CHAPTER 1

Chapter 1
Chemistry of peptidomimetic macrocycles and dendrimers: A brief review

1.1. Synthetic organic chemistry

In the mid-nineteenth century, there was a dramatic development in chemistry. Instead of simply analyzing the existing molecules, chemists began to synthesize molecules by developing specific strategies. Organic synthesis is an art and science of building molecules ranging from complex, biologically active natural or synthetic products to new materials starting from smaller entities. The integration of synthetic methodologies with traditional analytical methods changed the chemistry world, leading to a deep understanding of the fundamental principles of structure and reactivity which resulted in the emergence of the modern pharmaceutical and chemical industries. The inevitable role of synthetic organic chemistry in diverse area is demonstrated in figure 1.1.

Figure 1.1. Demonstration of few applications of organic molecules in diverse area.
Among the enormous applications, most essential focus of synthetic organic chemistry is in pharmaceutical industry, for the cost-effective synthesis of complicated drug molecules and active pharmaceutical intermediates. Other than drug discovery, some advanced research areas of synthetic organic chemistry include synthetic coordination chemistry, catalysis, synthetic supramolecular chemistry, chemical biology and biological chemistry, polymer materials etc. This science has developed as a vast area of research and the role of a synthetic organic chemist in contemporary research world is shown in figure 1.2.

![Figure 1.2](image)

**Figure 1.2.** Role of a synthetic organic chemist in the contemporary research world.

For the synthesis of any organic scaffold applicable in any discipline, the most essential one is the design and development of a synthetic strategy to afford the desired product which means the heart of organic synthesis is the development of effective synthetic routes to a molecule. Hence synthetic organic chemists are facing the challenge of designing and developing efficacious strategies for the synthesis of functional organic molecules in few synthetic steps. My research work was mainly focused on the 4th point shown in figure 1.2 i.e. the development of step-economic and cost-effective methodologies for the synthesis of potential organic molecules applicable to various research areas. Among the various types of organic molecules, we had a keen interest in developing macrocycles and dendritic architectures due to their ineffable applications in medicinal and material chemistry.
1.2. Macrocycles

In general, macrocycles have been defined as a ring system consisting of 12 or more atoms.\(^7\) However, 8 membered ring systems have also been included in macrocycle family.\(^8\) Coordination chemists define a macrocycle as a cyclic molecule with three or more potential donor atoms that can coordinate to a metal center.\(^9\) There are many examples for the amazing macrocyclic systems developed by the nature to justify the definition given by coordination chemists. For example macrocyclic ligands found in many cofactors in proteins and enzymes like heme, the active site in the hemoglobin is a porphyrin ring containing iron, chlorophyll, the green photosynthetic pigment found in plants contains a chlorin ring, vitamin B\(_{12}\) contains a corrin ring etc. In the history of organic chemistry, crown ethers are the first subclass of synthetic macrocycles that showed a specific relationship between structure and function. There are different classes of macrocycles, including peptidic and nonpeptidic natural products, peptidic and nonpeptidic non-natural (synthetic) macrocycles etc.

1.3. Macrocycles in drug discovery

Over the past 30 years, uninjured and desirable pharmaceutical products have been designed and marketed and most of them are based on two major categories of organic molecules. One class is small molecule drugs; usually work by interacting with receptors or enzymes of compact binding sites. These molecules are synthetic compounds strictly obeying Lipinski ‘Rule of 5’.\(^{10}\) However, for disrupting protein–protein interactions (PPIs) small molecule drugs are inefficient and therefore biological drugs derived from proteins or peptides have been used. These biologics can effectively interact over a large surface area or extended binding sites.\(^{11}\) Antibodies or soluble receptors are main part of this drug space. Semi-synthetic versions of such biologics such as adnectins TM, avimers, and aptamers etc. are also known with high efficiency and unique selectivity. However, the size of these molecules significantly restricts membrane permeability. Thus there remains a need for compounds that possess enough size and functionality to interact with protein surfaces like biologicals while maintaining the small molecule-like properties such
as cell penetration and oral bioavailability. The limitations of small molecule drugs and biologics have been resolved by the introduction of macrocyclic therapeutics. These potential scaffolds can maintain the properties of both small molecule and biological drugs. Thus among the pharmacologically active compounds, macrocycles occupied the middle seat between small molecules and biologicals as shown in figure 1.3.\textsuperscript{12}

![Figure 1.3](image)

Figure 1.3. Graph demonstrating the importance of macrocycles in drug discovery. Macrocycles occupy the position between small molecule drugs and biological drugs.

