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New Artificial Macrocycles accessed by Ugi four-component reaction (U-4CR)

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Abstract: The use of drug-like artificial *macrocycles* is *emerging* as an exciting area in drug discovery as these compounds offer the potential to modulate difficult targets and largely underexploited part of chemical space. Macrocycles can have advantages over their natural twins such as better control over synthesis, physicochemical properties resulting in drug-like properties. Approaches towards libraries of artificial macrocyclic compounds based on macrocyclizations using Ugi-4CR and applications of these technology platforms are introduced in this review.

Keywords: Artificial macrocycle; Macrocyclic drugs; Multicomponent reaction; Ugi-4CR; Synthetic pathway

Introduction

Macrocyclic motifs employ fascinating chemical architectures, enclosing ring-systems consisting of 12 or more atoms. Over the past years, their chemical diversity sparked significantly, compelled new approach in bioinformatics and synthetic methodology. They have gained enormous popularity in medicinal chemistry [1].

The reason behind for considerable attention are several, including exploiting access to novel chemical space, many potential applications in supramolecular and material chemistry, made better pharmacokinetics for relatively large as well as small molecules [2]. Despite their high molecular weight, polar backbone, macrocycles have capability to diversify their conformation and therefore regarded as more drug-like than expected to show unique physicochemical and pharmaceutical target classes [3].

For example from the field of protease, evolution standpoint has the development of rigidified peptide ligand mimics as well as agonists and antagonists of G protein-coupled receptors (GPCRs) have been bringing about with macrocyclic structures.

Due to their large and flat surface area, the

potential utility of macrocycles is to target proteins which are crucial to handle by typical drug modalities such as protein-binding interactions. In continuation, they have huge potential to drive modern postgenomic targets that are challenging to target by small molecules, like protein-protein interactions (PPI), which are currently therapeutically relevant targets covered by antibodies [4-6]. This behaviour can be generated by conformational changes due to transfer between intra- and intermolecular hydrogen bonding. Thus, there has been increased focus to study different approaches for developing therapeutically novel inhibitors for a variety of protein targets that are not conventionally ‘‘druggable’’ [7]. IL17 with approved antibodies is an example of an exciting PPI target use in rheumatoid arthritis. Macrocyclic small-molecule drugs are ideal idea, more than 100 macrocyclic drugs and clinical candidates are currently marketed or in drug discovery programs [8].

Historically, natural product erythromycin, the first well-known macrolide antibiotic was available commercially in 1952 [9], and after that many more macrocyclic drugs (e.g., rifampicin, vancomycin, and epothilone) [10-12] have been identified (Figure 1).

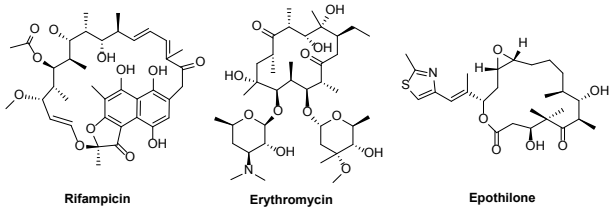


Figure 1. Representative macrocyclic small-molecule drugs

Peptide macrocyclic stems are the second traditional source from peptides, some of which are natural products. The favorable impact of aacrocyclization in peptide chemistry are restrict peptide conformation, reduce polarity, increase proteolytic stability, pharmacokinetic properties like passive permeability, stability, and consequently improve druggability [13-16]. Researchers accessed a library of macrocyclic peptides including the incorporation of non-peptidic macrocycles having diverse confirmations (head to tail, side chain to side chain, head to side chain) [17]. Several drugs having macrocyclic peptides from synthetic or natural sources have been discovered such as octreotide, cyclosporin,, eptifibatide, and caspofungin (Figure 2) [18-19].

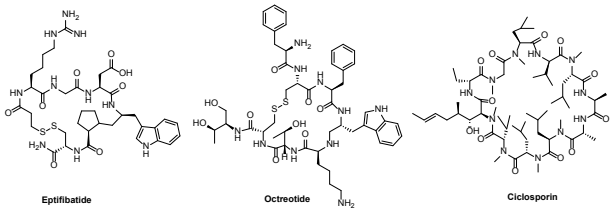


Figure 2. Representative several drugs having macrocyclic peptides from synthetic or natural sources

More and more frequently, macrocyclization is applied in medicinal chemistry programs as a standard strategy to improve the properties of compounds as well as to generate novel chemotypes. These efforts are reflected in the publication of a large number of research papers summarized in a series of review articles covering the field. In the recent past, macrocyclic natural products or derivatives thereof but also synthetic de novo designed macrocyclic compounds were approved by the FDA or are in clinical trials (Figure 3) [20-24].

