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New Ag(I) and Pd(II) complexes derived from symmetrical and asymmetrical NHC precursors: Synthesis, Characterization, Antibacterial activity, and Theoretical calculations

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ABSTRACT

New symmetric and asymmetric imidazolium salts namely 1-methyl-3-(2,5-dimethylphenyl)-acetamideimidazolium chloride (**2**), 1-benzyl-3-(2,5-dimethylphenyl)-acetamideimidazolium chloride (**3**) and 1,3-bis-(2,5-dimethylphenyl)-acetamideimidazolium chloride (**4**) were synthesized. *In situ* deprotonation technique was employed to synthesize Ag(I)-NHC complexes (**5**-**7**) from the reaction of Ag_2O with the abovementioned ligand precursors. Subsequent reactions of Ag(I)-NHC complexes with $[PdCl_2(MeCN)_2]$ resulted the Pd(II)-NHC complexes (**8**-**10**) via transmetallation method. All the synthesized compounds were characterized using various techniques such as ^1H and ^{13}C NMR, FTIR and CHN analysis. The antibacterial activity of all the compounds was evaluated against bacterial strains *E. coli* as gram-negative and *S. aureus* as gram-positive bacteria using azithromycin as a standard antibiotic. The density functional theory (DFT) method was used to optimize the structures of the synthesized compounds using Gaussian 09 and Molecular Graphic Laboratory (MGL). Electronic energy, HOMO, LUMO, and dipole moment were calculated as well. Further, the estimated anticancer activity of the compounds was determined using docking calculations.

1. Introduction

Since its first isolation by Arduengo in 1991, and due to its remarkable applications particularly in catalytic and biological ones, N-heterocyclic carbene (NHC) chemistry has undergone incredible expansion [1-6]. NHCs have a strength highly favored forming complexes with a series of metals than heterocycles that have a P, N, O, and S atoms, also the metal-carbene bond is more reactive than the other types of metal-complexes such as phosphine complexes [7]. Two important factors can affect the stabilization of NHCs, the first is π-bonding by a resonance effect, and the second is σ-bonding by an inductive effect [8]. The bonding properties of NHC may be better as σ-donors compared to those of known trialkyl phosphines, makes them good candidates for the stabilization of transition-metal catalysis in various oxidation states during biological activities [9,10]. In addition, the shape and size of NHCs may easily be modified by the introduction of various substituents on the heterocycle [11,12].

The interest in the chemistry of Ag(I)-NHC complexes has greatly expanded during the last two decades. This is because of different strength points including; synthetic strategies, structural diversity, and their usefulness in several applications. So, many research articles and reviews focusing on the structure and applications of silver(I)-NHC complexes have been published [13-19]. So far, the carbene transfer method which is used in the synthesis of different transition metal-NHC complexes is the most significant application for Ag(I)-NHCs. This method was discovered by Lin and co-workers and used to synthesize palladium(II)- and gold(I)-NHC complexes [20]. Later, it has been applied successfully in the synthesis of many NHC complexes with a variety of metals, such as nickel, ruthenium, rhodium, platinum, gold, iridium and ..etc [12,21,22]. In this context, silver(I)–NHC complexes are important for the preparation of active species in homogeneous catalysis by transmetallation to other transition metal–NHC complexes [23]. Furthermore, silver-NHC complexes showed another significant applications includes their potential use as antifungal [24,25], an-

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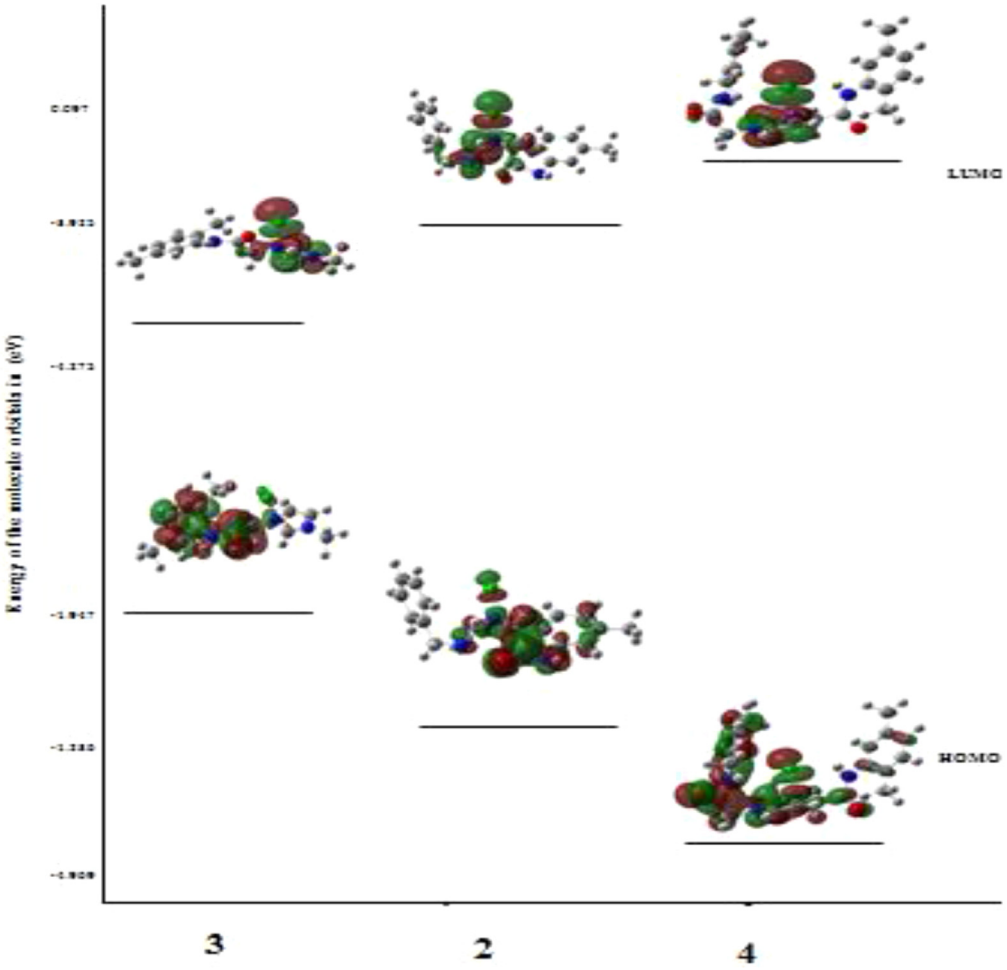


Fig. 1. Energy levels HOMO and LUMO orbitals of compounds 2-4.

timicrobial [18,19,26], and anti-cancer agents [18,21,22,26,27-29]. Recently, according to theoretical calculations, some imidazolium salts and Ag-NHC complexes showed activity against the novel COVID-19 and could act as potential inhibitors for the virus [30,31]. The chemistry of Pd(II)-NHC complexes is still considered very recent, despite it has a history of two decades or some more. The potential of catalytic properties of this class of complexes particularly in coupling reactions was recognized by Herrmann and co-workers [7]. Later, this field has grown widely into different types of catalysis research. So, these complexes are studied extensively in catalysis ranging from C-C coupling to olefin polymerizations [11,32,33].

Biological applications of Pd(II)-NHC complexes are reported first time by Ray and co-workers in 2007 [34], as some of Pd(II)-NHC complexes are examined for their potency as anticancer agents and found to be active against various cancer cell lines. After that, various studies focused on the biological applications of these complexes, especially in the field of anticancer agents being these complexes are mimics to the platinum complexes that have such activity [18,22,35]. In the present work, we report the synthesis and characterization of new symmetrical and asymmetrical NHC precursors derived from 1,3-disubstituted imidazole and their corresponding mononuclear Ag(I) and Pd(II) complexes. All the prepared compounds were examined for their in-vitro antibacterial activity against bacterial strains *E. coli* and *S. aureus*. Further, DFT and docking studies were used to have a deep insight into more properties for the prepared compounds.

