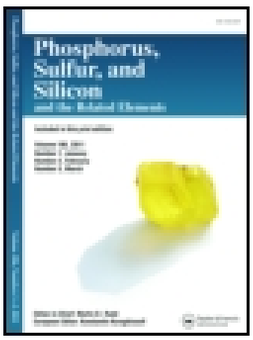

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Synthesis of 1,2,3-triazol derivatives of 4-methyl benzenesulfonamide

N,N'-(hexane-1,6-diyl)bis(N-((1-aryl/alkyl-1H-1,2,3-triazol-4-yl)methyl)-4-methyl benzenesulfonamide): Synthesis, antibacterial, antioxidant, and DNA-cleavage activities

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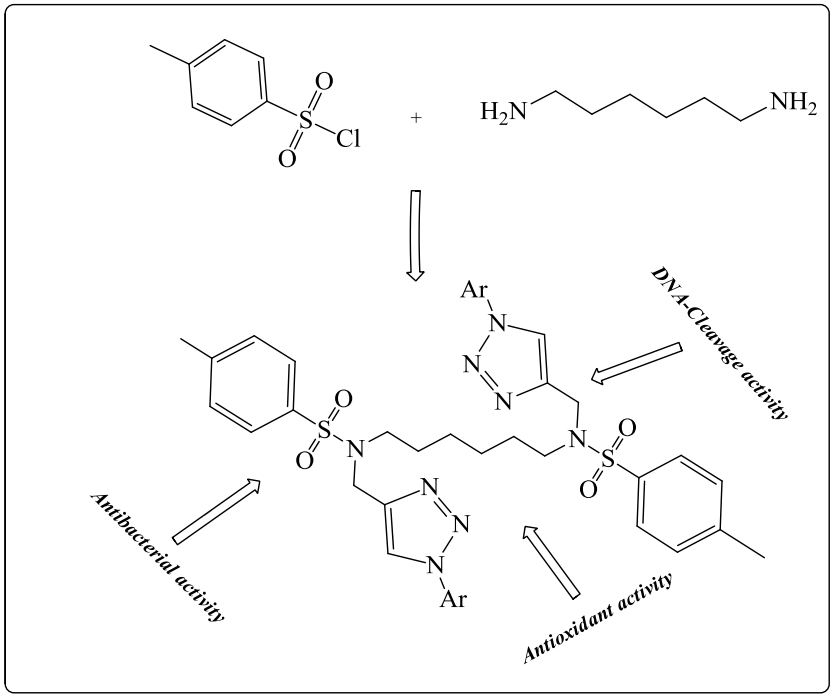
Abstract

Thirteen novel bis-1,2,3-triazole derivatives were synthesized under copper (I)-catalyzed azide-alkyne 1, 3-dipolar cycloaddition of N,N'-(hexane-1,6-diyl)bis(4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide) with different aryl azides and evaluated their biological activity. All the newly synthesized compounds were confirmed by ^{1}H-NMR, IR and ESI-MS spectral studies. The synthesized bis-1, 2, 3-triazoles were evaluated for their antioxidant activity and some of them found to exhibit good to excellent antioxidant activity ($IC_{50:}$ 11.13 ± 1.5 to 98.98 ± 1.7 μM) in comparison with standard references Trolox (11.73 ± 1.5 μM) and ascorbic acid (3.34 ± 1.8 μM). The bistriazoles also exhibited excellent to moderate anti-bacterial activity (MIC: 2.253 to 75 μg mL^{-1} against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* when compared with Streptomycin. N,N'-(hexane-1,6-diyl)bis(N-((1-(3,5-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methyl benzenesulfonamide) has completely cleaved DNA at 100 mg mL^{-1} concentration and the remaining compounds have partially cleaved the DNA.



Keywords

Bis-1, 4-disubstituted 1, 2, 3-triazoles, antioxidant, antibacterial, DNA-cleavage activity.

