

## Contents

**List of Contributors** XV

**Preface** XXI

### **1 Different Roles of Carboxylic Functions in Pharmaceuticals and Agrochemicals 1**

*Clemens Lamberth and Jürgen Dinges*

- 1.1 Introduction 1
- 1.2 Solubilizer 1
- 1.3 Pharmacophore 3
- 1.4 Prodrug 4
- 1.5 Bioisosteric Replacement 6
- 1.6 Scaffold 8
- 1.7 Conclusion 9
- References 9

### **Part I Neurology 13**

### **2 Carboxylic Ester Containing Norepinephrine–Dopamine Reuptake Inhibitors (NDRIs) 15**

*David J. O'Neill*

- 2.1 Introduction 15
- 2.2 History 15
- 2.3 Synthesis 17
- 2.4 Mode of Action 21
- 2.5 Structure–Activity Relationships 22
- References 25

### **3 Analgesic and Anesthetic Amides 27**

*Thomas Erhard*

- 3.1 Introduction 27
- 3.2 History 27
- 3.3 Synthesis 30

- 3.4 Mode of Action 33
- 3.5 Structure–Activity Relationships 34
- References 37

## Part II Cardiovascular Diseases 39

- 4 **Fibrate Acids and Esters for the Treatment of Hyperlipidemia (PPAR $\alpha$  Activators) 41**  
*Gavin O'Mahony*
  - 4.1 Introduction 41
  - 4.2 History 42
  - 4.3 Synthesis 45
  - 4.4 Mode of Action 48
  - 4.5 Structure–Activity Relationships 50
  - References 54
- 5 **Antiplatelet 2-Hydroxy Thienopyridine Ester Derivatives for the Reduction of Thrombotic Cardiovascular Events 57**  
*Modesto de Candia, Nunzio Denora, and Cosimo D. Altomare*
  - 5.1 Introduction 57
  - 5.2 History 57
  - 5.3 Synthesis 60
  - 5.4 Mode of Action 62
  - 5.5 Structure–Activity Relationships 67
  - References 70
- 6 **Carboxylic Acids and Lactones as HMG-CoA Reductase Inhibitors 71**  
*Xiang-Yang Ye and Pratik Devasthale*
  - 6.1 Introduction 71
  - 6.2 History 72
  - 6.3 Synthesis 73
  - 6.4 Mode of Action 80
  - 6.5 Structure–Activity Relationship 81
  - References 83
- 7 **Angiotensin II Receptor Antagonists with Carboxylic Functionalities in Cardiovascular Disease 87**  
*Steve Swann and Simone Bigi*
  - 7.1 Introduction 87
  - 7.2 History 89
  - 7.3 Synthesis 90
  - 7.4 Mode of Action 95

|           |                                                                                                           |            |
|-----------|-----------------------------------------------------------------------------------------------------------|------------|
| 7.5       | Structure–Activity Relationships                                                                          | 96         |
|           | References                                                                                                | 99         |
| <b>8</b>  | <b>Carboxylic Acid Containing Direct Thrombin Inhibitors for the Treatment of Thromboembolic Diseases</b> | <b>103</b> |
|           | <i>Harry R. Chobanian and Mathew M. Yanik</i>                                                             |            |
| 8.1       | Introduction                                                                                              | 103        |
| 8.2       | History                                                                                                   | 104        |
| 8.3       | Synthesis                                                                                                 | 106        |
| 8.4       | Mode of Action                                                                                            | 108        |
| 8.5       | Structure–Activity Relationship                                                                           | 109        |
|           | References                                                                                                | 113        |
|           | <b>Part III Infectious Diseases</b>                                                                       | <b>115</b> |
| <b>9</b>  | <b>Tetracycline Amide Antibiotics</b>                                                                     | <b>117</b> |
|           | <i>Ingo Janser</i>                                                                                        |            |
| 9.1       | Introduction                                                                                              | 117        |
| 9.2       | History                                                                                                   | 120        |
| 9.2.1     | First-Generation Tetracyclines – The Discovery                                                            | 120        |
| 9.2.2     | Second-Generation Semisynthetic Tetracyclines                                                             | 121        |
| 9.2.3     | Tetracycline Resistance                                                                                   | 122        |
| 9.2.4     | Third-Generation Tetracyclines                                                                            | 123        |
| 9.3       | Synthesis                                                                                                 | 123        |
| 9.4       | Mode of Action                                                                                            | 127        |
| 9.5       | Structure–Activity Relationships                                                                          | 128        |
|           | References                                                                                                | 130        |
| <b>10</b> | <b>Carboxylic-Acid-Based Neuraminidase Inhibitors</b>                                                     | <b>133</b> |
|           | <i>Stacy Van Epps</i>                                                                                     |            |
| 10.1      | Introduction                                                                                              | 133        |
| 10.2      | History                                                                                                   | 133        |
| 10.3      | Synthesis                                                                                                 | 136        |
| 10.4      | Mode of Action                                                                                            | 142        |
| 10.5      | Structure–Activity Relationships                                                                          | 143        |
|           | References                                                                                                | 146        |
| <b>11</b> | <b>Oxazolidinone Amide Antibiotics</b>                                                                    | <b>149</b> |
|           | <i>Cristiana A. Zaharia, Saverio Cellamare, and Cosimo D. Altomare</i>                                    |            |
| 11.1      | Introduction                                                                                              | 149        |
| 11.2      | History                                                                                                   | 150        |
| 11.3      | Synthesis                                                                                                 | 153        |
| 11.4      | Mechanism of Action                                                                                       | 156        |
| 11.5      | Structure–Activity Relationships                                                                          | 162        |
|           | References                                                                                                | 164        |