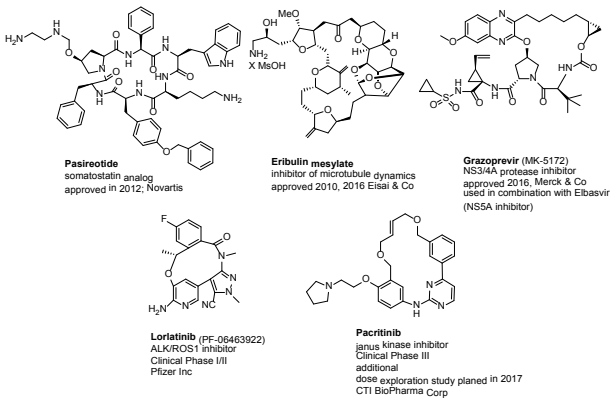


Figure 3. Macrocyclic drugs which were approved or are in clinical trials

Due to the increasing importance of macrocycles in medicinal chemistry, there is a great demand for advanced and new approaches to chemically synthesize these compounds. Recently in drug discovery, artificial non-peptide macrocycles became highly attractive as a novel research field. Macrocycles can have advantages over their natural twins such as better control over synthesis, physicochemical properties resulting in druglike properties [25].

For exploration, the synthesis of the artificial macrocycle cyclisation over oligo- or polymerization is the major challenge. Paul Ruggli and Karl Ziegler have introduced the high-dilution principle, according to which low concentrations of the starting acyclic precursor favour cyclization over chain formation [26]. Many synthetic protocols toward macrocycles have been successfully explored including speedy and dynamic methodologies such as DNA encoded chemistry, enzyme-catalyzed ring closures, and accessing peptide macrocycles from genetically encoded polypeptides [27]. Remarkably, most of procedure focuses towards peptide macrocycles.

In comparison to the conventional stepwise synthesis approach, multicomponent reactions (MCRs), involves one-pot combination of various simple reactants into the complex. Moreover, MCRs involve the formation of multiple new bonds in a single operation, ideally without isolating the intermediates, changing the reaction conditions or adding further reagents. Therefore, MCRs cover by definition topics such as sustainability, atom- and eco-efficiency, high convergence (process efficiency), and reduction of the number of intermediate steps or functional group manipulations, thus reducing time and energy, known as step efficiency (Figure 4) [28].

Therefore, in both academic and industrial research multicomponent reactions emerged as valuable tools for the synthesis of heterocyclic molecules.

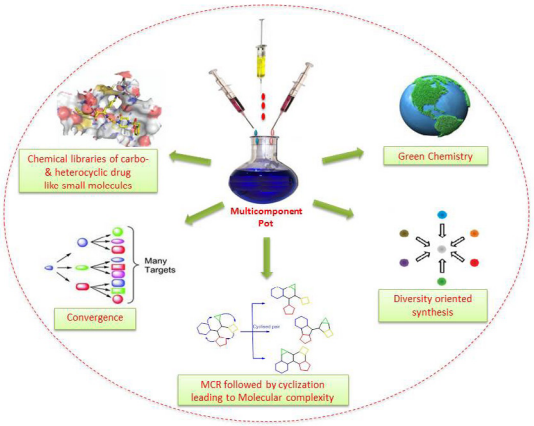


Figure 4. Representation and application of multicomponent reaction

Among the MCRs, the majorly used methodologies for the synthesis of complex molecules are Biginelli, Mannich, Passerini, Petasis, Strecker and Ugi-4CR. In recent years, many modifications of the traditional Ugi-4CR and post-Ugi modification have been done for the synthesis of various heterocyclic molecules, from small molecule scaffolds to macrocyclic libraries [29].

Multi-component Ugi reaction involves a ketone or aldehyde, an amine, an isocyanide, and a carboxylic acid to form a bis-amide. The reaction is named after Ivar Karl Ugi, who first reported this reaction in 1959 (Figure 5) [30].

