# Synthesis and characterization of novel acyclic asymmetrical and symmetrical enediyne-triazole conjugates

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**Abstract**
A novel group of asymmetrical and symmetrical acyclic enediyne-triazole conjugates have been synthesized by using Sonogashira coupling and Click chemistry.

**Keywords:** Acyclic enediynes-triazole conjugates, Sonogashira coupling, Click chemistry

## Introduction

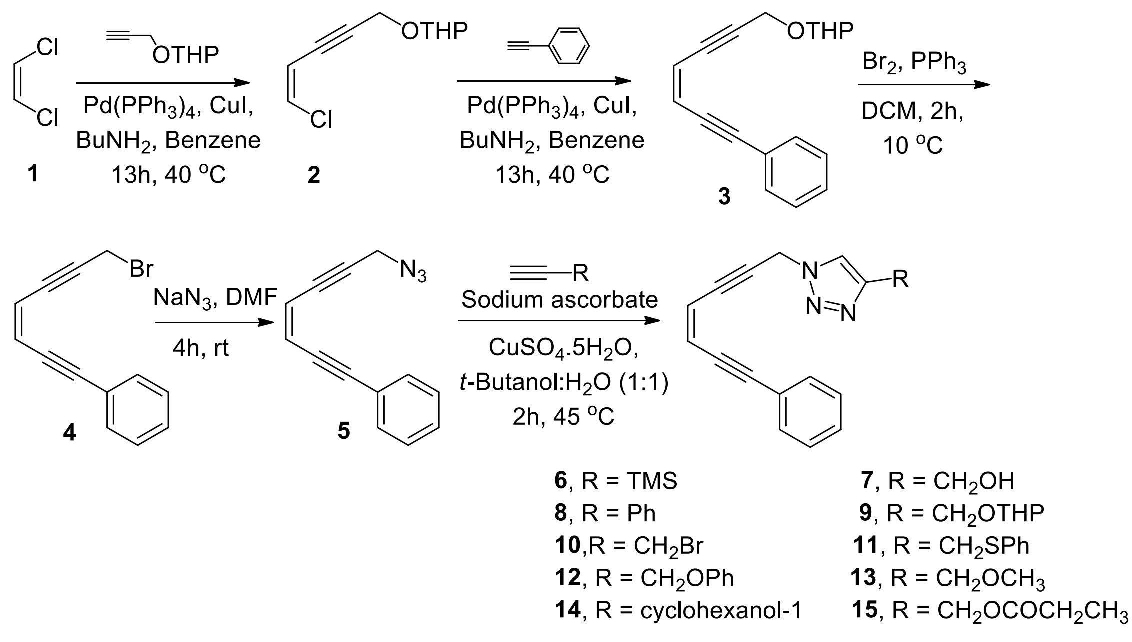
In the decade of 1970`s and 1980`s enediyne chemistry captured the imagination of chemists and biologists throughout the world since the discovery of highly potent anticancer and antimicrobial agents natural product enediynes such as calicheamicin,[1] esperamicin,[2] dynamicin,[3] neocarzinostatin,[4] N1999-A2,[5] maduroptin,[6] namenamicin,[7] shishijimicins,[8] and uncialamycin.[9] The anticancer activity of these compounds is due to the presence of highly unsaturated 1,5-diyne-3-ene unit that undergoes cycloaromatization and generates benzene-1,4-diradical,[10,11] which causes cell death.[12] In order to improve the biological activity of the enediynes, efforts are being made to synthesize analogues with better efficacy.[13-15] Apart from anticancer activity, synthetic enediynes are known to exhibit cytotoxicity against various cell lines,[16,17] protein degradation activity.[18] and topoisomerase inhibitory activity.[19] To the best of our knowledge, none of the synthetic enediynes were synthesized as triazole conjugates, which could be the new area of research. To this end, we have synthesized,[20,21] and explored various approaches,[20,21] for improving the biological activity of enediyne based compounds and this paper deals with the syntheses and characterization of a novel group of acyclic asymmetrical and symmetrical enediynes-triazole conjugates by using standard Sonogashira coupling and "click chemistry".[22-26]

## Results and Discussion

(7-Azidohept-3-ene-1,5-diynyl)benzene **5** was used as an intermediate for the syntheses of acyclic enediynes-triazole conjugates **6-15**, (Scheme 1). *Cis*-dichloroethylene **1** (1.0 equiv.) reacts with 2-(prop-2-ynyloxy)tetrahydropyran (1.0 equiv.) under standard Sonogashira coupling conditions to give 2-(5-chloropent-4-en-2-ynyloxy)tetrahydropyran **2**, which undergoes a second Sonogashira coupling to give 2-(7-phenylhept-4-ene-2,6-diynyloxy)tetrahydropyran **3**. Bromination of enediyne **3** in presence of $PPh_3/Br_2$ affords (7-bromohept-3-ene-1,5-diynyl)benzene **4** (Scheme 1).[27] Later enediyne **4** was reacted with $NaN_3$, (6.0 equiv.) to give (7-azidohept-3-ene-1,5-diynyl)benzene **5** in very good yield, which has been used as an intermediate for the synthesis of acyclic asymmetrical enediyne-triazole conjugates.

