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Synthesis, Characterization, and Molecular Docking of Ag(I) Complex with Schiff Base Functionalized *N*-Heterocyclic Carbene

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Abstract

A novel precursor (**1a**) of a Schiff base-functionalized N-heterocyclic carbene ligand and its corresponding Ag(I) complex (**2b**) were synthesized via an in-situ deprotonation method using a Schiff base/imidazolium salt and silver oxide. The compounds were thoroughly characterized employing UV-Vis, FTIR, ^{1}H-NMR, and ^{13}C-NMR spectroscopies along with elemental analysis techniques. Molecular docking analysis was conducted to elucidate the binding interactions between the silver complex and the active sites of survivin dimer H. sapiens protein (PDB ID: 1E31).

Keywords: Ag(I)-*N*-heterocyclic carbene, Docking study, Imidazolium salts**,** Schiff base.

1.Introduction

In organometallic chemistry, N-heterocyclic carbene (NHC) ligands have generated a great interest[1]. 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 and a free carbene led to the first NHC-Ag(I) complex isolated in 1993 by[2] . The most common method reported of synthesis has been the deprotonation with a silver base such as Ag_2O, Ag_2CO_3 and AgOAc [3-5].

NHC-Ag(I) complexes have been widely used as sources of different metal complexes via transmetallation [6-11] These compounds have antimicrobial and anticancer properties[3, 12- 14].

The term Schiff base was given in honour of the German chemist Hugo Schiff, who first described the products resulting from the reactions between primary amines with carbonyl compounds.[15]

In medicinal chemistry, the development of powerful and effective medicinal drugs has been extensively explored. The derivatives of Schiff bases represent a significant category of compounds that have found multiple applications in therapeutic chemistry because of their wide range of pharmacokinetic properties and their prominence in drug discovery programs [1617]. Schiff base derivatives and their complexes have reportedly demonstrated a variety of biological properties, such as anti-inflammatory[18], antibacterial [16], antifungal[19], antiviral[20], anticancer [21-26]. Conjugation of Schiff bases to NHCs represents a synergistic approach toward the development of new anticancer agents. By incorporating NHC fragments into Schiff base frameworks, in this study we aim to capitalize on the combined pharmacological benefits of both scaffolds. The resulting Schiff Base-NHC complexes may exhibit enhanced stability, selectivity, and cellular uptake, thus enhancing their anticancer efficacy.

2.Synthesis part

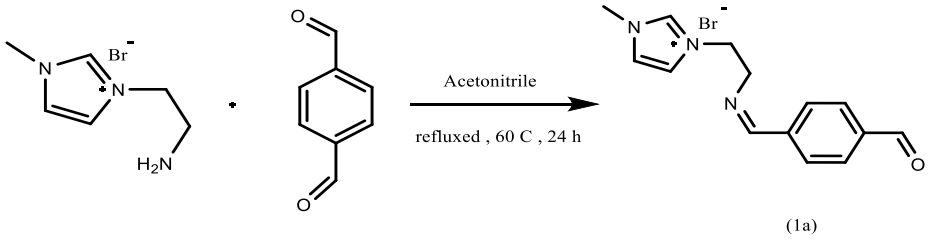
2.1 Materials and methods

All chemicals and solvents, used as supplied from commercial sources. Nuclear magnetic resonance (NMR) spectra were recorded using Bruker 400 MHz spectrometers at ambient temperature. The infrared spectra were recorded with FT-IR spectrophotometer (FTIR-

8400s, Bruker). UV-Visible spectrometer double beam was assigned on (Biochrom Libra S60) and the elemental analysis (CHN) were carried out on (PerkinElmer series II, 2400 microanalyzer). Thin Layer Chromatography (TLC) was carried out on Machery-Nagel polygamist/G/UV254 pre-coated plates. Melting points analysis were recorded using an Electrothermal 9100 melting point apparatus.

