A Novel Strategy of Ugi-4CR/Huisgen 1,3-Dipolar Synthesis of 1*H*-1,2,3-Triazole-Modified Peptidoimetics

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ABSTRACT: *In this protocol, we report a novel approach for the synthesis of a new class of heterocyclic 1H-1,2,3-triazole-modified peptidoimetic compounds. The process consists of an Ugi four-component condensation reaction of amines, an isocyanide, an aldehyde and acids followed by a Huisgen 1,3-dipolar cycloaddition reaction with an azide group in the presence of a catalytic amount of $CuSO_4.5H_2O$/sodium ascorbate. The copper-catalyzed Huisgen cycloaddition reactions provide such a general synthetic method, with the resulting 1,2,3-triazoles being good peptide bond mimics. This protocol was highly efficient for structurally diverse heterocyclic molecules containing an active aldehyde group and will find applications in combinatorial chemistry, diversity-oriented synthesis, and drug discovery.*

KEYWORDS: *1H-1,2,3-Triazole; 1,3-Dipolar cycloaddition; Ugi four-component; Isocyanide.*

INTRODUCTION

Triazoles chemistry has been increasing rapidly, mainly as a result of the heterocyclic functionality in medicinal chemistry which plays as a metabolically stable surrogate for carboxylic acid functionalities [1-4]. Recently, rigidification of the core scaffold from the Ugi-Azide MCR has led to the generation of unique cyclic scaffolds such as ketopipirazine-tetrazoles [5], azipine-tetrazoles [6], benzodiazepine-tetrazoles [7], quinoxaline-tetrazoles [8] and triazole-modified peptidomimetics (I and II) compounds [9]. It is important to note that the triazole-modified peptidomimetics are important nonnatural compounds for drug discovery because of their many biological activities [10-13]. Some of biologically examples 1,2,3-triazoles include HIV-1 protease inhibitor III [14], potential anticancer agent IV [15], or non-nucleoside reverse transcriptase inhibitor V (Fig. 1) [16].

Recently, the synthesis of triazoles in terminal, center, or side chain position of peptide that linked to sugars or other peptides has been reported *via* the multi-step approaches which required many protecting groups [17-20]. In modern therapeutic discovery, the rapid synthesis of organic compounds without protecting groups is gaining considerable interest. Isocyanide-based MultiComponent Reactions (IMCRs) are an important strategy in the synthesis of complex and biologically relevant molecules. By simply varying each component in the multicomponent method, especially IMCRs, large libraries of organic molecules could be synthesized.

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1021-9986/2018/2/73-84 12/$/6.02

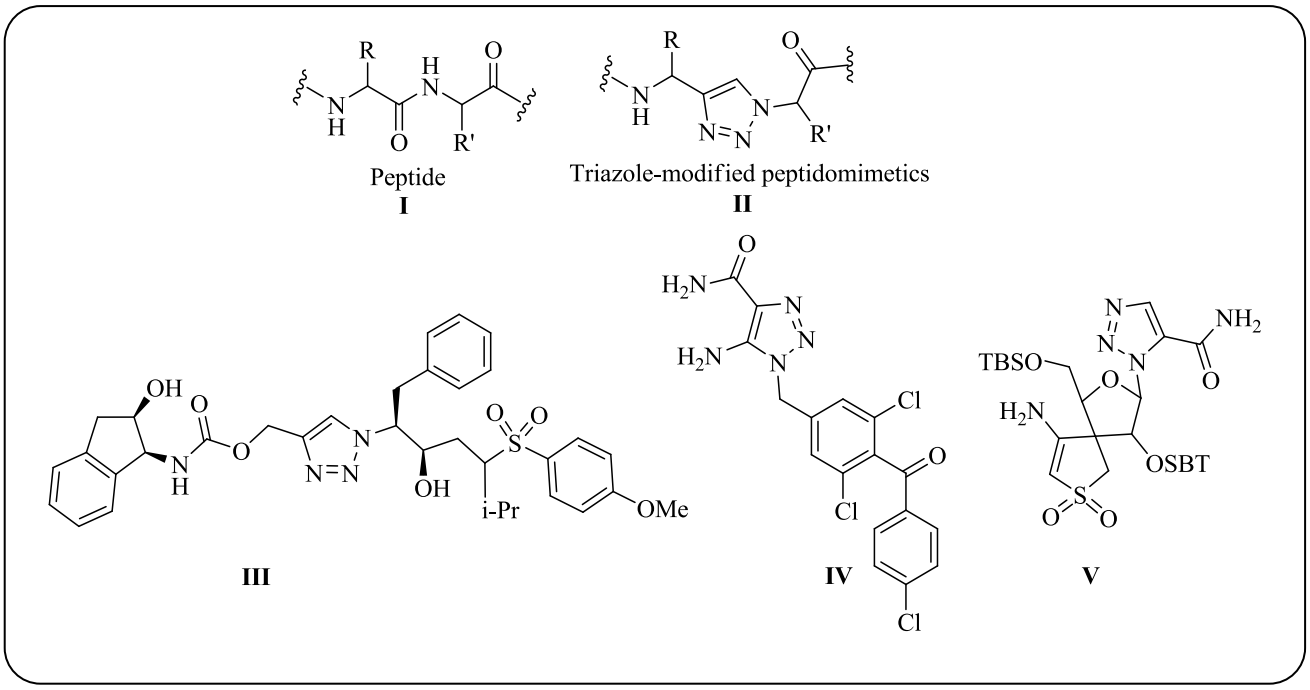


Fig. 1c: General structures of peptide (I), 1H-1,2,3-triazole-modified peptidomimetics (II) and examples of medicinal 1,2,3-triazole derivatives (III-V).

The Ugi four-component reactions (Ugi 4CR) is one of the cornerstones in this field, and great efforts have been devoted to the exploration of the potential of this transformation [21-24].

EXPERIMENTAL SECTION

General

Melting points were measured on an Electrothermal 9200 apparatus. Mass spectra were recorded on a Shimadzu GCMS-QP1100EX mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H NMR Spectra were recorded on a Bruker DRX-300 Avance spectrometer 300.13 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR Spectra are reported in order: number of protons, multiplicity and approximate coupling constant (*J* value) in Hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad signal) and Ar (aryl). The ^{13}C NMR spectra were recorded at 75.47 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). The elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL. All the products are new compounds, which were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectra and Mass spectral data.

A typical procedure for the preparation of azidoacetic acid 4

Sodium azide (0.15 g, 2.30 mmol, 2.10 equiv) was suspended in DMSO (6.25 mL) and stirred at ambient temperature for 1.5 h to obtain a clear yellow solution. *α*- Bromoacetic acid (0.15 g, 1.10 mmol, 1.00 equiv) was dissolved in DMSO and added dropwise, upon which the solution turned clear orange. After 12 h, the reaction was diluted with water (5 mL) and acidified using concentrated hydrochloric acid (1 mL). The aqueous solution was then extracted with ethyl acetate three times. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give 0.09 g (85% yield) of the desired product as a pale yellow oil [36].

General procedure for the preparation of 2-azido-acetamides 7a–h

Amines **1** (1.00 mmol), aldehydes **3** (1.00 mmol) in EtOH (5 mL) were stirred at room temperature for 1 h. Then, azidoacetic acid **4** (1.00 mmol), and cyclohexyl isocyanide **2** (1.00 mmol) were added and stirred at room temperature for 6 h. After completion of the reaction, as indicated by TLC (ethyl acetate/n-hexane, 3/1), the mixture was filtered and the solid precipitate washed

with H_2O and *n*-hexane (20 mL). Further purification was followed by crystallization from ethanol to give pure crystalline products **7a—h**.

General procedure for the preparation of 1H-1,2,3-triazoles 6a—h

To the products **7a—h** (1.0 mmol) in the presence of $CuSO_4.5H_2O$ (0.02 g, 10 mol %), sodium ascorbate (0.04 g, 20 mol %) in *t*-BuOH:H_2O (10 mL, 1:1) was added propargylated aldehydes **5** (1.0 mmol) and stirred at 70 °C for 12 h. Then, the reaction mixture was cooled and the resulting solid was filtered to provide products **6a—h**. Finally, the pure products **6a—h** were obtained after recrystallization from ethanol.

