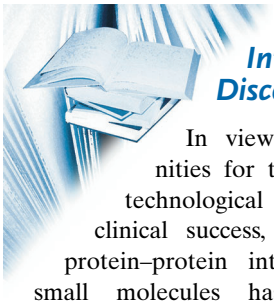


Protein–Protein Interactions in Drug Discovery

In view of the vast opportunities for therapeutic intervention, technological advances, and emerging clinical success, the field of targeting protein–protein interactions (PPIs) using small molecules has recently undergone explosive growth. The editor of this book, Alexander Dömling, and the series editors Raimund Mannhold, Hugo Kubinyi, and Gerd Folkers have done an excellent job in providing a balanced overview of this area, although without claiming to deliver an exhaustive account (as they explain in the Foreword). The book is a thoughtfully selected compilation of chapters aimed at acquainting readers with this area, and the authors' diverse viewpoints and backgrounds appropriately reflect the interdisciplinary work devoted to this field. A large number of case studies illustrating the challenges and opportunities in targeting PPIs make this book practical and useful to medicinal chemists as well as to scientists in related areas.

Chapter 1 provides a concise introductory overview of PPI approaches to drug discovery and of the relevant compound classes, discussing aspects such as the role of PPIs in human physiology and the structural features of PPI interfaces, illustrated by a number of examples. Chapter 2 is concerned with defining and predicting the protein–protein interactome, using various techniques of systems biology. The reader is given fascinating insights into the efforts devoted to unraveling PPI networks, and understanding their significance for disease and opportunities for therapeutic intervention.

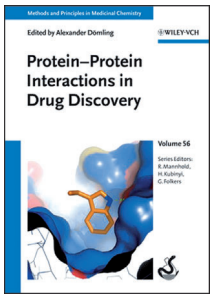
In Chapter 3, the authors make a case for the importance of three-dimensionality in the chemical structures of protein PPI inhibitors, based on an analysis of data from the Protein Data Bank. This is not a new concept, and the chapter would have benefited from an overview of previous work and the knowledge gained by other researchers. With this caveat, the authors' study is nevertheless insightful and a good read thanks to a clear and concise discussion. Chapter 4 presents an in-depth analysis of the chemical space of PPI inhibitors for four of the most thoroughly studied PPIs in the literature (p53/MDM2, XIAP/Smac, Bcl/Bak, and ICAM-1/LFA-1). The conclusion, similar to that in studies done by others, is a tendency for greater hydrophobicity, aromaticity, and molecular weight of effective PPI inhibitors, compared to traditional enzyme inhibitors, with the curious observation that the published XIAP inhibitors appeared significantly more drug-like. Chapter 5 discusses computational tools for assessing ligand binding ability of protein–protein interfaces, and predicting effective small-molecule inhibitors on the basis of virtual screening exercises. One of the tools highlighted, AnchorQuery, allows performing pharmacophore searches by virtual screening, tapping into the vast chemical space of Ugi multi-component reaction products. The authors give practical guidance on how to utilize this and other open-access interactive computational tools as part of a workflow for developing PPI inhibitors.

Chapter 6 is devoted to the Src homology 3 (SH3) domain, a conserved protein fold that mediates a large number of PPIs. Structure, degree of conservation, and typical binding motifs of inhibitor molecules described in the literature are critically discussed, as well as strategies for achieving selectivity between SH3 domains of different proteins.

The interaction between the tumor suppressor p53 and its negative regulator MDM2, discussed in Chapter 7, is one of the most thoroughly studied PPIs, with many examples of small-molecule inhibitors existing in the literature, and some compounds in clinical evaluation. The authors highlight the discovery, structure–activity relationships, and in vivo characterization of key compounds in various programs reported by industrial and academic groups. The case studies in this chapter are informative, but could have benefited from a more critical discussion. Chapter 8 gives an account of work on the well-studied class of LFA-1/ICAM inhibitors, treated in a more critically evaluating style than the previous chapter.

Chapter 9 covers a protein feature that can be exploited for ligand binding, the PIF pocket, a conserved regulatory element that is specific for AGC kinases. Binders to this pocket have been particularly well studied in the kinase PDK1, and allosteric inhibition of the interaction with substrate proteins has been demonstrated. The author does an excellent job of explaining the rationale for pursuing this approach as an alternative to ATP-competitive inhibition and provides an insightful overview of the field. Particularly valuable is the thoughtful and critical discussion of the ligand binding ability of the PIF pocket, providing useful guidance for medicinal chemists interested in this area.

Chapter 10 relates the story of the discovery of the oxytocin antagonists retosiban and epelsiban chosen as candidates for clinical development. Oxytocin is a G-protein coupled receptor, and inclusion of this topic in a book focused on protein–protein interactions is surprising. Nonetheless, it is a very well-written review, including a highly instructive summary of the lead optimization process.



Protein–Protein Interactions in Drug Discovery (Series: Methods and Principles in Medicinal Chemistry, Vol. 56) Edited by Alexander Dömling. Wiley-VCH, Weinheim, 2013. 334 pp., hardcover, € 138.00.—ISBN 978-3527331079

The book ends with two chapters on peptidic ligands as starting points for identifying PPI inhibitors. Chapter 11 focuses on RGD-containing peptides as inhibitors of the interaction between integrins and their substrates. Conformational rigidification by cyclization and the systematic use of techniques of conformational modification led to highly selective ligands, culminating in the case of αv inhibitors in the discovery of the antiangiogenic compound "cilengitide". This compound is currently in clinical trials, and it is to be hoped that the author's forecast of "first antiangiogenic RGD peptide that will reach the market" will come true, despite a recent Phase III failure in glioblastoma trials. Chapter 12 describes a computationally-guided iterative process of sequentially replacing peptide fragments of peptidic ligands with non-peptidic fragments (termed REPLACE), for generating non-ATP-competitive inhibitors of the cell cycle kinases CDK2 and PLK1. As in the previous chapter on the PIF pocket in AGC kinases, the rationale of these endeavors is to achieve isoform specificity, which is difficult to attain using ATP-competitive kinase inhibitor approaches.

The layout, graphics, and illustrations are impeccable, making this book a pleasure to read. However, one of the main shortcomings is the large number of typos, especially in Chapter 7. Hopefully, these mistakes will be corrected in a second printing.

Considered altogether, this book is a very useful and instructive overview of the field of small-molecule PPI inhibitors, and I strongly recommend it to chemists and other scientists interested in this challenging and fascinating area of drug discovery.

Joachim Rudolph
Genentech, San Francisco (USA)

DOI: 10.1002/anie.201307711

