Phenylphthalimide 衍生物合成及生物活性之研究

Synthesis and Bioactive Studies on phenylphthalimide analogues

中文摘要

Thalidomide [N(a)-phthalimidoglutarimide] 是一個鎮靜劑，但是它會引起嬰孩出生肢幹嚴重畸形。因此，被撤出市場。最近研究顯示它可以用於治療發炎、愛滋病病患體欉虛耗、口瘡潰瘍、眼睛斑狀退化、乳癌,攝護腺癌、腦癌、愛滋病病患常見的 Kaposi's 腫瘤，和其他的相關疾病等。這些疾病治療可能是 thalidomide 能夠調節，由 monocyctes 或是 macrophages 所分泌的腫瘤壞死因子 (tumor necrotic factor, TNF-a)，然而，thalidomide 的光學結構容易消旋 (racemize) 和水解 (hydrolysis)。因此，本實驗嘗試簡化 thalidomide 的 glutarimide 的部份，獲得 phthalimide 衍生物，包括四個系列 phenyl-phthalimide、pyridyl-phthalimide 、aminobenzyl-phtalimide 及 diphenylazo-phtalimide analogues；本實驗亦嘗試採用數個 anhydrides 修飾 phthalimide 中 1H-isoindole 的部分，以進行結構與活性關係之探討。本實驗利用 phthalic anhydride 及 anhydrides 與 amino substrates 於高溫鹼性條件下，以封管加熱反應，製備一系列化合物。並進行 HL-60、HEP-2、HEP G2、HONE-1、NUGC 五種癌細胞的體外細胞毒性試驗，結果大部分不具細胞毒性。另外本實驗利用 thalidomide 及 thalidomide analogues 合成物來探討對 NO 之抑制作用機制。研究數據顯示，thalidomide 和所合成的 thalidomide analogues 合成物具有抑制 NO 的作用。此結果將有助於研究此類化合物抑制 iNOS 形成 NO 的相關免疫性疾病、癌症生長與血管增生。

英文摘要

Thalidomide [N(a)-phthalimidoglutarimide] is a sedative agent, but withdraw from the market, because it caused infants born with a severe deformity of the limbs. At present, this drug is useful to treat inflammation common to a host of diseases, and combat weight loss and aphthous ulcers in AIDS patients, on the eye disease macular degeneration, on breast, prostate and brain cancer, on Kaposi's sarcoma (a form of cancer common in AIDS patients), and other related diseases. The treatment for these diseases may result from thalidomide can regulate tumor necrotic factor (TNF-a), which secreted mainly by activated monocyctes or macrophages. Because optically pure forms of thalidomide readily racemize and undergo hydrolysis, we tried to simplify the part of glutarimide of thalidomide to obtain four series of phthalimide derivatives, including phenyl-phthalimide, pyridyl-phthalimide, aminobezyl-phthalimide, and diphenylazo-phthalimide analogues. In order to further structural studies and bioactivities, we used anhydrides to replace the 1H-isoindole moiety of phthalimide derivatives to obtain related compounds. We used anhydrides and amino

substrates to prepare all the above compounds and to evaluate the bioactivities. The compounds were evaluated in vitro cytotoxicity against five human tumor cell growth (HL-60，Hep-2，Hep G2，HONE-1 and NUGC). The data indicated that almost compounds are non-cytotoxicity. On the other hand, we evaluated the effects of thalidomide and the thalidomide-like compounds on the synthesis of nitric oxide (NO). The data suggest that thalidomide and the thalidomide-like compounds potent inhibiting activities on NO. The results are helpful to further studies on immunological diseases, tumor growth and angiogenesis.