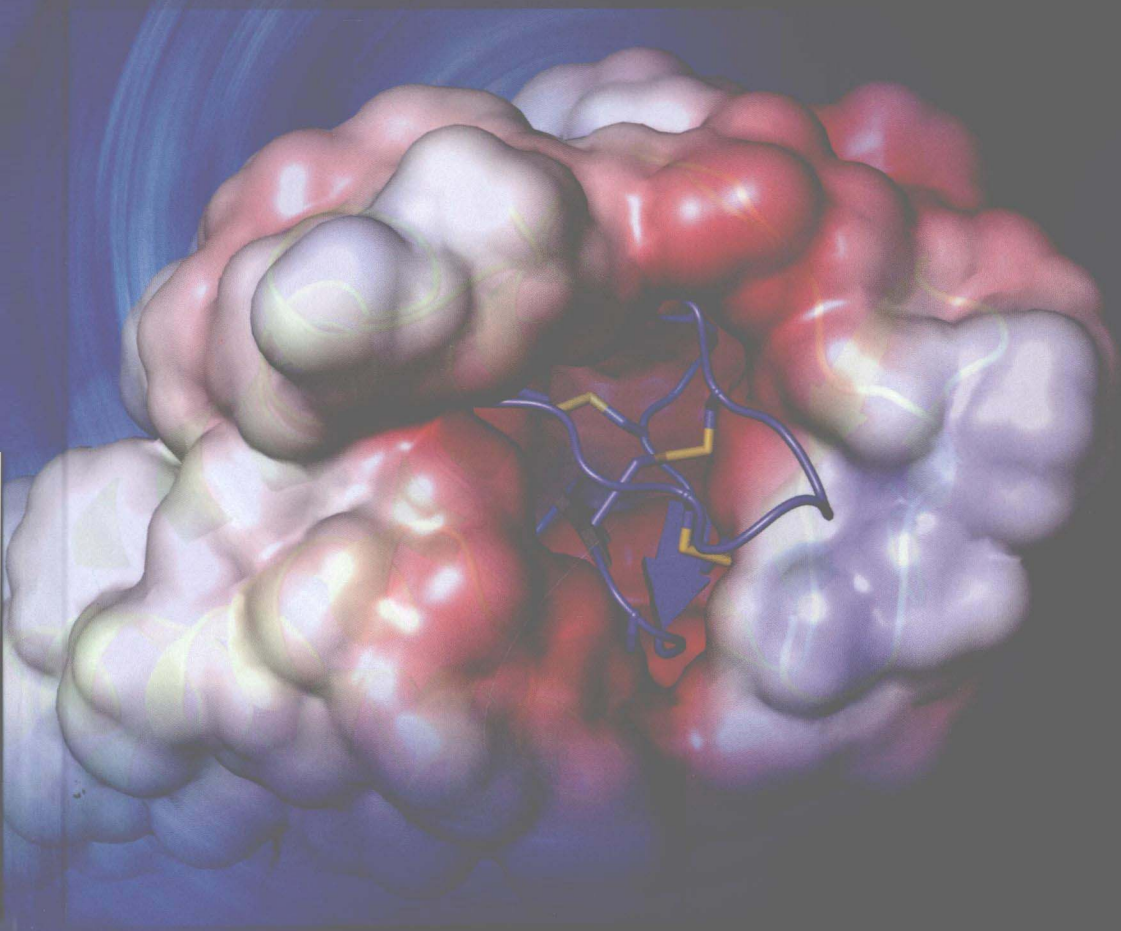
Peptide Chemistry and Drug Design



Edited by

Ben M. Dunn

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PREFACE

This book is result of many conversations with peptide scientists at a variety of meetings, including American Peptide Society Symposia, meetings of the European Peptide Society, the Japanese Peptide Society, and the Australian Peptide Society. Some of these conversations were with the authors of the chapters in this book. One additional influence was a meeting in Dubai, where I had an excellent dinner with Waleed Danho, then with Roche Nutley. Waleed had given an excellent talk about the value of peptide chemistry and peptides as elements in the drug-discovery process. Over a delicious dinner of baked fish and many other courses, we discussed the history of drug discovery and the role that peptides have played in the past. Waleed made the strong point that peptides still have great value in the discovery process and, with appropriate methods to deal with delivery and metabolism issues, can provide excellent drugs for the future.

