Methods and Principles in Medicinal Chemistry

Edited by
Hugo Kubinyi, Gerhard Müller

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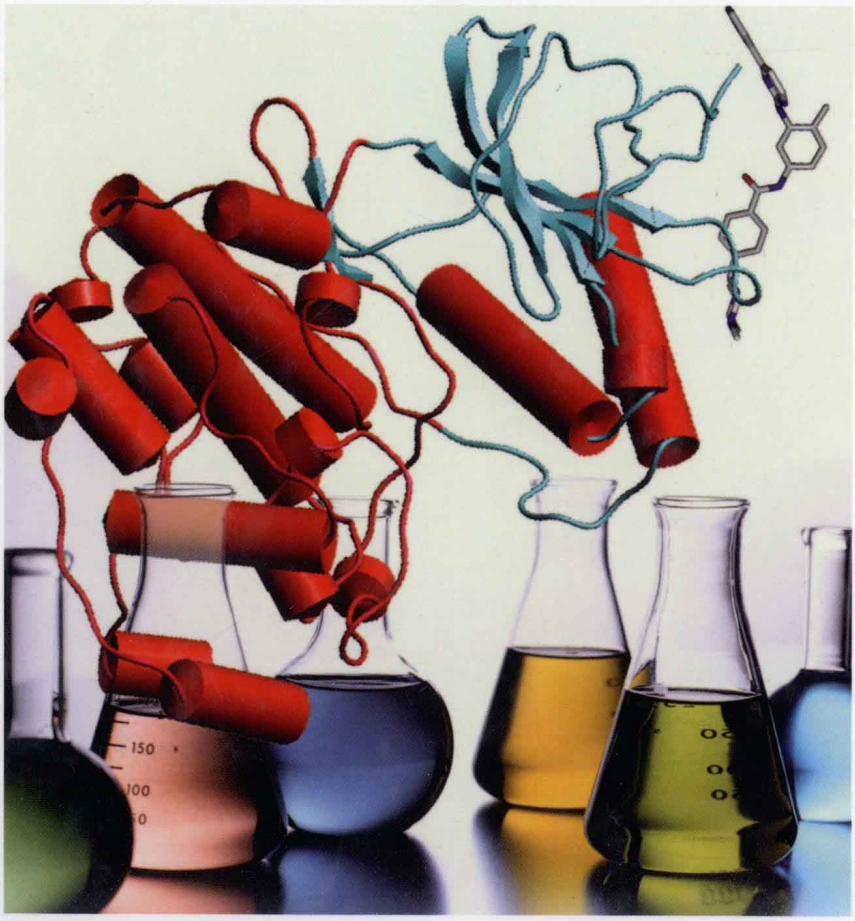
Chemogenomics in Drug Discovery

A Medicinical Chemistry Perspective



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Dedicated to the memory of the great medicinal chemist
Dr. Paul Janssen (1926–2003),
the discoverer of many breakthrough medicines.

Preface

The term chemogenomics is applied to a diversity of approaches that use chemical compounds to probe biological systems. While all of the approaches have at least some relevance to drug discovery, the methods can be differentiated according to the extent to which they employ stochastic versus directed approaches. Stochastic chemogenomics approaches probe the global response of a biological system on exposure to chemical compounds. Focused chemogenomics approaches use chemicals as detailed probes of biochemical pathways that can play a key role in target identification and validation. An integrated chemogenomics platform uses affinity-based screening, directed combinatorial chemistry, and structure-based drug design to rapidly develop drug-like tool compounds that can validate a target-based therapeutic hypothesis *in vivo*.

Chemogenomics approaches are evolving to overcome key problems limiting the efficiency of drug discovery in the postgenomic era. Many of these limits stem from the low success rates in finding drugs for novel genomics targets whose biochemical properties and therapeutic relevance is poorly understood. The fundamental objective of chemogenomics is to find and optimize chemical compounds that can be used to directly test the therapeutic relevance of new targets revealed through genome sequencing. The chemogenomics approach defers investment in biological target validation to a later stage in the discovery cycle, where resources can be deployed more efficiently and with a higher probability of success, thus providing a more direct route to finding new drugs.

The present volume on "Chemogenomics in Drug Discovery" is organized in three main sections. General aspects in the first section are dedicated to privileged structures as target family-directed masterkeys (G. Müller), drug discovery from side effects (H. Kubinyi), the value of chemical genetics in drug discovery (K. Russell) and structural aspects of binding site similarity (A. Bergner and J. Günther).

The second section focuses on target families such as kinases (R. Buijsman), ion channel modulators (K.-H. Baringhaus and G. Hessler), and phosphodiesterases (M. Hendrix and C. Kallus). In addition, the contribution of molecular informatics for chemogenomics (E. Jacoby et al.), chemical kinomics (B. Klebl), as well as proteochemometrics (J. Wikberg et al.) are discussed.

Chemical libraries are the topic of the final section and cover chemogenomics in compound library and template design for GPCRs (T. R. Webb), computational filters in lead generation (W. Guba), navigation in chemical space (G. Schneider

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and P. Schneider), natural product derived combinatorial libraries (M. A. Koch and H. Waldmann), and combinatorial chemistry in chemical genomics age (R. Joseph and P. Arya).

We are grateful to the Volume Editors for their enthusiasm to organize this volume and to work with such a fine selection of authors. We also want to express our gratitude to Frank Weinreich from Wiley-VCH for his valuable contributions to this project.

Dr. Paul A. J. Janssen, former Director of Janssen Pharmaceutica N. V., Beerse Belgium, and founder of the Center for Molecular Design, Vosselaar, Belgium, unexpectedly died on November 11, 2003. As he was one of the most prominent medicinal chemists and discoverer of many breakthrough medicines, the Volume and Series Editors would like to dedicate this book to the memory of this great man.

