

Contents

Foreword	xv
Preface	xvii
Abbreviations	xix
CHAPTER 1 General Aspects of Cancer Chemotherapy.....	1
1 Introduction: Some General Comments About Cancer	1
2 Tumorigenesis and Oncogenes: Pharmacogenomics	2
3 Early Diagnosis of Cancer and Its Therapeutic Relevance	5
4 A Brief History of Cancer Chemotherapy	6
5 General Comments About Anticancer Drug Discovery	8
6 Combination Therapy and Personalized Anticancer Treatments	11
7 Natural Products in Cancer Chemotherapy.....	13
8 A Brief Comment About Cancer Nanotechnology	14
9 Summary of FDA-Approved Anticancer Drugs	15
References.....	21
CHAPTER 2 Antimetabolites That Interfere with Nucleic Acid Biosynthesis.....	23
1 Introduction.....	24
2 Inhibitors of the Biosynthesis of Uridylic Acid.....	25
3 Inhibitors of Ribonucleotide Reductase	26
3.1 Structure and Catalytic Cycle of Ribonucleotide Reductase.....	26
3.2 Gallium Salts and Complexes	28
3.3 Radical Scavengers.....	30
3.4 Substrate Analogs as Ribonucleotide Reductase Inhibitors	31
3.5 Allosteric Inhibition of Ribonucleotide Reductase via Inhibition of Purine Nucleoside Phosphorylase	35
4 Inhibitors of the Biosynthesis of Thymidilic Acid	37
4.1 Thymidylate Synthase	37
4.2 5-Fluorouracil and Floxuridine	38
4.3 5-Fluorouracil Prodrugs.....	41
4.4 Modulation of 5-Fluorouracil Activity.....	45
4.5 Trifluridine.....	48
4.6 Folate-Based Thymidylate Synthase Inhibitors	49
5 Inhibitors of Dihydrofolate Reductase	54
5.1 Classical DHFR Inhibitors	56
5.2 Nonclassical (Lipophilic) DHFR Inhibitors.....	59

6	Inhibitors of the <i>De Novo</i> Purine Biosynthesis Pathway.....	59
6.1	Inhibitors of PRPP Amidotransferase	60
6.2	Inhibitors of Glycinamide Ribonucleotide Formyltransferase	61
6.3	Inhibitors of Phosphoribosylformylglycinamide Synthetase	62
6.4	Inhibitors of 5-Aminoimidazole-4-Carboxamide Ribonucleotide Formyltransferase	65
6.5	Thiopurines and Related Compounds	65
7	Inhibitors of Adenosine Deaminase	66
8	Inhibitors of Late Stages in DNA Synthesis.....	70
8.1	Pyrimidine Nucleosides	72
8.2	Purine Nucleosides	75
9	Antimetabolite Enzymes.....	76
	References.....	77

CHAPTER 3	Anticancer Drugs That Modulate Hormone Action.....	81
1	Introduction.....	82
2	Estrogens and Their Involvement in Carcinogenesis	82
3	Antiestrogens as Antitumor Drugs	87
3.1	Nonsteroidal Antiestrogens (Selective Estrogen Receptor Modulators).....	87
3.2	Steroidal Antiestrogens.....	92
4	Aromatase Inhibitors	96
4.1	Aromatase Mechanism of Action.....	97
4.2	Steroidal Aromatase Inhibitors (Type I Inhibitors)	98
4.3	C-19 Modified Substrate Analogs.....	99
4.4	4-Hydroxyandrostenedione Derivatives	100
4.5	Steroids with Additional Unsaturation at the A and B Rings.....	100
4.6	Structure–Activity Relationships in Steroidal Aromatase Inhibitors	102
4.7	Nonsteroidal Aromatase Inhibitors (Type II)	102
5	Steroid Sulfatase Inhibitors	105
6	Androgen-Related Antitumor Agents	105
6.1	Antiandrogens.....	107
6.2	Inhibitors of Androgen Biosynthesis.....	110
7	Regulation of Gonadotropin-Releasing Hormone: Control of the Hypothalamic–Pituitary–Gonadal axis.....	116
7.1	Introduction.....	116
7.2	GnRH (LHRH) Agonists	118
7.3	GnRH (LHRH) Antagonists	118
8	Miscellaneous Steroid Hormone-Related Anticancer Therapy	121
8.1	Gestagens as Antitumor Agents	121
8.2	Glucocorticoids and Inhibitors of Their Biosynthesis as Antitumor Agents.....	122

