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Efficient synthesis of triazlolic peptidomimetics *via* copper-catalyzed azide-alkyne [3+2] cycloaddition

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ABSTRACT

A practical synthetic protocol affording regioselectively various types of 1,2,3-triazole-containing peptidomimetics ***(9-23)*** *in moderate to excellent yields (33-99%) is described. Such peptidomimetics were obtained by clicking alkyne-N-protected-L-serine derivatives* ***(1-3)*** *and azide-tagged compounds* ***(4-8)*** *under the copper-catalyzed azide-alkyne [3+2] cycloaddition (CuAAC) regime. Various peptidomimetic substrates containing sugar moieties with potential biological and medical relevance are reported.*

Keywords*:* peptidomimetics, amino acids, 1,2,3-triazole, [3+2] cycloaddition, CuAAC, click chemistry.

INTRODUCTION

Naturally occurring peptides and amino acid polymers constitute a vital class of organic compounds, being essential for the function of an enormous variety of biological processes. However, their use and manufacture as potential new drugs is limited by their low bioavailability, enzymatic degradation within biological environments as well as their suffering from non-specific recognition [1]. To circumvent these liabilities, the development of new stable molecules-mimicking the naturally occurring peptides with structural resistance to the metabolic environment appears to be of major importance, in view of synthesizing new biologically active target-molecules [2]. So, the replacement of the classical amide bond in a peptide by a non-classical heterocyclic bioisostere linkage such as 1,2,3-triazole appears to be a promising therapeutic-strategy for the synthesis of biologically relevant peptidomimetic substances [3,4]. Indeed, the triazole unit is found to be reluctant to the enzymatic degradation, hydrolysis and oxidation processes, a feature that promotes it as an alternative to replace the more labile linkers in biologically active molecules. In fact, 1,2,3-triazoles and their derivatives have been reported to serve as synthetic intermediates for the preparation of many drugs that exhibit a wide range of biological activities including antiviral, anticarcinogenic and antibacterial abilities [5-9]. Additionally, the 1,2,3-triazole resembles the amide function both from structurally and physicochemically viewpoints (Fig. 1) [10]. In this context, the Cu-catalyzed azide-alkyne [3+2] cycloaddition (hereafter referred to as CuAAC) that regioselectively yields the 1,4-regioisomer 1,2,3-triazole

has been successfully used to ligate two small molecules, generating a biologically active compound that mimic the known HIV-1 protease inhibitor amprenavir, with the triazole moiety occupying the same position normally adopted by the amide unit of amprenavir. The central nitrogen atom of the triazole was suitably positioned to establish a hydrogen bond with a water molecule present in the protease active site [11].

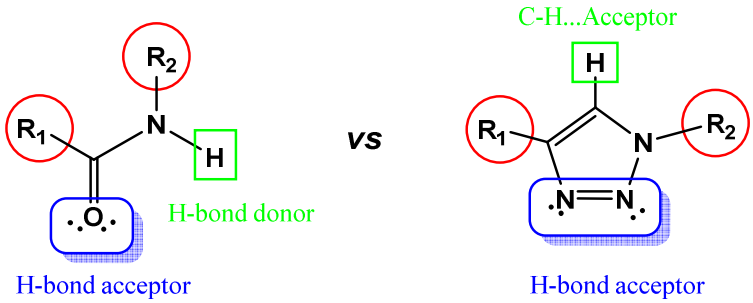
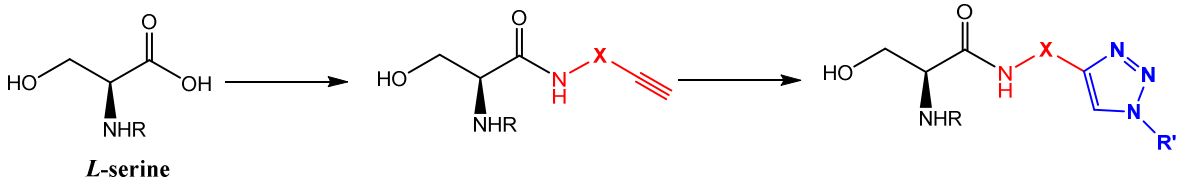


Figure 1. Topological and electronic analogies of the amide bonds and 1,4-disubstitued 1,2,3-triazoles

In order to address the issue of discovering new peptidomimetic drugs, containing the 1,2,3-triazole ring as non-classical bioisostere, we conceived a synthetic strategy based on the coupling of *L*-serine, (a known non-essential amino acid), particularly important for the proper functioning of the brain and central nervous system with acetylic derivatives followed by the transformation of the triple bond into 1,2,3-triazolic unit via CuAAC with azide-tagged molecules, including sugar ones (Scheme 1) [12].



Scheme 1. Synthetic strategy of peptidomimetics with triazole functionality, starting from *N*-protected-*L*-serine

MATERIALS AND METHODS

All the reagents and solvents employed were of highly pure grade and they were used as received. The azide-tagged sugars **4-6** and the azide-tagged compounds **7** and **8** were prepared as reported elsewhere.[16] Column chromatography was performed on silica gel 60 (Merck 230-400 mesh). All the reactions were monitored by thin-layer chromatography TLC on Silica gel 60 F_{254} aluminum sheets. NMR spectra were recorded in dimethyl sulfoxide (DMSO-d_6) on a Bruker AC-300 instrument. The melting points were determined using a Stuart melting point apparatus SMP3 and employing the capillary tube method. The high resolution mass spectra (HRMS) were recorded in the EI (70 eV) or FAB mode at the mass Spectrometry Service of the Universidad de Valencia. The elemental analysis (C, H and N) were carried out on a EuroEA3000 analyzer by the Servei Central d'Instrumentació Científica at the University of Jaume I. The optical rotations were recorded on a PERKIN-ELMER 241 polarimeter equipped with a sodium lamp and working at room temperature in methanol (MeOH).

