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Facile and Rapid Green Route for the Synthesis of Privileged Peptidotriazoles Based on Oxazolonic Acids by Click Fragment Assembly

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A convenient synthetic pathway to triazole-functionalized oxazolone peptidomimetics by click fragment assembly is described. The target molecules were obtained by the ligation of oxazolone-based peptides with azidopeptides via Cu(I)-catalyzed Huisgen cycloaddition reaction ("Click Chemistry").

One of the most exciting and potentially rewarding challenges in modern drug discovery is the design of chemical reaction sequences that can provide maximum structural complexity, diversity, and drug-like properties in a minimum number of synthetic steps.[1] Fragment-based assembly has emerged as an efficient strategy to generate structural diversity and complexity in drug leads for the development of small molecule inhibitors, with multiple binding pockets in their active sites.[2a] There are two major issues in fragment-based drug discovery. One is the selection and availability of a robust, high yielding, and low cost chemical reaction that can provide functionally diverse and structurally complex fragments. The second one is the availability of a modular reaction that can mimic the "nature's creation strategy" for the assembly of fragments. These two issues stimulated the effort toward the search for new green chemical methods for fragment generation and fragment assembly.[2b,2c]

In recent years, many new reaction methodologies have been developed for the generation of scaffolds that can fit in drug leads.[3] Among such methods, multicomponent reactions (MCRs) are particularly useful to produce smart molecular fragments preferably in a one-pot and one-step manner with high atom economy and less resource consumption.[3] Among the various MCRs, isocyanide-based MCRs like Ugi and Passerini reactions are well known for creating small peptide like molecules, with high degree of structural complexity and for the incorporation of stereogenic centers in scaffolds, which is often positively related with bioactivity.[4]

Among the various ligation techniques, the Cu(I)-catalyzed Huisgen cycloaddition between two structural fragments, suitably functionalized with pairing handles such as an alkyne in one fragment and azide in the second one has greatly advanced in the last decade.[5] This cycloaddition provides a 1,2,3-triazole linker between two scaffolds, which will ultimately change a non-peptidic molecule to a peptide like one with enhanced physicochemical properties such as proteolytic stability, selectivity, bioavailability, etc.[6–8]

Oxazolones, also known as azalactones, are internal anhydrides of acylamino acids and can be easily prepared from *N*-acylamino acids via. cyclodehydration.[9] They possess important biological activities such as antimicrobial,[10] anti-inflammatory,[11] anticancer,[12a,12b] anti-HIV,[13] antiangiogenic,[14] antitumor, antagonistic, and sedative properties.[15] Interesting examples include spirocyclopropyl oxazolone (**a**)[13] and pancratistatin (**b**) (Figure 1).[12c] The former represents a new class of herpes protease inhibitor[13] and the later is a phenanthrene alkaloid-based anticancer drug[16] obtained from the intramolecular Diels–Alder reaction of phenacycloxazolone.

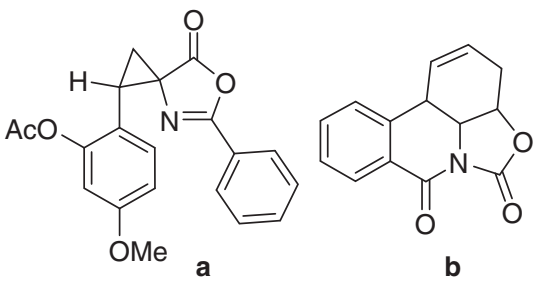

Figure 1. Classical examples of oxazolone-derived drugs.

Moreover, the oxazolone ring resembles a cyclic ester and, its amide like geometric parameters make it a peptide bond isoster.[17] In recent years, peptide-based drugs have emerged as a new class of therapeutic agents and more than 60 FDA-approved peptide based drugs are available on the market. Most of these peptide drugs contain β-amino acids, nonnatural amino acids or peptidomimetics as a core structural scaffold.[18,19] Such complex molecules are prepared by adopting a tailoring pharmacology approach based on the combination of heterocyclic functional parts and small peptide-like backbones.[20] The final molecule may exert multiple agonistic functions. These relatively high molecular weight peptidomimetics can easily link with intercellular targets, a task that cannot be addressed by small molecule approaches.

In continuation of our ongoing research for the development of heterogenized peptidomimetics, herein we report our recent results in the synthesis of a new series of small β-peptide-functionalized oxazolonic acid mimics with general structure **A** or **B** (Figure 2) based on MCR and click strategy. The overall reaction in most cases involves two multicomponent reactions and a "click" cycloaddition.

