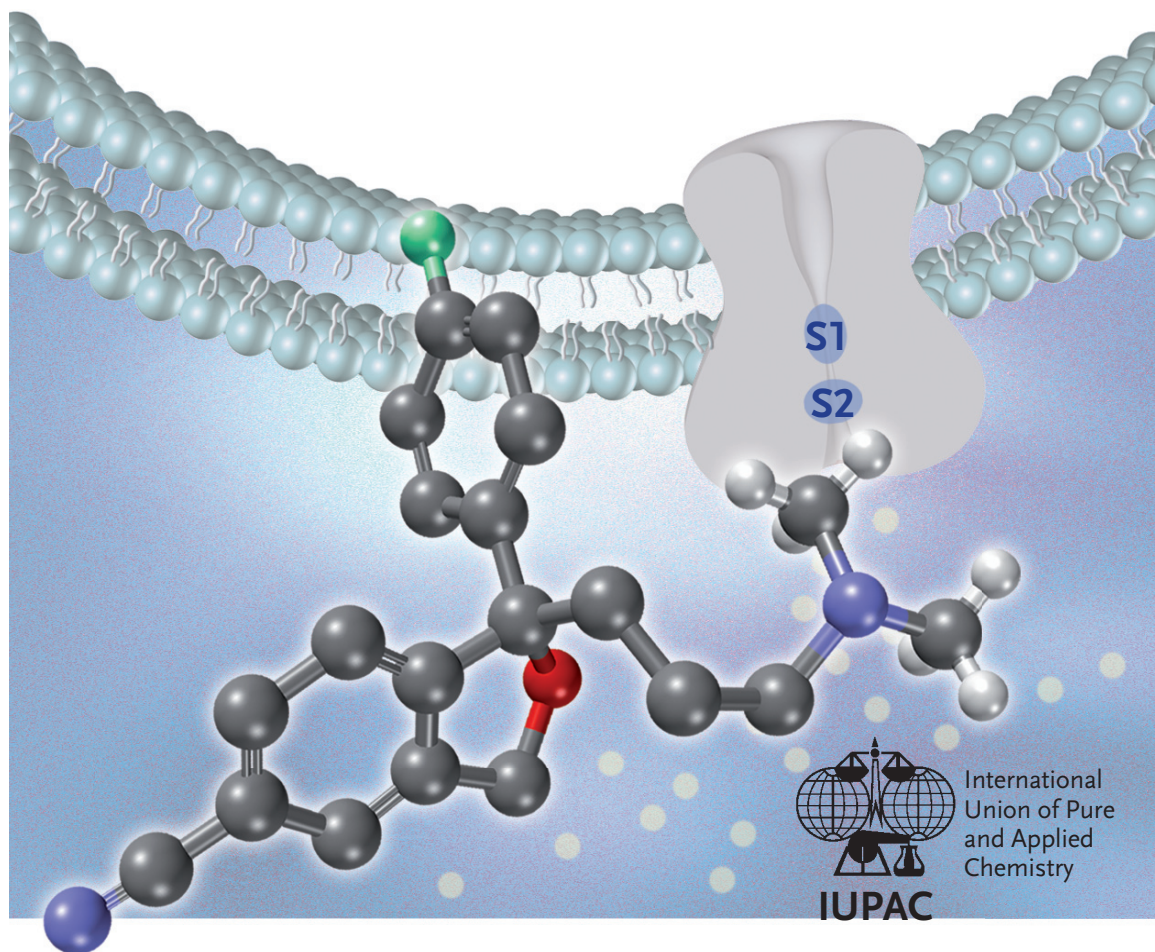


Edited by János Fischer,  
C. Robin Ganellin and David P. Rotella

 WILEY-VCH

# Analogue-based Drug Discovery III





*Edited by János Fischer,  
C. Robin Ganellin and  
David P. Rotella*

**Analogue-based Drug Discovery III**

## ***Related Titles***

Fischer, J., Ganellin, C. R. (Eds.)

### **Analogue-based Drug Discovery II**

2010

ISBN: 978-3-527-32549-8

IUPAC, Fischer, J., Ganellin, C. R. (Eds.)

### **Analogue-based Drug Discovery**

2006

ISBN: 978-3-527-31257-3

Abraham, D. J., Rotella, D. P.

### **Burger's Medicinal Chemistry, Drug Discovery and Development**

**8 Volume Set**

2010

ISBN: 978-0-470-27815-4

Li, J. J., Johnson, D. S. (eds.)

### **Modern Drug Synthesis**

2010

ISBN: 978-0-470-52583-8

Lednicer, D.

### **Strategies for Organic Drug Synthesis and Design**

2008

ISBN: 978-0-470-19039-5

Chorghade, M. S. (ed.)

### **Drug Discovery and Development**

**2 Volume Set**

2007

ISBN: 978-0-471-39846-2

*Edited by János Fischer, C. Robin Ganellin  
and David P. Rotella*

## **Analogue-based Drug Discovery III**



WILEY-VCH Verlag GmbH & Co. KGaA

## The Editors

### **Prof. Dr. János Fischer**

Gedeon Richter Plc.  
Gyömrői út 30  
1103 Budapest  
Hungary

### **Prof. Dr. C. Robin Ganellin**

University College London  
Department of Chemistry  
20 Gordon Street  
London WC1H 0AJ  
United Kingdom

### **Prof. Dr. David P. Rotella**

Montclair State University  
Department of Chemistry & Biochemistry  
Montclair, NJ 07043  
USA

Supported by the international Union of  
Pure and Applied Chemistry (IUPAC)  
Chemistry and Human Health Division  
PO Box 13757  
Research Triangle Park, NC 2770-3757  
USA

All books published by **Wiley-VCH** are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

**Library of Congress Card No.:** applied for

### **British Library Cataloguing-in-Publication Data**

A catalogue record for this book is available from the British Library.