General procedure for the synthesis of N-protected-L-serine-N-propargylamide

To a solution of *N*-protected-*L*-serine (2 g, 9.57 mmol for *N*-benzoyl derivative and 9.75 mmol for the *N*-Boc derivative), HOBt (1.42 g, 10.5 mmol) and DCC (2.17 g, 10.51mmol) in chloroform (20 mL); propargylamine (11.48 mmol for *N*-benzoyl and 11.69 mmol for *N*-Boc derivative) and trimethylamine (3 mL, 2.2 equ.) were added. The reaction mixture was stirred at room temperature for 24 h. A white solid was precipitated and it was removed by filtration. The filtrate was evaporated under vacuum and the resulting residue extracted by ethyl acetate. The extracts were combined and the solvent removed in vacuum. The crude obtained was purified by column chromatography.

General procedure for the synthesis of N-Boc-L-serine-N-phenylamide

To a mixture of *N*-protected-*L*-Serine (2 g, 9.75 mmol), HOBt (1.42 g, 10.5 mmol) and DCC (2.17 g, 10.51 mmol) in chloroform (20 mL) were added 4-ethynylaniline (11.36 mmol) and triethylamine (3 mL, 2.2 equ.). The reaction

mixture was stirred at room temperature for 24 h. A white solid was formed and filtered off. The resulting filtrate was evaporated under vacuum and the reaction residue obtained was extracted several times with ethyl acetate. The extracts were combined and the solvent removed under vacuum. The crude obtained was purified by column chromatography by using ethyl acetate. The obtained solids were subsequently recrystallized from a mixture of dichloromethane / hexane.

N-Boc-L-serine-N-propargylamide ***(1)***
White solid. Yield: 85 %; R_f= 0.57 (Ethyl acetate); mp: 153 °C; $[\alpha]^{20}_D$ = -2.3 (*c* = 0.6 in MeOH); ^{1}H NMR (300 MHz, DMSO): δ 1.35 (s, 9H, 3 CH_3), 3.06 (t, 1H, HC≡, *J* = 2.4Hz) ; 3.06 (t, 2H, CH_2C, *J* = 2.4Hz); 3.49 (dd, 2H, CH_2OH, J_1 = 4,2Hz, J_2 = 4,5Hz); 3.82 (m,1H, CHN-); 4.78 (t, 1H, OH, *J* = 6Hz); 6.57 (d, 1H, NHBoc, *J* = 8.4Hz); 8.20 (t,1H,NHCO, *J* = 5.4Hz). ^{13}C NMR (75 MHz, DMSO): δ 28.1-28.3 (3 CH_3); 33.6 (CH_2NH); 38.9 (CH_2OH); 53.1 (BocNHCH); 56.8 (C≡); 62.2 (HC≡); 81.27 (C-O); 155.3 (CO); 170.3 (CO). HRMS (FAB^+): Calcd. for $C_{11}H_{20}N_2O_4$: 244.1453; Found: 243.1375.

N-benzoyl-L-serine-N-propargylamide ***(2)***
White solid. Yield: 75% **;** R_f= 0.5 (Ethyl acetate) ; mp: 161°C; $[\alpha]^{20}_D$ = +5.4 (*c* = 0.1 in MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.08 (t,1H, HC≡, *J* = 2.4Hz) ; 3.70 (m, 4H, 2 CH_2); 4.40 (t, 1H, OH, *J* = 7.2Hz) ; 4.93 (m, 1H, CH-CH_2) ; 7.45 (m, 3H, 3 CH_{arom}) ; 7.89 (d, 2H, 2 CH_{arom}, *J* = 7.2Hz) ; 8.25 (m,2H, 2 NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ 33.6 (CH_2NH) ; 53.1 (CHNH) ; 67.2 (CH_2OH); 72.6 (HC≡); 80.7 (C≡); 133.1-133.7 (5C_{arom}); 165.9 (CO); 169.4 (CO). HRMS (FAB^+): Calcd. for $C_{13}H_{15}N_2O_3$: 248.1161; Found: 248.1201.

N-Boc-L-serine-N-4-ethynylphenylamide ***(3)***
White solid. Yield: 76%; R_f= 0.53 (Ethyl acetate); mp: 122°C; $[\alpha]^{20}_D$ = -2.5 (*c* = 0.4 in MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.46 (s, 9H, 3 CH_3); 3.05 (t, 1H, HC≡, *J* = 2.4Hz); 3.51 (dd, 2H, CH_2OH, J_1 = 5Hz, J_2 = 5.2Hz); 3.87 (m,1H, CH_{serine}); 4.76 (t, 1H, OH, *J* = 6Hz); 6.60 (d, 1H, NH, *J* = 8.4Hz); 7.45 (m,4H,C_6H_4) ; 8.25 (m,1H, NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.1-28.3 (3 CH_3); 38.9 (CH_2OH); 53.1 (CH_{serine}); 81.3 (C-O); 82.0 (HC≡) ; 82.1 (C≡); 118.20(C_{arom}); 120.4 (2CH_{arom}); 130.56(2CH_{arom}); 137.4 (C_{arom}); 154.2 (CO); 170.8 (CO). HRMS (FAB^+): Calcd. for $C_{16}H_{21}N_2O_4$: 306.1580; Found: 306.1610.

