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Synthesis of some novel imidazole-based dicationic carbazolophanes as potential antibacterials

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ABSTRACT

Synthesis of fluorescent imidazole-based dicationic carbazolophanes incorporating various spacer units is described. Interestingly, the cyclophanes **2a** and **5a** incorporating a pyridine moiety exhibited superior antibacterial activity against most of the pathogenic bacteria in the tested concentrations as compared to the other cyclophanes as well as the test control, benzalkonium chloride (BAC), cetylpyridinium chloride (CPC) and tetracycline.

Supramolecular systems with a fluorescence tag play an important role in biology.[1] Carbazole-based fluorophoric receptors find application as phosphate[2] and fluoride ion sensors[3] and as fluorescence markers for cancer cells.[4] Cyclophanes have received much attention in the areas of host–guest complexation, molecular self-assembly and specific receptor activity. Imidazole-based dicationic cyclophanes have been used for the synthesis of carbenoid[5] and silver complexes[6] and these also exhibit interesting conformational behavior.[7] Amphiphilic quaternary ammonium compounds (QACs)[8] are generally known to be antibacterial substances due to their electrostatic and hydrophobic interactions with negatively charged bacterial membranes. In medicine, QACs such as benzalkonium chloride (BAC) and cetylpyridinium chloride (CPC) are still broadly used as antibiotics. The synthesis and antimicrobial activity of various QACs including imidazolium and pyrrolidinonium salts,[9] 4,4′-(α,ω-polymethylenedithio)bis(1-alkylpyridinium iodide)s[10] and fluorinated bis-ammonium salts[11] are known in the literature. Kawabata et al.[12] have synthesized 3′-(3-aminopyrazolium)cephalosporins-based QACs which show good antibacterial activity with Gram-positive and Gram-negative bacteria. Pernak and Chwala et al.[13] reported a quantitative relation between MIC against bacteria and water–octanol partition coefficient (*P*) for choline-like quaternary ammonium chlorides. Amphiphilc dendrimers[14] and macrocyclic cavitand containing quaternary alkyl ammonium groups at the periphery[15] act as bactericidic agent with high efficacy and good selectivity. Dicationic imidazolophanes with various spacers like pyridine,[16] *m*-terphenyl[17] and chiral binaphthol[18] have been reported from our laboratory. However, to the best of our knowledge, imidazole-based cationic macrocycles with carbazole unit have not been reported. Herein, we wish to report the synthesis and antibacterial activity of imidazole-based dicationic carbazolophanes **1**–**6**.

The purpose of the synthesis of cationic carbazolophanes **1**–**6** is to examine the antibacterial activity, due to their electrostatic and hydrophobic interactions with negatively charged bacterial membranes. Hence, antibacterial activity of the carbazolophanes **1**–**6b** was assayed against *Proteus vulgaris*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella typhi* and *Staphylococcus aureus* at different concentrations.

The synthetic pathway leading to the synthesis of precyclophane **10** and **11** is outlined in Scheme 1. Reaction of 1 equiv of *N*-ethylcarbazole (**7**) with 2.1 equiv of *p*-toluoyl chloride in the presence of $AlCl_3$ in dry DCM at room temperature gave the diketo compound **8** in 92% yield. NBS bromination of **8** in the presence of Bz_2O_2 in dry CCl_4 at reflux for 2 h gave the dibromide **9** in 78% yield. The reaction of 2.1 equiv benzimidazole with 1 equiv of dibromide **9** in 25% aq NaOH gave the precyclophane **10** in 62% yield. Similarly the precyclophane **11** was also obtained in 42% yield by the reaction of 2.1 equiv imidazole with 1 equiv of dibromide **9** in the presence of 25% aq NaOH. The structure of precyclophanes **10** and **11** was also completely characterized from spectral and analytical data.[19,20] In the ^{1}H NMR spectrum of precyclophane **10**, the –*N*–CH_2– and –*N*=*CH*–*N*- protons of benzimidazole appeared as singlets at δ 5.71 and δ 9.32 and in the ^{13}C NMR spectrum, the –*N*–CH_2– carbon of benzimidazole and carbonyl carbon appeared at δ 48.8 and δ 195.2 in addition to other carbons.

