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Synthesis and Antimicrobial Evaluation of 4-Amino/Dimethylamino-1-Aryl/Alkylpyridinium Bromide

A. Yasodha[1], G. Arunachalam[1], A. Puratchikody[*2]

[1]*Department of Pharmaceutical Chemistry, PGP college of Pharmaceutical Science and Research Institute, Namakkal-637207, Tamilnadu, India.*
[2*]*Department of Pharmaceutical Technology, Anna University Chennai, BIT Campus, Tiruchirappalli-620024, Tamilnadu, India.*

Abstract:
A series of bromides (RCH_2Br) containing aryl / alkyl group readily reacted with 4-amino / dimethylaminopyridine to give stable pyridinium bromide **(1-30)**. The physical and spectral (IR, ^1H & ^{13}C NMR and MS) data for **1-30** were collected to confirm the structure (s) assigned. *Invitro* antibacterial and antifungal activities of **1-30** against Gram positive / Gram negative and fungal species were evaluated. The 4-amino / dimethylamino-1-alkylpyridinium bromides (Group III & IV) were found higher antibacterial and antifungal activity than the standard drugs ciprofloxacin / fluconazole respectively.
Key words: Antimicrobial activity, 4-aminopyridine, 4-dimethylaminopyridine (DMAP), Pyridinium bromides.

INTRODUCTION

Quaternary ammonium salts were reported as good antimicrobial agents [1-4]. Antimicrobial activity of quat salts was endorsed to their effect on the cell wall resulting in a direct and indirect lethal effect on the cell viability [5]. Pyridinium salts are considered as one of the categories of quaternary ammonium salts which are heterocyclic compounds having different functional groups [6]. Pyridinium salts have wide range of therapeutic properties like antibacterial [7-8], antifungal [9], antimycobacterial [10], antiviral [11], antitumoral [12], antiAChE [13], antimalarial [14] and hepatoprotective activities [15]. Several well-known drugs contain pyridinium nucleus such as Cephaloridine, Pralidoxime, Pyridostigmine, Cefalonium, Stilbazium, Fazadinium etc, indicating the fact that pyridinium nucleus possess vast spectrum of biological activities. These activities indicate that pyridinium frame work plays an essential role in drug discovery and represents an interesting template for combinatorial and medicinal chemistry [16]. It is, therefore, part of interest to prepare some pyridinium salts with different functional groups at 4-and 1-position of pyridine nucleus with a view to knowing their biological activity. The present investigation is one more addition to the pyridine derivatives of biological interest.

MATERIALS AND METHODS

Melting points determined are uncorrected. IR (KBr) spectra of the compounds **1-30** were recorded on Perkin Elmer 1600 FT spectrophotometer. ^1H CNMR spectra were recorded in DMSO – d_6 on a Bruker AC, 300MHz spectrometer using TMS as standard and Mass Spectra on API 3000 Centroid Turbo Spray Analyzer.

General Procedure for Synthesis of 1-aryl / alkyl-4-amino / dimethylaminopyridinium bromides (1-30): 4-amino/dimethylaminopyridine in dry acetone (30 ml) was added in to the solution containing required amount of aryl or alkyl bromide (0.1mol) in acetone (25 ml). The reaction mixer was stirred at room temperature for 2-12 h. The solid that separated was filtered off, washed with toluene, dried in vaccum and recrystallized from chloroform and acetone (1:1) to give **1-30**.

4-amino-1-(phenylmethyl)pyridinium bromide (1): ^1H-NMR (DMSO-d_6) δ: 8.37-8.36 (d, 2H, C_2- and C_6-H), 8.28 (s, 2H, NH_2), 7.45-7.35 (m, 5H, CH_2-Ph), 7.07-7.06 (d, 2H, C_3- and C_5-H), 5.40 (s, 2H, N^+-CH_2). ^{13}C-NMR (DMSO-d_6) δ: 158.70, 155.85, 142.95, 142.00, 135.80, 135.65, 129.00, 128.63, 128.01 (aromatic carbons), 109.56, 108.00 (N^+-CH_2), 59.47, 59.13. IR (KBr) cm^{-1}: 3337, 3171, 2649, 2077, 1653, 1542, 1449, 1381. ESIMS *m/z*: 185 (Calcd for $C_{12}H_{13}BrN_2$: 185.03). MS *m/z*: (M^+). *Anal.* calcd for $C_{12}H_{13}BrN_2$: C, 77.83; H, 7.02; N, 15.13. Found: C, 77.81; H, 7.03; N, 15.12.

4-amino-1-[(4-bromophenyl)methyl]pyridinium bromide (2): ^1H-NMR (DMSO-d_6) δ: 8.32-8.29 (d, 2H, C_2- and C_6-H), 8.23 (s, 2H, NH_2), 7.63-7.61 (d, 2H, C'_3- and C'_5-H), 7.38-7.35 (d, 2H, C'_2 and C'_6-H), 6.89-6.87 (d, 2H, C_3- and C_5-H), 5.38 (s, 2H, N^+-CH_2). ^{13}C-NMR (DMSO-d_6) δ: 158.74, 142.94, 134.97, 131.22, 130.30 (-C_4-Br), 122.01 (aromatic carbons), 109.64 (N^+-CH_2), 58.74. IR (KBr) cm^{-1}: 3280, 3128, 2690, 2064, 1668, 1544, 1490, 1174, 818. ESIMS *m/z*: 263 (Calcd for $C_{12}H_{12}Br_2N_2$: 262.94). MS *m/z*: (M^+). *Anal.* calcd for $C_{12}H_{12}Br_2N_2$: C, 54.56; H, 4.58; N, 10.60. Found: C, 54.54; H, 4.56; N, 10.59.

4-amino-1-[(4-nitrophenyl)methyl]pyridinium bromide (3): ^1H-NMR (DMSO-d_6) δ: 8.33-8.30 (d, 2H, C_2- and C_6-H), 8.25 (s, 2H, NH_2), 7.62-7.61 (d, 2H, C'_2- and C'_6-H), 7.35-7.34 (d, 2H, C'_3- and C'_5-H), 7.06-7.05 (d, 2H, C_3-and C_5-H), 5.30 (s, 2H, N^+-CH_2). ^{13}C-NMR (DMSO-d_6) δ: 155.96, 147.52, 143.01, 142.18, 124.06 (aromatic carbons), 108.14 (N^+-CH_2), 58.30, 40.97 (C_4-NO_2). IR (KBr) cm^{-1}: 3399, 3035, 2717, 2064, 1648, 1565, 1344, 1168, 803. ESIMS *m/z*: 230 (Calcd for $C_{12}H_{12}BrN_3O_2$: 230.01). MS *m/z*: (M^+). *Anal.* calcd for $C_{12}H_{12}BrN_3O_2$: C, 62.60; H, 5.21; N, 18.26. Found: C, 62.58; H, 5.20; N, 18.27.

