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Original article

Synthesis, structural characterization of silver(I)-NHC complexes and their antimicrobial, antioxidant and antitumor activities

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ABSTRACT

To prepare a novel series of silver (I) complexes, the interaction of benzimidazolium salts having their two nitrogen atoms substituted by bulky groups with Ag_2O in DMF has been carried out. Their structures were characterized by elemental analyses, ^1H NMR, ^{13}C NMR and IR spectroscopy techniques. Further, the antibacterial properties of both the salts and their silver(I)-NHC complexes were tested against positive and negative bacteria using the agar dilution procedure. The results show that silver complexes are effective against *Salmonella Typhimurium*, *Listeria monocytogenes*, and *Micrococcus luteus* with moderate to high activity, and their minimum inhibitory concentrations ranging from 0.0024 to 1.25 mg/ml. Moreover, the antioxidant activity determination of these compounds were studied with the DPPH, and compared with (gallic acid "GA"and butylatedhydroxytoluene "BHT "). They exhibited significant antioxidant activities. In addition, the of benzimidazoles salts **2a-j** and silver-NHC complexes **3a-j** were screened for their antitumor activity. The highest antitumor activity was observed for **3e** and **3d** Complexes and they exhibited IC50 values 6.85 μg/mL against MCF-7 and 10.75 μg/mL against T47D, respectively.

1. Introduction

In organometallic chemistry, N-heterocyclic carbene (NHC) ligands have generated a great interest (ArduengoIII and Harlow, 1991). They can form stable metal complexes with strong metal-carbon bonds. Silver complexes are of considerable importance among the NHC-metal complex. The reaction of AgO Tf and a free carbene led to the first NHC-Ag(I) complex isolated in 1993 by ArduengoIII et al. (1993). The most common method reported fot synthesis has been the deprotonation with a silver base such as Ag_2O, Ag_2CO_3 and AgOAc (Xia et al., 2017; Patil et al., 2010a,b; Gok et al., 2013). NHC-Ag(I) complexes have been widely used as sources of different metal complexes via transmetallation (Nakamura et al., 2016; Baquero et al.,2013; Deng et al., 2013; Hameury et al., 2014; Iwasaki et al., 2016; Monticelli et al., 2016; Wan et al., 2016; Chardon et al., 2017). These compounds have antimicrobial and anticancer properties (Shahini et al., 2017a,b; Haque et al., 2015; Karatas et al., 2016; Iqbal et al., 2015; Anchez et al., 2016). Also, they have been studied as luminescent materials (Syu et al.,2017; Adhikary et al., 2012; Seth et al., 2013; Lin et al., 2013). There have been limited number of reports related to the use of NHC-Ag(I) complexes in catalysis (Yoshida et al., 2014; Fu et al., 2011; Kilincarslan et al., 2016; Li et al., 2013; Samantaray et al., 2006; Balcan et al.,2013; Fujii et al.,2009; Tasci et al., 2017; Avinash et al., 2008; Datani et al., 2012). The biological interest of benzimidazole derivatives structure comes from their similarity with naturally occurring nucleotides (Cavallo et al.,2005). For this reason, we synthesized a series of new Ag(I) complexes. The study was conducted with two primary objectives. The first objective was to synthetize a series of new Ag(I) complexes and the second objective was to evaluate the antimicrobial, antioxidant and

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antitumor activities of these compounds. All new benzimidazoles and silver complexes were characterized by elemental analysis including ^{13}C NMR, ^{1}H NMR and FT-IR spectroscopy

2. Experimental

2.1. Preparation of benzimidazolium salts

Reaction of 1-isobutyl-benzimidazole (1 mmol) (1) with various alkyl chloride(1,1mmol) in dimethylformamide (DMF; 5 mL) at 80 °C for 24 h afford benzimidazole salts **2a-j**. A white crystalline solid was obtained after adding Diethyl ether (15 mL), which was subsequently filtered off. After washing with diethyl ether (3*10 mL) the solid was dried under vacuum, and the crude product was recrystallized from Dichloromethane/diethyl ether (1:3 ratio).

2.2. 1-(isobutyl)-3-(benzyl) benzimidazolium chloride, 2a

Yield 89%, Mp: 128.3 °C, ν(CN) = 1650.9 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.06 (d, 6H, CH_3 (a,b), J = 4 Hz), 2.44 (Hep, 1H, $H_{2'}$, J = 8 Hz), 4.44 (d, 2H, $H_{1'}$), 5.95 (s, 2H, $H_{1''}$), 7.30–7.71 (m, 9H, $H_{4,\ 5,\ 6,\ 7,\ 3'',\ 4'',\ 5'',\ 6'',\ 7''}$), 12.07 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.8 ($C_{a,b}$), 28.8 ($C_{2'}$), 51.3 ($C_{1''}$), 54.4 ($C_{1'}$), 113.1 (C_4), 113.8 (C_7), 127.0 (C_6), 127.1 (C_5), 128.3 ($C_{3'';7''}$), 129.1 ($C_{5''}$), 129.3 ($C_{4'';6''}$), 131.1 (C_9), 131.7 (C_8), 132.9 ($C_{2''}$), 144.0 (C_2). Elemental analysis % calcd. (found) for $C_{18}H_{21}ClN_2$:C, 71.866% (71.9); H, 7.036% (7.1); N, 9.312 (9.2).

2.3. 1-(Isobutyl)-3-(benzyl)-5.6-dimethylbenzimidazolium chloride, 2b

Yield 95%, Mp: 238.9 °C, ν(CN) = 1566.9 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.04 (d, 6H, $CH_{3(a,b)}$, J = 8 Hz), 2.38 (s, 3H, $CH_{3(c)}$), 2.42 (s, 3H, $CH_{3(d)}$), 2.44 (Hep, 1H, $H_{2'}$, J = 8 Hz), 4.36 (d, 2H, $H_{1'}$, J = 8 Hz), 5.86 (s, 2H, $H_{1''}$), 7.30–7.49 (m, 7H, $H_{4,\ 7,\ 3'',\ 4'',\ 5'',\ 6'',\ 7''}$), 11.81 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.8 ($C_{c,d}$), 20.7 ($C_{a,b}$), 28.7 ($C_{2'}$), 51.0 ($C_{1''}$), 54.2 ($C_{1'}$), 112.8 (C_4), 113.3 (C_7), 128.1 ($C_{3'';7''}$), 129.0 ($C_{5''}$), 129.3 ($C_{4'';C6''}$), 129.6 (C_8), 130.2 (C_9), 133.2 ($C_{5;6}$), 137.3 ($C_{2''}$), 142.8 (C_2). Elemental analysis % calcd. (found) for $C_{20}H_{25}ClN_2$: C, 73.040 (73.1); H, 7.662% (7.7); N, 8.518% (8.6).

2.4. 1-(Isobutyl)-3-(2.3.5.6-tetramethylbenzyl) benzimidazolium chloride, 2c

Yield 89%, Mp: 176.3 °C, ν(CN) = 1660.1 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.02 (d, 6H, $CH_{3\ (a,b)}$, J = 8 Hz), 2.25 (s, 12H, $CH_{3(c,d,e,f)}$), 2.38 (Hep, 1H, $H_{2'}$, J = 8 Hz), 4.49 (d, 2H, $H_{1'}$, J = 8 Hz), 5.97 (s, 2H, $H_{1''}$), 7.07–7.69 (m, 5H, $H_{4,\ 5,\ 6,\ 7,\ 5''}$), 11.44 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 16.12 ($C_{c,f}$), 19.7 ($C_{d,e}$), 20.5 ($C_{a,b}$), 28.8 ($C_{2'}$), 48.0 ($C_{1''}$), 54.2 ($C_{1'}$), 113.0 (C_4), 113.8 (C_7), 126.8 (C_6), 127.0 (C_5), 127.9 ($C_{5''}$), 131.3 (C_8), 131.8 (C_9), 133.5 ($C_{3'',7''}$), 134.0 ($C_{4'',6''}$), 135.0 ($C_{2''}$), 143.9 (C_2).Elemental analysis % calcd. (found) for $C_{22}H_{29}ClN_2$:C, 74.030% (74.1); H, 8.189% (8.2); N, 7.848%(7.9).

2.5. 1-(Isobutyl)-3-(2.3.5.6 tetramethylbenzyl)-5.6-dimethylbenzimidazolium chloride, 2d

Yield 87%, Mp: 113.1 °C, ν(CN) = 1558 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm0.99 (d, 6H, CH_3 ($_{a,b}$), J = 4 Hz), 2.30 (m, 18H, $CH_{3(c,d,e,f,g,h)}$), 2.38 (Hep, 1H, $H_{2'}$, J = 8 Hz), 4.43 (d, 2H, $H_{1'}$, J = 8 Hz), 5.86 (s, 2H, $H_{1''}$), 6.94–7.36 (m, 3H, $H_{4,\ 7,\ 5''}$), 11.08 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm)16.1 ($C_{e,h}$), 18.4 ($C_{c,d}$), 19.7 ($C_{a,b,f,g}$), 28.8 ($C_{2'}$), 47.6 ($C_{1''}$), 54.1 ($C_{1'}$), 112.7 (C_4), 113.5 (C_7), 128.0 ($C_{5''}$), 129.9 (C_8), 130.3 (C_9), 133.4 ($C_{3''}$), 133.0 ($C_{7''}$), 134.9 ($C_{5;6}$), 136.9 ($C_{4''}$), 136.9 ($C_{6''}$),142.5 ($C_{2''}$), 142.6 (C_2). Elemental analysis % calcd. (found) for $C_{24}H_{33}ClN_2$: C, 74.875% (74.9); H, 8.640% (8.7); N, 7.276% (7.2).