2. Experimental

2.1. Materials and instrumentation

All chemicals and solvents were of high analytical grade and used as it is without further purification. Nuclear magnetic resonance (NMR) spectra were recorded using Bruker 400 MHz spectrometers at ambient temperature. ^{1}HNMR chemical shifts were referenced to the solvent signals. FT-IR spectra were recorded with a Shimadzu FTIR-8400s spectrophotometer. The elemental analysis (CHN) was carried out on PerkinElmer series II, 2400 microanalyzer. Palladium chloride $PdCl_2$ was converted to its corresponding $[PdCl_2(MeCN)_2]$ using a reported method. [36].

2.2. Syntheses of ligand precursors

2.2.1. Preparation of 2-chloro-N-(2,5-dimethylphenyl)-acetamide (1)

2-chloro-*N*-(2,5-dimethylphenyl)acetamide was synthesized according to a reported procedure [37], by mixing (5 ml, 40 mmol) of 2,5-dimethylaniline in benzene (10 ml) then 1.5 ml of trimethylamine was added. The mixture was stirred for 20 min then chloroacetyl chloride (3 ml, 40 mmol) was added dropwise. The stirring was continued for another 30 min at room temperature. After completion of the reaction, the resulted white precipitate was filtered and washed with distilled water and then recrystallized using ethanol. Yield (5.9 g, 75 %), (m.p = 140-142 °C).

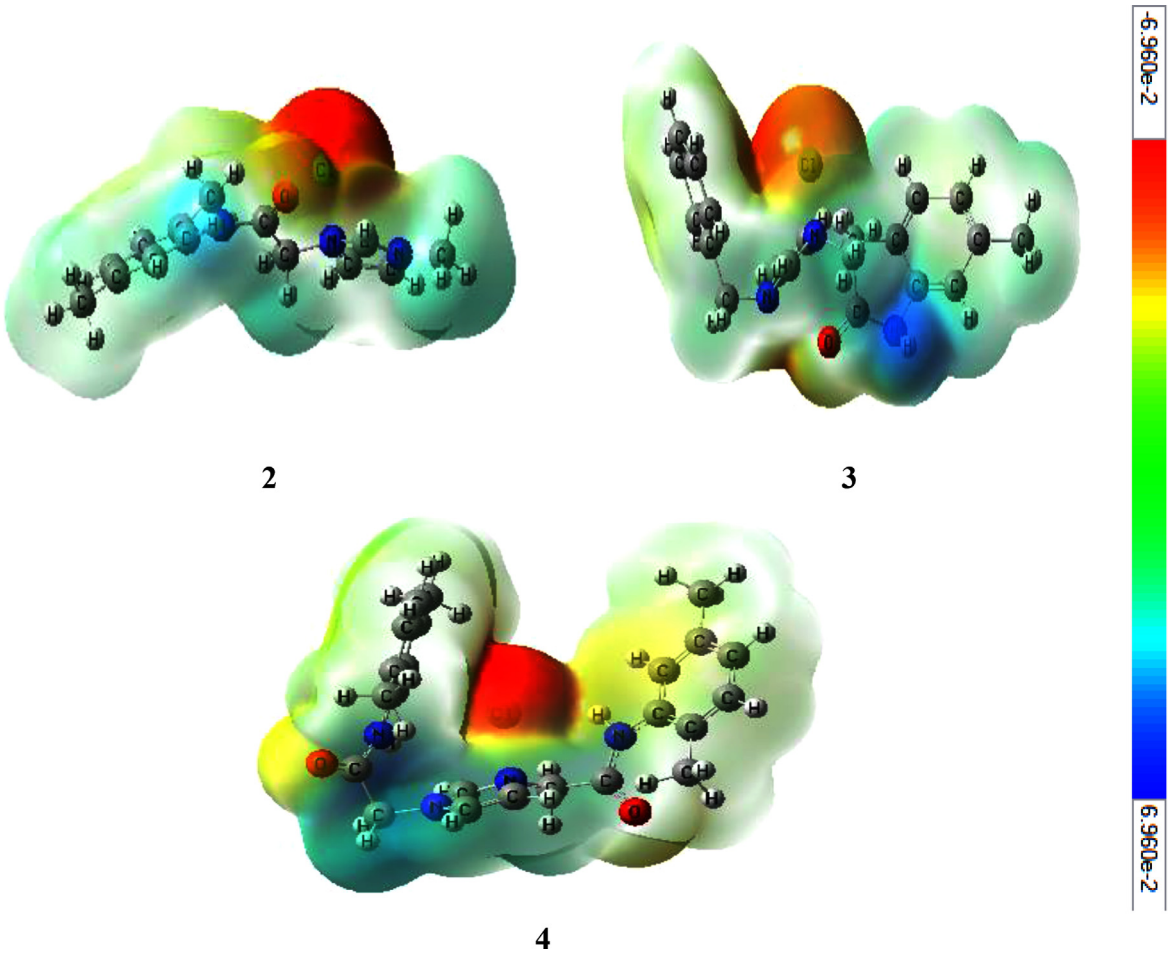


Fig. 2. TED maps of compounds 2-4.

2.2.2. 1-methyl-3-(2,5-dimethylphenyl)acetamide imidazolium chloride (2)

In a 50 mL round bottom flask, 1-methylimidazole (1 g, 12.1 mmol) in 10 ml of dioxane was placed, then 2-chloro-N-(2,5-dimethylphenyl)acetamide (2.4 g, 12.1 mmol) dissolved in 20 ml of dioxane was added dropwise. The mixture was refluxed with stirring at 90 °C for 24 hrs. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude product was washed with diethyl ether and dichloromethane to get the product as a white powder. Yield: (2.4 gm 82%), (m.p = 157-159°C). FT-IR cm^{-1}: 3268 m ν(N-H), 1667 m ν(C=O), 1583 m ν(C-N). ^{1}HNMR (400 MHz, d_6-DMSO) δppm: 9.96 (1H, s, N-H), 8.12 (1H, s, imidazolium H2′), 7.72 (2H, d, J = 7 Hz, Ar-H), 7.62 (1H, d, J = 8 Hz, imidazolium H5′), 7.31 (1H, s, Ar-H), 7.24 (1H, d, J = 8 Hz, imidazolium H4′), 5.52 (2H, s, $COCH_2N$), 4.0 (3H, s, N-CH_3), 2.52 (3H, s, CH_3Ar) and 2.51(3H, s, CH_3Ar). ^{13}CNMR (100 MHz, d_6-DMSO) δppm: 158.3 (N-CO), 139.3 (imidazolium C2′), 135.4, 133.2, 129.1, 128.5, 125.6, 123.3 ($C_{aromatic}$), 124.7, 121.9 ((imidazolium C5′ & and C4′), 55.8 (CO-CH_2N), 37.2 (N-CH_3), 20.8 (Ar-CH_3), 18.3 (Ar-CH_3). Anal. Calc. for $C_{14}H_{18}N_3OCl$: C, 60.10; H, 6.49; N, 15.02. Found. C, 60.35; H, 6.99; N, 15.19.