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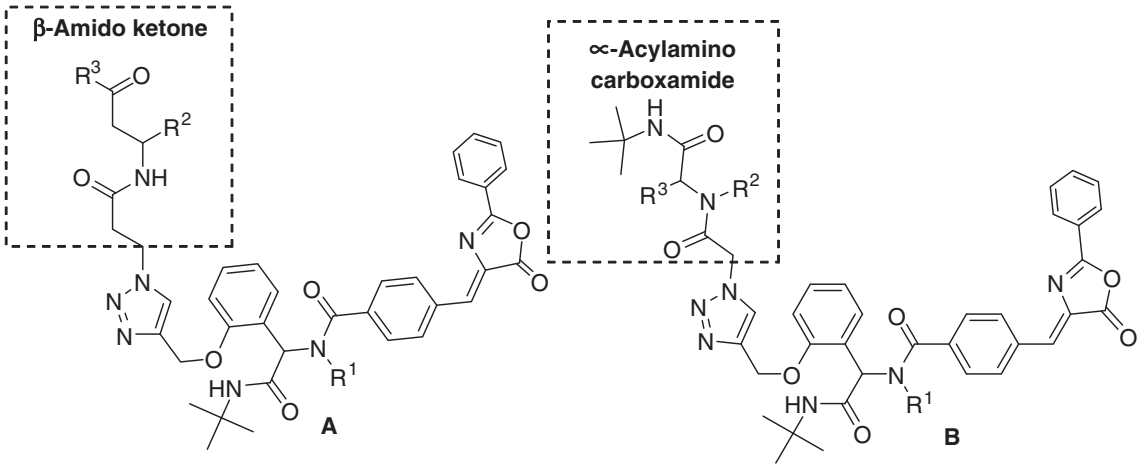
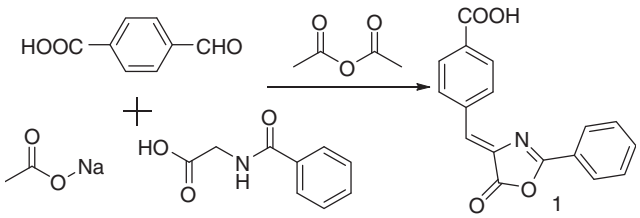


Figure 2. Triazole-linked peptidomimetics connecting oxazolone-based tripeptides with carboxamide residues.



Scheme 1. Synthesis of oxazolone **1** via. Erlenmeyer–Polchi reaction.

Results and Discussion

Our primary targets were tripeptidomimetics like structure **B** (Schemes 1 and 2 and Figure 3) which were obtained from Ugi reactions of oxazolonic acid **1**, propargylated aldehydes and amines with isocyanides. Oxazolonic acid **1** with *Z* configuration (confirmed from ^{1}H NMR)[9b] was prepared in good to excellent yield by following the classical Erlenmeyer–Polchi reaction of formyl benzoic acid and hippuric acid with sodium acetate and acetic anhydride[9] (Scheme 1).

Having synthesized the oxazolonic acid **1**, we next preceded to the synthesis of oxazolonic acid-based tripeptides **2a**–**2c**. The reaction was initiated by stirring *o*-propargylated benzaldehyde with butylamine in methanol for 30 min. To this, oxazolonic acid and *tert*-butylisocyanide were added and the stirring was continued with TLC examinations at regular intervals. After 46 h, the solvent was removed and crude mixture was repeatedly washed with petroleum ether to obtain the desired product **2a** (60%).

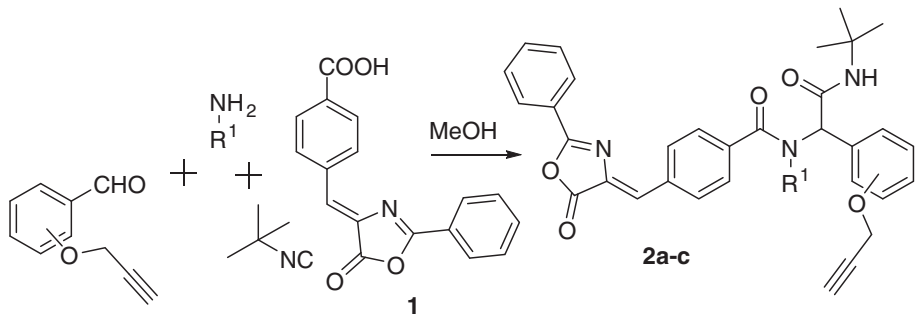
The process was repeated with benzylamine in two different combinations and the small peptide-like scaffolds **2b** and **2c** were also isolated in good yield (Figure 3).