2.2 Synthesis of the Schiff Base/NHC ligand precursor 1a

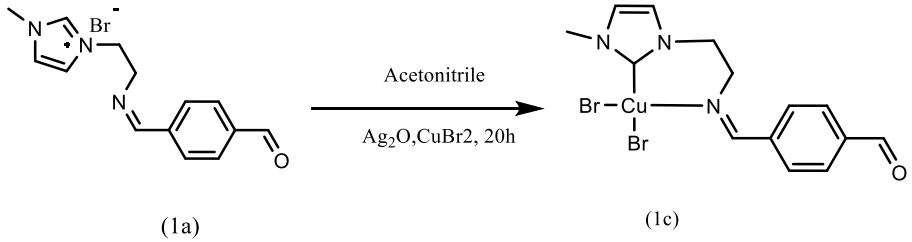
Into a dry Schleck flask with a stirrer bar and nitrogen gas was placed an equimolar amount of both the Schiff base a (0.24 g, 1 mmol) and the **1**-methyl imidazole b (0.82 g, 1 mmol) in 20ml acetonitrile. The mixture was refluxed at 60 ^{o}C for 24 hours, with the progress of reaction monitored using TLC. After the completion of reaction, the solvent was evaporated then recrystallized using methanol, 0.8g (75% yield) as a brown powder (m.p = 288-290 ℃). Scheme 1.



Scheme 1. Synthesis of (**1a**)

2.1.2. Synthesis of Silver(I)- Schiff base /NHC Complex 1b.

Silver oxide (1.15g, 0.005 mol) was added to a solution of compound **1a** (0.32, 0.01 mol) in 20 mL acetonitrile. The mixture was stirrer for 24 hr. in glassware, covered by aluminum foil. After the black suspension was filtered through the celite to remove the excess Ag_2O, the solvent was removed to give the product as a brown solid 0.8 g (61 % yield) (m.p = 223-225 ℃). Scheme 2.



Scheme 2. Synthesis of (**1b**)

2.3 Theoretical approach

It was possible to make precise predictions about the chemical and biological characteristics of the substances based on the molecular indices that were generated from them. The MOE-2015 software program was employed to simulate the interaction between ligands and protein receptors in the complexes. Using information from the Protein Data Bank, the survivin dimer H. sapiens protein—which corresponds to PDB ID: 1E31—was chosen as the protein receptor in this investigation. A number of crucial procedures were carried out before docking, such as anchoring the protein chain, adding hydrogen, removing solvent molecules, and identifying active sites. Using Merck Molecular Force Field calculations, the docking of the investigated chemicals was optimized. This includes atomic charge calculation, potential energy adjustment, energy minimization, and binding energy determination.

Results and discussion

3. Synthesis and characterization

3.1 NMR study

The ^{1}H NMR for **1a** in d_6-DMSO showed the singlet peak at (9.48) ppm was assigned to aldehyde proton (HCO). The signal of imidazolium proton H2′ appeared at (9.27) ppm as a singlet peak. The singlet peak at (8.53) ppm was assigned to Schiff base proton (HC=N). In addition, aromatic protons were seen as a multiplet at around 6.54 to 7.24 ppm due to the deshielding effects of the positively charged imidazolium ring system. The -CH_2 proton peaks bonding to the (-N-CH_2-CH_2-N-) has been observed as triplets at (3.85,3.74) ppm respectively. Figure (3.1).

