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Research Article

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Synthesis, Antimicrobial and Molecular Docking Studies of Benzimidazole and Benzotriazole based Dicationic Sulphonophanes

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Abstract: The synthesis of benzimidazole and benzotriazole based dicationic sulphonophanes incorporating various spacer units is described. The result of the antimicrobial studies of sulphonophanes correlates well with the molecular docking studies performed on protein DNA gyrase B from *Escherichia coli*. Further, the theoretical evaluations of ADMET properties reveal that the dicationic sulphonophanes could be good candidates as antibacterial and antifungal.

Keywords: Benzimidazole; Benzotriazole; Antimicrobial; ADMET Properties

1. INTRODUCTION

The synthesis of cyclophanes has attracted the synthetic chemists because of their diverse applications in supramolecular chemistry [1], host-guest complexation and molecular recognition [2]. Cyclophanes with well defined cavity size are efficient in encapsulating and stabilizing guest molecules through various non-covalent interactions [3]. This unique property of the cyclophanes has been widely exploited in novel materials [4] as well as in biological sciences [5]. Cationic compounds are widely used in the biomedical field, in which amphiphilic quaternary ammonium compounds (QACs) are generally known to exhibit antimicrobial [6], disinfectant [7] and antiseptic [8] activity.

However, the design and synthesis of cationic macrocyclic structures and the incorporation of various bioactive organic residues are important research topics in medicinal chemistry. Many cationic cyclophanes exhibit biological activities such as antibacterial [9], antiproliferative [10], human choline kinase inhibitors [11] and activated K^+ channel [12]. Imidazolium and benzimidazolium cyclophanes have been used for the synthesis of silver complexes [13], selective anion recognition [14] and they also exhibit interesting conformational behavior [15]. Imidazole and benzimidazole nuclei are the important and well known pharmacophores in drug discovery [16, 17].

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Recently, the dicationic acridinophanes [18], quinolinophanes [19] imidazolophanes [20] and imidazole based sulphonophanes [21] using various spacers like pyridine, *m*-terphenyl and chiral binaphthol have been reported from our laboratory. Benzimidazolo and triazolo sulphonophanes could improve their antimicrobial activity due to the combined effect of benzimidazole and benzotriazole units with sulphone functionality respectively. However, to the best of our knowledge, benzimidazole and benzotriazole based dicationic sulphonophanes have not been reported so far. Here, we report the synthesis of sulphonophanes **1-8** (Figure 1) along with their antimicrobial activity against human pathogens and attention has also been focused on docking studies in order to know the mechanism of the antimicrobial activity of sulphonophanes. Further, theoretical evolution of ADMET properties have been also investigated.

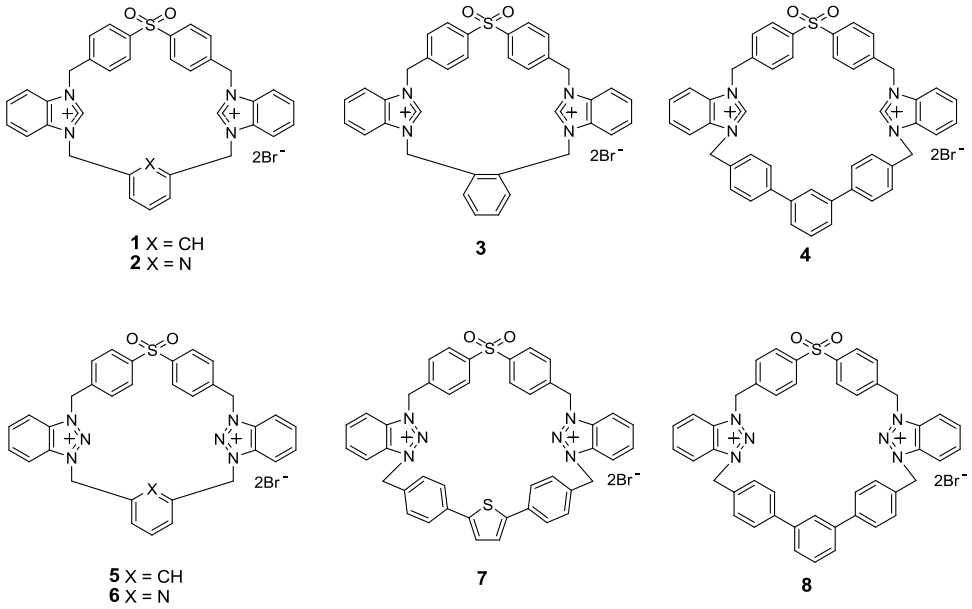

Figure 1. Structure of sulphonophanes **1-8**.