From a chemistry point of view, macrocycles can tolerate diverse functionality and stereochemical complexity in a conformationally restricted manner. Moreover, macrocycles can offer highly favorable drug-like properties; including excellent solubility, high lipophilicity, enhanced cell membrane penetration, improved metabolic stability, and exceptional oral bioavailability with desirable pharmacokinetic and pharmacodynamic properties.\textsuperscript{13} These properties made macrocycles a unique class of compounds that has an unavoidable role in modern drug discovery.
There are 100 or more macrocyclic drugs available in the market in which most of them are obtained from natural product sources. Numerous biologically active macrocycles, including antibiotic, antifungal, antitumor etc. have been isolated from natural sources for example, vancomycin, erythromycin, amphotericin B, rifamycin B, rapamycin etc. to name a few. However, the isolation of natural molecules in appreciable quantity, identification of the bioactive
component, post isolation modifications for studying structure–activity relationship etc. is laborious. Moreover, for a large number of therapeutic targets, no macrocyclic ligands are available from natural sources. This motivated synthetic organic chemists to mimic the nature by synthesizing potential macrocyclic molecules in the laboratory using efficient synthetic methodologies. Consequent to this, synthetic macrocyclic drugs like TZP101, robotnikinin, FK506, FK520 etc. are now available in the market. Structure and functions of few natural/synthetic macrocyclic drugs are shown in figure 1.4.

1.4. Synthetic strategies for macrocyclization

Several groups have made the synthetic version of potential natural macrocyclic molecules or their analogs using step by step synthesis. These compounds after bioassay showed the same potential as that of their natural versions. However, such multistep strategies are expensive and resource intensive. The renaissance in new synthetic protocols such as multicomponent reactions paved a new wave in macrocycle synthesis. A ‘build-pair’ strategy in which the back bone structures made by either multi-step or multicomponent coupling process and cyclization via following any one of the traditional cyclization methodologies such as macrolactonization, macrolactamation and various other strategies like transition metal catalyzed cross coupling reactions, ring closing metathesis etc. are the most accepted protocol to access synthetic macrocycles.

1.4.1. Classical build/pair strategy for macrocyclization

1.4.1.1. Macrolactonization and Macrolactamization

Macrolactones and macrolactams are significant part of naturally occurring macrocycles, with diverse biological activities. Corey and Nicolaou reported the first macrolactonization via thioesterification of hydroxyl acid. Based on Corey and Nicolaou’s thioester procedure, more efficacious protocols and reagents were subsequently developed including Corey and Clark, Corey and Brunelle, Schmidt, and Wollenberg to enhance the esterification efficiency. Along with Corey and Nicolaou, other alternative methods are also widely used for finding
synthetic applications including macrolide antibiotics.\textsuperscript{32} For example, recently, Yang and coworkers\textsuperscript{33} synthesized Batatoside L,\textsuperscript{34} bearing an 18-membered macrolactone system, using Corey-Nicolaou macrolactonization approach. As illustrated in scheme 1.1, after multi-step synthesis of glycosidic acid 1.1, the construction of the macrolactone core structure 1.2 was achieved by adopting the Corey-Nicolaou macrolactonization approach. Batatoside L 1.3 could be generated from glycosylation of heterodisaccharide macrolactone 1.2 and exocyclic dirhamnose trichloroacetimidate, following appropriate deprotections.

**Scheme 1.1.** Key macrolactonization step involved in the total synthesis of Batatoside L.

![Scheme 1.1](image)

Compared to macrolactones, the macrolactams are much less commonly present in many natural products and peptides. Among various strategies for synthesizing lactams, the most common and efficient approach is to react an amino group with activated carboxylic acid moiety. For example, the multi-step synthesis of hirsutellide A 1.5 was achieved by following a key macrolactamization step of

**Scheme 1.2.** Key macrolactamization step for the total synthesis of hirsutellide A.

![Scheme 1.2](image)
1.4 Using phosphorus activating reagent BOP-Cl and DIPEA in a highly diluted DMF solution (scheme 1.2).\textsuperscript{35}

1.4.1.2. C-C, C-O, and C-N Coupling Reactions

For creating new C-C, C-O or C-N bonds, the best synthetic tool is transition metal catalyzed cross coupling reactions. From the synthetic point of view, diversely functionalized and complex scaffolds can be easily developed via these coupling reactions to provide a broad range of applications in organic synthesis.\textsuperscript{36} The convenience of constructing new C-C, C-O, C-N and other carbon-hetero (C-X) bonds makes coupling reactions a powerful and attractive pairing tool for macrocyclization. Many research groups have explored this synthetic strategy for the building of naturally occurring macrocycles. Few examples are discussed below.

