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Substrate exploitation of multicomponent reactions toward diverse scaffolds and applications in medicinal chemistry

Li, Jingyao

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Substrate Exploitation of
Multicomponent Reactions
Toward Diverse Scaffolds
and Applications in Medicinal Chemistry

Jingyao Li

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Substrate Exploitation of
Multicomponent Reactions
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and Applications in Medicinal Chemistry

PhD thesis

to obtain the degree of PhD at the
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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 12 January 2021 at 11.00 hours

by

Jingyao Li

born on 05 January 1993
in Shandong, China

SUPERVISORS

Prof. A.S.S. Dömling

Prof. T.A. Holak

ASSESSMENT COMMITTEE

Prof. F.J. Dekker

Prof. P.H. Elsinga

Prof. T.J.J. Müller

TO

MY FAMILY AND FRIENDS

WHO BRING ALL THE PLEASANT MOMENTS TO MY LIFE

PARANYMPHS

Zefeng Wang

Mojgan Hadian

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Aim and Scope of the Thesis

AIM AND SCOPE

Multicomponent reactions (MCRs) are reactions which involve three and more starting materials. In this one-pot reaction, a single complex is synthesized, retaining the majority of the atoms of the starting material¹. MCRs are perfect tools for enlarging scaffold diversity and providing easy access to a number of complicated compounds with the very straightforward protocol. Recently, owing to the properties of easy accessibility, efficiency, and capability of multi-substitution, MCR has revealed to have broad acceptance in general organic and medicinal chemistry as well.

Figure 1. Representative multicomponent reactions

Isocyanide-based multicomponent reaction (IMCR), in which an isocyanide reagent is incorporated, is one of the most well-known and extensively-developed MCR². Additionally, a majority of celebrated name reactions are IMCRs, such as Ugi reaction³, Passerini reaction^{4,5}, and GBB reaction⁶⁻⁸ (**Figure 1**). However, the limited commercial availability, instability, and notorious stench of isocyanides result in unpleasant utilization of this approach. One of the solutions to eliminate these drawbacks is the use of so-called convertible isocyanides, which can be easily transformed into other ordinary functional groups such as acids, esters or amides. In **chapter 1**, the use of 2-nitrobenzyl isocyanide as a convertible isocyanide in multicomponent reactions is reported. This isocyanide is defined as a truly universal convertible isocyanide, owing to its applicability in both

Ugi-four-component reactions and Ugi-tetrazole reactions. In addition, this isocyanide could be cleaved in both acidic and basic conditions as well.

The strategy of using multifunctional building blocks as starting materials in MCRs are extensively applied to enlarge the diversity of the MCR products or synthesize specific molecules for particular applications, for instance, medicinal purpose. Among all the components, isocyanides could only afford limited scaffold diversity owing to their unstable properties and scant commercial availability. Besides isocyanides, aldehyde components are generally necessary for the majority of MCRs as well. The modification of commercially available aldehydes to access bi- or multifunctional building blocks, followed by incorporating them in MCRs in the next step, is a common strategy to achieve target multifunctional complex. In **chapter 2**, a series of tetrazole containing aldehydes were synthesized as building blocks to provide tetrazole scaffolds in the corresponding MCR products. In this chapter, the synthesis of modified tetrazole containing aldehydes is conducted by the MCR process and Swern oxidation. This tetrazole containing aldehyde was applicable in both Ugi-four-component, Ugi-tetrazole, and Passerini reactions.

Although MCRs stands out as a mighty approach to provide serviceable compounds, most of the corresponding products are linear constructions, which lack drug-like physicochemical properties. Post-cyclization of the MCR products could change their properties dramatically leading to beneficial performance, such as increasing permeability or stability to metabolism, and rigidify and generate a conformation similar to the receptor-bound structure. Particularly, owing to the enormous diversity of MCR products, post-MCR cyclization could access the conformation of numerous highly functionalized heterocyclic compounds. In **chapter 3**, a two-step approach, which involves a multicomponent reaction followed by cyclization, is reported to achieve the transition from basic moieties to charge neutral heterocyclic derivatives. A series of multi-substituted oxazolidinones, oxazinanones, oxazepanones as well as their thio- and sulfur-derivatives are synthesized from readily available building blocks with mild conditions and high yields.

