

## Contents

Preface XIII

A Personal Foreword XV

List of Contributors XVII

### Part I Introduction

#### 1 Pharmacophores: Historical Perspective and Viewpoint from a Medicinal Chemist 3

*Camille G. Wermuth*

1.1 Definitions 3

1.1.1 Functional Groups Considered as Pharmacophores:  
the Privileged Structure Concept 4

1.2 Historical Perspective 4

1.2.1 Early Considerations About Structure–Activity Relationships 4

1.2.2 Early Considerations About the Concept of Receptors 5

1.2.3 Ehrlich's "Magic Bullet" 5

1.2.4 Fischer's "Lock and Key" 6

1.3 Pharmacophores: the Viewpoint of a Medicinal Chemist 6

1.3.1 Two-dimensional Pharmacophores 6

1.3.1.1 Sulfonamides and PABA 6

1.3.1.2 Estrogens 7

1.3.2 An Early Three-dimensional Approach: the Three-point Contact  
Model 7

1.3.2.1 Clonidine and Its Interaction with the  $\alpha$ -Adrenergic Receptor 8

1.3.3 Criteria for a Satisfactory Pharmacophore Model 9

1.3.4 Combination of Pharmacophores 10

1.4 Conclusion 11

References 11

**Part II Pharmacophore Approaches**

- 2 Pharmacophore Model Generation Software Tools 17**  
*Konstantin Poptodorov, Tien Luu, and Rémy D. Hoffmann*
- 2.1 Introduction 17
- 2.2 Molecular Alignments 18
- 2.2.1 Handling Flexibility 18
- 2.2.2 Alignment Techniques 19
- 2.2.3 Scoring and Optimization 20
- 2.3 Pharmacophore Modeling 21
- 2.3.1 Compound Structures and Conformations 21
- 2.3.2 Representation of Interactions in the Pharmacophore Models 22
- 2.3.3 Conformational Expansion 22
- 2.3.4 Comparison 23
- 2.3.5 Pharmacophores, Validation and Usage 23
- 2.4 Automated Pharmacophore Generation Methods 23
- 2.4.1 Methods Using Pharmacophore Features and Geometric Constraints 24
- 2.4.1.1 DISCO, GASP and GALAHAD 24
- 2.4.1.2 Catalyst 27
- 2.4.1.3 Phase 32
- 2.4.1.4 Pharmacophores in MOE 34
- 2.4.2 Field-based Methods 36
- 2.4.2.1 CoMFA 36
- 2.4.2.2 XED 37
- 2.4.3 Pharmacophore Fingerprints 38
- 2.4.3.1 ChemX/ChemDiverse, PharmPrint, OSPPREYS, 3D Keys, Tuples 39
- 2.5 Other Methods 40
- 2.5.1 SCAMPI 40
- 2.5.2 THINK 41
- 2.5.3 Feature Trees 43
- 2.5.4 ILP 43
- 2.6 Conclusions 43
- References 44
- 3 Alignment-free Pharmacophore Patterns –  
A Correlation-vector Approach 49**  
*Steffen Renner, Uli Fechner, and Gisbert Schneider 49*
- 3.1 Introduction 49
- 3.2 The Correlation-vector Approach 51
- 3.2.1 The Concept 51
- 3.2.2 Comparison of Molecular Topology: CATS 52
- 3.2.3 Comparison of Molecular Conformation: CATS3D 56
- 3.2.4 Comparison of Molecular Surfaces: SURFCATS 57

