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Multicomponent Reactions in High Throughput Synthesis and Medicinal Chemistry

Gao, Li

DOI:
[10.33612/diss.202801320](https://doi.org/10.33612/diss.202801320)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Gao, L. (2022). *Multicomponent Reactions in High Throughput Synthesis and Medicinal Chemistry*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.
<https://doi.org/10.33612/diss.202801320>

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Multicomponent Reactions in High Throughput Synthesis and Medicinal Chemistry

Li Gao

2022

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. The work was financially supported by the China Scholarship Council (CSC).

Printing of this thesis was financially supported by the University Library and the Graduate School of Science, Faculty of Science and Engineering, University of Groningen, The Netherlands.

Layout:

Cover design:

Printing: IPSKAMP printing

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university of
 groningen

Multicomponent Reactions in High Throughput Synthesis and Medicinal Chemistry

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

Tuesday 22 March 2022 at 11.00 hours

by

Li Gao

born on 24 November 1988
in Sichuan, China

Supervisors

Prof. A.S.S. Dömling

Prof. M.R. Groves

Assessment committee

Prof. F. J. Dekker

Prof. A. J. Minnaard

Prof. T. A. Holak

To

to my family and friends

who has always been by my side

Paranymphs

Mojgan Hadian

Xiaochen Du

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OUTLINE OF THE THESIS

1. Outlook

Drugs are substances used in the diagnosis, cure, mitigation, treatment, or prevention of disease or used to improve health state. Drug discovery and drug design have been through a long historical development from random drug discovery to the later rational drug design based on disease-related targets.¹ An example of accidental drug discovery is Penicillin found in 1928 by Alexander Fleming, and its structure was not determined until the year 1940 by Dorothy Hodgkin using X-ray crystallography. Since the 1960s, modern drug design has immensely evolved alongside the remarkable advances in fields such as organic chemistry, analytical chemistry, physical chemistry, biochemistry, pharmacology, and molecular biology, etc. Typical stages of modern drug design is indicated in **Figure 1**.

Figure 1. Typical stages of modern drug design.

Meanwhile, drug development has also laid the foundation for establishing a novel interdisciplinary subject: medicinal chemistry, which is rooted in organic synthesis and concerns the discovery, development, identification and interpretation of the mode of action of biologically active compounds at the molecular and cellular level.² Medicinal chemistry focuses on the lead discovery and lead modification processes aiming at the discovery and development of new therapeutic agents. Common sources of lead compounds can be the following¹: 1) Natural ligands or substances for the disease-related target; 2) Already existing substances for the target; 3) Random or targeted screening; 4) Fragment-based screening; 5) Computational approaches. After a lead compound is discovered, it will proceed to the next stage, lead modification based on some notable drug properties, e.g. potency, selectivity, and ADME (Absorption, Distribution, Metabolism, Excretion). This thesis is titled *“Multicomponent Reactions in High Throughput Synthesis and Medicinal Chemistry”*, and its aim, in brief, is to explore the application of multicomponent reactions in medicinal chemistry.

Undoubtedly, the tremendous progress in organic chemistry has greatly speeded up modern drug discovery and drug design, e.g., determining binding affinity mode requires accurate chemical structures of both drug molecules and proteins. In the field of organic chemistry, there is a particular branch, multicomponent reactions (MCRs).³⁻⁵ By definition, in MCRs, three or more reactants are combined in a one-pot reaction fashion, as opposed to conventional reactions in which only one or two reactants are involved. (An intuitive view of MCRs vs Traditional organic reactions is demonstrated in **Figure 2**). MCR chemistry is atom economic and synthesis convergent. It has been known for over 170 years since 1850. Owing to the pioneering work of Ivar Karl Ugi who has made a significant contribution to MCRs,⁶ MCR chemistry is then evolving rapidly. Hitherto, there is a diverse variety of MCRs. And so far, more than 300 scaffolds have been obtained, e.g. Ugi 4-component reaction (Ugi-4CR),⁷ Passerini 3-component reaction (Passerini-3CR),⁸ Groebke-Blackburn-Bienaymé Reaction (GBB reactions),⁹⁻¹² Orru reaction (Orru-3CR),¹³ and van Leusen reaction (vL-3CR),¹⁴ etc.

Figure 2: An intuitive view of MCRs vs Traditional organic reactions.

Figure 3: (1) Clinical and marketed drugs incorporating MCRs. (2) an example of a three-step synthesis of Praziquantel involving Ugi-4CR and Pictet-Spengler reactions.

MCR chemistry is gaining increasing popularity because of its application in materials science, agriculture, and medicinal chemistry. Notably, only in the recent decades has MCR chemistry

earned its place in pharmaceutical industry. Two main reasons may explain for MCRs being historically neglected in drug discovery: 1) unfamiliarity of MCR chemistry among students and researchers in both academia and industry due to little introduction of MCRs in organic textbooks. 2) MCR libraries are generally regarded as compounds with poor drug-like properties. Nevertheless, along with increasing reports in chemical literature and widely recognized advantages of MCRs such as diversity-oriented synthesis and molecular complexity, an increasing number of clinical and marketed drugs were discovered and assembled by MCRs. (shown in **Figure 3**).

