Book Reviews

Annual Reports in Medicinal Chemistry. Volume 32. Editor-in-Chief: James A. Bristol. Academic Press, San Diego, CA. 1997. xi + 378 pp. 17 × 25 cm. ISBN 0-12-040532-6. $70.00.

Annual Reports in Medicinal Chemistry is sponsored by the Division of Medicinal Chemistry of the American Chemical Society, and it is received by all members of the Division. As a result, this annual series of reviews of important topics in medicinal chemistry and emerging new areas in the biological sciences is well-known and appreciated by almost all medicinal chemists. Volume 32 continues with the style and format of previous volumes in the series.

The 31 approximately 10-page reviews that comprise the present volume are grouped into seven sections: (I) Central Nervous System Diseases; (II) Cardiovascular and Pulmonary Diseases; (III) Cancer and Infectious Diseases; (IV) Immunology, Endocrinology and Metabolic Diseases; (V) Topics in Biology; (VI) Topics in Drug Design and Discovery; and (VII) Trends and Perspectives. Section I consists of six reviews that deal with aspects of migraine therapy, Alzheimer's disease, obesity, melatonin receptor ligands, corticotropin-releasing hormone (CRH) receptors, and neurokinin receptor antagonists. Section II is comprised of reviews that consider endothelin inhibitors, antithrombotics and serine proteases, leukotriene modulators in inflammatory diseases, and new approaches to the treatment of atherosclerosis. Section III presents reviews dealing with agents and approaches to overcome bacterial resistance, bacterial genomics, resistance to antiretroviral drug treatment, non-HIV antivirals, antifungals, angiogenesis inhibitors, and chemical inhibitors of cyclin-dependent kinases. The final disease-oriented section (IV) reviews T lymphocyte potassium channel blockers, male contraception, new antipsoriasis agents, cyclooxygenase-2 inhibitors, and growth hormone secretagogues. As in previous volumes, the next two sections consider important topics in medicinal chemistry, biology, and drug design. Thus, section V has three reviews entitled "Novel Gene Switches for the Regulation of Gene Expression", "Agents that Block TNF-alpha Synthesis or Activity", and "Nuclear Orphan Receptors: Scientific Progress and Therapeutic Opportunities". Section VI is in keeping with the current focus toward mechanism-directed drug discovery and newer technologies. It includes chapters that deal with combinatorial mixtures as discovery tools, mass spectrometry of noncovalent adducts, nonpeptide agonists of peptide receptors, natural products, and cytochrome P-450. The final section (VII) concludes with the usual "To Market, To Market" chapter that describes the 38 new chemical entities (NCEs) for human therapeutic use introduced into the world market for the first time in 1996.

The volume concludes with indexes listing compound name, code number, and subjects for Volume 32, cumulative chapter titles for Volumes 1−32, cumulative NCE introductions, 1983−1996, and cumulative NCE introductions, 1983−1996 (by indication).

Annual Reports in Medicinal Chemistry. Volume 32, like previous volumes in this series, presents timely reviews of important areas of active, ongoing medicinal chemical research, emerging topics in the biological sciences that may lead to future novel therapies, newer methodologies to enable new drug design and drug discovery, and the marketed medicinal chemistry accomplishments (i.e., NCEs) of the previous year. Clearly, this volume will be important to all medicinal chemists as well as to other researchers concerned with the derivation and development of new drug products.

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Anti-Infectives. Recent Advances in Chemistry and Structure−Activity Relationships. Edited by P. H. Bentley and P. J. O'Hanlon. The Royal Society of Chemistry, Cambrige, U.K. 1997. xi + 338 pp. 16 × 24 cm. ISBN 0-85404-707-7. $174.00.

This volume is based on the proceedings of the Second International Symposium on Recent Advances in the Chemistry of Anti-infective Agents held July 7−10, 1996, at Cambridge University. This symposium series actually originated in 1976 and has been held at the same site every four years. Initially, it was devoted only to β-lactam antibiotics, but this symposium and its predecessor have been expanded to include other antibacterial agents as well as antifungals and antivirals.

The book is divided into three sections: (1) Advances in Antibacterials/Antibiotics, (2) Advances in Antifungals, and (3) Advances in Antivirals. The first section begins with a description of the elegant work carried out by Dudley Williams and his group at Cambridge on the structure and mechanism of action of the glycopeptide class of antibiotics which includes vancomycin. Clinically, vancomycin has been the last line of defense against β-lactam resistant strains of bacteria, but new strains are constantly evolving, and vancomycin resistant ones have now been encountered. Williams describes a new semisynthetic glycopeptide antibiotic derived from chloroeremomycin by scientists at Eli Lilly that is active against the vancomycin resistant strains and proposes a binding mechanism to account for its unexpected antibacterial spectrum. The search for new antibacterial agents which can effectively deal with continuing emergence of resistant strains is a general theme of this section which also includes chapters on synthetic oxazolidinones, pristinamycins, salinomycin, β-lactams with novel mechanisms of action, polyether macrolides, and siderophore-mediated drug delivery.

