腫瘤的活性。由於 coumarin 具有許多的生物活性因此進而引起我們的興趣來合成一些具有 coumarin 結構的衍生物，其中本實驗以四羥基香豆素(4-hydroxycoumarin)爲起始原料，以各種酸酐化合物和氮丙啶(aziridine)合成一系列具有 coumarin 結構的衍生物。4-hydroxycoumarins 是一種醫藥中間體(intermediates)，用於合成 Warfarin、Dicumarol、Acenocoumarol 和 Novobicin 等具有抗凝血和抗細菌 (Antibacteria) 活性的化合物。文獻也指出 4-hydroxycoumarins 爲 HIV 的抑制劑，另外也是一種香料亦可用於香水工業。其中本實驗以抗菌活性爲標的結合各式酸酐類和活化型氮丙啶 (N-activated aziridine) 爲基礎合成具有 coumarin 結構的化合物。藉由下列方法：先把 4-hydroxycoumarin 和酸酐化合物置於反應瓶，加熱到 150℃迴流反應 3 小時，另外再同上述方法把溫度提高到 180℃以上其目的是使其發生重排的現象。另一系列 N-activated aziridine 衍生物則是先將 4-hydroxycoumarin 加上 CH3ONa 在室溫下反應 1 小時，再加上 N-activated aziridine 加熱到 110℃迴流反應。所得到的化合物再經由再結晶、TLC Plate 純化方法純化出來，然後再經由核磁共振儀、紅外光光譜儀、高解析度質譜儀確定結構。並進行抗細菌活性測試。結果顯示化合物主要對革蘭氏陽性菌有抑制效果。其中化合物 23 (N-[2-Methyl-2-(coumarin-4-yloxy)-propyl]-benzamide) 顯現出和 Penicillin G 有一樣的抑菌效果。

英文摘要

Coumarins are widely distributed in nature and have reported to exhibit various interesting biological activities. Coumarins could be extracted from Tonka Bean and also synthesized by organic process. Coumarin derivatives are lactone compounds that are used as additives to food and cosmetics, laser dyes and some medicines. In medical field, coumarin derivatives have also been used as anticoagulants and antibacterial agents (e.g Novobiocin、Coumermycin A1). However, some bioactivity compounds with 4-hydroxycoumarin structure aroused our interest in 4-hydroxycoumarin derivatives. 4-hydroxycoumarin is a intermediate which could be used in synthesing some anticoagulant and antibacterial compounds (e.g Warfarin、Dicumarol and Novobicin). Furthermore, 4-hydroxycoumarin derivatives have been found to have antiretroviral and antiallergic activities. Here we focus on antibacterial activity and try to synthesize a series of 4-hydroxycoumarin

derivatives. Firstly, we used 4-hydroxycoumarin derivatives (4-hydroxy-5-methyl-coumarin,4-hydroxycoumarin-5,6-dimethyl-coumarin and 4-hydroxy-7-methoxy- coumarin) as starting materials with anhydrides in synthesing a series of 3-acyl-4-hydroxycoumarin derivatives via intramolecular acyl-lactone rearrangement under temperature control. Secondly, we use 4-hydroxycoumarin as starting material reacting with some N-activated aziridines in synthesing some 4-hydroxycoumarin-aziridine derivatives. All of the 4-hydroxycoumarin derivatives were measured by 1H-NMR, IR, High-resolution mass spectrometry. In addition, we evaluated these compounds in antibacterial activity and found some of our new compounds with antibacterial activities.