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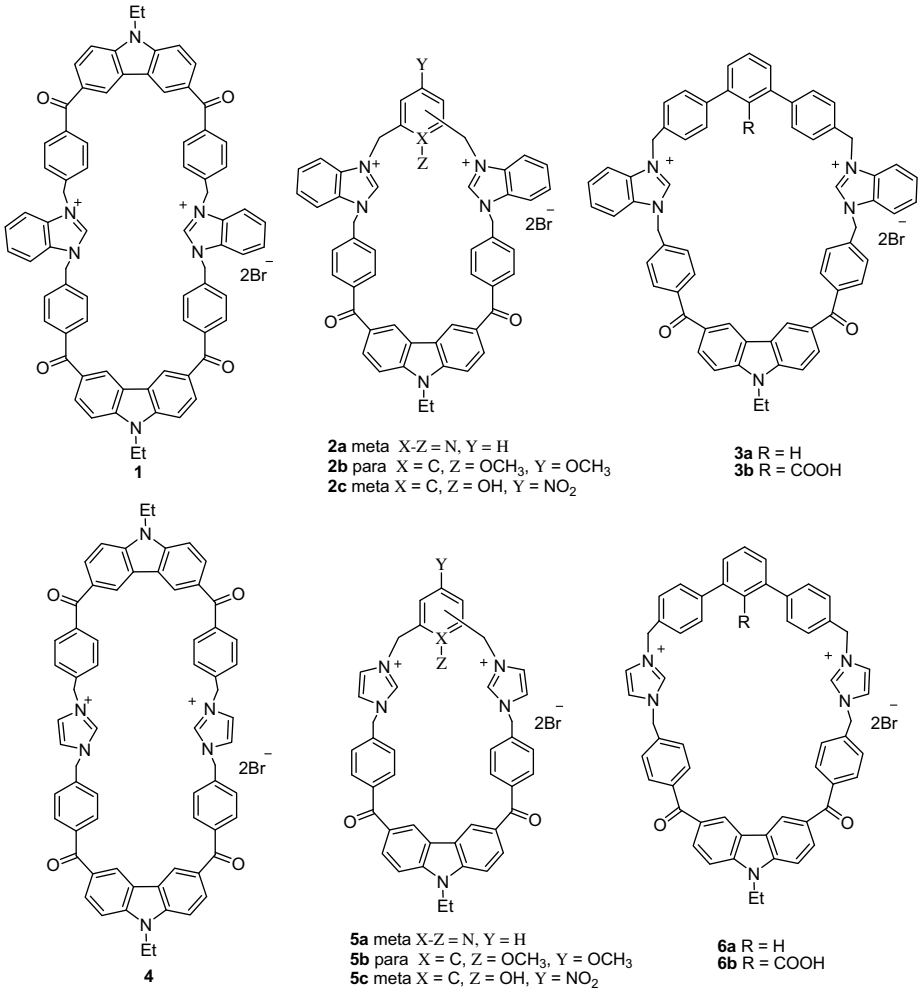


