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Graphical Abstract

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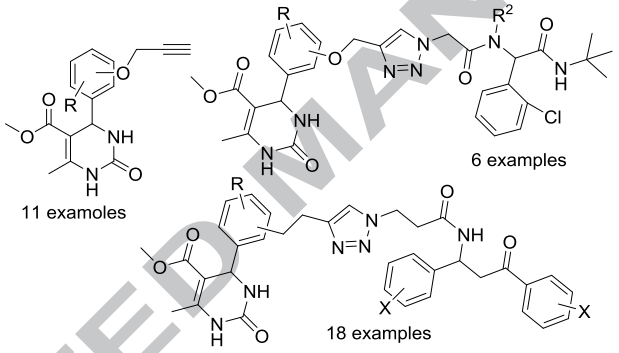

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A novel green synthesis of *α*/*β*-amino acid functionalized pyrimidinone peptidomimetics using triazole ligation through click-multi-component reactions

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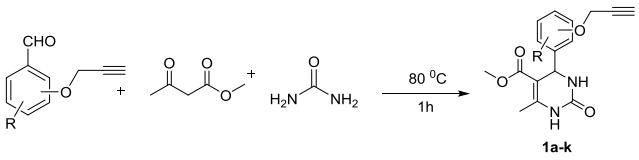
ABSTRACT

An innovative synthetic pathway for the preparation of a new series of triazole-decorated dihydropyrimidinone peptidomimetics with skeletal *α* or *β*-amino acid residue is reported. The protocol involves two synthetic steps with an initial solvent-free and catalyst-free synthesis of propargylated dihydropyrimidinones precursors using Biginelli condensations. The subsequent cycloaddition reactions of pyrimidinone alkynes with small peptide like azides prepared from Ugi or alternate Mannich type multi-component reactions afforded the triazole decorated pyrimidinone peptide conjugates in excellent yield with high regio and stereospecificity. In total, a scaffold diversity contains 11 new pyrimidinone alkynes and 18 new pyrimidinone peptidomimetics were introduced to the chemical space.

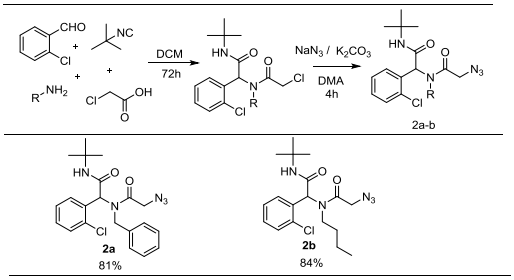
Development of structural scaffolds with skeletal diversity suitable to populate the chemical space of drug leads has been used in the algorithm of diversity oriented synthesis (DOS).[1, 2] One of the important strategies to achieve DOS is the explorations in multicomponent reactions (MCRs) [3] which are useful tools for building large heterocyclic libraries in one-pot, one step manner.[4] These class of reactions are also amenable to suitable design strategies for increasing the scaffold diversity in manifold with desirable bio-profiles. Interesting examples in this type of diversity intensification includes the union of MCRs[4] or 'clicking' [5] one of the MCR scaffolds with a different type of privileged scaffold.[6] Among the two, the latter one is more versatile for the creation of stereo and / or regiospecific 1,4-disubstituted 1,2,3-triazole derivatives. Many of such triazole derivatives possess valuable clinical profiles like anti-HIV, anti-allergic, anti-fungal or anti-viral properties.[7-12]

Dihydropyrimidinone derivatives also displays a wide range of biological activities and these have led to the development of a number of therapeutics including calcium channel blockers, antiviral, antitumor, antibacterial, anti-inflammatory and antihypertensive agents.[13-15] As part of our ongoing programmes for developing green protocols for scaffold synthesis, we decided to work on pyrimidinone chemistry and the subject matter of this paper is the development of a solvent-free Biginelli condensation route to functionalized pyrimidinones with cooperative functionalities and subsequent structural diversifications based on click chemistry to produce pyrimidinone-peptide conjugates. The studies were started with the alkyne functionalization of various hydroxyl aldehydes by base catalysed condensation reaction with propargyl bromide and six such aldehydes with one or more



Scheme 1. Synthesis of alkyne functionalized dihydropyrimidinones by solvent free Biginelli reaction

alkyne functionalities were prepared.. For performing Biginelli reaction, methyl acetoacetate and ethyl cyanoacetate were taken as the CH acidic oxo components and urea as the diamide component.