At around this time, I was contacted by Jonathan Rose of John Wiley & Sons who asked if I would be interested in editing a book on peptides and drug discovery. Sometimes life provides a nice juxtaposition of ideas and I immediately accepted the invitation. Over the following years, I spoke with many scientists, emailed some more, and worked on putting together the chapters for this book. I want to thank Jonathan as well as Kari Capone of John Wiley for their patience and advice over the years it took to bring this together.

The book starts with a chapter provided by Nader Fatouhi, discussing the current state of peptides in drug discovery. I heard Nader speak at the 23rd American Peptide Symposium in the Kona region of the Big Island of Hawaii. As I felt that his presentation provided an update on the thoughts first revealed to me by Waleed Danho, I asked Nader to contribute the opening chapter of the book, as this sets the stage for what follows. In his chapter, Nader discusses the rising importance of peptides as

molecules for drug development as well as the issues facing scientists in this field, including cell penetration, stability, and targeting. Tools and techniques are available to address each of these limitations at this time.

Chapter 2 was contributed by Fernando Albericio and colleagues. This presents modern methods of peptide synthesis in a very readable format. Included are sections on solid supports for solid-phase peptide synthesis, which dominates most research level approaches, linkers, protecting groups, methods for peptide-bond formation, and a variety of methods to modify peptides to limit metabolism. In all cases the latest reagents and techniques are featured, thus making this chapter a great starting point for scientists starting out in the peptide field. The authors go on to discuss synthesis of peptides in solution, which still has great value in certain applications, including production of peptides in bulk. In addition, the combination of both solution- and solid-phase methods is discussed for cases where fragment condensation is used to prepare ever larger peptides. This discussion includes native chemical ligation, which permits selectively linking N-termini and C-termini of fragments, and which has several variations with more coming each year. The chapter concludes with a very valuable discussion of separation methods and methods for the analysis of the products of peptide synthesis. Again, this chapter is recommended as a great starting place for new scientists.

Anamika Singh and Carrie Haskell-Luevano have provided Chapter 3 that discusses the important topic of membrane receptors as targets for drug discovery. Due to the vital role of membrane receptors in cell signaling and control of metabolic events, a significant percentage of drugs in current use exert their function by interfering or stimulating binding and signaling events at membrane receptors, also known as G-protein coupled receptors (GPRCs). This chapter provides a catalog of systems where peptides are known to be involved and where it has been shown that synthetic peptides can modulate function. The Haskell-Luevano lab has provided outstanding research on the melanocortin receptors, but this chapter takes a broader approach and discusses a wide variety of these systems, including structural information as known and as modeled by other labs. Anyone involved in aspects of membrane signaling will find this chapter a highly valuable resource for methods, approaches, and strategies for attacking this important area of biology.

Gregg Fields and colleagues present Chapter 4 to introduce the use of peptides as inhibitors of enzymes. In the first part, the authors introduce enzymes and their classification and present several classical examples of the use of peptides to come up with compounds that provide the desired change in enzyme function to overcome a metabolic defect. In a second section, the area of HIV-1 infection and progression to AIDS is described, with emphasis on the value of peptides as modulators of growth and infection. As the human immunodeficiency virus goes through a complicated life cycle, the authors point out that there are multiple targets for approaching therapy and a combination strategy, known as HAART (highly active antiretroviral therapy) has provided the optimal approach to treatment of affected individuals. The Fields lab has made major contributions to discoveries in the area of matrix metalloproteinases and this chapter presents a thorough discussion of this system. The enzymes in this family provide a great example of the development of inhibitors through a process of

discovery of aspects of structure and function that can guide the process. The chapter continues with nice discussions of several other systems where peptide chemistry has been key in new discoveries that have driven the drug-development process.

