Chapter 1
Introduction and Scope of the Thesis

Part of this thesis was published in:

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Chem. Record, 2015, 15, 981-996.
Abstract

Multicomponent reactions (MCRs), which are located between 1- and 2-component and polymerization reactions, provide a number of valuable conceptual and synthetic advantages over stepwise sequential approaches towards complex and valuable molecules. To address current limitations in number of MCR and resulting scaffolds the concept of union of MCRs was introduced two decades ago by Dömling and Ugi and is rapidly advancing apparent by several recently published work. MCR technology is now widely recognized for its impact on drug discovery projects and is strongly endorsed by industry in addition to academia. Clearly, novel scaffolds accessible in few steps including MCR will further enhance the field of applications. Additionally, broad expansion of MCR applications in fields such as imaging, material science, medical devices, agriculture, or futuristic applications in stem cell therapy and theragnostics or solar energy and superconductivity are predicted.
1. Multicomponent reactions

Reactions in organic chemistry can be classified according to the number of participating starting materials. There are one-component reactions, two-component reactions, multi-component reactions (MCR) and polymerizations (Figure 1). An example of a one-component reaction is the classical Claisen rearrangement.[1] One-component reactions involve one starting material and if necessary a catalyst and yield one or two products. In a two-component reaction two starting materials are combined into one product.[2] Reactions involving three and more starting materials are known as MCRs. Prototypical examples are the Mannich reaction and the Ugi reaction.[3] According to a generally accepted definition “MCRs are reactions with three and more starting materials where the majority of the atoms of the starting materials are incorporated into the product.”[4] An important subgroup of MCRs are so called unions of MCRs where a MCR is combined with a secondary reaction e.g. MCR in the same flask, even enhancing the diversity and potential usefulness of the reactions.[5] MCRs bridge one- and two-component reactions with polymerizations, where one or several starting materials combine repetitively to form a polymer of varying length. The majority of organic textbook chemistry consist of one- and two-component reactions and polymerizations. Surprisingly, the wealth of MCRs is not adequately represented in modern teaching of organic chemistry despite the many contemporary and important applications in chemistry. This small review gives a personalized glimpse of modern MCR with a focus on higher MCRs and some intriguing recent applications underscoring the immense potential of navigating the MCR space.[6]

![Figure 1. Schematic presentation of different reactions based on number of starting materials.](image-url)
1.1 Classes of MCRs

Many of the classical MCRs are named reactions and all have proven their wide applicability in chemistry with multiple commercial products on the market (Table 1).

TaniaPhos® for example is a commercial application of the Mannich-3CR reaction. It is a chiral ligand for a catalyst used in the asymmetric hydrogenations and can be synthesized from the (R)-Ugi amine in two steps.[7] The (R)-Ugi amine can be synthesized via a Mannich reaction between ferrocene, dimethyl amine and acetaldehyde (Table 1, entry 1).[8]

α,α-Disubstituted amino acids have attracted increasing attention as unnatural amino acid analogues due to their applications in peptide-mimetics and in the de novo design of proteins. The Strecker-3CR was used for the synthesis of ((S)-N-ethoxycarbonyl-α-methylvaline) where 3-methyl-2-butanone and NaCN were treated with NH₄Cl in the presence of MgSO₄ in NH₃/MeOH at 30°C. Further steps involve the formation of the tartrate salt and the preparation of (S)-2-ethoxycarbonylamino-2,3-dimethylbutyric acid dicyclohexylamine salt (Table 1, entry 2).[9]

The Passerini reaction affords the fungicidal compound mandipropamid in just 2 steps. The first step involves the Passerini reaction of an in situ synthesized isocyanide, an aldehyde and a carboxylic acid to form the α-acyloxycarboxamide. The second step involves the alkylation with propargyl bromide to yield Micora (Mandipropamid®) (Table 1, entry 3).[10]

Lidocaine (Xylocain®) is a very popular local anesthetic. Its synthesis can be accomplished by the Ugi-3CR of formaldehyde, diethyl amine and 2,6-dimethyl-phenylisocyanide. This synthesis comprises an early application of IMCR in production of commercial drugs (Table 1, entry 4).[11]

