Liriodenine 類似物之化學合成研究

Synthesis of Liriodenine Analogs

中文摘要

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Liriodenine(1) 是從 Liriodendron tulipifera L 之 heartwood 中分離出的 7-oxoaporphine 的生物鹼。最近的報告證實 liriodenine 爲一種很強 topoisomerase Ⅱ抑制劑，利用其平面的分子結構， 如同 DNA 的崁入劑般發揮抗癌作用。此外有一些體內的藥理研究報告證明 lirodenine 也有抗心律不整的作用。Liriodenine 經藥理活性篩選發現其對於 carbachol 誘發天竺鼠支氣管平滑肌之收縮具有鬆弛作用，但對心臟強心作用之活性僅爲平滑肌鬆弛作用之十分之一而已。這些藥理作用證實 liriodenine 也是屬於一選擇性的 M3 receptor 抑制劑，且其結構與其他的選擇性的 M3 receptor 抑制劑(如, 4-DAMP)有很大的不同。因此，本實驗室的研究重點將著重於發展並找出新又簡易之合成 liriodenine 的方法，並嘗試去合成更多與 liriodenine 結構類似的衍生物，以利於將來的新藥的研發。本實驗室之採用兩種方法進行 liriodenine 的合成。方法一、二，皆是先利用 piperonal 及 aminoacetaldehyde dimethyl acetal 進行縮合反應後再運用 Pomeranz-Fritsch reaction 進行 isoquinoline 環化反應來製備 6,7-methylenedioxyisoquinoline (23)，然後再將 23 與 benzoyl chloride 及 trimethylsilyl cyanide 去製備 isoquinoline reissert 化合物 24 。接下來，方法一則是將 24 與 2-bromobenzaldehyde 反應形成 benzylisoquinoline ester 27，經水解得到 16，與 tributyltin hydride 進行自由基分子內的環化反應即可得到 liriodenine (產率 35%) 及一副產物 32 (產率 55%)。第二種方法是將 24 與 2-bromobenzyl chloride 反應形成 1-bromobenzyl-6,7-methylene-dioxyisoquinoline (34) 後再運用 Bu3SnH/AIBN 進行環化反應，所得之中間體沒有分離出來使直接經由空氣中自行氧化得到 liriodenine (產率 15%)，從研究結果發現所採用的方法較文獻所述簡單，但 liriodenine 的總產率並無提高，又本化合物由方法一總產率較方法二微高。本研究也合成兩種 liriodenine 衍生物 38 及 39，係由化合物 1 分別與 hydroxylamine hydrochloride 及 hydrazine hydrate 反應而得 (產率約 80%)。

英文摘要

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Liriodenine (1) ， an 7-oxoaporphine alkaloid was isolated from the heartwood of Liriodendron tulipifera L。 Recently，it was found that the nature product exhibited inhibitory activity against Topo Ⅱ because of its planar molecule having DNA intercalation capability。 The in vivo biological studies also know that liriodenine

possessed a prominent antiarrhythmic activity ， antimicrobial action，antibacterial，antifungal activity，mutagenicity andantiplatelet actions。Tracheal contraction of guinea-pig induced by carbachol was inhibited by liriodenine。 The cardiotonic effect of this agent was just only one tenth potency compared with smooth muscle relaxation effect。It demonstrated that liriodenine is a selective muscarinic M3 subtype receptor antagonist。 Since the natural product is structurally different from the known M3 antagonist (e.g. 4-DAMP)。 It is of great interest to develop a new and facile synthesis route for liriodenine, and its analogs as selective M3 antagonists。 Two methods were applied for the synthesis of liriodenine。The natural product 1 was prepared by starting from the reaction of piperonal and aminoacetaldehyde dimethyl acetal to form 6,7-methylenedioxyisoquinoline 23 via Promeranz-Fritsch reaction in 4 steps。Compound 23 was then treated with benzoyl chloride，followed with trimethylsilyl cyanide to yield isoquinoline Reissert compound 24 in good yield。In Method 1: Compound 24 was reacted with 2-bromobenzaldehyde to form benzylisoquinoline ester 27，which was then hydrolyzed to afford 16。Treatment of compound 16 with tributyltin hydride followed with air autooxidation to give the desired product 1 together with by-product 32，Alternatively (method 2): compound 24 was reacted with 2-bromobenzyl chloride to give 1-bromobenzyl-6,7-methyleedioxyisoquinoline (34)，which was further treated with Bu3SnH/AIBN and air autooxidation in one-pot reaction to afford liriodenine (1) in low yield 。 The present results showed that the overall yield of liriodenine by Method 1 was slightly higher than that by Method 2。Two new analogues of liriodenine，compounds 38 and 39，were also prepared in high yield (80%) by the reaction of compound 1 with hydroxylamine hydrochloride and hydrazine hydrate，respectively。