2. EXPERIMENTAL

2.1 General

All melting points were determined using a Toshniwal melting point apparatus by the open capillary tube method and are uncorrected. ^{1}H NMR and ^{13}CNMR spectra were recorded on Bruker 300 MHz instrument. The mass spectra (ESI) were recorded on a Jeol DX-303 mass spectrophotometer. Elemental analyses were carried out using a Perkin-Elmer CHNS 2400 instrument. Column chromatography was performed on silica gel (ACME, 100-200 mesh). Routine monitoring of the reaction was made using thin layer chromatography developed on glass plates coated with silica gel-G (ACME) of 25 mm thickness and visualized with iodine.

*2.2 General procedure for the synthesis of precyclophanes **10** and **11***

To a solution of benzimidazole/ benzotriazole (2.1 equiv) in MeCN (50 mL), aq NaOH (25%, 5 mL) was added and the mixture was stirred for 10 min. 4,4'-Sulfonylbis((bromomethyl)benzene) **9** (1.0 equiv) in MeCN (20 mL) was added in one portion and the reaction was stirred at room temperature for 48 h. After completion of the reaction, the solvent was evaporated under vacuum and the residue was extracted with $CHCl_3$ (3 x 100 mL) washed with brine (150 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel.

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*Precyclophane **10***

Yellow solid; 73% yield; mp 180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.65 (s, 4H); 7.52-7.59 (m, 8H); 7.69 (d, 4H, *J* = 8.1Hz); 7.89 (d, 4H, J = 8.1 Hz); 8.62 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.4, 119.8, 127.4, 127.8, 128.1, 128.4, 129.5, 137.6, 138.4, 141.3, 143.0, 155.8. ESI-MS *m/z* 479.5 $(M+H)^+$. Elemental Anal. calcd for $C_{28}H_{22}N_4O_2S$: C, 70.27; H, 4.63; N, 11.71. Found: C, 70.06; H, 4.71; N, 11.57.

*Precyclophane **11***

Pale yellow solid; 75% yield; mp 189 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87 (s, 4H); 7.32-7.41 (m, 8H); 7.56 (d, 4H, *J* = 8.4 Hz); 7.82 (d, 4H, *J* = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.8, 109.9, 119.8, 121.9, 124.2, 127.7, 133.1, 139.0, 146.1, 148.2, 148.6. ESI-MS *m/z* 481 $(M+H)^+$. Elemental Anal. Calcd for $C_{26}H_{20}N_6O_2S$: C, 64.98; H, 4.20; N, 17.49. Found: C, 65.23; H, 4.31; N, 17.23

*2.3 General procedure for the Synthesis of dicationic sulphonophanes **1-8***

To a solution of precyclophanes **10/ 11** (1.0 equiv) in anhydrous MeCN (250 mL), dibromide (1.0 equiv.) was added in one portion and the mixture was refluxed for 4 days until the bromide was consumed (reaction monitored by TLC). When the reaction was complete, the mixture was concentrated, cooled and the cationic sulphonophanes **1-8** were isolated as the bromide salt by filtration.

*Sulphonophane **1***

Colourless solid; 76% yield; mp 176 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.70 (s, 4H); 5.75 (s, 4H); 7.44 (d, 4H, *J* =7.5 Hz); 7.68-7.73 (m, 8H); 7.86 (d, 4H, *J* = 8.4 Hz); 7.92-7.95 (m, 4H); 9.26 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 49.2, 51.2, 113.7, 114.1, 122.6, 127.0, 127.2, 127.9, 128.1, 128.3, 129.4, 131.2, 131.6, 138.6, 141.3, 142.2, 153.7. ESI-MS *m/z* 742.7 $(M)^+$, 743.7 $(M+H)^+$. Elemental analy. Calcd. for $C_{36}H_{30}Br_2N_4O_2S$: C, 58.23; H, 4.07; N, 7.55. Found: C, 58.44; H, 4.12; N, 7.64.

