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Synthesis and antibacterial activity of some novel imidazole-based dicationic quinolinophanes

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ABSTRACT

Synthesis of novel quinoline based dicationic benzimidazolophanes and imidazolophanes incorporating various spacer units is described. Some of the quinolinophanes **1b**, **3a, 3b** and **4a** exhibit good antibacterial activity against most of the human pathogenic bacteria in the tested concentrations as compared to the other cyclophanes as well as the test control, streptomycin.

Supramolecular systems with a fluorescence tag play an important role in biology.[1] Quinoline based fluorophoric system find application as fluoride ion[2] and metal ions sensor.[3] Quinoline derivatives are well known for their biological activities such as bactericidal, antifungal, antiprotozoic, herbicidal and antiproliferative activity.[4] Cyclophanes have received much attention in the area of host–guest complexation, molecular self assembly and specific receptor activity. Imidazole based dicationic cyclophanes have been used for the synthesis of carbenoid complexes,[5] silver complexes,[6] anionic binding properties,[7] transition metal catalysis and have higher donor abilities than most of the phosphine ligands[8] and also exhibited interesting conformational behaviour.[9] Imidazole and benzimidazole nucleus are well known and important pharmacophore in drug discovery.[10] Amphiphilic quaternary ammonium compounds (QACs)[11] are well known for antibacterial activity due to their electrostatic and hydrophobic interaction with negatively charged bacterial membranes. Many quaternary compounds incorporating imidazolium and benzimidazolium unit shows remarkable antibacterial activity.[12,13] Bisbenzimidazole dications strongly bind to DNA AT rich sequence.[10] Interestingly, the silver nanoparticle of 1,3-disubstituted imidazolinium cations and halogen ions in hydroxyl functionalized ionic liquids (HFIL) show high antimicrobial activity.[14] The synthesis and antibacterial activity of imidazole based carbazolophanes,[15] antifungal activity of ferrocenyl imidazolophanes[8] and antimicrobial activity of silver(I) complex of imidazolophane derivatives are known in the literature.[16] Synthesis of chiral cyclophanes incorporating binaphthol has been reported in our laboratory.[17] Synthesis and antibacterial activity of fluorescent supramolecules with chiral core units[18] would be more fascinating. Recently, dicationic imidazolophanes with various spacers like pyridine, *m*-terphenyl and oxadiazole have been reported.[19] Synthesis and properties of quinoline based cyclophanes are found to be of great interest[20–23] during recent times. However to the best of our knowledge, synthesis and antibacterial activity of imidazole based dicationic macrocycles with quinoline have not been reported. Herein, we wish to report the synthesis and antibacterial activity of imidazole based dicationic quinolinophanes **1a**, **1b**, **2a**, **2b**, **3a**, **3b**, **4a** and **4b** incorporating catechol and *S*-(−)-BINOL units.

The synthetic pathway leading to the synthesis of dicationic quinolinophanes **1a** and **1b** is outlined in Scheme 1. 2-Chloro-3-formylquinoline **5** was synthesized from acetanilide via Vilsmeier–Haack approach.[24] The reaction 1 equiv of *S*-(−)-BINOL with 2.1 equiv of 2-chloro-3-formylquinoline in DMF and in the presence of K_2CO_3 gave the dialdehyde **6**, which was reduced to diol **7** using $NaBH_4$ in MeOH, followed by reaction with PBr_3 to give the dibromide **8** in 71% yield. Reaction of the dibromide **8** with 2.1 equiv of benzimidazole in CH_3CN in the presence of 25% aq NaOH for 2 days afforded the precyclophane **9**[25] in 69% yield. Coupling of the precyclophane **9** with 1 equiv of 2,6-bis(bromomethyl)pyridine under reflux and under high dilution conditions for 5 days gave the quinolinophane **1a** in 67% yield.