2.6. 1-(Isobutyl)-3-(2.3.4.5.6-pentamethylbenzyl) benzimidazolium chloride, 2e

Yield 92%, Mp: 198.2 °C, ν(CN) = 1546 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.05 (d, 6H, $C_{H3\ (a,b),}$ J = 4 Hz), 2.24 (s, 6H, $CH_{3(c,g)}$), 2.28 (s, 6H, $CH_{3(d,f)}$), 2.28 (s, 3H, $CH_{3(e)}$), 2.38 (Hep, 1H, $H_{2'}$), 4.51 (d, 2H, $H_{1'}$), 5.94 (s, 2H, $H_{1''}$), 7.22–7.70 (m, 4H, $H_{4,\ 5,\ 6,\ 7}$), 11.29 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 16.9 ($C_{c,g}$), 17.1 ($C_{d,f}$), 17.3 (C_e), 19.7 ($C_{a,b}$), 28.8 ($C_{2'}$), 48.5($C_{1''}$), 54.2 ($C_{1'}$), 113.0 (C_4), 113.9 (C_7), 125.1 ($C_{5''}$), 126.8 (C_5), 127.00(C_6), 131.3 ($C_{4''}$), 131.8 ($C_{6''}$), 133.5 ($C_{3'';7''}$), 133.8 ($C_{8;9}$), 137.2 ($C_{2''}$), 143.7 (C_2). Elemental analysis % calcd. (found) for $C_{23}H_{31}ClN_2$: C, 74.468% % (74.5); H, 8.423% (8.5); N, 7.552% (7.4).

2.7. 1-(Isobutyl)-3-(2.3.4.5.6-pentamethylbenzyl)-5.6-dimethylbenzimidazolium chloride, 2f

Yield 93%, Mp: 219.9 °C, ν(CN) = 1550 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.98 (d, 6H, $CH_{3(a,b)}$, J = 8 Hz), 2.14 (Hep, 1H, $H_{2'}$, J = 8 Hz), 2.25 (s, 6H, $CH_{3(c,d)}$), 2.30 (t, 12H, $CH_{3(e,f,h,i)}$), 2.41 (s, 3H, $CH_{3(g)}$), 2.37 (Hep, 1H, $H_{2'}$), 4.46 (d, 2H, $H_{1'}$), 5.80 (s, 2H, $H_{1''}$), 7.05 (s, 1H, H_7), 7.38 (s, 1H, H_4), 10.48 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 16.9 ($C_{f,h}$), 17.1 ($C_{e,i}$), 17.3 (C_g), 19.7 ($C_{a,b}$), 20.6 ($C_{c,d}$), 28.7 ($C_{2'}$), 47.9 ($C_{1''}$), 54.1 ($C_{1'}$), 112.7 (C_4), 113.4 (C_7), 125.2 ($C_{5''}$), 129.9 (C_8), 130.4 (C_9), 133.8 ($C_{3'';7''}$), 133.5 ($C_{4'';6''}$), 136.8 (C_5), 136.9 (C_6), 137.1 ($C_{2''}$), 142.3 (C_2). Elemental analysis % calcd. (found) for $C_{25}H_{35}ClN_2$: C, 75.253% (75.3); H, 8.841% (8.9); N, 7.021% (7.1).

2.8. 1-(Isobutyl)-3-(4- methylbenzyl) benzimidazolium chloride 2g

Yield 87%, Mp: 176.1 °C, ν(CN) = 1550 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.05 (d, 6H, $CH_{3(a,b)}$), 2.31 (s, 3H, $CH_{3(c)}$), 2.43 (Hep, 1H, $H_{2'}$), 4.44 (d, 2H, $H_{1'}$), 5.88 (s, 2H, $H_{1''}$), 7.15–7.71 (m, 8H, $H_{4,\ 5,\ 6,\ 7,\ 3'',\ 4'',\ 6'',7''}$), 12.05 (s, 1H, H_2).). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.8 ($C_{a,b}$), 21.1 (C_c), 28.9 ($C_{2'}$), 51.2 ($C_{1''}$), 54.3 ($C_{1'}$), 113.1 (C_4), 113.9 (C_7), 127.0 ($C_{5;6}$), 128.3 ($C_{3'';7''}$), 129.9 ($C_{5''}$), 129.9 ($C_{4'';6''}$), 131.0 (C_8), 131.7 (C_9), 139.1 ($C_{2''}$), 143.9 (C_2). Elemental analysis % calcd. (found) for $C_{19}H_{23}ClN_2$: C, 72.480% (72.5); H, 7.363% (7.4); N, 8.897% (8.9).

2.9. 1-(Isobutyl)-3-(2.4.6-trimethylbenzyl) −5.6-dimethylbenzimidazolium chloride 2h

Yield 89%, Mp: 249.7 °C, ν(CN) = 1550 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.01 (d, 6H, $CH_{3(a,b)}$), 2.29 (d, 6H, $CH_{3(c,d)}$), 2.32 (s, 6H, $CH_{3(e,g)}$), 2.40 (s, 3H, $CH_{3(f)}$), 2.44 (Hep, 1H, $H_{2'}$), 4.40 (d, 2H, $H_{1'}$), 5.84 (s, 2H, $H_{1''}$), 6.9–7.38 (m, 4H, $H_{4,\ 7,\ 4'',\ 6''}$), 11.34 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7 ($C_{a,b}$), 20.2 ($C_{c,d}$), 20.6 (C_e), 20.8 (C_g), 21.0 (C_f), 28.7 ($C_{2'}$), 47.1 ($C_{1''}$), 54.1 ($C_{1'}$), 112.6 (C_4), 113.5 (C_7), 125.4 ($C_{4'';6''}$), 130.0 ($C_{3'';\ 5'';7''}$), 137.02 ($C_{8;9}$), 137.89 ($C_{5;6}$), 139.52 ($C_{2''}$), 142.91 (C_2). Elemental analysis % calcd. (found) for $C_{23}H_{31}ClN_2$: C, 74.468% (74.5); H, 8.423% (8.5); N, 7.552% (7.6).

2.10. 1-(Isobutyl)-3-(naphthyl)-5.6-dimethylbenzimidazolium chloride 2i

Yield 98%, Mp: 178.3 °C, ν(CN) = 1550 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.04 (d, 6H, $CH_{3(a,b)}$), 2.33 (s, 3H, $CH_{3(d)}$), 2.39

(s, 3H, $CH_{3(c)}$), 2.44 (Hep, 1H, $H_{2'}$), 4.38 (d, 2H, $H_{1'}$), 6.04 (s, 2H, $H_{1''}$), 7.28–7.96 (m, 9H, $H_{4,\ 7,\ 3'',\ 5'',\ 6'',\ 7'',\ 8'',\ 10'',\ 11''}$), 11.52 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) (ppm)19.8 ($C_{a,b}$), 20.6 ($C_{c,d}$), 28.8 ($C_{2'}$), 51.2($C_{1''}$), 54.3 ($C_{1'}$), 112.8 (C_4), 113.4 (C_7), 125.0 ($C_{7''}$), 126.7 ($C_{3''}$), 126.8 ($C_{10''}$), 127.6 ($C_{5''}$), 127.7 ($C_{8''}$), 128.1 ($C_{6''}$), 129.4 ($C_{11''}$), 130.4 ($C_{8;9}$), 133.2 ($C_{5;6}$), 137.4 ($C_{2''}$), 141.9 (C_2). Elemental analysis % calcd. (found) for $C_{24}H_{27}BrN_2$: C, 68.083% (68.1); H, 6.428% (6.5); N, 6.616% (6.7).

2.11. 1-(Isobutyl)-3-(anthracen-9-ylmethyl)-5.6-dimethylbenzimidazolium chloride 2j

Yield 97%, Mp: 269,7 °C, ν(CN) = 1666 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.00 (d, 6H, CH_3 (a,b)), 1.91 (s, 3H, $CH_{3(d)}$), 2.23 (s, 3H, $CH_{3(c)}$), 2.34 (Hep, 1H, $H_{2'}$), 4.32 (d, 2H, $H_{1'}$), 6.90 (s, 2H, $H_{1''}$), 6.65 (s, 1H, $H_{9''}$), 7.23–8.58 (m, 10H, $H_{4,\ 7,\ 4'',\ 5'',\ 6'',\ 7'',\ 11'',\ 12'',\ 13'',\ 14''}$), 11.95 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 19.7 ($C_{a,b}$), 20.4 (C_c), 20.4 (C_d), 28.6 ($C_{2'}$), 45.2 ($C_{1''}$), 54.2 ($C_{1'}$), 112.3 (C4), 114.2 (C_7), 122.1 ($C_{9''}$), 123.1 ($C_{5'',\ 6'',\ 12'',\ 13''}$), 125.4 ($C_{4'',\ 14''}$), 128.0 ($C_{7'',\ 11''}$), 129.7 ($C_{4'',\ 15''}$), 129.8 ($C_8$), 130.1 ($C_9$), 130.4 ($C_{8''}$), 130.9 ($C_{10''}$), 131.2 ($C_{2''}$), 136.65 ($C_5$), 136.72 ($C_6$), 143.04 ($C_2$). Elemental analysis % calcd. (found) for $C_{28}H_{29}ClN_2$: C, 78.392% (78.4); H, 6.814% (6.9); N, 6.530% (6.6).

