

# New Ionic Liquid Microemulsion-Mediated Synthesis of Silver Nanoparticles for Skin Bacterial Infection Treatments

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## 1. Materials and Instrumentation

Chemicals were obtained from the following suppliers and used without further purification: toluene, cumene, tert-butylbenzene, 1-methylimidazole, 1-n-butylimidazole lithium bis(trifluoromethanesulfonimide), and anhydrous MgCl<sub>2</sub> (Sigma–Aldrich); Zinc iodide (Acros).

*Melting points were measured* using a BÜCHI Melting point B-540 apparatus; all *melting points were measured in open glass capillaries* and are uncorrected. Elemental analyses for C, H, N, were performed with a Perkin–Elmer 263 elemental analyzer. FT-IR spectra were recorded on a BRUKER Tensor-37 FT-IR spectrophotometer in the range 400–4000 cm<sup>-1</sup> as KBr disc in the 4000-550 cm<sup>-1</sup> region with 2 cm<sup>-1</sup> resolution or with an ATR (attenuated total reflection) unit (Platinum ATR-QL, diamond). For signal intensities the following abbreviations were used: br (broad), sh (sharp), w (weak), m (medium), s (strong), vs (very strong). UV/Vis spectra were measured at 25 °C in ethanol (10<sup>-5</sup> mol/L) on a Shimadzu UV-2450 spectrophotometer using quartz cuvettes (1 cm). NMR-spectra were obtained with a Bruker Avance DRX200 (200 MHz for <sup>1</sup>H) or Bruker Avance DRX500 (125 and 470 MHz for <sup>13</sup>C and <sup>19</sup>F respectively) spectrometer with calibration to the residual proton solvent signal in DMSO-*d*<sub>6</sub> (<sup>1</sup>H NMR: 2.52 ppm, <sup>13</sup>C NMR: 39.5 ppm), CDCl<sub>3</sub> (<sup>1</sup>H NMR: 7.26 ppm, <sup>13</sup>C NMR: 77.16 ppm) against TMS ( $\delta = 0.00$  ppm) for <sup>1</sup>H and <sup>13</sup>C, 85% phosphoric acid ( $\delta = 0.00$  ppm) for <sup>31</sup>P and CFCl<sub>3</sub> ( $\delta = 0.00$  ppm) for <sup>19</sup>F NMR. Multiplicities of the signals were specified s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). The ESI-MS of the synthesized compounds were acquired in the linear mode for positive ions on a UHR-QTOF maXis 4G (Bruker Daltonics) and BRUKER Ultraflex MALDI-TOF instrument equipped with a 337 nm nitrogen laser pulsing at a repetition rate of 10 Hz. The 2+ charge assignment of ions in HR-ESI-MS was confirmed by the m/z = 0.5 difference between the isotope peaks (x, x+1, x+2). Peaks with chlorine showed the isotope ratio <sup>35/37</sup>Cl = 75.8:24.2.

## 2. Synthesis of 1-alkyl-4-(chloromethyl)benzene (1a-c)

General procedure: A flask was charged with 5 mol% of ZnI<sub>2</sub> (1.3 mmol), chlorosulfonic acid (31 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (30 mL), followed by dropwise addition of dimethoxymethane (31 mmol) at -10 °C. After stirring the reaction mixture at -10°C for 30min, the aromatic compound (26 mmol) was slowly added. The resulting mixture was then stirred at 5-10 °C for the time 0.5 - 2 h. The reaction was monitored by TLC analysis.

After completion, the reaction was quenched by addition of water (10 mL) in an ice bath. After extraction with  $\text{CH}_2\text{Cl}_2$  (3 x 20 mL), the organic phase was washed with 5% sodium carbonate solution (2 x 10 mL), water (2 x 10 mL) and brine (2 x 20 mL), then evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography on a silica gel using petroleum ether (boiling range: 60-90°C) and ethyl acetate as eluents to give the desired product.

*1-(Chloromethyl)-4-isopropylbenzene (1b)* [24]: Colorless liquid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.41 (d,  $J = 8.1$  Hz, 2H), 7.32 (d,  $J = 8.1$  Hz, 2H), 4.66 (s, 2H), 3.05–2.93 (m, 1H), 1.35 (d,  $J = 7.4$  Hz, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 146.3, 138.7, 128.6, 126.7, 46.0, 33.9, 23.9.

