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论文

腺苷酸琥珀酸合成酶与其抑制剂的分子机制研究

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摘要:

利用密度泛函B3LYP方法选择6-31G(*d*)基组对腺苷酸琥珀酸合成酶(AdSS)天然抑制剂及其衍生物的结构进行优化, 并对其稳定性进行了分析, 同时采用Mulliken键序、原子电荷分布、表观静电势等对AdSS抑制剂及其衍生物电子结构与其生物活性相关性进行了理论研究. 基于腺苷酸琥珀酸合成酶(AdSS)与其底物肌苷单磷酸(IMP)复合物的晶体结构以及获得的天然抑制剂衍生物稳定构象, 利用分子对接、分子力学优化及常温分子动力学模拟对AdSS酶与天然抑制剂及其衍生物的相互作用复合物结构进行理论预测. 结果表明, AdSS酶的系列抑制剂中磷酸根基团和乙内酰脲(Hydantoin)官能团构成药效团模型, 识别过程中范德华相互作用能的贡献大于静电相互作用能.

关键词: 腺苷酸琥珀酸合成酶; 抑制剂; 分子对接; 密度泛函理论

Molecular Mechanism Studies on Interactions Between Adenylosuccinate Synthetase and Its Inhibitors

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Abstract:

By density functional theory B3LYP method with 6-31G(*d*) basis set, the geometry and electronic structure of the natural inhibitor and derivatives of Adenylosuccinate synthetase(AdSS) were optimized and their thermodynamic stability was also analyzed. The relationship between their electronic structures and bioactivities were discussed based on the Mulliken bond order, atomic net charge distribution and molecular surface electrostatic potential. According to the complex structure of AdSS and its substrate IMP as well as the optimized stable conformation of natural inhibitors, the interaction mode between AdSS and its inhibitors was studied with molecular docking, mechanical optimization and molecular dynamics simulation methods. These results show that the phosphate group and the hydantoin ring of the inhibitors form the pharmacophore model. The van der Waals energy played more important role in binding compared with the electrostatic energy. Furthermore, the inhibitors were mainly located in the hydrophobic cavity of the AdSS.

Keywords: Adenylosuccinate synthetase(AdSS); Inhibitor; Molecule docking; Density functional theory

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