1.4.1.2.1 C-C Bond Formation

Rhizopodin 1.8 was isolated from the culture broth of the myxobacterium \textit{Myxococcus stipitatus}, exhibited antifungal and antiproliferative cytotoxicity against a panel of cancer cell lines.\textsuperscript{37} It possesses a C2-symmetric 38-membered macrolide ring system containing 18 stereogenic centers. Due to its unique and complex structure, this natural product target has attracted the attention of the synthetic community. The Menche group has developed Rhizopodin 1.8 using multi-step strategy with Heck reaction as the macrocyclization step (scheme 1.3).\textsuperscript{38} The terminal allylic iodide was coupled with the terminal alkene of 1.6 in presence of Pd catalyst to afford the alkene functionalized macrocycle 1.7.

\begin{center}
\includegraphics[width=\textwidth]{scheme13.png}
\end{center}

Scheme 1.3. Heck reaction as the key macrocyclization step for the synthesis of Rhizopodin.
1.4.1.2.2 C-O Bond Formation

Ullmann reaction is the best strategy among the transition metal catalyzed cross coupling reactions for C-O bond formation.\(^{39}\) Recently; it became an efficient macrocyclization tool in the total synthesis of natural product macrocycles. Hirsutellone B 1.12 was isolated from insect pathogenic fungus *Hirsutella nivea* BCC 2594 and act as excellent antituberculosis agent.\(^{40}\) This molecule has a highly strained 13-membered cyclic ring and a tricyclic decahydrofluorene present in its skeleton. Using multi-step approach, Uchiro et al. recently synthesized hirsutellone B by using copper-catalyzed Ullmann-type reaction as critical macrocyclization step (scheme 1.4).\(^{41}\) The MOM-protected enol ether 1.10 was obtained after reacting 1.9 with MOMCl in the presence of Cs₂CO₃. Then, the 13-membered macrocycle core 1.11 could be built by intramolecular Ullmann-type etherification of 1.10 using CuI as catalyst and 1,10-phenanthroline as ligand. Following several transformations, the desired target hirsutellone B 1.12 was obtained in good yield.

![Scheme 1.4.](image)

**Scheme 1.4.** Ullmann-type reaction as the macrocyclization tool for the total synthesis of hirsutellone B.

1.4.1.2.3 C-N Bond Formation

The building of C-N bond is easily accomplished using Buchwald-Hartwig coupling reaction.\(^{42}\) Attracted by the excellent cytotoxicity of SNX-5422 1.13 against Hsp90 in proliferation assay\(^{43}\) Zapf and coworkers designed and synthesized a series of macrocyclic \(\alpha\)-aminobenzamide Hsp90 inhibitors, such as 1.14 and 1.15.\(^{44}\) These derivatives showed coequal inhibitory activity against Hsp90 with enhanced solubility and microsomal stability. Recently, the same group has reported a more complex variant of these macrocyclic lead compounds via conjugating amino-based heterocycles to the macrocycles using Buchwald-Hartwig coupling reaction between arylhalide and alkyl to afford 1.18 as shown in scheme 1.5.\(^{45}\)
1.4.1.3. Ring-Closing Metathesis (RCM) Reaction

The metathesis reaction especially, ring closing metathesis reaction (RCM), has emerged as an extremely efficient pairing tool for the formation of macrocycles. A novel cytotoxic 20-membered macrolactone Dactylolide 1.19, was isolated from a marine sponge of the genus *Dactylospongia* by Riccio and coworkers. Due to their unique macrolide scaffold and guaranteed biological activity, the synthetic organic community is fascinated to develop these macrocycles. Lee and coworkers reported the synthesis of (−)-Dactylolide via multi-step synthetic approach for the linear precursor 1.20 followed by RCM to afford beautifully decorated macrolactone 1.21 (scheme 1.6).

Even though the synthesis of macrocyclic natural product drugs or their derivatives in the laboratory is a milestone in the drug discovery process, this multistep synthetic approach has many synthetic limitations such as high cost, time consuming, less efficient, low yield, limited diversity per step etc. The hurdles associated with the conventional multi-step synthesis, forced the synthetic organic
chemists to develop more economic, efficacious and advanced synthetic strategies for the construction of these potential molecular scaffolds.

1.4.2. Advanced build/pair strategy for macrocyclization

1.4.2.1. Multicomponent reaction

An advanced synthetic strategy to overcome the hurdles associated with multistep synthesis and to construct the potential building blocks in a step-economic and cost-effective manner is the use of ‘Multicomponent reaction’ (MCR). Multicomponent reaction is defined as a reaction in which more than two starting compounds react to form a product in such a way that the majority of the atoms of the starting material can be found in the product thereby increase molecular complexity and diversity. The first documented multicomponent reaction was the Strecker synthesis\(^5\) of \(\alpha\)-amino cyanides in 1850 from which \(\alpha\)-amino acids could be derived. Figure 1.5 gives a clear idea about the reason why the chemists are keen to replace multistep synthesis with multicomponent reaction in the advanced research scenario.

