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Synthesis, characterization, antibacterial activity and molecular docking studies on triazolophanes with benzophenone and S(-)-BINOL functionalization at the intra annular position

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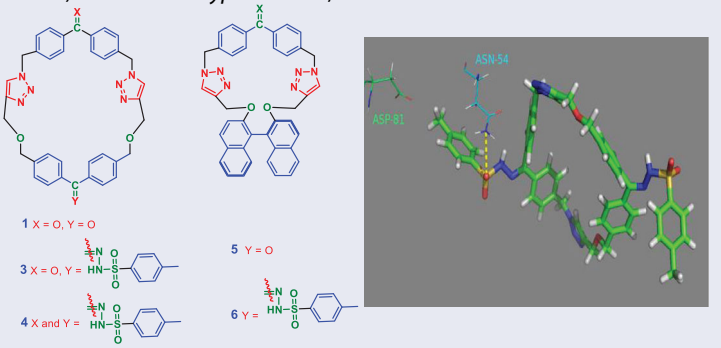
ABSTRACT

Triazolophanes with benzophenone and S(-)-BINOL functionalization at the intra annular position have been synthesized by the click reaction of 4,4′-bis(azidomethyl) benzophenone with the corresponding bispropargyloxy compounds. The newly synthesized triazolophanes were characterized by spectral and analytical methods. Triazolophane with S(-)-BINOL and benzophenone functionality at the intra annular position shows good target binding ability in molecular docking studies and also better antibacterial activity against all the four tested pathogens viz. *Staphylococcus aureus, Bacillus subtilis, Salmonella typhimurium*, and *Escherichia coli* bacteria.

GRAPHICAL ABSTRACT

Synthesis and antibacterial activity of triazolophanes against *S. aureus, B. subtilis S. typhimurium*, and *E. coli* bacteria.



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KEYWORDS
Antibacterial; click chemistry; molecular docking; triazolophane

Introduction

Cyclophanes with heterocyclic ring systems possess a binding site for metal ions[1] and propitiate the properties as molecular hosts. Molecular recognition in supramolecular chemistry,[2] play a vital role in a biological system involving host–guest interactions.

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Supplemental data for this article can be accessed on the publisher's website

Molecular recognition in supramolecular chemistry is regulated by non-covalent intermolecular interactions such as hydrogen bonding, metal coordination, hydrophobic π–π stacking, van der Waals' and electrostatic interactions. Cyclophanes with a preorganized cavity can interact through hydrogen bonding with various guest molecules[3] Cyclophanes can function as selective probes for various guest molecules through non-covalent interactions as well as by forming inclusion complexes. Cyclophanes with binding sites for metal ions can function as a molecular host.[4]

Macrocyclic systems with triazole unit have attracted the synthetic chemists because of their various applications in supramolecular chemistry. Triazolophanes[5] are the new class of cyclophanes containing 1,2,3-triazole motif, which can exhibit strong interactions with halides, transition metal ions, and neutral molecules,[6] and are also of biological importance.[7] Triazolophanes are a new motif that can participate in multiple non-covalent interactions such as metal coordination,[8] anion recognition,[9] self-assembly,[10] and also can exhibit wide applications in biology if used in the synthesis of rigid cavity cyclophanes and hence can have the ability to form complexes with a selectivity that can sharply change the spectral properties. Triazolophane moiety functions as multiple targets due to their auspicious properties such as solubility, bioavailability, hydrophilic and pharmacophoric nature. Further, triazole moiety can enhance the hydrophilicity and binding with macromolecules as seen in drug molecules such as sildenafil, imatinib.[11,12]

Cu(I)-catalyzed azide-alkyne (CuAAC)[13] click chemistry is used for the synthesis of 1,2,3-triazoles regioselectively, which could be a very interesting and promising method. 1,2,3-triazole unit finds their due to the many applications in biology as well as in material science[14] S(-)-BINOL and benzophenone are used in electron transfer and electron exchange devices and also have been widely used in various fields such as textile, drug synthesis,[3] lubricant additives,[12] flavoring agents,[15] personal care,[16] plastics,[14] pharmaceuticals,[17] household products and for the synthesis of antibacterial agent,[18] and so on. However, the biological activity of the triazolophanes is rarely reported.[19] Triazolophanes with BINOL and benzophenone could furnish supramolecular sensing, recognition, and self-assembling properties. We wish to report herein the synthesis, characterization, and antibacterial activity of the new class of triazolophanes **1–6** obtained from the suitable azide and terminal alkyne by click reaction (Fig. 1).

Results and discussion

Triazolophanes **1–6** can be synthesized by the reaction of the corresponding bispropargyloxy precyclophane with various bisazides. The corresponding bispropargyloxy precyclophane can be obtained by the reaction of bis(4-(bromomethyl)phenyl) methanone with propargyl alcohol. In order to synthesis the triazolophanes **1–6** using click chemistry, synthesis of the azides **9**, **11**, and the alkynes **10**, **12**, **14**. is focused. Synthesis of the precyclophanes **9**, **10**, **11**, **12**, and **14** is shown in Scheme 1. Reaction of 4-methyl benzoyl chloride with toluene in the presence of anhydrous $AlCl_3$ at 0 °C to room temperature (rt) afforded 4, 4′-dimethylbenzophenone **7** in 85% yield. Reaction of 4,4′-dimethylbenzophenone **7** with 2.1 equiv. of NBS in the presence of benzyl peroxide in