Figure 5. The Ugi multi-component reaction in organic chemistry

Nowadays, these Ugi reactions are applied for macrocyclization directly or to carry out

linear precursors synthesis exploiting Ugi tetrazole chemistry, pursued by post-Ugi macrocyclization using another Passerini or Ugi multicomponent reaction (MCR) [31-32].

The accepted idea for artificial macrocycles was described via shorter sequence involving an initial linear diversification, followed by a rapid change diversification with the step of macrocyclization using Ugi MCR, resulted in the 2-step synthesis of complex macrocycles (Figure 6).

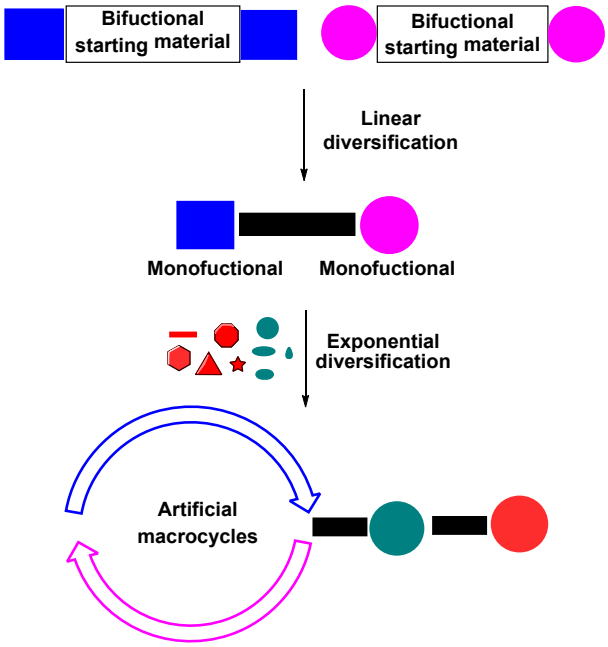
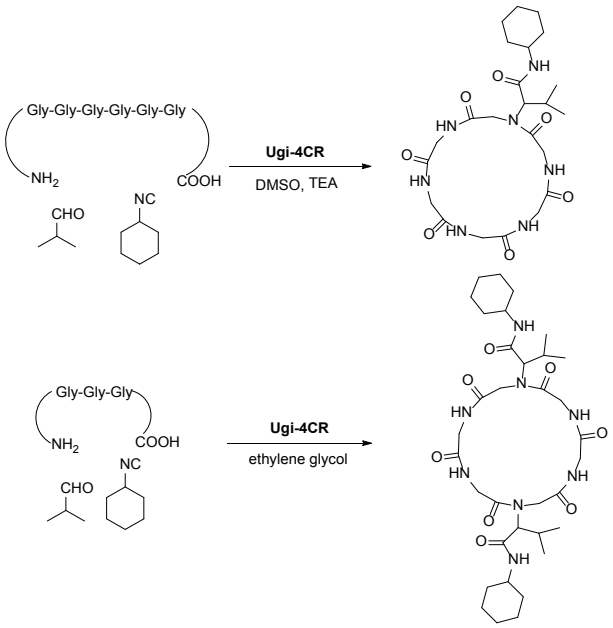


Figure 6. Synthetic concept of rapid generation of artificial macrocycles

In regards for the synthesis of many diverse libraries of macrocycles, isocyanide-based multicomponent Ugi followed by post-cyclization approach have been greatly utilized. This review highlights the representative of an attractive and large chemical space of artificial macrocycles synthesis via shorter sequence involving an initial linear diversification, followed by an exponential diversification step of macrocyclization using Ugi multicomponent reaction.

Synthetic Approaches toward Artificial Macrocycles Using MCR

The fist macrocycles were synthesized in 1979 by Failli and Immer [33] using Ugi MCR for the one-pot macrocyclization of N, C-terminal unprotected linear hexapeptides to head-to-tail cyclic peptide. Surprisingly, the product which was isolated from the reaction of triglycine with isobutyraldehyde and cyclohexyl isocyanide was the substituted cyclic hexaglycine derived from a double MCR of the starting materials (Scheme 1).

