高等学校化学学报 2010, 31(2) 374-378 DOI: ISSN: 0251-0790 CN: 22-1131/O6

论文

Apicidin选择性抑制Class Ⅰ HDACs分子动力学研究

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摘要:

采用模拟方法研究组蛋白脱乙酰酶抑制剂(Apicidin)选择性抑制组蛋白去乙酰化酶(Histone deacetylases, HDACs)中的HDAC1和HDAC8. 通过HDAC8晶体结构同源模建HDAC1三维结构模型, 将Apicidin分别与HDAC1和HDAC8对接并进行分子动力学模拟, 结果表明, HDAC1活性口袋入口处的Arg270是Apicidin-HDAC1形成稳定结构的重要因素; HDAC1中Tyr303及His178与Apicidin形成2个持续存在的氢键, 而在HDAC8中未发现, 这是Apicidin选择性抑制HDAC1高于HDAC8的另一重要原因.

关键词: 组蛋白脱乙酰酶抑制剂; 组蛋白去乙酰化酶(HDACs); 分子动力学; 同源模建; 分子对接

Selective Inhibition Study of Apicidin Towards Class I HDACs by Molecular Dynamics Simulation

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Abstract:

The selective inhibitory activity of cyclic tetrapeptides apicidin towards class I histone deacetylases (HDACs) was studied by molecular dynamics simulation. The 3D structure of HDAC1 was constructed by homology modeling using the X-ray structure of HDAC8 as template. Furthermore, the 3500 ps molecular dynamics simulations were performed on both apicidin-HDAC1 and apicidin-HDAC8 complexes, which were obtained by molecular docking. As a result, the Arg270 locating at the entrance of the HDAC1 active pocket played a crucial role in forming stable interactions with apicidin. There were two lasting hydrogen bonds between apicidin and HDAC1 during the molecular dynamics simulation, while none between apicidin and HDAC8. This difference could be another important reason for the high inhibitory activity of apicidin to HDAC1.

Keywords: Apicidin; Histone deacetylase; Molecular dynamics; Homology modeling; Molecular docking

收稿日期 2009-03-17 修回日期 网络版发布日期

DOI:

基金项目:

国家“八六三”计划项目(批准号: 2007AA021604)资助.

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