2.2.3. 1-benzyl-3-(2- N-2,5-dimethylphenylacetamide)imidazolium chloride (3)

This compound was synthesized in a similar method to that for **2**, except using of benzylimidazole instead of methylimidazole. White gummy product. Yield: (1.8 gm, 72%), (m.p= 165-166 °C). FT-IR cm^{-1}: 3287 m ν(N-H), 1647 s ν(C=O), 1589 s ν(C-N). ^{1}HNMR (400 MHz, d_6-DMSO) δppm: 10.12 (1H, s, N-H), 9.33 (1H, s, imidazolium H2′), 7.93 (2H, d, J = 7 Hz, Ar-H), 7.64 (H, d, J = 8 Hz, imidazolium H5′), 7.42-7.25 (7H, m, Ar-H, imidazolium H4′), 5.62 (2H, s, CO-CH_2N), 5.35 (2H, s, benzylic CH_2), 2.55 (3H, s, CH_3-Ar) and 2.53 (3H, s, CH_3-Ar). ^{13}CNMR (100 MHz, d_6-DMSO) δppm: 158.6 (N-CO), 138.8 (imidazolium C2′), 136.2, 135.1, 134.4, 133.6, 129.3, 128.5, 127.6, 125.4, 124.2, 123.1 (Ar-C), 122.8, 121.6 ((imidazolium C5′ & and C4′), 54.9 (CO-CH_2N), 52.2 (benzylic C), 21.3 (Ar-CH_3), 17.9 (Ar-CH_3). Anal. Calc. for $C_{20}H_{22}N_3OCl$: C, 67.50; H, 6.23; N, 11.81. Found. C, 67.32; H, 6.12; N, 11.68.

2.2.4. 1,3-(bis[3-N-2,5-dimethylphenylacetamide])imidazolium chloride (4)

This compound was synthesized in a similar method to that for **3,** but using 2 mole of **1.** White powder product. Yield: (2.5 gm, 89%), (m.p = 250-252 °C). FT-IR cm^{-1}: 3266 w ν(N-H), 1658 s ν(C=O), 1584 s ν(C-N). ^{1}HNMR (400 MHz, d^6-DMSO), δppm: 9.3 (2H, s, 2 × N-H), 8.3 (1H, s, imidazolium H2′), 7.8 (2H, s, imidazolium H5′ & H4′), 7.2 (4H, d, J = 7 Hz, Ar-H), 7.16 (2H, s, Ar-H), 5.3 (4H, s, 2 × CO-CH_2N), 2.3 (6H, s, CH_3Ar) and 2.2 (6H, s, CH_3Ar). ^{13}CNMR (100 MHz, d_6-DMSO) δppm: 162.2 (N-CO), 138.9 (imidazolium C2′), 136.5, 135.3, 129.6, 128.2, 125.1, 114.3 (Ar-C), 123.7, 122.9 ((imidazolium C5′ & and C4′), 53.8 (CO-CH_2N), 21.6 (Ar-CH_3), 20.2 (Ar-CH_3). Anal. Calc. for $C_{23}H_{27}N_4O_2Cl$: C, 64.70; H, 6.37; N, 13.12. Found. C, 64.67; H, 6.61; N, 13.31.

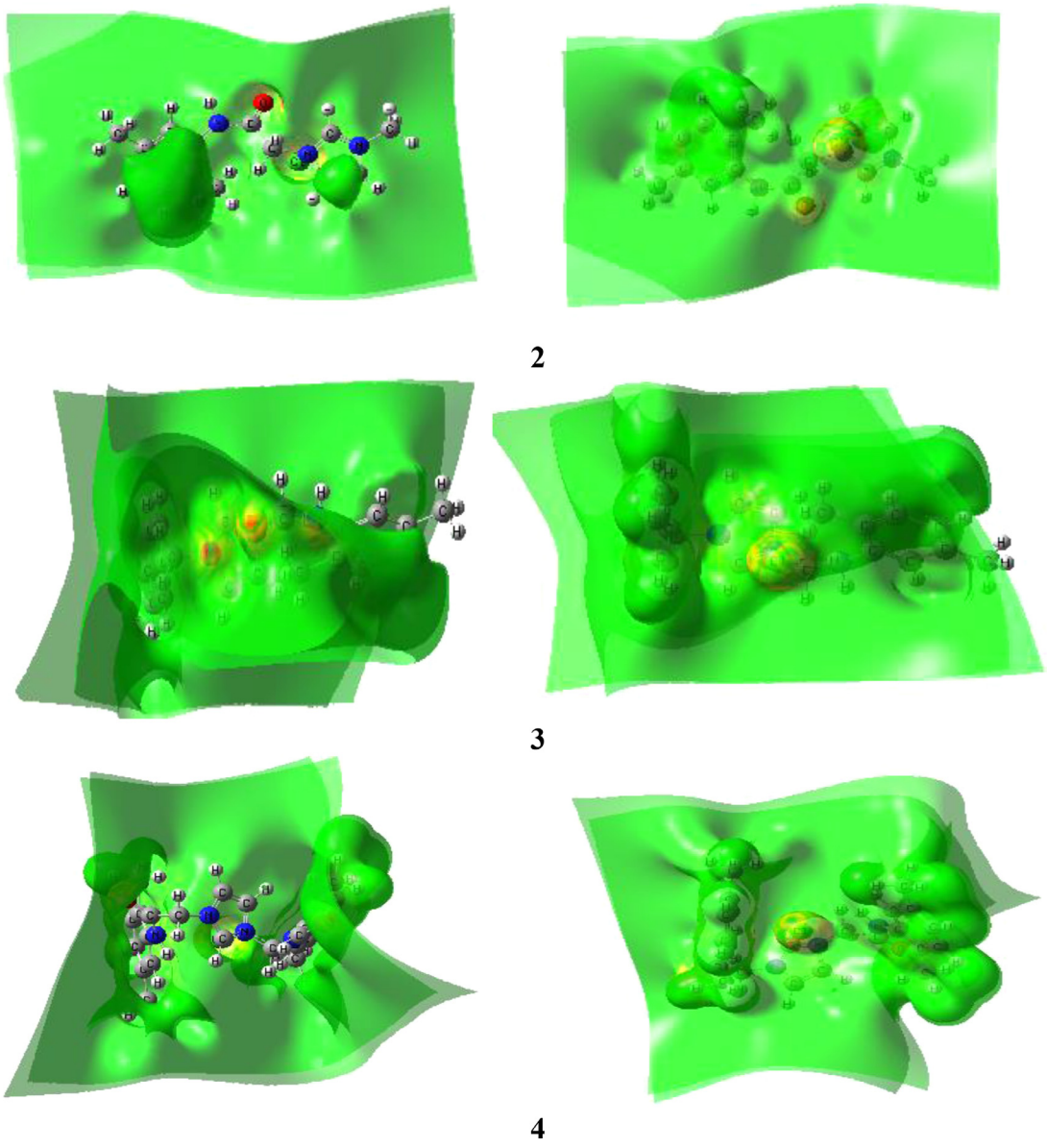


Fig. 3. ESP maps of the compounds 2-4.

