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研究论文

非经典三铂核药物与DNA作用的理论研究

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摘要 利用分子力学、分子动力学和量子化学等计算方法研究了新型临床二期抗癌药物BBR3464([{*trans*-PtCl$(NH_3)_2$}$_2$-*μ*-{*trans*-Pt$(NH_3)_2(NH_2(CH_2)_6NH_2)_2$}]$^{4+}$)与寡聚DNA片段复合物的几何构型及其电子结构. 结果表明, 利用分子力学和分子动力学确定的复合物结构与实验的基本吻合. BBR3464为+4价高电荷铂药, 与两端的铂相连的两个Cl配体间的距离是2.74 nm, 这使得药物与DNA交联速度快, 形成远程的1,4-链间交联. 计算结果表明, BBR3464与DNA识别能力强, 结合稳定. 所形成的复合物中既有Pt-N7间较强的配位键, 也存在许多氢键、弱氢键及静电作用. 复合物中结合位点及结合位点外的嘌呤碱基的构象发生了不同程度的改变. 复合物结构特征说明, DNA在键合药物后其构型并未发生定域的链弯曲, 而是离域的嘌呤碱基的构象转化, 其对DNA所造成离域性损伤与经典的药物不同. DNA是铂抗肿瘤药物的靶点, 多点键合和离域性损伤的结构特征与BBR3464的独特生物活性和临床表现相关.

关键词 BBR3464([{*trans*-PtCl$(NH_3)_2$}$_2$-*μ*-{*trans*-Pt$(NH_3)_2(NH_2(CH_2)_6NH_2)_2$}]$^{4+}$) DNA片段 分子力学方法 分子动力学方法 量子化学方法

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Theoretical Investigation of Interaction Between Unclassical Trinuclear Antitumor Platinum Complex and DNA Duplex

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Abstract BBR3464([{*trans*-PtCl$(NH_3)_2$}$_2$-*μ*-{*trans*-Pt$(NH_3)_2(NH_2(CH_2)_6NH_2)_2$}]$^{4+}$) is currently in phase Ⅱ clinical trials. It is of considerable interest to understand the patterns of DNA damage. Detailed stu-dies about the geometrical and electrical configurations of the adduct of the trinuclear platinum compound and the 12-mer duplex 5'-d(ATATG*TACATAT)$_2$-3' was made with the molecular mechanics, molecular dyna-mics and quantum chemistry methods. The investigating results show that the coordinate bonds between platinum atoms of the trinuclear platinum complex and two N7's of guanines four base apart on opposite DNA strands are the most important interaction and hydrogen bond interactions are critical factors influencing on the configuration of the adduct. The strong H8-H1' intraresiding electrostatic interaction for purine residues(G5, G17, A3, A7, A9, and A13) is consistent with a *syn*-conformation of the nucleoside unit, suggesting a delocalized structure and extensive conformational changes in solution. Since DNA is the major pharmacological target of platinum drugs, the unique structural characteristic may be related to the increased cytotoxicity and antitumor activity of BBR3464 as compared to *cis*-platin(*cis*-DDP).

Key words BBR3464([{*trans*-PtCl$(NH_3)_2$}$_2$-*μ*-{*trans*-Pt$(NH_3)_2(NH_2(CH_2)_6NH_2)_2$}]$^{4+}$); DNA duplex; Molecular mechanics method; Molecular dynamics method; Quantum chemistry method

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