Book Reviews

Voltage-Gated Ion Channels as Drug Targets. Edited by D. J. Triggle, M. Gopalakrishnan, D. Rampe, and W. Zheng. Wiley/VCH, Weinheim, Germany. 2006. xii + 479 pp. 17.5 × 24.5 cm. ISBN 3-527-31258-7. $175.00.

The voltage-gated ion channel family consists of more than 140 structurally related membrane proteins. These heteromeric pore-forming structures are typically classified on the basis of their selectivity for inorganic ions. While their widespread distribution and functional diversity make them tempting targets for drug development, such efforts have been frustrated by a lack of inexpensive, high-throughput assays and the difficulty in identifying pharmacophores that interact selectively with these sites. Their chemical promiscuity is evidenced by the fact that scores of drugs, including tricyclic antidepressants and certain antipsychotics and analgesics, display some affinity for them, although in many cases the extent to which these interactions contribute to their therapeutic responses remains uncertain. Nonetheless, the clinical utility of procaine and other sodium channel blockers, verapamil and other L-type calcium channel antagonists, and of glyburide and related inhibitors of ATP-sensitive potassium channels illustrates the value of these channels as drug targets.

Contained in this work, which is volume 29 of the Methods and Principles of Medicinal Chemistry series edited by R. Mannhold, H. Kubinyi, and G. Folkers, is a comprehensive review of this topic by an outstanding group of contributors. The book is divided into eight sections, half of which provide background material, with the other half containing individual units on calcium, sodium, and potassium channels and on channelopathies. The introductory chapters by Gopalakrishnan et al. and by Catterall are excellent overviews, with the offering by Leishman and Waldron being a particularly useful review of contemporary laboratory techniques.

The chapters devoted to the individual channels are uniformly excellent, as exemplified by the Triggle offering on L-type calcium channels and the Chandy et al. presentation on Kvl.3 potassium channels. In all cases there is a discussion of the molecular, structural, biophysical, and functional characteristics of the site, a consideration of structure−activity relationships, a review of pharmacological data, and suggestions for future research. The final section underscores the biological importance of voltage-gated ion channels with a discussion of pathologies associated with gene mutations. Among these are Bartter's syndrome type 2 (Kirl.l), long QT syndrome (KCNQ1, Navl.5, Cavl.2, and hERG), epilepsy (Navl.l, Navl.2, Cav3.2), and migraine (Cav2.1). There is also a section describing laboratory models for predicting hERG blockade. The book is enhanced by the number and quality of color illustrations and the extensive display of chemical structures. Literature coverage is through 2004, with a few citations to work published in 2005.

This volume makes an excellent case for initiating, continuing, or broadening studies to identify voltage-gated ion channel agonists and antagonists. The most compelling arguments are buttressed by data indicating that such drugs are of benefit in treating conditions as diverse as epilepsy, neuropathic pain, hypertension, angina, diabetes, obesity, multiple sclerosis, rheumatoid arthritis, and neurodegeneration. Given these findings and the advances made in developing more rapid and reliable lead validation assays, this volume should be of interest to a broad range of medicinal chemists and pharmacologists.

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