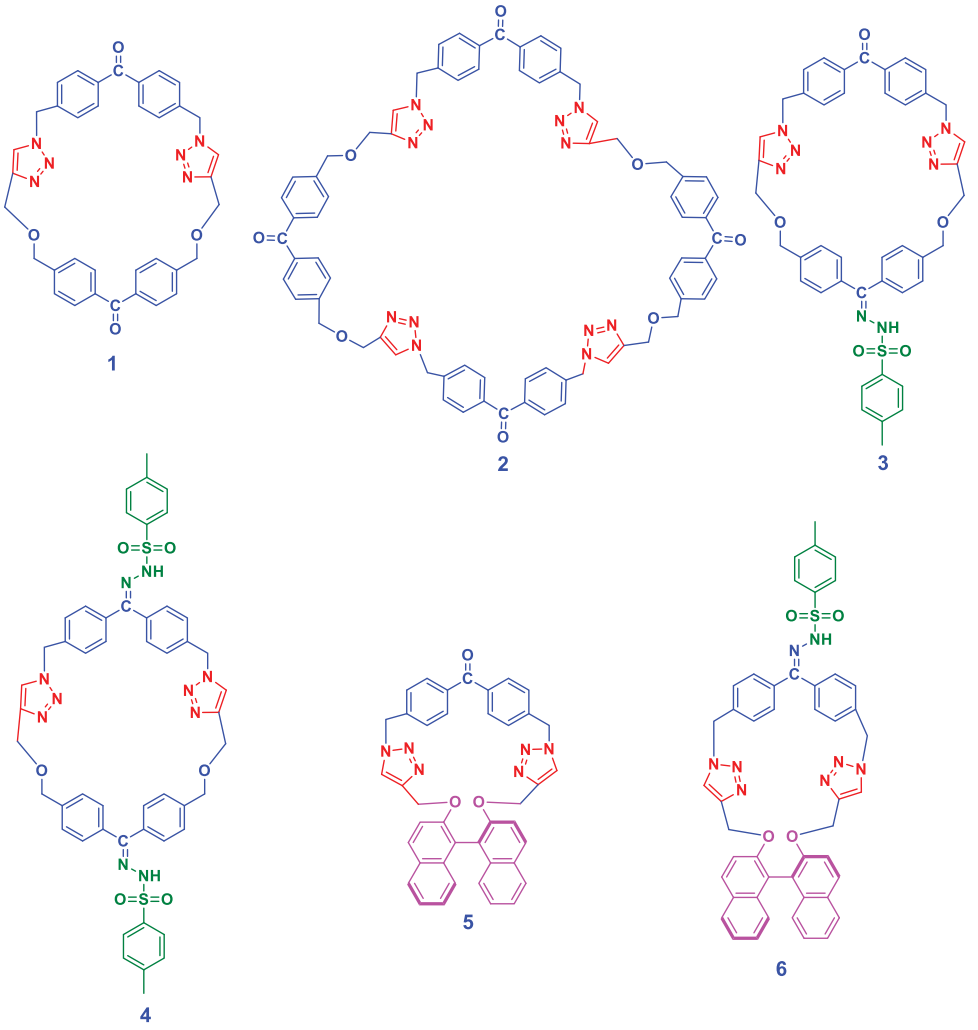
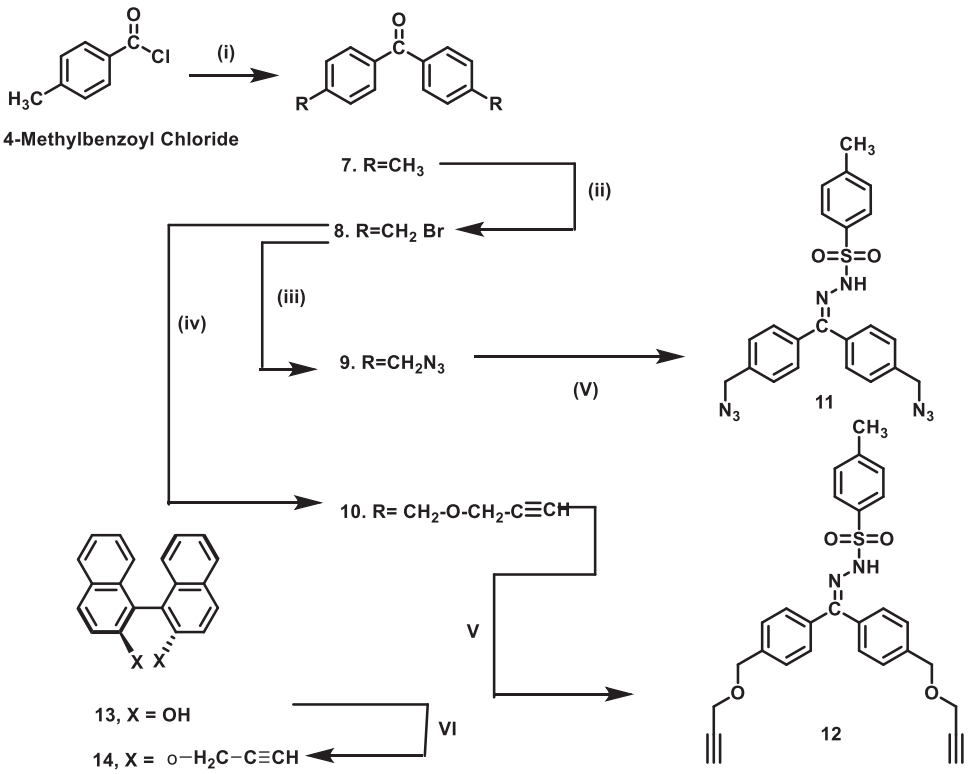


Figure 1. Molecular structure of triazolophanes **1–6** with S(-)-BINOL and benzophenone functionalization at the intra annular position.

CCl_4 gave bis(4′-(bromomethyl)phenyl) methanone **8** in an 85% yield. Further, azidation of **8** with 2.1 equiv. of NaN_3 in a mixture of acetone water (4:1) at 60 °C gave bis(4′-(azidomethyl)phenyl) methanone 9 in 72% yield. Propargylation of bromomethyl compound **8** with 2.1 equiv. of propargyl bromide in the presence of K_2CO_3 in dry DMF gave bis(4′-(propargylmethyl)phenyl methanone **10** in 72% yield.

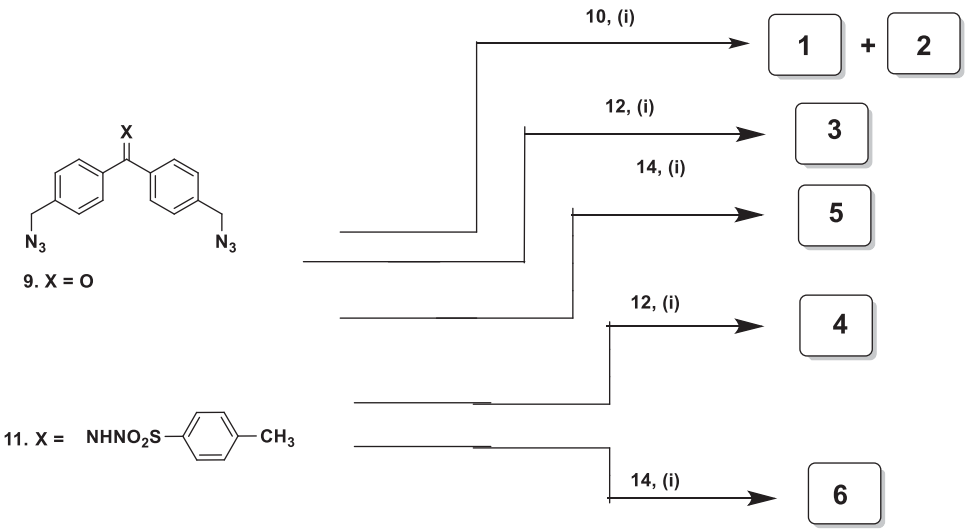
The reaction of 1.0 equiv. of the bisazide **9** and the bispropargyloxy compound **10** with 1.0 equiv. of *p*-Tolylsulphonyl hydrazide in a mixture of toluene-ethanol (2:3) gave the precyclophanes **11** and **12** in 60 and 62% yields, respectively. (Scheme 1). Having successfully synthesized the precyclophanes **11** and **12**, synthesis of bispropargyloxy *S* (-) BINOL 14 was then focused on. The reaction of 1.0 equiv. of *S* (-)BINOL with 2.1 equiv. of propargyl bromide in the presence of K_2CO_3 in dry DMF gave the bispropargyloxy BINOL 14 in 75% yield.



