Edited by
János Fischer and C. Robin Ganellin

Analogue-based Drug Discovery II

WILEY-VCH Verlag GmbH & Co. KGaA

Edited by
János Fischer and
C. Robin Ganellin

Analogue-based Drug Discovery II

Related Titles

Faller, B., Urban, L. (eds.)

Hit and Lead Profiling

Identification and Optimization of Drug-like Molecules

2009

ISBN: 978-3-527-32331-9

Chorghade, M. S. (ed.)

Drug Discovery and Development

2 Volume Set

2007

ISBN: 978-0-471-39846-2

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

The Art of Drug Synthesis

2007

ISBN: 978-0-471-75215-8

IUPAC / Fischer, János / Ganellin, C. Robin (eds.)

Analogue-based Drug Discovery

2006

ISBN-13: 978-3-527-31257-3

Lednicer, Daniel

New Drug Discovery and Development

2006

ISBN-13: 978-0-470-00750-1

Edited by
János Fischer and C. Robin Ganellin

Analogue-based Drug Discovery II

WILEY-VCH Verlag GmbH & Co. KGaA

The Editors

Prof. Dr. János Fischer
Richter Plc
Gyömröi ut 30
1103 Budapest
Hungary

Prof. Dr. C. Robin Ganellin
University College London
Department of Chemistry
20 Gordon Street
London WC1H OAJ
United Kingdom

Supported by

The International Union of Pure and Applied Chemistry (IUPAC)
Chemistry and Human Health Devision
PO Box 13757
Research Triangle Park, NC 27709-3757
USA

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.

Cover Design Adam Design, Weinheim
Typesetting Thomson Digital, Noida, India
Printing and Binding Strauss GmbH, Mörlenbach

Printed in the Federal Republic of Germany
Printed on acid-free paper

ISBN: 978-3-527-32549-8

Contents

Analogue-based Drug Discovery II. Edited by János Fischer and C. Robin Ganellin

ISBN: 978-3-527-32549-8

Preface

The positive response to the first volume stimulated the editors to continue beyond the well-received book.

Three very important facts supported this feeling.

1) All copies of the book "*Analogue-Based Drug Discovery*" were sold within 18 months after its publication in February 2006.
2) The *Journal of Medicinal Chemistry* in its very positive review recommended the book for teaching of medicinal chemistry.
3) Last, but not the least Wiley-VCH, and, personally, Dr. Frank O. Weinreich welcomed the idea of the continuation.

We started to collect new topics at the beginning of 2008. We have continued to study the general aspects of "Analogue-Based Drug Discovery" with the help of the chapters that describe how analogues optimize drug therapy. In a separate chapter on standalone drugs, we demonstrate that in the case of a minor number of drugs, the pioneer drug could not (or not yet) be optimized. These standalone drugs can always challenge the medicinal chemistry researchers because, as existing drugs, they can serve as starting points for researchers.

We are grateful again to the IUPAC (International Union of Pure and Applied Chemistry), which supported this activity in projects. The Subcommittee for Medicinal Chemistry and Drug Development and the Division of Chemistry and Human Health provided the opportunity to the editors to discuss this work with other experts of medicinal chemistry.

We are grateful for the participation of all the contributors. Many authors of the book played an important role as inventors who discovered valuable drugs, and their chapters carry a high credibility either as an analogue class study or as a case history of a drug.

We are very much obliged to the helpful reviewing work done by many colleagues, whose names are as follows: Karl-H. Baringhaus, Jozsef Bódi, Derek Buckle, Mark Bunnage, Duane Burnett, Neal Castagnoli, Jonathan B. Chaires, Mukund Chorghade, Erik De Clercq, Duncan Curley, György Domány, Joelle Dubois, Andrew Fensome, Tom Heightman, Bastian Hengerer, Duy H. Hua, Robert Jones, Dale

Analogue-based Drug Discovery II. Edited by János Fischer and C. Robin Ganellin

ISBN: 978-3-527-32549-8

Kempf, Karsten Krohn, K.H. Lee, John Lowe III, Frank C. Odds, Eckhard Ottow, Tom Perun, István Polgár, Dominick Quagliato, Waldemar Priebe, Graham Robertson, Romano Silvestri, László Szabó, Károly Tihanyi, Edwin B. Villhauer, Niels Vrang, Richard White, Michael Williams, and Puwen Zhang. All these colleagues contributed to the quality of this second volume.

