Preface

As is well known, ion channels are crucial components of living cells. The physiological function of ion channels had been observed long before they were known to exist. They figure in a wide variety of biological processes that involve changes in cells, such as cardiac, skeletal, and smooth muscle contraction, epithelial transport of nutrients and ions, T-cell activation, and pancreatic β-cell insulin release. Thus being the crucial components of living cells, ion channels are important targets of therapeutic agents. Historically, it has been challenging to develop drugs on this target class. A major issue with target-based ion channel drug development is identification of good small chemical leads for medicinal chemistry optimization to clinical candidate status. Thus, enough attention has been paid to the study of structure and functions of ion channels and their potential inhibitors. The present book compiles a few important articles authored by eminent workers in the field to cover some recent advances in the studies on the structure and functions of some ion channels, e.g., Na^+, K^+, Ca^{2+}, Cl^-, and their inhibitors. The book may be of great use to the students and scientists working in the area of molecular biology, biochemistry, physiology, and neurobiology.

The book contains 11 articles in total. Ion channels, in fact, are transmembrane proteins that selectively allow a given species of ion to pass through them. In Chap. 1 entitled *Structural and Functional Discrimination of Membrane Proteins*, Gromiha et al. discuss all aspects of these membrane proteins right from their structural discrimination to resulting functional discrimination and drug–target interactions. In Chap. 2, Bois et al. present the pharmacology of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. HCN channels generate and/or regulate neuronal and cardiac excitability. Several physiological roles have been ascribed to HCN channels which are the consequence of their particular biophysical properties. In Chap. 3 entitled *Advanced Molecular Modeling Techniques Applied to Ion Channels Blockers*, Hannongbua et al. describe some important advanced molecular modeling techniques used to design and develop the potent ion channel blockers. These techniques include 2D-, 3D-, and 4D-QSARs, ADMET prediction, molecular dynamics simulations, molecular docking, quantum chemical

calculations, and QM/MM calculations. These techniques have been widely applied to the drug design.

Of the various ion channels, sodium ion channels have been of great significance. An article on this with the title *Advances in Design and Development of Sodium Channel Blockers* has been exclusively written by Zuliani et al. to describe briefly the recent advances in the development of isoform-specific and state-selective sodium channel blockers and the medicinal chemistry involved, surveying the emerging therapeutic fields. Abnormal activity of sodium channels is related to several pathological processes, including cardiac arrhythmias, epilepsy, chronic pain, neurodegenerative diseases, and spasticity.

The potassium ion channels play no less important role in the human body. They constitute the important target for the development of antiarrhythmic agents. Therefore, in Chap. 5, You et al. have presented the development of potassium channel blockers as antiarrhythmic agents. Although there are a variety of potassium channels, scientists have developed immense interest in human *ether-a-go-go*-related gene (*hERG*) potassium channels due to their involvement in life-threatening cardiac arrhythmia. Therefore, an article on *hERG* channels has been presented by Singh and Sharma to describe their functions and dysfunctions, therapeutic agents modulating these channels, and associated QT prolongation. In the next article, Schiesaro and Ecker describe structure- and ligand-based approaches to develop models which shed light on the molecular basis of hERG channel inhibition and present an overview on recent approaches for prediction of hERG channel blockers. In continuation to this, an article on *Advances in Structure–Activity Relationship Studies on Potassium Channel Modulators* has been contributed by Sharma et al., highlighting the mode of functions of potassium ion channel modulators.

Calcium ions are a ubiquitous second messenger and their entry into the cytosol is mediated by multiple types of calcium channels, each with a distinct physiological role. They constitute an important target to develop drugs against several cardiovascular and noncardiovascular diseases, such as angina, hypertension, arrhythmias, asthma, dysmenorrhea, premature labor, cancer, epilepsy, and glaucoma. In Chap. 9, therefore, Hadjipavlou-Litina presents a vivid description of calcium ion channels, their subtypes, and their blockers, with detailed structure–activity relationships of blockers. N-type voltage-gated Ca^{2+} channels (NCCs) play dominant roles in neuropathic pain and cerebral ischemia. An article on this type of calcium ion channels, therefore, has been presented by Gopi Mohan et al. to mainly focus on their blockers and the pharmaceutical importance thereof.

Chloride ion channels have been found to play crucial roles in the development of human diseases, e.g., mutations in the genes encoding Cl^- channels lead to a variety of deleterious diseases in muscle, kidney, bone, and brain, including myotonia congenita, dystrophia myotonica, cystic fibrosis, osteopetrosis, and epilepsy, and similarly their activation is supposed to be responsible for the progression of glioma in the brain and the growth of malaria parasite in the red blood cells. Thus, the study of the structure, function, and blockers of Cl^- channels seems to be of great importance. The last article entitled *Chloride Ion Channels: Structure,*

Functions and Inhibitors, therefore, has been written by Gupta and Kaur to describe all important classes of Cl^- channels with a detail of their structures, functions, and inhibitors.

Thus, an attempt has been made to make the book an interesting reading by selecting the articles of varying taste for all those involved in research on ion channels and their blockers. As an editor of this book, I have greatly enjoyed reading all the articles and hope so will do all the readers. I gratefully acknowledge the enthusiasm of all the authors for contributing the excellent articles in this book.

Meerut, Uttar Pradesh, India Satya P. Gupta
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