4-amino-1-[(4-methylphenyl)methyl]pyridinium bromide (4): ^1H-NMR (DMSO-d_6) δ: 8.31-8.30 (d, 2H, C_2- and C_6-H), 8.21 (s, 2H, NH_2), 7.30-7.29 (d, 2H, C'_3- and C'_5-H), 7.22-7.21 (d, 2H, C'_2- and C'_6-H), 6.88-6.86 (d, 2H,

C_3- and C_5-H), 5.33 (s, 2H, N^+-CH_2), 2.29 (s, 3H, C_4-CH_3). ^{13}C-NMR (DMSO-d_6) δ: 158.86, 142.86, 138.12, 132.61, 129.54, 128.08 (aromatic carbons), 109.55(N^+-CH_2), 59.37, 20.68 (C_4-CH_3). IR (KBr) cm^{-1}: 3289, 3122, 2699, 2150, 1652, 1530, 1368, 1167. ESIMS *m/z*: 199 (Calcd for $C_{13}H_{15}BrN_2$: 199.04). MS *m/z*: (M^+). *Anal.* calcd for $C_{13}H_{15}BrN_2$: C, 78.39; H, 7.53; N, 14.07. Found: C, 78.38; H, 7.51; N, 14.10.

4-amino-1-(2-oxo-2-phenylethyl)pyridinium bromide (5): ^{1}H-NMR (DMSO-d_6) δ: 8.37-8.36 (d, 2H, C_2- and C_6-H), 8.28 (s, 2H, NH_2), 7.45-7.35 (m, 5H, CO-Ph), 7.07-7.06 (d, 2H, C_3- and C_5-H), 5.41 (s, 2H, N^+-CH_2). ^{13}C-NMR (DMSO-d_6) δ: 193.12 (C=O), 154.17, 149.41, 137.21, 131.62, 129.02, 128.99, 127.00 (aromatic carbons), 108.82 (N^+-CH_2), 58.36. IR (KBr) cm^{-1}: 3437, 3096, 2764, 2052, 1649, 1506, 1443, 1332, 1215. ESIMS *m/z*: 213 (Calcd for $C_{13}H_{13}BrN_2O$: 213.02). MS *m/z*: (M^+). *Anal.* calcd for $C_{13}H_{13}BrN_2O$: C, 73.23; H, 6.10; N, 13.14. Found: C, 73.21; H, 6.09; N, 13.12.

4-dimethylamino-1-(phenylmethyl)pyridinium bromide (6): ^{1}H-NMR (DMSO-d_6) δ: 8.46-8.45 (d, 2H, C_2- and C_6-H), 7.42-7.37 (m, 5H, CH_2-Ph), 7.08-7.06 (d, 2H, C_3- and C_5-H), 5.44 (s, 2H, N^+ CH_2-), 3.18 (s, 6H, N-$(CH_3)_2$). ^{13}C-NMR (DMSO-d_6) δ: 155.88, 142.01, 135.80, 129.01, 128.65, 127.97 (aromatic carbons), 107.99 (N^+-CH_2), 59.23 (N-$(CH_3)_2$). IR (KBr) cm^{-1}: 3038, 2953, 2083, 1644, 1568, 1397, 1157. ESIMS *m/z*: 213 (Calcd for $C_{14}H_{17}BrN_2$: 213.06). MS *m/z*: (M^+). *Anal.* calcd for $C_{14}H_{17}BrN_2$: C, 78.87; H, 7.98; N, 13.14. Found: C, 78.85; H, 7.96; N, 13.13.

4-dimethylamino-1-[(4-bromophenyl)methyl] pyridinium bromide (7) : ^{1}H-NMR (DMSO-d_6) δ: 8.34-8.32 (d, 2H, C_2- and C_6-H), 7.61-7.59 (d, 2H, C'$_3$- and C'$_5$-H), 7.36-7.34 (d, 2H, C'$_2$- and C'$_6$-H), 7.02-7.00 (d, 2H, C_3- and C_5-H), 5.37 (s, 2H, N^+-CH_2), 3.16 (s, 6H, N-$(CH_3)_2$). ^{13}C-NMR (DMSO-d_6) δ: 155.85, 141.84, 134.87, 131.93, 130.24 (C'$_4$-Br), 122.06 (aromatic carbons), 107.94 (N^+-CH_2), 58.62 (N-$(CH_3)_2$). IR (KBr) cm^{-1}: 3045, 2963, 1928, 1641, 1579, 1345, 1158, 823. ESIMS *m/z*: 291 (Calcd for $C_{14}H_{16}Br_2N_2$: 290.97). MS *m/z*: (M^+). *Anal.* calcd for $C_{14}H_{16}Br_2N_2$: C, 57.93; H, 5.51; N, 9.65. Found: C, 57.91; H, 5.50; N, 9.6.

4-dimethylamino-1-[(4-nitrophenyl)methyl]pyridinium bromide (8): ^{1}H-NMR (DMSO-d_6) δ: 8.29-8.26 (d, 2H, C'$_3$- and C'$_5$-H), 8.31-8.29 (d, 2H, C_2- and C_6-H), 7.62-7.60 (d, 2H, C'$_2$- and C'$_6$-H), 6.89-6.87 (d, 2H, C_3-and C_5-H), 5.36 (s, 2H, N^+-CH_2), 3.17 (s, 6H, N-$(CH_3)_2$). ^{13}C-NMR, (DMSO-d_6) δ: 158.86, 154.44, 148.90, 147.52, 143.19, 142.90, 129.09, 124.05 (aromatic carbons), 109.80 (N^+-CH_2), 58.60 (N-$(CH_3)_2$), 41.18 (C'$_4$- NO_2). IR (KBr) cm^{-1}: 3192, 2923, 2052, 1663, 1517, 1345, 1219, 837. ESIMS *m/z*: 259 (Calcd for $C_{14}H_{16}BrN_3O_2$: 258.04). MS *m/z*: (M^+). *Anal.* calcd for $C_{14}H_{16}BrN_3O_2$: C, 65.11; H, 6.20; N, 16.27. Found: C, 65.10; H, 6.19; N, 16.25.