We express special thanks to reviewers Derek Buckle, John Lowe III, Bruce E. Maryanoff, Lester A. Mitscher, and Dominick Quagliato, who each corrected the language, and Eckhard Ottow, who corrected the structures, of a whole chapter.

Some authors, besides the editors, also served as reviewers. Our thanks are due to these authors and reviewers as follows: Giovanni Gaviraghi, John Proudfoot, and David Rotella.

J.F. thanks the Alexander von Humboldt Foundation (Bonn) for a fellowship in 2008 and 2009.

We hope that the second volume will also be well received and that it will contribute in some way to help the experts in drug discovery and students of medicinal chemistry.

October 2009 *János Fischer and C. Robin Ganellin*
Budapest and London

Introduction

János Fischer and C. Robin Ganellin

Analogy plays a very important role in scientific research and especially in applied research. This is certainly true for the medicinal chemist searching for new drugs to treat diseases. The chemical structure and the similarities and differences in chemical and biological properties between compounds help guide the researcher in deciding where to position a new molecule in comparison to what is already known about other compounds.

Medicinal chemistry is a relatively "young" science that spanned the whole of the twentieth century. In the first half of the century, new drug research was dominated by organic chemistry, and researchers sought improved drugs among structurally similar compounds. *Full analogues* (see below) dominated this kind of research. The latter half of the century saw a much greater contribution from biochemistry and pharmacology, and many *pioneer drugs* were discovered. This opened the way for researchers to seek to improve upon these drugs by investigating analogues.

The first volume of *Analogue-Based Drug Discovery* focused on an important segment of medicinal chemistry, where an existing drug was selected as a lead compound and the research had, as a goal, to improve upon the lead by synthesizing and testing analogues. The chemical structure and main biological activity of such an analogue were often similar to the lead drug. Thus, the researchers generally sought a *structural and pharmacological analogue* (more simply called a *full analogue*) or if the pharmacophores were the same, a *direct analogue*. Usually, the aim was to achieve an improved biological activity profile, with a greater potency.

The first volume included a description of many well-established analogue classes of drug that are indispensable nowadays for the treatment of peptic ulcer disease, gastroesophageal reflux disease, prevention of cardiovascular diseases (e.g., anti-hypertensives, cholesterol-lowering agents, calcium antagonists, and beta-adrenergic receptor blocking agents), pain (e.g., opioid analgesics), and many other diseases.

The last two decades, however, have witnessed great changes in the chemical and biological methods for generating a lead compound. Combinatorial chemistry affords many more compounds than traditional synthetic methods and these are tested very rapidly by high-throughput screening (HTS) to deliver new hit and lead molecules. This procedure often paves the way for new types of structures for drug research thereby decreasing the importance of having chemical similarity. At the

Analogue-based Drug Discovery II. Edited by János Fischer and C. Robin Ganellin

ISBN: 978-3-527-32549-8

same time, this provides a better opportunity for novelty and therefore for patenting. This also gives rise to a greater need to compare the biological properties of these new lead compounds in order to arrive at the best *pharmacological analogue*.

Analogue-based drug discovery (ABDD) is not a simple research method, but it is a way of thinking that, in addition to organic synthesis, uses most of the procedures that are now available to medicinal chemists, such as

i. investigation of structure–activity relationships,
ii. molecular modeling,
iii. structure-based drug discovery,
iv. fragment-based drug discovery,
v. early recognition of drug distribution properties and avoidance of potential toxicities.

Analogue-based drug discovery has the merit that the therapeutic target is already validated, but it carries the hazard of potentially losing out to competitors who may start from the same approach at about the same time.

This second volume of *Analogue-Based Drug Discovery* has a broader scope than the first volume. The book not only contains descriptions of full analogues but also includes several pharmacological analogues. The book is divided into three parts:

1) General Aspects of Analogue-Based Drug Discovery
2) Analogue Classes
3) Case Histories

General Aspects

The opening chapter summarizes various possibilities exemplifying how the properties of a drug may be modified to give a new drug analogue that improves patient drug therapy. There are 12 principles exemplified and within some of these principles there are several methods; hence this chapter gives a broad overview.

A small number of the *pioneer drugs* remain without successful analogues; we describe these by the term *standalone drugs*. Among the most frequently used 100 drugs, 9 such *standalone drugs* can be identified. Their history and present situation may be used to initiate a new research activity to make their analogues.