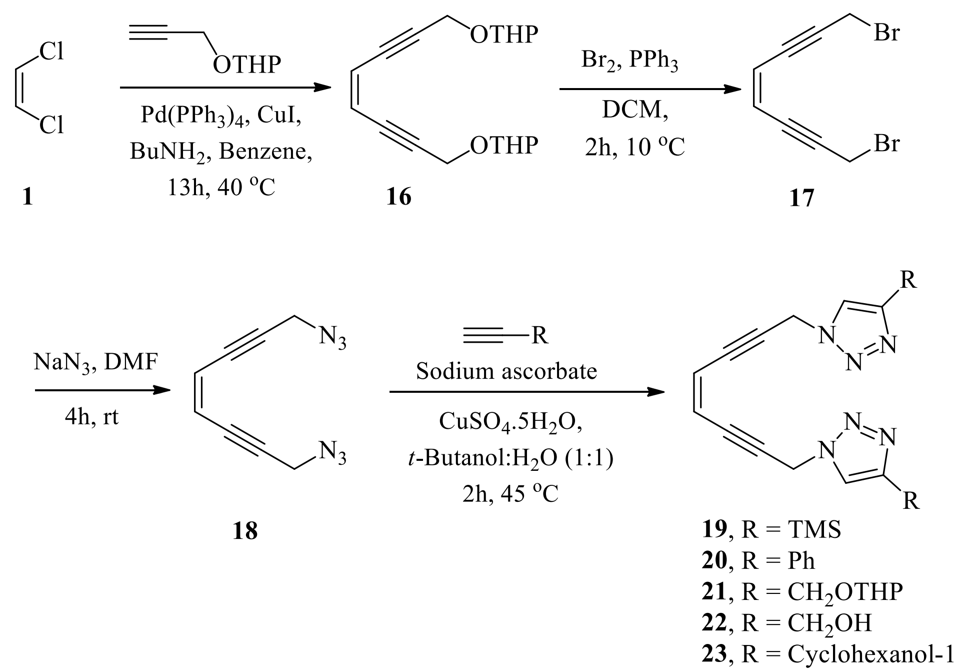
The classic Huisgen 1,3-dipolar cycloaddition often gives mixtures of regioisomers, but the copper-catalyzed reaction allows the synthesis of the 1,4-disubstituted regioisomer specifically.[23,29] Thus the intermediate **5** (1.0 equiv.) reacted with different substituted terminal alkynes (4.3 equiv.) in presence of sodium ascorbate (0.4 equiv.), $CuSO_4.5H_2O$ (0.22 equiv.) in *t*-BuOH/$H_2O$ (1:1) leads to the formation of acyclic asymmetrical enediyne-triazole conjugates **6-15**, (Scheme 1).




**Scheme 1**

At the same time 1,8-diazidooct-4-ene-2,6-diyne **18** was used as an intermediate for the synthesis of acyclic symmetrical enediyne-triazole conjugates. *cis*-Dichloroethylene **1** (1.0 equiv.) and 2-prop-2-ynyloxytetrahydropyran (2.0 equiv.) undergo Sonogashira coupling, to give 1,8-bis(tetrahydropyran-2-yloxy)oct-4-ene-2,6-diyne **16** which undergoes bromination in presence of $PPh_3/Br_2$ to afford the intermediate 1,8-dibromooct-4-ene-2,6-diyne **17** (Scheme 2).[28] Reaction of enediyne **17** with $NaN_3$ (12.0 equiv.) then led to the formation of an intermediate 1,8-diazidooct-4-ene-2,6-diyne **18** in very good yield.

The intermediate enediyne **18** (1.0 equiv.) reacted with substituted terminal alkynes (10.0 equiv.) in presence of sodium ascorbate (0.8 equiv.), $CuSO_4.5H_2O$ (0.5 equiv.) in *t*-BuOH/$H_2O$ (1:1) as a solvent, to afford symmetrical acyclic enediyne-triazole conjugates **19-23**, (Scheme 2) in moderate to good yields.




