

Edited by
Evamarie Hey-Hawkins and Clara Viñas Teixidor

Boron-Based Compounds

Potential and Emerging
Applications in Medicine



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Edited by

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Contents

List of Contributors *xiii*

Preface *xvii*

Part 1 Design of New Boron-based Drugs 1

- 1.1 Carboranes as Hydrophobic Pharmacophores: Applications for Design of Nuclear Receptor Ligands 3
Yasuyuki Endo
 - 1.1.1 Roles of Hydrophobic Pharmacophores in Medicinal Drug Design 3
 - 1.1.2 Carboranes as Hydrophobic Structures for Medicinal Drug Design 4
 - 1.1.3 Estrogen Receptor Ligands Bearing a Carborane Cage 5
 - 1.1.3.1 Estrogen Agonists 5
 - 1.1.3.2 Estrogen Antagonists and Selective Estrogen-Receptor Modulators (SERMs) 7
 - 1.1.4 Androgen Receptor Ligands Bearing a Carborane Cage 7
 - 1.1.4.1 Androgen Antagonists 7
 - 1.1.4.2 Improvement of Carborane-Containing Androgen Antagonists as Candidates for Anti-Prostate Cancer Therapy 9
 - 1.1.5 Retinoic Acid Receptor (RAR) and Retinoic Acid X Receptor (RXR) Ligands Bearing a Carborane Cage 11
 - 1.1.5.1 RAR Agonists and Antagonists 11
 - 1.1.5.2 RXR Agonists and Antagonists 12
 - 1.1.6 Vitamin D Receptor Ligands Bearing a Carborane Cage 12
 - 1.1.7 Determination of the Hydrophobicity Constant π for Carboranes and Quantitative Structure–Activity Relationships in ER Ligands 13
 - 1.1.7.1 Determination of the Hydrophobicity Constant π for Carboranes 13
 - 1.1.7.2 Quantitative Structure–Activity Relationships of Carboranylphenols with Estrogenic Activity 14
 - 1.1.8 Conclusion and Prospects 16
 - References 16

1.2	Boron Cluster Modifications with Antiviral, Anticancer, and Modulation of Purinergic Receptors' Activities Based on Nucleoside Structures	20
	<i>Anna Adamska-Bartłomiejczyk, Katarzyna Bednarska, Magdalena Białek-Pietras, Zofia M. Kiliańska, Adam Mieczkowski, Agnieszka B. Olejniczak, Edyta Paradowska, Mirosława Studzińska, Zofia Sułowska, Jolanta D. Żołnierczyk, and Zbigniew J. Lesnikowski</i>	
1.2.1	Introduction	20
1.2.2	Boron Clusters as Tools in Medicinal Chemistry	21
1.2.3	Modification of Selected Antiviral Drugs with Lipophilic Boron Cluster Modulators and New Antiviral Nucleosides Bearing Boron Clusters	23
1.2.4	<i>In Vitro</i> Antileukemic Activity of Adenosine Derivatives Bearing Boron Cluster Modification	26
1.2.5	Adenosine–Boron Cluster Conjugates as Prospective Modulators of Purinergic Receptor Activity	28
1.2.6	Summary	30
	Acknowledgments	30
	References	30
1.3	Design of Carborane-Based Hypoxia-Inducible Factor Inhibitors	35
	<i>Guangzhe Li, Hyun Seung Ban, and Hiroyuki Nakamura</i>	
1.3.1	Introduction	35
1.3.2	Boron-Containing Phenoxyacetanilides	36
1.3.2.1	Synthesis of Boron-Containing Phenoxyacetanilides	36
1.3.2.2	Biological Activity of Boron-Containing Phenoxyacetanilides	38
1.3.3	Target Identification of GN26361	39
1.3.3.1	Design of GN26361 Chemical Probes	39
1.3.3.2	Synthesis of GN26361 Chemical Probes	39
1.3.3.3	Target Identification of GN26361	40
1.3.4	Carborane-Containing HSP60 Inhibitors	40
1.3.4.1	Design of <i>Ortho</i> - and <i>Meta</i> -Carborane Analogs of GN26361	40
1.3.4.2	Synthesis of GN26361 Analogs	41
1.3.4.3	HIF Inhibitory Activity of Carborane Analogs of GN26361	46
1.3.4.4	HSP60 Inhibitory Activity of Carborane Analogs of GN26361	47
1.3.5	Carborane-Containing Manassantin Mimics	49
1.3.5.1	Synthesis of Carborane-Containing Manassantin Mimics	49
1.3.5.2	Biological Activity of Carborane-Containing Manassantin Mimics	51
1.3.6	Carborane-Containing Combretastatin A-4 Mimics	52
1.3.6.1	Design of <i>Ortho</i> -Carborane Analogs of Combretastatin A-4	52
1.3.6.2	Synthesis of Carborane Analogs of Combretastatin A4	53
1.3.6.3	HIF Inhibitory Activity of Carborane Analogs of Combretastatin A4	54
1.3.7	Conclusion	56
	References	57
1.4	Half- and Mixed-Sandwich Transition Metal Dicarbolides and <i>nido</i>-Carboranes(–1) for Medicinal Applications	60
	<i>Benedikt Schwarze, Marta Gozzi, and Evamarie Hey-Hawkins</i>	
1.4.1	Introduction	60
1.4.2	Synthetic Approaches to <i>nido</i> -Carborane $[C_2B_9H_{12}]^-$ Derivatives	66

