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研究论文

白色念珠菌*N*-肉豆蔻酰基转移酶中药物结合位点的MCSS分析

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摘要 采用多拷贝同时搜寻方法(MCSS)分析得到了CaNMT活性位点的疏水区域、氢键结合位点和负电性区域. MCSS计算结果显示, CaNMT活性位点有两个疏水性比较强的区域: 一个由Tyr107, Tyr109, Val108, Phe117, Phe123, Ala127, Phe176和Leu337等残基组成; 另一个由Phe115, Phe240和Phe339组成. CaNMT活性位点发现有两个氢键作用区域, 其中Tyr119, His227, Asn392和Leu451是与已有抑制剂的氢键结合位点, Tyr107, Asn175, Thr211和Asp412是新发现的氢键结合位点, 而且在NMT家族中高度稳定, 它们对设计新结构类型的CaNMT抑制剂具有重要作用. Leu451是负电性兼氢键作用位点, 是抑制剂设计时所必需考虑的位点.

关键词 *N*-肉豆蔻酰基转移酶 抗真菌 多拷贝同时搜寻 药物结合位点 药物设计

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MCSS Analysis of Drug Binding Sites for *Candida albicans N*-Myristoyltransferase

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Abstract NMT is a promising target for the development of novel anfifungal agents with a new mode of action. In order to know the important functional residues and regions in the active site of *Candida albicans N*-myristoyltransferase(CaNMT) in detail, multiple copy simultaneous search(MCSS) was used to identify the hydrophobic pockets, hydrogen-bonding sites and electrostatic negative sites. The results from MCSS calculation reveal that there were two hydrophobic pockets. One pocket was lined with Tyr107, Tyr119, Val108, Phe117, Phe123, Ala127, Phe176 and Leu33, the other pocket was lined with Phe115, Phe240 and Phe339. Moreover, two hydrogen-bonding sites were identified by MCSS calculations. Among those hydrogen-bonding residues, Tyr119, His227, Asn392 and Leu451 could form hydrogen bond with the benzofuran inhibitors and Tyr107, Asn175, Thr211 and Asp412 were newly discovered hydrogen-bonding residues, which were highly conserved residues across the NMT family and would play an important role in the design of NMT inhibitors with novel chemical scaffold. Important functional residue Leu451 could serve as both hydrogen-bonding site and electrostatic negative site, which was indispensable in inhibitor design. The above results could provide important clues for the de novo design and virtual high-throughput screening of novel NMT inhibitors.

Key words *N*-Myristoyltransferase Antifungal Multiple copy simultaneous search Drug binding site Drug design

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