



## 2-Hydroxybenzylidene-4-(4-Substituted Phenyl)-2-amino Thiazole and Their Pt (II) Complexes: Synthesis, Characterization and Biological Study



Zahra Aldelfy\*, Zeki Al-Shamkani, Mohammed Al-assadi

Department of Chemistry, College of Science, University of Basrah, Iraq.

NEWLY prepared Schiff bases; 2-Hydroxybenzylidene-4-x-phenyl)-2-aminothiazole, where  $x=H, NO_2^-, CH_3, ^-OCH_3, ^-F,$  and  $^-Cl$  (L1-L6), and their corresponding Pt (II) complexes (Pt(L1)<sub>2</sub>-Pt(L6)<sub>2</sub>) were synthesized. The ligands and their own complexes were structurally characterized using, FT-IR, <sup>1</sup>HNMR, <sup>13</sup>CNMR, mass spectra, elemental analysis and SEM technique. The spectral data revealed that these bases are bonded to the Pt ion via both, the deprotonated hydroxyl and the imine groups, suggesting a square planar geometry. Human DNA interaction with Schiff bases and their metal complexes were investigated spectrophotometrically, intercalation mechanism was found to dominate those links. Antioxidant activity measurements of the prepared ligands and their platinum complexes, also, were performed by linoleic acid free radical scavenging method. The methoxy derivative, L4 was found to be the most active species relatively to BHT and the sequence of activity, apparently arranged as following order:



Anti-proliferative activity of the bases and their Pt(II) complexes was carried out on the MCF-7 cancer cell lines following the MTT assay.

**Keywords:** Schiff base of phenyl thiazole, Platinum complexes, Antioxidant, DNA interaction, Anticancer.

### Introduction

Thiazole is a five-membered ring in which heteroatoms (N and S) are parts of the ring at 1, 3-positions.

Thiazole derivatives and their metal complexes had been gambling an important function in medicinal chemistry[1]. They display quite a vast spectrum of biological activities that have observed applications inside the remedy of allergies[2], anti-inflammatory[3], antioxidant[4], antitubercular[5], most cancers[6], microbial infections and HIV infections[7,8]. Thiazoles also have emerged as a brand new elegance of robust antimicrobial marketers[9], which might be reported to inhibit bacteria with the aid of blocking off the biosynthesis of positive bacterial lipids and/or by extra

mechanism.

The chemistry of Schiff bases plays important dealing in the promotion of chemistry science[10]. An azomethine compound or Schiff bases is a practical organization that includes a carbon, nitrogen double bond (N=CH-) (imine) institution that formed between the primary amine and aldehyde[11,12].

The coordination chemistry of Schiff bases has allured the attention of several researchers[13-17]. Schiff base ligands are capable to chelate metals via nitrogen in the imine group and a donor atom nearby[18]. The presence of the basic donor N atom and the stability of the imine function render Schiff bases as the most favored ligands that have the ability to stabilize metal ions in different

\*Corresponding author e-mail: zaldelfy95@gmail.com

Received 26/2/2019; Accepted 10/4/2019

DOI: 10.21608/ejchem.2019.10039.1661

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oxidation states[19].

Schiff base metal complexes have received a great attention due to their remarkable biological activities, as they can be used a medicinal models compounds[20,21], as well as, their versatility and diverse range of biological application. Their Transition metal complexes were found to be as effective inhibitors of DNA synthesis, besides, their feasible pharmacological applications[22,23].

The observed anticancer platinum (II) complexes have been a very exciting topic in medicinal inorganic chemistry over the last decades, as cisplatin has played a crucial drug for this purpose.

A series of water-soluble platinum (II) complexes of reduced amino acid Schiff bases were synthesized as potential anticancer agents. These compounds have been tested for interaction with salmon sperm DNA, and there in vitro anticancer activities[24].

However, this emerging field of research remains in need to more different biological active bases coordinated to an interesting ion such as platinum to increase the dimensionality of this area of research. Schiff bases such as 2-Hydroxybenzylidene-4-(4-substitutedphenyl)2-amino thiazole have not been mentioned, yet, in literature. Therefore, it is good opportunity to synthesize such ligands and to conduct variable studies alongside with their corresponding Pt(II) complexes. Investigation of this work includes

antioxidant activity measurements, DNA interaction and toxicity studies.

## Experimental

### Reagents

2-Amin 4-(4-sudstitutedphenyl) thiazole was Prepared according to literature[25], salicylaldehyde was obtained from Prolabo and  $K_2PtCl_4$  was obtained from Sigma-Aldrich.