INTRODUCTION

The world population had been suffering from infectious disease due to the multi-drug resistant pathogens against man made antibiotics. Among them, bacterial infections are second most leading death causing diseases after cardiovascular disease in the world, due to their rapid spread, toxicity and resistance towards the existing antibiotic drugs. [1-3] The importance of 1, 2, 3-triazoles in biological systems has attracted great interest due to their medicinal and pharmacological characteristics. Many compounds containing the 1,2,3-triazole moiety have found widespread biological activities, which include antimicrobial, [4] anticancer,[5, 6] antioxidant, [7] anti-HIV, [8, 9] anti-inflammatory, [10] antiprotozoal, [11] anticonvulsant, [12] antihistamine, [13] and antitubercular properties. [14] Such compounds have also been reported as β3-selective adrenergic receptor agonists, [15] kinase inhibitors [16, 17] and other enzyme inhibitors.[18,19]

The Cu-catalyzed [3+2] cycloaddition reaction using azide-alkyne was discovered individually by Sharpless and Meldal and led to the fundamental development of the Huisgen thermal reaction and offers a unique approach for the regio selective synthesis of 1,4-disubstituted 1,2,3-triazoles. [20, 21] The 1,4-disubstituted 1,2,3-triazoles can also be prepared by one-pot three component reaction of substituted halides, sodium azide and terminal alkynes in the presence of a copper catalyst. [22-24] Therefore, in continuation of our research towards the synthesis of biologically potent 1, 2, 3-triazole derivatives, [25-28] we report herein, one-pot three component and simple two component synthesis of a small library of N,N'-(hexane-1,6-diyl)bis(4-methylbenzenesulfonamide) linked bis1,4-disubstituted 1,2,3-triazole conjugates and their antibacterial, antioxidant and DNA cleavage activities.

RESULTS AND DISCUSSION

Chemistry

The target bis-1,2,3-triazoles (**5a-h**) and (**6a-e**) were synthesized as outlined in **Scheme S1**. The intermediates **3** and **4** were prepared according to the known reported synthetic route.[29] *p*-toluenesulfonyl chloride (**1**) reacted with hexamethylenediamine(**2**) to form *N, N'*- (hexane-1,6-diyl) bis (4-methyl benzene sulfonamide) (**3**). Compound **4** was obtained by the reaction of compound **3** with propargyl bromide and ^{t}BuOK in DMF at room temperature. The treatment of compound **4** with substituted azides in the presence of a copper (I) catalyst afforded title compounds (**5a-h**). Compound **4** was treated with organic halides, sodium azide and CuI in the presence of THF-H_2O mixture to obtain the desired compounds (**6a-e**) in good to excellent yields.

All the newly synthesized bis triazoles were well characterized by IR, ^{1}H NMR, elemental analysis and mass (ESI-MS) spectral techniques. The IR spectrum of a representative compound **5a** showed absorption bands in the region 3137-3076 cm^{-1}, which were recognized to = C--H stretching vibrations of the triazole ring. The ^{1}H NMR spectrum of compound **5a** showed one characteristic singlet at δ 8.01 due to the presence of two triazole protons. A sharp singlet at δ 5.32 confirmed the presence of four protons of two -CH_2 groups attached to the triazole ring. The presence of two sharp singlet peaks at δ 3.86 and 2.39, corresponded to the -OCH_3 and --CH_3 protons attached to the aromatic ring. One triplet signal was observed at δ 3.14, accounted for the protons of the N-CH_2- group. Further, all the aromatic protons were observed in the region δ 7.01--7.68. The presence of two multiplets in the region δ 1.34-1.13, confirmed the methylene protons of hexamethylenediamine (-N-CH_2-$(CH2)_4$-CH_2 -N-). The mass spectrum of compound

5a exhibited two signals at m/z 800.2 and m/z 822.4 corresponding to [M+H] and [M+Na], which are in agreement with calculated values.

Antioxidant activity

All the synthesized compounds (**5a-h** and **6a-e)** were screened for *in vitro* antioxidant activity[30] and results are presented in Table S 1 (Supplemental Materials). The evaluation of the antioxidant activity revealed that the most of the tested compounds exhibited moderate to strong DPPH radical scavenging ability compared with the positive controls Trolox and ascorbic acid. Among them, the compound bearing 3-(trifluoromethyl)phenyl (**5h)** and 3,5-dichloro phenyl (**5b)** on the triazole ring were found to be more effective and potent DPPH radical scavenging ability as compared with positive control drug Trolax. Remaining compounds have shown good to moderate radical scavenging activity with IC_{50} values in the range of 28.62 ± 1.890 - 97.18 ± 2.051 μM. From the above results it is obvious that compounds bearing electron attracting groups on the triazole attached phenyl group have found to possess potent radical scavenging ability.