Scheme 1. Reagents and conditions: (i) Toluene, Anhydrous $AlCl_3$, DCM, 0 °C to rt, 3 h, **7** (85%), (ii) 2.1 equiv. of NBS, dry CCl_4, BPO, reflux, 12 h, **8** (85%). (iii) 2.5 equiv. of NaN_3, acetone/H_2O, (4:1) 60 °C, 3 h, 9 (72%). (iv) 2.1 equiv. of propargyl bromide, dry DMF, rt, 24 h 10 (72%). (v) *P*-Tosylhydrazide, (1.0 equiv.), Toluene/ethanol (2:3), rt, N_2, 24 h, **11** (60%),**12** (62%). (vi) 2.1 equiv. of propargyl bromide, dry DMF, rt, 24 h, 14 (75%).

Synthesis of the triazolophanes **1**, **2**, **3**, **4**, **5**, and **6** is shown in Scheme 2. The reaction of 1.0 equiv. of the bisazide **9** with 1.0 equiv. of each of the bispropargyloxy derivatives **10**, **12**, and **14** in the presence of $CuSO_4{\cdot}5H_2O$ (5 mol%) and NaAsc (10 mol%) in a mixture of THF-H_2O (3:1) at rt under click reaction conditions gave the triazolophanes **1**, **3** and **5** in 35, 25, and 62% yields, respectively. Similarly, the reaction of 1.0 equiv. of the hydrazide **11** with 1.0 equiv. of each of the propargyloxy derivative **12** and **14** gave the triazolophanes **4** and **6** in 65%, and 30% yields, respectively (Scheme 2). However in the case of the coupling between the azide **9** and the bispropargyloxy ketone **10**, 2:2 oligomer **2** was also obtained in 41% yield. But the formation of such oligomers is not observed in the other coupling reactions.

The ^{1}H NMR spectrum of the triazolophane **1** displayed three singlets at δ 4.70, 4.74, and 5.63 for the *O*-CH_2, *N*-CH_2, and benzylic protons, respectively, in addition to the signals for the aromatic protons in the region at δ 7.29–7.81. The ^{13}C NMR spectrum of the triazolophane **1** showed signals at δ 53.6, 63.9, and 71.9 for the *O*-CH_2, *N*-CH_2, and benzylic carbon and the aromatic carbons appeared in the region at δ 122.7–145.6 and the ester carbonyl carbon appeared at δ 196.1.



Scheme 2. Reagents and conditions: (i) $CuSO_4.5H_2O$ (5 mol%), sodium ascorbate (10 mol%), H_2O/THF (1:1), rt, 10 h. **1** (35%), **2** (41%), **3** (25%), **4** (65%). **5** (62%), **6** (30%).

The mass spectrum of the triazolophane **1** showed the molecular ion peak at *m*/*z* 610 [M^+]. Further, the structure of the triazolophane **1** was also confirmed from the analytical data. Similarly, the structure of the triazolophanes **2**, **3**, **4**, **5**, and **6** were characterized by spectral and analytical data. (Supplementary Information)

Antibacterial activity of the triazolophanes 1–6

The emergence of drug resistance in bacteria makes it difficult to control both community and hospital-acquired infections. Hence, there is a need to develop new antibacterial drugs. As a result of the drug resistance, there is a major threat to global health and the available drugs will no longer be effective in treating infections due to increasing drug resistance against bacteria. As one of the approaches to screen for the new antibacterial agents that may inhibit and also act as drug targets through a unique binding, we studied the antibacterial activity of the newly synthesized triazolophanes, which is also supported by docking studies.

The antibacterial activity of the newly synthesized cyclophanes was investigated by the Agar well diffusion method against Gram-positive bacteria (*aureus* and *subtilis*) and Gram-negative bacteria (*typhi* and *coli)* strains. All the cyclophanes at various concentrations viz. 50, 100, and 150 µg/mL were dissolved in DMSO. In brief, the incubated bacterial cultures were swabbed on MHA plates and different concentrations of samples were loaded into the well. Streptomycin 25 µg/mL was used as the stranded control and the plates were maintained overnight at 37 °C. After the incubation, a clear zone appeared around the well and was measured as a zone of inhibition against bacteria.

Figure 2 shows the zone of inhibition when the triazolophanes are tested by Agar well diffusion method against both Gram-positive and Gram-negative bacteria. 10% DMSO in water is used as the control which did not show inhibition against all the tested bacteria. At higher concentrations, all the triazolophanes significantly inhibited