**12      Sovaldi, an NS5B RNA Polymerase-Inhibiting Carboxylic Acid Ester  
Used for the Treatment of Hepatitis C Infection   167**

*Alastair Donald*

12.1      Introduction   167

12.2      History   168

12.3      Synthesis   170

12.4      Mode of Action   172

12.5      Structure–Activity Relationships   173

References   174

**Part IV      Metabolic Diseases   177**

**13      Dipeptidyl Peptidase-4 (DPP-4)-Inhibiting Amides for the Treatment of  
Diabetes   179**

*Naomi S. Rajapaksa and Xiaodong Lin*

13.1      Introduction   179

13.2      History   179

13.3      Synthesis   184

13.4      Mode of Action   187

13.5      Structure–Activity Relationships   188

References   193

**Part V      Oncology   197**

**14      Ibrutinib, a Carboxylic Acid Amide Inhibitor of Bruton's Tyrosine  
Kinase   199**

*Timothy D. Owens*

14.1      Introduction   199

14.2      History   199

14.3      Synthesis   201

14.4      Mechanism of Action   202

14.5      Structure–Activity Relationships   203

References   207

**Part VI      Anti-Inflammatory Drugs   209**

**15      Fumaric Acid Esters   211**

*Tony S. Gibson*

15.1      Introduction   211

15.2      History   211

15.3      Synthesis   213

15.4      Mode of Action   213

15.5      Structure–Activity Relationships   215

References   218

**16 Carboxylic Acid Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) 221**  
*Yan Lou and Jiang Zhu*

- 16.1 Introduction 221
- 16.2 History 222
- 16.3 Synthesis 224
- 16.4 Mode of Action 228
- 16.5 Structure–Activity Relationships 230
- References 234

**17 Carboxylic-Acid-Containing Antihistamines 237**  
*Irini Akritopoulou-Zanze*

- 17.1 Introduction 237
- 17.2 History 237
- 17.3 Synthesis 239
- 17.4 Mode of Action 241
- 17.5 Structure–Activity Relationship 241
- References 243

**18 Corticosteroid Carboxylic Acid Esters 245**  
*Maurizio Franzini*

- 18.1 Introduction 245
- 18.2 History 249
- 18.3 Synthesis 252
- 18.4 Mode of Action 258
- 18.5 Structure–Activity Relationships 261
- References 264

**Part VII Ophthalmology 269**

**19 Prostaglandins with Carboxylic Functionalities for the Treatment of Glaucoma 271**

*Fabrizio Carta and Claudiu T. Supuran*

- 19.1 Introduction 271
- 19.2 History 271
- 19.3 Synthesis 272
- 19.4 Mode of Action 276
- 19.5 Structure–Activity–Relationship (SAR) 278
- References 279