1.4.3	Biologically Active Organometallic <i>nido</i> -Carborane Complexes and Organic <i>nido</i> -Carborane Derivatives	72
1.4.3.1	Biologically Active Half- and Mixed-Sandwich Metallocarborane Complexes	72
1.4.3.1.1	Half-Sandwich Complexes of Rhenium(I) and Technetium(I)-99m as Radio-Imaging and Radiotherapeutic Agents	72
1.4.3.1.2	<i>nido</i> -Carborane(−1) Anions as Pharmacophores for Metal-Based Drugs	79
1.4.3.2	Biologically Active Compounds Containing a <i>nido</i> -Carborane(−1) Core	83
1.4.3.2.1	Radiotherapy and Radio-Imaging	83
1.4.3.2.2	Pharmacophores	91
1.4.4	Conclusions and Future Challenges	95
	Appendix: Abbreviations	96
	Acknowledgments	97
	References	98
1.5	Ionic Boron Clusters as Superchaotropic Anions: Implications for Drug Design	109
	<i>Khaleel I. Assaf, Joanna Wilińska, and Detlef Gabel</i>	
1.5.1	Introduction	109
1.5.2	Water Structure and Coordinating Properties	110
1.5.3	Host–Guest Chemistry of Boron Clusters	112
1.5.4	Ionic Boron Clusters in Protein Interactions	116
1.5.4.1	Interactions of Boron Clusters with Lipid Bilayers	118
1.5.5	Implications for Drug Design	120
1.5.5.1	Binding to Proteins	120
1.5.5.2	Penetration through Membranes	120
1.5.5.3	Computational Methods	120
1.5.6	Conclusions	121
	References	121
1.6	Quantum Mechanical and Molecular Mechanical Calculations on Substituted Boron Clusters and Their Interactions with Proteins	126
	<i>Jindřich Fanfrlík, Adam Pecina, Jan Řezáč, Pavel Hobza, and Martin Lepšík</i>	
1.6.1	Introduction	126
1.6.2	Plethora of Noncovalent Interactions of Boron Clusters	127
1.6.3	Computational Methods	129
1.6.3.1	Advanced Methods for Models Systems in Vacuum	129
1.6.3.2	Approximate Methods for Extended Systems Including the Environment	129
1.6.3.2.1	SQM Methods	130
1.6.3.2.2	MM Methods	130
1.6.3.2.3	Solvation and Ion Models	131
1.6.3.2.4	pKa Calculations	131
1.6.3.2.5	Docking and Scoring	131
1.6.4	Boron Cluster Interactions with Proteins	131
1.6.5	Conclusions	135
	References	135

Part 2 Boron Compounds in Drug Delivery and Imaging 139

2.1 Closures: An Icosahedral Platform for Drug Delivery 141

Satish S. Jalisatgi

- 2.1.1 Introduction 141
- 2.1.2 Synthesis and Chemistry of [*closo*-B₁₂H₁₂]²⁻ 143
- 2.1.3 Hydroxylation of [*closo*-B₁₂H₁₂]²⁻ 143
- 2.1.4 Ether and Ester Closures 144
- 2.1.5 Carbonate and Carbamate Closures 145
- 2.1.6 Azido Closures 146
- 2.1.7 Methods of Vertex Differentiation for Multifunctional Closures 148
- 2.1.7.1 Vertex Differentiation by Selective Derivatization of [*closo*-B₁₂(OH)₁₂]²⁻, 1 148
- 2.1.7.2 Vertex Differentiation by Functionalizing the B₁₂²⁻ Core Prior to the Cage Hydroxylation 151
- 2.1.8 Conclusions 155
- References 155

2.2 Cobaltabisdicarbollide-based Synthetic Vesicles: From Biological Interaction to *in vivo* Imaging 159

Clara Viñas Teixidor, Francesc Teixidor, and Adrian J. Harwood

- 2.2.1 Introduction 159
- 2.2.2 A Synthetic Membrane System 160
- 2.2.3 Crossing Lipid Bilayers 161
- 2.2.4 Visualization of COSAN within Cells 162
- 2.2.5 COSAN Interactions with Living Cells 163
- 2.2.6 Enhancing Cellular Effects of COSAN 165
- 2.2.7 Tracking the *in vivo* Distribution of I-COSAN 167
- 2.2.8 Discussion and Potential Applications 168
- 2.2.9 Summary 170
- Appendix: Abbreviations 170
- Acknowledgments 171
- References 171

2.3 Boronic Acid-Based Sensors for Determination of Sugars 174

Igor B. Sivaev and Vladimir I. Bregadze

- 2.3.1 Introduction 174
- 2.3.2 Interactions of Boronic Acids with Carbohydrates 175
- 2.3.3 Fluorescence Carbohydrate Sensors 179
- 2.3.3.1 Intramolecular Charge Transfer Sensors 180
- 2.3.3.2 Photoinduced Electron Transfer Sensors 186
- 2.3.3.3 Fluorescence Resonance Energy Transfer Sensors 196
- 2.3.4 Colorimetric Sensors 197
- 2.3.5 Conclusions 199
- References 199

2.4	Boron Compounds in Molecular Imaging	205
	<i>Bhaskar C. Das, Devi Prasan Ojha, Sasmita Das, and Todd Evans</i>	
2.4.1	Introduction	205
2.4.2	Molecular Imaging in Biomedical Research	207
2.4.3	Molecular Imaging Modalities	207
2.4.4	Boron Compounds in Molecular Imaging	210
2.4.5	Boron-Based Imaging Probes	213
2.4.5.1	Boron-Based Optical Probes	213
2.4.5.2	Boron-Based Nuclear Probes	216
2.4.5.3	Boron-Based MRI Probes	219
2.4.5.4	Boron-Based Molecular Probes for Disease	220
2.4.6	Future Perspectives	224
	Appendix: Companies Offering Imaging Instruments and Reagents	225
	References	225
2.5	Radiolabeling Strategies for Boron Clusters: Toward Fast Development and Efficient Assessment of BNCT Drug Candidates	232
	<i>Kiran B. Gona, Vanessa Gómez-Vallejo, Irina Manea, Jonas Malmquist, Jacek Koziorowski, and Jordi Llop</i>	
2.5.1	Boron Neutron Capture Therapy	232
2.5.1.1	Boron: The Element	232
2.5.1.2	The Principle behind Boron Neutron Capture Therapy (BNCT)	232
2.5.2	Boron Clusters	235
2.5.2.1	Boranes	236
2.5.2.2	Carboranes	236
2.5.2.3	Metallocarboranes	238
2.5.3	Nuclear Imaging: Definition and History	238
2.5.3.1	Radioactivity: The Basis of Nuclear Imaging	239
2.5.3.2	Single-Photon Emission Computerized Tomography	240
2.5.3.3	Positron Emission Tomography	241
2.5.3.4	Multimodal Imaging	243
2.5.3.5	Nuclear Imaging and the Need for Radiolabeling	243
2.5.4	Radiolabeling of Boron Clusters	244
2.5.4.1	Radiohalogenation	245
2.5.4.1.1	Radioastatination of Boron Clusters	245
2.5.4.1.2	Radioiodination of Boron Clusters	246
2.5.4.1.3	Radiofluorination of Boron Clusters	248
2.5.4.1.4	Radiobromination of Boron Clusters	250
2.5.4.2	Radiometallation	251
2.5.4.2.1	Radiolabeling using other Radionuclides	253
2.5.5	The use of Radiolabeling in BNCT Drug Development: Illustrative Examples	254
2.5.6	Conclusion and Future Perspectives	259
	References	259