Jeffrey-Tri Nguyen and Yoshiaki Kiso have provided Chapter 5, which continues the discussion of enzyme inhibitors from the aspect of peptides. The highly productive Kiso lab has led the way in creating a very large catalog of peptide derivatives for use in drug discovery in several systems. They begin this chapter by discussing the advantages and disadvantages of peptides as potential drugs and come down on the side of the beneficial role that peptides play. In particular, they make the important point that the use of peptides can frequently define the pharmacophore, or structural model, which can then be transformed into a small molecule of non-peptide nature for further development as a potential drug. This chapter further focuses on the process of the design of potential inhibitors and reviews the history of discovery from natural sources as well as through *ab initio* design. They discuss the advantages of learning from the natural substrates of an enzyme and introduce the important concept of the transition state analog; the critical role that structural information on the target protein can provide. This chapter provides an excellent discussion of systems where targeting with peptide molecules may provide opportunities for further drug discovery.

Sónia T. Henriques and David J. Craik describe many peptide inhibitors from natural sources in Chapter 6. The introduction to their chapter discusses the value of finding compounds from nature and describes a number of sources, including the antimicrobial peptides from many bacteria. In both bacterial and plant worlds, there is a continual war between competing systems, and this has led to the development through evolution of many natural peptides that serve as defensive molecules. The authors discuss the cyclotides, peptides that are connected end to end and that have multiple disulfide bonds. This arrangement is very stable and the molecules are found in venoms of several species as well as in plants. After this introduction, the authors turn to a discussion of the drug discovery process from their perspective. The chapter continues with an in depth discussion of a variety of systems where many methods are used to modify molecules isolated from nature and where the activity against many targets is tested. The wide diversity of structures and targets is featured in this chapter and the many discoveries have pushed research and drug discovery forward significantly.

Isuru R. Kumarasinghe and Victor J. Hruby have taken on the task of describing methods to limit the metabolism of peptide molecules in humans. This leads to a very detailed discussion of the chemistry of peptide modification. As Victor Hruby is the world leader in this aspect of peptides, the chapter is thoroughly exciting and interesting. A main concern is the digestion of peptides by proteolytic enzymes present in both the digestive tract and the circulation. The first step is to define the pharmacophore residues of a naturally occurring and effective peptide. This will show the absolutely critical functional groups and their stereochemical relationships that must be maintained. Then replacement of some nonessential amino acids by non-natural amino acids, with the D-amino acid isomer, or with peptide-bond isosteres may be sufficient to block degradation by proteases. In addition, cyclization can sometimes provide more stability and also enhance passage of peptides through

the blood–brain-barrier. Other strategies include replacement of specific the amino acids with the *N*-methyl derivatives, with topographically constrained derivatives, or with the halogenated derivatives of aromatic amino acids. Finally, the use of the "multiple-antigenic-peptide" approach where many molecules are attached to a carrier with multiple attachment points can produce molecules that, due to their size, are not recognized by proteases. This chapter emphasizes the role of creative synthetic chemistry is the modification of peptides to achieve stability and bioavailability.

The book concludes with Chapter 8, provided by Jeffrey-Tri Nguyen Yoshiaki Kiso, that discusses the important area of peptide delivery. While progress in the past 50 years has permitted peptide chemists to make almost any sequence of amino acids that is desired in high yield and purity, getting those molecules into humans and into the specific area in the body where they can exert a therapeutic effect is a problem that has not progressed as rapidly. Thus, this chapter is very important for future advances in drug discovery based on peptides. Many of the readers may already be familiar with the Lipinski's Rule of Five that includes recommendations for the size of a molecule, the number of hydrogen bonding atoms, and the lipophilicity. These rules are discussed in this chapter, but much more information is provided regarding solubility, membrane transport, and metabolic stability.

In conclusion, this book provides a primer for anyone in the field of drug discovery and specifically in the area of the use of peptides as molecules for both the discovery phase and, in favorable cases, the final phase of the creation of new molecular entities that can be moved into further studies to evaluate their potential as therapeutic drugs. I want to thank the authors of the chapters for their friendship, for many discussions, and for their excellent writing for this book.

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