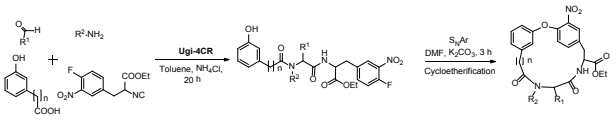


Scheme 1. First in time peptide macrocyclization strategy using the Ugi-4CR

Next, Zhu *et al.* [34] used readily accessible starting materials for the Ugi four-component reaction (Ugi-4CR) followed by an intramolecular SNAr-based cycloetherification to synthesize macrocycles with an *endo* aryl-aryl ether bond (Scheme 2). The nitro group serves as an activator for the macrocyclization and provides a handle for the introduction of functional group diversity into the existing macrocycles.

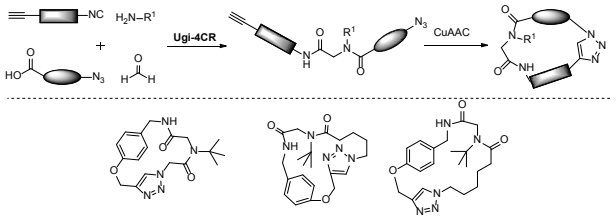
Thus, the construction of the peptide backbone

incorporating biaryl ether containing macrocycles, first the Ugi reaction of an aldehyde, an amine, an ω-(3-hydroxyphenyl) alkanecarboxylic acid, and an isocyanide afforded the dipeptide amides backbone as a mixture of two diastereomers in a ratio of 1:1. Then, cycloetherification has been done smoothly in DMF using potassium carbonate as a base to form 16-membered macrocycle in very good yield (Scheme 2).



Scheme 2. Synthesis of biaryl ether containing macrocycle using Ugi-4CR/SNAr

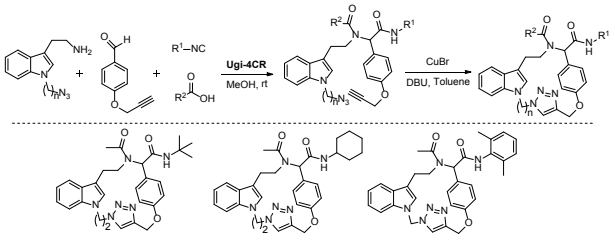
Oliver Kappe and coworkers [35] described the synthesis of triazole containing cyclic peptide utilizing Ugi four-component reaction followed by click cycloaddition. The central transformation of this process was an Ugi four-component reaction generating the peptidomimetic core structure then subsequent intramolecular copper-catalyzed azide-alkyne cycloaddition (Scheme 3).



Scheme 3. General synthetic strategy for the synthesis of cyclic peptidomimetic scaffolds using Ugi-4CR/click reaction

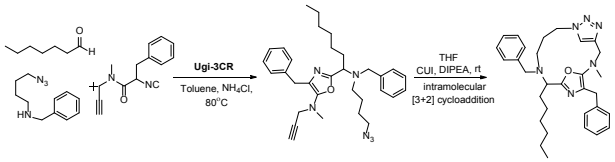
Miranda and co-workers [36] developed a methodology for the synthesis of macrocyclic structures with various ring sizes that would contain a peptoid moiety, a 1,3-substituted indole (tryptamine-based), and a triazole ring using an Ugi 4-CR/click-cycloaddition sequential reaction protocol.

The construction of the peptoid motif backbone incorporating triazole containing macrocycles, first the Ugi reaction of an alkyne containing aldehyde, an N-alkylated tryptamine, carboxylic acid, and an isocyanide afforded the azide-alkyne backbone. Then, CuAAC has been utilized as an efficient protocol to close macrocycles of different sizes by the formation of 1,4-triazoles in very good yield (Scheme 4).



Scheme 4. Construction of macrocycles containing a 1,3-substituted indole, a peptoid moiety and a triazole using Ugi 4-CR/click-cycloaddition

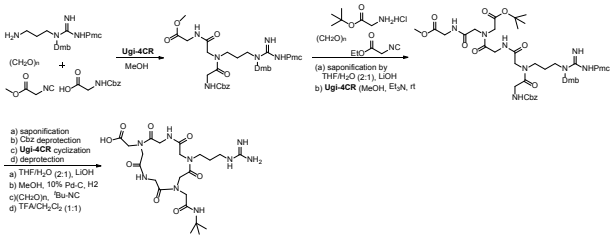
Again, Zhu *et al.*[37] also introduced a tandem Ugi-3CR reaction followed by a copper-catalyzed intramolecular [3+2] cycloaddition of alkyne and azide took place to afford complex macrocycles in moderate to good yields. The reaction between an aldehyde, an ω-azidoamine, and an isocyanoacetamide gives 5-aminooxazole as an intermediate which undergoes intramolecular [3+2] cycloaddition between alkyne and azide to afford triazole containing macrocycle. By this method different 14-, 15-, and 16-membered ring macrocycles were synthesized in 24–76% yields (Scheme 5).