The section on antifungals contains chapters that deal with further refinement of the azole class of antifungal agents to produce much more effective agents such as fluconazole and Sch 56592. Also covered are agents that interfere with tubulin function, cell wall biosynthesis, and mitochondrial respiration. The antiviral section comprises nine chapters that cover novel nucleosides and nucleotides as well as inhibitors of viral proteases, sialidase, and reverse transcriptase. An unusual class of antivirals called TSOA derivatives are silylated nucleosides that inhibit HIV-1 by binding in an allosteric, hydrophobic pocket of reverse transcriptase rather than acting as substrate mimics.

The chapters are generally well written and contain ample rationale for the design of anti-infective agents based on proposed mechanisms of action. The references at the end of each chapter are current, including several 1996 citations. There is a short subject index that is of limited value. Although this book will be of interest to medicinal chemists involved in anti-infective research, its high price makes it unattractive except for an institutional library copy.

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Modern Strategy for Preclinical Pharmaceutical R&D: Towards the Virtual Research Company. By David Cavalla, with contributions from John Flack and Richard Jennings. John Wiley & Sons, Chichester, England. 1997. x + 218 pp. 15.5 × 23.5 cm. ISBN 0-471-97117-0. Price Unavailable: (hbk: alk. paper).

There is no doubt that the 1990s have been a decade of tremendous change for the pharmaceutical industry. A seemingly endless series of mergers, acquisitions, downsizings, and rightsizings among major pharmaceutical companies has paved the way for the formation of a growing number of startup research and contract R&D companies. These new companies hope to use their small size, flexibility, and specialized expertise to carve niche markets out of gaps in R&D programs left by the apparent retreat of many multinational corporations from long-term, large-scale commitments to basic research and new drug development.

In *Modern Strategy for Preclinical Pharmaceutical R&D: Towards the Virtual Research Company*, David Cavalla attempts to analyze and understand this trend of replacing pharmaceutical research and development at large, centralized corporate facilities with looser and more flexible contractual and collaborative relationships among a number of smaller, highly specialized scientific businesses. Cavalla begins the book with an excellent summarization of the methods and costs of "traditional" drug discovery programs at vertically integrated multinational corporations, which in the past sought to completely control the entire development process from discovery to marketing. The general trend toward downsizing and outsourcing R&D functions, of course, is a response to the rapidly burgeoning complexity and cost of this traditional process of bringing a new drug to market—different sources cited by Cavalla provide estimates ranging from $230M in 1987 to $597M in 1994.

Cavalla devotes the second and third chapters of the book to reviewing the advantages and disadvantages of seeking to control the costs and the inherent risks of pharmaceutical R&D by contracting out well-defined chunks of the development process to specialized companies, or by establishing research collaborations among companies that possess mutually complementary specialized skills or technologies particularly relevant to the development project at hand. Advantages include benefits from increased efficiency due to the specialization and localization of expertise and equipment at the contract R&D firm, reducing the cost of the risk of failure with the ability to quickly terminate a program which proves nonproductive or prohibitively expensive, the speed and flexibility with which smaller firms can allocate resources to a project or switch over to more promising avenues of research, and the strong motivations such contract R&D companies have to maximize the quality and productivity of their work while minimizing costs to their customers. Disadvantages include the difficulty in finding an appropriate, reliable contractor to meet the pharmaceutical company's needs at an overall cost less than the work could be done in-house and the administrative burden of keeping a project on track despite differences in geographic locales and corporate cultures.

Chapter four explores the growing role of academic research institutes as discovery collaborators or providers of contract research services to industry. Although Cavalla stresses that industry and academia already rely heavily on one another in their exchange of funding for knowledge and trained scientists and that research collaborations between industry and academia show a great deal of promise, he does point out the two most significant problems which have yet to be satisfactorily resolved: the control over intellectual property rights and problems with conflicts arising from the fundamentally different cultures and world-views of academic institutions and the for-profit developers of pharmaceuticals.

Cavalla explores the expanding role of contract research organizations and small research companies in the fifth chapter. He briefly traces the history of the development and growth of this niche industry through the 1970s, 1980s, and 1990s, and how by this time such specialized businesses can provide nearly a full range of drug discovery and development services. He describes a number of companies that can provide services spanning discovery chemistry, combinatorial chemistry, development chemistry, molecular biology and biochemistry, pharmacology, pharmaceutics, toxicology, and ultimately, clinical trials and registration.

The final chapter of the book wraps up Cavalla's observations by describing these trends as a movement to what he calls the virtual research company. At its most extreme case, such a virtual research company would be headed by an umbrella organization that sets goals, distributes funds, and manages and coordinates the efforts of a flexible and ever-changing number of partners or subcontractors. Cavalla provides some