General procedure for the Cu-catalyzed Huisgen [3+2] cycloaddition of alkynes with azides
To a solution of alkyne (1mmol) and azide (1.1 mmol) in a mixture of ethanol / water (10 mL /10 mL); $CuSO_4{\cdot}5H_2O$ (0.3 mmol) and sodium ascorbate (0.6 mmol) were added successively. The reaction mixture was stirred at room temperature for 24h. The solvent was removed under vacuum and the resulting residual was extracted by dichloromethane, dried over sulfate magnesium, and filtered. The solvent was evaporated under vacuum and the residue obtained was purified by column chromatography.

N-Boc-L-Serine-N-[(1-galactose-1H-1,2,3-triazole)methylamide] ***(9)***
Colorless oil. Yield: 99%; R_f: 0.42 (Ethyl acetate); $[\alpha]^{20}_D$ = -0.4 (*c* = 1.0 in MeOH); ^{1}H NMR δ (ppm) (300 MHz, DMSO-d_6): 1.37 (m, 21H, 7 CH_3); 4.40 (m, 12H, 6CH+3CH_2); 5.29 (s, 1H, NH); 5.48 (d, 1H, NH, *J* = 4.8Hz); 5.79 (t, 1H, OH, *J* = 6.3Hz); 7.28 (s, 1H, $CH_{triazole}$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.3 (CH_2NH); 26.30 (4 CH_3); 28.67 (3 CH_3); 34.26 (CH_2N); 49.46 (CH_{serine}); 63.29 (CH_2NH); 67.5-71.5 (5 CH (gal)); 80.6 (C-O); 96.5 ($CH_{triazole}$); 109.5 ($C_{triazole}$); 110.3 (C-O); 156.3 (CO). HRMS (FAB^+): Calcd. for $C_{23}H_{39}N_5O_9$: 529.2748; Found: 528.2808.

N-Boc-L-Serine-N-[(1-glucose-1H-1,2,3-triazole)methylamide] ***(10)***
White solid. Yield: 50%; R_f= 0.3 (Ethyl acetate); mp: 125°C; $[\alpha]^{20}_D$ = +40 (*c* = 0.1 in MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.27 (m, 21H, 7 CH_3); 2.50 (m, 2H, OCH_2 (glu)); 3.50 (m, 3H, NCH_2 + OH); 3.93 (m, 1H, CHN (glu)); 4.17 (m, 1H, CH (glu)); 4.33 (dd, 2H, CH_2OH, J_1 = 4.2Hz, J_2 = 4.5Hz); 4.53 (m, 1H, CH (glu)); 4.84 (m, 2H, CH_2NH); 5.14 (m, 1H, CH $_{serine}$); 5.92 (s, 1H, CH (glu)); 6.60 (m, 1H, NHBoc); 7.90 (s, 1H, $CH_{triazole}$); 8.34 (s, 1H, $NHCH_2$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.8 (CH (glu)); 26.6 (2CH_3 (glu)); 26.8 (2CH_3 (glu)); 28.9 (3CH_3 Boc); 33.8 (CH_2N); 34.5 (CH_2NH); 62.3 (CH_{serine}); 62.5 (CH_2OH); 65.4 (CH_2O); 75.8 (CH (glu)); 77.5 (CH (glu)); 78.6 (C-O); 79.5 (CH (glu)); 104.6 (OCHO (glu)); 109.3 (O-C-O); 113.0 (O-C-O); 123.5 ($CH_{triazole}$); 145.2 ($C_{triazole}$); 155.6 (CO); 170.8 (CO). HRMS (FAB^+): Calcd. for $C_{24}H_{40}N_5O_9$: 542.565; Found: 542.561.

N-Boc-L-Serine-N-[(1-ribose-1H-1,2,3-triazole)methylamide] ***(11)***
Colorless oil. Yield: 60%. R_f= 0.29 (Ethyl acetate). $[\alpha]^{20}_D$ = -13.4 (*c* = 0.1 in MeOH); ^{1}H NMR δ (ppm) (300 MHz, DMSO-d_6): δ 1.35 (s, 15H, 2CH_3+ 3CH_3); 3.24 (s, 3H, OCH_3); 4.42 (m, 7H, 2CH (rib)+ CH_2N + CH_2 + OH); 4.64 (

d, 1H, CH (rib), *J* = 5.7Hz); 4.77 (d, 1H, OCHO (rib), *J* = 5.7Hz); 4.93 (s, 2H, CH_2NH); 5.07 (m, 1H, CH_{serine}); 6.61 (d, 1H, NHBoc, *J* = 7.5Hz); 7.89 (s, 1H, $CH_{triazole}$); 8.40 (t, 1H, $NHCH_2$, J=5.7Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.9 (OCH_3); 26.5 (2 CH_3); 28.5 ($3CH_3$); 34.8 (CH_2NH); 52.5 (CH_2N); 55.2 (CH_{serine}); 62.1 (CH_2O); 79.2 (C-O); 81.6-85.0 (3CH (rib)); 109.6 (O-CH-O (rib)); 112.4(O-C-O); 123.5 ($CH_{triazole}$); 145.5 ($C_{triazole}$); 155.8 (CO); 171.3 (CO). HRMS (FAB^+): Calcd. for $C_{20}H_{34}N_5O_8$: 472.480; Found 472.476.

