

CONTENTS

Preface to the Fourth Edition	(vii)
Preface to the First Edition	(ix)

CHAPTER 1: Drug Design—A Rational Approach	1
---	----------

1. Introduction	2
2. Analogues and Prodrugs	3
3. Concept of Lead	3
3.1. Examples	3
4. Factors Governing Drug-Design	6
5. Rational Approach to Drug-Design	6
5.1. Quantum Mechanical Approach	7
5.2. Molecular Orbital Approach	7
5.3. Molecular Connectivity Approach	7
5.4. Linear Free Energy Approaches	7
6. Drug-Design : The Method of Variation	7
6.1. Drug Design Through Disjunction	8
6.2. Drug Design Through Conjunction	10
7. Drug Design and Development: An Overview	11
7.1. Preamble	11
7.2. Revolutions in Drug Discovery	13
7.3. Research and Development Strategies	14
8. Molecular Hybridization	14
9. Rigidity and Flexibility Vs Drug Design	16
9.1. Increased Rigidity	16
9.2. Increased Flexibility	18
10. Tailoring of Drugs	18
11. General Considerations	18

CHAPTER 2: Physical-Chemical Factors and Biological Activities	21
---	-----------

1. Introduction	22
2. Physical Properties	23
2.1. Features Governing Drug Action in Active Site	23
2.2. Structurally Specific Drugs	23
2.3. Structurally Non-Specific Drugs	24

2.4. Thermodynamic Activity	24
2.5. Meyer-Overton and Meyer-Hemmi Theory	24
2.6. Ferguson's Theory	25
2.7. Van der Waal's Constants	25
2.8. The Cut-off Point	26
2.9. Steric Factors	27
2.9.1. Taft's Steric Factor (Es)	28
2.9.2. Molar Refractivity (MR)	31
2.9.3. Verloop Steric Parameter	32
2.10. Hansch Equation	33
2.11. The Craig Plot	35
2.12. The Topliss Scheme	36
3. Factors Governing Ability of Drugs to Reach Active Site	40
3.1. Absorption	40
3.2. Distribution	41
3.3. Metabolism (Biotransformation)	41
3.4. Excretion	42
3.5. Intramolecular Distances and Biological Activity	42
4. Dissociation Constants	43
4.1 Drug Exerting Action as Undissociated Molecules	43
4.2. Drugs Exerting Action as Ionized Molecules	44
5. Isosterism and Bio-Isosterism	44
5.1. Classical Bioisosteres	46
5.2. Nonclassical Bioisosteres	48
6. Stereochemistry and Drug Action	50
6.1. Enantiomers	50
6.2. Diastereoisomers	51
6.3. Stereochemistry and Biologic Activity	53
6.3.1. Positional Isomers (or Constitutional Isomers)	54
6.3.2. Geometrical Isomers	54
6.3.3. Absolute Configuration	55
6.3.4. Easson-Stedman Theory	55
6.3.5. Conformationally Flexible to Conformationally Rigid Molecule	55
7. Chemical Properties	56
7.1. Molecule Negentropy	56
7.2. Cammarata Correlation	56

1. Introduction	60
2. Methodologies : Molecular Modeling	61
2.1. Molecular Mechanics	61
2.2. Quantum Mechanics (or Quantum Mechanical Methods)	63
2.2.1. Charge and Electrostatics	63
2.2.2. Parameterization of Force Fields	65
2.2.3. Chemical Reaction(s) Modeling and Design of Transition State Inhibitors	65
3. Known Receptor Sites	66
3.1. 3D Structure of Macromolecular Targets	66
3.2. Structure-Based Drug-Design	66
3.3. Major Steps in Structure-Based Drug Design	67
3.4. Ligand Receptor Recognition	68
3.5. Active Site for a Target Molecule	69
3.6. Meaning of Site	71
3.7. Characterization of Site	72
3.7.1. Hydrogen Bonding and Other Group Binding Sites	72
3.7.2. Electrostatic and Hydrophobic Fields	73
3.8. Design of Ligands	73
3.8.1. Visually Assisted Design	73
3.8.2. 3D Databases	74
3.8.3. ‘Divide and Rule’ Concept in Design of Ligands	75
3.8.4. <i>De Novo</i> Design	80
3.9. Calculation of Affinity	80
3.9.1. Components of Bonding Affinity	81
3.9.2. Binding Energetics and Comparisons	82
3.9.3. Simulations and the Thermodynamic Cycle	82
3.9.4. Multiple Binding Modes	83
4. Unknown Receptor Sites	84
4.1. Pharmacophore <i>Vs</i> Binding-site Models	85
4.1.1. Pharmacophore Models	85
4.1.2. Binding-Site Models	85
4.1.3. Molecular Extensions	86
4.1.4. Activity <i>Vs</i> Affinity	87
4.2. Searching for Similarity	88
4.2.1. Simple Comparisons	88
4.2.2. Visualization of Molecular Properties	88
4.3. Molecular Comparisons	89

