

# Contents

		xxvi
		xxxvii
<b>List of Contributors</b>		xxvi
<b>Preface</b>		xxxvii
<b>1 <sup>3</sup>Li Lithium Metallotherapeutics</b>		1
	<i>Robin S.B. Williams and Adrian J. Harwood</i>	
<b>1.1 Introduction</b>		1
<b>1.2 The Inorganic Chemistry of Lithium</b>		2
<b>1.3 Biology of Lithium</b>		3
1.3.1 The history of lithium therapeutics		3
1.3.2 Lithium and the body		4
<b>1.4 Targets of Lithium</b>		5
1.4.1 Glycogen synthase kinase-3		5
1.4.2 Inositol phosphate signalling		8
<b>1.5 Lithium Therapeutics</b>		10
1.5.1 Bipolar disorder and schizophrenia		10
1.5.2 Alzheimer's disease		12
1.5.3 Ischemia (stroke)		14
1.5.4 Adverse effects		14
<b>Acknowledgements</b>		15
<b>References</b>		15

## 2

 **$^{10}\text{B}$  Boron Compounds as Therapeutic Drugs**

19

*Geeta Rana, Kamesh Vyakaranam, John A. Maguire and Narayan S. Hosmane*

<b>2.1</b>	<b>Boron Neutron Capture Therapy</b>	19
<b>2.2</b>	<b>Classes of Boron Compounds for Potential Use in BNCT</b>	22
2.2.1	DNA binders	22
2.2.2	Boron-containing amino acids and related peptides	24
2.2.3	Boron-containing nucleic acid precursors	27
<b>2.3</b>	<b>Phosphates, Phosphonates and Phosphoramidates</b>	31
<b>2.4</b>	<b>Amines</b>	33
<b>2.5</b>	<b>Boron Analogues of Pyrophosphates</b>	33
<b>2.6</b>	<b>Boronated Polyamines</b>	34
<b>2.7</b>	<b>Carbohydrates</b>	36
<b>2.8</b>	<b>Lipoproteins</b>	36
<b>2.9</b>	<b>Lipids and Phospholipids</b>	37
<b>2.10</b>	<b>Radiation Sensitizers</b>	38
<b>2.11</b>	<b>Cyclic Thiourea Derivatives</b>	38
<b>2.12</b>	<b>Central Nervous System (CNS) Depressants: Promazines, Hydantoins and Barbiturates</b>	39
<b>2.13</b>	<b>Hydantoins and Barbiturates</b>	39
<b>2.14</b>	<b>Oligonucleotide Antisense Agents</b>	40
<b>2.15</b>	<b>Hormones</b>	42
<b>2.16</b>	<b>Liposomes</b>	44

<b>2.17</b>	<b>Conclusions</b>	45
	<b>Acknowledgements</b>	46
	<b>References</b>	46
<b>3</b>	<b><sup>12</sup>Mg The Role of Magnesium as a Metallotherapeutic Drug</b>	51
	<i>Pietro Delva</i>	
<b>3.1</b>	<b>Introduction</b>	51
<b>3.2</b>	<b>Magnesium as a Drug</b>	53
	3.2.1 Gestational hypertension, preeclampsia and eclampsia	53
	3.2.2 Asthma	54
	3.2.3 Stroke	55
	3.2.4 Acute myocardial infarction	57
	3.2.5 Arrhythmias	60
	3.2.6 Miscellaneous	61
	<b>References</b>	62
<b>4</b>	<b><sup>13</sup>Al Aluminum Metallotherapeutics</b>	65
	<i>Thanos Salifoglou</i>	
<b>4.1</b>	<b>Introduction</b>	65
<b>4.2</b>	<b>Adjuvants</b>	66
	4.2.1 Alum	66
	4.2.2 Al(OH) <sub>3</sub>	67
	4.2.3 Aluminum phosphate	69
<b>4.3</b>	<b>Antacids</b>	69
	4.3.1 Aluminum hydroxide	69
	4.3.2 Aluminum glycinate	70
	4.3.3 Peptic ulcer disease	70
	4.3.4 Bismuth aluminum carbonate	73
	4.3.5 Bismuth–magnesium–sodium alumino-silicate	73
<b>4.4</b>	<b>Phosphate Binders</b>	73
	4.4.1 Basic aluminum carbonate	75
	4.4.2 Alumino-silicates	75

