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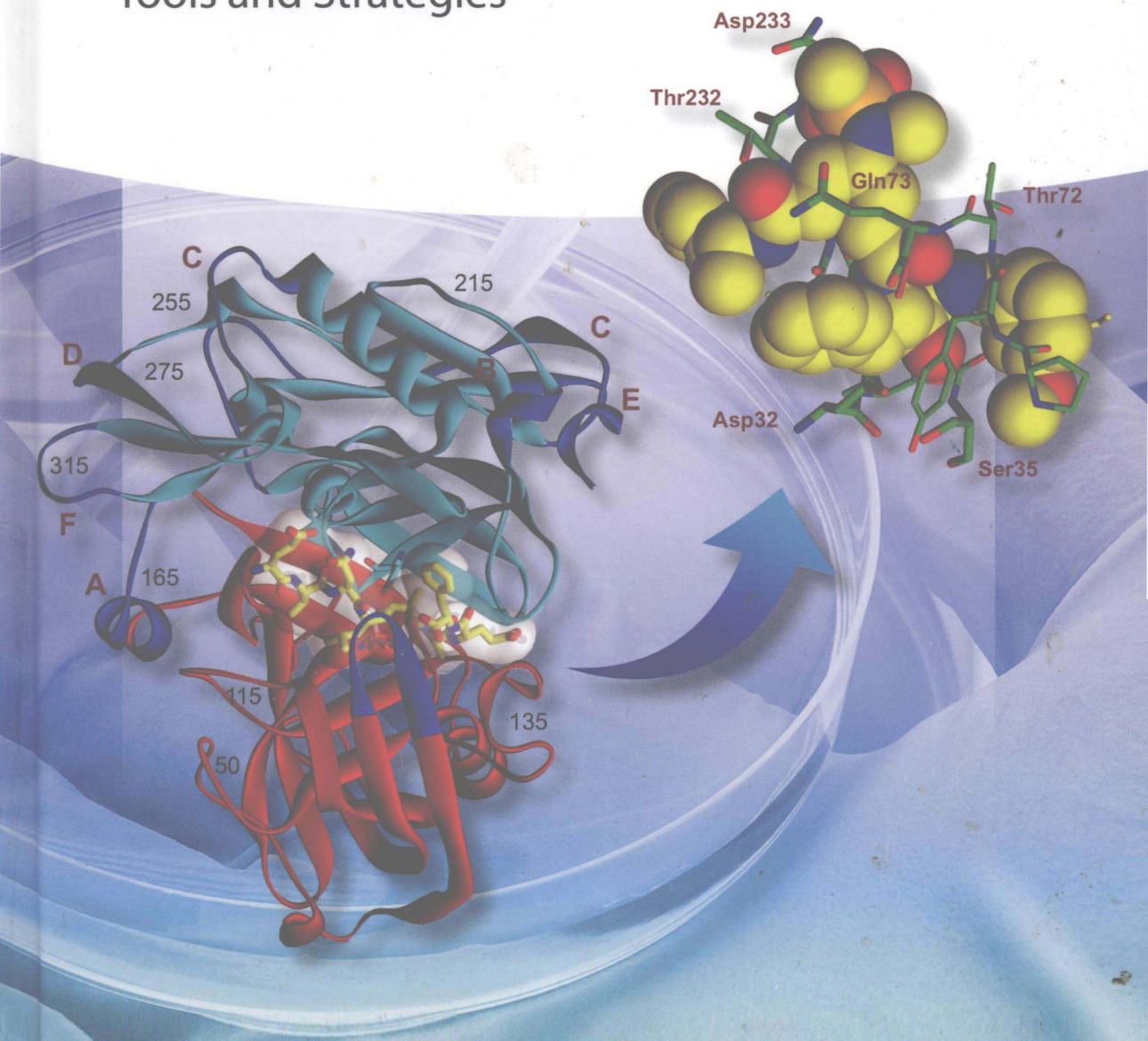
Arun K. Ghosh and Sandra Gemma

Structure-based Design of Drugs and Other Bioactive Molecules

Tools and Strategies



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Drug design is a complex, challenging and innovative research area. Structure-based molecular design has transformed the drug discovery approach in modern medicine. Traditionally, focus has been placed on computational, structural or synthetic methods only in isolation. This one-of-a-kind guide integrates all three skill sets for a complete picture of contemporary structure-based design.