### **Bibliographic information published by the Deutsche Nationalbibliothek**

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

©2013 Wiley-VCH Verlag GmbH & Co. KGaA,  
Boschstr. 12, 69469 Weinheim, Germany

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

**Print ISBN:** 978-3-527-33073-7

**ePDF ISBN:** 978-3-527-65111-5

**ePub ISBN:** 978-3-527-65110-8

**mobi ISBN:** 978-3-527-65109-2

**oBook ISBN:** 978-3-527-65108-5

**Cover Design** Grafik-Design Schulz, Fußgönheim

**Typesetting** Thomson Digital, Noida, India

**Printing and Binding** Markono Print Media Pte Ltd,  
Singapore

Printed on acid-free paper

## Contents

**Preface** *XIII*

**List of Contributors** *XV*

### **Part I      General Aspects    1**

#### **1            Pioneer and Analogue Drugs    3**

*János Fischer, C. Robin Ganellin, and David P. Rotella*

- 1.1      Monotarget Drugs    5
  - 1.1.1    H<sub>2</sub> Receptor Histamine Antagonists    5
  - 1.1.2    ACE Inhibitors    6
  - 1.1.3    DPP IV Inhibitors    7
  - 1.1.4    Univalent Direct Thrombin Inhibitors    8
- 1.2      Dual-Acting Drugs    10
  - 1.2.1    Monotarget Drugs from Dual-Acting Drugs    10
    - 1.2.1.1    Optimization of Beta-Adrenergic Receptor Blockers    10
  - 1.2.2    Dual-Acting Drugs from Monotarget Drugs    11
    - 1.2.2.1    Dual-Acting Opioid Drugs    11
- 1.3      Multitarget Drugs    12
  - 1.3.1    Multitarget Drug Analogue to Eliminate a Side Effect    12
    - 1.3.1.1    Clozapine and Olanzapine    12
  - 1.3.2    Selective Drug Analogue from a Pioneer Multitarget Drug    13
    - 1.3.2.1    Selective Serotonin Reuptake Inhibitors    13
- 1.4      Summary    16
- Acknowledgments    16
- References    16

#### **2            Competition in the Pharmaceutical Drug Development    21**

*Christian Tyrchan and Fabrizio Giordanetto*

- 2.1      Introduction    21
- 2.2      Analogue-Based Drugs: Just Copies?    22

2.3	How Often Does Analogue-Based Activity Occur? Insights from the GPCR Patent Space	25
	References	32
<b>3</b>	<b>Metabolic Stability and Analogue-Based Drug Discovery</b>	<b>37</b>
	<i>Amit S. Kalgutkar and Antonia F. Stepan</i>	
	List of Abbreviations	37
3.1	Introduction	37
3.2	Metabolism-Guided Drug Design	39
3.3	Indirect Modulation of Metabolism by Fluorine Substitution	42
3.4	Modulation of Low Clearance/Long Half-Life via Metabolism-Guided Design	45
3.5	Tactics to Resolve Metabolism Liabilities Due to Non-CYP Enzymes	46
3.5.1	Aldehyde Oxidase	46
3.5.2	Monoamine Oxidases	48
3.5.3	Phase II Conjugating Enzymes (UGT and Sulfotransferases)	49
3.6	Eliminating RM Liabilities in Drug Design	51
3.7	Eliminating Metabolism-Dependent Mutagenicity	51
3.8	Eliminating Mechanism-Based Inactivation of CYP Enzymes	54
3.9	Identification (and Elimination) of Electrophilic Lead Chemical Matter	60
3.10	Mitigating Risks of Idiosyncratic Toxicity via Elimination of RM Formation	61
3.11	Case Studies on Elimination of RM Liability in Drug Discovery	62
3.12	Concluding Remarks	67
	References	68
<b>4</b>	<b>Use of Macrocycles in Drug Design Exemplified with Ulimorelin, a Potential Ghrelin Agonist for Gastrointestinal Motility Disorders</b>	<b>77</b>
	<i>Mark L. Peterson, Hamid Hoveyda, Graeme Fraser, Éric Marsault, and René Gagnon</i>	
4.1	Introduction	77
4.1.1	Ghrelin as a Novel Pharmacological Target for GI Motility Disorders	77
4.1.2	Macrocycles in Drug Discovery	79
4.1.3	Tranzyme Technology	80
4.2	High-Throughput Screening Results and Hit Selection	82
4.3	Macrocycle Structure–Activity Relationships	83
4.3.1	Preliminary SAR	83
4.3.2	Ring Size and Tether	83
4.3.3	Amino Acid Components	87
4.3.4	Further Tether Optimization	89
4.4	PK–ADME Considerations	92
4.5	Structural Studies	95
4.6	Preclinical Evaluation	96

- 4.6.1 Additional Compound Profiling 97
- 4.6.2 Additional Pharmacokinetic Data 98
- 4.6.3 Animal Models for Preclinical Efficacy 100
- 4.7 Clinical Results and Current Status 100
- 4.8 Summary 103
- References 104

## Part II Drug Classes 111

### 5 The Discovery of Anticancer Drugs Targeting Epigenetic Enzymes 113

*A. Ganesan*

List of Abbreviations 113

- 5.1 Epigenetics 114
- 5.2 DNA Methyltransferases 116
- 5.3 5-Azacytidine (Azacitidine, Vidaza) and 5-Aza-2'-deoxycytidine (Decitabine, Dacogen) 118
- 5.4 Other Nucleoside DNMT Inhibitors 122
- 5.5 Preclinical DNMT Inhibitors 123
- 5.6 Zinc-Dependent Histone Deacetylases 124
- 5.7 Suberoylanilide Hydroxamic Acid (SAHA, Vorinostat, Zolinza) 125
- 5.8 FK228 (Depsipeptide, Romidepsin, Istodax) 127
- 5.9 Carboxylic Acid and Benzamide HDAC Inhibitors 131
- 5.10 Prospects for HDAC Inhibitors 132
- 5.11 Epigenetic Drugs – A Slow Start but a Bright Future 133
- Acknowledgments 133
- References 134

### 6 Thienopyridyl and Direct-Acting P2Y<sub>12</sub> Receptor Antagonist Antiplatelet Drugs 141

*Joseph A. Jakubowski and Atsuhiko Sugidachi*

List of Abbreviations 141

- 6.1 Introduction 142
- 6.1.1 Platelet Involvement in Atherothrombosis 142
- 6.2 Thienopyridines 143
- 6.2.1 Ticlopidine: 5-[(2-Chlorophenyl)methyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine 144
- 6.2.2 Clopidogrel: (+)-(S)- $\alpha$ -(2-Chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H) acetate 145
- 6.2.3 Prasugrel: 5-[(1RS)-2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate 147
- 6.3 Direct-Acting P2Y<sub>12</sub> Antagonists 152
- 6.3.1 Nucleoside-Containing Antagonists 152
- 6.3.1.1 Cangrelor: [Dichloro-[[[(2R,3S,4R,5R)-3,4-dihydroxy-5-[6-(2-methylsulfanylethylamino)-2-(3,3,3-trifluoropropylsulfanyl)purin-9-yl]oxolan-2-yl]methoxy-hydroxyphosphoryl]oxy-hydroxyphosphoryl]methyl]phosphonic acid 153