Scheme 2. Synthesis of α-amino acid type azides by U-4CR

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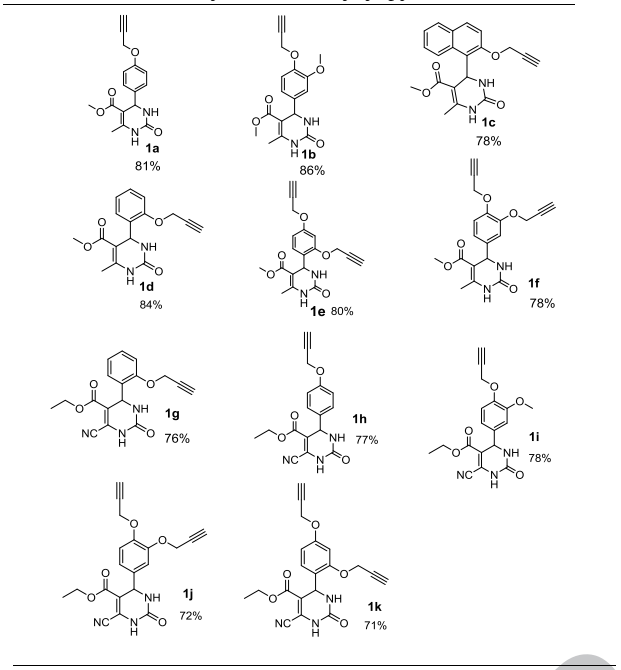
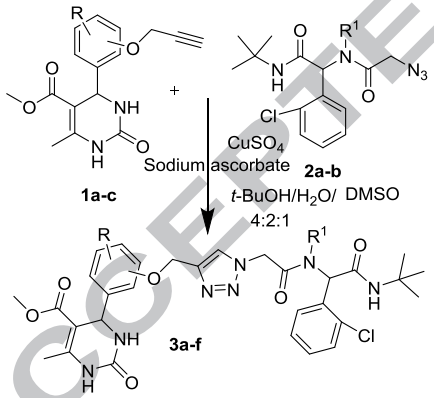
In an initial reaction, the components were mixed in equimolar quantities and heated to 80 ^{o}C in an oil bath. After 1h, the viscous mass obtained was cooled to room temperature and the solid mass was then stirred with water to obtain the precipitate of the alkynyl pyrimidinone derivative **1** in pure form (Scheme 1).[16] Accordingly, pyrimidinones **1a-k** were synthesized in 71-86% yield without the aid of a catalyst or solvent. The results are presented in Table 1.

Table 1. Solvent-free synthesis of alkynyl pyrimidinone scaffolds





Scheme 3. Synthesis of 1,4-disubstituted triazolyl DHPMs with skeletal α-amino acid residues via Cu (I) catalyzed Huisgen cycloaddition.

We then moved onto the demonstration of an amenable chemistry for increasing the skeletal diversity of some of the pyrimidinones listed in Table 1. For this, we decided to functionalize pyrimidinones **1a-c** with *α*-amino acid residues or *β*-amido ketone residues through 'click' cycloaddition to form highly diversified triazole derivatives of pyrimidinone peptidomimetics.