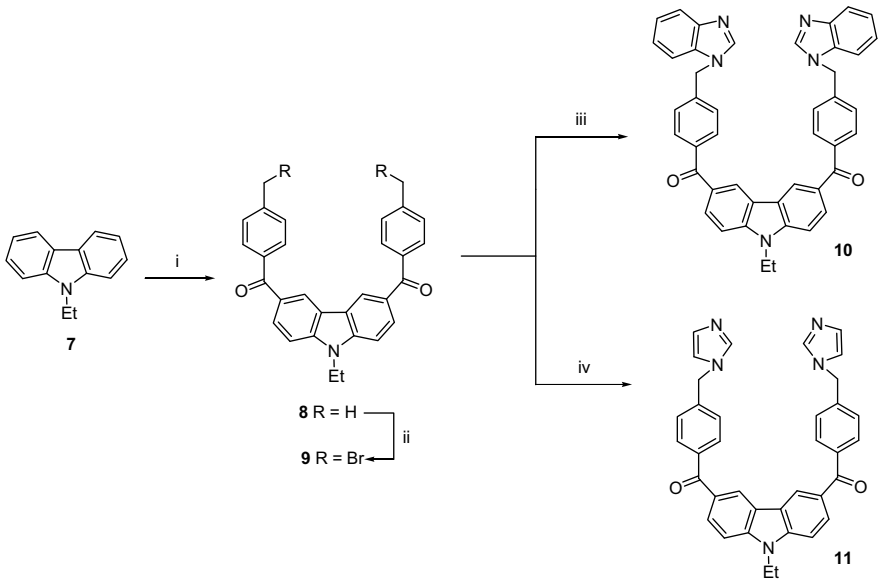
Treatment of the precyclophane **10** with 1 equiv of dibromide **9** in CH_3CN under reflux for 4 days afforded the carbazolophane **1** in 38% yield. The ^1H NMR spectrum of carbazolophane **1**[21] displayed two broad singlets at δ 1.37 and δ 4.57 for the methylene and methyl protons of the *N*-Et unit, and a singlet at δ 6.07 for the –*N*–CH_2– protons attached to the benzimidazole. The –*N*–*CH*=*N*– protons appeared as a singlet at δ 10.42 in addition to the aromatic protons. In the ^{13}C NMR spectrum, the *N*-Et carbons appeared at δ 13.7 and δ 38.1 and the –*N*–CH_2– carbons attached to the benzimidazole unit at δ 49.7, a peak at δ 194.7 for carbonyl carbon and in addition to the other aromatic carbons.

In order to test the synthetic utility of precyclophane **10** for the synthesis of various dicationic carbazolophanes, one equiv of precyclophane **10** was coupled with each one equiv of 2,6-bis(bromomethyl)pyridine (**12**),[22] 1,4-bis(bromomethyl)-2,5-dimethoxybenzene (**13**),[23] 1,3-bis-(bromomethyl)-4-nitrophenol (**14**),[24] and *m*-terphenyl dibromides **15a**–**b**[25] to give the carbazolophanes **2a**, **2b**, **2c**, **3a** and **3b** in 42%, 44%, 41%, 38% and 33% yields, respectively, after usual purification (Scheme 2).

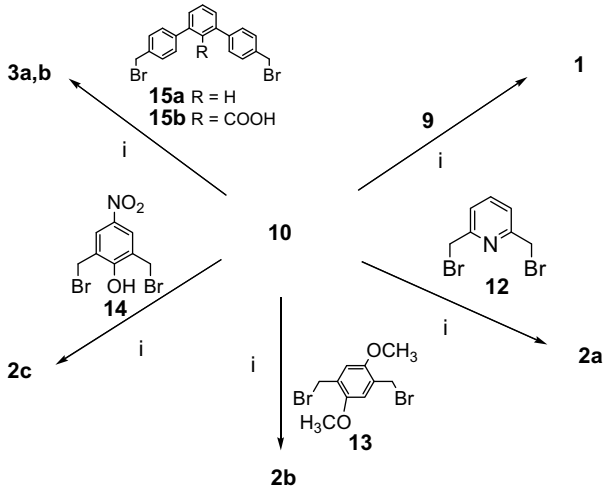
The ^1H NMR spectrum of carbazolophane **2a**[26] showed two singlets at δ 5.93 and δ 5.95 for CH_2– protons attached to *N* atom of benzimidazole units. The benzimidazole –*N*–*CH*=*N*– protons appeared as singlet at δ 10.25 in addition to other protons of carbazole and imidazole unit. In the ^{13}C NMR spectrum, the –*N*–CH_2– carbon attached to the benzimidazole unit at δ 49.7 and δ 50.9 and the carbonyl carbon appeared at δ 195.0 and in addition to the other carbons. Similarly, the structure of other carbazolophanes **2b**–**c**, **3a**–**b** was confirmed from spectral and analytical data.[27–29]

By similar procedure, dicationic cyclophanes **4**, **5a**–**c**, **6a**–**b** were prepared in excellent yields by the reaction of 1 equiv of the precyclophane **11** with one equiv of the dibromides **9**, **12**, **13**, **14** and **15a**–**b** in CH_3CN under reflux for 4 days (Scheme 3). The structure of dicationic carbazolophanes **4**, **5a**–**c** and **6a**–**b** were completely characterized from spectral and analytical data.[30–34]

