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Microwave-assisted synthesis of novel imidazolium, pyridinium and pyridazinium-based ionic liquids and/or salts and prediction of physico-chemical properties for their toxicity and antibacterial activity

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ABSTRACT

An efficient, eco-friendly, simple and facile synthesis of a novel class of imidazolium, pyridinium and pyridazinium-based ionic liquids and/or salts is described under both conventional procedure and microwave irradiation. The newly synthesized ILs were well-characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis. Their *in vitro* antibacterial against a panel of Gram-positive and Gram-negative bacteria was measured by determination of the inhibition zone (IZ), minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) and the results revealed that ILs containing imidazolium cation are very effective antibacterial agents, especially, *1,2-dimethyl-3-(3-phenoxypropyl)-1H-imidazol-3-ium bromide* **8**. A correlation of structure and activities relationship of these ILs with respect to Lipinski rule of Five, drug likeness, toxicity profiles and other physico-chemical properties of drugs are described and verified experimentally.

1. Introduction

Nowadays, Considerable challenges surveys by many chemical industries have been directed toward finding alternatives to toxic or hazardous volatile organic compounds (VOCs). For these problems Ionic liquids (ILs) appear as suitable solution due to their several outstanding properties such as zero- vapor pressure, good chemical and thermal stability, low flammability, excellent solubility for many organic and inorganic compounds and high ionic conductivity and [1–3] The general definition of ILs are organic salts with a melting-point below 100 °C which contained organic cation, combined with various organic and inorganic anions [4–5]. The numerous combinations made between the cation and the anion permits the design of appropriate ILs for a particular application.

Based on these unique characteristics, ILs have been widely investigated in various fields and reported such as media for electrodeposition of metals [6], as a catalyst and biocatalyst [7–8], as potential corrosion inhibitors [9–10], in polymer science [11], in food chemical science [12], as electrolytes for batteries [13,14], and in many other area of research.

Additionally, several studies have shown the very interesting biological activity of ILs against both environmental and clinically important microorganisms [15–17].

On the other hand, efficient and eco-friendly green methods such microwave and ultrasound irradiation gained popularity for a clean synthesis of ILs and compared with its conventional preparation. The most important advantages provided by the use of these eco-friendly technologies are the large reduction time of reaction and the simplicity in handling and processing [18–19].

Thus, the purpose of this work was the synthesis of new class of imidazolium, pyridinium and pyridazinium-based ionic liquids. Furthermore, the antimicrobial activity of the new synthesized ILs were tested against six types of human pathogen was investigated in order to assess to their potential toxicities.

2. Materials and methods

2.1. Apparatus

All new compounds were characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and LCMS. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured in DMSO and D_2O at room temperature.

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Chemical shifts (δ) were reported in ppm, with tetramethylsilane (TMS) as an internal standard. The LCMS spectra were measured with a Micromass LCT mass spectrometer. IR spectra were recorded on a KBr disc with a Schimadzu 8201 PC FT-IR spectrophotometer (ν_{max} in cm^{-1}). The microwave-assisted reactions were performed using a controllable single-mode microwave reactor, CEM Discovery, designed for synthetic use. The reactor is equipped with a magnetic stirrer as well as a pressure, temperature and power controls. The maximum operating pressure of the reactor is 2.10^6 Pa. The power and temperature range are 15–300 W and 60–250 °C, respectively. The elemental analysis was given by using the 2400 Series II CHNS/O Elemental Analyzer.

2.2. Synthesis

2.2.1. General procedures for the synthesis of IL/salt (**1**–**14**) using conventional method

To the solution of picoline, pyridazine and/or imidazole derivatives (1 eq) in toluene, was added (2-bromoethoxy)benzene and/or (3-bromopropoxy)benzene (1.1 eq) at room temperature, followed by stirring at 80 °C for 18 h. The completion of the reaction was marked by the separation of oil or solid from the initially obtained clear and homogenous mixture of amine and alkyl bromide in toluene. The product was isolated by extraction or filtration to remove the unreacted starting materials and solvent. Subsequently, the picolinium, pyridazinium and/or imidazolium salt was washed with ethyl acetate. In each case, the IL/salt was finally dried at a reduced pressure to get rid of all the volatile organic compounds.

