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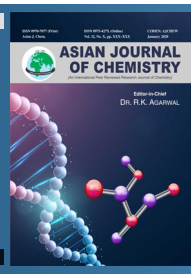

Design, Sustainable Synthesis, Characterization, Antimicrobial Evaluation and *in silico* ADMET Prediction of New Functionalized Imidazolium Based Ionic Liquids

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A series of sixteen new ionic liquids (ILs) bearing imidazolium moiety were designed and synthesized under sustainable and green conditions which were confirmed by analytical and spectral techniques using ^{1}H- & ^{13}C-NMR, FT-IR, mass and elemental analysis. A panel of clinically isolated strains was used for *in vitro* inhibitory antimicrobial activities screening of synthesized ionic liquids. The results of antimicrobial assay showed that some of synthesized ionic liquids showed moderate to good activity. Among these ILs, ionic liquids **3**, **4** and **5** (bearing alkyl chain with a phenyl group) significantly inhibited cell growth of strains. In this regard, these ionic liquids considered as promising antibacterial agents when compared with standard antibiotics. By encouraging *in vitro* antimicrobial screening, *in silico* ADMET evaluation has been performed and found excellent pharmacokinetic, bioavailability and toxicity profiles. Synthesized ionic liquids has found to be safe and non-toxic according to calculated *in vivo* computed LD_{50} values (2.49-2.80 mg/kg) for rat acute toxicity.

Keywords: Functionalized immidazolium, Ionic liquids, ADMET, Antimicrobial assay.

INTRODUCTION

With increasing human industrial activity and the growth of global energy demand, the pollution has become a global phenomenon that threatens the security and stability of environmental components [1-3]. Therefore, it was necessary to resort to policies and methods that prevent or reduce the negative effects on the environment resulting from chemical manufacturing processes and the creation of new environmentally friendly materials [4-7].

Volatile organic compounds (VOCs) are one of the sources of pollution involved in many chemical manufacturing processes, which in turn need to be replaced by vehicles that are less harmful to the environment [8-12]. Recently, ionic liquids [13,14] have emerged as environmentally friendly compounds and a successful alternative to VOCs because they possess many advantages [15-19]. The above properties in addition to other properties are what give ionic liquids a wide range of applications. Despite several positive properties of ionic liquids, they also have some negative characteristics such as high levels of toxicity in some of them, as well as the difficulty of biodegradation [20,21]. The toxicity of ionic liquids can be tested using bacteria because of the short life of their generations compared to other microorganisms. Indirectly, these tests (toxicity tests) opened up a new wide field to ionic fluids as antimicrobial agents [22].

The synthesis of ionic liquids may use traditional techniques or green technologies. When using conventional techniques or methods, they require high power consumption, longer time and no higher yields. But when using green technologies, they briefly consume less energy, much shorter time than their traditional counterparts and can get high-yield and more purity [23-25].

The main objective of this study is preparation of a new series of room temperature ionic liquids (RTILs) bearing imidazolium with a different functional groups. Also, alkyl chains

were selected at diverse lengths to learn the consequence of chain length on the properties and applications of the resulting ionic liquids. Taking into account the above, green technologies (microwave as an energy source) were used in the synthesis of these new compounds. Several principles of green chemistry have been applied in the process of synthesis, such as the principle of atomic economy, minimize use of hazardous solvents and waste disposal in a proper ways that do not cause pollution to the environment.

EXPERIMENTAL

The reagents and solvents were used to the minimum limit. Synthesized ionic liquids characterized by spectroscopic analysis. The mass spectrometer was used to measure the molecular mass of the compound and the resulting fragments. The mass spectra were measured with a Bruker MS-TOF-MS. The melting point was ignored and not measured, since all the ionic fluids prepared were RTILs. Microwave-assisted reactions were performed using microwave oven with a temperature controller (300 W) and a higher temperature limit (100 ºC) with nitrogen gas being used as a cooling agent if the temperature inside the reaction chamber increased.

Microwave irradiation synthesis (1-16): To a solution of 1-pentyl-1*H*-imidazole (1 eq.) in toluene, was added alkyl halides (1.1 eq) were exposed under irradiation for 20 min in closed vessel at 100 ºC. The completion of the reaction was marked by the separation of oil or solid from the initially obtained clear and homogenous mixture of 1-pentylimidazole and alkyl halide in toluene. Filtered or extracted the product and followed by washing with ethyl acetate. In each case, the IL/salt was finally dried at a reduced pressure.

Conventional synthesis (1-16): A solution of 1-pentylimidazole (1 eq.) in toluene, was added alkyl halide (1.1 eq.) were placed in a closed vessel at room temperature and stirred at 80 ºC for 18 h. Filtered the ionic liquid and washed with ethyl acetate. The ionic liquid was filtered again and then evaporated ethyl acetate to obtain pure ionic liquid.

Spectral data

1-Pentyl-3-phenethyl-1*H*-imidazol-3-ium bromide (1): Brown oil, yield = 88 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1560 (C=N), 2910 and 2980 (Ar-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.77 (t, 3H, CH_3), 1.11-1.21 (m, 4H, CH_2), 1.73 (quintet, 2H, CH_2), 3.17 (t, 2H, CH_2), 4.14 (t, 2H, CH_2), 4.57 (t, 2H, CH_2), 7.14 (m, 5H, Ar-H), 7.37 (d, 1H, Ar-H), 7.45 (d, 1H, Ar-H), 10.02 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.7 (CH_3), 21.9 (CH_2), 28.0, (CH_2), 29.8 (CH_2), 36.4 (CH_2), 49.9 (CH_2), 50.8 (CH_2), 121.9 (CH), 122.7 (CH), 127.7 (CH), 128.1 (CH), 128.8 (CH), 128.8 (CH), 129.0 (CH), 135.8 (C), 136.5 (CH). MS (M+)-Br^- 243.19 found for $C_{16}H_{23}N_2^+$.

1-Pentyl-3-(3-phenylpropyl)-1*H*-imidazol-3-ium bromide (2): Brown oil, yield = 86 % FT-IR (KBr, ν_{max}, cm^{-1}): 1560 (C=N), 2910 and 2980 (Ar-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.76 (t, 3H, CH_3), 1.20 (m, 4H, CH_2), 1.79 (quintet, 2H, CH_2), 2.17 (quintet, 2H, CH_2), 2.60 (t, 2H, CH_2), 4.19 (t, 2H, CH_2), 4.28 (t, 2H, CH_2), 7.06-7.13 (m, 5H, Ar-H), 7.43 (d, 1H, Ar-H), 7.49 (d, 1H, Ar-H), 10.23 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.8 (CH_3), 22.0 (CH_2), 28.1, (CH_2), 29.8 (CH_2), 31.6 (CH_2), 32.3 (CH_2), 49.4 (CH_2), 49.9 (CH_2), 122.2 (CH), 122.4 (CH), 126.3 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.9 (CH), 136.6 (CH), 139.7 (C); MS (M+)-Br^- 257.20 found for $C_{17}H_{25}N_2^+$.