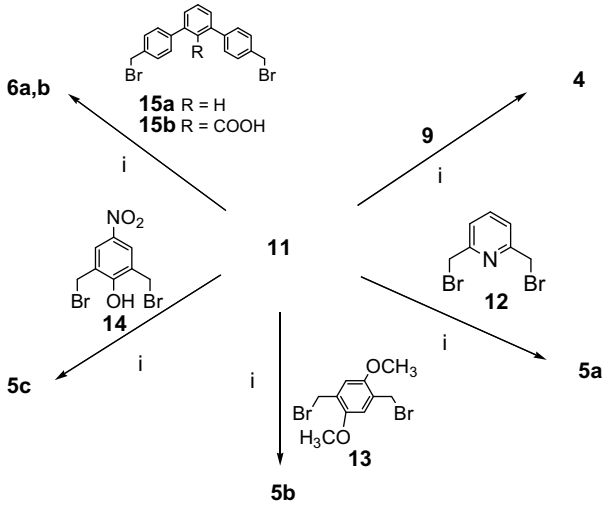
Antibacterial activity: The antibacterial activity of the compounds was evaluated against five human pathogenic bacteria namely, *P. vulgaris*, *P. mirabilis*, *P. aeruginosa*, *S. typhi* and *S. aureus* by the agar diffusion method. Among the carbazolophanes **1**–**6**, the four cyclophanes namely, **2a**, **2c**, **5a** and **5c** exerted various levels of inhibitory effects against the pathogenic bacteria (Table 1). Among **2a**, **2c**, **5a** and **5c** compound **2a** exhibited significant activity towards all the above mentioned bacteria followed by compound **2c** which also revealed remarkable activity. The minimum inhibitory concentration (MIC) of compound **2a** was determined between 8 and 20 μg/ml as against 12 and 30 μg/ml for benzalkonium chloride (BAC), 18 and 42 μg/ml for CPC and 15 and 35 μg/ml for tetracycline. Carbazolophane **5a** and **5c** also exhibited relatively better activity when compare to the commercially available antibiotic like BAC, CPC and tetracycline in inhibiting the growth of the above mentioned bacteria. The antimicrobial activity[35] of the test macrocycles was



Scheme 1. Reagents and conditions: (i) $AlCl_3$, *p*-toluoyl chloride, DCM(dry), rt, 8 h, **8** (92%); (ii) NBS, CCl_4(dry), Bz_2O_2, 2 h, **9** (78%); (iii) benzimidazole, 25% NaOH, CH_3CN, rt, 2 days, **10** (62%); (iv) imidazole, 25% NaOH, CH_3CN, rt, 2 days, **11** (42%).



Scheme 2. Reagents and conditions: (i) CH_3CN, reflux, 4 days, **1** (38%), **2a** (42%), **2b** (44%), **2c** (41%), **3a** (38%), and **3b** (33%).



Scheme 3. Reagents and conditions: (i) CH_3CN, reflux, 4 days, **4** (33%), **5a** (47%), **5b** (41%), **5c** (38%), **6a** (35%), and **6b** (31%).

dose-dependent and it was remarkable at higher concentrations. Other cyclophanes **1**, **2b**, **3a**, **3b**, **4**, **5b**, **6a** and **6b** were less effective than **2a**, **2c**, **5a** and **5c**. Overall analysis of the antibacterial activity revealed that cyclophanes **1**, **2a**, **2c**, **4**, **5a** and **5c** remarkably inhibited the growth of all the pathogenic bacteria in most of the tested concentrations as compared to other compounds and the control (Table 1).

In conclusion, the dicationic carbazolophanes **2a**, **2c**, **5a** and **5c** with pyridine and nitro phenol spacer unit exhibited good antibacterial activity against all five human pathogenic bacteria. The compounds **2a** and **5a** may be developed further as antibiotic drugs as these showed better activity against all the test pathogens than the other compounds. However, further studies are required to determine their potential against a wide range of human pathogens and its mode of action. Syntheses of other similar dicationic carbazolophanes and their antibacterial activity as well as molecular recognition towards various biologically important anions are under investigation.

