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Multicomponent reactions, applications in medicinal chemistry & new modalities in drug discovery

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MULTICOMPONENT REACTIONS, APPLICATIONS IN MEDICINAL CHEMISTRY & NEW MODALITIES IN DRUG DISCOVERY

Markella Konstantinidou

2020

**Marie Skłodowska-Curie
Actions**

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Multicomponent reactions, applications in medicinal chemistry & new modalities in drug discovery

PhD Thesis

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 University of Groningen
 on the authority of the
 Rector Magnificus Prof. C. Wijmenga
 and in accordance with
 the decision by the College of Deans.

This thesis will be defended in public on

Friday 14 February 2020 at 14.30 hours

by

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*To
to my family
who has always been by my side*

Paranymphs

Qian Wang

Jingyao Li

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OUTLINE OF THE THESIS

OUTLOOK

Medicinal chemistry plays a key role in the drug discovery process, including the early stages of hit identification, the lead optimization (hit-to-lead) and process chemistry. It is considered a multi-disciplinary field and medicinal chemists are key players in interactions with computational chemists, biologists and pharmacologists. In the last few decades, the two main approaches used in drug design (high-throughput screening (HTS)^[1] and fragment-based drug discovery (FBDD)^[2-3]) had also an effect on medicinal chemistry. The first approach required a large number of compounds for screening, which gave rise to combinatorial chemistry. On the contrary, in the second approach, a smaller number of compounds was needed in the first screening steps, but medicinal chemists had the non-tedious task of designing routes for growing, merging and linking fragment hits together towards drug-like molecules. Nowadays, the growing interest of pharmaceutical industries and academia in difficult or “undruggable” targets, has brought into the research fields a considerable amount of protein – protein interactions (PPIs).^[4-5] PPIs tend to lack well-defined binding sites and are largely flat, hydrophobic areas. Therefore, medicinal chemistry also needed to shift from small molecules designed for typical, well-defined binding sites to new modalities. In the last few years, the medicinal chemistry toolbox was enriched with macrocycles, stapled peptides, antisense oligonucleotides and proteolysis targeting chimeras (PROTACs).^[6]

In this thesis, new targets in medicinal chemistry, in particular the PPI of PD-1/PD-L1, novel synthetic methodologies towards scaffolds with diverse biological applications and lastly PROTACs, as a highly promising new modality in drug discovery, are discussed.

The accumulation of biological data and better understanding of the immune checkpoints has made the field of immune-oncology a very promising and competitive area in cancer research.^[7] In particular, the identification of monoclonal antibodies (mAbs) targeting the PD-1/PD-L1 axis and the first approvals by FDA in 2014 have revived the field. Although monoclonal antibodies for these targets have shown impressive clinical outcomes, there are still certain disadvantages. In general, mAbs are not orally bioavailable and have a high molecular weight, which leads to poor diffusion, especially in large tumors. Production costs are also very high. In **chapter 1**, promising small molecules targeting the PPI of PD-1/PD-L1 that were disclosed in patents in the last couple of years are discussed. In **chapter 2**, a structural analysis, is provided, based on co-crystal structures of mAbs, small molecules and macrocycles that aim to block the interaction.

In the drug discovery process, time has always been a key factor. The development of medicinal chemistry and the hit-to-lead optimization are still considered a rate-limiting step. In an interesting analysis regarding the type of reactions most commonly employed in drug discovery, it was shown that there is a tendency to rely on known synthetic routes, with a high prevalence of amide coupling reactions and C-C coupling steps.^[8-9] As a result of this trend, certain types of molecular shapes are prevailing and the chemical space explored is limited. There is still a constant need for

optimizing reaction schemes, reducing the required time and number of steps and minimizing waste. Most of these requirements are met by multicomponent reaction chemistry (MCR), which in contrast to classical synthetic routes relies at using at least 3 starting materials in a single synthetic step to access complex scaffolds and covers rapidly unexplored chemical space.

Figure 1. Advantages of multicomponent reactions.