In the next step, syntheses of specially designed azido peptides required for the ligations were undertaken. β-Acetamido ketone or amino ketone residues were selected as the backbone structure of azides because of their known biological and pharmacological properties.[21] These compounds were prepared by an alternate Mannich-type reaction which involves the one-pot condensation of a non-enolizable aldehyde with an enolizable ketone in the presence of a bromonitrile and acetyl chloride.[22] We have screened various catalysts like $BF_3 \cdot Et_2O$, Mont.K10, selectfluor, phthalocyanin, $CuSO_4$, etc.[22,23] and found that copper sulfate was very efficient for promoting this reaction to form bromo derivative of the β-amido ketone. The copper sulfate-assisted process was adopted as the chosen methodology[23c] and the bromo functionalized β-amido ketones **3a** and **3b** thus prepared were then converted to the corresponding azides **4a** and **4b** in appreciable yield (Scheme 3).[23e]

Having synthesized the alkynes and azides, we then turned our attention toward the final assembly of substrates by copper(I)-catalyzed alkyne-azide click chemistry (CuAAC). As shown in Scheme 4, the coupling was done using modified Sharpless conditions.[24a] The alkynes and azides were mixed with 0.2 equiv of $CuSO_4$ and 0.4 equiv of sodium ascorbate in a solvent mixture contain *t*-BuOH, water and DMSO (4:2:1) at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (10 h), the aqueous workup of the mixture afforded the desired peptidomimetic. The process was repeated in various combinations and the peptidomimetics **5a**–**5f** were isolated in 65–75% with sufficient purity (Figure 4). The molecules were then characterized using ^{1}H NMR and EI-MS spectroscopy.

In order to suggest the regio- and stereoselectivity in triazole formation, we have compared the spectral data of the peptidomimetics with literature values.[24] The ^{1}H NMR spectra showed a downfield signal around 7.8 ppm in most cases, corresponding to the ethylenic proton of an *anti*-1,4-substituted 1,2,3-triazole. This value is well in agreement with the reported spectral values.[24] It should be noted that the cycloaddition reactions of tripeptides **2a**–**2c** with the azide **4b** took more reaction time (15 h) compared to the **4a** analogues (10 h) and, afforded products **5c**, **5d**, and **5f** respectively. This may be due to the presence of the electron-withdrawing bromine atom at the *para* position of the aromatic rings.[25]

The purity of the samples were again confirmed by performing HPLC analysis. As shown in Figure 5, all the click products gave only one peak corresponds to the molecular ion in the HPLC profile. This again confirmed that, the molecules were formed as a single isomer (For HPLC profiles of all the click products, see Supporting Information).



Scheme 2. Synthesis of oxazolonic acid-functionalized α-acylamino carboxamide alkynes **2a**–**2c** by *U*-4CR.