2.2.2. General procedure for the synthesis of IL/salt (**1**–**14**) using under Microwave irradiation

Picoline, pyridazine and/or imidazole derivatives (1 eq) and the appropriate alkyl bromide (1 eq) were placed in a closed vessel and exposed to irradiation for 20 using a Microwave irradiatiom. The product was then collected as described in the conventional procedure outlined earlier.

2.3. Characterization

2-methyl-1-(2-phenoxyethyl)pyridinium bromide **1**. This compound was obtained as brown solid; Mp 148–150 °C, ^{1}H NMR (D_2O, 400 MHz,): δ = 2.77 (s, 3H), 4.38 (t, J = 7.6 Hz, 2H), 4.84 (t, J = 7.6 Hz, 2H), 6.80 (d, 2Ar-H), 6.89 (t, 1Ar-H), 7.19 (t, 2Ar-H), 7.76 (m, 2Ar-H), 8.23 (t, 1Ar-H), 8.66 (d, 1Ar-H); ^{13}C NMR (D_2O, 100 MHz,): δ = 20.0 (CH_3), 56.6 (CH_2), 65.5 (CH_2), 114.5 (CH), 122.9 (CH), 125.3 (CH), 129.8 (CH), 130.1 (CH), 145.6 (CH), 155.8 (C), 157.2 (C); IR (KBr) ν_{max} 3132 (C-H Ar), 1599–1472 (C═C), 1169 (C—N), 1083 (C—O) cm^{-1}; LCMS (M^+)-Br^- 214.1 found for $C_{14}H_{16}NO^+$.

2-methyl-1-(3-phenoxypropyl)pyridinium bromide **2**. This compound was obtained as white solid; Mp 166–168 °C, ^{1}H NMR (D_2O, 400 MHz,): δ = 2.33 (quint, 2H), 2.73 (s, 3H), 4.06 (t, J = 7.6 Hz, 2H), 4.67 (t, J = 7.6 Hz, 2H), 6.79 (d, 2Ar-H), 6.95 (t, 1Ar-H), 7.25 (t, 2Ar-H), 7.71 (t, 1Ar-H), 7.80 (d, 1Ar-H), 8.25 (t, 1Ar-H), 8.61 (d, 1Ar-H); ^{13}C NMR (D_2O, 100 MHz,): δ = 17.6 (CH_3), 29.5 (CH_2), 59.3 (CH_2), 64.6 (CH_2), 114.4 (CH), 121.5 (CH), 127.4 (CH), 129.8 (CH), 139.8 (C), 141.4 (CH), 143.9 (CH), 146,1 (CH), 157.4 (C); IR (KBr) ν_{max} 3133 (C—H Ar), 1600–1471 (C═C), 1166(C—N), 1083 (C—O) cm^{-1}; LCMS (M^+)-Br^- 228.1 found for $C_{15}H_{18}NO^+$.

3-methyl-1-(2-phenoxyethyl)pyridinium bromide **3**. This compound was obtained as brown solid; Mp 116–118 °C, ^{1}H NMR (D_2O, 400 MHz,): δ = 2.49 (s, 3H), 4.51 (t, J = 7.6 Hz, 2H), 4.92 (t, J = 7.6 Hz, 2H), 6.90–7.01 (m, 3Ar-H), 7.29 (t, 2Ar-H), 7.90 (t, 1Ar-H), 8.31 (d, 1Ar-H), 8.71 (m, 2Ar-H); ^{13}C NMR (D_2O, 100 MHz,): δ = 17.7 (CH_3), 60.7 (CH_2), 66.2 (CH_2), 114.7 (CH), 122.1 (CH), 127.4 (CH), 129.9 (CH), 139.8 (CH), 141.9 (CH), 144.2 (CH), 146.6 (CH), 157.2 (C); IR (KBr) ν_{max} 3132 (C-H Ar), 1601–1469 (C═C), 1167(C—N), 1081 (C—O) cm^{-1}; LCMS (M^+)-Br^- 214.1 found for $C_{14}H_{16}NO^+$.