The azide derivatives of the *α*-amino acid residues **2a-b** were synthesized form the post condensation modification of chloro derivatives of the *α*-acylamino carboxamides obtained from Ugi MCR [17] as shown in Scheme 2.[18] Cycloaddition reactions between **1a** and **2a** was carried out at modified Sharpless condition.[7c] In a representative reaction, an equimolar mixture of **1a** and **2a** were mixed with 0. 2 equivalant of $CuSO_4$ and 0.4 equivalent of sodium ascorbate in a mixed solvent system containing *tert*-butanol, water and DMSO (4:2:1) at room temperature (Scheme 3). After 12 h, the reaction mixture was diluted with cold water to afford the click product **3a** (83% yield) in solid form.[19] The results of the studies with azides **2a-b** and alkynes **1a-c** are presented in Table 2. The regioselectivity in triazole formation was confirmed from ^{1}H NMR spectra in which the appearance of a singlet in between δ8-8.5ppm corresponds to the hydrogen on the 5-position of the 1,4-disubstituted 1,2,3-triazole regioisomer.[7c,d]

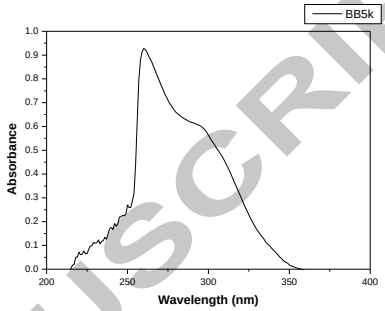


Figure 1. Absorption spectrum of compound **5k** ($2.805x10^{-5}$M) in DMSO. λabs.max. (nm): 260.0

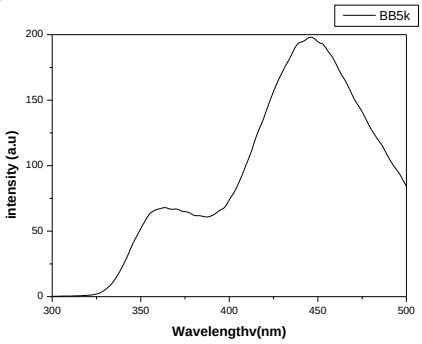
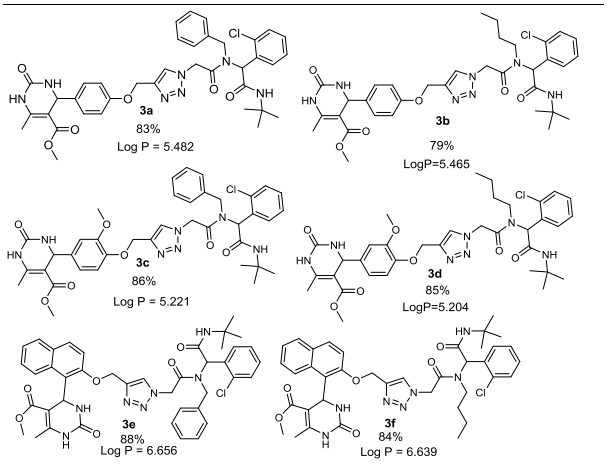


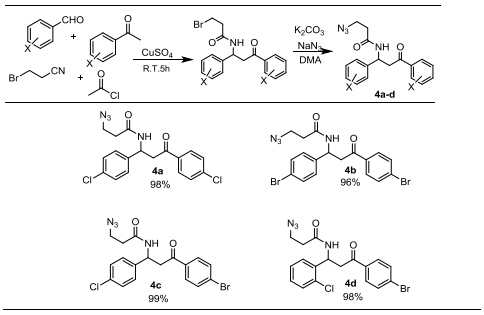
Figure 2. Emission spectrum of compound **5k** ($2.805x10^{-5}$M**)** in DMSO. λem.max. (nm): 364.0 and 446.0

Table 2. List of 1, 4-disubstituted triazolyl DHPMs with skeletal *α*-amino acid residues.



The skeletal diversity expansion studies were further extended with *β*-amino acid type azides **4a-d.** The azides **4a-d** were obtained from a two-step process as shown in Scheme 4.