5. Predictive ADME	90
6. Reverse Designing	92
6.1. High Throughput Screening	92
6.2. Combinatorial Chemistry	92
7. CADD-Methods : Comparison for Determining Relative Binding Affinities of COX-2 Inhibitors	95

CHAPTER 4: General Anaesthetics	105
--	------------

1. Introduction	106
2. Classification	106
2.1. Inhalation Anaesthetics	106
2.2. Intravenous Anaesthetics	111
2.3. Basal Anaesthetics	116
3. Mode of Action of General Anaesthetics	118
3.1. Lipid Theory	118
3.2. Physical Theory	119
3.3. Biochemical Theory	119
3.4. Miscellaneous Theory	119
3.5. Meyer-Overton Theory	119
3.6. Minimum Alveolar Concentration (MAC)	119
3.7. Stereochemical Effects	120
3.8. Ion Channel and Protein Receptor Hypotheses	121
4. Mechanism of Action General Anaesthetics	121

CHAPTER 5: Local Anaesthetics	127
--------------------------------------	------------

1. Introduction	128
2. Classification	131
2.1. The Esters	131
2.2. Piperidine or Tropane Derivatives	140
2.3. The Amides	143
2.4. The Quinoline and Iso-Quinoline Analogues	149
2.5. Miscellaneous Type	152
3. Chemical Considerations of Local Anaesthetic Drug Substances	155
3.1. Löfgren's Classification	155
3.1.1. Lipophilic Entity	156
3.1.2. Intermediate Chain	160
3.1.3. Hydrophilic Entity	160

4. Benzoic Acid and Aniline Analogues with Potential Local Anaesthetic Profile	161
5. Mode of Action of Some Selected Local Anaesthetics	164

CHAPTER 6: Sedatives and Hypnotics	169
---	------------

1. Introduction	170
2. Classification	171
2.1. Barbiturates	171
2.2. Non barbiturates	190
3. Mode of Action of Barbiturates	194
4. Mechanism of Action	194
5. Barbiturates Vs Benzodiazepines	195
6. Structure-Activity Relationship	195
7. Barbiturates Vs Dissociation Constant (pKa)	196
8. Substitutions on Hetero Atoms in Barbiturates	197
9. OH ⁻ Catalyzed Degradation of Barbiturates	197
10. Specific Mechanism of Action of Some Sedatives and Hypnotics	198

CHAPTER 7: Anticonvulsants	203
-----------------------------------	------------

1. Introduction	204
2. Classification	205
2.1. Barbiturates	205
2.2. Hydantoin Derivatives	206
2.3. Oxazolidinediones	209
2.4. Succinimides	210
2.5. Miscellaneous	214
3. Chemotherapy of Epilepsy	216
4. Mechanisms of Action for the Anticonvulsants	218
5. Specific Mechanisms of Selected Anticonvulsants	220

CHAPTER 8: Muscle Relaxants	225
------------------------------------	------------

1. Introduction	226
2. Classification	226
2.1. Neuromuscular Blocking Drugs	226
2.2. Centrally Acting Muscle Relaxants	235
3. General Mechanism of Action of Muscle Relaxants	244
4. Mode of Action of Some Specific Muscle Relaxants	247

