

Contents

List of Contributors *XI*

Preface *XV*

A Personal Foreword *XVII*

Part One Principles 1

1 Bioisosterism in Medicinal Chemistry 3

Nathan Brown

1.1 Introduction 3

1.2 Isosterism 3

1.3 Bioisosterism 6

1.4 Bioisosterism in Lead Optimization 9

1.4.1 Common Replacements in Medicinal Chemistry 9

1.4.2 Structure-Based Drug Design 9

1.4.3 Multiobjective Optimization 12

1.5 Conclusions 13

References 14

2 Classical Bioisosteres 15

Caterina Barillari and Nathan Brown

2.1 Introduction 15

2.2 Historical Background 15

2.3 Classical Bioisosteres 17

2.3.1 Monovalent Atoms and Groups 17

2.3.2 Bivalent Atoms and Groups 17

2.3.3 Trivalent Atoms and Groups 18

2.3.4 Tetravalent Atoms 19

2.3.5 Ring Equivalents 19

2.4 Nonclassical Bioisosteres 20

2.4.1 Carbonyl Group 20

2.4.2 Carboxylic Acid 21

2.4.3 Hydroxyl Group 22

2.4.4 Catechol 22

2.4.5	Halogens	23
2.4.6	Amide and Esters	24
2.4.7	Thiourea	25
2.4.8	Pyridine	26
2.4.9	Cyclic Versus Noncyclic Systems	27
2.5	Summary	27
	References	27
3	Consequences of Bioisosteric Replacement	31
	<i>Dennis A. Smith and David S. Millan</i>	
3.1	Introduction	31
3.2	Bioisosteric Groupings to Improve Permeability	32
3.3	Bioisosteric Groupings to Lower Intrinsic Clearance	40
3.4	Bioisosteric Groupings to Improve Target Potency	43
3.5	Conclusions and Future Perspectives	47
	References	49
Part Two	Data	53
4	BIOSTER: A Database of Bioisosteres and Bioanalogues	55
	<i>István Ujváry and Julian Hayward</i>	
4.1	Introduction	55
4.2	Historical Overview and the Development of BIOSTER	56
4.2.1	Representation of Chemical Transformations for Reaction Databases	56
4.2.2	The Concept of “Biosteric Transformation”	57
4.2.3	Other Analogue and Bioisostere Databases	58
4.3	Description of BIOSTER Database	59
4.3.1	Coverage and Selection Criteria	59
4.3.2	Sources	59
4.3.3	Description of the Layout of Database Records	60
4.3.3.1	ID Code	60
4.3.3.2	Biosteric Transformation	60
4.3.3.3	Citation(s)	62
4.3.3.4	Activity	63
4.3.3.5	Fragments	63
4.3.3.6	Component Molecules and Fragments	64
4.4	Examples	64
4.4.1	Benzodioxole Bioisosteres	65
4.4.2	Phenol Bioisosteres	66
4.4.3	Ketoamides	66
4.5	Applications	69
4.6	Summary	70
4.7	Appendix	70
	References	71

5	Mining the Cambridge Structural Database for Bioisosteres	75
	<i>Colin R. Groom, Tjelvar S. G. Olsson, John W. Liebeschuetz, David A. Bardwell, Ian J. Bruno, and Frank H. Allen</i>	
5.1	Introduction	75
5.2	The Cambridge Structural Database	76
5.3	The Cambridge Structural Database System	78
5.3.1	ConQuest	78
5.3.2	Mercury	78
5.3.3	WebCSD	79
5.3.4	Knowledge-Based Libraries Derived from the CSD	80
5.4	The Relevance of the CSD to Drug Discovery	83
5.5	Assessing Bioisosteres: Conformational Aspects	84
5.6	Assessing Bioisosteres: Nonbonded Interactions	86
5.7	Finding Bioisosteres in the CSD: Scaffold Hopping and Fragment Linking	91
5.7.1	Scaffold Hopping	91
5.7.2	Fragment Linking	92
5.8	A Case Study: Bioisosterism of 1 <i>H</i> -Tetrazole and Carboxylic Acid Groups	94
5.8.1	Conformational Mimicry	94
5.8.2	Intermolecular Interactions	94
5.9	Conclusions	97
	References	98
 6	 Mining for Context-Sensitive Bioisosteric Replacements in Large Chemical Databases	 103
	<i>George Papadatos, Michael J. Bodkin, Valerie J. Gillet, and Peter Willett</i>	
6.1	Introduction	103
6.2	Definitions	104
6.3	Background	105
6.4	Materials and Methods	109
6.4.1	Human Microsomal Metabolic Stability	109
6.4.2	Data Preprocessing	109
6.4.3	Generation of Matched Molecular Pairs	110
6.4.4	Context Descriptors	111
6.4.4.1	Whole Molecule Descriptors	111
6.4.4.2	Local Environment Descriptors	112
6.4.5	Binning of ΔP Values	112
6.4.6	Charts and Statistics	112
6.5	Results and Discussion	113
6.5.1	General Considerations	123
6.6	Conclusions	124
	References	125

