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C. Robin Ganellin and David P. Rotella

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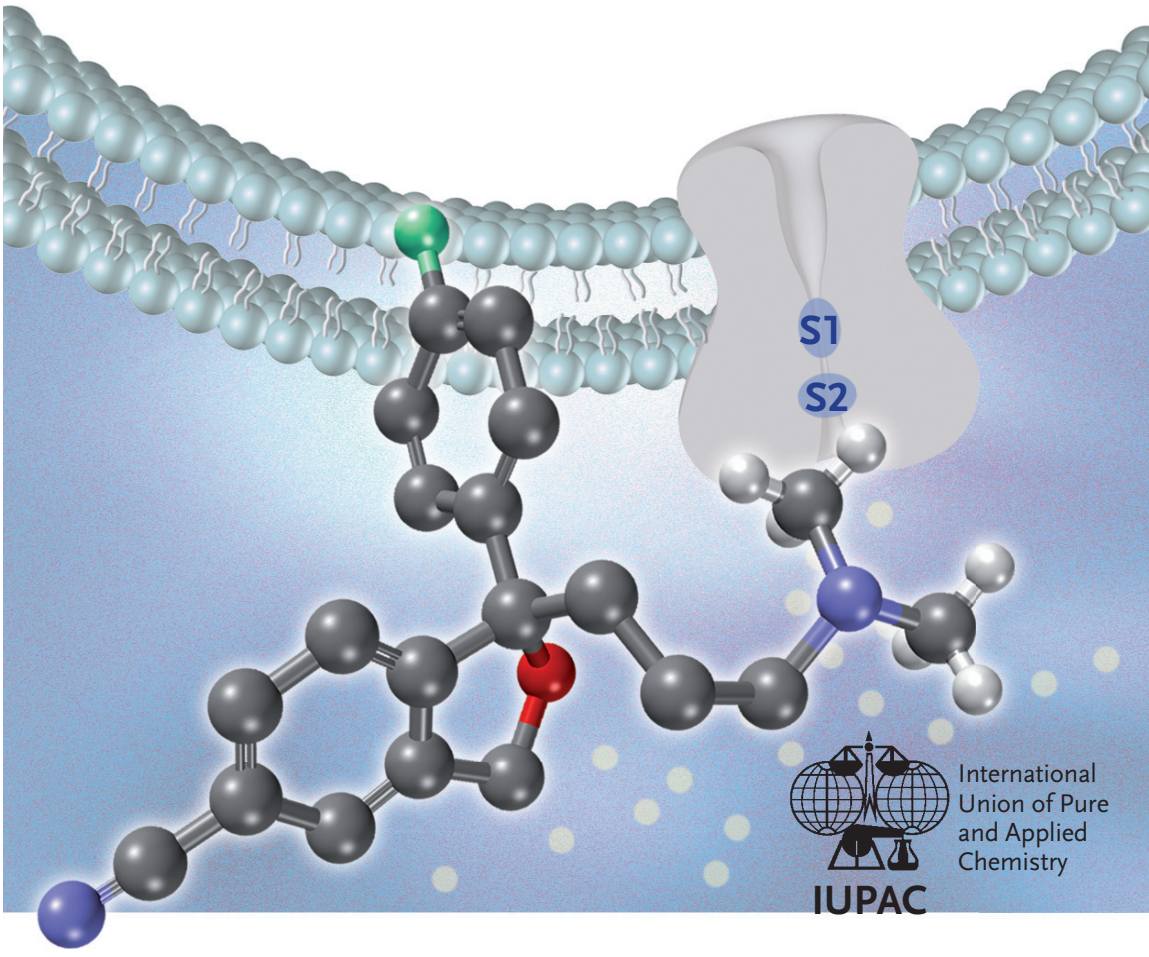
Analogue-based Drug Discovery III



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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

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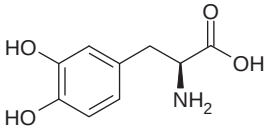
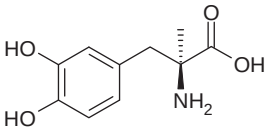
Methyldopa (first synthesized at Merck Sharp & Dohme) has a dual mechanism of action: it is a competitive inhibitor of the enzyme DOPA decarboxylase and its metabolite acts as an α-adrenergic agonist.



levodopa

1

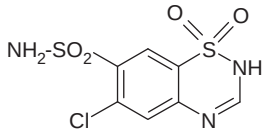


methyldopa

2

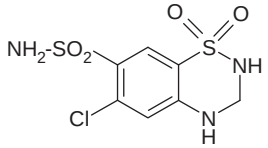
Levodopa and methyldopa are not analogues from the viewpoint of medicinal chemistry. Both are pioneer drugs in their respective therapeutic fields and can be considered as stand-alone drugs, because they have no successful analogues.

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

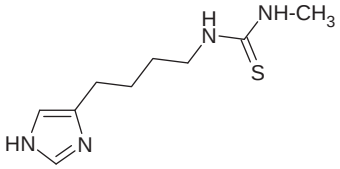
Chlorothiazide and hydrochlorothiazide are *direct analogues*, which term emphasizes their close relationship.

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

1.1
Monotarget Drugs

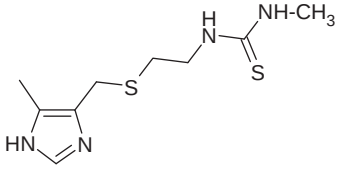
1.1.1
H_2 Receptor Histamine Antagonists

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_2 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.