2.12. General procedure for the preparation of silver(I)-NHC complexes

A solution of benzimidazolium salt (1.0 mmol) (**2a-j**), Ag_2O (1.0 mmol) in dichloromethane (15 mL) was stirred for 24 h at room temperature in dark condition. The reaction mixture was filtered through celite and the solvent removed under reduced pressure. The crude product was recrystallized from dichloromethane/diethyl ether (1:3).

2.13. Chloro[1-isobutyl-3-(benzyl) benzimidazole-2-ylidene] silver(I) (3a)

Yield 75%, Mp: 188 °C, ν(CN) = 1466 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.02 (d, 6H, $CH_{3(a,b)}$, *J* = 8 Hz), 2.38 (Hep, 1H, $H_{2'}$, *J* = 8 Hz), 4.425 (d, 2H, $H_{1'}$, *J* = 8 Hz), 5.63 (s, 2H, $H_{1''}$), 7.25–7.38 (m, 9H, $H_{4,\ 5,\ 6,\ 7,\ 3'',\ 4'',\ 5'',\ 6'',\ 7''}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 20.3 ($C_{a,b}$), 29.3 ($C_{2'}$), 53.4 ($C_{1''}$), 56.8 ($_{C1'}$), 111.7 (C_4), 112.2 (C_7), 124.2 (C_5), 124.2 (C_6), 127.0 ($C_{3'';7''}$), 127.1 (C_8), 127.1(C_9), 128.5($C_{5''}$), 129.1 ($C_{4'';6''}$), 134.8 ($C_{2''}$), C_2: Ag-$C_{carbene}$: not observed. Elemental analysis % calcd. (found) for $C_{18}H_{20}AgClN_2$: C, 53.029%% (53.1); H, 4.945% (4.8); N, 6.871% (6.9).

2.14. Chloro[1-isobutyl-3-(benzyl)-5.6-dimethylbenzimidazole-2-ylidene] silver(I) (3b)

Yield 78%, Mp: 208.2 °C, ν(CN) = 1400 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.00 (d, 6H, $CH_{3(a,b)}$, *J* = 4 Hz), 2.31 (s, 3H, $CH_{3(c)}$), 2.37 (s, 3H, $CH_{3(d)}$), 2.37 (Hep, 1H, $H_{2'}$, *J* = 8 Hz), 4.18 (d, 2H, $H_{1'}$, *J* = 8 Hz), 5.56 (s, 2H, $H_{1''}$), 7.08–7.32 (m, 7H, $H_{4,\ 7,\ 3'',\ 4'',\ 5'',\ 6'',\ 7''}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 20.3 ($C_{c,d}$), 20.4 ($C_{a,b}$), 29.2 ($C_{2'}$), 53.1 ($C_{1''}$), 56.7 ($C_{1'}$), 111.2 (C_4), 112.8 (C_7), 126.8 ($C_{3'';7''}$), 128.3 ($_{5''}$), 129.0 ($C_{4'';\ 6''}$), 132.2 (C_8), 132.7 (C_9), 133.6 (C_5), 133.7 (C_6), 135.1 ($C_{2''}$), C_2: Ag-$C_{carbene}$: not observed. Elemental analysis % calcd. (found) for $C_{20}H_{24}AgClN_2$: C, 53.029%% (53.1); H, 4.945% (4.8); N, 6.871% (6.9).

2.15. Chloro[1-isobutyl-3-(2.3.5.6-tetramethylbenzyl)benzimidazole-2-ylidene]silver 3c

Yield 85%, Mp: 227.3 °C, ν(CN) = 1450 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.94 (d, 6H, $CH_{3(a,b)}$, *J* = 8 Hz), 2.15 (s, 6H, $CH_{3(d,e)}$), 2.29 (s, 6H, $CH_{3(c,f)}$), 2.33 (Hep, 1H, $H_{2'}$, *J* = 8 Hz), 4.17 (d, 2H, $H_{1'}$, *J* = 8 Hz), 5.49 (s, 2H, $H_{1''}$), 7.14–7.49 (m, 5H, $H_{4,\ 5,\ 6,\ 7,\ 5''}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm)16.1(Cc,f), 20.2 (Cd,e), 20.7 (Ca,b), 29.3 (C2′), 47.6 ($C_{1''}$), 57.3 ($C_{1'}$), 111.4 (C_4), 111.5 (C_7), 124.0 (C_5), 124.2(C_6), 129.6 ($C_{5''}$), 133.1 ($C_{3'';7''}$), 133.5 ($C_{4'';6''}$), 133.1 ($C_{2''}$), 135.3 ($C_{8;9}$), 189.3 (C_2). Elemental analysis % calcd. (found) for $C_{22}H_{28}AgClN_2$: C, 56.973% (56.8); H, 6.085% (6.1); N, 6.040% (6.1).

2.16. Chloro[1-isobutyl-3-(2.3.5.6-tetramethylbenzyl)-5.6-dimethylbenzimidazole-2-ylidene]silver 3d

Yield 82%, Mp: 231.4 °C, ν(CN) = 1466 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.92 (d, 6H, $CH_{3(a,b)}$, *J* = 8 Hz), 2.13 (s, 6H, $CH_{3(f,g)}$), 2.29 (s, 6H, $CH_{3(e,h)}$), 2.30 (Hep, 1H, $H_{2'}$, *J* = 8 Hz), 2.4 (s, 6H, $CH_{3(c,d)}$), 4.09 (d, 2H, $H_{1'}$, *J* = 8 Hz), 5.40 (s, 2H, $H_{1''}$), 7.14 (s, 1H, $H_{5''}$), 7.21 (d, 2H, $H_{4,7}$, *J* = 4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm)16.1 ($C_{e,h}$), 20.2 ($C_{c,d}$), 20.7 ($C_{a,b,f,g}$), 29.2 ($C_{2'}$), 47.1 ($C_{1''}$), 57.3 ($C_{1'}$), 111.5 (C_4), 111.8 (C_7), 129.9 ($C_{5''}$), 133.0 ($C_{8;9}$), 133.3 ($C_{3'';4''}$), 133.4 ($C_{5;6}$), 133.5 ($C_{4'';6''}$), 135.5 ($C_{2''}$), C_2: Ag-$C_{carbene}$: not observed. Elemental analysis % calcd. (found) for $C_{24}H_{32}AgClN_2$: C, 58.607% (58.7); H, 6.558% (6.6); N, 5.696% (5.7).

2.17. Chloro[1-isobutyl-3-(2.3.4.5.6-pentamethylbenzyl) benzimidazole-2-ylidene]silver 3e

Yield 86%, Mp: 275.3 °C, ν(CN) = 1458 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.93 (d, 6H, $CH_{3(a,b)}$, *J* = 4 Hz), 2.19 (s, 6H, $CH_{3(d,f)}$), 2.28 (s, 6H, $CH_{3(c,g)}$), 2.30 (Hep, 1H, $H_{2'}$, *J* = 8 Hz), 2.33 (s, 3H, $CH_{3(e)}$), 4.15 (d, 2H, $H_{1'}$, *J* = 8 Hz), 5.48 (s, 2H, $H_{1''}$), 7.27–7.48 (m, 4H, $H_{4,\ 5,\ 6,\ 7}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm)17.1 ($C_{c,d,f,g}$), 17.3 (C_e), 20.2 ($C_{a,b}$), 29.3 ($C_{2'}$), 47.8 ($C_{1''}$), 57.3 ($C_{1'}$), 111.4 (C_4), 111.6 (C_7), 123.9 (C_5), 124.1 (C_6), 126.5 ($C_{5''}$), 132.9 ($C_{4'';6''}$), 133.2 ($C_{8;9;3'';7''}$), 137.2($C_{2''}$), 189.0 (C_2). Elemental analysis % calcd. (found) for $C_{23}H_{30}AgClN_2$: C, 57.814% (57.9); H, 6.328% (6.4); N, 5.863% (5.9).

2.18. Chloro[1-isobutyl-3-(2.3.5.6-tetramethylbenzyl)-5.6-dimethylbenzimidazole-2-ylidene]silver 3f

Yield 89%, Mp: 208.3 °C, ν(CN) = 1591 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.91 (d, 6H, $CH_{3(a,b)}$, *J* = 8 Hz), 2.18 (s, 6H, $CH_{3(f,h)}$), 2.24 (Hep, 1H, $H_{2'}$, *J* = 8 Hz), 2.28 (s, 6H, $CH_{3(e,i)}$), 2.33 (s, 3H, $CH_{3(g)}$), 2.41(s, 6H, $CH_{3(c,d)}$), 4.08 (d, 2H, $H_{1'}$, *J* = 8 Hz), 5.39 (s, 2H, $H_{1''}$), 7.20 (s, 1H, H_4), 7.27 (s, 1H, H_7). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 17.0 ($C_{f,h}$), 17.1 ($C_{e,i}$), 17.3 (C_g), 20.4 ($C_{a,b}$), 20.4 (C_c), 20.5 (C_d), 29.1 ($C_{2'}$), 47.3 ($C_{1''}$), 57.3 ($C_{1'}$), 111.5 (C_4), 111.8 (C_7), 126.7 ($C_{5''}$), 132.9 ($C_{8;9}$), 133.2($C_{3''}$), 133.5 ($C_{7''}$), 134.2 ($C_{5;6;4'';6''}$), 137.1 ($C_{2''}$), 185.2 (C_2). Elemental analysis % calcd. (found) for $C_{25}H_{34}AgClN_2$: C, 59.356% (59.4); H, 6.774% (6.8); N, 5.538% (5.6).

