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Topics in Heterocyclic Chemistry

Aims and Scope

The series Topics in Heterocyclic Chemistry presents critical reviews on present and future trends in the research of heterocyclic compounds. Overall the scope is to cover topics dealing with all areas within heterocyclic chemistry, both experimental and theoretical, of interest to the general heterocyclic chemistry community.

The series consists of topic related volumes edited by renowned editors with contributions of experts in the field.

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Zdenko Časar
Editor

Synthesis of Heterocycles in Contemporary Medicinal Chemistry

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Preface

Heterocyclic compounds have had a central role in medicinal chemistry, and they have made notable contributions to the quality of life for humanity. It is difficult to imagine the progress in public health and the increased life expectancy that we have witnessed in the last 70 years without drugs such as β-lactam antibiotics, ACE inhibitors, calcium channel blockers, and others. Over the last decade, some particular compounds, like the statins, have established their position as important drugs, while many new therapeutic classes of compounds have emerged that have provided important advances in the area of modern medicinal chemistry. Indeed, statins, and in particular their heterocyclic derivatives that are frequently called the super-statins, have markedly improved the management of hypercholesterolemia, which has led to reduced risk of atherosclerosis and cardiovascular disease. Nowadays, these drugs are facing a patent cliff, which will allow the market entry of generic versions of these drugs and thus increase their access to patients worldwide. Then, early in this decade, a major breakthrough was achieved in the treatment of hepatitis C virus (HCV) infections. Several compound classes have emerged that can now provide significantly improved rates of sustained virological response in a few months of oral therapy, thus avoiding the use of less efficient and more difficult to tolerate ribavirin/pegylated interferon therapies. Among these compounds, sofosbuvir (NS5B HCV polymerase/protease inhibitor) and simeprevir (NS3/4A HCV protease inhibitors) and its analogs have a central role in the battle against hepatitis C. The treatment of type 2 diabetes has also moved to inhibition of glucose reabsorption in the kidney, which leads to reduced blood sugar levels. This has been achieved with a new class of compounds that inhibit sodium-glucose transport protein 2 (SGLT2), which are now referred to as the "gliflozin" drugs. Over the past 5 years, several gliflozin family members have been put on the market: canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, and tofogliflozin. These arose from the fascinating new arsenal of synthetic chemistry that was constructed for their efficient preparation. HIV treatment has also witnessed notable progress in the last decade, and one recently approved drug that might change the landscape of anti-HIV therapies is the second-generation HIV integrase strand transfer inhibitor dolutegravir, with its impressive efficacy and good patient tolerability. Anticancer

drugs have also made significant progress in the last decade. Among these, the so-called tinibs and the tyrosine kinase inhibitors have had a pivotal role. At the same time, astonishing results have been achieved in the area of natural product derivatives, where eribulin was introduced into clinical practice recently for the treatment of metastatic breast cancer and inoperable liposarcoma. Based on its complex polyether macrolide structure with 19 stereocenters, the total synthesis for eribulin production requires more than 60 steps. This is an outstanding achievement in industrial synthesis, and it represents the longest commercial drug synthesis to date.

Therefore, all of these achievements have provided impetus for the assembly of this volume of *Topics in Heterocyclic Chemistry*, entitled *Synthesis of Heterocycles in Contemporary Medicinal Chemistry*, which highlights in detail the abovementioned achievements. This volume is special in several aspects. First, it was composed by industrial medicinal and process chemists with decades of industrial experience. Secondly, it is dedicated to the heterocyclic drug compounds that have particularly marked the area of medicinal chemistry over the last decade. As this volume contains a good blend of synthetic organic, medicinal, and process chemistry, it should be appealing to a broad area of chemistry professionals and graduate students. I hope that it will inspire current and future process and medicinal chemists to design new drugs in efficient and sustainable manners.

Gallou provides a chapter on the development of a manufacturing process for the formation of a hepatitis C drug candidate with immense tutorial value from the process chemistry perspective. Lemaire and Schils describe the synthetic and process chemistry aspects of SGLT2 inhibitors for the treatment of type 2 diabetes. Schöne et al. give a detailed overview of synthetic routes to sofosbuvir, one of the best selling drugs of this decade. Prof. Tsantrizos discusses the discovery, early synthetic chemistry, and process chemistry of macrocyclic HCV NS3/NS4A protease inhibitors for the case of ciluprevir (BILN-2061), which brought olefin metathesis to the industrial scale and paved the way for the assembly of the marketed analogs simeprevir, paritaprevir, and vaniprevir. The chapter that I have contributed reviews the recent progress in super-statin chemistry. Schreiner et al. provide an overview and detailed analysis of the synthetic routes to dolutegravir. Bauer summarizes the discovery and the initial synthetic routes toward eribulin and its analogs and describes the recent synthetic advances in the area.

To finish, I would like to thank the series editor, Prof. Slovenko Polanc, for giving me an outstanding opportunity to compile this volume of *Topics in Heterocyclic Chemistry*. I am also grateful to Prof. Janez Košmrlj for his support in this matter. I must also express my gratitude to the entire editorial and support staff at Springer for their prompt support and guidance during the preparation of this work. I would like to express my appreciation to all of the authors of this volume, for their hard work and outstanding contributions. I extend my sincere gratitude to Sandoz/Lek management for providing an inspiring scientific environment and, in particular, to Dr. Josef Egerbacher, Dr. Susanne Raehs, Mr. Matjaž Tršek, Dr. Bojan Mitrović, and Mr. Pavel Drnovšek, who have been supportive in all my scientific endeavors. I would also like to acknowledge Prof. Stanislav Gobec for his support

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Ljubljana, Slovenia Zdenko Časar
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