In addition to the traditional structure–activity relationship (SAR) studies, molecular modeling is the most important method that can help the medicinal chemist to find a new drug analogue. The chapter discusses several useful examples of molecular modeling in analogue research.

Patenting activity is one of the basic tasks of drug research. Patents mostly concern a group of *direct analogues*; therefore, the first claim of a patent contains a general structure that describes this group of compounds. The chapter gives an overview of some of the issues that can affect the commercial protection of the discoveries made by medicinal chemists.

Analogue Classes

The discovery of dipeptidyl peptidase IV inhibitors has opened a promising chapter for the treatment of type 2 diabetes. The *pioneer drug* sitagliptin has been followed by several analogues in order to obtain more potent and longer acting derivatives.

Serendipitous clinical observation afforded the *pioneer drug* sildenafil. Several analogues have been found that have optimized its properties (e.g., selectivity, duration of action).

Rifamycins are antibacterial antibiotics derived from fermentation. Analogue-based drug research afforded more potent derivatives. One of the derivatives, the poorly absorbed rifaximin, has a promising application for the treatment of irritable bowel syndrome.

Three analogue classes of monoterpenoid indole alkaloids are discussed: (i) vincamine derivatives, (ii) dimeric vinca alkaloid analogues, and (iii) camptothecin analogues. The successful natural product *direct analogues* are applied for the treatment of cerebral insufficiencies and cancer.

The natural product doxorubicin is an anthracycline antibiotic used to treat a wide range of cancers, but it has a cardiotoxic adverse effect. The research into *direct analogues* had a goal to obtain drugs with a better therapeutic index.

Paclitaxel and epothilone analogues are also examples of how natural product drugs can be used to initiate analogue-based drug research to afford new drug analogues with better properties as anticancer agents.

The selective serotonin reuptake inhibitors (SSRIs) are *pharmacological analogues* that revolutionized antidepressant therapy. The structurally different SSRIs have different profiles for inhibiting uptake of the neurotransmitters: serotonin, dopamine, and norepinephrine.

The modification of naturally occurring tropane alkaloids afforded the quaternary ammonium salts ipratropium and tiotropium, which are important drugs used for treating chronic obstructive pulmonary disease. Tiotropium, as a result of analogue-based drug discovery, has a longer duration of action that enables a once-daily dosing.

The natural product adrenaline (epinephrine) was the starting point for drug research into β-adrenoreceptor agonists. From isoprenaline (isoproterenol) through the selectively acting salbutamol, and on to salmeterol, analogue research resulted in selective, more potent, and longer acting analogues with different PK profiles, which are important drugs in asthma therapy.

Case Histories

Eight case histories are described by their inventors.

Liraglutide is a new antidiabetic drug, an analogue of the natural product glucagon-like peptide 1. Among the acylated GLP-1 analogues liraglutide has been developed for a once-daily treatment.

Eplerenone is a spironolactone analogue for treating hypertension that has a greater selectivity for the mineralocorticoid receptor and reduced sexual side effects.

Clevudine is a new drug for the treatment of the chronic hepatitis B virus (HBV) infection, which belongs to the class of nucleoside reverse transcriptase inhibitors.

Tipranavir is a new anti-HIV agent that is a protease inhibitor. The discovery of tipranavir used structure-based and fragment-based drug design and its long discovery process started from warfarin, which is a weak HIV-1 protease inhibitor.

Dasatinib can be regarded as a *pharmacological analogue* of imatinib. Dasatinib is more potent and it can be used in imatinib-resistant cases for the treatment of chronic myelogenous leukemia (CML).

Lapatinib can be regarded as a *pharmacological analogue* of erlotinib. It is a tyrosine kinase inhibitor and was first approved for the treatment of solid tumors such as in breast cancer.

Venlafaxine is the first marketed serotonin/norepinephrine reuptake inhibitor (SNRI) and is used for the treatment of deep depression. Its active metabolite is desvenlafaxine, which has some advantageous properties; for example, it has a more favorable metabolic profile compared to venlafaxine.

Rilpivirine is a new HIV-1 nonnucleoside reverse transcriptase inhibitor (NNRTI), an analogue of etravirine. Rilpivirine is highly potent also against strains that are resistant to the first-generation NNRTI drugs.

