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C. Robin Ganellin and
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Analogue-based Drug Discovery III

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Analogue-based Drug Discovery III

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Contents

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 $P2Y_{12}$ 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 Phramaceutical 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 Hauel, Andreas Clemens, Herbert Nar, Henning Priepke, 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 semisynthetic taxane, a new anticancer drug. Srikanth Venkatraman, Andrew Prongay, and George F. Njoroge (Merck) summarize the discovery of boceprevir and narlaprevir, 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
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Part I
General Aspects

Analogue-based Drug Discovery III, First Edition. Edited by János Fischer, C. Robin Ganellin, and David P. Rotella.

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.

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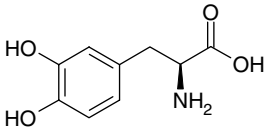
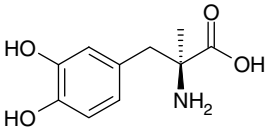
Methyldopa (first synthesized at Merck Sharp & Dohme) has a dual mechanism of action: it is a competitive inhibitor of the enzyme DOPA decarboxylase and its metabolite acts as an α-adrenergic agonist.



levodopa

1

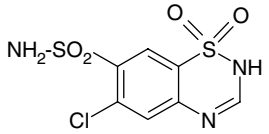


methyldopa

2

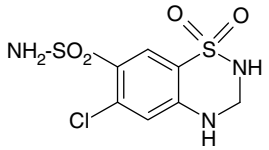
Levodopa and methyldopa are not analogues from the viewpoint of medicinal chemistry. Both are pioneer drugs in their respective therapeutic fields and can be considered as stand-alone drugs, because they have no successful analogues.

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.