2.19. Chloro[1-isobutyl-3-(4–methylbenzyl) benzimidazole-2-ylidene] silver 3g

Yield 79%, Mp: 202.3 °C, ν(CN) = 1468 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.01 (d, 6H, $CH_{3(a,b)}$, *J* = 8 Hz), 2.31 (s, 3H, $CH_{3(c)}$), 2.83 (Hep, 1H, $H_{2'}$, *J* = 8 Hz), 4.24 (d, 2H, $H_{1'}$, *J* = 8 Hz), 5.57 (s, 2H, $H_{1''}$), 7.11–7.48 (m, 8H, $H_{4,\ 5,\ 6,\ 7,\ 3'',\ 4'',\ 6'',7''}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 20.3 ($C_{a,b}$), 21.1 (C_c), 29.3 ($C_{2'}$), 53.3 ($C_{1''}$), 56.8 ($C_{1'}$), 112.2 (C_4), 111.6 (C_7), 124.1 (C_5), 124.2 (C_6), 127.1 ($C_{3'';7''}$), 129.7 ($C_{4'';6''}$), 131.8 ($C_{5''}$), 133.6 (C_8), 134.2 (C_9), 138.4 ($C_{2''}$), C_2: Ag-$C_{carbene}$: not observed. Elemental analysis % calcd. (found) for $C_{19}H_{22}AgClN_2$: C, 54.114% (54.2); H, 5.258% (5.3); N, 6.643% (6.7).

2.20. Chloro[1-isobutyl-3-(2.4.6-trimethylbenzyl)-5.6-dimethylbenzimidazole-2-ylidene]silver 3h

Yield 86%, Mp: 273.4 °C, ν(CN) = 1458 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.94 (d, 6H, $CH_{3(a,b)}$, *J* = 4 Hz), 2.23 (s, 6H, $CH_{3(c,d)}$), 2.28 (Hep, 1H, $H_{2'}$, *J* = 8 Hz), 2.34 (s, 3H, $CH_{3(e)}$), 2.35 (s, 3H, $CH_{3(f)}$), 2.38 (s, 3H, $CH_{3(g)}$), 4.11 (d, 2H, $H_{1'}$, *J* = 8 Hz), 5.40 (s, 2H, $H_{1''}$), 6.97 (s, 2H, H $_{4'', 6''}$), 7.18 (s, 2H, H $_{4, 7}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 20.2 ($C_{(c,d)}$), 20.3 (C $_{(a,b)}$), 20.4 (Ce), 20.5 (Cg), 21.1 (C f), 29.2 ($C_{2'}$), 47.4 ($C_{1''}$), 57.1 ($C_{1'}$), 111.7 (C_4), 111.8 (C_7), 126.8 ($C_{4''6''}$), 130.2 ($C_{3''5''7''}$), 133.3 ($C_{8;9}$), 137.4 ($C_{5;6}$), 139.4 ($C_{2''}$), 187.9 (C_2).Elemental analysis % calcd. (found) for $C_{23}H_{30}AgClN_2$: C, 57.814% (57.9); H, 6.328% (6.4); N, 5.863% (5.9).

2.21. Chloro[1-isobutyl-3-(3-(naphthyl)-5.6-dimethylbenzimidazole-2-ylidene] silver 3i

Yield 85%, Mp: 284.6 °C, ν(CN) = 1400 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.98 (d, 6H, $CH_{3(a,b)}$), *J* = 8 Hz), 2,26 (s, 3H, CH_3(d)), 2.35 (s, 3H, CH_3(c)), 2.36 (Hep, 1H, $H_{2'}$, *J* = 8 Hz), 4.19 (d, 2H, H1′), *J* = 8 Hz), 5.71 (s, 2H, $H_{1''}$), 7.10–7.76 (m, 9H, $H_{4, 7, 3'', 5'', 6'', 7'', 8'', 10'', 11''}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 20.3 (C $_{(a,b)}$), 20.3 (C $_{(c,d)}$), 29.2 ($C_{2'}$), 53.2 ($C_{1''}$), 56.6 ($C_{1'}$), 111.8 (C_4), 112.2 (C_7), 124.4 ($C_{7''}$), 125.9($C_{3''}$), 126.3 ($C_{10''}$), 126.5($C_{5''}$), 127.7 ($C_{8''}$), 127.9 ($C_{6''}$), 129.0 ($C_{11''}$), 132.3 (C_8), 132.8 (C_9), 133.0 (C_5), 133.1 (C_6), 133.6 ($C_{2''}$), 168.6 (C_2). Elemental analysis % calcd. (found) for $C_{24}H_{26}AgClN_2$: C, 59.337% (59.4); H, 5.395% (5.4); N, 5.766% (5.8).

2.22. Chloro[1-isobutyl-3-(anthracen-9-ylmethyl) dimethylbenzimidazole-2-ylidene]silver 3j

Yield 86%, Mp: 214.2, ν(CN) = 1468 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.90 (d, 6H, $CH_{3(a,b)}$, *J* = 4 Hz), 2.12 (s, 3H, $CH_{3(d)}$), 2.22 (Hep, 1H, $H_{2'}$, *J* = 8 Hz), 2.31 (s, 3H, $CH_{3(c)}$), 4.08 (d, 2H, $H_{1'}$, *J* = 4 Hz), 6.38 (s, 2H, $H_{1''}$), 7.87–8.22 (m, 11H, $H_{4, 7, 4'', 5'', 6'', 7'', 9'', 11'', 12'', 13'', 14''}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 20.2(C (a,b)), 20.3 (C (c)), 20.4 (C (d)), 29.1 ($C_{2'}$), 46.2 ($C_{1''}$), 57.0 ($C_{1'}$), 111.7 (C_4), 112.3 (C_7), 122.9 ($C_{9''}$), 125.2 ($C_{5''; 6''; 12''; 13''}$), 127.5 ($C_{4''; 7''; 11''; 14''}$), 129.9 ($C_{3'', 8'', 10'', 15''}$), 131.1 ($C_{8;9}$), 131.4 ($C_{5;6}$), 132.7 ($C_{2''}$), C_2: Ag-$C_{carbene}$: not observed. Elemental analysis % calcd. (found) for $C_{28}H_{28}AgClN_2$: C, 62.759% (62.8); H, 5.267% (5.3); N, 5.228% (5.3).

Antibacterial activities were prepared according the reported procedures (boubakri et al., 2018)

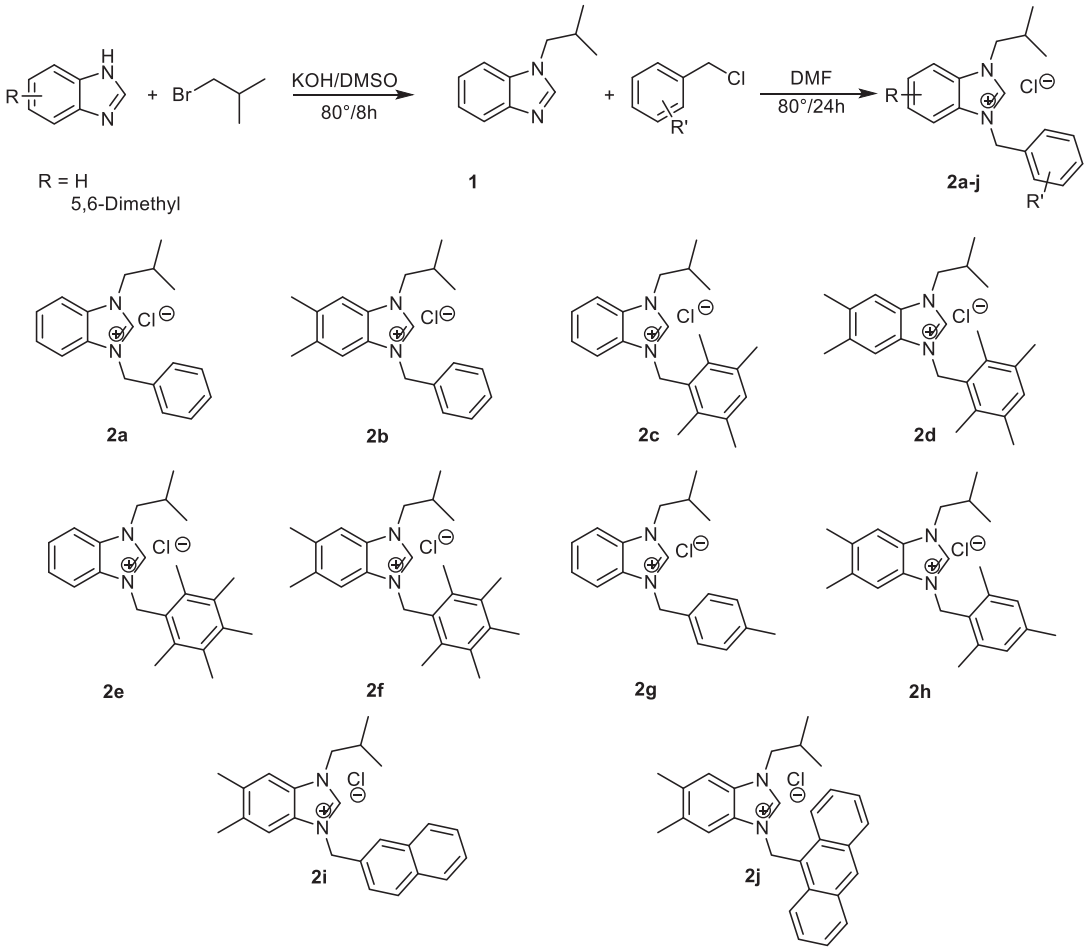
2.23. Cytotoxicity assay

Cytotoxicity of benzimidazoles salts **2a-j** and silver–NHC complexes **3a-j** was assessed using the reported procedures (Song et al., 2010).

