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Topics in Medicinal Chemistry

Aims and Scope

Drug research requires interdisciplinary team-work at the interface between chemistry, biology and medicine. Therefore, the new topic-related series *Topics in Medicinal Chemistry* will cover all relevant aspects of drug research, e.g. pathobiochemistry of diseases, identification and validation of (emerging) drug targets, structural biology, drugability of targets, drug design approaches, chemogenomics, synthetic chemistry including combinatorial methods, bioorganic chemistry, natural compounds, high-throughput screening, pharmacological in vitro and in vivo investigations, drug-receptor interactions on the molecular level, structure-activity relationships, drug absorption, distribution, metabolism, elimination, toxicology and pharmacogenomics.

In general, special volumes are edited by well known guest editors.

In references *Topics in Medicinal Chemistry* is abbreviated *Top Med Chem* and is cited as a journal.

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Nicholas A. Meanwell
Editor

Tactics in Contemporary Drug Design

With contributions by

U.M. Hanumegowda · J.G. Kenna · A.G. Leach · D.J. Leishman · N.A. Meanwell · T. Noeske · Z. Rankovic · A. Regueiro-Ren · M.W. Sinz · S.H. Stahl · M.A. Walker · R.J. Young

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Editor
Nicholas A. Meanwell
Bristol-Myers Squibb
Wallingford
Connecticut
USA

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Preface to the Series

Medicinal chemistry is both science and art. The science of medicinal chemistry offers mankind one of its best hopes for improving the quality of life. The art of medicinal chemistry continues to challenge its practitioners with the need for both intuition and experience to discover new drugs. Hence sharing the experience of drug discovery is uniquely beneficial to the field of medicinal chemistry.

The series Topics in Medicinal Chemistry is designed to help both novice and experienced medicinal chemists share insights from the drug discovery process. For the novice, the introductory chapter to each volume provides background and valuable perspective on a field of medicinal chemistry not available elsewhere. Succeeding chapters then provide examples of successful drug discovery efforts that describe the most up-to-date work from this field.

The editors have chosen topics from both important therapeutic areas and from work that advances the discipline of medicinal chemistry. For example, cancer, metabolic syndrome and Alzheimer's disease are fields in which academia and industry are heavily invested to discover new drugs because of their considerable unmet medical need. The editors have therefore prioritized covering new developments in medicinal chemistry in these fields. In addition, important advances in the discipline, such as fragment-based drug design and other aspects of new lead-seeking approaches, are also planned for early volumes in this series. Each volume thus offers a unique opportunity to capture the most up-to-date perspective in an area of medicinal chemistry.

Dr. Peter R. Bernstein
Prof. Dr. Armin Buschauer
Prof. Dr. Gunda I. Georg
A. K. Saxena
Dr. Claudiu T. Supuran
Dr. John Lowe
Dr. Hans Ulrich Stilz

Preface

Contemporary drug discovery practices have evolved considerably over the last 30 years as our knowledge and understanding of the attributes and profiles of successful drugs have both deepened and become more sophisticated. These advances have contributed to the effort to enhance compound durability and improve overall success rates in an industry where drug candidate failure is still overwhelmingly the more common outcome of a development program. In 1990, the principal reasons for drug failure were distributed almost evenly between toxicity, lack of efficacy, and poor pharmacokinetic (PK) properties. Advances in preclinical profiling have enhanced the ability to predict human PK parameters to an extent that this has been reduced significantly as a source of drug failure. Despite this development, drug discovery output over the last 25 years has remained stubbornly low, with failure rates for small molecules not changing significantly as toxicity and lack of efficacy have emerged as the major sources of candidate demise. However, improved preclinical practices are more effectively selecting drug candidates suitable for testing a particular mechanistic hypothesis in Phase II clinical trials. Clinical success is dependent upon demonstrating exposure of a drug at the site of action, the engagement of the target and an expression of the pharmacological effect that is anticipated based on the underlying theory. A heightened awareness of drug physical properties, developability issues and side effects is reflected by the implementation of a broad range of in vitro and in vivo assays designed to remove candidate compounds with a higher potential to fail or to precipitate unacceptable effects in a clinical setting.

This volume of the *Topics in Medicinal Chemistry* series focuses on exploring tactical approaches to solving problems in drug design that affect candidate developability and quality and which are encountered frequently in drug development programs. In the chapter "Physical Properties in Drug Design" Robert J. Young summarizes the importance of controlling and modulating physical properties during the drug design and optimization phase. This is an area of fundamental importance that has been the subject of considerable scrutiny by the medicinal chemistry community over the last decade as it has focused an introspective lens on developing a deeper understanding of what factors drive compound durability.

Designing better molecules at the outset requires a fuller appreciation of the factors governing drug–target interactions and the several efficiency metrics that have been devised provide useful guideposts for the medicinal chemist. Ligand lipophilic efficiency (LLE or LipE) has emerged as one of the most prominent and effective means of assessing compound quality by providing a basic understanding of the contribution of the lipophilicity of a molecule to the affinity for its cognate target. By routinely applying this metric during the analysis of structure–activity relationships, the current trend in drug design of depending on flat, sp^2 center-rich, lipophilic molecules that derive much of their potency from non-specific entropic effects rather than more specific enthalpy-based drug–target interactions may be reversed.

Drug solubility is fundamentally dependent on the inherent physical properties of a molecule and contemporary practices are clearly producing poorly soluble compounds that require the application of sophisticated formulation strategies to facilitate drug delivery in vivo. Indeed, there is a burgeoning reliance on spray-dried dispersions to deliver drug candidates both pre-clinically and clinically, a reflection on the chemical space being explored in many discovery programs. This may be a function of the nature of a biological target or the design practices of the medicinal chemist or a combination of these phenomena. In the chapter "Improving Solubility via Structural Modification" Michael A. Walker reviews the importance of solubility in drug delivery and provides a synopsis of approaches that have been applied to the design of drug candidates with enhanced pharmaceutical properties.