4-dimethylamino-1-[(4-methylphenyl)methyl]pyridinium bromide (9): ^{1}H-NMR (DMSO-d_6) δ: 8.346-8.45 (d, 2H, C_2- and C_6-H)), 7.42-7.41 (d, 2H, C'$_2$- and C'$_6$-H), 7.38-7.37 (d, 2H, C'$_3$- and C'$_5$-H), 7.08-7.06 (d, 2H, C_3- and C_5-H), 5.44 (s, 2H, N^+-CH_2-), 3.18 (s, 6H, N-$(CH_3)_2$), 2.51 (s, 3H, C'$_4$-CH_3). ^{13}C-NMR (DMSO-d_6) δ: 155.88, 142.01, 135.80, 129.01, 128.65, 127.97 (aromatic carbons), 107.99 (N^+CH_2), 59.23 (N-$(CH_3)_2$), 21.45 (C'$_4$-CH_3); IR (KBr) cm^{-1}: 3018, 2414, 1967, 1647, 1572, 1387, 1164. ESIMS*m/z*: 227 (Calcd for $C_{15}H_{19}BrN_2$: 227.07). MS *m/z*: (M^+). *Anal.* calcd for $C_{15}H_{19}BrN_2$: C, 79.26; H, 8.37; N, 12.33. Found: C, 79.27; H, 8.35; N, 12.31.

4-dimethylamino-1-(2-oxo-2-phenylethyl)pyridinium bromide (10): ^{1}H-NMR (DMSO-d_6) δ: 8.48-8.46 (d, 2H, C_2- and C_6-H), 7.48-7.37 (m, 5H, CO-Ph), 7.08-7.06 (d, 2H, C_3-and C_5-H), 5.44 (s, 2H, N^+-CH_2), 3.18 (s, 6H, N-$(CH_3)_2$). ^{13}C-NMR (DMSO-d_6) δ: 194.57 (C=O), 156.50, 142.01, 135.80, 129.01, 128.65, 127.97, 107.44 (N^+-CH_2), 59.23 (N-$(CH_3)_2$). IR (KBr) cm^{-1}: 3021, 2995, 2125, 1701, 1649, 1558, 1390, 1215**.** ESIMS *m/z*: 241 (Calcd for $C_{15}H_{17}BrN_2O$: 241.97). MS *m/z*: (M^+). *Anal.* calcd for $C_{15}H_{17}BrN_2O$: C, 74.68; H, 7.05; N, 11.61. Found: 74.67; H, 7.03; N, 11.60.

4-amino-1-propylpyridinium bromide (11): ^{1}H-NMR (DMSO-d_6) δ: 7.98-7.97 (d, 2H, C_2- and C_6-H), 6.47-6.46 (d, 2H, C_3-and C_5-H), 6.01 (s, 2H, NH_2), 3.72-3.70 (t, 2H, N^+-CH_2), 2.57(m, 5H, CH_2-CH_2-CH_3). ^{13}C-NMR (DMSO-d_6) δ: 154.24, 149.33, 139.50, 108.82 (N^+-CH_2), 46.10, 20.10, 18.03 (CH_2-CH_3). IR (KBr) cm^{-1}: 3506, 3331, 2334, 2054, 1646, 1422, 1324, 1203. ESIMS *m/z*: 137 (Calcd for $C_8H_{13}BrN_2$: 137.03). MS *m/z*: (M^+). *Anal.* calcd for $C_8H_{13}BrN_2$: C, 70.07; H, 9.48; N, 20.43. Found: C, 70.05; H, 9.47; N, 20.42.

4-amino-1-butylpyridinium bromide (12): ^{1}H-NMR (DMSO-d_6) δ: 8.20-8.18 (d, 2H, C_2- and C_6-H), 7.96 (s, 2H, NH_2), 6.85-6.82 (d, 2H, C_3- and C_5-H), 3.51-3.46 (m, 9H, N^+CH_2-CH_2-CH_2-CH_3). ^{13}C-NMR (DMSO-d_6) δ: 158.52, 154.20, 149.33, 142.80, 109.33, 108.81 (N^+-CH_2), 65.68, 56.70, 32.17, 18.66, 13.30 (CH_2-CH_2-CH_3). IR (KBr) cm^{-1}: 3434, 3300, 3100, 2538, 1646, 1531, 1435, 1332; ESIMS *m/z*: 151 (Calcd for $C_9H_{15}BrN_2$: 151.04). MS *m/z*: (M^+). *Anal.* calcd for $C_9H_{15}BrN_2$: C, 71.52; H, 9.93; N, 9.27. Found: C, 71.51; H, 9.91; N, 9.26.

4-amino-1-pentylpyridinium bromide (13): ^{1}H-NMR (DMSO-d_6) δ: 8.36-8.25 (d, 2H, C_2- and C_6-H), 8.19 (s, 2H, NH_2), 6.88-6.87 (d, 2H, C_3- and C_5-H), 4.15-4.12 (t, 2H, N^+-CH_2), 3.42-2.50 (m, 6H, N^+-CH_2-CH_2-CH_2-CH_2-CH_3), 1.19-1.15 (t, 3H, N^+-CH_2-CH_2-CH_2-CH_2-CH_3). ^{13}C-NMR (DMSO-d_6) δ: 158.59, 154.28, 149.19, 142.81, 109.26, 108.79 (N^+-CH_2), 56.41, 29.49, 21.70 (CH_2-CH_2-CH_2-CH_3). IR (KBr) cm^{-1}: 3428, 3209, 2938, 2055, 1651, 1542, 1437, 1381. ESIMS *m/z*: 165 (Calcd for $C_{10}H_{17}BrN_2$: 165.06). MS *m/z*: (M^+). *Anal.* calcd for $C_{10}H_{17}BrN_2$: C, 72.72; H, 10.30. Found: C, 72.70; H, 10.28; N, 16.96.

4-amino-1-hexylpyridinium bromide (14): ^{1}H-NMR (DMSO-d_6) δ: 8.10 (s, 2H, NH_2), 7.98-7.96 (d, 2H, C_2- and C_6-H), 6.47-6.45 (d, 2H, C_3-and C_5-H), 4.16-4.15 (t, 2H, N^+-CH_2), 1.75-1.23 (m, 11H, N^+-CH_2-CH_2-CH_2-CH_2-CH_3). ^{13}C-NMR (DMSO-d_6) δ: 154.82, 141.95, 108.19 (N^+-CH_2), 60.43, 56.50, 48.26, 34.99, 32.20, 31.93, 30.07, 24.65 (CH_2-CH_2-CH_2-CH_3). IR (KBr) cm^{-1}: 3306, 3095, 2698, 2052, 1649, 1506, 1435, 1334. ESIMS *m/z*: 179 (Calcd for $C_{11}H_{19}BrN_2$: 179.07). MS *m/z*: (M^+). *Anal.* calcd for $C_{11}H_{19}BrN_2$: C, 73.74; H, 10.61; N, 15.64. Found: C, 73.72; H, 10.60; N, 15.63.