3-(2-Chlorobenzyl)-1-pentyl-1*H*-imidazol-3-ium chloride (3): Brown oil, yield = 90 % FT-IR (KBr, ν_{max}, cm^{-1}): 1560 (C=N), 2910 and 2980 (Ar-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.82 (t, 3H, CH_3), 1.27 (m, 4H, CH_2), 1.86 (quintet, 2H, CH_2), 4.27 (t, 2H, CH_2), 5.70 (s, 2H, CH_2), 7.29-7.48 (m, 4H, Ar-H), 7.51 (d, 1H, Ar-H), 7.76 (d, 1H, Ar-H), 10.60 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.8 (CH_3), 22.0 (CH_2), 28.2, (CH_2), 29.9 (CH_2), 50.1 (CH_2), 50.5 (CH_2), 121.9 (CH), 122.3 (CH), 128.2 (CH), 130.0 (CH), 131.0 (CH), 131.2 (CH), 132.2 (CH), 134.0 (C), 137.5 (CH). MS (M+)-Cl^- 263.13 found for $C_{15}H_{20}ClN_2^+$.

1-Pentyl-3-(2-phenoxyethyl)-1*H*-imidazol-3-ium bromide (4): Brown oil, yield = 87 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1250 (C-O), 1600 (C=N), 2910 and 2980 (Ar-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.78 (t, 3H, CH_3), 1.17-1.23 (m, 4H, CH_2), 1.83 (quintet, 2H, CH_2), 4.23 (t, 2H, CH_2), 4.30 (t, 2H, CH_2), 4.80 (t, 2H, CH_2) 6.80, (d, 2H, Ar-H), 6.87 (t, 1H, Ar-H), 7.17 (t, 2H, Ar-H), 7.46 (d, 1H, Ar-H), 7.73 (d, 1H, Ar-H), 10.19 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.7 (CH_3), 21.9 (CH_2), 28.1, (CH_2), 29.8 (CH_2), 49.3 (CH_2), 50.1 (CH_2), 66.1 (CH_2), 114.4 (CH), 121.7 (CH), 121.9 (CH), 123.3 (CH), 128.15 (CH), 128.9 (CH), 129.6 (CH), 136.9 (CH), 157.4 (C-O); MS (M+)-Br^- 259.18 found for $C_{16}H_{23}N_2O^{+\cdot}$

1-Pentyl-3-(3-phenoxypropyl)-1*H*-imidazol-3-ium bromide (5): Brown oil, yield = 89 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1250 (C-O), 1600 (C=N), 2910 and 2980 (Ar-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.75 (t, 3H, CH_3), 1.19 (m, 4H, CH_2), 1.76 (quintet, 2H, CH_2), 2.35 (quintet, 2H, CH_2), 3.93 (t, 2H, CH_2), 4.17 (t, 2H, CH_2), 4.51 (t, 2H, CH_2), 6.74 (d, 2H, Ar-H), 6.82 (t, 1H, Ar-H), 7.14 (t, 2H, Ar-H), 7.46 (d, 1H, Ar-H), 7.54 (d, 1H, Ar-H), 10.20 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.7 (CH_3), 21.9 (CH_2), 28.1, (CH_2), 29.8 (CH_2), 29.9 (CH_2), 47.2 (CH_2), 50.0 (CH_2), 64.0 (CH_2), 114.3 (CH), 121.2 (CH), 122.1 (CH), 122.8 (CH), 129.5 (CH), 136.7 (CH), 158.0 (C-O); MS (M+)-Br^- 273.20 found for $C_{17}H_{25}N_2O^+$.

1-Pentyl-3-(2-methoxyethyl)-1*H*-imidazol-3-ium bromid (6): Brown oil, yield = 86 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1150 (C-O), 1550 (C=N), 2910 and 2950 (Ar-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.82 (t, 3H, CH_3), 1.27 (m, 4H, CH_2), 1.88, (m, 2H, CH_2), 3.30 (s, 3H, CH_3), 3.72 (m, 2H, CH_2), 4.24-4.26 (t, 2H, CH_2), 4.55 (t, 2H, CH_2), 7.46 (d, 2H, Ar-H), 7.59 (d, 2H, Ar-H), 10.08 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.8 (CH_3), 22.0 (CH_2), 28.2 (CH_2), 29.9 (CH_2), 49.7 (CH_2), 50.0 (CH_2), 59.0 (OCH_3), 70.25 (OCH_2), 121.7 (CH), 123.3 (CH), 136.7 (CH). MS (M+)-Br^- 197.16 found for $C_{11}H_{21}N_2O^+$

1-Pentyl-3-(3-methoxypropyl)-1*H*-imidazol-3-ium bromide (7): Brown oil, yield = 86 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1110 (C-O), 1560 (C=N), 2910 and 2950 (Al-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.79 (t, 3H, CH_3), 1.06 (t, 3H, CH_3), 1.24 (m, 4H, CH_2), 1.83 (quintet, 2H, CH_2), 3.42 (t, 2H, CH_2), 3.72 (t, 2H, CH_2), 4.25 (q, 2H, CH_2), 4.51 (t, 2H, CH_2), 7.49

(d, 2H, Ar-H), 7.56 (d, 2H, Ar-H), 10.06 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.8 (CH_3), 14.9 (CH_3), 22.0 (CH_2), 28.1 (CH_2), 29.9 (CH_2), 49.9 (CH_2), 50.0 (CH_2), 66.7 (OCH_2), 68.2 (OCH_2), 121.8 (CH), 123.3 (CH), 136.7 (CH); MS (M+)-Br^- 211.18 found for $C_{12}H_{23}N_2O^+$.

3-(Hydroxymethyl)-1-pentyl-1*H*-imidazol-3-ium bromide (8): Brown oil, yield = 85 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1580 (C=N), 2910 and 2950 (Ar-H), 3310 (O-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.86 (t, 3H, CH_3), 1.30 (m, 6H, CH_2), 1.89 (quintet, 2H, CH_2), 2.10 (quintet, 2H, CH_2), 3.58 (quintet, 2H, CH_2), 4.28 (t, 2H, CH_2), 4.49 (t, 2H, CH_2), 7.43 (d, 1H, Ar-H), 7.75 (d, 1H, Ar-H), 9.96 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.9 (CH_3), 22.0 (CH_2), 28.2 (CH_2), 29.9 (CH_2), 30.0 (CH_2), 32.6 (CH_2), 47.0 (CH_2), 50.0 (CH_2), 57.1 (CH_2O), 121.9 (CH), 123.0 (CH), 136.7 (CH). LCMS (M+)-Cl^- 211.18 found for $C_{12}H_{23}N_2O^+$.