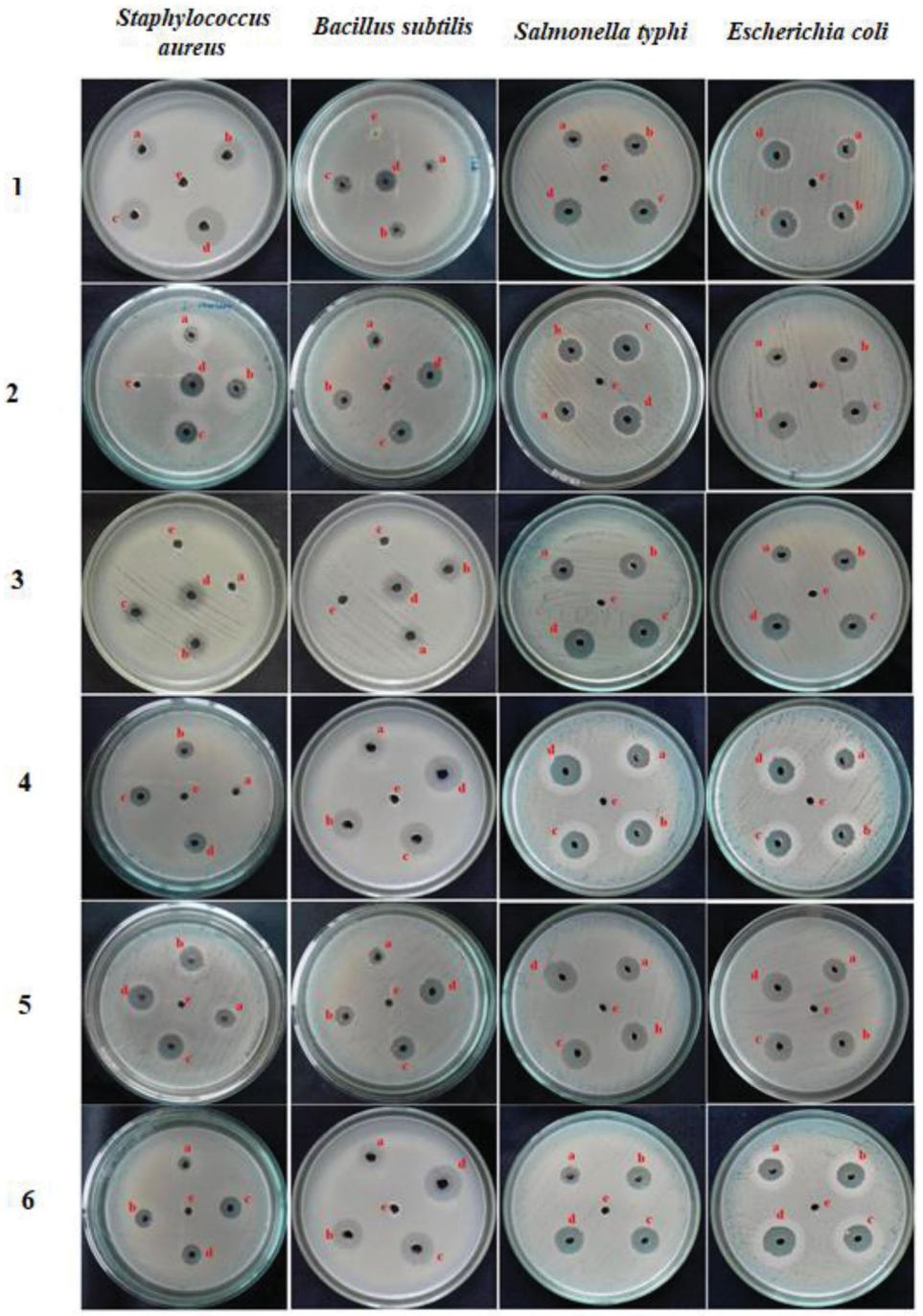


Figure 2. Antibacterial activity of triazolophanes **1**, **2**, **3**, **4**, **5**, and **6** against both Gram positive (*S. aureus*) and Gram negative (*S. typhimurium* and *E. coli*) bacteria strains. Zone of inhibition in mm diameter (a) 50 μg, (b) 100 μg, (c) 150 μg, (d) 25 μg standard (Streptomycin) and (e) 10% DMSO (control).

Table 1. Antibacterial activity of Triazolophanes **1–6**.

	Zone of inhibition in mm																			
	Gram Positive bacteria										Gram Negative bacteria									
	Staphylococcus aureus					*Bacillus subtilis*					*Salmonella typhi*					*Escherichia coli*				
Triazolophane	a	b	c	d	e	a	b	c	d	e	a	b	c	d	e	a	b	c	d	e
1	NA	7.5	9	13	NA	10	11	12	13	NA	1.5	3	5.5	8	NA	10	12	13	14	NA
2	2	4.5	8	10	NA	10	12	13	14	NA	3.5	4.5	7	8	NA	10	11	12	13	NA
3	NA	1.5	2	9	NA	11	13	14	15	NA	NA	NA	1.5	9	NA	10	11	12	13	NA
4	NA	4.5	5.5	7	NA	11	12	13	15	NA	NA	6	8	10	NA	10	11	12	12.5	NA
5	5.0	7	8	9	NA	11	12	14	15.5	NA	2.5	4.5	7	8	NA	11	12	13	14.5	NA
6	2.0	4.5	6	8	NA	10	11.5	13	14	NA	NA	9	11	13	NA	11	12	12	14	NA

(a) 50 μg, (b) 100 μg, (c) 150 μg, (d) 25 μg of the standard drug (streptomycin) and (e) 10% DMSO (negative control). NA: nil activity.

the growth of both Gram-positive and Gram-negative bacteria. The inhibition of the bacterial growth was directly proportional to the concentration of the triazolophanes. All the tested cyclophanes inhibit the growth of bacteria *subtilis* and *coli* effectively.

The average diameter of the inhibition zones of the triazolophanes is determined and listed in Table 1. These values indicate that the inhibition zone increases with an increase in the concentration of the triazolophanes from 50–150μg/mL in 10% DMSO water medium. The present study clearly shows that the triazolophanes are solely responsible for the antibacterial activity against both Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Salmonella typhimurium*) bacteria.[20]

The antibacterial mechanism of samples can be attributed due to the formation of reactive oxygen species (ROS), which results in cell death. It has been reported[21] that the rupture of the bacterial outer membrane can weaken the cells, which is caused by the interaction of the sample surface with bacterial membrane.

Triazolophane **5** shows better antibacterial activity against *aureus* at all tested concentration and all the synthesized triazolophanes show good antibacterial activity at the concentration of 100 μg/mL and the zone of inhibition is almost equal to that of the standard drug viz. Streptomycin. All the triazolophanes **1–6** exhibit almost equal antibacterial effect to that of the standard viz. streptomycin at a concentration 100 μg/mL. However, most of the triazolophanes show poor antibacterial activity or nil activity at the lower concentration of 50 μg/mL with respect to the microorganism *Salmonella typhi* and at higher concentration of the 100 μg/mL Triazolophanes **2**, **5** and **6** at concentration of 150 μg/mL show almost equal activity to that of the standard viz., streptomycin. The antibacterial activity of all triazolophanes **1–6** is comparable to that of the standard even at a lower concentration of 50 μg/mL with respect to bacterial *Escherichia coli*. The antibacterial activity against the bacteria *E. coli* at higher concentration viz. 100 μg/mL is almost the same as that of a lower concentration viz. 50 μg/mL. Hence, with respect to *E. coli* bacteria, the antibacterial activity is dose-independent. From the above observation, triazolophanes **5** and **6** show better antibacterial activity against all the four tested pathogens than that of the triazolophanes **1**, **2**, **3**, and **4.** Triazolophanes **1**, **2**, **4**, **5**, and **6** show antibacterial activity against *S. aureus* at a higher concentration of 150 mg comparable to that of the

Table 2. Molecular docking of triazolophanes **1**, **3**, **4**, **5**, and **6** with target proteins (PDB-3U2D).

Cyclophanes	Glide score	Glide energy (kcal/mol)	Hydrogen bond interactions D–H … A	Distance (Å)
1	−4.164	−60.007	(SER-129) O–H … N	2.7
			(THR-173) O–H … O	3.0
3	−8.410	−74.450	(ASN-54) N–H … O	3.0
			C–H … O (TYR-63)	2.9
			(ARG-84) N–H … N	3.2
			(THR-173) O … O	2.7
4	−4.232	−67.671		
5	−7.556	−68.065		
6	−4.274	−51.921		

standard drug viz., streptomycin. All the synthesized triazolophanes **1–6** show concentration-independent antibacterial activity toward *Bacillus subtilis* and comparable to that of the standard. Triazolophanes **2**, **4**, **5**, and **6** show antibacterial activity agent *Salmonella typhi* comparable to that of the standard only at a higher concentration of 150 mg. The antibacterial activity of the triazolophanes **1–6** is concentration-dependent with respect to *E. coli* and comparable to that of the standard