3-methyl-1-(3-phenoxypropyl)pyridinium bromide **4**. This compound was obtained as white solid; Mp 120–122 °C, ^{1}H NMR (D_2O, 400 MHz,): δ = 2.33 (m, 5H), 3.97 (t, J = 7.6 Hz, 2H), 4.62 (t, J = 7.6 Hz, 2H), 6.69 (d, 2Ar-H), 6.89 (t, 1Ar-H), 7.20 (t, 2Ar-H), 7.75 (t, 1Ar-H), 8.21 (d, 1Ar-H), 8.51 (d, 1Ar-H), 8.53 (s, 1Ar-H); ^{13}C NMR (D_2O, 100 MHz,): δ = 17.6 (CH_3), 29.5 (CH_2), 59.3 (CH_2), 64.6 (CH_2), 114.4 (CH), 121.5 (CH), 127.4 (CH), 129.8 (CH), 139.8 (C), 141.4 (CH), 143.9 (CH), 146,1 (CH), 157.4 (C); IR (KBr) ν_{max} 3129 (C—H Ar), 1599–1471 (C═C), 1167(C—N), 1080 (C—O) cm^{-1}; LCMS (M^+)-Br^- 228.1 found for $C_{15}H_{18}NO^+$.

4-methyl-1-(2-phenoxyethyl)pyridinium bromide **5**. This compound was obtained as brown solid; Mp 78–80 °C, ^{1}H NMR (D_2O, 400 MHz,): δ = 2.46 (s, 3H), 4.35 (t, J = 7.6 Hz, 2H), 4.76 (t, J = 7.6 Hz, 2H), 6.77–6.88 (m, 3Ar-H), 7.16 (t, 2Ar-H), 7.67 (d, 2Ar-H), 8.54 (d, 2Ar-H); ^{13}C NMR (D_2O, 100 MHz,): δ = 21.3 (CH_3), 59.8 (CH_2), 66.1 (CH_2), 114.6 (CH), 121.9 (CH), 128.4 (CH), 129.8 (CH), 143.5 (CH), 157.8 (C), 160.6 (C); IR (KBr) ν_{max} 3133 (C-H Ar), 1601–1473 (C═C), 1164(C—N), 1080 (C—O) cm^{-1}; LCMS (M^+)-Br^- 214.1 found for $C_{14}H_{16}NO^+$.

4-methyl-1-(3-phenoxypropyl)pyridinium bromide **6**. This compound was obtained as brown solid; Mp 134–136 °C, ^{1}H NMR (D_2O, 400 MHz,): δ = 2.34 (quint, J = 7.6 Hz, 2H), 2.50 (s, 3H), 3.98 (t, J = 7.6 Hz, 2H), 4.60 (t, J = 7.6 Hz, 2H), 6.72 (d, 2Ar-H), 6.91 (t, 1Ar-H), 7.21 (t, 2Ar-H), 7.66 (d, 2Ar-H), 8.48 (d, 2Ar-H); ^{13}C NMR (D_2O, 100 MHz,): δ = 21.2 (CH_3), 29.4 (CH_2), 58.5 (CH_2), 64.5 (CH_2), 114.4 (CH), 121.5 (CH), 128.5 (CH), 129.8 (CH), 143.2 (CH), 157.4 (C), 160.1 (C); IR (KBr) ν_{max} 3132 (C—H Ar), 1600–1470 (C═C), 1167(C—N), 1078 (C—O) cm^{-1}; LCMS (M^+)-Br^- 228.1 found for $C_{15}H_{18}NO^+$.