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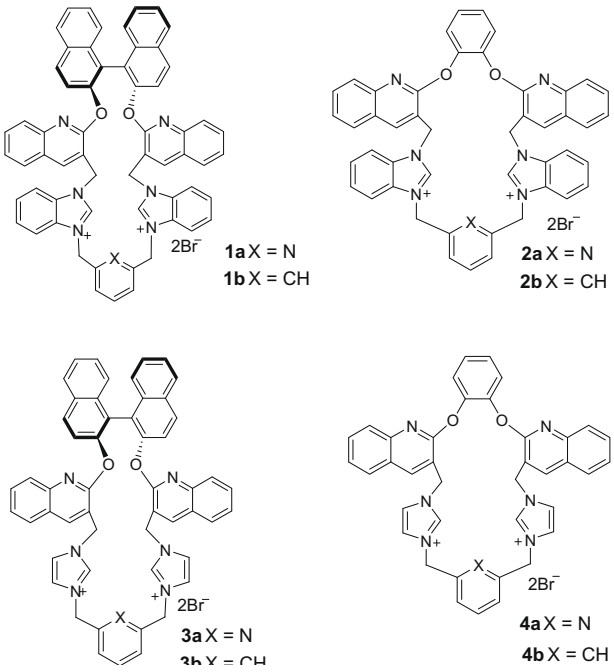


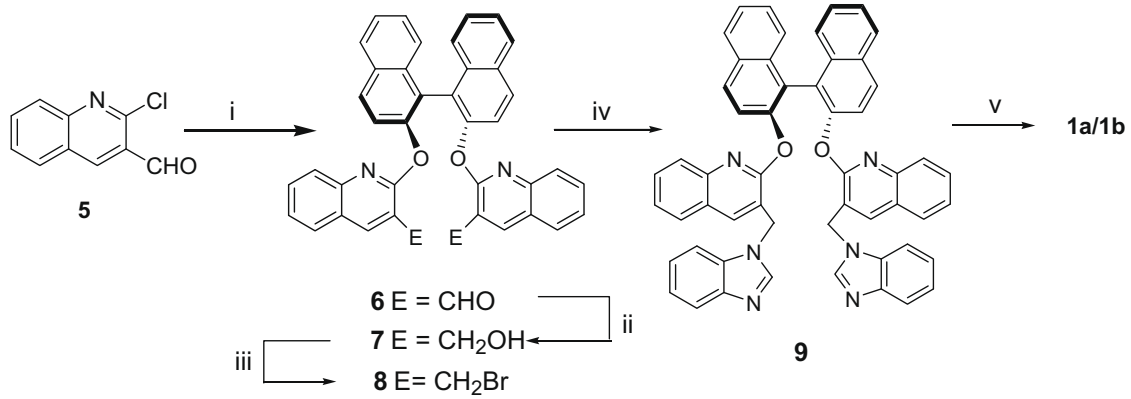
^{1}H NMR spectrum of **1a**[29] displayed *N*-methylene protons (–*N*–CH_2–) as doublets at δ 5.37 and δ 5.77, the methine proton of benzimidazole ring (–*N*–CH=*N*–) appeared as a singlet at δ 9.57, in addition to aromatic protons. In ^{13}C NMR spectrum, the –*N*–CH_2– was observed at δ 45.48, 50.12 along with other aromatic carbons. A similar sequence was followed using *m*-xylene dibromide and precyclophane **9** to give the quinolinophane **1b** in 65% yield (Scheme 1). The structure of quinolinophane **1b** was also confirmed from spectral and analytical data.[30]

Attention was then focused on the synthesis of quinolinophanes **2a** and **2b** by similar methodology. Treatment of 1 equiv of catechol with 2.1 equiv of 2-chloro-3-formylquinoline **5** gave the dialdehyde **10**, which was reduced with $NaBH_4$ to give diol **11**. Reaction of the diol **11** with PBr_3 gave the dibromide **12** in 69% yield, which was than reacted with 2.1 equiv of benzimidazole in CH_3CN in presence of 25% aq NaOH to give precyclophane **13**[26] in 72% yield. The precyclophane **13** was coupled with 1 equiv of 2,6-bis(bromomethyl)pyridine and *m*-xylene dibromide to give the cyclophanes **2a** and **2b** in 65% and 61% yields, respectively (Scheme 2). The ^{1}H NMR spectrum of **2a**[31] displayed *N*-methylene protons as singlets at δ 5.83 and δ 6.01, respectively, and the benzimidazole proton (–*N*–CH=*N*–) appeared as singlet at 10.09 in addition to aromatic protons. In ^{13}C NMR spectrum the –*N*–CH_2– appeared at δ 45.60 and δ 50.58 in addition to the aromatic carbons. The structure of cyclophane **2b** was also characterized from spectral and analytical data.[32]