Molecular docking study on triazolophanes 1, 3, 4, 5, and 6

The molecular docking study helps us to find the interactions between ligand/compound with a protein of interest (target).[22] The binding of any ligand in the active pocket of the protein inhibits the catalytic functions. Further, molecular docking could explain the mode of action of the ligands that bind to the target proteins. Hence, the synthesized triazolophane derivatives **1**, **3**, **4**, **5**, and **6** have been subjected to molecular docking studies with the target protein of *S. aureus* GyrB. A molecular docking study was carried out using the Schrodinger suite. DNA gyrase is an essential enzyme in bacteria.[23] The inhibition of DNA gyrase results in disruption of DNA synthesis and subsequently cell death. DNA gyrase consisting of the subunits GyrA and GyrB and is one of the members of the type II family of topoisomerases that control the topological state of DNA in cells.[24] This enzyme plays a vital role in the replication of DNA by coupling with the ATP, which helps the supercoiling of the DNA. It has been known as a fascinating target for antibacterial drugs.[25] The 3D structure of *S. aureus* GyrB was taken from the protein data bank (PDB ID: 3U2D), in which the crystal structure was solved at 1.85 Å resolution. *Staphylococcus aureus* GyrB protein was prepared and refined by protein preparation module and their energy minimized using default constraint of 0.3 Å RMSD and OPLS 2005 force field. (Schrödinger suite). ASP-81, ARG-84, ARG-144, and THR-173 are the active site residues of the protein. The synthesized triazolophanes derivative structures were built using Maestro v9.1 and geometrically minimized using OPLS_2005 force field by LigPrep module of Maestro 9.1 (Schrödinger suite). LigPrep produces a minimized low-energy 3D conformation of each input structure with various ring conformations, ionization states, and tautomer using various criteria including molecular weight and types of functional groups present.

The triazolophanes **1**, **3**, **4**, **5**, and **6** show excellent binding with the amino acids in the active pocket of the protein with good binding energy and docking score, and

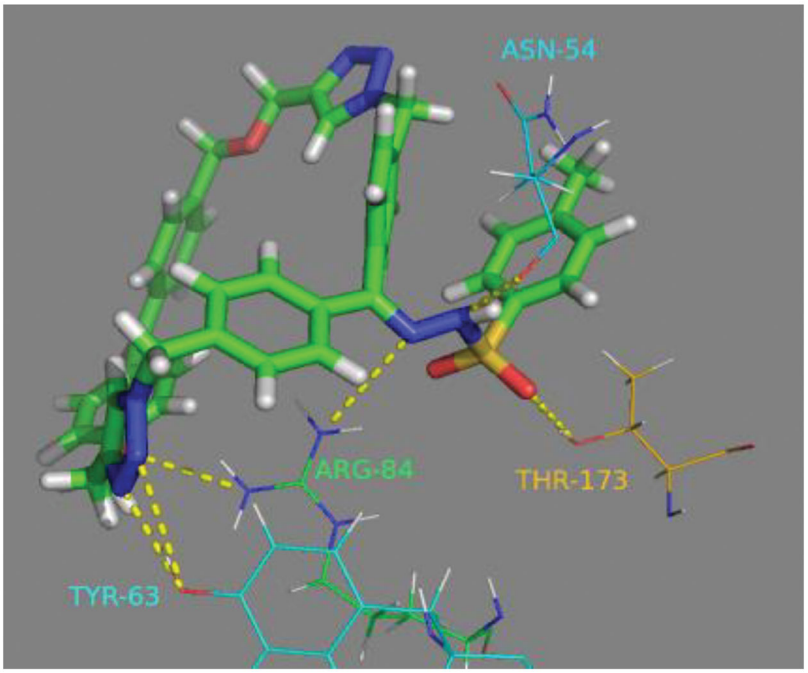


Figure 3. Pymol view of the interaction between triazolophane 3 and *S. aureus* GryB.

the results are tabulated in Table 2. However, the docking study could not be carried out with the triazolophane **2** due to its larger size and higher molecular mass.

Among the five derivatives, the triazolophane **5** closely binds with the active site of the target protein. The sulphonyl group on the right side of the triazolophane **3** forms hydrogen bonding interaction with the side chain of the hydroxyl group of THR-173 (2.7 Å). An additional nitrogen atom of triazolophane **3** has a hydrogen bond interaction with the nitro group of ARG-84 (3.2 Å) as shown in Figure 3. Triazolophane **3** has the highest glide score of −8.410 and glide energy of −74.450 with the target protein of *S. aureus* GryB as shown in Table 2. The carboxyl group of the triazolophane **1** shows hydrogen bond interaction with the side chain of the hydroxyl group of THR-173 (3.0 Å). However, the triazolophanes **4** and **6** do not bind with the active site of the target protein *S. aureus* GryB. Pymol view of the interaction between the triazolophanes **3**, 1, **4**, **5**, and **6** and *S. aureus* GryB is shown in Figures 3–7, respectively.

Experimental

General information

All the reagents and solvents were commercially available in the best grade and used without further purification. The melting points were determined using a Toshiwal melting point apparatus by open capillary tube method and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz NMR spectrometer. The

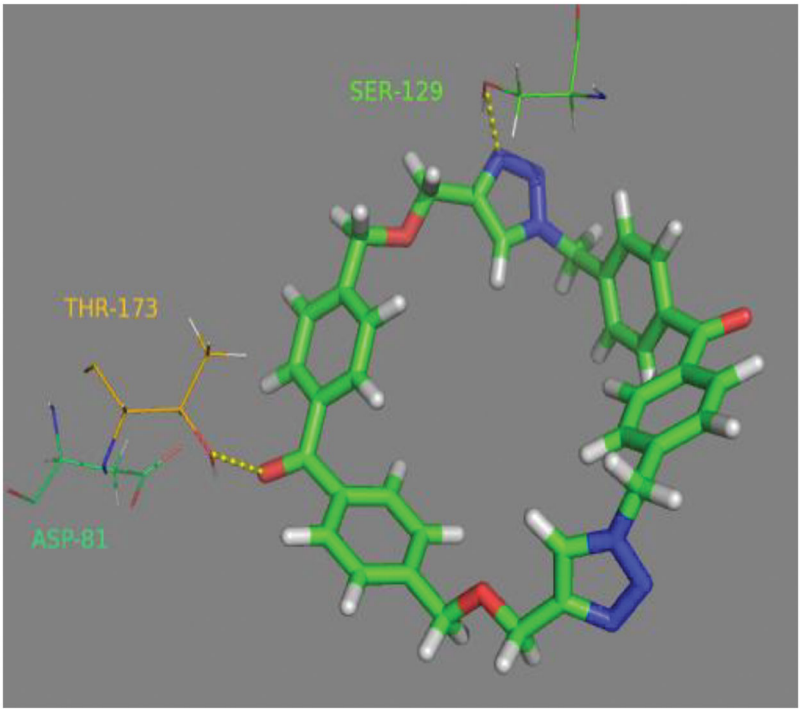


Figure 4. Pymol view of the interaction between triazolophane 1 and *S. aureus* GryB.

