• 系統編號	RB8610-1888
• 計畫中文名稱	異奎琳化合物活性成分之化學修飾研究
• 計畫英文名稱	Structural Modification Studies on the Bioactive Isoquinolines.
• 主管機關	行政院國家科學委員會
• 計畫編號	NSC85-2331-B038-030-M25
• 執行機構	私立台北醫學院藥學系
• 本期期間	8408 ~ 8507
• 報告頁數	0 頁
• 使用語言	中文；英文
• 研究人員	陳繼明 Chen, Chi-Ming
• 中文關鍵字	異奎琳類；化學合成；抗心律不整；構造與藥效關係
• 英文關鍵字	Isoquinoline；Chemical synthesis；Antiarrhythmia；Structur alactivity relationship (SAR)；Spirobenzylisoquinoline
• 中文摘要	JKL1067 (2,3-methylenedioxy-9,10-dimethoxyspirobenzylisoquinoline)(1)是爲合成之螺旋芊基異？？衍生物,研究發現除增加心收縮力和減緩自發性的心跳速率外,對於 ouabain 或缺氧所引起的心律不整有抑制的作用。爲研究其化學結構與心臟作用藥效的關係,我們利用化學合成的方法合成了八個螺旋芊基異？？之類似化合物 1、2、3、4、5、6、7 和 8。 化學製備係先合成原小蘗鹼型衍生物爲關鍵性中間化合物,再與 CH/sub 3/I 反應生成 N-methiodide salts 後,在 Dimsyl sodium 催化進行 Stevens 之重排反應,生成三級螺旋芊基異？？類似物 1、2、3 和 4。四種三級類似物與 CH/sub 3/I 反應生成四級螺旋芊基異？？類似物 5、6、7 和 8。 八種螺旋芊基異？？類似物是以大白鼠之離體心臟進行有關心收縮力與心跳速率之藥理活性測試。結果顯示,三級的螺旋芊基異？？類似物 2 和 4 可增加心收縮力和減緩自發性的心跳速率,作用強度與 JKL1067 相當。而化合物 3 則較 JKL1067 有更強之心收縮力但具較弱之減緩心跳速率。至於四級的螺旋芊基異？？類似物 5、6、7 和 8 可能因爲極性的關係對心臟並沒有任何活性。
• 英文摘要	JKL1067 (2,3-methylenedioxy-9,10-dimethoxyspirobenzylisoquinoline) (1), a synthetic spirobenzylisoquinoline, exhibited a positive inotropic effect and negative chronotropic effect. It also possessed antiarrhythmic activity against cardiac arhythmia induced by ouabain or hypoxemia. In order to study the relationship between the structure and activity on cardiovascular system, eight spirobenzylisoquinoline analogues, such as 1, 2, 3, 4, 5, 6, 7, and 8 have been prepared by chemical synthesis. Protoberberine derivatives were used as key intermediates. Treatment of protoberbines with methiodide afforded

N-methyltetrahydroprotoberberinium iodides. Tertiary spirobenzylisoquinolines 1, 2, 3 and 4 were prepared by Stevens rearrangement of the N-methyl quarternary salts catalyzed by dimsyl sodium in DMSO. N-Methylation of spirobenzylisoquinolines 1, 2, 3 and 4 with methiodide afforded N,N-dimethylspirobenzylisoquinolinium iodides 5, 6, 7 and 8. Eight spirobenzylisoquinolines 1-8 were evaluated with the isolated heart preparation from rats to determine the chronotropic and inotropic effects. The results indicated that tertiary spirobenzylisoquinoline analogues 2 and 4 have equal effects in positive inotropic and negative chronotropic activities with JKL1067 in cardiac tissues. Compound 3 showed a stronger inotropic effect and a weaker chronotropic effect than that of JKL1067. However none of the quarternary spirobenzylisoquinoline analogues was active in cardiac preparations.