

Contents

Contributors	page vii
Preface	ix
1 Progress and issues for computationally guided lead discovery and optimization	1
<i>William L. Jorgensen</i>	
PART I. STRUCTURAL BIOLOGY	
2 X-ray crystallography in the service of structure-based drug design	17
<i>Gregory A. Petsko and Dagmar Ringe</i>	
3 Fragment-based structure-guided drug discovery: strategy, process, and lessons from human protein kinases	30
<i>Stephen K. Burley, Gavin Hirst, Paul Sprengeler, and Siegfried Reich</i>	
4 NMR in fragment-based drug discovery	41
<i>Christopher A. Lepre, Peter J. Connolly, and Jonathan M. Moore</i>	
PART II. COMPUTATIONAL CHEMISTRY METHODOLOGY	
5 Free-energy calculations in structure-based drug design	61
<i>Michael R. Shirts, David L. Mobley, and Scott P. Brown</i>	
6 Studies of drug resistance and the dynamic behavior of HIV-1 protease through molecular dynamics simulations	87
<i>Fangyu Ding and Carlos Simmerling</i>	
7 Docking: a domesday report	98
<i>Martha S. Head</i>	
8 The role of quantum mechanics in structure-based drug design	120
<i>Kenneth M. Merz, Jr.</i>	
9 Pharmacophore methods	137
<i>Steven L. Dixon</i>	
10 QSAR in drug discovery	151
<i>Alexander Tropsha</i>	
11 Predicting ADME properties in drug discovery	165
<i>William J. Egan</i>	

PART III: APPLICATIONS TO DRUG DISCOVERY

12 Computer-aided drug design: a practical guide to protein-structure-based modeling	181
<i>Charles H. Reynolds</i>	
13 Structure-based drug design case study: p38	197
<i>Arthur M. Doweyko</i>	
14 Structure-based design of novel P2-P4 macrocyclic inhibitors of hepatitis C NS3/4A protease	209
<i>M. Katharine Holloway and Nigel J. Liverton</i>	
15 Purine nucleoside phosphorylases as targets for transition-state analog design	215
<i>Andrew S. Murkin and Vern L. Schramm</i>	
16 GPCR 3D modeling	248
<i>Frank U. Axe</i>	
17 Structure-based design of potent glycogen phosphorylase inhibitors	257
<i>Qiaolin Deng</i>	
Index	265