Prostaglandins have antioxidant and ionophoric activities. The Pauson-Khand 3CR is used as the key step for the regio- and stereoselective synthesis of prostaglandin B₁. The Pauson-Khand reaction involved a silyl- protected propargyl acetylene, ethylene and octacarbonyl dicobalt as a carbon monoxide source to afford the 3-tert-butyldimethylsilyloxymethyl-2-substituted-cyclopent-2-en-1-one at room temperature in good yield (Table 1, entry 5).[12]

p38 MAP kinase is involved in the inflammatory pathway and inhibitors of the p38 MAP kinase are widely investigated as potential drugs. 1,4,5-trisubstituted imidazoles were synthesized as p38 MAP kinase inhibitors using the van Leussen-3CR of an α-substituted tosylmethyl isocyanide, a primary amine and an aldehyde in the presence of a base. The reaction has been described on a 500 kg batch scale to provide enough material for phase III clinical trials (Table 1, entry 6).[13]

The Gewald-3CR generally affords bioisosteres of anthranilic acids. 2-Amino-3-carbonyl thiophene is the starting material for the synthesis of several drugs e.g. Olanzapine (Zyprexa®), an atypical antipsychotic drug. This thiophene-phenol bioisostere can be easily prepared by the Gewald-3CR using cyanoacetamides, a-methylene active aldehydes or ketones, and sulfur (Table 1, entry 7).[14]

The Hantzsch-3CR was used for the synthesis of the calcium channel blocker Nifedipine (Procardia®). Synthesis of the dihydropyridine derivative involves condensation of a 2-nitro benzaldehyde with 2 equivalents of methyl acetoacetate and ammonia (Table 1, entry 8).[15]
Ezetimibe (Zetia®) is a lipid-lowering compound which selectively inhibits the intestinal absorption of cholesterol. It is synthesised by using the Staudinger-3CR as a key reaction. The imine formed from p-fluoroaniline and benzylxybenzaldehyde was treated with methyl 5-chloro-5-oxopentanoate in the presence of tributylamine and toluene to form the β-lactam ring. This reaction involves the formation of an intermediate ketene which undergoes a [2+2] cycloaddition reaction with the imine to form regioselectively the β-lactam ring giving the trans isomer as the major product (Table 1, entry 9).[16]

### Table 1

<table>
<thead>
<tr>
<th>Name Reaction</th>
<th>Reaction</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mannich 3CR[17]</td>
<td><img src="image1" alt="Mannich reaction" /></td>
<td><img src="image2" alt="Mannich product" /></td>
</tr>
<tr>
<td>2 Strecker 3CR[9]</td>
<td><img src="image3" alt="Strecker reaction" /></td>
<td><img src="image4" alt="Strecker product" /></td>
</tr>
<tr>
<td>3 Passerini 3CR[10]</td>
<td><img src="image5" alt="Passerini reaction" /></td>
<td><img src="image6" alt="Passerini product" /></td>
</tr>
<tr>
<td>4 Ugi 3CR[11]</td>
<td><img src="image7" alt="Ugi reaction" /></td>
<td><img src="image8" alt="Ugi product" /></td>
</tr>
<tr>
<td>5 Pauson-Khand 3CR[12]</td>
<td><img src="image9" alt="Pauson-Khand reaction" /></td>
<td><img src="image10" alt="Pauson-Khand product" /></td>
</tr>
<tr>
<td>6 Van Leusen 3CR[13]</td>
<td><img src="image11" alt="Van Leusen reaction" /></td>
<td><img src="image12" alt="Van Leusen product" /></td>
</tr>
</tbody>
</table>
2. Multicomponent Reaction and Subsequent Transformations