4.5	<b>Alginate Raft Formulations</b>	75
4.6	<b>Blistering Diseases in the Elderly</b>	77
4.7	<b>Metabolic Diseases and Aluminum</b>	77
4.8	<b>Anti-malarial Substances</b>	78
4.9	<b>Potential Aluminum Toxicity</b>	79
4.10	<b>Conclusions</b>	80
	<b>References</b>	80
<b>5</b>	<b><sup>14</sup>Si Biological Activity of Organosilicon Compounds</b>	83
	<i>Edmunds Lukevics and Luba Ignatovich</i>	
5.1	<b>Introduction</b>	83
5.2	<b>Organosilicon Modification</b>	84
	5.2.1 O-, S- and N-Silylation	84
	5.2.2 C-Silylation	89
5.3	<b>Sila Analogues</b>	92
5.4	<b>Specific Organosilicon Compounds</b>	94
	<b>References</b>	96
<b>6</b>	<b><sup>20</sup>Ca The Role of Calcium as a Metallotherapeutic Drug</b>	109
	<i>Mario Barbagallo and Ligia J. Dominguez</i>	
6.1	<b>Introduction</b>	109
6.2	<b>Calcium Homeostasis</b>	110
6.3	<b>Hormonal Regulation of Calcium Metabolism</b>	111
6.4	<b>Optimal Amount of Dietary Calcium Intake and Benefits of Calcium Supplementation</b>	112

6.5	<b>Osteoporosis</b>	115
6.6	<b>Hypertension</b>	116
6.7	<b>Hypertension in Pregnancy and Preeclampsia</b>	118
6.8	<b>Colon Cancer</b>	119
6.9	<b>Weight Control and Regulation of Body Fat</b>	119
6.10	<b>Periodontal Disease</b>	120
6.11	<b>Kidney Stones</b>	121
6.12	<b>Calcium Supplements: Side Effects</b>	121
6.13	<b>Conclusions</b>	122
	<b>References</b>	123
<b>7</b>	<b><sup>22</sup>Ti Anti-tumor Titanium Drugs</b>	125
	<i>Erich Dubler</i>	
7.1	<b>Introduction</b>	125
7.2	<b>The Biochemistry of Titanium</b>	126
7.3	<b>Titanium Anti-cancer Drugs</b>	127
7.4	<b>Budotitane</b>	130
	7.4.1 Chemistry and anti-cancer activity	130
	7.4.2 Isomer abundance of budotitane	131
	7.4.3 Reaction with biomolecules	133
	7.4.4 Animal studies	134
	7.4.5 Clinical investigations	134
7.5	<b>Titanocene Dichloride</b>	135
	7.5.1 Chemistry and anti-cancer activity	135
	7.5.2 Reaction with biomolecules	136
	7.5.3 Animal studies	137
	7.5.4 Clinical investigations	138
	7.5.5 Perspectives of titanocene dichloride	138

<b>7.6</b>	<b>Conclusions</b>	139
	<b>Acknowledgements</b>	140
	<b>References</b>	140
<b>8</b>	<b><math>^{23}\text{V}</math> Insulin-Mimetic Vanadium-Containing Compounds</b>	143
	<i>Tamás Kiss and Tamás Jakusch</i>	
<b>8.1</b>	<b>Chemistry of Vanadium</b>	143
<b>8.2</b>	<b>Biological and Medicinal Aspects of Vanadium</b>	144
<b>8.3</b>	<b>The Role of Insulin in Glucose Metabolism</b>	144
<b>8.4</b>	<b>Vanadium Complexes with Biological Activity</b>	145
<b>8.5</b>	<b>Biological Activity and Toxicity of Various Vanadium(IV/V) Compounds</b>	148
<b>8.6</b>	<b>Speciation of VI(IV) Complexes in Biological Fluids</b>	149
<b>8.7</b>	<b>Possible Mechanism for <i>in vivo</i> Vanadium Action</b>	153
<b>8.8</b>	<b>Conclusion</b>	155
	<b>Acknowledgements</b>	156
	<b>References</b>	156
<b>9</b>	<b><math>^{25}\text{Mn}</math> Manganese Metallotherapeutics</b>	159
	<i>Jeanne H. Freeland-Graves, Tanushree Bose and Abbass Karbassian</i>	
<b>9.1</b>	<b>Prevalence in the Environment</b>	159
<b>9.2</b>	<b>Diet and Water</b>	160
<b>9.3</b>	<b>Functions</b>	160