This practical approach provides the tools to develop a high-affinity ligand with drug-like properties for a given drug target for which a high-resolution structure exists. The authors use numerous examples of recently developed drugs to present "best practice" methods in structure-based drug design with both newcomers and practicing researchers in mind. By way of a carefully balanced mix of theoretical background and case studies from medicinal chemistry applications, readers will quickly and efficiently master the basic skills of successful drug design.

This book is aimed at new and active medicinal chemists, biochemists, pharmacologists, natural product chemists and those working in drug discovery in the pharmaceutical industry. It is highly recommended as a desk reference to guide students in medicinal and chemical sciences as well as to aid researchers engaged in drug design today.

Arun K. Ghosh *received his BS and MS in Chemistry at the University of Calcutta and the Indian Institute of Technology, Kanpur, respectively. He obtained his Ph.D. (1985) at the University of Pittsburgh. He then pursued post-doctoral research with Professor E. J. Corey at Harvard University (1985–1988). He was a research fellow at Merck Research Laboratories prior to joining the University of Illinois, Chicago as an assistant Professor in 1994. In 2005, he moved to Purdue University where he is currently the Ian P. Rothwell Distinguished Professor of Chemistry and Medicinal Chemistry. His notable honors include: ACS Medicinal Chemistry Hall of Fame, National Institutes of Health MERIT Award, CRSI medal from the Chemical Research Society of India, IUPAC Richter Award, ACS Arthur C. Cope Scholar Award, ACS Robert Scarborough Medicinal Chemistry Award, American Association for the Advancement of Science, University of Illinois University Scholar, National Merit Scholar of India. He has published over 260 research papers, edited a book on aspartic acid proteases and holds numerous patents. His research interests include diverse areas of organic, bioorganic, and medicinal chemistry with particular emphasis on organic synthesis and protein-structure-based design of biomolecules.*

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Preface

As our knowledge of the structure and function of proteins has expanded, new techniques employing this knowledge as the basis for drug design and discovery have emerged and taken the lead. The impact of structure-based design strategies has been dramatic and far-reaching, resulting in the discovery and development of numerous FDA-approved drugs, many of which are first-in-class medicines. Major advancements in molecular biology and technology have led to in-depth structural knowledge of new disease-relevant target enzymes. Improvements in X-ray crystallographic techniques have created an important database and enabled a better understanding of the role of enzyme–ligand interactions. Progress in computer analysis has also played a vital role in advancing structure-based design capabilities since the 1980s. Today, structure-based design has become one of the most innovative and dynamic areas of drug design and discovery.

Over the years, the Ghosh laboratories have gained extensive experience with structure-based design. The development of conceptually novel inhibitors against HIV-1 protease for the treatment of HIV/AIDS has been an important area of research that led to the design and discovery of darunavir, the first FDA-approved treatment for drug-resistant HIV/AIDS. Structure-based design of β-secretase 1 (BACE1) inhibitors for the treatment of Alzheimer's disease also started in the Ghosh laboratories with the design and synthesis of the first substrate-based transition-state inhibitors, determination of the first X-ray crystal structure of inhibitor-bound BACE1, followed by design and development of potent and selective inhibitors with clinical potential. The Ghosh laboratories have also led the design of coronavirus 3CLPro and PLpro inhibitors for possible treatment of SARS/Mers and the design of methyltransferase inhibitors for possible treatment of dengue virus infection. Our experience in structure-based design in these diverse areas is detailed within this book.

A significant body of structure-based design work for many approved therapeutic drugs and preclinical and clinical candidates has been reported by numerous academic and pharmaceutical scientists. This work has led to the development of tools, strategies, and concepts that aid the process of structure-based design. A substantial part of this work has been an integral part of the lecture notes of one of the authors for teaching fundamentals and concepts of drug discovery and design to students at Purdue University. During these research and teaching endeavors, an

important need for writing this book was recognized. Although there are many elegant reports of the structure-based design of therapeutic drugs that span three decades now, a systematic presentation of the evolution of the field, principles, and applications had not yet been compiled. The materials of this treatise are organized with these objectives in mind. This book covers a critical overview of the history of structure-based drug design, an analysis of the underlying principles, and an up-to-date description of the X-ray techniques and methods that led to the structure determination of many important biomolecules. The book also highlights the structure-based design and drug development process covering a broad array of FDA-approved medications. The reader will gain a sense of how a drug interacts with its biological target at the molecular level and how the drug–target interactions can be optimized in order to increase affinity with desired physicochemical and drug-like properties. Furthermore, the reader will gain knowledge of how other factors such as *in vivo* efficacy and physicochemical and pharmacokinetic parameters need to be optimized in order to convert a lead compound into a clinical drug structure.