Part 3 Boron Compounds for Boron Neutron Capture Therapy 269

3.1 Twenty Years of Research on 3-Carboranyl Thymidine Analogs (3CTAs): A Critical Perspective 271

Werner Tjarks

- 3.1.1 Introduction 271
- 3.1.2 Boron Neutron Capture Therapy 272
- 3.1.3 Carboranes 273
- 3.1.4 Rational Design of 3CTAs 274
- 3.1.5 Synthesis and Initial Screening of 3CTAs as TK1 Substrates 275
 - 3.1.5.1 First-Generation 3CTAs 275
 - 3.1.5.2 Second-Generation 3CTAs 277
- 3.1.6 Enzyme Kinetic and Inhibitory Studies 279
- 3.1.7 Cell Culture Studies 279
- 3.1.8 Metabolic Studies 280
- 3.1.9 Cellular Influx and Efflux Studies 282
- 3.1.10 *In vivo* Uptake and Preclinical BNCT Studies 282
- 3.1.11 Potential Non-BNCT Applications for 3CTAs 284
- 3.1.12 Conclusion 285
- Acknowledgments 286
- References 286

3.2 Recent Advances in Boron Delivery Agents for Boron Neutron Capture Therapy (BNCT) 298

Sunting Xuan and Maria da Graça H. Vicente

- 3.2.1 Introduction 298
 - 3.2.1.1 Mechanisms of BNCT 298
 - 3.2.1.2 General Criteria for BNCT Agents 299
 - 3.2.1.3 Main Categories of BNCT Agents 299
- 3.2.2 Amino Acids and Peptides 300
- 3.2.3 Nucleosides 304
- 3.2.4 Antibodies 305
- 3.2.5 Porphyrin Derivatives 307
 - 3.2.5.1 Porphyrin Macrocycles 307
 - 3.2.5.2 Chlorin Macrocycles 314
 - 3.2.5.3 Phthalocyanine Macrocycles 316
- 3.2.6 Boron Dipyrromethenes 318
- 3.2.7 Liposomes 321
- 3.2.8 Nanoparticles 324
- 3.2.9 Conclusions 330
- References 331

3.3 Carborane Derivatives of Porphyrins and Chlorins for Photodynamic and Boron Neutron Capture Therapies: Synthetic Strategies 343

Valentina A. Ol'shevskaya, Andrei V. Zaitsev, and Alexander A. Shtil

- 3.3.1 Introduction 343
- 3.3.2 Recent Synthetic Routes to Carboranyl-Substituted Derivatives of 5,10,15,20-Tetraphenylporphyrin 344

3.3.3	Synthesis of Carborane Containing Porphyrins and Chlorins from Pentafluorophenyl-Substituted Porphyrin	350
3.3.4	Carborane Containing Derivatives of Chlorins: New Properties for PDT and Beyond	355
3.3.4.1	Carborane Containing Derivatives of Pyropheophorbide <i>a</i> and Pheophorbide <i>a</i>	356
3.3.4.2	Carborane Containing Derivatives of Chlorin <i>e</i> ₆	358
3.3.4.3	Carborane Containing Derivatives of Purpurin-18 and Bacteriopurpurinimide	362
3.3.5	Conclusion	364
	Acknowledgments	364
	References	365
3.4	Nanostructured Boron Compounds for Boron Neutron Capture Therapy (BNCT) in Cancer Treatment	371
	<i>Shanmin Gao, Yinghuai Zhu, and Narayan Hosmane</i>	
3.4.1	Introduction	371
3.4.2	Boron Neutron Capture Therapy (BNCT)	373
3.4.2.1	Principles of BNCT	373
3.4.2.2	Liposome-Based BNCT Agents	375
3.4.2.3	Carbon Nanotubes	377
3.4.2.4	Boron and Boron Nitride Nanotubes	377
3.4.2.5	Magnetic Nanoparticles-Based BNCT Carriers	379
3.4.2.6	Other Boron-Enriched Nanoparticles	382
3.4.3	Summary and Outlook	383
	References	383
3.5	New Boronated Compounds for an Imaging-Guided Personalized Neutron Capture Therapy	389
	<i>Nicoletta Protti, Annamaria Deagostino, Paolo Boggio, Diego Alberti, and Simonetta Geninatti Crich</i>	
3.5.1	General Introduction on BNCT: Rationale and Application	389
3.5.2	Imaging-Guided NCT: Personalization of the Neutron Irradiation Protocol	392
3.5.2.1	Positron Emission Tomography	392
3.5.2.2	Single-Photon Emission Computed Tomography	395
3.5.2.3	Magnetic Resonance Imaging and Spectroscopy	396
3.5.2.3.1	¹ H-MRI	396
3.5.2.3.2	MRS Spectroscopy	398
3.5.2.3.3	¹⁰ B and ¹¹ B NMR	398
3.5.2.4	Optical Imaging	400
3.5.2.5	Boron Microdistribution	401
3.5.3	Targeted BNCT: Personalization of <i>in vivo</i> Boron-Selective Distribution	402
3.5.3.1	Small-Sized Boron Carriers	402
3.5.3.2	Nanosized Boron Carriers	406
3.5.4	Combination of BNCT with Other Conventional and Nonconventional Therapies	407

