book reviews

Vitomir Šunjić and Michael J. Parnham
Signposts to Chiral Drugs Organic Synthesis in Action

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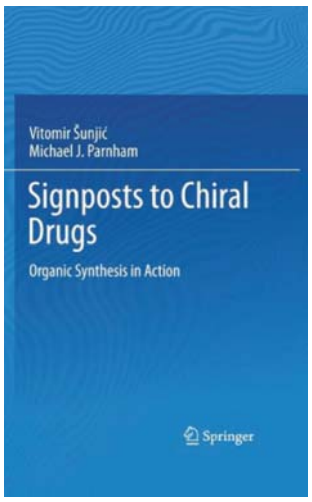

Dr Vitomir Šunjić, professor at the Department of Chemistry, Faculty of Science, University of Zagreb and Dr Michael J. Parnham, professor at the Goethe University, Frankfurt, and visiting scientist at the University Hospital for Infectious Diseases "Dr. Fran Mihaljević " in Zagreb, have decided to write a book. An original and very interesting book. Springer, the renowned publisher, supported them and the authors started by solving fifteen "cases". The synthetic "cases " of their choice in which the target molecules are mostly chiral, enantiopure drugs. Some of them are established drugs, the others are candidates for drugs under clinical research. One is a natural product with broad application and the other the library of lead molecules. The authors' approach to the synthesis of target molecules was that of capable detectives making use of all possible means to successfully solve the "cases". In the description of the specific compounds or structural classes of compounds the authors included mechanistic and stereochemical aspects of often enantioselective transformations. They have also described many new methodologies such as click chemistry, multi-component syntheses without forgetting the green chemistry criteria. Furthermore, the information on the biological targets, mechanisms of action and biological and therapeutic profiles of target compounds has been given in order to complete the picture of the all chosen "cases".

Each chapter of this exceptional book is complete in itself. Therefore, the reader can choose and read with more attention the chapters of their interest. Each chapter begins with a very informative Abstract that offers you a clear idea of the strategy of synthesis and the therapeutic profile of the compound or a family of compounds described in that chapter. At that point you can decide whether that chapter is the one that you want to read in detail or browse through it or parts of it. Let us start from the beginning. Chapter 2 describes aliskiren fumarate, an antihypertensive drug used in the oral treatment of high blood pressure. The 2-aryloxy-propionic derivative (R)-K-13675, a lead candidate compound in the development of cholesterol-lowering drugs, is described in Chapter 3. Chapter 4 is concerned with sitagliptin phosphate monohydrate which is used in the treatment of type 2 diabetes mellitus. In Chapter 5 the synthesis of biaryl units common to valsartan and vancomycin are described. While valsartan is a leading drug in the treatment of hypertension, vancomycin is a broad spectrum antibiotic to be administered intravenously. Chapter 6 is concerned with a group of related molecules, 3-amino-1,4-benzodiazepines. Privileged structures in that minor changes can produce a wide variety of biological actions. Three of the four described illustrative structures are candidate molecules to be used in the therapy of Alzheimer's disease, and the fourth one is a potential antiarrythmic agent. Chapter 7 deals with the synthesis of sertraline, an aryl-substituted tetrahydronaphthalene derivative which is widely used as a drug in the treatment of depression and anxiety-related disorders. Chapter 8 is devoted to a synthetic process leading to enantiopure 1,2-dihydroquinolines, a group of related molecules which are possible candidates for use as selective, non-steroidal antagonists at the glucocorticoid receptor. Such antagonists have the potentiality to be used in adrenocortical hyperplasia, as in Cushing's disease. Chapter 9 is concerned with the synthesis of (–)-menthol, a natural terpenoid and a household medicament widely used as local anaesthetic and analgesic, in order to reduce itching, as gastric sedative agent and as a decongestant. The described synthetic process has been already scaled-up to the production of 1,000 tons/year. Fexofenadine hydrochloride is a racemic carboxylic analogue of terfenadine and a highly hydrophylic amino acid, a second-generation antihistaminic drug lacking sedative activity, used in the treatment of allergic diseases. The possibilities of its synthesis in the R (+) enantiomeric form, although not feasible at this moment from the cost-benefit point of view, are examined in Chapter 10. In Chapter 11 the synthesis of montelukast sodium which is a 7-chloroquinoline derivative of the leukotriene D_4 is described. The molecule is used in the oral treatment of chronic, particularly nocturnal asthma. The compound has been recognized as one of the most significant advances in asthma therapy in the last 25 years. Chapter 12 is dedicated to the class of compounds, thiolactone macrocylic peptides which act as antibacterials, naturally regulating the growth of bacteria. One of compounds from this class not in use as a drug has been chosen to describe the latest strategies used in the development of peptide synthesis. Chapter 13 is dedicated to efavirenz, a non-nucleoside analogue which is a drug of choice in the therapy for patients with HIV-1 infection. The chapter is of special interest since the AIDS epidemic remains a challenge to worldwide healthcare and billions of dollars have been spent on AIDS research. Paclitaxel (taxol) is a natural polysubstituted macrocyclic compound isolated from the bark of the Pacific yew tree. It is an efficient anticancer agent with a broad spectrum of activity against tumors. Three selected synthetic pathways leading to paclitaxel are described in Chapter 14. The synthesis of this compound is necessary in order to enhance the availability of the drug and avoid the unsustainable use of yew trees. In Chapter 15 the synthesis of 1,2,3-triazole-linked, diphenyl-substituted neoglycoconjugate has been described. It has been selected as a lead compound from a small library of compounds with potential in the treatment of inflammation and cancer. And finally, another potential anticancer agent, 12-aza-epothilone, a representative of a class of natural macrocyclic azathilones has been described in Chapter 16. In search of new lead compounds natural macrocyclic molecules have been previously subjected to both extensive and peripheral structural modifications. An example of this synthetic approach is antibiotic azithromycin. 12-Aza-epothilones, on the contrary, must be approached by total synthesis. The description of these compounds ends the list of interesting target molecules that the authors chose to present. Every chapter has its own short conclusion. Instead of

