Contents

Chapter 1  Drugs and their Structural Motifs  1

       Alexander A. Alex and R. Ian Storer

1.1 Introduction  1

1.2 Launched Drugs  6
   1.2.1 Target Space of Launched Drugs  7
   1.2.2 Chemical Space of Launched Drugs  9
   1.2.3 Molecular Properties of Launched Drugs  10
   1.2.4 Polypharmacology  13

1.3 Drugs Bound to their Targets  15
   1.3.1 Comparison of Binding Sites of Drugs Bound in their Biological Targets  25
   1.3.2 Phosphodiesterase 5 (PDE5) Drugs  25
   1.3.3 Cyclooxygenase (Cox) Drugs  26
   1.3.4 Classes of Drugs with High Structural Similarity  28

1.4 Privileged Substructures in Drugs  28
   1.4.1 Examples of Privileged Substructures  30
   1.4.2 Benzodiazepines  30
   1.4.3 Arylsulfonamides and Drugs Derived from them  31
   1.4.4 Chemokine Receptor 5 (CCR5)  37
   1.4.5 Diaryl Heterocycles such as Cyclooxygenase Inhibitors (COX-2)  39
   1.4.6 Aminoheterocycles as Kinases Inhibitors  41
   1.4.7 HMG-CoA Reductase Inhibitors  44

1.5 Discussion of Privileged Substructures and Chemical Space  44
Chapter 2  ADMET for the Medicinal Chemist


2.1 Introduction
   2.1.1 Physicochemical Principles for ADME
   2.1.2 Physicochemistry Summary

2.2 Delivery of Drugs and Bioavailability
   2.2.1 Oral Delivery
   2.2.2 Intranasal Delivery
   2.2.3 Inhaled Delivery
   2.2.4 Sublingual Delivery
   2.2.5 Rectal Delivery
   2.2.6 Transdermal Delivery
   2.2.7 Subcutaneous and Intramuscular Administration

2.3 Tissue Distribution of Drugs
   2.3.1 Distribution to the Central Nervous System

2.4 Clearance, Extraction, Metabolism and Excretion
   2.4.1 Clearance
   2.4.2 Clearance by the Liver
   2.4.3 Metabolism
   2.4.4 Biliary Elimination
   2.4.5 Clearance by the Kidney
   2.4.6 Clearance Summary

2.5 Toxicology related to ADME

References

Chapter 3  Carboxylic Acids and their Bioisosteres

Amit S. Kalgutkar and J. Scott Daniels

3.1 Introduction

3.2 Carboxylic Acid Containing Non-steroidal Anti-inflammatory Drugs (NSAIDs)
   3.2.1 Discovery of Aspirin
   3.2.2 Mode of Inhibition of COX Activity by NSAIDs
   3.2.3 Molecular and Structural Basis for COX Inhibition by NSAIDs

3.3 Carboxylic Acid Containing β-Lactam Antibiotics
   3.3.1 Discovery of Penicillins
   3.3.2 Mechanism of Action of β-Lactam Antibiotics
3.4 Carboxylic Acid Containing Statins 110
3.4.1 Discovery of the Statins 111
3.4.2 Molecular and Structural Basis for Inhibition of HMG-CoA Reductase by Statins 113
3.5 Carboxylic Acid Containing Fibrates 113
3.6 From Terfenadine to Fexofenadine—an Interesting Case Study on the Utility of the Carboxylic Acid Moiety in Drug Discovery 115
3.7 Bioisosteres of the Carboxylic Acid Moiety 116
3.7.1 Non-classical Bioisosteres of the Hydroxyl Portion of the Carboxylic Acid Group 117
3.7.2 Non-classical Bioisosteres of the Entire COOH Moiety 119
3.8 Absorption, Distribution, Metabolism and Excretion (ADME) Profile of Carboxylic Acids 122
3.8.1 Oral Absorption 122
3.8.2 Distribution and Clearance 125
3.8.3 Metabolism of the Carboxylic Acid Moiety 126
3.8.4 P450 Isozymes Involved in the Oxidative Metabolism of Carboxylic Acid Derivatives 140
3.8.5 Hepatobiliary Disposition of Carboxylic Acids 141
3.9 ADME Profile of Tetrazoles 143
3.9.1 Metabolism of the Tetrazole Motif 145
3.9.2 Role of Transporters in the Disposition of Tetrazole-based Angiotensin II Receptor Antagonists 146
3.10 ADME Profile of Thiazolidinedione Derivatives 146
3.10.1 Clearance and Oral Bioavailability 147
3.10.2 Metabolism of the Thiazolidinedione Ring System 147
3.10.3 P450 isozymes Responsible for the Metabolism of ‘glitazones’—DDI Potential 148
3.11 ADME Profile of Esters and Amides 149
3.12 Boronic Acid Derivatives 150
3.13 Concluding Remarks: Carboxylic Acid and Drug Safety 151
References 154