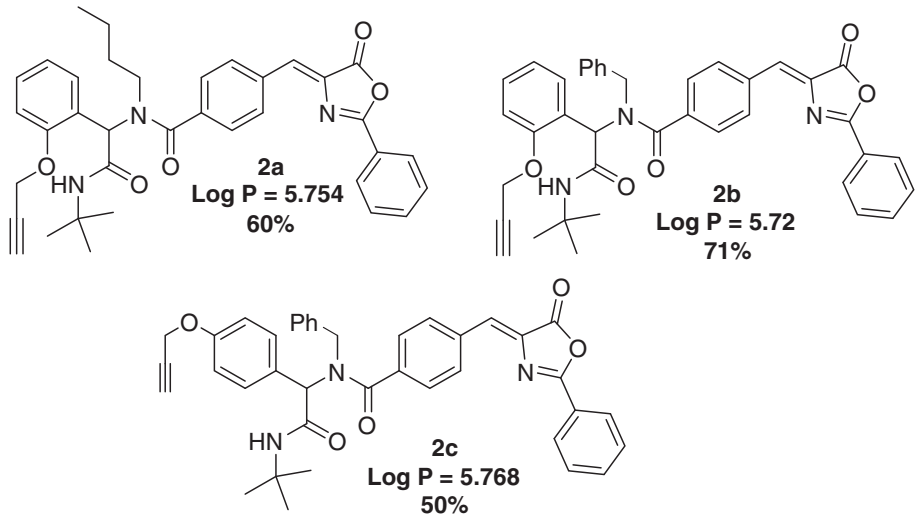
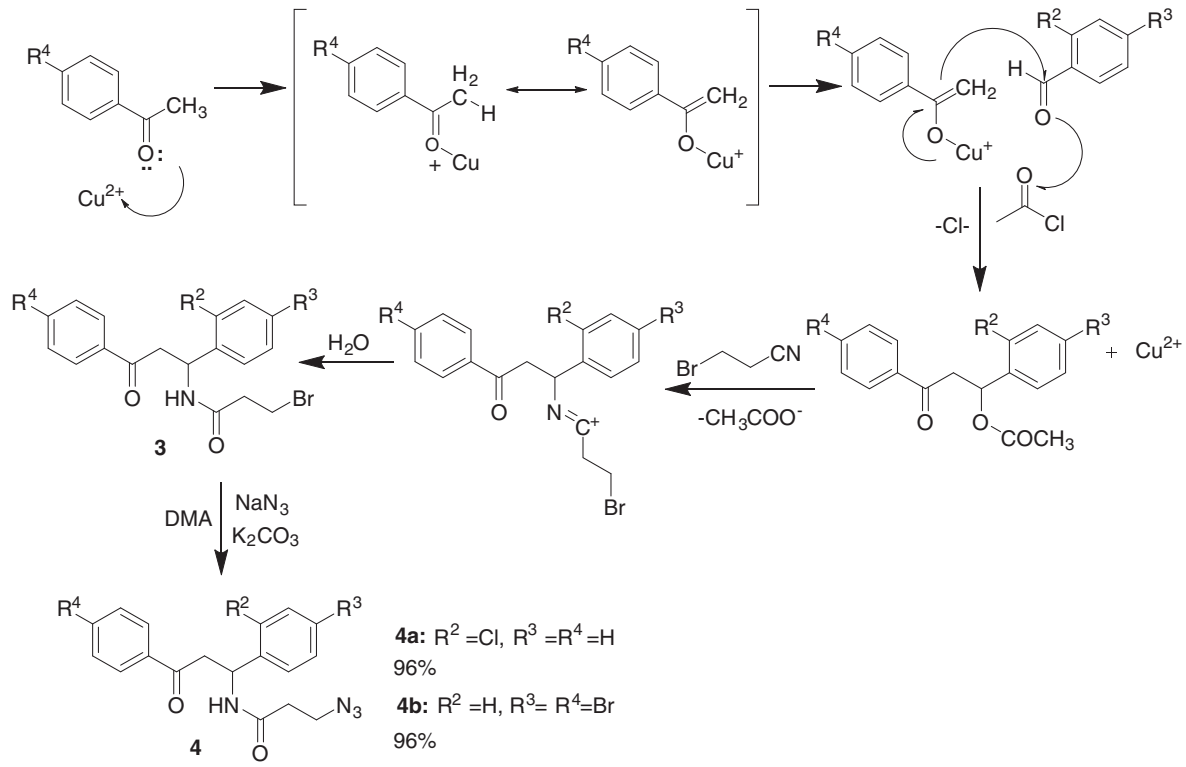
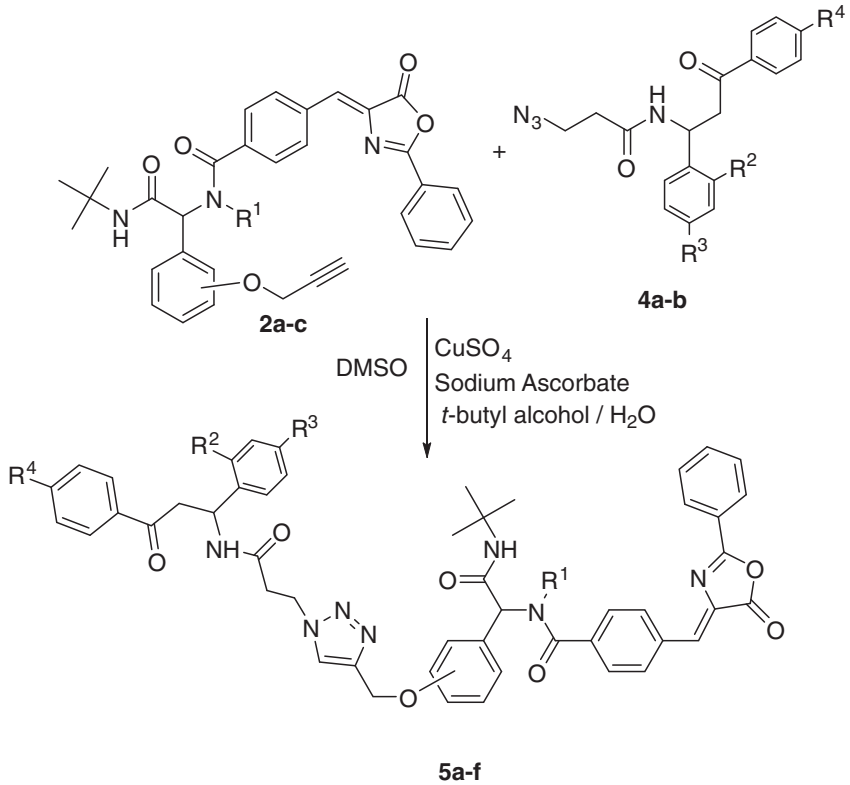


Figure 3. Structures of alkyne fragments **2a**–**2c** obtained from *U*-4CR.