N-Boc-L-Serine-N-[(1-benzyle-1H-1,2,3-triazole)methylamide] ***(12)***
Colorless oil. Yield: 62%; R_f= 0.25 (Ethyl acetate); $[\alpha]^{20}_D$ = -6.0 (*c* = 0.1 in MeOH). ^1H NMR δ (ppm) (300 MHz, DMSO-d_6): δ 1.24 (s, 9H, $3CH_3$); 3.50 (dd, 2H, CH_2OH, J_1=5.7Hz, J_2 = 5.8Hz); 3.96 (m, 1H, CH_{serine}); 4.31 (d, 2H, CH_2NH, *J* = 5.7Hz); 4.84 (t, 1H, OH, *J* = 6.0Hz); 5.60 (s, 2H, CH_2 Ph); 6.64 (d, 1H, NHBoc, *J* = 8.1Hz); 7.32 (m, 5H, $5CH_{arom}$); 7.90 (s, 1H, $CH_{triazole}$); 8.33 (t, 1H, $NHCH_2$, *J*=5.7Hz). ^{13}C NMR (75 MHz, DMS-d_6): δ (28.6 ($3CH_3$); 34.9 (CH_2N); 53.2 (CH_2N); 57.3 (CH_{serine}); 62.3 (CH_2O); 78.6 (C-O); 123.2 ($CH_{triazole}$); 128.3-129.2 (3 CH_{arom}); 136.5 (Cq $_{arom}$); 145.8 ($C_{triazole}$); 155.6 (CO); 170.9 (CO). HRMS (FAB^+): Calcd. for $C_{18}H_{25}N_5O_4$: 376.401; Found: 376.398.

N-Boc-L-Serine-N-[(1-tetradecane-1H-1,2,3-triazole)methylamide] ***(13)***
White solid. Yield: 40%; R_f= 0.2 (Ethyl acetate); mp: 83°C; $[\alpha]^{20}_D$ = -2.1 (*c*= 0.1 in MeOH). ^1H NMR) (300 MHz, DMSO-d_6): δ 0.89 (t, 3H, CH_3CH_2, *J* = 6.2Hz); 1.30 (m, 31H, $3CH_3$ + $11CH_2$); 1.75 (m, 2H, CH_2CH_2N); 3.55 (dd, 2H, CH_2OH, J_1 = 4.9 Hz, J_2= 5 Hz); 3.96 (m, 1H, CH_{serine}); 4.32 (m, 4H, CH_2 NH + CH_2N); 4.84 (t, 1H, OH, *J* = 5.7Hz); 6.65 (d, 1H, NHBoc, *J* = 7.5Hz); 7.82 (s, 1H, $CH_{triazole}$); 8.33 (t, 1H, $NHCH_2$, *J* = 5.4Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.2 (CH_3); 23-34.9 ($12CH_2$); 28.8 ($3CH_3$); 49.7 (CH_2NH); 57.34 (CH_{serine}); 62.3 (CH_2O); 78.6 (C-O); 122.9 ($CH_{triazole}$); 145.4 ($C_{triazole}$); 155.7 (CO); 170.9 (CO). HRMS (FAB^+): Calcd. for $C_{25}H_{47}N_5O_4$: 482.637; Found: 482.632.

N-benzoyl-L-Serine-N-[(1-galactose-1H-1,2,3-triazole)methylamide] ***(14)***
Colorless oil. Yield 98%; R_f= 0.19 (Ethyl acetate); $[\alpha]^{20}_D$ = +0.3 (*c* = 0.5 in MeOH). ^1H NMR δ (ppm) (300 MHz, DMSO-d_6): δ 1.25 (m, 12H, $4CH_3$); 3.65 (m,2H, CH_2NH); 4.08 (m, 3H, CH_2OH + CH_{serine}); 4.28 (m, 2H, CH_2N); 4.46 (m, 4H, OCH); 4.66 (m,1H, O-CH-O); 5.38 (t, 1H, OH, *J*=4.8Hz); 7.4 (m,5H, CH_{arom}); 7.61 (s, 1H, $CH_{triazole}$); 7.72 (m, 2H, 2NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.8-26.3 ($4CH_3$); 35.4 (CH_2NH); 51.0 (NCH_2); 63.2 (CH_2OH); 127.67-132.3 (5CH-O); 168.2-171.3 (2CO). HRMS (FAB^+): Calcd. for $C_{25}H_{34}N_5O_8$: 532.573; Found: 532.571.

N-benzoyl-L-Serine-N-[(1-glucose-1H-1,2,3-triazole)methylamide] ***(15)***
Colorless oil. Yield 65%; R_f= 0.19 (Ethyl acetate); $[\alpha]^{20}_D$ = -0.4 (*c* = 1.0 in MeOH). ^1H NMR (300 MHz, DMSO-d_6): δ 1.3 (4s, 12H, $4CH_3$); 3.50-5.30 (m, 15H, 6CH + $4CH_2$ + CH_{serine}); 5.85 (t, 1H, OH, *J* = 5Hz); 7.28 (m, $3CH_{arom}$); 7.68 (m, 4H, $2CH_{arom}$+NH+$CH_{triazole}$); 7.996 (s, 1H, NH_{serine}). ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.1-26.9 (4 CH_3); 35.0 (CH_2N); 53.9 (C-N); 55.7 (CHNH); 63.1 (CH-CH_2 (glu)); 63.3 (CH_2NH); 66.2 (CH_2O); 66.3 (C_{arom}); 66.4 (CH_2OH); 75.8 (CH-O); 78.4 (CH-O); 79.5 (CH-O); 104.6 ($CH_{triazole}$); 110.4 (C-O); 114.18 (C-O); 123.4 (O-CH-O); 127.7 (C_{arom}); 128.1 (C_{arom}); 128.9 (C_{arom}); 129.10 C_{arom}); 132.3 (C_{arom}); 168.2 (CO); 171.3 (CO). HRMS (FAB^+): Calcd. for $C_{25}H_{33}N_5O_8$: 532.528; Found: 532.522.