General procedure for the preparation of 13a—n

Primary amines **1** (1.00 mmol) were added to a solution of propargylated aldehydes **5** (1.00 mmol) in EtOH (10 mL), and the mixture stirred at room temperature for 1 h. Then, acids **11** (1.00 mmol) were added and stirring continued for 15 min, followed by addition of cyclohexyl isocyanide **2** (1.00 mmol). The resulting solution was stirred for 24 h at room temperature. Next, 1-azido-3-nitrobenzene **12** (1.00 mmol), $CuSO_4$ (0.02 g, 10 mol %), sodium ascorbate (0.04 g, 20 mol %) and H_2O (10 mL) were added. The resulting mixture was stirred for 12 h at 60 °C. After completion of the reaction, as indicated by TLC (ethyl acetate/n-hexane, 3/1), the product was precipitated by addition of 10 mL of water. Finally, the pure products **13a—n** were obtained after recrystallization from ethanol.

N-Cyclohexyl-2-(2-(4-((2-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamido)-2-phenylacetamide (6a)

Light yellow powder; mp 245–247°C. IR (KBr) cm^{-1}: 3248, 3078, 2927, 2850, 1675, 1646, 1598, 1563, 1492, 1396, 1283, 1240, 1051. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 0.95-1.65 (10H, m, $5CH_2$ of cyclohexyl), 3.57 (1H, s, CH-NH), 4.92 (2H, m, CH_2-CO), 5.35 (2H, s, CH_2), 6.02 (1H, s, CH), 6.90-8.02 (16H, m, CH-Ar), 8.20 (1H, br s, NH-CO), 10.34 (1H, s, CHO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 32.7, 48.4, 121.6, 128.3, 129.2, 130.6, 131.4. Anal. Calcd for $C_{32}H_{33}N_5O_4$: C, 69.67; H, 6.03; N, 12.70; found C, 69.58; H, 6.11; N, 12.58.

N-Cyclohexyl-2-(2-(4-((2-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamido)-2-(3-nitrophenyl) acetamide (6b)

White powder; mp 239–241°C. IR (KBr) cm^{-1}: 3263, 3159, 3089, 2933, 2854, 1684, 1598, 1532, 1488, 1453, 1396, 1349, 1290, 1237. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 0.93-1.64 (10H, m, $5CH_2$ of cyclohexyl), 3.57 (1H, s, CH-NH), 4.97 (2H, ABq, J = 16.95 Hz, CH_2-CO), 5.36 (2H, s, CH_2), 6.16 (1H, s, CH), 7.08-8.21 (15H, m, H-Ar and NH-CO), 10.34 (1H, s, CHO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.8, 24.9, 25.6, 32.5, 48.4, 52.0, 62.6, 63.6, 114.6, 121.6, 123.4, 124.9, 125.3, 126.8, 128.1, 129.1, 129.5, 130.0, 131.4, 136.8, 137.3, 137.4, 137.8, 142.4, 147.5, 160.9, 165.8, 167.7, 189.5. Anal. Calcd for $C_{32}H_{32}N_6O_6$: C, 64.42; H, 5.41; N, 14.09; found C, 64.50; H, 5.32; N, 13.94.

2-(4-Chlorophenyl)-N-cyclohexyl-2-(2-(4- ((2-formylphenoxy) methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamido) acetamide (6c)

Light yellow powder; mp 219–222°C. IR (KBr) cm^{-1}: 3444, 3267, 3078, 2932, 2852, 1673, 1650, 1597, 1559, 1493, 1455, 1396, 1286, 1237, 1094, 1019. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 0.90-1.22 (10H, m, $5CH_2$ of cyclohexyl), 4.90 (2H, ABq, J = 14.67 Hz, CH_2-CO), 5.35 (2H, s, CH_2), 6.00 (1H, s, CH), 6.90-8.25 (15H, m, H-Ar and NH-CO), 10.33 (1H, s, CHO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 25.0, 25.6, 31.2, 32.5, 48.4, 62.6, 79.0, 79.4, 114.5, 128.3, 129.3, 131.3, 132.4, 136.8, 177.8, 189.5. Anal. Calcd for $C_{32}H_{32}ClN_5O_4$: C, 65.58; H, 5.50; N, 11.95; found C, 65.46; H, 5.62; N, 11.75.

N-Benzyl-N-(2-(cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-2-(4-((2-formylphenoxy)methyl) -1H-1,2,3-triazol-1-yl)acetamide (6d)

White powder; mp 173–175°C. IR (KBr) cm^{-1}: 3271, 3164, 3080, 2932, 2851, 1694, 1678, 1653, 1603, 1565, 1514, 1455, 1403, 1346, 1294, 1248, 1194, 1173. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.12-1.63 (10H, m, $5CH_2$ of cyclohexyl), 3.53 (1H, s, CH-NH), 3.70 (3H, s, CH_3), 4.50-5.22 (4H, m, $2CH_2$), 5.35 (2H, s, CH_2), 6.05 (1H, s, CH), 6.83-8.25 (15H, m, CH-Ar, and NH-CO), 10.33 (1H, s, CHO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.85, 25.59, 32.63, 48.18, 51.78, 55.53, 62.58, 114.20, 114.66, 121.56, 124.91, 126.42, 127.02, 127.54, 127.71, 128.10, 128.73, 130.41, 131.17, 136.83, 138.27,

142.50, 159.42, 160.89, 167.56, 168.67, 189.57. Anal. Calcd for $C_{34}H_{37}N_5O_5$: C, 68.55; H, 6.26; N, 11.76; found C, 68.55; H, 6.26; N, 11.76.

N-Cyclohexyl-2-(2-(4-((1-formylnaphthalen-2-yloxy)methyl)-1H-1,2,3- triazol-1-yl) -N-phenylacetamido) -2-(3-methoxyphenyl) acetamide (6e)

Brown powder; mp 238–240°C. IR (KBr) cm^{-1}: 3469, 3261, 3160, 3084, 2920, 2844, 1676, 1648, 1587, 1514, 1253. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.18-1.63 (10H, m, $5CH_2$ of cyclohexyl), 3.63 (4H, s, CH-NH and CH_3), 4.91 (2H, s, CH_2-CO), 5.53 (2H, s, CH_2), 5.99 (1H, s, CH), 6.66-9.08 (17H, m, H-Ar and NH-CO), 10.74 (1H, s, CHO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 25.1, 25.6, 32.6, 48.3, 52.0, 55.3, 57.8, 63.9, 113.7, 115.7, 116.6, 124.4, 125.3, 126.9, 128.8, 129.0, 130.2, 131.0, 131.4, 131.9, 138.3, 142.3, 159.1, 163.4, 165.5, 168.9, 191.7. Anal. Calcd for $C_{37}H_{37}N_5O_5$: C, 70.35; H, 5.90; N, 11.09; found C, 70.55; H, 5.70; N, 10.93.

N-Cyclohexyl-2-(2-(4-((1-formylnaphthalen-2-yloxy)methyl) -1H-1,2,3 -triazol-1-yl) -N-phenylacetamido) -2-(4-hydroxyphenyl)acetamide (6f)

Light brown powder; mp 164–166°C. IR (KBr) cm^{-1}: 3438, 3261, 3154, 3078, 2926, 2857, 1674, 1648, 1613, 1594, 1514, 1442, 1272, 1238. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 0.90-1.63 (10H, m, $5CH_2$ of cyclohexyl), 3.56 (1H, s, CH-NH), 4.90 (2H, ABq, J = 16.30 Hz, CH_2-CO), 5.15 (1H, s, OH), 5.52 (2H, s, CH_2), 5.92 (1H, s, CH), 6.48-9.37 (17H, m, H-Ar and NH-CO), 10.73 (1H, s, CHO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.9, 25.1, 25.6, 32.7, 48.3, 52.1, 57.9, 63.5, 115.2, 115.6, 115.7, 116.6, 124.4, 125.1, 125.3, 125.5, 126.9, 128.7, 128.8, 129.0, 130.2, 131.0, 131.5, 131.8, 138.1, 138.3, 157.3, 163.4, 165.4, 169.0, 191.7. Anal. Calcd for $C_{36}H_{35}N_5O_5$: C, 70.00; H, 5.71; N, 11.34; found C, 69.80; H, 5.80; N, 11.50.