2.3. Synthesis of silver (I)-NHC complexes (5-7)

2.3.1. Bis(1-methyl-3-(2,5-dimethylphenyl)-acetamideimidazolium)silver chloride (5)

Excess of silver oxide (0.7g, 2.1 mmol) was added to compound **2** (0.5 g, 2.1 mmol) in 20 ml of acetonitrile. The mixture was stirred for 8 h in glassware wrapped with aluminum foil at 50 °C. The black suspension was filtered through a pad of celite to remove the excess Ag_2O, and the solvent was removed under vacuum. The resulted white solid washed twice with fresh diethyl ether. Yield = (0.84 gm, 65 %), (m.p= 130-132 °C). FT-IR cm^{-1}: 3265 s ν(N-H), 1668 s ν(C=O), 1590 w ν(C-N). ^{1}HNMR (400 MHz, d_6-DMSO) δppm: 9.93 (2H, s, 2 × N-H), 7.82 (2H, d, J = 7 Hz, Ar-H), 7.25 (1H, s, Ar-H), 7.25-7.20 (2H, m, 2 × imidazolium H5′), 6.99-6.90 (2H, m, 2 × imidazolium H4′), 5.3 (4H, s, 2 × CO-CH_2N), 4.2 (6H, s, 2 × N-CH_3), 2.3 (6H, s, 2 × Ar-CH_3), and 2.2 (6H, s, 2 × Ar-CH_3). ^{13}CNMR (100 MHz, d^6-DMSO) 178.4 ($C_{carbene}$-Ag), 158.8 (N-CO), 135.8, 134.3, 131.2, 129.7, 126.5, 124.8 ($C_{aromatic}$), 123.6, 122.8 (imidazolium C5′ & and C4′), 55.2 (CO-CH_2N), 37.5 (N-CH_3), 21.2 (Ar-CH_3), 18.8 (Ar-CH_3). Anal. Calc. for $C_{28}H_{34}AgN_6O_2Cl$: C, 53.39; H, 5.44; N, 13.34. Found. C, 53.07; H, 5.12; N, 12.98.

2.3.2. Bis(1-benzyl-3-(2,5-dimethylphenyl)-acetamideimidazolium)silver chloride (6)

This compound was synthesized in a similar method to that for **5,** but using 2 mole of compound **2**. White solid. Yield: (1.25 gm, 73 %), (m.p = 150-152 °C). FT-IR cm^{-1}: 3279 m ν(N-H), 1664 s ν(C=O), 1594 m ν(C-N). ^{1}HNMR (400 MHz, d^6-DMSO) δppm: 9.83 (2H, s, 2 × NH), 7.84 (4H, d, J = 7 Hz, 2 × Ar-H), 7.47 (2H, d, J = 8 Hz, 2 × imidazolium H5′), 7.28-7.21 (14H, m, 2 × Ar-H, 2 × imidazolium H4′), 5.2 (4H, s, 2 × benzylic CH_2), 5.3 (4H, s, 2 × CO-CH_2N), 2.3 (6H, s, 2 × Ar-CH_3) and 2.2 (6H, s, 2 × Ar-CH_3). ^{13}CNMR (100 MHz, d_6-DMSO) δppm: 177.8 ($C_{carbene}$-Ag), 158.2 (N-CO), 136.6, 135.3, 133.9, 133.7, 129.7, 128.8, 127.3, 125.6, 123.8, 123.2 (Ar-C), 122.5, 121.3 (imidazolium C5′ & and C4′), 55.1 (CO-CH_2N), 52.6 (benzylic C), 21.5 (Ar-CH_3), 18.4 (Ar-CH_3). Anal. Calc.

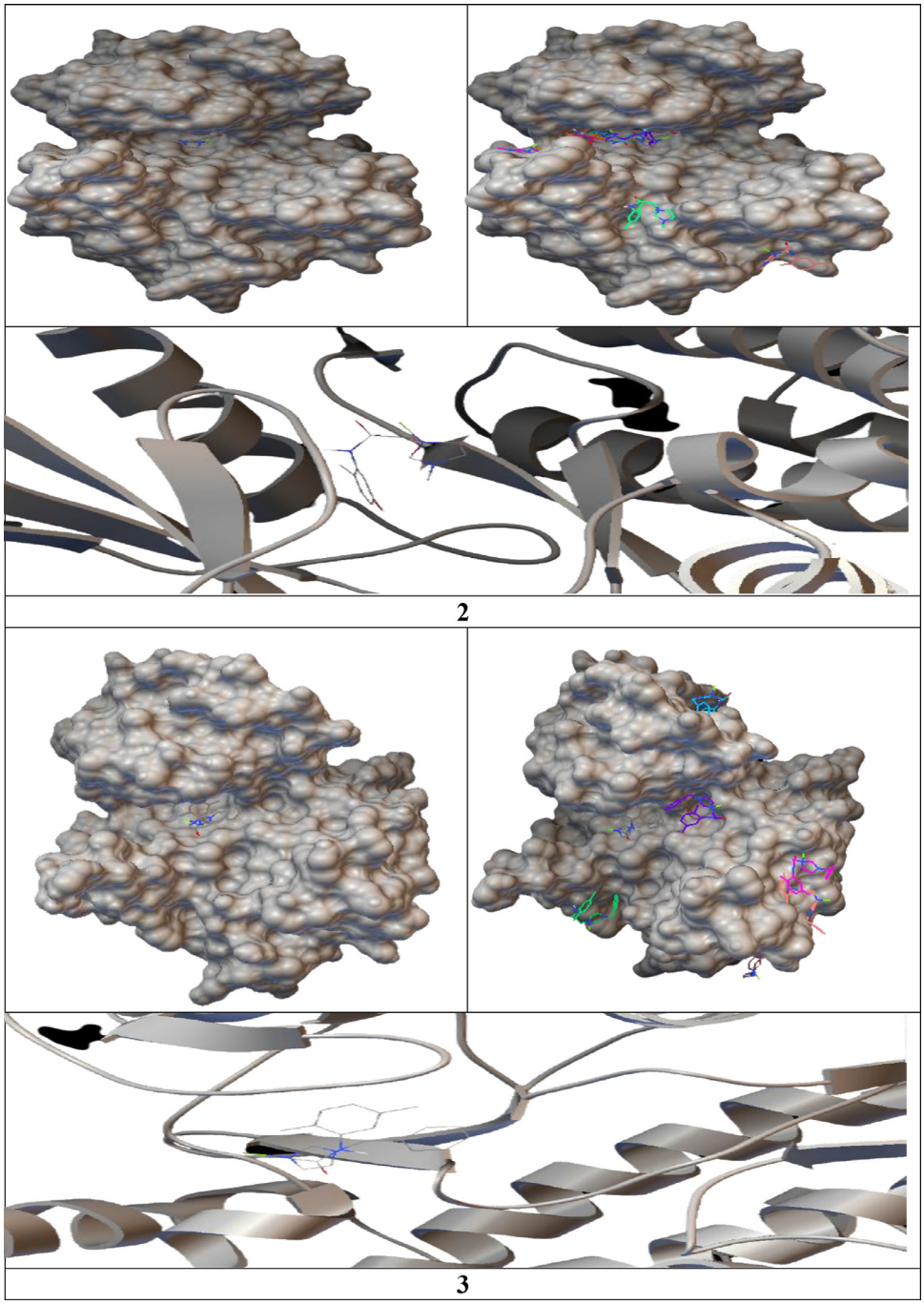


Fig. 4. Molecular interactions between LDH-5 and compounds 2-4.

for $C_{40}H_{42}N_6AgO_2Cl$: C, 61.43; H, 5.41; N, 10.75. Found. C, 61.67; H, 6.02; N, 10.44.

2.3.3. Bis[1,3-(bis[3-N-2,5-dimethylphenylacetamide])imidazolium]silver chloride (7)

This compound was synthesized in a similar method to that for **5,** but using 2 mole of compound **3**. White solid. Yield: (1.37 gm, 72 %), (m.p = 150-152 °C). FT-IR cm^{-1}: 3271 m ν(N-H), 1662 s ν(C=O), 1597 s ν(C-N). ^{1}HNMR (400 MHz, d^6-DMSO), δppm: 9.6 (4H, s, 4 × N-H), 7.7 (4H, s, 2 × imidazolium H5′ & H4′), 7.42 (8H, d, J = 7 Hz, 2 × Ar-H), 7.08 (4H, s, 2 × Ar-H), 5.2 (8H, s, 2 × CO-CH_2N), 2.3 (12H, s, 4 × CH_3Ar) and 2.2 (12H, s, 4 × CH_3Ar). ^{13}CNMR (100 MHz, d_6-DMSO) δppm: 178.9 ($C_{carbene}$-Ag), 161.1 (N-CO), 135.9, 135.0, 128.8, 128.3, 124.7, 113.6 (Ar-C), 123.8 (imidazolium C5′ & and C4′), 52.4 (CO-CH_2N), 21.9 (Ar-CH_3), 20.8 (Ar-CH_3). Anal. Calc. for $C_{46}H_{52}N_8AgO_4Cl$: C, 59.78; H, 5.67; N, 12.12. Found. C, 59.97; H, 5.88; N, 12.41.

