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论文

吩噻嗪类化合物抑制肿瘤细胞多药耐药及蛋白激酶C活性的三维构效关系研究

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摘要：

目的：利用本室诱导建立的耐药细胞株K562/A02,研究在体外条件下吩噻嗪类衍生物(PTZs)逆转多药耐药(MDR)活性的构效关系。方法与结果：利用已知PKC Cys 2功能区晶体结构，结合计算化学和分子图形学手段对PKC抑制剂与PKC蛋白分子间可能的相互作用模式进行探讨。结果表明，2位取代各种基团逆转MDR作用强度依次为：COC_3H_7 > CF_3 > $COCH_3$ >H。边链哌嗪环4′-位取代基作用强度为:CH_3 > $COOC_2H_5$ > C_2H_4OH。结论：选出代表性化合物测定对鼠脑的抑制活性，初步三维构效关系研究表明，PTZs抑制PKC活性确实与特定的立体结构特征有关。本研究为进一步探索PTZs，PKC和MDR三者间的内在机制和设计有效PKC抑制剂或多药耐药逆转剂提供了新的途径。

关键词： 吩噻嗪类衍生物 多药耐药 逆转剂 蛋白激酶C

STRUCTURE-ACTIVITY RELATIONSHIP OF PHENOTHIAZINES FOR INHIBITION OF PROTEIN KINASE C AND REVERSAL OF MULTIDRUG RESISTANCE

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Abstract:

AIM: To study the structure-activity relationship of phenothiazines(PTZs) for inhibition of protein kinase C (PKC) and reversal of multidrug resistance (MDR) *in vitro*. METHODS and RESULTS: The possible binding model of PTZs to PKC based upon the X-ray structure of PMA(phorbol myristic acetate) in complex with PKC Cys 2 with DOCK program was explored. The results showed that the order of potency of reversal effect of PTZs on MDR is as follows: 2-COC_3H_7 > 2-CF_3 > 2-$COCH_3$ >H. The type of piperazinyl substitution also significantly affected potency against MDR. The result showed the order: CH_3 > $COOC_2H_5$ > C_2H_4OH. CONCLUSION: Some derivatives of PTZ was tested for inhibition of PKC. The observation indicates that PTZs inhibit PKC in a manner related to specific structural feature. Our molecular-modeling study suggests preliminarily how these PTZs bind to PKC and provide a structural basis for the design of high affinity PKC-modulator. Our structure-activity studies offer a way to understand which molecular structure affects activity, and this information may be used in the rational design of more effective drugs.

Keywords: multidrug resistance reversal agent protein kinase C phenothiazines

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