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论文

组织蛋白酶K拟肽腈类抑制剂的合成、表征及抑制效应检测

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摘要:

针对组织蛋白酶K(Cat K)的活性位点的化学结构特征设计合成了一系列拟肽腈类抑制剂, 并检测了其抑制效果, 得到了高效且具有较高选择性的抑制剂(其中抑制剂b和f对Cat K的抑制常数K_i值分别为15.9和19.1 nmol/L). 构效关系分析表明, P_2与P_3位连接部分以及P_3基团的结构不同可使其抑制效果产生100倍以上的差异.

关键词: 组织蛋白酶K; 肽腈化合物; 抑制剂; 构效关系

Synthesis, Characterization and Enzyme Activity Assays of Peptides Nitriles as Inhibitors of Cathepsin K

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Abstract:

Cathepsins are a family of cystein proteases that is specifically expressed in the osteoclasts. They are responsible for terminal protein degradation in acidic environment, and therefore are involved in many serious human diseases, such as osteoporosis, osteoarthritis, and bone cancer and so on. Of all the 11 human cystein cathepsins, Cathepsin K is the predominant one as it is an important drug target and has gained special attention recently. According to the structural characteristics of the active site in cathepsin K, we designed and synthesized a series of dipeptide nitriles as inhibitors of cathepsins and have gained a potent and high selective inhibitor of it, b(K_i=15.9 nmol/L) and f(K_i=19.1 nmol/L). Inhibition activity was tested by measuring the hydrolysis of initially quenched fluorogenic peptide substrates. Studies on structure-activity relationship reveal large differences of 100-fold in activity suppression as a result of difference in NH linker between P_3 aryl and P_2 leucinamide moieties and P_3 moieties. Our results also suggest that less amide bonds may be good for the selectivity of peptide nitriles to cathepsins.

Keywords: Cathepsin K; Peptide nitrile; Inhibitor; Structure-activity relationship

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参考文献:

1. Lecaille F., Kaleta J., Brömme D.. Chem. Rev.[J], 2002, 102: 4459—4488
2. Otto H. H., Schirmeister T.. Chem. Rev. [J], 1997, 97: 133—171
3. Falgueyret J. P., Oballa R. M., Okamoto O., *et al*.. J. Med. Chem.[J], 2001, 44: 94—104
4. LIU Hai-Dong(刘海东), XIAO Jun-Hai(肖军海), LI Song(李松). Letters in Biotechnology(生物技术通讯)[J], 2006, 17: 119—122
5. WU Yan(吴艳), WANG Yi(王毅), YANG Gang-Yi(杨刚毅). Chinese Journal of Osteoporosis(中国骨质疏松杂志)[J], 2006, 12: 522—524
6. Löser R., Schilling K., Dimming E., *et al*.. J. Med. Chem.[J], 2005, 48: 7688—7707
7. Palmer J. T., Bryant C., Wang D. X., *et al*.. J. Med. Chem.[J], 2005, 48: 7520—7534
8. Ma L. J., Liu Y. F., Wu Y. Q.. Chem. Commun.[J], 2006, 25: 2702—2704
9. WANG Hua(王华), ZHAO Mi-Feng(赵密锋), LI Gang(李刚), *et al*.. Chem. J. Chinese Universities(高等学校化学学报)[J], 2006, 27(2): 240—243
10. WANG Ding(王鼎), ZHANG Qi-Han(张奇涵), XU Jia-Xi(许家喜). Chem. J. Chinese Universities(高等学校化学学报)[J], 2006, 27(4): 669—671
11. Falgueyret J. P., Black W. C., Cromlish W., *et al*.. Anal. Biochem.[J], 2004, 335: 218—227
12. Robichaud J., Bayly C., Oballa R., *et al*.. Bioorg. Med. Chem. Lett.[J], 2004, 14: 4291—4295
13. Setti E. L., Venkatraman S., Palmer J. T., *et al*.. Bioorg. Med. Chem. Lett.[J], 2006, 16: 4296—4299

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