Scheme 5. One-pot synthesis of macrocycles by tandem Ugi-3CR/click ring closure

Wessjohann and co-workers [38], other pioneers

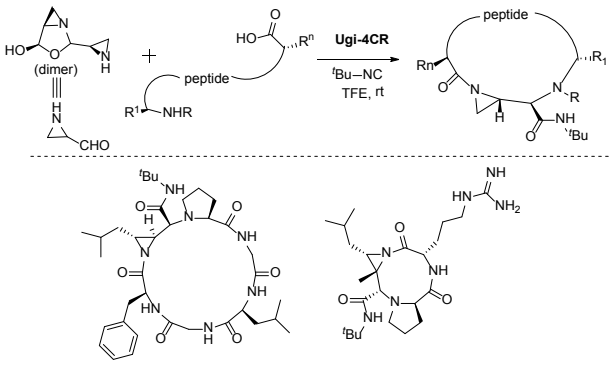
in MCR macrocycle chemistry developed consecutive Ugi reactions for the assembly of the acyclic peptoid and for the ring closure strategy. The first Ugi reaction was performed followed by hydrolysis of the Ugi adduct, the resulting acid was used in a subsequent second Ugi reaction to give ester in high yield (85%, Scheme 6). The amino acid precursor for the cyclization was obtained after ester hydrolysis and Cbz deprotection and was reacted with *tert*-butyl isocyanide and paraformaldehyde under pseudo-high-dilution conditions to avoid oligomerization, giving cyclopeptoid in 33% yield after removal of the protecting groups with 1:1 TFA/CH_2Cl_2. The results confirm the versatility and efficiency of the method for the preparation of cyclic oligopeptoids.



Scheme 6. One-pot synthesis of macrocycles by tandem Ugi-3CR/click ring closure

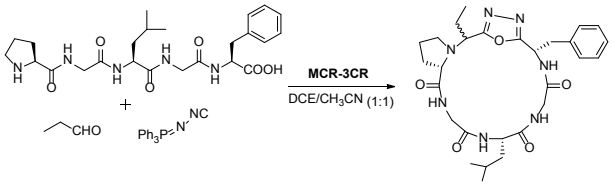
Yudin group [39] developed a general strategy for the synthesis of cyclic peptides and derivatives by amphoteric aziridine aldehyde dimers. This versatile synthetic approach leads to a multitude of cyclic peptide derivatives of different ring size with useful point for conjugation to various side chains via nucleophilic ring opening. This strategy has also been used for the synchronized synthesis of peptide-based macrocycles by digital microfluidics which is of potential interest for the fast and automated synthesis of libraries of compounds for applications in drug discovery and high-throughput screening.

Cyclic peptides were synthesized based on the Ugi-4CR by using amphiphilic aziridine aldehydes. Firstly, amino aldehyde and a linear peptide form an imine, which undergoes cyclization in the presence of isocyanide to give peptidic macrocycles with various ring sizes (9–18 atoms) depending on the used linear peptide (Scheme 7).



Scheme 7. General one-pot synthetic strategy of aziridine containing macrocycles by Ugi-4CR

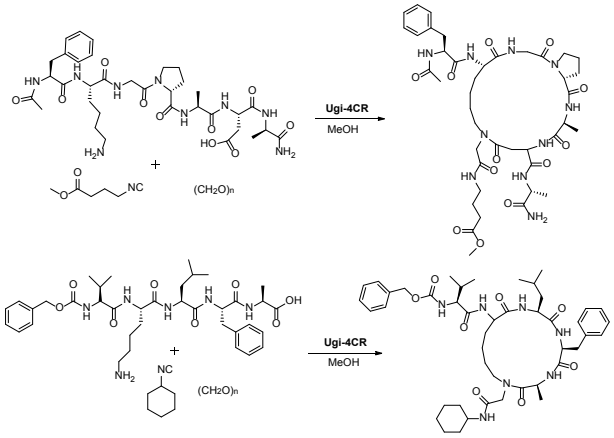
Yudin group also report the oxadiazole-containing macrocycles formation for the head-to-tail synthesis of 15-, 18-, 21-, and 24- membered rings between a linear peptide, an aldehyde and (N-isocyanimino)triphenylphosphorane [40]. This process generates head-to-tail cyclic peptidomimetics in a single step (Scheme 8). This method is tolerant of variation in the peptide and aldehyde components. Interestingly all of the oxadiazole-containing macrocycles tested in the PAMPA assay displayed higher membrane permeability than cyclosporin A, the prototype of a macrocyclic bioavailable drug.