4-dimethylamino-1-propylpyridinium bromide (15): ^{1}H-NMR (DMSO-d_6) δ: 8.11-8.10 (d, 2H, C_2- and C_6-H), 6.59 (d, 2H, C_3- and C_5-H), 2.95 (s, 6H, N-$(CH_3)_2$), 2.51-2.50 (m, 7H, N^+-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_3}$). ^{13}C NMR (DMSO-d_6) δ: 153.93, 149.25, 106.67 (N^+-CH_2), 59.60 (N-$(CH_3)_2$), 40.02, 39.02, 38.56 (CH_2-CH_3). IR (KBr) cm^{-1}: 2906, 2821, 2123, 1604, 1440, 1370, 1217. ESIMS *m/z*: 165 (Calcd for $C_{10}H_{17}BrN_2$: 165.06). MS *m/z*: (M^+). *Anal.* calcd for $C_{10}H_{17}BrN_2$: C, 72.72; H, 10.30; N, 16.96. Found: C, 72.70; H, 10.31; N, 16.95.

4-dimethylamino-1-butylpyridinium bromide (16): ^{1}H-NMR (DMSO-d_6) δ: 8.10-8.09 (d, 2H, C_2- and C_6-H), 6.58 (d, 2H, C_3- and C_5-H), 3.51 (s, 6H, N-$(CH_3)_2$), 2.51 (m, 9H, N^+-CH_2-CH_2-CH_2-CH_3). ^{13}C-NMR (DMSO-d_6) δ: 154.40, 149.78, 107.16 (N^+-CH_2), 58.52 (N-$(CH_3)_2$), 39.05, 28.40, 22.60 (CH_2-CH_2-CH_3). IR (KBr) cm^{-1}: 3032, 2920, 2123, 1604, 1513, 1370, 1228. ESIMS *m/z*: 179 (Calcd for $C_{11}H_{19}BrN_2$: 179.07). MS *m/z*: (M^+). *Anal.* calcd for $C_{11}H_{19}BrN_2$: C, 73.74; H, 10.61; N, 15.64. Found: C, 73.71; H, 10.60; N, 15.62.

4-dimethylamino-1-pentylpyridinium bromide (17): ^{1}H-NMR (DMSO-d_6) δ: 8.11-8.10 (d, 2H, C_2- and C_6-H), 6.58-6.57 (d, 2H, C_3- and C_5-H), 3.19 (s, 6H, N-$(CH_3)_2$), 2.51-2.50 (t, 2H, N^+-CH_2), 1.30-1.10 (m, 9H, N^+-CH_2-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_3}$). ^{13}C-NMR (DMSO-d_6) δ: 158.59, 154.40, 149.78, 107.00 (N^+-CH_2), 59.50 (N-$(CH_3)_2$), 39.07, 28.50, 23.50, 21.54 (CH_2-CH_2-CH_2-CH_3). IR (KBr) cm^{-1}: 2906, 2541, 2123, 1603, 1525, 1440, 1218. ESIMS *m/z*: 183 (Calcd for $C_{12}H_{21}BrN_2$: 183.09). MS *m/z*: (M^+). *Anal.* calcd for $C_{12}H_{21}BrN_2$: C, 78.68; H, 11.47; N, 15.30. Found: C, 78.69; H, 11.45; N, 15.29.

4-dimethylamino-1-hexylpyridinium bromide (18): ^{1}H-NMR (DMSO-d_6) δ: 8.11-8.10 (d, 2H, C_2- and C_6-H), 6.58-6.57 (d, 2H, C_3- and C_5-H), 3.19 (s, 6H, N-$(CH_3)_2$), 2.51-2.50 (t, 2H, N^+-CH_2), 1.30-1.10 (m, 9H, N^+-CH_2-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_3}$). ^{13}C-NMR (DMSO-d_6) δ: 158.59, 154.40, 149.78, 107.00 (N^+-CH_2), 59.50 (N-$(CH_3)_2$), 39.07, 28.50, 23.50, 21.54 (CH_2-CH_2-CH_2-CH_3). IR (KBr) cm^{-1}: 2906, 2541, 2123, 1603, 1525, 1440, 1218. ESIMS *m/z*: 207 (Calcd for $C_{13}H_{23}BrN_2$: 207.10). MS *m/z*: (M^+). *Anal.* calcd for $C_{13}H_{23}BrN_2$: C, 75.36; H, 11.11; N, 13.52. Found: C, 75.34; H, 11.10; N, 13.50.

4-amino-1-(3-bromopropyl)pyridinium bromide (19): ^{1}H-NMR (DMSO-d_6) δ: 8.21 (s, 2H, NH_2), 7.96-7.95 (d, 2H, C_2- and C_6-H), 6.46-6.44 (d, 2H, C_3- and C_5-H), 4.20-4.17(t, 2H, N^+-CH_2), 2.50 (m, 4H, N^+-CH_2-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{Br}$). ^{13}C-NMR (DMSO-d_6) δ: 158.66, 154.19, 142.80, 109.44 (N^+-CH_2), 66.18 (CH_2-Br), 53.92, 46.10. IR (KBr) cm^{-1}: 3437, 3308, 2916, 2540, 1669, 1508, 1334, 1269, 823. ESIMS *m/z*: 214 (Calcd for $C_8H_{12}Br_2N_2$: 214.14). MS *m/z*: (M^+). *Anal.* calcd for $C_8H_{12}Br_2N_2$: C, 44.85; H, 5.60; N, 13.08. Found: C, 44.84; H, 5.61; N, 13.07.

4-amino-1-(4-bromobutyl)pyridinium bromide (20): ^{1}H-NMR (DMSO-d_6) δ: 8.18 (s, 2H, NH_2), 7.96-7.94 (d, 2H, C_2- and C_6-H), 6.86-6.85 (d, 2H, C_3- and C_5-H), 4.17 (t, 2H, N^+-CH_2), 2.50-1.71 (m, 6H, N^+-CH_2-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-Br). ^{13}C-NMR (DMSO-d_6) δ: 158.57, 154.22, 149.30, 142.79, 109.38, 108.79 (N^+-CH_2), 56.16 (CH_2-Br), 26.79. IR (KBr) cm^{-1}: 3437, 3304, 2698, 2540, 1600, 1508, 1435, 1217, 823. ESIMS *m/z*: 229 (Calcd for $C_9H_{14}Br_2N_2$: 228.95). MS *m/z*: (M^+). *Anal.* calcd for $C_9H_{14}Br_2N_2$: C, 47.36; H, 6.14; N, 12.28. Found: C, 47.35; H, 6.12; N, 12.27.