- 6.3.1.2 Ticagrelor: (1*S*,2*S*,3*R*,5*S*)-3-[7-[(1*R*,2*S*)-2-(3,4-Difluorophenyl)cyclopropylamino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol 154
- 6.3.2 Non-Nucleoside P2Y<sub>12</sub> Antagonists 157
- 6.3.2.1 Elinogrel: *N*-[(5-Chlorothiophen-2-yl)sulfonyl]-*N'*-[4-[6-fluoro-7-(methylamino)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]phenyl]urea 157
- 6.4 Summary 158
- References 158

## 7 Selective Estrogen Receptor Modulators 165

*Amarjit Luniwal, Rachael Jetson, and Paul Erhardt*

List of Abbreviations 165

- 7.1 Introduction 166
- 7.1.1 Working Definition 166
- 7.1.2 Early ABDD Leading to a Pioneer SERM 167
- 7.1.3 Discovery and Development of Clomiphene 169
- 7.1.4 SERM-Directed ABDD: General Considerations 170
- 7.2 Tamoxifen 171
- 7.2.1 Early Development 171
- 7.2.2 Clinical Indications and Molecular Action 172
- 7.2.3 Pharmacokinetics and Major Metabolic Pathways 174
- 7.2.4 Clinical Toxicity and New Tamoxifen Analogues 175
- 7.3 Raloxifene 175
- 7.3.1 Need for New Antiestrogens 176
- 7.3.2 Design and Initial Biological Data on Raloxifene 176
- 7.3.3 RUTH Study 177
- 7.3.4 STAR Study 177
- 7.3.5 Binding to the Estrogen Receptor 178
- 7.3.6 ADME 179
- 7.3.7 Further Research 179
- 7.4 Summary 179
- References 180

## 8 Discovery of Nonpeptide Vasopressin V<sub>2</sub> Receptor Antagonists 187

*Kazumi Kondo and Hidenori Ogawa*

List of Abbreviations 187

- 8.1 Introduction 187
- 8.2 Peptide AVP Agonists and Antagonists 188
- 8.3 Lead Generation Strategies 189
- 8.4 Lead Generation Strategy-2, V<sub>2</sub> Receptor Affinity 192
- 8.5 Lead Optimization 197
- 8.6 Reported Nonpeptide Vasopressin V<sub>2</sub> Receptor Antagonist Compounds 199
- 8.6.1 Sanofi 199

8.6.2	Astellas (Yamanouchi)	199
8.6.3	Wyeth	201
8.6.4	Johnson & Johnson	201
8.6.5	Wakamoto Pharmaceutical Co. Ltd	202
8.6.6	Japan Tobacco Inc.	202
8.7	Conclusions	203
	References	203

## **9 The Development of Cysteinyl Leukotriene Receptor Antagonists 211**

*Peter R. Bernstein*

List of Abbreviations 211

9.1	Introduction	212
9.2	Scope of the Drug Discovery Effort on Leukotriene Modulators	214
9.3	Synthetic Leukotriene Production and Benefits Derived from this Effort	215
9.4	Bioassays and General Drug Discovery Testing Cascade	216
9.5	Development of Antagonists – General Approaches	218
9.6	Discovery of Zafirlukast	218
9.7	Discovery of Montelukast	224
9.8	Discovery of Pranlukast	227
9.9	Comparative Analysis and Crossover Impact	229
9.10	Postmarketing Issues	231
9.11	Conclusions	232
	Acknowledgment	232
	Disclaimer	232
	References	233

## **Part III Case Studies 241**

### **10 The Discovery of Dabigatran Etxilate 243**

*Norbert Huel, Andreas Clemens, Herbert Nar, Henning Priepke, Joanne van Ryn, and Wolfgang Wienen*

List of Abbreviations 243

10.1	Introduction	243
10.2	Dabigatran Design Story	246
10.3	Preclinical Pharmacology Molecular Mechanism of Action of Dabigatran	254
10.3.1	<i>In Vitro</i> Antithrombotic Effects of Dabigatran	255
10.3.2	<i>Ex Vivo</i> Antithrombotic Effects of Dabigatran/Dabigatran Etxilate	256
10.3.3	Venous and Arterial Antithrombotic Effects of Dabigatran/Dabigatran Etxilate	256
10.3.4	Mechanical Heart Valves	257
10.3.5	Cancer	257
10.3.6	Fibrosis	257
10.3.7	Atherosclerosis	258

10.4	Clinical Studies and Indications	258
10.4.1	Prevention of Deep Venous Thrombosis	259
10.4.2	Therapy of Venous Thromboembolism	259
10.4.3	Stroke Prevention in Patients with Atrial Fibrillation	260
10.4.4	Prevention of Recurrent Myocardial Infarction in Patients with Acute Coronary Syndrome	260
10.5	Summary	260
	References	261
<b>11</b>	<b>The Discovery of Citalopram and Its Refinement to Escitalopram</b>	<b>269</b>
	<i>Klaus P. Bøgesø and Connie Sánchez</i>	
	List of Abbreviations	269
11.1	Introduction	270
11.2	Discovery of Talopram	271
11.3	Discovery of Citalopram	272
11.4	Synthesis and Production of Citalopram	275
11.5	The Pharmacological Profile of Citalopram	276
11.6	Clinical Efficacy of Citalopram	277
11.7	Synthesis and Production of Escitalopram	278
11.8	The Pharmacological Profile of the Citalopram Enantiomers	279
11.9	R-Citalopram's Surprising Inhibition of Escitalopram	279
11.10	Binding Site(s) for Escitalopram on the Serotonin Transporter	283
11.11	Future Perspectives on the Molecular Basis for Escitalopram's Interaction with the SERT	286
11.12	Clinical Efficacy of Escitalopram	287
11.13	Conclusions	288
	References	288
<b>12</b>	<b>Tapentadol – From Morphine and Tramadol to the Discovery of Tapentadol</b>	<b>295</b>
	<i>Helmut Buschmann</i>	
	List of Abbreviations	295
12.1	Introduction	296
12.1.1	Pain and Current Pain Treatment Options	297
12.1.2	Pain Research Today	300
12.1.3	The Complex Mode of Action of Tramadol	301
12.2	The Discovery of Tapentadol	302
12.2.1	From the Tramadol Structure to Tapentadol	303
12.2.2	Synthetic Pathways to Tapentadol	306
12.3	The Preclinical and Clinical Profile of Tapentadol	310
12.3.1	Preclinical Pharmacology of Tapentadol	311
12.3.2	Clinical Trials	312
12.3.3	Pharmacokinetics and Drug–Drug Interactions of Tapentadol	314
12.4	Summary	315
	References	315