<b>9.4</b>	<b>MnSOD</b>	160
<b>9.5</b>	<b>Deficiency</b>	161
	9.5.1 Animals	161
	9.5.2 Humans	162
<b>9.6</b>	<b>Toxicity</b>	162
<b>9.7</b>	<b>Therapeutic Manganese-Related Agents</b>	163
<b>9.8</b>	<b>Therapeutic Uses</b>	165
	9.8.1 Arthritis	165
	9.8.2 Cancer	166
	9.8.3 Cardiovascular diseases	167
	9.8.4 Dermatitis	168
	9.8.5 Diabetes	168
	9.8.6 Epilepsy	169
	9.8.7 Human immunodeficiency virus	169
	9.8.8 Inflammatory pain and response	170
	9.8.9 Ischemia and reperfusion injury	171
	9.8.10 Osteoporosis	171
	9.8.11 Peritoneal adhesions	172
	9.8.12 Premenstrual syndrome	172
	9.8.13 Shortened life span (premature aging)	173
	9.8.14 Other disorders	174
<b>9.9</b>	<b>Magnetic Resonance Imaging (MRI)</b>	174
<b>9.10</b>	<b>Future Implications</b>	175
	<b>Acknowledgements</b>	175
	<b>References</b>	176
<b>10</b>	<b><math>^{26}\text{Fe}</math> The Use of Iron-Based Drugs in Medicine</b>	179
	<i>Xiang Wu and Mei Lin Go</i>	
<b>10.1</b>	<b>Introduction</b>	179
<b>10.2</b>	<b>Ferrocene</b>	180

<b>10.3</b>	<b>TMH Ferrocene</b>	181
<b>10.4</b>	<b>Ferrocene in Drug Design</b>	181
10.4.1	Examples where introduction of ferrocene has resulted in a loss or no change in activity	182
10.4.2	Examples where introduction of ferrocene has resulted in enhanced activity or a change in activity profile	183
<b>10.5</b>	<b>Ferrochloroquine</b>	185
<b>10.6</b>	<b>Other Ferrocenyl Anti-plasmodial Agents</b>	191
<b>10.7</b>	<b>Organoiron as Anti-cancer Agents</b>	193
<b>10.8</b>	<b>Conclusions</b>	197
	<b>References</b>	198
<b>11</b>	<b><sup>27</sup>Co Cobalt Complexes as Potential Pharmaceutical Agents</b>	201
	<i>Hui Chao and Liang-Nian Ji</i>	
<b>11.1</b>	<b>Introduction</b>	201
<b>11.2</b>	<b>Enzyme Inhibition/Induction</b>	202
11.2.1	Serine protease inhibitors	202
11.2.2	Topoisomerase II inhibitors	202
11.2.3	Heme oxygenase-1 inducers	203
<b>11.3</b>	<b>Nucleic Acid Binding and Cleavage</b>	204
11.3.1	Cobalt(III) polypyridyl complexes	204
11.3.2	Cobalt(III) bleomycin complexes	206
11.3.3	Cobalt(III) polyamine complexes	208
<b>11.4</b>	<b>Miscellaneous</b>	209
11.4.1	Cobalamin conjugates as drug delivery devices	209
11.4.2	Hypoxic selective agents	211
11.4.3	PET imaging agents	213
<b>11.5</b>	<b>Conclusions</b>	214