Scheme 3. β-Amido ketone azides **4a** and **4b** obtained from alternative Mannich type MCR.[22a–22c]



Scheme 4. Synthesis of triazole-linked peptidomimetics **5a**–**5f** using β-amido ketone azides.

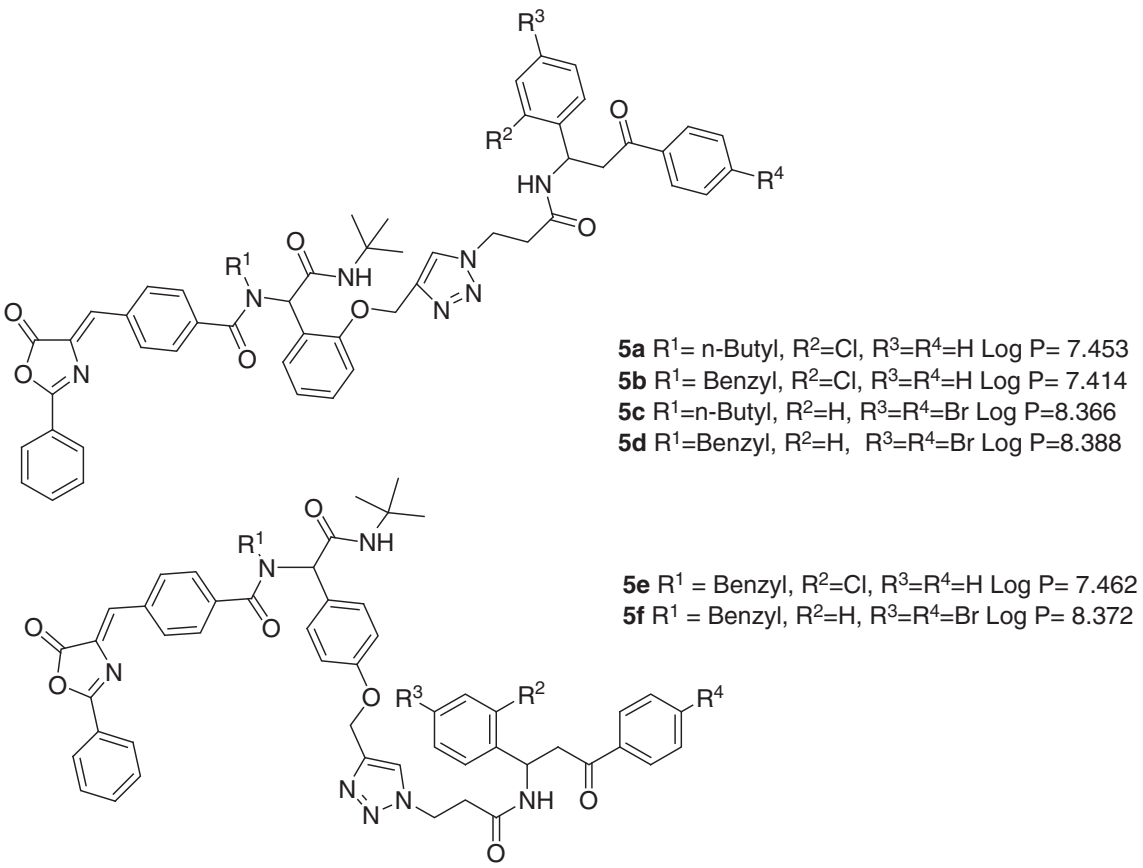


Figure 4. List of peptidomimetics obtained from Cu(I)-catalyzed alkyne–azide cycloaddition between alkynes **2a**–**2c** and azides **4a** and **4b**.