**Scheme 2**

## Experimental Section

**General.** All of the chemicals used in the synthesis were purchased from Sigma-Aldrich and were used as such. Thin layer chromatography was used to monitor the progress of the reactions. All of the compounds were purified over silica gel column (60-120 mesh). Solvents were distilled prior to use. Melting points were determined on a Glassco melting point apparatus (Cat. no. 514.303.01). IR(KBr) spectra were recorded using Perkin-Elmer FT-IR spectrophotometer and the values are expressed as $\nu_{max}$ $cm^{-1}$. Mass spectral data were recorded on a Jeol (Japan) JMS-DX303 and micromass LCT, Mass Spectrometer/Data system. The, $^1H$ NMR and, $^{13}C$ NMR spectra were recorded on Bruker Spectrospin spectrometer at 300 MHz and 75.5 MHz, respectively using TMS as an internal standard. The chemical shift values are recorded on δ (ppm) scale and the coupling constants (*J*) are in Hz. Elemental analysis for all compounds were performed on a Carlo Erba Model EA-1108 elemental analyzer and data of C, H and N is within ±0.4% of calculated values. Differential scanning calorimetry (DSC) traces were recorded on a Pyris 6 Differential scanning calorimeter of Perkin Elmer Corporation as a peak value at a heating rate of 10 $^oC.min^{-1}$. The maximum temperature mentioned in the data is for, an exothermic peak. At that highest temperature the compound either decomposed, cyclized or forms diradical.

### General procedure and spectral data

**2-(7-Phenylhept-4-ene-2,6-diynyloxy)tetrahydropyran (3).**[27] To a stirred suspension of $Pd(PPh_3)_4$ (1.15 g, 0.99 mmol), CuI (0.76 g, 0.39 mmol), *n*-butylamine (7.29 g, 99.75 mmol) in benzene (40 mL), phenylacetylene (2.24 g, 21.94 mmol) was added dropwise at 40 $^oC$ followed by the dropwise addition of 2-(5-chloropent-4-en-2-ynyloxy)tetrahydropyran **2** (4.0 g, 19.95 mmol) after 15 min. Then reaction mixture was stirred for an additional 13 h at the same temperature. The progress of reaction was monitored by TLC. The excess of solvent was evaporated under vacuo. Residue was purified over $SiO_2$ column using 10% EtOAc/hexane as an eluent. Yield: 74%; DSC: 158.56 $^oC$; Light yellow semisolid, IR (KBr, $cm^{-1}$): 3054, 2943, 2852, 2190, 1598, 1489, 1441, 1344, 1201, 1116, 1054, 1023. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 1.47-1.73 (m, 6H), 3.54 (m, 1H), 3.87 (m, 1H), 4.50 (s, 2H), 4.92 (t, 1H), 5.91 (d, $J$ = 10.8 Hz, 1H), 6.06 (d, $J$ = 10.8 Hz, 1H), 7.30-7.33 (m, 3H), 7.46-7.50 (m, 2H); MS (*m/z*): 267 (M+H, 100%), 182 (32), 166 (38).

**(7-Bromohept-3-ene-1,5-diynyl)benzene (4).**[27] To a stirred suspension of $PPh_3$ (5.67 g, 21.63 mmol) in $CH_2Cl_2$ (50 mL) at 10-15 $^oC$ under nitrogen atmosphere, followed by the careful and slow addition of bromine (3.46 g, 21.63 mmol). Then, 2-(7-phenylhept-4-ene-2,6-diynyloxy)tetrahydropyran **3** (3.60 g, 13.52 mmol) was added dropwise to the reaction mixture at the same temperature. The reaction mixture was stirred at room temperature for 45 min and the progress of reaction was monitored by thin layer chromatography. Excess of solvent was removed under vacuo and crude product was washed by cold hexane and purified over $SiO_2$ column using 5% EtOAc/hexane as an eluent. Yield: 98%; DSC: 158.56 $^oC$; Dark brown liquid; IR (KBr, $cm^{-1}$): 3046, 2924, 2851, 2190, 1597, 1488, 1441, 1225, 1200, 1140, 1028. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 4.16 (s, 2H), 5.91 (d, $J$ = 10.8 Hz, 1H), 6.10 (d, $J$ = 10.8 Hz, 1H), 7.32-7.34 (m, 3H), 7.50-7.52 (m, 2H); MS (*m/z*): 245 (M+, 100%), 247 (M+2, 89), 166 (41).