9	Compounds Acting on Other Proteins of the Nuclear Receptor Superfamily:	
	Retinoids	123
10	PPAR Ligands as Antitumor Agents.....	126
11	Somatostatin Analogs in Neuroendocrine Tumors	127
	References	129

CHAPTER 4 Anticancer Drugs Acting via Radical Species: Radiotherapy and Photodynamic Therapy of Cancer 133

1	Introduction: Radicals and Other Reactive Oxygen Species.....	134
2	Biological Effects of Reactive Oxygen Species	135
	2.1 Membrane Phospholipid Peroxidation	136
	2.2 Malondialdehyde Generation and Its Consequences	137
	2.3 DNA Strand Cleavage	139
	2.4 Oxidation of DNA Bases.....	142
	2.5 Formaldehyde Generation	145
	2.6 ROS as Signaling Molecules.....	145
	2.7 Oxidative Stress Induction as a Strategy in Cancer Treatment.....	145
3	Anthracyclines and Their Analogs.....	146
4	Mitoxantrone and Related Quinones.....	156
5	Actinomycin D.....	159
6	Chartreusin, Elsamicin A, and Related Compounds	160
7	Bleomycins	161
8	Enediyne Antibiotics	165
9	Tirapazamine	171
10	Penclomedine.....	172
11	Radiotherapy and Radiosensitizers	173
	11.1 Radiotherapy.....	173
	11.2 Drugs Used to Improve the Results of Radiotherapy.....	179
12	Photodynamic Therapy of Cancer.....	183
	12.1 Porphyrins as Photosensitizers	185
	12.2 Non-Porphyrin Photosensitizers	188
	12.3 Other Applications of Photodynamic Therapy	190
	References	191

CHAPTER 5 DNA Alkylating Agents 197

1	Introduction.....	197
2	Nitrogen Mustards	198
	2.1 Introduction.....	198
	2.2 DNA Alkylation by Nitrogen Mustards and Cytotoxicity Mechanisms	200
	2.3 Structure–Activity Relationships in Nitrogen Mustards.....	202
	2.4 Site-Directed Nitrogen Mustards.....	205

3	Aziridines (Ethyleneimines)	212
4	Epoxides	216
5	Methanesulfonates	218
6	Nitrosoureas	219
7	Triazenes	225
8	Methylhydrazines	227
9	1,3,5-Triazines: Hexamethylmelamine and Trimelamol	228
10	Transition Metal Species	229
	10.1 Platinum Complexes	229
	10.2 Ruthenium Complexes	236
	10.3 Titanocenes	236
11	Miscellaneous Alkylating and Acylating Antitumor Agents	237
	References	238

CHAPTER 6	Anticancer Drugs That Interact with the DNA Minor Groove	243
1	Introduction	243
2	Netropsin, Distamycin, and Related Compounds	243
3	Mitomycins	249
4	Tetrahydroisoquinoline Alkaloids	257
5	Cyclopropylindole Alkylating Agents	264
6	Irofulven	267
7	Pyrrolo[1,4]benzodiazepines	268
	References	269

CHAPTER 7	Other Anticancer Drugs Targeting DNA and DNA-Associated Enzymes	273
1	DNA Intercalation and Its Consequences	274
2	Monofunctional Intercalating Agents	276
	2.1 Ellipticine and Its Analogs	276
	2.2 Actinomycins	279
	2.3 Fused Quinolines	280
	2.4 Naphthalimides and Related Compounds	281
	2.5 Chartreusin, Elsamicin A, and Related Compounds	281
	2.6 Other Monofunctional Intercalating Agents	282
3	Bifunctional Intercalating Agents	282
4	Indirect DNA Damage by DNA Topoisomerase Inhibitors	285
	4.1 Topoisomerase I Mechanism	285
	4.2 Topoisomerase II Mechanism	286