3.3	Applications	58
3.3.1	Retrospective Screening Studies	58
3.3.2	Scaffold-hopping Potential	64
3.3.3	Prospective Virtual Screening	69
3.4	New Methods Influenced by the Correlation-vector Approach	72
3.4.1	“Fuzzy” Pharmacophores: SQUID	72
3.4.2	Feature Point Pharmacophores: FEPOPS	76
3.5	Conclusions	76
	Acknowledgments	77
	Abbreviations	77
	References	78
<b>4</b>	<b>Feature Trees: Theory and Applications from Large-scale Virtual Screening to Data Analysis</b>	<b>81</b>
	<i>Matthias Rarey, Patrick Fricker, Sally Hindle, Günther Metz, Christian Rummey, and Marc Zimmermann</i>	
4.1	Introduction: from Linear to Non-linear Molecular Descriptors	81
4.2	Creating Feature Trees from Molecules	82
4.3	Algorithms for Pairwise Comparison of Feature Trees	85
4.3.1	Recursive Division: the Split-search Algorithm	86
4.3.2	Subsequently Growing Matchings: the Match-search Algorithm	87
4.3.3	Match-Search with Gaps: the Dynamic Match-search Algorithm	89
4.3.4	Building Multiple Feature Tree Models	91
4.4	Feature Trees in Similarity Searching and Virtual Screening	92
4.4.1	Virtual Screening	92
4.4.2	Virtual Screening Based on Multiple Query Compounds	95
4.4.3	Tagged Feature Trees	97
4.5	Searching Combinatorial Fragment Spaces with Feature Trees	99
4.5.1	Search Algorithm	100
4.5.2	Set-up of Fragment Spaces	102
4.5.3	Searching in Fragment Spaces	105
4.6	Multiple Feature Tree Models: Applications in HTS Data Analysis	108
4.7	Drawing Similar Compounds in 2D Using Feature Tree Mappings	111
4.8	Conclusion	113
	Acknowledgments	113
	References	114
<b>5</b>	<b>Concept and Applications of Pseudoreceptors</b>	<b>117</b>
	<i>Klaus-Jürgen Schleifer</i>	
5.1	Introduction	117
5.2	Methodology	118
5.3	Application of Pseudoreceptors	123
5.4	Conclusion	129
	References	130

<b>6</b>	<b>Pharmacophores from Macromolecular Complexes with LigandScout</b>	<b>131</b>
	<i>Gerhard Wolber and Robert Kosara</i>	
6.1	Introduction	131
6.1.1	Structure-based Drug Design Methods	131
6.1.2	Why Structure-based Pharmacophores?	132
6.2	The Data Source: Clean-up and Interpretation of PDB Ligand Molecules	132
6.2.1	Topological Analysis	133
6.2.2	Geometric and Semantic Analysis	135
6.2.3	Double Bond Distribution	136
6.3	Chemical Feature-based Pharmacophores Used by LigandScout	136
6.3.1	Characteristics of Chemical Features: Specific or Comparable?	137
6.3.2	Fully Automated Perception of Chemical Features	138
6.3.3	Vectors: Hydrogen Bonding	139
6.3.4	Points: Lipophilic Contacts and Charge-transfer Interactions	139
6.3.4.1	Hydrophobic Contacts	139
6.3.4.2	Positive and Negative Ionizable Areas	140
6.4	Overlaying Chemical Features	140
6.5	3D Visualization and Interaction	141
6.5.1	Core and Environment Visualization	141
6.5.2	Pharmacophore Visualization	143
6.5.3	Interaction	144
6.6	Application Examples: Pharmacophore Generation and Screening	145
6.6.1	HRV Coat Protein Inhibitor	146
6.6.2	ABL Tyrosine Kinase Inhibitor	146
6.7	Conclusion	147
	Acknowledgments	148
	References	148
<b>7</b>	<b>GRID-based Pharmacophore Models: Concept and Application Examples</b>	<b>151</b>
	<i>Francesco Ortuso, Stefano Alcaro, and Thierry Langer</i>	
7.1	Introduction	151
7.2	Theoretical Basis of the GBPM Method	152
7.3	Application Examples	155
7.3.1	Protein–Protein Interaction: XIAP	155
7.3.2	Protein–Protein Interaction: the Interleukin 8 Dimer	159
7.3.3	DNA-Ligand Interaction	162
7.4	Conclusions	168
	References	168

