化学学报 2002 60 (6): 1116-1121 ISSN: 0567-7351 CN: 31-1320/06

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胰蛋白酶和苯酰氨类抑制剂结合自由能的预测

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收稿日期 修回日期 网络版发布日期 接受日期

摘要 用基于线性响应近似的自由能预测方法计算胰蛋白酶和苯酰氨类抑制剂的结合自由能。计算结果表明，单参数，双参数和三参数模型具有相似的线性回归系数，但三参数和双参数模型的交互验证回归系数要明显优于单参数模型。从预测能力来 看，双参数模型和三参数模型都能够很好地预测测试集中抑制剂的结合自由能，其中双参数模型预测的结果要略优于三参数模型的预测结果。对测试集中的抑制剂，双参数模型预测得到的预测自由能和实际自由能之间平均绝对误差仅为1.15 kJ/mol。自由能计算模型以及分子动力学轨迹能很好地解释抑制剂结构和活性的 关系，为药物设计提供了重要的结构信息。

关键词 胰蛋白酶 抑制剂 药物 分子动力学

分类号 06

Prediction of Binding Free Energies between Benzamides and Trypsin

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Abstract Binding affinities of a series of benzamide inhibitors for trypsin were evaluated by molecular dynamics (MD) simulations using a linear response approach. The calculated results show that for models with one, two or three parameters, the coefficients of linear regression are similar, while the coefficients of "leave-one-out" cross- validation of the two-parameter and three-parameter models are obviously superior to that of the one-parameter model. Moreover, the binding free energies of these compounds in the test set can be well predicted by the two-parameter and three-parameter models. The predictions by the two-parameter model are a little better than those by the three-parameter model. To the compounds in the test set, the average error is only 1.15 kJ/mol between the actual and the predicted binding free energies by the two-parameter model. The relationships between the structures and activities of the benzamides can be derived from the binding free energies and the trajectories from MD simulations, which provide us with some important structural information about development of new drugs.

Key words TRYPSIN INHIBITOR INHIBITOR DRUGS KINETIC STUDY

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