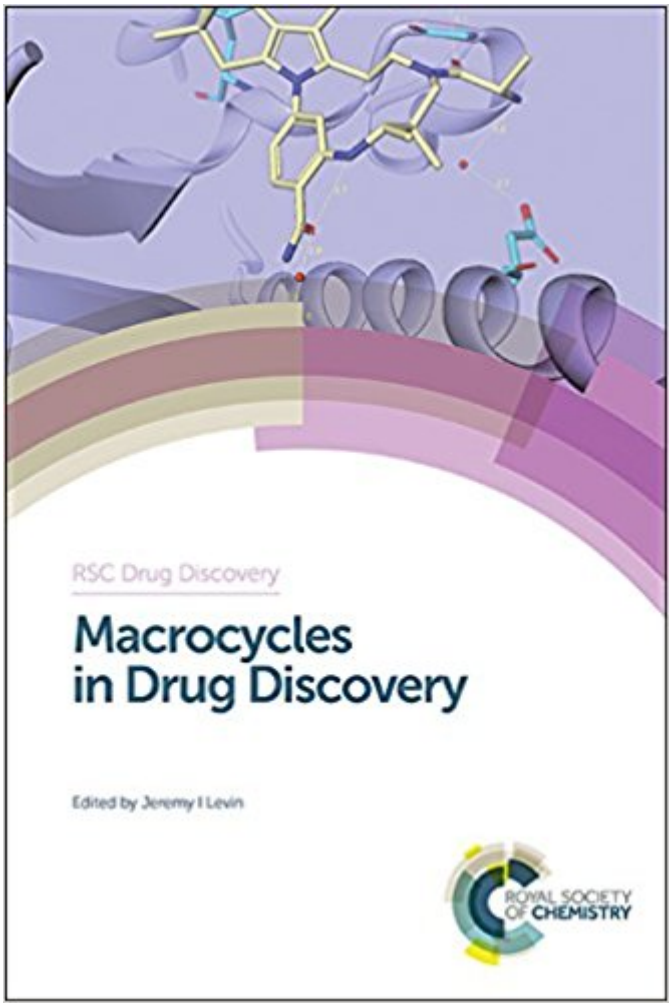
Macrocycles In Drug Discovery



Synopsis

This book reviews macrocycles in drug discovery, both those of natural origin and semi-synthetic derivatives of natural products, and those designed and synthesized based on principles of medicinal chemistry. The medicinal chemistry of macrocyclic natural products is interesting in itself, but lessons learned from these compounds, in terms of the relationship between structure and desirable physicochemical properties, are now informing the design of fully synthetic macrocyclic drug candidates against a variety of targets including kinases, ATPases, proteases, GPCRs and others. Furthermore, as more non-classical drug targets, such as proteinÃ¢â ¬â œprotein interactions, are pursued in the pharmaceutical industry, macrocyclic molecules are generating increasing interest as they offer a way to provide drugÃ¢â ¬â œprotein interactions that cover a larger surface area than traditional small molecules.A variety of macrocycles have become important drugs or have been identified as leads to marketed drugs. This text will discuss these compounds, their pharmacology and synthesis, in the context of their broad chemotype as compounds composed of large rings. Providing a wide reaching review of this important area in a single volume, this book will be of interest to biochemists, pharmaceutical scientists and medicinal chemists working in industry or academia.

Book Information

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Customer Reviews

"The book is a wellmade snapshot of current research, describing development stories of