**(7-Azidohept-3-ene-1,5-diynyl)benzene (5).** To a stirred solution of (7-bromohept-3-ene-1,5-diynyl)benzene **4** (3.57 g, 14.56 mmol) in DMF (20 mL), $NaN_3$ (5.68 g, 87.38 mmol) was added at room temperature. Progress of reaction was monitored by TLC and reaction took 4-6 h to complete. The reaction mixture was extracted with $CHCl_3$ (6 × 30 mL), and combined organic layer was washed with water (6 × 250 mL). The organic layer was dried ($Na_2SO_4$) and solvent was removed under reduced pressure. The crude product was purified over $SiO_2$ column using 5% EtOAc/hexanes as an eluent. Yield: 95%; Dark brown liquid; IR (KBr, $cm^{-1}$): 3049, 2918, 2191, 2128, 2103, 1598, 1489, 1441, 1336, 1246, 1132, 1028. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 4.08 (s, 2H), 5.86 (d, $J$ = 10.8 Hz, 1H), 6.07 (d, $J$ = 10.8 Hz, 1H), 7.18-7.27 (m, 3H), 7.40-7.43

(m, 2H). $^{13}$C NMR (300 MHz, $CDCl_3$) δ: 38.1, 81.9, 83.6, 87.9, 90.4, 119.1, 126.6, 127.2, 127.4, 127.6, 129.5; MS (*m/z*): 207 (M+, 98%), 181 (15), 166 (47); Anal. calcd. for $C_{13}H_9N_3$: C, 75.4; H, 4.4; N, 20.3. Found: C, 75.3; H, 4.4; N, 20.3.

**General method for the synthesis of asymmetrical enediyne-triazole conjugates (6-15)**

To a vigorously stirred suspension of (7-azidohept-3-ene-1,5-diynyl)benzene **5** (1.0 equiv.) and alkynes (4.2 equiv.) in *t*-butyl alcohol, a solution of $CuSO_4.5H_2O$ (0.22 equiv.) and sodium ascorbate (0.4 equiv.) in distilled water was added. The amount of *t*-butyl alcohol and distilled water was kept 1:1. The deep yellow mixture was stirred vigorously at 45 $^o$C for 2-3 h. The progress of reaction was monitored by thin layer chromatography. Then the crude mixture was extracted with $CHCl_3$ (5 × 10 mL) and dried over anhydrous $Na_2SO_4$. Excess of solvent was removed under vacuo. The crude reaction mixture was purified over $SiO_2$ column using EtOAc/hexane as an eluent.

**4-Trimethylsilyl-1-(7-phenylhept-4-ene-2,6-diynyl)-1*H*-[1,2,3]triazole (6).** Yield: 68%; DSC: 147.85 $^o$C; Dark brown liquid; IR (KBr, cm$^{-1}$): 3054, 2958, 2851, 2192, 1598, 1489, 1442, 1343, 1250, 1193, 1045. $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.25 (s, 9H), 5.46 (s, 2H), 5.93 (d, *J* = 10.8 Hz, 1H), 6.18 (d, *J* = 10.8 Hz, 1H), 7.34-7.39 (m, 5H), 7.82 (s, 1H). $^{13}$C NMR (300 MHz, $CDCl_3$) δ: 0.9, 38.8, 83.1, 84.4, 86.2, 95.3, 121.4, 126.8, 127.10, 127.4, 127.8, 128.0, 129.8, 130.7, 131.1; MS (*m/z*): 305 (M+, 100%), 233 (22), 181 (12), 166 (31); Anal. calcd. for $C_{18}H_{19}N_3Si$: C, 70.8; H, 6.3; N, 13.8. Found: C, 71.0; H, 6.3; N, 13.7.

**4-Hydroxymethyl-1-(7-phenylhept-4-ene-2,6-diynyl)-1*H*-[1,2,3]triazole (7).** Yield: 80%; Dark green liquid; IR (KBr, cm$^{-1}$): 3351, 2926, 2855, 2192, 1598, 1489, 1442, 1347, 1227, 1140, 1040. $^1$H NMR (300 MHz, $CDCl_3$) δ: 3.01 (brs, 1H), 4.61 (s, 2H), 5.40 (s, 2H), 5.90 (d, *J* = 10.8 Hz, 1H), 6.19 (d, *J* = 10.8 Hz, 1H), 7.34-7.42 (m, 5H), 7.87 (s, 1H). $^{13}$C NMR (300 MHz, $CDCl_3$) δ: 40.0, 61.2, 83.1, 84.8, 86.4, 95.4, 122.0, 125.8, 127.3, 127.3, 127.7, 128.1, 130.2, 131.1, 148.6; MS (*m/z*): 264 (M+H, 100%), 247 (29), 181 (11), 166 (40); Anal. calcd. for $C_{16}H_{13}N_3O$: C, 73.0; H, 5.0; N, 16.0. Found: C, 73.0; H, 5.0; N, 16.0.