*1-(tert-Butyl)-4-(chloromethyl)benzene (1c)* [24]: Colorless liquid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm):  $\delta$ H 7.46 (d,  $J = 8.4$  Hz, 2H), 7.42–7.39 (m, 2H), 4.64 (s, 2H), 1.40 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 151.4, 134.5, 128.3, 125.6, 46.0, 34.5, 31.3.

### 3. Synthesis of benzyl alkyl imidazolium chloride [ $\text{R}^1\text{BnImR}^2$ ] $^+\text{Cl}^-$ ionic liquids (2a-f)

Into a three-neck round-bottom flask, benzyl chloride derivatives (0.03 mol) were added dropwise to a solution of 1-alkylimidazole (0.03 mol) in acetonitrile (ACN) (30 mL) at room temperature under stirring. The mixture was then heated under reflux in a  $\text{N}_2$  atmosphere for about 48 h, until no starting material was detected by thin layer chromatography (TLC). After the reaction was completed, ACN was evaporated into vacuo, and the yellowish oily product was washed three times with refluxing ethyl acetate (25 mL) at 353 K to eliminate any residual unreacted starting materials. The pure oily products were then dried for 48 h in a vacuum oven (40 mbar) at 333 K. Samples of the produced TBAILs (2a-f) were characterized as follows:

**3-benzyl-1-methyl-1H-imidazol-3-ium chloride** [ $\text{BnMIm}$ ] $\text{Cl}$  (2a): Obtained in a 93% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm); 9.39 (1H, s, Im-H), 7.89 (1H, d,  $J = 1.9$  Hz, Im-H), 7.75 (1H, d,  $J = 1.9$  Hz, Im-H), 7.69–7.45 (5H, m, Ar-H), 5.52 (2H, 2, Ph- $\underline{\text{CH}_2}$ ), 3.84 (3H, s, N- $\underline{\text{CH}_3}$ ). ESI-MS (positive mode): 173.2 m/z [ $\text{M} - \text{Cl}^-$ ,  $\text{C}_{11}\text{H}_{13}\text{N}_2$ ] $^+$

**3-(4-isopropylbenzyl)-1-methyl-1H-imidazol-3-ium chloride** [ $^{\text{iso}}\text{PBnMIm}$ ] $\text{Cl}$  (2b): Obtained in a 90% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm); 9.48 (1H, s, Im-H), 7.91 (1H, d,  $J = 1.8$  Hz, Im-H), 7.71 (1H, d,  $J = 1.8$  Hz, Im-H), 7.47–7.30 (4H, m, Ar-H), 5.57 (2H, 2, Ar- $\underline{\text{CH}_2}$ ), 3.98 (3H, s, N- $\underline{\text{CH}_3}$ ), 3.32 (1H, p,  $J = 1.9$  Hz,  $\underline{\text{CH}}(\text{CH}_3)_2$ ), 1.23 (6H, d,  $J = 7.0$  Hz,  $\text{CH}(\underline{\text{CH}_3})_2$ ). ESI-MS (positive mode): 215.2 m/z [ $\text{M} - \text{Cl}^-$ ,  $\text{C}_{14}\text{H}_{19}\text{N}_2$ ] $^+$

**3-(4-(tert-butyl)benzyl)-1-methyl-1H-imidazol-3-ium chloride** [ $^{\text{tert}}\text{BBnMIm}$ ] $\text{Cl}$  (2c): Obtained in a 92% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm); 9.83 (1H, s, Im-H), 7.89 (1H, d,  $J = 1.8$  Hz, Im-H), 7.72 (1H, d,  $J = 1.8$  Hz, Im-H), 7.51–7.26 (4H, m, Ar-H), 5.58 (2H, 2, Ar- $\underline{\text{CH}_2}$ ), 4.01 (3H, s, N- $\underline{\text{CH}_3}$ ), 1.40 (9H, s, C( $\underline{\text{CH}_3}$ ) $_3$ ). ESI-MS (positive mode): 229.2 m/z [ $\text{M} - \text{Cl}^-$ ,  $\text{C}_{15}\text{H}_{21}\text{N}_2$ ] $^+$

