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An easy two step synthesis of macrocyclic peptidotriazoles via a four-component reaction and copper catalyzed intramolecular azide–alkyne [3+2] click cycloaddition

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ABSTRACT

A two-step macrocyclization strategy for the synthesis of 12- and 14-membered cyclic peptidotriazoles by combining a one pot four-component reaction and an intramolecular [3+2] azide–alkyne click cycloaddition reaction is described. Macrocycles are obtained in good to excellent yield from the aqueous work-up of the reaction mixture and it is possible to expand or contract the ring size by adjusting the length of the nitrile moiety used in the MCR stage.

Macrocyclic compounds have unique physicochemical and topological properties that allow them to exhibit unusual biological properties.[1] Macrocycles are generally considered as molecules containing at least one large ring composed of 12 or more atoms. Macrocycles are more conformationally restricted (due to the presence decreased number of rotatable bonds) than their acyclic analogues and have the ability to exhibit high target binding affinity, selectivity, and improved oral bioavailability. Additionally, macrocyclization is an efficient way of increasing cellular penetration via the decrease in polarity of peptidic drug leads.[2] Macrocycles have been proven to be efficient as protease inhibitors,[3] G protein-coupled receptors (GPCRs),[4] and protein–protein interaction inhibitors.[5] Natural products are one of the sources of bioactive macrocycles such as erythromycin, rapamycin, vancomycin, cyclosporine, and epothilone.[6] Natural products exhibit enormous structural diversity.[7] However, there are several problems associated with their use in screening experiments including difficulties with purification, bioactive component identification, structural assignment, chemical modification, and analogue synthesis.[8] These difficulties have motivated medicinal chemistry researchers to develop strategies such as diversity oriented synthesis (DOS) of macrocyclic compounds with known bioactive domains such as peptide motifs.[9] Peptide motifs are present in many biologically active molecules, and many peptides are drugs.[10] However, molecules of such classes are proven to be largely inadequate for modifying more challenging biological targets.

One of the methods for improving the bioactivity of peptidic molecules is the introduction of bioisosteric functionalities in them.[11] The resulting molecules are known as peptidomimetics, and they usually present improved stability, bioavailability, and selectivity toward a particular target.[12] Many of these molecules are made by the stepwise creation of a core structure followed by the ring closure using standard reactions like ring closing metathesis, lactonizations, and lactamizations.[13,14] Although, these reactions are proven to be useful, but still proceed with low yields and require high dilution to counterbalance the entropic loss associated with the formation of a preferred conformation.

An alternative method developed for addressing problems such as yield, selectivity, step economy, and structural diversity of peptidomimetics is the use of multi-component reactions (MCRs)[15,16] to construct the core structure with pairable functionalities and subsequent functional group pairing to effect the chemoselective ring closure.[17] The ring closure is usually carried out by using Huisgen 1,3-dipolar cycloaddition reaction between the azides and alkynes in a 'click chemistry' manner to produce a 1,2,3-triazole functionality.[18] The introduction of the triazole ring imparts rigidity to the molecule and mimics either the *cis*- or the *trans*-like configuration of the amide bond.[19] Consequently, many bioactive macrocycles with diversity and complexity are now readily available in chemist's showcases.[12a,20] Even though, multi-component reactions have proven to be very fruitful routes for the construction of

