

论文

噻唑烷二酮和芳酮酸类PPAR γ 激动剂三维定量构效关系研究

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摘要:

目的建立PPAR γ 激动剂-噻唑烷二酮和芳酮酸类化合物的三维定量构效关系, 为设计高活性PPAR γ 激动剂提供结构信息。方法与结果用比较分子力场分析方法得到噻唑烷二酮和芳酮酸类化合物CoMFA模型, 其交叉验证相关系数 $R^2=0.656$, 非交叉验证相关系数 $R^2=0.982$, $F_{10,37}=201.1$, 绝对误差 $SE=0.115$ 。结论从CoMFA系数等势图中揭示芳酮酸类化合物较噻唑烷二酮类化合物活性更高的原因, 提示芳酮酸类化合物与PPAR γ 结合时形成了不同于BRL-PPAR γ 复合物晶体的结合腔。

关键词: 过氧化酶体增殖激活 γ 受体(PPAR γ) PPAR γ 激动剂 比较分子力场分析 噻唑烷二酮 芳酮酸

STUDY ON 3D-QSAR OF PPAR γ AGONISTS WITH THIAZOLIDINEDIONE AND ARYLKETO-ACID MOIETIES

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Abstract:

AIM To build a model of two series of PPAR γ agonists thiazolidinedione and arylketo-acid derivatives using 3D-QSAR method, and to reveal the structural features affecting the binding activity to PPAR γ , which relates to antihyperglycemic and antihyperlipidemic activity and has a potential application to the treatment of type II diabetes. METHODS and RESULTS 48 agonists with selective activity for PPAR γ were analyzed using CoMFA. Based upon the active conformation of rosiglitazone (BRL) extracted from its complex with PPAR γ all agonists were aligned. The model from CoMFA showed a high ability to explain and predict the activity of PPAR γ agonists with cross-validation correlation coefficient $R^2=0.656$, that of non-cross-validation $R^2=0.982$, $F_{10,37}=201.1$, and $SE=0.115$. CONCLUSION The CoMFA contour map indicates that the steric fields mainly contribute to the binding effect, and especially a bulky group in the arylketo-acid series favors in the increase of affinity for PPAR γ , as compared to the thiazolidinedione.

Keywords: PPAR γ agonists CoMFA thiazolidinedione arylketo-acid peroxisome proliferator-activated receptor- γ (PPAR γ)

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