<b>13</b>	<b>Novel Taxanes: Cabazitaxel Case Study</b>	<b>319</b>
	<i>Hervé Bouchard, Dorothée Semiond, Marie-Laure Risse, and Patricia Vrignaud</i>	
	List of Abbreviations	319
13.1	Introduction	320
13.1.1	Isolation and Chemical Synthesis of Taxanes	321
13.1.2	Drug Resistance and Novel Taxanes	322
13.2	Cabazitaxel Structure–Activity Relationships and Chemical Synthesis	323
13.2.1	Chemical and Physical Properties	323
13.2.2	Structure–Activity Relationships of Cabazitaxel	324
13.2.3	Chemical Synthesis of Cabazitaxel	325
13.3	Cabazitaxel Preclinical and Clinical Development	328
13.3.1	Preclinical Development	328
13.3.2	Clinical Studies	330
13.3.2.1	Phase I and II Studies	332
13.3.2.2	Clinical Pharmacokinetics	333
13.3.2.3	Phase III Trial	334
13.3.3	Other Ongoing Trials	335
13.4	Summary	336
	Acknowledgments	337
	References	337
<b>14</b>	<b>Discovery of Boceprevir and Narlaprevir: A Case Study for Role of Structure-Based Drug Design</b>	<b>343</b>
	<i>Srikanth Venkatraman, Andrew Prongay, and George F. Njoroge</i>	
	List of Abbreviations	343
	References	359
<b>15</b>	<b>A New-Generation Uric Acid Production Inhibitor: Febuxostat</b>	<b>365</b>
	<i>Ken Okamoto, Shiro Kondo, and Takeshi Nishino</i>	
	List of Abbreviations	365
15.1	Introduction	365
15.2	Xanthine Oxidoreductase – Target Protein for Gout Treatment	367
15.3	Mechanism of XOR Inhibition by Allopurinol	368
15.4	Development of Nonpurine Analogue Inhibitor of XOR: Febuxostat	369
15.5	Mechanism of XOR Inhibition by Febuxostat	370
15.6	Excretion of XOR Inhibitors	372
15.7	Results of Clinical Trials of Febuxostat in Patients with Hyperuricemia and Gout	372
15.8	Summary	373
15.9	Added in proof	373
	References	373
	<b>Index</b>	<b>377</b>



## Preface

The editors of the third volume of the book series “Analogue-Based Drug Discovery” thank the International Union of Pure and Applied Chemistry (IUPAC) for supporting this book project. We also thank the coworkers at Wiley-VCH, Dr. Frank Weinreich and Waltraud Wüst, for their excellent help, and last but not least we are grateful to all the contributors of this book. Special thanks are due to the following reviewers who helped both the authors and the editors: Klaus Peter Bøgesø, Helmut Buschmann, Paul W. Erhardt, Staffan Erickson, Susan B. Horwitz, Manfred Jung, Amit Kalgutkar, Danijel Kikelj, Andrew MacMillan, Eckhard Ottow, Jens-Uwe Peters, Henning Priepke, John Proudfoot, Stephen C. Smith, Bernard Testa, and Han van de Waterbeemd.

Analogue-based drug discovery is a basic principle of drug research. In this book series, we focused on analogues of existing drugs. In the first volume (2006), we discussed structural and pharmacological analogues, whereas the second volume (2010) also included analogues with pharmacological similarities.

In this volume, we continued the same concept, recognizing that in several cases there is only a narrow gap between a pioneer and an analogue drug because of the strong competitive environment in the industry. A new promising molecular biological target inspires parallel research efforts at several companies. It can happen that the first discovery does not lead to a marketed drug; instead, a molecule discovered later proves to be the first to be launched. As a result of the strong competition, it can also happen that two pioneer drugs are introduced nearly simultaneously in the market, and these drugs often have chemical and pharmacological similarities.

The third volume of Analogue-Based Drug Discovery consists of three parts.

### Part I (General Aspects)

The introductory chapter discusses the relationship between the pioneer and analogue drugs, where their overlapping character can be observed. A chapter by Christian Tyrchan and Fabrizio Giordanetto (AstraZeneca) analyzes competition in pharmaceutical drug development. Amit S. Kalgutkar and Antonia F. Stepan (Pfizer) study the important role of metabolic stability in drug research. Mark L. Peterson, Hamit Hoveyda, Graeme Fraser, Éric Marsault, and René Gagnon

(Tranzyme Pharma Inc.) write on the use of peptide-based macrocycles in drug design exemplified with the discovery of ulimorelin.

## Part II (Drug Classes)

A. Ganesan (University of East Anglia) gives an overview of discovery research into anticancer epigenetic drugs. Joseph A. Jakubowski (Lilly) and Atsushiro Sugidachi (Daiichi Sankyo) evaluate the structurally diverse drug class of the antithrombotic P2Y<sub>12</sub> receptor antagonists. Paul Erhardt, Amarjit Luniwal, and Rachael Jetson (University of Toledo, USA) summarize the medicinal chemistry of selective estrogen receptor modulators. Kazumi Kondo and Hidenori Ogawa (Otsuka Pharmaceutical Co., Japan) describe the discovery of aquaretics that are vasopressin V2 receptor antagonists. Peter R. Bernstein (PharmaB LLC) evokes the discovery of cysteinyl leukotriene receptor antagonists that are important in the treatment of asthma.