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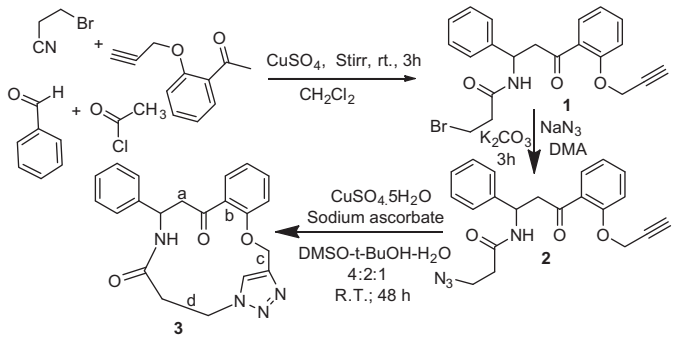
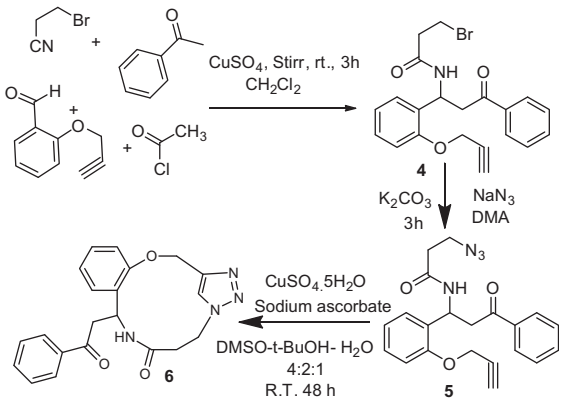


Scheme 1. MCR and click method for the synthesis of 14-membered macrocycles.



Scheme 2. MCR and click method for the synthesis of 12-membered macrocycles.

libraries, only limited attention has been directed toward their potential for accessing the macrocyclic target class.

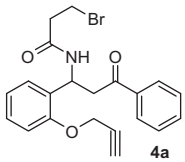
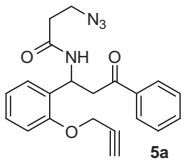
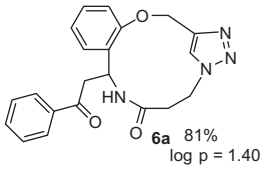
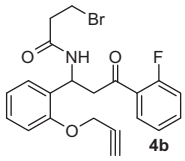
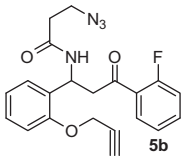
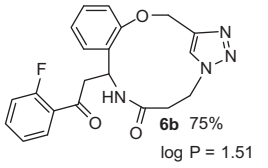
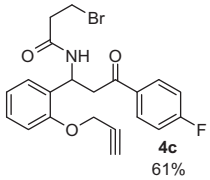
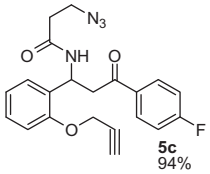
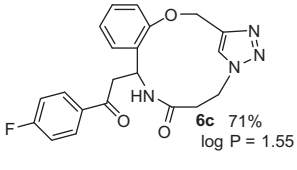
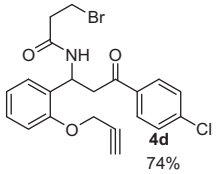
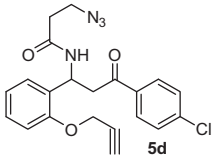
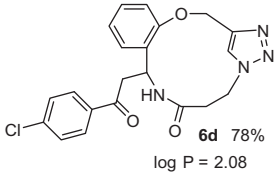
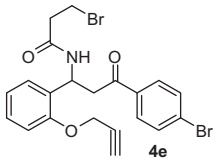
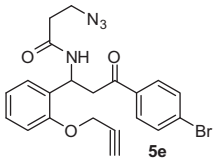
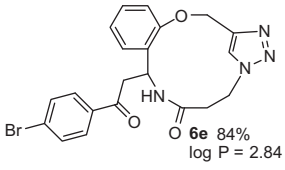
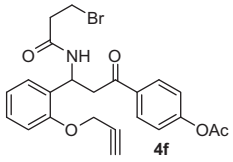
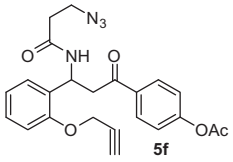
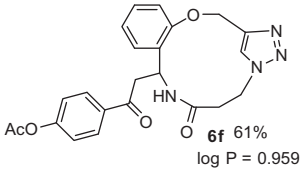
β-Ketoamides are important building blocks for the synthesis of 1,3-amino alcohols and β-lactams. The former is a structural part of peptidyl nucleoside antibiotics such as nikkomycins and polyoxins[21] and the latter is found in β-lactamase inhibitors such as 6-β-bromopenicillanic acid.[22] We have recently reported a couple of protocols for the synthesis of β-ketoamide structures based on a four-component catalytic MCR.[23] Our interest in multi-component reactions and peptidomimetics[24] prompted us to look into the possibilities of functionalizing the β-ketoamide structures with azide and alkynes for synthesizing macrocycles with 1,2,3-triazole modifications. The overall strategy is depicted in Scheme 1.