N-Cyclohexyl-2- (2-(4- ((1-formylnaphthalen -2-yloxy) methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamido) -2-(3-nitrophenyl)acetamide (6g)

Light brown powder; mp 260 >°C. IR (KBr) cm^{-1}: 3488, 3261, 3166, 3084, 2926, 2850, 1676, 1651, 1536, 1347, 1234. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 0.95-1.72 (10H, m, $5CH_2$ of cyclohexyl), 3.58 (1H, s, CH-NH), 4.97 (2H, m, CH_2-CO), 5.54 (2H, s, CH_2), 6.15 (1H, s, CH), 7.23-8.32 (16H, m, H-Ar and NH-CO), 9.09 (1H, d, J = 8.37 Hz, H-Ar), 10.72 (1H, s, CHO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.8, 32.5, 36.8, 37.1, 37.4, 48.4, 63.6, 115.8, 116.6, 123.4, 125.3, 126.9, 129.1, 129.5, 130.2, 131.4, 147.5, 191.8. MS *m/z*: 175 (100), 133 (70), 57 (15), 41 (18). Anal. Calcd for $C_{36}H_{34}N_6O_6$: C, 66.86; H, 5.30; N, 13.00; found C, 66.78; H, 5.18; N, 13.10.

2-(4-Chlorophenyl)-N-cyclohexyl-2-(2-(4-((1-formylnaphthalen -2-yloxy)methyl)- 1H-1,2,3-triazol-1-yl) -N-phenylacetamido) acetamide (6h)

Light brown powder; mp 260 >°C. IR (KBr) cm^{-1}: 3444, 3280, 3084, 2933, 2844, 2775, 1670, 1651, 1562, 1493, 1234, 1095, 1019. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-1.65 (10H, m, $5CH_2$ of cyclohexyl), 3.56 (1H, s, CH-NH), 4.91 (2H, m, CH_2-CO), 5.53 (2H, s, CH_2), 5.99 (1H, s, CH), 7.05-8.22 (16H, m, H-Ar and NH-CO), 9.10 (1H, d, J = 8.58, H-Ar), 10.72 (1H, s, CHO). Anal. Calcd for $C_{36}H_{34}ClN_5O_4$: C, 67.97; H, 5.39; N, 11.01; found C, 67.88; H, 5.40; N, 11.10. (Due to the low solubility product was not possible to obtain carbon spectra.)

N-(1-(5-Bromo-2-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)- 2-(cyclohexylamino) -2- oxoethyl)-N-phenyl-1H-indole-2-carboxamide (13a)

Colorless crystals; mp 175–178°C . IR (KBr) cm^{-1}: 3279, 3148, 3049, 2934, 2845, 1695, 1617, 1586, 1534, 1492. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.00 (10H, m, $5CH_2$ of cyclohexyl), 3.60 (1H, m, CH of cyclohexyl), 5.44 (2H, br s, CH_2), 6.49 (1H, br s), 6.60-8.70 (19H, Ar and NH-CO) , 11.56 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 25.0, 25.1, 25.6, 29.5, 32.7, 48.4, 59.1, 62.0, 111.9, 115.2, 120.8, 123.2, 124.0, 126.5, 128.6, 128.7, 130.0, 130.3, 132.2, 136.9, 137.5, 139.2, 144.6, 145.3, 149.0, 156.3, 165.9, 168.7, 169.1. MS *m/z*: 747 (M^+). Anal. Calcd for $C_{38}H_{34}BrN_7O_5$: C, 60.97; H, 4.58; N, 13.10; found C, 60.97; H, 4.57; N, 13.15.

N-Benzyl-N-(2-(cyclohexylamino) -1-(2- ((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-2-oxoethyl)-1H-indole-2-carboxamide (13b)

Colorless crystals; mp 204–206°C . IR (KBr) cm^{-1}: 3451, 3294, 3159, 3112, 3065, 2929, 2845, 1669, 1593,

1535, 1491, 1455, 1418, 1351. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.00 (10H, m, 5CH_2 of cyclohexyl), 3.64 (1H, br s, CH of cyclohexyl), 4.88-5.30 (4H, m, 2CH_2), 6.38 (1H, s, CH), 6.49-8.80 (20H, Ar and NH-CO), 11.77 (1H, s, NH). MS *m/z*: 683 (M^+). Anal. Calcd for $C_{39}H_{37}N_7O_5$: C, 68.51; H, 5.45; N, 14.34; found C, 68.51; H, 5.40; N, 14.24. (Due to the low solubility product was not possible to obtain carbon spectra.)

2-Bromo-N- (1-(5-bromo-2-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl) -2-(cyclohexylamino)-2-oxoethyl)-N-phenylacetamide (13c)

Colorless crystals; mp 147–150°C . IR (KBr) cm^{-1}: 3368, 3274, 3148, 3101, 3059, 3023, 2929, 2845, 1678, 1650, 1601, 1536, 1491, 1455, 1350, 1314. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.00 (10H, m, 5CH_2 of cyclohexyl), 3.47 (1H, s, CH of cyclohexyl), 3.61 (2H, s, CH_2), 5.31 (2H, s, CH_2), 6.31 (1H, s, CH), 6.76-8.80 (14H, Ar and NH-CO). MS *m/z*: 724 (M^+). Anal. Calcd for $C_{31}H_{30}Br_2N_6O_5$: C, 51.26; H, 4.16; N, 11.57; found C, 51.22; H, 4.10; N, 11.47. (Due to the low solubility product was not possible to obtain carbon spectra.)

2-Bromo-N-(2-(cyclohexylamino)-1-(2-((1-(3-nitrophenyl) -1H-1,2,3-triazol-4-yl)methoxy)phenyl)-2-oxoethyl)-N-phenylacetamide (13d)

Colorless crystals; mp 220–222°C . IR (KBr) cm^{-1}: 3289, 3153, 3106, 3065, 3012, 2930, 2850, 1684, 1647, 1597, 1537, 1493, 1455, 1413, 1382, 1348. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.00 (10H, m, 5CH_2 of cyclohexyl), 3.59 (1H, br s, CH of cyclohexyl), 3.69 (1H, s, CH_2), 5.31 (2H, s, CH_2), 6.37 (1H, s, CH), 6.60-8.80 (15H, Ar and NH-CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 25.0, 25.1, 25.6, 32.6, 48.4, 58.7, 60.9, 61.8, 111.9, 115.1, 120.7, 121.8, 123.2, 123.7, 124.0, 126.5, 128.3, 128.7, 129.0, 129.9, 130.4, 132.2, 137.5, 138.3, 145.2, 149.0, 156.3, 169.1, 171.8. MS *m/z*: 646 (M^+). Anal. Calcd for $C_{31}H_{31}BrN_6O_5$: C, 57.50; H, 4.83; N, 12.98; found C, 57.55; H, 4.80; N, 12.95.

N-(2-(Cyclohexylamino)-1-(2-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl) -2-oxoethyl) -N-phenylpropionamide (13e)

Colorless crystals; mp 205–207°C . IR (KBr) cm^{-1}: 3279, 3101, 3065, 2934, 2850, 1675, 1645, 1591, 1534, 1493, 1455, 1392, 1353. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.20 (15H, m, 6CH_2 of cyclohexyl and CH_3), 3.59 (1H, m, CH of cyclohexyl), 5.30 (2H, br s, CH_2), 6.42 (1H, s, CH), 6.60-8.80 (15H, Ar and NH-CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 9.9, 25.0, 25.2, 25.6, 28,1, 32.6, 32.7, 48.4, 58.3, 61.9, 111.8, 115.0, 120.7, 123.0, 123.8, 124.8, 126.3, 127.8, 128.6, 129.7, 130.4, 130.5, 132.2, 137.5, 140.4, 145.4, 149.1, 156.3, 169.4, 173.0. MS *m/z*: 582 (M^+). Anal. Calcd for $C_{32}H_{34}N_6O_5$: C, 65.96; H, 5.88; N, 14.42; found C, 65.93; H, 5.80; N, 14.42.

N-(1-(5-Bromo-2-((1-(3-nitrophenyl) -1H-1,2,3-triazol-4-yl) methoxy)phenyl) -2-(cyclohexylamino)-2-oxoethyl)-N-phenylpropionamide (13f)

Colorless crystals; mp 163–165°C . IR (KBr) cm^{-1}: 3279, 3143, 3101, 2929, 2850, 1674, 1633, 1617, 1532, 1492, 1460, 1397. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.20 (15H, m, 6CH_2 of cyclohexyl and CH_3), 3.57 (1H, m, CH of cyclohexyl), 5.29 (2H, br s, CH_2), 6.33 (1H, s, CH), 7.10-8.74 (14H, Ar and NH-CO). MS *m/z*: 660 (M^+). Anal. Calcd for $C_{32}H_{33}BrN_6O_5$: C, 58.10; H, 5.03; N, 12.70; found C, 58.08; H, 5.06; N, 12.66. (Due to the low solubility product was not possible to obtain carbon spectra.)