2.4. Synthesis of Palladiun(II)-NHC complexes (8-10)

2.4.1. Bis(1-methyl-3-(2,5-dimethylphenyl)-acetamideimidazolium)Palladium dichloride (8)

Palladium complex [Pd($CH_3CN)_2Cl_2$] (0.04 gm, 0.15 mmol) dissolved in methanol (7.5 ml) add dropwise to complex **5** (0.13 gm,

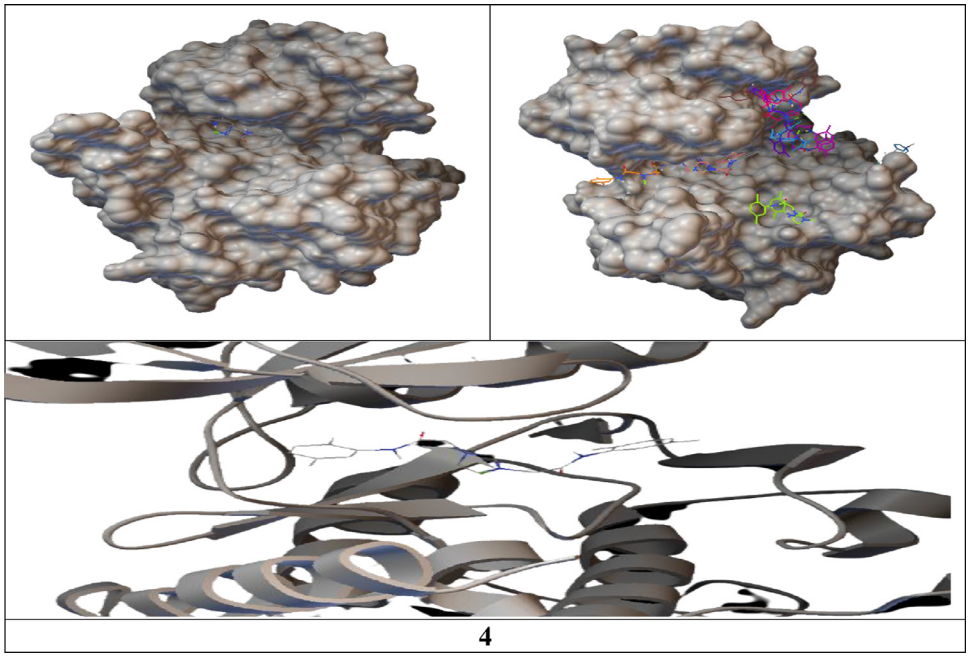


Fig. 4. Continued

0.15 mmol) that dissolved in methanol (7.5 ml), then the mixture was stirred for 6 hrs at room temperature . The mixture was filtered using celite to remove silver particles. The resulted solution was minimized to 1 ml using reduced pressure and 10 ml of petroleum ether was added to give the complex as a pale-brown precipitate which was filtered and dried at ambient temperature. Yield: (0.13 gm, 82 %), (m.p = 170-174 °C). FT-IR cm^{-1}: 3267 m ν(N-H), 1663 s ν(C=O), 1592 s ν(C-N). ^{1}HNMR (400 MHz, d^6-DMSO) δppm: 9.96 (2H, s, 2 × N-H), 8.20 (4H, d, J = 7 Hz, 4 × Ar-H), 7.84 (2H, d, J = 8 Hz, 2 × imidazolium H5′), 7.37 (2H, s, 2 × Ar-H), 7.32 (2H, d, J = 8 Hz, 2 × imidazolium H4′), 5.5 (4H, s, 2 × CO-CH_2N), 4.0 (6H, s, 2 × N-CH_3), 2.3 (6H, s, 2 × Ar-CH_3) and 2.1 (6H, s, 2 × Ar-CH_3). ^{13}CNMR (100 MHz, d^6-DMSO) 168.12 ($C_{carbene}$-Pd), 156.9 (N-CO), 135.4, 133.9, 132.1, 129.5, 127.2, 125.2 ($C_{aromatic}$), 124.8, 123.3 (imidazolium C5′ & and C4′), 55.6 (CO-CH_2N), 36.8 (N-CH_3), 22.1 (Ar-CH_3), 19.3 (Ar-CH_3). Anal. Calc. For $C_{28}H_{34}Cl_2N_6O_2Pd$: C, 50.65; H, 5.16; N, 12.66. Found. C, 50.39; H, 5.08; N, 12.41.

2.4.2. Bis(1-benzyl-3-(2,5-dimethylphenyl)-acetamideimidazolium)Palladium dichloride (9)

This complex was prepared in similar method, except using complex **6** instead of **5**. The complex resulted as a pale-brown solid. Yield: (0.16 gm, 85 %), (m.p = 108-110 °C). FT-IR cm^{-1}: 3280 m ν(N-H), 1667 s ν(C=O), 1596 s ν(C-N). ^{1}HNMR (400 MHz, d^6-DMSO) δppm: 9.63 (2H, s, 2 × NH), 7.94 (4H, d, J = 7 Hz, 2 × Ar-H), 7.36 (2H, d, J = 8 Hz, 2 × imidazolium H5′), 7.24-7.18 (14H, m, 2 × Ar-H, 2 × imidazolium H4′), 4.95 (4H, s, 2 × benzylic CH_2), 4.73 (4H, s, 2 × CO-CH_2N), 2.27 (6H, s, 2 × Ar-CH_3) and 2.16 (6H, s, 2 × Ar-CH_3). ^{13}CNMR (100 MHz, d_6-DMSO) δppm: 167.8 ($C_{carbene}$-Pd), 158.32 (N-CO), 136.2, 135.7, 133.6, 133.3, 130.1, 128.9, 127.5, 125.4, 123.6, 123.4 (Ar-C), 122.8, 121.2 (imidazolium C5′ & and C4′), 55.3 (CO-CH_2N), 52.7 (benzylic C), 21.7 (Ar-CH_3), 19.2 (Ar-CH_3). Anal. Calc. for $C_{40}H_{42}N_6PdO_2Cl_2$: C, 58.87; H, 5.19; N, 10.30. Found. C, 58.98; H, 5.42; N, 10.61.