The first volume of *Analogue-Based Drug Discovery* discussed mostly well-established drugs. This second volume also opens the door to new drug discoveries and the editors hope that, like the first volume, all of the drugs discussed in this book will have a bright future.

Abbreviations

ABC	ATP binding cassette
ABDD	analogue-based drug discovery
ABPM	ambulatory blood pressure monitoring
ACAT	acyl-CoA:cholesterol acyltransferase
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotropic hormone
ADMET	absorption, distribution, metabolism, excretion and toxicity
AFC	7-amino-4-trifluoromethylcoumarin
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ALL	acute lymphoblastic leukemia
AMP	amprenavir
cAMP	cyclic 3′,5′-adenosine monophosphate
ANDA	Abbreviated New Drug Application
α-APA	α-anilinophenylacetamide
APV	amprenavir
AR	androgen receptor
ATP	adenosine triphosphate
AUC	area under the curve
AZT	azidothymidine
BBB	blood-brain-barrier
Bcr-Abl	Breakpoint cluster region - Abelson
BG	blood glucose
b.i.d.	twice a day (from Latin *bis in die*)
BOC	t-butoxycarbonyl
CBF	cerebral blood flow
CC_{50}	50% cytotoxic concentration
β-CCE	ethyl β-carboline-3-carboxylate
CGI	Clinical Global Impressions Scale
CHB	chronic hepatitis B
CK	creatine kinase
CL	clearance
CL_R	renal clearance

Analogue-based Drug Discovery II. Edited by János Fischer and C. Robin Ganellin

ISBN: 978-3-527-32549-8

CL_T	total clearance
CLV	clevudine
CLV-TP	clevudine triphosphate
CML	chronic myelogenogenous leukemia
CMRglc	cerebral metabolic rate of glucose
CNS	central nervous system
COBP	chronic obstructive broncho-pneumopathies
COPD	chronic obstructive pulmonary disease
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
CPI/r	comparator protease inhibitor boosted with ritonavir
CPT	camptothecin
CRC	colorectal cancer
CYP	cytochrome P450 isoenzyme
DA	dopamine
10-DAB	10-deacetyl-baccatin
DAPY	diarylpyrimidine
DATA	diaryltriazine
dCK	deoxycytidine kinase
DNA	desoxyribonucleic acid
cDNA	complementary deoxyribonucleic acid
cccDNA	covalently closed circular DNA
mtDNA	mitochondrial DNA
DOC	deoxycorticosterone
DOCA	deoxycorticosterone acetate
DPP-4	dipeptidyl peptidase 4
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, third edition
EBV	Epstein-Barr virus
EC_{50}	effective concentration 50
ED	erectile dysfunction
EFS	electric field stimulation
EGFR	epidermal growth factor receptor
EMEA	European Medicines Agency
EPA	Environmental Protection Agency
EPO	European Patent Office
EPS	exprapyramidal side effect
Erk	extracellularly regulated kinase
ETC	emtricitabine
FAAH	fatty acid amide hydrolase
FBDD	fragment-based drug design
FDA	Food and Drug Administration
L-FEAU	1-(2′-deoxy-2′-fluoro-β-L-arabinofuranosyl)-5-ethyluridine
FEV	forced expiratory volume
L-FMAU	L-2′-fluoro-5-methyl-β-L-arabinofuranosyluracil

$GABA_A$	gamma-aminobutyric acid A
GAD	generalized anxiety disorder
GI	growth inhibition
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
cGMP	cyclic 3′,5′-guanosine monophosphate
GPIIb/IIIa	glycoprotein IIb/IIIa
HA	heavy atom
HAART	Highly Active Antiretroviral Therapy
HA/ACTH	histamine-induced adrenocorticotropic hormone
HAM-A	Hamilton Anxiety Taring Scale
HAM-D	Hamilton Depression Rating Scale
HbA_{1c}	glycosylated haemoglobin
HBV	hepatitis B virus
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e antigen
HbsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis delta virus
hERG	human ether-a-go-go-related gene
HFB	human foreskin fibroblast
HIAA	5-hydroxy-indole acetic acid
HIV	human immunodeficiency virus
HIV PR	HIV protease
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
5-HT	5-hydroxytryptamine (serotonin)
5-HTP	5-hydroxytryptophan
HTS	high-throughput screening
IBMX	isobutylmethylxanthine
IC_{50}	inhibitory concentration 50
pIC_{50}	$-\log IC_{50}$
ICS	inhaled corticosteroids
IDR	idarubicin
IDV	indinavir
i.m.	intramuscular
IND	Investigational New Drug
INN	International Nonproprietary Name
IOPY	iodophenoxypyridone
i.p.	intraperitoneal
i.v.	intravenous
K_i	inhibitory constant
LABA	long-acting β_2-agonist
Lck	lymphocyte specific kinase
hLck	human Lck