## Part III (Case Histories)

Norbert Hael, Andreas Clemens, Herbert Nar, Henning Pripke, Joanne van Ryn, and Wolfgang Wienen (Boehringer Ingelheim, Biberach, Germany) report on the discovery of dabigatran etexilate, an oral direct thrombin inhibitor approved for use in the treatment of acute thrombosis. Klaus P. Bøgesø and Connie Sánchez (Lundbeck) describe the discovery of escitalopram, which is one of the most successful selective serotonin reuptake inhibitors in the treatment of depressive disorders. Helmut Buschmann (Pharma-Consulting, Aachen, Germany) analyzes the discovery of tapentadol, a novel centrally acting synthetic analgesic with a dual mechanism of action. Hervé Bouchard, Drothée Semiond, Marie-Laure Risse, and Patricia Vrignaud (Sanofi) describe the discovery of cabazitaxel, a novel semi-synthetic taxane, a new anticancer drug. Srikanth Venkatraman, Andrew Prongay, and George F. Njoroge (Merck) summarize the discovery of boceprevir and nartlaprevir, hepatitis C protease inhibitors. Ken Okamoto, Shiro Kondo, and Takeshi Nishino (Nippon Medical School, Teijin Ltd, and University of Tokyo) describe the discovery of febuxostat, a new uric acid production inhibitor.

The above 15 chapters of the book with 40 authors from 9 countries bring important and successful drug discoveries closer to the medicinal chemists and to all who are interested in the complicated history of drug discoveries.

The major parts of the chapters are written by key inventors.

We hope that also the third volume of this book series will be well received by people interested in medicinal chemistry.

May 2012  
Budapest, Hungary  
London, UK  
Montclair, NJ, USA

János Fischer  
C. Robin Ganellin  
David P. Rotella

## List of Contributors

**Peter R. Bernstein**

PhaRmaB LLC  
14 Forest View Road  
Rose Valley, PA 1908-6721  
USA

**Klaus P. Bøgesø**

H. Lundbeck A/S  
Lundbeck Research Denmark  
9 Ottiliavej  
2500 Valby  
Denmark

**Hervé Bouchard**

Sanofi  
LGCR/Natural Product & Protein  
Chemistry (NPPC)  
13 quai Jules Guesde  
94400 Vitry-sur-Seine  
France

**Helmut Buschmann**

Sperberweg 15  
52076 Aachen  
Germany

**Andreas Clemens**

Boehringer Ingelheim Pharma  
GmbH & Co. KG  
Department of Medicinal Chemistry  
Birkendorfer Straße 65  
88400 Biberach an der Riß  
Germany

**Paul Erhardt**

The University of Toledo  
College of Pharmacy  
2801 West Bancroft Street  
Toledo, OH 43606-3390  
USA

**János Fischer**

Gedeon Richter Plc.  
Department of Medicinal Chemistry  
Gyömrői út 19/21  
1103 Budapest  
Hungary

**Graeme Fraser**

Tranzyme Pharma, Inc.  
3001, 12th Avenue Nord  
Sherbrooke, Quebec J1H 5N4  
Canada

**René Gagnon**

Tranzyme Pharma, Inc.  
3001, 12th Avenue Nord  
Sherbrooke, Quebec J1H 5N4  
Canada

**C. Robin Ganellin**

University College London  
Department of Chemistry  
20 Gordon Street  
London WC1H 0AJ  
UK

**A. Ganesan**

School of Pharmacy  
University of East Anglia  
Norwich NR4 7TJ  
United Kingdom

**Fabrizio Giordanetto**

AstraZeneca CV/GI  
Lead Generation Department  
Pepparedsleden 1  
43150 Mölndal  
Sweden

**Norbert Hael**

Boehringer Ingelheim Pharma  
GmbH & Co. KG  
Department of Medicinal Chemistry  
Birkendorfer Straße 65  
88400 Biberach an der Riß  
Germany

**Hamid Hoveyda**

Tranzyme Pharma, Inc.  
3001, 12th Avenue Nord  
Sherbrooke, Quebec J1H 5N4  
Canada

**Joseph A. Jakubowski**

Eli Lilly and Company  
Lilly Research Laboratories  
Indianapolis, IN 46285  
USA

**Rachael Jetson**

The University of Toledo  
College of Pharmacy  
2801 West Bancroft Street  
Toledo, OH 43606-3390  
USA

**Amit S. Kalgutkar**

Pfizer Worldwide Research and  
Development  
Department of Pharmacokinetics,  
Dynamics, and Metabolism  
MS 8220-3529  
Groton CT 06340  
USA

**Kazumi Kondo**

Otsuka Pharmaceutical Co. Ltd.  
Qs' Research Institute  
463-10 Kagasuno, Kawauchicho  
Tokushima 771-0192  
Japan

**Shiro Kondo**

Teijin Ltd.  
Kondo Laboratory  
4-3-2 Asahigaoka, Hino  
Tokyo 191-8512  
Japan

**Amarjit Luniwal**

The University of Toledo  
College of Pharmacy  
2801 West Bancroft Street  
Toledo, OH 43606-3390  
USA

**Éric Marsault**

Tranzyme Pharma, Inc.  
3001, 12th Avenue Nord  
Sherbrooke, Quebec J1H 5N4  
Canada

**Herbert Nar**

Boehringer Ingelheim Pharma  
GmbH & Co. KG  
Department of Medicinal Chemistry  
Birkendorfer Straße 65  
88400 Biberach an der Riß  
Germany

**Takeshi Nishino**

The University of Tokyo  
Graduate School of Agricultural and  
Life Sciences  
Department of Applied Biological  
Chemistry  
1-1-1 Yayoi, Bunkyo-Ku  
Tokyo 113-8657  
Japan

**George F. Njoroge**

Eli Lilly and Company  
Lilly Research Laboratories  
Indianapolis, IN 46285  
USA

**Hidenori Ogawa**

Otsuka Pharmaceutical Co. Ltd.  
Qs' Research Institute  
463-10 Kagasuno, Kawauchicho  
Tokushima 771-0192  
Japan

**Ken Okamoto**

Nippon Medical School  
Department of Biochemistry  
1-1-5 Sendagi, Bunkyo-ku  
Tokyo 113-8602  
Japan

**Mark L. Peterson**

Tranzyme Pharma, Inc.  
3001, 12th Avenue Nord  
Sherbrooke, Quebec J1H 5N4  
Canada

**Henning Priepke**

Boehringer Ingelheim Pharma  
GmbH & Co. KG  
Department of Medicinal Chemistry  
Birkendorfer Straße 65  
88400 Biberach an der Riß  
Germany

**Andrew Prongay**

Merck Research Laboratories  
Chemical Research  
2015 Galloping Hill Road  
Kenilworth, NJ 07033  
USA

**Marie-Laure Risse**

Sanofi Oncology  
Centre de Recherche de  
Vitry-Alfortville  
13 quai Jules Guesde  
94400 Vitry-sur-Seine  
France