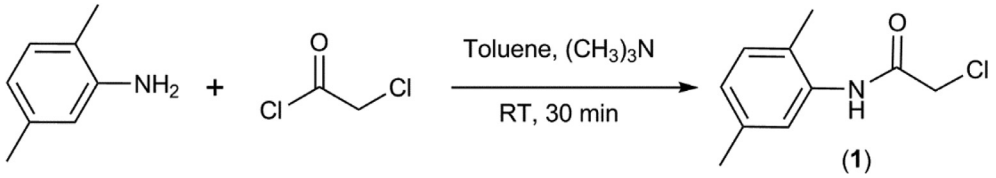
2.4.3. Bis[1,3-(bis(2-N-2,5-dimethylphenylacetamide)imidazolium]Palladium(II) dichloride (10)

This complex was prepared in similar method, except using complex **7** instead of **5**. The complex resulted as a pale-brown solid. Yield: (0.11 gm, 79 %), (m.p = 170-174 °C). FT-IR cm^{-1}: 3269 m ν(N-H), 1663 s ν(C=O), 1599 s ν(C-N). ^{1}HNMR (400 MHz, d^6-DMSO), δppm: 9.5 (4H, s, 4 × N-H), 7.9 (4H, s, 2 × imidazolium H5′ & H4′), 7.32 (8H, d, J = 7 Hz, 2 × Ar-H), 7.04 (4H, s, 2 × Ar-H), 5.3 (8H, s, 4 × CO-CH_2N), 2.3 (12H, s, 4 × CH_3Ar) and 2.1 (12H, s, 4 × CH_3Ar). ^{13}CNMR (100 MHz, d_6-DMSO) δppm: 168.6 ($C_{carbene}$-Pd), 159.7 (N-CO), 135.7, 134.5, 128.2, 127.8, 124.6, 112.9 (Ar-C), 123.4 (imidazolium C5′ & and C4′), 53.0 (CO-CH_2N), 21.3 (Ar-CH_3), 19.6 (Ar-CH_3). Anal. Calc. for $C_{46}H_{52}N_8PdO_4Cl_2$: C, 57.66; H, 5.47; N, 11.69. Found. C, 57.84; H, 5.68; N, 11.93.

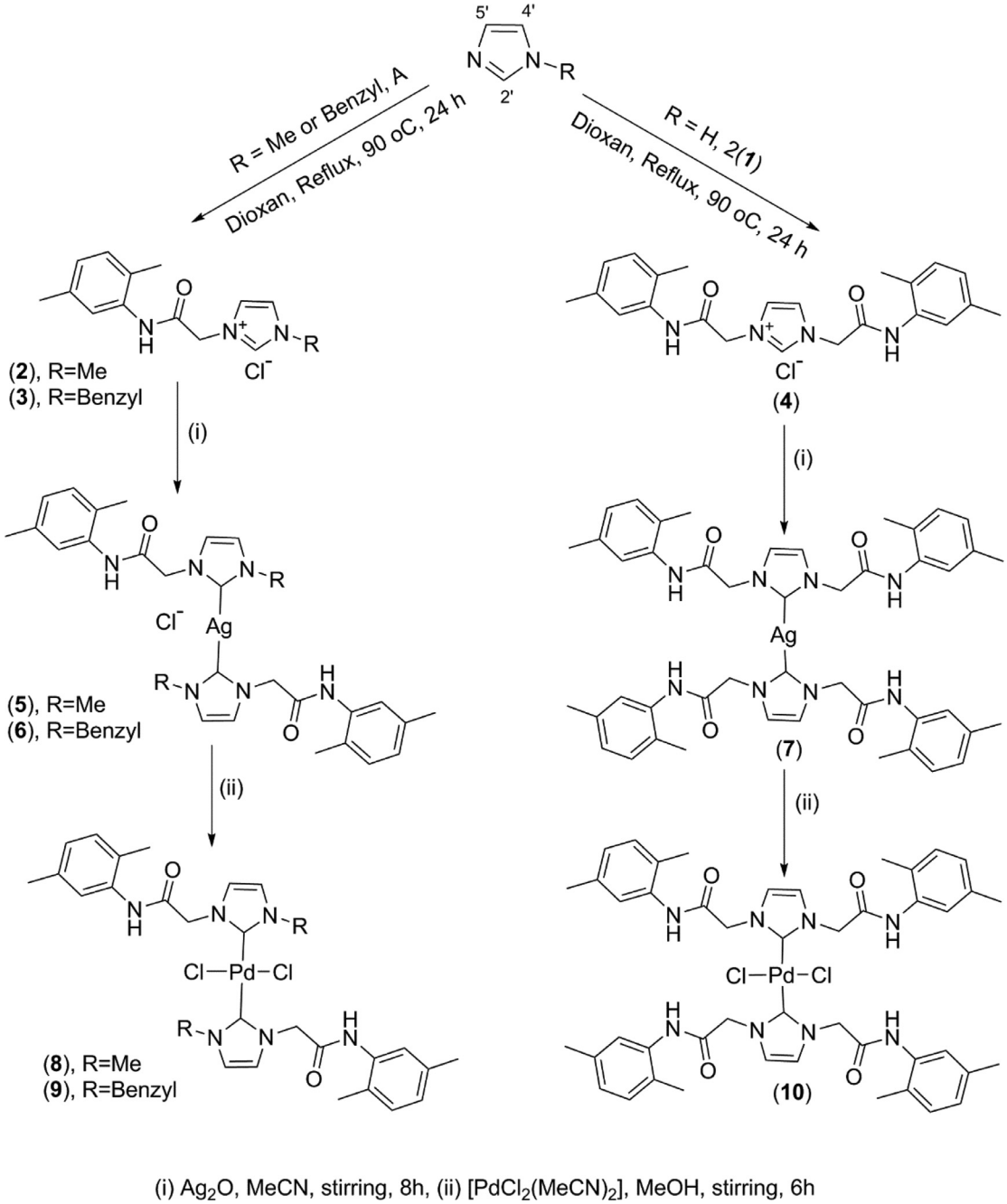
2.5. Calculations Models

In the current study, The software Gaussian (Gauss View 0.9) and Molecular Graphic Laboratory (MGL) tools were used [38-40]. The geometrical optimization for the complexes was suggested by Density Functional Theory (DFT) with LanL2DZ basis set [41]. Physical properties such as Total energy, Dipole moment, bond lengths, HOMO-LUMO energies, ESP, and TED are included in DFT calculation. Docking calculations were done for the studied complexes as inhibitors for colon cancer cell LDH-5. (Research Collaboratory for Structural Bioinformatics) RCSB [42] was used to download the protein structure (1T2F). For each component, LDH-5 and coordinates of drugs have been selected using Autodock tools (ADT, version 1.5.6). The structures of protein and complexes are transformed into a recognized format ADT (*.pdbqt files).

Gasteiger charges and polar hydrogen atoms were taken into consideration in the calculations as well. The Autodock also tries to identify the root of the molecule if the consumer does not indicate it. The root was selected automatically Autodock. The atomic affinity maps were calculated with the support of Autogrid (version 4.2.6) for all ligand atomic groups and electrostatic [43]. DSV software gives the interactions of the cell with the complexes.



Scheme 1. Synthesis of 1.



Scheme 2. Synthesis of NHC precursors (2-4), and their coresponding Ag(I)-NHC (5-7), and Pd(II)-NHC (8-10) complexes.

2.6. Antibacterial activity

The compounds **2, 3, 5, 6, 9,** and **10** were screened for their antibacterial activity against Escherichia coli and Staphylococcus aureus in Muller Hinton agar by measuring the inhibition zone, using Azithromycin (AZ,100 µg/ µL and 200 µg/ µL) as a standard antibacterial drug. Each bacteria isolate was inoculated onto the Muller-Hinton Agar (sterilize in autoclave) by dipping a cotton swab into the suspension and streaking it over the surface of the agar plates. Then, in the solidified medium, four holes were made. These holes were filled with (0.5 ml) of the prepared compounds ((100 µg/ µL and 200 µg/ µL) of the compound dissolved in 1ml of DMSO sol-

vent). These plates were incubated at 37 °C and measured zone of inhibition after 48 hours.

3. Results and discussion

3.1. NHC precursors and complexes

The compound 2-chloro-(2,5-dimethyl phenyl) acetamide (**1**) was prepared according to a reported procedure (Scheme 1), which was then used to prepare compounds **2, 3**, and **4**.