3-(2-Hydroxyethyl)-1-pentyl-1*H*-imidazol-3-ium bromide (9): Dark brown oil, yield = 91 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1580 (C=N), 2910 and 2950 (Ar-H), 3310 (O-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.87 (t, 3H, CH_3), 1.32 (m, 4H, CH_2), 1.89 (quintet, 2H, CH_2), 3.87 (t, 2H, CH_2), 4.26 (t, 2H, CH_2), 4.49 (t, 2H, CH_2), 7.42 (d, 1H, Ar-H), 7.70 (d, 1H, Ar-H), 9.58 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.9 (CH_3), 22.0 (CH_2), 28.3 (CH_2), 29.8 (CH_2), 50.1 (CH_2) 52.2 (CH_2), 60.0 (CH_2-O), 121.7 (CH), 123.4 (CH), 136.3 (CH); MS (M+)-Br^- 169.13 found for $C_9H_{17}N_2O^+$.

3-(2-Ethoxy-2-oxoethyl)-1-pentyl-1*H*-imidazol-3-ium chloride (10): Brown oil, yield = 87 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1210 (C-O), 1550 (C=N), 1750 (C=O), 2850 and 2910 (Ar-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.71 (t, 3H, CH_3), 1.10-1.15 (m, 7H), 1.75 (quintet, 2H, CH_2), 4.06 (t, 2H, CH_2), 4.14 (q, 2H, CH_2), 5.34 (s, 2H, CH_2), 7.44 (d, 1H, Ar-H), 7.67 (d, 1H, Ar-H), 10.21 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.6 (CH_3), 13.9 (CH_3), 21.8 (CH_2), 28.0 (CH_2), 29.7 (CH_2), 49.9 (CH_2), 50.0 (CH_2), 62.6 (CH_2), 121.6 (CH), 124.0 (CH), 137.9 (CH), 166.2 (C=O); MS (M+)-Cl^- 225.16 found for $C_{12}H_{21}N_2O_2^+$.

3-(3-Ethoxy-3-oxopropyl)-1-pentyl-1*H*-imidazol-3-ium chloride (11): Brown oil, yield = 88 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1150 (C-O), 1550 (C=N), 1710 (C=O), 2910 and 2950 (Ar-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.80 (t, 3H, CH_3), 1.15 (t, 3H, CH_3), 1.26 (m, 4H, CH_2), 1.85 (quintet, 2H, CH_2), 2.18 (quintet, 2H, CH_2), 2.36 (t, 2H, CH_2), 4.03 (q, 2H, CH_2), 4.26 (t, 2H, CH_2), 4.42 (t, 2H, CH_2), 7.52 (d, 1H, Ar-H), 7.60 (d, 1H, Ar-H), 10.25 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.8 (CH_3), 14.1 (CH_3), 22.0 (CH_2), 25.6 (CH_2), 28.2 (CH_2), 29.9 (CH_2), 30.5 (CH_2), 48.8 (CH_2), 50.0 (CH_2), 60.8 (CH_2), 122.3 (CH), 122.5 (CH), 136.7 (CH), 172.1 (C=O); MS (M+)-Cl^- 225.16 found for $C_{14}H_{25}N_2O_2^+$.

3-(5-Ethoxy-5-oxopentyl)-1-pentyl-1*H*-imidazol-3-ium bromide (12): Brown oil, yield = 90 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1283 (C-O), 1639 (C=N), 1740 (C=O), 2890 and 2967 (Al-H), 3078 (Ar-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.69 (t, 3H, CH_3), 1.03 (t, 3H, CH_3), 1.14 (m, 4H, CH_2), 1.47 (quintet, 2H, CH_2), 1.74-1.83 (m, 4H, CH_2), 2.18 (t, 2H, CH_2), 3.90 (q, 2H, CH_2), 4.15 (t, 2H, CH_2), 4.24 (t, 2H, CH_2), 7.47 (d, 1H, Ar-H), 7.56 (d, 1H, Ar-H), 10.14 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.7 (CH_3), 14.0 (CH_3), 21.2 (CH_2), 21.9 (CH_2), 28.0 (CH_2), 29.4 (CH_2), 29.8 (CH_2), 33.1 (CH_2), 49.4 (CH_2), 49.8 (CH_2), 60.3 (CH_2), 122.3 (CH), 122.5 (CH), 136.4 (CH), 172.7 (C=O). MS (M+)-Br^- 267.21 found for $C_{15}H_{27}N_2O_2^+$.

3-(6-Ethoxy-6-oxohexyl)-1-pentyl-1*H*-imidazol-3-ium bromide (13): Brown oil, yield = 90 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1550 (C=N), 2220 (CN), 2910 and 2950 (Ar-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.71 (t, 3H, CH_3), 1.08 (t, 3H, CH_3), 1.16 (m, 6H, CH_2), 1.49 (quintet, 2H, CH_2), 1.78-1.80 (m, 4H, CH_2), 2.13-2.17 (m, 2H, CH_2), 3.91-3.93 (q, 2H, CH_2), 4.18-4.22 (m, 4H, CH_2), 7.48 (d, 1H, Ar-H), 7.53 (d, 1H, Ar-H), 10.15 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.7 (CH_3), 14.1 (CH_3), 21.9 (CH_2), 23.9, (CH_2), 25.4 (CH_2), 28.1 (CH_2), 29.8 (CH_2), 29.9 (CH_2), 33.7 (CH_2), 49.5 (CH_2), 49.8 (CH_2), 60.2 (CH_2), 122.3 (CH), 122.4 (CH), 136.5 (CH), 173.2 (C=O). MS (M+)-Br^- 281.22 found for $C_{16}H_{29}N_2O_2^+$.

3-(4-Acetoxybutyl)-1-pentyl-1*H*-imidazol-3-ium bromide (14): Dark brown oil, yield = 87 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1210 (C-O), 1550 (C=N), 1720 (C=O), 2910 and 2950 (Ar-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.83 (t, 3H, CH_3), 1.28 (m, 4H, CH_2), 1.66 (quintet, 2H, CH_2), 1.88 (quintet, 2H, CH_2), 1.98 (m, 5H, CH_3, CH_2), 4.04 (t, 2H, CH_2), 4.28 (t, 2H, CH_2), 4.41 (t, 2H, CH_2), 7.50 (d, 1H, Ar-H), 7.64 (d, 1H, Ar-H), 10.36 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.8 (CH_3), 21.0 (CH_3), 22.0 (CH_2), 25.3, (CH_2), 27.1 (CH_2), 28.2 (CH_2), 29.9 (CH_2), 49.4 (CH_2), 50.0 (CH_2), 63.2 (CH_2), 122.2 (CH), 122.5 (CH), 136.8 (CH), 171.06 (C=O). MS (M+)-Br^- 253.19 found for $C_{14}H_{25}N_2O_2^+$.