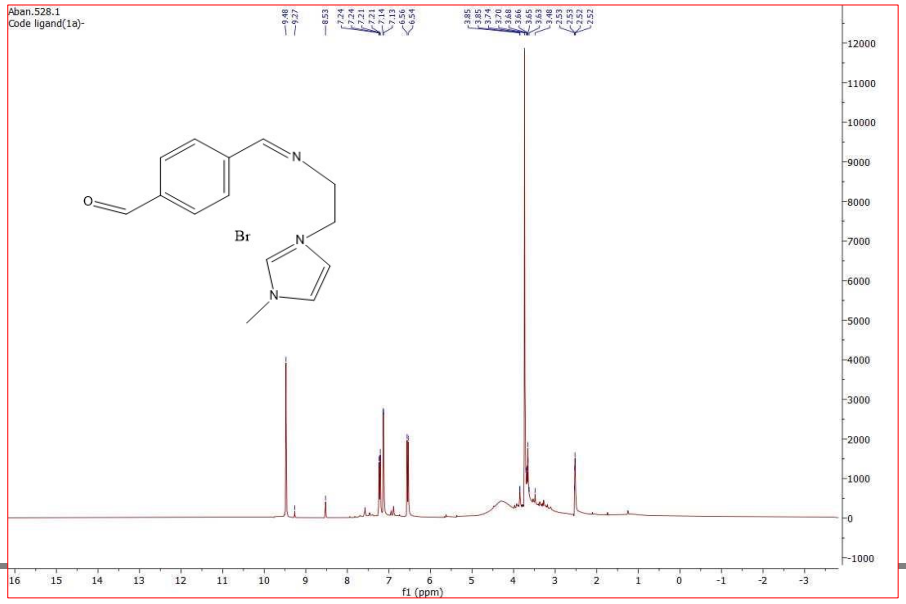


Figure 3.1: ^{1}H NMR Spectrum of 1**a** in d_6-DMSO

The ^{1}H NMR for **1b** in d_6-DMSO showed the singlet peaks at (9.78) ppm were assigned to aldehyde proton (HCO). The singlet peak at (8.12) ppm was assigned to Schiff base proton (HC=N). In addition, aromatic protons were seen as a multiplet at around 7.01 to 7.45 ppm. The -CH_2 proton peaks bonding to the (-N-CH_2-CH_2-N-) has been observed as triplets at (3.85, 3.73) ppm respectively. Figure (3.2).

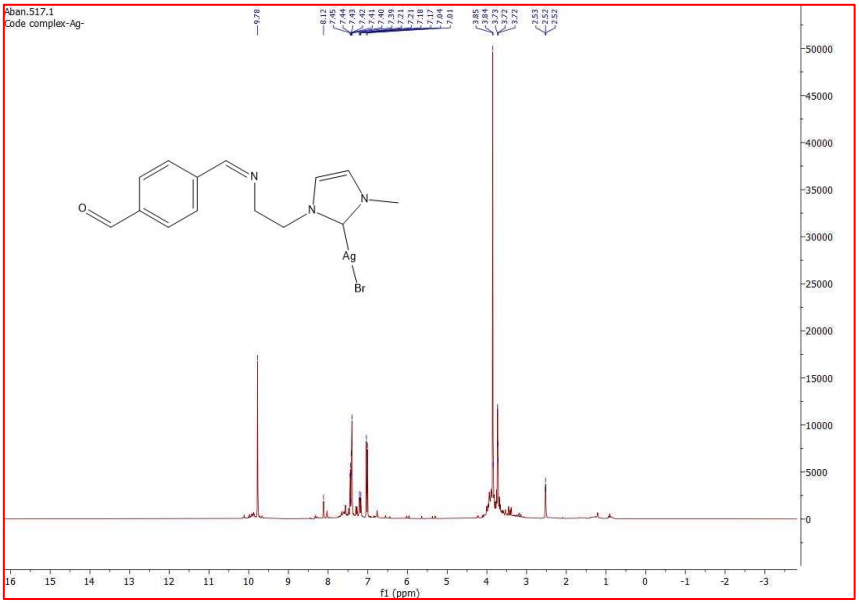


Figure 3.2: 1H NMR Spectrum of 1**b** in d_6-DMSO

The successful coordination of Ag-NHC in 1**b** complex via deprotonation of C2 is the absence of characteristic singlet protons (9.27) ppm compared with (**A**) ligand spectra[27] Figure (3.2) .

