
Introduction to Medicinal Chemistry

How Drugs Act and Why

Alex Gringauz



WILEY-VCH

New York • Chichester • Weinheim • Brisbane • Singapore • Toronto

Contents

Chapter 1. Basic Considerations of Drug Activity	1
1.1 Introduction	1
1.2 Factors Affecting Bioactivity	1
1.3 Theories of Drug Activity	21
1.4 Quantitative Aspects of Drug Action: An Overview	26
1.5 Receptor Concept of Drug Action Mechanisms	32
1.6 Receptor Characterization	40
References	48
Suggested Readings	48
Chapter 2. Mechanisms of Drug Action	49
2.1 Introduction	49
2.2 Enzyme Stimulation	50
2.3 Enzyme Inhibition	51
2.4 Sulfonamides	61
2.5 Membrane-Active Drugs	67
References	76
Suggested Readings	76
Chapter 3. Drug Metabolism and Inactivation	77
3.1 Introduction	77
3.2 Biotransformations	79
3.3 Metabolic Reactions	80
3.4 Conjugation Reactions	87

Chapter 4. Anticancer Drugs and Their Mechanism of Action 93

4.1	Introduction	93
4.2	Chemical Carcinogenesis	94
4.3	Cancer and Genetics	96
4.4	Cancer and Nutrition	96
4.5	Radiation	97
4.6	Viruses and Cancer	97
4.7	Cancer Chemotherapy—Special Problems	98
4.8	Drug Resistance	102
4.9	Drug Discovery Strategies	102
4.10	The Cell Cycle	103
4.11	Alkylating Agents	104
4.12	Antimetabolites	115
4.13	Carcinolytic Antibiotics	125
4.14	Mitotic Inhibitors	130
4.15	Hormonal Agents	132
4.16	Miscellaneous Carcinolytics	136
4.17	Development of New Modalities	137
	References	138
	Suggested Readings	139

Chapter 5. Analgetics and Nonsteroidal Antiinflammatory Agents 141

5.1	Introduction	141
5.2	Classification of Pain	141
5.3	Classification of Analgetics	142
5.4	Mild Analgetics	143
5.5	Prostaglandins	150
5.6	The Nonsteroidal Antiinflammatory Drugs	161
5.7	Nontraditional Antirheumatoid Drugs	165
5.8	Opium—and the Strong Analgetics Emanating from It	168
5.9	Narcotic Antagonists	175
5.10	Agonist/Antagonist Analgetics	176
5.11	The Opiate Receptor	180
5.12	Endogenous Opiate Receptor Ligands	185
5.13	Multiple Opiate Receptors	187
	References	189
	Suggested Readings	189

Chapter 6. Antimicrobial Drugs I 191

6.1	The Antibiotics	191
6.2	Cell Wall Synthesis Inhibitors	191
6.3	Cell Wall Biosynthesis	194

6.4	The β -Lactam Ring—The Enchanting Structure	201
6.5	Antipseudomonal Penicillins	211
6.6	Penicillin-Binding Proteins	213
6.7	Other Bicyclic β -Lactams	226
6.8	Monobactams	228
6.9	β -Lactamase Enzymes	231
6.10	β -Lactamase Inhibitors	233
6.11	Antibiotics Inhibiting Protein Synthesis	236
	References	262
	Suggested Readings	263

Chapter 7. Antimicrobial Drugs II 265

7.1	The 4-Quinolones	265
7.2	Nonbenzenoid Nitro Compounds	271
7.3	Parasitic Diseases	275
7.4	Chemotherapy of Malaria	278
7.5	Other Antiprotozoal Drugs	290
7.6	Antifungal Drugs	295
7.7	Anthelmintics	305
7.8	Antiviral Chemotherapy	317
	References	328
	Suggested Readings	329

Chapter 8. Drugs Affecting Cholinergic Mechanisms 331

8.1	Introduction	331
8.2	Aspects of the Cholinergic System	337
8.3	Cholinergic Drugs	349
8.4	Anticholinesterase Agents	352
8.5	Antidotes for AChE Inhibitors	357
8.6	Memory and Alzheimer's Disease	359
8.7	Cholinergic Blocking Agents	360
8.8	Neuromuscular Blocking Agents— Nicotinic Antagonists	374
	References	381
	Suggested Readings	382

Chapter 9. Drugs Affecting Adrenergic Mechanisms 383

9.1	Adrenergic Concepts and Synthesis	383
9.2	Catabolism	389
9.3	Catecholaminergic Receptors	393
9.4	Indirect Sympathomimetics	408
9.5	The α -Receptors	413
	References	415
	Suggested Readings	416

Chapter 10. Drugs and the Cardiovascular Diseases 417

10.1	Introduction	417
10.2	Cardiovascular Diseases	417
10.3	Drugs	422
	References	498
	Suggested Readings	498

Chapter 11. Drugs and the Cardiovascular Diseases II 501

11.1	Clotting Prevention and Lysis	501
11.2	Antithrombotics	507
11.3	Cyclooxygenase Inhibitors	508
11.4	Prostacyclins	512
11.5	Thrombolytics	515
11.6	Plasminogen Activators	517
11.7	Hypolipidemic–Hypocholesterolemic Drugs	519
11.8	Drugs and Diabetes	528
11.9	Sickle Cell Disease or Anemia	537
11.10	Thyroid Functions and Drugs Affecting Them	539
	References	542
	Suggested Readings	543

Chapter 12. Psychoactive Drugs—Chemotherapy of the Mind 545

12.1	Historical Overview	546
12.2	Neurotransmitters	550
12.3	CNS Depressants	564
12.4	Buspirone—Is Anxioreselectivity Possible?	588
12.5	Antiepileptic Drugs	589
12.6	Neurochemistry of Mental Disease	593
12.7	Antipsychotic Drugs—The Neuroleptics	599
12.8	The Butyrophenones—Serendipity and Drug Development	603
12.9	Antidepressants	608
12.10	Stereochemical Aspects of Psychotropic Drugs	615
	References	618
	Suggested Readings	619

Chapter 13. Histamine Antagonists and Local Anesthetics 621

13.1	Histamine Antagonists	621
13.2	Inhibition of Mediator Release	629
13.3	Peptic Ulcer Disease	630
13.4	Proton Pump Inhibitors (H ⁺ –K ⁺ -ATPase)	638
13.5	Prostaglandins	639

13.6	Local Anesthetics	643
13.7	Mechanism of Action	651
	References	652
	Suggested Readings	653

Chapter 14. Steroids 655

14.1	Introduction	655
14.2	The Steroid Hormones of the Adrenal Cortex	657
14.3	Mechanism of Action	670
14.4	The Sex Hormones	671
14.5	Progesterone, Progestins, and Their Receptors	674
14.6	Oral Contraceptives (OC)	676
14.7	Androgens	676
14.8	Antiandrogens	680
	References	680
	Suggested Readings	681

Chapter 15. New Developments and New Problems 683

15.1	Introduction	683
15.2	Gene Therapy	684
15.3	Drug Resistance	686
15.4	Antisense Drugs	688
15.5	Cytokines	690
15.6	Computers as Drug Design Aids	693
	References	695
	Suggested Readings	697

Index 699