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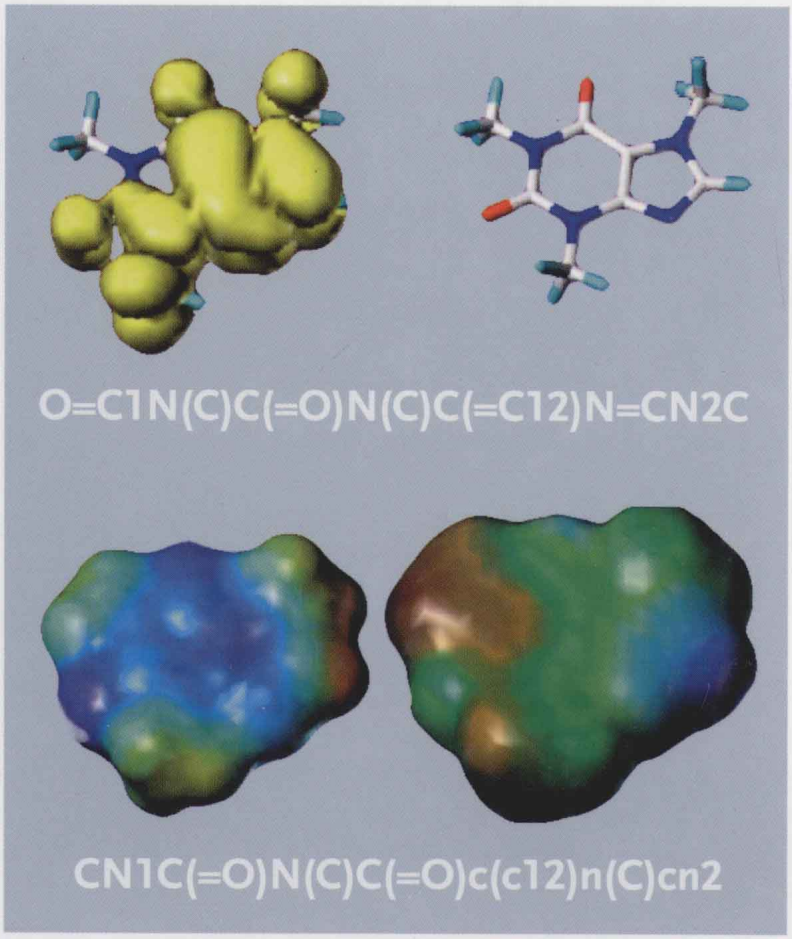

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A Personal Foreword

This volume brings together contributions from academic and industrial scientists who develop and apply chemoinformatics strategies and tools in drug discovery. From chemical inventory and compound registration to candidate drug nomination, chemoinformatics integrates data via computer-assisted manipulation of chemical structures. Linked with computational chemistry, physical (organic) chemistry, pharmacodynamics and pharmacokinetics, chemoinformatics provides unique capabilities in the areas of lead and drug discovery. This book aims to offer knowledge and practical insights into the use of chemoinformatics in preclinical research.

Divided in four sections, the book opens with a first-hand account from Garland Marshall, spanning four decades of chemoinformatics and pharmaceutical research and development. Part one sets the stage for virtual screening and lead discovery. Hit and lead discovery via *in silico* technologies are highlighted in part two. In part three, data collection and mining using chemical databases are discussed in the context of chemical libraries. Specific applications and examples are collected in part four, which brings together industrial and academic perspectives. The book concludes with another personal account by Don Abraham, who presents drug discovery from an academic perspective.

The progression hit identification → lead generation → lead optimization → candidate drug nomination is served by a variety of chemoinformatics tools and strategies, most of them supporting the decision-making process. Key procedures and steps, from virtual screening to *in silico* lead optimization and from compound acquisition to library design, underscore our progress in grasping the preclinical drug discovery process, its needs for novel technologies and for integrated informatics support. We now have the ability to identify novel chemotypes in a rational manner, and *in silico* methods are deep-rooted in the process of systematic discovery. Our increased knowledge in a variety of seemingly unrelated phenomena, from atomic level issues related to drug–receptor binding to bulk properties of drugs and pharmacokinetics profiling, is likely to lead us on a better path for the discovery of orally bioavailable drugs, at the same time paving the way for novel, unexpected therapeutics.

I want to acknowledge all the contributors who made this book possible. Their insights, examples and personal accounts move beyond the sometimes dry language of science, turning this volume into an interesting and fascinating book to read.

Finally, I thank Frank Weinreich and Hugo Kubinyi for their encouragement and timely pressure to prepare this book on time.

Albuquerque, January 2005 *Tudor I. Oprea*

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Preface

The term "chemoinformatics" was introduced in 1998 by Dr. Frank K. Brown in the Annual Reports of Medicinal Chemistry. In his article "Chemoinformatics: What is it and How does it Impact Drug Discovery", he defines chemoinformatics as follows: "*The use of information technology and management has become a critical part of the drug discovery process. Chemoinformatics is the mixing of those information resources to transform data into information and information into knowledge for the intended purpose of making better decisions faster in the area of drug lead identification and organization*".

In fact, Chemoinformatics is a generic term that encompasses the design, creation, organization, management, retrieval, analysis, dissemination, visualization and use of chemical information. Related terms of chemoinformatics are cheminformatics, chemi-informatics, chemometrics, computational chemistry, chemical informatics, and chemical information management/science.

Reflecting the above given definitions, the present volume on "Chemoinformatics in Drug Discovery"covers its most important aspects within four main sections. After an introduction to chemoinformatics in drug discovery by Garland Marshall, the first section is focused on *Virtual Screening*. T. Oprea describes the use of "Chemoinformatics in Lead Discovery" and M.M. Hann et al. deal with "Computational Chemistry, Molecular Complexity and Screening Set Design". Then, M. Rarey et al. review "Algorithmic Engines in Virtual Screening" and D. Horvath et al. review the "Strengths and Limitations of Pharmacophore-Based Virtual Screening". The next section is dedicated to *Hit and Lead Discovery* with chapters of I.J. McFadyen et al. on "Enhancing Hit Quality and Diversity Within Assay Throughput Constraints", of C.L. Cavallaro et al. on "Molecular Diversity in Lead Discovery", and of C. Ho on "In Silico Lead Optimization". Topics of the third section refer to *Databases and Libraries*. They include chapters on "WOMBAT: World of Molecular Bioactivity" by M. Olah et al., on "Cabinet – Chemical and Biological Informatics Network" by V. Povolna et al., on "Structure Modification in Chemical Databases" by P.W. Kenney and J. Sadowski, and on the "Rational Design of GPCR-specific Combinational Libraries Based on the Concept of Privileged Substructures" by N.P. Savchuk et al.

According to our intention, to provide in this series on "Methods and Principles in Medicinal Chemistry" practice-oriented monographs, the book closes with a section on *Chemoinformatics Applications*. These are exemplified by G.M. Maggiora et al. in a chapter on "A Practical Strategy for Directed Compound Acquisition", by

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K.-H. Baringhaus and H. Matter on "Efficient Strategies for Lead Optimization by Simultaneously Addressing Affinity, Selectivity and Pharmacokinetic Parameters", by R.A. Goodnow et al. on "Chemoinformatic Tools for Library Design and the Hit-to-Lead Process" and by A. Tropsha on the "Application of Predictive QSAR Models to Database Mining". The section is concluded by a chapter of D.J. Abraham on "Drug Discovery from an Academic Perspective".

The series editors would like to thank Tudor Oprea for his 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.

September 2004

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