**4-Phenyl-1-(7-phenylhept-4-ene-2,6-diynyl)-1*H*-[1,2,3]triazole (8).** Yield: 78%; mp 98-101 $^o$C; DSC: 140.77 $^o$C; Dark green solid powder; IR (KBr, cm$^{-1}$): 3052, 2925, 2853, 2191, 1598, 1486, 1440, 1344, 1225, 1072, 1043. $^1$H NMR (300 MHz, $CDCl_3$) δ: 5.46 (s, 2H), 5.93 (d, *J* = 10.8 Hz, 1H), 6.19 (d, *J* = 10.8 Hz, 1H), 7.16-7.37 (m, 8H), 7.69-7.71 (m, 2H), 8.08 (s, 1H). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ: 39.6, 83.5, 85.1, 86.4, 96.8, 116.2, 118.0, 120.6, 121.1, 124.5, 126.9, 127.2, 127.5, 127.7, 129.1, 130.4, 146.8; MS (*m/z*): 309 (M+, 100%), 233 (24), 181 (18), 166 (53); Anal. calcd. for $C_{21}H_{15}N_3$: C, 81.5; H, 4.9; N, 13.6. Found: C, 81.6; H, 5.0; N, 13.6.

**1-(7-Phenylhept-4-ene-2,6-diynyl)-4-(tetrahydropyran-2-yloxymethyl)-1*H*-[1,2,3]triazole (9).** Yield: 72%; Light yellow viscous liquid; IR (KBr, cm$^{-1}$): 3052, 2944, 2870, 2192, 1570, 1489, 1441, 1350, 1201, 1120, 1034. $^1$H NMR (300 MHz, $CDCl_3$) δ: 1.41-1.73 (m, 6H), 3.46 (m, 1H), 3.79 (m, 1H), 4.48 (s, 2H), 4.62 (t, 1H), 5.33 (s, 2H), 5.84 (d, *J* = 10.8 Hz, 1H), 6.11 (d, *J* = 10.8 Hz, 1H), 7.19-7.34 (m, 5H), 7.81 (m, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ: 14.2, 19.3, 21.0, 25.4, 30.4, 40.8, 60.3, 62.2, 85.4, 87.1, 88.3, 98.1, 117.5, 121.9, 122.4, 128.4, 128.5, 129.0, 130.8, 131.8, 131.8, 131.9; MS (*m/z*): 348 (M+H, 100%), 263 (20), 247 (8), 181 (13), 166 (37); Anal. calcd. for $C_{21}H_{21}N_3O_2$: C, 72.6; H, 6.1; N, 12.1. Found: C, 72.6; H, 6.1; N, 12.1.

**4-Bromomethyl-1-(7-phenylhept-4-ene-2,6-diynyl)-1*H*-[1,2,3]triazole (10).** Yield: 54%; Dark brown viscous liquid; IR (KBr, $cm^{-1}$): 3140, 3052, 2927, 2854, 2192, 1597, 1488, 1441, 1349, 1215, 1116, 1046. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 4.34 (s, 2H), 5.42 (s, 2H), 6.16 (d, *J* = 10.8 Hz, 1H), 6.24 (d, *J* = 10.8 Hz, 1H), 7.35-7.37 (m, 5H), 7.93 (s, 1H). $^{13}C$ NMR (300 MHz, $CDCl_3$) δ: 33.9, 39.2, 82.8, 84.4, 86.2, 96.3, 119.1, 125.7, 126.9, 127.1, 127.4, 130.5, 131.0, 142.8; MS (*m/z*): 325 (M+, 100%), 327 (M+2, 80), 247 (10), 233 (17), 218 (30), 166 (59); Anal. calcd. for $C_{16}H_{12}BrN_3$: C, 59.0; H, 3.7; N, 12.9. Found: C, 59.0; H, 3.7; N, 12.8.