a general conclusion at the end of the book the authors give, chapter by chapter, short descriptions of synthetic methods and concepts discussed in the relevant chapter.

A wide variety of compounds or classes of compounds have been selected to be presented in this book which demonstrates the breadth of knowledge and professional interests of the authors. It does not surprise if one considers the basic biographical notes which are given on the authors. Thus, professor Šunjić, a graduate chemist, has a long-standing experience in teaching of organic chemistry at the Chemistry Department of the Faculty of Science, both at the undergraduate and graduate levels. Beside teaching, his whole professional career has been devoted to research in the field of organic chemistry, mostly in research Institutes and closely related to pharmaceutical industries where he had as well been employed for several years. The results of his years of research are visible in a great number of scientific publications, projects and patents. Michael J. Parnham, a graduate pharmacologist, professor of pharmacology and toxicology at Goethe University in Frankfurt, spent a number of years in research centers of German and Croatian pharmaceutical industries. His list of authored books, monographs and scientific publications is impressive.

But, let us return to the beginning. In Chapter 1 the authors give a precise explanation of motives that induced them to write this book. The focal point has been the discovery and development of new drugs, and in this context organic synthesis as a crucial part in the creation of novel, biologically active, safe target molecules. Every new cognition on the preparation, action and new possibilities of a bioactive compound found in Nature, modified or synthesized as a target molecule, is welcomed and useful in the continuing human effort to preserve health as well as considering the intrinsic human need to fight illness. **Only** 15 “cases ” are discussed in this book. Therefore, I expect the research of new “cases ” to be continued. I hope that the authors will not stop at this point.

The book will be of interest to everybody concerned with natural sciences, medicine, pharmacology, not only chemistry or more specifically organic synthetic chemistry. It is worth having it in one’s personal library, on any book shelf. It does not necessarily have to be placed among chemistry textbooks or monographs. I can easily imagine it in the company of good detective stories.

My recommendation is: read the book!

Srđanka Tomić-Pisarović