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Book Review

Annual Review of Pharmacology and Toxicology. Volume 50. Edited by Arthur K. Cho, Terrence F. Blaschke, Paul A. Insel, and Horace H. Loh.. Annual Reviews, Palo Alto, CA. 2010. ix +483 pp. 24 × 19 cm. ISBN 978-0-8243-0450-8. $84.00.

This is the current volume of the consistently high-quality and essential *Annual Review of Pharmacology and Toxicology*. This volume contains 17 chapters covering a variety of topics that represent the wide scope of pharmacology and toxicology as they are currently practiced. Topics include (listed in sequential order) allosteric receptors with an emphasis on nicotinic receptors, pharmacogenetics of drug dependence, adverse effects of small particle size solids interacting with biological systems, GPCR interacting proteins (GIPs) in the nervous system, c-MYC nuclease hypersensitive element interactions, RNA polymerase I, lysophosphatidic acid (LPA) receptors, clock genes in pharmacology, toxicological modification of tyrosine phosphatases, aptamers, antisense oligonucleotides targeting RNA, metabotropic glutamate receptors (mGluRs), protective mechanisims of heme oxygenase-1, exchange protein directly activiated by cAMP (Epac), clock genes in pharmacology, economic aspects of pharmacogenomics, and the renin−angiotensin−aldosterone system. Although all topics are relevant to modern pharmacology and toxicology, only those reviews with particular relevance to medicinal chemistry will be addressed below.

Changeux presents an excellent first-person narrative detailing the initial identification of the acetylcholine receptor from early studies with electric fish and the electric eel *Electrophorus electricus*. Subsequent details are presented as a sequence of events driven both by the unique character of each scientist and by emerging technical advances. A summary of the current understanding of constitutive activity at the receptor level as well at the CNS anatomical level and its relevance to memory, cognition, and therapeutic relevance is exemplary. Bockaert presents a lucid pharmacologically based overview of GCPR interacting proteins (GIPs). This narrative emphasizes signaling pathways and participating proteins, especially Homer proteins and β-arrestins. Clear presentation of all abbreviations familiar to the pharmacologist, but often alien to the medicinal chemist, with a well-organized presentation permits a clear and comprehensive understanding of the material. Topics of particular interest for drug development include the role of mGluRs in fragile X syndrome, the role of Homer protein subtypes in epilepsy, the interplay of β-arrestins and spinophilin in memory, addiction, neuronal plasticity, and perhaps most intriguingly the role of GIPs with 5HT receptors of the subtypes 2c and 1b. The role of long-term modification of these 5HT receptor subtypes (and perhaps related receptor subtypes) has implications for multiple mood disorders including schizophrenia and depression. Hurley gives a lucid presentation of the function and regulation of c-MYC, associated transcription factors, and a structural analysis of the c-MYC G-quadraplex DNA complex. DNA constructs are given not only in diagrammatic form but also in actual H-bonding interaction form. The putative therapeutic relevance of the c-MYC G-quadraplex structure is presented in broad general terms of gene silencing, but specific relevance is given for two Burkett's lymphoma cell lines. Grummt presents a well-organized presentation of the RNA polymerase I construct. All associated proteins are fully explained. Contributory roles of cell cycle, receptor tyrosine kinases (RTKs), and ERK signaling pathways are well presented. This review should be essential background reading for medicinal chemistry researchers interested in oncology. Chun presents the structure, ligands, physiological distribution, and biological effects for the five currently identified LPA receptors. Likely therapeutic application targeting the vasculature, immune system, uterine implantation, cancer, connective tissue disorders, and adipocyte metabolism of glucose is discussed. Samet analyzes the toxicological disruption of tyrosine phosphatases. The description of active-site cystine sulfhydryl group modification by normal or toxic mechanisms should be essential reading for medicinal chemists conducting PTPase research. Bennett provides a comprehensive overview of RNA targeting antisense therapeutic agents including 35 drugs that are either approved (fomiversen) or in clinical trials. This structure-based biochemical analysis of the action of this class of therapeutic is an excellent starting point for understanding this emergent therapeutic strategy. A comprehensive review of mGluR pharmacology is given by Niswender and Connn. Receptor subtype, splice variation, physiological and neuroanatomical variation, and strategies for secondary signaling coupling are presented. A list of 40 ligands with well-characterized interaction plus an analysis of relevant therapeutic areas including depression, pain, schizophrenia, Alzheimer's disease, and Parkinson's disease should provide a solid opportunity for many medicinal chemistry projects. Bos presents an emerging site for cAMP action: exchange protein directly activated by cAMP (EPAC). This normally autoinhibited protein is activated upon cAMP binding and activates pathways relevant to cardiac muscle contraction, insulin secretion, and inflammatory response. There are currently two isoforms of this protein known, and their selectivity of action is likely to arise predominately from subcellular compartmentalization. Arguably the best presentation of the chronotherapeutic relevance of chemotherapeutic agents is given in an article by Levi et al. From a medicinal chemistry perspective, 40 standard drugs and agents are given with their primary pharmacological target of action. These agents are then analyzed by therapeutic class in the context of modification by or on circadian rhythm. An excellent mathematical presentation on chronotoxicity or chronoefficacy ensues. Any academic medicinal chemist or practicing medicinal chemist involved in any aspect of oncology should read this article.