In addition, the ^{13}C NMR spectrum of **1a** showed the characteristic imidazolium C2 signal at 137.40 ppm. The carbon alpha to imine (N=C) appears at 161.92 ppm while the carbon atom that caries the aldehyde group was observed around 191.37 ppm. Figure (3.3)

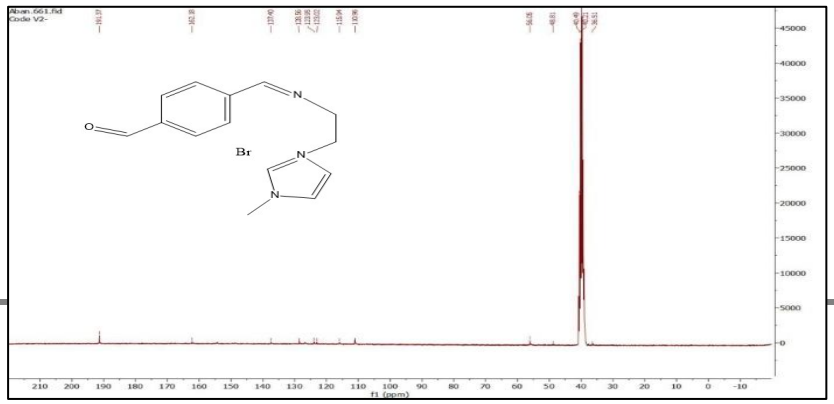


Figure 3.3: ^{13}C NMR Spectrum of 1**b** in d_6-DMSO

The ^{13}C NMR spectra of **1b** showed that the imidazolium C2 signal at (137.40) ppm C2 is absent compared to the ligand **1a** spectra, indicating the formation of an Ag-C bond. Figure (3.4). The other peaks were listed in Table (3-11)

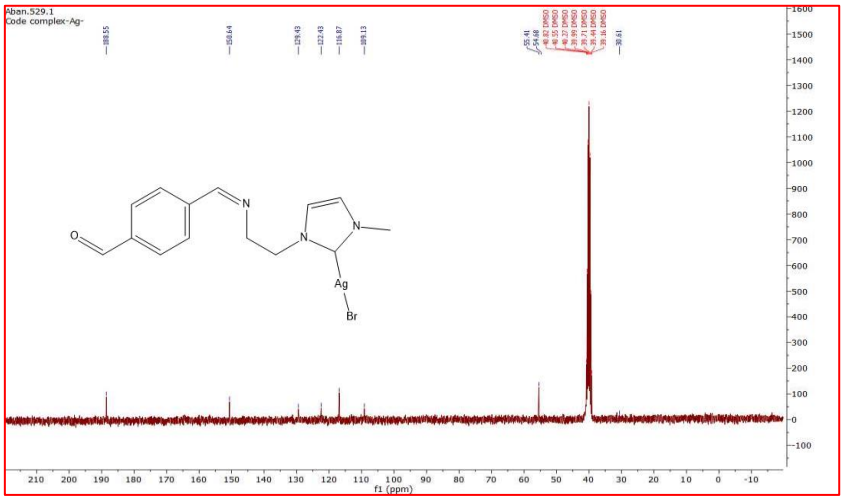


Figure 3.4: ^{13}C NMR Spectrum of 1**b** in d_6-DMSO

Table (3.1): ^{13}C NMR Chemical Shift Range of 1a and 1b

Functional group	^{13}CNMR Chemical shift range (ppm)	
	1a	2b
C=O	191.37	188.55
HC=N-	162.38	150.46
CH – imidazole	137.40	……..
Ar-C aromatic ring	111.03-128.51	109.13-129.34
-CH_2-CH_2-	48.81-56.06	54.68-55.41

CH_3-imidazole	30.51	30.61

3.2 UV-Vis Study

The spectra of ligand were recorded in methanol. The **1a** spectrum showed two distinguishable bands at (**283 and 310**) nm these bands can be indicating to π-π* and n-π* for the imidazole ring.