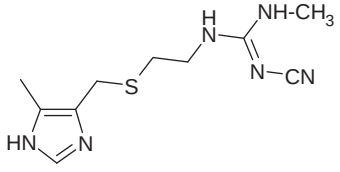
burimamide

5



metiamide

6

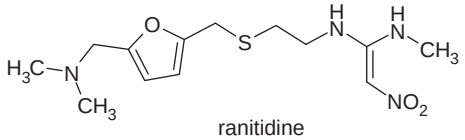


cimetidine

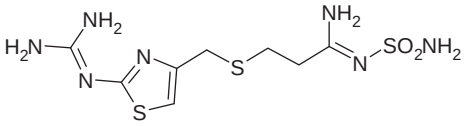
7

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
8



famotidine
9

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

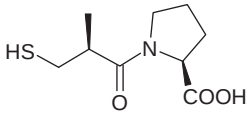
A natural product, the nonapeptide teprotide (**10**), was the pioneer drug for angiotensin-converting enzyme (ACE) inhibitors. Teprotide [8] was used as an active antihypertensive drug in patients with essential hypertension. It could only be administered parenterally, which is a great drawback for 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

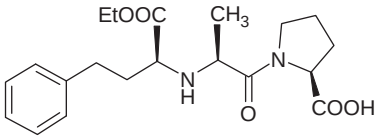
teprotide

10



captopril

11



enalapril

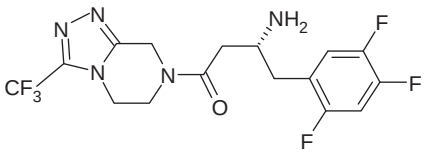
12

Summary:

Pioneer ACE inhibitor drug: teprotide.
First orally active ACE inhibitor drug: captopril.
First orally long-acting ACE inhibitor drug: enalapril.

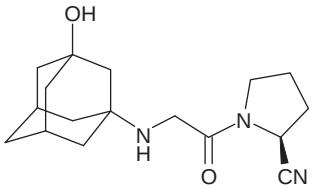
1.1.3 DPP IV Inhibitors

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



vildagliptin

14

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:

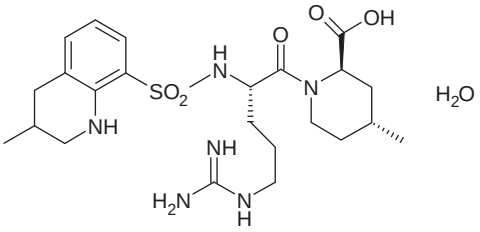
Pioneer DPP IV inhibitor drug: sitagliptin (long-acting inhibitor).
First DPP IV inhibitor analogue drug: vildagliptin (short-acting inhibitor).

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.

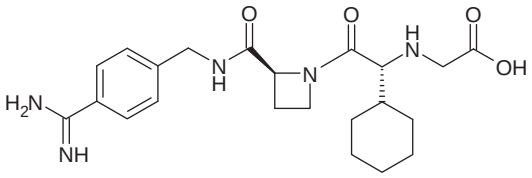
The pioneer univalent direct thrombin inhibitor is argatroban monohydrate (**15**) [15] that was launched by Daiichi Pharmaceutical and Mitsubishi Pharma in 1990. Argatroban was approved by the FDA for prophylactic anticoagulation in the treatment of thrombosis in patients with heparin-induced thrombocytopenia. 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)



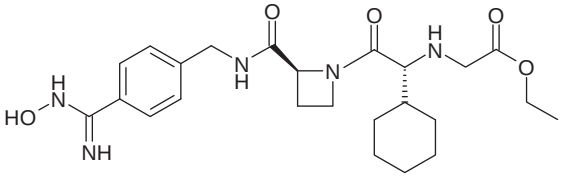
argatroban monohydrate

15



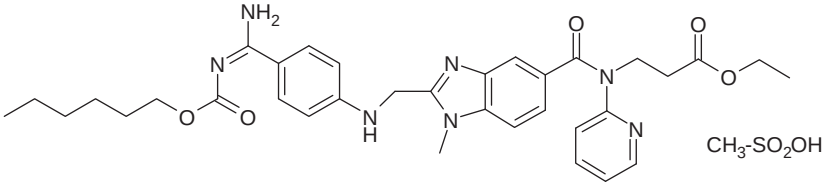
melagatran

16



ximelagatran

17



dabigatran etexilate mesylate

18

Summary:

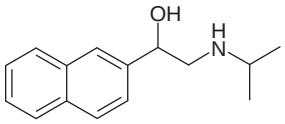
Pioneer univalent direct thrombin inhibitor drug: argatroban.
First orally active univalent thrombin inhibitor: ximelagatran.
First orally active univalent thrombin inhibitor without adverse liver affects: dabigatran etexilate.

1.2 Dual-Acting Drugs

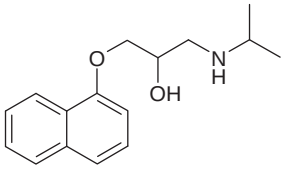
1.2.1 Monotarget Drugs from Dual-Acting Drugs

1.2.1.1 Optimization of Beta-Adrenergic Receptor Blockers

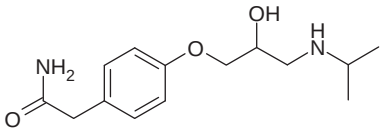
James W. Black and coworkers at ICI invented propranolol as a product of analogue-based drug discovery (ABDD) using their prototype drug, pronethalol (**19**), as a lead compound. Pronethalol [20] was an active drug for the treatment of angina pectoris in humans, but its development was discontinued 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-napthyl group and the secondary alcohol moiety of pronethalol. Propranolol [21] was more potent than pronethalol. Propranolol became the pioneer nonselective β-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