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FULL PAPER

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Non–symmetrically *p*–nitrobenzyl–substituted *N*–heterocyclic carbene–silver(I) complexes as metallopharmaceutical agents

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In the present work, a series of eight new imidazole, 4,5–dichloroimidazole, 4,5–diphenylimidazole and benzimidazole based nitro–functionalized mono–*N*–heterocyclic carbene (NHC)–silver(I) acetate (**7a–d**) and bis–NHC–silver(I) hexafluorophosphate complexes (**8a–d**) were synthesised by the reaction of the corresponding azolium hexafluorophosphate salts (**6a–d**) with silver(I) acetate and silver(I) oxide in methanol and acetonitrile, respectively. All the synthesised compounds were fully characterized by various spectroscopic techniques and elemental analyses. Additionally, the structure of bis–(1–benzyl–3–(*p*–nitrobenzyl)–4,5–dichloroimidazole–2–ylidene)silver(I) hexafluorophosphate complex (**8b**) was confirmed by single crystal X–ray diffraction analysis. Preliminary *in vitro* antibacterial evaluation was conducted for all the compounds (**6a–d**), (**7a–d**), and (**8a–d**) by Kirby–Bauer's disc diffusion method followed by the determination of Minimum Inhibitory Concentration (MIC) from broth macrodilution method against five standard bacteria; two Gram–positive bacterial strains (*Staphylococcus aureus and Bacillus subtilis)* and three Gram–negative bacterial strains *(Escherichia coli, Shigella sonnei,* and *Salmonella typhi).* All the hexafluorophosphate salts (**6a–d**) were found inactive against the tested bacterial strains and their corresponding mono– and bis–NHC–silver(I) complexes (**7a–d** and **8a–d**) exhibited moderate to high antibacterial activity with MIC value in the range 8–128 μg/mL. In addition, preliminary *in vitro* anticancer potential of all the silver(I) complexes (**7a–d** and **8a–d**) was determined against the human derived breast adenocarcinoma cells (MCF 7) by MTT assay. All the mono– and bis–NHC–silver(I) complexes (**7a–d** and **8a–d**) orchestrated high anticancer potential with IC_{50} values ranging from 10.39 to 59.56 nM. In comparison, mono– NHC–silver(I) complexes performed better than the bis–NHC–silver(I) complexes.

KEYWORDS

antibacterial drugs, anticancer agents, MCF 7, *N*–heterocyclic carbene, silver, synthesis and characterization

1 | INTRODUCTION

Cancer is the second highest cause of death threatening millions of lives worldwide with an alarming increase in mortality each year.[1] With this incentive, recent research has devised diverse approaches to combat the death dealing effects of cancer, among which chemotherapy is eminent and is widely applied. Cisplatin, the most common chemotherapeutic agent and its derivative, carboplatin, treat ovarian, lung, bladder, head and neck cancers.[2,3] In spite of being

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excessively efficient, they pose disturbing side effects[4,5] and the recent reports of chemo–resistance is of growing concern.[6] On the other hand, an upswing in drug resistance in bacterial strains are unsettling, to overcome which is the dire need of an equally competitive alternate. Among the best alternatives counted are the NHC–metal complexes that have been in the foreground since the discovery and isolation of free NHCs.[7–12] NHC–metal complexes are being explored for numerous applications like pharmaceutical, catalysis, luminescence, functional materials, etc. till date[13,14] and they have been exhibiting favourable results in preclinical investigations and are attaining prominence for the ease of synthesis, stability and diversity that can be achieved by varying the *N*–heterocyclic core, the substituents, and the metal centre.[14–17]

Since the first reports of biological importance of NHC–silver(I) compounds by Youngs *et al*., researchers have delved into designing an effective prescription for cancer as well as bacterial infections utilising silver, owing to the employment of silver in medicine since antique times and its low toxicity.[18–22] In addition to the metal centre, the other components of an effective NHC–metal complex are the *N*–heterocyclic core and the N,N′–substituents, whose right combination results in an excellent drug with precise lipophilicity to penetrate in to an infected cell and the ability to release the metal ions at a controlled rate.[23–25] Further, the variety of drug design employed in NHC-silver complexes for biological applications has been thoroughly reviewed[2,26–28] which served as a motivation to accomplish the present work that examines and compares the effect of different cores viz., imidazole, 4,5–dichloroimidazole, 4,5–diphenylimidazole and benzimidazole on the antibacterial and anticancer activity of the corresponding mono– and bis–NHC–silver(I) complexes against both Gram–positive and Gram–negative bacterial species and the human derived breast adenocarcinoma cells (MCF 7), respectively. However, as the N,N′–substituents play a crucial role in the biological relevance of the complexes, the study involves *p*–nitrobenzyl substitution on the aforementioned core molecules as it is well known for being utilised in the synthesis of medically relevant molecules ranging from antipyretics and analgesics to antipsychotic drugs.[29–32] Having the symmetric substitution previously reported complex with silver(I) acetate,[33] the current investigation deals with asymmetric compounds of mono– and bis–NHC–silver(I) complexes. Moreover, a reported 1–benzyl–3–*p*–nitrobenzyl benzimidazolium salt similar to (**5d**) did not deal with the targeted biological studies.[34] Therefore, the core of the study is to compare the preliminary biological activities of the hexafluorophosphate salts (**6a–d**) and their corresponding NHC–silver(I) complexes (**7a–d** and **8a–d**). Further, a comparison can be made on the biological efficacies of mono– and bis–NHC–silver(I) complexes, which facilitates to establish a structure activity relationship.

We hereby report the synthesis, characterization and preliminary *in vitro* antibacterial and anticancer activities of a series of non–symmetrically *p*–nitrobenzyl–substituted mono– and bis–NHC–silver(I) complexes.

2 | EXPERIMENTAL PROTOCOL

2.1 | Materials and methods

All the reactions were carried out under aerobic conditions in oven–dried glassware with magnetic stirring. Imidazole, benzimidazole, 4,5–diphenylimidazole, 4,5–dichloroimidazole, benzyl bromide, *p*–nitrobenzyl bromide, potassium hydroxide, potassium hexafluorophosphate, silver(I) acetate and silver(I) oxide were procured commercially from Sigma–Aldrich chemical company and were used without further purification. Heating was accomplished by either a heating mantle or silicone oil bath. Reactions were monitored by thin–layer chromatography (TLC) performed on 0.25 mm Merck TLC silica gel plates, using UV light as a visualizing agent. Concentration under vacuum refers to the removal of volatile solvent using a rotary evaporator attached to a dry diaphragm pump (10–15 mm Hg) followed by pumping to a constant weight with an oil pump (<300 mTorr). ^{1}H NMR spectra were recorded on Bruker 300 MHz or Bruker AVANCE III 400 MHz spectrometer, and are reported relative to DMSO–d_6 (δ 2.50 ppm). ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz) and multiplicities are designated as, s (singlet), d (doublet), t (triplet), m (multiplet). Proton–decoupled ^{13}C NMR spectra were recorded at 75 MHz or 100 MHz and reported relative to DMSO–d_6 (δ 39.5 ppm). ATR–IR spectra were recorded on a Bruker ECO–ATR spectrophotometer in the range 600–4000 cm^{-1}. Elemental analyses were performed using a PerkinElmer 2400 Series II CHN/S microanalyzer. X–ray intensity data of 6686 reflections (of which 3027 unique) were collected at room temperature on a Bruker X8 Proteum diffractometer equipped with graphite monochromated CuK\a radiation (k = 1.54178 Å). The crystal used for data collection was of dimensions 0.30 x 0.29 x 0.27 mm. The intensities were measured by ϕ and ω scan mode for θ ranges 5.38–64.45. The structure was solved by direct methods using SHELXS97.[35] Full–matrix least squares refinement was carried out using SHELXL97.[35] The Ag(1), P(1), F(1), F(2), F(3), F(4), F(5) and F(6) atoms lie on a special position, and the occupancy factors are all 0.5. All the hydrogen atoms bound to carbon atoms were placed at idealized positions and refined as riding atoms. All non-hydrogen atoms were refined anisotropically on F^2 by full-matrix least–square using all unique data; the goodness of fit on F^2 was 1.023. The final refinement cycles converged to an

R = 0.0741 and wR (F2) = 0.2037 for the observed data. Residual electron densities ranged from −2.453 to 2.316 e Å $^{-3}$. Crystallographic data of the structure reported in this article was deposited with the Cambridge Crystallographic Data Center with the deposition number 1517151. A copy of the data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336–033; e–mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk/deposit].

3 | SYNTHESIS

3.1 | General experimental procedure for the synthesis of 1–benzyl azoles (3a–d)

1–Benzyl azoles were synthesized according to the literature procedure with slight modifications.[36] A mixture of imidazole/4,5–dichloroimidazole/4,5–diphenylimidazole/benzimidazole (1 mmol) and potassium hydroxide (0.08 g, 1.5 mmol) were stirred at 100 °C for 2 h in minimum amount of DMSO. The temperature of the reaction mixture was reduced to 40 °C and then benzyl bromide (**2**) (0.11 mL, 1.0 mmol) was added in one portion, and stirring was continued for further 2 h. Later, the reaction mixture was cooled to room temperature and ice cold water was added. The precipitate was separated by decantation and washed with water (3 x 10 mL). The product was then extracted using chloroform and reduced under vacuum to obtain pure (**3a–d**).

3.2 | Synthesis of 1–benzyl–1*H*–imidazole (3a)

Compound (**3a**) was synthesized from imidazole (**1a**) (0.06 g, 1.0 mmol), according to the general procedure. Pale yellow solid. Yield: 89.92% (0.14 g).

3.3 | Synthesis of 1–benzyl–4,5–dichloro–1*H*–imidazole (3b)

Compound (**3b**) was synthesized from 4,5–dichloroimidazole (**1b**) (0.13 g, 1.0 mmol), according to the general procedure. White solid. Yield: 71.54% (0.16 g).