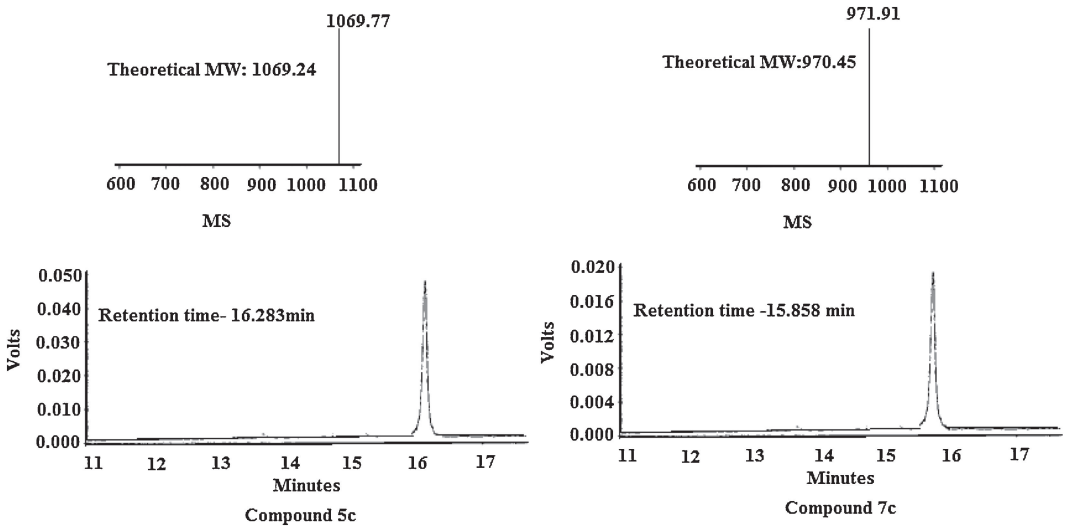
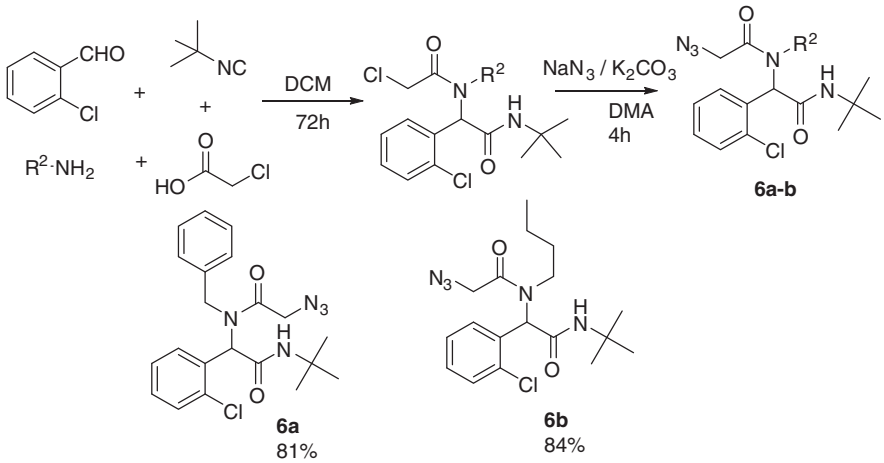


Figure 5. Representative HPLC profiles. Analytical HPLC profiles of compounds **5c** and **7c** and the MS of the same samples.

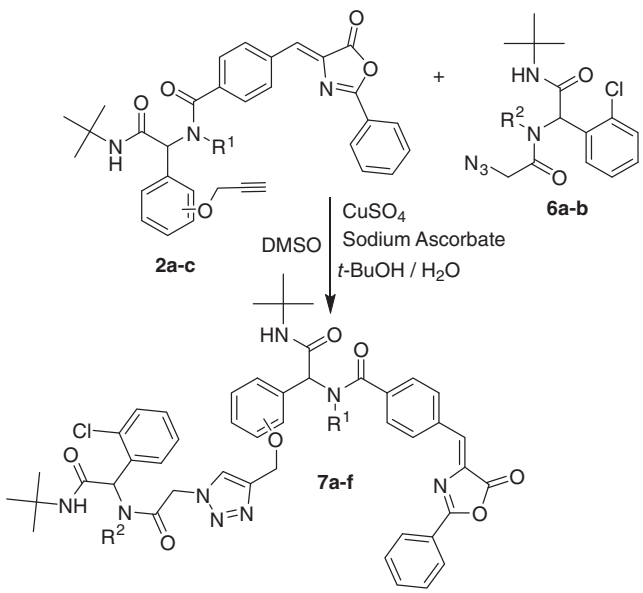


Scheme 5. Synthesis of azides **6a** and **6b** from *U*-4CR.

As an extension, the ligation studies were conducted with a second set of azides **6a** and **6b** containing α-acylamino carboxamide moieties. **6a** and **6b** were prepared by following an Ugi reaction of chlorobenzaldehyde, chloroacetic acid, and *tert*-butylisocyanide with an amine in dichloromethane at room temperature.[4] After 72 h of stirring, the reaction afforded the chloro derivative of the α-acylamino carboxamides in high yield. The subsequent N_3 substitution in the Ugi reaction products by treating the chlorides with sodium azide in the presence of potassium carbonate in dimethylacetamide at room temperature resulted in the formation of the α-acylamino carboxamide azides **6a** and **6b** in appreciable yield (Scheme 5).