In addition to the absorption peaks (**273, 314**) nm due to electronic transitions in ligand, the novel Ag-NHC complex **1b** showed a new absorption peak at (**349**) nm, related to MLCT (metal-ligand charge transfer)

This complex couldn't show any d-d transition due to its d^{10} configuration because of d- d transitions are forbidden by the Laporte selection rule, which confirms the absence of any (d-d) transitions and absence of visible region absorptions in their electronic spectra. The difference in absorption peaks and the appearance of new absorption peaks confirm the complexity process figure (3.5)

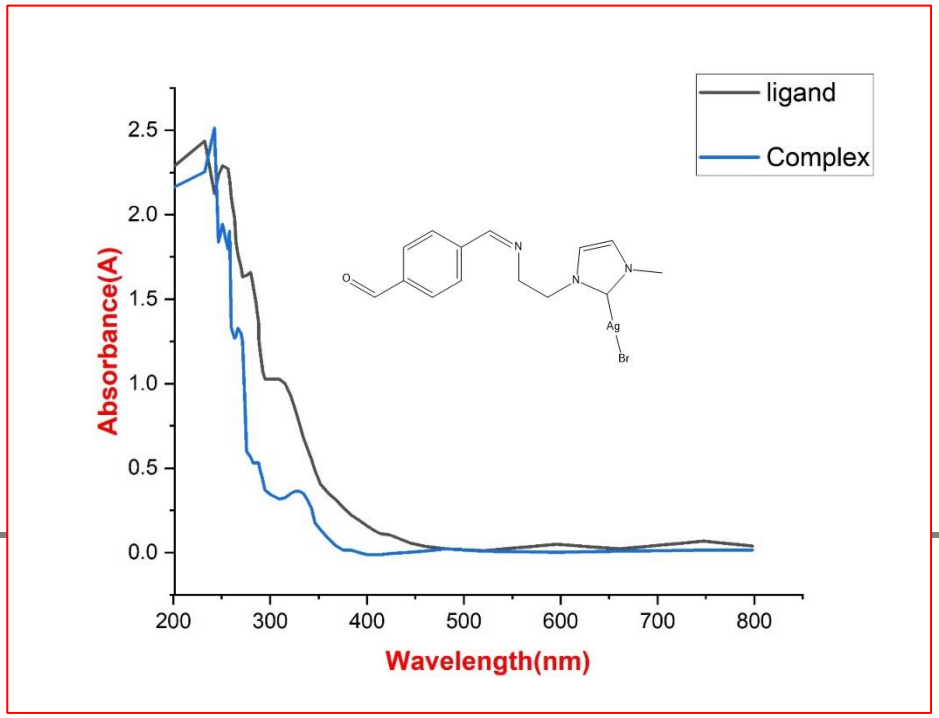


Figure 3.5: UV-Vis Spectrum of 1**a** and 1**b**

3.3 FT-IR Study

The FT-IR spectrum of ligand **1a**, was gave the following peaks which was assigned as following, a band at 1700 cm^{-1} due to (C=O) stretching vibration, 1643 cm^{-1} due to (HC=N) group. Figure (3.6).

The FTIR spectra of complex **2b,** Figure (3.7) showed the following characteristic peaks; bands at **1698** cm^{-1} for the (C=O), the peak 1644 cm^{-1} for the (HC=N). The slight shifting at the (HC=N) peak may be evidence of the lack of coordination bond with the silver ion. Figure (3.7). The other bands were listed in Table (3-2).