Many MCRs have been described in the past one and a half century and recently many fundamental advances in finding new MCRs have been made. A strategy to enhance the size and diversity of current MCR chemical space is the concept of combining a MCR and a subsequent secondary reaction, examples involve postcondensations or the Ugi-deprotection-cyclization (UDC) strategy. Herein, bifunctional orthogonally protected starting materials are used and cyclizations can take place in a secondary step upon deprotection of the orthogonal functional groups. Many different scaffolds have been recently described using this strategy. A recent example of such a postcondensation strategy is shown in Scheme 1. It is based on a recently discovered variation of the Ugi reaction of α-amino acids (1), oxo components (2), and isocyanides (3), now including primary and secondary amines (4) and can afford highly substituted isoindolones (5), pyrolidindiones (6), di (7), tri (8), and tetra (9)-cyclic scaffolds reminding to alkaloids, quinocarcin and notoamide B. The MCR is stereoselective as the chiral α-amino acid can be used under stereoretention (Scheme 1).
3. Union of Multicomponent Reactions

The term "union of MCR" was coined by Dömling and Ugi in the publication "The seven component reaction" performing the one-pot combination of a modified Asinger-4CR\cite{19} and the Ugi-4CR (Scheme 2).\cite{20}

![Scheme 2. "The seven component reaction" (Asinger-Ugi-7CR).](image)

The union of MCRs is a strategy for the rational design of novel MCRs combining two (or more) different types of MCRs in a one-pot process. The presence of orthogonal reactive groups in the product of the primary MCR, which is either formed during the primary MCR or present in one of the inputs, allows the union with the secondary MCR.\cite{21} The union of MCRs is an intriguing concept to increase even more the complexity and efficiency and provide new scaffold types. Several new examples have been elaborated recently.
Besides various 5- and 6-CRs, the first example of an eight component reaction, currently the highest number of different compounds used in a one-pot procedure, was published by the Orru group in 2009. This 8-CR unifies three different MCRs, with nine new bonds formed, creating highly complex and structurally versatile drug-like compounds with eleven points of diversity (Scheme 3).

In the first of the three MCRs imidazoline intermediate (19) was formed through a three component reaction utilizing the sodium salt of glycine (18), which provided the carboxylic acid handle for the latter Ugi-4CR. The N-(cyanomethyl)amide-intermediate (23) was accessed via a second three component reaction. Here the authors made use of the difference in reactivity of the two isocyanides in 2,5-diisocyanopentanamide (20) to produce compound (23) in good yield, carrying an isocyanide handle for the subsequent MCR. Multicomponent products (19) and (23) could be formed either in separate reaction vessels (sequential manner) or in a single reaction vessel. In the case of a one-pot procedure, first the formation of (19) was established, whereafter the second set of starting materials was added to give intermediate (23). Finally, the reaction mixture was neutralised to activate the carboxylic acid, and a final set of reagents (i.e. aldehyde and amine) was added, generating the final product (24) in an impressive 24% yield (85% yield per bond forming step).

Scheme 3. Combination of three multicomponent reactions leading to an 8CR.

One of the first MCRs combining more than four different components making use of an orthogonal functionality was reported by Bienayme in 1998. In a modified Bredereck reaction a secondary amine morpholine (25), N-formylimidazole diethyl acetal (26) and methyl isocyanooacetate (27) were
reacted to produce the intermediate isocyanide (28) exclusively as the (z)-stereoisomer (Scheme 4). After the subsequent addition of a carboxylic acid (e.g. benzoic acid) and an aldehyde (e.g. cyclohexane carboxyaldehyde) a Passerini-3CR takes place, resulting in the formation of product (29) which is a racemic mixture in a fair yield (30%), accounting for an 80% yield per bond forming step (five new bonds).

Scheme 4. Combination of a Bredereck - Passerini-3CR.

The combination of a Petasis-3CR[26] and an Ugi-4CR (Pt-U-6CR) was recently described by Portlock and co-workers (Scheme 5).[27] With six new bonds formed and the introduction of six points of diversity, dipeptide amides (34) could be obtained as 1:1 mixtures of racemic diastereomers with yields ranging from 80–95% per bond forming step. As shown in Scheme 5 amino acid (33), formed by the Petasis-3CR, serves as the carboxylic acid component in the following Ugi-4CR. Despite the readily achievable high structural diversity, a solvent change is required for the second MCR to proceed, hence limiting the applicability of this approach in the rapid preparation of structurally diverse, drug-like compound libraries. To overcome this drawback, the same authors showed that this reaction sequence could be translated to a solid support, thus allowing the exploration of a larger chemical space, though at the cost of one point of diversity as a result of the linkage to a resin.[28]

Scheme 5. Combination of Petasis-3CR and Ugi-4CR.