The cycloaddition reactions of alkynes **2a**–**2c** with **6a** and **6b** were conducted in the same conditions mentioned for the reactions between **2a**–**2c** and **4a** and **4b**, and took place with the formation of the *anti*-1,4-substituted 1,2,3-triazoles **7a**–**7f** in 80–88% yield (Scheme 6). The results are presented in Figure 6.

The log P values of compounds **5a**–**5f** and **7a**–**7f** were also calculated using an online calculation service (www.molinspiration.com) and are presented in Figures 4 and 6. The



Scheme 6. Cu(I)-catalyzed [3 + 2] cycloaddition between alkynes **2a**–**2c** and α-acylamino carboxamide azides **6a** and **6b**.

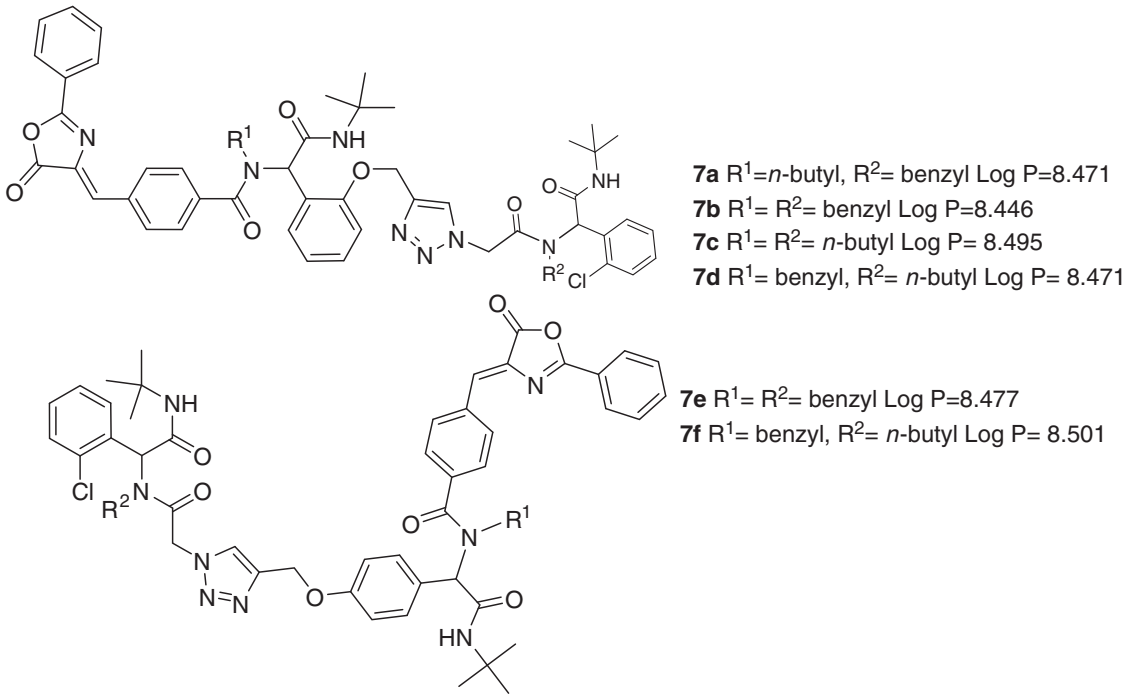


Figure 6. List of peptidomimetics obtained from Cu(I)-catalyzed azide–alkyne cycloadditon of alkynes **2a**–**2c** with azides **6a** and **6b**.

peptidomimetics **5a**–**5f** and **7a**–**7f** are made up with functionalities like amide bonds and its isosteres such as 1,2,3-triazole, oxazolone, keto-methylene (CH_2–CO), alkyl ether (O–CH_2), etc.[17] Thus, it can be envisioned that employment of these peptide bond isosteres can impart a significant amount of proteolytic stability in the final molecule. Compounds **5a**–**5f** contain three amide bonds and four of its isosteres and **7a**–**7f** contain four amide bonds and three of its isosteres. Hence, these compounds can be considered as heptapeptides (or peptidomimetics) with three points where scaffold diversity can be introduced (see positions marked as R^1, R^2, and R^3 in structures **A** and **B** of Figure 2).

Conclusion

In summary, we have prepared a small library of peptidomimetics comprised of triazole–oxazolone–amide functionality by the click reactions between the two types of small peptide-like scaffolds generated from multicomponent synthetic approach. The synthetic strategy involves the combination of MCR chemistry with click chemistry and both reactions are prototype models of green chemistry. Structural features of the compounds indicates that these molecules are promising in the lead discovery process.