![Diagram of Multistep vs Multicomponent Reactions]

Figure 1.5. Comparison between multistep reactions and multicomponent reactions.

A myriad of multicomponent reactions are available today, of which the isocyanide based MCRs are the most documented, for example Ugi reaction,\(^5\) Passerini reaction,\(^5\) Van Leusen reaction\(^5\) etc. Examples for non isocyanide based
MCRs are mainly Strecker reaction,\textsuperscript{50} Hantzsch reaction,\textsuperscript{54} Biginelli reaction,\textsuperscript{55} Mannich reaction,\textsuperscript{56} etc. Other examples of multicomponent reactions include free-radical mediated MCRs,\textsuperscript{57} MCRs based on organoboron compounds (Petasis reaction)\textsuperscript{58} and metal-catalyzed MCRs.\textsuperscript{59}

There are ineffable applications of MCR in drug discovery and many other fields of interest. Direct one pot synthesis of drug molecules or its analogs are easily afforded with MCR while multistep synthetic approach will take several steps to accomplish the target.\textsuperscript{40b} The figure 1.6 shows the structure of Azinomycin B analog \textbf{1.22} which is a natural product drug isolated from Streptomyces sahachiroi. This strong DNA binding and alkylating antibiotic was easily synthesized in the laboratory via one pot Passerini three component reaction using an acid, aldehyde and isocyanide moieties.\textsuperscript{60}

![Figure 1.6](image)

\textbf{Figure 1.6.} Synthesis of analogs of Azinomycin (DNA binding and alkylating antibiotic) using three component Passerini reaction.

Biginelli reaction is a three component reaction between aldehyde, β ketoester and urea to afford dihydropyrimidinone (DHPM). The most attractive part for this motif is its high biological activity. Biological activity of DHPMs extended to diverse range showing potent antiviral, antibacterial, antitumor, anti-inflammatory, analgesic and also cardiovascular activity. It can also be the part of nucleic acid mimetic.\textsuperscript{49d,61} The structure of DHPM is shown in figure 1.7
MCR can be effectively utilized as the tool for the synthesis of core structure of potential drug molecules. For example, versatile four component Ugi reaction using an isocyanide 1.24, acid 1.25, aldehyde 1.26 and amine 1.27 to afford α-acylamino carboxamide 1.28 was used as a tool for the development of core structure of the antibiotic Bicyclomycin 1.29, a natural product isolated from *Streptomyces sapporonensis* (scheme 1.7).62

Figure 1.7. structure of highly bioactive dihydropyrimidinone (product of Biginelli three component reaction).

A milestone in the use of multicomponent reactions in drug discovery was the core structure synthesis of HIV protease inhibitor Crixivan (piperazine carboxamide 1.34) using one-step one-pot Ugi reaction (scheme 1.8).63

Scheme 1.7. Ugi MCR used for the core structure synthesis to afford antibiotic Bicyclomycin.

Scheme 1.8. The Ugi MCR for piperazine carboxamide synthesis (core structure of HIV protease inhibitor Crixivan).
So far we have discussed the use of MCR as a direct methodology for drug development or as a tool for core structure or building block synthesis to afford the targeted drug molecule. This discussion will help the readers to get an idea about why multicomponent reaction are used to substitute multistep synthetic approach for the efficacious synthesis of potential scaffolds. Influenced by the potential of MCR in drug discovery and other area of interest, we also had designed an MCR based synthetic methodology for the synthesis of highly functionalized organic scaffolds.

For this, we have optimized a ‘Mannich type three component reaction’ to construct the core structure β-amidoketone 1.38 which is an important building block for the synthesis of 1,3-amino alcohols and β-lactams. The former is a

![Scheme 1.9. General synthetic strategy for the alternative Mannich type reaction to afford β-amidoketone core structure (synthetic strategy used for build phase) and the proposed reaction mechanism.](image-url)
structural part of peptidyl nucleoside antibiotics such as nikkomycins and polyoxins\textsuperscript{65} and the latter is found in β-lactamase inhibitors such as 6-β-bromopenicillanic acid.\textsuperscript{66} This catalytic reaction needs an aldehyde 1.35, a nitrile component 1.36 and an enolizable ketone 1.37 and small amount of an acid chloride to realize the product. General synthetic strategy and the proposed reaction mechanism which illustrates the formation of β-amido ketone scaffold is given in scheme 1.9. The reaction is initiated by the complexation of the carbonyl oxygen of the ketone to the metal atom of the catalyst to produce a sterically hindered enolate anion 1 with a more nucleophilic α carbon. Subsequent reactions of this metal enolate with aldehyde component and acid chloride resulted in the carbon-carbon bond formation to produce a β-acyloxy ketone derivative 2. The acyloxy group in 2 then displaced by nucleophilic nitrogen of the nitrile component to produce a stable cation intermediate 3. Addition of water or other reactive species like HOCl formed during the reaction leads to the formation of β-amido ketone scaffold 4 and closes the catalytic cycle.