As shown in Scheme 1, the alkyne **1** with a β-amido-ketone core was synthesized in a one pot manner by the reaction of a propargylated acetophenone with benzaldehyde and bromopropionitrile in the presence of acetyl chloride using copper sulfate as catalyst at room temperature. The bromine in alkyne **1** was subsequently replaced with an azide group by treatment with sodium azide in basic conditions. The introduction of the azide functionality was found to be chemoselective with the ring halogens remaining intact. Using the azido alkyne **2a** as the model compound, optimization of the macrocyclization was carried out by intramolecular [3+2] azide–alkyne cycloaddition using various copper sources. The studies were initiated using freshly purified copper iodide in THF in the presence of excess amount of diisopropyl amine at room temperature.[25] TLC examination in constant intervals up to several hours revealed the failure of this methodology to effect cycloaddition. We have then examined the utility of copper sulfate–sodium ascorbate system in different solvents. The cycloaddition was

Table 1
List of 14-membered macrocycles prepared and its substrates

Bromo alkynes	Azdo alkynes	Macrocycle
1a 58%	**2a** 73%	**3a** 70% log P = 1.40
1b 64%	**2b** 91%	**3b** 71% log P = 1.52
1c 74%	**2c** 71%	**3c** 78% log P = 2.03
1d 72%	**2d** 73%	**3d** 79% log P = 2.6

Table 2
List of 12-membered macrocycles prepared and its substrates

Bromo alkynes	Azdo alkynes	Macrocycle
 **4a** 66%	 **5a** 91%	 **6a** 81% log p = 1.40
 **4b** 67%	 **5b** 88%	 **6b** 75% log P = 1.51
 **4c** 61%	 **5c** 94%	 **6c** 71% log P = 1.55
 **4d** 74%	 **5d** 71%	 **6d** 78% log P = 2.08
 **4e** 72%	 **5e** 65%	 **6e** 84% log P = 2.84
 **4f** 65%	 **5f** 68%	 **6f** 61% log P = 0.959