4-(dimethylamino)-1-(2-phenoxyethyl)pyridinium bromide **7**. This compound was obtained as brown solid; Mp 178–180 °C, ^{1}H NMR (D_2O, 400 MHz,): δ = 2.85 (s, 6H), 4.11 (t, J = 7.6 Hz, 2H), 4.28 (t, J = 7.6 Hz, 2H), 6.55 (d, 2Ar-H), 6.69–6.73 (m, 3Ar-H), 7.03 (t, 2Ar-H), 7.80 (d, 2Ar-H); ^{13}C NMR (D_2O, 100 MHz,): δ = 39.3 ($2CH_3$), 56.5 (CH_2), 66.5 (CH_2), 107.2 (CH), 114.4 (CH), 121.7 (CH), 129.7 (CH), 141.6 (CH), 155.9 (C), 157.3 (C); IR (KBr) ν_{max} 3132 (C—H Ar), 1600–1471 (C═C), 1166(C—N), 1082 (C—O) cm^{-1}; LCMS (M^+)-Br^- 243.1 found for $C_{15}H_{19}N_2O^+$.

4-(dimethylamino)-1-(3-phenoxypropyl)pyridinium bromide **8**. This compound was obtained as white solid; Mp 134–136 °C, ^{1}H NMR (D_2O, 400 MHz,): δ = 2.12 (quint, J = 7.6 Hz, 2H), 2.92 (s, 6H), 3.83 (t, J = 7.6 Hz, 2H), 4.12 (t, J = 7.6 Hz, 2H), 6.55 (d, 2Ar-H), 6.67 (d, 2Ar-H), 6.81 (t, 1Ar-H), 7.12 (t, 2Ar-H), 7.75 (d, 2Ar-H); ^{13}C NMR (D_2O, 100 MHz,): δ = 29.17 (CH_2), 39.4 ($2CH_3$), 54.8 (CH_2), 64.5 (CH_2), 107.4 (CH), 114.4 (CH), 121.4 (CH), 129.7 (CH), 141.3 (CH), 156.0 (C), 157.6 (C); IR (KBr) ν_{max} 3131 (C—H Ar), 1599–1470 (C═C), 1164 (C—N), 1083 (C—O) cm^{-1}; LCMS (M^+)-Br^- 257.1 found for $C_{16}H_{21}N_2O^+$.

1-(2-phenoxyethyl)pyridazin-1-ium bromide **9**. This compound was obtained as brown solid; Mp 160–161 °C, ^{1}H NMR (D_2O, 400 MHz,): δ = 4.54 (t, J = 7.2, Hz 2H), 5.14 (t, J = 7.6 Hz, 2H), 6.82–6.93 (m, 3H, Ar-H), 7.19–7.23 (m, 2H, Ar-H), 8.39–8.50 (m, 2H), 9.38 (d, 1H), 9.67 (d, 1H); ^{13}C NMR (D_2O, 100 MHz,): δ = 64.7 (CH_2), 65.1 (CH_2), 114.7 (CH), 122.1 (CH), 129.9 (CH), 135.6 (CH), 137.1 (CH), 150.3 (CH), 154.7 (CH), 157.1 (C); IR (KBr) ν_{max} 3131 (C—H Ar), 1598–1469 (C═C), 1165(C—N), 1081 (C—O) cm^{-1}; LCMS (M^+)-Br^- 201.1 found for $C_{12}H_{13}N_2O^+$.

1-(3-phenoxypropyl)pyridazin-1-ium bromide **10**. This compound was obtained as brown solid; Mp 190–192 °C, ^{1}H NMR (D_2O, 400 MHz,): δ = 2.49 (quint, J = 7.6 Hz, 2H), 4.06 (t, J = 7.2, Hz 2H), 4.96 (t, J = 7.6 Hz, 2H), 6.69–6.92 (m, 3H, Ar-H), 7.19–7.23 (m, 2H, Ar-H), 8.39–8.42 (m, 2H), 9.34 (d, 1H), 9.60 (d, 1H); ^{13}C NMR (D_2O, 100 MHz,): δ = 28.7 (CH_2), 63.5 (CH_2), 64.9 (CH_2), 114.4 (CH), 121.5 (CH), 129.8 (CH), 135.7 (CH), 136.7 (CH), 149.6 (CH), 154.4 (CH), 157.3 (C); IR (KBr) ν_{max} 3132 (C—H Ar), 1599–1471 (C═C), 1165(C—N), 1082 (C—O) cm^{-1}; LCMS (M^+)-Br^- 215.1 found for $C_{13}H_{15}N_2O^+$.