Chapter 1

Introduction

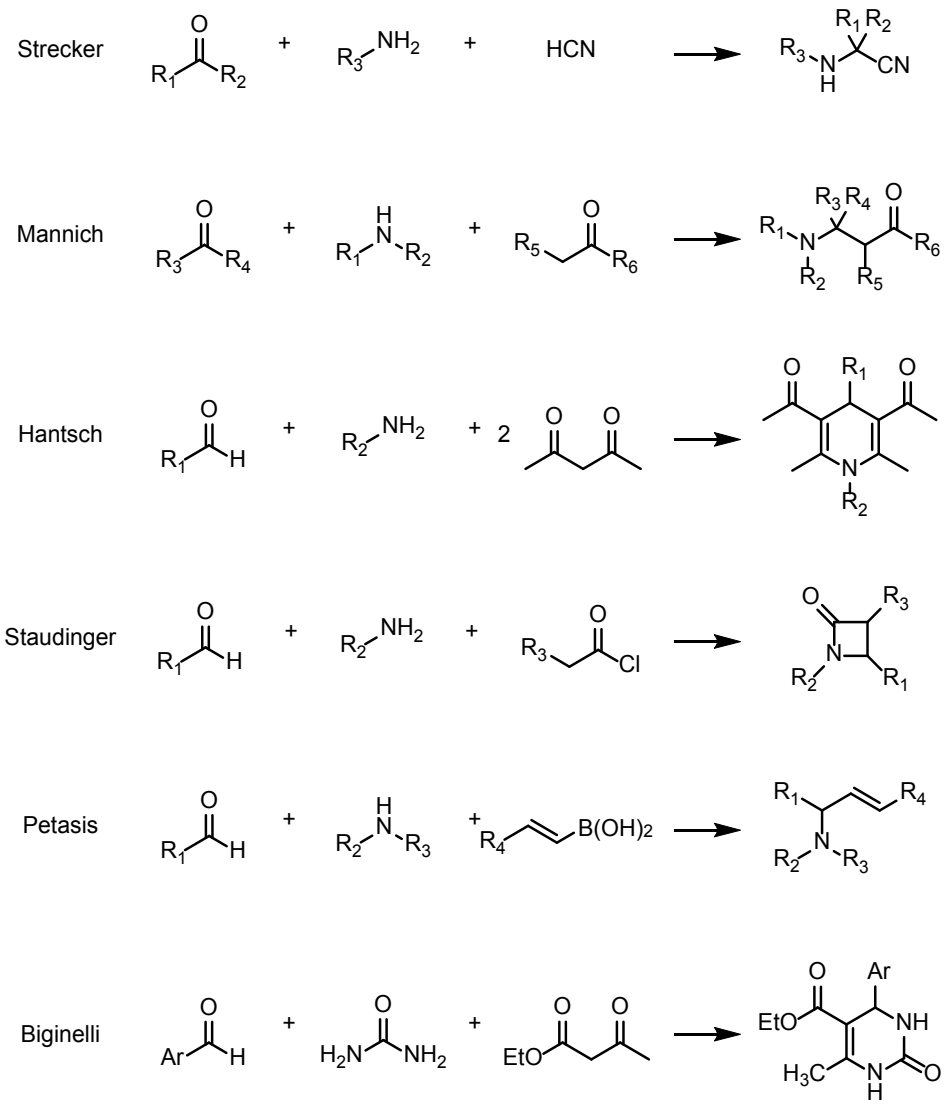
MCR introduction, Perspective and Outline

Multicomponent reactions

Multicomponent reactions (MCRs) are a special class of chemical transformations, which produce complex scaffolds in a single step by employing three or more starting materials, in which most of the atoms are present in the final product.[1] This type of chemistry can be classified as a domino reaction. Similar to polymer chemistry, MCRs proceed through a cascade of intermediate reactions, however, yielding a complex but small molecule. The first example of a MCR reaction is the Strecker amino acid synthesis, developed almost 170 years ago in 1850. The Strecker reaction is a 3-component reaction (3-CR) between an aldehyde or ketone, ammonia and potassium cyanide and yields an α-aminonitrile, subsequent hydrolysis gives access to synthetic α-amino acids (Scheme 1).[2] The high atom economy, efficiency, convergent nature and very high bond forming index of MCR reactions make this class extremely useful for drug exploration.[3]

Scheme 1. The Strecker amino acid synthesis.