3.5.4.1	Chemotherapy	408
3.5.4.2	Photodynamic Therapy (PDT)	408
3.5.4.3	Standard Radiotherapy	408
3.5.5	Conclusions	410
	References	410

3.6 Optimizing the Therapeutic Efficacy of Boron Neutron Capture Therapy (BNCT) for Different Pathologies: Research in Animal Models Employing Different Boron Compounds and Administration Strategies 416

Amanda E. Schwint, Andrea Monti Hughes, Marcela A. Garabalino, Emiliano C.C. Pozzi, Elisa M. Heber, and Veronica A. Trivillin

3.6.1	BNCT Radiobiology	416
3.6.2	An Ideal Boron Compound	417
3.6.3	Clinical Trials, Clinical Investigations, and Translational Research	418
3.6.4	Boron Carriers	419
3.6.5	Optimizing Boron Targeting of Tumors by Employing Boron Carriers Approved for Use in Humans	422
3.6.6	BNCT Studies in the Hamster Cheek Pouch Oral Cancer Model	422
3.6.6.1	The Hamster Cheek Pouch Oral Cancer Model	422
3.6.6.2	BNCT Mediated by BPA	425
3.6.6.3	BNCT Mediated by GB-10 or by GB-10 + BPA	425
3.6.6.4	Sequential BNCT	428
3.6.6.5	Tumor Blood Vessel Normalization to Improve Boron Targeting for BNCT	430
3.6.6.6	Tumor Blood Vessel Normalization + Seq-BNCT	432
3.6.6.7	Electroporation + BNCT	432
3.6.6.8	Assessing Novel Boron Compounds	433
3.6.7	BNCT Studies in a Model of Oral Precancer in the Hamster Cheek Pouch for Long-Term Follow-up	435
3.6.8	BNCT Studies in a Model of Liver Metastases in BDIX Rats	438
3.6.9	BNCT Studies in a Model of Diffuse Lung Metastases in BDIX Rats	441
3.6.10	BNCT Studies in a Model of Arthritis in Rabbits	442
3.6.11	Preclinical BNCT Studies in Cats and Dogs with Head and Neck Cancer with no Treatment Option	445
3.6.12	Future Perspectives	446
	References	446

Index 462

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Preface

Today, medicinal chemistry is still clearly dominated by organic chemistry, and most commercial drugs are purely organic molecules, which, besides carbon and hydrogen, can incorporate nitrogen, oxygen, sulfur, phosphorus, and halogens, all of which are to the right of carbon in the periodic table, whereas boron is located to the left. Boron and carbon are elements that have the ability to build molecules of unlimited size by covalent self-bonding. However, commercial boron-based drugs are still rare. Bortezomib, tavorole (AN2690), crisaborole (AN2728), epetraborole (AN3365), SCYX-7158 (AN5568), 4-(dihydroxyboryl)phenylalanine (BPA), and sodium mercapto-undecahydro-*closo*-dodecaborate (BSH) are used as drugs, the last two compounds in boron neutron capture therapy (BNCT). All of these boron-containing drugs are derivatives of boronic acids except BSH, which contains an anionic boron cluster. While the pharmacological uses of boron compounds have been known for several decades, recent progress is closely related to the discovery of further boron-containing compounds as prospective drugs. While first developments of the medicinal chemistry of boron were stipulated by applications in BNCT of cancers, knowledge accumulated during the past decades on the chemistry and biology of bioorganic and bioinorganic boron compounds laid the foundation for the emergence of a new area of study and application of boron compounds as skeletal structures and hydrophobic pharmacophores for biologically active molecules. These and other recent findings clearly show that there is still a great, unexplored potential in medicinal applications of boron-containing compounds.

This book summarizes the present status and further promotes the development of new boron-containing drugs and boron-based materials for diagnostics by bringing together renowned experts in the field of medicinal chemistry of boron compounds. It aims to provide a balanced overview of the vibrant and growing field of the emerging and potential applications of boron compounds in medicinal chemistry and chemical biology. The book is aimed at academics and professional researchers in this field, but also at scientists who want to get a better overview on the state of the art of this rapidly advancing area. It contains reviews of important topics, which are divided into three main sections: (1) “Design of New Boron-based Drugs”, (2) “Boron Compounds in Drug Delivery and Imaging”, and (3) “Boron Compounds for Boron Neutron Capture Therapy”.

The first section, “Design of New Boron-Based Drugs”, consists of six reviews dealing with the use of carborane derivatives for the development of novel drugs. In his review (Chapter 1.1), Yasuyuki Endo, one of the pioneers in the development of carboranes as

hydrophobic pharmacophores almost 20 years ago, describes the development of a variety of potent nuclear receptor ligands with carborane structures as hydrophobic moieties. Nucleoside drugs have been in clinical use for several decades and have become cornerstones of treatment for patients with cancer or viral infections. One of the new developments in the medicinal chemistry of nucleosides is derivatives comprising a boron component such as a boron cluster, as described in the review by Zbigniew J. Lesnikowski and coworkers (Chapter 1.2), whose group has long-standing expertise in the introduction of boron clusters into molecules with diverse biological activity, where they serve as pharmacophores, building blocks, and modulators of the physicochemical and biological properties. An alternative approach to battling cancer is described by Hiroyuki Nakamura *et al.* in their chapter on the design of carborane-based hypoxia-inducible factor (HIF) inhibitors (Chapter 1.3). Overexpression of HIF1 α has been observed in human cancers, including brain, breast, colon, lung, ovary, and prostate cancers; thus, HIF1 α is a novel target of cancer therapy, and the Nakamura group has shown carborane-based HIF1 inhibitors to be very promising targets. Another emerging type of boron-based drugs are metallacarboranes. The group of Evamarie Hey-Hawkins has been involved in carborane chemistry for more than 20 years. In Chapter 1.4, they report recent examples of biologically active half- and mixed-sandwich metallacarborane complexes of the dicarbollide ligand, as well as hybrid organic-inorganic compounds containing a *nido*-carborane(–1) as appended moiety. Their potentially beneficial properties, such as stability in aqueous environments and new binding modes due to their lipophilicity, are described. Prospective applications in radio-imaging, radiotherapy, and drug design are envisaged. In Chapter 1.5, Detlef Gabel and coworkers focus on ionic boron clusters that are soluble in water as well as in nonpolar solvents. This highly interesting feature sets them apart from other ionic and nonionic pharmacophores and renders them interesting new entities for drug design. The final review (Chapter 1.6) by Pavel Hobza, Martin Lepšík, and coworkers on the current status of structure-based computer-aided drug design tools for boron-cluster-containing protein ligands concludes this first section.

