

Contents

Chapter 1	Introduction	1
1.1	Aims	1
1.2	The Classification of Drugs	1
1.3	Targets for the Medicinal Chemist	2
1.3.1	Hormones as Targets	2
1.3.2	Cellular Structures as Targets	4
1.4	The Stages in the Development of a Drug	5
1.5	The Synthesis of a Drug	6
1.6	The History of Medicinal Chemistry	8
Chapter 2	General Principles of Medicinal Chemistry	20
2.1	Aims	20
2.2	Administration and Absorption	20
2.3	The Gastrointestinal Tract	21
2.4	Other Routes of Administration	23
2.5	Physico-Chemical Measurements	23
2.6	Formulation	24
2.7	Drug Metabolism	25
2.8	Oxidation by Cytochrome P ₄₅₀ s	26
2.9	The Hydroxylation of Aromatic Rings	27
2.10	The Hydroxylation of Aliphatic Systems	29
2.11	The Monoamine Oxidases	30
2.12	Other Phase One Changes	31
2.13	Phase Two Changes	32
2.14	Excretion	33
2.15	Pro-Drugs	33
2.16	Quantitative Structure: Activity Relationships	35
2.17	Hansch QSAR Analyses	36
2.18	Craig Plots and the Topliss Decision Tree	38
2.19	Drug: Receptor Interactions	39
Chapter 3	Neurotransmitters as Targets	41
3.1	Aims	41
3.2	Introduction	41
3.3	The Nervous System	42

3.4	The Neurotransmitters	44
3.5	Cell-Surface Receptors	45
3.6	Ion-Channel-Linked Receptors	45
3.7	Kinase-Linked Receptors	45
3.8	G-Protein-Linked Receptors	46
3.9	Agonists and Antagonists	48
3.10	Acetylcholine	48
3.11	Neuromuscular Blocking Agents in Surgery	49
3.12	Muscarinic Agonists	51
3.13	Local Anaesthetics	52
3.14	Catecholamines as Neurotransmitters	53
3.15	The Adrenergic Receptors	55
3.16	α -Adrenergic Receptor Agonists	55
3.17	β -Adrenergic Receptor Agonists - The Development of Anti-Asthma Drugs	56
3.18	β_1 -Adrenergic Antagonists ‘ β -Blockers’	59
3.19	The Treatment of Hypertension	61
Chapter 4	Medicinal Chemistry and the Central Nervous System	64
4.1	Aims	64
4.2	Introduction	64
4.3	The Treatment of Neurodegenerative Diseases	66
4.3.1	Alzheimer’s Disease	66
4.3.2	Parkinson’s Disease	67
4.4	Dopamine Antagonists as Neuroleptic Agents	70
4.5	Serotonin as a Neurotransmitter	72
4.6	The Treatment of Depression	73
4.7	GABA as a Neurotransmitter	76
4.8	The Treatment of Epilepsy	77
4.9	Benzodiazepines as Anxiolytic Agents	78
4.10	Barbiturate Sleeping Tablets	80
4.11	Opioids as Analgesics	81
Chapter 5	Local and Circulatory Hormone Targets	85
5.1	Aims	85
5.2	Introduction	85
5.3	Histamine as a Target	86
5.4	Histamine Antagonists in the Treatment of Peptic Ulcers	87
5.5	The Prostaglandins and Non-Steroidal Anti-Inflammatory Agents	90
5.6	The Development of Ibuprofen	92

5.7	The Mechanism of Action of Aspirin	94
5.8	Medicinal Uses of Prostaglandins	95
5.9	The Sterols and Steroid Hormones	96
5.10	The Biosynthesis of the Steroids	98
5.11	The Control of Cholesterol Biosynthesis	100
5.12	The Steroidal Anti-Inflammatory Agents	101
5.13	The Steroidal Oral Contraceptives	103
5.14	The Role of Nitric Oxide	104
Chapter 6	Anti-infective Agents	105
6.1	Aims	105
6.2	Introduction	105
6.3	Bacterial Diseases	106
6.4	Antiseptics	107
6.5	The Sulfonamide Anti-Bacterial Agents	108
6.6	The Penicillins	111
6.6.1	Semi-Synthetic Penicillins	114
6.7	Clavulanic Acid and the Inhibition of β -Lactamases	114
6.8	The Cephalosporins	115
6.9	The Mode of Action of the β -Lactam Antibiotics	115
6.10	Other Antibiotics	117
6.11	Synthetic Anti-Bacterial Agents	118
6.12	Anti-Viral Agents	118
6.12.1	Viral Diseases	118
6.12.2	Viral Structure and Replication	119
6.12.3	Targets for Anti-Viral Agents	120
6.13	The Inhibition of Nucleic Acid Biosynthesis	120
6.14	Inhibitors of Reverse Transcriptase	121
6.15	Neuraminidase Inhibitors	122
6.16	The Synthesis of Nucleoside Analogues	122
6.17	Anti-Fungal Agents	124
6.18	Ergosterol Biosynthesis Inhibitors	124
6.19	Other Anti-Fungal Agents	126
6.20	Parasitic Infections	126
6.20.1	The Treatment of Malaria	126
Chapter 7	Cancer Chemotherapy	129
7.1	Aims	129
7.2	Introduction	129
7.3	The Cell Cycle	129
7.4	Cancer Chemotherapy	131
7.5	Anti-Metabolites	131

7.6	Alkylating Agents	134
7.7	Intercalating Agents	137
7.8	Anti-Mitotic Agents	138
7.9	Interference with Selected Developmental Processes	138
	7.9.1 The Treatment of Breast Cancer	138
7.10	Monoclonal Antibodies	140
7.11	Prostate Cancer	141
	Further Reading	142
	Glossary	144
	Subject Index	151