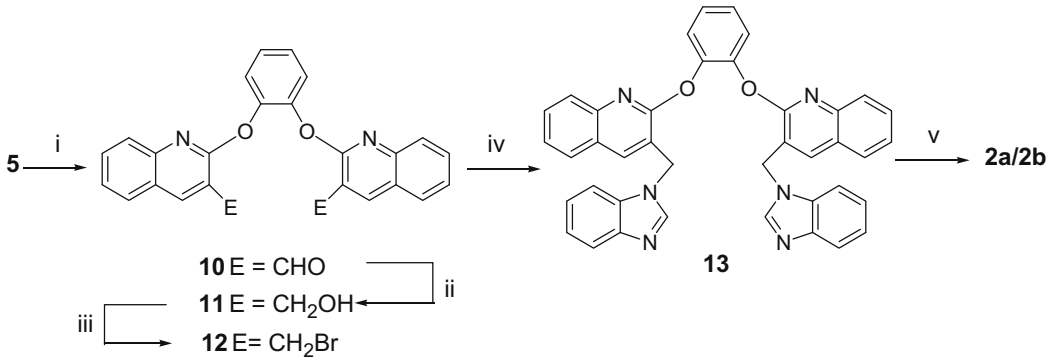
In order to test the synthetic utility of above sequence for the synthesis of imidazole based chiral quinolinophanes, the precyclophane **14** was prepared from the chiral dibromide **8** by similar synthetic sequence as mentioned in Scheme 1. Reaction of the chiral dibromide **8** with 2.1 equiv of imidazole in CH_3CN in the presence of 25% NaOH gave precyclophane **14**[27] in 46% yield. Coupling of the precyclophane **14** with 1 equiv of 2,6-bis(bromomethyl)pyridine and xylene dibromide gave cyclophanes **3a** and **3b** in 38% and 45% yields, respectively (Scheme 3). The ^{1}H NMR spectrum of **3a**[33] displayed *N*-methylene proton (–*N*–CH_2–) as doublets at δ 5.15 and δ 5.46 and the methine proton of imidazole ring (–*N*–CH=N–) as a singlet at δ 9.62, in addition to aromatic protons. In ^{13}C NMR spectrum the –*N*–CH_2– appeared at δ 53.36 and δ 57.82, along with other aromatic carbons. Similarly the structure of the quinolinophane **3b** was also confirmed from spectral and analytical data.[34]

Similarly, cyclophanes **4a** and **4b** were also synthesized in 42% and 34% yields, respectively, from precyclophane **15** and 2,6-bis(bromomethyl)pyridine and *m*-xylene dibromide (Scheme 4). Precyclophane **15**[28] was obtained in 41% yield by the reaction of dibromide **12** with 2.1 equiv of imidazole. The structure of quinolinophanes **4a** and **4b** was characterized from spectral and analytical data.[35,36]

