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MCR-Based Exploitation and Application of Diverse (Poly)Heterocyclic Scaffolds

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Qian Wang

2020

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university of
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MCR-Based Exploitation and Application of Diverse (Poly)Heterocyclic Scaffolds

PhD thesis

to obtain the degree of PhD at the
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

Monday 5 October 2020 at 18.00 hours

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TO
MY FAMILY AND FRIENDS
WHO HAVE ALWAYS BEEN BY MY SIDE

Paranymphs

Lin Zhou

Roberto Butera

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OUTLINE OF THE THESIS

OUTLOOK

Nowadays, people can enjoy longer and healthier lives and unquestionably one of the main drivers for that are the significant developments in drug discovery. Drug discovery is the process through which potential new candidate medications are identified. It involves a wide range of scientific disciplines, including biology, chemistry and pharmacology. There are multiple defined stages for drug discovery process, indicated in Figure 1.¹

Figure 1. The drug discovery process.

It can be easily recognized from Figure 1 that medicinal chemistry plays a crucial role in the drug discovery process. Medicinal chemists prepare and/or select appropriate compounds for biological evaluation that, if found to be active, could serve as lead compounds. They then evaluate the structure-activity relationships (SARs) of analogous compounds with regard to their *in vitro* and *in vivo* efficacy and safety.² With the increasing demand for efficacy, time is becoming a critical factor. The time cost has escalated sharply to up to an estimated US \$1.2 billion for the development a single new drug.³

Chemical synthesis represents the most time-consuming aspect of medicinal chemistry, so medicinal chemistry has added combinatorial chemistry and high-speed parallel synthesis in lead discovery and optimisation to more quickly generate novel chemical structures, the multi-component reaction (MCR) therefore has seen a resurgence of interest.⁴ MCR is a specific type of cascade reaction that combines three or more different starting materials as chemical structure inputs and yield the final product in a one-pot procedure. Opposite to other classical organic reactions, MCRs are superior to allow for the easy and fast generation of chemical diversity and complexity in just a single synthetic operation with high atom economy and bond-forming efficiency.⁵ The scaffold diversity of MCRs and the window in chemical space have been undoubtedly recognized by the synthetic community in industry and academia as a great tool to design and discover biologically active compounds (Figure 2).⁶ Moreover, MCR scaffolds can withstand a myriad of post-transformations depending on the functional groups introduced during the MCR, thus leading to the synthesis of several pharmacologically important heterocyclic scaffolds, mostly in two operational steps.⁷⁻⁸

Figure 2. Multicomponent reactions and their advantages.

These features of MCR make it an attractive technology in drug research and development.⁹ Examples of drugs and candidates synthesized by MCR clearly show the immense advantages of them.¹⁰ However, the number of applications in drug discovery is rather limited regarding the superb advantages of this chemistry.¹¹ An analysis of the currently marketed drugs, however, shows that approximately 5% can be synthesized with the use of MCR, even so they are synthesized by a classical sequential pathway.¹²

Lidocaine	Praziquantel	Telaprevir	Levetiracetam
Olanzapine	Almorexant	Carfentanil	Epelsiban
Clopidogrel	Lacosamide	Ivosidenib	Atorvastatin

Figure 3. Examples of marketed drugs and drugs in clinical trials which have been discovered using MCR chemistry.

In this thesis, environmentally friendly building block in MCR, novel synthetic methodologies towards drug-like privileged structures and lastly PROTACs, as a highly promising new modality in drug discovery, are discussed.

The Ugi reaction is most appealing among MCRs which is well suited for diversity oriented synthesis applicable in drug discovery.¹³ The nature of the amine component in Ugi reactions may vary widely¹⁴ and the utilization of ammonia herein will be valuable because it is one of the most-produced and cheapest bulk chemicals and permits reduced waste. In **chapter 1**, the developments of ammonia-Ugi reactions and successful applications in the formation of complex peptides, heterocyclic scaffolds, macrocycles, and natural products, are discussed.

The association of a MCR with an efficient post-MCR transformation, typically a cyclization process, has been proven to be a powerful strategy to generate highly functionalized heterocyclic compounds.¹⁵ In **chapters 2-7**, sequential multi-component reaction, Huisgen reaction or transition-metal-catalyzed domino reactions in alliance with the Ugi reaction is also especially useful for synthesizing a number of privileged scaffolds (Figure 4).

Figure 4. Ugi-4CR and post-transformations for the generation of complex architectures.

In **chapter 2**, the direct usage of C,N-unprotected amino acids is discussed regarding the synthesis of a novel class of acid-tetrazole compounds. Two sequential MCRs afforded complex tetrazole-peptidomimetics with a high level of structural diversity, providing a platform for the production of functionalized building blocks for novel bioactive molecules and nontraditional scaffolds which previously were not accessible.

In **chapter 3**, 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 late-stage functionalization were also well-tolerated.

In **chapter 4**, 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 5**, easy operation, readily accessible starting materials, and short syntheses of the privileged scaffold indeno[1,2-c]isoquinolinone was achieved by a MCR-based protocol via an ammonia-Ugi-4CR/Copper-catalyzed annulation sequence. Optimization and scope and limitations of this short and general sequence are described. The methodology allows an efficient construction of a wide variety of indenoisoquinolinones in just two steps.

In **chapter 6**, a Cu-catalyzed cascade reaction were successfully applied in the Ugi postcyclization strategy by using ammonia and 2-halobenzoic acids as key building blocks. Privileged polysubstituted isoquinolin-1(2*H*)-ones were constructed in a combinatorial format with generally moderate to good yield. The protocol, with ligand-free catalytic system, shows broad substrate scope and good functional groups tolerance towards excellent molecular diversity. Moreover, free 4-carboxy-isoquinolinone are now for the first time generally accessible by a convergent multicomponent reaction protocol.

In **chapter 7**, a one-pot procedure is discussed regarding the synthesis of beta-carboline 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.

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 8**, 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.

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