Another interesting example of creating complexity and structural diversity by the combination of two successive MCRs was published recently by Al-Tel and co-workers.[29] By combining the Groebke-Bienaymé-Blackburn reaction[30] an acid-mediated isocyanide addition to 2-iminopyridines yielding fused pyridine-imidazoles (38) with a Passerini-3CR or an Ugi-4CR, a 5- or 6CR was developed, generating structurally diverse (up to ten points of diversity), highly substituted, drug-like heterocyclic compounds (39) and (40) respectively in an efficient manner (>90% yield per bond forming step). The formylbenzoic acids (36) react with 2-aminopyridine (35) and isocyanides (37) selectively on the aldehyde group and the benzoic acid moiety is left intact. Thus the orthogonal reactivity of the carboxylic acid in the Groebke-Bienayme-Blackburn reaction was used as a functional handle in the subsequent MCRs i.e. Ugi or Passerini (Scheme 6).
4. Recent MCR Applications

Several interesting recent applications of MCR chemistry going beyond simple combinatorial applications are discussed in the following.

Large scale pharmacophore based virtual screening of MCR libraries: ANCHOR.QUERY

Two decades ago, MCR chemistry was almost generally neglected in pharmaceutical and agrochemical industry. The knowledge of these reactions was often low and it was generally believed that MCR scaffolds are associated with useless drug-like properties e.g. absorption, distribution, metabolism, excretion, and toxicity (ADMET). During the times of combinatorial chemistry, however, MCR offered a major technology to produce in a reliable fashion large compound libraries to fill the screening decks. Now MCR technology is widely recognized for its impact on drug discovery projects and is strongly endorsed by industry as well as academia.[31] These examples show that pharmaceutical and agrochemical compounds with preferred ADMET properties and superior activities can be engineered based on MCR chemistry. The very high compound numbers per scaffold based on MCR may be regarded as a friend or foe. On the one hand, it can be fortunate to have a MCR product as a medicinal chemistry starting point, since a fast and efficient SAR elaboration can be accomplished; on the other hand, the known chemical space based on MCRs is incredibly large and can neither be screened nor exhaustively synthesized with reasonable efforts. The currently preferred path to medicinal chemistry starting points in industry, the high-throughput screening (HTS), however, is an expensive process with rather low efficiency yielding hits often only in low double-digit or single-digit percentage. Modern postgenomic targets often yield zero hits. The initial hits are often ineffective to elaborate due to their complex multistep synthesis. Thus, neither the screening even
of a very small fraction of the chemical space accessible by the classical Ugi-4CR and other scaffolds, nor the synthesis is possible.

Recent advances in computational chemical space enumeration and screening, however, allow for an alternative process to efficiently foster a very large chemical space. The free web-, anchor-, and pharmacophore-based server AnchorQuery™ (anchorquery.ccbb.pitt.edu/), for example, allows for the screening of a very large virtual MCR library with over a billion members. AnchorQuery builds on the role deeply buried amino acid side chains or other anchors play in protein-protein interactions. Based on the efficient and convergent nature of MCR chemistry proposed virtual screening hits can be instantaneously synthesized and tested. The software was instrumental to the discovery of multiple potent and selective MCR-based antagonists of the protein–protein interaction between p53 and MDM2. Thus, computational approaches to screen MCR libraries will likely play a more and more important role in the early drug discovery process in the future. More and more high-resolution structural information on MCR molecules bound to biological receptors is available (Scheme 7). With the advent of structure-based design and fragment-based approaches in drug discovery, access to binding information of MCR molecules to their receptors is becoming crucial. Once the binding mode of an MCR molecule is defined, hit-to-lead transitions become more facile and time to market can be shortened and attrition rate in later clinical trials can be potentially reduced with the knowledge to engineer the physicochemical properties of the target compounds.