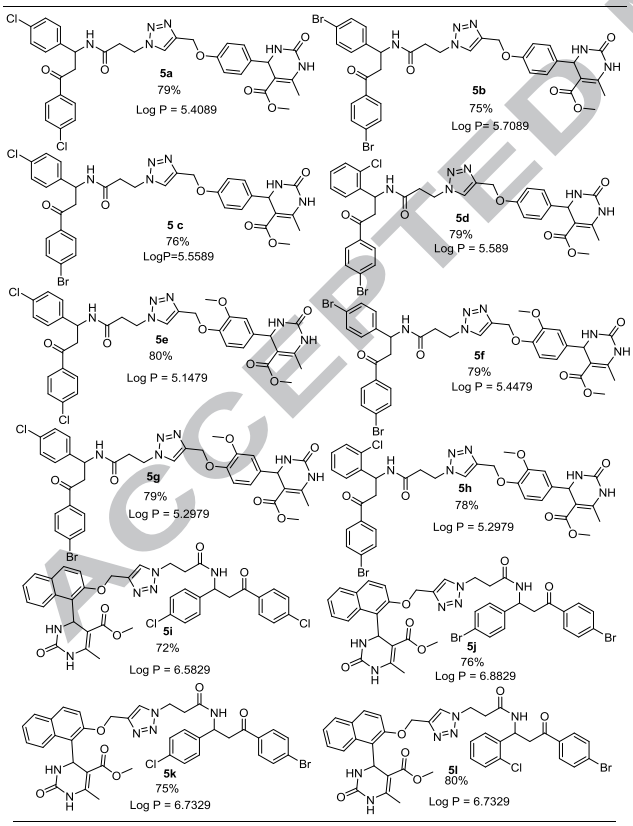
A $CuSO_4$ catalyzed alternate Mannich type four-component reaction[20] of bromopropionitrile with enolizable and non-enolizable oxo compounds in presence of an acid chloride afforded the bromoamido ketones. [20, 21]



Scheme 4. Synthesis of β-amido ketone azides by alternate Mannich reaction.

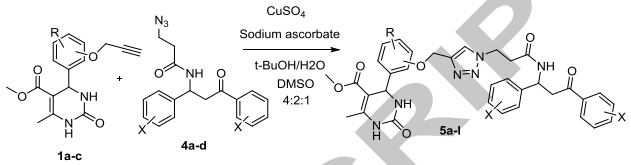
The bromoamido ketones were then converted to the azides **4a-d** in moderate to good yield and purity and are used for the azide-alkyne [3+2] click cycloaddition reactions with **1a-c** (Scheme 5). The reaction conditions applied was identical with the same adopted for click chemistry with azides **2a-b**. The resulting 1,4-disubstituted 1,2,3-triazolyl pyrimidinone peptidomimetics **5a-l** were obtained in 70-80% yield (Table 3).

Table 3. List of 1,4-disubstituted triazolyl DHPMs with skeletal β-amino acid residues.



Compounds **3a-f** and **5a-l** are promising in terms of their structural features. The presence a 1,4-disubstituted 1,2,3-triazole linker in between the pyrimidinone ring and the peptide residue may impart better stability to the molecules. The liphophilicity constant value (Log P) for both the sets of peptide conjugates **3a-f** and **5a-l** was also calculated using an online calculation service at www.molinspiration.com and the values are presented under the corresponding structures in Tables 2 and 3.

We have also carried out some preliminary investigations on the optical properties of compounds **3a-f** and **5a-l** by UV/Vis and fluorescence spectroscopy. A typical absorption and emission spectra of compound **5k** is given as Figures 1&2. All of the compounds have absorption wavelengths (λabs) in the UV region (266–286.5 nm), and have their emission wavelengths (λem) in the UV or visible region (332–446 nm).[22] Slight deviation from general behavior is observed in compounds with naphthyl groups. Compounds with naphthyl groups for example **5k** have showed two emission maxima.