Antibacterial activity

In vitro antibacterial activity was examined using broth dilution method [31] and results are presented in Table S 2 (Supplemental Materials). The evaluation of antibacterial data revealed that the most of the tested compounds exhibited moderate to excellent antibacterial activity. Among them, compound **5a** has exhibited excellent activity against *B.Subtilis* (MIC = 2.253 μg mL^{-1}) and S.aureus (MIC = 4.587 μg mL^{-1}). Similarly, compound **5h** showed good activity against *B.Subtilis* (MIC = 6.350 μg mL^{-1}) and *P.aeroginosa* (MIC = 4.687μg mL^{-1}). Compound **6c** also exhibited good activity against *E. coli* (MIC = 2.343 μg mL^{-1}). The remaining

compounds also showed moderate activity against tested microbial strains with MIC ranging from 9.575 to 75 μg mL^{-1}.

DNA cleavage activity

The DNA cleavage activity of the titled compounds (**5a-h** & **6a-e**) was determined using agarose gel electrophoresis method [32, 33] as depicted in Figure S 1. The gel after electrophoresis clearly revealed that, the plasmid pUC18 having three forms of DNA, whereas in case of standard $FeSO_4$ (10 mg mL^{-1}) complete DNA and partial cleavage was observed. Compared to standard $FeSO_4$, compound **5g** have completely cleaved the DNA at 100 mg mL^{-1}. The compounds **5b**, **5e** and **6b** showed partial cleavage at 100 mg mL^{-1}.

EXPERIMENTAL

All the solvents and the starting materials were purchased from commercial sources and used without further purification. Column chromatography was performed on silica gel 60--120 mesh. Melting points were determined using a Cintex apparatus. Elemental analysis was measured by means of Perkin Elmer 2400 CHN elemental analyzer. 400 MHz NMR spectrometer was used to acquire ^{1}H-NMR spectra. Coupling constant (J) values are presented in Hertz and spin multiples are given as s (singlet), d (doublet), t (triplet), and m (multiplet). Mass spectra were recorded by using ESI--MS.

Synthesis of N,N'-(hexane-1,6-diyl)bis(4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide) (4): To a stirred solution of compound **3** (11.8 mmol) in N, N-dimethylformamide (50 mL) was added ^{t}BuOK (47.16 mmol) at 0°C and the reaction mixture was stirred for 2 h under N_2 atmosphere. After 2 h, propargyl bromide (35.3 mmol) was added drop wise to the reaction mass and stirred at room temperature for 6h. After completion of the reaction by TLC, the reaction

mixture was poured carefully into ice-cold water (100 mL), The solid was filtered off, washed with water and dried to afford N,N'-(hexane-1,6-diyl)bis(4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide). Yield: 68%; mp: 74-76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 4H), 7.43 (d, *J* = 8.2 Hz, 4H), 4.71 (s, 4H, C***H*****$_2$**), 3.08 (t, *J* = 4.0 Hz, 4H, N-C***H*****$_2$**-CH_2-), 2.41(s, 6H, Ar-CH_3), 2.29 (s, 2H, alkyne-*H*), 1.33 (m, 4H, N-CH_2-*C*H**$_2$**-CH_2-),1.15 (m, 4H, N-CH_2-*C*H_2-C***H*****$_2$**-); ESI-MS m/z: 501.7 [M+H] & 523.4 [M+Na]. Anal. Cal for $C_{26}H_{32}N_2O_4S_2$: C, 62.37; H, 6.44; N, 5.60; found: C, 62.41; H, 6.47; N, 5.54.

General procedure for 5a-h

To a solution of compound **4** (0.2 g, 0.4 mmol) and arylazide (1.2 mmol) in THF (15mL) was added copper iodide (20 mol-%). The reaction mixture was stirred at room temperature for 8-10 h and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (15 mL) and the product was extracted with ethyl acetate (2×20 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under vacuum and the crude product obtained was purified by column chromatography (hexane/ethyl acetate gradient) to afford the pure desired product.