N-Benzyl-N-(2-(cyclohexylamino)-1-(2-((1-(3-nitrophenyl) -1H-1,2,3- triazol-4-yl) methoxy) phenyl) -2-oxoethyl) propionamide (13g)

Colorless crystals; mp 216–218°C . IR (KBr) cm^{-1}: 3289, 3148, 3091, 3059, 2934, 2855, 1678, 1623, 1537, 1491, 1455. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.10 (15H, m, 6CH_2 of cyclohexyl and CH_3), 3.45 (1H, m, CH of cyclohexyl), 4.22 (1H, ABq, *J* = 16.77 Hz, CH), 4.60 (1H, ABq, *J* = 16.77 Hz, CH), 5.47 (2H, br s, CH_2), 6.56 (1H, br s), 7.00-8.80 (15H, Ar and NH-CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.9, 25.6, 26.2, 26.9, 32.5, 48.2, 55.9, 61.0, 111.5, 114.9, 121.0, 121.8, 122.7, 123.7, 124.9, 125.9, 126.2, 126.6, 127.2, 127.6, 128.0, 128.2, 129.8, 132.0, 137.6, 149.1, 169.3, 173.8. MS *m/z*: 596 (M^+). Anal. Calcd for $C_{33}H_{36}N_6O_5$: C, 66.43; H, 6.08; N, 14.08; found C, 66.33; H, 6.05; N, 14.00.

N-Benzyl-N-(1-(5-bromo-2-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-2-(cyclohexylamino)-2-oxoethyl) propionamide (13h)

Colorless crystals; mp 215–218°C . IR (KBr) cm^{-1}: 3300, 3086, 2934, 2856, 1664, 1627, 1560, 1538, 1490,

1455, 1351, 1283, 1247. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.10 (15H, m, 6CH_2 of cyclohexyl and CH_3), 3.50 (1H, m, CH of cyclohexyl), 4.60-5.19 (4H, m, 2CH_2), 6.46 (1H, s, CH), 6.80-8.80 (14H, Ar and NH-CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.8, 25.5, 26.8, 32.1, 32.4, 48.1, 55.7, 61.4, 62.4, 112.3, 112.4, 113.7, 114.9, 115.2, 122.9, 123.8, 126, 126.3, 126.6, 127.3, 128.3, 131.7, 132.2, 137.5, 145.1, 149.0, 155.9, 168.5, 173.8. MS *m/z*: 674 (M^+). Anal. Calcd for $C_{33}H_{35}BrN_6O_5$: C, 58.67; H, 5.22; N, 12.44; found C, 58.62; H, 5.22; N, 12.34.

N-Cyclohexyl-2-(2-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-2-(N-phenylacetamido)acetamide (13i)

Colorless crystals; mp 197–199 °C . IR (KBr) cm^{-1}: 3441, 3284, 3148, 3106, 3070, 2934, 2850, 1681, 1637, 1596, 1534, 1493. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.00 (13H, m, 5CH_2 of cyclohexyl and CH_3), 3.59 (1H, m, CH of cyclohexyl), 5.29 (2H, br s, CH_2), 6.38 (1H, br s), 6.64-8.80 (15H, Ar and NH-CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 23.5, 25.0, 25.1, 25.6, 32.6, 32.7, 48.4, 58.4, 61.8, 111.9, 115.0, 120.7, 123.1, 123.6, 123.7, 124.8, 125.0, 126.4, 126.6, 128.0, 128.2, 128.5, 129.7, 130.4, 132.2, 136.9, 137.6, 140.9, 145.4, 149.1, 156.3, 169.3, 169.8. MS *m/z*: 568 (M^+). Anal. Calcd for $C_{31}H_{32}N_6O_5$: C, 65.48; H, 5.67; N, 14.78; found C, 65.48; H, 5.67; N, 14.78.

2-(2-((1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-2-(N-benzylacetamido)-N-cyclohexylacetamide (13j)

Colorless crystals; mp 187–189°C . IR (KBr) cm^{-1}: 3445, 3284, 3154, 3107, 3070, 2934, 2850, 1681, 1637, 1596, 1533, 1493, 1455, 1350, 1250. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.00 (13H, m, 5CH_2 of cyclohexyl and CH_3), 3.50 (1H, m, CH of cyclohexyl), 4.65-5.01 (4H, m, 2CH_2), 5.67 (2H, s, CH_2), 6.74 (1H, s, CH), 6.80-8.28 (16H, Ar and NH-CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 22.0, 25.6, 32.4, 32.5, 32.6, 47.4, 48.1, 53.2, 59.0, 61.4, 93.4, 111.6, 120.8, 124.6, 125.0, 126.0, 126.5, 127.1, 127.5, 128.2, 128.5, 128.6, 129.2, 129.7, 130.0, 136.5, 139.0, 139.4, 144.0, 156.9, 168.7, 171.5. MS *m/z*: 551 (M^+). Anal. Calcd for $C_{33}H_{37}N_5O_3$: C, 71.84; H, 6.76; N, 12.69; found C, 71.74; H, 6.66; N, 12.59.

2-(5-Bromo-2-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl) methoxy)phenyl)-N-cyclohexyl-2-(2-(naphthalen-1-yl)-N-phenylacetamido)acetamide (13k)

Colorless crystals; mp 215–217°C. IR (KBr) cm^{-1}: 3436, 3143, 3101,3049, 2934, 2850, 1674, 1643, 1591, 1534, 1486, 1460, 1397, 1350. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.00 (10H, m, 5CH_2 of cyclohexyl), 3.62 (1H, m, CH of cyclohexyl), 3.66 (2H, m, CH_2), 5.48 (2H, s, CH_2), 6.52 (1H, s, CH), 6.80-8.90 (21H, Ar and NH-CO). MS *m/z*: 772 (M^+). Anal. Calcd for $C_{41}H_{37}BrN_6O_5$: C, 63.65; H, 4.82; N, 10.86; found C, 63.60; H, 4.72; N, 10.76. (Due to the low solubility product was not possible to obtain carbon spectra.)

N-(1-(5-Bromo-2-((1-(3-nitrophenyl)-1H-1,2,3 -triazol-4-yl)methoxy)phenyl)-2-(cyclohexylamino)-2-oxoethyl) -2,2,2-trifluoro-N-phenylacetamide (13l):

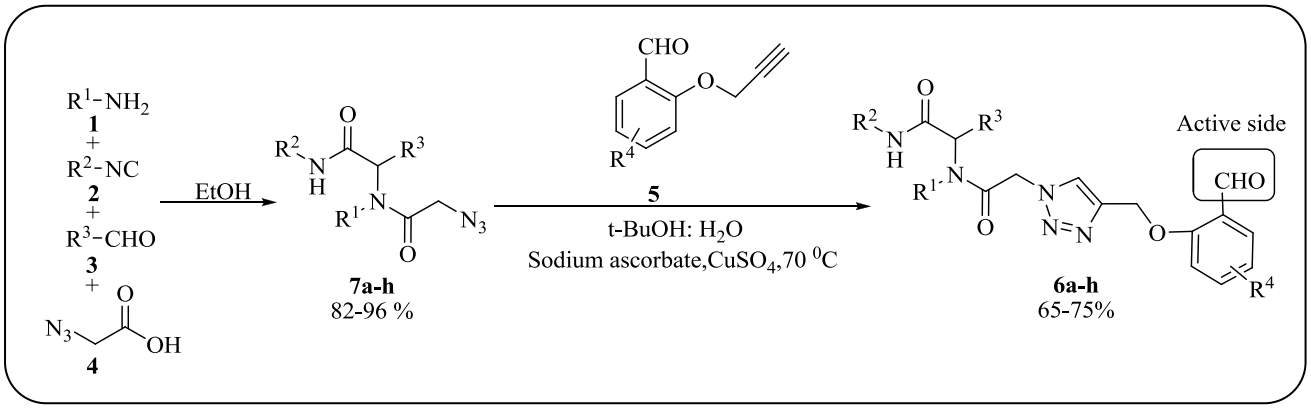
Colorless crystals; mp 149–151°C. IR (KBr) cm^{-1}: 3331, 3164, 3117, 3065, 2929, 2845, 1678, 1602, 1538, 1491, 1461, 1351, 1314, 1288. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.00 (10H, m, 5CH_2 of cyclohexyl), 3.61 (1H, m, CH of cyclohexyl), 5.31 (2H, br s, CH_2), 6.19 (1H, br s), 6.85-8.70 (14H, Ar and NH-CO). MS *m/z*: 700 (M^+). Anal. Calcd for $C_{31}H_{28}BrF_3N_6O_5$: C, 53.08; H, 4.02; N, 11.98; found C, 53.00; H, 4.01; N, 11.90. (Due to the low solubility product was not possible to obtain carbon spectra.)