**1-(7-Phenylhept-4-ene-2,6-diynyl)-4-phenylsulfanylmethyl-1*H*-[1,2,3]triazole (11).** Yield: 78%; Dark brown viscous liquid; IR (KBr, $cm^{-1}$): 3139, 3055, 2925, 2852, 2191, 1582, 1482, 1439, 1348, 1222, 1222, 1116, 1044. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 4.06 (s, 2H), 5.33 (s, 2H), 5.93 (d, *J* = 10.8 Hz, 1H), 6.18 (d, *J* = 10.8 Hz, 1H), 7.18-7.40 (m, 10H), 7.67 (s, 1H). $^{13}C$ NMR (300 MHz, $CDCl_3$) δ: 38.7, 41.3, 84.0, 85.2, 86.8, 96.1, 120.1, 121.4, 123.2, 126.7, 126.9, 127.6, 127.9, 128.0, 134.0, 134.3, 149.2, 150.4; MS (*m/z*): 356 (M+H, 20%), 355 (M+, 100), 279 (26), 247 (34), 233 (21), 181 (13), 166 (52); Anal. calcd. for $C_{22}H_{17}N_3S$: C, 74.3; H, 4.8; N, 11.8. Found: C, 74.4; H, 4.8; N, 11.8.

**4-Phenoxymethyl-1-(7-phenylhept-4-ene-2,6-diynyl)-1*H*-[1,2,3]triazole (12).** Yield: 90%; Dark green liquid; IR (KBr, $cm^{-1}$): 3136, 3056, 2931, 2872, 2192, 1597, 1491, 1347, 1232, 1174, 1032. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 4.91 (s, 2H), 5.27 (s, 2H), 5.79 (d, *J* = 10.8 Hz, 1H), 6.06 (d, *J* = 10.8 Hz, 1H), 6.79-6.87 (m, 4H), 7.13-7.30 (m, 6H). $^{13}C$ NMR (300 MHz, $CDCl_3$) δ: 42.0, 65.4, 83.8, 85.9, 86.6, 95.8, 115.7, 120.0, 122.8, 127.6, 127.4, 127.8, 128.0, 128.2, 131.2, 134.3, 153.4, 155.0; MS (*m/z*): 341 (M+H, 21%), 339 (M+, 100), 263 (29), 247 (30), 181 (11), 166 (45); Anal. calcd. for $C_{22}H_{17}N_3O$: C, 77.9; H, 5.1; N, 12.4. Found: C, 77.8; H, 5.0; N, 12.3.

**4-Methoxymethyl-1-(7-phenylhept-4-ene-2,6-diynyl)-1*H*-[1,2,3]triazole (13).** Yield: 75%; Dark green liquid; IR (KBr, $cm^{-1}$): 3052, 2926, 2878, 2191, 1598, 1489, 1444, 1347, 1222, 1093, 1047. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 3.26 (s, 3H), 4.37 (s, 2H), 5.34 (s, 2H), 5.84 (d, *J* = 10.8 Hz, 1H), 6.11 (d, *J* = 10.8 Hz, 1H), 7.19-7.35 (m, 5H), 7.81 (s, 1H). $^{13}C$ NMR (300 MHz, $CDCl_3$) δ: 40.2, 58.2, 66.1, 83.3, 84.9, 86.5, 94.7, 119.0, 127.6, 127.7, 127.9, 128.0, 131.4, 133.6, 148.2; MS (*m/z*): 277 (M+, 100%), 263 (14), 247 (32), 233 (20), 181 (7), 166 (55); Anal. calcd. for $C_{17}H_{15}N_3O$: C, 73.6; H, 5.5; N, 15.2. Found: C, 73.6; H, 5.4; N, 15.2.

**1-[1-(7-Phenylhept-4-ene-2,6-diynyl)-*1H*-[1,2,3]triazole-4-yl]cyclohexanol (14).** Yield: 45%; Dark green liquid; IR (KBr, $cm^{-1}$): 3394, 3053, 2931, 2856, 2191, 1488, 1445 1346, 1156, 1046. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 1.25-1.86 (m, 10H), 2.08 (s, 1H), 5.40 (s, 2H), 5.92 (d, *J* = 10.8 Hz, 1H), 6.18 (d, *J* = 10.8 Hz, 1H), 7.32-7.43 (m, 5H), 7.74 (s, 1H). $^{13}C$ NMR (300 MHz, $CDCl_3$) δ: 21.8, 26.5, 38.7, 39.9, 74.3, 83.4, 84.7, 86.5, 95.6, 120.1, 126.3, 126.8, 127.6, 127.9, 131.0, 132.0, 138.9; MS (*m/z*): 355 (M+Na, 78%), 331 (M+, 99), 315 (22), 233 (17), 181 (9), 166 (41); Anal. calcd. for $C_{21}H_{21}N_3O$: C, 76.1; H, 6.4; N, 12.7. Found: C, 76.1; H, 6.5; N, 12.7.

