

论文

取代苄基/萘甲基异喹啉类及有关季铵衍生物的合成与生物活性

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摘要:

以具心血管活性的异喹啉类生物碱为先导物,结合某些钾通道阻滞剂的结构特征,设计合成了28个3,4-二氢(I_{1~4})和1,2,3,4-四氢苄基/萘甲基异喹啉化合物(II_{1~18})及有关季铵衍生物(I_{5,6}和II_{19~22})。药理试验表明:除化合物I₄有一定升压作用外,大多化合物有不同程度的降压和减慢心率活性,其中化合物II₁的降压活性最强。分析定量构效关系发现:化合物母核氮原子电荷愈大(即其绝对值愈小),降压作用愈强;反之,减慢心率作用愈强。异喹啉母核氮原子电荷可能为影响作用于血管或心脏组织的重要因素之一。

关键词: 异喹啉类 季铵衍生物 降压药 抗心律失常药 构效关系

SYNTHESIS AND BIOLOGICAL ACTIVITY OF SUBSTITUTED BENZYL / NAPHTHYLMETHYL ISOQUINOLINES AND RELATED QUATERNARY AMMONIUM DERIVATIVES

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Abstract:

In an attempt to search for novel antihypertensive or antiarrhythmic agents, especially compounds mainly acting on calcium or potassium channels, with the isoquinoline alkaloids which possessed cardiovascular effects as lead compounds, and on the basis of previous works of our laboratory as well as integration of the structural feature of certain potassium channel blockers, 28 compounds (I_{1~6} and II_{1~22}) were designed and synthesized among which 24 were not reported previously. 3,4-Dihydroisoquinolines were first synthesized by the Bischler-Napieralski cyclization with 3,4-disubstituted phenethylamine and aromatic acetic acid as starting materials. N-alkyl substituted tetrahydroisoquinolines were prepared by the alkylation of tetrahydroisoquinolines with corresponding substituted benzyl halides, or by the reduction of dihydroisoquinoline quaternary ammonium derivatives. Preliminary pharmacological studies *in vivo* showed that most of these compounds exhibited various degrees of hypotensive and bradycardial effects except I₄ which exhibited hypertensive activity. The hypotensive effect of II₁ was the most potent among these compounds in anaesthetized normotensive Sprague-Dawley rats. Analysis of the QSAR between hypotensive/bradycardial activities of certain compounds and their structural parameters of molecular mechanics (MM₂) showed that the hypotension/bradycardia increased with the increase/decrease of the charge of the nitrogen atom in the isoquinoline nucleus. Thus, the charge of the nitrogen atom might be one of the important factors which could enhance the selectivity of the compounds acting on blood vessels or cardiac tissues.

Keywords: Quaternary ammonium derivatives Hypotensive agents Antiarrhythmic agents QSAR This work was supported by a grant from the National Natural Science Foundation. Isoquinolines

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