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published in
Drug Discovery Today: Technologies
2018

DOI (link to publisher)
10.1016/j.ddtec.2018.11.002

document version
Publisher's PDF, also known as Version of record

ELSEVIER

DRUG DISCOVERY TODAY TECHNOLOGIES

Drug Discovery Today: Technologies Vol. 29, 2018

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EDITORIAL

Multicomponent reactions in drug discovery and medicinal chemistry

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Eelco Ruijter (1977) carried out his graduate studies with Prof. Ludger Wessjohann at the Vrije Universiteit (VU) Amsterdam and the Leibniz Institute of Plant Biochemistry (Halle/Saale, Germany) and was awarded his PhD in 2005. By then, he had joined Prof. Rob Liskamp's group at Utrecht University as a postdoctoral fellow working on chemistry-based proteomics. In December 2006, he returned to the VU Amsterdam as a tenure track assistant professor at the Department of Chemistry & Pharmaceutical Sciences. He received tenure in 2012 and was promoted to associate professor in 2018. His research interests include the development of new synthetic strategies towards complex molecules of high biological relevance making use of cascade processes and asymmetric catalysis. He is author of 88 publications in international, peer-reviewed scientific journals (*h*-index: 32) and five book chapters, editor of two volumes in a book series, and co-inventor of three patents.

Romano V.A. Orru obtained his PhD in 1994 with prof Ae. De Groot at the Agricultural University in Wageningen, The Netherlands, on synthetic methodology towards sesquiterpene total syntheses. From 1996 to 2000 he worked on synthetic applications of biotransformations in the group of prof. K. Faber at the Technical and Karl-Franszens Universities in Graz, Austria. In 2000 he was appointed assistant professor and later associate professor at the VU Amsterdam. Since 2007, he holds the chair of Synthetic & Bio-organic Chemistry in Amsterdam running a group of 15–20 researchers.

Quality of life has increased tremendously over the past century and unquestionably one of the main drivers for that are the amazing developments in medicine. Nowadays, people can enjoy longer and healthier lives as effective treatment is available for many previously incurable diseases. Indeed, pharmaceuticals have come a long way from simple compounds like paracetamol and aspirin to today's modern drugs, with their potency and selectivity molecules reflected in increasingly complex molecular structures. However, as valuable as drugs may be, they currently lack an important feature: the ability to be produced in a sustainable and affordable way. Synthetic chemistry, despite also having seen outstanding progress in the last century, has not quite been able to keep up the pace with the discoveries in medicine: in general, drugs are produced via tedious, multistage, highly wasteful processes, often using toxic materials. Thus, the manufacturing side of the pharmaceutical industry is cost- and resource-inefficient and environ-

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[1] See Appendix A.

1740-6749/$ https://doi.org/10.1016/j.ddtec.2018.11.002

mentally unfriendly. Surely, the high value of the products – the medicines – justifies the means, but improvements are dearly needed in this area as well.

Developing more efficient techniques for synthesising complex drug molecules is a painstaking process. Multicomponent and other cascade reactions (processes comprising several consecutive reactions in one pot) allow scientists to carry out chemical syntheses in fewer steps than conventional approaches. Generally, they improve the eco-friendliness and time/cost efficiency associated with the synthesis of drugs and other high-value organic molecules. Therefore, these one-pot processes have the potential to reduce our environmental impact, as well as the overall costs associated with producing life-saving medicines. A multicomponent reaction, or MCR, is a specific type of cascade reaction that combines three or more reactants in one reaction vessel to form a new product. This product often contains all the atoms that were present in the reactants. As a result, there is very little waste or unwanted by-product formation compared to more traditional syntheses. Therefore, MCRs are powerful tools for the synthesis of complex, biologically relevant molecules. The atom economy of MCRs, their convergent character, operational simplicity, and the structural diversity and complexity of the resulting products make this chemistry exceptionally useful for discovery and optimisation processes in the pharmaceutical industry.

In this special issue, contributions from renowned (synthetic) chemists highlight several aspects of MCRs in drug discovery and medicinal chemistry. From the laboratory in Genova a contribution of Luca Banfi & Renata Riva discusses the application of biocatalysis to MCR processes in order to address stereochemistry issues connected to many of these cascade reactions. Another aspect is highlighted by Alex Dömling and coworkers from the University of Groningen. In their contribution efficient access to highly potent macrocyclic (semi)peptides is described. The MCR approach allows quick synthesis of analogs facilitating SAR. A completely different type of application is described by Thomas Müller from University of Düsseldorf. His lab is known for the use of MCR cascade sequences to produce luminescent materials, which can be used to visualize pharmacologically important processes in e.g. cells. Thomas Nielsen from the University of Copenhagen in turn disclosed a very nice and to the point entry to the use of the Petasis three-component reactions in medicinal chemistry. Benzynes become more and more important as building blocks in MCR chemistry and the contribution of Tracey Pirali and Marta Serafini from the Università del Piemonte Orientale provides a brief introduction into that emerging area.

The discovery of new variations of classical MCRs remains a fruitful strategy for the development of new flexible multicomponent processes. Sunliang Cui and Bo Huang of Zhejiang University discuss their use of ynamide as isocyanide homologs in new MCRs based on the Ugi and Passerini reactions. Andrei Yudin and Joanne Tan of the University of Toronto highlight the use of borylated reagents in multicomponent chemistry and application of the resulting products in synthetic and medicinal chemistry. Erik Van der Eycken and co-workers present an overview of gold-catalysed cyclisation reactions of MCR products accessing complex polycyclic scaffold structures. Finally, Rodolfo Lavilla and Ouldouz Ghashghaei of the University of Barcelona together with colleagues of the University of the Basque Country review recent applications of the Povarov reaction in medicinal chemistry.

In summary, this special issue of Drug Discovery Today: Technologies may serve as an excellent starting point for the non-specialized medicinal chemist as an entry to MCRs in drug discovery and medicinal chemistry. We hope you all enjoy reading it and may try some of the chemistry yourself in the lab!

Appendix A

Profile of the Synthetic & BioOrganic Chemistry Group

The research of the SyBOrCh group (http://syborch.com/) focuses on sustainable synthetic method development employing cascade (or domino, tandem) processes. These are applied to the diversity-oriented synthesis of small focused libraries of high added value small molecules, including building blocks for pharmaceuticals or ligands for catalysis. Since entering the field the group has developed important novel entries in the highly competitive area of multicomponent reactions (MCRs) and strategies for diversity-oriented synthesis, often involving bio- and transition metal catalysis. We especially focus on mechanistic and stereochemical aspects, as well as on optimization toward robust procedures of high synthetic utility. The group's chemistry has proven successful in the synthesis of potentially biologically active molecules (antitumor, antibiotics, hepatitis C) as well as ligands relevant to catalysis. Eelco Ruijter and Romano Orru are leading players in the field of multicomponent and cascade reactions for diversity-oriented synthesis.