N-benzoyl-L-Serine-N-[(1-ribose-1H-1,2,3-triazole)methylamide] ***(16)***
Colorless oil. Yield 63%; R_f= 0.20 (Ethyl acetate); $[\alpha]^{20}_D$ = +0.1 (*c* = 1.0 in MeOH). ^1H NMR δ (ppm) (300 MHz, DMSO-d_6): δ 1.2 (m, 6H, $2CH_3$); 3.24 (s, 3H, OCH_3); 3.68 (m, 1H, CH_{serine}); 3.98 (dd, 2H, CH_2OH, J_1 = 4.7Hz, J_2 = 5Hz); 4.27 (m, 2H, CH_2NH); 4.42 (m, 3H, CH_2N+CH-O); 4.54 (m, 1H, CH-O); 4.67 (m, 2H, CH-O+O-CH-O); 4.88 (t, 1H, OH, *J*=4.8Hz); 7.36 (m, 3H, $3CH_{arom}$); 7.62 (m, 2H, $CH_{triazole}$ + $NHCH_2$); 7.7 (m, 2H, CH_{arom}); 8.03 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.8 (CH_3); 25.3 (CH_3); 34.0(CH_2NH); 52.1 (CH_2N); 54.4 (OCH_3); 54.5 (CHCO); 62.0 (CH_2OH); 80.7-83.9-84.0 (3CH (rib)); 109 (O-CH-O (rib)); 111.8 (O-C-O); 121.9; 122.1; 126.3; 127.4; 130.8 (C_{arom}); 132.3 (C-N); 134.8 (C-CO); 166.7 (CO); 170.1 (CO). HRMS (FAB^+): Calcd. for $C_{22}H_{29}N_5O_7$: 476.475; Found: 476.469.

N-Benzoyl-L-Serine-N-[(1-benzyle-1H-1,2,3-triazole)methylamide] ***(17)***
White solid. Yield: 50%; R_f= 0.24 (Ethyl acetate); mp: 148°C; $[\alpha]^{20}_D$ = +12.5 (*c* = 0.1 in MeOH). ^1H NMR (300 MHz, DMSO-d_6): δ 3.72 (dd,2H,CH_2OH, J_1 = 5.0Hz, J_2=5.5Hz); 4.32 (d,2H,CH_2NH, *J* = 5.7Hz); 4.47 (m, 1H, CH_{serine}, *J* = 6.0Hz); 4.97 (t, 1H, OH, *J* = 6Hz); 5.56 (s, 2H, CH_2Ph); 7.40 (m, 8H, $8CH_{arom}$); 7.88 (m, 3H, $CH_{triazole}$ + $2CH_{arom}$); 8.30 (d, 1H, NHCH, *J* = 9.0Hz); 8.49 (t,1H,$NHCH_2$, *J* = 6.0Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ

35.0(CH_2N); 53.2 (CH_2N); 56.8 (CH_{serine}); 62.1 (CH_2O); 123.3 ($CH_{triazole}$); 128.0-131.8 ($6CH_{arom}$); 134.5 (C_{arom}); 136.5 (C_{arom}); 145.9 ($C_{triazole}$); 166.8 (CO); 170.6 (CO). HRMS (FAB^+): Calcd. for $C_{20}H_{21}N_5O_3$: 380.401; Found: 380.166.

N-Benzoyl-L-Serine-N-[(1-tetradecane-1H-1,2,3-triazole)methylamide] ***(18)***

White solid. Yield: 68%; R_f= 0.22 (Ethyl acetate); mp: 136°C; $[\alpha]^{20}_D$ = +26.9 (*c* = 0.1 in MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.97 (t, 3H, CH_3CH_2, *J* = 6Hz); 1.5 (m, 11H, $11CH_2$); 2.15 (m, 2H, CH_2CH_2N); 3.46 (dd, 2H, CH_2OH, J_1 = 4.7 Hz, J_2= 5 Hz); 4.10 (m, 1H, CH_{serine}); 4.32 (m, 4H, CH_2 NH + CH_2N); 4.73 (t, 1H, OH, *J* = 5.7Hz); 6.65 (d, 1H, NHCH, *J* = 7.5Hz); 7.35 (m, 3H, $3CH_{arom}$); 7.52 (s, 1H, $CH_{triazole}$); 7.7 (m, 2H, CH_{arom}); 8.33 (t, 1H, $NHCH_2$, *J*= 5.4Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 15.5 (CH_3); 21-35.7 ($12CH_2$); 29.1 ($3CH_3$); 48.9 (CH_2NH); 55.2 (CH_{serine}); 65.2 (CH_2O); 76.9 (C-O); 121.2 ($CH_{triazole}$); 123.0; 125.4; 127.1; 129.3; 131.9 (C_{arom}); 145.4 ($C_{triazole}$); 155.7 (CO); 170.9 (CO). HRMS (FAB^+): Calcd. for $C_{25}H_{47}N_5O_4$: 482.637; Found: 482,631.

