Sulfanilamide 和 Thiazole 的 Imide 衍生物合成及生物活性之研究

Study on the Synthesis and Bioactivity of Sulfanilamide and Thiazole analogues

中文摘要

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磺胺藥在臨床上爲葉酸拮抗劑，用於治療細菌感染，另一方面 sulfanilamide 爲重要的活性官能基，以其爲 lead molecule 發展出多種廣泛不同活性的藥物,包括:抗菌劑，碳酸酐胺抑制劑、利尿劑、降血糖劑、抗 HIV 病毒、metalloprotease 抑制劑等;根據最近的文獻報導，一群新的 sulfanilamide 衍生物在體內及體外試驗皆顯示具抗腫瘤活性，它們具有共同的芳香環/異環 sulfanilamide 結構，其抗癌基轉包括: 抑制碳酸酐胺，破壞細胞週期 G1 期，阻止微小管聚合，抑制轉錄活化因子 NF-Y 功能，及抑制血管增生等;其 SAR 探討結果顯示，sulfanilamide 爲活性必要基團，因此我們嘗試以 sulfanilamide 爲起始原料，以各種酸酐類化合物合成一系列之磺胺衍生物，先前本實驗室已將磺胺類衍化合物導入 cantharidin 合成一系列醯亞胺化合物，並發現部分化合物有抗肝癌活性，因此本實驗室進一步利用各式酸酐類化合物取代 cantharidin 之結構，合成得到一系列之磺胺衍生物 (compounds 1-34)，藉由以下方法:將 sulfaniamide 和酸酐化合物置於高壓封管，加熱到 200℃反應兩個小時，待冷卻後，進行脫水反應，利用 TLC Plate 純化，另一 thiazole 系列(compounds 35-57)，也藉由同樣的反應條件合成。合成的化合物，已由核磁共振儀、紅外光光譜儀、質譜儀確定結構。此外也針對磺胺衍生物在抗肝癌細胞藥理活性測試, 結果顯示 sulfanilamide 衍生物大部分不具細胞毒性,而另一系列 thiazole 衍生物 細胞毒性則待測中。

英文摘要

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Abstract

The sulfanilamides were the first effective antibacterial drug which is folic acid antagonist. The sulfanilamide lead molecule constituted the basis for the development of all these types of pharmacological agents which such a varied spectrum of biological actions, as exemplified below for antibacterial agent, carbonic anhydrase inhibitor, diuretic agent, hypoglycemic agent, HIV protease inhibitor, metalloprotease inhibitor. A host of structurally novel sulfonamide derivatives have recently been reported to show substantial antitumor activity in vitro and in vivo. Although they have a common chemical motif of aromatic/

heterocyclic sulfonamide, there are a variety of mechanisms of their antitumor action, such as carbonic anhydrase inhibition, cell cycle arrest in the G1 phase, disruption of microtuble assembly, functional suppression of the transcription activitor NF-Y, and angiogenesis (matreix metalloproteinase) inhibition among others. Previously, we usedsulfanilamide analogues to attach cantharidin to synthesis a series of imide compounds and founded a part compounds had antihepatocellular carcinoma activity. In order to further structural study, we used various anhydrides replace the structure of cantharidin to synthesis a series of sulfanilamides analogues
(compounds 1- 34) by the following method: sulfanilamide or other analogues were dealed with various anhydrides by heated to 200℃ in a sealed tube for 2 hours. After cooling, the residuals were removed from the tube, and were further evaporated and purified by TLC plate. Another series of thiazole analogues (compounds 35-57) were synthesized by the same method. All of these sulfanilamide and thiazole imide analogues were measured by H-NMR, IR, mass spectrometry. Besides, the series synthetic compounds of the sulfa and thiazole were tested for their capability to suppress growth of human hepatocellular carcinoma cell line. The data indicated that almost compounds of sulfanilamide are non- cytotoxicity. Another series of thiazole analogues would be tested .