N,N'-(hexane-1,6-diyl)bis(N-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methyl benzenesulfonamide) (5a): Yield: 68%; mp: 97-99 °C; 8 h; IR (KBr): 3137, 1678, 1594, 1489 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01(s, 2H, triazole-***H***), 7.68 (d, *J* = 8.0 Hz, 4H, Ar-***H***), 7.61(d, *J* = 8.0, 4H, Ar-***H***), 7.41(d, *J* = 8.2 Hz, 4H, Ar-***H***), 7.01(d, *J* = 8.0, 4H, Ar-***H***), 5.32 (s, 4H, N = N-C***H*****$_2$**), 3.86 (s, 6H, -OC***H*****$_3$**) 3.14 (t, *J* = 4.4 Hz, 4H, N-C***H*****$_2$**-CH_2-), 2.39 (s, 6H, Ar-C***H*****$_3$**), 1.32-1.28 (m, 4H, N-CH_2-*C*H**$_2$**-CH_2-), 1.18- 1.06 (m, 4H, N-CH_2-*C*H_2-C***H*****$_2$**-); ESI-MS

m/z: 800.2 [M+H], 822.4 [M+Na]. Anal. Cal for $C_{40}H_{46}N_8O_6S_2$: C, 60.13; H, 5.80; N, 14.02; found: C, 60.10; H, 5.86; N, 14.08.

N,N'-(hexane-1,6-diyl)bis(N-((1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methyl benzenesulfonamide) (**5b**): Yield: 58%; mp: 112-114 °C; 10 h; IR (KBr): 3152, 1677, 1589, 1492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 2H, triazole-***H***), 7.82 (s, 2H, Ar-***H***), 7.72 (d, *J* = 8.0 Hz, 4H, Ar-***H***), 7.62 (s, 4H, Ar-***H***), 7.44 (d, *J* = 8.0 Hz, 4H, Ar-***H***), 5.36 (s, 4H, N = N-C***H₂***), 3.17 (t, *J* = 4.0 Hz, 4H, N-C***H₂***-CH_2-), 2.44 (s, 6H, Ar-C***H***$_3$), 1.42-1.30 (m, 4H, N-CH_2-*C****H₂***-CH_2-), 1.19-1.10 (m, 4H, N-CH_2-*C*H_2-C***H₂***-); ESI-MS m/z: 877.4 [M+H]. Anal. Cal for $C_{38}H_{38}Cl_4N_8O_4S_2$: C, 52.06; H, 4.37; N, 12.78; found: C, 52.14; H, 4.40; N, 12.80.

N,N'-(hexane-1,6-diyl)bis(N-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methyl benzenesulfonamide) (5c): Yield: 62%; mp: 107-109 °C; 8 h; IR (KBr): 3147, 1680, 1597, 1495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 2H, triazole-***H***), 7.71 (d, *J* = 8.2 Hz, 4H, Ar-***H***), 7.66 (d, *J* = 7.8 Hz, 4H, Ar-***H***), 7.59-7.43 (m, 8H, Ar-***H***), 5.34 (s, 4H, N-C***H₂***), 3.14 (t, *J* = 4.0 Hz, 4H, N-C***H₂***-CH_2-), 2.42 (s, 6H, Ar-C***H***$_3$), 1.41-1.29 (m, 4H, N-CH_2-*C****H₂***-CH_2-), 1.21- 1.08 (m, 4H, N-CH_2-*C*H_2-C***H₂***-); ESI-MS m/z: 808.3 [M+H]. 830.7 [M+Na]. Anal. Cal for $C_{38}H_{40}Cl_2N_8O_4S_2$: C, 56.50; H, 4.99; N, 13.87; found: C, 56.45; H, 4.91; N, 13.79;

N,N'-(hexane-1,6-diyl)bis(N-((1-(4-chloro-3,5-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methylbenzenesulfonamide) (**5d**): Yield: 47%; mp: 128-130 °C; 12 h; IR (KBr): 3139, 1689, 1593, 1494 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 2H, triazole-***H***), 7.74 (d, *J* = 8.2 Hz, 4H, Ar-***H***), 7.54 (s, 4H, Ar-***H***), 7.41(d, *J* = 8.2 Hz, 4H, Ar-***H***), 5.33 (s, 4H, N = N-C***H₂***), 3.88 (s, 6H, -OC***H***$_3$), 3.84 (s, 6H, -OC***H***$_3$), 3.18 (t, *J* = 4.4 Hz, 4H, N-C***H₂***-CH_2-), 2.41 (s, 6H, Ar-CH_3), 1.42- 1.32 (m, 4H, N-CH_2-*C****H₂***-CH_2-), 1.18-1.08 (m, 4H, N-CH_2-*C*H_2-C***H₂***-); ESI-

MS m/z: 950.7 [M+Na]. Anal. Cal for $C_{42}H_{48}Cl_2N_8O_8S_2$: C, 54.36; H, 5.21; N, 12.08; found: C, 54.40; H, 5.19; N, 12.13.