Scheme 8. MCR synthesis of oxadiazole containing macrocyclic peptides

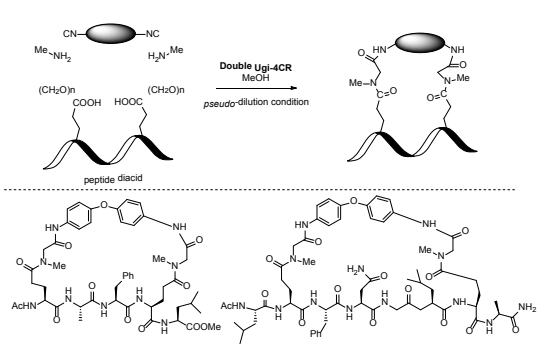
Recently, in order to improve pharmacological properties through the N-alkylation of the macrocycles, Rivera's group [41a] developed the use of Ugi reaction for the macrocyclization

of peptide side chains, thus leading to cyclic peptides bearing a tertiary lactam bridge instead of a secondary one, i.e., N-substituted cyclic peptides. Linear peptide building blocks were first synthesized either by a standard Fmoc solid-phase procedure or by stepwise solution-phase synthesis, and then Ugi strategy was applied in the cyclization step by using commercially available isocyanides (Scheme 9).



Scheme 9. Side Chain-to-Side Chain and side-chain to terminus peptide Macrocyclizations by the Ugi-4CR

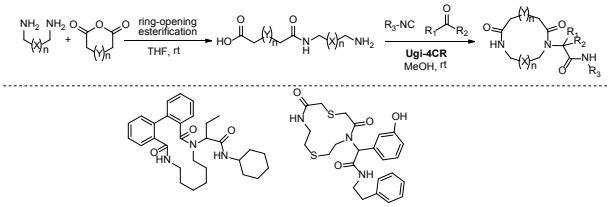
Revera group [41b] also introduced the diversity of peptide cyclization methods for accessing new types of macrocyclic chemotypes featuring a wide variety of ring sizes and topologies via bidirectional macrocyclization of peptides by double multicomponent reactions. This procedure shows prospects for the rapid scanning of the chemical space of macrocyclic peptides for applications in chemical biology and drug discovery.



Scheme 10. Side chain-to-side chain bidirectional macrocyclization of peptides by double Ugi-4CR

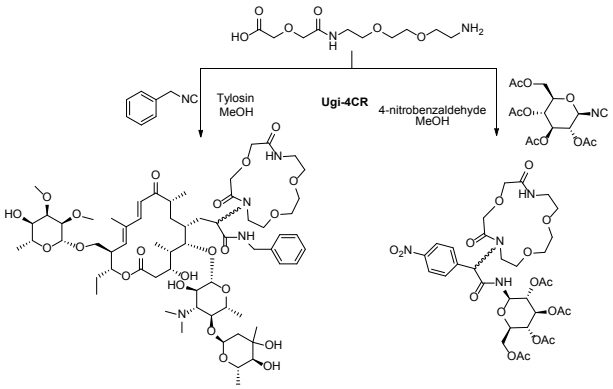
Recently Domling and co-workers [42] first introduced the different pathways to form macrocycles based on bifunctional starting materials using the Ugi-4CR reaction. Applying this concept, they have developed methods that can quickly and accurately convert small molecules into macrocycles via Ugi reaction. This approach provides a very short and versatile pathway to synthesize macrocycle libraries through isocyanide-based multicomponent reactions (IMCRs).

