Textbook presentation: "Rational Design of Bioactive Compounds: From Theoretical to the Practical Approach" by authors: Milan Mladenovic, Rino Ragno, Nevena Stankovic, Nezrina Mihovic,

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The textbook entitled: "RATIONAL DESIGN OF BIOACTIVE COMPOUNDS: From Theoretical to Practical Approach" was created as a result of the scientific and teaching-pedagogical collaboration between the Faculty of Science and Mathematics of the University of Kragujevac and the Faculty of Pharmacy and Medicine of the Sapienza University of Rome. The authors of the textbook have incorporated their knowledge of biochemistry, pharmacy and medical chemistry into a textbook that will bring medical chemistry closer to the broader academic community in Serbia and present the basic concepts of rational design of bioactive compounds with the ultimate goal of designing compounds that will be used as pharmaceuticals.

The textbook is an upgrade of biochemistry knowledge and answers the basic question in biochemistry: How does a bioactive molecule (substrate, inhibitor, agonist, partial agonist, antagonist ...) interact with its molecular target (enzyme, receptor or nucleic acid)? The authors, through the concept of crystal structures of co-crystallized complexes of biomolecules and proteins, present to the reader the activity of biomolecules as a direct consequence of the interactions that the biomolecule exerts in the

crystal structure with the active center of the enzyme or receptor. The specificity of this textbook is to consider biomolecule-protein interactions by using accredited and recognized computer methods, with a simple premise: biomolecule-protein interactions will be better understood if viewed on a monitor screen. In this way, future readers will easily adopt a new way of understanding biochemistry and fully understand the importance of biomolecule interactions with proteins. The manuscript focuses not on the metabolic pathways of biomolecules, but on the interactions of biomolecules with proteins and the consequences that these interactions have on human physiology.

The book is thematically divided into nine chapters:

Chapter I: Crystallography as a method for the definition of bioactive conformations of inhibitors and antagonists of enzymatic reactions

Chapter II: Preparation of crystal structures of biomolecules in the complex with native protein

Chapter III: Three-dimensional quantitative correlation between the bioactive conformation and the activity of biomolecules

Chapter IV: Generating 3-D QSAR studies

Chapter V: Generation of bioactive conformations by molecular target structure: molecular docking

Chapter VI: Practical applications of molecular docking

Chapter VII: Defining bioactive conformations according to crystal structure of inhibitors or agonists: alignment biomolecules

Chapter VIII: Practical application of biomolecule alignment

Chapter IX: Rational design of bioactive compounds

The major emphasis in the textbook is on the understanding the biophysical phenomena that lead to the generation of the bioactive conformation (Chapters III and IV). In other words, it explains in detail how the interaction between biomolecules and proteins occurs. The textbook is based on the recently published study of the rational design of novel monoamine oxidase B (MAO B) inhibitors (Chapter III), an enzyme whose disruption of activity leads to the oxidative stress at the level of mitochondrial DNA and the subsequent development of Parkinson's disease. The authors presented to readers simply and understandably how diversity in the structure of MAO B inhibitors affects activity. MAO B inhibitor activity was quantified through the concept of Three-Dimensional Structure Activity Relationships (3-D QSAR) and presented in detail how statistically significant 3-D QSAR models are generated and how they are interpreted, with minimal use of complex mathematical formulations of chemometrics, at the level at which it is necessary to understand how chemoinformatic methods are used in medicinal chemistry.

The authors' view is that medical chemistry cannot be learnt only by reading university and scientific literature, but mainly through practical work; all the methods of generating 3-D QSAR studies and other manuscript methods that are described in the scientific literature are descriptively presented in a case study of a human dihydrofolate reductase inhibitor (Chapters II, IV, VI, and VIII), an enzyme whose disruption in catalytic activity leads to the development of leukemia. Within the practical chapters, the authors, using Linux as an operating system, bash and Python programming, present to readers in detail the most popular practical methods for the rational design of bioactive compounds.

The practical chapters represent the greatest value of this textbook. All of the molecular modeling tools that are presented are completely free to the academic community. Generation of 3-D QSAR studies will be learnt by readers through the use of Open3DALIGN (Chapter IV).

From the theoretical and practical point of view, both molecular docking methods (Chapter V) and the alignment of three-dimensional structures of biomolecules (Chapter VII) are addressed in the textbook. Methods that are complementary to 3-D QSAR studies and used to predict the bioactive conformations of compounds whose activities are known but not their interactions with proteins of interest are also presented. Although the methods presented are supported by appropriate mathematical formulations, greater emphasis is placed on understanding of the methods and the purpose of their applications. Readers are told how to choose the best method to predict the bioactive conformation of a new molecule based on the structure of the molecular target or known inhibitors or antagonists. Molecular docking requires the practical application of AutoDock4.2, AutoDock Wines and DOCK6 (Chapter VI), while the Balloon/ShaEP and Obconformer/Open3DALIGN programs (Chapter VIII) are used to compare the three-dimensional structures of biomolecules.

The textbook concludes with the presentation of the rational design concepts of novel monoamine oxidase B inhibitors, using all the methods learnt (Chapter IX). By understanding the content, readers will understand that the rational design of new biomolecules is based solely on the interactions that the molecule will accomplish with the molecular target of interest, and after adopting all the methods presented in the manuscript, readers will be able to critically review the biomolecular-molecular interaction target and to experimentally work (synthesis and biochemical evaluation of compounds) based on the rational knowledge.

The concept that each theoretical title is followed by a chapter in which the methods of computational medicinal chemistry are practically

taught is certainly different from the usual formats of university textbooks, forcing the reader to apply what has been learnt previously. Mastering the methods presented in the book, readers will understand that the activity of biomolecules and future drugs is a result of the interactions that the biomolecule has with the active center of the enzyme or a receptor and will acquire the ability to rationally design new bioactive molecules.