N-Boc-L-Serine-N-[(1-galactose-1H-1,2,3-triazole)phenylamide] ***(19)***

Colorless oil. Yield: 35%; R_f= 0.33 (Ethyl acetate / Hexane ; 2/1 v/v); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (m, 21H, $4CH_3$+ $3CH_3$); 3.64 (dd, 2H, CH_2OH, J_1 = 4.9Hz, J_2 = 5.3Hz); 4.29 (m, 5H, CH_{serine} + 4CH (gal)); 4.66 (m, 2H, CH_2N); 4.97 (t, 1H, OH, *J* = 5.8Hz); 5.42 (m, 1H, O-CH-O (gal)); 6.78 (d, 1H, NHBoc, *J* = 7.5Hz); 7.73 (4H, $4CHa_{rom}$, *J* = 7.8Hz); 8.47 (s, 1H, $C_{triazole}$); 10.05 (s, 1H, NHPh). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.7-26.4 (4 CH_3); 29.4 ($3CH_3$); 50.7 (CH_2N); 57.8 (CH_{serine}); 62.3 (CH_2O); 67.8-71.0 (4CH (gal)); 78.7 (C-O); 95.99 (O-CH-O); 108.6 (O-C-O); 109.3 (O-C-O); 120.0 ($2C_{arom}$); 125.9 ($2C_{arom}$); 126.2 (C_{arom}); 139.0 (C_{arom}); 146.3 ($CH_{triazole}$); 155.7 (CO); 169.9 (CO). HRMS (FAB^+): Calcd. for $C_{28}H_{40}N_5O_9$: 590,281; Found: 590,278.

N-Boc-L-Serine-N-[(1-glucose-1H-1,2,3-triazole)phenylamide] ***(20)***

Colorless oil. Yield: 33%; R_f= 0.5 (Ethyl acetate / Hexane ; 2/1 v/v); $[\alpha]^{20}_D$ = +43.3 (*c* = 0.1 in MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.27 (m, 21H, $3CH_3$ + $4CH_3$); 3.61 (m, 1H, NCH (glu)); 3.99 (m, 1H, O-CH (glu)); 4.22 (t, 1H, OH, *J* = 5.3Hz); 4.25 (2H, OCH_2 (glu), *J* = 5.4Hz); 4.69 (q, 1H, OCH (glu), *J* = 5.1Hz); 4.89 (t, 1H, O-CH (glu), *J* = 3.9Hz); 4.96 (dd, 2H, CH_2OH, J_1 = 5.3Hz, J_2 = 5,5); 5.21 (m, 1H, CH_{serine}); 5.95 (d, 1H, O-CH-O (glu), *J*=3.6Hz); 6.78 (d, 1H, NHBoc, *J*= 7.8Hz); 7.81 (AB, 4H, $4CH_{arom}$, *J*=4.8Hz); 8.59 (s, 1H, $CH_{triazole}$); 10.06 (s, 1H, NHPh). ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.37-26.8 ($4CH_3$); 28.6 ($3CH_3$); 57.8 (CH (glu)); 62.3 (CH_2OH); 62.6 (CH_{serine}); 65.7 (CH_2O (glu)); 75.71-79.5 (3CH (glu)); 78.7 (C-O); 104.6 (CH (glu)); 109.4 (CH_2); 113.0 (O-C-O); 120.3 ($CH_{triazole}$); 121.89-126.1 ($4CH_{arom}$); 126.3 (C_{arom}); 139.1 (C_{arom}); 146.2 ($C_{triazole}$); 155.7 (CO); 169.9 (CO). HRMS (FAB^+): Calcd. for $C_{29}H_{41}N_5O_9$: 604.634; Found: 604.629.

N-Boc-L-Serine-N-[(1-ribose-1H-1,2,3-triazole)phenylamide] ***(21)***

White solid. Yield: 50%; R_f= 0.21 (Ethyl acetate / Hexane ; 2/1 v/v); mp: 164°C; $[\alpha]^{20}_D$ = -30.0 (*c* = 0.1 in MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.39 (2s, 15H, $2CH_3$+ $3CH_3$); 3.28 (s, 3H, OCH_3); 3.65 (dd, 2H, CH_2OH, J_1 = 4.7Hz, J_2 = 4.9Hz); 4.15 (m, 1H, CH_{serine}, *J* = 7.2Hz); 4.52 (m, 5H, 2CH (rib) + CH_2NH + OH); 4.69 (d, 1H, CH (rib), *J* = 6.0Hz); 4.83 (d, 1H, CH-OCH_3, *J* = 5.7Hz); 6.79 (d, 1H, NHBoc, *J* = 8.1Hz); 7.74 (4H, $4CH_{arom}$, *J* = 8.7Hz); 8.60 (s, 1H, $CH_{triazole}$); 10.06 (s, 1H, NHPh). ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.5 (OCH_3); 26.65 ($2CH_3$); 28.6 ($3CH_3$); 53.0 (CH_2N); 55.2 (CH_{serine}); 62.2 (CH_2O); 78.7 (C-O); 81.67-109.5 (4CH-O); 112.2 (O-C-O); 119.99 ($2CH_{arom}$); 121.5 ($CH_{triazole}$); 126.0 ($2CH_{arom}$); 126.13 (C_{arom}); 139.1 (C_{arom}); 146.76 ($C_{triazole}$); 154.5 (CO); 169.98 (CO). HRMS (FAB^+): Calcd. for $C_{25}H_{33}N_5O_8$: 532.535; Found: 533.530.