3-(3,5-Dinitrobenzoyl)-1-pentyl-1*H*-imidazol-3-ium chloride (15): Black oil, yield = 92 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1560 (C=N), 2910 and 2980 (Ar-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.83 (t, 3H, CH_3), 1.29 (m, 4H, CH_2), 1.88 (quintet, 2H, CH_2), 4.25 (t, 2H, CH_2), 7.19 (d, 1H, Ar-H), 7.46 (d, 1H, Ar-H), 9.07-9.21 (m, 4H, Ar-H; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.8 (CH_3), 22.0 (CH_2), 28.3, (CH_2), 30.0 (CH_2), 49.9 (CH_2), 120.3 (CH), 120.7 (CH), 122.2 (CH), 129.7 (CH), 134.8 (C), 135.0 (C), 148.6 (C), 164.1 (C=O). MS (M+)-Cl^- 333.12 found for $C_{18}H_{17}ClN_4O_5^+$.

3-(3-Cyanopropyl)-1-pentyl-1*H*-imidazol-3-ium chloride (16): Dark brown oil, yield = 89 %. FT-IR (KBr, ν_{max}, cm^{-1}): 1550 (C=N), 2220 (CN), 2910 and 2950 (Ar-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.87 (t, 3H, CH_3), 1.31 (m, 6H, CH_2), 1.91 (quintet, 4H, CH_2), 2.68 (t, 2H, CH_2), 4.32 (t, 2H, CH_2), 7.44 (d, 1H, Ar-H), 7.88 (d, 1H, Ar-H), 10.33 (s, 1H, Ar-H), ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.8 (CH_3), 14.5 (CH_3), 22.0 (CH_2), 26.3 (CH_2), 28.2 (CH_2), 29.8 (CH_2), 48.3 (CH_2), 50.2 (CH_2), 118.1 (C), 122.0 (CH), 123.1 (CH), 137.1 (CH), MS (M+)-Cl^- 220.11 found for $C_{12}H_{20}N_3^+$.

Antibacterial activity: Synthesized ionic liquids were tested against selected clinical pathogenic bacteria including Gram positive strains (*i.e. Staphylococcus aureus, Bacillus cereus* and *Bacillus amyloliquefaciens*) and Gram negative (*i.e. Escherichia coli*, *Acinetobacter baumannii*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa*). Bacterial strains were selected as being recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for antimicrobial susceptibility testing [26].

Antimicrobial activities for tested compounds have been primarily evaluated by determination of their ability to inhibit bacterial growth *via* inhibition zone (IZ) measurements, which was determined by agar disc diffusion method using bacterial strains cultured. Freshly 24 h subcultured bacterial strains were suspended in sterile distilled water and 0.1 mL was transferred and homogenously streaked onto the surface. Dry filter paper discs (6 mm i.d.) impregnated with 10 µg of tested compounds (1 µg/µL) were shifted on surface of the inoculated plates and left for 2 h at 4 ºC. Filter paper discs loaded sterile distilled water was used as a control. Plates were incubated for 24 h at 37 ºC and then, the diameter of the produced inhibition zones were measured (in mm). Antibacterial potentials were evaluated by determination of the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) as being described by CLSI microdilution assay [27]. A stock test compound concentration of 512 µg/mL in Mueller-Hinton broth (Becton Dickinson, USA) [28] was prepared and two-fold serially diluted in a 96-well microtiter plate. Aliquots of 100 µL of bacterial suspensions prepared in Muller-Hinton broth (1×10^8 CFU/mL) were mixed with 100 µL serially diluted tested compounds in microtiterplate [29]. Uninoculated Muller-Hinton broth in wells was used as a control sample. The MIC was defined as the lowest concentration of test compound producing no visible growth after 24 h incubation of microtiter plates at 37 ºC. The MBC on the other hand, was determined by transferring aliquots from wells containing no growth onto nutrient agar plates and tested for colony formation after 24 h incubation at 37 ºC. MIC and MBC values were determined in a range from 0 to 256 µg/mL [27] and evaluated in comparison with four standard antibiotics; ampicillin, rifampicin, clindamycin and kanamycin. All experiments were performed in triplicate.

RESULTS AND DISCUSSION

By encouraging our previous research work, which deals in synthesis of ionic liquids (ILs) bearing diversity of functional groups, herein we report on a combination of ILs based on imidazolium moiety **1-16** by using conventional radiation and microwave irradiation methods **(Scheme-I)**.

At first, the known pentyl-1H-imidazolium based derivatives **1**, **2** and **3** was synthesized by reaction of 1-pentylimidazole with (2-bromoethyl)benzene, (3-bromopropyl)benzene and 1-chloro-2-(chloromethyl)benzene in toluene at 80 ºC for 18 h when we using conventional radiation methods, and also in toluene at 100 ºC for 20 min when used microwave irradiation.

The quaternization reaction has taken place to give the resultant imidazolium halides **1**, **2** and **3** by attacking nitrogen lone pair on alkyl halides and found 74-90 % yield as oils (Table-1). Microwave irradiation reactions have also been used in the present work for the synthesis of 1-pentyl-1*H*-imidazolium-based ILs **1**, **2** and **3**. Reactants were exposed under microwave irradiation in a closed vessel. Monitoring of ILs formation was confirmed when two phase formed because of ILs are insoluble in toluene. Short period was required under irradiation for completion and good yields were achieved.