<b>8</b>	<b>“Hot Spot” Analysis of Protein-binding Sites as a Prerequisite for Structure-based Virtual Screening and Lead Optimization</b>	<b>171</b>
	<i>Ruth Brenk and Gerhard Klebe</i>	
8.1	Introduction	171
8.2	Calculating “Hot Spots”	171
8.3	From “Hot Spots” to Molecules	174
8.4	Real-life Examples	177
8.5	Replacement of Active-site Water Molecules	185
8.6	Conclusions	190
	Acknowledgments	190
	References	191
<b>9</b>	<b>Application of Pharmacophore Fingerprints to Structure-based Design and Data Mining</b>	<b>193</b>
	<i>Prabha Karnachi and Amit Kulkarni</i>	
9.1	Introduction	193
9.2	Applications of 3D Pharmacophore Fingerprints	194
9.2.1	Focused/Diverse Library Design Using Pharmacophore Fingerprints	194
9.2.2	Analyzing Protein–Ligand Interactions Using Pharmacophore Fingerprints	195
9.2.3	Virtual High-throughput Screen (vHTS) and Protein Selectivity	196
9.2.3.1	Application of FLIP Technology	199
9.3	Conclusion	203
	Acknowledgments	204
	References	204
<b>10</b>	<b>SIFt: Analysis, Organization and Database Mining for Protein-Inhibitor Complexes. Application to Protein Kinase Inhibitors</b>	<b>207</b>
	<i>Juswinder Singh, Zhan Deng, and Claudio Chuaqui</i>	
10.1	Introduction	207
10.2	How to Generate a SIFt Fingerprint	208
10.3	Profile-based SIFts	210
10.4	SIFt and the Analysis of Protein Kinase – Inhibitor Complexes	211
10.5	Canonical Protein – Small Molecule Interactions in the Kinase Family	212
10.6	Clustering of Kinase Inhibitors Based on Interaction Fingerprints	212
10.7	Profile Analysis of ATP, p38 and CDK2 Complexes	215
10.8	Virtual Screening	218
10.9	Use of p-SIFt to Enrich Selectively p38, CDK2 and ATP Complexes	219
10.10	Conclusion	220
	Acknowledgments	222
	References	222

<b>11</b>	<b>Application of Structure-based Alignment Methods for 3D QSAR Analyses</b> 223
	<i>Wolfgang Sippl</i>
11.1	Introduction 223
11.2	Why is 3D QSAR So Attractive? 225
11.3	CoMFA and Related Methods 226
11.3.1	CoMFA 226
11.3.2	CoMSIA 227
11.3.3	GRID/GOLPE 227
11.4	Reliability of 3D QSAR Models 228
11.5	Structure-based Alignments Within 3D QSAR 230
11.6	Conclusion 241
	Acknowledgments 243
	References 244
<b>Part III</b>	<b>Pharmacophores for Hit Identification and Lead Profiling: Applications and Validation</b>
<b>12</b>	<b>Application of Pharmacophore Models in Medicinal Chemistry</b> 253
	<i>Fabrizio Manetti, Maurizio Botta, and Andrea Tafi</i>
12.1	Introduction 253
12.2	Building Pharmacophore Models Able to Account for the Molecular Features Required to Target the $\alpha_1$ Adrenergic Receptor ( $\alpha_1$ -AR) and its Subtypes 254
12.2.1	A Pharmacophore Model for $\alpha_1$ -AR Antagonists 254
12.2.1.1	Pharmacophore Building 254
12.2.1.2	Pharmacophore Analysis 257
12.2.1.3	Validation of the Pharmacophore Model 259
12.2.1.4	Hit Search Through Database Mining 260
12.2.2	Towards a Pharmacophore Model for the $\alpha_{1D}$ -AR Subtype 261
12.2.2.1	A Preliminary Model 261
12.2.2.2	An Improved (Simplified) Model 264
12.3	Use of Excluded Volume Features in the Rationalization of the Activity Data of Azole Antifungal Agents 268
12.3.1	Excluded Volume Spheres in Structure-based and Ligand-based Pharmacophore Studies 268
12.3.2	Issues Inherent in the Rational Design of Azole Antifungal Agents 270
12.4	Conclusion 277
	References 279