*Sulphonophane **2***

Colourless solid; 72% yield; mp 188 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.10 (s, 4H); 5.45 (s, 4H); 7.58 (d, 4H, *J* = 7.2 Hz); 7.62-7.84 (m, 8H); 7.86-7.87 (m, 3H); 7.92 (d, 4H, *J* = 8.2 Hz); 9.00 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.2, 57.6, 110.0, 120.1, 120.6, 122.3, 123.2, 128.2, 128.6, 128.9, 133.6, 138.4, 143.4, 143.5. ESI-MS *m/z* 744.5 $(M+H)^+$. Elemental analy. calcd. for $C_{35}H_{29}Br_2N_5O_2S$: C, 56.54; H, 3.93; N, 9.42. Found: C, 56.38; H, 4.17; N, 9.18.

*Sulphonophane **3***

Colourless solid; 75% yield; mp 178 - 180 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.76 (s, 4H); 5.78 (s, 4H); 7.40 (d, 4H, *J* = 7.8 Hz); 7.64-7.71 (m, 4H); 7.73-7.77 (m, 2H); 7.87-7.96 (m, 6H); 8.34 (d, 4H, *J* = 8.1 Hz); 9.75 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 47.7, 49.4, 114.1, 127.2, 128.0, 128.2, 128.3, 128.5, 129.2, 130.9, 131.2, 131.7, 132.0, 138.5, 141.7, 147.2. ESI-MS *m/z* 742.7 $(M+H)^+$. Elmental analy. calcd. for $C_{36}H_{30}Br_2N_4O_2S$: C, 58.23; H, 4.07; N, 7.55. Found: C, 58.34; H, 4.19; N, 7.48.

*Sulphonophane **4***

Pale brown solid; 73% yield; mp 284 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.02 (s, 4H); 5.54 (s, 4H); 7.27-7.30 (m, 8H); 7.44 (d, 4H, *J* = 8.2 Hz); 7.55-7.63 (m, 6H); 7.68-7.72 (m, 6H); 7.90 (d, 4H, *J* = 8.2 Hz); 9.11(s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.6, 57.8, 123.1, 123.5, 126.7, 127.9, 128.1, 128.4, 128.6, 128.7, 128.9, 129.2, 129.4, 130.7, 133.5, 136.8, 137.4, 140.5, 141.2, 141.4, 142.8. ESI-MS *m/z* 895.4 $(M+H)^+$. Elemental analy. calcd. for $C_{48}H_{38}Br_2N_4O_2S$: C, 64.44, H, 4.28; N, 6.26. Found: C, 64.68, H, 4.12; N, 6.38.

*Sulphonophane **5***

Pale yellow solid; 73% yield; mp 182 - 184 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.88 (s, 4H); 6.00 (s, 4H); 7.54 (d, 4H, *J* = 7.5 Hz); 7.65-7.77 (m, 8H); 7.81-7.97 (m, 4H); 8.02-8.10 (m, 4H). ^{13}C NMR

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(75 MHz, DMSO-d_6): δ 49.3, 52.6, 119.4, 119.7, 119.9, 120.6, 121.4, 121.6, 124.7, 125.0, 125.8, 127.6, 128.8, 129.2, 132.7, 136.9, 142.2. ESI-MS *m/z* 745.7 $(M+H)^+$. Elemental analy. calcd. for $C_{34}H_{28}Br_2N_6O_2S$: C, 54.85; H, 3.79; N, 11.29. Found: C, 54.55; H, 3.62; N, 11.42.

Sulphonophane ***6***

Pale brown solid; 70% yield; mp 176 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.89 (s, 4H); 6.01 (s, 4H); 7.49-7.52 (m, 2H); 7.71-7.76 (m, 6H); 7.80-7.93 (m, 5H); 7.99-8.08 (m, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 51.7, 54.9, 119.0, 122.7, 123.7, 126.9, 128.2, 129.9, 131.4, 132.8, 133.9, 134.2, 135.1, 138.7, 141.2. ESI-MS *m/z* 746.2 $(M+H)^+$. Elemental analy. calcd. for $C_{33}H_{27}Br_2N_7O_2S$: C, 53.17; H, 3.65; N, 13.15. Found: C, 52.98; H, 3.72; N, 13.01.