N-Benzyl-N-(1-(5-bromo-2-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-2-(cyclohexylamino)-2-oxoethyl) -2,2,2-trifluoroacetamide (13m)

Colorless crystals; mp 188–190 °C. IR (KBr) cm^{-1}: 3343, 3273, 3101, 3059, 3022, 2929, 2845, 1678, 1649, 1601, 1536, 1350, 1247. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.00 (10H, m, 5CH_2 of cyclohexyl), 3.63 (1H, br s, CH of cyclohexyl), 4.67 (1H, ABq, J = 9.87 Hz, CH), 5.01 (1H, ABq, J = 9.87 Hz, CH), 5.49 (2H, s, CH_2), 6.77 (1H, s, CH), 6.80-8.80 (14H, Ar and NH-CO). MS *m/z*: 714 (M^+). Anal. Calcd for $C_{32}H_{30}BrF_3N_6O_5$: C, 53.72; H, 4.23; N, 11.75; found C, 53.72; H, 4.13; N, 11.65. (Due to the low solubility product was not possible to obtain carbon spectra.)

N-((2-((1-(3-Nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy) phenyl) (cyclohexylcarbamoyl)methyl) -2-methyl-N-phenylbenzamide (13n)

Colorless crystals; mp 217–220 °C . IR (KBr) cm^{-1}: 3279, 3122, 3096, 3054, 2929, 2856, 1669, 1636, 1597, 1534, 1493, 1455, 1407, 1384, 1353. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00-2.00 (10H, m, 5CH_2 of cyclohexyl), 2.07 (3H, s, CH_3), 3.68 (1H, m, CH of cyclohexyl), 5.24 (2H, br s, CH_2), 6.51 (1H, br s, CH),



Scheme 1: Synthesis of 1H-1,2,3-triazole-modified peptidoimetics 6a-h.

6.70-8.78 (19H, Ar and NH-CO). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 19.1, 25.1, 25.7, 32.6, 48.5, 59.0, 61.4, 111.6, 115.1, 120.6, 121.8, 123.7, 124.2, 125.0, 126.5, 126.6, 127.2, 127.7, 128.0, 128.3, 130.0, 130.3, 130.6, 132.0, 132.3, 137.5, 139.9, 149.0, 156.3, 169.3, 175.0. MS *m/z*: 644 (M^+). Anal. Calcd for $C_{37}H_{36}N_6O_5$: C, 68.93; H, 5.63; N, 13.04; found C, 68.93; H, 5.61; N, 13.00.

RESULTS AND DISCUSSION

Inspired by the above investigation and our continued interest in the development of new synthetic methods for the generation of biologically active heterocyclic compounds [25-35], herein we wish to report the synthesis of a new class of heterocyclic 1H-1,2,3-triazole-modified peptidoimetic compounds with an activated aldehyde side **6a-h** *via* a five component two sequential condensation reaction of an amine **1**, an isocyanide **2**, an aldehyde **3**, azidoacetic acid **4** and a propargylated aldehyde **5** in good yields (Scheme 1).

This reaction is two-step and in the first step, amines **1**, isocyanides **2**, aldehydes **3** and azidoacetic acid **4** in ethanol were stirred at room temperature. After 6 h, the reaction was completed (monitored by TLC method) and target 2-azido-acetamide derivatives **7a-h** were obtained. In the second step, different aromatic propargylated aldehydes **5** and intermediates **7a-h** were selected to undergo Huisgen 1,3-dipolar cycloaddition reaction in the presence of catalytic amounts of $CuSO_4.5H_2O$ (10 mol %) and sodium ascorbate (20 mol %) as a reducing agent for Cu(Π) in the mixture of t-BuOH and H_2O with 1:1 ratio at 70 °C. As shown in Fig. 2, the reaction proceeds under mild conditions and is compatible with some functional groups. Four substitutions in the products can be varied independently of each other. The results of this study and the structure of target compounds **6a-h** are represented in Fig. 2.

For the synthesis of compound **7a** in the first step, α-bromoacetic acid **8** can be used instead of azidoacetic acid **4**. In this regard, aniline, cyclohexyl isocyanide, benzaldehyde and α-bromoacetic acid **8** performed in ethanol at room temperature to give the target peptide 2-bromo-N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-N-phenylacetamide **9a** in 95% yield (Scheme 2).

The Ugi intermediate **9a** contains a functional group which is suitable for further nucleophilic reaction with sodium azide **10** without any catalysts or separation and afforded compound **7a** as the sole product. This one-pot synthesis of 2-azido-N-(2-(cyclohexylamino)-2-oxo-1-phenylethyl) -N-phenylacetamide **7a** required up to 42 h for being completed which it was a time-consuming reaction. After successful application of this route to the synthesis of 1H-1,2,3-triazole derivatives **6a-h**, the reaction was extended to various carboxylic acids instead of azidoacetic acid for the synthesis of compounds **13a-n** *via* a one-pot procedure strategy. In the first step, amines **1**, cyclohexyl isocyanide **2**, propargylated aldehydes **5** and carboxylic acids **11** in ethanol were stirred at room temperature for 24 h to give the target peptides **14a-n**. Then, 1-azido-3-nitrobenzene **12**, $CuSO_4$ (10 mol %) sodium ascorbate (20 mol %) and H_2O were added at 60 °C (Scheme 3).

The reaction proceeds under mild conditions and is compatible with some functional groups. Three substitutions in the products can be varied independently of each other. The results of this study and the structure of target compounds **13a-n** are represented in Fig. 3.

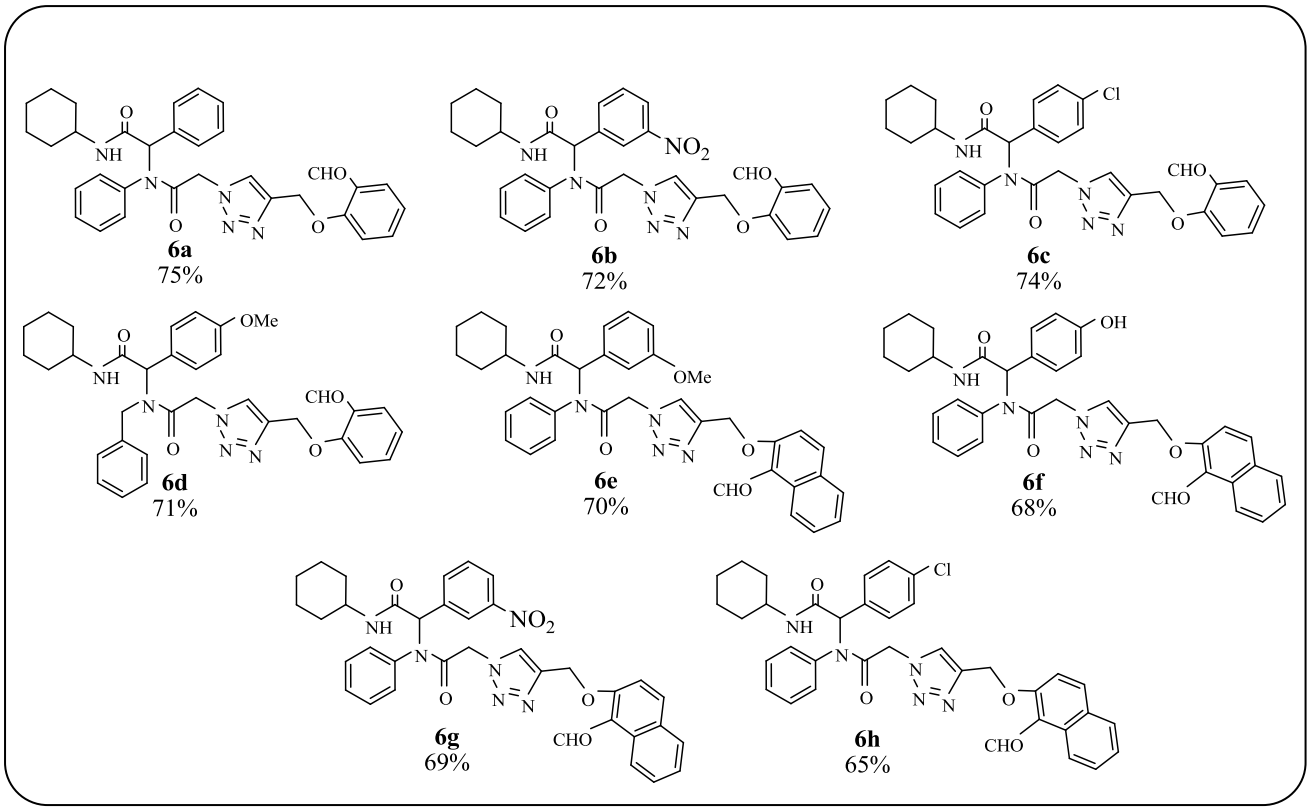
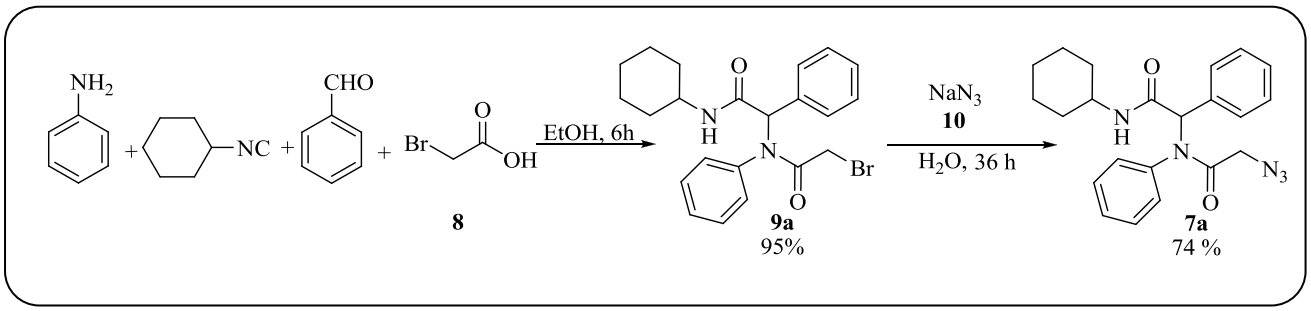