3.4 | Synthesis of 1–benzyl–4,5–diphenyl–1*H*–imidazole (3c)

Compound (**3c**) was synthesized from 4,5–diphenylimidazole (**1c**) (0.22 g, 1.0 mmol), according to the general procedure. White solid. Yield: 74.93% (0.23 g).

3.5 | Synthesis of 1–benzyl–1*H*–benzimidazole (3d)

Compound (**3d**) was synthesized from benzimidazole (**1d**) (0.11 g, 1.0 mmol), according to the general procedure. Pale yellow solid. Yield: 88.35% (0.18 g).

3.6 | General experimental procedure for the synthesis of 1–benzyl–3–(4–nitrobenzyl)–azolium bromides (5a–d)

A mixture of 1–benzyl azole (1.0 mmol) and *p*–nitrobenzyl bromide (**4**) (0.21 g, 1.0 mmol) in dioxane (30 mL) was stirred at 100 °C for 24 h. Then the reaction mixture was cooled to room temperature. The precipitate was filtered, washed with fresh dioxane (30 mL) and dried under vacuum to get pure **5a–d**.

3.7 | Synthesis of 1–benzyl–3–(4–nitrobenzyl) imidazolium bromide (5a)

Compound (**5a**) was synthesized from 1–benzyl–1*H*–imidazole **(3a)** (0.15 g, 1.0 mmol), according to the general procedure. Pale yellow viscous liquid. Yield: 90.12% (0.33 g).

3.8 | Synthesis of 1–benzyl–3–(4–nitrobenzyl)–4,5–dichloroimidazolium bromide (5b)

Compound (**5b**) was synthesized from 1–benzyl–4,5–dichloro–1*H*–imidazole **(3b)** (0.22 g, 1.0 mmol), according to the general procedure. White solid. Yield: 72.58% (0.32 g).

3.9 | Synthesis of 1–benzyl–3–(4–nitrobenzyl)–4,5–diphenylimidazolium bromide (5c)

Compound (**5c**) was synthesized from 1–benzyl–4,5–diphenyl–1*H*–imidazole **(3c)** (0.31 g, 1.0 mmol), according to the general procedure. White solid. Yield: 73.48% (0.38 g).

3.10 | Synthesis of 1–benzyl–3–(4–nitrobenzyl) benzimidazolium bromide (5d)

Compound (**5d**) was synthesized from 1–benzyl–1*H*–benzimidazole **(3d)** (0.20 g, 1.0 mmol), according to the general procedure. White solid. Yield: 83.32% (0.35 g).

3.11 | General experimental procedure for the synthesis of 1–benzyl–3–(4–nitrobenzyl)azolium hexaflourophosphates (6a–d)

The bromide salts **(5a–d)** (1.0 mmol) were directly converted into their hexafluorophosphate counterpart by salt metathesis reaction using KPF_6 (0.27 g, 1.5 mmol) in a mixture of methanol (20 mL) and water (5 mL). The resultant mixture was

stirred for 4 h at room temperature and poured into water (100 mL). The separated precipitate was filtered and washed with water (100 mL) and dried under vacuum to obtain (**6a–d**) in high purity.

3.12 | Synthesis of 1–benzyl–3–(4–nitrobenzyl) imidazolium hexafluorophosphate (6a)

Compound (**6a**) was synthesized from 1–benzyl–3–(4–nitrobenzyl)imidazolium bromide **(5a)** (0.32 g, 1.0 mmol), according to the general procedure. White solid. Yield: 74.51% (0.32 g). ^{1}H NMR (δ ppm, DMSO–d_6, 300 MHz): 9.39 (s, 1H, NCHN), 8.31 (d, J = 8.7 Hz, 2H, $CH_{Nitrobenzyl}$), 7.86 (s, 2H, $CH_{Nitrobenzyl}$), 7.68 (d, J = 8.7 Hz, 2H, CH_{Imid}), 7.43 (m, 5H, CH_{Benzyl}), 5.59 (s, 2H, CH_2), 5.44 (s, 2H, CH_2). ^{13}C NMR (δ ppm DMSO–d_6, 75 MHz, proton decoupled): 142.4, 137.2, 135.0, 130.0, 129.5, 129.3, 128.8, 124.5, 123.6 (NCN + C_{Imid} + $C_{Nitrobenzyl}$), 52.6 (CH_2), 51.6 (CH_2). ATR–IR (cm^{-1}): 2954.4 (w), 1566.7 (m), 1516.8 (s), 1343.0 (s), 1207.3 (m), 1160.4 (m), 1108.3 (m), 1035.9 (m), 955.2 (m), 840.6 (s), 804.9 (s), 737.3 (s), 708.6 (s), 660.0 (m), 629.8 (m). Micro Analysis Calculated for $C_{17}H_{16}N_3O_2PF_6$: C, 46.5; H, 3.7; N, 9.6%; Found: C, 46.5; H, 3.7; N, 9.6%.

3.13 | Synthesis of 1–benzyl–3–(4–nitrobenzyl)–4,5–dichloroimidazolium hexafluorophosphate (6b)

Compound (**6b**) was synthesized from 1–benzyl–3–(4–nitrobenzyl)–4,5–dichloroimidazolium bromide **(5b)** (0.39 g, 1.0 mmol), according to the general procedure. White solid. Yield: 64.76% (0.32 g). ^{1}H NMR (δ ppm, DMSO–d_6, 300 MHz): 9.68 (NCHN), 8.33 (d, J = 8.7 Hz, 2H, $CH_{Nitrobenzyl}$), 7.73 (d, J = 8.7 Hz, 2H, $CH_{Nitrobenzyl}$), 7.48–7.45 (m, 5H, CH_{Benzyl}), 5.71 (CH_2), 5.54 (CH_2). ^{13}C NMR (δ ppm DMSO–d_6, 75 MHz, proton decoupled): 148.1, 140.54, 137.6, 132.9, 129.9, 129.4, 219.4, 128.8, 124.4, 119.9, 119.7 (CCl + C_{Benzyl} + $C_{Nitrobenzyl}$), 52.1 (CH_2), 51.2 (CH_2). ATR–IR (cm^{-1}): 2851.0 (w), 1551.5 (m), 1451.6 (m), 1425.1 (m), 1344.1 (s), 1185.0 (m), 1143.9 (m), 1115.9 (m), 1083.1 (m), 1006.1 (m), 961.8 (m), 931.7 (m), 848.5 (m), 799.8 (s). Micro Analysis Calculated for $C_{17}H_{14}N_3O_2Cl_2PF_6$: C, 40.2; H, 2.8; N, 8.3%; Found: C, 41.26; H, 3.54; N, 8.39%.

3.14 | Synthesis of 1–benzyl–3–(4–nitrobenzyl)–4,5–diphenylimidazolium hexafluorophosphate (6c)

Compound (**6c**) was synthesized from 1–benzyl–3–(4–nitrobenzyl)–4,5–diphenylimidazolium bromide **(5c)** (0.48 g, 1.0 mmol), according to the general procedure. White solid. Yield: 68.03% (0.40 g). ^{1}H NMR (δ ppm DMSO–d_6, 400 MHz): 9.04 (s, 1H, NCHN), 7.99 (d, J = 8.4 Hz, 2H, $CH_{Nitrobenzyl}$), 7.38–6.98 (m, 17H, $CH_{Nitrobenzyl}$ + CH_{Benzyl} + CH_{Imid}), 5.41 (s, 2H, CH_2), 5.27 (s, 2H, CH_2). ^{13}C NMR (δ ppm DMSO–d_6, 100 MHz, proton decoupled): 147.7, 141.9, 137.5, 134.6, 132.4, 132.2, 131.2, 131.2, 130.6, 129.5, 129.2, 128.9, 128.4, 125.3, 125.2, 124.1 (C_{Imid} + $C_{Nitrobenzyl}$ + C_{Benzyl}), 51.12 (CH_2), 50.34 (CH_2). ATR–IR (cm^{-1}): 2896.6 (w), 1555.3 (m), 1445.7 (m), 1344.8 (s), 1181.3 (m), 1106.7 (m), 1070.6 (m), 1022.4 (m), 972.3 (m), 849.66 (m), 766.5 (s). Micro Analysis Calculated for $C_{29}H_{24}N_3O_2PF_6$: C, 58.9; H, 4.1; N, 7.1%; Found: C, 60.1; H, 4.3; N, 7.7%.

3.15 | Synthesis of 1–benzyl–3–(4–nitrobenzyl) benzimidazolium hexafluorophosphate (6d)

Compound (**6d**) was synthesized from 1–benzyl–3–(4–nitrobenzyl)benzimidazolium bromide **(5d)** (0.37 g, 1.0 mmol), according to the general procedure. White solid. Yield: 81.30% (0.39 g). ^{1}H NMR (δ ppm DMSO–d_6, 300 MHz): 10.14 (m, 1H, NCHN), 8.30 − 8.28 (m, 2H, $CH_{Nitrobenzyl}$), 8.00–7.98 (m, 2H, $CH_{Nitrobenzyl}$), 7.94–7.91 (m, 2H, $CH_{Benzimid}$), 7.81–7.77 (m, 2H, $CH_{Benzimid}$), 7.67–7.62 (m, 5H, CH_{Benzyl}), 5.98 (s, 2H, CH_2), 5.82 (s, 2H, CH_2). ^{13}C NMR (δ ppm DMSO–d_6, 75 MHz, proton decoupled): 148.0, 143.6, 141.7, 134.2, 131.5, 131.5, 129.9, 129.4, 129.25, 128.8, 127.4, 127.3, 124.4, 114.5, 114.3 (NCN + $C_{Benzmid}$ + $C_{Nitrobenzyl}$ + C_{Benzyl}), 50.62 (CH_2), 49.70 (CH_2). ATR–IR (cm^{-1}): 2950.8 (w), 1553.8 (m), 1485.4 (m), 1423.2 (m), 1338.9 (s), 1217.0 (m), 1183.8 (m), 1106.3 (m), 1015.8 (m), 854.7 (m), 802.1 (m), 750.4 (s), 705.2 (s). Micro Analysis Calculated for $C_{21}H_{18}N_3O_2PF_6$: C, 51.5; H, 3.7; N, 8.6%; Found: C, 52.6; H, 4.3; N, 8.9%.