3. Results and discussion

3.1. Preparation of benzimidazolium salts

benzimidazoles salts (**2a-j**) were prepared via the two step N-alkylation process as depicted in Scheme 1. Compound 1 was



Scheme 1. Synthesis of the benzimidazoles salts (**2a-j**).

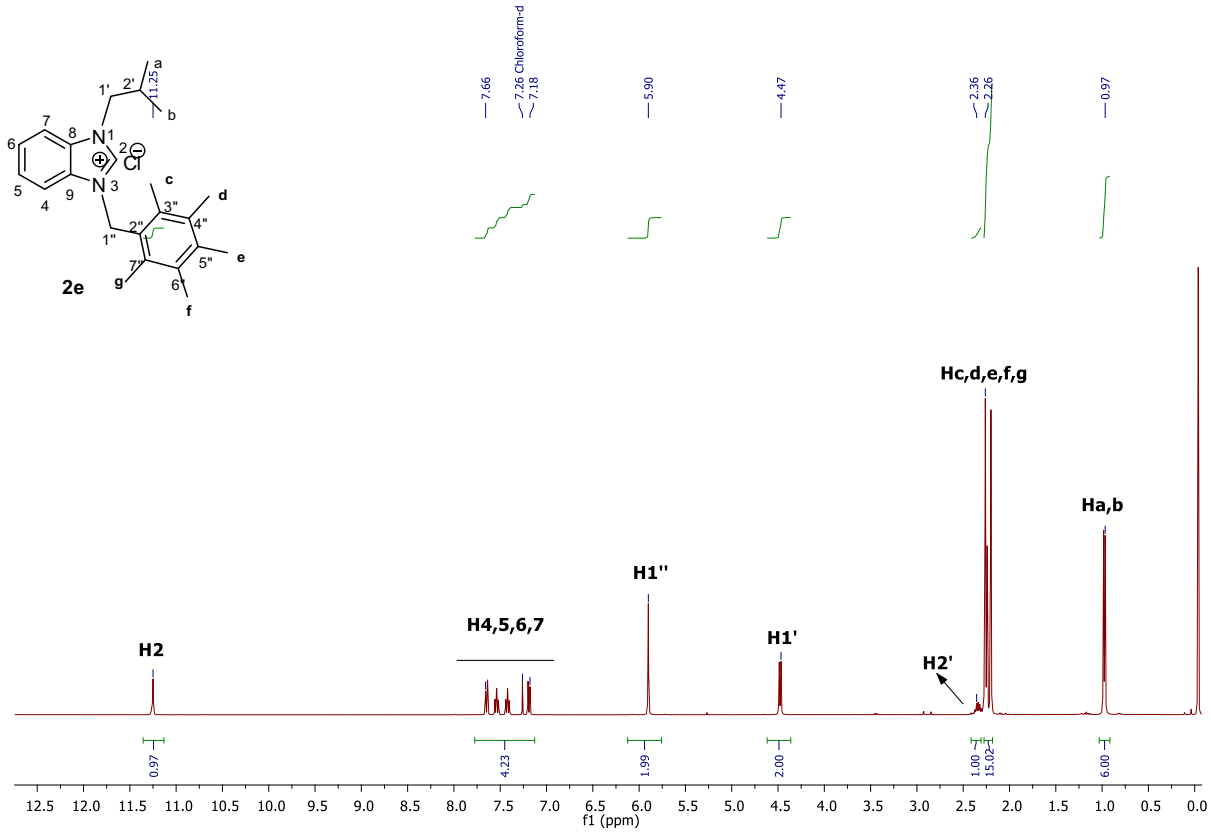


Fig. 1. ^{1}H NMR spectra of benzimidazole salt **2e** in $CDCl_3$.

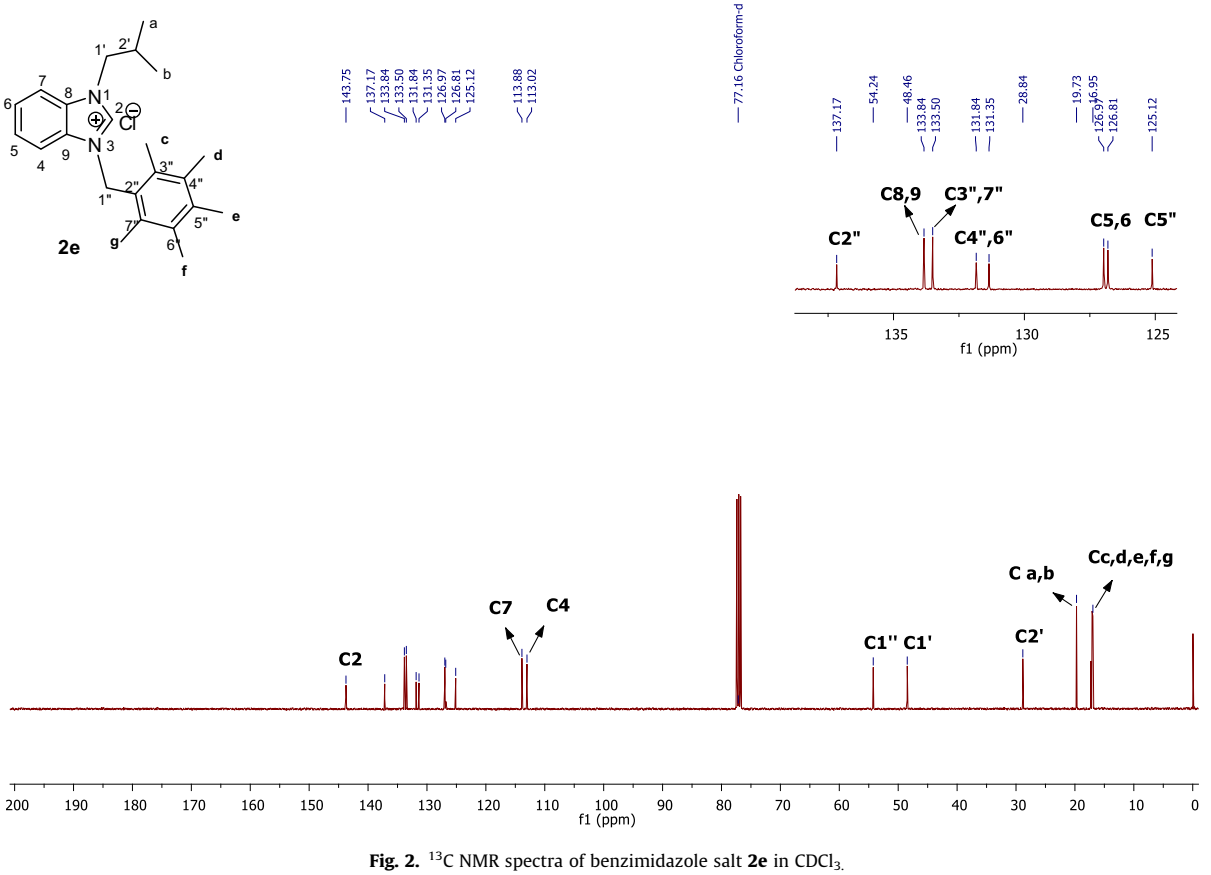


Fig. 2. ^{13}C NMR spectra of benzimidazole salt **2e** in $CDCl_3$.

obtained by N-alkylation of benzimidazole with isobutyl bromide (1-Bromo-2-methylpropane) in the presence of KOH in DMSO at 80 °C for 8 h. The benzimidazolium salts (**2a-j**) were prepared by reacting N-(isobutyl)-benzimidazole (**1**) with various aryl chloride in DMF at 80 °C for 24 h (Scheme 1). The reaction has been monitored following thin layer chromatography, and after this time the formation of salts (**2a-j**), has been observed for every target compound. The benzimidazolium salts (**2a-j**) were air- and moisture-stable both in the solid state and in solution.

The FTIR spectroscopy, ^{1}H- and ^{13}C{1H} NMR spectroscopy, and elemental analysis data of the title compounds confirm the proposed structures.

