论文

苯并呋喃类*N*-肉豆蔻酰基转移酶抑制剂的三维定量构效关系研究

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摘要：

摘要采用比较分子力场分析法(CoMFA)和比较分子相似性指数分析法(CoMSIA), 系统地研究了40个苯并呋喃类N-肉豆蔻酰基转移酶(NMT)抑制剂的三维定量构效关系. 在CoMFA研究中, 考察了网格点步长对模型统计结果的影响. 在CoMSIA研究中, 研究了各种分子场组合、 网格点步长和衰减因子对模型统计结果的影响, 发现立体场、 静电场、 疏水场和氢键受体场的组合可得到最佳模型. 所建立的CoMFA和CoMSIA模型的交叉相关系数q^2值分别为0.759和0.730, 均具有较强的预测能力. 利用CoMFA和CoMSIA模型的三维等值线图直观地解释了化合物的构效关系, 阐明了化合物结构中苯并呋喃环上各位置取代基对抑酶活性的影响, 为进一步结构优化提供了重要依据.

关键词：　苯并呋喃; NMT抑制剂; 抗真菌; 三维定量构效关系; 比较分子力场分析(CoMFA); 比较分子相似性指数分析(CoMSIA)

3D-QSAR Study of a Series of Novel Benzofuran NMT Inhibitors

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Abstract:

AbstractUsing comparative molecular field analysis(CoMFA) and comparative molecular similarity indices analysis(CoMSIA), three dimensional structure activity relationship(3D-QSAR) studies were carried out on a series of benzofuran N-myristoyl transferase(NMT) inhibitors. Variation of grid spacing was used during the optimization of the CoMFA model. For the CoMSIA study, the influence of the combination of different field types was evaluated and the best combination was considered to be steric, electrostatic, hydrophobic and H bonding acceptor fields. Variation of grid spacing and attenuation factor was used to obtained the best CoMSIA model. The resulting CoMFA and CoMSIA models had a cross validated coeffiecient(q^2) of 0.759 and 0.730 respectively, which showed a strong predictive ability on both test-set and training set. The tri-dimensional contour maps of CoMFA and CoMSIA provided smooth and interpretable explanation of the structure-activity relationship of the compounds. The analysis of the tri-dimensional contour maps permitted interesting conclusions about the effects of different substituents of different positions of the benzofuran group on the antifungal activity, which will guide the design of novel NMT inhibitors with a higher activity.

Keywords: KeywordsBenzofuran; NMT inhibitors; Antifungal; 3D-QSAR; Comparative molecular field analysis(CoMFA); Comparative molecular similarity indices analysis(CoMSIA)

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