CHAPTER 9: Central Nervous System Stimulants	253
1. Introduction	254
2. Classification	255
2.1. Xanthine Derivatives	256
2.2. Analeptics	260
2.3. Miscellaneous Central Nervous System Stimulants	264
3. CNS-Peptides, S-Glutamate and Blockade of NMDA Induced Responses	267
3.1. CNS-Peptides	267
3.2. S-Glutamate and Blockade of NMDA-Induced Responses	268
4. Mechanism of Action of Selected CNS-Stimulants	269
CHAPTER 10: Antipyretic Analgesics	273
1. Introduction	274
2. Classification	275
2.1. Aniline and <i>p</i> -Aminophenol Analogues	275
2.2. Salicylic Acid Analogues	279
2.3. Quinoline Derivatives	285
2.4. Pyrazolones and Pyrazolidiones	287
2.5. The N-Arylanthranilic Acids	294
3. Mechanism of Action	296
4. Mechanism of Action of Selected Antipyretic-Analgesics	297
CHAPTER 11: Narcotic Analgesics (Opiate Analgesics)	303
1. Introduction	304
2. Limitations of Opiate Analgesics	305
3. Characteristics Features of Opioids	306
3.1. Opioid Peptides	306
3.2. Opioid Receptors	307
3.3. Orphan Opioid Receptors	307
3.4. Mu Opioid Receptors	307
3.5. Kappa Opioid Receptors	308
3.6. Delta Opioid Receptors	310
3.7. Opioid Receptors: Identification and Activation	311
4. Classification	312
4.1. Morphine Analogues	312
4.2. Morphinan Analogues	317
4.3. Morphan Analogues	320

4.4. 4-Phenylpiperidine Analogues	322
4.5. Phenylpropylamine Analogues	327
4.6. Miscellaneous Analogues	330
5. Narcotic Antagonists	332
6. Morphine: Structural Representations	334
7. Mechanism of Action of Certain Narcotic Analgesics	336

CHAPTER 12: Cardiovascular Drugs	343
---	------------

1. Introduction	344
2. Classification	345
3. Cardiac Glycosides	345
3.1. Designing the Cardiac Glycoside Receptor	345
3.2. Mechanism of Action	348
4. Antihypertensive and Hypotensive Drugs	348
4.1. Renin-Angiotensin Pathway	349
4.2. Angiotensin II Receptor Antagonists	349
4.3. Potential Dependent Calcium Channels	350
4.4. Mechanism of Action of Selected Antihypertensive and Hypotensive Drugs	354
5. Antiarrhythmic Agents	355
5.1. Membrane-Stabilizing Agents	358
5.1.1. Mechanism of Action of Membrane Stabilizing Agents	362
5.2. Antisynthetic Drugs	363
5.2.1. Mechanism of Action	364
5.3. Prolonging Cardiac Action	364
5.3.1. Mechanism of Action	366
5.4. Interference with Calcium Conductance	366
5.4.1. Mechanism of Action	367
6. Vasopressor Drugs	367
6.1. Mechanism of Action	370

CHAPTER 13: Autonomic Drugs	373
------------------------------------	------------

1. Introduction	374
2. Classification	375
3. Sympathomimetic Drugs	375
3.1. Mechanism of Action	384
3.2. Structure Activity Relationships (SARs)	385