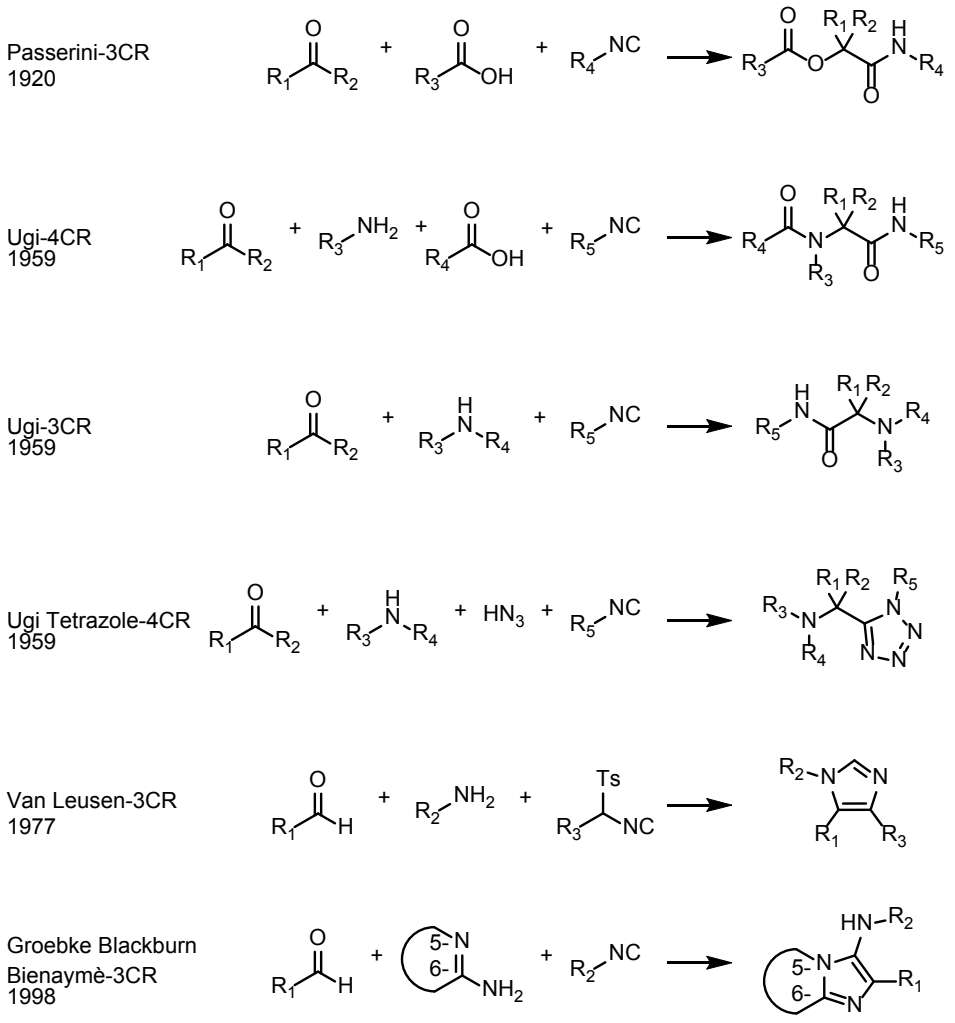
MCRs are often considered to be complex, because the formation of the final products proceed via a number of intermediate steps. In order to understand the complex nature of MCRs, a breakdown of the reaction into intermediate steps could aid in comprehension of the underlying mechanism. Difference in reactivity of each of the individual components is the driving force behind selective reactions, resulting in a predefined order in which each component will react. The most common studied and therefore well-developed early type of MCRs evolve around the reactivity of imine groups, usually obtained through reacting carbonyl compounds with amines. The resulting imines or Schiff bases are electrophiles and can react via electrophilic addition to for example α-methylene carbonyls in the Mannich 3-CR, to β-ketoesters in the Biginelli 3-CR, to boronates (from boronic acids) in the Petasis 3-CR and many other reactions, described in scheme 2.[4-8] The formation of the Schiff base is performed in the presence of the third component, the electrophile, in a one-pot fashion, which in practice comes down to adding all the reactants together in a suitable solvent and stir the multicomponent reaction, often under ambient conditions. The selective order generally allows for a clean reaction with little byproducts and high conversion towards a single product.



Scheme 2. Overview of the most common MCR 3-CR of amines, carbonyl compounds and nucleophiles.