Fig. 2: Structures of 1H-1,2,3-triazoles-modified peptidoimetics 6a-h.

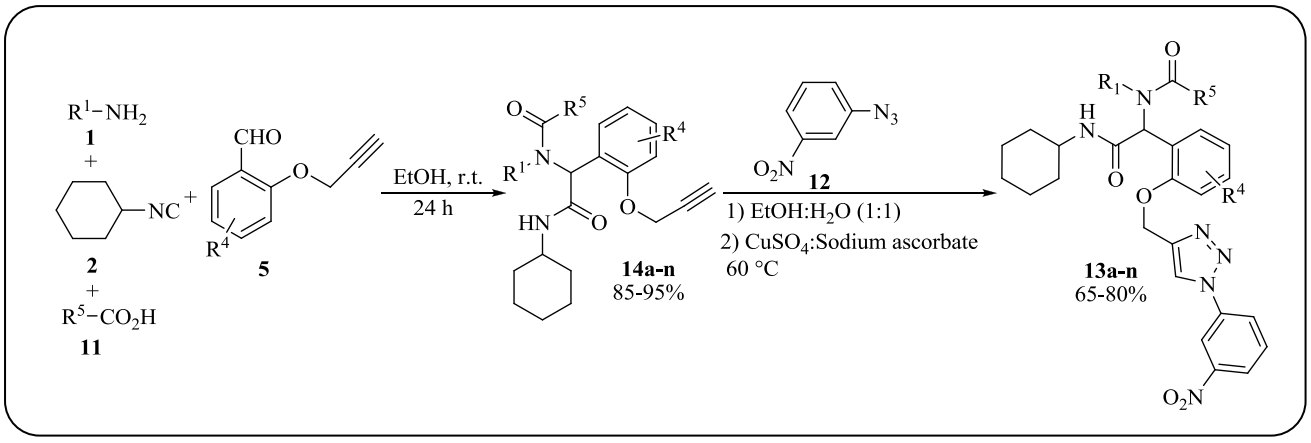


Scheme 2: Synthesis of 2-azido-acetamide derivatives 7a.

A possible mechanism for the formation of product **6** is shown in Scheme 4. The reaction was started with the commonly accepted Ugi-4CR mechanism, the amines **1**, aldehydes **3**, and acids **4** are in equilibrium with iminium carboxylates **15** in the reaction medium. The addition of the carbenoid C atom of the isocyanides onto the iminium group followed by the addition of the carboxylate ion onto the C atom of the nitrillium ion leads to the formation of the adduct **16**, which undergoes an intramolecular acylation known as Mumm rearrangement to give the stable Ugi adduct **7**. Finally, the Huisgen 1,3-dipolar cycloaddition reaction between the propargyloxy group of **5** and azide group of **7** takes place to produce the products **6**. It is important to note that in Copper(I)-Catalyzed Triazole formation step, the role of Cu (I) is to control regioselectivity of reaction [37].

CONCLUSIONS

In summary, we have successfully demonstrated a mild and straightforward strategy for the synthesis of unique fused triazole ring systems and a wide variety of peptidomimetics with an active aldehyde side through a combination of Ugi-4CR/Huisgen 1,3-dipolar intermolecular azide-alkyne cyclization in good yields. These protocols



Scheme 3: Synthesis of 1H-1,2,3-triazole-modified peptidoimetic derivatives 13a-n.

