

## PREFACE

This book presents basic and advanced principles underlying the multivalent interactions that are prevalent in biological systems. To illustrate important or complex concepts, the book provides up-to-date examples of synthetic multivalent molecules, their design, and their biological benefits. Functional roles displayed by such molecules of both natural and synthetic origin are well documented in biology, where they exert unique and crucial activities at a level not readily achievable by monovalent molecules. The concept of multivalent design is now accepted as an effective strategy—in particular, for designing ligands, inhibitors, and drugs that influence biological systems potently and selectively.

Over the past 15 years, diverse disciplines have generated a growing interest in the biomedical application of multivalent design. The goal of this book is to share the findings in this exciting area of research by providing a systematic summary of experimentally tested case studies of multivalency. I believe that a single book serves best to collect such scattered research material in one place and to discuss it in a consistent and introductory format.

The book focuses on practical examples of synthetic multivalent molecules reported broadly in the literature. It consists of five chapters. In Chapter 1 I introduce the multivalent molecule and its structural elements, describe the mechanistic basis that accounts for the benefits of multivalent interaction, and provide a short summary of biological functions displayed by multivalent molecules. In Chapters 2 to 4 I provide practical examples derived from biological targets in viral, bacterial, and mammalian cells, respectively. In each chapter I review in a similar format the design concept, synthesis, and biological activity of multivalent molecules: in particular, those of synthetic origin.

Typically, the chapter format begins with a brief description of a target from a structural and functional viewpoint to provide a rationale for multivalent design, followed by the main discussion. In Chapter 5 I summarize various aspects of synthetic methods used in the synthesis of multivalent molecules, and I conclude with a summary of combinatorial approaches developed in the library design of multivalent molecules. The book ends with an appendix that presents tabular summaries of both examples treated in this book and untreated. The targets selected for discussion are comprehensive but, of course, do not purport to be a complete list.

The book is written for a broad community of audiences, comprising educators, graduate students, and professional researchers in academia and the (bio)pharmaceutical industry, particularly those who perform interdisciplinary research in organic chemistry, chemical biology, biological chemistry, medicinal chemistry, pharmacology, and medicine. Specifically, it would be most valuable as a reference book for those scientists interested in finding new ideas and developments in areas of receptor–ligand interaction, carbohydrate-based medicines, enzyme inhibitors, toxin inhibitors, DNA(RNA)–drug association, antibiotics, antiviral agents, anti-inflammatory drugs, and anticancer therapeutics.

It is my pleasure to express great gratitude to Professor Koji Nakanishi of Columbia University, who introduced me to the importance of multidisciplinary bioorganic studies and encouraged this publication. I am also indebted to Professor George M. Whitesides of Harvard University and sincerely appreciate his directing me to continue research in multivalency. In 1996, Professor Whitesides and several colleagues, including Professor John Griffin of Stanford University, Dr. Mathai Mammen of Harvard, and James Tananbaum of Sierra Ventures, founded Advanced Medicine, Inc. to develop opportunities in multivalent drug research and development. I joined Advanced Medicine in 1997 to help further develop ideas in multivalent drug design. Today, Advanced Medicine has evolved into a vibrant pharmaceutical company, Theravance, Inc., under the guidance of our Chairman, Roy Vagelos (former CEO of Merck Pharmaceuticals), and current CEO, Rick Wainwright. I am indebted to my colleagues at Theravance for ongoing collaborations in medicinal chemistry. In particular, I am sincerely thankful to Dr. Ed Moran, Dr. Thomas Jenkins, and Dr. Mathai Mammen for their editorial assistance with this manuscript.

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