3.16 | General experimental procedure for the synthesis of (1–benzyl–3–(4–nitrobenzyl)azol–2–ylidene)silver(I) acetates (7a–d)

A mixture of 1–benzyl–3–(4–nitrobenzyl)azolium hexaflourophosphate (1.0 mmol) and silver(I) acetate (0.33 g, 2.0 mmol) in methanol (20 mL) was stirred at room temperature for 24 h under dark in round bottom flask wrapped with aluminium foil. Then the reaction mixture was filtered through a Celite bed and the filtrate was reduced under vacuum to afford an off–white sticky solid. The solid was washed with excess diethyl ether and dried under vacuum to obtain pure (**7a–d**).

3.17 | Synthesis of (1–benzyl–3–(4–nitrobenzyl)imidazole–2–ylidene)silver(I) acetate (7a)

Compound (**7a**) was synthesized from 1–benzyl–3–(4–nitrobenzyl)imidazolium hexafluorophosphate **(6a)** (0.43 g,

1.0 mmol), according to the general procedure. White solid. Yield: 71.39% (0.33 g). ^{1}H NMR (δ ppm, DMSO–d_6, 400 MHz): 8.27 (d, J = 8.4 Hz, 2H, $CH_{Nitrobenzyl}$), 7.83 (s, 2H, $CH_{Nitrobenzyl}$), 7.66 (d, J = 8.8 Hz, 2H, CH_{Imid}), 7.422–7.37 (m, 5H, C_{Benzyl}), 5.58 (s, 2H, CH_2), 5.42 (s, 2H, CH_2), 1.86 (s, 3H, $COCH_3$). ^{13}C NMR (δ ppm DMSO–d_6, 100 MHz, proton decoupled): 180.8 (NCN), 173.1 (C = O), 148.1, 142.3, 137.2, 134.9, 130.0, 129.4, 129.2, 128.8, 124.4, 123.5, 123.5 (C_{Imid} + C_{Benzyl} + $C_{Nitrobenzyl}$), 52.6 (CH_2), 51.6 (CH_2), 21.9 ($COCH_3$). ATR–IR (cm^{-1}): 2950.2 (w), 1604.5 (m), 1566.4 (m), 1515.9 (s), 1447.8 (m), 1398.7 (m), 1342.7 (s), 1160.9 (m), 1108.8 (m), 1030.6 (m), 842.9 (s), 807.6 (s), 712.6 (s), 663.9 (m). Micro Analysis Calculated for $C_{19}H_{18}N_3O_4Ag$: C, 49.6; H, 3.9; N, 9.1%; Found: C, 50.1; H, 4.6; N, 9.9%.

3.18 | Synthesis of (1–benzyl–3–(4–nitrobenzyl)–4,5–dichloroimidazole–2–ylidene)silver(I) acetate (7b)

Compound (**7b**) was synthesized from 1–benzyl–3–(4–nitrobenzyl)–4,5–dichloroimidazolium hexafluorophosphate **(6b)** (0.50 g, 1.0 mmol), according to the general procedure. White solid. Yield: 60.13% (0.31 g). ^{1}H NMR (δ ppm DMSO–d_6, 400 MHz): 8.02 (d, J = 8.8 Hz, 2H, $CH_{Nitrobenzyl}$), 7.36 (d, J = 8.4 Hz, 2H, $CH_{Nitrobenzyl}$), 7.24–7.16 (m, 3H, CH_{Benzyl}), 7.17 (m, 2H, CH_{Benzyl}), 5.58 (s, 2H, CH_2), 5.40 (s, 2H, CH_2), 1.62 (s, 3H, OCH_3). ^{13}C NMR (δ ppm DMSO–d_6, 100 MHz, proton decoupled): 183.3 (NCN), 171.9 (C = O), 147.6, 143.1, 135.5, 129.2, 128.6, 128.3, 127.4, 124.2, 118.3, 118.0 (C_{Imid} + C_{Benzyl} + $C_{Nitrobenzyl}$), 54.0 (CH_2), 53.1 (CH_2), 22.9 ($COCH_3$). ATR–IR (cm^{-1}): 2845.9 (w), 1652.3(s), 1572.3 (m), 1519.2 (s), 1435.9 (m), 1387.1 (m), 1342.4 (m), 1315.3 (s), 1263.7 (m), 1108.4 (m), 1013.7 (m), 979.5 (m), 836.4 (m), 797.8 (m), 732.5 (s). Micro Analysis Calculated for $C_{19}H_{16}N_3O_4Cl_2Ag$: C, 43.1; H, 3.0; N, 8.3%; Found: C, 41.3; H, 3.5; N, 7.9%.

3.19 | Synthesis of (1–benzyl–3–(4–nitrobenzyl)–4,5–diphenylimidazole–2–ylidene)silver(I) acetate (7c)

Compound (**7c**) was synthesized from 1–benzyl–3–(4–nitrobenzyl)–4,5–diphenylimidazolium hexafluorophosphate **(6c)** (0.59 g, 1.0 mmol), according to the general procedure. White solid. Yield: 68.91% (0.42 g). ^{1}H NMR (δ ppm DMSO–d_6, 400 MHz): 8.12 (d, J = 8.0 Hz, 2H, $CH_{Nitrobenzyl}$), 7.39–7.24 (m, 15H, CH_{Imid} + CH_{Benzyl}), 7.126–7.09 (m, 2H, $CH_{Nitrobenzyl}$), 5.63 (s, 2H, CH_2), 5.44 (s, 3H, CH_2), 1.63 (s, 3H, OCH_3). ^{13}C NMR (δ ppm DMSO–d_6, 100 MHz, proton decoupled): 181.9 (NCN), 171.9 (C = O), 147.2, 144.7, 137.1, 133.0, 132.7, 131.0, 130.9, 129.7, 129.7, 129.2, 129.0, 128.9, 128.3, 128.1, 128.0, 127.6, 127.5, 127.0, 123.9 (C_{Imid} + C_{Benzyl} + $C_{Nitrobenzyl}$), 52.9 (CH_2), 52.3 (CH_2), 22.9 ($COCH_3$). ATR–IR (cm^{-1}): 2913.1 (w), 1620.1 (s), 1561.0 (m), 1519.2 (s), 1445.1 (m), 1375.0 (m), 1339.3 (s), 1216.1 (m), 1160.5 (m), 1105.1 (m), 1074.7 (m), 1014.1 (m), 977.8 (m), 927.8 (m), 847.3 (m), 800.8 (m), 755.3 (m), 729.4 (s). Micro Analysis Calculated for $C_{31}H_{26}N_3O_4Ag$: C, 60.8; H, 4.3; N, 6.9%; Found: C, 61.0; H, 4.4; N, 6.6%.

3.20 | Synthesis of (1–benzyl–3–(4–nitrobenzyl)benzimidazole–2–ylidene) silver(I) acetate (7d)

Compound (**7d**) was synthesized from 1–benzyl–3–(4–nitrobenzyl)benzimidazolium hexafluorophosphate **(6d)** (0.48 g, 1.0 mmol), according to the general procedure. White solid. Yield: 71.52% (0.36 g). ^{1}H NMR (δ ppm DMSO–d_6, 400 MHz): 8.23 (m, 2H, $CH_{Nitrobenzyl}$), 8.09–8.04 (m, 2H, $CH_{Nitrobenzyl}$), 7.87 (d, J = 7.6 Hz, 2H, $CH_{Benzimid}$), 7.76 (d, J = 8.8 Hz, 2H, $CH_{Benzimid}$), 7.68–7.55 (m, 3H, C_{Benzyl}), 7.48–7.39 (m, 2H, C_{Benzyl}), 5.96 (s, 2H, CH_2), 4.57–4.51 (s, 2H, CH_2), 1.70 (s, 3H, $COCH_3$). ^{13}C NMR (δ ppm DMSO–d_6, 100 MHz, proton decoupled): 190.9 (NCN), 172.0 (C = O), 147.5, 144.3, 136.6, 133.9, 133.9, 129.2, 128.5, 128.4, 127.6, 124.8, 124.2, 113.0, 112.6 ($C_{Benzmid}$ + $C_{Nitrobenzyl}$ + C_{Benzyl}), 52.4 (CH_2), 51.4 (CH_2), 22.9 ($COCH_3$). ATR–IR (cm^{-1}): 2847.5 (w), 1652.9 (s), 1519.5 (m), 1514.6 (s), 1481.9 (m), 1441.2 (m), 1395.7 (m), 1342.0 (s), 1263.3 (m), 1203.7 (m), 1175.5 (m), 1106.0 (m), 1081.2 (m), 1021.2 (m), 857.6 (m), 807.6 (m), 743.9 (s), 706.2 (s). Micro Analysis Calculated for $C_{23}H_{20}N_3O_4Ag$: C, 54.1; H, 3.9; N, 8.2%; Found: C, 54.9; H, 4.0; N, 9.1%.

3.21 | General experimental procedure for the synthesis of bis–(1–benzyl–3–(4–nitrobenzyl) azol–2–ylidene)silver(I) hexafluorophosphates (8a–d)

A mixture of 1–benzyl–3–(4–nitrobenzyl)–azolium hexafluorophosphate (1.0 mmol) and silver(I) oxide (0.27 g, 1.2 mmol) in acetonitrile (20 mL) was stirred at 45 °C for 24 h. Light was eliminated during the reaction by wrapping the reaction vessel with aluminium foil. Then the reaction mixture was filtered through a Celite bed and the resulted filtrate was concentrated to 3 mL under vacuum. The fine white precipitate was afforded by addition of diethyl ether (30 mL). The precipitate was filtered, washed with diethyl ether (30 mL), and dried under vacuum to yield pure (**8a–d**).