![Scheme 7. p53 – mdm2 inhibitors synthesized by Ugi-4CR.](image)

Active compounds were reported based on anchoring of a 6-chloro-indole moiety onto Trp23 of p53 in the p53 mdm2 interaction, designed through special computational software AnchorQuery™ and synthesized through Ugi and other multicomponent chemistry. The most potent compounds are (41) (PDB: 3TJ2), (42) (PDB: 4MDQ), and (43) (PDB: 4MDN) with IC₅₀ values of 400 nM, 1.2 μM, and 600 nM, respectively.

Compounds (41) and (42) mimic three distinct aminoacids of p53 (Phe19, Trp23, and Leu26), but compound (43) induced an additional hydrophobic pocket on the MDM2 surface and unveiled for the first time a four-point binding mode (Scheme 7).
Figure 2. The use of ANCHOR.QUERY in structure-based drug discovery. Above: a) The endogenous interaction of p53 in Mdm2 with the hot spot amino acids Phe19, Trp23 and Leu26. b) Pharmacophore model and screening of a very large virtual library of MCR products allows for the efficient discovery of novel and potent scaffolds. c) Three MCR molecules mimicking the p53 interaction with Mdm2.

Figure 3. A potent p53-Mdm2 antagonist comprising of four pharmacophore points based on the Ugi-4CR discovered with AnchorQuery™ technology (PDB ID 4MDN). The AnchorQuery™ (http://anchorquery.ccbb.pitt.edu/) derived p53-Mdm2 antagonists based on MCR chemistry. The hotspot of the protein protein interaction of p53 (green sticks) on Mdm2 (redish surface) different ligand areas important for the ligand-protein interaction are projected onto the receptor surface and presented by different colors: isocyanide blue, aldehyde red, amine green and orange. The acid component (formic) does not make major contributions but rather points into solvent.
Besides applications in structure based drug design and medicinal chemistry, MCR chemistry recently also finds application in the design and synthesis of libraries with unusual 3D and physicochemical properties for applications in high throughput screening campaigns, such as the European Lead Factory (https://www.europeanleadfactory.eu/).

**Natural Products**

The use of MCR in natural product synthesis is currently totally underinvestigated however several recent examples are discussed in the following.

While the Bucherer-Bergs and the related Strecker synthesis are well established methods for the one-pot synthesis of natural and unnatural amino acids and provide very early examples of MCR triggered natural product syntheses, the complex antibiotic penicillin was synthesized 50 years ago in a highly convergent approach by Ivar Ugi using two MCRs, the Asinger reaction and his own reaction (Scheme 8).\(^{[38]}\)

![Scheme 8. Penicillin synthesis via the union of Asinger-4CR and Ugi-4CR MCRs.](image)

Although early example of the advantageous use of MCR in the conscious total synthesis of complex natural products leads the way, its use has been neglected for decades and only recently realized by a few organic chemists.\(^{[39-44]}\)

A novel MCR approach towards Aspergillamide A (54) was described by Dömling et al. using an Ugi-4CR between N-acetylleucin (50), methylamine (51), phenylacetaldehyde (52) and E/Z-3-(2-isocyanoethen)-indole (53), the natural product was obtained in one step (Scheme 9).\(^{[45]}\)

![Scheme 9. Synthesis of Aspergillamide A via the Ugi-4CR.](image)

The natural product and proteasome inhibitor Omuralide (59) has been synthesized in a stereo controlled manner using an intramolecular U-4CR of the ketocarboxylic acid (55) as a key step (Scheme 10).\(^{[46]}\) Herein a novel convertible isocyanide, 1-isocyano-2-(2,2-dimethoxyethyl) benzene
(56) was used, which was introduced independently by two groups. The p-methoxybenzylamine (57) is used as an ammonia surrogate. The indole acyl of the intermediate (58) resulting from the convertible isocyanide can be cleaved under very mild conditions to produce the final product.