**Acknowledgements** 214

**References** 214

## 12 <sup>29</sup>Cu Chemotherapeutic Copper Compounds

*Francisco González-Vílchez and Rosario Vilaplana* 219

**12.1 Introduction** 219

**12.2 Copper-Purine Derivatives Complexes** 220

**12.3 Copper-Thiosemicarbazone Complexes** 223

**12.4 Copper-Benzohydroxamic Acid Complexes** 230

**12.5 Copper-Imidazole Derivatives Complexes** 230

**12.6 Copper-Polycarboxylate Complexes** 233

**Acknowledgements** 234

**References** 235

## 13 <sup>30</sup>Zn The Role of Zinc as a Metallotherapeutic Agent

*Jane V. Higdon and Emily Ho* 237

**13.1 Introduction** 237

**13.2 Functions** 237

13.2.1 Catalytic functions 238

13.2.2 Structural functions 238

13.2.3 Regulatory functions 238

**13.3 Zinc Deficiency** 238

13.3.1 Severe zinc deficiency 239

13.3.2 Mild zinc deficiency 239

13.3.3 Growth retardation 239

<b>13.4</b>	<b>Increased Susceptibility to Infectious Disease</b>	240
	13.4.1 Diarrhea	240
	13.4.2 Pneumonia	240
	13.4.3 Malaria	240
<b>13.5</b>	<b>Risk Factors for Zinc Deficiency</b>	241
	13.5.1 Dietary factors that decrease zinc absorption	241
	13.5.2 Intake recommendations	241
<b>13.6</b>	<b>Therapeutic Uses of Zinc</b>	243
	13.6.1 Wilson disease	243
	13.6.2 Age-related macular degeneration	243
	13.6.3 Human immunodeficiency virus (HIV) infection	243
	13.6.4 Type 1 diabetes	244
	13.6.5 Wound healing	244
<b>13.7</b>	<b>Common Cold</b>	245
	13.7.1 Oral zinc	245
	13.7.2 Intranasal zinc	245
<b>13.8</b>	<b>Zinc Status and Its Relevance to Cancer</b>	245
	13.8.1 Zinc deficiency and oxidative stress	246
	13.8.2 Zinc and DNA repair	247
	13.8.3 Zinc and prostate cancer	249
<b>13.9</b>	<b>Safety</b>	251
	13.9.1 Toxicity	251
	13.9.2 Drug interactions	252
<b>13.10</b>	<b>Conclusions</b>	252
	<b>References</b>	252
<b>14</b>	<b><sup>31</sup>Ga Therapeutic Gallium Compounds</b>	259
	<i>Lawrence R. Bernstein</i>	
<b>14.1</b>	<b>Introduction</b>	259
<b>14.2</b>	<b>Chemistry and Mechanisms of Action</b>	260
	14.2.1 Aqueous biochemistry	260

	14.2.2 Gallium and iron	261
	14.2.3 Mechanisms of action	264
<b>14.3</b>	<b>Therapeutic Gallium Compounds</b>	265
	14.3.1 Gallium nitrate and citrated gallium nitrate	265
	14.3.2 Gallium chloride	269
	14.3.3 Gallium 8-quinolinolate	269
	14.3.4 Gallium maltolate	270
	14.3.5 Other gallium compounds	271
	<b>Abbreviations Used</b>	273
	<b>References</b>	273
<b>15</b>	<b><sup>32</sup>Ge Biological Activity of Organogermanium Compounds</b>	279
	<i>Edmunds Lukevics and Luba Ignatovich</i>	
<b>15.1</b>	<b>Introduction</b>	279
<b>15.2</b>	<b>Biological Activity</b>	282
	15.2.1 2-Carboxyethylgermanium sesquioxide	282
	15.2.2 Spirogermanium	285
	15.2.3 Germatranes	286
	15.2.4 Germanium modified organic compounds	288
	<b>References</b>	290
<b>16</b>	<b><sup>33</sup>As Metallotherapeutic Arsenic Compounds</b>	297
	<i>Paul C. Ho</i>	
<b>16.1</b>	<b>Introduction</b>	297
<b>16.2</b>	<b>Chemistry of Arsenic</b>	299
<b>16.3</b>	<b>Mechanisms of Action</b>	300
	16.3.1 Modulation of PML and PML-RAR $\alpha$ genes	301
	16.3.2 Induction of intracellular reactive oxygen species (ROS)	302
	16.3.3 Collapse of the mitochondrial membrane potential	303