3.22 | Synthesis of bis–(1–benzyl–3–(4–nitrobenzyl)imidazole–2–ylidene)silver(I) hexafluorophosphate complex (8a)

Compound (**8a**) was synthesized from 1–benzyl–3–(4–nitrobenzyl)imidazolium hexafluorophosphate **(6a)** (0.43 g,

1.0 mmol), according to the general procedure. White solid. Yield: 73.54% (0.61 g). ^{1}H NMR (δ ppm DMSO–d_6, 400 MHz): 8.11 (d, J = 8.4 Hz, 2H, $CH_{Nitrobenzyl}$), 7.56 (s, 2H, $CH_{Nitrobenzyl}$), 7.37–7.18 (m, 7H, $CH_{Nitrobenzyl}$ + C_{Benzyl}), 5.45 (s, 2H, CH_2), 5.30 (s, 2H, CH_2). ^{13}C NMR (δ ppm DMSO–d_6, 100 MHz, proton decoupled): 181.0 (NCN), 147.4, 145.1, 137.5, 129.1, 128.6, 128.4, 127.7, 124.2, 123.4, 123.3 (C_{Imid} + C_{Benzyl} + $C_{Nitrobenzyl}$), 54.7 (CH_2), 53.7 (CH_2). ATR–IR (cm^{-1}): 2945.1 (w), 1527.2 (m), 1412.6 (m), 1345.9 (s), 1233.3 (m), 1205.8 (m), 1159.3 (m), 1109.7 (m), 1037.6 (m), 828.8 (s), 725.8 (s). Micro Analysis Calculated for $C_{34}H_{30}N_6O_4PF_6Ag$: C, 48.6; H, 3.6; N, 10.0%; Found: C, 48.8; H, 3.8; N, 10.0%.

3.23 | Synthesis of bis–(1–benzyl–3–(4–nitrobenzyl)–4,5–dichloroimidazole–2–ylidene) silver(I) hexafluorophosphate complex (8b)

Compound (**8b**) was synthesized from 1–benzyl–3–(4–nitrobenzyl)–4,5–dichloroimidazolium hexafluorophosphate **(6b)** (0.50 g, 1.0 mmol), according to the general procedure. White solid. Yield: 62.39% (0.56 g). ^{1}H NMR (δ ppm DMSO–d_6, 400 MHz): 8.11 (d, J = 8.8 Hz, 2H, $CH_{Nitrobenzyl}$), 7.41 (d, J = 8.8 Hz, 2H, $CH_{Nitrobenzyl}$), 7.31–7.20 (m, 5H, CH_{Benzyl}), 5.60 (s, 2H, CH_2), 5.43 (s, 2H, CH_2). ^{13}C NMR (δ ppm DMSO–d_6, 100 MHz, proton decoupled): 183.3 (NCN), 147.5, 143.1, 135.6, 129.2, 128.6, 128.3, 127.4, 124.2, 118.3, 118.0 (C_{Imid} + C_{Benzyl} + $C_{Nitrobenzyl}$), 54.0 (CH_2), 53.1 (CH_2). ATR–IR (cm^{-1}): 2830.8 (w), 1565.1 (m), 1515.9 (s), 1437.2 (m), 1386.8 (m), 1337.5 (s), 1197.7 (m), 1118.4 (m), 822.7 (s), 741.6 (s). Micro Analysis Calculated for $C_{34}H_{26}N_6O_4Cl_2PF_6Ag$: C, 45.1; H, 2.9; N, 9.3%; Found: C, 45.2; H, 3.1; N, 9.6%.

3.24 | Synthesis of bis–(1–benzyl–3–(4–nitrobenzyl)–4,5–diphenylimidazole–2–ylidene) silver(I) hexafluorophosphate complex (8c)

Compound (**8c**) was synthesized from 1–benzyl–3–(4–nitrobenzyl)–4,5–diphenylimidazolium hexafluorophosphate **(6c)** (0.27 g, 1.0 mmol), according to the general procedure. White solid. Yield: 69.33% (0.79 g). ^{1}H NMR (δ ppm DMSO–d_6, 400 MHz): 7.99 (d, J = 8.8 Hz, 2H, $CH_{Nitrobenzyl}$), 7.31–7.11 (m, 15H, CH_{Imid} + CH_{Benzyl}), 6.90–6.88 (m, 2H, $CH_{Nitrobenzyl}$), 5.40 (s, 2H, CH_2), 5.26 (s, 2H, CH_2). ^{13}C NMR (δ ppm DMSO–d_6, 100 MHz, proton decoupled): 151.9 (NCN), 149.5, 141.8, 137.7, 137.4, 135.7, 135.7, 134.4, 133.7, 132.8, 132.8, 132.4, 132.2, 131.8, 128.7 (C_{Imid} + C_{Benzyl} + $C_{Nitrobenzyl}$), 57.6 (CH_2), 57.0 (CH_2). ATR–IR (cm^{-1}): 2905.7 (w), 1523.5 (m), 1342.5 (s), 1179.0 (m), 1108.5 (m), 1074.3 (m), 1019.0 (m), 831.5 (s), 765.3 (s), 730.1 (s). Micro Analysis Calculated for $C_{58}H_{46}N_6O_4PF_6Ag$ (1143.85): C, 60.9; H, 4.1; N, 7.4%; Found: C, 61.0; H, 4.2; N, 7.5%.

3.25 | Synthesis of bis–(1–benzyl–3–(4–nitrobenzyl)benzimidazole–2–ylidene)silver (I) hexafluorophosphate complex (8d)

Compound (**8d**) was synthesized from 1–benzyl–3–(4–nitrobenzyl)benzimidazolium hexafluorophosphate **(6d)** (0.48 g, 1.0 mmol), according to the general procedure. White solid. Yield: 78.80% (0.74 g). ^{1}H NMR (δ ppm DMSO–d_6, 400 MHz): 8.09 (d, J = 8.8 Hz, 2H, $CH_{Nitrobenzyl}$), 7.71–7.68 (m, 2H, $CH_{Nitrobenzyl}$), 7.47–7.45 (m, 2H, $CH_{Nitrobenzyl}$), 7.39–7.34 (m, 2H, $CH_{Nitrobenzyl}$), 7.32–7.22 (m, 5H, CH_{Benzyl}), 5.91 (s, 2H, CH_2), 5.75 (s, 2H, CH_2). ^{13}C NMR (δ ppm DMSO–d_6, 100 MHz, proton decoupled): 173.7 (NCN), 148.0, 143.9, 143.6, 141.9, 131.6, 130.2, 129.8, 128.5, 127.2, 124.3, 122.8, 122.5, 121.7, 119.8, 114.3, 114.1, 112.5, 110.7 ($C_{Benzmid}$ + $C_{Nitrobenzyl}$ + C_{Benzyl}), 49.4 (CH_2), 42.7 (CH_2). ATR–IR (cm^{-1}): 2830.6 (w), 1551.2 (m), 1435.2 (m), 1339.5 (s), 1181.3 (m), 1109.1 (m), 1032.6 (m), 824.2 (s), 745.8 (s). Micro Analysis Calculated for $C_{42}H_{34}N_6O_4PF_6Ag$: C, 53.7; H, 3.7; N, 8.9%; Found: C, 54.0; H, 3.8; N, 9.0%.

4 | BIOLOGICAL EVALUATION

4.1 | Antibacterial screening

Preliminary *in vitro* antibacterial activity of NHC–precursors (**6a–d**) and their corresponding mono– and bis–NHC–silver(I) complexes (**7a–d** and **8a–d**) were evaluated by Kirby–Bauer's disc diffusion method followed by the determination of Minimum Inhibitory Concentration from broth macrodilution method against standard five bacterial strains *Staphylococcus aureus* (*S. aureus), Bacillus subtilis* (*B. subtilis*), *Escherichia coli (E. coli), Shigella sonnei (S. sonnei),* and *Salmonella typhi (S. typhi)* with standard Ampicillin.

4.2 | Kirby–Bauer's disc diffusion method

The bacterial strains were individually cultured from a single colony in sterile Muller–Hinton agar medium overnight at 37 °C. Then, a single colony was picked and introduced to nutrient broth and the absorbance was adjusted to McFarland standard 0.5. For each strain, 100 μL of culture were spread evenly on nutrient agar medium. Five 6 mm diametre Whatman paper discs were placed evenly separated on each plate. Stock solution of every compound was prepared at 800.0 μg/mL in DMSO. Each plate was tested with control, 3.0 μL, 6.0 μL, 9.0 μL and 12.0 μL of stock solution. The plates were covered and placed in an incubator at 37 °C for

24 h. The plates were then removed and the diameter of zone of inhibition for each sample was measured in millimetres against the standard Amphicillin.

4.3 | Determination of MIC by broth macrodilution method

A series of concentrations ranging from 1.0 μg/mL to 256.0 μg/mL of all the test compounds were obtained by serial dilution. Then, 1.0 mL of bacterial suspension was added to the series after adjusting the absorbance to McFarland standard 0.5 to derive a concentration range of 0.5–128.0 μg/mL. The sample tubes, along with the control and standard tubes were incubated at 37 °C for 16 h. MIC was determined visually as the lowest concentration of the test compound that inhibited bacterial growth.