4. Beta Adrenergic Receptor Stimulants	386
4.1. Mechanism of Action	387
5. Adrenergic Receptor Blocking Agents	388
5.1. α -Adrenergic Blocking Agents	388
5.1.1. Mechanism of Action	391
5.2. β -Adrenoreceptor Blocking Agents	391
5.2.1. First Generation β -Blockers	392
5.2.2. Second Generation β -Blockers (Selective β_1 -Blockers)	396
5.2.3. Third Generation β -Blockers	397
5.3. Alpha- and Beta-Adrenergic Receptor Blocking Agent	399
6. Cholinomimetic (Parasympathomimetic) Drugs	399
6.1. Directly Acting	399
6.2. Indirectly Acting (Anticholinesterase) Drugs	403
6.2.1. Mechanism of Action	407
7. Antimuscarinic (Anticholinergic) Agents	408
7.1. Aminoalcohol Esters	409
7.2. Aminoalcohol Ethers	416
7.3. Aminoalcohol Carbamates	416
7.4. Aminoalcohols	417
7.5. Aminoamides	417
7.6. Diamines	420
7.7. Miscellaneous Amines	420
7.8. Mechanism of Action	423
8. Ganglionic Blocking Agents	426
8.1. Mechanism of Action	430
9. Adrenergic Neurone Blocking Agents	431
9.1. Mechanism of Action	433

CHAPTER 14: Diuretics	437
------------------------------	------------

1. Introduction	438
2. Classification	438
2.1. Mercurial Diuretics	439
2.2. Non-Mercurial Diuretics	444
2.2.1. Thiazides (Benzothiazines)	444
2.2.2. Carbonic Anhydrase Inhibitors	456
2.2.3. Miscellaneous Sulphonamide Diuretics	462

2.2.4. ‘Loop’ and ‘High-Ceiling’ Diuretics	467
2.2.5. Aldosterone Inhibitors	471
2.2.6. Purine or Xanthine Diuretics	473
2.2.7. Pyrimidine Diuretics	474
2.2.8. Osmotic Diuretics	475
2.2.9. Acidotic Diuretics	477
2.2.10. Miscellaneous Diuretics	478

CHAPTER 15: Antihistamines	483
-----------------------------------	------------

1. Introduction	484
2. Classification	485
2.1. Histamine H ₁ -Receptor Antagonists	485
2.1.1. Aminoalkylethers	486
2.1.2. Ethylenediamines	490
2.1.3. Thiophene Derivatives	494
2.1.4. Cyclic Basic Chain Analogues	497
2.1.5. Phenothiazine Derivatives	501
2.1.6. Second Generation Nonsedating Antihistamines	505
2.1.7. Miscellaneous Agents	510
2.2. Prevention of Histamine Release	515
2.2.1. Mechanism of Action	516
2.3. Histamine (H ₂) Receptor Blockers	516
2.3.1. Mechanism of Action	517

CHAPTER 16: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	521
---	------------

1. Introduction	522
2. Classification	523
2.1. Heteroarylacetic Acid Analogues	523
2.1.1. Mechanism of Action	526
2.2. Arylpropionic Acid Analogues	527
2.2.1. Mechanism of Action	529
2.3. Arylpropionic Acid Analogues	530
2.3.1. Mechanism of Action	532
2.4. Naphthalene Acetic Acid Analogues	533
2.4.1. Mechanism of Action	534
2.5. Gold Compounds	534
2.5.1. Mechanism of Action	537

2.6. Miscellaneous Anti-Inflammatory Drugs	538
2.6.1. Antimalarial Agents	538
2.6.2. Uricosuric Agents	538
2.7. Salicylic Acid Analogues	542
2.8. Pyrazolones and Pyrazolodiones	542

CHAPTER 17: Antiparkinsonism Agents	545
--	------------

1. Introduction	546
1.1. Etiology	546
1.2. Parkinsonism Produced by MPTP	548
2. Classification	549
2.1. Piperidine Analogues	549
2.1.1. Mechanism of Action	552
2.2. Pyrrolidine Analogue	553
2.2.1. Mechanism of Action	554
2.3. Phenothiazine Analogue	554
2.3.1. Mechanism of Action	555
2.4. Miscellaneous Drugs	556
2.4.1. Mechanism of Action	560

CHAPTER 18: Expectorants and Antitussives	565
--	------------

1. Introduction	566
2. Classification	568
2.1. Sedative Expectorants	568
2.2. Stimulant (Irritant) Expectorants	571
2.3. Centrally Acting Antitussive Agents	573