**David P. Rotella**

Montclair State University  
Department of Chemistry &  
Biochemistry  
1 Normal Ave  
Montclair, NJ 07043  
USA

**Connie Sánchez**

Lundbeck Research USA  
Department of Neuroscience  
215 College Road  
Paramus, NJ 07652  
USA

**Dorothée Semiond**

Sanofi  
Centre de Recherche de  
Vitry-Alfortville  
Department of Disposition, Safety  
and Animal Research (DSAR)  
13 quai Jules Guesde  
94400 Vitry-sur-Seine  
France

**Antonia F. Stepan**

Pfizer Worldwide Research and  
Development  
Neuroscience Medicinal Chemistry  
700 Main Street  
Cambridge, MA 02139  
USA

**Atsuhiko Sugidachi**

Daiichi Sankyo Co., Ltd.  
Biological Research Laboratories  
1-2-58 Hiromachi, Shinagawa-ku  
Tokyo 140-8710  
Japan

**Christian Tyrchan**

AstraZeneca CV/GI  
Lead Generation Department  
Pepparedsleden 1  
43150 Mölndal  
Sweden

**Joanne van Ryn**

Boehringer Ingelheim Pharma  
GmbH & Co. KG  
Department of Medicinal Chemistry  
Birkendorfer Straße 65  
88400 Biberach an der Riß  
Germany

**Srikanth Venkatraman**

Schering-Plough Research Institute  
Department of Medicinal Chemistry  
2015 Galloping Hill Road  
Kenilworth, NJ 07033-1335  
USA

**Patricia Vrignaud**

Sanofi Oncology  
Centre de Recherche de  
Vitry-Alfortville  
13 quai Jules Guesde  
94400 Vitry-sur-Seine  
France

**Wolfgang Wienen**

Boehringer Ingelheim Pharma  
GmbH & Co. KG  
Department of Medicinal Chemistry  
Birkendorfer Straße 65  
88400 Biberach an der Riß  
Germany

## Part I

### General Aspects



## 1

## Pioneer and Analogue Drugs

János Fischer, C. Robin Ganellin, and David P. Rotella

A *pioneer drug* (“first in class”) represents a breakthrough invention that affords a marketed drug where no structurally and/or pharmacologically similar drug was known before its introduction. The majority of drugs, however, are *analogue drugs*, which have structural and/or pharmacological similarities to a pioneer drug or, as in some cases, to other analogue drugs.

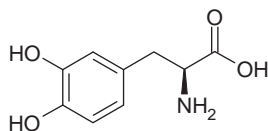
The aim of this chapter is to discuss these two drug types [1].

The term “pioneer drug” is not used very often, because only a small fraction of drugs belongs to this type and in many cases the pioneer drugs lose their importance when similar but better drugs are discovered. A pioneer drug and its analogues form a drug class in which subsequent optimization may be observed. Analogue drugs typically offer benefits such as improved efficacy and/or side effect profiles or dose frequency than a pioneer drug to be successful on the market.

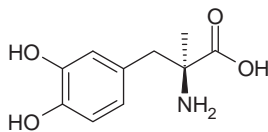
The discovery of both *pioneer* and *analogue drugs* needs some serendipity. A pioneer drug must clinically validate the safety and efficacy of a new molecular target and mechanism of action based on a novel chemical structure. In the case of an analogue drug, it is helpful that a pioneer or an analogue exists; nevertheless, some serendipity is needed to discover a new and better drug analogue, because there are no general guidelines on how such molecules can be identified preclinically. The analogue approach is very fruitful in new drug research, because there is a higher probability of finding a better drug than to discover a pioneer one. A significant risk with this approach is based on the potential for one of the many competitors in the drug discovery area to succeed prior to others.

The similarity between two drugs cannot be simply defined. Even a minor modification of a drug structure can completely modify the properties of a molecule. Levodopa (1) and methyldopa (2) are applied in different therapeutic fields; however, their structures differ only in a methyl group. Both molecules have the same stereochemistry as derivatives of L-tyrosine. Levodopa [2] is used for the treatment of Parkinson's disease as a dopamine precursor, whereas methyldopa [3] was an important antihypertensive agent before safer and more efficacious molecules (e.g., ACE inhibitors) appeared on the market.

Methyldopa (first synthesized at Merck Sharp & Dohme) has a dual mechanism of action: it is a competitive inhibitor of the enzyme DOPA decarboxylase and its metabolite acts as an  $\alpha$ -adrenergic agonist.



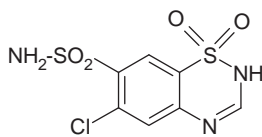
levodopa  
1



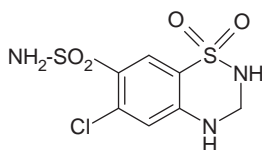
methyldopa  
2

Levodopa and methyldopa are not analogues from the viewpoint of medicinal chemistry. Both are pioneer drugs in their respective therapeutic fields and can be considered as stand-alone drugs, because they have no successful analogues.

There are several examples, and it is a usual case that a minor modification of a drug molecule affords a much more active drug in the same therapeutic field. The pioneer drug chlorothiazide (3) and its analogue hydrochlorothiazide (4) from Merck Sharp & Dohme differ only by two hydrogen atoms; however, the diuretic effect of hydrochlorothiazide [4] is 10 times higher than that of the original drug. The pioneer drug chlorothiazide is rarely used, but its analogue, hydrochlorothiazide, is an important first-line component in current antihypertensive therapy as a single agent and in combination with other compounds.



chlorothiazide  
3



hydrochlorothiazide  
4

Chlorothiazide and hydrochlorothiazide are *direct analogues*, which term emphasizes their close relationship.

The terms “pioneer drugs” and “analogue drugs” will be discussed in the following sections.