Scheme 5. Synthesis of 1,4-disubstituted triazolyl DHPMs with skeletal β-amino acid residues via Cu (I) catalyzed Huisgen cycloaddition

In summary, we have introduced a new class of pyrimidinone scaffolds as well as pyrimidinone peptidomimetics to the chemical space by sharing the principles of green chemistry wherever possible. The procedure is simple with no requirements of sophisticated experimental set-up. We hope that, these new peptidomimetic molecules with a biological base can find application in the search for new drug leads or flurophores.

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16. *Typical experimental procedure for the synthesis of alkynyl pyrimidinone **1a***: A mixture of propargylated aromatic aldehyde (300 mg, 1mmol), methylacetoacetate (183 mg, 1 mmol) and urea (142 mg, 1. 5 mmol) were stirred and refluxed at 80 ºC for 1h in an oil bath. The completion of reaction was monitored by TLC. After cooling, the reaction mixture was poured into crushed ice. The separated solid was filtered and dried in vacuum to afford the crude product. Recrystallization from hot ethanol provides the analytically pure product **1a (**0. 243g, 81%) as white solid. Mp. 120-122 ^{o}C. IR (KBr) (νmax, cm^{-1}): 3277, 3247, 3115, 2115, 1716, 1651, 1608, 1304, 1175. ^{1}H-NMR (DMSO-(d_6) 400MHz) δ_H (ppm): 2.24 (s, 3H), 3.34 (s, 1H), 3.53 (s, 3H), 4.75 (s, 2H), 5.09 (s, 1H), 6.91-6.93 (m, 2H), 7.14-7.16 (m, 2H), 7.68 (s, 1H), 9.18 (s, 1H). ^{13}C-NMR (DMSO-(d_6), 100MHz) δ_C (ppm): 17.8, 50.6, 53.1, 55.6, 78.1, 79.2, 101.7, 114.2, 114.6, 127.3, 127.9, 137.5, 145.4, 152.1, 167.4. EI-MS: 301.1 (M^+).
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18. *Typical procedure for the synthesis of α-amino acid type azide **2a***: An equimolar amount of 2-chlorobenzaldehyde (140 mg, 1mmol), and benzyl amine (107 mg, 1mmol), are taken in dichloromethane (8 ml), and stirred at room temperature for 20 min. to form the Schiff-base. To this, one equiv. of *tert*- butyl isocyanide (94 mg, 1 mmol) and chloroacetic acid (83 mg, 1 mmol) were added and stirring was continued at room temperature. The reaction was monitored by TLC and found to complete after 72h. The solvent was evaporated under vacuum and the residue was washed with peteroleum ether (5x15ml) to afford the chloro derivative of the Ugi product. In a subsequent step, the Ugi chloride (407 mg, 1 mmol), K_2CO_3 (414mg, 3 mmol) and NaN_3 (65 mg, 1 mmol) are stirred at room temperature for 4h in dimethyl acetamide. After completion of the reaction, the reaction mixture was poured into ice cold water. The solid product was filtered and dried under vacuum to afford 2-{[N-benzyl-(N-1-azidopropan-2-one)-N-tert-butyl-2-(2- chlorophenyl)]} acetamide **2a** (0.335g, 81%) as white solid: IR (KBr) (ν_{max}, cm^{-1}): 3304, 2100, 1685, 1640, 1552. ^{1}H-NMR ($CDCl_3$, 500MHz) δ_H (ppm): 1.25 (s, 9H), 1.62 (s, 2H), 4.58 (s, 2H), 6.38 (s, 1H, -CH), 6.95-7.26 (m, 9H), 7.53 (s, 1H). ^{13}C-NMR (DMSO- (d_6), 125MHz) δ_C (ppm): 31.1, 42.7, 48.3, 51.7, 52.2, 126.8, 127.2, 128.4, 129.6, 129.7, 130.1, 132.5, 134.7, 137.7, 137.9, 167.0, 167.2. EI-MS: 414.4 (M^+).