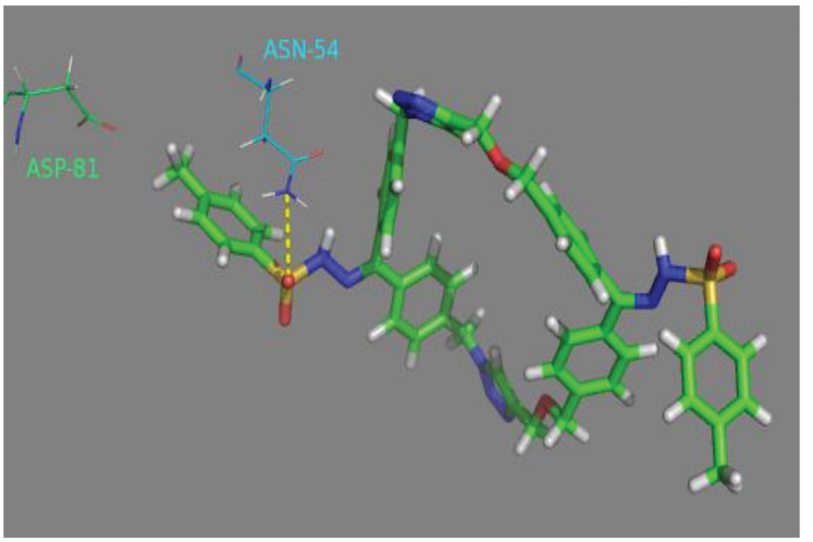


Figure 5. Pymol view of the interaction between triazolophane 4 and *S. aureus* GryB.

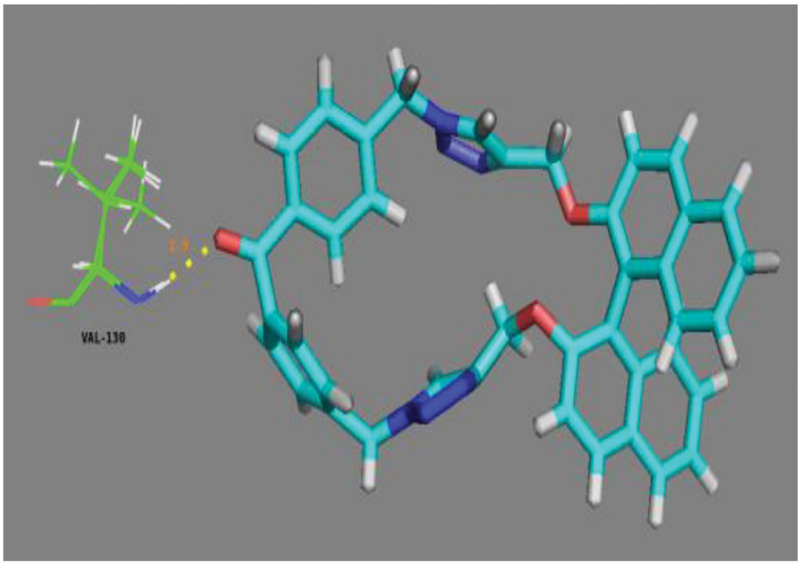


Figure 6. Pymol view of the interaction between triazolophane 5 and *S. aureus* GryB.

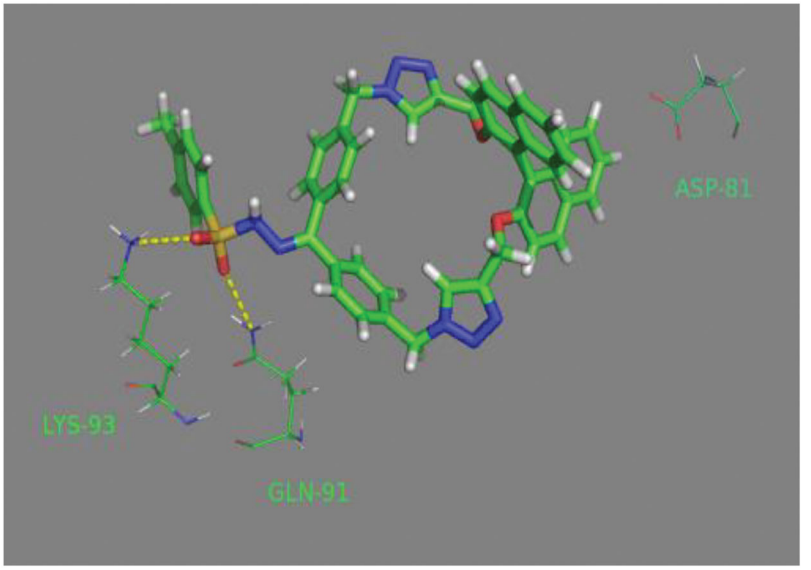


Figure 7. Pymol view of the interaction between triazolophane 6 and *S. aureus* GryB.

chemical shifts are reported in ppm (δ) with TMS as an internal standard and the coupling constants (*J*) are expressed in Hz. Elemental analyses were performed on a Perkin-Elmer 240B elemental analyzer. Electrospray ionization mass spectra (ESI-MS) were recorded with an LCQ AD mass spectrometer.

General procedure for the Cu (I) catalyzed click reaction (procedure A)

A mixture of acetylenic derivative (1.0 mmol, 1 equiv.) and azido derivative (1.1 mmol, 1.1 equiv.) was dissolved in THF/H_2O (1:1; 8 mL) and added sodium ascorbate (0.4 mmol, 0.4 equiv.) followed by $CuSO_4.5H_2O$ (0.2 mmol, 0.2 equiv.). The reaction mixture was stirred overnight at rt. The solvent was evaporated and the crude product was dissolved with EtOAc (2 × 100 mL), washed with NH_4Cl solution (50 mL) and brine solution (50 mL), dried over Na_2SO_4 and concentrated to give a residue, which was purified by column chromatography (SiO_2), using the eluent as mentioned under each compound.

General procedure for the synthesis of bispropargyloxy compound by O-alkylation (procedure B)

A mixture of 1.0 equiv. of the dihydroxyl compound and 2.2 equiv. of propargyl bromide with potassium carbonate (3.0 equiv.) in anhydrous DMF (5 mL) was stirred at 60 °C for 48 h under nitrogen. The reaction mixture was allowed to cool to rt and poured into ice water (500 mL) and extracted with $CHCl_3$ (2 × 100 mL) and the combined organic layer was washed with water (2 × 50 mL) brine (50 mL) and dried over anhydrous Na_2SO_4 The crude product obtained after the removal of the solvent, was subjected to column chromatography over SiO_2 using hexane:$CHCl_3$ (1:2) as the eluent to give the corresponding bispropargyloxy compound.

General procedure for the conversion of dendritic chloride to azide (procedure C)

Dendritic chloride (1.0 mmol, 1.0 equiv.) was dissolved in a mixture of acetone:water (4:1; 8 mL) and added NaN_3 (1.5 mmol, 1.5 equiv.), and the mixture was heated to 60 °C for 3 h. The reaction mixture was cooled to rt, acetone was evaporated, diluted with water (100 mL), and extracted with EtOAc (2 × 100 mL). The organic layer was washed with saturated NaCl (100 mL), dried over Na_2SO_4 and evaporated to give the corresponding azido compounds.

