Introduction

Knud J. Jensen

The aim of this book is to provide a comprehensive introduction to the concepts and methods behind the design of peptides and small proteins. The individual chapters are written by experts in each field. We have striven to coordinate the chapters to create coherence in the book. Inevitably, there is some constructive overlap between the topics in the chapters, and the chapters refer to one another.

Chapter 2, ‘Computational Approaches in Peptide and Protein Design: An Overview’, by Gregory V. Nikiforovich and Garland R. Marshall, provides a comprehensive overview of computational approaches to the modelling of peptides and proteins. This chapter surveys computational methods and principles as well as some of the available software. The authors illustrate their points with specific examples, such as the design of cyclopentapeptides as inhibitors of CXCR4. Here they describe the conformational study of both the cyclopentapeptides, as a 3D pharmacophore model for FC131, and of the G-protein-coupled receptor CXCR4, where they build on a 3D model of the transmembrane region of CXCR4. They then discuss docking of the peptide FC131 to CXCR4.

Chapter 3, ‘Aspects of Peptidomimetics’, by Veronique Maes and Dirk Tourwé, provides an overview of a hierarchical approach to peptidomimetic design. This includes the role of cyclic peptides in the development of peptidomimetics, referring to Chapter 4. Maes and Tourwé then
describe the concept of retroinverso structures and deliver an extensive overview of backbone modifications, before discussing side-chain constraints. They describe peptoids and secondary structure mimetics – a topic that is taken up again in Chapter 6 – as well as topomimetics. An important aspect of Chapter 3 is the examples given of modifications of peptide hormones, especially of somatostatin, as peptidomimetics. The chapter also covers a range of protease inhibitors.

Chapter 4, ‘Design of Cyclic Peptides’, by Oliver Demmer, Andreas O. Frank and Horst Kessler, provides a comprehensive overview of its topic. It starts with naturally-occurring cyclic peptides (cyclosporin A, for example) and moves on to different ways of cyclizing peptides. Then some backbone modifications are discussed, a theme covered in Chapter 3, as well as other modifications of cyclic peptides. A central part of the chapter is a description of the conformation and dynamics of cyclic peptides, especially the reduction in conformational space. The authors describe turn structures in cyclic peptides and concepts in the rational design of cyclic peptides, leading to the outline of a general strategy for finding active hits. The text exemplifies this with the development of the peptide drug candidate Cilengitide as an integrin inhibitor and CXCR4 antagonist.

Chapter 5, ‘Carbohydrates in Peptide and Protein Design’, by Jesper Brask and the editor, describes how carbohydrates are used to introduce new structural and conformational features to peptides and proteins. The topics in this chapter include sugar amino acids, cyclodextrins and carbohydrates as templates in the design of peptides and proteins.

Chapter 6, ‘De Novo Design of Proteins’, by the editor, gives an overview of concepts in the design of proteins from general principles, rather than through a redesign of natural structures. The focus is on structural aspects, especially rules for the design of secondary structural elements such as α-helical peptides, and the assembly of these into tertiary structures. Some de novo turn motifs, used to connect the secondary structural elements, are also included. The chapter features an introduction to foldamers, especially β- and γ-peptides. It ends with examples of biopharmaceutical applications of de novo design.

Chapter 7, ‘Design of Insulin Variants for Improved Treatment of Diabetes’, by Thomas Hoeg-Jensen, provides a comprehensive overview of the classical therapeutic peptide hormone insulin. The focus is on insulin as a modern biopharmaceutical drug and the development of new insulin variants with modulated therapeutic profiles, e.g. prolonged-acting vs. fast-acting insulins, either by modifications in the
51 AA structure or by appending moieties. Novel glucose-sensitive insulins and insulin mimetics are also covered.

As mentioned above, there is some constructive overlap between chapters. We have striven to make the index a powerful tool in accessing topics across chapters.