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论文

5-HT$_3$受体拮抗剂药效团模型的构建

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摘要:

以31个来源于MDDR数据库中具有抑制鼠Bezold-Jarisch反射作用的5-HT$_3$受体拮抗剂作为训练集化合物, 构建5-HT$_3$受体拮抗剂药效团模型. 训练集化合物具备结构多样性, 来源于相同药理模型, 活性值ED_{50}范围为0.05~320 μg/kg *i.v.*. 利用Catalyst计算5-HT$_3$受体拮抗剂的最优药效团由一个氢键受体、一个疏水基团、一个正电离子化基团、一个芳香环特征和6个排除体积组成; Fixed cost值、Null cost 值、Δcost值和Configuration cost值分别为112.6, 172.0, 59.4和7.248. 训练集化合物活性的计算值与实测值相关系数为0.9031, 偏差值为0.8976, 基于Fischer的交叉验证结果表明药效团模型具有较高的置信度, 所得药效团对训练集化合物活性值的预测结果显示有较好的预测能力, 可用于数据库搜索指导发现新的具有该活性的先导化合物, 也可用于中药或天然产物药物研究开发.

关键词: 5-HT$_3$受体拮抗剂 三维药效团 数据库搜索

Pharmacophore Model Construction of 5-HT$_3$ Receptor Antagonist

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Abstract:

A three-dimensional pharmacophore model of 5-HT$_3$ Receptor Antagonists was developed based on 31 5-HT$_3$ Receptor Antagonists which antagonizes the von Bezold-Jarisch reflex evoked by 5-HT in anesthetized rats. The antagonists were selected with great diversity in both molecular structure and bioactivity as required by HypoGen program in the Catalyst software. The antagonists in training set show 5-HT$_3$ Receptor inhibiting activity with ED_{50} values, and the range of values is 0.05—320 μg/kg *i.v.*. The best statistical hypothesis, consisting of four features, one hydrogen-bond acceptor, one hydrophobic region, one ring aromatic feature, one positive ionizable and six excluded volumes, has a correlation coefficient of 0.9031, a root-mean-square deviation of0.8976, a fixed cost of112.6, a null cost of 172.0, a configuration cost of 7.248. The pharmacophore model has a highly predictive ability, which was approved by the results of the activity estimated by mapping the compounds of training set with it. On the basis of Fischer method, the cross-validation provided a strong confidence on this hypothesis. This pharmacophore model can contribute to the finding and designing of new-type 5-HT$_3$ Receptor Antagonists.

Keywords: 5-HT$_3$ receptor antagonists Three-dimensional pharmacophore Database searching

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