斑蝥胺素及其類似衍生物合成與生物活性之研究

Study on the Synthesis and Bioactivity of Cantharidinimides and Their Analogues

中文摘要

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斑蝥素（Cantharidin; exo,exo-2,3-dimethyl-7-oxabicyclo[2.2.1] heptane-2,3-dicarboxlic acid anhydride），爲翹翅目、莞青科、斑莞青屬的昆蟲於抵禦外侮時所分泌的化合物，具有顯著的生物活性如引泡發赤、抗腫瘤劑、刺激毛髮及除草劑等作用。最近曾有研究指出斑蝥素之 N-衍生物類斑蝥胺具有一定的抗腫瘤效果且副作用較低。基於減少其毒性增加療效的目的，本研究進行 cantharidin 之化學修飾，合成系列之 N-衍生物，並進一步作生物活性評估。經由 cantharidin 或其它酸酐衍生物與含胺基之取代物於高溫（約 200℃）在鹼性條件下封管加溫 2 小時後，餾去溶媒純化後得到一系列之斑蝥胺素 N-衍生物（sulfa 和 ethanolamine 系列）。另外，藉由 Aziridine 的開環反應將反應物嘗試在不同的條件下經由位向及之立體空間障礙的考量，合成另一系列衍生物。已合成的化合物，斑蝥素之 N-衍生物及酸酐素之 N-衍生物，已由核磁共振儀、紅外線光譜儀、質譜儀和元素分析儀確定結構。此外也針對 sulfa 系列和 Aziridine 開環系列等產物在抗肝癌細胞 Hep 3B 的抑制性進行測試，而結果顯示化合物 6 的抗肝癌細胞 Hep 3B 毒性最強，且優於斑蝥素。

英文摘要

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Abstract

Cantharidin (exo,exo-2,3-dimethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxlic acid anhydride), is produced by beetles, belonging to the order of Coleotera, and family of Melodae, as a defense against predators. It has remarkable biological activity, and can be used as an acantholytic, an antitumor agent, a hair-growth stimulator and a pesticide.

It has been shown in animal studies that N-derivatives of cantharidin have certain inhibitory action on tumors with less side effects. Furthermore, in order to study the bioactivity and toxicity of related compounds, we synthesized a series of cantharidinimide by the following method: Cantharidin or other analogues were dealed with amino-containing substrate by heated to 200oC in a sealed tube for 2 hours. After cooling, the residuals were removed from the tube, and were further evaporated and purified by column chromatography (SiO_2). Another series of N-cantharidinimide analogues were synthesized by the method of ring-opening of activated aziridine dealed with NaH at 80oC for 24 hours.

All of these cantharidinimides and their derivatives were measured by 1H-NMR, IR,

mass spectrometry and elemental analysis. Besides, the series synthetic compounds of the sulfa and aziridine were tested for their capability to suppress growth of human hepatocellular carcinoma call line, Hep 3B. The results showed that compound 6 was the most potent, and it was more effective than cantharidin