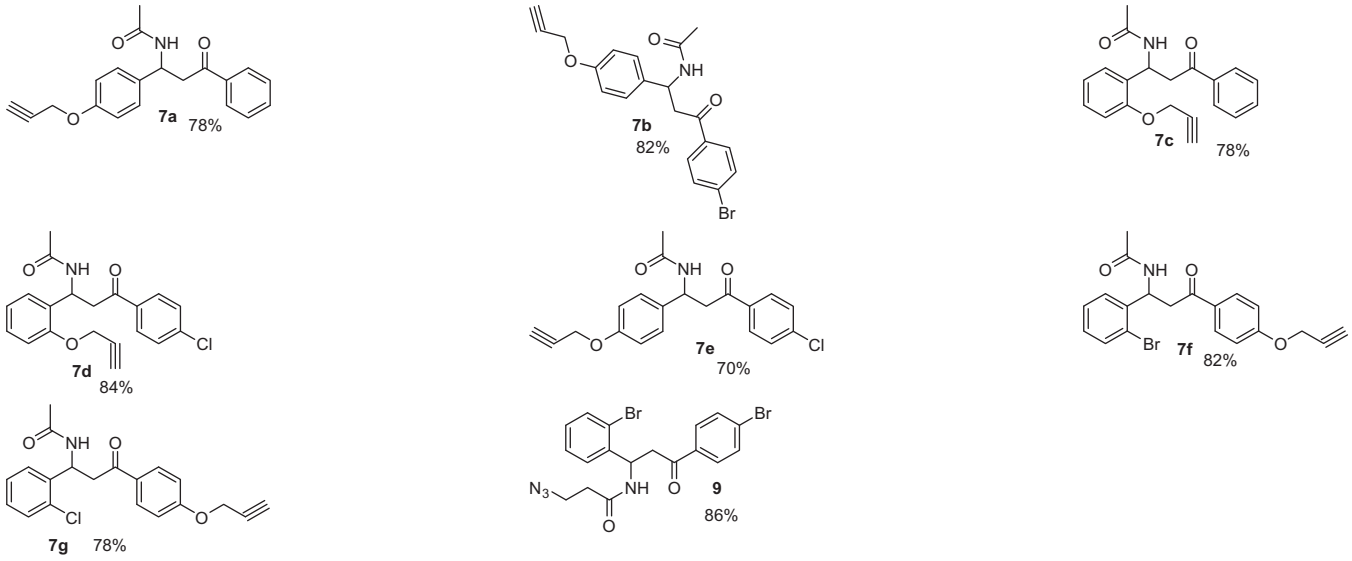
found to be efficient in a solvent system of DMSO/*t*-BuOH/H_2O in the ratio 4:2:1 to produce a 14-membered macrocycle **3a** in 70% yield.[26] The progress of the reaction was found to be slow and took 48 h to reach completion. The work-up was done by aqueous precipitation followed by simple solvent wash. The generality of the method was examined by synthesizing azido–alkynes **2b**–**2d** with chlorine, bromine, and fluorine in the *o*-position of the aldehyde fragment of the β-amido ketone core and subsequent macrocyclizations. The macrocycles **3a**–**3d** prepared are shown in Table 1. Among the compounds, the azido–alkynes with chlorine and bromine in the *o*-position of the aldehyde part of the β-amido ketone core gave slightly higher yield for the desired product.

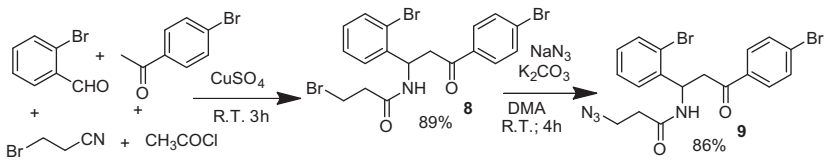
An interesting feature of this macrocyclic system is the presence of an amide and a triazole functionality along with an endocyclic keto alkyl and an akyl ether group in the ring. A survey of peptide bond isosteres revealed that amide bond is boisosteric with $-CH_2-CO-$, $-CH_2O-$, and 1,2,3-triazole functionalities with difference in the magnitude of stability factor.[27] Since compounds **3a**–**3d** contain an amide and three of its isosteres (the alkene functionality contributed by the benzene ring is excluded) these compounds can be considered as a macrocyclic tetrapeptide (or peptidomimetic) with at least four points where stereochemical or scaffold diversity can be introduced (see positions marked as a, b, c, and d in **3**, Scheme 1).

We have then turned our attention toward the synthesis of a 12-membered ring system by putting the alkyne functionality in the aldehyde part of the azido–alkyne **5**. As shown in Scheme 2, the one pot reaction of the propargylated benzaldehyde and acetophenone with 3-bromopropionitrile in the presence of acetyl chloride and copper sulfate afforded the bromo alkyne **4** in excellent yield.