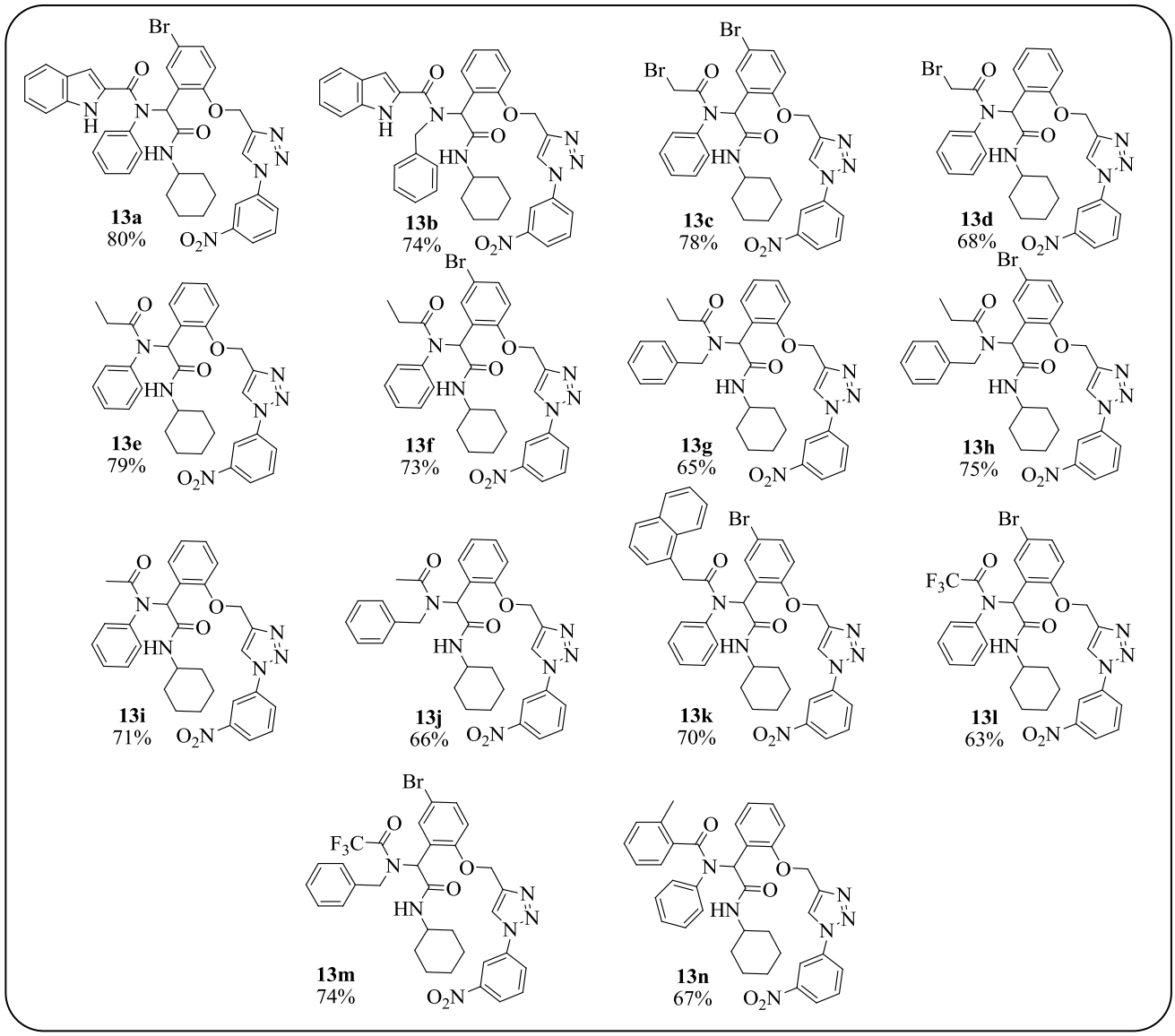
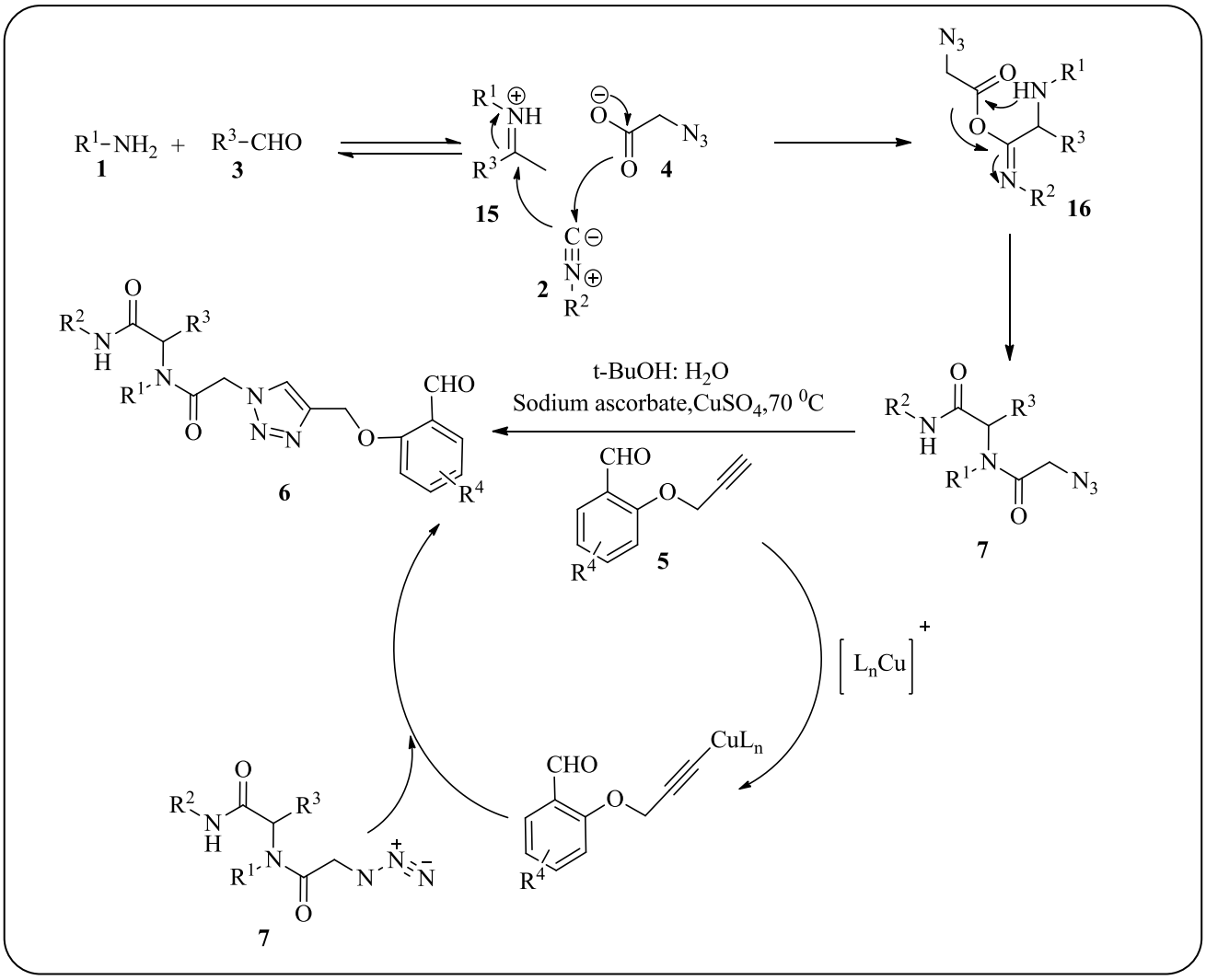


Fig. 3: Structures of 1H-1,2,3-triazole-modified peptidoimetics 13a-n.



Scheme 4: Proposed Mechanism for the Formation of Products 6.

may have interesting implications on the construction of structurally diverse heterocyclic molecules and will find applications in combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

Acknowledgments

We gratefully acknowledge financial support from the Iran National Elites Foundation (INEF) and Research Council of Shahid Beheshti University.

Received : Oct. 25, 2015 ; Accepted : Sep. 25, 2017

REFERENCES

[1] (a) Banfi L., Riva R., The Passerini Reaction, *Org. React.*, **65**: 1-140 (2005).

(b) Niu T. F., Cai C., Yi L., A One-Pot Tandem Ugi Multicomponent Reaction (MCR)/Click Reaction as an Efficient Protecting-Group-Free Route to 1H-1,2,3-Triazole-Modified a-Amino Acid Derivatives and Peptidomimetics, *Helv. Chim. Acta*, **95**: 87-99 (2012).

[2] (a) Zhu J., Recent Developments in the Isonitrile-Based Multicomponent Synthesis of Heterocycles, *Eur. J. Org. Chem.*, **7**: 1133–1144 (2003);

(b) Salvador C. E. M., Pieber B., Neu P. M., Torvisco A., Andrade C. K. Z., Kappe C. O., A Sequential Ugi Multicomponent/Cu-Catalyzed Azide-Alkyne Cycloaddition Approach for the Continuous Flow Generation of Cyclic Peptoids, *J. Org. Chem.*, **80** (9)**:** 4590–4602 (2015).

[3] Ugi I., Werner B., Domling A., The Chemistry of Isocyanides, Their MultiComponent Reactions and Their Libraries, *Molecules*, **8**: 53-66 (2003).

[4] Hulme C., Gore V., Multi-Component Reactions: Emerging Chemistry in Drug Discovery from Xylocain to Crixivan, *Curr. Med. Chem.*, **10**: 51-80 (2003).

[5] Nixey T., Kelly M., Hulme C., The One-Pot Solution Phase Preparation of Fused Tetrazole-Ketopiperazines, *Tetrahedron Lett.*, **41**: 8729-8733 (2000).

[6] Nixey T., Kelly M., Semin D., Hulme C., Short Solution Phase Preparation of Fused Azepine-tetrazoles *via* a UDC (Ugi/de-Boc/Cyclize) Strategy, *Tetrahedron Lett.*, **43**: 3681-3684 (2002).

[7] Gunawan S., Ayaz M., De Moliner F., Frett B., Kaiser C., Patrick N., Xu Z., Hulme C., Synthesis of Tetrazolo-Fused Benzodiazepines and Benzodiazepinones by a Two-Step Protocol Using an Ugi-Azide Reaction for Initial Diversity Generation, *Tetrahedron*, **68**: 5606-5611 (2012).

[8] Gunawan S., Nichol G., Hulme C., Concise Route to A Series of Novel 3-(Tetrazol-5-yl)quinoxalin-2(1H)-ones, *Tetrahedron Lett.*, **53**: 1664-1667 (2012).

[9] Niu T.-f., Gu L., Yi W.-b., Cai C., Copper-Free Route to Triazole-Modified Peptidomimetic by the Combination of Two Multicomponent Reactions in One Pot, *ACS Comb. Sci.*, **14**: 309–315 (2012).

[10] Horne W.S., Yadav M.K., Stout C.D., Ghadiri M.R., Heterocyclic Peptide Backbone Modifications in an Alpha-Helical Coiled Coil, *J. Am. Chem. Soc.*, **126**: 15366-15367 (2004).