Table 1
Antibacterial activity (minimum inhibitory concentration μg/ml) of imidazolium dicationic carbazolophanes

Dicationic carbazolophanes	*P. vulgaris*	*P. mirabilis*	*P. aeruginosa*	*S. typhi*	*S. aureus*
1	30	30	35	25	26
2a	15	10	20	15	8
2b	45	55	70	40	NI
2c	35	30	30	15	20
3a	50	50	65	45	45
3b	60	55	70	50	NI
4	40	35	55	25	25
5a	25	20	30	15	12
5b	60	55	80	50	75
5c	30	20	35	20	20
6a	70	75	75	55	75
6b	65	50	80	35	35
BAC	28	12	30	20	15
CPC	30	25	42	20	18
Tetracycline	35	20	35	15	20
Control	NI	NI	NI	NI	NI

NI, no inhibition.

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19. *Precyclophane* **10:** Yield 62%; mp 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.43 (t, 3H, J = 7.2 Hz); 4.38 (q, 2H, J = 7.2 Hz); 5.71 (s, 4H); 7.18–7.36 (m, 10H); 7.45 (d, 2H, J = 8.8 Hz); 7.74 (d, 4H, J = 7.6 Hz); 7.83 (br s, 2H); 8.04 (d, 2H, J = 8.4 Hz); 8.39 (s, 2H); 9.32 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.7, 38.2, 48.8, 108.8, 110.2, 120.0, 121.7, 122.9, 123.0, 123.8, 123.9, 124.4, 125.2, 127.0, 129.0, 129.5, 130.5, 138.9, 139.1, 143.4, 195.2. (FAB-MS) 663 (M^+). Elemental Anal. Calcd for $C_{44}H_{33}N_5O_2$: C, 79.62; H, 5.01; N, 10.55. Found: 79.74; H, 5.16; N, 10.68.
20. *Precyclophane* **11**: Yield 42%; mp 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.41 (t, 3H, J = 7.2 Hz); 4.36 (q, 2H, J = 7.2 Hz); 5.16 (s, 4H); 6.90 (br s, 2H); 7.04 (br s, 2H); 7.18 (d, 4H, J = 7.2 Hz); 7.40 (d, 2H, J = 8.4 Hz); 7.58 (br s, 2H); 7.70 (d, 4H, J = 7.6 Hz); 7.92 (d, 2H, J = 8.4 Hz); 8.46 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.7, 38.1, 50.3, 108.9, 119.4, 122.6, 123.5, 126.1, 126.9, 128.9, 130.4, 137.5, 138.3, 139.9, 143.2, 195.4; (FAB-MS) 563 (M^+). Elemental Anal. Calcd for $C_{36}H_{29}N_5O_2$: C, 76.71; H, 5.19; N, 12.43. Found: 76.86; H, 5.31; N, 12.56.
21. *Cyclophane* **1**: Yield 38%; mp 274 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.37 (br s, 6H); 4.57 (br s, 4H); 6.07 (s, 8H); 7.35–8.10 (m, 32H); 8.73 (s, 4H); 10.42 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 13.7, 38.1, 49.7, 114.0, 121.5, 122.1, 123.7, 125.5, 126.0, 126.9, 128.3, 128.6, 130.0, 131.1, 137.6, 138.4, 142.9, 194.7; m/z (FAB-MS) 1253 (M^+). Elemental Anal. Calcd for $C_{74}H_{56}Br_2N_6O_4$: C, 70.93; H, 4.50; N, 6.71. Found: 70.81; H, 4.63; N, 6.84.
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26. *Cyclophane* **2a**: Yield 42%; mp 300–302 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.39 (t, 3H, J = 7.2 Hz); 4.62 (q, 2H, J = 7.2 Hz); 5.93 (s, 4H); 5.95 (s, 4H); 7.33–7.46 (s, 4H); 7.69–7.83 (m, 16H); 7.95 (d, 2H, J = 9.3 Hz); 8.09 (t, 1H, J = 7.5 Hz); 8.18 (s, 2H); 10.25 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 13.8, 37.1, 49.7, 50.9, 110.8, 113.8, 114.0, 121.0, 123.3, 124.1, 126.2, 126.3, 127.6, 128.5, 128.7, 129.8, 130.5, 131.4, 137.4, 138.5, 139.1, 142.9, 153.0, 195.0; m/z (FAB-MS) 928 (M^+). Elemental Anal. Calcd for $C_{51}H_{40}Br_2N_6O_2$: C, 65.96; H, 4.34; N, 9.05. Found: 65.82; H, 4.24; N, 9.18.