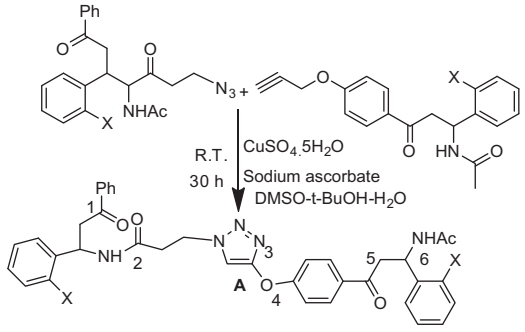
The chemoselective replacement of the side chain bromine with an azide group afforded the azido–alkyne **5**. The intramolecular [3+2] azide–alkyne cycloaddition of **5** afforded the 12-membered cyclic peptidomimetic **6** in appreciable yield. **6** also contains one amide bond and three amide isosteres in which the macrocyclic system occupies the amide and two of its isosteres and the third amide isostere is present in the form of an *exo* alkyl keto group. Lists of 12-membered macrocycles synthesized are given in Table 2.

Table 3
Alkyne and azide building blocks used for the synthesis of acyclic peptidomimetics **10–16**





Scheme 3. One pot **4** component synthesis of β-bromo-propionamido ketone and is conversion to azide **9**.



Scheme 4. Copper catalyzed azide–alkyne cycloaddition reaction for the synthesis of linear peptidotriazole **A** with two amide bonds and four amide bond isosteres.

As seen in Tables 1 and 2, the overall yields of the macrocycles are in the appreciable range with slight dependence to the ring size and the nature of the substituents. The yield obtained for the 12-membered ring systems are slightly higher than for the corresponding 14-membered counterparts. Similarly azido–alkynes containing a bromine substituent afforded slightly higher yield for the macrocycles.

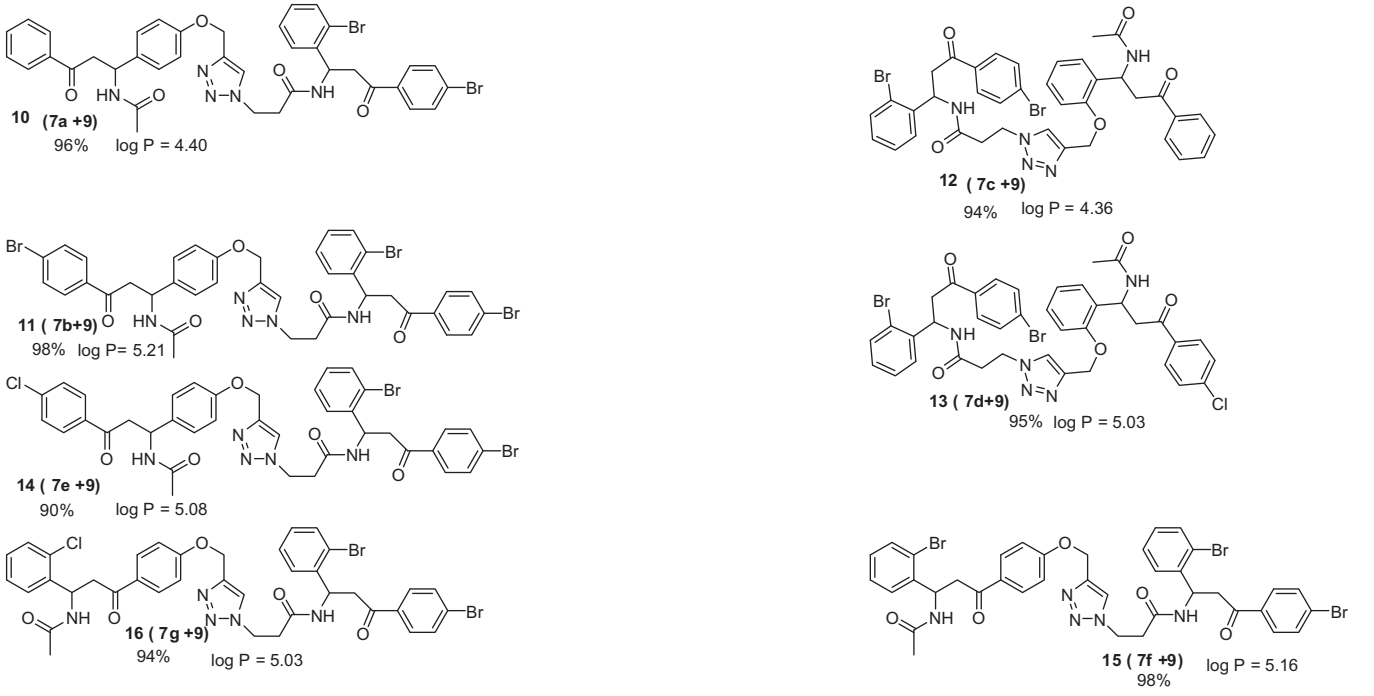
An interesting feature of this methodology is the possibility for the expansion or contraction of the ring size by adjusting the length of the nitrile source used for the MCR synthesis of azido–alkynes. For example, the uses of bromo-valeronitrile can step-up the ring size to **15**.

