

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 α 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
8	Carboxylic Acid Containing Direct Thrombin Inhibitors for the Treatment of Thromboembolic Diseases	103
	<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
	Part III Infectious Diseases	115
9	Tetracycline Amide Antibiotics	117
	<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
10	Carboxylic-Acid-Based Neuraminidase Inhibitors	133
	<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
11	Oxazolidinone Amide Antibiotics	149
	<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
21	Chloroacetamide Herbicides	293
	<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
22	Carboxylic-Acid-Containing Sulfonylurea Herbicides	303
	<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
23	Amino Acids as Nonselective Herbicides	315
	<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
24	Herbicidal Aryloxyphenoxypropionate Inhibitors of Acetyl-CoA Carboxylase	325
	<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

- 25 Pyridines Substituted by an Imidazolinone and a Carboxylic Acid as Acetoxyacid-Synthase-Inhibiting Herbicides 339**
Dale Shaner
- 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
- 26 Carboxylic-Acid-Containing Protoporphyrinogen-IX-Oxidase-Inhibiting Herbicides 347**
George Theodoridis
- 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
- Part IX Disease Control 357**
- 27 Phenylamide Fungicides 359**
Laura Quaranta
- 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
- 28 Complex III Inhibiting Strobilurin Esters, Amides, and Carbamates as Broad-Spectrum Fungicides 371**
Clemens Lamberth
- 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
- 29 Scytalone-Dehydratase-Inhibiting Carboxamides for the Control of Rice Blast 385**
Andrew E. Taggi
- 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
- 30 Carboxylic Acid Amide Fungicides for the Control of Downy Mildew Diseases 395**
Clemens Lamberth
- 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
- 31 Fungicidal Succinate-Dehydrogenase-Inhibiting Carboxamides 405**
Harald Walter
- 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
	<i>Sebastian Rendler</i>	
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	<i>N</i>-Benzoyl-<i>N'</i>-Phenyl Ureas as Insecticides, Acaricides, and Termiticides	439
	<i>Peter Jeschke</i>	
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
	<i>Régis Mondière and Fides Benfatti</i>	
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
	<i>Ottmar F. Hüter</i>	
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

36	Diamide Insecticides as Ryanodine Receptor Activators	479
	<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
	Index	491