**4-Methyl ester-1-(7-phenylhept-4-ene-2,6-diynyl)-1*H*-[1,2,3]triazole propionic acid (15).** Yield: 65%; Dark green liquid; IR (KBr, $cm^{-1}$): 3144, 2980, 2192, 1737, 1460, 1352, 1178, 1048.

$^1$H NMR (300 MHz, $CDCl_3$) δ: 1.07-1.12 (t, 3H), 2.25-2.34 (m, 2H), 5.08 (s, 2H), 5.42 (s, 2H), 5.92 (d, $J$ = 10.8 Hz, 1H), 6.19 (d, $J$ = 10.8 Hz, 1H), 7.29-7.41 (m, 5H), 7.92 (s, 1H). $^{13}$C NMR (300 MHz, $CDCl_3$) δ: 8.6, 28.2, 39.9, 57.4, 83.6, 84.9, 86.7, 93.1, 119.3, 126.3, 126.8, 127.3, 127.6, 129.9, 131.6, 142.8, 178.9; MS (*m/z*): 320 (M+H, 16%), 319 (M+,100), 263 (25), 247 (14), 181 (10), 166 (34); Anal. calcd. for $C_{19}H_{17}N_3O_2$: C, 71.5; H, 5.4; N, 13.2. Found: C, 71.4; H, 5.4; N, 13.1.

**1,8-Diazidooct-4-ene-2,6-diyne (18)**

To a stirred suspension of 1,8-dibromooct-4-ene-2,6-diyne **17** (4.0 g, 15.26 mmol) in DMF (20 mL), $NaN_3$ (11.9 g, 183.20 mmol) was added at room temperature and reaction allowed to stirred for additional 4 h. The progress of reaction was monitored by TLC. After completion of reaction, reaction mixture was extracted with $CHCl_3$ (630 mL), and combined organic layer was washed with water (6 × 250 mL). The organic layer was dried (anhydrous $Na_2SO_4$) and solvent was removed under reduced pressure. The crude product was purified over $SiO_2$ column using 10% EtOAc/hexanes as an eluent. Yield: 88%; DSC: 120 $^oC$; Dark brown liquid; IR (KBr, $cm^{-1}$): 3052, 2924, 2856, 2106, 1586, 1440, 1336, 1247, 1161, 1099. $^1$H NMR (400 MHz, $CDCl_3$) δ: 4.12 (s, 4H), 5.96 (s, 2H). $^{13}$C NMR (300 MHz, $CDCl_3$) δ: 37.2, 81.7, 86.4, 127.1; MS (*m/z*): 186 ($M^+$, 100%), 134 (15), 104 (33); Anal. calcd. for $C_8H_6N_6$: C, 51.6; H, 3.3; N, 45.1. Found: C, 51.7; H, 3.3; N, 45.2.

**General method for the synthesis of symmetrical enediyne-triazole conjugates (19-23)**

To a vigorously stirred solution of 1,8-diazidooct-4-ene-2,6-diyne **19** (1.0 equiv.) and alkynes (9.0 equiv.) in *t*-butyl alcohol, a solution of $CuSO_4.5H_2O$ (0.46 equiv.) and sodium ascorbate (0.86 equiv.) in distilled water was added. The amount of *t*-butyl alcohol and distilled water was kept 1:1. The deep yellow mixture was stirred vigorously at ca. 45 $^oC$ for 2-3 h. The progress of reaction was monitored by thin layer chromatography. After completion of reaction, the reaction mixture was extracted with $CHCl_3$ (5 × 10 mL) and dried (anhydrous $Na_2SO_4$). Excess of solvent was removed under vacuo. The crude mixture was purified over $SiO_2$ column using EtOAc/hexane as an eluent.

**1,8-Bis-[(4-trimethylsilyl-1*H*-(1,2,3-triazol-1-yl)]oct-4-ene-2,6-diyne (19).** Yield: 60%; Dark brown viscous liquid; IR (KBr, $cm^{-1}$): 3124, 2960, 2855, 2108, 1488, 1345, 1253, 1100, 1045. $^1$H NMR (300 MHz, $CDCl_3$) δ: 0.25 (s, 18H), 5.33 (s, 4H), 5.88 (s, 2H), 7.66 (s, 2H). $^{13}$C NMR (300 MHz, $CDCl_3$) δ: 1.1, 38.6, 82.1, 87.6, 126.2, 129.2, 130.4; MS (*m/z*): 382 (M+, 99%), 238 (42), 134 (18), 104 (27); Anal. calcd. for $C_{18}H_{26}N_6Si_2$: C, 56.5; H, 6.9; N, 22.0. Found: C, 56.5; H, 6.8; N, 22.0.