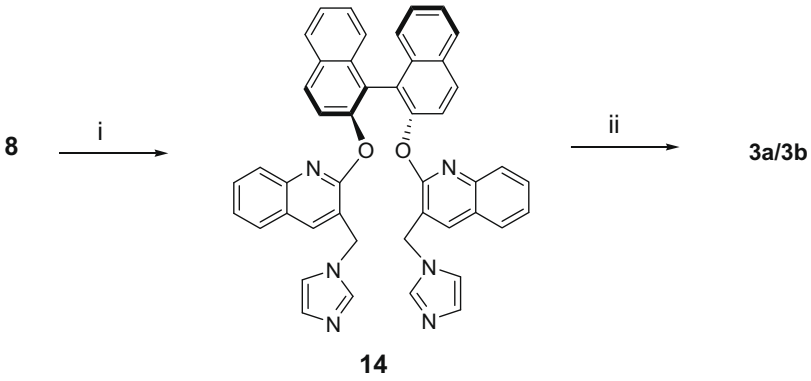
The antibacterial activity of the quinolinophanes was evaluated against six human pathogenic bacteria namely *Staphylococcus aureus, Pseudomonas aeruginosa, Shigella* sp. *Klebsiella pneumoniae*, *Escherichia coli* and *Vibrio cholera* by the agar well diffusion method.[37,38] Among the quinolinophanes **1–4** (**a**, **b**), the inhibitory effects were observed and exert moderate levels of the selected pathogenic bacteria (Table 1). The antibacterial activity of the test compounds was dose dependent and remarkable at higher concentrations. Among the compounds tested the quinolinophanes **1b**, **3a**, **3b** and **4a** were more effective than **1a**, **2a**, **2b** and **4b**. Over all analysis on the antibacterial activity revealed that the quinolinophanes **1b**, **3a**, **3b** and **4a** remarkably inhibited all the pathogenic bacteria in most of the tested concentrations as compared to other compounds and control. Further the compounds **1b**, **3a** and **3b** were also found to be superior then the commercial antibiotic viz. streptomycin. The minimum inhibitory concentrations (MIC) of quinolinophanes **1b**, **3a** and **3b** were determined between



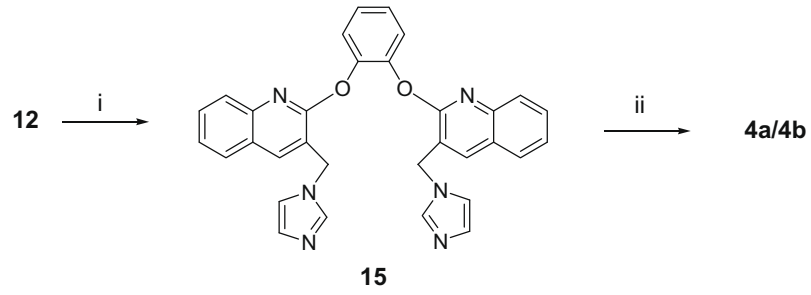
Scheme 1. Reagents and conditions: (i) (*S*)-BINOL, K_2CO_3, DMF, 60 °C, 2 days, **6** (71%); (ii) $NaBH_4$, MeOH, 6 h, **7** (80%); (iii) PBr_3, CH_2Cl_2, 0 °C, 4 h, **8** (71%); (iv) 2.1 equiv benzimidazole, 25% aq NaOH, CH_3CN, rt, 2 days, **9** (69%); (v) 2,6-bis (bromomethyl) pyridine, CH_3CN, reflux, 5 days, **1a** (67%); *m*-xylene dibromide, CH_3CN, reflux 5 days, **1b** (65%).



Scheme 2. Reagents and conditions: (i) catechol**,** K_2CO_3, DMF, 60 °C, 2 days, **10** (67%); (ii) $NaBH_4$, MeOH, 6 h, **11** (81%); (iii) PBr_3, CH_2Cl_2, 0 °C, 4 h, **12** (69%); (iv) 2.1 equiv of benzimidazole, 25% aq NaOH, CH_3CN, rt, 2 days, **13** (72%); (v) 2,6-bis (bromomethyl) pyridine, CH_3CN, reflux 5 days, **2a** 65%, *m*-xylene dibromide, CH_3CN, reflux 5 days, **2b** (61%).



Scheme 3. Reagents and conditions: (i) 2.1 equiv of imidazole, 25% aq NaOH, CH_3CN, rt, 2 days, **14** (46%); (ii) 2,6-bis(bromomethyl)pyridine, CH_3CN, reflux, 5 days, **3a** (38%), *m*-xylene dibromide, CH_3CN, reflux, 5 days, **3b** (45%).