**3-benzyl-1-butyl-1H-imidazol-3-ium chloride** [ $\text{BnBIm}$ ] $\text{Cl}$  (2d): Obtained in a 89% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm); 9.39 (1H, s, Im-H), 7.89 (1H, d,  $J = 1.9$  Hz, Im-H), 7.75 (1H, d,  $J = 1.9$  Hz, Im-H), 7.69–7.45 (5H, m, Ar-H), 5.52 (2H, 2, Ph- $\underline{\text{CH}_2}$ ), 3.84 (3H, s, N- $\underline{\text{CH}_3}$ ). ESI-MS (positive mode): 215.2 m/z [ $\text{M} - \text{Cl}^-$ ,  $\text{C}_{14}\text{H}_{19}\text{N}_2$ ] $^+$

**3-(4-isopropylbenzyl)-1-butyl-1H-imidazol-3-ium chloride** [ $^{\text{iso}}\text{PBnBIm}$ ] $\text{Cl}$  (2e): Obtained in a 83% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm); 9.48 (1H, s, Im-H), 7.91 (1H, d,  $J = 1.8$  Hz, Im-H), 7.71 (1H, d,  $J = 1.8$  Hz, Im-H), 7.47–7.30 (4H, m, Ar-H), 5.57 (2H, 2, Ar- $\underline{\text{CH}_2}$ ), 3.98 (3H, s, N- $\underline{\text{CH}_3}$ ), 3.32 (1H, p,  $J = 6.9$  Hz,  $\underline{\text{CH}}(\text{CH}_3)_2$ ), 1.23 (6H, d,  $J = 7.0$  Hz,  $\text{CH}(\underline{\text{CH}_3})_2$ ). ESI-MS (positive mode): 257.3 m/z [ $\text{M} - \text{Cl}^-$ ,  $\text{C}_{17}\text{H}_{25}\text{N}_2$ ] $^+$

**3-(4-(tert-butyl)benzyl)-1-butyl-1H-imidazol-3-ium chloride** [ $^{\text{tert}}\text{BBnBIm}$ ] $\text{Cl}$  (2f): Obtained in a 87% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm); 9.83 (1H, s, Im-H), 7.89 (1H, d,  $J = 2.0$  Hz, Im-H), 7.72 (1H, d,  $J = 2.0$  Hz, Im-H), 7.51–7.26 (4H, m, Ar-H), 5.58 (2H, 2, Ar- $\underline{\text{CH}_2}$ ), 4.01 (3H, s, N- $\underline{\text{CH}_3}$ ), 1.40 (9H, s, C( $\underline{\text{CH}_3}$ ) $_3$ ). ESI-MS (positive mode): 271.3 m/z [ $\text{M} - \text{Cl}^-$ ,  $\text{C}_{18}\text{H}_{27}\text{N}_2$ ] $^+$

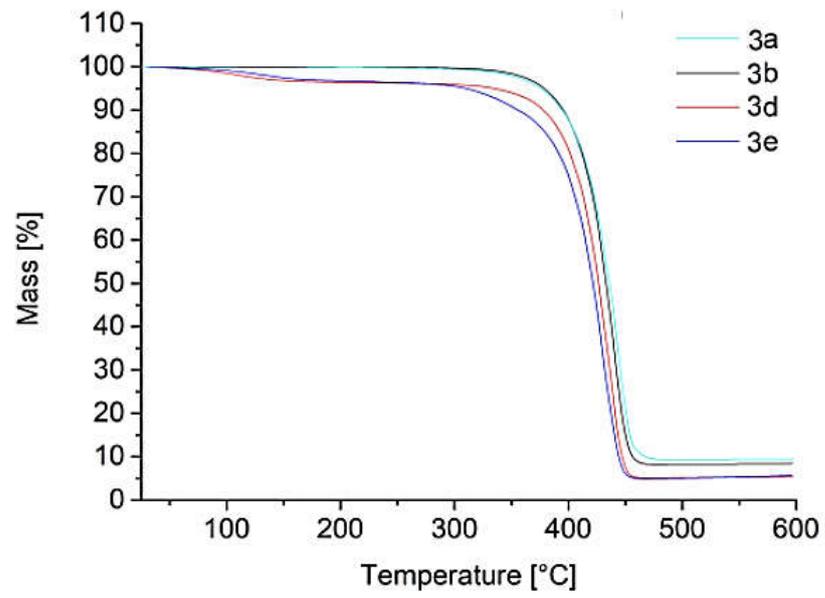
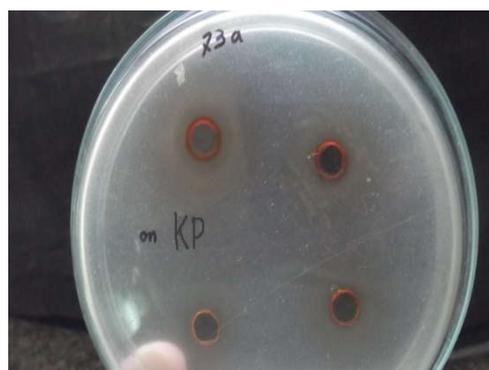