Chapter 1 provides a historical perspective of drug discovery encompassing discovery through serendipity and natural product screening to the evolution of the field of structure-based design of today's medicines. Chapters 2–7 outline general principles for design of enzyme inhibitors covering aspartic acid proteases, serine proteases, cysteine proteases, metalloproteases, threonine proteases, and protein kinases. These chapters highlight the key protein–ligand interactions and evolution of ligands, scaffolds, and templates to aid molecular design of lead inhibitors and their optimization. These chapters also cover the synthesis of a selection of ligands, templates, and isosteres generally utilized for structure-based design. Chapter 8 reviews recent progress in gaining high-resolution structural knowledge of biologically relevant proteins and G-protein-coupled receptors (GPCRs), particularly the methods of X-ray crystallography and their application in lead discovery. Chapter 9 covers recent developments in the structure-based design of novel ligands for GPCRs, an exciting new dimension for GPCR research.

Chapters 10–20 cover an array of recently FDA-approved drugs developed by utilizing structure-based design strategies. These chapters highlight the mechanism of action associated with each drug class, in-depth structural analysis of protein–ligand interactions, structural design, and optimization of ligand binding to protein structures. Chapter 10 is devoted to the design of the first ACE inhibitor, captopril, which marks the beginning of structure-based design. Chapters 11–19 cover the design and development of HIV-1 protease inhibitors such as saquinavir, indinavir, and darunavir (Chapter 11); kinase inhibitor drugs imatinib, nilotinib, and dasatinib (Chapter 12); NS3/4A serine protease inhibitor drugs boceprevir and telaprevir for the treatment of HCV (Chapter 13); proteasome inhibitor drugs bortezomib and carfilzomib for the treatment of relapsed multiple myeloma (Chapter 14); development of direct thrombin inhibitor dabigatran etexilate (Chapter 15); non-nucleoside HIV reverse-transcriptase inhibitors etravirine and rilpivirine (Chapter 16); development of renin inhibitor aliskiren (Chapter 17); neuraminidase inhibitors zanamivir and oseltamivir for the treatment of influenza (Chapter 18); and carbonic

anhydrase inhibitor dorzolamide (Chapter 19) for the treatment of glaucoma. The last chapter outlines the development of β-secretase inhibitors that are at various stages of preclinical and clinical development for possible treatment of Alzheimer's disease.

Overall, this book will greatly enhance the readers' understanding of structure-based design and drug discovery, its potential, underlying principles, feasibility, and limitations. We believe that the book will be an excellent resource for new and practicing medicinal chemists, biologists, biochemists, and pharmacologists who are interested in working in the field of molecular design for discovery and development of human medicine. Structure-based design has a critical role in today's drug design and discovery, and it will continue to play a very prominent role in drug design and medicinal chemistry endeavors throughout the twenty-first century. We hope that the book will be helpful to researchers involved in drug discovery and the pursuit of knowledge in structure-based design and related areas.

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We very much enjoyed working with Drs. Frank Weinreich and Lesley Belfit and the Wiley-VCH editorial team. We sincerely appreciate their help and support throughout this project. We would like to thank Dr. Hiroaki Mitsuya, Dr. Jordan Tang and Dr. Irene Weber for longstanding and productive research collaboration. We would like to express our appreciation and thanks to our research colleagues from Purdue University, Dr. Venkateswararao Kalapala, Dr. Navanth Gavande, Ms. Heather Osswald, Mr. Anindya Sarkar, Ms. Kelsey Cantwell and Mr. Anthony Tomaine for their invaluable help with proofreading and reviewing of this work. We wish to convey special thanks and appreciation to Dr. Jody Ghosh for her help and support and Mrs. JoAnna Hadley for her help with the manuscript preparation and organization. Finally, we wish to thank our families for their love, support, and inspiration.

Purdue University — *Arun K. Ghosh*
Purdue University & University of Siena — *Sandra Gemma*

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