Sulphonophane ***7***

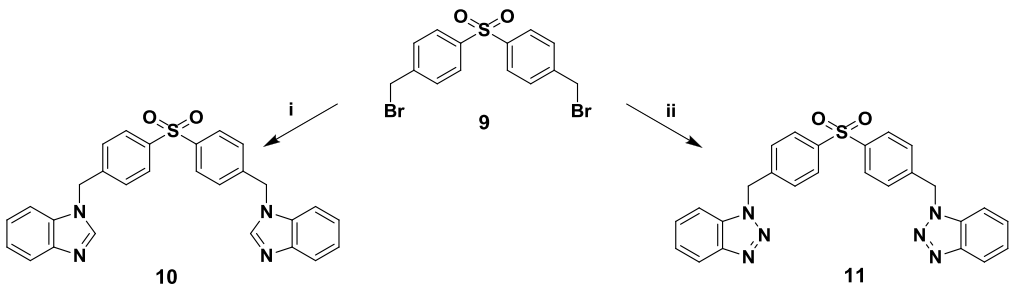
Brown solid; 71% yield; mp 189 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.90 (s, 4H); 5.02 (s, 4H); 7.44-7.51 (m, 4H); 7.54-7.60 (m, 2H); 7.71 (d, 4H, *J* = 7.5 Hz); 7.81-7.91 (m, 4H); 7.94-8.00 (m, 4H); 8.03 -8.09 (m, 8H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 53.4, 56.7, 109.9, 113.8, 119.8, 124.6, 124.7, 126.2, 127.9, 128.1, 128.3, 128.7, 128.9, 129.5, 134.5, 136.7, 142.9. ESI-MS *m/z* 903.7 $(M+H)^+$. Elemental analy. calcd. for $C_{44}H_{34}Br_2N_6O_2S_2$: C, 58.54, H, 3.80; N, 9.31. Found: C, 58.62; H, 3.68; N, 9.18.

Sulphonophane ***8***

Pale brown solid; 74% yield; mp 245 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.28 (s, 4H); 6.36 (s, 4H); 7.22 (d, 4H, *J* = 7.5 Hz); 7.32-7.40 (m, 4H); 7.55-7.60 (m, 6H); 7.68-7.79 (m, 8H); 7.93-7.99 (m, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 53.5, 54.3, 119.2, 124.9, 125.6, 126.7, 127.3, 127.5, 127.9, 128.1, 128.3, 129.5, 129.6, 130.5, 131.5, 134.7, 134.9, 137.1, 139.9, 140.9. ESI-MS *m/z* 897.5 $(M+H)^+$. Elemental analy. calcd, for $C_{46}H_{36}Br_2N_6O_2S$: C, 61.61; H, 4.05; N, 9.37. Found: C, 61.82; H, 4.89; N, 9.24.

3. RESULT AND DISCUSSION

The synthesis of diaryl sulphone based precyclophanes **10** and **11** has been achieved *via* an *N*-alkylation route using benzimidazole and benzotriazole as bridging units. The reaction of 4,4'-sulfonylbis((bromomethyl)benzene) **9** [22] with 2.1 equiv. of benzimidazole and benzotriazole in the presence of 25% aqueous NaOH in CH_3CN at room temperature for 2 days gave the precyclophanes **10** and **11** in 73% and 75% yields, respectively (Scheme 1).



Scheme 1. Reagents and conditions**:** (i) Benzimidazole (2.1 equiv.), aq. NaOH 25%, MeCN, rt., 48 h, **10** (73%). (ii) Benzotriazole (2.1 equiv.), aq. NaOH 25%, MeCN, rt., 48 h **11** (75%).

The ^{1}H NMR spectrum of precyclophanes **10** and **11** showed the *N*-CH_2- protons at δ 5.65 and δ 5.87 for **10** and **11** respectively**,** in addition to the signals for aromatic protons. The ^{13}C NMR spectrum of