CHAPTER 19: Sulphonamides	581
----------------------------------	------------

1. Introduction	582
2. Classification	584
2.1. Sulphonamides for General Infections	584
2.1.1. Mechanism of Action	592
2.2. Sulphonamides for Urinary Infections	595
2.2.1. Mechanism of Action	598
2.3. Sulphonamides for Intestinal Infections	598
2.3.1. Mechanism of Action	602
2.4. Sulphonamide for Local Infection	603
2.4.1. Mechanism of Action	604

2.5. Sulphonamide Related Compounds	604
2.5.1. Mechanism of Action	606
3. Ionizaton of Sulphonamides	607
4. Sulphonamide Inhibition and Probable Mechanisms of Bacterial Resistance to Sulphonamides	607
5. Chemotherapeutic Consideration	608

CHAPTER 20: Antimalarials	611
----------------------------------	------------

1. Introduction	612
2. Classification	614
2.1. 4-Aminoquinoline Analogues	614
2.1.1. Mechanism of Action	621
2.2. 8-Aminoquinoline Analogues	623
2.2.1. Mechanism of Action	631
2.3. 9-Aminoacridines	632
2.3.1. Mechanism of Action	636
2.4. Guanidine Analogues (Biguanides)	637
2.4.1. Mechanism of Action	640
2.5. Pyrimidine Analogues (Diaminopyrimidines)	640
2.5.1. Mechanism of Action	644
2.6. Sulfones	644
2.6.1. Mechanism of Action	645
2.7. Quinine Analogues	646
2.7.1. Mechanism of Action	646
2.8. New Antimalarial Drugs	646

CHAPTER 21: Anthelmintics	651
----------------------------------	------------

1. Introduction	652
2. Classification	653
2.1. Piperazines	654
2.2. Benzimidazoles	655
2.3. Heterocyclics	659
2.4. Antimalarials	661
2.5. Natural Products	661

CHAPTER 22: Insulin and Oral Hypoglycemic Agents	667
---	------------

1. Introduction	668
2. Insulin-Primary Structure	669
2.1. Variants of Insulin Products	670

3. Oral Hypoglycemic Agents	672
3.1. Sulfonylureas	672
3.1.1. First-Generation Sulfonylureas	673
3.1.2. Second-Generation Sulfonylureas	676
3.2. Non-Sulfonylureas-Metaglinides	678
3.3. Thiazolidinediones	680
3.4. Bisguanides	681
3.5. α -Glucosidase Inhibitors	682

CHAPTER 23: Steroids	685
-----------------------------	------------

1. Introduction	686
2. Steroid Nomenclature, Numbering, Double Bonds and Stereochemistry	686
3. Classification	690
3.1. Sterols	690
3.2. Sex Hormones	691
3.2.1. Classification	691
3.2.2. Androgens	691
3.2.3. Oestrogens	698
3.2.4. Gestogens	707
3.3. Cardiac Glycosides	709
3.3.1. Mechanism of Action	712
3.4. Bile Acids	712
3.5. Sapogenins	713

CHAPTER 24: Adrenocortical Steroids	717
--	------------

1. Introduction	718
2. Classification	720
2.1. Short to Medium Acting Glucocorticoids	720
2.2. Intermediate Acting Glucocorticoids	727
2.3. Long Acting Glucocorticoids	728
2.4. Mineralocorticoids	731

CHAPTER 25: Antibiotics	735
--------------------------------	------------

1. Introduction	736
2. Classification	737
3. β -Lactam Antibiotics	737
3.1. Penicillins	737
3.2. Cephalosporins	754

4. Aminoglycoside Antibiotics	763
5. Chloramphenicol	767
5.1. Structure of Chloramphenicol	767
5.2. Synthesis of Chloramphenicol	769
5.3. Structure Activity Relationship	771
6. Tetracyclines	772
6.1. Salient Features of Tetracyclines	772
6.2. Nomenclature	772
6.3. General Characteristics of the Tetracyclines	773
6.4. Structure Activity Relationship (SAR)	776
6.5. Newer Tetracyclines	777