4-amino-1-(5-bromopentyl)pyridinium bromide (21): ^{1}H-NMR (DMSO-d_6) δ: 8.27-8.25 (d, 2H, C_2- and C_6-H), 8.19 (s, 2H, NH_2), 6.88-6.87 (d, 2H, C_3-and C_5-H), 4.15–4.12 (t, 2H, N^+-CH_2), 2.50-1.15 (m, 8H, N^+-CH_2-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-Br). ^{13}C-NMR (DMSO-d_6) δ: 158.5, 154.28, 149.19, 142.84, 109.26, 108.79 (N^+-CH_2), 56.41 (CH_2-Br), 29.49, 21.70. IR (KBr) cm^{-1}: 3397, 3143, 2930, 2076, 1655, 1540, 1368, 1186, 834. ESIMS *m/z*: 242 (Calcd for $C_{10}H_{16}Br_2N_2$: 242.97). MS *m/z*: (M^+). *Anal.* calcd for $C_{10}H_{16}Br_2N_2$: C, 49.58; H, 6.61; N, 11.57. Found: C, 49.58; H, 6.61; N, 11.57.

4-amino-1-(6-bromohexyl)pyridinium bromide (22): ^{1}H-NMR (DMSO-d_6) δ: 8.25-8.24 (d, 2H, C_2- and C_6-H), 8.17 (s, 2H, NH_2), 7.95-7.94 (d, 2H, C_3- and C_5-H), 4.14– 4.10 (t, 2H, N^+-CH_2), 2.50-1.23 (m, 10H, N^+-CH_2-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-Br). ^{13}C-NMR (DMSO-d_6) δ: 158.50, 154.29, 149.17, 142.81, 109.26, 108.75 (N^+-CH_2), 56.70 (CH_2-Br), 29.91, 24.74. IR (KBr) cm^{-1}: 3311, 3136, 2935, 2065, 1602, 1539, 1371, 1188, 839. ESIMS *m/z*: 256 (Calcd for $C_{11}H_{18}Br_2N_2$: 256.98). MS *m/z*: (M^+). *Anal.* calcd for $C_{11}H_{18}Br_2N_2$: C, 51.56; H, 7.03; N, 10.90. Found: 51.54; H, 7.02; N, 10.90.

4-dimethylamino-1-(3-bromopropyl)pyridinium bromide (23): ^{1}H-NMR (DMSO-d_6) δ: 8.32-8.30 (d, 2H, C_2- and C_6-H), 7.06-7.04 (d, 2H, C_3-and C_5-H), 4.27-4.25 (t, 2H, N^+-CH_2), 3.2 (s, 6H, N-$(CH_3)_2$), 2.51-2.34 (m, 4H, N^+-CH_2-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{Br}$). ^{13}C-NMR (DMSO-d_6) δ: 155.86, 141.94, 107.77 (N^+-CH_2), 53.77 (CH_2-Br), 47.80 (N-$(CH_3)_2$), 45.52. IR (KBr) cm^{-1}: 3066, 2946, 2069, 1650, 1570, 1337, 1183, 827. ESIMS *m/z*: 243 (Calcd for $C_{10}H_{16}Br_2N_2$: 242.97). MS *m/z*: (M^+). *Anal.* calcd for $C_{10}H_{16}Br_2N_2$: C, 49.58; H, 6.61; N, 11.57. Found: C, 49.56; H, 6.60; N, 11.55.

4-dimethylamino-1-(4-bromobutyl)pyridinium bromide (24): ^{1}H-NMR (DMSO-d_6) δ: 8.39-8.37 (d, 2H, C_2- and C_6-H), 7.07-7.05 (d, 2H, C_3- and C_5-H), 4.26-4.21 (t, 2H, N^+-CH_2), 3.19 (s, 6H, N-$(CH_3)_2$), 2.51-1.36 (m, 6H, N^+-CH_2-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-Br). ^{13}C-NMR (DMSO-d_6) δ: 156.31, 142.46, 139.70, 108.24, 108.15, 107.46 (N^+-CH_2), 60.40 (CH_2-Br), 57.01, 56.21(N-$(CH_3)_2$), 29.24, 27.76, 27.42. IR (KBr) cm^{-1}: 3061, 2949, 2360, 1651, 1566, 1404, 1174, 839. ESIMS *m/z*: 257 (Calcd for $C_{11}H_{18}Br_2N_2$: 256.98). MS *m/z*: (M^+). *Anal.* calcd for $C_{11}H_{18}Br_2N_2$: C, 51.56; H, 7.03; N, 10.93. Found: C, 51.55; H, 7.02; N, 10.91.

4-dimethylamino-1-(5-bromopentyl)pyridinium bromide (25): ^{1}H-NMR (DMSO-d_6) δ: 8.37-8.35 (d, 2H, C_2- and C_6-H), 7.06-7.04 (d, 2H, C_3-and C_5-H), 4.20-4.18 (t, 2H, N^+-CH_2), 3.19 (s, 6H, N-$(CH_3)_2$), 2.51-1.18 (m, 8H, N^+-CH_2-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-Br). ^{13}C-NMR (DMSO-d_6) δ: 155.78, 142.00, 107.66 (N^+-CH_2), 56.14(CH_2-Br), 41.17 (N-$(CH_3)_2$), 29.57, 21.77. IR (KBr) cm^{-1}: 3063, 2933, 2065, 1649, 1567, 1391, 1177, 828. ESIMS *m/z*: 271 (Calcd for $C_{12}H_{20}Br_2N_2$: 271.0). MS *m/z*: (M^+). *Anal.* calcd for $C_{12}H_{20}Br_2N_2$: C, 53.13; H, 7.38; N, 10.33. Found: C, 53.11; H, 7.37; N, 10.32.

4-dimethylamino-1-(6-bromohexyl)pyridinium bromide (26): ^{1}H-NMR (DMSO-d_6) δ: 8.36-8.34 (d, 2H, C_2- and C_6-

H), 7.09-7.08 (d, 2H, C_3- and C_5-H), 4.20– 4.18 (t, 2H, N^+-CH_2), 3.19 (s, 6H, N-$(CH_3)_2$), 2.59-1.18 (m, 10H, N^+-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-Br). ^{13}C-NMR (DMSO-d_6) δ: 155.78, 142.00, 107.66 (N^+-CH_2), 56.77 (CH_2-Br), 42.77 (N-$(CH_3)_2$), 40.37, 29.57, 21.77. IR (KBr) cm^{-1}: 3414, 2935, 2360, 1653, 1568, 1402, 1178, 831. ESIMS *m/z*: 285 (Calcd for $C_{13}H_{22}Br_2N_2$: 285.0). MS *m/z*: (M^+). ***Anal.*** calcd for $C_{13}H_{22}Br_2N_2$: C, 54.73; H, 7.71; N, 9.82. Found: C, 54.72; H, 7.70; N, 9.81.