4.4 | Anticancer screening

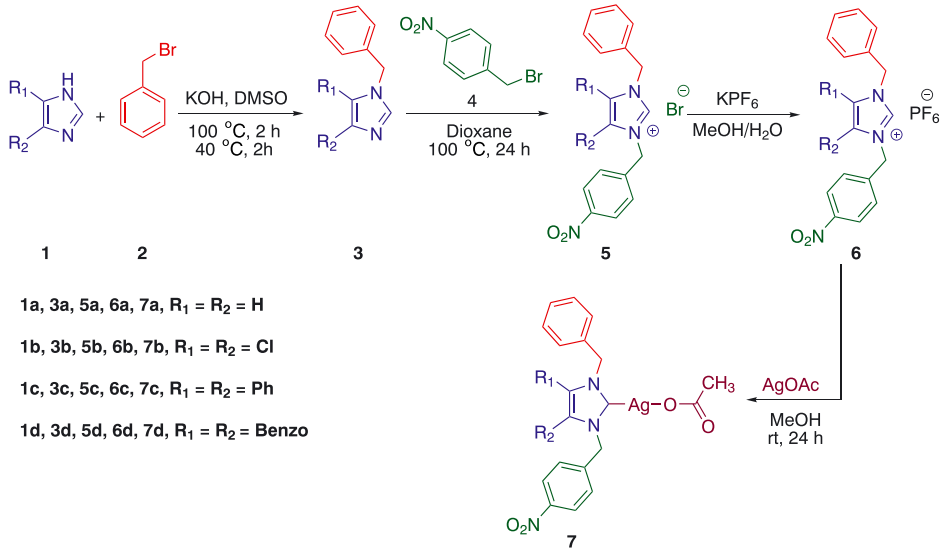
Preliminary *in vitro* anticancer potential of mono– and bis–NHC–silver(I) complexes (**7a–d** and **8a–d**) was performed on human breast adenocarcinoma (MCF–7) cell line (procured from NCCS, Pune). The cell line was maintained in 96 wells micro titre plate containing Minimum Essential Medium (MEM) supplemented with 10% heat inactivated fetal calf serum (FCS) containing 5% of mixture of Gentamicin (10.0 μg), Penicillin (100 units/mL) and Streptomycin (100.0 μg/mL) in the presence of 5% CO_2 at 37 °C for 48–72 h. Preliminary *in vitro* growth inhibition effect of test compounds was assessed by calorimetric or spectrophotometric determination of conversion of MTT into Formazan blue by living cells. The supernatant from the plate was removed and added fresh MEM solution followed by treatment with different concentrations of the compound appropriately diluted with DMSO to respective wells containing 100.0 μL of the medium in order to obtain final concentrations of 10.0, 20.0, 25.0, 30.0 and 50.0 μg/mL. Control group contained only DMSO. After 48 h of incubation at 37 °C in a humidified atmosphere of 5% CO_2, stock solution of MTT was added to each well (20.0 μL, 5.0 mg/mL in sterile PBS) for further incubation of 4 h. The supernatant was then carefully aspirated and the precipitated crystals of Formazan blue were solubilised by adding DMSO (100.0 μL) and optical density was measured at wavelength of 570 nm by using LISA plus. The results represent the mean of five readings.

5 | RESULTS AND DISCUSSION

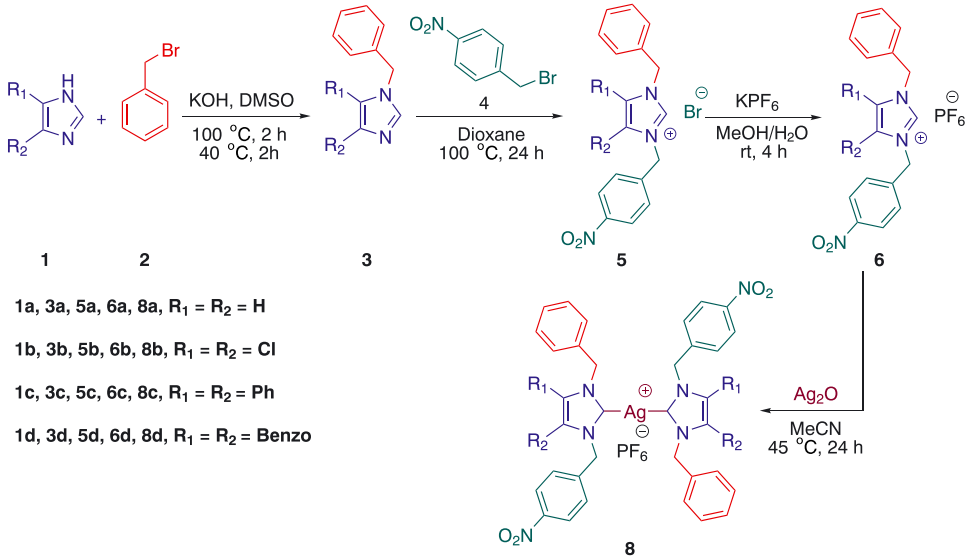
5.1 | Synthesis and characterization

The synthetic route for novel non–symmetrically *p*–nitrobenzyl–substituted *N*–heterocyclic carbenes as ligand precursors (**6a–d**) and their corresponding silver(I) complexes (**7a–d** and **8a–d**) depicted in the present work is outlined in Schemes 1 and 2, respectively. 1–Benzyl azoles **(3a–d)** were prepared by stirring imidazoles [imidazole **(1a)**, 4,5–dichloroimidazole **(1b)**, 4,5–diphenylimidazole **(1c)** and benzimidazole **(1d)**] with one equivalent of benzyl bromide **(2)** in the presence of potassium hydroxide as a base in DMSO at 100–110 °C for 4 h. The bromide salts (**5a–d**) were prepared by reacting one equivalent of *p*–nitrobenzyl bromide **(4)** with 1–benzyl azoles [1–benzyl–1*H*–imidazole **(3a)**, 1–benzyl–4,5–dichloro–1*H*–imidazole **(3b)**, 1–benzyl–4,5–diphenyl–1*H*–imidazole **(3c)**, and 1–benzyl–1*H*–benzimidazole **(3d)**] in dioxane at 100 °C for 24 h, with variable yields between 71.54%–89.92%. All the hexafluorophoaphate salts (**6a–d**) were prepared by the reaction of their corresponding bromide salts (**5a–d**) with KPF_6 in a mixture of methanol and water at room temperature for 4 h as an air and moisture stable white powders, with moderate to good yields (64.76%–81.30%). The prepared NHC hexafluorophosphate salts (**6a–d**) were easily soluble in organic solvents such as acetone, acetonitrile, DMF and DMSO and insoluble in common organic solvents such as pentane, hexane, toluene, and diethyl ether. Structures of all the newly synthesized hexafluorophosphate salts (**6a–d**) were confirmed by ^{1}H, ^{13}C NMR and ATR–IR spectroscopic techniques and elemental analysis.

The ^{1}H NMR spectra of all the newly synthesised hexafluorophosphate salts (**6a–d**) displayed a characteristic downfield resonance in the range δ = 9.04–10.14 ppm attributed to the resonance of NCHN protons indicated the successful formation of desired hexafluorophosphate salts (**6a–d**). The spectra also evidenced the presence of a set of peaks in the range δ = 8.33–6.98 ppm ascribed to the resonance of aromatic protons ($CH_{Azole} + CH_{Benzyl} + CH_{Nitrobenzyl}$). In addition, two singlet peaks were observed in the range δ = 5.98–5.27 ppm which are due to the methylene (CH_2) protons of *p*–nitrobenzyl and benzyl module attached to the nitrogen atoms of the N–heterocyclic core. The ^{13}C NMR spectra of all the hexafluorophosphate salts (**6a–d**) revealed the presence of peaks in the range δ = 148.18–114.38 ppm attributed to the aromatic carbon atoms (NCN, $C_{Azole} + C_{Benzyl} + C_{Nitrobenzyl}$). Also, two peaks were observed in the range δ = 52.66–49.70 ppm ascribed to the methylene (CH_2) carbon atoms of *p*–nitrobenzyl and benzyl module attached to the nitrogen atoms of the *N*–heterocyclic core. In the ATR–IR spectra of hexafluorophosphate salts (**6a–d**), stretching vibrational bands of nitro functionality was observed as two medium intensity bands at *ca.* 1566–1551 and 1344–1338 cm^{-1}.[33,34] Further, the ATR–IR spectra of (**6a–d**) displayed a sharp band of medium intensity in the range 2954–2851 cm^{-1}, attributed to the aromatic ν(C–H) stretching vibrations. In addition, the results



SCHEME 1 General reaction scheme for the synthesis of nitro–functionalized NHC precursors (**6a–d**) and their corresponding mono–NHC–silver(I) acetate complexes (**7a–d**)



SCHEME 2 General reaction scheme for the synthesis of nitro–functionalized NHC precursors (**6a–d**) and their corresponding bis–NHC–silver(I) complexes (**8a–d**)

obtained from the elemental analysis are in good agreement with the proposed structures of the hexafluorophosphate salts (**6a–d**).

The mono–NHC–silver(I) acetate complexes (**7a–d**) were synthesized by the reaction of the hexafluorophosphate salts (**6a–d**) with two equivalents of silver(I) acetate in methanol. The reaction mixture was stirred for 24 h at room temperature in dark to afford the mono NHC–silver(I) acetate complexes (**7a–d**) as off white solids in 60.13 to 71.52% yield. All the newly synthesized mono NHC–silver(I) acetate complexes were fully characterized by ^{1}H, ^{13}C NMR, ATR–IR spectroscopic techniques and elemental analyses.

The complete disappearance of a downfield NCHN signal and appearance of new signals at $\delta = 1.62$ to 1.86 ppm for the acetate (O_2CCH_3) protons in all the ^{1}H NMR spectra for (**7a–d**), indicates a successful NHC–silver(I) acetate complex formation. The ^{13}C NMR resonances of the carbene carbon atoms in complexes (**7a–d**) observed in the range $\delta = 180.82$–190.92 ppm. These resonances are shifted to downfield region compared to their corresponding hexafluorophosphate salts (**6a–d**) carbene carbons resonance at the range 148.1–142.4 ppm, which further reveals the formation of expected mono–NHC–silver(I) acetate complexes. Furthermore, the presence of the ^{13}C NMR resonances for the carbonyl and methyl carbons of the acetate

group of NHC–silver(I) acetate complexes (**7a–d**) in the range δ = 171.9–173.1 and 21.9–22.9 ppm, respectively demonstrated the formation of the targeted mono–NHC–silver(I) acetate complexes. The ATR–IR spectra of all mono–NHC–silver(I) acetate complexes (**7a–d**) exhibit strong bands in the region 1604–1652 and 1263–1160 cm^{-1} respectively, attributed to the acetate ν(C = O) and ν(C–O) stretching vibrations, which further confirms the successful NHC–silver(I) acetate complex formation. Medium intensities stretching vibrational bands in the region 1566–1519 and 1342–1339 cm^{-1}, indicate the presence of nitro moiety. Further, the ATR–IR spectra of all the mono–NHC–silver(I) acetate complexes (**7a–d**) displayed one sharp band of medium intensity around 2950–2845 cm^{-1}, attributed to the aromatic ν(C–H) stretching vibrations. Additionally, elemental analysis results are in good agreement with the proposed structures of the mono–NHC–silver(I) acetate complexes (**7a–d**).