16.3.4	Roles of glutathione	303
16.3.5	Down-regulation of bcl-2	304
16.3.6	Involvement of p53	304
16.3.7	Activation of caspases	305
16.3.8	Other mechanisms of arsenic-induced apoptosis	305
<b>16.4</b>	<b>Pharmacokinetic Profiles</b>	306
16.4.1	Absorption, distribution and excretion	306
16.4.2	Metabolism	306
<b>16.5</b>	<b>Toxic Side Effects of As<sub>2</sub>O<sub>3</sub></b>	307
<b>16.6</b>	<b>Indications and Uses of As<sub>2</sub>O<sub>3</sub></b>	308
<b>16.7</b>	<b>Summary and Conclusions</b>	308
	<b>Acknowledgements</b>	309
	<b>References</b>	309
<b>17</b>	<b><sup>34</sup>Se The Use of Selenium-Based Drugs in Medicine</b>	313
	<i>Michael Carland and Tahli Fenner</i>	
<b>17.1</b>	<b>Introduction to Selenium and its Biochemistry</b>	313
<b>17.2</b>	<b>Diseases Associated with Selenium Deficiency</b>	315
17.2.1	Asthma	316
17.2.2	Keshan disease	316
17.2.3	Human immunodeficiency virus (HIV)	317
<b>17.3</b>	<b>Therapeutic Uses of Supranutritional Doses of Selenium</b>	317
17.3.1	Arsenism	317
17.3.2	Cancer prevention	318
<b>17.4</b>	<b>Synthetic Selenium-Containing Therapeutics</b>	321
17.4.1	Anti-oxidants and anti-inflammatory agents	321
17.4.2	Anti-cancer	324
17.4.3	Anti-hypertensives	327
17.4.4	Anti-virals and anti-bacterials	327

<b>17.5</b>	<b>Conclusion</b>	328
	<b>References</b>	328
<b>18</b>	<b><sup>43</sup>Tc Technetium in Medicine</b>	333
	<i>Oyebola O. Sogbein and John F. Valliant</i>	
<b>18.1</b>	<b>Overview</b>	333
<b>18.2</b>	<b>Technetium: Historical Accounts and Properties Relevant to Nuclear Medicine</b>	334
<b>18.3</b>	<b>Technetium Radiopharmaceuticals</b>	336
	18.3.1 Tc-essential compounds	336
	18.3.2 Tc-tagged compounds	338
<b>18.4</b>	<b>Peptide-Targeted Radiopharmaceuticals</b>	343
<b>18.5</b>	<b>Current Areas of Research</b>	344
	18.5.1 Bioorganometallic chemistry	344
	18.5.2 Tc and solid supports	345
	18.5.3 Technetium-94m	349
<b>18.6</b>	<b>Outlook</b>	350
	<b>References</b>	352
<b>19</b>	<b><sup>44</sup>Ru Perspectives of Ruthenium Complexes in Cancer Therapy</b>	359
	<i>Olivier Lentzen, Cécile Moucheron and Andrée Kirsch-De Mesmaeker</i>	
<b>19.1</b>	<b>Introduction</b>	359
<b>19.2</b>	<b>Ruthenium Complexes that Mimic Platinum Drugs</b>	360
	19.2.1 Chloro-ammino derivatives	361
	19.2.2 Dimethyl-sulfoxide complexes	362
	19.2.3 Complexes with mixed chloride and heterocyclic ligands	364