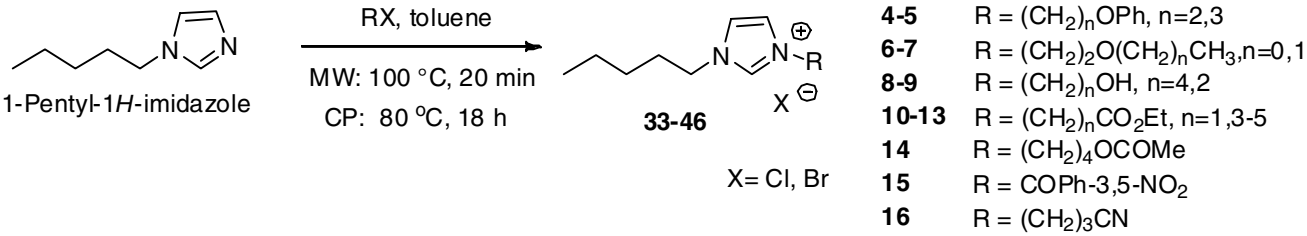
TABLE-1
PREPARATION OF IONIC LIQUIDS (**1–16**) USING CONVENTIONAL PROCEDURE (CP) AND MICROWAVE IRRADIATION (MW)

Compd.	RX	Yield (%) of the quaternization step	
		CP_1 [a]	MW [b]
1	$C_6H_5(CH_2)_2Br$	75	88
2	$C_6H_5(CH_2)_3Br$	74	86
3	Cl-2-Ph CH_2Cl	77	90
4	$PhO(CH_2)_2Br$	73	87
5	$PhO(CH_2)_3Br$	75	89
6	$CH_3O(CH_2)_2Br$	72	86
7	$CH_3CH_2O(CH_2)_2Br$	72	86
8	$OH(CH_2)_4Cl$	68	85
9	$OH(CH_2)_2Br$	77	91
10	EtO_2CCH_2Cl	75	87
11	$EtO_2C(CH_2)_3Cl$	70	88
12	$EtO_2C(CH_2)_4Br$	73	90
13	$EtO_2C(CH_2)_5Br$	76	90
14	$CH_3CO_2(CH_2)_4Cl$	75	87
15	NO_2-3,5-PhCOBr	80	92
16	$NC(CH_2)_3Cl$	76	89

[a]Time (18 h), Temperature (80 °C) in toluene; [b]Time (20 min), Temperature (100 °C) in toluene

3-(2-chlorobenzyl)-1-pentyl-1*H*-imidazol-3-ium chloride **3** was chosen for explaining spectral data to establish the structure of IL **1-3**.

1-Pentyl-1*H*-imidazole with 1-chloro-2-(chloromethyl)-benzene (**3**) confirmed in ^{1}H NMR, methyl protons of pentyl group was arise as triplet at 0.83 ppm and one multiplet around 1.27 ppm assigned for methylene protons of $CH_3CH_2CH_2$ and one quintet around 1.86 ppm was assign for methylene protons



Scheme-I

of $CH_2CH_2CH_2$ and one triplet around 4.27 ppm due to the methylene protons of N-CH_2CH_2 and one signals around 5.70 ppm assign for methylene protons of N-CH_2Ph . The ^{1}H NMR spectrum for compound **3** contained also two doublets signals at 7.51, 7.76 and singlet at 10.60 ppm for imidazolium ring protons. Signal at 7.29-7.48 ppm was observed for aromatic protons of the pendent aromatic rings in IL **3**.

Carbon signal for imidazolium ring in ^{13}C NMR spectrum of IL **3** was arise at range of δ_C 121-137 ppm. Furthermore, corresponding signals to CH_2 and CH_3 groups in ^{13}C NMR spectrum arise with usual chemical shifts and confirmed without doubt by APT ^{13}C-NMR. Absorption band 2910 and 2980 cm^{-1} in FT-IR designate for Ar-H. Furthermore, C=N group shown peak at 1560 cm^{-1}, which also confirmed by mass spectrum with desired mass 263.13 *m/z* as $[M-Cl]^+$ ions. In the same manner, rest of new RTILs were prepared **(Scheme-I)**.

Structures of the desired ILs **4-7**, containing an ether as functional group (Table-1) were elucidated. The IL containing 1-pently-3-(3-phenoxypropyl) moiety **(5)** was chosen for explaining spectral data to verify the quaternization reaction of 1-pentyl-1*H*-imidazole with (3-bromopropoxy)benzene. ^{1}H-NMR analysis has established structure of ILs **5**. Quintet signal at 2.35 ppm arises for methylene protons of $CH_2CH_2CH_2O$ and two triplets around 3.93, 4.17 and 4.51 due to the methylene protons of two N-CH_2CH_2, and methylene protons of OCH_2CH_2. ^{1}H NMR spectrum of **5** has shown signals as doublet at 7.46, 7.54 and a singlet 7.92 ppm for imidazolium protons. Aromatic protons of IL **5** shown signal at 6.82-7.14 ppm. The ^{13}C NMR spectrum of IL **5** shows signal in the range of 114-136 ppm owing to aromatic region. Furthermore, CH_2 and CH_3 groups showed standard chemical shifts in ^{13}C NMR, which further established without doubt by DEPT-135 NMR. Characteristic band at 1250 cm^{-1} in FT-IR assign for etheric C-O and molecular ion peak $[M-Br]^+$at 273.20 *m/z* established structure of IL **5**.

Present communication is focused also on the synthesis of ionic liquids based imidazolium derivatives bearing an alkyl chain having alcohol functionality (**Scheme-I**). Previous attention for reward of using microwave irradiation was mentioned (Table-1). The success of the alkylation was verified using spectral data of the resulted ILs **8** & **9**. The ionic liquid, 3-(4-hydroxy-butyl)-1-pentyl-1*H*-imidazol-3-ium chloride (**8**) was chosen for confirmation. However, previously discussed ILs **3** and **5** have some parts of IL **8**. From the H-NMR spectrum of IL **8** two quintet around 1.89 and 2.10 ppm assigned to methylene protons of N-CH_2CH_2 CH_2 and O-CH_2CH_2 CH_2 and two triplets around 3.58 and 4.49 assigned for methylene protons of N-CH_2CH_2 and O-CH_2CH_2 and one brad singlet around 4.63 ppm owing to the protons of CH_2OH. Proton spectrum for IL **8** contained also two doublets signals at 7.43, 7.75 and singlet at 9.96 ppm assigned to imidazolium ring protons.

In APT ^{13}C-NMR spectrum of IL **8**, there are seven signs indicating the number CH_2 of the resulting composite between δ_C 22 to 57 ppm. The CH_3 groups have found at their usual chemical shifts. Absorption band of IL **8** in FT-IR was attain at around 3310 cm^{-1} for characteristic hydroxyl group and molecular ion peak $[M-Cl]^+$ at 211.18 *m/z* established the structure IL **8**.

In continuation to work on the synthesis of ILs with different functional group, with improved reaction conditions. In this article, a combination of imidazolium-based ILs newly enhanced with alkyl chain with an ester functional is also reported. Corresponding imidazolium halides ILs **10-14** has been synthesized by quaternization reaction with 70-90% yield (**Scheme-I**). These reactions were carried out using traditional techniques and green techniques (microwave) as an energy source. Again, the results were in favour of green technologies in terms of shorter time, less energy use and high yields (Table-1).

From spectral analysis data, structures of ionic liquids (ILs) **10-14** could be established. Ionic liquid, 3-(5-ethoxy-5 oxo-pentyl)-1-pentyl-1*H*-imidazol-3-ium bromide (**13**) has been chosen from ILs **10-14** for explaining spectral data.