In the second section, the focus is on “Boron Compounds in Drug Delivery and Imaging”. Satish S. Jalisatgi, a collaborator of Frederick Hawthorne, who was the pioneer of boron cluster chemistry almost 60 years ago, gives an overview of closo-polyhedral drug delivery platforms based on an icosahedral polyhedral borane scaffold (Chapter 2.1). The resulting monodisperse nanostructures are capable of performing a combination of therapeutic, diagnostic, and targeting functions, which is highly useful for emerging applications. A complementary approach is described in the review by Clara Viñas Teixidor (Chapter 2.2), one of the founders of EuroBoron conference, and her colleagues. The anionic boron-based cobaltabis(dicarbollide) can form atypical monolayer membranes with the shape of vesicles and micelles with similar dimensions to those seen in nature, but of a very different chemical composition. These vesicles interact with liposomes and biological membranes to accumulate inside living cells. Their particular properties offer new opportunities for the development of nanoscale platforms to directly introduce new functionality for use in cancer therapy, drug design, and molecular delivery systems.

Diabetes is a chronic disease that has devastating human, social, and economic consequences. A tight control of blood glucose is the most important goal in dealing with diabetes. The majority of blood glucose monitoring tools relies on the glucose

oxidase enzyme (GOx), but they have some drawbacks. A powerful approach for detecting glucose in fluids is the development of boronic acid-based saccharide sensors. The main principles of their design and factors governing their selectivity are discussed by Igor B. Sivaev and Vladimir I. Bregadze in Chapter 2.3.

Drug development is a lengthy process requiring identification of a biological target, validation of the target, and development of pharmacological agents designed and subsequently confirmed by *in vivo* studies. Molecular and functional imaging applied in the initial stages of drug development can provide evidence of biological activity and confirm on-target drug effects. In their contributions, Bhaskar C. Das *et al.* focus on various boron-containing molecular probes used in molecular imaging (Chapter 2.4), and Jordi Llop *et al.* provide an overview of nuclear imaging techniques, as well as the different radiolabeling strategies reported so far for the incorporation of positron and gamma emitters into boron clusters (Chapter 2.5). Finally, some illustrative examples on how radiolabeling and *in vivo* imaging can aid in the process of drug development are described, focusing on BNCT drug candidates containing boron clusters, linking this chapter to the third section dedicated to “Boron Compounds for Boron Neutron Capture Therapy”.

Cancer is the second leading cause of death globally, and was responsible for 8.8 million deaths in 2015. Treatment typically comprises surgery, radiotherapy, and chemotherapy. BNCT is a unique binary therapy that was developed during the last five to six decades. With the availability of accelerator-based neutron sources at clinics, selective boron compounds for use in BNCT will become very important. In this third section, several novel classes of potential BNCT agents are described. Werner Tjarks critically reviews aspects of the design, synthesis, and biological evaluation of 3-carboranyl thymidine analogs (3CTAs) as boron delivery agents for BNCT over a time span of approximately 20 years (Chapter 3.1). Potential future non-BNCT applications of 3CTAs are also discussed, linking this review to the first section on boron-based drug design. Maria da Graça H. Vicente and Sunting Xuan describe different classes of third-generation boron delivery agents with enhanced tumor-localizing properties, which are under investigation for use in BNCT (Chapter 3.2), and the contribution by Valentina A. Ol'shevskaya and colleagues deals with synthetic approaches leading to tumor-selective boronated porphyrins and chlorins with potential applications in diagnosis, drug delivery, and treatment. This study emphasizes the role of boron in rendering the photoactivatable tetrapyrrolic scaffolds more potent in photodynamic therapy (Chapter 3.3). A highly innovative approach is described in the review by Narayan Hosmane, one of the founders of Boron in the Americas (BORAM), and his coworkers covering the recent developments in the use of nanoparticles as adjuncts to boron-containing compounds in BNCT, involving boron nanotubes (BNTs) and boron nitride nanotubes (BNNTs) (Chapter 3.4). For further implementation of BNCT at the clinical level, new specifically targeted boron carriers for BNCT, conjugated with functional groups detectable by highly sensitive imaging tools, are required. This allows the determination of the local boron concentration, which is crucial to personalize the treatment for each patient. Simonetta Geninatti Crich and coworkers cover this important topic in Chapter 3.5. Furthermore, *in vivo* research in appropriate animal models is important to expand BNCT radiobiology and optimize its therapeutic efficacy for different pathologies. This highly interdisciplinary topic is covered by Amanda E. Schwint and coworkers in their comprehensive contribution in Chapter 3.6.

We are very grateful to all the authors for their contributions and their patience. Last but not least, we would like to thank the Wiley team, especially Sarah Higginbotham and Emma Strickland, for their continuous support in planning and compiling this book, which gives a timely overview of the evolving potential and emerging applications of boron-based compounds in medicine.