1.4.2.2. MCR as advanced build phase for macrocyclization

One of the vital synthetic applications of multicomponent reaction is scaffolding the macrocyclization through preorganized synthesis of potential core structures. These core scaffolds are cyclized via terminal functional group pairing using both traditional macrocyclization strategies like macrolactonization, macrolactamization and also various other strategies like transition metal catalyzed cross coupling reactions, ring closing metathesis etc. The net result is the development of highly decorated macrocyclic architectures with excellent complexity and diversity within two or three simple synthetic steps unlike conventional multistep synthetic approach for macrocyclization.

Domling et al. reported the syntheses of macrocycles using multicomponent reactions like Passerini and Ugi variants for core structures (build phase) with terminal alkene functionalities and were cyclized via ring-closing metathesis (pair phase). This strategy favored the synthesis of complex and diverse natural product-like macrocycles 1.44 within two synthetic steps and opened space for the discovery
of new bioactive agents. The general scheme for this synthetic strategy is shown below.

![Diagram of synthetic strategy](image)

**Scheme 1.10.** Two step Ugi/RCM strategy for the synthesis of potential macrocycles.

Cai and coworkers reported an efficient strategy to generate 14 and 15 membered macrocycles by the combination of two multicomponent reactions in a one-pot chemo-selective manner followed by intramolecular Pd-catalyzed Sonogashira cross-coupling. These researchers used an initial Ugi MCR to produce the product 1.49 and used 1.49 along with 1.50 and 1.51 for the 2nd MCR to produce 1.52. 1.52 then subjected to an intramolecular Sonogashira coupling to afford 1.53. Three classes of macrocycles have been successfully synthesized by this method and the diversity can be easily generated by varying the substitutions on the amine, aldehyde, acid and isonitrile used in the initial Ugi reaction. The whole synthetic strategy is shown in scheme1.11.

![Scheme 1.11](image)

**Scheme 1.11.** Chemoselective synthesis of potential macrocyclic components by tandem multicomponent reactions followed by intramolecular Sonogashira cross-coupling reaction.
Since synthetic organic chemists are always restless, they thought about connecting MCR with a more straight forward and orthogonal synthetic strategy to develop potential macrocycles. So there was an ever-increasing need for the rapid reactions that meet the three main criteria of an ideal synthesis: efficiency, versatility and selectivity.\textsuperscript{59} Development of such reactions would be an asset for the modern synthetic organic community and the foremost example for such class of ideal synthetic strategy is ‘Click reaction’.\textsuperscript{70}

1.4.2.3. Click reaction as advanced pair phase for macrocyclization

Sharpless et al. defined a click reaction as “Strategy for the rapid and efficient assembly of molecules with diverse functionality…enabled by a few nearly perfect reactions, it guarantees reliable synthesis of the desired products in high yield and purity”.\textsuperscript{71} According to Sharpless the criteria for useful click reactions are wide scope, very high yield, selectivity, simple conditions, temperatures, readily available starting materials, no solvent or a benign solvent, or an easily removed solvent, simple isolation of the product like crystallization or distillation and no chromatography is used, stability of the new bond, for example under physiological conditions in the case of drugs etc.\textsuperscript{70a}

According to the definition and criteria of click reaction, this reaction can be classified into different classes as follows

- Cu(I)-catalyzed azide-alkyne[3+2] cycloaddition referred simply as Click reactions
- Copper free click reactions such as enamine and enolate mediated organocatalytic [3+2]-cycloaddition reactions
- Strain-promoted azide-alkyne reactions
- Sulfer fluoride exchange reactions (SuFex)
- Thiol-ene reaction
- Diels-Alder reaction and inverse electron demand Diels-Alder reaction
- [4+1] cycloadditions between isonitriles (isocyanides) and tetrazines

- Nucleophilic substitution to small strained rings like epoxy and aziridine compounds

- Carbonyl-chemistry like formation of urea but not reactions of the aldol type due to low thermodynamic driving force.