<b>19.3</b>	<b>Design of New Anti-cancer Compounds based on the Photoreactivity of Polyazaaromatic Ruthenium(II) Complexes</b>	365
19.3.1	Energy transfer processes leading to photo-cleavages	367
19.3.2	Photoelectron transfer processes leading to DNA cleavages	368
19.3.3	Photoelectron transfer processes leading to photoadduct formation	371
<b>19.4</b>	<b>Targeting Base Residues of Specific Sequences</b>	373
<b>19.5</b>	<b>Conclusions</b>	375
	<b>References</b>	376
<b>20</b>	<b><sup>45</sup>Rh Rhodium in Medicine</b>	379
	<i>Florian P. Pruchnik</i>	
<b>20.1</b>	<b>Introduction</b>	379
<b>20.2</b>	<b>Anti-tumor Activity of Rhodium Complexes</b>	379
20.2.1	Rhodium(I) complexes	380
20.2.2	Rhodium(II) complexes	381
20.2.3	Rhodium(III) complexes	385
<b>20.3</b>	<b>Anti-bacterial and Anti-parasitic Activity</b>	388
<b>20.4</b>	<b>Radorhodium Agents</b>	390
<b>20.5</b>	<b>Photochemotherapy</b>	391
<b>20.6</b>	<b>Toxicity of Rhodium Complexes</b>	392
	<b>References</b>	394
<b>21</b>	<b><sup>46</sup>Pd The Use of Palladium Complexes in Medicine</b>	399
	<i>Achilleas Garoufis, Sotiris K. Hadjikakou and Nick Hadjiliadis</i>	
<b>21.1</b>	<b>Introduction</b>	399

<b>21.2</b>	<b>Anti-viral, Anti-fungal and Anti-microbial Activity of Pd(II) Complexes</b>	400
21.2.1	Sulfur-donor ligands	400
21.2.2	Metal complexes of drugs used as ligands	404
21.2.3	Palladium(II) complexes with Schiff base ligands	405
21.2.4	Miscellaneous	406
<b>21.3</b>	<b>Anti-tumor Activity of Pd(II) Complexes</b>	407
21.3.1	Sulfur-donor ligands	407
21.3.2	Nitrogen and other donor atoms	410
<b>21.4</b>	<b>Concluding Remarks</b>	414
	<b>References</b>	415
<b>22</b>	<b><sup>50</sup>Sn Tin Compounds and Their Therapeutic Potential</b>	421
	<i>Marcel Gielen and Edward R.T. Tiekink</i>	
<b>22.1</b>	<b>Introduction</b>	421
<b>22.2</b>	<b>Structures of Organotin Compounds in Solution</b>	422
<b>22.3</b>	<b>Anti-tumour Pre-screening</b>	422
<b>22.4</b>	<b>Early <i>In Vitro</i> Cytotoxicity Testing of Diorganotin Carboxylates</b>	423
<b>22.5</b>	<b>The Di-<i>n</i>-Butyltin Analogue of Carboplatin</b>	425
<b>22.6</b>	<b>Anti-tumour Potential of Triorganotin Carboxylates</b>	426
<b>22.7</b>	<b>Anti-tumour Screening of Organotin Derivatives of Biologically Relevant Substrates</b>	427
<b>22.8</b>	<b>Anti-tumour Potential of Fluorine-Substituted Organotin Carboxylates</b>	428
<b>22.9</b>	<b>Anti-tumour Potential of Boron-Containing Organotin Carboxylates</b>	428

<b>22.10</b>	<b>Anti-tumour Potential of Organotin Carboxylates-Containing Polyoxaalkyl Moieties</b>	430
<b>22.11</b>	<b>Mode of Action of Cytotoxic Organotin Compounds</b>	431
<b>22.12</b>	<b>Other Therapeutic Potential of Organotin Compounds</b>	431
<b>22.13</b>	<b>Therapeutic Potential of Tin Compounds Without Tin-to-Carbon Bonds</b>	433
<b>22.14</b>	<b>Conclusions</b>	435
	<b>Acknowledgements</b>	435
	<b>References</b>	435
<b>23</b>	<b><sup>51</sup>Sb Antimony in Medicine</b>	441
	<i>Siucheong Yan, Lan Jin and Hongzhe Sun</i>	
<b>23.1</b>	<b>Introduction</b>	441
<b>23.2</b>	<b>The Chemistry of Antimony</b>	441
<b>23.3</b>	<b>Antimony in Medicine</b>	443
	23.3.1 Historic view of antimony drugs	443
	23.3.2 Applications of antimony drugs as anti-leishmanial agents	444
	23.3.3 Other medicinal applications	445
<b>23.4</b>	<b>Pharmacology, Toxicology and Metabolism of Antimony Drugs</b>	447
	23.4.1 Pharmacology and human toxicology of antimony drugs	447
	23.4.2 Pharmacokinetics studies and clinical aspect of antimony drugs	448
<b>23.5</b>	<b>Possible Mechanism of Action of Antimony Drugs: Interaction of Antimony with Biologically Relevant Molecules</b>	449