Chapter 4 Primary, Secondary and Tertiary Amines and their Isosteres 168
D. K. Walker, R. M. Jones, A. N. R. Nedderman and P. A. Wright

4.1 Introduction 168
4.1.1 Amines that Interact with Aminergic Receptors 169
4.1.2 Amines that Interact with Acetylcholine 170
4.1.3 Amines that Interact with Opioid Receptors 170
4.1.4 Amines that Interact with Ion Channels 171
4.1.5 Amine Antimalarial Drugs 171
4.1.6 Miscellaneous Amine Drugs 172
4.1.7 Amine Isosteres 172

4.2 Physicochemical Properties of Amines 173
4.2.1 Polarity of Amines 173
4.2.2 Basicity of Amines 174

4.3 Absorption Properties of Amine Containing Drugs 176
4.3.1 Solubility and Absorption 176
4.3.2 Membrane Permeability and Absorption 177
4.3.3 Impact of P-glycoprotein on Absorption 180

4.4 Systemic Behaviour of Amine Containing Drugs 181
4.4.1 Tissue Affinity and its Impact on Distribution 181
4.4.2 Distribution and Duration 181
4.4.3 Additional Specific Interactions Enhancing Tissue Affinity 183
4.4.4 Distribution Dependent on pH 183
4.4.5 Plasma Protein Binding 184
4.4.6 Brain Distribution 185

4.5 Clearance of Amine Containing Drugs 185
4.5.1 Metabolic Clearance 185
4.5.2 Phase 1 Metabolism 186
4.5.3 Phase 2 Metabolism 192
4.5.4 Non-metabolic Clearance 195
4.5.5 Renal Clearance 195
4.5.6 Biliary Clearance 195

4.6 Amines as Toxicophores and Toxicity of Amine Containing Drugs 196

4.7 Zwitterions 199

4.8 Prodrugs of Amines to Change Physicochemical Properties 200
4.8.1 Prodrugs to Enhance Absorption 201
4.8.2 Prodrugs to Achieve Tissue Specificity 202
4.8.3 Prodrugs Utilising Amine Functionality 203

References 204

Chapter 5  Sulfonamide as an Essential Functional Group in Drug Design 210
Amit S. Kalgutkar Rhys Jones and Aarti Sawant

5.1 Introduction 210
5.1.1 Sulfanilamide Antibacterial Agents 212
Chapter 7 Influence of Heteroaromatic Rings on ADME Properties of Drugs
Deepak Dalvie, Ping Kang, Cho-Ming Loi, Lance Goulet and Sajiv Nair

7.1 Introduction 328
7.2 Types of Heteroaromatic Rings and their Physicochemical Properties 333
7.3 Influence of Heteroaromatic Rings on ADME Properties of Compounds 338
   7.3.1 Absorption 339
   7.3.2 Distribution 344
   7.3.3 Metabolism 348
   7.3.4 Excretion 354
7.4 Influence of Heteroaromatic rings on Toxicity of Compounds 357
7.5 Summary 364
References 365