However, previously discussed ILs **3** contains some parts of IL **13**, thus only the new peaks are discussed. Methyl protons of OCH_2CH_3 group in IL **13** has shown the characteristic own triplet respectively at 1.03 ppm, and two quintet around 1.47 and 1.74 due to the methylene protons of $CH_2CH_2CH_2$ and two triplets respectively at 2.18 ppm for methylene protons of $COCH_2CH_2$, at 4.24 ppm assigned to methylene protons of N-CH_2CH_2. One quartet due to the methylene protons of OCH_2CH_3 appeared around 3.90 ppm. IL **13** also contained two doublets signals at 7.47, 7.56 and one singlet around 10.14 ppm.

In ^{13}C-NMR, IL **13** has shown signal around δ_C 172 ppm for characteristic carbonyl group. The CH_2 and CH_3 of ester group (OCH_2CH_3) have been observed at their standard chemical shifts. Signal at around 50 ppm assigned for corresponding NCH_2CO which was also established by APT ^{13}C-NMR. Standard signal was also found for five other methylene groups.

FT-IR spectrum of IL **13** showed a band around 1283 cm^{-1} for corresponding C-O. Also contained an absorption band at 1639 (C=N) and 1740 (C=O). Furthermore, due to Ar-H groups a peak at 2890, 2967 and 3078 cm^{-1} were found which also supported by desired mass ions $[M-Br]^+$ 267.21 *m/z*.

^{1}H NMR spectrum of IL **15** has shown one triplet around 4.25 ppm assigned for methylene protons of N-CH_2CH_2. Ionic liquid **15** contained also two doublets signals at 7.19, 7.46 and a singlet at 9.04 ppm. Signal at 9.07-9.24 ppm has assigned for phenyl protons of the pendent aromatic rings and band at 1690 cm^{-1} arised to corresponding carbonyl group in FT-IR which was further supported by molecular ion peak $[M-Cl]^+$ at 333.12 *m/z* in mass spectra. The ^{13}C NMR of IL **15** bearing aromatic carbons including imidazolium ring have showed signals at 120-135 ppm. Additionally, carbon of the carbonyl group appeared around δ_C 164.1 ppm. The ^{13}C NMR spectrum and DEPT-135 NMR of IL **15** have confirmed without doubt and shown standard signals corresponding to CH_2 and CH_3 groups.

From ^{1}H NMR spectrum of IL **16**, one quintet around 1.91 ppm due to the methylene protons of $CH_2CH_2CH_2$ and two triplets around 2.68, 4.32 due to the methylene protons of N-CH_2CH_2 . Two doublets at 7.44, 7.88 and one singlet at 10.33 ppm has been assigned for protons of imidazolium. In ^{13}C NMR spectrum of IL **16**, the carbon of cyano group appeared around δ_C 118 ppm. The CH_2 and CH_3 groups have been observed at their standard chemical shifts. A characteristic band at 2220

cm^{-1} confirmed presence of CN group which also supported by molecular ion peak $[M\text{-}Cl]^+$ at 220.12 *m/z* in mass spectra.

Antibacterial activity: It has been recently reported that ILs have promising biological and antimicrobial activities [30-32]. In this study, another set of newly synthesized ILs have significant antibacterial activities against pathogenic bacteria with varying degrees. Except for ILs **6**-**9**, **10**-**12** and **14**, all other synthesized compounds were very potent against all bacterial strains with IZ values ranging from 10 to 30 mm and MIC values found for some compounds (Table-2). Based on MIC values, it is assumed that ILs **3**, **4** and **5** demonstrated good activity profile against tested pathogenic bacteria except for *P. aeruginosa* (Table-2). The ILs-sensitive bacterial strains are known for their frequent development of antimicrobial drug resistance [33-35]. In this regard, ILs **3**, **4** and **5** might be capable antibacterial agents when compared with standard antibiotics.

Ionic liquid **4** exhibited a remarkable activity against *S. aureus* and *B. amyloliquefaciens* with MIC value 8 µg/mL. Further, it can be concluded that synthesized IL **4** has shown good MIC values (16 µg/mL) against *B. cereus* and *K. pneumonia* and 32 µg/mL for *E. coli* and *A. baumannii*. Ionic liquid **5** has also shown potent activity with good MIC values (4 µg/mL) against *B. amyloliquefaciens* and 8 µg/mL for *S. aureus* and *B. cereus*. It also showed a fair MIC value 32 µg/mL for *A. baumannii*

TABLE-2
ANTIMICROBIAL ACTIVITY OF IONIC LIQUIDS (**1–16**) EXPRESSED AS IZ (mm), MIC AND MBC (µg/mL)[a]

ILs	*S. aureus*			*B. cereus*			*B. amyloliquefaciens*			*E. coli*		
	IZ (mm)	MIC (µg/mL)	MBC (µg/mL)	IZ (mm)	MIC (µg/mL)	MBC (µg/mL)	IZ (mm)	MIC (µg/mL)	MBC (µg/mL)	IZ (mm)	MIC (µg/mL)	MBC (µg/mL)
1	30	8	8	15	64	64	22	16	32	11	128	128
2	23	16	16	22	32	32	28	8	8	18	16	32
3	21	32	32	21	8	16	29	8	8	12	64	128
4	28	8	8	23	16	16	27	8	8	14	32	32
5	25	8	8	23	8	16	30	4	8	12	64	64
6	0	-	-	0	-	-	0	-	-	0	-	-
7	9	> 256	> 256	0	-	-	8	> 256	> 256	0	-	-
8	21	64	64	0	-	-	0	-	-	0	-	-
9	0	-	-	0	-	-	0	-	-	0	-	-
10	0	-	-	0	-	-	0	-	-	0	-	-
11	6	> 256	> 256	0	-	-	0	-	-	0	-	-
12	11	128	128	8	> 256	> 256	9	> 256	> 256	8	> 256	> 256
13	14	64	128	9	128	128	10	128	128	7	> 256	> 256
14	6	> 256	> 256	0	-	-	8	> 256	> 256	0	-	-
15	0	-	-	8	128	128	19	64	128	18	32	64
16	9	> 256	> 256	0	-	-	15	64	128	0	-	-
Amp	17	16	16	7	64	64	25	8	8	0	-	-
RD	40	4	4	15	16	32	17	16	16	0	-	-
DA	39	4	4	21	8	8	24	8	8	0	-	-
K	21	16	16	14	32	32	30	8	8	19	16	16