Bader gives a comprehensive, current, and very well-presented description of the rennin−angiotensin−aldosterone system. The rennin−angiotensin system is presented from the primary protein structure of angiotensinogen, rennin processing, tissue distribution of AT receptors, to AT1 receptor pharmacology at the organ, tissue, and cellular level. The pharmacology of aldosterone is presented primarily from an analysis of site of action and interaction with AT1 receptors. The quality and comprehensive nature of this review recommends this article as essential for understanding current rennin−angiotensin−aldosterone pharmacology for all medicinal chemists.

Overall this volume presents the leading edge of pharmacology. There is varying relevance to either practicing or academic medicinal chemists by article. This issue includes, although not uniformly, a boxed detailed list of summary points and future issues. This feature is not uniformly effective but can function to solidify central themes after reading the article. Minimally, any serious medicinal chemist should routinely read this publication and any scientific library should contain this series. An electronic form/subscription is also available. For researchers actively involved in any of the areas highlighted above, purchase is strongly recommended; the moderate price and high quality of content (including color graphics) make this a recommended and very welcome addition to the personal library of any medicinal chemist.

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Handbook of Cyclization Reactions. Volumes 1 and 2. Edited by Shengming Ma.. Wiley-VCH, Weinheim, Germany. 2010. xviii + 623 pp (Volume 1) and xxiv + 640 pp (Volume 2). 17.5 × 24.5 cm. ISBN 978-3-527-32088-2. $430.00.

This two-volume set consists of separately authored specialist reviews covering a broad spectrum of synthetic methods for cyclizations in organic synthesis. While the topics have received coverage elsewhere in occasional journal article reviews, compiling so many updated reviews together in these volumes allows the reader to compare current methods with relative ease. Assembling this breadth of up-to-date review articles on one's own would be a daunting task, so this compendium will neatly address a need of the synthesis community.

Each of the 25 chapters begins with some brief introductory material regarding the general features of the synthetic methods at hand. Then it delves into specific examples of the main reaction types, illustrating scope and limitations. Coverage is broad but not exhaustive, and it gives sufficient leading references to initiate deeper searches. Most of the chapters include numerous examples of applications in complex target-oriented synthesis. Finally, each author has reproduced a set of representative experimental procedures from primary literature sources; this offers additional practical insights that may help the reader to select the most appropriate synthetic method to suit a prospective application. The detail with which these experimental procedures are presented varies significantly from chapter to chapter; a chemically meaningful title, literature citation, and scheme cross-reference are not always given, leaving it up to the reader to sort out the connections to the chapter text and references. A graphic depicting product structure for each experimental would have been welcome.

Volume 1 begins with three chapters on concerted cycloadditions (Diels−Alder, hetero-Diels−Alder, and 1,3-dipolar). Next is a chapter on 1,2- and 1,4-addition to carbonyl or imino compounds, followed by eight chapters on cyclizations via metal-catalyzed coupling and metathesis chemistry. Volume 2 continues with chapters on metal-catalyzed cycloisomerization and nucleophilic cyclizations of enynes. Then it moves through epoxidation, aziridination, and cyclizations and annulations of cyclopropane-containing compounds. These are followed by metal-catalyzed ring-expansion cyclizations and cyclizations initiated by hydrometalation. Another chapter on 1,3-dipolar cycloaddition of alkynes with azides and nitrile oxides is placed here, in the middle of Volume 2 rather than in Volume 1 with the other 1,3-dipolar cycloadditions.

Electrophilic cyclizations (e.g., iodolactonization), metal-catalyzed cyclizations involving C−H activation, Friedel−Crafts cyclizations, and lactone and lactam macrocyclizations are covered, and then Volume 2 finishes with free radical, photochemical, and organocatalytic cyclizations. The rationale for the ordering of chapters, especially of Volume 2, is not clear; for example, it is unclear why iodolactonization would be interjected between various types of metal catalyzed transformations. This is a minor criticism though, and the organization should not interfere with use of selected chapters as a reference resource.

With so many authors in a project of this magnitude, there are bound to be some areas of potential overlap. Some of these issues have been addressed in well-defined ways, such as in the coverage of metathesis; Chapter 12 focuses only on alkyne metathesis, while diene and enyne metatheses are handled in Chapter 11. However, there are some minor redundancies still present, such as organocatalytic reactions that appear in several chapters but are also covered in Chapter 25.

The authors generally cite content from the primary research literature through 2008. There is a subject index provided at the end of Volume 2, covering both volumes.

Chemistry libraries should include Handbook of Cyclization Reactions in their holdings, as researchers at all levels will find it a useful resource. In this book, bench chemists will find direction to the appropriate primary literature needed to move their projects forward while research directors will find a valuable tool for proposal preparation and related amusements.

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