N,N'-(hexane-1,6-diyl)bis(N-((1-(4-butylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methyl benzenesulfonamide) (**5e**): Yield: 55%; mp: 83-85 °C; 11h; IR (KBr): 3144, 1667, 1594, 1488 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 2H, triazole-***H***), 7.74-7.66 (m, 8H, Ar-***H***), 7.52-7.38 (m, 8H, Ar-***H***), 5.32 (s, 4H, N = N-C***H*****$_2$**), 3.11 (t, *J* = 4.4 Hz, 4H, N-C***H*****$_2$**-CH_2-), 2.52-2.41 (m, 10H, Ar-C***H***$_3$ & Ar-*C***H**$_2$-CH_2-), 1.60-1.52 (m, 4H, Ar-CH_2-*C***H**$_2$-), 1.34-1.24 (m, 8H, N-CH_2-*C***H**$_2$-CH_2- & Ar-CH_2-CH_2-*C***H**$_2$-CH_3), 1.18-1.10 (m, 4H, N-CH_2-*C*H_2-C***H*****$_2$-**), 0.98 (t, *J* = 6.0 Hz, 6H, Ar-CH_2-CH_2-CH_2-C***H***$_3$); ESI-MS m/z: 852.2 [M+H]. Anal. Cal for $C_{46}H_{58}N_8O_4S_2$: C, 64.91; H, 6.87; N, 13.17; found: C, 64.88; H, 6.79; N, 13.24.

N,N'-(hexane-1,6-diyl)bis(4-methyl-N-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide) (**5f**): Yield: 57%; mp: 116-118 °C; 11 h; IR (KBr): 3141, 1689, 1594, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 7.8 Hz, 4H, Ar-***H***), 8.18 (s, 2H, triazole-***H***), 7.88 (d, *J* = 7.8 Hz, 4H, Ar-***H***), 7.72 (d, *J* = 8.0 Hz, 4H, Ar-***H***), 7.46 (d, *J* = 8.2 Hz, 4H, Ar-***H***), 5.36 (s, 4H, N = N-C***H*****$_2$**), 3.18 (t, *J* = 4.4 Hz, 4H, N-C***H*****$_2$**-CH_2-), 2.44 (s, 6H, Ar-C***H***$_3$), 1.42-1.30 (m, 4H, N-CH_2-*C***H**$_2$-CH_2-), 1.22-1.10 (m, 4H, N-CH_2-*C*H_2-C***H*****$_2$-**); ESI-MS m/z: 852.6 [M+Na]. Anal. Cal for $C_{38}H_{40}N_{10}O_8S_2$: C, 55.06; H, 4.86; N, 16.90; found: C, 55.12; H, 4.78; N, 16.94.

N,N'-(hexane-1,6-diyl)bis(N-((1-(3,5-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methyl benzenesulfonamide) (5g): Yield: 66%; mp: 96-98 °C; 10 h; IR (KBr): 3142, 1682, 1592, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 2H, triazole-***H***), 7.69 (d, *J* = 8.0 Hz, 4H, Ar), 7.43 (d, *J* = 8.2 Hz, 4H, Ar-***H***),7.35 (s, 4H, Ar), 7.16 (s, 2H, Ar), 5.33 (s, 4H, N = N-

C***H₂***), 3.19-3.08 (m, 4H, N-C***H₂***-CH_2-), 2.40 (s, 6H, Ar-CH_3), 2.38 (s, 12H, Ar-C***H₃***), 1.46-1.26 (m, 4H, N-CH_2-*C****H₂***-CH_2-), 1.20-1.10 (m, 4H, N-CH_2-*C*H_2-C***H₂***-); ESI-MS m/z: 796.4 [M+H]. Anal. Cal for $C_{42}H_{50}N_8O_4S_2$: C, 63.45; H, 6.34; N, 14.09; found: C, 63.51; H, 6.39; N, 14.14.