ILs	*A. baumannii*			*K. pneumonia*			*P. aeruginosa*		
	IZ (mm)	MIC (µg/mL)	MBC (µg/mL)	IZ (mm)	MIC (µg/mL)	MBC (µg/mL)	IZ (mm)	MIC (µg/mL)	MBC (µg/mL)
1	10	128	128	9	128	128	0	-	-
2	14	32	32	10	128	128	0	-	-
3	12	64	128	15	16	16	8	> 256	> 256
4	13	32	32	14	16	16	8	> 256	> 256
5	13	32	64	11	64	64	7	> 256	> 256
6	0	-	-	0	-	-	0	-	-
7	0	-	-	8	> 256	> 256	7	> 256	> 256
8	0	-	-	7	> 256	> 256	0	-	-
9	0	-	-	0	-	-	0	-	-
10	0	-	-	0	-	-	0	-	-
11	0	-	-	0	-	-	0	-	-
12	7	> 256	> 256	8	> 256	> 256	0	-	-
13	7	> 256	> 256	8	> 256	> 256	0	-	-
14	0	-	-	7	> 256	> 256	7	> 256	> 256
15	8	> 256	> 256	7	> 256	> 256	0	-	-
16	0	-	-	9	128	128	7	> 256	> 256
Amp	0	-	-	0	-	-	0	-	-
RD	13	32	32	7	64	64	13	32	64
DA	0	-	-	0	-	-	0	-	-
K	0	-	-	0	-	-	22	16	16

[a]Results are the mean of three repetitions.

and a moderate activity (64 µg/mL) against *E. coli* and *K. pneumonia*. Next to **ILs 4** and **5** comes **IL 3**, which was efficient compound with wide profile. **IL 3** has shown good values (8 µg/mL) against *B. cereus* and *B. amyloliquefaciens* and 16 µg/mL for *K. pneumonia* and 32 µg/mL for *S. aureus*. Antimicrobial screening results has demonstrated prominent impact (64 µg/mL) against *E. coli* and *A. baumannii*. *K. pneumonia*, *A. baumannii*and *E. coli* are known to acquire simultaneous resistance mechanisms and cause nosocomial infections [36-38]. Consequently, **ILs 3**, **4** and **5**, which do possess remarkable antibacterial activities.

Ionic liquid **1** was effective with MIC value of 8 µg/mL against *S. aureus*. Results has demonstrated 32 and 64 µg/mL value for *B. amyloliquefaciens* and *B. cereus*, respectively. It showed a week antibacterial activities against *Escherichia coli*, *Acinetobacter baumannii*, *Klebsiella pneumonia* with MIC values of 128 µg/mL. *S. aureus* in particular is a problematic clinical pathogen due to its frequent development of multidrug resistance and wide spread of nosocomial infections. Methicillin resistant *S. aureus* (MRSA) and vancomycin resistant strains (VRSA) are the most common pathogens that raised up the public concern [39]. Beside Methicillin and vancomycin resistance, *S. aureus* strains have recently acquired multiple resistance to a wide range of antibiotics including β-lactam ones like ampicillin [40]. In this regard, development of newly synthesized antimicrobial agents is a must. Newly synthesized **ILs 1, 4** and **5** showed a remarkable antibacterial potency against *S. aureus* with MIC value of 8 µg/mL, which makes them a convenient candidate as antibacterial agent against *S.aureus* compared to ampicillin and kanamycin antibiotics.

In addition, IL **2** showed a potential antibacterial activity against *B. amyloliquefaciens*, *S. aureus*, *E. coli* and *A. baumannii* with MIC values of 8, 16, 32 and 64 µg/mL, respectively. Ionic liquids **8** and **13** showed a modest to week activities (MIC 64 to 128 µg/mL) against *S. aureus* and *B. amyloliquefaciens*. Ionic liquid **16** showed a moderate to week antibacterial activities against *B. amyloliquefaciens* and *K. pneumonia* only with estimated MIC values of 64 and 128 µg/mL, respectively. Ionic liquids **6**, **7**, **9-12** and **14** had no antibacterial activities. Newly synthesized (ILs **3**, **4** and **5** in particular) represent a promising compounds and attribute this without ambiguity to the presence of phenoxy or chloro-substituted phenyl groups [26,41].

In drug designing and development process, to predict the bioavailability of lead drug, Lipinski's rule of five is generally used. It is assumed that those compounds follow Lipinski's rule of five, will likely be orally active. Drug property descriptor such as molecular weight (MW) and topological surface area (TPSA) [42] were calculated and tabulated in Table-3. Drug like molecules usually have molecular weight less than 500 daltons [43]. All the ionic liquids did not violate any of the Lipinski's rules of five and were expected to be orally active. It seems that all ionic liquids are to be easily diffused, absorbed and transported because have molecular weight was found to be less than 500. TPSA of synthesized derivatives were observed in the range of 3.24-111 Å and are well below the limit of 160 Å. Rest of calculated properties is in good agreement and qualifies as drug candidate. Prediction results of molecular properties (TPSA, GPCR ligand and ICM) are demonstrated in Table-3 and are in good agreement.

Good liphophilicity is required for permeability across the cell membrane and depend on Log P value. Liphophilc potency calculated by Log P that measures the potency of any drug. Low Log P value means that high liphophilicity and resultant cross the cell membrane. Log P value (octanol/water partition coefficient) were calculated and found to be in acceptable range according to Lipinski's rule which are shown in Table-5. All ionic liquid has shown Log P value less than 5, except compound **2** which suggested high membrane permeability across the cell.

In silico toxicity study is a necessary parameter to find out drug to be safe for administration. To confirm the toxicity nature of synthesized ionic liquids, *in silico* mutagenicity and carcinogenicity has been calculated and tabulated in Table-5. Thus, all compounds are safe for carcinogenicity and mutag-

TABLE-3
in silico PREDICTION OF PHYSICO-CHEMICAL CALCULATIONS OF IONIC LIQUIDS (**1-16**)

Compd.	m.w. (g/mol)	Physico-chemical properties				Drug likeness					
		TPSA	O/NH	VIOL	VOL	GPC	ICM	KI	NRL	PI	EN
1	323	3.24	0	0	279	0.09	0.04	-0.19	-0.05	-0.05	0.09
2	337	3.24	0	1	295	0.16	0.06	-0.12	0.04	0.02	0.12
3	299	3.24	0	0	271	0.03	-0.02	-0.20	-0.08	-0.15	-0.01
4	339	12.47	0	0	288	0.05	-0.05	-0.11	-0.07	-0.08	0.04
5	353	12.47	0	0	304	0.08	-0.05	-0.07	0.09	-0.05	0.05
6	277	12.47	0	0	233	-0.35	-0.20	-0.53	-0.53	-0.47	-0.15
7	291	12.47	0	0	250	-0.28	-0.14	-0.47	-0.39	-0.38	-0.10
8	247	23.47	1	0	244	-0.10	0.02	-0.32	-0.18	-0.23	0.10
9	263	23.47	1	0	215	-0.30	-0.09	-0.54	-0.48	-0.47	-0.03
10	261	29.54	0	0	247	-0.23	-0.10	-0.58	-0.30	-0.25	-0.09
11	289	29.54	0	0	281	-0.06	-0.05	-0.36	-0.08	-0.10	0.05
12	247	29.54	0	0	302	-0.03	-0.06	-0.31	-0.04	-0.06	0.06
13	361	29.54	0	0	319	0.00	-0.06	-0.26	-0.00	-0.02	0.06
14	289	29.54	0	0	281	0.00	-0.03	-0.31	-0.06	-0.06	0.10
15	413	112	0	0	311	-0.08	-0.14	-0.17	-0.16	-0.09	-0.10
16	242	27.03	0	0	236	-0.32	-0.48	-0.48	-0.53	-0.41	-0.09