19. *Typical procedure for the synthesis of 1, 4-disubstituted triazolyl DHPMs with skeletal α-amino acid residue **3a**:* An equi-molar amount of **2a** (69 mg, 0.2 mmol) and **1a** (50 mg, 0.2mmol) are dissolved in minimum amount of DMSO. To this, 2 ml of *tert*-BuOH, 1ml of water, $CuSO_4.5H_2O$ (11 mg) and sodium ascorbate (50 mg) are added and stirred in room temperature for 12 h. After 12h, the mixture was poured in to cold water. The precipitated solid was collected and washed with water and dried. The dried product was washed with diethyl ether (3x 5ml) to afford **3a (**0.138g, 83%) as white solid. IR (KBr) (ν_{max}, cm^{-1}): 3331, 3296, 3225, 1687, 1658, 1604, 1549, 1316, 1176; ^{1}H-NMR (DMSO-(d_6), 400MHz) δ_H (ppm): 1.29 (s, 9H), 2.24 (s, 3H), 3.52 (s, 3H), 4.46 (s, 2H), 4.69 (s, 2H), 5.12 (s, 2H), 5.48 (s, 1H), 6.29 (s, 1H), 6.86-7.88 (m, 14H, ArH, -CH), 8.07 (s, 1H), 9.18 (s, 1H), 9.87 (s, 1H). ^{13}C-NMR (DMSO-(d_6), 100MHz) δ_C (ppm): 17.4, 31.8, 46.2, 48.1, 49.3, 52.0, 56.6, 72.3, 102.4, 113.2, 121.2, 127.2, 128.2, 128.4, 129.0, 129.1, 129.7, 129.8, 130.1, 132.0, 132.1, 132.2, 132.5, 133.2, 135.1, 137.7, 142.0, 148.2, 151.1, 158.8, 167.5, 168.6, 169.9. EI-MS: 714.0 (M^+).
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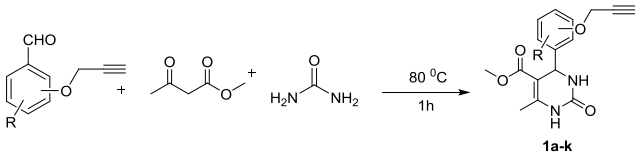
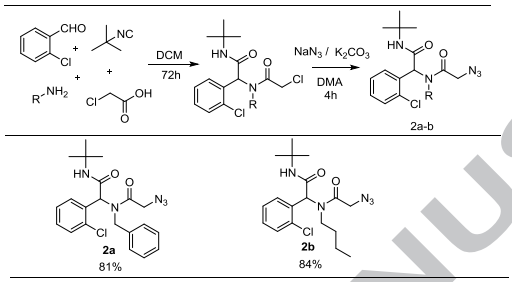
21. *Typical procedure for the synthesis of β-amido ketone azide **4a**:* A mixture of 4-chloroacetophenone (140 mg, 1 mmol), 2-chloro benzaldehyde (154mg, 1mmol), and 3-bromopropionitrile (133mg, 1mmol) in acetonitrile (8 ml) was stirred in the presence of 5 mol% $CuSO_4$ at room temperature for 8h. After completion of the reaction as indicated by TLC, the reaction mixture was poured into ice cold water and extracted with CH_2Cl_2 (15 ml). Evaporation of the solvent followed by purification on silica gel (100-200 mesh), ethyl acetate/hexane (3:1) afford 3-bromo-N-[1-(2-chlorophenyl)-3-(4-chlorophenyl)-3-oxopropyl] propanamide. The resulted bromide (426 mg, 1 mmol), K_2CO_3 (414 mg, 3 mmol), NaN_3 (65 mg, 1 mmol) were dissolved in dimethylacetamide and stirred for 6-8h. After completion, the reaction mixture was poured into ice cold water and the precipitate was filtered, dried under vacuum to afford the azide **4a** (.0.332g, 86%) as white solid. IR (KBr) (ν_{max}, cm^{-1}): 3296, 2107, 1685, 1645, 1588. ^{1}H-NMR ($CDCl_3$, 500MHz) δ_H (ppm): 1.73 (t, 2H), 2.45 (t, 2H), 2.67 (dd, 1H), 3.38 (dd, 1H), 5.53 (m, 1H), 6.89-7.43 (m, 8H, ArH), 7.83 (d, J=7.5Hz, 1H). ^{13}C-NMR ($CDCl_3$, 125MHz) δ_C (ppm): 35.6, 46.4, 48.2, 77.3, 128.3, 128.4, 128.9, 129.0, 129.6, 129.9, 130.3, 132.4, 134.7, 137.6, 140.2, 141.1, 169.1, 197.5. EI-MS: 391.0 (M^+).
22. Cornec, A.-S.; Baudequin, C.; Fiol-Petit, C.; Plé, N.; Dupas, G.; Ramondenc, Y. *Eur. J. Org. Chem.* **2013**, 1908-1915.