23.5.1	General hypothesis on the mechanisms of action of antimony anti-leishmanial compounds	449
23.5.2	<i>In vitro</i> and <i>in vivo</i> reduction of antimony(V) drugs	449
23.5.3	Interaction of antimony(III) compounds with thiolate molecules	450
23.5.4	Inhibition of topoisomerase I from <i>Leishmania donovani</i> and formation of DNA-protein complexes by Sb <sup>V</sup>	453
23.5.5	Antimony-mediated DNA fragmentation, apoptosis and Ca <sup>2+</sup> -related programmed cell death in <i>Leishmania</i>	454
23.5.6	Interference of the exclusive purine scavenge pathway of <i>Leishmania</i>	454
23.5.7	Modulation and increase of cellular signaling of the host macrophage as a means of intracellular <i>Leishmania</i> elimination	455
<b>23.6</b>	<b>Concluding Remarks</b>	457
	<b>Abbreviations</b>	457
	<b>Acknowledgement</b>	457
	<b>References</b>	457
<b>24</b>	<b><sup>75</sup>Re Therapeutic Rhenium Radiopharmaceuticals</b>	463
	<i>Jonathan R. Dilworth and Paul S. Donnelly</i>	
<b>24.1</b>	<b>Introduction</b>	463
<b>24.2</b>	<b>Synthetic Aspects of Rhenium Radiopharmaceuticals</b>	466
24.2.1	Complexes of bifunctional ligands	467
<b>24.3</b>	<b>The Radiopharmaceutical Chemistry of Rhenium</b>	467
24.3.1	Complexes with oxo-cores	467
24.3.2	Complexes with cores containing metal–nitrogen multiple bonds	472
24.3.3	Complexes of the Re(I) tricarbonyl core	474

24.3.4	Organometallic approaches	479
24.3.5	Miscellaneous approaches	480
<b>24.4</b>	<b>'First-Generation' Rhenium Agents</b>	482
24.4.1	Bone-targeting phosphonate complexes	482
24.4.2	[Re(V)-oxo(DMSA)]	483
24.4.3	Rhenium agents for endovascular radiation therapy	484
24.4.4	Rhenium agents for radiation synovectomy	485
<b>24.5</b>	<b>Summary</b>	485
	<b>References</b>	486
<b>25</b>	<b><sup>78</sup>Pt Platinum-Based Drugs</b>	489
	<i>Viktor Brabec and Jana Kasparkova</i>	
<b>25.1</b>	<b>Introduction, Anti-tumor Activity of Cisplatin</b>	489
<b>25.2</b>	<b>Anti-tumor Activity of Carboplatin, Oxaliplatin and Nedaplatin</b>	490
<b>25.3</b>	<b>Mechanism of Action of Cisplatin</b>	491
<b>25.4</b>	<b>Mechanism of Action of Carboplatin, Oxaliplatin and Nedaplatin</b>	494
<b>25.5</b>	<b>Activation of <i>trans</i> Geometry</b>	495
<b>25.6</b>	<b>Polynuclear Platinum Compounds</b>	498
<b>25.7</b>	<b>Platinum(IV) Compounds</b>	499
<b>25.8</b>	<b>Targeted Analogues</b>	500
<b>25.9</b>	<b>Anti-viral Activity</b>	501
<b>25.10</b>	<b>Combinations of Platinum Complexes with Other Agents</b>	502
<b>25.11</b>	<b>Conclusions</b>	502
	<b>Acknowledgements</b>	503
	<b>References</b>	503