They developed bifunctional strategy for the synthesis of artificial medium- and macrocycles (Schemes 11) involves the ring opening of cyclic carboxylic acid anhydrides with diamines which was then applied to the head-to-tail cyclization. The targeted complex macrocycles pathway consists of the formation of intermediate α-amino-ω-carboxylic acids by suitable ring opening of cyclic anhydrides with diamines, amino acid derived isocyanide coupling, and finally, macrocyclization through an exponential diversification step using Ugi -4CR (Scheme 11) [42]. The last step of the macrocycle synthesis was performed by using several commercially available aliphatic, aromatic, and heterocyclic aldehydes and ketones as oxo-components to afford macrocyclic derivatives in moderate yields of 21−66% after purification by column chromatography.



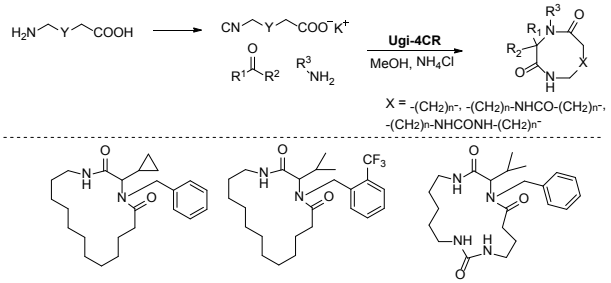
Scheme 11. Bifunctional strategy for the synthesis of artificial macrocycles from α,ω-amino carboxylic acids using Ugi-4CR

With these optimized conditions, they have synthesized a small library 8- to 19-membered medium to macrocycles in 22 to 75% yields. Fascinatingly, all these isocyanides reacted very smoothly and resulted in a variety of macrocycles in good yields. The ability of the designed macrocyclization to address complexity was assessed by using tylosin as an oxo component. Under this condition they have synthesised tylosin- and sugar-based macrocycles (Scheme 12). This example nicely underscores the mildness of the procedure, which was shown to be compatible with free hydroxy groups, α,β-unsaturated ketones, esters, and acetals [42].



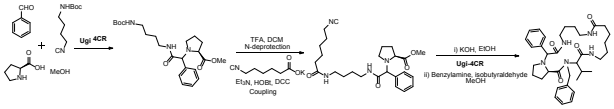
Scheme 12. Synthesis of tylosin- and sugar-based macrocycles using Ugi-4CR

Domling group [43] also introduced the direct macrocycle synthesis of α-isocyano-ω-carboxylic acids of different lengths (Scheme 13), which can be reacted with the oxo and amine components to yield various 12- to 16-membered macrocycles through an Ugi ring closure. Surprisingly, in this approach free isocyano carboxylic acid does not work, but the corresponding potassium salt with NH_4Cl additive works nicely, and under the optimized conditions macrocycles with various size and different substituted α-isocyano-ω-carboxylic acids with additional amide and urea motifs can be synthesized. Side chains with aliphatic, small, bulky, and aromatic substituents can be introduced.



Scheme 13. Macrocycle Synthesis by Ugi-4CR-derived pathway and some examples with Macrocyclization

Next, they chose another well-established Ugi MCR to introduce diversity into the macrocycle linker portion. In the U-4CR, an unprotected α-amino acid is reacting with an oxo component and an isocyanide in methanol to yield imino dicarboxylic acid mono amides, often with very high stereoinduction by the α-amino acid component.[38] They used diamine-derived monoisocyanide in order to provide the isocyano-ω-carboxylic acid linker, which was macrocyclized with the help of a second Ugi-4CR (Scheme 14).

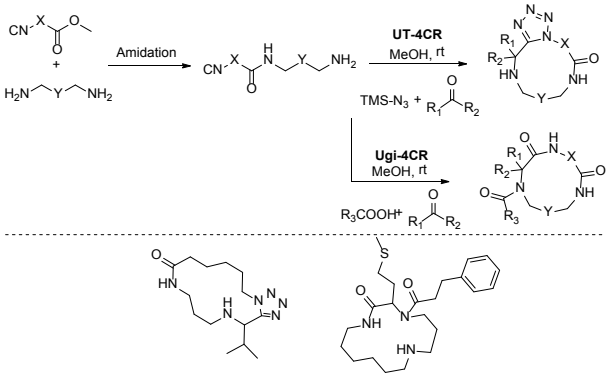


Scheme 14. Mixed MCR strategy derived macrocycle synthesis pathway

Again Dömling and co-workers [44] developed another IMCR macrocyclization strategy involves simple starting materials such as diamines, isocyanide esters, and aldehydes which leads to 11−19-membered macrocylces with three points of diversity.