Supplementary Material: Copies of NMR, FT-IR and Mass spectrum of new compounds.

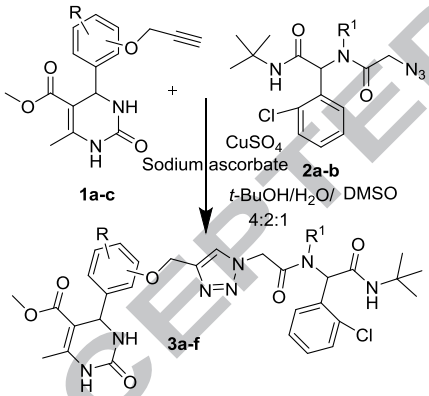
List of Figures



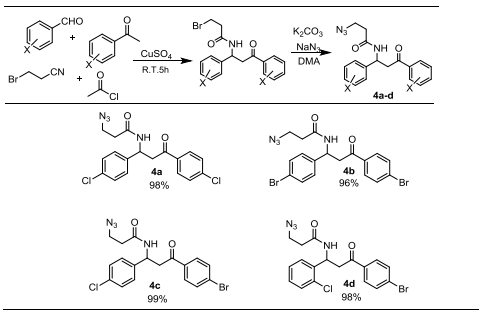
Scheme 1. Synthesis of alkyne functionalized dihydropyrimidinones by solvent free Biginelli reaction



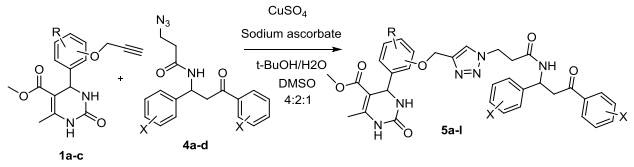
Scheme 2. Synthesis of α-amino acid type azides by U-4CR



Scheme 3. Synthesis of 1,4-disubstituted triazolyl DHPMs with skeletal α-amino acid residues via Cu (I)catalyzed Huisgen cycloaddition.



Scheme 4. Synthesis of β-amido ketone azides by alternate Mannich reaction.