N,N'-(hexane-1,6-diyl)bis(4-methyl-N-((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl) methyl)benzenesulfonamide) (**5h**): Yield: 51%; mp: 124-126 °C; 11 h; IR (KBr): 3161, 1678, 1593, 1496 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 2H, triazole-***H***), 8.03 (s, 2H, Ar), 7.83-7.75 (m, 6H, Ar-***H***), 7.72 (d, *J* = 8.0 Hz, 4H, Ar-***H***), 7.45 (d, *J* = 8.2 Hz, 4H, Ar-***H***), 5.37 (s, 4H, N = N-C***H₂***), 3.18 (t, 4H, N-C***H₂***-CH_2-), 2.44 (s, 6H, Ar-CH_3), 1.42-1.31 (m, 4H, N-CH_2-*C****H₂***-CH_2-), 1.28-1.12 (m, 4H, N-CH_2-*C*H_2-C***H₂***-); ESI-MS m/z: 897.8 [M+Na]. Anal. Cal for $C_{40}H_{40}F_6N_8O_4S_2$: C, 54.91; H, 4.61; N, 12.81; found: C, 54.88; H, 4.58; N, 12.78.

General procedure for 6a-e

To a solution of compound **4** (0.2 g, 0.4 mmol), organic halide (1.0mmol) and sodium azide (1.0 mmol) in THF-H_2O mixture (15mL) was added copper iodide (20 mol-%). The reaction mixture was stirred at 60 ^{o} C for 8 h and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (15 mL) and the product was extracted with ethyl acetate (2×20 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under vacuum and the crude product obtained was purified by column chromatography (hexane / ethyl acetate gradient) to afford the pure desired product.

N,N'-(hexane-1,6-diyl)bis(N-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-methylbenzene sulfonamide) (6a): Yield: 60%; mp: 80-82 °C; 8 h; IR (KBr): 3161, 1671, 1591, 1493 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 2H, triazole-***H***), 7.66 (d, *J* = 8.0 Hz, 4H, Ar-***H***), 7.42 (d, *J* =

8.2 Hz, 4H, Ar-***H***), 7.40-2-7.28 (m, 4H, Ar-***H***), 7.20-7.00 (m, 6H, Ar-***H***), 5.30 (s, 4H, N = N-C***H₂***), 5.20 (s, 4H, Ar-C***H***$_2$) 3.09 (t, *J* = 4.0 Hz, 4H, N-C***H₂***-CH$_2$-), 2.39 (s, 6H, Ar-C***H***$_3$), 1.42-1.28 (m, 4H, N-CH$_2$-*C****H₂***-CH$_2$-), 1.22-1.10 (m, 4H, N-CH$_2$-*C*H$_2$-C***H₂***-); ESI-MS m/z: 768.5 [M+H]. Anal. Cal for $C_{40}H_{46}N_8O_4S_2$: C, 62.64; H, 6.05; N, 14.61; found: C, 62.57; H, 6.11; N, 14.54

N,N'-(hexane-1,6-diyl)bis(4-methyl-N-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide) (6b): Yield: 58%; mp: 87-89 °C; 8 h; IR (KBr): 3152, 1675, 1594, 1490 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 2H, triazole-***H***), 7.70 (d, *J* = 8.0 Hz, 4H, Ar), 7.42 (d, *J* = 8.2 Hz, 4H, Ar), 7.37-7.27 (m, 4H, Ar), 7.24-7.17 (m, 4H, Ar), 5.31 (s, 4H, N = N-C***H₂***), 5.22 (s, 4H, Ar-CH$_2$), 3.11 (t, *J* = 4.4 Hz, 4H, N-C***H₂***-CH$_2$-), 2.44 (s, 6H, Ar-CH$_3$), 2.24 (s, 6H, Ar-CH$_3$), 1.42-1.28 (m, 4H, N-CH$_2$-*C****H₂***-CH$_2$-), 1.21-1.09 (m, 4H, N-CH$_2$-*C*H$_2$-C***H₂***-); ESI-MS m/z: 796.4 [M+H]. Anal. Cal for $C_{42}H_{50}N_8O_4S_2$: C, 63.45; H, 6.34; N, 14.09; found: C, 63.41; H, 6.27; N, 14.15.