In 1920, Passerini discovered the first isocyanide based MCR reaction (IMCR) and involves an isocyanide, an oxo component and a nucleophile.[9] The carbene like properties of the isocyanide group allow for some very interesting transformations, as this functional group can behave as nucleophile and then as electrophile at the same atom, resulting to the so-called α-adduct.[10] The IMCR subclass has complemented the field of MCR due to its versatile reactivity, variability and scaffolds and is currently the most widely used/applied type of MCR. Nevertheless it took roughly 40 years until more developments were made in this field, which can be attributed to the obnoxious smell of the isocyanides. The smell is

considered unpleasant, even in such a way that the US government investigated the use of isocyanides as non-lethal chemical weapons.[11] The considered 'constraint' is limited to the liquid isocyanides, as higher molecular weight isocyanides are often solid and have little to no smell. Regardless of this fact, the result is poor commercial availability, which is not necessarily problematic as isocyanides can readily be prepared from primary amines or aldehydes in one or two steps.[12-14]



Scheme 3. Some of the well-known IMCRs

A considerable amount of pioneering work with IMCRs was performed by Ugi in the late 1950s. The Ugi-4CR is defined as the reaction of an amine with an aldehyde or ketone, an isocyanide and a carboxylic acid (Scheme 3).[15] The limits of IMCRs were explored by Ivar Ugi and since the introduction of the Ugi 4-CR, many new IMCR reactions have found their way to the nowadays well accept-

ed field of MCR chemistry. The work described in this thesis is based on drug design, utilizing the Ugi reaction and several variations of the Ugi reaction to synthesize drug like compounds and medical probes.

Drug discovery and MCR.

Identification of biochemical pathways related to a disease and the intervention of potential targets is the first step in the discovery of new medicines. Luckily more and more molecular targets are being identified, allowing for target validation and development of small molecules. High throughput screening (HTS) is a common method in the pharmaceutical industry to discover new leads for molecular targets. Such screenings, however, are expensive, up to $10 million per screening, show low efficiency and have limited success rate. Therefore, academia aim at development of smarter design and selection criteria to enable screening of smaller focused compound collections to provide higher success rates and lower costs. Effective selection criteria can be obtained by analysis of the binding site in a co-crystal structure to identify a pharmacophore. This pharmacophore is used subsequently to design potential binders for screening. This approach relies heavily on the medicinal chemists knowledge of molecular interactions, more specifically the attractive interactions between two partner molecules in biological systems. Parallel synthesis is then applied to synthesize libraries of compounds for hit to lead optimization.

In drug discovery, synthesis of compound libraries is necessary to optimize a lead. Determination of the biological activity on a specified target can identify which moieties are important and which need optimizing for increasing its activity, selectivity often via a structure activity analysis. Compiling a library of 20 compounds, where stepwise the individual parts of the target molecule have to be chemically connected, the number of reaction and purification steps quickly exceeds 100. This is first of all time consuming and second very resource demanding. Looking at the MCR approach, the philosophy is to obtain products in just a single step, where the product contains all the desired properties. With this in mind, the MCR methodology deems to be a competitive alternative to ordinary parallel multistep synthesis.

To date there are many marketed drugs that can be prepared through a MCR (Figure 1). The local anesthetic lidocaine (Xylocaine®) is for example prepared by a Ugi-3CR in a single step by reacting formaldehyde, diethyl amine and 2,6-dimethyl-phenylisocyanide.[16] This example is an early adaption of IMCR in commercial drug production. Other examples of MCR directed/assisted drug synthesis are shown in figure 1.