5	Specific Topoisomerase I Inhibitors	290
5.1	Camptothecins	290
5.2	Non-Camptothecin Topoisomerase I Inhibitors.....	298
6	Topoisomerase II Poisons.....	301
6.1	Acridine Derivatives.....	301
6.2	Anthracyclines and Related Compounds	302
6.3	Non-Intercalating Topoisomerase II Poisons.....	305
7	Topoisomerase II Catalytic Inhibitors.....	309
7.1	Inhibitors of the Binding of Topoisomerase II to DNA	309
8	Telomerase Inhibitors and Other Anticancer Approaches Targeting Telomeres	311
8.1	G-Quadruplex Ligands	313
8.2	Inhibitors of Telomerase Reverse Transcriptase.....	316
8.3	Inhibitors of the RNA Domain Template	316
9	DNA Repair Inhibitors	317
	References.....	318

CHAPTER 8 Epigenetic Therapy of Cancer..... 325

1	Introduction.....	325
2	Inhibitors of DNA Methylation: Reactivation of Silenced Genes	328
2.1	Nucleoside Inhibitors of DNA Methyltransferases.....	329
2.2	Non-Nucleoside Inhibitors of DNA Methyltransferase	335
3	Inhibitors of Histone and Other Protein Deacetylases.....	337
3.1	Short-Chain Fatty Acids.....	339
3.2	Hydroxamic Acids.....	340
3.3	Cyclic Tetrapeptides	343
3.4	Benzamides.....	345
3.5	Thiols	345
3.6	Inhibitors of HDAC4.....	346
3.7	Inhibitors of Sirtuins.....	347
3.8	Bromodomain Inhibitors.....	348
4	Regulators of Histone Methylation	350
4.1	Inhibitors of Histone Methyltransferases	351
4.2	Lysine-Specific Demethylases (LSDs or KDMs) and Their Inhibitors	353
	References.....	356

CHAPTER 9 Anticancer Drugs Targeting Tubulin and Microtubules 359

1	Introduction.....	359
2	Drugs That Inhibit Microtubule Polymerization.....	361
2.1	Compounds Binding at the <i>Vinca</i> Site.....	361
2.2	Compounds Binding at the Colchicine Site.....	368

3	Microtubule-Stabilizing Agents: Compounds Binding at the Taxane Site.....	373
3.1	Taxanes	373
3.2	Epothilones	377
3.3	Miscellaneous Marine Compounds That Bind to the Taxane Site.....	380
3.4	Inhibitors of LIM Kinase.....	382
4	Miscellaneous Anticancer Drugs Acting on Novel Sites of Tubuline	383
5	Antivascular Effects of Microtubule-Targeted Agents.....	385
6	Mitotic Kinesin Inhibitors	386
	References.....	387

CHAPTER 10 Drugs That Inhibit Signaling Pathways for Tumor Cell

	Growth and Proliferation: Kinase Inhibitors.....	391
1	Introduction.....	392
2	Oncogenes and Signal Transduction.....	393
3	The Role of Protein Kinases in Cancer: Signaling Pathways Related to Kinases	394
4	Inhibitors of Tyrosine Kinases	402
4.1	Inhibitors of EGFR (HER-1).....	403
4.2	Inhibitors of HER-2.....	410
4.3	Inhibitors of HER-3.....	411
4.4	Pan-HER Inhibitors	411
4.5	Inhibitors of Insulin-Like Growth Factor Receptors (IGF-1R).....	411
4.6	Inhibitors of Hepatocyte Growth Factor Receptor (HGFR, c-Met)	413
4.7	Inhibitors of Pro-Angiogenic Tyrosine Kinases: Vascular Endothelial Growth Factor Receptor and Related Kinase Receptors	413
4.8	Inhibitors of FLT3 (CD135).....	421
4.9	Inhibitors of Bcr-Abl Tyrosine Kinase (Abelson Kinase).....	422
4.10	Anaplastic Lymphoma Kinase (ALK) Inhibitors	427
4.11	Inhibitors of JAK-STAT and PRL Pathways.....	431
4.12	Inhibitors of Bruton's Tyrosine Kinase (BTK).....	433
4.13	Inhibitors of Tropomyosin Receptor Kinase (Trk).....	434
5	Inhibitors of Serine-Threonine Kinases.....	434
5.1	Cyclin-Dependent Kinases (CDKs)	434
5.2	Polo-Like Kinases (PLKs).....	442
5.3	Checkpoint Kinases (CHKs)	443
5.4	PI3K/PDPK1/AKT/mTOR Kinases Pathway	445
5.5	Aurora Kinases	453
5.6	Protein Kinase C (PKC) Modulators	455
5.7	Inhibitors of Pim Kinases.....	458