[11] Bock V.D., Hiemstra H., Maarseveen J.H., Cu^{I}-Catalyzed Alkyne-Azide "Click" Cycloadditions from a Mechanistic and Synthetic Perspective, *Eur. J. Org. Chem.*, **1**: 51-68 (2005).

[12] Angell Y.L., Burgess K., Peptidomimetics *via* Copper-Catalyzed Azide-Alkyne Cycloadditions, *Chem. Soc. Rev.*, **36**: 1674-1689 (2007).

[13] Pedersen D.S., Abell A., 1,2,3-Triazoles in Peptidomimetic Chemistry, *Eur. J. Org. Chem.*, **13**: 2399-2411 (2011).

[14] Brik A., Muldoon J., Lin Y.C., Elder J.H., Goodsell D.S., Olson A.J., Fokin V.V., Sharpless K.B., Wong C.H., Rapid Diversity-Oriented Synthesis in Microtiter Plates for in Situ Screening of HIV Protease Inhibitors, *Chem. Bio. Chem.*, **4**: 1246-1248 (2003).

[15] Soltis M.J., Yeh H.J., Cole K.A., Whittaker N., Wersto R.P., Kohn E.C., Identification and Characterization of Human Metabolites of CAI [5-Amino-1-1(4'-chlorobenzoyl-3,5-dichlorobenzyl)-1,2,3-triazole-4-carboxamide, *Drug. Metab. Dispos.*, **24**: 799-806 (1996).

[16] Alvarez R., Velazquez S., San-Felix A., Aquaro S., De Clercq E., Perno C.F.N., Karlsson A., Balzarini J., Camarasa M.J., 1,2,3-Triazole-[2,5-Bis-O-(tert-butyldimethylsilyl)-beta-D-ribofuranosyl]-3'-spiro-5"-(4"-amino-1",2"-oxathiole 2",2"-dioxide) (TSAO) Analogs: Synthesis and Anti-HIV-1 Activity, *J. Med. Chem.*, **37**: 4185-4194 (1994).

[17] Beraa S., Zhanel G.G., Schweizera F., Evaluation of Amphiphilic Aminoglycoside-Peptide Triazole ConjuGates as Antibacterial Agents, *Bio. Med. Chem. Lett.*, **20**: 3031-3035 (2010).

[18] Bock V.D., Speijer D., Hiemstra H., Maarseveen J.H., 1,2,3-Triazoles as Peptide Bond Isosteres: Synthesis and Biological Evaluation of Cyclotetrapeptide Mimics, *Org. Biomol. Chem.*, **5**: 971-975 (2007).

[19] Nenajdenko V.G., Gulevich A.V., Sokolova N.V., Mironov A.V., Balenkova E.S., Chiral Isocyanoazides: Efficient Bifunctional Reagents for Bioconjugation, *Eur. J. Org. Chem.*, **8**: 1445–1449 (2010).

[20] Sokolova N.V., Latyshev G.V., Lukashev N.V., Nenajdenko V.G., Design and Synthesis of Bile Acid-Peptide Conjugates Linked *via* Triazole Moiety, *Org. Biomol. Chem.*, **9**: 4921-4926 (2011).

[21] Zhu J., Bienaymé H., (Eds.) "Multicomponent Reactions", Wiley-VCH: Weinheim, 33–75 (2005).

[22] Dömling A., Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry, *Chem. Rev.*, **106**: 17-89 (2006).

[23] Rouhi A.M., Traditional Methods Thrive Because Numerous Hurdles, Including Tough Luck, Slow Down the Commercialization of Catalytic Processes, *Chem. Eng. News*, **82**: 47-62 (2004).

[24] Kolb H.C., Finn M.G., Sharpless K.B., Click Chemistry: Diverse Chemical Function from a Few Good Reactions, *Angew. Chem. Int.*, **40**: 2004-2021 (2001).

[25] Shaabani A., Maleki A., Moghimi-Rad J., A Novel Isocyanide-Based Three-Component Reaction: Synthesis of Highly Substituted 1,6-Dihydropyrazine-2,3-dicarbonitrile Derivatives, *J. Org. Chem.*, **72**: 6309-6311 (2007).

[26] Shaabani A., Maleki A., Mofakham H., Moghimi-Rad J., A Novel One-Pot Pseudo-Five-Component Synthesis of 4,5,6,7-Tetrahydro-1*H*-1,4-diazepine-5-carboxamide Derivatives, *J. Org. Chem.*, **73**: 3925-3927 (2008).

[27] Shaabani A., Maleki A., Mofakham H., Khavasi H.R., Novel Isocyanide-Based Three-Component Synthesis of 3,4-Dihydroquinoxalin-2-amine Derivatives, *J. Comb. Chem.*, **10**: 323-326 (2008).

[28] Shaabani A., Maleki A., Mofakham H., Novel Multicomponent One-Pot Synthesis of Tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide Derivatives, *J. Comb. Chem.*, **10**: 595-598 (2008).

[29] Shaabani A., Maleki A., Mofakham H., Khavasi H.R., Novel Isocyanide-Based Three-Component One-Pot Synthesis of Cyanophenylamino-acetamide Derivatives, *J. Comb. Chem.*, **10**: 883-885 (2008).

[30] Shaabani A., Maleki A., Mofakham H., A Novel Synthesis of Highly Substituted Imidazo[1,5-a]pyrazine Derivatives by 3-CR/2-CR Sequence, *Mol. Divers.*, **13**: 63-67 (2009).

[31] Shaabani A., Mofakham H., Maleki A., Hajishaabanha F., Novel Isocyanide-Based One-Pot Multicomponent Syntheses of Tetrahydrobenzo[*b*][1,4]oxazepine and Malonamide Derivatives, *J. Comb. Chem.*, **12**: 630-632 (2010).

[32] Shaabani A., Maleki A., Hajishaabanha F., Mofakham H., Seyyedhamzeh M., Mahyari M., Novel Syntheses of Tetrahydrobenzodiazepines and Dihydropyrazines *via* Isocyanide-Based Multicomponent Reactions of Diamines, *J. Comb. Chem.*, **12**: 186-190 (2010).

[33] Shaabani A., Hajishaabanha F., Mahyari M., Mofakham H., Ng S.W., A Novel One-Pot Pseudo-Four-Component Isocyanide-Based Reaction: An Unexpected Approach for the Synthesis of Tetrahydrodiisoindoloquinoxalines and Tetrahydrobenzodiisoindoloquinoxalines, *Tetrahedron*, **67**: 8360-8366 (2011).

[34] Hajishaabanha F., Shaabani A., Synthesis of Oxazepin-Quinoxaline Bis-Heterocyclic Scaffolds *via* An Efficient Three Component Synthetic Protocol, *RSC Adv.*, **4**: 46844-46850 (2014).

[35] (a) Hajishaabanha F., Shaabani S., Shaabani A., Synthesis of Furan-Fused Quinoxaline Tetracyclic Scaffolds *via* A Three-Component Isocyanide-Based Reaction, *Res. Chem. Intermed.*, **42**: 4109-4120 (2016).

(b) Shaabani A., Ghadari R., Rezayan A. H., Synthesis of Functionalized Coumarins, *Iranian Journal of Chemistry and Chemical Engineering (IJCCE)*, **30**: 19-22 (2011);

(c) Shaabani A., Farhangi E., Shaabani S., A Rapid Combinatorial Library Synthesis of Benzazolo[2,1-b]quinazolinones and Triazolo[2,1-b]quinazolinones, *Iranian Journal of Chemistry and Chemical Engineering (IJCCE)*, **32**: 3-10 (2013).

[36] Banaszynski L.A., Liu C.W., Wandless T.J., Characterization of the FKBP Rapamycin FRB Ternary Complex, *J. Am. Chem. Soc.*, **127**: 4715-4721 (2005).

[37] (a) Rostovtsev V.V., Green L.G., Fokin V.V., Sharpless K. B., A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes, *Angew. Chem. Int. Ed.*, **41**: 2596-2599 (2002);

(b) Himo F., Lovell T., Hilgraf R., Rostovtsev V. V., Noodleman L., Sharpless K. B., Fokin V. V., Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates, *J. Am. Chem. Soc.*, **127**: 210-216 (2005).

(c) Amblard F., Cho J. H., Schinazi R. F., Cu(I)-Catalyzed Huisgen Azide-Alkyne 1,3-Dipolar Cycloaddition Reaction in Nucleoside, Nucleotide, and Oligonucleotide Chemistry, *Chem. Rev.*, **109**: 4207–4220 (2009).