Part Three Methods 129**7 Physicochemical Properties 131***Peter Ertl*

- 7.1 Introduction 131
- 7.2 Methods to Identify Bioisosteric Analogues 132
- 7.3 Descriptors to Characterize Properties of Substituents and Spacers 132
- 7.4 Classical Methods for Navigation in the Substituent Space 135
- 7.5 Tools to Identify Bioisosteric Groups Based on Similarity in Their Properties 136
- 7.6 Conclusions 138
- References 138

8 Molecular Topology 141*Nathan Brown*

- 8.1 Introduction 141
- 8.2 Controlled Fuzziness 141
- 8.3 Graph Theory 142
- 8.4 Data Mining 144
 - 8.4.1 Graph Matching 144
 - 8.4.2 Fragmentation Methods 145
- 8.5 Topological Pharmacophores 146
- 8.6 Reduced Graphs 149
- 8.7 Summary 151
- References 152

9 Molecular Shape 155*Pedro J. Ballester and Nathan Brown*

- 9.1 Methods 156
 - 9.1.1 Superposition-Based Shape Similarity Methods 156
 - 9.1.2 Superposition-Free Shape Similarity Methods 158
 - 9.1.3 Choosing a Shape Similarity Technique for a Particular Project 160
- 9.2 Applications 161
- 9.3 Future Prospects 164
- References 165

10 Protein Structure 167*James E. J. Mills*

- 10.1 Introduction 167
- 10.2 Database of Ligand–Protein Complexes 168
 - 10.2.1 Extraction of Ligands 168
 - 10.2.2 Assessment of Ligand and Protein Criteria 169

10.2.3	Cavity Generation	170
10.2.4	Generation and Validation of SMILES String	170
10.2.5	Generation of FASTA Sequence Files	171
10.2.6	Identification of Intermolecular Interactions	172
10.3	Generation of Ideas for Bioisosteres	173
10.3.1	Substructure Search	173
10.3.2	Sequence Search	175
10.3.3	Binding Pocket Superposition	175
10.3.4	Bioisostere Identification	176
10.4	Context-Specific Bioisostere Generation	177
10.5	Using Structure to Understand Common Bioisosteric Replacements	178
10.6	Conclusions	180
	References	180

Part Four Applications 183

11	The Drug Guru Project	185
	<i>Kent D. Stewart, Jason Shanley, Karam B. Alsayyed Ahmed, and J. Phillip Bowen</i>	
11.1	Introduction	185
11.2	Implementation of Drug Guru	187
11.3	Bioisosteres	188
11.4	Application of Drug Guru	194
11.5	Quantitative Assessment of Drug Guru Transformations	195
11.6	Related Work	197
11.7	Summary: The Abbott Experience with the Drug Guru Project	197
	References	198
12	Bioisosteres of an NPY-Y5 Antagonist	199
	<i>Nicholas P. Barton and Benjamin R. Bellenie</i>	
12.1	Introduction	199
12.2	Background	199
12.3	Potential Bioisostere Approaches	201
12.4	Template Molecule Preparation	204
12.5	Database Molecule Preparation	206
12.6	Alignment and Scoring	206
12.7	Results and Monomer Selection	207
12.8	Synthesis and Screening	208
12.9	Discussion	209
12.10	SAR and Developability Optimization	211
12.11	Summary and Conclusion	214
	References	214

13	Perspectives from Medicinal Chemistry	217
	<i>Nicholas A. Meanwell, Marcus Gastreich, Matthias Rarey, Mike Devereux, Paul L.A. Popelier, Gisbert Schneider, and Peter Willett</i>	
13.1	Introduction	217
13.2	Pragmatic Bioisostere Replacement in Medicinal Chemistry: A Software Maker's Viewpoint	219
13.3	The Role of Quantum Chemistry in Bioisostere Prediction	221
13.4	Learn from "Naturally Drug-Like" Compounds	223
13.5	Bioisosterism at the University of Sheffield	224
	References	227
	Index	231