- Addition reactions to carbon-carbon double bonds like dihydroxylation or the alkynes in the thiol-yne reaction.

Among these different class of reactions, Cu(1) catalyzed [3+2] cycloaddition reaction (CuAAC) is particularly versatile due to its ineffable applications in medicinal and material chemistry to date. This reaction was developed by Sharpless and coworkers in 2001, which involves a modified Huisgen 1,3-dipolar cycloaddition of an alkyne 1.55 and an azide 1.56 in the presence of copper (1) catalyst to generate a regioselective 1,4-disubstituted 1,2,3-triazole product 1.57 under mild reaction conditions. The general synthetic strategy and the proposed Cu (1) catalyzed cyclic mechanism to afford the triazole product is shown in scheme 1.12. In the initial step the Cu (1) complex interact with the acetylene to form a copper acetylide 1 by losing one ligand. In a subsequent step, the azide displaces another ligand and binds to the copper to form 2. Followed by this, an unusual six-membered copper (III) metallacycle 3 is formed. Ring contraction to a triazolyl-copper derivative 4 followed by protonolysis gives the triazole product 5.

Due to the high functional group tolerance of CuAAC reaction, any complex scaffold with azide functionality at one terminal and alkyne moiety at other end can be easily paired. This unique potential of this advanced synthetic tool has been advantageous for macrocyclization. Moreover, azide-alkyne pairing will results in the formation of a 1,2,3-triazole which is an interesting privileged scaffold in medicinal chemistry. 1,2,3-triazole moiety is commonly found in pharmaceutical and bioactive molecules.
Scheme 1.12. General synthetic protocol for Cu (1) catalyzed azide-alkyne [3+2] cycloaddition reaction and proposed mechanism.

Interestingly, this heterocyclic triazole ring possesses similar physicochemical properties with the trans-amide functionality so that it could serve as its isostere. Therefore, along with the other surrogates of amide bonds if any present in the MCR core structure (build phase) along with 1,2,3-triazole (pair phase) will result in the formation of highly decorated class of compounds called ‘peptidomimetic macrocycles’ which will maintain the unique properties of peptide macrocycles with better biological activity and improved metabolic stability and rigidity.

Sureshbabu et al. reported an effective Ugi MCR followed by CuAAC protocol to afford cyclic glycol peptidomimetics in a sequential manner. Poc-amino
alkyl isonitrile 1.60 was used in the initial MCR. The pairing between the alkyne moiety of Poc group (Poc-propargyloxycarbonyl) with azide functionality on the other terminal of 1.62 at the intramolecular CuAAC reaction step afforded the peptidomimetic macrocycle 1.63 (scheme 1.13).

![Scheme 1.13. Ugi/CuAAC strategy for the synthesis of peptidomimetic macrocycles.](image)

Miranda et al. developed an easy two step protocol for the synthesis of novel tryptamine-based macrocycles 1.69 using an Ugi 4-CR/click-cycloaddition reaction. The highlight of this macrocyclic scaffolds are the presence of a peptoid core structure and 1, 3-substituted indole provided by Ugi MCR and a triazole ring provided by CuAAC. The whole synthetic protocol is shown in scheme 1.14.

![Scheme 1.14. Two step Ugi/Click strategy for the synthesis of tryptamine based macrocycles.](image)

Kappe et al. reported the development of an efficacious continuous flow strategy for the synthesis of linear peptoids using Ugi MCR and a subsequent copper-catalyzed azide-alkyne cycloaddition for the formation of macrocyclic architectures. The isocyanide 1.70 was synthesized in a continuous process by the dehydration of the corresponding amide using Burgess reagent. Azide moiety 1.71 was developed in situ by the nucleophilic substitution of a bromide precursor with tetrabutylammonium azide. The resulting continuous synthesis generates the desired linear peptidomimetics 1.74 in good to excellent yields. The subsequent CuAAC macrocyclization takes place in a continuous flow reactor made of copper which will
skip the use of other active catalytic species to give the peptidomimetic monomeric or dimeric macrocycles 1.75. The whole continuous flow process was based on the synthesis of the peptoid core structure using U-4CR (scheme 1.15).