Compounds 1-methyl-3-(2,5-dimethylphenyl)-acetamideimidazolium chloride (**2**), and 1-benzyl-3-(2- N-2,5-dimethylphenylacetamide)imidazolium chloride (**3**), were prepared by reaction of **1** with 1-methy- or 1-benzylimidazole in 1:1 mole ratio, in dioxane and the mixture was refluxed with stirring at 90 °C for 24 hrs. While the compound 1,3-(bis[3-N-2,5-dimethylphenylacetamide])imidazolium chloride (**4**), was prepared by the reaction of imidazole with 2 moles of **1** at the same conditions). The prepared compounds resulted in their solid form after evaporation of the solvent and washing with diethyl ether. Moreover, they were stable to air and moisture, and soluble in common solvents such as ethanol, methanol, acetonitrile, dichloromethane, DMSO, and DMF, but insoluble in some solvents such as benzene, dioxane, and diethyl ether, and partially in the water.

Silver complexes **5**-**7** were prepared according to a reported procedure [20], by in situ reaction of silver oxide with corresponding imidazolium salts **2**-**4**, respectively. In glassware wrapped with aluminum foil to exclude the light, the reaction of excess silver oxide with imidazolium salt in refluxed acetonitrile for 8-10 h produced the complexes in good yields after appropriate treatment. In all reactions, a resulted black suspension was filtered off using a pad of celite to remove the excess of Ag_2O. Then, the solvent was removed under reduced pressure to give a white solid after washing with diethyl ether.

Palladium complexes **8**-**10** were synthesized by the transmetallation method [20]. The reaction of $[PdCl_2(MeCN)_2]$ with corresponding Ag(I)-NHC complexes in stirring methanol for 6 h at room temperature resulted in the Pd(II)-NHC complexes after suitable treatment in good yields. The black suspension resulted was filtered off using a pad of celite to remove AgCl precipitate. Then, the solvent was minimized under reduced pressure, followed by the addition of petroleum ether to give the complexes as pale yellow solids. Both Ag(I)-NHC and Pd(II)-NHC complexes were soluble in organic solvents such as ethanol, methanol, acetonitrile, dichloromethane, DMSO, and DMF but insoluble in water, diethyl ether, and benzene. Synthesis of compounds **2**-**10** shown in Scheme 2.

3.2. FT-IR Spectroscopy

There is some good information that could be deduced by using the FT-IR spectrum when comparing the ligands and their corresponding metal complexes. Infrared spectra were obtained for all imidazolium salts and their Ag(I) complexes using KBr disk method (Figs SI1). In the imidazolium salt, the bands observed at the range 3266-3287 cm-1 are assigned to the stretching of N-H. The stretching bands of C=O were observed at the range 1667-1647 cm-1. Another band was observed at the range 1583-1489 cm-1, which was assigned to the stretching of C-N. In Ag(I)- and Pd(II)-NHC complexes, most of the above-mentioned bands are shifted up or down, and this could be considered as a primary indicator for successful complexation with Ag and Pd, respectively [44]. The most important band which is showed a significant shifting is C-N. This band is shifted up at the range 5-15 cm-1. This shifting can be attributed to the back bonding of Ag and Pd electrons [45,46].

3.3. NMR spectroscopy

All NMR spectra of imidazolium salts and their corresponding Ag(I)- and Pd(II)-NHC complexes were collected in d_6-DMSO over the scan range of δ 0-12 and δ 0-200 for ^1H and ^{13}C, respectively (Figs SI2 and SI3). NMR spectra of all the synthesized compounds showed the expected signals for this class of compounds. In ^1H NMR of the imidazolium salts **2**-**4**, a singlet peak appeared at the range of δ 9.3-10.12 is assigned to the proton of N-H. The significant signal of imidazolium H2′ was observed at the range of δ 8.12-9.33 as a singlet peak. The arene protons Ar-H appeared at the range of δ 6.8-7.4 as multiplet peaks. While the imidazolium H5′/H4′ protons appeared at the range of δ 7.39-8.2 as variable peaks. In ^{13}C NMR, the most important signal is for C2′, which appeared at the range of δ 138-139.

In both synthesized Ag(I) and Pd(II) complexes, 1H NMR showed a full absence of H2′ signals, the characteristic one in imidazolium salts. According to the literature, this is attributed to the successful coordination with the metals used [19,22,25]. The Ar-H protons appeared at the range of δ 6.8-7.5 as multiplet peaks, while the imidazolium H5′/H4′ protons appeared at the range of δ 7.7-8.1. In ^{13}C NMR, the characteristic signals of $C_{carbene}$-Ag and $C_{carbene}$-Pd appeared at the ranges δ 177.8-178.9 for Ag(I)-NHC complexes, and δ 167.8-168.6 for Pd(II)-NHC complexes. All these observations are in good agreement with the data of the reported analogs imidazolium salts and complexes [47-49].

3.4. The antibacterial activity test

The antibacterial activity of substituted imidazolium salts and their Ag(I) and Pd(II) complexes were evaluated against the bacterial strains *E. coli* as gram-negative and *S. aureus* as gram-positive using azithromycin as a standard antibiotic. In comparing with azithromycin, all the imidazolium salts and their respective Ag(I) and Pd(II) complexes showed good activity against the tested bacteria (Table **1**). According to the tabulated results, the antibacterial activity of Ag(I) complex **5** is the highest, while, the lowest was for imidazolium salt **2**. Also, Pd(II) complex **9** showed good activity but less than **5**. Other compounds showed moderate activity, and there are no vast differences observed. The variance in the results is may be due to the changing of N-substituents on the NHC, which leads to a complete change in the stability of the complexes. This could enhance a slow sustained release of Ag+ ions, which is significant in the inhibition of bacterial growth [18,19]. Further, The sensitivity of the gram-negative bacteria increases as the volume of the complex suspensions increases.

3.5. Ground state of compounds

The bond/interaction distances (Å) of compounds **2**-**10** at the equilibrium (Table **2**) were calculated using the DFT method. Depeneding on the tabulated results, there are some differences in lengths. Also, a decrease found in total energy in the order **2**< **3**< **4**< **8**< **5**< **6**< **9**<**10**< **7**, which is directly proportional to the size of the geometrical and molecular structure of the studied compounds. The coordination bonds give more stability to compounds **5**-**10**, while the low stability of compounds **2, 3**, and **4** reveals the high activity of these compounds.

3.6. Activity and molucular orbitals

In this part, some physical properties are studied to refer to the activity [50,51] of the synthesized compounds (Table 3). There is a decrease in E_{LUMO} in the order 3< 2< 5< 9< 6< 10< 7< 8< 4, (Figs. 1 **and SI4**). The energy gap, the difference between HOMO and LUMO orbitals was in the order 3> 2> 7> 5> 8> 9> 6> 4>

Table 1
Antibacterial activities of compounds 2, 3, 5, 6, 9, and 10 against E.coli. and S. Aureus.

Compound	*E.coli.* Inhibition zone (mm)		*S. aureus* Inhibition zone (mm)	
	100 μg ml^{-1}	200 μg ml^{-1}	100 μg ml^{-1}	200 μg ml^{-1}
2	15	20	0	10
3	20	30	15	25
5	25	35	25	30
6	20	20	20	25
9	25	25	20	25
10	20	25	15	15
AZ	30	40	20	30

Table 2
Bond/interaction distances (Å) and total energy of the studied compounds.