4-amino-1-(2-ethoxy-2oxoethyl)pyridinium bromide (27): ^{1}H-NMR (DMSO-d_6) δ: 8.16-8.14 (d, 2H, C_2- and C_6-H), 6.91-6.90 (d, 2H, C_3-and C_5-H), 5.05 (s, 2H, N^+-CH_2), 4.21-4.16 (quadret, 2H, CH_2-CH_3), 2.51-2.50 (t, 3H, CH_2-CH_3). ^{13}C-NMR (DMSO-d_6) δ: 168.86 (carbon of ester gp), 167.58, 159.79, 158.93, 158.81, 143.98, 139.77, 108.96, 108.68 (N^+-CH_2), 61.74 (CH_2-CH_3), 57.12, 56.75 (CH_2-CH_3). IR (KBr) cm^{-1}: 3427, 2988, 2708, 2080, 1744, 1654, 1557, 1382, 1210, 1019. ESIMS *m/z*: 181 (Calcd for $C_9H_{13}BrN_2O_2$: 181.02). MS *m/z*: (M^+). ***Anal.*** calcd for $C_9H_{13}BrN_2O_2$: C, 59.66; H, 7.18; N, 15.46. Found: C, 59.64; H, 7.17; N, 15.45.

4-amino-1-allylpyridinium bromide (28): ^{1}H-NMR (DMSO-d_6) δ: 8.31-8.21 (d, 2H, C_2- and C_6-H), 8.0 (s, 2H, NH_2), 6.94-6.92 (d, 2H, C_3- and C_5-H), 6.07-6.05 (d, 2H, N^+-CH_2), 5.30-5.27 (d, 1H, CH_2-CH=CH_2), 4.84-4.83 (d, 2H, CH_2-CH=CH_2). ^{13}C-NMR (DMSO-d_6) δ: 158.60, 142.80, 138.25, 132.80 (CH=CH_2), 119.68 (CH=CH_2), 109.30 (N^+-CH_2), 58.51. IR (KBr) cm^{-1}: 3259, 3091, 2710, 2154, 1658, 1535, 1506, 1369, 1170. ESIMS *m/z*: 135 (Calcd for $C_8H_{11}BrN_2$: 135.01). MS *m/z*: (M^+). ***Anal.*** calcd for $C_8H_{11}BrN_2$: C, 71.11; H, 8.14; N, 20.74. Found: C, 71.10; H, 8.12; N, 20.73.

4-dimethylamino-1-(2-ethoxy-2oxoethyl)pyridinium bromide (29): ^{1}H-NMR (DMSO-d_6) δ: 8.29-8.27 (d, 2H, C_2- and C_6-H), 7.12-7.10 (d, 2H, C_3- and C_5-H), 4.21-4.17 (quadret, 2H, CH_2- CH_3), 5.25 (s, 2H, N^+-CH_2), 3.22 (s, 6H, N-$(CH_3)_2$), 1.25-1.22 (t, 3H, CH_2-CH_3). ^{13}C-NMR (DMSO-d_6) δ: 169.13 (carbon of ester gp), 168.10, 156.50, 143.59, 143.55, 107.86, 107.63, 107.44 (N^+-CH_2), 62.94 (CH_2-CH_3), 56.97 (CH_2-CH_3), 40.98 (N-$(CH_3)_2$). IR (KBr) cm^{-1}: 3060, 2419, 1970, 1750, 1650, 1564, 1388, 1212, 1020. ESIMS *m/z*: 209 (Calcd for $C_{11}H_{17}BrN_2O_2$: 209.05). MS *m/z*: (M^+). ***Anal.*** calcd for $C_{11}H_{17}BrN_2O_2$: C, 63.15; H, 8.13; N, 13.39. Found: C, 63.13; H, 8.11; N, 13.38.

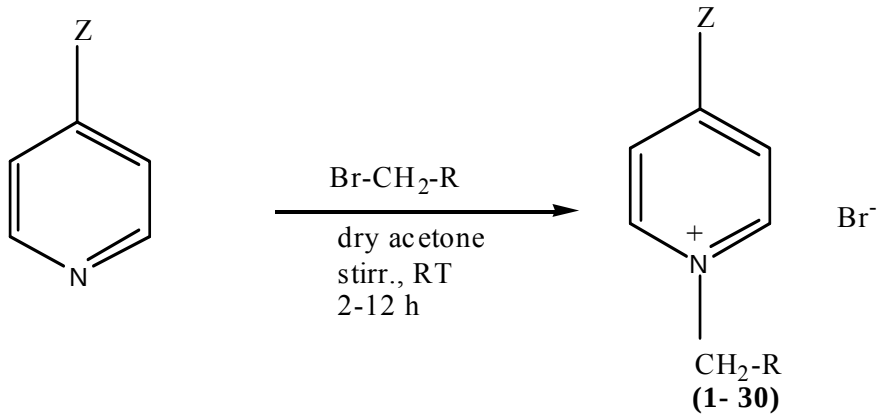
4-dimethylamino-1-allylpyridinium bromide (30): ^{1}H-NMR (DMSO-d_6) δ: 8.31-8.21 (d, 2H, C_2- and C_6-H), 6.94-6.92 (d, 2H, C_3- and C_5-H), 6.07-6.05 (d, 2H, N^+-CH_2), 5.27-5.22 (d, 1H, CH_2-CH=CH_2), 4.84-4.83 (d, 2H, CH_2-CH=CH_2), 3.16 (s, 6H, N-$(CH_3)_2$). ^{13}C-NMR (DMSO-d_6) δ: 158.85, 141.84, 134.87, 131.93, 130.24 (CH_2-CH=CH_2), 122.06 (CH_2-CH=CH_2), 107.94 (N^+-CH_2), 58.62 (N-$(CH_3)_2$). IR (KBr) cm^{-1}: 3061, 2949, 2017, 1658, 1535, 1506, 1369, 1170. ESIMS *m/z*: 163 (Calcd for $C_{10}H_{15}BrN_2$: 163.04). MS *m/z*: (M^+). ***Anal.*** calcd for $C_{10}H_{15}BrN_2$: C, 73.61; H, 9.20; N, 17.17. Found: C, 73.60; H, 9.18; N, 17.15.

Antimicrobial Screening:

The antibacterial activity was performed against Gram positive (*Staphylococcus aureus* and *Streptococcus mutants*) and Gram negative (*Escherichia coli* and *Klebesillap neumoniae*) bacteria and antifungal activity was performed against *Rhizopus arrhizus* and *Aspergillus niger* by tube dilution method [17]**.** Dilutions of test and standard compounds [ciprofloxacin (antibacterial) and fluconazole (antifungal)] were prepared in double strength nutrient broth – I.P. (bacteria) and Sabouraud dextrose broth I.P. (fungi). The samples were incubated at 37 °C for 24 h (bacteria), at 25 °C for 72 h (*Aspergillus niger*) and at 37 °C for 48 h (*Rhizopus arrhizus*), respectively, and the results were recorded in terms of minimum inhibitory concentration (MIC) (the lowest concentration of test substance which inhibited the growth of microorganisms).

