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喜树碱类抗肿瘤药物作用模式的柔性分子对接研究

宋云龙,张万年,季海涛,盛春泉,张珉,姚建忠,余建鑫,周有骏,朱驹,吕加国

中国人民解放军第二军医大学药学院

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摘要 研究采用柔性分子对接技术，将15个喜树碱类化合物对接到拓扑异构酶I (Topo I)-DNA切割复合物中，从原子水平和分子力场角度阐明了喜树碱类抗肿瘤药 物与DNA，Topo I的相互作用机制。研究发现，喜树碱分子插入Topp I-DNA复合物 的切割位点，并与Asn722，Asp533，Lys532和Lys720形成氢键作用网络。定量构效 关系研究进一步表明喜树碱分子可以与Topo I-DNA切割复合物形成电荷迁移作用。 该对接模型系统解释了喜树碱类化合物的构效关系、定点突变等诸多实验事实，为 下一步设计、合成新型高效的喜树碱类衍生物打下了坚实基础。

关键词 喜树碱 异构酶 抗肿瘤药 药物设计

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Flexible Molecular Docking Studies of Antineoplastic Camptothecin Derivatives on DNA-topoisomerase I Complex

Song Yunlong,Zhang Wannian,Ji Haitao,Sheng Chunquan,Zhang Min,Yao Jianzhong,Yu Jianxin,Zhou Youjun,Zhu Ju,Lu Jiaguo

School of Pharmacy, Second Military Medical University

Abstract Based on the crystallographic structure of human topoisomerase I (Topo I)-DNA covalent complex, a general model for the ternary drug-DNA- Topo I complex for camptothecin (CPT) derivatives has been developed using flexible docking teclmiques and thus elucidated the mode of action of CPT compounds interacting with Topo I and DNA from the atomic level for further design of novel potent CPT derivatives. In our model, CPT intercalated between the - 1 and + 1 base pail's of the cleavage site, stabilized further by H-bonding network between Asn722, Asp533, Lys532, Lys720 of Topo I and itself. Quantitative structure- activity relationship (QSAR) studies of 20 A-ring substituted CPT derivatives indicate that there may exist 7r-7t charge transfer interaction between CPT derivatives and Topo I-DNA complex. Our model of action for CPT provides an excellent fit between CPT and the binding site and is significantly consistent with the current knowledge of experimental mutations that render CFf resistant and structure-activity relationships of CPT derivatives, etc. This model provides a rational basis for further design and synthesis of novel potent CPT antitumor drugs.

Key words CATALYTIC ACTIVITY ISOMERASE ANTITUMOR DRUGS drug design

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通讯作者