Multicomponent reaction chemistry can significantly accelerate the synthesis of derivatives and allows the coverage of large chemical space. In most of the cases the reaction conditions are mild and inert atmosphere or dry solvents are not required. Moreover, functional groups are well-tolerated, thus the necessity of protecting and deprotecting steps is kept to a minimum. It is noteworthy that MCR scaffolds can withstand a large number of post-MCR modifications, including cyclizations, macrocyclizations and Pd catalyzed reactions^[10-12], just to name a few commonly used strategies. Depending on the choice of starting materials, properly selected functional groups can be employed at a secondary MCR.

The application of MCR synthetic methodologies is used either to improve an existing synthetic route or to access a scaffold that is not accessible with classical synthetic routes. In **chapter 3**, a synthetic route for glutarimide alkaloids was designed. The existing procedures don't provide an easy access neither to the natural products nor to their derivatives. In the described MCR-based methodology, the key step is an Ugi reaction, with two points of variations, thus significantly enabling the synthesis of derivatives.

In **chapter 4**, a one-pot procedure is discussed regarding the synthesis of *beta*-carbolinone analogues. The intermediate of the initial Ugi reaction undergoes an intramolecular cyclization towards the desired scaffold. The one-pot protocol reduces the number of purification steps.

In **chapter 5**, a successful combination of an Ugi reaction with a palladium-catalyzed cyclization to access tetracyclic indoloquinolines, a class of natural alkaloid analogues, is shown. Commercially available starting materials can be used and a library of derivatives was rapidly synthesized.

In **chapter 6**, the focus is the scaffold of 2-(imidazo[1,5-*a*]pyridine-1-yl)-1,3,4-oxadiazoles, a scaffold of biological importance for topoisomerase II inhibitors and 5HT₄ partial agonists. The existing synthetic routes require 6 steps in total and several purifications to access this type of scaffold. The novel designed protocol is based on simple building blocks for an Ugi-tetrazole reaction. With *in situ* deprotections and cyclizations, a diverse library of derivatives was synthesized. Remarkably, only one purification is required in the last step.

In **chapter 7**, Ugi-tetrazole and Huisgen reactions were combined to access the privileged scaffold of 2,5-disubstituted 1,3,4-oxadiazoles. A large number of functional groups was tolerated and great diversity was achieved through the three possible variation points. The synthesis showed good scalability and post-modifications were also well-tolerated.

In **chapter 8**, an application of MCR scaffolds on a medicinal chemistry target is presented. As target proteins the aspartic proteases were selected and in particular the member called endothiapepsin. The aim was to develop an anchor-centered docking approach in order to rationally design, select and optimize our selected scaffold. A series of Ugi-tetrazole products were designed, synthesized and biologically evaluated. Co-crystal structures of potent inhibitors with the target protein were obtained. MCR in this case gives rapid access to the library of potential inhibitors. Moreover, the developed docking protocol allows the enumeration of tailor-made virtual libraries from commercially available starting materials. This protocol gives access to novel virtual libraries that can be developed for diverse biological targets.

The last part of this thesis is focusing on an exciting new modality in drug discovery that has evolved rapidly after its first description in 2001. Proteolysis targeting chimeras (PROTACs) are heterobifunctional molecules comprising of a ligand targeting a protein of interest, a ligand targeting an E3 ligase and a connecting linker. The aim is instead of inhibiting the target to induce its proteasomal degradation. The concept relies on the natural protein degradation by ubiquitination, and it is proven so far to work effectively on a number of targets that are traditionally classified as challenging or even “undruggable”. In **chapter 9**, the advantages of PROTACs over classical inhibitors are discussed and an analysis of the existing co-crystal structures of ternary complexes is presented. Special cases, such as homoPROTACs, PROTACs targeting the Tau protein and the first PROTACs that entered clinical trials are discussed.

In **chapter 10**, the aim is to design, synthesize and evaluate the biological effects of PROTACs targeting the cyclin-dependent kinases 4 and 6 (CDK4/6). Using the FDA approved dual CDK4/6 kinase inhibitor, abemaciclib, after structural modifications, degraders were designed. A small

library, including different types of linkers was synthesized. Preliminary biological data indicate that the designed PROTACs are highly capable of degrading the protein of interest. In **chapter 11**, the focus is on the design and synthesis of PROTACs targeting leucine-rich kinase 2 (LRRK2), which has emerged as a potential target for Parkinson's disease. The rational for the design and synthesis is discussed. A hypothesis is presented regarding the features that make this kinase target challenging.

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