**1,8-Di-[(4-phenyl-1*H*-(1,2,3-triazole)]oct-4-ene-2,6-diyne (20).** Yield: 60%; mp 160-164 $^oC$; DSC: 161.78 $^oC$; Light brown solid powder; IR (KBr, $cm^{-1}$): 2922, 2886, 2189, 1460, 1353, 1224, 1075. $^1$H NMR (300 MHz, $CDCl_3$) δ: 5.28 (s, 4H), 5.97 (s, 2H), 7.26-7.41 (m, 6H), 7.80-7.83 (m, 4H), 7.96 (s, 2H). $^{13}$C NMR (300 MHz, $CDCl_3$+DMSO-$d_6$) δ: 38.5, 81.4, 88.3, 118.7, 119.2, 123.8, 126.4, 127.2, 128.9, 145.5; MS (*m/z*): 391 (M+H, 15%), 390 (M+, 100), 238 (13), 134 (25), 104 (32); Anal. calcd. for $C_{24}H_{18}N_6$: C, 73.8; H, 4.7; N, 21.5. Found: C, 73.8; H, 4.7; N, 21.6.

**1,8-Di-[(4-tetrahydropyranyl-2-yloxymethyl)-1*H*-(1,2,3-triazole)]oct-4-ene-2,6-diyne (21).** Yield: 60%; Dark green liquid; IR (KBr, $cm^{-1}$): 2936, 2855, 2185, 1541, 1456 1351, 1261, 1119, 1032. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 1.44-1.75 (m, 12H), 3.49 (m, 2H), 3.83 (m, 2H), 4.61 (s, 4H), 4.80 (m, 2H), 5.30 (s, 4H), 5.88 (s, 2H), 7.74 (s, 2H). $^{13}C$ NMR (300 MHz, $CDCl_3$) δ: 15.3, 21.4, 37.8, 39.2, 61.9, 65.0, 82.4, 88.0, 101.1, 127.1, 131.2, 148.1; MS (*m/z*): 467 (M+H, 19%), 466 (M+, 100), 298 (31), 238 (31), 134 (27), 104 (22); Anal. calcd. for $C_{24}H_{30}N_6O_4$: C, 61.8; H, 6.5; N, 18.0. Found: C, 61.8; H, 6.5; N, 18.0.

**1,8-Di-[4-hydroxymethyl-1*H*-(1,2,3-triazole)]oct-4-ene-2,6-diyne (22).** Yield: 50%; Dark brown liquid; IR (KBr, $cm^{-1}$): 3358, 2963, 2190, 1605, 1348, 1261, 1017. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 2.50 (s, 2H), 4.51 (s, 4H), 4.66 (s, 4H), 5.91 (s, 2H), 7.71 (s, 2H); $^{13}C$ NMR (300 MHz, $CDCl_3$) δ: 41.0, 61.6, 82.4, 88.4, 127.3, 130.9, 147.5; MS (*m/z*): 299 (M+H, 79%), 298 (M+, 100), 238 (29), 134(18), 104 (30); Anal. calcd. for $C_{14}H_{14}N_6O_2$: C, 56.4; H, 4.7; N, 28.2. Found: C, 56.3; H, 4.7; N, 28.1.

**1,8-Di-4-[1-hydroxycyclohexanyl-1*H*-(1,2,3-triazole)]oct-4-ene-2,6-diyne (23).** Yield: 77%; Dark brown liquid; IR (KBr, $cm^{-1}$): 3378 (brd), 2932, 2856, 2188, 1585, 1448, 1347, 1257, 1157, 1059. $^1H$ NMR (300 MHz, $CDCl_3$) δ: 1.25-2.04 (m, 20H), 3.20 (brs, 2H), 5.35 (s, 4H), 5.95 (s, 2H), 7.71 (s, 2H). $^{13}C$ NMR (300 MHz, $CDCl_3$) δ: 21.4, 26.1, 38.8, 40.8, 76.1, 82.5, 88.3, 127.3, 130.2, 135.1; MS (*m/z*): 434 (M+, 100%), 402 (15), 238 (25), 134 (35), 104 (44); Anal. calcd. for $C_{24}H_{30}N_6O_2$: C, 66.3; H, 7.0; N, 19.3. Found: C, 66.3; H, 6.9; N, 19.3.

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