6	Inhibitors of the Ras/Raf/MEK Signaling Pathway.....	458
6.1	Introduction to Ras Signaling.....	458
6.2	Inhibitors of Ras Protein Expression	462
6.3	Inhibitors of Ras Processing by Farnesyltransferase.....	462
6.4	Inhibitors of the Attachment of Farnesyl-Ras to the Cell Membrane	470
6.5	Inhibitors of Downstream Effectors of the Ras Function.....	470
7	Transforming Growth Factor-β-Smad Signaling.....	478
8	Glucose Metabolism and Cancer: Inhibitors of Kinases Involved in Anaerobic Glycolysis	480
	References.....	484

CHAPTER 11 Other Nonbiological Approaches to Targeted

	Cancer Chemotherapy	493
1	Introduction.....	494
2	Proteolytic Enzymes as Anticancer Targets	494
2.1	Anticancer Drugs Acting on the Ubiquitin-Proteasome System	494
2.2	Inhibitors of Matrix Metalloproteinases.....	508
2.3	Inhibitors of Aminopeptidases	512
2.4	Inhibitors of Cathepsins.....	512
3	Heparanase Inhibitors	515
3.1	Polysaccharides with <i>O</i> - or <i>N</i> -Sulfate Groups.....	516
3.2	Compounds with <i>C</i> -Sulfonate Groups	516
3.3	Neutral Inhibitors.....	517
3.4	Monoclonal Antibodies	517
4	Integrin Antagonists and Inhibitors of Chemokine Receptors	517
5	Endogenous Inhibitors of Angiogenesis	519
6	Miscellaneous Antiangiogenic Compounds	522
6.1	Squalamine.....	522
6.2	Thalidomide and Its Analogs	522
6.3	Fumagillin Analogs	524
7	Drugs Targeting Cancer Stem Cells.....	525
7.1	Wingless/ β -Catenin Signaling	526
7.2	Inhibitors of the Notch Signaling Pathway.....	529
7.3	Hedgehog Signaling/Smo Receptor Inhibitors.....	531
7.4	Mesenchymal Stem Cell-Mediated Gene Therapy for Cancer	533
8	Inhibitors of Oncogenic Protein-Protein Interactions	533
8.1	Anticancer Drugs Acting on Apoptotic Signaling Pathways	534
8.2	Inhibitors of Heat Shock Proteins and Other Chaperones.....	549
9	Anticancer Agents Targeted at the Lysosomes	553
	References.....	554

CHAPTER 12 Biological Therapy of Cancer	561
1 Introduction.....	561
2 Monoclonal Antibodies against Cancer Cells.....	562
2.1 mAbs Targeting Specific Antigens	564
2.2 Specific Immunomodulatory mAbs	566
2.3 Bispecific Antibodies	569
3 Cancer Immunotherapy: General Aspects	570
3.1 Regulatory T Cells.....	571
3.2 Myeloid-Derived Suppressor Cells	572
3.3 Toll-Like and NOD2 Receptors	573
4 Cancer Vaccines	575
4.1 Tumor Cell Vaccines and Vaccination Antigens.....	575
4.2 DNA and RNA Cancer Vaccines.....	576
4.3 Carbohydrate Vaccines.....	577
4.4 Peptide Vaccines.....	579
4.5 Telomerase-Targeted Vaccines	581
4.6 Vaccines against Oncogenic Viruses	582
5 Gene Therapy.....	582
5.1 Replacement of Deficient or Absent Tumor Suppressor Genes:	
Oncolytic Viruses	583
5.2 Gene Transfer (Suicide Gene) Therapy	584
5.3 Transfer of Resistance Genes for Chemoprotection	
of Hematopoietic Stem/Progenitor Cells	585
5.4 Immunomodulatory Gene Therapy	585
6 Antisense Oligonucleotides in Cancer Treatment.....	587
7 Bacteria and Bacterial Toxins in Cancer Therapy.....	589
References.....	589
 CHAPTER 13 Drug Targeting in Anticancer Chemotherapy.....	 595
1 Introduction.....	596
2 Small-Molecule prodrugs for Anticancer Drug Targeting	596
2.1 Selective Enzyme Expression in Tumor Cells.....	596
2.2 Hypoxia-Based Strategies for Tumor-Specific Prodrug Activation.....	598
2.3 Gene-Directed Enzyme Prodrug Therapy and Virus-Directed Enzyme	
Prodrug Therapy	610
2.4 Antibody-Directed Enzyme Prodrug Therapy	613
3 Therapeutic Nanoparticles for Drug Delivery in Cancer: General Aspects.....	617
4 Polymer Conjugates: Macromolecular Small-Drug Carrier Systems.....	617
4.1 PEGylated Conjugates.....	619
4.2 <i>N</i> -(2-Hydroxypropyl)Methacrylamide Polymers	620

