高等学校化学学报 2007 , 28 (8): 1503—1507 ISSN: 0251-0790 CN: 22-1131/O6

研究论文

新型5-HT重摄取抑制剂的设计、合成及活性评价

杨静, 王小芳, 杜冠华, 秦芳, 文辉, 杨光中

中国协和医科大学, 中国医学科学院药物研究所, 北京100050

收稿日期 2006-11-2 修回日期 网络版发布日期 2007-8-9 接受日期

摘要 在对已知各种结构类型的5-HT重摄取抑制剂分子结构全面分析的基础上, 建立了SSRIs药效团模型. 基于该模型应用UNITY程序对NCI-3D和Maybridge-3D数据库进行三维结构的限制性查询, 在获得的命中结构的信息指导下, 设计合成了3种全新结构类型的化合物, 并完成了初步的药理活性评价. 这些化合物均显示出不同程度的5-HT重摄取抑制活性, 其中5个化合物显示高抑制活性. 哌嗪取代的二苯脒类化合物的结构新颖, 较好地符合5-HT重摄取抑制剂药效团模型, 与SSRIs类化合物三维定量构效关系研究得到的CoMFA模型有较好的适配性.

关键词 选择性5-HT重摄取抑制剂(SSRIs) 抗抑郁 药效团

分类号 0626

Design, Synthesis and Activity Evaluation of Novel Selective Serotonin Reuptake Inhibitors

YANG Jing, WANG Xiao-Fang, DU Guan-Hua, QIN Fang, WEN Hui, YANG Guang-Zhong*

Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, China

Abstract Depression is a kind of common and severe mental illness. During the past two decades, selective serotonin reuptake inhibitors(SSRIs) have been proved to be a safer and more effective resistance than the first-generation antidepressants(TCAs and MAOIs), and have gained incredible popularity.Based on the conformation analysis and pharmacophore information of SSRIs, flexible database searching from the NCI-3D and Maybridge-3D database was performed. Three classes of the new compounds structures were designed and 27 analogues were prepared and evaluated as potential antidepressant agents. Biphenylbenzamidine derivative Ⅰ-19 showed good activity of affinity to the 5-HT transporter. It can be used as the lead structure for drug design with the objective of making more potent inhibitors against 5-HT transporter.

Key words Selective serotonin reuptake inhibitors(SSRIs) Antidepressants Pharmacophore

DOI:

通讯作者 杨光中 yanggzh@imm.ac.cn