![Scheme 10](image)

**Scheme 10.** Synthesis of Omuralide using an Ugi-4CR as a first step.

**Polymers – Materials**

Another application of MCR chemistry far from being leveraged to its full extent is in materials science. Precise engineering of macromolecular architectures is of utmost importance for designing future materials. Like no other technology, MCRs can help to meet this goal. Recently, the synthesis of sequence-defined macromolecules (64) without the utilization of any protecting group using a Passerini-3CR has been described (Scheme 11).[47]

![Scheme 11](image)

**Scheme 11.** Macromolecule synthesis via the Passerini-3CR.

Another sequence-specific polymer synthesis with biological applications comprises the peptide nucleic acids (PNAs), which are metabolically stable and can recognize DNA and RNA polymers which can be accomplished by the Ugi-4CR (Scheme 12).[48]

![Scheme 12](image)

**Scheme 12.** MCR approach to PNA polymers.

Yet another application of MCRs in materials science might underscore the potential opportunities to uncover. Ugi molecule-modified stationary phases have been recently introduced to efficiently separate immunoglobulins (Igs).[49] Currently, more than 300 monoclonal antibodies (mAbs) are moving toward the market. However, the efficient and high-yielding cleaning of the raw fermentation
Introduction and Scope of the Thesis

Brew is still a holy grail in technical antibody processing. Thus, it is estimated that approximately half of the fermentation yield of mAbs is lost during purification. Ugi-modified stationary phases (70) (Scheme 13) have been found in this context to be far superior to purification protocols based on natural Ig-binding proteins, which are expensive to produce, labile, unstable, and exhibit lot-to-lot variability.

![Scheme 13. Ugi-modified stationary phase.](image)

Fluorescent pharmacophores were discovered by the Groebke-Blackburn-Bienaymè MCR (GBB-3CR) with potential applications as specific imaging probes using a droplet array technique on glass slides. Another group described the discovery of BODIPY dyes for the in vivo imaging of phagocytotic macrophages and assembled by MCRs.

**Synthesis of Macrocycles**

Macrocyclic synthetic compounds or natural products structures recently became en-vogue due to many potential advantages over small molecular weight compounds. Macrocycles can have improved binding to the receptor and even can target proteins which otherwise are difficult to handle such as protein-protein interactions due to their large and flat surface area. Moreover some macrocycles show enhanced transport properties due to their cameleon-like behavior in hydrophobic and hydrophilic environments. This behaviour can be triggered by conformational changes induced by a shift between intra- and intermolecular hydrogen bondings.

Modular MCR chemistry is very well suitable for the fast and efficient synthesis of many diverse macrocycles. Pioneers using MCR for the macrocyclization step were Failli and Immer who synthesized bioactive cyclic hexa-peptides via a Ugi MCR of N-C-terminal unprotected linear hexapeptides. Later many other groups contributed to macrocycle synthesis via MCR. A recent outstanding example consists the macrocycle synthesis of Yudin involving amphiphilic aziridinoaldehydes (71) in Ugi-type reactions (Scheme 14).

The macrocycles synthesis is diverse in terms of ring size and starting materials. An interesting application of the macrocyclization in very small volumes has been recently disclosed.
Applications in Pharmaceutical and Agrochemical Industry

Other worthwhile applications of MCRs in medicinal chemistry are in route scouting for shorter, convergent, and cheaper syntheses. An excellent showcase is the synthesis of the recently approved HCV protease inhibitor Incivek® (Telaprevir) (75). The complex compound is industrially produced using a lengthy, highly linear strategy relying on standard peptide chemistry exceeding 20 synthetic steps. Orru et al.\textsuperscript{[55a,b]} were able to reduce the length and complexity of the synthesis of Incivek® (Telaprevir) by almost half using a biotransformation and two multicomponent reactions as the key steps. (Scheme 15) Recently Riva et al. reported on a second MCR approach towards Incivek® with an enantioselective enzymatic desymmetrization approach.\textsuperscript{[55c]}
Scheme 15. MCR approach towards Incivek® (Telaprevir).

Another example is the convergent synthesis of the schistosomiasis drug Biltricide® (Praziquantel) (89) using key Ugi and Pictet-Spengler reactions (Scheme 16).[56] Clearly, more synthetic targets are out there, which can be potentially accessed in a more convergent and cheaper way using MCR chemistry, thus potentially benefiting the patient.