<b>26</b>	<b><math>^{79}\text{Au}</math> Gold-Based Metallotherapeutics: Use and Potential</b>	507
	<i>Soo Yei Ho and Edward R.T. Tiekink</i>	
<b>26.1</b>	<b>Preamble</b>	507
<b>26.2</b>	<b>The Physical and Chemical Properties of Gold</b>	507
26.2.1	Physical properties of the element	507
26.2.2	Chemical reactivity of gold	508
26.2.3	Oxidation states and stereochemistries of gold complexes	508
<b>26.3</b>	<b>Gold in Medicine</b>	510
26.3.1	Historical perspective	510
26.3.2	Gold therapy for rheumatoid arthritis	511
<b>26.4</b>	<b>Metabolism of Gold Drugs</b>	514
26.4.1	Biological ligand exchange	514
26.4.2	Gold in cells: The thiol-shuttle model	514
26.4.3	Cyanide metabolites	515
<b>26.5</b>	<b>Pharmacological Potential of Gold Complexes</b>	516
26.5.1	Motivation for drug development	516
26.5.2	Anti-tumour properties of gold drugs	517
26.5.3	Tetrahedral gold(I) complexes	518
26.5.4	Auranofin analogues	518
26.5.5	Gold(III) complexes	520
<b>26.6</b>	<b>Other Potential Clinical Applications of Au(I) Complexes</b>	521
26.6.1	Anti-microbial activity	521
26.6.2	Anti-malaria activity	522
26.6.3	Treatment of bronchial asthma	523
26.6.4	Anti-HIV activity and AIDS	524
<b>26.7</b>	<b>Conclusions and Outlook</b>	524
	<b>Acknowledgements</b>	524
	<b>References</b>	524

<b>27</b>	<b><math>^{83}\text{Bi}</math> Bismuth-Based Pharmaceuticals</b>	529
	<i>Neil Burford and Melanie D. Eelman</i>	
<b>27.1</b>	<b>Introduction</b>	529
<b>27.2</b>	<b>Bismuth-Based Therapeutics</b>	529
<b>27.3</b>	<b>Fundamental Aspects of Bismuth Chemistry and Methods of Characterization</b>	530
<b>27.4</b>	<b>Hydroxycarboxylate Complexes of Bismuth</b>	531
<b>27.5</b>	<b>Development of Bioactive Bismuth Compounds</b>	534
<b>27.6</b>	<b>Interactions of Bismuth Compounds with Biological Molecules</b>	537
<b>27.7</b>	<b>Concluding Remarks</b>	539
	<b>References</b>	539
<b>28</b>	<b>Paramagnetic Metal Complexes as Contrast Agents for Magnetic Resonance Imaging</b>	541
	<i>Silvio Aime, Alessandro Barge, Eliana Gianolio, Simonetta Geninatti Crich, Walter Dastrù and Fulvio Uggeri</i>	
<b>28.1</b>	<b>Generalities on Magnetic Resonance Imaging (MRI) and Paramagnetic Contrast Agents</b>	541
<b>28.2</b>	<b>Determinants of the Relaxivity of Paramagnetic Metal Complexes</b>	544
<b>28.3</b>	<b>Responsive Agents</b>	548
	28.3.1 pH sensitive agents	549
	28.3.2 Agents sensitive to the redox potential	551
	28.3.3 Enzyme responsive agents	552

<b>28.4</b>	<b>Targeting Cells with Gd(III) Chelates</b>	554
<b>28.5</b>	<b>Concluding Remarks</b>	559
	<b>References</b>	559

**Index**

561

Department of Chemistry University of Toronto Toronto Ontario Canada	561
Michael Carugo Department of Chemistry University of Victoria Parkville Victoria 3052 Australia	561
Hai Cao Department of Chemistry The Key Laboratory of Ministry of Education State Key Laboratory of Materials and Technology Sun Yat-Sen University Guangzhou 510275 P.R. China	561
Giuseppe Crich Dipartimento di Chimica IFM e Centro per il Molecular Imaging 7 Via Pietro Giuria I-10125 Torino Italy	561
Walter Dastrù Dipartimento di Chimica IFM e Centro per il Molecular Imaging 7 Via Pietro Giuria I-10125 Torino Italy	561
Mario Barbagnolo Department of Internal Medicine and Geriatrics University of Palermo via F. Scudato 6/c I-90144 Palermo Italy	561
Alessandro Barigo Dipartimento di Chimica IFM e Centro per il Molecular Imaging 7 Via Pietro Giuria I-10125 Torino Italy	561
Lawrence R. Bernstein 285 Willow Road Menlo Park CA 94025 USA	561
Tanzhene Bose Department of Biology University of Isfahan Isfahan Iran	561