**Part VIII Weed Control 281**

**20 Herbicidal Carboxylic Acids as Synthetic Auxins 283**

*Paul Schmitzer, Jeffrey Epp, Roger Gast, William Lo, and Jeff Nelson*

- 20.1 Introduction 283
- 20.2 History 283

|           |                                                                                 |            |
|-----------|---------------------------------------------------------------------------------|------------|
| 20.3      | Synthesis                                                                       | 286        |
| 20.4      | Mode of Action                                                                  | 289        |
| 20.5      | Biological Activity                                                             | 289        |
|           | References                                                                      | 291        |
| <b>21</b> | <b>Chloroacetamide Herbicides</b>                                               | <b>293</b> |
|           | <i>Clemens Lamberth</i>                                                         |            |
| 21.1      | Introduction                                                                    | 293        |
| 21.2      | History                                                                         | 293        |
| 21.3      | Synthesis                                                                       | 296        |
| 21.4      | Mode of Action                                                                  | 297        |
| 21.5      | Biological Activity                                                             | 299        |
| 21.6      | Structure–Activity Relationship                                                 | 300        |
|           | References                                                                      | 302        |
| <b>22</b> | <b>Carboxylic-Acid-Containing Sulfonylurea Herbicides</b>                       | <b>303</b> |
|           | <i>Atul Puri and Paul H. Liang</i>                                              |            |
| 22.1      | Introduction                                                                    | 303        |
| 22.2      | History                                                                         | 303        |
| 22.3      | Synthesis                                                                       | 305        |
| 22.4      | Mode of Action                                                                  | 306        |
| 22.5      | Biological Activity                                                             | 308        |
| 22.6      | Structure–Activity Relationship                                                 | 309        |
|           | References                                                                      | 312        |
| <b>23</b> | <b>Amino Acids as Nonselective Herbicides</b>                                   | <b>315</b> |
|           | <i>Stephane Jeanmart</i>                                                        |            |
| 23.1      | Introduction                                                                    | 315        |
| 23.2      | History                                                                         | 316        |
| 23.3      | Synthesis                                                                       | 317        |
| 23.4      | Mode of Action                                                                  | 319        |
| 23.5      | Biological Activity                                                             | 320        |
| 23.6      | Structure–Activity Relationships                                                | 321        |
|           | References                                                                      | 323        |
| <b>24</b> | <b>Herbicidal Aryloxyphenoxypropionate Inhibitors of Acetyl-CoA Carboxylase</b> | <b>325</b> |
|           | <i>William G. Whittingham</i>                                                   |            |
| 24.1      | Introduction                                                                    | 325        |
| 24.2      | History                                                                         | 325        |
| 24.3      | Synthesis                                                                       | 327        |
| 24.4      | Mode of Action                                                                  | 329        |
| 24.5      | Biological Activity                                                             | 330        |
| 24.6      | Structure–Activity Relationships                                                | 331        |
|           | References                                                                      | 334        |

|               |                                                                                                                               |
|---------------|-------------------------------------------------------------------------------------------------------------------------------|
| <b>25</b>     | <b>Pyridines Substituted by an Imidazolinone and a Carboxylic Acid as Acetohydroxyacid-Synthase-Inhibiting Herbicides</b> 339 |
|               | <i>Dale Shaner</i>                                                                                                            |
| 25.1          | Introduction 339                                                                                                              |
| 25.2          | History 339                                                                                                                   |
| 25.3          | Synthesis 341                                                                                                                 |
| 25.4          | Mode of Action 342                                                                                                            |
| 25.5          | Biological Activity 342                                                                                                       |
| 25.6          | Structure–Activity Relationship 344                                                                                           |
|               | References 345                                                                                                                |
| <br><b>26</b> | <br><b>Carboxylic-Acid-Containing Protoporphyrinogen-IX-Oxidase-Inhibiting Herbicides</b> 347                                 |
|               | <i>George Theodoridis</i>                                                                                                     |
| 26.1          | Introduction 347                                                                                                              |
| 26.2          | History 347                                                                                                                   |
| 26.2.1        | Carboxylic Acid Functional Group Directly Attached to Aromatic Ring of Protox Herbicide 349                                   |
| 26.2.2        | Carboxylic Acid Functional Group Present but Not Directly Attached to Aromatic Ring of Protox Herbicide 350                   |
| 26.3          | Synthesis 350                                                                                                                 |
| 26.4          | Mode of Action 351                                                                                                            |
| 26.5          | Biological Activity 352                                                                                                       |
| 26.6          | Structure–Activity Relationship 352                                                                                           |
|               | References 354                                                                                                                |
| <br>          | <br>                                                                                                                          |
|               | <b>Part IX Disease Control</b> 357                                                                                            |
| <br><b>27</b> | <br><b>Phenylamide Fungicides</b> 359                                                                                         |
|               | <i>Laura Quaranta</i>                                                                                                         |
| 27.1          | Introduction 359                                                                                                              |
| 27.2          | History 359                                                                                                                   |
| 27.3          | Synthesis 362                                                                                                                 |
| 27.4          | Mode of Action 364                                                                                                            |
| 27.5          | Biological Activity 365                                                                                                       |
| 27.6          | Structure–Activity Relationship 365                                                                                           |
|               | References 367                                                                                                                |
| <br><b>28</b> | <br><b>Complex III Inhibiting Strobilurin Esters, Amides, and Carbamates as Broad-Spectrum Fungicides</b> 371                 |
|               | <i>Clemens Lamberth</i>                                                                                                       |
| 28.1          | Introduction 371                                                                                                              |
| 28.2          | History 371                                                                                                                   |
| 28.3          | Synthesis 375                                                                                                                 |
| 28.4          | Mode of Action 379                                                                                                            |