27. *Cyclophane* **2b**: Yield 44%; mp 262 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.34 (br s, 3H); 3.85 (s, 6H); 4.56 (br s, 2H); 5.52 (s, 4H); 5. 69 (s, 4H); 7.52–8.37 (m, 22H); 8.73 (s, 2H); 10.66 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.7, 37.4, 49.3, 56.2, 56.3, 113.8, 122.7, 123.1, 124.8, 126.1, 126.7, 127.0, 127.5, 128.1, 128.6, 129.4, 130.0, 130.3, 130.7, 131.0, 131.5, 137.9, 142.9, 151.3, 152.0, 194.8; m/z (FAB-MS) 987 (M^+). Elemental Anal. Calcd for $C_{54}H_{45}Br_2N_5O_4$: C, 65.66; H, 4.59; N, 7.09. Found: 65.51; H, 4.47; N, 7.21.
28. *Cyclophane* **2c**: Yield 41%; mp 212–214 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.40 (br s, 3H, J = 7.2 Hz); 4.60 (q, 2H, J = 7.2 Hz); 5.93 (s, 4H); 6.01 (s, 4H); 7.62–8.48 (m, 23H); 8.73 (s, 2H); 10.53 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 13.7, 37.7, 49.4, 49.9, 113.2, 121.1, 122.1, 122.6, 124.7, 126.1, 126.4, 126.8, 127.2, 127.6, 128.1, 128.6, 129.0, 130.0, 130.6, 131.0, 131.8, 138.2, 142.2, 142.8, 194.8; m/z (FAB-MS) 988 (M^+). Elemental Anal. Calcd for $C_{52}H_{40}Br_2N_6O_5$: C, 63.17; H, 4.08; N, 8.50. Found: 63.29; H, 4.21; N, 8.63.
29. *Cyclophane* **3a**: Yield 38%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.10 (br s, 3H); 4.31 (br s, 2H); 5.70 (s, 4H); 5.80 (s, 4H); 7.18–7.91 (m, 32H); 8.40 (s, 2H); 10.27 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 13.7, 37.7, 49.6, 49.8, 109.7, 114.1, 122.0, 123.7, 125.1, 126.1, 126.8, 127.0, 127.4, 127.5, 128.4, 128.6, 129.1, 129.2, 130.0, 130.2, 131.0, 131.1, 133.0, 137.8, 138.3, 140.0, 140.4, 142.6, 142.9, 194.7; m/z (FAB-MS) 1079 (M^+). Elemental Anal. Calcd for $C_{64}H_{49}Br_2N_5O_2$: C, 71.18; H, 4.57; N, 6.49. Found: 71.31; H, 4.42; N, 6.62.
30. *Cyclophane* **4**: Yield 33%; mp 263 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.37 (br s, 6H); 4.58 (br s, 4H); 5.63 (s, 8H); 7.52–8.06 (m, 28H); 8.74 (s, 4H); 9.60 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 13.7, 37.7, 51.7, 109.4, 120.0, 122.2, 123.1, 123.7, 128.1, 128.3, 128.7, 130.0, 136.8, 138.4, 143.0, 194.8; m/z (FAB-MS) 1153 (M^+). Elemental Anal. Calcd for $C_{66}H_{52}Br_2N_6O_4$: C, 68.75; H, 4.55; N, 7.29. Found: 68.59; H, 4.37; N, 7.16.
31. *Cyclophane* **5a**: Yield 47%; mp 298 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.38 (br s, 3H); 4.62 (br s, 2H); 5.61 (s, 4H); 5.66 (s, 4H); 7.56 (d, 4H, J = 8 Hz); 7.64 (d, 2H, J = 7.6 Hz); 7.81–7.85 (m, 8H); 7.94 (d, 2H, J = 8.8 Hz); 8.02 (t, 1H, J = 6.2 Hz); 8.12 (d, 2H, J = 8.8 Hz); 8.30 (s, 2H); 9.60 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.1, 37.3, 51.3, 52.7, 110.2, 120.9, 122.0, 122.4, 123.1, 123.6, 127.0, 127.7, 128.5, 129.3, 136.7, 137.5, 138.4, 142.5, 152.8, 194.2; m/z (FAB-MS) 828 (M^+). Elemental Anal. Calcd for $C_{43}H_{36}Br_2N_6O_2$: C, 62.33; H, 4.38; N, 10.14. Found: 62.47; H, 4.52; N, 10.28.