Bis(4-(bromomethyl)phenyl) methanone (8)

Bis(4-(bromomethyl)phenyl) methanone (**8**) was obtained by the radical bromination of di-p-tolylmethanone (2.6 g, 15.3 mmol) using NBS (1.6 g, 30.6 mmole) in CCl_4(100 mL) in the presence of pinch of benzyl peroxide as per the reported procedure. Yield: 85%.

Bis(4-(azidomethyl)phenyl) methanone (9)

Following the general procedure C, bis(4-(azidomethyl)phenyl) methanone (**9**) was obtained as white solid by the reaction of bis(4-(bromomethyl)phenyl) methanone (5.6 g, 15.3 mmol) with sodium azide (3.0 g, 45.9 mmol) in acetone at 60 °C for 8 hr. Yield: 3.2 g, 72%, mp: 120 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 4.46 (s, 4H); 7.45 (d, 4H, $J = 8.1$ Hz); 7.82 (d, 4H, $J = 8.1$ Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δc 54.3, 126.5,

127.9, 130.6, 137.3, 140.1, 195.6. MS (ESI): $m/z = 293$ [M + 1]. Anal. Calcd. For $C_{15}H_{12}N_6$ O: C, 61.64; H, 4.14; N, 28.75. Found: C, 61.52; H, 4.28; N, 28.68.

Bis(4′-(propargylmethyl)phenyl methanone (10)

A mixture of bis (4-(bromomethyl) phenyl) methanone (1.5 g, 0.004 mmol, 1.0 equiv.), propargyl alcohol (0.91 g, 0.016 mmol, 2.1 equiv.) and K_2CO_3 (3.0 equiv.) in DMF (10 mL) was stirred at rt for 24 h. After completion of the reaction, the reaction mixture was poured into water and the residue was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue obtained was purified by column chromatography with silica gel using $CHCl_3$:Hexane (4:1) as the eluent to give the diyne 10 as white solid, Yield: 3.2 g, 72%, mp: 120 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.51 (t, 2H, $J = 2.4$ Hz); 4.24 (d, 4H, $J = 2.1$ Hz); 4.69 (s, 4H); 7.48 (d, 4H, $J = 7.8$ Hz); 7.79 (d, 4H, $J = 7.8$ Hz); ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 57.6, 70.9, 75.0, 79.3, 127.5, 130.3, 137.1, 142.1, 196.0. ESI-MS: $m/z = 318$ [M^+]. Elemental Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70%. Found: C, 79.19; H, 5.69%.

N′-(bis(4-(azidomethyl)phenyl)methylene)-4-methylbenzenesulfonohydrazide (11)

Following the general procedure **C**, N′-(Bis(4-(azidomethyl)phenyl)methylene)-4-methylbenzenesulfonohydrazide **11** was obtained as white solid by the reaction of bis(4-(azidomethyl)phenyl) methanone **9** (2.5 g, 15.3 mmol) with *p* - tosylhydrazide (3.0 g, 45.9 mmol) in toluene, ethanol at rt for 24 h. Yield: 60%, mp: 180 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.44 (s, 3H); 4.31 (s, 2H); 4.46 (s, 2H); 7.16 (q, 2H) 7.26 (q, 2H); 7.36 (s, 2H); 7.48 (q, 4H); 7.16 (q, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δc 21.6,54.2, 54.3, 127.0, 129.9, 128.0, 128.8, 129.3, 129.7, 130.8, 135.3, 136.3, 137.2, 137.9, 144.3, 153.0. MS (ESI): $m/z = 460$ [M + 1]. Anal. Calcd. For $C_{22}H_{20}N_8O_2S$: C, 57.38; H, 4.38; N, 24.33. Found: C, 57.34; H, 4.39; N, 24.35.

N′-(bis(4-((prop-2-ynyloxy)methyl)phenyl)methylene)-4 methyl benzene sulfonohydrazide (12)

Following the general procedure **A**, N′-(Bis(4-((prop-2-ynyloxy)methyl)phenyl)methylene)-4 methyl benzene sulfonohydrazide 12 was obtained as white solid from Bis(4′-(propargylmethyl)phenyl methanone (**10**) and p-tolylsulphonyl hydrazide. Yield: 62%, mp: 180 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.44 (t, 3H, $J = 2.4$ Hz); 2.47 (s, 1H); 2.52 (t, 1H, $J = 2.1$ Hz); 4.16 (s, 2H) 4.28 (s, 2H); 4.58 (s, 2H); 4.68 (s, 2H); 7.12 (s, 2H); 7.28 (s, 1H) 7.34 (d, 2H) 7.42 (m, 2H); 7.53 (m, 3H) 7.86 (d, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δc 21.6, 57.8, 74.8, 75.1, 79.4, 125.3, 127.9, 128.4, 128.5, 128.7, 129.1, 129.7, 135.4, 136.0, 139.2, 139.8, 144.2, 153.8. MS (ESI): $m/z = 486$ [M + 1]. Anal. Calcd. For $C_{28}H_{26}N_2O_4$: C, 69.11; H,5.39; N, 5.76. Found: C, 69.22; H, 5.45; N, 5.85.

Bis (propargylic) S(-)- binaphthyl ether (14)

Following the general procedure B, the bispropargylic ether **14** was obtained as white solid from S(-)-BINOL and propargl bromide. Yield: 75%, mp: 104 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.38 (t, 2H, $J = 2.1$ Hz); 4.57 (s, 4H); 7.14 (s, 4H), 7.32 (d, 2H, $J = 8.4$ Hz); 7.54 (d, 2H, $J = 8.1$ Hz); 7.57 (t, 2H, $J = 7.1$ Hz); 7.86 (t, 2H, $J = 7.2$ Hz); 7.96 (d, 2H, $J = 9.0$ Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δc 57.3, 55.3, 79.3, 116.1, 120.6, 124.1, 125.6, 126.4, 127.9, 129.4, 129.8, 304.0, 153.2. MS (ESI): $m/z = 293$ [M + 1]. Anal. Calcd. For $C_{26}H_{18}O_2$: C, 86.20; H, 5.06. Found: C, 86.36; H, 5.20.

Triazolophane 1

Following the general procedure A, the triazolophane **9** was obtained as yellow solid from the precyclophane **10** (0.3 g, 0.65 mmol) and the bisazide **9** (0.16 g, 0.65 mmol). Yield: 35%, mp: 104 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 4.70 (s, 4H); 4.74 (s, 4H); 5.63 (s, 4H); 7.37 (d, 4H, $J = 7.8$ Hz); 7.59 (s, 4H); 7.66 (s, 2H); 7.71 (t, 4H, $J = 10.5$ Hz); 7.79 (t, 4H, $J = 7.8$ Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δc 54.3, 64.0, 71.9, 122.7, 126.5, 127.5, 127.9, 130.3, 136.5, 136.9, 140.3, 143.0, 145.5, 195.1, 195.3. MS (ESI): $m/z = 610$ [M + 1]. Anal. Calcd. For $C_{36}H_{30}N_6O_4$: C, 70.81; H,4.95; N, 13.76. Found: C, 70.93; H,5.07; N, 13.88.