As an extension of this methodology, the usefulness of the β-amido carbonyl scaffolds for the synthesis of acyclic peptidomimetics was also demonstrated by synthesizing compounds **10–16** via the intermolecular [3+2] azide–alkyne cycloaddition of aklynes **7a–7g** with azide **9**. Alkynes **7a–7e** (Table 3) were prepared by the one pot multi-component reactions of a suitably propargylated aldehyde with acetophenone derivatives in the presence of acetyl chloride and acetonitrile with the assistance of copper sulfate as catalyst at room temperature.

Similarly, alkynes **7f** and **7g** were prepared by the reactions of propargylated acetophenone derivatives with aldehyde, acetonitrile, and acid chloride by following the same procedure. All the reactions afforded good to excellent isolated yield for the desired products. Azide **9** was synthesized by a one step creation of the bromo derivative **8** and subsequent replacement of the bromine by treatment with NaN_3 (Scheme 3). [3+2] Cycloaddition reaction between the alkynes and azides was examined by following the same strategy adopted for the macrocyclization reactions. The reactions afforded acyclic peptidotriazole **10–16** with general structure A (Scheme 4, the isosteres are numbered as 1–6 in A) contain two amide bonds and four amide bond isosteres. The results are listed in Table 4.

In order to provide an indication about the drug-likeness of the macrocycles as well as the linear peptidotriazoles, we have calculated the lipophilicity constant (log*P*) values of the compounds using molinspiration Property calculation service (www.molinspiration.com) and the values obtained are given below the structures presented in respective Tables. Drug-like molecules usually have log*P* values in between −0.4 and 5.6 with a molecular weight <500.[28] According to the classification given in comprehensive medicinal chemistry database, the average log*P* value for anti-neoplastics, hypnotic, antihypertensive, and anti-infective drug classes are 1.59, 2.20, 1.97, and 2.38 respectively.[29] The log*P* values obtained for the present compounds indicate that, cyclic peptidomimetics **3a**, **3b**, **6a–6c,** and **6f** are in the range of anti-neoplastics, **3c** and **6d** are in the range of antihypertensive and **3d** and **6e** are

Table 4
List of acyclic peptidotriazoles prepared



in the range of anti-infective drug classes. The log*P* values of liner peptidotriazoles **10**–**16** are also in the qualifying range of drug-likeness.

In conclusion, we have demonstrated a two-step synthesis of cyclic as well as acyclic peptidomimetics based on an MCR and click strategy. Structural features as well as the preliminary assessment of drug-likeness contributing parameters such as log*P* indicate that, the macrocycles can find use in the search for drug leads.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.116.

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