32. *Cyclophane* **5b**: Yield 41%; mp 223 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.37 (br s, 3H); 3.58 (s, 6H); 4.55 (br s, 2H); 5.36 (s, 4H); 5.62 (s, 4H); 6.99–7.98 (m, 18H); 8.72 (s, 2H); 9.62 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 13.7, 37.3, 48.2, 55.8, 56.2, 109.9, 122.1, 122.6, 123.1, 123.7, 125.4, 128.1, 129.2, 130.0, 130.3, 136.3, 137.4, 138.7, 142.5, 149.6, 151.2, 195.3; m/z (FAB-MS) 887 (M^+). Elemental Anal. Calcd for $C_{46}H_{41}Br_2N_5O_4$: C, 62.24; H, 4.66; N, 7.89. Found: 62.41; H, 4.47; N, 7.72.
33. *Cyclophane* **5c**: Yield 38%; mp 223 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.36 (t, 3H, J = 7.1 Hz); 4.63 (q, 2H, J = 7.1 Hz); 5.62 (s, 4H); 5.66 (s, 4H); 7.56–7.64 (m, 4H); 7.79–7.93 (m, 15H); 8.71 (s, 2H); 9.50 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 13.7, 37.7, 51.2, 51.3, 109.6, 120.3, 122.1, 122.2, 123.7, 127.1, 128.2, 128.6, 129.2, 129.8, 130.0, 130.3, 135.6, 137.9, 138.3, 138.7, 142.9, 194.8; m/z (FAB-MS) 888 (M^+). Elemental Anal. Calcd for $C_{44}H_{36}Br_2N_6O_5$: C, 59.47; H, 4.08; N, 9.46. Found: 59.61; H, 4.23; N, 9.57.
34. *Cyclophane* **6a**: Yield 35%; mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.35 (br s, 3H); 4.54 (br s, 2H); 5.53 (s, 4H); 5.61 (s, 4H); 7.54–8.01 (m, 28H); 8.68 (s, 2H); 9.64 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 13.7, 37.7, 51.7, 51.8, 109.7, 122.1, 122.8, 123.1, 125.1, 126.1, 127.0, 127.4, 128.3, 128.6, 129.1, 129.2, 129.6, 130.1, 130.2, 136.1, 138.4, 139.9, 140.4, 142.9, 194.7; m/z (FAB-MS) 979 (M^+). Elemental Anal. Calcd for $C_{56}H_{45}Br_2N_5O_2$: C, 68.65; H, 4.63; N, 7.15. Found: 68.78; H, 4.72; N, 7.28.
35. *Antibacterial activity:* The cultures of human pathogenic bacteria *P. vulgaris*, *P. mirabilis*, *P. aeruginosa*, *S. typhi* and *S. aureus* used in this study were obtained from the Culture Collections of Biocontrol and Microbial Metabolites Laboratory, Centre for Advanced Studies in Botany, University of Madras and maintained on Nutrient Agar (NA), consisting of the following [(g/L) Beef extract 1.0; Yeast extract 2.0; Peptone 5.0; NaCl 5.0; Agar 15.0; Distilled H_2O 1 L; pH 7.2.] in slants or Petriplates at room temperature (28 ± 2 °C). The antibacterial activity of the compounds against human pathogens was evaluated by the agar diffusion method. About 1 ml of inoculum of each test pathogen was added to the molten Nutrient Agar (NA) medium and poured into sterile Petriplates under aseptic conditions. After solidification, a 5-mm well was made in the centre of each plate using a sterile cork borer. Each compound was dissolved in 10% DMSO to get different concentrations and filter was sterilized using 0.25 μm filter paper. Each well received 50 μL solution of each compound and the plates were incubated at room temperature. Sterile DMSO (10%) was used as control. After 48 h, the appearance of inhibition zone around the well was observed.