抗不整脈氧基小蘗鹼類似物之合成研究

Synthesis of 8-Oxoberberine Analogues as Potential Antiarrhythmic Agents

中文摘要

中 文 摘 要 抗不整脈藥物氧基小蘗鹼類似物之合成研究 8-氧基小蘗鹼(JKL 1073A)(2)是一個小蘗鹼(1)的衍生物，初步藥理實驗中發現其具有加強心臟收縮力及減緩心跳具有抗不整脈的作用，並對於缺氧及 ouabain 所引起的心律不整有改善的作用；為了進一步了解其化學結構與抗心律不整作用之間的相關性，我們使用化學合成方法製備了數種氧基小蘗鹼衍生物，以供藥理實驗測定之用。化學合成方法是以四級化原小蘗鹼型衍生物之鹽類作為關鍵性中間化合物，加入 30% NaOH 水溶液進行類似 Cannizzaro 機轉的反應，得到七種 8-氧基原小蘗鹼衍生物分別為化合物 2,14, 17, 58, 59, 60, 61, 63 及 64。取化合物 2 及 58，於鹽酸水溶液中加熱進行 O-demethylation 反應，得到化合物 63 及 64。第十三位氧化的原小蘗鹼衍生物也同時被製備，主要是利用小蘗鹼氯鹽(1)作為起始原料，先經 NaBH4 還原作用形成 dihydroberberine(15)，再以 m-chloroperbenzoicacid 氧化，即可得到第十三位氧化的 berberinephenolbetaine(26)，以此作為一重要的中間產物，當使用 1-propanol 為溶媒並以 NaBH4 還原時，可以得到 ophiocarpine(20)及 epiophiocarpine(21)兩種產物；若 berberinephenolbetaine(26)分別與鹽酸甲醇溶液或甲基碘試劑反應，則得到 13-hydroxyberberinium Chloride(65)或 13-methoxyberberiniumiodide(66)二種產物。以化學合成的十三種化合物均經紅外光譜、氫光譜、碳光譜及質譜等光譜分析鑑定結構。部份包含中間產物的二十個化合物是以大白鼠之離體心臟作有關心收縮力與心跳速率之藥理活性測試。結果顯示化合物 15 及 66 可增加心收縮力和減緩自發性的右心房心跳速率，作用較 JKL 1073A(2)為佳；而化合物 54 則是在加強右心室心收縮力方面比 JKL1073A(2)更強。後續部份化合物有關其抗心律不整的藥理活性，目前正在評估測試中。

英文摘要

AbstractSynthesis of 8-Oxoberberine Analogues as Potential Antiarrhythmic Agents 8-Oxoberberine (JKL 1073A) (2) is a analog of berberine (1), exhibited a positive inotropic effect and negative chronotropic effect. Besides the positive inotropic effect, it also possessed antiarrhythmic activity against cardiac arrhythmia induced by ouabain and hypoxia. Therefore, several analogues modeled after 8-oxoberberine (2) were prepared by chemical synthesis in order to evaluate the relationship between their structures and antiarrhythmic activity. Protoberberinium salts were used as key intermediates. Treatment of protoberberinium salts with 30% NaOH in aqueous solution, by the Cannizzaro mechanism, to yield seven

8-oxoprotoberberine derivatives 2, 14, 17, 58, 59, 60 and 61. O-Demethylation of compounds 2 and 58 with hydrochloric acid afforded the phenolic compounds 63 and 64.13-Oxygenated protoberberines were also perpared berberine chloride were reduced by NaBH4 to give dihydroberberine (15). Oxidation of dihydroberberine (15) by m-chloroperbenzoic acid gave berberine phenolbetaine (26) and following by NaBH4 reduction in 1-propanol to yield ophiocarpine (20) and epiophiocarpine (21). Reaction of berberinephenolbetaine (26) with hydrochloride or methyl iodide, gave the 13-hydroxyberberinium chloride (65) or 13-methoxyberberinium iodide (66). The structures of these synthetic analogues are consistent with the spectral data of IR, PMR, CMR and Mass spectra. Twenty compounds including intermediates were evaluated with the isolated heart preparation from rats to determine the chronotropic and inotropic effects. The result indicated that compounds 15 and 66 have stronger effects in postive inotropic and negative chronotropic activities than that of JKL 1073A 2. Compound 54 showed more potent in positive inotropic effect than that of JKL 1073A 2 in right ventricle preparation. The evaluation of some other synthetic analogues on the isolated heart preparation is under investigated.