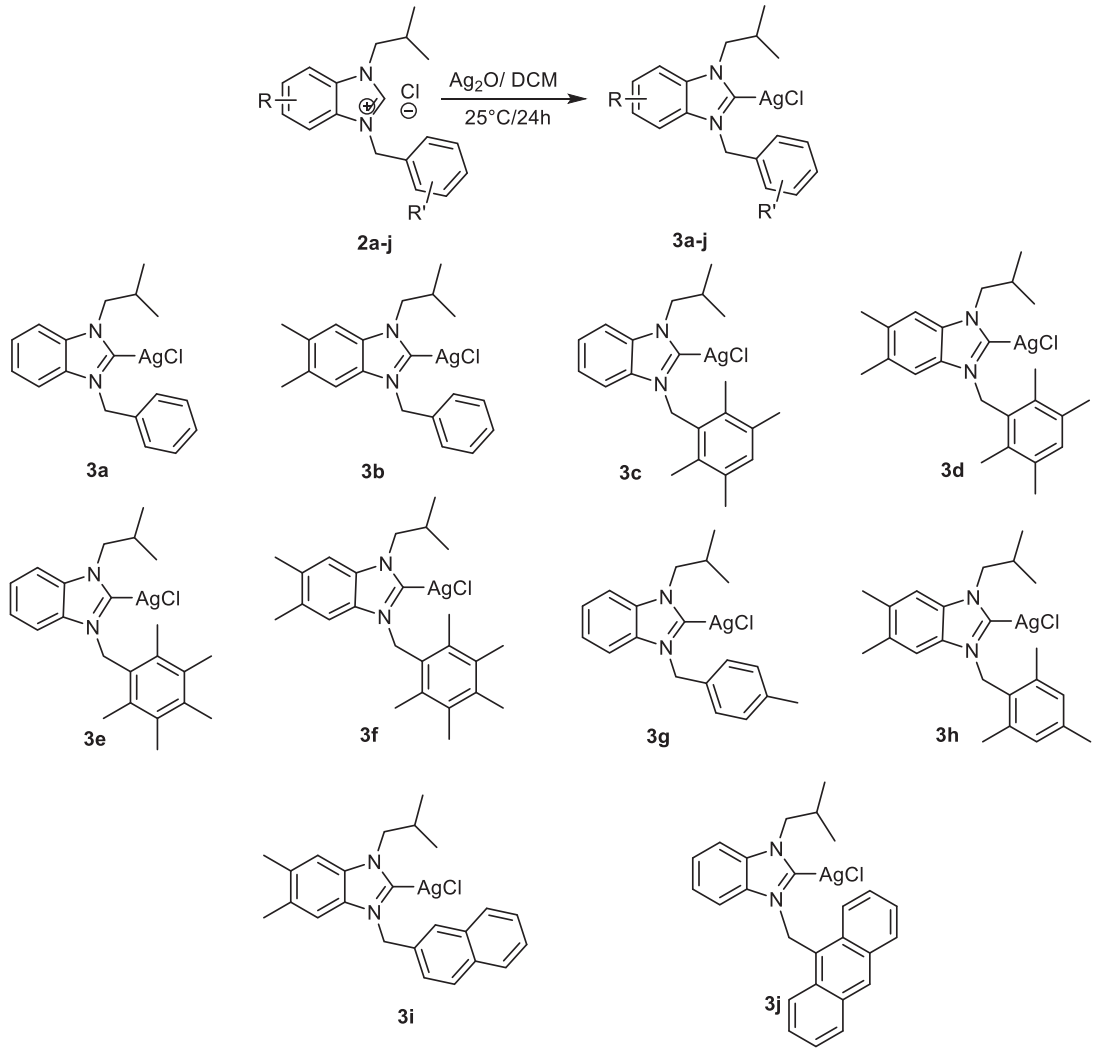
NMR spectra of all the compounds were analyzed in d-$CDCl_3$. In the ^{1}H NMR spectra, acidic protons (NCHN) for benzimidazolium salts (**2a-j**) were seen at 12.07, 11.81, 11.44, 11.08, 11.29, 10.48, 12.05, 11.34, 11.52 and 11.95 ppm, respectively, as a characteristic sharp singlet. In the ^{13}C{1H} NMR spectra of benzimidazoles salts (**2a-j**), the NCHN carbon were detected as typical singlets at 144.5, 142.8, 144.02, 142.66, 143.78, 142.39, 143.96, 142.91, 141.91 and 143.04 ppm, respectively. These values are consistent with related literature. (Hu et al.,2004; Doğan et al., 2001; Ozdemir et al., 2010; Iqbal et al., 2013).

In the IR spectra, the ν(C=N) bands for salts (**2a-j**) were observed at 1650, 1566, 1660, 1558, 1546, 1550, 1550, 1550, 1550 and 1666 cm^{-1} respectively.

Aromatic protons of benzimidazolium salts (**2a-j**) were detected in the range of 6.94–8.64 ppm. –CH– protons of isopropyl group on all benzimidazolium salts where seen as septets in the range of 2.34–2.44 ppm. Methylic protons of isopropyl group on benzimidazolium salts (**2a-j**) were resonated between 0.98 and 1.06 as doublets however methyl protons of benzimidazolium salts (**2a-j**) signaled at 2.24–2.44 ppm as singlets. In the ^{1}H NMR spectra of (**2a-j**) $H_{1'}$ protons appeared at 4.49 ppm while $H_{1''}$ protons were detected as typical singulets between at 5.90 ppm (Fig. 1).

The ^{13}C NMR spectra showed aromatic carbons of benzimidazolium salts (**2a-j**) in the range of 112.35–143.97 ppm. NCHN carbons on salts (**2a-j**) were observed at 144.5, 142.8, 144.02, 142.66, 143.78, 142.39, 143.96, 142.91, 141.91 and 143.04 ppm, respectively. Terminal carbons(a,b) of the isopropyl group of all benzimidazolium salts (**2a-j**) gave peaks at 19.86, 20.70, 20.57, 19.72, 19.79, 19.71, 19.86, 19.74, 19.87 and 19.73 respectively while –CH carbons of the isobutyl group were observed at 28.89, 28.77, 28.87, 28.87, 28.88, 28.79, 28.90, 28.77, 28.84, 28.69 respectively (Fig. 2).

The general procedure for the preparation of silver(I)-NHC complexes (**2a-j**) was performed according to the procedure of Organ (O'Brien et al., 2006). Benzimidazolium salts (**2a-j**) were incorporated into the silver(I)-NHC complexes (**3a-j**) by reaction with Ag_2O in dichloromethane for 24 h resulted in the silver-NHC complex as a white solid. Monitoring of the reaction by ^{1}H NMR



Scheme 2. Synthesis of silver(I) complexes **3a-j**.

spectroscopy in $CDCl_3$ showed that benzimidazolium salts were completely transformed into silver complexes with moderate yields (75–85%) under argon atmosphere. Ag(I) complexes were synthesized in the absence of light and all products were stored in the dark Scheme 2.

The silver complexes (**3a-j**) have a good solubility in polar solvents and are stable in the air and toward the moisture.

In the ^{1}H NMR spectra the acidic imino proton of benzimidazolium salts (NCHN) were not observed between δ10.48–12.07 ppm. Fig. 3 Similarly, in the ^{13}C NMR spectra, imino carbon of benzimidazolium salts (NCHN) were not observed between δ 141–144 ppm.

Therefore, in the ^{1}H NMR spectrum Ag(I)-NHC complexes (**3a-j**), the disappearance of an acidic proton is evidence of formation complex. In the^{13}C NMR spectra of salts (**2a-j**) the characteristic signals of carbon (NCHN) were seen as singlets at 144.5, 142.8, 144.02, 142.66, 143.78, 142.39, 143.96, 142.91, 141.91 and 143.04 ppm, respectively for benzimidazolium salts while for complex (**3a-j**) a signal of carbon (NCN) have shifted greatly downfield region compared to the corresponding benzimidazolium salt (**2a-j**) and were observed at 189.35, 189.06, 185.29, 187.95, 168.65, ppm respectively for complexes **3b**, **3e**, **3f**, **3h** and **3i** however, the rest of carbon signal for complexes **3a**, **3b**, **3e**, **3g** and **3j** were not observed. Fig. 4. These values, and the lack of the carben peak are in agreement with reported data for similar Ag-NHC complexes (Pytkowicz et al., 2001). At the same time, formation of the Ag(I)-NHC complexes (**3a-j**) was proven by IR spectra, which showed CN bond vibrations at 1466, 1400, 1450, 1466, 1458, 1591, 1468, 1458, 1400, 1468 cm^{-1}, respectively.

All the synthesized benzimidazolium salts (**2a-j**) and their corresponding silver(I) complexes (**3a-j**) were tested for antibacterial and antioxidant activities as per details given in the following text.

4. Biological activities

All the synthesized benzimidazolium salts (**2a-j**) and their corresponding silver(I) complexes (**3a-j**) were investigated for antibacterial against the both gram (+)/(−) bacterials. The DMSO did not exhibit any antimicrobial activity as reported earlier (Shahini et al., 2017; Patil et al., 2010a,b; Gleeson et al.,2008). The antimicrobial activities of the NHC precursors (**2a-j**) and their corresponding silver complexes (**3a-j**) are reported in Table 1.

Compound **3i** is more active than compounds **3h** and **3c** against the *Micrococcus luteus* LB 14110. The complexes have shown antibacterial activity to different extents, according on the typr of ligand. The silver complexes have shown enhanced activity compared with the benzimidazolium salts. The complexes exhibited enhanced antibacterial activity, which could be explained by the increased lipophilicity due to the synergistic effect of the complexes. Observed antibacterial activity of these complexes is comparable to that of our previous silver complexes (Achar et al., 2018a,b).

The MIC values of tested silver complexes and their starting material against *Listeria monocytogenes* ATCC 19117, *Salmonella Typhimurium* ATCC 14,028 and *Micrococcus luteus* are presented in Tables 2.