mLck	murine Lck
LDL-C	low-density lipoprotein-cholesterol
LE	ligand efficiency
LPV	lopinavir
LVEF	left ventricular ejection fraction
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
M_1	muscarinic receptor M_1 subtype
MAP	mitogen-activated protein
rMD	restrained molecular dynamics
MDD	major depressive disorder
MDR	multidrug resistance
MED	minimal effective dose
MES	maximal electroshock seizure
MIC	minimal inhibitory concentration
MR	mineralocorticoid receptor
MRP	multidrug resistance-associated protein
MTD	maximum tolerated dose
NAPQI	*N*-acetyl-p-benzoquinone imine
NCE	New Chemical Entity
NCI	National Cancer Institute
NDA	New Drug Application
NE	norepinephrine
NMR	nuclear magnetic resonance
NNRTI	nonnucleoside reverse transcriptase inhibitor
NO	nitric oxide
NPs	natural products
NPC1L1	Niemann-Pick C1-Like-1
NRIs	norepinephrine reuptake inhibitors
NRTI	nucleoside reverse transcriptase inhibitor
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
OADs	oral antidiabetic drugs
OC	ovarian cancer
OCD	obsessive-compulsive disorder
OGTT	oral glucose tolerance test
PCA	p-chloroamphetamine
PCF	plant cell fermentation
PCT	Patent Cooperation Treaty
PDEs	phosphodiesterases
PDGFR	platelet derived growth factor receptor
PEP	prolyl endopeptidase
PGE_1	prostaglandin E_1
PGE_2	prostaglandin E_2
P-gp	permeability glyocoprotein

Ph (+)	Philadelphia chromosome positive
PK	pharmakokinetic
PKG	protein kinase G
POMS	profile of mood state
PPCE	postproline cleaving enzyme
PR	progesterone receptor
QSAR	quantitative structure-activity relationship
q.d. or QD	once a day (from Latin *quaque die*)
RBA	relative binding affinity
RGD	arginine-glycine-aspartic acid
RNA	ribonucleic acid
RNApol	RNA polymerase
mRNA	messenger RNA
RT	reverse transcriptase
RTV	ritonavir
SAR	structure-activity relationship
SBDD	structure-based drug design
s.c.	subcutaneous
SCID	severe combined immunodeficient
SCLC	small-cell lung cancer
SEDDS	self-emulsifying drug delivery system
SEF	sodium excreting factor
SI	selectivity index
SIV	simian immunodeficiency virus
SMC	smooth muscle cell
SNRI	serotonin/norepinephrine reuptake inhibitor
SQV	saquinavir
Src	sarcoma
SRI	serotonin reuptake inhibitor
SSRIs	selective serotonin reuptake inhibitors
TCR	T-cell antigen receptor
TDF	tenofovir disoproxil fumarate
TGFα	tansforming growth factor-α
TI	tumor inhibition
TIBO	4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk]benzodiazepin-2(1*H*)-one
t.i.d.	three times daily
TK	thymidine kinase
TMPK	thymidylate kinase
TPV	tipranavir
TPV/r	tipranavir/ritonavir combination
TPT	topotecan
TRIPs	Trade-related Aspects of Intellectual Property Rights
TTP	time to progression
UDP	uridine diphosphate

UGT	uridine diphosphate glucuronyl transferase
USAN	United States Adopted Names
VEGFR	vascular endothelial growth factor receptor
VMS	vasomotor symptoms
VSMC	vascular smooth muscle cell
V_{SS}	steady-state volume
WBC	white blood cell
WHcAg	woodchick hepatitis virus core antigen
WHsAg	woodchuck hepatitis virus surface antigen
WHV	woodchuck hepatitis virus
WTO	World Trade Organization

Part I
General Aspects

Analogue-based Drug Discovery II. Edited by János Fischer and C. Robin Ganellin

ISBN: 978-3-527-32549-8