established macrocycle drugs and their properties, as well as new avenues in their development." "The book s 11 chapters, written by distinguished experts, are mostly dedicated to macrocycles for a specific protein target or target class." "Numerous examples presented along with the compounds potency, selectivity, permeability, bioavailability and other properties allow the reader to understand which determinants make a successful macrocyclic drug."--Christian Heinis "Chemistry World """"Macrocycles in Drug Discovery" provides an in-depth review with case studies of some of the major targets and areas that have been the focus of macro- cyclic drug discovery. It also provides useful insights into macrocycle cell permeability, oral bioavailability and methods for their synthesis." " rich in information " "I absolutely recommend "Macrocycles in Drug Discovery" to those that are active in the field, both in academia and the pharmaceutical industry. The different chapters provide stimulating reading for experts in macrocycles as well as for organic chemists and medicinal chemists in general. The comprehensive chapters also serve as a source of references with extensive citation of the primary literature."--Prof. Jan Kihlberg "Chemmedchem review in March 2015 issue ""Macrocycles are usually defined as having a structure that includes a ring of 12 or more heavy atoms. They are an interesting class of small molecules that have found wide use as antibiotics, as therapeutic agents in oncology, and for immunosuppression, but also across a large number of other indications. Many macrocyclic drugs are natural products that were isolated and discovered prior to the emergence of target- based drug discovery and high-through- put screening. Despite this precedent, macrocycles were largely out of focus in drug discovery research for a number of years. Interest in macrocycles has undergone a major revival over the past decade for several reasons. It has been argued that too strict an implementation of the Lipinski s rule of five (Ro5) has hampered the pharmaceutical industry from seizing opportunities involving novel but difficult targets. This has put the spotlight on compounds outside the Ro5 as tool agents in chemical biology and as leads for drug discovery. Macrocycles are of particular prominence in this space as they have been hypothesized to be better suited to modulate difficult targets with large and flat binding sites be- cause of their size, shape and flexibility. In addition, a number of natural-product-based and designed macrocycles are also cell permeable and orally bioavailable, making them of particular interest among the drugs outside the Ro5 guide- lines. "Macrocycles in Drug Discovery" provides an in-depth review with case studies of some of the major targets and areas that have been the focus of macro- cyclic drug discovery. It also provides useful insights into macrocycle cell permeability, oral bioavailability and methods for their synthesis. As Nature is the main source of macrocyclic drugs, it is appropriate that Chapter 1 of the book provides an overview of different classes of macrocyclic natural products. This ranges from sources of isolation and bio-

synthesis, via synthetic approaches, to pharmacological activities and clinical applications. Chapter 1, as all chapters in the book, is rich in information and therefore not bedside reading unless you are an expert in the field. In general, Chapters 2 7 review and discuss how macrocycles have been discovered and developed to modulate different targets of interest for the treatment of disease. Each chapter starts with an introduction to the field to whet the appetite of the reader, followed by a systematic overview of data and insights gathered, such as for different classes of macrocycles. These chapters also provide important lessons from historical macro- cycle drug discovery. Thus, macrocycles that target heat shock protein 90 (Hsp90), epothilones as stabilizers of microtubules, inhibitors of zinc-dependent histone deacetylases (HDACs) and macrocyclic kinase inhibitors, which are all used in oncology, are reviewed in Chapters 2 5. Chapters 6 and 7 discuss the use of anti-inflammatory macrolides to manage chronic neutrophilic inflammation and the recent discoveries of hepatitis C virus protease inhibitors. Chapter 8 provides an impressive overview of how cyclic mimetics of protein epitopes have been developed to target G-protein-coupled receptors (GPCRs), integrins and protein protein interactions (PPIs). In line with this theme, Chapter 9 is focused on macrocyclic a-helical peptides, in particular stapled peptides and their use to inhibit PPIs. Last but not least, Chapters 10 and 11 provide general and extensive overviews of properties that influence cell permeability and oral bioavailability of macrocycles, as well as methods for their synthesis, respectively. Chapter 10 has a particularly interesting introductory section on modelling of permeability and absorption. This is followed by a brief overview of oral bioavailability of macrocycles, which can be supplemented from citations throughout the book, particularly those in the introduction of Chapter 1. Chapter 11 provides a very extensive review of how macrocycles have been synthesized (434 references), but is easy to access from its systematic organization by the methodology used for the macrocyclization step. In particular, the section on how macrocyclizations have been scaled up in process chemistry departments illustrates how far chemistry has progressed in this field during recent years. Additional reading to this section should include the use of diversity- oriented synthesis (DOS) to generate synthetic libraries of macrocycles for drug discovery. All books will have some drawbacks and omissions; a few minor ones have been alluded to above in the overview of the different chapters. Additional topics that readers should be aware of include cyclosporine A for which substantial studies have been undertaken to explain how it crosses cell membranes. These studies form a historical basis for which current research aimed at identifying strategies for design of cell-permeable cyclic peptides are based. Chapter 9 on stapled peptides is written with a very optimistic viewpoint that differs somewhat from current discussions in the primary literature, as well as the more stringent tone of the other chapters. It would have