Scheme 4. Reagents and conditions: (i) 2.1 equiv of imidazole, 25% aq NaOH, CH_3CN, rt, 2 days, **15** (41%); (ii) 2,6-bis(bromomethyl)pyridine, CH_3CN, reflux, 5 days, **4a** (42%), *m*-xylene dibromide, CH_3CN, reflux, 5 days, **4b** (34%).

Table 1
The antibacterial activity (minimum inhibitory concentration in μg/ml) the selective quinolinophanes against different human pathogenic bacteria

Dicationic cyclophanes	Antibacterial activity (minimum inhibitory Concentration (μg/ml)					
	Staphylococcus aureus	*Pseudomonas aeruginosa*	*Shigella* sp.	*Klebsiella pneumonia*	*Escherichia coli*	*Vibrio cholera*
1a	45	20	45	30	30	45
1b	15	25	10	15	15	10
2a	35	25	40	45	35	30
2b	45	40	55	60	30	25
3a	15	20	10	15	10	10
3b	15	25	15	10	20	10
4a	30	25	25	25	20	15
4b	45	30	45	40	30	35
Streptomycin	25	45	25	25	20	25
Control	NI	NI	NI	NI	NI	NI

NI: No inhibition.

10 and 25 μg/ml as compared to 25 and 60 μg/ml for other compounds and streptomycin (Table 1). However, the antibacterial activity of quinolinophane **4a** was found to be equal to that of streptomycin on all the tested pathogens.

In conclusion, all the synthesized dicationic quinolinophanes particularly **2a**, **2b**, **4b**, **1a** and **4a** have elevated antibacterial activity against all the selected human pathogenic bacteria. The quinolinophanes **1a**, **3a, 3b** and **4a** may be developed further as antibiotic drugs as they exhibit better antibacterial activity against all the test pathogens than the other quinolinophanes as well as streptomycin. However, further studies are required to determine their mode of action and their potential application against wide range of human pathogens. Synthesis of fluorescence sensing quinoline based dicationic cyclophane and their antibacterial activity as well as molecular recognition towards various biologically important anions are under investigation.