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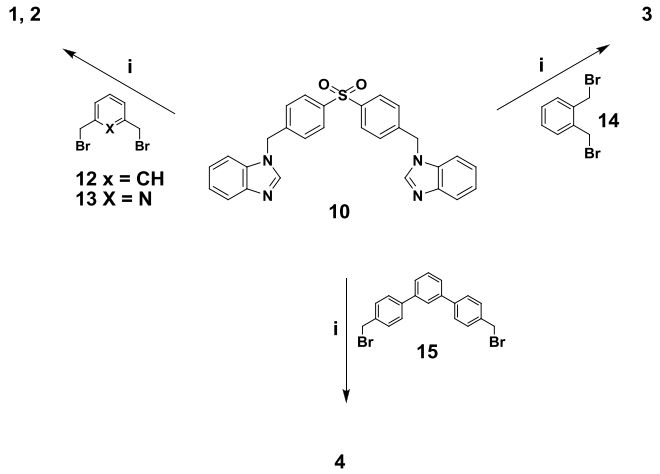
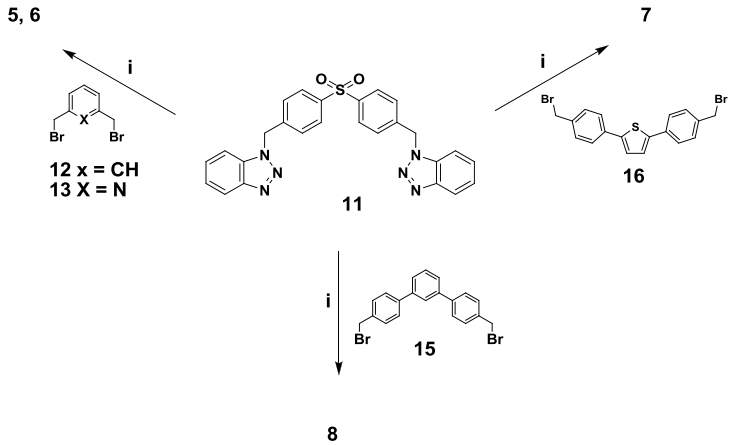
precyclophanes **10** and **11**, displayed *N*-CH_2- carbons at δ 52.4 and δ 53.8 for **10** and **11** respectively, in addition to the signals for aromatic carbons. Further, the structure of precyclophanes **10** and **11** was confirmed from the mass spectral and analytical data.

The cyclic skeleton consisting of quaternary ammonium and sulphonyl units has potential applications in the field of biology. Hence, it is of interest to design and synthesize benzimidazole and benzotriazole incorporated dicationic sulphonophanes. The quaternization of precyclophane **10** with 1.0 equiv. of dibromides **12-15** gave sulphonophanes **1-4** in 76%, 72%, 75% and 73% yields, respectively (Scheme 2).



Scheme 2. Reagents and conditions: (i) CH_3CN, reflux, 4 days, **1** (76%). **2** (72%), **3** (75%) and **4** (73%).

The ^{1}H NMR spectrum of sulphonophane **1** displayed the *N*-CH_2- protons as a set of singlets at δ 5.70 and δ 5.75 and the methine protons of the benzimidazole at δ 9.26, in addition to other signals for aromatic protons. In the ^{13}C NMR spectrum of **1**, the two types of *N*-CH_2- carbons appeared at δ 49.2 and δ 51.2, in addition to other aromatic carbon signals. The mass spectrum (ESI-MS) of **1** showed the molecular ion peak at *m/z* 742.7. The elemental analysis also supported the structure of the cyclophane **1**. Similarly, the structure of the cationic sulphonophanes **2-4** was also confirmed from the spectral and analytical data.



Scheme 3. Reagents and conditions**:** (i) CH_3CN, reflux, 4 days, **5** (73%). **6** (70%), **7** (71%) and **8** (74%).

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Table 1. *In vitro* antimicrobial activities (minimum inhibitory concentration in µg/mL) of sulphonophanes **1-8.**

Sulphonophanes	*B. subtilis*	*S. aureus*	*V. cholerae*	*E. coli*	*P. vulgaris*	*P. aeuroginosa*	*K. pneumoniae*	*S. typhimurium*	*S. marcescens*	*C. albicans*
1	30	70	60	35	25	35	60	35	20	35
2	25	20	15	15	55	20	20	30	20	10
3	30	70	60	20	25	20	NI	35	60	30
4	20	30	15	25	15	60	25	60	70	15
5	70	30	35	60	60	20	30	25	60	25
6	15	25	20	20	25	15	15	60	15	10
7	15	20	25	10	25	15	20	60	15	10
8	35	30	40	60	35	35	60	35	35	30
Ciprofloxacin	5	5	10	5	10	5	15	10	10	NA
Clotrimazole	NA[a]	NA	NA	NA	NA	NA	NA	NA	NA	5
Control	NI[b]	NI	NI	NI	NI	NI	NI	NI	NI	NI