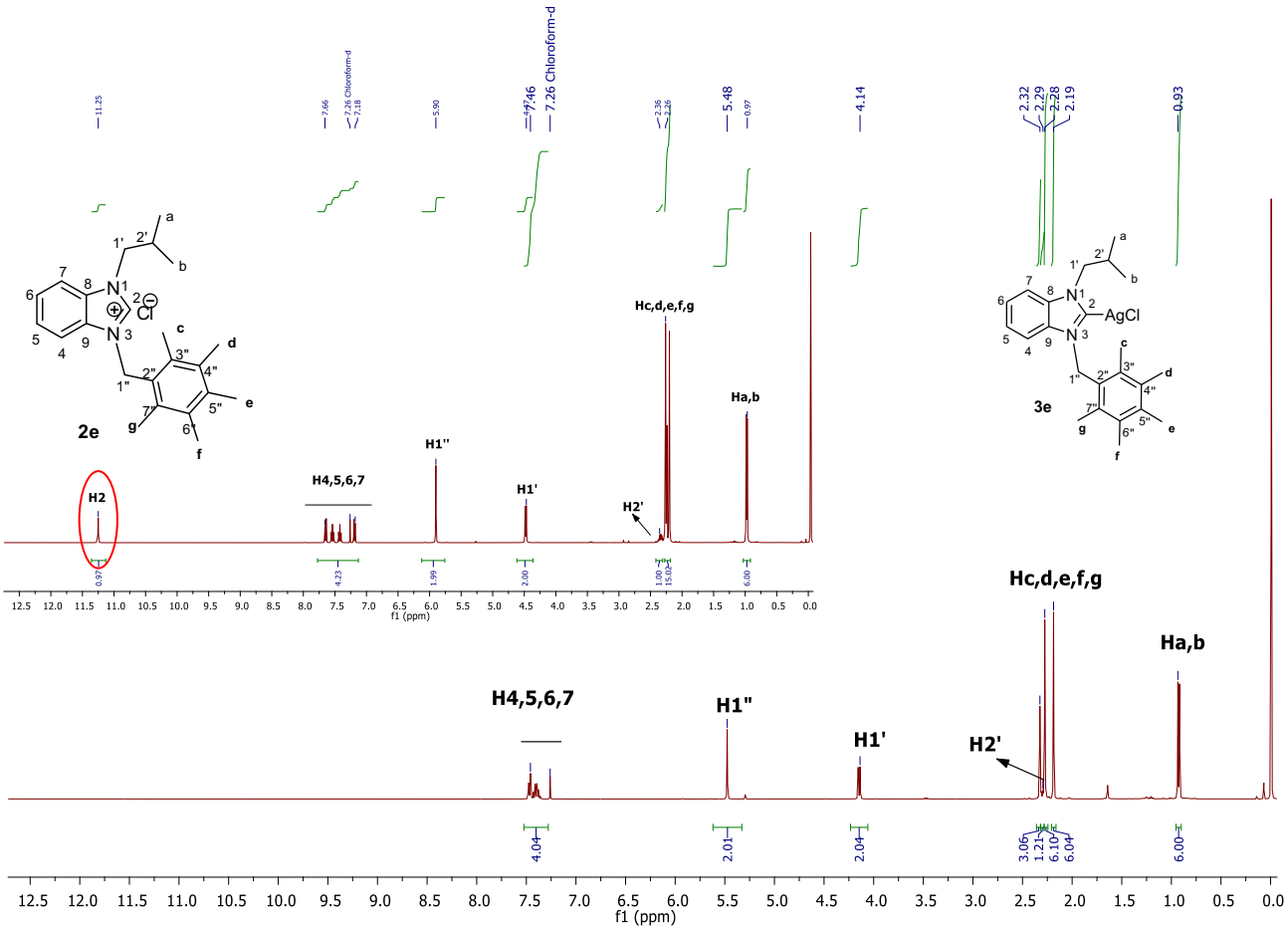


Fig. 3. ^{1}H NMR spectra of silver complex **3e** in $CDCl_3$.

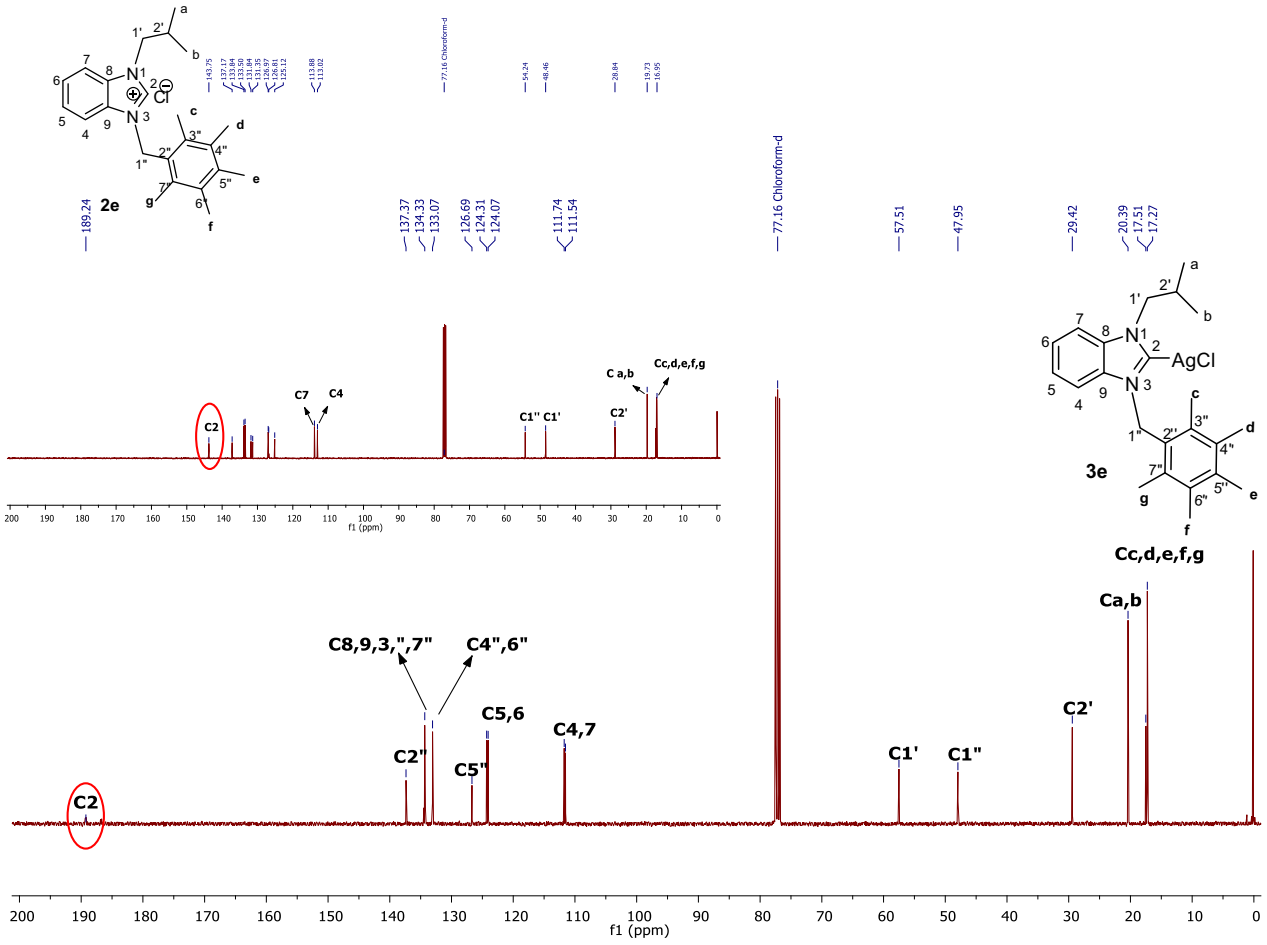


Fig. 4. ^{13}C NMR spectra of silver complex **3e** in $CDCl_3$.

Table 1
Zone of bacterial inhibition measured in mm of the synthesized salts and silver complexes.

Microorganisms Compounds	*Micrococcus luteus* LB 14,110	*Listeria monocytogenes* ATCC 19,117	*Salmonella Typhimurium* ATCC 14,028	*Staphylococcus aureus* ATCC 6538	*Pseudomonas aeruginosa*
3a	20 ± 0.6	14 ± 0.5	18 ± 0.54	16 ± 0.25	16 ± 0.13
3b	22 ± 0.6	15 ± 0.6	18 ± 0.5	17 ± 0.3	17 ± 0.14
3c	35 ± 0.5	16 ± 0.2	18 ± 0.5	18 ± 0.5	22 ± 0.2
3d	30 ± 0.5	14 ± 0.5	16 ± 0.10	18 ± 0.11	16 ± 0.19
3e	25 ± 0.33	22 ± 0.5	18 ± 0.5	18 ± 0.18	20 ± 0.45
3f	36 ± 0.2	16 ± 0.3	18 ± 0.5	20 ± 0.1	20 ± 0.4
3g	28 ± 0.32	16 ± 0.5	22 ± 0.44	18 ± 0.15	22 ± 0.5
3h	30 ± 0.4	16 ± 0.2	16 ± 0.2	20 ± 0.2	18 ± 0.2
3i	38 ± 0.2	22 ± 0.2	22 ± 0.3	22 ± 0.2	20 ± 0.4
3j	34 ± 0.44	22 ± 0.5	22 ± 0.15	22 ± 0.3	20 ± 0.25
2a	20 ± 0.22	–	22 ± 0.22	18 ± 0.05	18 ± 0.22
2b	18 ± 0.2	20 ± 0.2	16 ± 0.3	20 ± 0.2	18 ± 0.2
2c	16 ± 0.2	18 ± 0.3	18 ± 0.22	16 ± 0.0	16 ± 0.5
2d	22 ± 0.2	16 ± 0.2	14 ± 0.2	20 ± 0.2	16 ± 0.2
2e	18 ± 0.2	18 ± 0.22	18 ± 0.33	18 ± 0.23	18 ± 0.22
2f	30 ± 0.4	22 ± 0.7	30 ± 0.4	25 ± 0.2	18 ± 0.22
2g	22 ± 0.3	16 ± 0.4	22 ± 0.4	18 ± 0.2	18 ± 0.2
2h	10 ± 0.4	14 ± 0.5	12 ± 0.10	14 ± 0.15	16 ± 0.10
2i	32 ± 0.32	–	16 ± 0.15	18 ± 0.1	18 ± 0.15
2j	20 ± 0.4	18 ± 0.5	18 ± 0.24	18 ± 0.5	18 ± 0.16

