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药效团检索设计新的**HIV-1**蛋白酶抑制剂

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摘要 通过对自建的未开发化合物三维结构库进行药效团检索,得到了4个对HIV-1蛋白酶抑制活化的化合物,通过构象分析发现包含药效团的构象处于优势构象,而且4个结构都含有带两个邻位羟基的苯环和一个间位羰基的药效团以及公共子结构。通过计算发现它们的疏水参数都很小。在考虑满足包含药效团的结构特征和有适中的疏水参数两个因素的前提下,设计出了新的具有潜在抑制**HIV-1**蛋白酶活性的化合物。它们的结构都比检索得到的四个化合物更为简单,因此易于合成。

关键词 药效团 构象 蛋白酶 抑制剂 药物筛选 计算机辅助设计

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Design of new HIV-1 protease inhibitors by pharmacophore searching

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Abstract Four HIV-1 protease inhibitors were hit by pharmacophore searching against a 3D structural database (containing 30,000 newly reported compounds) developed by our group. By using conformation analysis we found that their favorable conformers contain the pharmacophore respectively. Additionally, all the four compounds have some common structural features such as an ortho-dihydroxyl substituted benzene ring with a carbonyl at para-position of the ring. Their hydrophobic parameters were calculated by Ghose-Crippen method integrated in the Spartan 5.0 program and found to be a little too small. In order to meet the two principal factors: containing the pharmacophore and having a moderate hydrophobic parameter, which were believed to be critical for an active HIV-1 protease inhibitor, some new structures were designed by modifying the structures of these four compounds. These designed structures are simpler and believed easier to synthesize than the hitting compounds.

Key words CONFORMATION PROTEASE INHIBITOR DRUG SCREENING COMPUTER AIDED DESIGN

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