[a]NA- not applicable, [b]NI- no inhibition

Moreover, the incorporation of benzotriazole and sulphone moieties into the macrocyclic system might increase the complexion, chelating and solublizing ability. Hence, it is of interest to synthesis the cyclophanes **5-8** (Figure 1). The precyclophane **11** was treated with 1.0 equiv. of the corresponding dibromides **12**, **13**, **15** and **16** in CH_3CN under refluxing conditions for 4 days to give the cationic sulphonophanes **5-8** in 73%, 70%, 71% and 74% yields, respectively (Scheme 3). In the ^{1}H NMR spectrum, the dicationic sulphonophane **5** showed two sharp singlets at δ 5.88 and δ 6.00 for two types of *N*-CH_2- protons attached to the benzotriazole moiety, in addition to other signals for the aromatic protons. The ^{13}C NMR spectrum of sulphonophane **5** displayed two *N*-CH_2- carbons at δ 49.3 and δ 52.6 in addition to the signals for other carbon. The mass spectrum (ESI-MS) of **5** showed the molecular ion peak at *m/z* 745.7 $(M+H)^+$. The structure of the cyclophane 5 was also supported by elemental analysis. Similarly, the structure of the cationic sulphonophanes **6-8** was also confirmed from the spectral and analytical data.

The *in vitro* antimicrobial activity of sulphonophanes **1-8** against gram positive and gram negative bacteria and human fungal pathogen is shown in Table 1. The results revealed that a majority of the synthesized compounds show varying degrees of inhibition against the tested human pathogenic microorganisms.

The antimicrobial activity of the sulphonophanes **1-8** was determined by the agar well diffusion assay against Gram positive human pathogenic bacteria *B. subtilis* and *S. aureus*, and Gram negative bacteria *V. cholera, E. coli*, *P. vulgaris*, *P. aeruginosa, K. pneumoniae*, *S. typhimurium*, *S. marcescens* and human fungal pathogen *C. albicans*. Ciprofloxacin and clotrimazole were used as the standard for antibacterial and antifungal activity, respectively. In order to ensure that the solvent has no effect on bacterial and fungal growth, a control test was performed containing broth supplemented with DMSO in the same dilution as the one used in the experiment. The MIC of the sulphonophanes **1-8** against the pathogens was effective in the range of 10 to 50 µg. Among all the cyclophanes, sulphonophane **2** was more effective and exhibits better activity against *V. cholera* and *K. pneumoniae* than other sulphonophanes. The sulphonophanes **4, 6** and **7** shows significant antimicrobial activity against the test pathogens. The sulphonophanes **1, 3, 5** and **8** displays moderate activity against the tested human

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pathogens.

Table 2. Binding free energy docking simulation results of sulphonophanes **1, 2, 3, 5** and **6.**

Sulphonophanes	Glide Score	Glide Energy kcal/mol	Hydrogen Bond	
			D-H…A	Distance(Å)
1	-6.698	-57.025	Lys N-H…O	3.07
			Gln N-H…O	3.08
			Arg N-H…O	2.90
2	-7.445	-64.367	LysN-H…O	3.28
			Gln N-H…O	3.12
			Asp N-H…O	2.40
3	-5.809	-48.019	Gln N-H…O	3.50
			Arg N-H…O	3.40
5	-6.097	-61.654	Lys N-H…O	3.16
			Asp N-H…O	2.80
6	-5.225	-49.776	Asp N-H…O	3.20
			Asp N-H…O	2.70
			Gln N-H…O	2.80
Simocyclinone D8	-6.565	-64.715	Asp N-H…O	3.30
			Arg N-H…O	2.70
			Gln N-H…O	2.20
			Ala N-H…O	2.70
			Ser N-H…O	3.50
			Lys N-H…O	3.23

The MIC values were determined at the lowest concentration that completely inhibited the visible growth of the microorganisms. The relationship between the structure of the sulphonophanes and antimicrobial activity revealed that the compounds having benzotriazole with sulphone moieties should exhibit moderate activity when compared with compounds having benzimidazole with sulphone moieties.

All the synthesized sulphonophanes are evaluated for their antifungal activity against *C. albicans* and their minimum inhibitory concentration (MIC) is determined. Among all the cyclophanes, sulphonophanes **2**, **6** and **7** shows good inhibition to that of the standard drug, *viz.*, clotrimazole. The sulphonophanes **4** exhibit significant activity against *C. albicans*. Further studies are in progress to develop various such novel antimicrobial agents.