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25. *Precyclophane* **9**: Yield 69%; $[\alpha]_D^{25}$ −110.76 (*c* 0.2, MeOH); mp 239 °C; ^{1}H NMR (300 MHz $CDCl_3$): δ (ppm) 4.44 (d, 2H, *J* = 17.1 Hz); 4.68 (d, 2H, 17.1); 6.91–6.93 (m, 4H); 6.99–7.10 (m, 6H); 7.14–7.18 (m, 4H); 7.20–7.30 (m, 4H); 7.44 (t, 2H, *J* = 7.5 Hz); 7.48–7.52 (m, 4H); 7.81 (d, 2H, *J* = 7.8 Hz); 7.85 (d, 2H, *J* = 9 Hz); 7.98 (d, 2H, *J* = 8.1 Hz); 8.14 (d, 2H, *J* = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 43.00, 109.92, 119.84, 120.36, 122.27, 123.04, 123.76, 124.64, 124.59, 125.84, 126.15, 126.54, 126.69, 127.06, 128.09, 129.37, 131.30, 133.63, 133.73, 135.80, 143.64, 143.7, 144.9, 148.8, 157.94. *m*/*z* (ESI) 801 (M^+). Anal. Calcd for $C_{54}H_{36}N_6O_2$: C, 80.98; H, 4.53; N, 10.49. Found: C, 80.85; H, 4.59; N, 10.63.
26. *Precyclophane* **13**: Yield 72%; mp 165 °C; ^{1}H NMR (300 MHz $CDCl_3$): δ (ppm) 4.80 (s, 4H); 6.83 (d, 2H, *J* = 8.1 Hz); 6.97 (t, 2H, *J* = 7.8 Hz); 7.13 (t, 2H, *J* = 7.8 Hz); 7.30–7.34 (m, 2H); 7.38–7.42 (m, 4H); 7.43–7.48 (m, 4H); 7.52 (d, 2H, *J* = 7.8 Hz); 7.56–7.59 (m, 4H); 7.71 (d, 2H, *J* = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 43.59, 109.41, 119.60, 120.38, 122.25, 123.04, 123.88, 126.09, 127.23, 127.36, 130.22, 133.44, 136.89, 143.49, 143.65, 144.35, 145.64, 157.46. *m*/*z* (ESI) 625 (M+) Anal. Calcd for $C_{40}H_{28}N_6O_2$: C, 76.91; H, 4.52; N, 13.45. Found: C, 76.74; H, 4.65; N, 13.54.
27. *Precyclophane* **14**: Yield 46%; $[\alpha]_D^{25}$ −342.39 (*c* 0.2, MeOH); mp 155 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.27 (d, 2H, *J* = 16.5 Hz); 4.43 (d, 2H, *J* = 16.5 Hz); 6.53 (s, 2H); 6.99 (d, 4H, *J* = 5.4 Hz); 7.06–7.13 (m, 8H); 7.16–7.31 (m, 4H); 7.40–7.45 (m, 4H); 7,77 (d, 2H, *J* = 8.7 Hz); 7.98 (d, 2H, *J* = 8.1 Hz); 8.08 (d, 2H, *J* = 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 44.94, 119.46, 120.93, 123.57, 123.99, 124.64, 125.09, 125.75, 126.11, 126.56, 126.62, 127.06, 128.02, 128.67, 129.41, 129.51, 129.70, 131.24, 133.69, 136.18, 137.56, 144.95, 148.93, 157.84. *m*/*z* (ESI) 701 (M+). Anal. Calcd for $C_{46}H_{32}N_6O_2$: C, 78.84; H, 4.60; N, 11.99. Found: C, 78.93; H, 4.48; N, 12.07.
28. *Precyclophane* **15**: Yield 41%; mp 173 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.67 (s, 4H); 6.58 (s, 2H); 6.91 (s, 2H); 7.18 (s, 2H); 7.39–7.41 (m, 8H); 7.49–7.54 (m, 2H); 7.61–7.66 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 45.48, 119.21, 120.99, 123.80, 125.53, 125.59, 126.11, 127.25, 127.41, 129.64, 130.26, 136.76, 137.46, 144.47, 145.69, 157.35. *m*/*z* (ESI) 525 (M+) Anal. Calcd for $C_{32}H_{24}N_6O_2$: C, 73.27; H, 4.61; N, 16.02. Found: C, 73.40; H, 4.69; N, 15.87.
29. *Cyclophane* **1a**: Yield 67%; $[\alpha]_D^{25}$ −136.68 (*c* 0.2, MeOH); mp 259 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 5.37 (d, 2H, *J* = 15.9 Hz); 5.77 (d, 2H, *J* = 15.9 Hz); 5.92 (d, 2H, *J* = 15.6 Hz); 5.99 (d, 2H, *J* = 15.9 Hz); 7.22–7.39 (m, 10H); 7.50–7.60 (m, 6H); 7.63–7.72 (m, 6H); 7.86–7.92 (m, 4H); 8.06–8.16 (m, 7H); 9.57 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 45.48, 50.12, 79.23, 113.34, 113.60, 117.43, 121.86, 122. 79, 123.13, 125.05, 125.21, 125.36, 126.19, 126.32, 126.61, 126.78, 127.65, 129.93, 130.49, 130.59, 130.72, 130.94, 133.00, 138.80, 139.46, 142.63, 145.32, 149.62, 152.53, 158.35. *m*/*z* (ESI) 986 (M+Br). Anal. Calcd for $C_{61}H_{43}Br_2N_7O_2$: C, 68.74; H, 4.07; N, 9.20. Found: C, 68.65; H, 4.16; N, 9.09.