Chapter 8 Peptidomimetics and Peptides as Drugs: Motifs Incorporated to Enhance Drug Characteristics
Tracey Boyden, Mark Niosi and Alfin Vaz

8.1 Introduction 370
8.2 Peptidomimetics for Aspartic Acid Proteases 371
8.3 Anticancer Peptidomimetics 379
   8.3.1 Summary 381
8.4 Peptide Drugs 382
   8.4.1 Insulin and Insulin Analogs 382
   8.4.2 Incetin Hormones 385
References 387

Chapter 9 Pharmacokinetics and Metabolism of Compounds that Mimic Enzyme Transition States
Iain Gardner, Chris Barber, Martin Howard, Aarti Sawant and Kenny Watson

9.1 Enzyme Transition States 390
9.2 Physicochemical Properties of Transition State Analogaes 393
9.3 ADME Properties of Transition State Analogue Inhibitors against Different Enzyme Targets 396
   9.3.1 Proteases 396
   9.3.2 Neuraminidase TSAI 427
   9.3.3 N-Ribosyltransferase TSAI 432

Contents
9.3.4 Nucleoside Deaminase TSAI 435
9.3.5 Inosine 5-monophosphate Dehydrogenase TSAI 440
9.3.6 Aspartate Carbamyl Transferase TSAI 441
9.3.7 Glycosidase Inhibitor TSAI 442

9.4 Conclusions 443
9.5 Abbreviations 444
References 445

Chapter 10 Alcohols and Phenols: Absorption, Distribution, Metabolism and Excretion 460

Zhuang Miao and R. Scott Obach

10.1 Physicochemical Properties of Alcohols and Phenols and their Prevalence in Drugs 460
10.2 Comparative Pharmacokinetics of Alcohols, Phenols and their Counterparts Lacking the Hydroxy Group 462
10.3 Biochemical Determinants of ADME Characteristics of Drugs Possessing Hydroxyl Groups 464
10.3.1 Plasma Protein Binding and Tissue Distribution 466
10.3.2 Interactions of Hydroxyl Group Containing Drugs with Drug Transporters and Impact on Absorption, Distribution and Excretion 467
10.3.3 Metabolism and Interaction with Drug-metabolising Enzymes 468
10.3.4 Fluorine as an Isostere of Hydroxy Groups 480

10.4 Conclusions 482
References 482

Chapter 11 Future Targets and Chemistry and ADME Needs 486

Dennis A. Smith and David S. Millan

11.1 The Human Genome 486
11.2 Drug Targets within the Genome 487
11.3 The Genome Gap 488
11.3.1 New Mechanisms and the Druggable Genome 490
11.4 The Need for New ADME tools 491
11.5 The Chemistry Gap 493
11.6 The Knowledge Gap in Drug Design 498
<table>
<thead>
<tr>
<th>11.7</th>
<th>Permeability of Membranes: A Pivotal Role in Drug Disposition</th>
<th>498</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.8</td>
<td>Future CNS Targets and ADME Space</td>
<td>503</td>
</tr>
<tr>
<td>11.9</td>
<td>Penetration into the Cell—Intracellular Drug Targets</td>
<td>506</td>
</tr>
<tr>
<td>11.10</td>
<td>Permeability and Large Molecules</td>
<td>507</td>
</tr>
<tr>
<td>11.11</td>
<td>Conclusion: Beyond PSA and ADME Space</td>
<td>508</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>509</td>
</tr>
</tbody>
</table>

**Subject Index**

512
Metabolism, Pharmacokinetics and Toxicity of Functional Groups
Impact of Chemical Building Blocks on ADMET
Smith, D.A. (Ed.)
2010, 530p., Hardcover
A product of Royal Society of Chemistry