N-Boc-L-Serine-N-[(1-benzyl-1H-1,2,3-triazole)phenylamide] ***(22)***

White solid. Yield: 35%; R_f= 0.51 (Ethyl acetate / Hexane ; 2/1 v/v); mp: 131°C; $[\alpha]^{20}_D$ = -14.8(*c* = 0.2 in MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.39 (s, 9H, $3CH_3$); 3.63 (dd, 2H, CH_2OH, J_1 = 5Hz, J_2 = 5.3Hz); 4.15 (m, 1H, CH_{serine}); 4.96 (t, 1H, OH, *J* = 5.7Hz); 5.63 (s, 2H, CH_2Ph); 6.78 (d, 1H, NHBoc, *J* = 7.8Hz); 7.37 (m, 5H, $5CH_{arom}$); 7.72 (4H, $4CH_{arom}$, *J* = 6.3Hz); 8.65 (s, 1H, $CH_{triazole}$); 10.04 (s, 1H, NHPh). ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.6 ($3CH_3$); 53.47 (CH_2N); 119.9 ($CH_{triazole}$); 126.0-129.2 (CH_{arom}). HRMS (FAB^+): Calcd. for $C_{23}H_{27}N_5O_4$: 438.475; Found: 438.47.

N-Boc-L-Serine-N-[(1-tetradecane-1H-1,2,3-triazole)phenylamide] ***(23)***

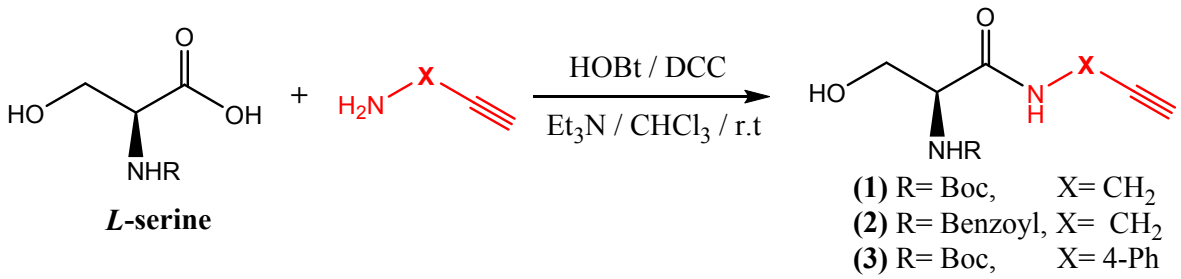
Colorless oil. Yield: 35%; R_f: 0.48 (Ethyl acetate / Hexane ; 2/1 v/v); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.84 (t, 3H, CH_3CH_2, *J* = 6.3Hz); 1.29 (m, 31H, $3CH_3$ + $11CH_2$); 1.86 (m, 2H, CH_2CH_2N); 3.63 (dd, 2H, CH_2OH, J_1 = 4.7Hz, J_2 = 5Hz); 4.16 (m, 1H, CH_{serine}, *J* = 7.2Hz); 4.36 (t, 2H, CH_2N, *J* = 6.9Hz); 4.96 (t, 1H, OH, *J* = 5.4Hz); 6.79 (d, 1H, NHBoc, *J* = 7.8Hz); 7.73 (4H, CH_{arom}, *J* = 8.7Hz); 8.5 (s, 1H, $CH_{triazole}$); 10.0 (s, 1H, NHPh). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.0 (CH_3); 22.5-31.7 ($12CH_2$); 28.6 ($3CH_3$); 49.9 (CH_2O); 57.8 (CH_{serine}); 62.3 (CH_2N);

78.7 (C-O); 119.9 ($CH_{triazole}$); 121.07-125.9 (4 CH_{arom}); 126.4 (C_{arom}); 139.0 (C_{arom}); 146.6 ($C_{triazole}$); 155.7 (CO); 169.9 (CO). HRMS (FAB^+): Calcd. for $C_{30}H_{49}N_5O_4$: 544.706; Found: 544,704.

RESULTS AND DISCUSSION

The amine group of the enantiomerically pure amino acid *L*-serine was firstly protected by either reaction with the anhydride di-*tert*-butyl dicarbonate (Boc_2O) or the benzoyl chloride in presence of sodium hydroxide (NaOH) or trimethylamine (Et_3N) as a base in methanol, yielding *N*-Boc- or *N*-benzyol-*L*-serine in good yields of 88 and 75%, respectively.

Later, the coupling of the *N*-protected-*L*-serine and a variety of acetylenic primary amine was conducted by using the combination of coupling agents 1-hydroxybenzotriazole (HOBt) and dicyclohexylcarbodiimide (DCC) in presence of Et_3N in chloroform at room temperature (Scheme 1). Purification by column chromatography using SiO_2 and ethyl acetate as eluent gave the acetylenic amides (**1-3**) as white crystalline solids in yields varying between 70 and 80%. The formation of the amide bond in compounds **1-3** was confirmed by ^1H and ^{13}C NMR, which indicate the presence of the typical chemical shifts of the hydrogen and carbon atoms of the amide unit at approximately 8.20 ppm and 170 ppm, respectively. Mass spectrometry also confirms the expected mass for obtained amide derivatives **1-3**.