RESULTS AND DISCUSSION

The reaction between aryl / alkyl bromide(s) (RCH_2Br) and 4-amino / dimethylaminopyridine reacts to give 4-amino / dimethylamino-1-aryl / alkylpyridinium bromide **(1-30)** in dry acetone at room temperature under stirring for 2-12 hours **(Scheme 1)**. The physical data of **1-30** were collected and are presented in **Table 1**. The physical (m.p., yield, etc.) data of some of the 4-aminopyridinium bromides and 4-dimethylaminopyridinium (DMAP) bromides are found comparable with their reported values elsewhere [18]. Each of 4-amino / dimethylaminopyridine is small organic molecule but is a potential nucleophile [19]. The presence of -NH_2 and -$N(CH_3)_2$ group at 4-position of pyridine has electron releasing property, whereas, the nitrogen at 1-position has electron accepting tendency. As a result the charge density on the endocyclic nitrogen is more than the exocyclic nitrogen [20]. Therefore, electrophile preferably attacks on the endocyclic nitrogen. In the case of aryl bromide, electron withdrawing group (EWG) at 4-position of benzene ring causes for C-Br bond to be more facile to cleave which makes the reaction faster and form more yield more (>80%) **(1-10)**. Whereas, C-Br cleavage is less facile in the case of alkyl bromide(s) **(11-18)** which results the less yield (70-80%). The isolated yield for **19-26** is found to be comparable with the yield of **1-10**. The presence of other bromine atom in the alkyl chain may cause for increasing the electrophilicity of the alkyl group. The reaction between 4-aminopyridine / DMAP and dibromoalkane under 1:1 mole ratio prefers to attack either one of the C-Br bonds [21]. Increasing the alkyl chain length is also favored for the approach of 4-aminopyridine / DMAP nucleophile which in turn increases the yield. The reaction between 4-aminopyridine / DMAP and carboethoxymethyl / allyl bromide gave the corresponding pyridinium salt (**27-30**) with poor yield. This may be due to the formation of carbocation which is to be stabilized by inductive and conjugative effect.



(1- 30)

Scheme 1. Synthetic route followed for the synthesis of 4-amino / dimethylamino-1-aryl / alkylpyridinium bromides.

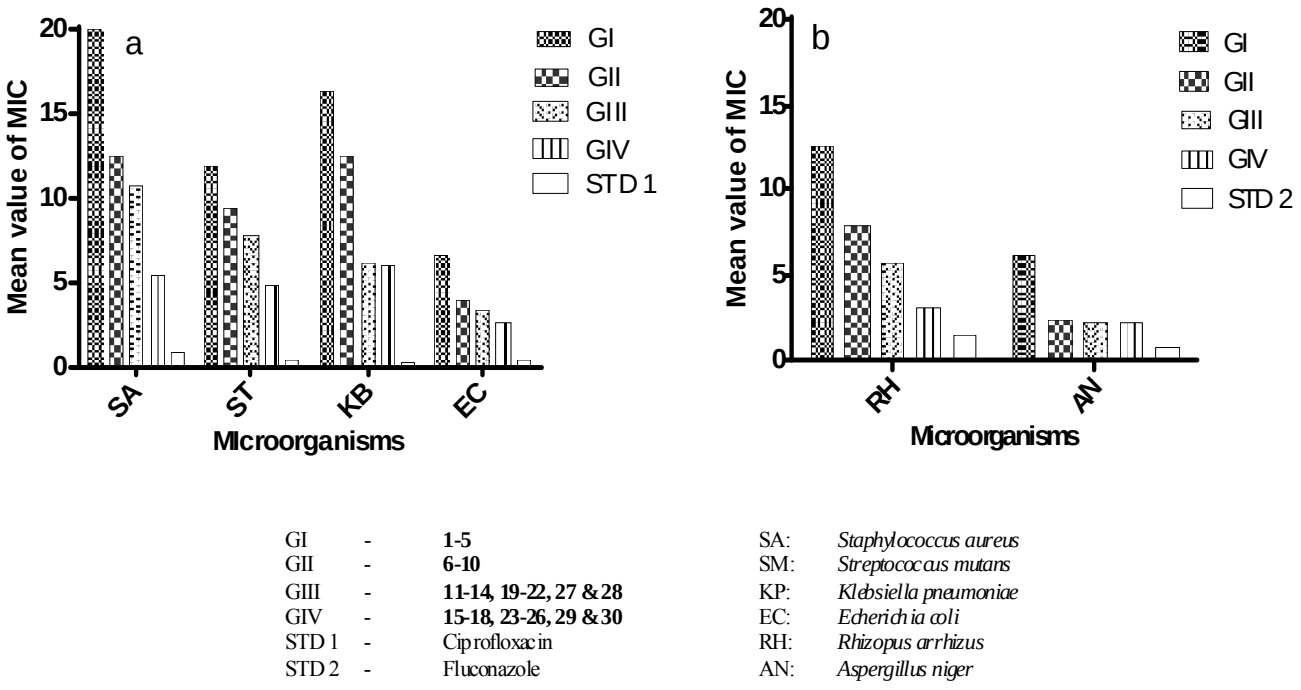
Compd. No	1	2	3	4	5	6	7	8	9	10
Z	$-NH_2$	$-NH_2$	$-NH_2$	$-NH_2$	$-NH_2$	$-N(CH_3)_2$	$-N(CH_3)_2$	$-N(CH_3)_2$	$-N(CH_3)_2$	$-N(CH_3)_2$
R	$-C_6H_5$	$-C_6H_4$-Br(4)	$-C_6H_4$-NO_2(4)	$-C_6H_4$-CH_3(4)	$-COC_6H_5$	$-C_6H_5$	$-C_6H_4$-Br(4)	$-C_6H_4$-NO_2(4)	$-C_6H_4$-CH_3(4)	$-COC_6H_5$

Compd. No	11	12	13	14	15	16	17	18	19	20
Z	$-NH_2$	$-NH_2$	$-NH_2$	$-NH_2$	$-N(CH_3)_2$	$-N(CH_3)_2$	$-N(CH_3)_2$	$-N(CH_3)_2$	$-NH_2$	$-NH_2$
R	$-CH_2CH_3$	$-(CH_2)_2$-CH_3	$-(CH_2)_2$-CH_3	$-(CH_2)_3$-CH_3	$-CH_2CH_3$	$-(CH_2)_2$-CH_3	$-(CH_2)_3$-CH_3	$-(CH_2)_4$-CH_3	$-CH_2$-CH_2Br	$-(CH_2)_2$-CH_2Br

Compd. No	21	22	23	24	25	26	27	28	29	30
Z	$-NH_2$	$-NH_2$	$-N(CH_3)_2$	$-N(CH_3)_2$	$-N(CH_3)_2$	$-N(CH_3)_2$	$-NH_2$	$-NH_2$	$-N(CH_3)_2$	$-N(CH_3)_2$
R	$-(CH_2)_3$-CH_2Br	$-(CH_2)_4$-CH_2Br	$-CH_2$-CH_2Br	$-(CH_2)_2$-CH_2Br	$-(CH_2)_3$-CH_2Br	$-(CH_2)_4$-CH_2Br	$-OCOCH_2CH_3$	$-CH=CH_2$	$-OCOCH_2CH_3$	$-CH=CH_2$

Table 1. Physical data of the synthesized compounds (**1-30**).