4.3 Poly-(L-Glutamic) Conjugates	625
4.4 Conjugates with Semisynthetic Hydrophilic Polyals.....	626
4.5 Neuropeptide Y Conjugates	628
4.6 Antibody–Drug Conjugates	629
5 Polymer-Directed Enzyme Prodrug Therapy Approaches	634
6 Folate Receptor-Targeted Chemotherapy	635
7 Liposomes and Other Nanoparticles in Anticancer Drug Targeting.....	640
7.1 Liposomes.....	641
7.2 Copolymer Micelles	645
7.3 Gold Nanoparticles	648
7.4 Dendrimers as Carriers for the Delivery of Chemotherapeutic Agents	649
7.5 Nanoparticle Albumin-Bound Technology	649
References.....	650

CHAPTER 14 Drugs That Modulate Resistance to Antitumor Agents..... 655

1 Introduction.....	656
2 ABC Efflux Pumps in Anticancer Drug Resistance	657
2.1 General Features of ABC Efflux Pumps.....	657
2.2 Inhibition of P-Glycoprotein	659
2.3 Indirect Inhibitors of MDR	668
2.4 Importance of the Pgp Inhibition Data in New Drug Applications	668
3 Glutathione and Glutathione S-Transferase in Anticancer Drug Resistance	668
3.1 Inhibitors of Glutathione Biosynthesis.....	669
3.2 Inhibitors of Glutathione S-Transferase	671
4 Chemosensitizers Targeting DNA Repair Systems	675
4.1 Inhibitors of <i>O</i> ⁶ -Alkylguanine DNA Alkyltransferase (MGMT or AGT)	677
4.2 Antitumor Adjuvants Targeting the BER Process.....	679
4.3 Inhibitors of Enzymes Involved in Double-Strand DNA Break Repair Pathways	688
5 Antitumor Drug Resistance Related to Cellular Adhesion Molecules.....	689
6 Antitumor Drug Resistance Related to the Extracellular pH: Tumor-Associated Carbonic Anhydrase as an Anticancer Target	690
7 The Role of the SPARC Protein in Drug Resistance	691
8 Radioresistance and Tumor Radiosensitization	691
9 Induced Tumor Chemoresistance.....	693
9.1 Chemoresistance to Anti-VEGF Therapies.....	693
9.2 Chemoresistance to EGFR-Targeted Therapies.....	693
9.3 Chemoresistance to ALK Mutations	695
References.....	696

CHAPTER 15 Cancer Chemoprevention.....	701
1 Introduction.....	701
2 Cancer Biomarkers, Molecular Medicine, and Individualized Treatments.....	702
3 Cancer Chemoprevention	703
4 Chemopreventive Agents	704
4.1 Estrogen Receptor Modulators and Antiandrogen Compounds	705
4.2 5-Fluorouracil and Eflornithine.....	706
4.3 Nonsteroidal Anti-Inflammatory Drugs as Cancer Chemopreventive Agents	707
4.4 Masoprocol and Ingenol Mebutate.....	709
4.5 Photodynamic Therapy.....	709
5 Nutritional Supplements	710
5.1 Antioxidants in Cancer Chemoprevention.....	710
5.2 Vitamin C (Ascorbic Acid)	711
5.3 Ergothioneine.....	712
5.4 Green Tea	713
5.5 Lycopene.....	714
5.6 Natural Products with Miscellaneous Protective Mechanisms.....	715
6 Ligands for Nuclear Receptors in Cancer Chemoprevention.....	718
References.....	721
 Index	 725