2. Scope and aim of the thesis

The rapid and easy access to biologically relevant compounds by MCRs and the scaffold diversity of MCRs have driven the application of MCRs in medicinal chemistry and drug design.¹⁵⁻¹⁷ To further address and fill in several research gaps concerning the potential application of MCRs in medicinal chemistry, three projects have been carried out and one review was written which are demonstrated in four chapters.

Chapter 1

In Chapter 1, we have thoroughly explored 16 classical MCR scaffolds' chemical space by applying a new acoustic dispensing technology. The chemical space of MCRs is vast and can neither be screened nor exhaustively synthesized with reasonable efforts using conventional bench chemistry. The currently preferred path is high-throughput synthesis (HTS), which is, however, an expensive process with relatively low efficiency. Due to these limitations, the chemical space of MCRs has not yet been systematically investigated. Herein, we introduce a new acoustic dispensing technology with automated, miniaturized, and accelerated synthesis to explore 16 different scaffolds of MCRs. In the end, a total of 1536 MCRs were automatically performed in a green, fast, and cost-saving fashion. The results were analysed by Supercritical Fluid Chromatography (SFC) quality control with *in-house* written Python software, consequently generating a 1536-format heatmap. The acoustic dispensing-enabled chemistry paves the way to highly accelerated synthesis and miniaturized reaction scouting, allowing for the first time access to the enormous chemical space of MCRs by establishing a library of 1536 compounds based on 16 MCR scaffolds. Further, we conducted a chemoinformatic analysis of our library and compared the properties with the Drugbank approved drugs to investigate its physiochemical and biopharmaceutical diversity.

Chapter 2

At the end of 2019, an unknown Infectious pneumonia hit the whole world. The scientists quickly found the virus that caused this pneumonia, and shared the genome sequence with the global scientists. The World Health Organisation (WHO) named it SARS-CoV-2 to distinguish it from the coronavirus SARS-CoV found in 2003, and the pneumonia caused by SARS-CoV-2 is called COVID-19. SARS-CoV-2 spreads through air very fast. This fast-spreading and deadly coronavirus has swept all over the world. What makes the situation worse, the virus keeps evolving into more contagious variants, e.g., from earlier Alfa, Beta, and Gamma variants to the current dominant Delta variant. The worldwide efforts by scientists, governments, companies, organizations, societies and individuals to curb this pandemic are still ongoing.

Due to the urgency of the COVID-19 pandemic and yet there is no specific medicine on the market to treat infected patients, we wrote and published a review paper, "*the Chemistry and Biology of SARS-CoV-2*" to give an overview of the current knowledge of the spread, disease course, and molecular biology of SARS-CoV-2. This paper is placed in my thesis as Chapter 2. In the paper, we give an opinion on the challenges and opportunities with COVID-19. Although development of

preventive and curative drugs for future corona outbreaks is long-term objectives, drug repurposing is likely to be the only short-term solution, and vaccination should be a middle-term aim. Our paper is focused on short-term solution, drug repurposing, for this purpose, we discussed different proteins of SARS-CoV-2, for instance, 3CLpro, PLpro, Spike glycoprotein, RdRp with their specific functions, structures and corresponding available molecule inhibitors to explore their potential as drug targets. In addition, we also investigated one of the host targets, AP2-associated protein kinase 1 (AAK1).

As exactly mentioned in our review on the middle-term aim to develop vaccines against COVID-19, even though in such a difficult time, with just one year, scientists from across the world have been working as hard as they can to save more lives and end this pandemic, and currently there are already several different vaccines being successfully rolled out in countries. Still, the degree to which these vaccines can protect us against COVID-19 remains to be seen. Also, long-term antiviral drugs must be developed in advance so that we are prepared for any future outbreak.

Chapter 3 and 4

MCR scaffolds can achieve high molecular diversity, therefore, it has great potential in developing drug inhibitors. In this thesis, I have investigated two specific MCR scaffolds, Ugi-tetrazole reaction (chapter 3) and GBB reaction (chapter 4), respectively.

Chapter 3

In this chapter, I aim to synthesize adenine mimics as bioactive compounds in a facile fashion. Kinases are attractive drug targets in several diseases. Previous research has identified a vast array of molecules that target the hinge region of ATP-binding pockets in the catalytic domain to compete with ATP. These molecule inhibitors mimic the adenine part of ATP. Therefore, adenine mimics are highly sought-after substructures. In this chapter, by application of GBB reactions, we report a one-pot, and high yielding mild synthesis of 2,3-di-substituted imidazo[1,2-a]pyrazin-8-amine derivatives as adenine mimics.

Chapter 4

1H-tetrazole moiety has gained popularity in medicinal chemistry as a bioisostere of the carboxylic acid group, not only because 1H-tetrazole moiety and carboxylic acids have a similar pKa with 4-5, but also due to the fact that 1H-tetrazole moiety has a 10-fold higher lipophilicity than carboxylic acids. In this chapter, I introduce an innovative and newly-designed 3,5-di-tert butyl 4-hydroxyl benzyl isocyanide as a convertible isocyanide in Ugi-tetrazole reactions. By following a second step of cleavage under mild condition, we have successfully obtained a diversified scaffold of 1H-tetrazoles.

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