N,N'-(hexane-1,6-diyl)bis(4-methyl-N-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide) (6c): Yield: 55%; mp: 93-95 °C; 8 h; IR (KBr): 3142, 1678, 1590, 1493 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 2H, triazole-***H***), 7.70 (d, *J* = 8.0 Hz, 4H, Ar-***H***),7.62 (d, *J* = 8.2 Hz, 4H, Ar-***H***), 7.50-7.40 (m, 4H, Ar-***H***), 7.38-7.18 (m, 4H, Ar-***H***), 5.31 (s, 4H, N = N-C***H₂***), 5.22 (s, 4H, Ar-C***H***$_2$) 3.11 (t, *J* = 4.0 Hz, 4H, N-C***H₂***-CH$_2$-), 2.42 (s, 6H, Ar-C***H***$_3$), 1.40-1.30 (m, 4H, N-CH$_2$-*C****H₂***-CH$_2$-), 1.22-1.10 (m, 4H, N-CH$_2$-*C*H$_2$-C***H₂***-); ESI-MS m/z: 858.3 [M+H]. Anal. Cal for $C_{40}H_{44}N_{10}O_8S_2$: C, 56.06; H, 5.18; N, 16.34; found: C, 56.01; H, 5.22; N, 16.28.

N,N'-(hexane-1,6-diyl)bis(N-((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)-4-methyl benzenesulfonamide) (6d): Yield: 62%; mp: 90-92 °C; 8 h; IR (KBr): 3144, 1667, 1592, 1490 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 2H, triazole-***H***), 7.71 (d, *J* = 8.0 Hz, 4H, Ar-***H***),7.64 (d, *J* = 8.2 Hz, 2H, Ar-***H***), 7.45 (d, *J* = 8.2 Hz, 2H, Ar-***H***), 7.36-7.18 (m, 6H, Ar-***H***), 6.92(d, *J* = 7.8 Hz, 2H, Ar-***H***), 5.33 (s, 4H, N = N-C***H₂***), 5.22 (s, 4H, Ar-C***H***$_2$), 3.82 (s, 6H, O-CH_3), 3.11 (t, *J* = 4.4 Hz, 4H, N-C***H₂***-CH_2-), 2.43 (s, 6H, Ar-CH_3), 1.42-1.30 (m, 4H, N-CH_2-*C****H₂***-CH_2-), 1.22-1.10 (m, 4H,N-CH_2-*C*H_2-C***H₂***-); ESI-MS m/z: 828.3 [M+H]. Anal. Cal for $C_{42}H_{50}N_8O_6S_2$: C, 61.00; H, 6.09; N, 13.55; found: C, 61.05; H, 6.16; N, 13.51.

N,N'-(hexane-1,6-diyl)bis(4-methyl-N-((1-(3-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl) benzenesulfonamide) (6e): Yield: 54%; mp: 86-88 °C; 8 h; IR (KBr): 3131, 1672, 1592, 1494 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 2H, triazole-***H***), 7.69 (d, *J* = 8.0 Hz, 4H, Ar-***H***), 7.40 (d, *J* = 8.2 Hz, 4H, Ar-***H***), 7.38-7.22 (m, 4H, Ar-***H***), 7.20-7.15 (m, 4H, Ar-***H***), 5.33 (s, 4H, N = N-C***H₂***), 5.18 (s, 4H, Ar-C***H***$_2$), 3.13 (t, *J* = 4.4 Hz, 4H, N-C***H₂***-CH_2-), 2.42 (s, 6H, Ar-C***H***$_3$), 2.34 (s, 6H, Ar-C***H***$_3$), 1.41-1.30 (m, 4H, N-CH_2-*C****H₂***-CH_2-),1.18-1.08 (m, 4H,N-CH_2-*C*H_2-C***H₂***-); ESI-MS m/z: 796.2 [M+H]. Anal. Cal for $C_{42}H_{50}N_8O_4S_2$: C, 63.45; H, 6.34; N, 14.09; found: C, 63.50; H, 6.37; N, 14.00.