*Evamarie Hey-Hawkins and
Clara Viñas Teixidor*

Part 1

Design of New Boron-based Drugs

1.1

Carboranes as Hydrophobic Pharmacophores: Applications for Design of Nuclear Receptor Ligands

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1.1.1 Roles of Hydrophobic Pharmacophores in Medicinal Drug Design

A pharmacophore is a partial structure in which important functional groups and hydrophobic structure are arranged in suitable positions for binding to a receptor [1]. Typically, hydrophilic functional groups of the pharmacophore interact with the receptor by hydrogen bonding and/or ionic bonding, and the hydrophobic structure interacts with a hydrophobic surface of the receptor. While hydrogen bonding plays a key role in specific ligand–receptor recognition, the hydrophobic interaction between receptor and drug molecule is especially important in determining the binding affinity. The difference of binding constants between a ligand having a suitable hydrophobic group and a ligand without such a group can be as large as 1000-fold. In medicinal drug design, the hydrophobic structures are often composed of aromatic and heteroaromatic rings, which also play a role in fixing the arrangement of functional groups appropriately for binding to the receptor. On the other hand, three-dimensional hydrophobic structures are not yet widely used in drug design, even though they could be well suited for interaction with the three-dimensional hydrophobic binding pockets of receptors. It is noteworthy that various steroid hormones target distinct steroid hormone receptors owing to differences of functionalization of the hydrophobic steroidal skeleton. The binding of the natural ligand 17 β -estradiol to human estrogen receptor- α (ER α) is illustrated in Figure 1.1.1 as an example. The large number of steroid hormones may be a consequence of evolutionary diversification of the functions of the steroidal skeleton. In this context, we aimed to establish a new three-dimensional hydrophobic skeletal structure for medicinal drug design.

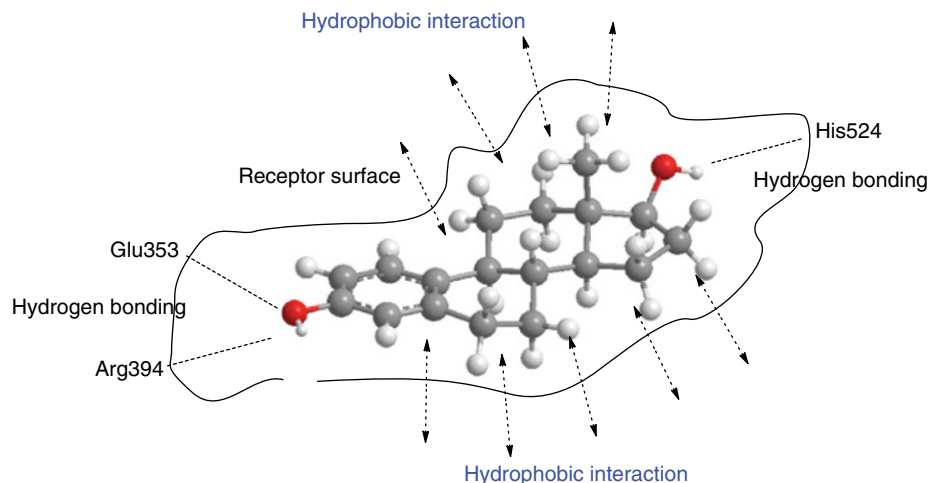


Figure 1.1.1 Interactions of ligand with receptor (example for 17β-estradiol with estrogen receptor-α).

1.1.2 Carboranes as Hydrophobic Structures for Medicinal Drug Design

In the past three decades, there has been increasing interest in globular molecules. In the 1980s, dodecahedrane, which consists of sp^3 carbons, was synthesized [2]; and in the 1990s, the chemistry of fullerene C_{60} , which also consists of sp^2 carbons, was explored [3]. However, the former is not easy to synthesize, while the latter molecule may have limited application because of its large molecular size. On the other hand, icosahedral carboranes [4] are topologically symmetrical, globular molecules, and have been known for more than half a century. The B–B and C–B bonds of 12-vertex carboranes are approximately 1.8 angstroms in length, and the molecular size of carboranes is somewhat larger than adamantane or the volume of a rotated benzene ring. Carboranes have a highly electron-delocalized hydrophobic surface, and are considered to be three-dimensional aromatic compounds [5] or inorganic benzenes. The structures of these compounds are illustrated in Figure 1.1.2. But, although the use of boron derivatives for boron neutron capture therapy (BNCT) of tumors has a long history [6], relatively little attention has yet been paid to the possible use of carboranes as components of biologically active molecules, despite their desirable hydrophobic character, spherical geometry, and convenient molecular size for use in the design and synthesis of medicinal drugs.

Carboranes have three isomers, *ortho*-, *meta*-, and *para*-carboranes (Figure 1.1.2), and their rigid and bulky cage structures hold substituents in well-defined spatial relationships. The two carbon atoms of carboranes have relatively acidic protons, which can readily be substituted with other organic groups [7]. Substituents can also be introduced selectively at certain boron atoms, to construct structures having three or more substituents, as illustrated in Figure 1.1.3 [8]. Carbocyclic skeletons often rearrange under acidic conditions, whereas carborane cage skeletons do not rearrange even in the presence of strong Lewis acids. Adamantane and bicyclo[2,2,2]octane are also available as hydrophobic skeletons, and substituents can readily be introduced at bridgehead carbons of adamantane, but selective introduction at other carbons is difficult, and chirality is also an issue.

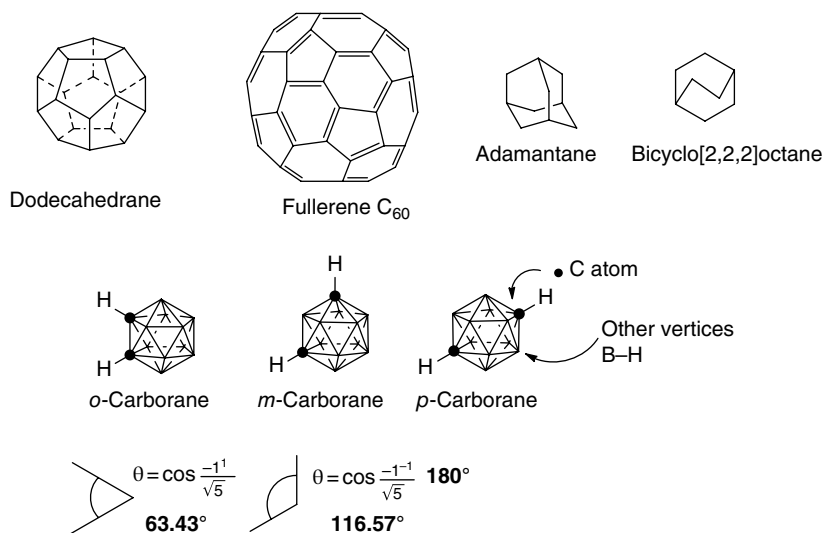
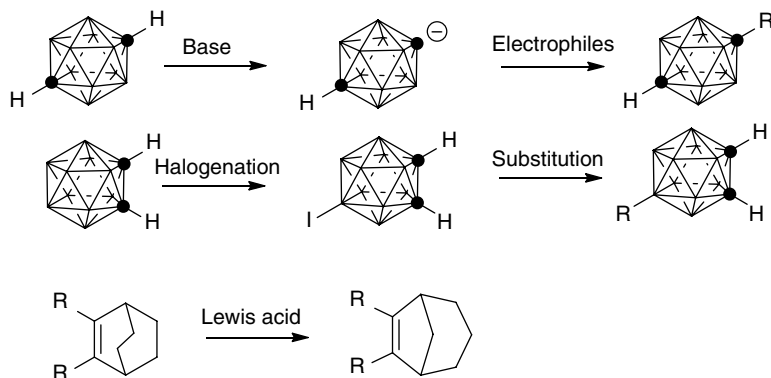