On the other hand, the bis–NHC–silver(I) hexafluorophosphate complexes (**8a–d**) were synthesized by treating the hexafluorophosphate salts (**6a–d**) with one equivalent of silver(I) oxide in acetonitrile at 45 °C for 24 h. All the newly synthesized bis–NHC–silver(I) hexafluorophosphate complexes (**8a–d**) were obtained in good yields ranging from 62.39 to 78.80%, and were characterized by ^{1}H, ^{13}C NMR, ATR–IR spectroscopic methods and elemental analyses.

The absence of a downfield NCHN signal in all the ^{1}H NMR spectra for (**8a–d**), indicates a successful bis–NHC–silver(I) hexafluorophosphate complex formation.[33,34] However, the resonances of aromatic and methylene protons of NHC–silver(I) complexes (**8a–d**) were observed with no or a negligible change with their respective hexafluorophosphate salts (**6a–d**). The ^{13}C NMR resonances of the carbene carbon atoms in complexes (**8a–d**) occur in the range δ = 183.3–151.9 ppm, respectively. These signals are shifted downfield compared to the corresponding precursors of (**6a–d**) carbene carbons resonance at δ = 148.1–142.4 ppm respectively, which further supports the formation of expected bis–NHC–silver(I) hexafluorophosphate complexes (**8a–d**). In the ATR–IR spectra of bis–NHC–silver(I) hexafluorophosphate complexes (**8a–d**), stretching vibrational bands of nitro moiety was observed as a medium intensities bands at 1565–1523 and 1345–1337 cm^{-1}. Further, all the bis–NHC–silver(I) complexes (**8a–d**) displayed one sharp band of medium intensity around 2945–2830 cm^{-1}, attributed to the aromatic ν(C–H) stretching vibrations. These spectral assignments are consistent with the similar reported compounds available in the literature.[34] In addition, the proposed structures of all the bis–NHC–silver(I) complexes (**8a–d**) were further confirmed from the elemental analysis results.

5.2 | Structural discussion

Suitable single crystals for X-ray diffraction analysis of bis-NHC-silver(I) complex **(8b)** were grown in saturated acetonitrile solution. A perspective view of compound **(8b)** is depicted in Figure 1. The crystal data and details concerning data collection and structure refinement are given in Table 1 and bond distances and bond angles are given in Table 2. Compound **(8b)** crystallized in the triclinic space group *P-1* with two motifs in a unit cell. The crystal structure consists of cation $[NHC\text{-}Ag\text{-}NHC]^{+}$ and PF_6^{-} anion. Consequently, the charge on complex **(8b)** is neutralised by the presence of PF_6 anion in the crystal lattice. Further, compound **(8b)** does not possess any lattice held water molecules or organic solvent molecules in the unit cell of the determined structure. The X-ray structure of **(8b)** revealed that the molecule is nonplanar in nature and the metal centre lies on the inversion centre. The silver(I) ion is coordinated to two carbene carbons of the 4,5-dichloroimidazolium rings in an *anti*–arrangement, in a perfect linear fashion with C(1)-Ag(1)-C(1′) (′ is reported by the symmetry operation -x, −y, −z) bond angle of 180° probably indicating that the steric bulk offered by the ligand does not hinder coordination geometry around the silver(I) centre while the bond distance between Ag(1)-C(1) is 2.093 (5) Å. Also, the bond distances and bond angles in the five-membered ring (NCNCC) compare well with those found in similar compounds bis-[1-benzyl-3-(4-nitrobenzyl) benzimidazolium]-silver(I) tetrafluoroborate and 1-hexyl-3-methyl-4,5-dichloroimidazolium iodide.[34,37] The C-C bond distances in aromatic rings are in the normal range of 1.328(8)-1.510(7) Å, which is characteristic of delocalized aromatic rings. The C-C-C bond angles in aromatic rings are close to 120°, it suggests that carbon atoms are sp^2 hybridized. The NO_2 [N(3) O(1) and N(3) O(2)] group

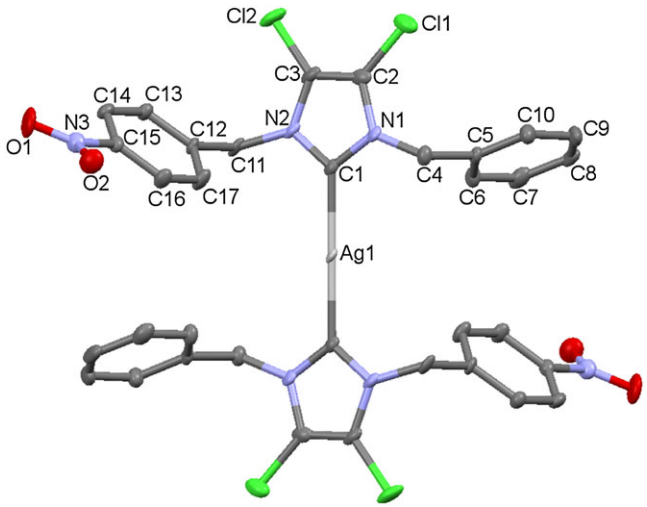


FIGURE 1 X-ray diffraction structure of compound (**8b**); thermal ellipsoids are drawn on the 50% probability level. Hydrogen atoms and hexafluorophosphate counterion are excluded for clarity

TABLE 1 The crystal data and structure refinement data of compound (**8b**)

Identification code	8b
Empirical formula	C_{17} H_{13} $Ag_{0.50}$ C_{l2} F_3 N_3 O_2 $P_{0.50}$
Formula weight	488.62
Temperature (K)	296(2)
Wavelength	1.54178
Crystal system	Triclinic
Space group	P–1
Unit cell dimensions	
a (Å)	8.0304(4)
b (Å)	9.7449(6)
c (Å)	12.3369(7)
α (°)	78.110(2)
β (°)	85.095(2)
γ (°)	78.871(2)
Volume ($Å^3$)	925.90(9)
Z	2
Density(calcd) (g/cm^3)	1.753
Absorption coefficient (mm^{-1})	8.139
F_{000}	488
Crystal size	0.30 x 0.29 x 0.27
θ range for data collection	5.38–64.45°
Index ranges	$-8 \le h \le 9$, $-11 \le k \le 11$, $-14 \le l \le 14$
Reflections collected	6686
Independent reflections	3027[R(int) = 0.0518]
Refinement method	Full–matrix least–squares on F^2
Completeness to θ_{max}	97.0%
Max. And min. Transmission	0.165 and 0.111
Data/ restrains/parameters	3027/0/256
Radiation (Å)	1.54178
θ min, max (°)	5.38–64.45
Goodness–of–fit on *F2*	1.039
Final *R* indices [$1 > 2\sigma(1)$]	$R = 0.0741$, wR = 0.2040
R indices (all data)	$R = 0.0741$, wR = 0.2037
Largest diff. Peak and hole (e $Å^{-3}$)	2.316 and −2.453

present in the complex is *trans* to methylene group. The compound (**8b**) lies in three planes with plane I [C(1) N (2) N(1) C(2) C(3) Cl(2) Cl(1), and Ag(1)] making a dihedral angle of 80.39° and 78.65° with plane II [C(11) C(17) C(12) C(13) C(14) C(15) C(16), and N(3)], and plane III [C(4) C(5) C(6) C(7) C(8) C(9), and C(10)], whereas the plane II forms a dihedral angle of 65.44° with plane III. However, the C(1)-Ag(1)-C(1′) plane is almost perpendicular to the plane of the aryl rings. The molecular packing of (**8b**) reveals a number of intermolecular and intramolecular hydrogen bond interactions where the fluoride of the hexafluorophosphate anion participates in a strong interaction with the silver(I) centre with an interaction distance of 3.07 Å which is followed in a diagonal pattern that results in a step-like arrangement (Figure 2). Additionally, the fluoride atoms are involved in strong interactions with N (2), C(1) and C(17) with interaction distances of 2.98, 2.97 and 2.99 Å respectively along with strong intramolecular hydrogen bonds between F(1) and H(6), F(2) and H(6), and F(2) and H(17) at distances of 2.52, 2.50 and 2.27 Å respectively.

TABLE 2 Selected bond lengths (Å) and bond angles (°) of compound (**8b**)

Bond lengths	[Å]	Bond angle	[°]
Ag(1)–C(1)	2.093 (5)	C(1)–ag(1)–C(1′)[a]	180.00
N(1)–C(1)	1.365 (7)	N(1)–C(1)–ag(1)	127.1 (4)
N(2)–C(1)	1.361(6)	N(2)–C(1)–ag(1)	127.5 (4)
N(1)–C(2)	1.392(6)	N(1)–C(1)–N(2)	105.0 (4)
N(2)–C(3)	1.388 (7)	C(1)–N(1)–C(2)	109.8 (4)
C(2)–C(3)	1.328(8)	C(3)–C(2)–N(1)	107.5 (5)
Cl(1)–C(2)	1.703(5)	C(2)–C(3)–N(2)	107.4 (5)
Cl(2)–C(3)	1.704(5)	C(1)–N(2)–C(3)	110.2 (4)
N(1)–C(4)	1.461(7)	N(1)–C(2)–Cl(1)	122.4 (4)
N(2)–C(11)	1.461(7)	C(3)–C(2)–Cl(1)	130.1 (4)
N(3)–O(1)	1.229(6)	C(2)–C(3)–Cl(2)	129.1 (4)
N(3)–O(2)	1.235(6)	N(2)–C(3)–Cl(2)	123.5 (4)

[a]is reported by the symmetry operation *-x,- y,- z*

5.3 | Pharmacological screening

Owing to the employment of nitro–aromatic compounds in the synthesis of effective pharmaceutical agents such as analgesics, antipyretics and antipsychotic drugs,[29–32] *p*–nitrobenzyl substituents were investigated as *N*–substitutents in different azolium compounds for antibacterial and anticancer properties against both Gram–positive and Gram–negative bacterial strains as well as human breast adenocarcinoma cell line (MCF 7).