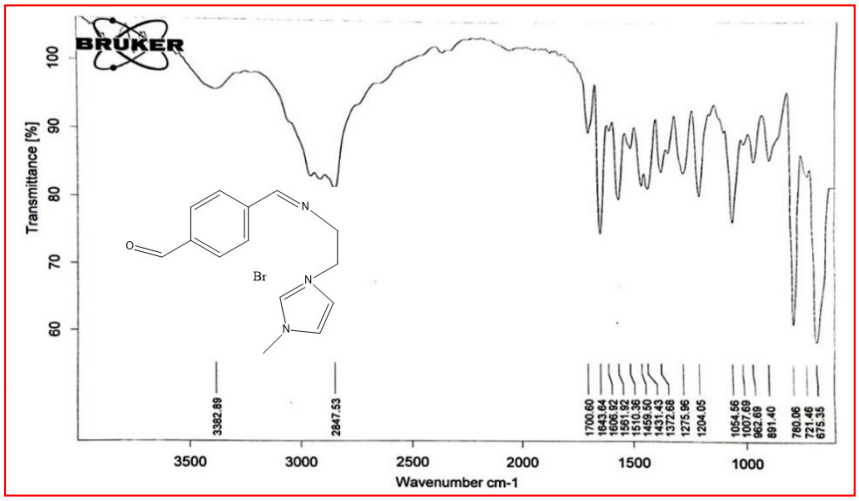


Figure 3. 6: FT-IR of compound 1a

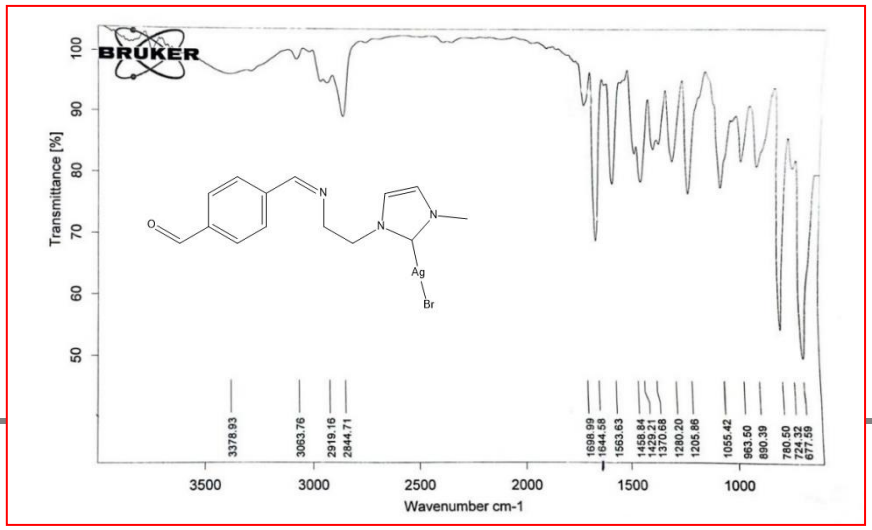


Figure 3.7: FT-IR of compound 1b

Table 3-2: FTIR peaks of 1a and 1b

Comp.	C-H ar.	C-H al.	C=O	HC=N	C=C
1a	3003	2847	1700	1643	1561
1b	3063	2919	1698	1644	1563

3.4 Molecular docking studies

Molecular docking is a valuable tool in structure design that enables the prediction of binding affinities and conformations between ligands and target receptor proteins. This knowledge greatly speeds up the development of medications [28],[29]. In order to explore the binding mechanisms, molecular docking experiments were conducted on compounds within the active sites of survivin dimer H. sapiens protein receptors (PDB ID: 1E31) to assess their binding interactions.

3.4.1 Molecular docking against 1E31

Interaction was facilitated by bringing the molecules into touch with one another by docking with 1E31. This exchange yields insightful information, as Figure 1 shows. The estimated score for the Ag(I) metal complex was S = -5.1989 kcal/mol with an RMSD of 1.5074 Å. Enhancing the Ag(I) complex resulted in a higher free ligand binding affinity. Coordination patterns showed that the free ligand bonded to particular amino acid residues to form H-acceptor and pi-H bonds, with bond lengths ranging from 3.03 to 4.47 Å. These residues included O 15 with ARG 18 (A), 6-ring with LYS 15 (A), and 6-ring with PHE 93 (A). In contrast, the Ag(I) complex used the Br 14, O 1, and O 2 atoms to produce two H-acceptor bonds and one H-donor bond in the 1E31 protein.