CONCLUSION

In conclusion, we have synthesized novel bis 1,4-disubstituted 1,2,3-triazoles in good yields, and evaluated their antibacterial, antioxidant and DNA cleavage activities. The compounds **5h** and **5b** showed very good antioxidant activity and the compounds **5a**, **5h** and **6c** showed remarkable antibacterial activity compared to standard drugs. Similarly, compound **5g** showed complete

DNA cleavage at 100 μg mL^{-1}. These results suggest that the synthesized compounds can be good candidates for future investigations.

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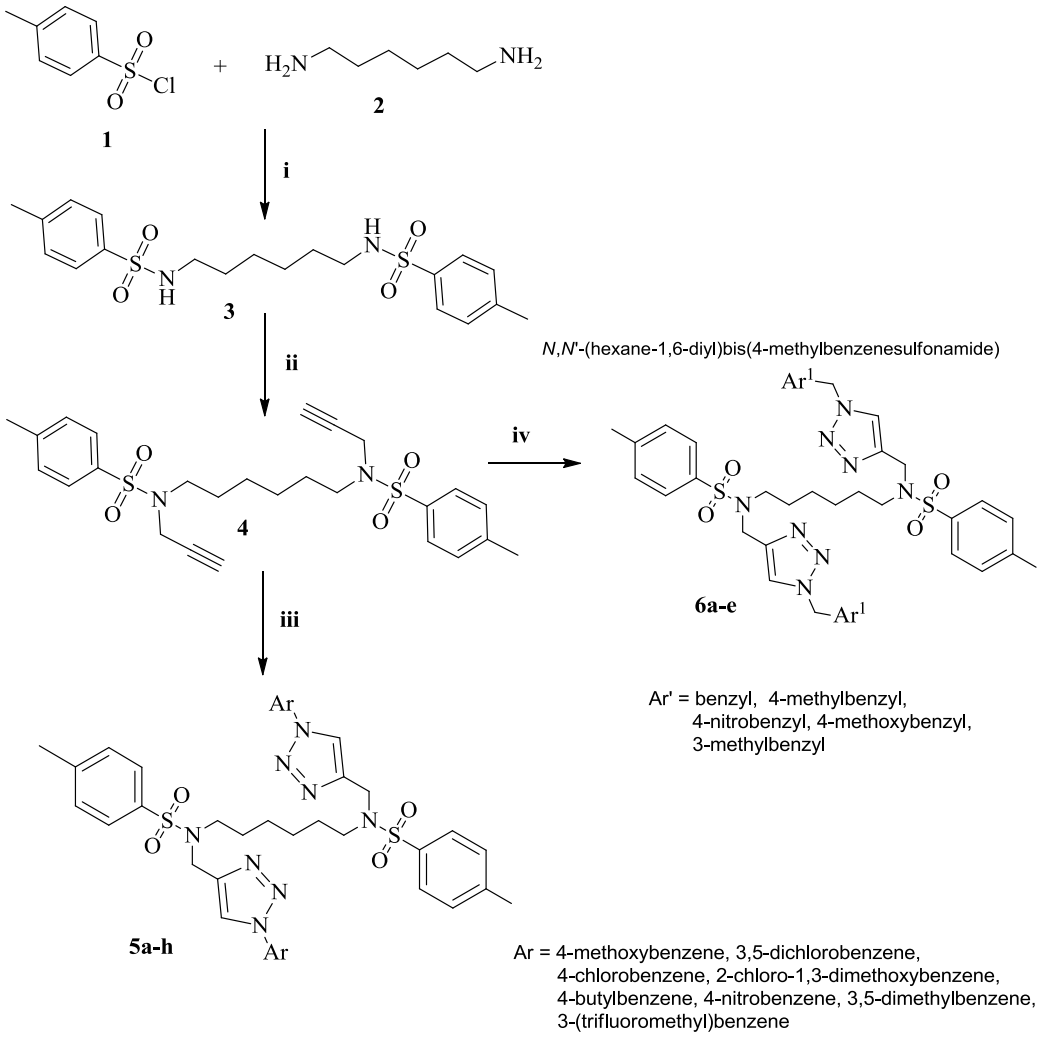

Scheme 1: Synthetic route: i) THF / 10% NaOH; ii) propargyl bromide/ ^{t}BuOK, DMF, rt, 12 h; iii) ArN_3/ CuI, THF, rt, 8-12 h; iv) Ar^1CH_2-Br / NaN_3, THF-H_2O, 60 °C, 8 h.