30. *Cyclophane* **1b**: Yield 65%; $[\alpha]_D^{25}$ −244.61 (*c* 0.2, MeOH); mp 247 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 5.67 (d, 2H, *J* = 16.50 Hz); 5.79 (s, 4H); 5.97 (d, 2H, *J* = 16.5 Hz); 7.26–7.27 (m, 4H); 7.36–7.42 (m, 6H); 7.57–7.63 (m, 7H); 7.63–7.70 (m, 4H); 7.75 (d, 2H, *J* = 8.1 Hz); 7.83 (d, 2H, *J* = 7.5 Hz); 7.92 (d, 2H, *J* = 8.1 Hz); 8.03–8.06 (m. 4H); 8.18 (d, 2H, *J* = 8.4 Hz); 8.35 (s, 1H); 9.92 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 45.46, 49.46, 79.22, 113.48, 113.71, 118.24, 121.74,122.78, 125.10, 125.37, 126.17, 126.79, 127.02,127.62, 127.88, 129.64, 129.90, 130.36, 130.59, 131.36, 133.01, 134.93, 142.99, 145.61, 158.09. *m*/*z* (ESI) 985 (M+Br). Anal. Calcd for $C_{62}H_{44}Br_2N_6O_2$: C, 69.93; H, 4.16; N, 7.89. Found: C, 69.79; H, 4.29; N, 7.81.
31. *Cyclophane* **2a**: Yield 65%; mp 262 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 5.83 (s, 4H); 6.01 (s, 4H); 7.37–7.39 (m, 2H); 7.49–7.51 (m, 7H); 7.75–7.64 (m, 4H); 7.76 (d, 2H, *J* = 7.8 Hz); 7.90–7.94 (m, 2H); 7.99 (d, 2H, *J* = 7.8 Hz); 8.06–8.10 (m, 4H); 8.19–8.22 (m, 2H); 10.09 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 45.60, 50.58, 79.33, 113.62, 113.84, 118.86, 123.77, 124.15, 125.31, 125.48, 126.41, 126.70, 126.91, 127.63, 130.19, 131.18, 131.22, 136.82, 139.13, 143.71, 143.94, 152.60, 156.88. *m*/*z* (ESI) 810 (M+Br). Anal. Calcd for $C_{47}H_{35}Br_2N_7O_2$: C, 63.45; H, 3.97; N, 11.02. Found: C, 63.66; H, 3.76; N, 11.15.
32. *Cyclophane* **2b**: Yield 61%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 5.85 (s, 4H); 5.99 (s, 4H); 7.40–7.45 (m, 4H); 7.56–7.64 (m, 6H); 7.68–7.73 (m, 2H); 7.78–7.82 (m, 7H); 7.98 (s, 1H); 8.13 (d, 4H); 8.45 (d, 2H, *J* = 8.1 Hz); 9.72 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 45.95, 50.12, 79.27, 113.50, 113.98, 119.75, 123.81, 125.30, 125.42, 126.62, 126.69, 127.10, 127.61, 130.22, 130.38, 131.66, 131.73, 132.15, 133.31, 136.07, 143.47, 143.85, 144.45, 157.10. *m*/*z* (ESI) 809 (M+Br). Anal. Calcd for $C_{48}H_{36}Br_2N_6O_2$: C, 64.88; H, 4.08; N, 9.46. Found: C, 64.75; H, 4.02; N, 9.54.
33. *Cyclophane* **3a**: Yield 38%; $[\alpha]_D^{25}$ −275.34 (*c* 0.2, MeOH); mp 267 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 5.15 (d, 2H, *J* = 14.1 Hz); 5.46 (d, 2H *J* = 14.7 Hz); 5.59 (d, 2H, *J* = 14.4 Hz); 5.69 (d, 2H, *J* = 15.0 Hz); 6.66 (s, 2H); 6.94 (t, 2H, *J* = 7.8 Hz); 7.23–7.28 (m, 2H); 7.30–7.33 (m, 4H); 7.38–7.43 (m, 3H); 7.61–7.68 (m, 7H, *J* = 7.8 Hz); 7.77 (d, 2H, *J* = 7.8 Hz); 7.83–7.87 (m, 4H); 7.90 (s, 1H); 8.45 (s, 2H); 9.62 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 38.41, 53.36, 57.82, 121.30, 125.83, 127.02, 128.19, 128.44, 130.04, 130.40,130.77, 131.35, 131.88, 132.49, 132.76, 134.35, 135.82, 135.86, 138.01, 141.04, 143.68, 147.04, 150.96, 153.88, 157.55, 163.84. *m*/*z* (ESI) 886 (M+Br). Anal. Calcd for $C_{53}H_{39}Br_2N_7O_2$: C, 65.92; H, 4.07; N, 10.15. Found: C, 65.78; H, 4.19; N, 10.01.
34. *Cyclophane* **3b**: Yield 45%; $[\alpha]_D^{25}$ −300.08 (*c* 0.2, MeOH); mp 251 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 5.26 (s, 4H); 5.29 (s, 4H); 6.17 (s, 2H); 6.92 (d, 2H, *J* = 9.0 Hz); 7.15–7.27 (m, 6H); 7.34–7.41 (m, 4H); 7.54 (t, 2H, *J* = 12 Hz); 7.66–7.77 (m, 6H); 7.85 (d, 2H, *J* = 9 Hz); 7.92–7.96 (m, 4H), 8.43 (s, 2H); 8.98 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 53.04, 56.95, 122.57, 126.68, 127.40, 127.95, 130.39, 130.57, 130.82,131.26, 131.46, 132.10, 132.37, 133.11, 133.35, 134.77, 134.94, 135.91, 136.25, 138.23, 140.54, 140.93, 147.14, 150.81, 154.16, 164.14. *m*/*z* (ESI) 885 (M+Br). Anal. Calcd for $C_{54}H_{40}Br_2N_6O_2$: C, 67.23; H, 4.18; N, 8.71. Found: C, 67.34; H, 4.37; N, 8.63.
35. *Cyclophane* **4a**: Yield 42%; mp 269 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 5.53 (d, 8H, *J* = 7.5 Hz); 6.82 (d, 4H, *J* = 5 Hz); 7.48–7.56 (m, 8H); 7.60–7.65 (m, 4H); 7.90–7.98 (m, 3H); 8.47 (s, 2H); 9.24 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 47.04, 52.25, 118.61, 120.46, 121.83, 123.15, 124.21, 125.25, 125.77, 126.60, 128.07, 131.02, 137.04, 138.40, 141.02, 144.89, 145.28, 152.95, 158.39.