Clinical candidates
Preterm labor is the major reason for neonatal morbidity and occurs in 10% of all birth worldwide. Currently, antagonistic derivatives of the neurohypophyseal nonapeptide hormone oxytocin are used to control preterm labors, however they are associated with the typical disadvantages of
peptide drugs, such as lacking oral bioavailability, short half life time and potential immunogenicity. The diketopiperazine scaffold (94) has been discovered in a HTS campaign which after further medicinal chemistry optimization developed to the first clinical class of small molecular weight oxytocin antagonists Retosiban (96) and Epelsiban (95) currently undergo human clinical trials. The later is also the first oxytocin antagonist drug developed for the treatment of premature ejaculation in men (Scheme 17).[57]

Interestingly, they show superior activity for the oxytocin receptor and selectivity toward the related vasopressin receptors than the peptide-based compounds currently used clinically. Perhaps against the intuition of many medicinal chemists, the Ugi diketopiperazines are orally bioavailable, while the currently used peptide derivatives are i.v. only and must be stabilized by the introduction of terminal protecting groups and unnatural amino acids.

Scheme 17. Oxytocin antagonists produced via the UDC methodology.

Because of the convergent and efficient nature of the MCR chemistry, detailed SAR of the scaffolds substituents could be performed giving rapid access to all eight stereoisomers of this Ugi DKP backbone in a landmark paper involving Ugi chemistry.[58]

5. MCR: Quo Vadis?

The immense scaffold diversity coupled with the ease of access of many different compounds and the resulting straightforward optimisation protocols make MCR chemistry an almost perfect technology to solve many of modern lifes issues. Whereas MCR has recently found broad acceptance in general organic and medicinal chemistry, other science and technology domains still do not appreciate the outstanding opportunities that MCR offers. We predict MCRs to become even more popular especially if new applications become introduced.
6. Aim and scope of this thesis

Since the importance of MCRs in the organic and medicinal chemistry is undisputed. To get biologically important molecules with high molecular diversity and complexity, in this thesis we developed a new MCR, checked the substrate scope in well-known Ugi and Passerini reaction. Furthermore, we also described the union of MCR and the applications of MCR towards complex molecules.

In **Chapter 1**, the MCR reactions, use in getting molecular diversity and complexity is discussed.

In **Chapter 2**, we give an overview of recent research about Passerini reaction. Passerini reaction’s scope, chirality and applications are discussed.

In **Chapter 3**, a new efficient method for the Passerini-type three component reaction (PT-3CR) is presented. The scope of the reaction is investigated with various aldehydes and isocyanides. Finally, the application of this method to get fused-tetrazole is briefly discussed.

In **Chapter 4**, the first time use of \(N\)-hydroxamic acids as acid isostere in Passerini reaction is described. The application of this method to get diverse and biologically important \(\alpha\)-hydroxy amides are discussed. Finally, the use of this reaction for the synthesis of oxyamines is discussed briefly.

In **Chapter 5**, we describe the successful use of the N-hydroxyimides as an acid isostere in the U-4CR for a direct route to the synthesis of \(\alpha\)-hydrazinoamides. This is the first time that Ugi-4CR is used for the synthesis of \(\alpha\)-hydrazino amides synthesis. Postmodification of this reaction for the synthesis of diverse molecules also discussed.

In **Chapter 6**, a novel three component reaction is reported for the synthesis of 1,5-tetrazole scaffold. The application of this reaction toward 1,5-disubstituted tetrazoles is reported. The usefulness of this method is also demonstrated in the synthesis of biologically important various fused tetrazole scaffolds and the marketed drug cilostazol.

**Chapter 7** focus on the union of Asinger and Ugi-tetrazole reaction for the synthesis of highly diastereoselective tetrazole-oxazinane synthesis.

In **Chapter 8**, the use of Passerini-2CR product for the direct amination reaction towards \(\alpha\)-amino amides is described. The diverse scope of this new amination methods is discussed.

In **Chapter 9**, a new universal convertible isocyanide is reported. The application of this cleavable isocyanide in Ugi-reactions and at different cleavage conditions is described.
References


Introduction and Scope of the Thesis