Inhibitors and inducers of the cyctochrome P450 (CYP 450) enzymes, important components of drug metabolism, are perpetrators of drug–drug interactions. This is of particular importance in an era when patients take some drugs chronically and may be prescribed with additional drugs that can be victims in a drug–drug interaction. CYP 450 inhibition can be of sufficient severity that the exposure of a victim drug can increase to levels where toxicity is evident; alternatively, efficacy can be severely compromised when CYP 450 induction occurs. In the chapter "Tactics to Avoid Inhibition of Cytochrome P450s" Andrew G. Leach examines CYP 450 structure and function and summarizes some of the strategies and tactics that have been employed to avoid CYP 450 inhibition. The pregnane X and constitutive aryl hydrocarbon nuclear receptors are important mediators of CYP 450 induction that sense xenobiotics and activation of these receptors by drugs is also a potential source of drug–drug interactions. In the chapter "Avoiding PXR and CAR Activation and CYP3A4 Enzyme Induction" Michael W. Sinz examines examples of drug molecules that activate these receptors and the current understanding of structure–activity relationships. In this chapter, an emphasis is placed on a discussion of the changes in molecular structure of modulators that have been observed to impact affinity and function.

The chapters "Strategies for Minimisation of the Cholestatic Liver Injury Liability Posed by Drug-Induced Bile Salt Export Pump (BSEP) Inhibition," "Drug Discovery vs hERG," and "Drug-Induced Phospholipidosis: Prediction, Detection, and Mitigation Strategies" focus attention on three prominent off-target effects of drug candidates that can be a significant source of drug toxicity and lead to

termination of a drug development program. Much of the increase in our understanding of these problems has been based on clinical observations and an iterative cycle of feedback to drug discovery. This has led to the implementation of preclinical screens designed to identify problematic molecules and eliminate them from consideration early in the drug discovery process. Drug-mediated inhibition of the bile salt export pump (BSEP) can precipitate cholestatic liver injury and this is an area of emerging concern. In the chapter "Strategies for Minimisation of the Cholestatic Liver Injury Liability Posed by Drug-Induced Bile Salt Export Pump (BSEP) Inhibition" J. Gerry Kenna and his colleagues capture the current understanding of the biochemical pharmacology associated with this transporter and attempt to equate inhibitory potency with the potential for the observation of clinical problems. This is a particularly daunting task given the current incomplete understanding of inhibitors of this transporter. The implementation of screening for inhibitors of the human ether-à-go-go gene product, a rapidly activating potassium channel that mediates the repolarizing I_{Kr} current in the cardiac action potential and commonly known as hERG, was precipitated by clinical observations with the antihistamine terfenadine. Terfenadine is a prodrug of the carboxylic acid metabolite fexofenadine and coadministration of this drug with the antifungal agent ketoconazole, a CYP P450 inhibitor, led to elevated levels of terfenadine which is a potent inhibitor of hERG channel function. Inhibition of the hERG channel leads to prolongation of the QT interval in the electrocardiogram which can take on a unique shape described as *torsades de pointes*. This can be manifested as a polymorphic ventricular tachycardia and lead to arrhythmias and, possibly, sudden death. In the chapter "Drug Discovery vs hERG" Zoran Rankovic and Derek J. Leishman discuss the structure of the hERG channel and describe the screening methodology that has become a mandatory part of the preclinical drug profiling landscape. They proceed to delineate the pharmacophore that has been developed for pore inhibitors and evaluate and summarize tactical approaches to structural modification of compounds that have been shown to reduce the propensity for hERG inhibition. Phospholipidosis is a disorder of lysosomal storage that is characterized by the accumulation of phospholipids in tissues. This phenomenon has been most prominently associated with lipophilic basic amines and many of structures that precipitate phospholipidosis overlap with the hERG inhibitor pharmacophore. In the chapter "Drug-Induced Phospholipidosis: Prediction, Detection, and Mitigation Strategies" Umesh M. Hanumegowda and Alicia Regueiro-Ren analyze this problem, summarize the physical chemical features associated with its occurrence and describe some of the strategies and tactics that have been successfully applied to mitigate the phenomenon in the design of drug candidates.

In the final chapter, "The Influence of Bioisosteres in Drug Design: Tactical Applications to Address Developability Problems," the application of effective structural mimics of a range of functional groups, commonly described as bioisosteres, to the process of drug design and optimization is discussed. The application of bioisosteres can be a useful approach to address many of the problems commonly encountered in contemporary drug discovery programs. In this chapter, these are annotated based on the nature of the problem encountered rather than by the more

traditional approach of grouping based on the nature of the functional group being emulated. However, the application of bioisosteres is very much contextual in nature with structural emulation highly dependent on the specific drug–target interactions under consideration.

I would very much like to express my gratitude to the authors for taking the time and care to compose and contribute their chapters to this enterprise. This volume will be successful if their thoughts and insights inspire ideas, concepts, approaches, and strategies that have utility in solving problems associated with drug optimization campaigns. Application of the principles that are described within these pages to solve specific problems is rarely completely repetitive in nature and, as most commonly practiced, requires some level of interpretation and improvisation to be successfully applied to a new context. This has been and will continue to be a natural part of the evolution of drug design practices and should be viewed as a source of intellectual stimulation rather than a limitation. Finally, I would like to thank Peter R. Bernstein for planting the seed for this book and his encouragement and support throughout the project.

Wallingford, CT, USA Nicholas A. Meanwell
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