Figure S1. TG curves of TBAILs.



**Figure S2.** Photographs of inhibition zones for the most active antibiotics (AgNPs-3e and AgNPs-3f).

**Table S1.** MIC and MBC values ( $\mu\text{g/mL}$ ) of new BAILs-supported AgNPs against different pathogens, in comparison to previously reported ones.

Sample	Size (nm)	SA		PA		KB		Ref.
		MIC $\pm$ SD	MBC $\pm$ SD	MIC $\pm$ SD	MBC $\pm$ SD	MIC $\pm$ SD	MBC $\pm$ SD	
AgNPs-3a	2.9	3.25 $\pm$ 0.25	3.75 $\pm$ 0.31	8.76 $\pm$ 0.32	8.85 $\pm$ 0.35	9.32 $\pm$ 0.34	9.50 $\pm$ 0.37	This work
AgNPs-3b	2.4	2.25 $\pm$ 0.12	2.25 $\pm$ 0.15	7.07 $\pm$ 0.19	7.15 $\pm$ 0.45	8.87 $\pm$ 0.11	8.05 $\pm$ 0.25	This work
AgNPs-3c	2.2	1.95 $\pm$ 0.15	2.07 $\pm$ 0.19	5.85 $\pm$ 0.25	5.95 $\pm$ 0.33	7.35 $\pm$ 0.37	7.48 $\pm$ 0.33	This work
AgNPs-3d	2.0	1.76 $\pm$ 0.15	1.95 $\pm$ 0.11	5.55 $\pm$ 0.29	5.65 $\pm$ 0.37	7.15 $\pm$ 0.21	7.23 $\pm$ 0.25	This work
AgNPs-3e	1.7	0.85 $\pm$ 0.11	0.95 $\pm$ 0.23	2.75 $\pm$ 0.36	2.85 $\pm$ 0.45	4.45 $\pm$ 0.29	4.55 $\pm$ 0.41	This work
AgNPs-3f	1.5	0.25 $\pm$ 0.12	0.35 $\pm$ 0.18	1.36 $\pm$ 0.27	1.39 $\pm$ 0.28	2.22 $\pm$ 0.15	2.25 $\pm$ 0.19	This work
AgNPs-C <sub>12</sub> Im <sup>a</sup>	9	16	16	32	32	NA	NA	[45]
AgNPs-C <sub>18</sub> Im <sup>b</sup>	8.6	256	256	256	256	NA	NA	[45]
AgNPs-C <sub>12</sub> Py <sup>c</sup>	18.49	16	16	64	64	NA	NA	[45]
AgNPs-C <sub>18</sub> Py <sup>d</sup>	6.71	128	128	128	128	NA	NA	[45]
AgNPs[BMIM][BF <sub>4</sub> ]	132	125	125	NA	NA	NA	NA	[46]
AgNPs[EMIM][BF <sub>4</sub> ]	360	500	500	NA	NA	NA	NA	[46]

NA= not assigned. <sup>a</sup>1-dodecyl-3-methylimidazolium chloride; <sup>b</sup> 1-octadecyl-3-methylimidazolium chloride; <sup>c</sup> 1-dodecyl pyridinium chloride; <sup>d</sup> 1-octadecyl pyridinium chloride; [BMIM][BF<sub>4</sub>].1-butyl-3-methylimidazolium tetrafluoroborate ; [EMIM][BF<sub>4</sub>].1-ethyl-3-methylimidazolium tetrafluoroborate.