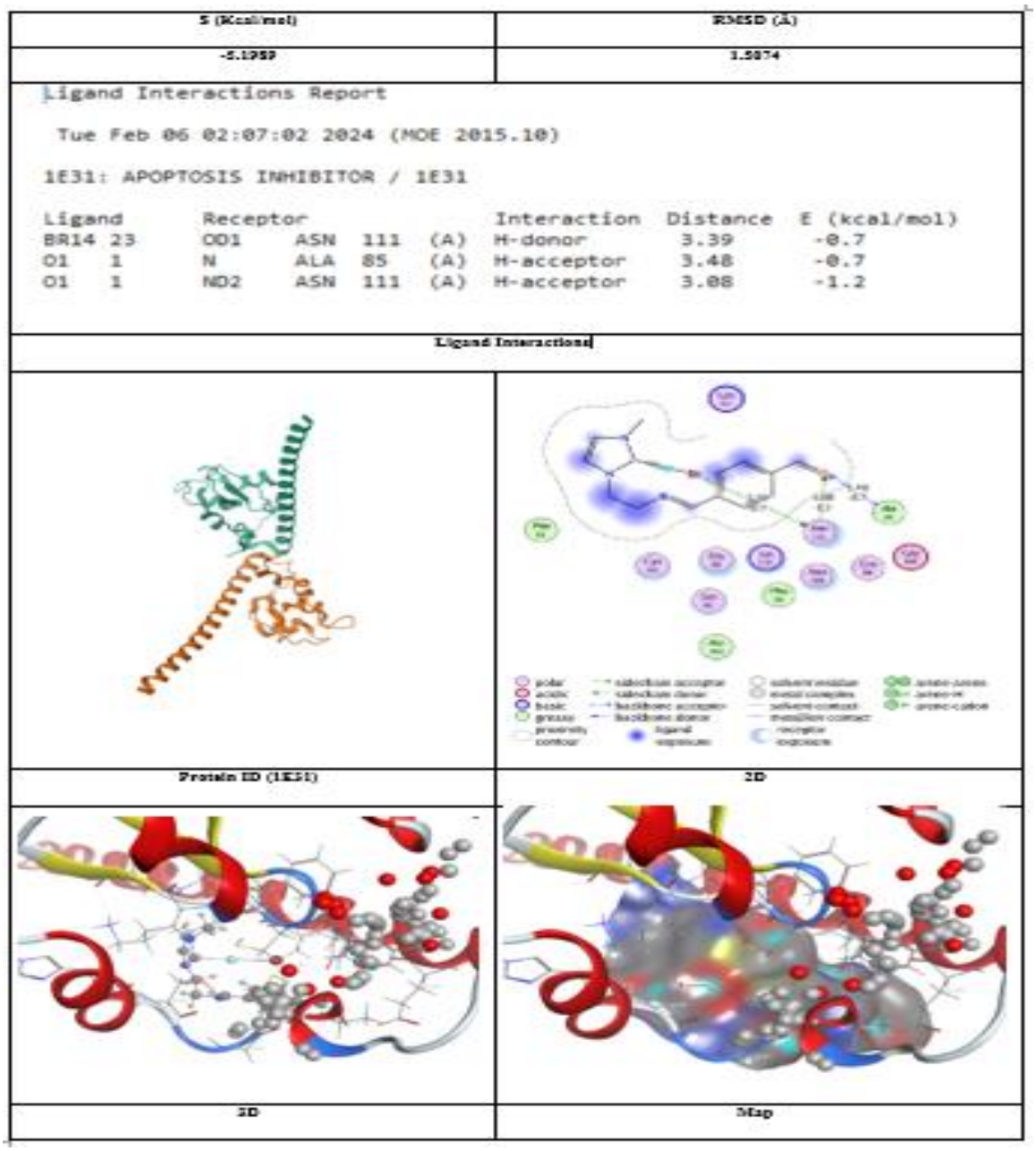


Figure 3.8: Detailed analysis of the interactions between protein 1E31 and Ag-Complex in 2D, 3D, and map views, (S = the final score is the score of the last step, RMSD_refine = the mean square deviation between the laying before refinement and after refinement pose).

3.5 Conclusion

our study successfully synthesized a novel Schiff base functionalized N-heterocyclic carbene silver(I) complex (**1b**) and characterized it using various analytical techniques.

Molecular docking studies revealed the binding interactions between the complex and selected biological targets, shedding light on its mode of action at the

molecular level. These findings underscore the significance of incorporating Schiff base ligands and *N*-heterocyclic carbenes in the design of silver-based anticancer agents. Further investigations into the biological activities and mechanisms of action of such complexes are warranted to fully exploit their therapeutic potential.

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