![Scheme 1.15. Continuous flow strategy for the synthesis of macrocycles via Ugi/click reaction.](image)

**1.5. Dendrimers**

Dendrimers can be defined as extremely branched highly symmetrical molecules with well-defined, homogeneous and monodisperse structure consisting of a core scaffold, branching units and decorated terminal functionalities. These highly branched molecules were first discovered by Fritz Vogtle in 1978. Later, Tomalia and coworkers synthesized dendrimers in 1985 and at the same time Newkome et al. also independently worked on these molecules. Since 1978, numerous books and about 22,000 articles have been published and over 100 dendrimeric structures have been realized. Due to the unique architectural design, extended branching possibility, multivalency and globular structure, dendrimers have made a revolution in polymer science and referred to as “Polymers of the 21st century”. Moreover, poor solubility, bioavailability, permeability, biocompatibility and toxicity of traditional polymers could be easily overcome by developing potential dendrimers. Also, unlike simple chain growth procedure of polymers, dendrimers undergo stepwise growth to afford nearly monodisperse product. The development of efficient, straightforward strategies for the synthesis of dendrimers provides well defined architectures suitable for advanced applications in medicine, materials, catalysis etc with reduced cost. The wide variety of applications of these
versatile molecules in the diverse research areas, made the researchers to think about the commercialization of dendrimers and it is now forthcoming. Some of the commercially available dendrimers are poly(amidoamine) (PAMAM), polyamide, bis(hydroxymethyl) propionic acid(bis-MPA), poly-L-Lysine (PLL), polyglycerol-

![Figure 1.8. Chemical structures of several commonly used commercially available dendrimer structures.](image)

**1.5.1. Structure of dendrimers**

Dendrimers possess three distinguished architectural components (figure 1.9) namely

(i) An initiator core.

(ii) Interior layers composed of branching units, radically attached to the interior core. Count branching points as generations G1, G2, G3 etc.

(iii) End points or terminal functionality attached to the outermost interior generations.
1.5.2. Types of dendrimer

Dendrimers are classified into different types and it is mainly based on their shape, end functional groups and internal cavities. The demonstration of different types of dendrimers known to date is shown in figure 1.10.

![Figure 1.9: General structure of a dendrimer. G stands for generation.](image)

![Figure 1.10: Types of dendrimeric architectures.](image)
1.5.3. Synthetic strategies for dendrimers

1.5.3.1. Classical synthetic strategy for dendrimers

Dendrimers are molecules that act between molecular chemistry and polymer chemistry. Scientists relate dendrimeric molecules to molecular chemistry world by means of their step-by-step controlled synthesis and to the polymer world due to their repetitive structure formed from monomers.\(^8^7\) For the synthesis of dendrimers, there are mainly two synthetic methods, a divergent method or a convergent method.\(^8^8\)

1.5.3.1.1. Divergent method

In the divergent approach introduced by Tomalia, the synthetic strategy starts from the core of the dendrimer to which the branches are connected by adding building blocks in a classical step-by-step manner to develop the higher generations. In this method a potential multi-functional core scaffold is generated first and then it is reacted with the reagent containing at least two protected branching units, followed by removal of the protecting groups to give the first generation dendrimers (G1). Then to develop the next generation dendrimer (G2) the process is repeated until the dendrimer of the desirable size is obtained.\(^8^1^a\) The whole synthetic method is demonstrated in figure 1.11. Polyamidoamines (PAMAMs) are the first synthesized dendrimers using this divergent synthetic approach.\(^8^4^d\)

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**Figure 1.11.** Demonstration of synthetic approach for dendrimers via divergent approach.
The major disadvantage of this synthetic approach is incomplete growth and many side reactions leading to imperfect dendrimers. The side reactions and imperfections can be reduced by the use of large excess of reagents.

1.5.3.1.2. Convergent method

In the convergent method, the dendrimer growth starts with the synthesis of branching units of the dendrimer with decorated surface groups. Then moves inward by gradually linking surface units together to afford the desired branching unit. Then this large branching unit called dendron is attached to the potential core scaffold to obtain a complete dendrimer molecule (figure1.12)

Figure 1.12. Demonstration of synthetic approach for dendrimers via convergent approach.

This approach has several advantages like easiness in purifying the desired product, limited imperfections in the final structure so that the final dendrimer will be more mono-disperse. However higher generation dendrimer synthesis using convergent approach is not easy as this method restricts the formation of large dendrimers due to the steric crowding which occurs during the reactions between the dendrons and the core molecule. This disadvantage limits the use of convergent method for the manufacture of a large molecule for drug loading purpose.

Even though the applications range from biomedical science to newer materials and catalysis, very few products utilizing dendrimers and only one drug have reached the market. This limited transfer of dendrimeric products from academia to industry is mainly due to difficulties associated with the synthesis and
puriﬁcation of these potential scaffolds. Therefore the traditional divergent or convergent synthetic approach must be replaced with some advanced synthetic strategies.