March 2004

Raimund Mannhold, Düsseldorf
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A Personal Foreword

Chemical Genomics versus Orthodox Drug Development is the title of an essay published in the February issue 2003 of Drug Discovery Today (Drug Discovery Today **8**, 157–159, 2003), discriminating between two pharmaceutical research approaches; the chemical genomics-based approach on one hand, as opposed to the classical way of drug development, adhering to the accepted traditional strategies on the other hand. Embedded in this apparent contradiction, defined by established medicinal chemistry and the post-genomic approaches characterized by -omes and -omics tags, this volume of *Methods and Principles in Medicinal Chemistry* attempts to re-position the core discipline of Medicinal Chemistry right into the centre of chemogenomics. Since chemogenomics is widely claimed to address key issues posed by the sharp decrease in pharmaceutical industry's productivity, the role and relevance of modern medicinal chemistry has to be re-emphasised in this context.

All contributions of this issue focus on aspects of the systematic investigation of molecular recognition phenomena that underlie drug–target interactions, and subsequent extrapolation either within compound classes or within target families with the ultimate aim to enhance efficiency of the drug discovery process.

G. Müller, H. Kubinyi, and K. Russell elaborate in their contributions on different aspects of classification and systematisation. The target family-directed masterkey concept conveyed by G. Müller intentionally takes advantage of privileged structures that are tailor-made to explore entire gene families, thus accounting for the required scalability of a once established chemistry concept in a chemogenomics framework. The systematic exploitation of observed side-effects associated to known drugs is described by H. Kubinyi as an efficient approach towards high-content leads for novel targets and respective diseases. In more general terms, K. Russell introduces into the manifold conceptual interfaces between biology and chemistry on a chemical genetics platform. Apart from the aspects of target identification and validation, the chemogenomics idea is developed out of the chemical genetics realm by extrapolating compounds from tools to high-quality leads.

Predominantly, the book covers systematic elaborations on pharmaceutically relevant target families with clear focus centred around systematic medicinal chemistry access routes towards the distinct members of those target clusters. Contributions by R. Buijsman and B. Klebl and colleagues provide detailed insights into the world of protein kinase inhibitors. While R. Buijsman systematically focuses on the detailed structural requirements of protein kinase binding sites that

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determine small molecule design strategies, B. Klebl and co-workers provide detailed insights into chemical kinomics, highlighting chemical genomics, chemical validation strategies, chemical genetics approaches, and a chemical proteomics technology, always emphasising the multiple purposes of specifically developed kinase inhibitors.

Medicinal Chemistry approaches towards the target family of phosphodiesterases, ion channels, and G protein-coupled receptors under a chemogenomics paradigm are introduced in three distinct contributions. M. Hendrix and C. Kallus elaborate the element of systematic strategies within medicinal chemistry for phosphodiesterase inhibitors where common substructures are described to address conserved features of an entire target family. Privileged chemotypes that qualify for a target family-directed library design concept form the basis for a chemogenomics-based discovery strategy pursued for ion channels, as described by K.-H. Baringhaus and G. Hessler. T. Webb refers to the area of G protein-coupled receptors, where ligand-derived information is systematically used to design target family-directed scaffolds that, upon further chemical variation, allow for rapid lead generation.

Contributions by R. Joseph and P. Arya as well as M. A. Koch and H. Waldmann focus on synthetic aspects towards lead structures originating from natural product-derived scaffolds. R. Joseph and P. Arya refer to two complementary approaches, the synthetic access to focussed libraries around bioactive natural product cores, and diversity-oriented synthesis aiming at 3D scaffold diversity for hit generation, respectively. On the other hand, M. A. Koch and H. Waldmann emphasise the correlation of natural product-based library concepts with structural features of targeted protein domains, thus strengthening the privileged structure concept from a bioorganic viewpoint.

Systematic application and conceptual combination of chemoinformatics, bioinformatics, and structural genomics approaches are covered by a variety of contributions in this book. E. Jacoby and colleagues report on design strategies for combinatorial compound libraries pursuing a system-based chemoproteomics approach that is exemplified on the target family of G protein-coupled receptors. Numerous aspects of ligand based *in-silico* design techniques are reviewed in detail by G. Schneider and P. Schneider, touching upon algorithms and applications of e.g. similarity searching, or pharmacophore models. W. Guba and O. Roche highlight pragmatic applications of computational strategies for addressing drug-like characteristics of chemotypes within the framework of lead finding and optimisation. A. Bergner and J. Günther propose a systematic approach towards a deeper understanding of target binding site characteristics and corresponding similarities, thus integrating unique and precious protein structure knowledge into the chemogenomics discussion. Finally, J. Wikberg and co-workers report on a novel bioinformatics approach, termed proteochemometrics, to develop detailed insights into molecular interaction space, by scrutinising binding data of different compound series targeted towards different receptor systems.

As the field of chemogenomics is still maturating, this book is an attempt to highlight the role of medicinal chemistry in the multi-disciplinary set-up that is

required for a successful drug discovery environment. Careful consideration of all aspects discussed within this book will undoubtedly facilitate the development of a clear definition of chemogenomics. In this context, the book will be helpful for numerous researchers in the life science community, currently addressing any aspect of drug discovery and development in pharmaceutical industry, as well as in academia.

All chapter authors are very much acknowledged for their great enthusiasm, their preparation of the manuscripts within a tough time frame and the high quality of their contributions. The Editors would also like to thank Dr. Frank Weinreich and the staff of Wiley-VCH for their engagement in the production of this monograph.

April 2004

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