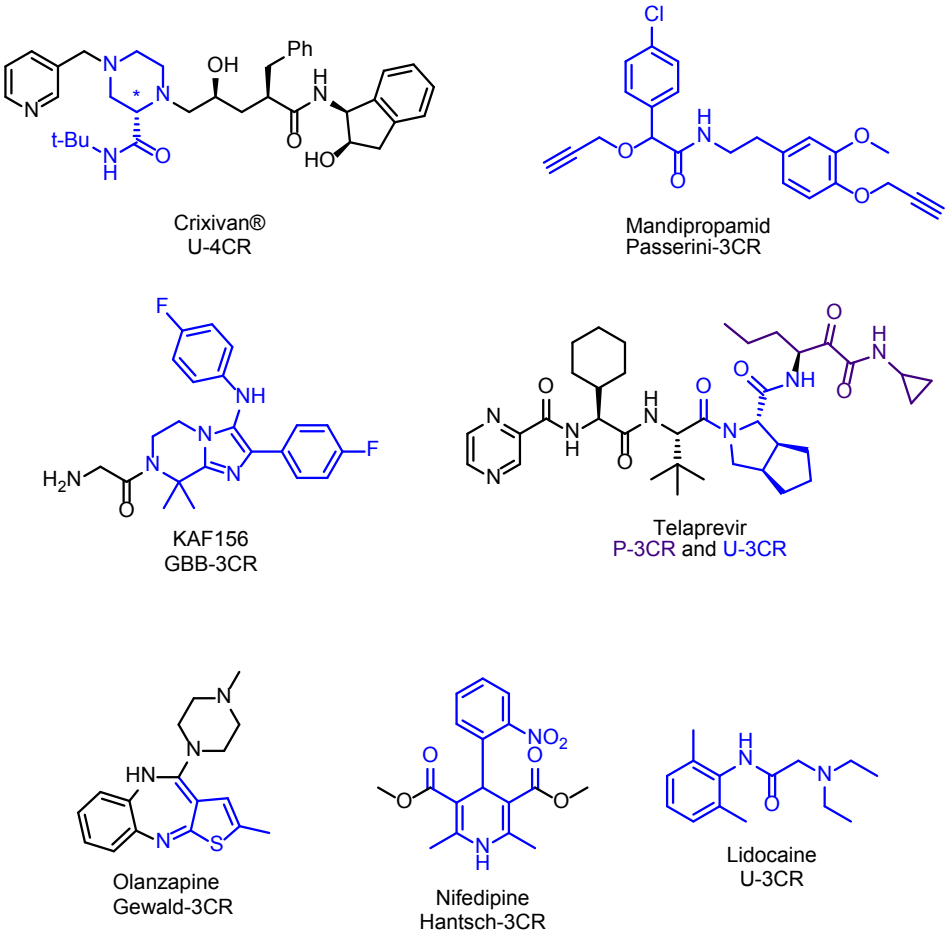


Figure 1. Various drug examples produced through the MCR methodology. The blue and purple color assigns the part of the molecule constructed with MCR chemistry.

Aim of the research described in this thesis

Drug design aims at the development of druglike compounds and probes which act as agonists or antagonists in biological processes. A pharmacophore model and complementing MCR methodologies can prove to be an invaluable asset in drug design. With the current state of the art in MCR chemistry, design and synthesis of vast libraries of compounds, targeting various identified biological targets is made possible. In turn, the MCR toolbox used for drug discovery is continuously expanded by the development of new scaffolds, simplification of existing chemistry with broader scope, better toleration towards sensitive functional groups and enables targeting of otherwise difficult to target binding sites such as flat surfaces. Noteworthy is the recent discovery of the catalytic enantioselective U-4CR, which proves that the rational design of MCR's has never been so important and widely applicable in drug discovery.[17-18] Development of new

probes and scaffolds using MCR chemistry and its application for the discovery of new drug like compounds is the main theme in this thesis.

Thesis Outline

In Chapter 2 selective inhibitors of Mdm4 are presented. The Mdm4 protein is a closely related protein to Mdm2 and it also binds to the same epitope of p53. Both Mdm2 and Mdm4 (MdmX) were characterized as druggable by analysis of the Mdm2-p53 co-crystal structure and are considered as an important oncology target.[19] All current known binders are highly specific for Mdm2. In a combinatorial synthetic approach, the U-4CR was applied to generate a library of peptidomimetic small molecules as potential Mdm2/4 binders. A selective Mdm4 binder was identified and subjected to subsequent hit-to-lead optimization.

Chapter 3 describes the improvements made in the preexisting U-4CR assisted synthesis of the anti-helminthic drug praziquantel. There are multiple methods to prepare praziquantel on industrial scale. The U-4CR method was developed in 2009, but was not adopted for industrial production up to date, likely due to the requirement of isocyanide chemistry. With the introduction of the *in situ* isocyanide methodology by Neochoritis et al., this constraint could be overcome, which was demonstrated in a preparation procedure, published in Organic Syntheses.[20-21]

Chapter 4 presents the post-MCR modification of ester containing UT-4CR products to obtain *N*-unsubstituted γ-and δ-lactams. The well-known UT-4CR allows for the introduction of the tetrazole moiety, which serves as a bio-isostere for carboxylic acids. In the experimental design tritylamine was used as a convertible amine component and an ester containing aldehyde as bi-functional building block, containing either 2 or 3 methylene groups. Removal of the tritylgroup results in compounds with both an amine and ester, which readily undergo aminolysis upon basic treatment, , resulting in intramolecular cyclization, thus formation of lactams. The peptidomimetic nature of the resulting tetrazolo-lactam motif can be applied as potent drugs attributed to the peptidomimetic proline cis-amide functionality.