Experimental

All chemicals, reagents, and solvents were purchased from Sigma Aldrich and Merck Ltd., India. ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker Avance 500 MHz spectrometer and the chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane, with J values in Hertz. The splitting patterns in ^{1}H NMR spectra are reported as follows: s = singlet; d = doublet; m = multiplet. High-resolution mass spectra were recorded under electron impact conditions using an AXMA CFR plus Kratos analytical Shimadzu. HPLC analysis were done using a Shimadzu LC-2010-HT system.

General Procedure for the Synthesis of 4-[(9Z)-5-Oxo-2-phenyloxazol-4(5*H*)-ylidenemethyl]benzoic Acid (1). A solution of formylbenzoic acid (0.3 g, 2 mmol), hippuric acid (0.378 g, 2 mmol), acetic anhydride (0.567 mL, 6 mmol), and anhydrous sodium acetate (0.162 g, 2 mmol) were refluxed under constant stirring for 3 h. After 3 h, the mixture was cooled and 20 mL of absolute ethanol was added slowly and allowed to stand for overnight. The crystallized crude product was filtered, washed with hot water and then with a small volume of 1:1 ice cold water–methanol mixture. The crude product obtained was dried and recrystallized in absolute ethanol to afford **1**.

General Procedure for the Synthesis of *N*-{(*tert*-Butylcarbamoyl)[2-(prop-2-ynyloxy)phenyl]methyl}-*N*-butyl-4-[(7*Z*)-5-oxo-2-phenyloxazol-4(5*H*)-ylidenemethyl]benzamide (2a). An equimolar amount of propargylated benzaldehyde (0.1 g, 0. 01 mol) and butyl amine (0.045 g, 0.01 mol) were taken in methanol (8 mL) and stirred at room temperature for 30 min. To this, one equivalent of *tert*-butyl isocyanide (0.051 g, 0.01 mol) and oxazolonic acid (0.183 g, 0.01 mol) were added and stirred at room temperature. The reaction was monitored by TLC and found to be complete after 46 h. The solvent was evaporated under vacuum and the crude product obtained upon repeated washings with petroleum ether (5 × 15 mL) afforded the pure **2a.**

General Procedure for the Synthesis of β-Ketoamide Azide (4a and 4b). A mixture of enolizable ketone (1 mmol), aldehydes (1 mmol), and 3-bromopropionitrile (1 mmol) in

acetonitrile (3 mL) was stirred in the presence of 5 mol % $CuSO_4$ at room temperature for 8 h. After completion of the reaction as indicated by TLC, the reaction mixture was poured into ice cold water and extracted with dichloromethane (15 mL). Evaporation of the solvent followed by purification on silica gel (100–200 mesh, ethyl acetate–hexane (3:1) afford pure functionalized bromo β-acetamidoketones. The resulting bromides (1 mmol), potassiumcarbonate (3 mmol), sodium azide (1 mmol) were dissolved in DMA. The reaction mixture was allowed to stir for 6–8 h and then poured into ice cold water. The precipitate was filtered, washed and dried in vacuum to afford **4a** and **4b**.

General Procedure for the Synthesis of Azides 6a and 6b. An equimolar amount of *Ugi chloride* (Ugi reaction product, 0. 0025 mol) and sodium azide (700 mg) are taken in dimethylacetamide (4 mL). To this K_2CO_3 (1 g) was added and stirred at room temperature for 4 h. The reaction mixture was then diluted with water. The white precipitate obtained was filtered and washed repeatedly with water to afford the pure azides **6a** and **6b**.

General Procedure for the Cu(I)-Promoted 1,3-Dipolar Cycloaddition Reactions. An equimolar amount of the azide **3a** (60 mg, 2 mmol) and the alkyne **2a** (83 mg, 2 mmol) are dissolved in minimum amount of DMSO. To this, 2 mL of *tert*-BuOH, 1 mL of water, $CuSO_4 \cdot 5H_2O$ (70 mg) and sodium ascorbate (83 mg) were added and stirred at room temperature. After 24 h, the mixture was poured in to cold water. The precipitated click product was filtered, washed with water and dried under vacuum to afford **5a**–**5f** and **7a**–**7f**.

Supporting Information

Copies of FT-IR, ^{1}H NMR and HRMS spectra of starting and final compounds **1**, **2a**–**2c**, **4a**, **4b**, **5a**–**5f**, **6a**, **6b**, **7a**–**7f** and HPLC profiles of **5a**–**5f** and **7a**–**7f**. This material is available free of charge on the Web at: http://www.csj.jp/journals/bcsj/.

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