1.5.3.1.3. Advanced click chemistry for dendrimer synthesis

In both convergent and divergent approach, sturdy orthogonality is the main requisite to maintain the purity and consequently the monodispersity of a dendrimer. Few reactions feature both high yields over 99% and good orthogonality to each other. Click reactions are the best example for such reactions and has been used as a key synthetic tool to many new dendritic architectures applicable in various advanced materials.91 All types of click reactions like thiol-alkene or thiol-alkyne,91,92 Diels-Alder reactions,93 Cu (1) catalyzed azide-alkyne cycloaddition reaction (CuAAC)94 etc. are used for the dendrimer synthesis.

Among these, CuAAC is the most important one due to its high functional group tolerance as it could accommodates both hydrophilic and hydrophobic substrates, the most highlighted characteristic for amphiphilic macromolecules. It can also operate in a wide range of pH values (5–12) and can drive the reaction at

![Figure 1.13. Demonstration of the convergent and divergent method for dendrimer synthesis using click reaction.](image)
room temperature. Moreover, the catalyst pair is somewhat green and cheap compared to a vast majority of organometallic compounds. Therefore it is not surprising that CuAAC reaction is still the most used strategy for dendrimer synthesis.\textsuperscript{95} Figure 1.13 shows the possibility of both convergent and divergent synthetic method for the dendrimer development using CuAAC reaction.

Multicomponent reactions especially isocyanide based ones like Passerni reaction, Ugi reaction etc are extensively used for the synthesis of dendrimers via both convergent and divergent approach. Rudick et al. reported the synthesis of dendrons and dendrimers following the convergent strategy using Passerini reaction.\textsuperscript{96} The advantage of this one pot multicomponent reaction to synthesize dendrimers is that surface-triblock dendrimers can be easily assessed in single step with three distinct clusters of surface functional groups.

Revera and coworkers demonstrated the library synthesis of first and second generation Janus-type dendrimeric architectures using divergent Ugi multicomponent reaction. A diverse peripheral group functionality and architectural diversity was introduced in the synthesized dendrimers. The core, branching repeat units, and peripheral groups were all synthesized through a series of divergent Ugi reactions.\textsuperscript{97}

There are also reports for the use of MCR for the synthesis of dendrons (branching unit) and other advanced synthetic strategies for connecting the core molecule with dendrons to construct desirable dendrimeric architectures. Meier et al. reported the combination of Passerini-3CR and olefin cross metathesis as a useful approach for the divergent synthesis of dendrimers containing ester and amide functionalities. Castor oil-derived platform chemicals were successfully applied for the synthesis of the core unit as well as for the branching of dendrimers using Passerini reactions.\textsuperscript{98} Zi-chen Li et al. demonstrated the combination of the orthogonal thiol-yne reaction and Passerini reaction as a highly efficient divergent approach for the dendrimer synthesis with structural diversity. The beauty of this synthetic work is dendrimers up to two generations were synthesized in three simple steps.\textsuperscript{91b}
We are also interested in the development of such synthetic strategy for dendrimer synthesis i.e. MCR for the branching unit synthesis and CuAAC reaction for pairing the branching unit with core scaffold. The amide bonds or its surrogates provided by MCR and the \textit{trans}-amide bond isostere 1,2,3 triazole provided by CuAAC will result in the formation of highly decorated ‘peptide mimetic dendrimers’.\textsuperscript{94a,99} Through this way, the synthetic difficulties like multi-step process, purification etc of peptide-decorated dendrimers (PPDs)\textsuperscript{100} can be easily solved and also could be able to maintain the unique properties of PDDs like excellent hydrogen bonding capability,\textsuperscript{101} mimicking the activities of biological molecules,\textsuperscript{102} proteolytic stability,\textsuperscript{103} absolute control over size, composition\textsuperscript{100c} etc.

In conclusion, “MCR-click” protocol has successfully replaced the classical multi-step synthetic approach for synthesizing potential natural product like complex macrocycles and highly decorated dendritic architectures. A myriad of applications are reported for macrocycles and dendrimers in both medicinal and material chemistry and thus these molecules become the quintessential part of contemporary research. Synthetic chemists are endeavoring hard to build these still underexplored scaffolds using newer and easier synthetic strategies. The ever-increasing need for the development of step-economic and cost-effective synthetic strategies for building advanced functional molecules have motivated us to work on this field. The subsequent chapters will give an extensive description on our effort towards the synthesis of highly decorated peptidomimetic macrocycles and dendritic architectures based on a build-pair strategy by combining MCR with click chemistry. The major part of the original research work presented in this thesis is on the building of peptidomimetic macrocycles using both intramolecular and intermolecular three step “MCR-Click” strategy and chapter 4 is on the development of dendrimeric architectures based on the same “MCR-Click” strategy. The graphical representation of the whole research work described in the thesis is shown below.
Figure 1.14. Graphical representation of the whole research work.
References


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