In chapter 5 a new generation of MRI contrast agents was introduced on the basis of the known metal chelator tetraxatan. In the current application of gadoteric acid, MRI contrast enhancement is achieved by the reduction of T1 relaxation times, more specifically by fast water exchange on the 9th coordination site of the gadolinium complex. Although the gadoteric acid complex is very stable with a stability constant (log K_{eq}) of 25.8, swift clearance from the body is important to prevent severe nephrotoxic adverse effects due to release of gadolinium ions by metabolic degradation of the gadolinium complex. Patients with renal failure are therefore susceptible to these side effects. Replacement of the appendant carboxylate arms with tetrazole bio-isosteres would tackle this unfavored leaching and its subsequent toxicity. The tetrazole is introduced in a two-step synthetic strategy using the UT-4CR and a deprotection step. The stability constant of the

complex was determined and the contract enhancing abilities were tested by *in vivo* experiments.

Chapter 6 highlights the developments of the GBB-3CR since its discovery in 1998. During the course of two decades the GBB-3CR reaction has emerged as a very important MCR, resulting in over a hundred patents and a great number of publications in various fields of interest. To celebrate this event, we would like to present an overview of the developments in the GBB-3CR, including an analysis of each of the three starting material classes, solvents and catalysts described. Additionally, a list of patents and their applications and a more in-depth summary of the biological targets that were addressed, including structural biology analysis, is given.

Chapter 7 focusses on the application of bis-amidines in the GBB-3CR. With multiple possible regioisomers, this amidine component could yield various unprecedented heterocyclic scaffolds. Pyrazine-2,3-diamine, however, is the only amidine affording products that did not show quick degradation at room temperature when exposed to air. The scaffold from this amidine, 2,3-di-substituted imidazo[1,2-a]pyrazin-8-amines represent a similar shape to adenine and thus could be applied for development of novel kinase inhibitors, mimicking the adenosine part in the ATP binding site. To strengthen our hypothesis we performed comprehensive docking studies with multiple potential targets where our imidazo[1,2-a]pyrazin-8-amine scaffold can bind.

References

1 I. Ugi, A. Dömling, W. Hörl, *Endeavour* **1994**, *18*, 115-122.

2 A. Strecker, *Justus Liebigs Annalen der Chemie* **1850**, *75*, 27-45.

3 L. F. Tietze, *Chemical Reviews* **1996**, *96*, 115-136.

4 N. A. Petasis, I. Akritopoulou, *Tetrahedron Letters* **1993**, *34*, 583-586.

5 A. Hantzsch, *Berichte der deutschen chemischen Gesellschaft* **1881**, *14*, 1637-1638.

6 P. Biginelli, *Berichte der deutschen chemischen Gesellschaft* **1891**, *24*, 2962-2967.

7 C. Mannich, W. Krösche, *Archiv der Pharmazie* **1912**, *250*, 647-667.

8 H. Staudinger, J. Meyer, *Helvetica Chimica Acta* **1919**, *2*, 635-646.

9 M. Passerini, L. Simone, *Gazz. Chim. Ital.* **1921**, *51*, 126-129.

10 A. Dömling, *Chemical Reviews* **2006**, *106*, 17-89.

11 M. C. Pirrung, S. Ghorai, *Journal of the American Chemical Society* **2006**, *128*, 11772-11773.

12 A. W. Hofmann, *Ann. Chem.* **1868**, *146*, 107.

13 I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, K. Offermann, *Angewandte Chemie International Edition in English* **1965**, *4*, 472-484.

14 C. G. Neochoritis, T. Zarganes-Tzitzikas, S. Stotani, A. Domling, E. Herdtweck, K. Khoury, A. Domling, *Acs Comb Sci* **2015**, *17*, 493-499.

15 I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner, *Angew Chem Int Edit* **1959**, *71*, 386-386.

16 A. Dömling, W. Wang, K. Wang, *Chemical Reviews* **2012**, *112*, 3083-3135.

17 S. Shaabani, A. Dömling, *Angewandte Chemie International Edition* **2018**, *57*, 16266-16268.

18 J. Zhang, P. Yu, S.-Y. Li, H. Sun, S.-H. Xiang, J. Wang, K. N. Houk, B. Tan, *Science* **2018**, *361*, eaas8707.

19 C. F. Cheok, C. S. Verma, J. Baselga, D. P. Lane, *Nature Reviews Clinical Oncology* **2010**, *8*, 25.

20 A. Boltjes, H. X. Liu, H. P. Liu, A. Dömling, *Org Synth* **2017**, *94*, 54-65.

21 C. G. Neochoritis, S. Stotani, B. Mishra, A. Dömling, *Org Lett* **2015**, *17*, 2002-2005.