Preface

Among all new technologies in drug research, structure-based ligand design is one of the most powerful approaches. The drugs Captopril, Dorzolamide and Zanamivir, to mention only some prominent examples, resulted from rational design, based on the knowledge and analysis of protein 3D structures. The discovery of some other drugs, e.g. the more recent HIV protease inhibitors Nelfinavir and Amprenavir, was at least supported by protein crystallography studies. Many other drug candidates that resulted from structure-based design are in clinical development.

Whereas some early attempts of structure-based design failed due to inappropriate physicochemical and pharmacokinetic properties of the ligands, modellers are nowadays aware of the pitfalls in ligand design. Large, greasy ligands are avoided, as well as too polar compounds. According to favorable lead and drug properties, defined e.g. by the Lipinski rule of five, ligand design focuses on compounds with relatively low molecular weight, an intermediate lipophilicity range, and a limited number of hydrogen bond donors and acceptors.

In 1997, Klaus Gubernator and Hans-Joachim Böhm edited a volume on structure-based ligand design in this book series. A comprehensive review by Robert Babine, one of the editors of the current book, and Steven Bender, also published in 1997, discussed the design of aspartic, serine, cysteine, and metalloprotease inhibitors, and of immunosuppressants. The present book deals with some other families of important biological targets, e.g. nuclear receptors and kinases. In addition, several other attractive drug targets are reviewed. A special topic, the design of orthogonal protein-ligand pairs, will become important in personalized medicine. The book closes with chapters on recent progress in technologies: protein engineering to promote crystallization, micro-crystallization, and high-throughput crystallography. With its broad perspective, the book provides a state-of-the-art overview on important results and techniques that are relevant for protein 3D structure-based drug design.

The series editors are grateful to Robert Babine and Sherin Abdel-Meguid for their engaged work and to Frank Weinreich, Wiley-VCH, for ongoing support during the preparation of the book. We expect that volume 20 of "Methods and Principles in Medicinal Chemistry" will be another highlight of this successful series, which started only ten years ago.

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