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Development of Novel Covalent Inhibitors and Other Scaffolds Through Multicomponent Reactions

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**DEVELOPMENT OF NOVEL COVALENT INHIBITORS
AND OTHER SCAFFOLDS
THROUGH MULTICOMPONENT REACTIONS**

**Fandi Sutanto
2020**

innovative
medicines
initiative

The research presented in this PhD thesis was performed in the group of Drug Design within the Groningen Research Institute of Pharmacy at the University of Groningen, The Netherlands.

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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 28 September 2020 at 16.15 hours

by

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to
My dearest family

Paranymphs

Qian Wang

Jingyao Li

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Outlook

OUTLOOK

Multicomponent reaction in drug discovery

Drug discovery is the process by which new medications are discovered. It requires an integrated set of disciplines that work together to support the series of necessary activities to identify and validate drug targets, to design or discover the so-called chemical probes which establish a desired pharmacological effect from the target, therefore optimizing these probes to provide drug-like candidates which fulfill safety, quality, and efficacy for treatment of a disease.¹

Multicomponent reaction (MCR) is a one-pot chemical reaction where at more than two components react to form a single product that fuses the atoms of the starting components (Fig. 1).² MCRs are flexible reactions for the rapid generation of complex molecules. Such molecules are often biologically relevant scaffold structures. Successful drug development relies on high efficiency and low cost, and short cycles of design-make-test, and therefore requires short and efficient synthetic sequences for lead discovery.³ MCRs are a unique tool that provides the opportunity to combine the entire above characteristic, as these reactions are atom ergonomic, step efficient, and have high exploratory power.^{4,5}

Fig. 1. The illustration of multicomponent reaction.

This thesis exhibits the advantage of MCR in generating novel scaffold. The strong focus of the work is about covalent inhibitors, however, other scaffolds are also presented herein. The first part of this thesis is focusing on covalent inhibitors, as the interest of covalent inhibitors as drugs is currently growing significantly. In **chapter 1**, we discuss a short review about covalent inhibitors. A brief history about covalent inhibitors and their current development are provided, including current candidate of the drugs in clinical trials.

The application of MCR synthetic methodologies towards the development of covalent inhibitors is not yet available. In **chapter 2**, the focus is the application of MCR in the synthesis of covalent inhibitors in mmol scale and a high-throughput synthesis on a nanoscale method. Diverse electrophiles were introduced on different scaffolds in one- or two-steps synthesis yielding in great number of synthesized compounds. In **chapter 3**, another approach to develop covalent inhibitors by means of MCR is presented. The Ugi reaction of (substituted) acrylic acid, ammonia, oxo components, and isocyanides were carried out, yielding highly substituted acrylamides. A

high-throughput synthesis on a nanoscale in an automated fashion and a large scale synthesis were also performed. In the end, the compounds were screened against PTP1B.

In **chapter 4**, the synthesis of 1-tetrazolyl-imidazo[1,5-*a*]pyridines is provided. The reaction sequence starts from an Ugi-tetrazole reaction, deprotection, and followed by acetic anhydride mediated N-acylation-cyclization. The methodology was further extended through the employment of commercial anhydrides, acid chlorides and acids as an acyl component. We demonstrate the usefulness of the method by an improved 3-step synthesis of guanylate cyclase stimulator.

In **chapter 5**, a successful synthesis of the scaffold 2-(imidazo[1,5-*a*]pyridin-1-yl)-1,3,4-oxadiazoles in short sequence synthesis is shown. This scaffold is of biological importance for topoisomerase II inhibitors and 5HT₄ partial agonists. An existing route to synthesize this scaffold requires six steps and several purifications. Our novel synthetic route utilizing MCR is based on simple building blocks for an Ugi-tetrazole reaction. By in situ deprotections and cyclizations, a diverse library of derivatives was synthesized with only one purification necessary in the last step.

In the last part of this thesis, **chapter 6**, an application of MCR scaffolds on a medicinal chemistry is provided. The aspartic protease, in particular endothiapepsin was selected as the target. A series of Ugi-tetrazole products were designed based on anchor-centered docking approach, which were then synthesized and biologically evaluated. Co-crystal structures of potent inhibitors with the target protein were obtained.

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