5.4 | Antibacterial activity

With the freshly prepared compounds on hand, we then proceeded to examine their antibacterial activity from Kirby–Bauer's disc diffusion method and MIC was

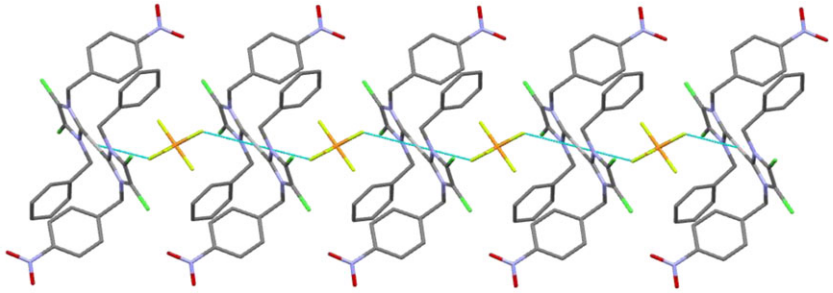


FIGURE 2 Interaction of the hexafluorophosphate anion with the metal centre. Hydrogen atoms are excluded for clarity

determined by broth macrodilution method towards *S. aureus, B. subtilis, E. coli, S. sonnei* and *S. typhi*. The solvent (DMSO) played no role in the inhibition of bacterial growth as reported earlier.[38,39] The outcome of antibacterial activities of hexafluorophosphate salts (**6a–d**) and their corresponding mono–NHC–silver(I) acetate (**7a–d**) and bis–NHC–silver(I) hexafluorophosphate complexes (**8a–d**) are depicted in Figures 3–7. The results are tabulated in Table 3.

In general the hexafluorophosphate salts (**6a–d**) showed no antibacterial activity. On the other hand, mono– and bis–NHC–silver(I) complexes (**7a–d** and **8a–d**) exhibited promising antibacterial activity. Bis–NHC–silver(I) complex (**8c**) orchestrated impressive antibacterial potential against *E. coli* at a concentration of 8 μg/mL. Similarly, mono–NHC–silver(I) complex (**7d**) displayed a high activity against *S. aureus* and *E. coli* at 8 μg/mL. Overall, mono– and bis–NHC–silver(I) complexes (**7a–d** and **8a–d**) showed high antibacterial activity against *S. aureus*, good to moderate activity against *E. coli* and *S. sonnei* and moderate to poor activity against *B. subtilis* and *S. typhi*. Though the results obtained by Kirby Bauer's disc diffusion

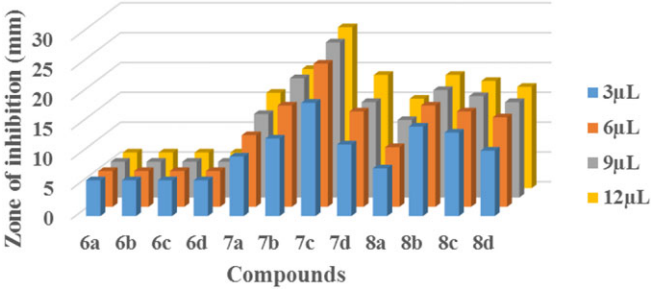


FIGURE 3 Area of clearance on *S. aureus* by (**6a–d**), (**7a–d**), and (**8a–d**)

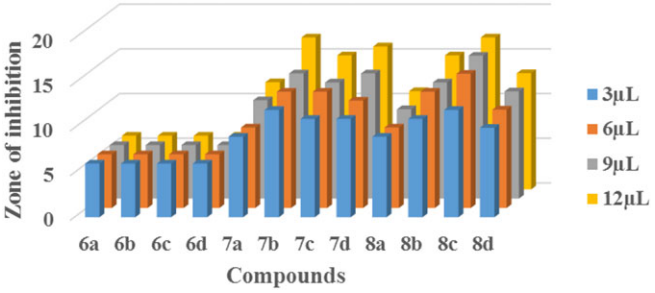


FIGURE 4 Area of clearance on *B. subtilis* by (**6a–d**), (**7a–d**), and (**8a–d**)

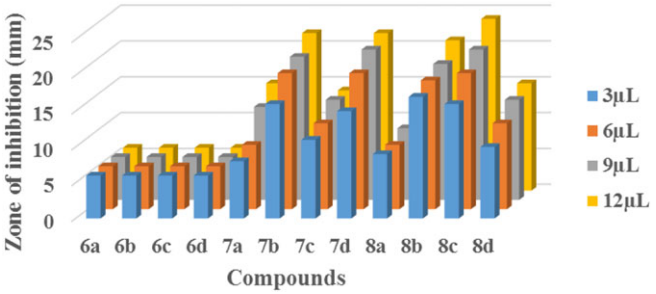


FIGURE 5 Area of clearance on *E. coli* by (**6a–d**), (**7a–d**), and (**8a–d**)

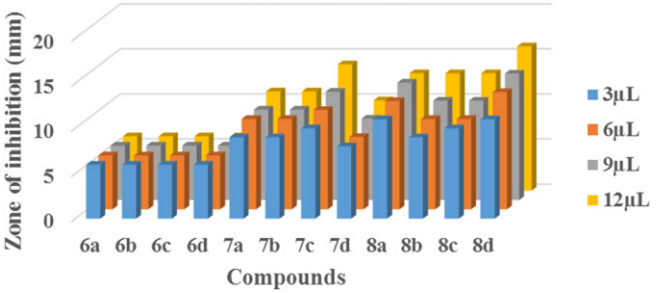


FIGURE 6 Area of clearance on *S. sonnei* by (**6a–d**), (**7a–d**), and (**8a–d**)

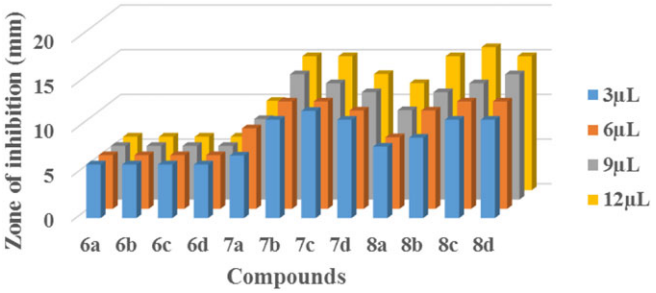


FIGURE 7 Area of clearance on *S. typhi* by (**6a–d**), (**7a–d**), and (**8a–d**)

TABLE 3 Preliminary *in vitro* antimicrobial activity data of compounds (**6a–d**), (**7a–d**), and (**8a–d**) towards gram–positive and gram–negative bacterial strains[a]

