Peptide and Protein Design for Biopharmaceutical Applications
Contents

List of Contributors ix
Preface xi

1 Introduction 1
Knud J. Jensen

2 Computational Approaches in Peptide and Protein Design: An Overview 5
Gregory V. Nikiforovich and Garland R. Marshall

2.1 Introduction 5
2.2 Basics and Tools 6
2.2.1 The Importance of Computational Approaches 6
2.2.2 Tools and Procedures: Force Fields and Sampling 9
2.3 Computational Study of Cyclopentapeptide Inhibitors of CXCR4 31
2.3.1 The 3D Pharmacophore Model for FC131 32
2.3.2 A 3D Model of the TM Region of CXCR4 36
2.3.3 Docking of FC131 to CXCR4 39
Acknowledgements 42
References 42

3 Aspects of Peptidomimetics 49
Veronique Maes and Dirk Tourwé

3.1 Introduction 49
3.2 Modified Peptides 51
3.3 Pseudopeptides 65
3.4 Secondary Structure Mimics (Excluding Turn Mimics)  75
  3.4.1 β-strand Mimetics  75
  3.4.2 Helix Mimetics  87
3.5 Examples of Peptidomimetics  92
3.6 Conclusion  104
References  105

4 Design of Cyclic Peptides  133
Oliver Demmer, Andreas O. Frank and Horst Kessler

4.1 Introduction  133
  4.1.1 Pharmaceutical Research Today  133
  4.1.2 General Advantages of Cyclic Peptide Structures  134
  4.1.3 Examples of Cyclic Peptides of Medicinal Interest  135
  4.1.4 General Considerations  137
4.2 Peptide Cyclization  138
  4.2.1 Possibilities of Peptide Cyclization  138
  4.2.2 Synthesis of Cyclic Peptides  139
  4.2.3 Chemical Modifications of Cyclic Peptides  141
  4.2.4 Concluding Remarks  146
4.3 Conformation and Dynamics of Cyclic Peptides  146
  4.3.1 Reductions in Conformational Space  146
  4.3.2 Conformational Arrangements in Cyclic Structures  148
  4.3.3 Flexibility of Cyclized Scaffolds  151
  4.3.4 Experimental Structure Characterization  152
4.4 Concepts in the Rational Design of Cyclic Peptides  154
  4.4.1 The Influence of Amino Acid Composition  154
  4.4.2 The Dunitz–Waser Concept  155
  4.4.3 The Spatial Screening Technique  156
  4.4.4 General Strategy for Finding Active Hits  157
4.5 Examples of Cyclic Peptides as Drug Candidates  159
  4.5.1 Cilengitide as Integrin Inhibitor  159
  4.5.2 CXCR4 Antagonists  163
  4.5.3 Sandostatin and the Veber–Hirschmann Peptide as Examples of Rational Design  164
4.6 Conclusion  166
References  166
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Preface

Ever since the discovery of the therapeutic value of insulin, at the beginning of the twentieth century, peptides have been successfully applied as drugs. In the fifties and sixties, with the advent of new methodologies for isolation, identification and total synthesis, the range of peptide hormones was further expanded and additional peptide drugs were launched. Since then, a generally upward trend has been seen, despite occasional statements to the contrary. Improvements in techniques have allowed the identification of many naturally occurring peptides, which have provided the starting point for the design of peptide drug candidates. In addition, de novo design has emerged as a new approach for the invention of peptide drug candidates. Designed peptides and small proteins have become ubiquitous tools for biochemical and biophysical studies. The latter studies have had a significant impact on the design of peptides as potential drug candidates, and are thus to some extent covered in the present volume.

This book comprehensively presents central topics in the design of peptides and proteins, especially those with the goal of biopharmaceutical applications. It starts with an outline of computational methods, then moves on to cyclic peptides, which are often important in the development of peptide drug candidates; it provides an overview of peptidomimetics, carbohydrates in the design of peptides and proteins, de novo design of proteins, and finally, as a key example, the design of new insulin variants. This book is aimed at peptide scientists in academia and in industry, as well as at graduate students entering the field.

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1

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