<b>13</b>	<b>GPCR <i>Anti-target</i> Modeling: Pharmacophore Models to Avoid GPCR-mediated Side-effects</b>	<b>283</b>
	<i>Thomas Klabunde</i>	
13.1	Introduction: GPCRs as Anti-targets	283
13.2	In Silico Tools for GPCR Anti-target Modeling	285
13.3	GPCR Anti-target Pharmacophore Modeling: the $\alpha_{1a}$ Adrenergic Receptor	285
13.3.1	Generation of Cross-chemotype Pharmacophore Models	286
13.3.2	Description of Cross-chemotype Pharmacophore Models	287
13.3.3	Validation of Anti-target Pharmacophore Models	289
13.3.3.1	Virtual Screening: Hit Rates and Yields	289
13.3.3.2	Virtual Screening: Fit Values and Enrichment Factors	290
13.3.4	Mapping of Pharmacophore Models into Receptor Site	292
13.3.5	Guidance of Chemical Optimization to Avoid GPCR-mediated Side-effects	294
13.4	Conclusion	295
	References	296
<b>14</b>	<b>Pharmacophores for Human ADME/Tox-related Proteins</b>	<b>299</b>
	<i>Cheng Chang and Sean Ekins</i>	
14.1	Introduction	299
14.2	Cytochrome P450	301
14.3	UDP-glucuronosyltransferase	304
14.4	P-glycoprotein (P-gp)	304
14.5	Human Peptide Transporter 1	306
14.6	Apical Sodium-dependent Bile Acid Transporter (ASBT))	307
14.7	Sodium Taurocholate-transporting Polypeptide (NTCP)	307
14.8	Nucleoside Transporters	307
14.9	Organic Cation Transporter 1 and 2	308
14.10	Organic Anion-transporting Polypeptides (OATPs)	309
14.11	Breast Cancer Resistance Protein (BRCP)	311
14.12	The Nuclear Hormone Receptors	312
14.13	Human Ether-a-go-go Related Gene	314
14.14	Conclusion	315
	Acknowledgments	316
	References	316
<b>15</b>	<b>Are You Sure You Have a Good Model?</b>	<b>325</b>
	<i>Nicolas Triballeau, Hugues-Olivier Bertrand, and Francine Acher</i>	
15.1	Introduction	325
15.2	Validation Methods: Different Answers Brought to Different Questions	326
15.2.1	Software-related Validation Methods	326
15.2.1.1	Ligand-based Pharmacophore Research	326
15.2.1.2	Protein Structure-based Pharmacophore Research	329

15.2.1.3	Critical Remarks Regarding Structure-based Pharmacophore Models	329
15.2.2	Visual Inspection	330
15.2.3	Consistency with Structure – Activity Relationships	331
15.2.3.1	Some Limitations of Computer Programs	331
15.2.3.2	Retained Chemical Features	332
15.2.3.3	Spatial Arrangement	332
15.2.3.4	3D-QSAR Pharmacophore Models	333
15.2.4	External Data to Back Up a Pharmacophore Model	335
15.2.4.1	Biophysical Data	335
15.2.4.2	Other Published Pharmacophore Models	335
15.2.4.3	The “Test Set” Approach and the Kubinyi Paradox	336
15.2.5	Database Mining	337
15.2.5.1	Some Metrics to Assess Screening Performances	338
15.2.5.2	The ROC Curve Approach	341
15.3	A Successful Application: the Ultimate Validation Proof	343
15.3.1	Validation of Pharmacophore Models for Virtual Screening	343
15.3.1.1	Which Validation Method Should One Insist On?	344
15.3.2	Validation of Pharmacophore Models to Guide Medicinal and Computational Chemistry	345
15.3.3	Validation of Pharmacophore Models for Activity Prediction	346
15.3.3.1	Which Validation Method Should One Insist On?	346
15.4	Case Study: a New Pharmacophore Model for mGlu4R Agonists	348
15.4.1	Metabotropic Glutamate Receptors as Potential Therapeutic Targets	348
15.4.2	Pharmacology of Metabotropic Glutamate Receptor Subtype 4 (mGlu4)	348
15.4.3	Training Set Elaboration	351
15.4.4	Strategy for Perceiving the Pharmacophore	352
15.4.5	Four Criteria to Validate our Pharmacophore Model	353
15.4.6	Results of Our Pharmacophore Model Research with Catalyst-HypoGen and HypoRefine	354
15.4.7	Description of the Two Retained Pharmacophore Models	356
15.4.7.1	Hypothesis 1 (Catalyst-HypoRefine with Variable Weights)	356
15.4.7.2	Hypothesis 2 (Catalyst-HypoRefine with Variable Weights and Tolerances)	357
15.4.7.3	Comparison of the Two Retained Hypotheses	358
15.4.8	Further Validation: Virtual Screening of the CAP Database	360
15.5	Conclusion	361
	Acknowledgments	362
	References	362

**Subject Index** 365