Compd. No	MF	Colour	Yield (%)	MP (°C)
1.	$C_{12}H_{13}BrN_2$	Colourless	81	165-166
2.	$C_{12}H_{12}Br_2N_2$	Pale yellow	85	230-232
3.	$C_{12}H_{12}BrN_3O_2$	Yellow	83	110-112
4.	$C_{13}H_{15}BrN_2$	Pale Yellow	80	222-224
5.	$C_{13}H_{13}BrN_2O$	Pale yellow	92	122-124
6.	$C_{14}H_{17}BrN_2$	Yellow	82	150-154
7.	$C_{14}H_{16}Br_2N_2$	Colourless	80	262-264
8.	$C_{14}H_{16}BrN_3O_2$	Yellow	84	90-91
9.	$C_{15}H_{19}BrN_2$	Pale Yellow	80	136-138
10.	$C_{15}H_{17}BrN_2O$	Yellow	90	214-216
11.	$C_8H_{13}BrN_2$	Pale Yellow	78	102-104
12.	$C_9H_{15}BrN_2$	Colourless	80	112-114
13.	$C_{10}H_{17}BrN_2$	Pale Yellow	76	104-106
14.	$C_{11}H_{19}BrN_2$	Yellow	74	118-120
15.	$C_{10}H_{17}BrN_2$	Colourless	78	106-108
16.	$C_{11}H_{19}BrN_2$	Yellow	73	114-116
17.	$C_{12}H_{21}BrN_2$	Colourless	80	94-96
18.	$C_{13}H_{23}BrN_2$	Yellow	78	106-108
19.	$C_8H_{12}Br_2N_2$	Colourless	87	58-60
20.	$C_9H_{14}Br_2N_2$	Colourless	91	263-264
21.	$C_{10}H_{16}Br_2N_2$	Colourless	92	236-238
22.	$C_{11}H_{18}Br_2N_2$	Colourless	93	185-186
23.	$C_{10}H_{16}Br_2N_2$	Colourless	88	68-70
24.	$C_{11}H_{18}Br_2N_2$	Colourless	90	258-260
25.	$C_{12}H_{20}Br_2N_2$	Yellow	92	235-237
26.	$C_{13}H_{22}Br_2N_2$	Colourless	94	187-189
27.	$C_9H_{13}BrN_2O_2$	Yellow	66	220-222
28.	$C_8H_{11}BrN_2$	Pale yellow	55	180-182
29.	$C_{11}H_{17}BrN_2O_2$	Yellow	69	208-210
30.	$C_{10}H_{15}BrN_2$	Pale yellow	53	115-120



GI	-	**1-5**
GII	-	**6-10**
GIII	-	**11-14, 19-22, 27 & 28**
GIV	-	**15-18, 23-26, 29 & 30**
STD 1	-	Ciprofloxacin
STD 2	-	Fluconazole

SA:	*Staphylococcus aureus*
SM:	*Streptococcus mutans*
KP:	*Klebsiella pneumoniae*
EC:	*Echerichia coli*
RH:	*Rhizopus arrhizus*
AN:	*Aspergillus niger*

Figure 1. Graph showing relation between the mean value of MIC of compounds 1-30 against bacterial (a) & fungal (b) microorganisms.

ANTIMICROBIAL ACTIVITY:

The minimum inhibitory concentration (MIC) assay of the 4-amino / dimethylamino-1-aryl / alkylpyridinium bromides (Group I, II, III & IV) showed a significant activity against all the mentioned pathogenic organisms **(Figure 1).**

Antibacterial Activity:

Pyridinium bromides (Group III) with amino moiety and alkyl side chain displayed excellent activity against both Gram positive and Gram negative bacteria at the low range of MIC value (25 -0.39 µg/mL). In addition , the same (Group III) compounds with the substitution of bromine atom at the end of the alkyl side chain displayed strong inhibitory action against both of the Gram negative bacteria *Escherichia coli* and *Klebesilla pneumoniae* (MIC range 25-0.39 µg/mL). The compounds (Group IV) with dimethylamino moiety bearing substitution of bromine at the end of the aliphatic side chain exerted remarkable activity against *Escherichia coli* (6.25-0.39 µg/mL) and promising activity against *Staphylococcus aureus* (12.5 - 0.39 µg/mL).

Antifungal Activity:

Investigation on antifungal screening revealed that the synthesized compounds showed variable degree of inhibition against the tested fungi. Pyridinium bromides (Group III & IV) with amino / dimethylamino moiety bearing alkyl side chain exhibited higher inhibitory effect (6.25 -0.39 µg/mL) than others (Group I & II) against *Rhizopus arrhizus.* Pyridinium bromides (Group III) with dimethylamino moiety containing aliphatic side chain displayed excellent inhibition against *Aspergillus niger* (6.25-0.39 µg/mL). The synthesized compounds with aryl side chain bearing amino and dimethylamino moiety (Group I & II) showed substantial activity against *Aspergillus niger* (12.5 -0.78 µg/mL).

4-Amino / dimethylamino-1-alkylpyridinium bromides (Group III & IV) have showed a good deal of activity than 4-amino / dimethylamino-1-arylpyridinium bromides (Group I & II). It is worth noting that the presence of a polar amino substituted pyridinium head group and the long liphophilic carbon chain could give rise to surfactant like activity. This surfactant like character may be helpful in achieving successful penetration into the lipid cell membrane and better biological activity for the compounds [6].In addition, it was proved that the factors such as molecular hydrophobicity [22,23] and electron density of the pyridinium nitrogen atom [24,25] control their antimicrobial activity.

CONCLUSION

This study clearly shows that quaternary 4-amino / dimethylamino-1-alkylpyridinium bromides are not only active against Gram negative, Gram positive bacteria and also active against opportunistic pathogenic fungi ultimately, these compounds have potential to be explored as a broad spectrum antimicrobial agent. These compounds are rather simple, easy to prepare in large scale and show interesting biological activity. Thus, there is a good scope for large-scale preparation of these compounds and application as both bactericide and fungicide.

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