m/*z* (ESI) 710 (M+Br). Anal. Calcd for $C_{39}H_{31}Br_2N_7O_2$: C, 59.33; H, 3.96; N, 12.42. Found: C, 59.41; H, 3.83; N, 12.51.

36. *Cyclophane* **4b**: Yield 34%; mp 242 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 5.47 (s, 4H); 5.59 (s, 4H); 7.21 (s, 2H); 7.38–7.44 (m, 5H); 7.51–7.55 (m, 7H); 7.61–7.64 (m, 4H); 7.71 (s, 2H); 7.93 (d, 2H, J = 7.8 Hz); 8.23 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 47.70, 52.08, 79.09, 117.75, 119.33, 122.15, 122.80, 123.61, 125.32, 125.66, 125.93, 126.62, 127.88, 129.58, 130.70, 134.89, 137.15, 138.86, 144.22, 144.98, 157.75. *m*/*z* (ESI) 709 (M+Br). Anal. Calcd for $C_{40}H_{32}Br_2N_6O_2$: C, 60.93; H, 4.09; N, 10.66. Found: C, 61.09; H, 4.17; N, 10.52.
37. Parekh, J.; Chanda, S. V. *Turk J. Biol.* **2007**, *31*, 53.
38. *Antibacterial activity*: Antibacterial activity of the cyclophanes against the selected human pathogens was evaluated by the agar well diffusion method. About 1 ml of inoculums of each test pathogen was added to the molten NA medium and poured into sterile Petri plates under aseptic conditions. After solidification, a 5 mm well was made in four wells of each plate using a sterile cork borer. Each compound was dissolved in 10% DMSO to get different concentrations and filtered using 0.25 μm sterilized filter paper. Each well received 50 μl solutions of each compound and the plates incubated at room temperature. Sterile DMSO (10%) was used as control. After 48 h, the appearance of inhibition zone around the well was observed. The plates were incubated overnight at 37 °C. Microbial growth was determined by measuring the minimum inhibitory concentration in μl/ml. For each bacterial strain, controls and commercial antibiotics were maintained.