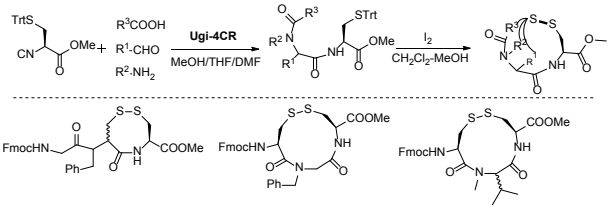
In this strategy the isocyanide based multicomponent reactions (IMCRs) involving simple starting materials like α-isocyano-ω-amine and aldehyde in the presence of the azide source $TMSN_3$ to access tetrazole macrocycle (Scheme 15).

The last step of the macrocycle synthesis was performed through Ugi tetrazole reaction (UT-MCR) by using several commercially available aliphatic, aromatic, and heterocyclic aldehydes and ketones as oxo-components to afford macrocycles of size 11–19 in moderate yields of 21−66% after purification by column chromatography (Scheme 15).



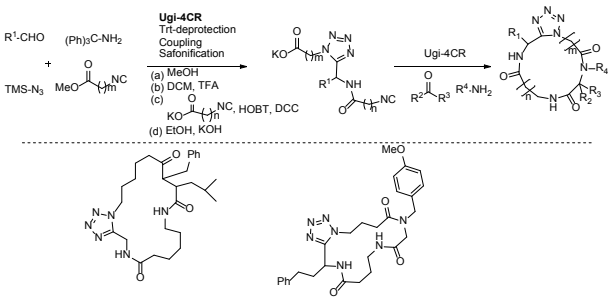
Scheme 15. Two-Step macrocycle synthesis by classical Ugi Reaction

They have also introduced the concept for the efficient synthetic access of disulfide-bridged cyclic peptidomimetics artificial macrocycles via a Ugi four-component reaction (Ugi-4CR) followed by oxidative cyclization [45]. The double-mercapto input is proposed for use in the Ugi reaction, thereby yielding all six topologically possible combinations. Reaction of Fmoc-Cys(Trt)-OH, amine, cysteine isocyanide, and aldehyde in a MeOH/THF/DMF solvent mixture afforded Ugi adduct, followed by iodine-mediated oxidative cyclization to give disulfide-bridged peptidomimetics in good to excellent yields (Scheme 16).



Scheme 16. Sulfur-Switch Ugi-4CR for synthesis macrocyclic Disulfide-Bridged peptidomimetics

Next, they introduced a general strategy for the synthesis of artificial macrocycles via union of two orthogonal MCRs, by using UT-MCR, an MCR of great interest due to the formation of α-amino tetrazoles, bioisosteres to cis-amides [46]. The linker α-isocyano- ω-carboxylic acids were then macrocyclized by an Ugi-4CR in the presence of primary amine and oxo component (Scheme 17). The first UT-MCR was performed by the reaction of an aldehyde, tritylamine, $TMSN_3$, and a bifunctional ester protected amino acid derived isocyanide to give α-amino tetrazole in excellent yields, followed by deprotection and coupling reaction with an isocyano carboxylic acid to yield the α-isocyano-ω-carboxylic acid linker. Next, Ugi reaction for the macrocyclic ring closure was carried out in the presence of a primary amine and an oxo component in methanol as solvent to afford highly decorated macrocycles of size 12–21 in moderate yields. In another approach, the Passerini MCR was used for the macrocyclic ring-closure step by using aliphatic, aromatic, and heterocyclic oxo components as aldehydes and ketones to yield macrocyclic depsipeptides as shown in Scheme 17 [46]. The resulting macrocyclic depsipeptides are model compounds for natural products and could find applications in drug discovery.



Scheme 17. Artificial Macrocycles Depsipeptides by Ugi Reaction

Conclusions

Artificial macrocycles are an emerging and largely underexploited part of chemical space for the future drug discovery. However, synthetic accessibility and tunability of properties in a timely and economical fashion is an issue with currently available macrocycles syntheses. MCR can be a solution! Maximal diversity can be reached by the concept of unions of MCR which was recently introduced in this review. The Ugi-4CR chemistry allows to access interesting artificial macrocycles with broad functional group compatibility. In future, the introduction of drug like properties into artificial macrocycles is key for successful use of this compound class in pharmaceutical industry.

Acknowledgments

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