Figure 1.1.2 Structures of globular molecules and characteristics of carboranes.



Rearrangement of hydrocarbon skeleton (for example)

Figure 1.1.3 Advantages of carborane skeleton for synthesis.

1.1.3 Estrogen Receptor Ligands Bearing a Carborane Cage

1.1.3.1 Estrogen Agonists

Estrogen mediates a wide variety of cellular responses through its binding to a specific estrogen receptor (ER). The hormone-bound ER forms an active dimer, which binds to the ER-responsive element of DNA and regulates gene transcription. Endogenous estrogen, such as 17 β -estradiol, plays an important role in the female reproductive system, and also in bone maintenance, the central nervous system, and the cardiovascular system. Recent studies on the three-dimensional structure of the complex formed by estradiol and the human ER α ligand-binding domain have identified the structural requirements for estrogenic activity [9]. 17 β -Estradiol is oriented in the ligand-binding

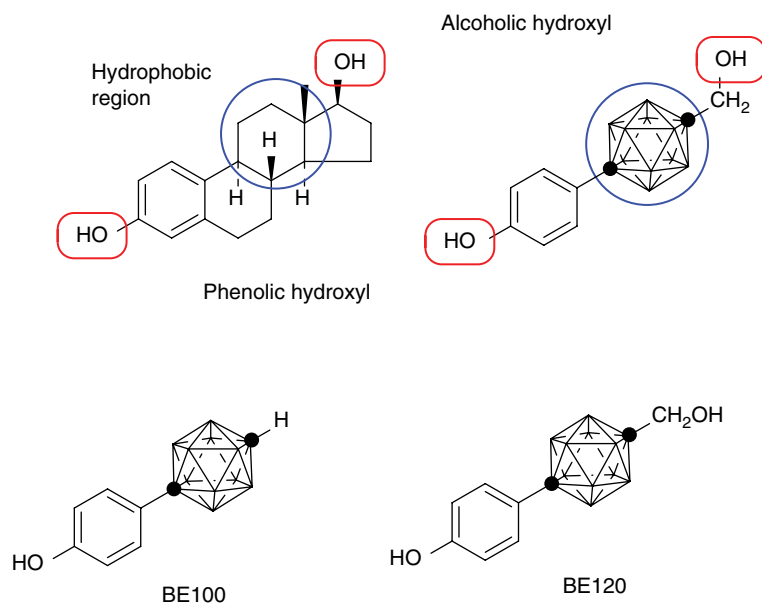


Figure 1.1.4 Structures of β -estradiol and designed molecule bearing *p*-carborane.

pocket by two types of contacts: hydrogen bonding from the phenolic hydroxyl group to Glu353 and Arg394, and from the 17 β -hydroxyl group to the nitrogen of His524, and hydrophobic interaction along the body of the skeleton (see Figure 1.1.1). Therefore, we designed a simple compound with a 4-phenolic residue and a hydroxymethylated *p*-carborane, together with some derivatives (Figure 1.1.4) [10].

The estrogenic activities of the synthesized compounds were examined by means of receptor binding assays. Surprisingly, the simple 4-(*p*-carboranyl)phenol BE100 exhibited potent ER α -binding affinity, comparable with that of estradiol, and the most active compound, BE120, was several times more potent than estradiol. In transcriptional assay, the simple 4-(*p*-carboranyl)phenol BE100 exhibited potent agonistic activity, comparable with that of estradiol. The activity was increased by the introduction of a hydroxymethyl group onto carbon of the carborane cage, and the resulting compound, BE120, was at least 10-fold more potent than estradiol. In a docking simulation of BE120 with the receptor based on the crystal structure of the estradiol-ER α complex, the phenolic hydroxyl group and hydroxymethyl group of BE120 appeared to play similar roles to those in the case of estradiol. The higher activity of BE120 suggests that the carborane cage binds to the hydrophobic cavity of the receptor more tightly than does the equivalent structure of estradiol [11].

BE120 also showed potent *in vivo* effects. Uterine atrophy due to estrogen deficiency or ovariectomy is blocked by estrogen administration, and this forms the basis of a typical *in vivo* assay for estrogenic activity. Estradiol and BE120 at 100 ng per day both restored the uterine weight, indicating that BE120 reproduces the biological activity of estradiol. Similarly, decrease of the bone mineral density of ovariectomized mice was blocked by administration of either estradiol or BE120, with similar potency [12].

1.1.3.2 Estrogen Antagonists and Selective Estrogen-Receptor Modulators (SERMs)

Since estrogen agonists increase the risk of carcinogenesis in breast and uterus [13], estrogen antagonists can be used as anticancer agents. On the other hand, estrogen agonists may be useful for the control of osteoporosis, if the risk of carcinogenesis can be avoided. Therefore, there is great interest in SERMs that selectively affect different organs, especially agents with agonistic activity in bone, but no effect or antagonistic activity in the reproductive organs. Among SERMs so far developed, tamoxifen is used to treat breast cancer [14], and raloxifene to treat osteoporosis [15].