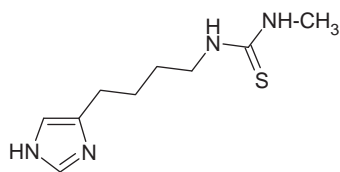
## 1.1

## Monotarget Drugs

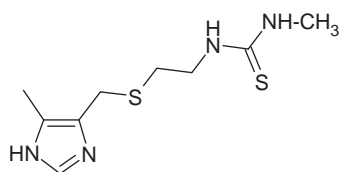
## 1.1.1

**H<sub>2</sub> Receptor Histamine Antagonists**

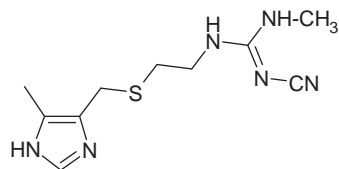
Before the launch of cimetidine (1976), only short-acting neutralization of gastric acid was possible by administration of various antacids (e.g., sodium bicarbonate, magnesium hydroxide, aluminum hydroxide, etc.) that did not affect gastric acid secretion. Cimetidine [5], the first successful H<sub>2</sub> receptor histamine antagonist, a pioneer drug for the treatment of gastric hyperacidity and peptic ulcer disease, was discovered by researchers at Smith, Kline & French. The inhibition of histamine-stimulated gastric acid secretion was first studied in rats. Burimamide (**5**) was the first lead compound, a prototype drug, that also served as a proof of concept for inhibition of acid secretion in human subjects when administered intravenously, but its oral activity was insufficient. Its analogue, metiamide (**6**), was orally active, but its clinical studies had to be discontinued because of a low incidence of granulocytopenia. Replacing the thiourea moiety in metiamide with a cyanoguanidino moiety afforded cimetidine (**7**). Its use provided clinical proof for inhibition of gastric acid secretion and ulcer healing and was a great commercial and clinical success in the treatment of peptic ulcer disease.



burimamide

**5**

metiamide

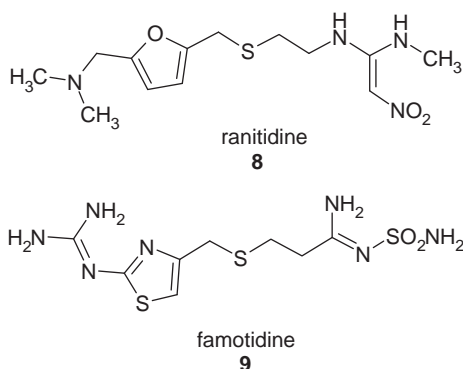
**6**

cimetidine

**7**

Although cimetidine was very effective for the treatment of peptic ulcer disease and related problems of acid hypersecretion, there were some side effects associated with its use, albeit at a very low level. A low incidence of gynecomastia in men can occur at high doses of cimetidine due to its antiandrogen effect. Cimetidine also inhibits cytochrome P450, an important drug metabolizing enzyme. It is therefore advisable to avoid coadministration of cimetidine with certain drugs such as propranolol, warfarin, diazepam, and theophylline.

Cimetidine led to the initiation of analogue-based drug research affording more potent analogue drugs such as ranitidine (8) and famotidine (9) that lack the above side effects of cimetidine.



Ranitidine [6] also has a pioneer character, because ranitidine is the first  $H_2$  receptor histamine antagonist that has no antiandrogen adverse effect and does not inhibit the cytochrome CYP450 enzymes. Famotidine is the most potent member of this drug class, which has been discussed in Volume I of this series [7].

#### Summary:

Pioneer  $H_2$  receptor histamine antagonist: cimetidine.

First  $H_2$  receptor histamine antagonist with no antiandrogen adverse effects and without inhibition of P450 enzymes: ranitidine.

### 1.1.2

#### ACE Inhibitors

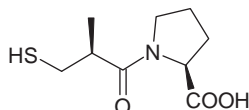
A natural product, the nonapeptide teprotide (10), was the pioneer drug for angiotensin-converting enzyme (ACE) inhibitors. Teprotide [8] was used as an active antihypertensive drug in patients with essential hypertension. It could only be administered parenterally, which is a great drawback for chronic use of a drug. A breakthrough occurred with the approval of the first orally active ACE inhibitor captopril (11) in 1980 by Squibb. Captopril [9] has a short onset time (0.5–1 h), and its duration of action is also relatively short (6–12 h); as a result, two to three daily doses are necessary. Captopril can be regarded as a pharmacological analogue of teprotide, but it is also the pioneer orally active ACE inhibitor. Captopril's discovery

initiated intensive research by several other drug companies to discover longer acting ACE inhibitors. Enalapril (**12**) was introduced by Merck in 1984. Enalapril [10] can be regarded as the first long-acting oral ACE inhibitor. The long-acting ACE inhibitors are once-daily antihypertensive drugs. There are several long-acting ACE inhibitors, whose differences have been discussed in the first volume of this book series [11].

pyro-Glu - Trp - Pro - Arg - Pro - Gln - Ile - Pro - Pro -OH

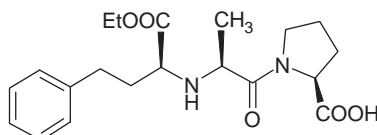
teprotide

**10**



captopril

**11**



enalapril

**12**

#### Summary:

Pioneer ACE inhibitor drug: teprotide.

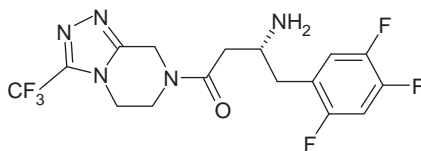
First orally active ACE inhibitor drug: captopril.

First orally long-acting ACE inhibitor drug: enalapril.

#### 1.1.3

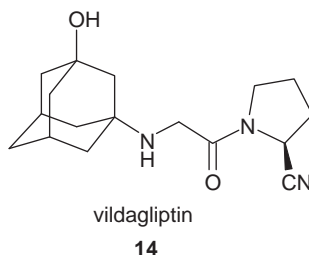
#### DPP IV Inhibitors

Sitagliptin (**13**) [12], a pioneer dipeptidyl peptidase IV (DPP IV) inhibitor, was launched in 2006 by Merck for the treatment of type 2 diabetes. The medicinal chemistry team began its research in 1999 when some DPP IV inhibitor molecules were known as substrate-based analogues. The lead molecule derived from this research was vildagliptin (**14**) [13]; discovered at Novartis in 1998, it was the second compound to be introduced to the market.



sitagliptin

**13**



The pioneer drug sitagliptin is a commercial success with 2010 sales greater than USD 3 billion. Vildagliptin was the first successful discovery in this drug class, but its development time was longer and it was introduced in 2007, after sitagliptin. Vildagliptin is only moderately selective over DPP-8 and DPP-9 compared to sitagliptin that is a highly selective DPP IV inhibitor. Based on long-term safety studies, these selectivity differences do not influence the toxicity of vildagliptin. Sitagliptin and vildagliptin show similar clinical efficacies. Vildagliptin has a short half-life (3 h) and its dosing regimen is twice a day, whereas sitagliptin has a long half-life (12 h) and once-daily dosing is used. DPP IV inhibitors are typical early-phase analogues that result from a highly competitive industry, and not the first candidate (vildagliptin) but a follow-on drug (sitagliptin) became the pioneer drug on the market (“first-in-class drug”). Further DPP IV inhibitors are available (alogliptin, saxagliptin, and linagliptin) and the individual compounds differ significantly in their mode of metabolism and excretion and these differences help the treatment of patients with type 2 diabetes in an individual way [14] (see Chapter 5 of Volume II of this book series).