CHAPTER 26: Antimycobacterial Drugs	781
--	------------

1. Introduction	782
2. Classification	784
2.1. First-Line Drugs	784
2.2. Second-Line Drugs	785

CHAPTER 27: Antineoplastic Agents	793
--	------------

1. Introduction	794
1.1. Chemotherapeutic Intervention	796
1.1.1. Phase Specificity	796
1.1.2. Tumour Selectivity and Response	797
1.1.3. Determinants of Sensitivity and Selectivity	798
1.1.4. Requirements for Kill	799
1.1.5. Combination Chemotherapy	799
1.1.6. Log Cell-Kill Principle	799
1.1.7. Drug Resistance	800
2. Classification	801
2.1. Alkylating Agents	801
2.1.1. Mustards	801
2.1.2. Methanesulphonates	806
2.1.3. Ethylenimines	807
2.1.4. Nitrosoureas	808
2.2. Antimetabolites	811
2.2.1. Antifolic Acid Compounds	811
2.2.2. Analogues of Purines	813
2.2.3. Analogues of Pyrimidines	815
2.2.4. Amino Acid Antagonists	817

2.3. Antibiotics	817
2.3.1. Mechanism of Action	819
2.4. Plant Products	819
2.4.1. Imides and Amides	820
2.4.2. Tertiary Amines	821
2.4.3. Heterocyclic Amines	824
2.4.4. Lactones	824
2.4.5. Glycosides	825
2.5. Miscellaneous Compounds	826
2.5.1. Mechanism of Action	828
2.6. Hormones	830
2.6.1. Mechanism of Action	831
2.7. Immunotherapy	831
2.7.1. Mechanism of Action	832

CHAPTER 28: Antipsychotics (Tranquilizers)	835
---	------------

1. Introduction	836
2. Classification	837
2.1. Reserpine and Related Alkaloids	837
2.1.1. Mechanism of Action	839
2.2. Alkylene Diols	839
2.3. Diphenylmethane Compounds	840
2.3.1. Mechanism of Action	843
2.4. Phenothiazine Compounds	843
2.4.1. Mechanism of Action	846
2.5. Dibenzazepines	847
2.5.1. Mechanism of Action	848
2.6. Butyrophenones	859
2.6.1. Mechanism of Action	850
2.7. Azaspirodecanediones	850
2.7.1. Mechanism of Action	851

CHAPTER 29: Antiviral Drugs	853
------------------------------------	------------

1. Introduction	853
1.1. Replication and Transformation	855
2. Classification	855
2.1. Substances that Inhibit Early Stages of Viral Replication	855
2.1.1. Mechanism of Action	856

2.2. Substances that Interfere with Viral Nucleic Acid Replication	857
2.2.1 Mechanism of Action	859
2.3. Substances that Affect Translation on Cell Ribosomes	860
2.3.1. Mechanism of Action	861

CHAPTER 30: Newer Drugs for Newer Diseases	863
---	------------

1. Introduction	864
2. Newer Drugs	864
2.1. Prostaglandins and Other Eicosanoids	865
2.1.1. Nomenclature	865
2.2. Antilipemic Drugs	869
2.2.1. Mechanism of Action	870
2.3. Hormone Antagonists	870
2.3.1. Antiestrogens	871
2.3.2. Antiandrogens	872
2.3.3. Aldosterone Antagonists	874
2.3.4. Antiprogestational Steroids	874
2.4. Antithyroid Drugs	875
2.4.1. Mechanism of Action	876
2.5. Antimycobacterial Drugs	877
2.5.1. Antitubercular Drugs	882
2.6. Cardiac Steroids and Related Inotropic Drugs	882
2.6.1. Cardiac Steroids	882
2.6.2. Phosphodiesterase Inhibitors	883
2.6.3. Adenylate Cyclase Stimulants	884
2.6.4. Drugs that Enhance the Ca^{2+} Sensitivity of Myocardial Contractile Proteins	885
2.7. Heparine	886
2.8. Radiosensitizer	887
2.8.1. Therapeutic Radioisotopes	887
2.8.2. Imaging Radioisotopes	888
2.9. Cromakalim	889
2.10. Drugs to Combat AIDS	890
Index	897