Scheme 5. Synthesis of 1,4-disubstituted triazolyl DHPMs with skeletal β-amino acid residues via Cu (I) catalyzed Huisgen cycloaddition

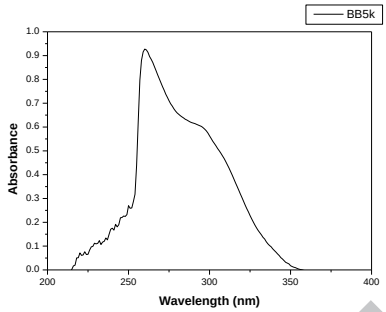


Figure 1. Absorption spectrum of compound **5k** (2.805x10^{-5}M) in DMSO. λabs.max. (nm): 260.0

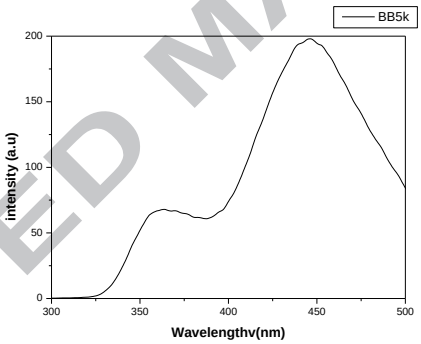


Figure 2. Emission spectrum of compound **5k** (2.805x10^{-5}M**)** in DMSO. λem.max. (nm): 364.0 and 446.0

List of Tables

Table 1. Solvent-free synthesis of alkynyl pyrimidinone scaffolds

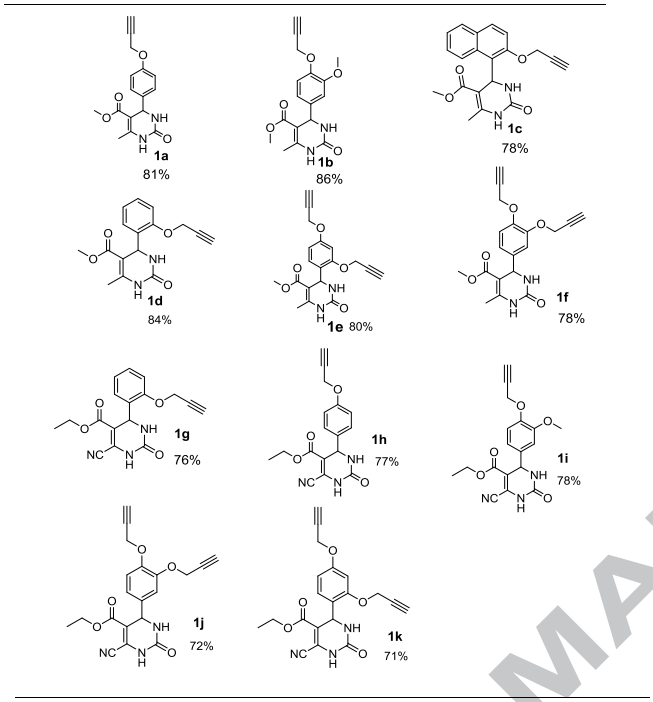


Table 2. List of 1, 4-disubstituted triazolyl DHPMs with skeletal *α*-amino acid residues.

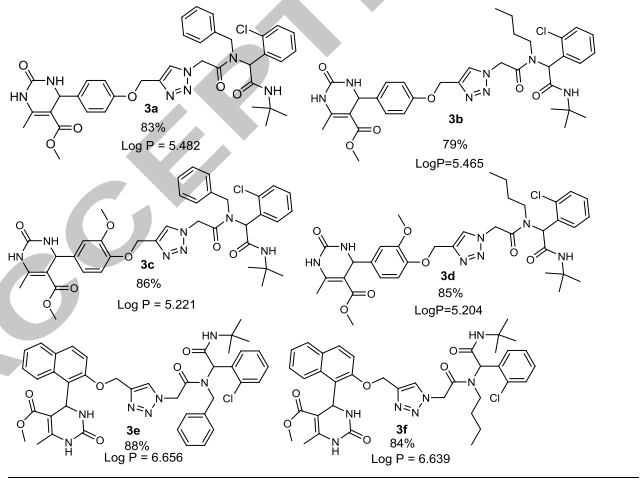


Table 3. **List of 1,4-disubstituted triazolyl DHPMs with skeletal β-amino acid residues**