The acid component is one of the most essential components in the Passerini reaction. Carboxylic acids, as the primary, most studied, and utilized acid, limit the scaffold diversity of the Passerini products. In recent decades, several alternatives for carboxylic acids have been discovered and applied to the Passerini reaction. However, all of the known acid components are OH-based acids which lead to a C-O bond in the product.

In **chapter 4**, a unique methodology, by replacing the OH-based acid component with NH-based acids in Passerini reactions, is reported. Phthalimide and its derivatives are the acidic donors by the presence of N-formylformamide. The substrate scope reveals an excellent tolerance of this approach. Further cleavages of phthalimide leading to β -amidine alcohols and β -amide alcohols are discussed as well.

The last part of the thesis is focusing on the combination of MCRs and medicinal chemistry. Medicinal chemistry is one of the fundamental roles of the drug discovery process. In the past few decades, high-throughput screening (HTS)⁹ which discovers highly active lead compounds by screening a large amount of high-quality molecules, and fragment-based drug discovery (FBDD)¹⁰⁻¹³ which transfers the fragment hit to higher affinity lead by the optimization and connection of the known fragments, are the two main research protocols to find drug-like molecules. Even so, owing to the large flat and hydrophobic protein-protein interaction surfaces, several proteins are still difficult to target by an only single small molecule, and therefore, are called “undruggable” targets. In terms of that, macrocycles, peptides, proteolysis targeting chimeras (PROTACs) and several other approaches are developed to enriched the toolbox of medicinal chemistry. In **chapter 5**, a review, illustrating the benefits, classification, and recent researches on PROTACs is presented. Co-crystal structures, computational tools, the kinetics of PROTACs, and specific cases including homo-PROTACs, Tau-PROTACs and PROTACs in clinical trials, are explained as well.

In **chapter 6**, a series of small molecules targeting interleukine-17 cytokine (IL-17) are designed and synthesized utilizing MCR methodology. 12 initial hits were identified from a primary ligand series of 40 members and 4 displayed good MST binding curves on the nM scale. Docking analysis of the potent compound is also displayed in this chapter.

REFERENCES

- [1] Zarganes-Tzitzikas, T., Chandgude, A. L., & Dömling, A. (2015). *The Chemical Record*, 15(5), 981-996.
- [2] Rudick, J. G., Shaabani, S., & Dömling, A. (2020). *Frontiers in Chemistry*, 7, 918.
- [3] Ugi, I., & Steinbrückner, C. (1960). *Angewandte Chemie International Edition*, 72 (7-8), 267-268.
- [4] Passerini, M. (1921). Isonitriles. II. *Gazz. Chim. Ital*, 51, 181-189.
- [5] Chandgude, A. L., & Dömling, A. (2016). *Green Chemistry*, 18(13), 3718-3721.
- [6] Bienayme, H., & Bouzid, K. (1998). *Angewandte Chemie International Edition*, 37(16), 2234-2237.
- [7] Blackburn, C. (1998). *Tetrahedron letters*, 39(31), 5469-5472.
- [8] Groebke, K., Weber, L., & Mehlin, F. (1998). *Synlett*, 1998(06), 661-663.
- [9] Hajare, A. A., Salunkhe, S. S., Mali, S. S., Gorde, S. S., Nadaf, S. J., & Pishawikar, S. A. (2013). *Am. J. PharmTech. Res*, 4, 112-129.
- [10] Murray, C. W., & Rees, D. C. (2009). *Nature chemistry*, 1(3), 187-192.
- [11] Chessari, G., & Woodhead, A. J. (2009). *Drug discovery today*, 14(13-14), 668-675.
- [12] Mashalidis, E. H., Ślędź, P., Lang, S., & Abell, C. (2013). *Nature protocols*, 8(11), 2309-2324.
- [13] Scott, D. E., Coyne, A. G., Hudson, S. A., & Abell, C. (2012). *Biochemistry*, 51(25), 4990-5003.