|           |                                                                                             |            |
|-----------|---------------------------------------------------------------------------------------------|------------|
| 28.5      | Biological Activity                                                                         | 380        |
| 28.6      | Structure–Activity Relationship                                                             | 381        |
|           | References                                                                                  | 383        |
| <b>29</b> | <b>Scytalone-Dehydratase-Inhibiting Carboxamides for the Control of Rice Blast</b>          | <b>385</b> |
|           | <i>Andrew E. Taggi</i>                                                                      |            |
| 29.1      | Introduction                                                                                | 385        |
| 29.2      | History                                                                                     | 385        |
| 29.3      | Synthesis                                                                                   | 389        |
| 29.4      | Mode of Action                                                                              | 390        |
| 29.5      | Biological Activity                                                                         | 391        |
| 29.6      | Structure–Activity Relationships                                                            | 392        |
|           | References                                                                                  | 392        |
| <b>30</b> | <b>Carboxylic Acid Amide Fungicides for the Control of Downy Mildew Diseases</b>            | <b>395</b> |
|           | <i>Clemens Lamberth</i>                                                                     |            |
| 30.1      | Introduction                                                                                | 395        |
| 30.2      | History                                                                                     | 395        |
| 30.3      | Synthesis                                                                                   | 397        |
| 30.4      | Mode of Action                                                                              | 399        |
| 30.5      | Biological Activity                                                                         | 400        |
| 30.6      | Structure–Activity Relationship                                                             | 400        |
|           | References                                                                                  | 403        |
| <b>31</b> | <b>Fungicidal Succinate-Dehydrogenase-Inhibiting Carboxamides</b>                           | <b>405</b> |
|           | <i>Harald Walter</i>                                                                        |            |
| 31.1      | Introduction                                                                                | 405        |
| 31.2      | History                                                                                     | 406        |
| 31.3      | Synthesis                                                                                   | 409        |
| 31.4      | Mode of Action and Importance of Respiration Inhibitors                                     | 415        |
| 31.5      | Biological Activity and Market Impact                                                       | 416        |
| 31.5.1    | The Foliar SDHI Carboxamides                                                                | 416        |
| 31.5.2    | The Seed Treatment SDHI Carboxamides                                                        | 417        |
| 31.6      | Structure–Activity Relationships                                                            | 418        |
| 31.6.1    | General Structure-Activity Relationship Considerations of the Pyrazole Carboxamide Class IV | 418        |
| 31.6.2    | Replacement of the Pyrazole Ring by Phenyl or Pyridyl                                       | 420        |
| 31.6.3    | Replacement of the Pyrazole Ring by Other Five-Membered Heterocycles                        | 420        |
| 31.6.4    | Carboxamides not derived from Aromatic Amines                                               | 421        |
|           | Acknowledgments                                                                             | 422        |
|           | References                                                                                  | 422        |



**Part X      Insect Control    427****32      Esters and Carbamates as Insecticidal Juvenile Hormone Mimics    429***Sebastian Rendler*

- 32.1      Introduction    429
- 32.2      History    429
- 32.3      Synthesis    431
- 32.4      Mode of Action    433
- 32.5      Biological Activity    434
- 32.6      Structure–Activity Relationship    434
- References    437

**33      *N*-Benzoyl-*N'*-Phenyl Ureas as Insecticides, Acaricides, and Termiticides    439***Peter Jeschke*

- 33.1      Introduction    439
- 33.2      History    439
- 33.3      Synthesis    442
- 33.4      Mode of Action    445
- 33.5      Biological Activity    446
- 33.6      Structure–Activity Relationship    448
- References    451

**34      Pyrethroid Esters for the Control of Insect Pests    453***Régis Mondière and Fides Benfatti*

- 34.1      Introduction    453
- 34.2      History    454
- 34.3      Synthesis    457
- 34.4      Mode of Action    459
- 34.5      Biological Activity    461
- 34.6      Structure–Activity Relationship    462
- References    465

**35      Ecdysone Receptor Agonistic Dibenzoyl Hydrazine Insecticides    467***Ottmar F. Hüter*

- 35.1      Introduction    467
- 35.2      History    467
- 35.3      Synthesis    468
- 35.4      Mode of Action    471
- 35.5      Biological Activity    473
- 35.6      Structure–Activity Relationship    473
- References    476

|           |                                                              |            |
|-----------|--------------------------------------------------------------|------------|
| <b>36</b> | <b>Diamide Insecticides as Ryanodine Receptor Activators</b> | <b>479</b> |
|           | <i>André Jeanguenat</i>                                      |            |
| 36.1      | Introduction                                                 | 479        |
| 36.2      | History                                                      | 479        |
| 36.3      | Synthesis                                                    | 481        |
| 36.4      | Mode of Action                                               | 485        |
| 36.5      | Biological Activity                                          | 485        |
| 36.6      | Structure–Activity Relationship                              | 486        |
|           | References                                                   | 489        |
|           | <b>Index</b>                                                 | <b>491</b> |