抗心律不整藥物螺旋卞基異奎琳類似物之合成研究

Synthesis of Spirobenzymisoquinoline Analogues as Potential Antiarrhymic Agents

中文摘要

中文摘要抗心律不整藥物螺旋卞基異奎琳類似物之合成研究 JKL 1067 (2,3-methylenedioxy-9,10-dimethoxyspirobenzyliso-quinoline) (33)是個合成的螺旋卞基異奎琳類，具增強心收縮力及減緩自發性的心跳速率，此外，對於 ouabain 所引起的心律不整有抑制作用。具有發展成爲抗心律不整藥物的潛力。爲了進一步研究其化學結構與心臟血管作用的關係，今就 JKL 1067 (33)分子結構加以修飾,我們利用化學合成方法,製備了七個螺旋卞基異奎琳類似物 38, 42, 46, 48, 62, 63 和 67。 合成方法，係以 berberine chloride (30)和 palmatine chloride (64)爲起始物，berberine chloride (30)在強鹼條件下，與丙銅反應形成 berberine acetone 附加物(34)，而後與 CH3I 進行反應，生成 13-甲基化合物 35。另一合成是 berberine chloride (30)爲起始物，分別在 urea 與 C2H5I 存在下各反應生成第 9 位有 hydorxy 取代基的酚性化合物 39 及第 9 位有 ethoxy 取代的化合物 43，然後將化合物 30, 35, 39, 43 和 64 再經 NaBH4 還原，成爲四氫原小蘗鹼型衍生物 31, 36, 40, 44 和 65，而後再與 CH3I 甲基化反應形成四級 N-methiodide 32, 37, 41, 45 和 66。另化合物 31 經苯乙基化反應形成四級 N-benzyl protoberberium bromide 47。化合物 32, 37, 41, 45, 47 和 66 於室溫下 dimsyl sodium 強鹼催化下，進行 Stevens 重排反應，可得螺旋卞基異奎琳類生物鹼之類似物 33, 38, 42,46, 48, 62 和 67。 另一化學合成原小蘗鹼型途徑係以 vanillin 爲原料，經 OH 爲保護基後，經數步反應形成 phenylethylamine 之衍生物 54，而後與 2,3-methylenedioxyphenylethylacyl chloride 縮合成醯胺類 57，再經 Bischler-Napieralski 環化反應及 NaBH4 還原後得四氫基異奎琳衍生物 59，之後與甲醛在酸性條件下進行 Mannich 縮合反應形成原小蘗鹼形衍生物 60，而後與前述化合物相同處理步驟，反應合成螺旋卞基異奎琳類似化合物 62，最後經 18 % HCl 反應，去除 benzyl 的保護基生成酚性衍生物 63。四個原小蘗鹼型衍生物 36a, 36b, 37, 40 和 44 及兩個螺旋卞基異奎琳類似物 38, 42，以大白鼠之離體心臟，評估有關心臟收縮力與心跳速率之藥理活性測試。目前研究結果顯示，原小蘗鹼型生衍生物 37 可增加心收縮力及減緩自發性的心跳速率，螺旋卞基異奎琳類似化合物 38, 42 並無明顯作用，另部份之原小蘗鹼型衍生物 43 及螺旋卞基異奎琳類似化合物 46, 48,62, 63, 67 目前藥理之評估正在進行中。

英文摘要

Synthesis of Spirobenzylisoquinoline Analogues as Potential Antiarrhymic AgentsAbstract JKL 1067 (2,3-methyenedioxy-9,10-

dimethoxyspirobenzyliso-quinoline) (33), exhibited a positive inotropic and negative chronotropic effect. It also possessed antiarrythmic activity against cardiac arrhythmia induced by ouabain. In order to study the relationship between the structure and cardiovascular activity. Seven spirobenzylisoquinoline analogues 38, 42, 46, 48, 62, 63 and 67 modeled after JKL 1067 (33) have been prepared by chemical synthesis. Following the usual synthetic procedures, berberine chloride (30) and palmatine chloride (64) were as starting materials. Treatment of berberine chloride (30) with acetone under base condition afforded berberine acetone adduate (34), and then reacted with methyl iodide to give 13-methyl compound 35. Berberine chloride (30) was heated with urea to produce 9-hydroxyl compound 39 and following alkylated with ethyl iodide to give 9-ethoxyl compound 43. Compound 30, 35, 39, 43 and 64 were reduced by sodium borohydride to give the tetrahydro-protoberberine 31, 36, 40, 44 and 65. After quarterization with methyl iodide, the N-methiodide salts of 32, 37, 41, 45 and 66 were produced. Compound 31 was reacted with benzyl bromide to afford the quaternary N-benzylprotoberberium bromide 47. Spirobenzyl-isoquinoline 33, 38, 42, 46, 48 and 67 were prepared by Stevens Rearrangement in the presence of dimsyl sodium in dimthyl sulfoxide. Phenolic protoberberine 60 was produced from O-benzyl protected vanillin and then converted to corresponding phenylethylamine 54. After condensation with 2,3-methylenedioxyphenylethylacyl chloride to amide 57, followed by Bischler-Napieralski cyclization and sodium borohydride reduction gave tetrahydroisoquinoline 59. Mannich condensation of 59 with form aldehyde in acidic condition gave protoberberine 60. Stevens Rearrangement of the N-methyl salts of 61 yieded spirobenzylisoquinoline 62. Compound 62 was treacted with 18% HCl to remove benzyl protecting group to give the phenolic spirobenzylisoquinoline 63. Four protoberberine 36a, 36b, 37, 40, 44 and two spirobenzyl-isoquinoline analogues 38, 42 were evaluated their antiarrhymic activity with an isolated heart preparation from rats. The results indicated protoberberine 37 have an equal effect in positive inotrpoic and negative chronotropic activities however spirobenzylisoquinoline analogues 38, 42 have no activity effect. Protoberberine 43 and other five spiro-benzylisoquinoline analogues 46, 48, 62, 63, 67 are evaluated their pharmacological activity is at present time.