In order to analyze the binding affinity of the sulphonophanes, they were screened using the High Throughput Virtual Screening Method (HTVS) with the target protein DNA gyrase B [23] (pdb code: 2Y3P). After the screening, based on the top glide score and binding energy five compounds were selected for Induced Fit Docking studies (IFD). A considerable number of interactions with the active site receptor are obtained from the IFD results. It is found that sulphonophanes binds well to the active site and maintained at least three interactions to establish the binding affinity. Table 2 shows the interactions with the key residues of the receptor, glide score and binding energy.

The activity study shows that five compounds yielded comparable results with simocyclinone D8 [24] in the case of *E. coli*. It may be due to the fact that their binding site is close to that of antibiotic drug

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Table 3. Theoretically predicted ADMET properties of synthesized sulphonophanes **1**-**8**.

Sulphonophanes	CNS[a]	SASA[b]	Donor H-Bond[c]	Acceptor H-Bond[d]	Qplogs[e]	% of human oral abs.	Lipinski's Rule
1	1	811.945	0	9	-0.392	61.751	1
2	1	811.125	0	8	-0.901	65.008	1
3	1	742.520	0	8	-4.201	72.038	2
4	-1	807.792	2	5	-7.357	100	2
5	-1	811.866	2	6	-7.081	100	2
6	-1	935.612	2	5	-9.776	100	2
7	-2	994.388	2	5	-10.403	100	2
8	-2	897.328	0	16	2	34.488	2

[a] *Predicted central nervous system (CNS) activity on a -2 (inactive) to +2 (active) scale.*
[b] *Total solvent accessible surface area (SASA) in square ång-ströms using a probe with a 1.4Å radius.*
[c] *Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution (donorHB)*
[d] *Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution (accptHB)*
[e] *Predicted aqueous solubility, log S. S in moles/liter is the concentration of the solute in a saturated solution that is in equilibrium with the crystalline solid.(Qplogs).*

simocyclinone D8 when compared to the other compounds, as revealed by the docking studies. Among sulphonophanes, **1**, **2**, **3, 5** and **6** showed good inhibition of the DNA gyrase B enzyme. In general, the binding affinity of the ligand (compounds or drugs) towards the enzyme DNA gyrase B affects its catalytic activity. Prior to unwinding, the DNA binds to the side chain A of the DNA gyrase B. As the DNA gyrase B is necessary for the DNA unwinding [25-26], the binding of the sulphonophanes inhibits the interaction of the DNA enzyme complex and the sulphonophanes were docked at the active site of the receptor. It was interesting to observe that even though the core structure of all the compounds was the same, the degree of interaction and the binding site were found to be different. As a result, it can be concluded that this kind of docking and anti-pathogenic screening studies would help in the design of drug targets. The variation in the bioactivity is mainly due to the difference in their binding site and binding ability.

The sulphonophane **2** potentially interacted with the key residues (Lys, Gln, Asp) of the receptor with a binding energy of -64.367 kcal/mol and a glide score of -7.445 when compared to the simocyclinone D8 with a binding energy of -64.715 kcal/mol and a glide score of -6.565. Similarly, the sulphonophanes **1** and **3**-**8** showed good binding affinity with active site residues of the receptor with significant binding energy and glide score as shown in Table 2. In order to better understand the overall properties of the described sulphonophanes, the lipophilicity (expressed as the octanol/water partition coefficient and herein called logP), was calculated using the QikProp 3.4, Schrödinger, 2011 [27]. The theoretical prediction of the Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties based on logP and the number of hydrogen donors and acceptors have been studied for sulphonophanes **1**-**8** and the results are presented in Table 3. The ADMET parameters shows that all the reported sulphonophanes could be effectively absorbed under oral conditions and hence sulphonophanes may have the potential application as drug candidates.

4. CONCLUSION

In conclusion, we have synthesized series dicationic sulphonophanes via *N*-alkylation using benzimidazole and benzotriazole as building units. The sulphonophane **2** exhibit excellent antibacterial activity against *V. cholera*, *K. pneumoniae* and also good antifungal activity against *C. albicans*. The

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strong inhibitory activity of sulphonophones was supported by molecular docking studies. Further, the described sulphonophanes have favorable ADMET properties. Hence, further understanding of the various interactions between the ligands and enzyme active sites in detail would help to design novel potent sulphonophane that can function as excellent antibacterial and antifungal agent.

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SUPLLEMENTARY INFORMATION

Full experiment details including an antimicrobial and docking studies, the ^{1}H NMR, ^{13}C NMR, ESI-MS spectra and docking figures are available online.

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The authors declare no conflict of interest

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