2	N-Cl	C=O	N-C	E_{total} (a.u)
	1.87	1.20	1.36	-1244.06
3	N-Cl	C=O	N-C	-1474.64
	1.88	1.25	1.46	
4	N-Cl	C=O	N-C	-1722.56
	2.02	1.20	1.36	
5	Ag-Cl	Ag-C	C=O	-1726.67
	2.32	2.11	1.20	
6	Ag-Cl	Ag-C	C=O	-2188.65
	2.32	2.10	1.20	
7	Ag-Cl	Ag-C	C=O	-2682.15
	1.72	1.59	1.20	
8	Pd-Cl	Pd-C	C=O	-1722.56
	2.24	2.03	1.20	
9	Pd-Cl	Pd-C	C=O	-2184.56
	2.25	2.05	1.20	
10	Pd-Cl	Pd-C	C=O	-2679.12
	2.25	2.03	1.20	

10, which also represents the order of activity. The ionization energy (IE) is the amount of energy required for removing the electron of an atom. Low ionization energy gives high efficiency for inhibition.

$$IE = -EHOMO \quad (1)$$

According to the IE, the activity of the studied compounds ordered as:

2> 7> 3> 8> 5> 6> 4> 9> 10

Electronic affinity (EA) is the amount of energy released when an electron is added to a neutral atom. The higher value of electron affinity, the less stability and gives high efficiency for inhibition.

$$EA = -ELUMO \quad (2)$$

According to EA, the activity of the studied compounds is as follows:

4> 8> 7> 10> 6> 9> 5> 2> 3

Hardness (η) is defined as the second derivative of the E, which gives an indicator for both the stability and reactivity of the molecule.

$$\eta = \frac{IE - EA}{2} \quad (3)$$

According to η, the order is as follows:

3> 2> 7> 5> 8> 9> 6> 4> 10

The global softness (S) is the inverse of the global hardness. Softness is one of the important properties that measure molecular stability and reactivity.

$$S = \frac{1}{\eta} \quad (4)$$

According to S, the order is:

3> 2> 7> 5> 8> 9> 6> 4> 10

In a covalent bond, the electronegativity (χ) is the ability of an atom to attract shared electrons.

$$X = -\mu = \frac{IE + EA}{2} \quad (5)$$

If χ decreases, the efficiency of inhibition increases, and the order will be:

3> 5> 9> 10> 2> 6> 8> 4> 7

For the dipole moment (μ), the high value of μ is proportional to the efficiency for inhibition. So, the order will be as follows:

8> 6> 10> 7> 9> 2> 5> 4>3

According to the above-mentioned parameters, the significant activity was for compounds **2,3** and **4**. So, they will take into consideration in the next part.

3.7. TED and ESP maps

The present compounds in this part **2, 3**, and **4** are the more active among the studied compounds. The electron density is known as the total electron density (TED). In Figs. **2** and **SI5**, the red color represents the negative sites, which refers to N and O, the more electronegative atoms in the molecules. while the blue color indicates the more positive sites (metal), that could accept electrons from the donor [52].

The electrostatic surface potential (ESP) shows the direction of the adsorption of the molecule on the metal surface (Figs. **3** and

Table 3
Quantum chemical parameters for the studied molecules calculated in vacuum using DFT method.

Comp.	E_{HOMO}[a]	E_{LUMO}[a]	IE[a]	EA[a]	E_{gap}[a]	η[a]	S[b]	μ[c]	χ[a]
2	-3.9258	-1.2365	3.9258	1.2365	2.6893	1.3446	0.7436	6.09	2.5811
3	-4.2752	-1.9472	4.2752	1.9472	2.3279	1.1639	0.8591	3.91	3.1112
4	-4.9694	0.0971	4.9694	-0.0971	5.0666	2.5333	0.3947	4.40	2.4361
5	-4.8429	-0.9222	4.8429	0.9222	3.9207	1.9603	0.5101	5.70	2.8825
6	-4.8538	-0.1303	4.8538	0.1303	4.7234	2.3617	0.4234	11.2	2.4920
7	-4.8538	-0.0593	3.5318	0.0593	3.4725	1.7362	0.5759	7.13	1.7955
8	-3.5318	0.0884	4.4954	-0.0884	4.5838	2.2919	0.4363	14.4	2.2034
9	-4.4954	-0.3992	5.0203	0.3992	4.6211	2.3105	0.4327	6.12	2.7097
10	-5.1879	-0.1058	5.1879	0.1058	5.0821	2.5410	0.3935	9.63	2.6469

a: in eV, b: in eV^{-1}, c: in Debye.

Table 4
Binding energy values and efficiency of the studied compounds.

Comp.	E_b	L_E	Best position
2	-4.36	-0.23	L7
3	-4.70	-0.19	L2
4	-5.70	-0.14	L6
5	-3.68	-0.10	L8
6	-2.90	-0.06	L4
7	-3.68	-0.10	L8
8	-3.24	-0.08	L10
9	-2.07	-0.04	L3
10	-2.82	-0.11	L2

SI6), which is the same direction of the carbonyl group and chloride atoms in some double bonds [53].

3.11. Docking results

All the synthesized compounds **2**-**10** were investigated for their anticancer activity. Increasing glucose uptake in tumor cells leads to increasing glycolytic activity, which in turn elevating the levels of lactate production [54,55]. Lactate release is regulated by lactate dehydrogenase-5 (LDH-5) found in tumor cells [56]. Recently, LDH-5 inhibitors have been reported as potential antitumor agents [57]. Confirming that inhibition of LDH-5 is a significant target to obtain new candidates with improved anticancer activity.

Molecular docking was performed to study the LDH-5 inhibitory effect of the new compounds. The crystal structure of LDH-5 was obtained from Protein Data Bank (1T2F) [58]. The interaction between LDH-5 and inhibitors is considered by binding energy Eb (The measure of the affinity of compounds to the receptor) and ligand efficiency LE (binding energy per atom of ligand to receptor protein) [59,60]. According to the E_b (Kcal/mol) values of compounds **2**-**10** (Table 4), it is noted that compounds **2, 3**, and **4** have more probability to inhibit the LDH-5. There are different favorite positions (L) on the receptor, where L = 1-10, and the favorite ones for compounds **2, 3**, and **4** are L7, L2, and L3, respectively (Figs. 4 **and SI7**). The order of the compounds for inhibition of LDH-5 is **3**> **4**> **2.**

4. Conclusions

New Ag(I)-and Pd(II)-NHC complexes **5**-**10** were prepared from symmetrical and asymmetrical imidazolium salt **2**-**4** as NHC precursor ligands. Ag(I)-NHC complexes were synthesized by in situ reaction of the ligands and Ag_2O. While Pd(II)-NHC complexes were synthesized by the transmetallation method. The ligands and their respective complexes were characterized using ^{1}H-NMR spectroscopy, FT-IR spectrophotometer, CHN elemental analysis. Using azithromycin as a standard, some of the synthesized compounds were examined for their antibacterial activity against E.coli and S. aureus, as gram-positive and gram-negative, respectively. All the examined compounds showed good activity against the above-mentioned bacterial strains, especially compound **5**. Further, DFT studies were used to get deep insight into some physical properties of the synthesized compounds, which revealed a good activity for compounds **2, 3**, and **4**.

According to TED and ESP maps, theoretical calculations predicted that oxygen, nitrogen, and chloride atoms have the highest electron density in all studied compounds. The Autodock study explains the possibility of using the compounds as anticancer agents, which was revealed a good activity for the same compounds **2, 3**, and **4**.

Declaration of Competing Interest

The authors declare that no conflict of interest.

CRediT authorship contribution statement

Mohammed Z. Ghdhayeb: Supervision, Methodology. **Karem J. Sabah:** Visualization, Investigation. **Abbas Washeel Salman:** Writing – review & editing. **Mustafa Mohammed Kadhim:** Methodology, Software.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.131254.

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