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Book Reviews

Molecular design. Concepts and applications

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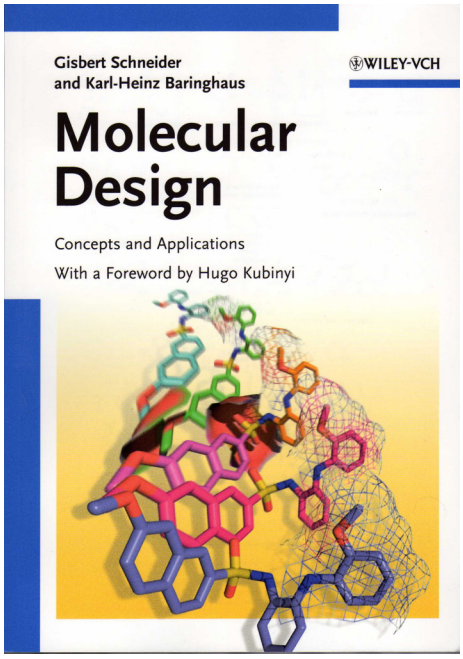
This book focuses on how different concepts and molecular modeling strategies could be exploited to design the molecular architecture of ligands for specific targets, as new drug candidates. The authors have large experience in drug discovery, occupying head positions in European pharmaceutical industries, which was crucial to their particular form to address the main design-related medicinal chemistry topics along the five chapters of the book. The foreword written by Hugo Kubinyi describes the importance of integrated and multidisciplinary work for the successful of rational drug design process. So, Schneider and Baringhaus used an easy and clear language to show the main advantages and disadvantages of several different approaches and technologies applied in molecular design of new chemical entities, highlighting the pitfalls and risks of the complex task of discovery a new drug. The first chapter presents the principal structural elements related to the molecules and what features should be persecuted to avoid or minimize the probability of unsuccessful during the clinical trials due to inadequate ADMET properties. In addition to the description of druglikeness properties, an important discussion about the importance of getting informations about the shape and the bioactive conformation of the bioligands is included. The second one introduces the phenomena related to receptor-ligand interactions pointing the more frequent types of bonds involved in the binding and how the enthalpic and entropic contributions could benefit the formation of stable complexes. At this point, the classical QSAR methods are introduced, demonstrating their evolution for the tridimensional (3D) approaches to access, indirectly, the structure of



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target bioreceptors. It includes the 3D-QSAR metods, like CoMFA, and the pharmacophore mapping strategies. Moreover, the limitations of these methods are discussed and associated to the possibility of different binding modes of distinct, but structurally-related, ligands pointing for the alternative investigation of the binding mode through docking approaches. Chapter 3 highlights the need of rational drug design strategies, including the computer-assisted molecular design (CAMD), to compensate the apparent creativity crisis evidenced by the ever smaller number of new drugs approved by FDA and it describes different molecular design methods that are assisted by *in silico* tools, including the systematic search in chemical compound libraries using druglikeness filters, the use of natural products as source of inspiration, the structure-based and "de novo" design strategies. The next chapter outines the virtual screening as an emerging tool to investigate in association with high-throughput screening (HTS) all the diversity of possible chemical space. The authors pointed examples of virtual screening cascades applied to structure-based positive design of new hits presenting minimal druglike properties and the steps to overcome before they could be considered leads. The final chapter is dedicated to the use of *in silico* tools to anticipate the ADME behavior of a new drug candidate and eventually introduce structural changes that are able optimize the bioavailability profile. The concepts of pro-drugs and bioisosteric changes are introduced as important molecular modification strategies and examples of drug discovery case studies are presented at the end. "Molecular design" is fully illustrated and adequately supported by actual bibliography. It should be recommended for graduate students and medicinal chemistry practitioners, especially those interested in the use of bioinformatics approaches in drug design. On the other hand, several other useful and classical strategies of molecular modification and design, as molecular simplification, molecular hybridization, conformational constraining and also the bioisosterism are not addressed in a manner less dependent of computer methods, reducing the value of chemical intuition and SAR understanding in drug discovery process.