*Summary:*

Pioneer DPP IV inhibitor drug: sitagliptin (long-acting inhibitor).

First DPP IV inhibitor analogue drug: vildagliptin (short-acting inhibitor).

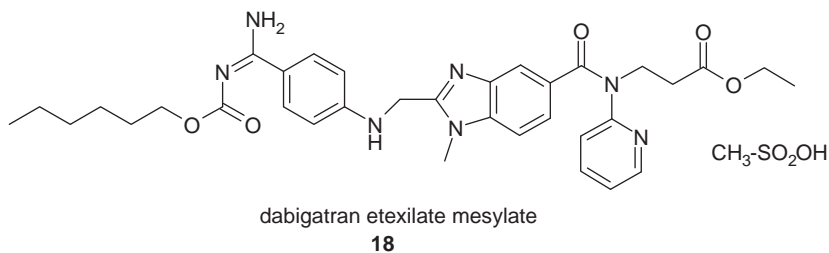
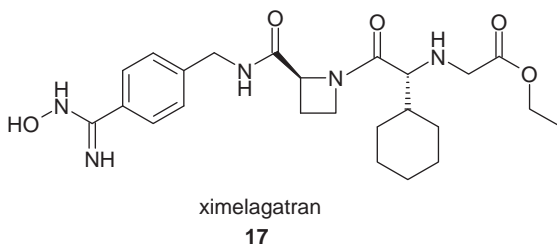
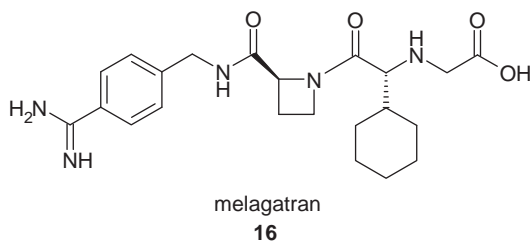
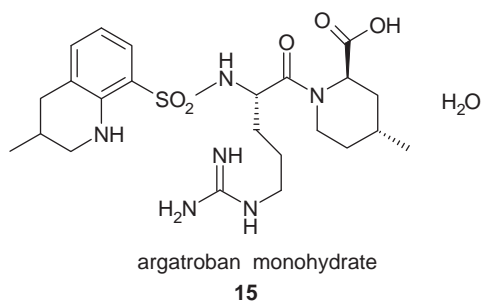
#### 1.1.4

##### Univalent Direct Thrombin Inhibitors

Thrombin is a serine protease enzyme whose inhibition plays an important role in the mechanism of several anticoagulants. Univalent direct thrombin inhibitors bind only to the active site of the enzyme, whereas bivalent direct thrombin inhibitors (e.g., hirudin and bivalirudin) block thrombin at both the active site and exosite 1.

The pioneer univalent direct thrombin inhibitor is argatroban monohydrate (**15**) [15] that was launched by Daiichi Pharmaceutical and Mitsubishi Pharma in 1990. Argatroban was approved by the FDA for prophylactic anticoagulation in the treatment of thrombosis in patients with heparin-induced thrombocytopenia. Argatroban is a rather selective reversible inhibitor for human thrombin. Despite its low molecular weight, argatroban is administered parenterally due to the presence of the highly basic guanidine moiety that prevents absorption from the

gastrointestinal tract. This characteristic limits the clinical use of the compound. The first oral direct thrombin inhibitor was ximelagatran (**17**) [16], which was introduced in 2004 by AstraZeneca. Ximelagatran is a double prodrug derivative of melagatran (**16**) with a bioavailability of about 20%, a measurable improvement compared to melagatran with oral bioavailability of 5.8%. Ximelagatran was withdrawn from the market in 2006 because of unacceptable hepatic side effects (alanine aminotransferase increased threefold and bilirubin level increased twofold above the normal upper limit) [17]. In this drug class, dabigatran etexilate (**18**) [18] was discovered by Boehringer Ingelheim as a new direct thrombin inhibitor without adverse liver effects [19] (see Chapter 10)



*Summary:*

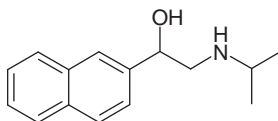
Pioneer univalent direct thrombin inhibitor drug: argatroban.

First orally active univalent thrombin inhibitor: ximelagatran.

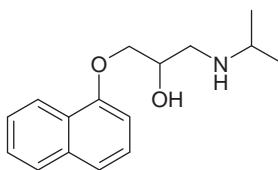
First orally active univalent thrombin inhibitor without adverse liver affects: dabigatran etexilate.

**1.2****Dual-Acting Drugs****1.2.1****Monotarget Drugs from Dual-Acting Drugs****1.2.1.1 Optimization of Beta-Adrenergic Receptor Blockers**

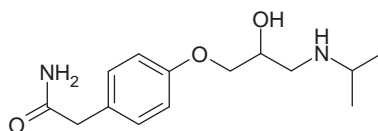
James W. Black and coworkers at ICI invented propranolol as a product of analogue-based drug discovery (ABDD) using their prototype drug, pronethalol (**19**), as a lead compound. Pronethalol [20] was an active drug for the treatment of angina pectoris in humans, but its development was discontinued because it proved to be carcinogenic in mice in long-term toxicology studies. Continuation of the analogue-based drug discovery afforded propranolol (**20**), where an oxymethylene link was inserted between the 1-naphthyl group and the secondary alcohol moiety of pronethalol. Propranolol [21] was more potent than pronethalol. Propranolol became the pioneer nonselective  $\beta$ -adrenergic receptor antagonist, a true antagonist without partial agonist properties (intrinsic sympathomimetic activity). It was a breakthrough discovery for the treatment of arrhythmias, angina pectoris, and hypertension.



pronethalol  
**19**



propranolol  
**20**



atenolol  
**21**