TABLE-4
in silico PHARMACOKINETICS PREDICTION OF **1-16**

Compound	GI absorption	BBB permeant	P-gp	CYP1A2 inhibitor	CYP2D6 inhibitor	log K_p (skin permeation) (cm/s)
1	High	Yes	No	Yes	Yes	-4.82
2	High	Yes	No	Yes	Yes	-4.65
3	High	Yes	No	Yes	Yes	-4.67
4	High	Yes	No	Yes	Yes	-5.12
5	High	No	No	Yes	Yes	-4.95
6	High	Yes	No	No	No	-6.03
7	High	Yes	No	No	No	-5.86
8	High	Yes	No	No	No	-5.84
9	High	Yes	No	No	No	-6.33
10	High	Yes	No	No	No	-5.74
11	High	Yes	No	No	No	-5.73
12	High	Yes	No	No	No	-5.71
13	High	Yes	No	No	No	-5.54
14	High	Yes	No	No	No	-5.74
15	High	No	No	Yes	No	-5.98
16	High	Yes	No	No	No	-5.80

GI: Gastro Intestinal; P-gp: P-glycoprotein; BBB: Blood Brain Barrier; CYP1A2: Cytochrome P450 family 1 subfamily A member 2 (PDB: 2HI4); CYP2D6: Cytochrome P450 family 2 subfamily D member 6 (PDB: 5TFT)

enecity, except compounds **15** and **16** for *in silico* mutagencity only. *In silico* computed LD_{50} (mol/kg) has been calculated and tabultated in Table-4. *In vivo* calculated computed LD_{50} (mol/kg) value (2.49-2.80) to be safe range and non toxic.

Oral bioavailability and pharmacokinetic parameter plays a critical role and necessary in assessing the quality of potential clinical candidate. For this purpose, *in silico* pharmacokinetic parameter were calculated and summarized in Table-4. The skin permeability (P_{Skin}) of pharmaceuticals is a key feature [44] and the calculated P_{Skin} (-4.65-6.03 indicating least permeability through the skin. The distribution properties were evaluated in terms of BBB permeability proposing that moderate amount of ILs will pass the BBB. The computed metabolism of ILs (Table-5) revealed no inhibitor of CYP1A2 and CYP2D6.

In silico bioavailability calculation has been displayed in Table-6. Bioactivityis measured by bioavailability score. It is assumed that bioactivity score is more than 0.00 than compound is biological active [45]. From Table-6, it is clear that all ionic liquids has respect Lipinski's rule, Ghose and Veber rule, except compounds **12** and **13** in case of veber rule. Biological score is 0.55 which is acceptable range and predict all ionic liquids were biological active and follow rule for bioavailability.

TABLE-5
in silico SCREENING OF TOXICITY AND log p OF IONIC LIQUIDS (**1-16**)

Compd.	AMES toxicity	Carcino-genecity	Rat acute toxicity LD_{50} (mol/kg)	log P
1	Non-toxic	Non-toxic	2.61	4.51
2	Non-toxic	Non-toxic	2.61	5.03
3	Non-toxic	Non-toxic	2.49	4.61
4	Non-toxic	Non-toxic	2.71	4.39
5	Non-toxic	Non-toxic	2.77	4.66
6	Non-toxic	Non-toxic	2.80	2.69
7	Non-toxic	Non-toxic	2.78	3.07
8	Non-toxic	Non-toxic	2.55	2.49
9	Non-toxic	Non-toxic	2.52	2.08
10	Non-toxic	Non-toxic	2.71	2.82
11	Non-toxic	Non-toxic	2.75	3.05
12	Non-toxic	Non-toxic	2.75	3.69
13	Non-toxic	Non-toxic	2.75	4.19
14	Non-toxic	Non-toxic	2.77	3.18
15	Toxic	Non-toxic	2.59	3.59
16	Toxic	Non-toxic	2.64	2.31

TABLE-6
in silico BIOAVAILABILITY PREDICTION

Compd.	*in silico* Bioavailability			
	Lipinski	Ghose	Veber	Bioavailability score
1	Yes	Yes	Yes	0.55
2	Yes	Yes	Yes	0.55
3	Yes	Yes	Yes	0.55
4	Yes	Yes	Yes	0.55
5	Yes	Yes	Yes	0.55
6	Yes	Yes	Yes	0.55
7	Yes	Yes	Yes	0.55
8	Yes	Yes	Yes	0.55
9	Yes	Yes	Yes	0.55
10	Yes	Yes	Yes	0.55
11	Yes	Yes	Yes	0.55
12	Yes	Yes	No, 1 Violation	0.55
13	Yes	Yes	No, 1 Violation	0.55
14	Yes	Yes	Yes	0.55
15	Yes	Yes	Yes	0.55
16	Yes	Yes	Yes	0.55

Conclusion

It can be concluded that all sixteen novel RTILs have been prepared through quaternization of 1-pentylimidazole by treatment it with a variety of functional group by using microwave irradiation in comparison with the conventional synthesis. It is found that microwave assisted interaction can improve the yield of target molecules and in much shorter than traditional synthesis. The biological activity of synthesized ILs showed that some ILs (**3**, **4** and **5**) has prominent antibacterial activity, which showed due to phenyl group bearing alkyl chain. *In silico* results has also proven that all ionic liquids follow Lipinski's

rule to qualify as drug candidate. Molecular property prediction has showed that compounds were in acceptance range and respect Log P value to be eligible for liphophilicity, Moreover, *in silico* pharmacokinetic results has demonstrated that all compounds are safe for BBA permeability and has good bioavailability score *i.e.* 0.55. Computed *in vivo* LD_{50} (mg/kg) for rat acute toxicity was in acceptance range (2.49-2.80) and non-toxic for further study. Pharmacokinetic results have shown that calculated P_{skin} (-4.65-6.03) indicated least permeability through the skin and found to be safe.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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