The balance of activities depends on the precise ligand–receptor complex structure, which influences subsequent binding with co-factors and other proteins, leading to different physiological actions. In the case of tamoxifen [14], the bulky dimethylaminoethoxyphenyl group plays a key role in the antagonistic activity. Taking this into account, we designed compounds containing *o*- and *m*-carborane skeletons, as shown in Figure 1.1.5.

The *o*-carborane derivative BE362 inhibited the activity of estradiol in the concentration range of 10^{-7} M in a transcriptional activity assay, being equipotent with tamoxifen. The *m*-carborane derivative BE262 was somewhat less potent than BE362. In this assay, synthetic intermediate BE360 also exhibited antagonistic activity, although its potency was somewhat weaker than that of BE362 [16]. In spite of its very simple structure, BE360 exhibited strong binding affinity for ER [17]. Therefore, we focused on BE360 as a candidate SERM. Loss of bone mineral density of ovariectomized mice was blocked by administration of BE360 at 1–30 mg/day [18]. BE360 was 1000-fold less potent than estradiol, but was almost equipotent with the osteoporosis drug raloxifene. On the other hand, BE360 did not affect uterine weight at this concentration. Thus, BE360 is a promising lead compound for development of therapeutically useful SERMs.

We next investigated structural development of BE360. Insertion of a methylene group (BE380) changed the partial agonist–antagonist character of BE360 to weak agonist, and insertion of two methylene units generated a potent antagonist (BE381). Replacing the carborane cage with a bicyclo[2,2,2]octane skeleton caused a drastic change of biological activity, affording a potent full agonist (BE1060). It seems clear that altering the three-dimensional hydrophobic core structure is a promising strategy for control of the agonist–antagonist activity balance toward ER [19].

In addition, we have recently reported that BE360 has antidepressant and antidementia effects through enhancement of hippocampal cell proliferation in olfactory bulbectomized mice [20]. Thus, BE360 may have potential for treatment of depression and neurodegenerative diseases, such as Alzheimer's disease.

1.1.4 Androgen Receptor Ligands Bearing a Carborane Cage

1.1.4.1 Androgen Antagonists

Like estrogen, androgen mediates cellular responses through binding to a specific androgen receptor (AR). The hormone-bound AR forms a dimer, which binds to the AR-responsive element of DNA and regulates gene transcription. Endogenous androgen, such as testosterone and dihydrotestosterone, plays an important role in the

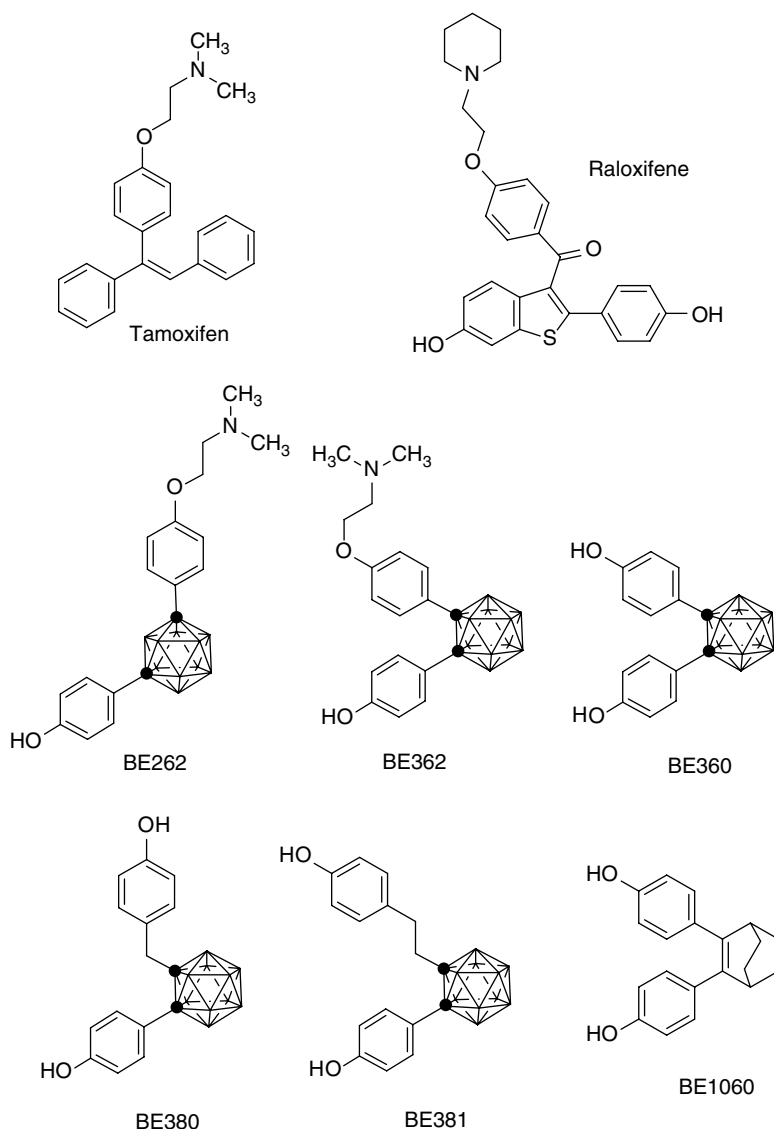


Figure 1.1.5 Structures of selective estrogen receptor modulators: tamoxifen and raloxifene, and designed molecules bearing carborane.

male reproductive system, and also in prostate enlargement, body hair growth, and muscle development. The X-ray structure of the complex of AR ligand-binding domain with an androgen agonist has been reported [21]. The overall structure of the ligand-binding domain is very similar to that of ER, but there are differences in the structures surrounding the ligand-binding pocket. One of the differences between AR and ER ligands is that the aliphatic cyclohexene A-ring of the steroid skeleton bears an 18-methyl group, so that the structure is bulky compared with the flat aromatic A-ring of estrogen. In addition, a ketone is present instead of the phenolic hydroxyl group in