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论文

氮唑类抗真菌药物药效构象及其与酶活性位点对接

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摘要：

目的： 研究氮唑类抗真菌药物与其受体蛋白活性位点相互作用机理。方法： 用随机构象搜寻和分子动力学模拟退火法确定15个4种不同类型的氮唑类抗真菌药物最低能量构象；用活性类似物法限定药物分子药效基团之间的距离，搜寻到各化合物药效构象；将各化合物药效构象对接到白色念珠菌羊毛甾醇14α去甲基化酶活性位点中。结果： 4种结构类型的氮唑类药物在酶活性位点中有相似的对接位置；真菌和哺乳动物的活性位点结构特异性的残基分布在F螺旋C端、β6-1和β6-2区中；氮唑类抗真菌药物共同的卤代芳环结构落入相同的疏水空穴中，其中Y132的侧链羟苯基结构可与抑制剂卤代芳环形成电子迁移复合物。结论： 对接结果与已知SAR分析结论相符，阐明了氮唑类药物与活性位点的氨基酸残基作用方式，探讨结构选择性药物的结构需求。

关键词： 羊毛甾醇14α去甲基化酶；氮唑类抗真菌药物；药效构象；对接；白色念珠菌

PHARMACOPHORIC CONFORMATIONS OF AZOLE ANTIFUNGALS AND THEIR INTERACTION WITH ACTIVE SITE OF TARGET ENZYME

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Abstract:

AIM: To study the interactive mechanism of azole antifungals and functional residues of the active site of lanosterol 14α demethylase of *Candida albicans*. METHODS: The global minimum-energy conformations of 15 azole antifungals which belong to 4 different structural categories were determined by random conformation search and molecular dynamics simulated annealing. Active analogue approach was empolyed to search for the pharmacophoric conformations of all compounds. The resulting bioactive conformations were docked into the active site of lanosterol 14α demethylase of *Candida albicans*. RESULTS: All 15 azole antifungals was shown to have similar docking position in the active site. To compare with mammalian enzyme, the structurally selective residues of the active site of fungal lanosterol 14α demethylase were distributed in C terminus of F helix, β6-1 sheet and β6-2 sheet. The common halogenated benzene substructure of azole inhibitors was located deep in the same hydrophobic cavity. The π～π charge transfer complex may exist between halogenated benzene ring of azoles and the hydroxyl benzene side chain of residue Y132 of lanosterol 14α demethylase of *Candida albicans*. CONCLUSION: The dock results were in accord with SAR analysis. The interactive mode of azole antifungals with active site residues of lanosterol 14α demethylase of *Candida albicans* was elucidated. The structrual selectivity of the fungal target enzyme to its inhibitors was investigated at the same time.

Keywords: azole antifungals pharmacophoric conformation docking *Candida albicans* lanosterol 14α demethylase

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