benefitted from a more extensive discussion of cell penetration of macrocyclic a-helical peptides. As written, the reader is left with the understanding that stapled peptides rely on active transport processes to enter cells, where they then elicit their pharmacological effect. However, a discussion of the current research on whether these transport processes allow general and re- producible drug delivery to a diverse population of patients is lacking. Another lingering question is whether or not there are limitations to whether stapled peptides reach their destinations inside the cell after active uptake. In spite of the minor concerns indicated above, I absolutely recommend "Macrocycles in Drug Discovery" to those that are active in the field, both in academia and the pharmaceutical industry. The different chapters provide stimulating reading for experts in macrocycles as well as for organic chemists and medicinal chemists in general. The comprehensive chapters also serve as a source of references with extensive citation of the primary literature. In addition, the chapters are well organized, and it is therefore easy to locate the reader s particular topic of interest. However, "Macrocycles in Drug Discovery" is best red one chapter at a time, not from cover to cover, due to the vast amount of information it summarizes. Each reader that has taken the time to carefully read through this book will be better positioned for retrospective analysis of macrocyclic drug discovery and speculation on what the future may look like.--Prof. Jan Kihlberg, Uppsala University (Sweden) "Chemmedchem review in March 2015 issue ""Macrocycles are ring-shaped molecules containing12 or more ring atoms. Many important drugs belong to this structural class, for example the immunosuppressant cyclosporine or the antibiotic vancomycin. Macrocycles' ability to bind difficult targets that are considered 'undruggable' by traditional small molecule drugs has produced much interest. Recent innovations for designing de novo macrocycles and for screening large combinatorial macrocycle libraries have given an additional impulse to the field's development. The book is a well-made snapshot of current research, describing development stories of established macrocycle drugs and their properties, as well as new avenues in their development. The book's 11chapters, written by distinguished experts, are mostly dedicated to macrocycles for a specific protein target or target class. The targets discussed include heat shock protein, tubulin, histone deacetylases, kinases, proteases, G-protein coupled receptors, integrins, and protein protein interactions. Several authors provide introductory sections about the general characteristics of macrocycles, meaning that there is a small overlap between some chapters. However, this is not negative at all as it offers different perspectives on the topic. Most established macrocyclic drugs are based on natural products that were identified in bacteria, fungi, plants or other organisms. Consequently, the majority of molecules discussed are natural products or derivatives thereof. As nature does not offer macrocycles for every therapeutic target, scientists have designed new

macrocycles, which are also covered in the book. Chapters are dedicated to the design of kinase inhibitors and to intriguing strategies for developing macrocycles de novo by mimicking protein epitopes such as hairpins or helices. To develop novel macrocycles, it is essential to understand the factors that affect their permeability and bioavailability-important topics that are discussed in the penultimate chapter. The book concludes with a comprehensive chapter on synthetic strategies for the production of macrocycles. In summary, this title is an in depth discussion of macrocycle drug discovery. Numerous examples presented along with the compounds' potency, selectivity, permeability, bioavailability and other properties allow the reader to understand which determinants make a successful macrocyclic drug.--Christian Heinis "Chemistry World ""

A variety of macrocycles have become important drugs or have been identified as leads to marketed drugs. This text will discuss these compounds, their pharmacology and synthesis, in the context of their broad chemotype as compounds composed of large rings. Providing a wide reaching review of this important area in a single volume, this book will be of interest to biochemists, pharmaceutical scientists and medicinal chemists working in industry or academia.