Scheme 2. Coupling of the *N*-protected-*L*-serine and acetylenic primary amines

The 1,3-dipoles containing sugar moieties **4-6** were prepared by partial appropriate protection of *D*-galactose, *D*-glucose [13,14] and *D*-ribose [15], followed by specific tosylation of the unprotected hydroxyl group using tosyl chloride [15]. The introduction of the azide function was carried out by reaction of the tosyl derivatives with sodium azide, affording azide-tagged sugars **4-6** (Figure 2) [16]. Meanwhile, the other two azide derivatives, namely benzyl azide (**7**) and tetradecane azide (**8**) were obtained by reaction of their respective bromo derivative with sodium azide in acetone as solvent [13].

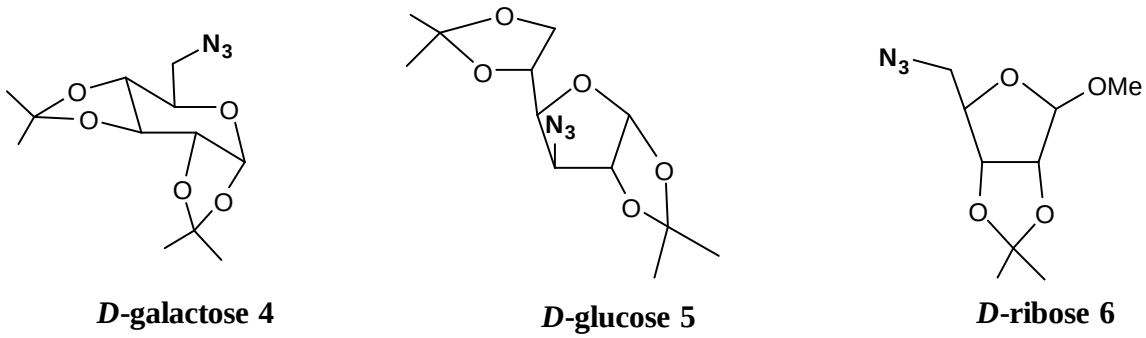


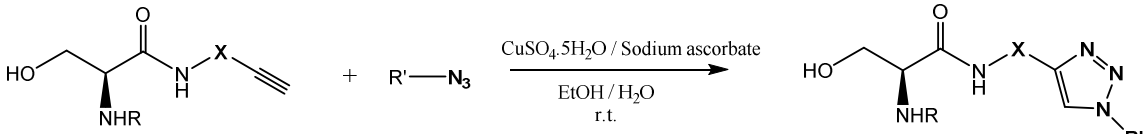
Figure 2. Azide –tagged sugars moieties employed in this study

The [2+3] cycloaddtion between the differents 1,3-dipoles azide and the *N*-protected-L-serine acetylenic derivatives regioselectively lead to the 1,2,3-triazolic products **9-23** under CuAAC by using $CuSO_4 \cdot 5H_2O$ as catalyst and sodium ascorbate as reducing agent of generate the catalytically active Cu(I) species. The cycloaddition reaction was conducted in a water/ethanol solvent mixture at room temperature until completion of the reaction as confirmed by TLC. The triazolic amino acid compounds **9-23** were obtained after purification by column chromatography in

moderate to excellent yields (33-99%) and their molecular structures that correspond to the 1,4-regioisomer was confirmed by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry analysis and elemental analysis (Table 1).

^{1}H NMR spectra show a signal corresponding to the new triazolic proton H5 that is located at 7.73 and 8.56 ppm for the peptidomimetic compounds **9-18** and the new amino acid triazolic compounds **19-23**, respectively. An AB system shifting at 7.73, 7.81, 7.74, 7.72 and 7.73 was observed for compounds **19** to **23** respectively, corresponding to the 4H of the phenyl amide group. ^{13}C NMR spectra show typical chemical shifts of the residual carbonyl-amide group of the peptidomimetics at 155.7 and 169.4 ppm and the new formed carbons of the triazolic unit, chemically shifting around 123 and 145 ppm for the tertiary and quaternary carbon atoms, respectively. Mass spectrometry analysis supports the expected molecular mass for all the isolated peptidomimetics. The optical properties of the obtained 1,2,3-triazoles-containing peptidomimetics, which is a specific property of amino acids and naturally occurring peptides, were also studied by measuring their optical rotations. The values found support that these peptidomimetics are still optically actives.

Table 1. Synthesis of 1,2,3-triazoles- containing peptidomimetics 9-23



9-23

R= Boc, X= CH_2 **1**
R= Benzoyl, X= CH_2 **2**
R= Boc, X= 4-Ph **3**

R'= *D*-galactose **4**
R´= *D*-glucose **5**
R'= *D*-ribose **6**
R'= Benzyl **7**
R'= *n*-$C_{14}H_{29}$ **8**

Entry	Alkyne	Azide	Peptidomimetic	Yield (%)
1	1	4	**9**	99
2	1	5	**10**	50
3	1	6	**11**	60
4	1	7	**12**	62
5	1	8	**13**	40
6	2	4	**14**	98
7	2	5	**15**	65
8	2	6	**16**	63
9	2	7	**17**	50
10	2	8	**18**	68
11	3	4	**19**	35
12	3	5	**20**	33
13	3	6	**21**	50
14	3	7	**22**	35
15	3	8	**23**	35

CONCLUSION

In summary, we have regioselectively synthesized various types of pseudomimetic **9-23** with 1,2,3-triazole as functional unit, bearing glycosyl moieties in a practical and simpler manner. Their structures were confirmed by a set of spectroscopic methods and their optical properties were verified too. Further evaluation of their cytotoxicity and anti-inflammatory activity is planned.

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