Minimum inhibitory concentration (MIC) determination

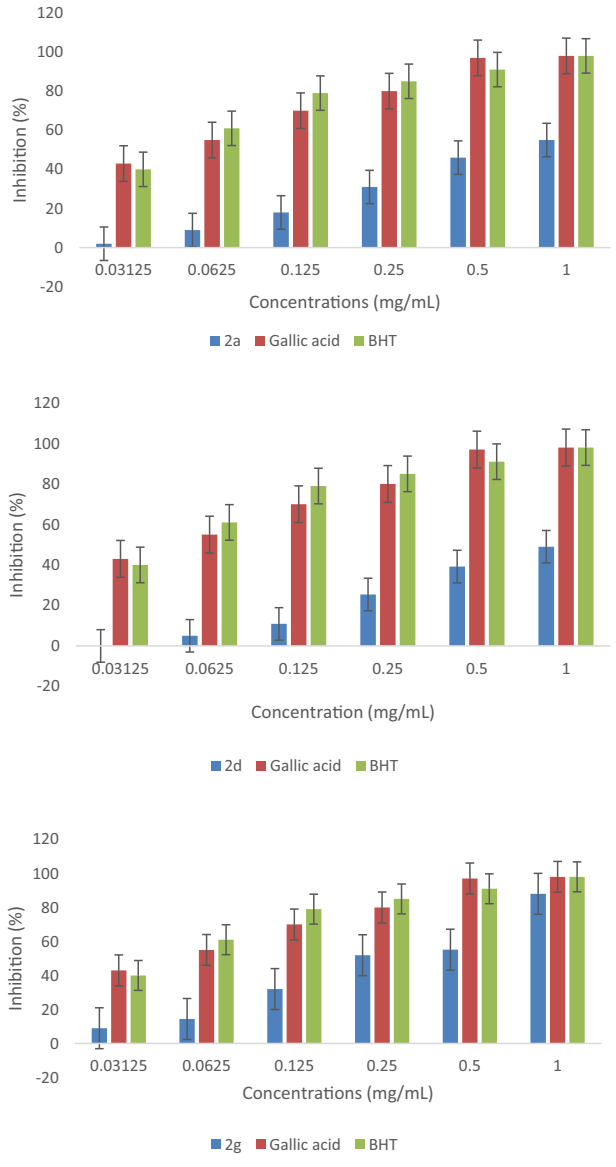
Silver complex **3f** showed good activity than that of ampicillin against Micrococcus luteus with a MIC of 0.0024 mg/mL. while a MIC of 0.048 mg/mL was observed in the case of Salmonella Typhimurium for the silver complex **3f**. MICs of other compounds remained within the tested range.

4.1. Antioxydant activities

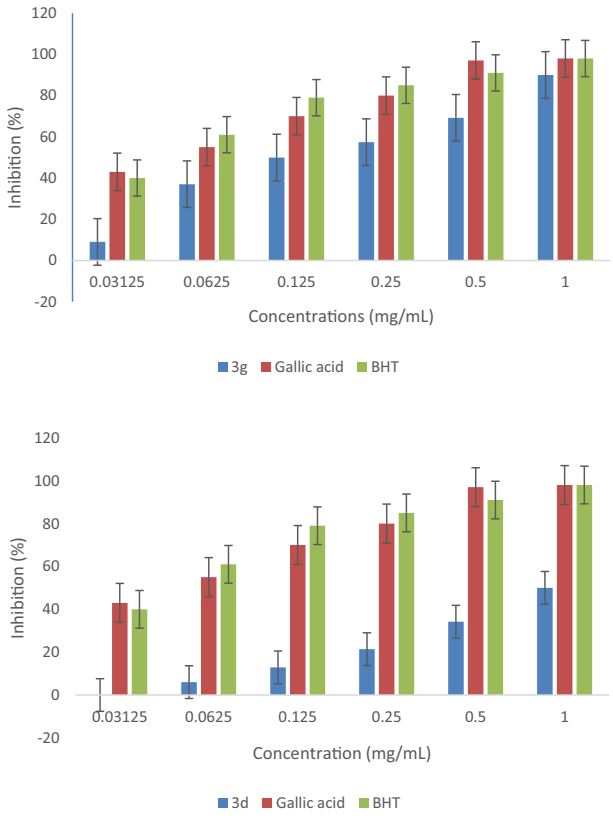
The scavenging activity of the synthesized of the NHC precursors (Scheme 3) and silver complexes with DPPH (1,1-diphenyl-2-picrylhydrazyl) is represented in Scheme 4.

Table 2
Minimal bacterial inhibitory concentration measured in mg/mL of benzimidazoles salts and silver–NHC complexes.

Microorganismindicator	Compounds	MIC (mg/ml)
Listeria monocytogenes ATCC 19,117	**2h**	1,25
	2j	0,625
	3f	0,0048
	Ampicillin	0.039
Salmonella Typhimurium ATCC 14,028	**2h**	1,25
	2j	0,039
	3f	0,0024
	Ampicillin	0,625
Micrococcus luteus	**2h**	0,3125
	2j	0,3125
	3f	0,0024
	Ampicillin	0,0195



Scheme 3. DPPH radicals scavenging activity of benzimidazoles salts, **2a**, **2d**, **2g**.



Scheme 4. DPPH radicals scavenging activity of (Ag-NHC) complexes, **3d**, **3g**.

Table 3
Anticancer of synthesized of benzimidazoles salts **2a-j** and silver–NHC complexes **3a-j**.

benzimidazoles salts **2a-j** and silver–NHC complexes **3a-j**	Anticancer activity LC_{50} in μg/ml	
3a	MCF7	MDA-MB-231
3b	4.2 ± 3.6	2.5 ± 4.3
3c	3.1 ± 3.1	2.6 ± 5.9
3d	1.7 ± 3.1	16 ± 2.8
3e	4.3 ± 1.8	0.0 ± 00
3f	0.68 ± 3.2	1.93 ± 2.6
3g	1.3 ± 4.1	3.3 ± 2.9
3h	2.0 ± 3.2	2.8 ± 2.9
3i	0.62 ± 3.1	1.95 ± 2.5
3j	1.3 ± 4.1	3.4 ± 2.9
2a	2.0 ± 3.2	2.7 ± 2.8
2b	NA	NA
2c	3.1 ± 5.9	6.3 ± 3.2
2d	NA	NA
2e	0.6 ± 2.9	3.1 ± 5.9
2f	Higher than 100 μg/ml	Higher than 100 μg/ml
2g	Higher than 100 μg/ml	Higher than 100 μg/ml
2h	Higher than 100 μg/ml	Higher than 100 μg/ml
2i	Higher than 100 μg/ml	Higher than 100 μg/ml
2j	Higher than 100 μg/ml	Higher than 100 μg/ml
Tetracycline[a]	NT	NT

Values are mean value ± standard deviation of three different replicates.
[a] The concentration was 30 μg, NT: not tested, NA: not active.

The analysis of the results showed that the profiles of obtained antiradical activity of the tested synthetic products **3g** and **3d** have a very important anti-radical activity and showed higher antioxidant activity than other products. For a used concentration (0.0625 mg/ml), the product 2d has the lowest radical activity comparing to the gallic acid and BHT (butylated hydroxytoluene). On the same way the compounds **2a**, **2g**, and **3d** for a concentration

equal to 0.0625 mg/ml had a lower radical activity than gallic acid and BHT (butylated hydroxytoluene). At a concentration of 1 mg/ml, these products **2a**, **2d**, **2g**, **3g** and **3d** revealed a significant activity of DPPH compared with the synthetic antioxidants.

Cytotoxic Activities

In order to evaluate their cytotoxicity, the benzimidazoles salts **2a-j** and silver–NHC complexes **3a-j** were screened against the two human cancer cell lines, MDA-MB-231 and MCF7. The results are presented in Table 3

As shown in Table 3, the cytotoxicity of **3i** and **3f** were much greater in MCF7 with IC_{50} values 0.68 and 0.6 μg/ml, respectively as compared to their activity on MDA-MB-231 cells. The cytotoxicity of compound **3j** in MCF7 and MDA-MB-231 cells was 2.3 and 3.4 μg/ml, while the IC_{50} values of compound on **2a** were 2 and 2.7 μg/ml against MCF7 and MDA-MB-231, respectively. For the compounds **2f-j** their IC50 values were more than 100 μg/ml. The compound **2d** was inactive.

5. Conclusion

In this study six benzimidazolium salts and their silver(I)–NHC complexes have been prepared and characterized by ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. In addition, these compounds showed significant activities compared with standard antibiotic. In addition, the silver(I)–NHC complexes showed significant antitumor activity against the cell lines MCF-7 and MDA-MB-231. In the aim to determine the antimicrobial activity specificity and spectra of action, studies are now in progress including a larger collection of bacteria of different species in order to provide possible application in different fields. Also advanced investigations focusing on new Au and Ag–NHC complexes as metallopharmaceutical compounds are in process.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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