		Gram–positive bacteria				Gram–negative bacteria					
	Test volume	*S. aureus*		*B. subtilis*		*E. coli*		*S. Sonnei*		*S. Typhi*	
Compounds (#)	(μL)	ZOI	MIC	ZOI	MIC	ZOI	MIC	ZOI	MIC	ZOI	MIC
6a	3	6 ± 1	>128	6 ± 1	>128	6 ± 1	>128	6 ± 1	>128	6 ± 1	>128
	6	6 ± 1		6 ± 1		6 ± 1		6 ± 1		6 ± 1	
	9	6 ± 1		6 ± 1		6 ± 1		6 ± 1		6 ± 1	
	12	6 ± 1		6 ± 1		6 ± 1		6 ± 1		6 ± 1	
6b	3	6 ± 1	>128	6 ± 1	>128	6 ± 1	>128	6 ± 1	>128	6 ± 1	>128
	6	6 ± 1		6 ± 1		6 ± 1		6 ± 1		6 ± 1	
	9	6 ± 1		6 ± 1		6 ± 1		6 ± 1		6 ± 1	
	12	6 ± 1		6 ± 1		6 ± 1		6 ± 1		6 ± 1	
6c	3	6 ± 1	>128	6 ± 1	>128	6 ± 1	>128	6 ± 1	>128	6 ± 1	>128
	6	6 ± 1		6 ± 1		6 ± 1		6 ± 1		6 ± 1	
	9	6 ± 1		6 ± 1		6 ± 1		6 ± 1		6 ± 1	
	12	6 ± 1		6 ± 1		6 ± 1		6 ± 1		6 ± 1	
6d	3	6 ± 1	>128	6 ± 1	>128	6 ± 1	>128	6 ± 1	>128	6 ± 1	>128
	6	6 ± 1		6 ± 1		6 ± 1		6 ± 1		6 ± 1	
	9	6 ± 1		6 ± 1		6 ± 1		6 ± 1		6 ± 1	
	12	6 ± 1		6 ± 1		6 ± 1		6 ± 1		6 ± 1	
7a	3	10 ± 1	16	9 ± 1	128	8 ± 1	32	9 ± 1	64	7 ± 1	128
	6	12 ± 1		9 ± 1		9 ± 1		10 ± 1		9 ± 1	
	9	14 ± 1		11 ± 1		13 ± 1		10 ± 1		9 ± 1	
	12	16 ± 1		12 ± 1		15 ± 1		11 ± 1		10 ± 1	
7b	3	13 ± 1	16	12 ± 1	128	16 ± 1	16	9 ± 1	128	11 ± 1	128
	6	17 ± 1		13 ± 1		19 ± 1		10 ± 1		12 ± 1	
	9	20 ± 1		14 ± 1		20 ± 1		10 ± 1		14 ± 1	
	12	20 ± 1		17 ± 1		22 ± 1		11 ± 1		15 ± 1	
7c	3	19 ± 1	16	11 ± 1	64	11 ± 1	16	10 ± 1	64	12 ± 1	64
	6	24 ± 1		13 ± 1		12 ± 1		11 ± 1		12 ± 1	
	9	26 ± 1		13 ± 1		14 ± 1		12 ± 1		13 ± 1	
	12	27 ± 1		15 ± 1		14 ± 1		14 ± 1		15 ± 1	
7d	3	12 ± 1	8	11 ± 1	128	15 ± 1	8	8 ± 1	128	11 ± 1	128
	6	16 ± 1		12 ± 1		19 ± 1		8 ± 1		11 ± 1	
	9	16 ± 1		14 ± 1		21 ± 1		9 ± 1		12 ± 1	
	12	19 ± 1		16 ± 1		22 ± 1		10 ± 1		13 ± 1	
8a	3	8 ± 1	16	9 ± 1	128	9 ± 1	64	11 ± 1	64	8 ± 1	128
	6	10 ± 1		9 ± 1		9 ± 1		12 ± 1		8 ± 1	
	9	13 ± 1		10 ± 1		10 ± 1		13 ± 1		10 ± 1	
	12	15 ± 1		11 ± 1		13 ± 1		13 ± 1		12 ± 1	
8b	3	15 ± 1	16	11 ± 1	64	17 ± 1	16	9 ± 1	64	9 ± 1	128
	6	17 ± 1		13 ± 1		18 ± 1		10 ± 1		11 ± 1	
	9	18 ± 1		13 ± 1		19 ± 1		11 ± 1		12 ± 1	
	12	19 ± 1		15 ± 1		21 ± 1		13 ± 1		15 ± 1	
8c	3	14 ± 1	16	12 ± 1	64	16 ± 1	8	10 ± 1	64	11 ± 1	64
	6	16 ± 1		15 ± 1		19 ± 1		10 ± 1		12 ± 1	
	9	17 ± 1		16 ± 1		21 ± 1		11 ± 1		13 ± 1	
	12	18 ± 1		17 ± 1		24 ± 1		13 ± 1		16 ± 1	
8d	3	11 ± 1	16	10 ± 1	128	10 ± 1	64	11 ± 1	64	11 ± 1	128
	6	15 ± 1		11 ± 1		12 ± 1		13 ± 1		12 ± 1	
	9	16 ± 1		12 ± 1		14 ± 1		14 ± 1		14 ± 1	

(*Continues*)

TABLE 3 (Continued)

Compounds (#)	Test volume (μL)	Gram–positive bacteria				Gram–negative bacteria					
		S. aureus		*B. subtilis*		*E. coli*		*S. Sonnei*		*S. Typhi*	
		ZOI	MIC	ZOI	MIC	ZOI	MIC	ZOI	MIC	ZOI	MIC
	12	17 ± 1		13 ± 1		15 ± 1		16 ± 1		15 ± 1	
Ampicillin	3	23 ± 1	<0.5	CI	<0.5	16 ± 1	<0.5	CI	<0.5	CI	<0.5
	6	24 ± 1		CI		19 ± 1		CI		CI	
	9	25 ± 1		CI		21 ± 1		CI		CI	
	12	27 ± 1		CI		24 ± 1		CI		CI	

[a]ZOI: Zone of inhibition (mm); MIC: Minimal bacterial inhibitory concentration (μg/mL); CI: Complete inhibition.

method is comparable with that of MIC values, slight deviations could be attributed to the nature of medium employed for the purpose, where the compounds diffuse through an agar based medium in Kirby Bauer's disc diffusion method, whereas the components are easily available in a broth medium during MIC determination. Also, an evident amount of difference could not be drawn between the activity of mono–NHC–silver(I) acetate complexes (**7a–d**) and bis–NHC–silver(I) hexafluorophosphate complexes (**8a–d**), which reflects that more number of NHC ligands do not add to the targeted biological activity.

Comparing the overall activity of the *N*–heterocyclic cores in the corresponding complexes, 4,5–diphenylimidazole based complexes exhibit higher activity than benzimidazole based complexes that were better than imidazole and 4,5–dichloroimidazole based complexes that are comparable. It is also noteworthy that the difference in activity brought about by different *N*–heterocyclic cores is not bold.

5.5 | Anticancer activity

The anticancer study of the hexafluorophosphate salts (**6a–d**) was excluded as the focus of the study was on the effectiveness of silver upon complexation with the rationally designed NHC ligands. Hence, anticancer potential of the mono– and bis–NHC–silver(I) complexes (**7a–d** and **8a–d**) was evaluated by MTT assay against human derived breast adenocarcinoma cell line (MCF 7). The inhibition of cell proliferation along varying concentrations of the mono– and bis–NHC–silver(I) complexes (**7a–d** and **8a–d**) is depicted in Figures 8 and 9. The compounds displayed excellent activity with IC_{50} values at nanomolar level. Bis–NHC silver(I) complex (**8b**) exhibited a high anticancer potential with an IC_{50} value of 10.39 nM, whereas complexes (**7a–d**) presented with appreciable IC_{50} values ranging from 13.28 to 16.74 nM. While complexes (**8c** and **8d**) illustrated IC_{50} values of 33.18 and 36.56 nM respectively, that of (**8a**) exceeded the tested range. On the whole, mono–NHC complexes surfaced as better candidates than the bis–NHC analogues, with an exception of (**8b**). Hence, it can be deduced that possession of two NHC based ligands do not result in a better drug candidate

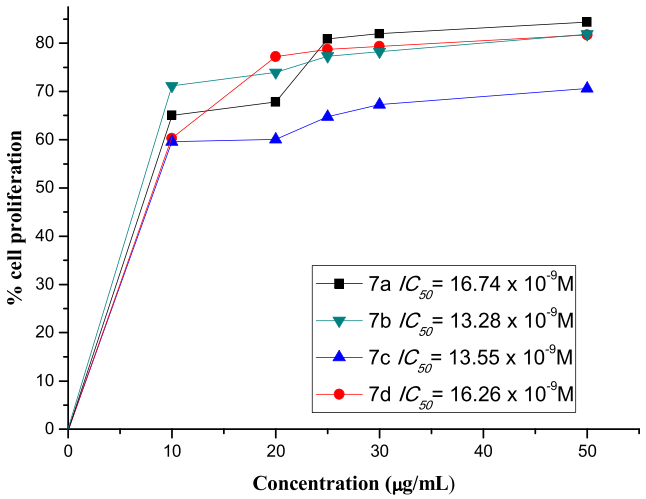


FIGURE 8 Cytotoxicity curves from typical MTT assays showing the effect of compounds (**7a–d**) on the cell proliferation of MCF 7 cells

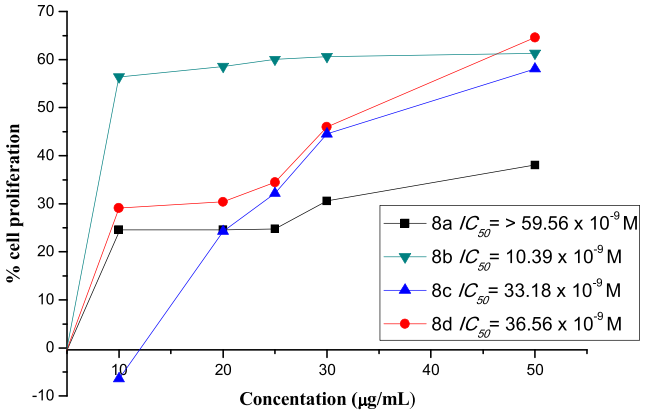


FIGURE 9 Cytotoxicity curves from typical MTT assays showing the effect of compounds (**8a–d**) on the cell proliferation of MCF 7 cells

and the phenomenon is in agreement with that of the antibacterial examination.

6 | CONCLUSION AND OUTLOOK

Several new non–symmetrically *p*–nitrobenzyl–substituted mono–NHC–silver(I) acetate and bis–NHC–silver(I) hexafluorophosphate derivatives (**7a–d** and **8a–d**) were synthesised through the reaction of corresponding non–symmetrically *p*–nitrobenzyl–substituted azolium salts (**6a–d**) with silver(I) acetate and silver(I) oxide, and appropriately characterized using various spectroscopic techniques as well as elemental analysis. Additionally, the structure of (**8b**) was unambiguously established by single crystal X–ray diffraction method. Summarising, it can be said that all the presented NHC–silver(I) complexes are easily accessible from low–cost starting materials with good yields and the preparation does not require any harsh conditions. The compound (**7d**) exhibited high antibacterial activity towards *S. aureus* and *E. coli*, whereas (**8c**) was equally effective against *E. coli,* at 8 μg/mL. Furthermore, all the NHC–silver(I) complexes (**7a–d** and **8a–d**) demonstrated exceptional anticancer activity with IC_{50} values at nano molar range. While the bis–NHC–silver(I) complex (**8b**) demonstrated the best anticancer potential with an IC_{50} value of 10.39 nM, other complexes (**7a–d, 8c–d**) exhibited proficient activity with IC_{50} values ranging from 13.28 to 36.56 nM against human breast adenocarcinoma cell line, MCF 7. Also, the difference in the antibacterial activity between mono and bis–NHC–silver(I) complexes (**7a–d** and **8a–d**) was not pronounced, whereas the former (**7a–d**) possessed better anticancer potential than the latter (**8a, 8c and 8d**). Therefore, the outcomes obtained from this study could afford valuable hints for the design and discovery of new NHC–silver (I) based antimicrobial and anticancer agents.

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