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论文

药物分子设计的策略：苗头和先导物的品质决定新药的成败

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摘要：

苗头化合物-先导物-候选药物是创制新药的三个重要里程碑，其中候选药物的确定是新药创制的关键环节，将创制过程分成研究和开发两个阶段，并且开发阶段所有环节都取决于候选药物的化学结构，所以决定了临床前和临床研究的命运。候选药物质量的高低又受制于先导化合物的类药性和苗头化合物的品质，苗头化合物演化成先导物是将新药的研究植根于有研发前景的结构上，先导物的优化是将活性化合物转化成候选药物的过程，是在药效、药代、安全性和物化性质等多维空间中的优化操作。本文结合实例讨论了发现苗头、确定先导物、先导物优化和确定候选药物的策略原则。

关键词： 分子设计 苗头化合物 先导物 候选药物 配体效率 优化

Strategy of molecular drug design: hits, leads and drug candidates

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Abstract:

Hits, leads and drug candidates constitute three millstones in the course of drug discovery and development. The definition of drug candidates is a critical point in the value chain of drug innovation, which not only differentiates the research and development stages, but more importantly, determines the perspective and destiny of the pre-clinical and clinical studies. All outcomes from the development stage are actually attributed to the chemical structure of candidates. The quality of candidates, however, is restricted by the drug-likeness of lead compounds, which in turn is decided by the characteristics of hits. The hit-to-lead is to provide a promising and druggable structure for further development, whereas the optimization of lead compounds is a process to transform an active compound into a drug, which in essence is molecular manipulation in multi-dimensional space related to pharmacodynamic, pharmacokinetic, physico-chemical, and safety properties. This review discusses the strategic principles in hit discovery, lead identification and optimization, as well as drug candidate definition with practical examples.

Keywords: hit lead drug candidate ligand efficiency optimization molecular drug design

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1．贾红;郭彦伸;葛轶昱;文辉;杨静;杨秀颖;杜冠华;杨光中.基于酶结构的新型基质金属蛋白酶抑制剂设计、合成与活性评价[J]. 药学学报, 2007,42(12): 1271-1281

2．郭宗儒.药物分子设计的策略: 分子的宏观性质与微观结构的统一[J]. 药学学报, 2008,43(3): 227-233

3．黄流生;陶国新;李兰燕;迟翰林.HIV-1蛋白酶解聚型抑制剂的计算机辅助分子设计[J]. 药学学报, 1999,34(5): 353-357

4．陶国新;李兰燕;迟翰林.小分子非肽类HIV蛋白酶抑制剂的计算机辅助分子设计[J]. 药学学报, 2000,35(4): 265-268

5．郭宗儒.药物分子设计的策略：双靶标药物设计[J]. 药学学报, 2009,44(3): 209-218

6．郭彦伸 郭宗儒.多靶点药物分子设计[J]. 药学学报, 2009,44(3): 276-281

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