METHODS IN MOLECULAR BIOLOGY

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Rational Drug Design

Methods and Protocols

Edited by

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Preface

As you set out on the way to Ithaca
hope that the road is a long one,
filled with adventures, filled with discoveries.
The Laestrygonians and the Cyclopes,
Poseidon in his anger: do not fear them, . . .
And if you find her poor, Ithaca didn't deceive you.
As wise as you will have become, with so much experience,
you will understand, by then, these Ithacas; what they mean.

C. P. Cavafy
Translated by Daniel Mendelsohn

What excites us as guest editors in the rational drug design is the decision of beginning a trip toward Ithaca that can lead to the liberation from the thefts that steal our health. This trip that involves Laestrygonians and Cyclops is exciting and adventure. We do not mind if our Ithaca did not fill our expectations. We become mature and happy as we discover new avenues for reaching a new Ithaca. The rational drug design is an Odyssey that never ends and this is the essence of life.

This volume of Methods in Molecular Biology covers several aspects of rational drug design. Such aspects include (a) synthesis of novel bioactive drugs; (b) development and application of new methodologies to tackle problems related to discovery of potent molecules; (c) comprehend on concepts strictly related to the bioactivity, i.e., lipophilicity; (d) development and application of computational methods valuable toward the establishment of new approaches in the Ithaca trip of drug discovery; and (e) the effects of physicochemical and ADMET properties of the designed potential drugs.

Hereby is given an outline of the chapters covered in the volume. The first three chapters are dedicated to the design of peptides and peptidomimetics targeting the amyloid deposits and multiple sclerosis. Chapter 4 offers applications and comprehends on saturation transfer difference (STD) NMR in the mapping of the protein-ligand interface. In the fifth chapter the performance of docking tools is assessed. The use of structural biology in drug design is reviewed in the sixth chapter. Chapter 7 introduces new essential cheminformatic tools in ligand-based drug design. In Chapter 8 a thorough method of bioguided design of trypanosomicidal compounds is explained. The use of hybrid screening protocols is given in Chapter 9. Chapter 10 explains a novel method for the determination of unlabeled compound kinetics using the technique of time-resolved fluorescence resonance energy transfer. The new computational method of dynamic undocking is introduced in Chapter 11. The importance of lipophilicity in drug discovery is explained in Chapter 12. Chapters 13 and 14 explore the polypharmacology and the development of nuclear receptor modulators. An extensible orthogonal protocol that combines structure-based and ligand-based screening tools is introduced in Chapter 15. In Chapter 16 the synthesis of various adamantane derivatives with σ-receptor affinity is described. Examples of supervised molecular dynamics approaches are reviewed in Chapter 17. In Chapter 18 the synergistic action of biomolecular NMR methodologies is explained. Chapter 19 introduces the use of the dynamic and in silico pharmacophore approach in drug discovery. Chapters 20 and 21 deal with the rational design of inhibitors targeting MAGL and methyllysine reader protein spindlin1. The design

of natural product hybrids bearing triple antiplatelet profile is described in Chapter 22. Pharmacophore generation using phase is explained in Chapter 23. The design of inhibitors targeting histone deacetylases by filtering through ADMET, physicochemical and ligand-target flexibility properties is provided in Chapter 24. The occurrence of reactions in NMR tubes that may lead to new drug leads is explored in Chapter 25. The two last chapters deal with the angiotensin II type 1 receptor (AT1R). Chapter 26 provides the application of structure-based methods to develop new antagonists of the receptor, while Chapter 27 explores the importance homology modeling played in the case of AT1R.

This book, as can be understood from the analysis of its contents, was made possible through the generous contributions of many scientists, who shared their knowledge, for which we are very grateful. We are also sincerely grateful to the series editor, Professor John Walker, for his help, advice, and patient guidance in preparing this volume.

Athens, Greece

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