2:2 Oligomeric triazolophane 2

The triazolophane **2** was also obtained obtained as yellow solid from the precyclophane **10** (0.3 g, 0.65 mmol) and the bisazide **9** (0.16 g, 0.65 mmol). Yield: 41%, mp: 104 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 4.69 (d, 8H, $J = 2.7$ Hz); 4.73 (s, 8H); 5.62 (s, 8H); 7.38 (d, 8H, $J = 8.1$ Hz); 7.45 (t, 8H, $J = 7.5$ Hz); 7.59 (s, 4H); 7.69 (t, 8H, $J = 7.8$ Hz); 7.78 (d, 8H, $J = 6.9$ Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δc 53.6, 64.0, 71.9, 122.7, 126.5, 127.9, 130.2, 130.7, 137.5, 142.1, 143.0, 143.3, 145.5, 195.0, 195.1. MS (ESI): $m/z = 1220$ [M + 1]. Anal. Calcd. For $C_{75}H_{60}N_{12}O_8$: C, 70.81; H,4.95; N, 13.76. Found: C, 70.96; H,4.99; N, 13.84.

Triazolophane 3

Following the general procedure A, the triazolophane **3** was obtained as yellow solid from the precyclophane **12** (0.3 g, 0.65 mmol) and the bisazide **9** (0.16 g, 0.65 mmol). Yield: 25%, mp: 104 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H 2.35 (s, 3H); 4.38 (s, 2H); 4.60 (s, 4H); 4.69 (s, 2H); 5.57 (s, 4H); 7.01 (d, 2H, $J = 7.8$ Hz); 7.32 (s, 2H); 7.34–7.46 (m, 11H); 7.75 (t, 7H, $J = 8.4$ Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δc 2 1.6, 54.2, 64.1, 71.9, 122.6, 127.6, 127.8, 128.5, 128.9, 129.6, 130.5, 130.7, 135.5, 136.9, 137.7, 138.9, 140.3, 144.2, 195.3. MS (ESI): $m/z = 778$ [M + 1]. Anal. Calcd. For $C_{43}H_{38}N_8O_5S$: C, 66.31; H, 4.92; N, 14.39. Found: C, 66.55; H, 5.08; N, 14.55.

Triazolophane 4

Following the general procedure **A**, the triazolophane **4** was obtained as yellow solid from the precyclophane **12** (0.3 g, 0.65 mmol) and the bisazide **11** (0.16 g, 0.65 mmol). Yield: 65%, mp: 104 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H: ^{1}H NMR, $CDCl_3$: 2.42 (s, 6H); 4.60 (s, 4H); 4.65 (s, 4H); 5.50 (s, 2H); 5.63 (s, 2H); 7.09–7.19 (m, 6H); 7.31 (s, 1H); 7.33 (s, 1H); 7.45 (t, 14H, $J = 8.4$ Hz); 7.63 (s, 1H); 7.83 (d, 4H, $J = 7.2$ Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δc 21.6, 54.4, 63.4, 71.7, 127.4, 127.7, 128.5, 128.7, 129.1, 129.7, 129.8, 130.9, 135.4 MS (ESI): $m/z = 946[M + 1]$. Anal. Calcd. For C_{50} H_{46} N_{10} O_6S_2: C, 63.41; H,4.90; N, 14.90. Found: C, 63.62; H,5.25; N, 15.02.

Triazolophane 5

Following the general procedure A, the triazolophane **5** was obtained as yellow solid from the precyclophane **14** (0.3 g, 0.65 mmol) and the bisazide **9** (0.16 g, 0.65 mmol).Yield: 62%, mp: 104 °C. ^{1}H NMR: (300 MHz, $CDCl_3$): δ_H: 5.16 (s, 2H); 5.20 (s, 2H); 5.30 (s, 4H); 7.14 (t, 9H, $J = 8.1$ Hz); 7.43 (t, 3H, $J = 8.7$ Hz); 7.70–7.75 (m, 5H); 7.80 (d, 3H, $J = 8.1$ Hz); 7.86–7.89 (m, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δc 29.7, 53.3, 63.9, 116.0, 120.7, 122.8, 124.0, 125.4, 126.5, 126.7, 127.7, 128.0, 129.1, 129.5, 130.4, 130.6, 133.9, 137.2, 138.2, 153.6. MS (ESI): $m/z = 654$ $[M + 1]$. Anal. Calcd. For C_{41} H_{30} N_6 O_3: C, 75.21; H,4.62; N, 12.84. Found: C, 75.39; H,4.86; N, 12.95.

Triazolophane 6

Following the general procedure A, the triazolophane **6** was obtained as yellow solid from the precyclophane **14** (0.3 g, 0.65 mmol) and the bisazide **11** (0.16 g, 0.65 mmol). Yield: 30%, mp: 104 °C. ^{1}H NMR, $CDCl_3$: 2.31 (s, 3H); 4.94 (t, 8H, $J = 7.2$ Hz); 6.44 (t, 2H, $J = 6$ Hz); 6.71 (s, 3H); 6.94 (d, 14H, $J = 21.9$ Hz); 7.79 (s, 8H); ^{13}C NMR, $CDCl_3$: 21.6, 57.0, 71.8, 114.1, 115.4, 115.9, 120, 2, 122.6, 124.0, 125.4, 126.4, 127.3, 127.9, 128.9, 129.7, 130.9, 132.4, 133.9, 135.4, 139.3, 144.3, 152.6, 153.5. MS (ESI): $m/z = 822$ $[M + 1]$. Anal. Calcd. For C_{48} H_{38} N_8 O_4 S: C, 70.06; H,4.65; N, 13.62. Found: C, 70.31; H,4.82; N, 13.76.

Conclusions

In conclusion, S(-)-BINOL and benzophenone based triazolophanes **1–6** were obtained in moderate to excellent yield by click chemistry. All the triazolophanes show excellent inhibitory activity against both Gram-positive and Gram-negative bacteria viz. *S. aureus*, *B. Subtilis*, *S. typhimurium*, and *E. Coli* The triazolophane **5** shows a better antibacterial activity against all the four tested pathogens than that of the triazolophanes **1**, **2**, **3**, **4**, and **6**. However, with respect to *E. coli* bacteria triazolophane **4** also shows better antibacterial activity comparable to that of the triazolophane **5**. The antibacterial activity of all the synthesized cyclophanes is dose-dependent against *aureus*, *subtilis*, *typhi* bacteria but with respect to *E. coli* the antibacterial activity of the synthesized cyclophane is dose-independent.

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