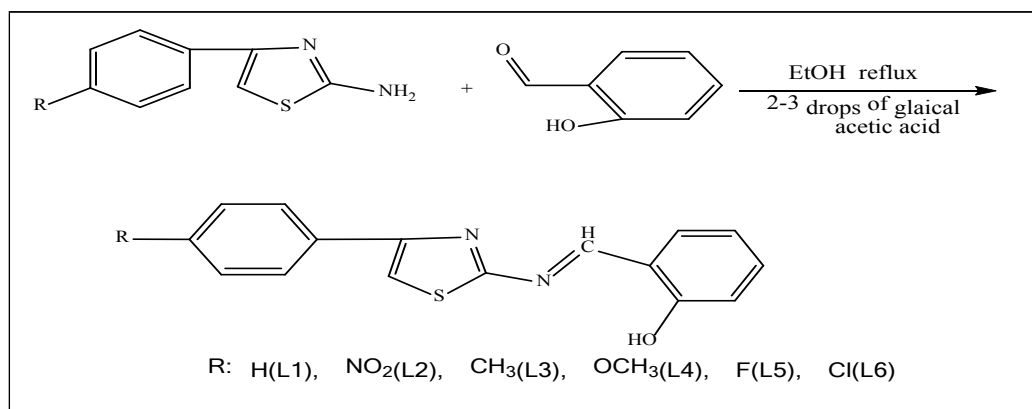
### Instruments

Melting points were measured using a Buchi thermal point apparatus with open capillaries and are uncorrected. Elemental analyses were determined on an Elemental Vario EL elemental analyzer. The IR spectra were recorded using (KBr disc) in the region (400-4000)  $cm^{-1}$  SHIMADZU. The  $^1H$ NMR The  $^{13}C$ NMR spectra were measured in DMSO- $d_6$  on a Bruker 500MHz and 125MHz respectively. The mass spectra were recorded by using Agilent Technology (HP) MS.5975C spectrometer, using EI-technique of (70ev) with (direct probe).

### Preparation of the ligands and their complexes

#### Synthesis Schiff base of thiazole derivatives (General Procedure)

A mixture of 2-amine -4(4-substituted phenyl) thiazole (1mmole) in 30ml absolute ethanol, salicylaldehyde (1mmole) in 20ml ethanol and catalytical amount of glacial acetic acid (2-3 drops) was refluxed with stirring for (8-12) hrs. Monitored of reaction by progress was carried out by TLC technique using (hexane: ethyl acetate) (8: 2) eluent. The reaction mixture was then cooled at room temperature, and the obtained yellow solid was collected, washed with DCM and finally with ether followed by recrystallized with DMF, and



Scheme 1. Synthesis Schiff bases

finally washed with ethanol absolute. The synthesis of the Schiff base ligands showed in Scheme 1.

*2-Hydroxybenzylidene-4-phenyl - 2-amino thiazole L1*: Brown, M.P 159-162, yield 76%. IR (KBr, cm<sup>-1</sup>) v: 3356 (OH), sy1689, asy1616 (C=N), sy1350 asy1334 (C-N), sy1276 asy1230 (C-O), sy1076 asy1030 (C-S), 3155 (Ar-H). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ ppm: 11.66 (s, OH), 9.52 (s, HC=N), 6.8-7.8 (m, 9H, Ar-H + CH thiazole). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) δ ppm: 167, 164, 153, 144, 138, 136, 134, 127.3, 127.1, 124.9, 124.2, 118, 114, 113. MS=m/z 280. Anal. calcd for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>SO: C 68.57%, H 4.28%, N 10%, S 11.42%; found: C 68.01%, H 3.9%, N 9.49%, S 10.56%.

*2-Hydroxybenzylidene-4-(4-nitrophenyl)-2-amino thiazole L2*: Pale yellow, M.P 194-195, yield 72%. IR (KBr, cm<sup>-1</sup>) v: 3373 (OH), sy1622 asy1606 (C=N), sy1278 asy1230 (C-O), sy1085 asy1020 (C-S), <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ ppm: 11.59 (s, OH), 9.8 (s, HC=N), 6.8-8.2 (m, 8H, Ar-H + CH thiazole). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) δ: 173, 163.7, 163, 152, 148, 140, 132, 130, 127, 125, 123, 119, 113, 107. MS=m/z 325. Anal. calcd for C<sub>16</sub>H<sub>12</sub>N<sub>3</sub>SO<sub>3</sub>: C 59.07%, H 3.38%, N 12.92%, S 9.84%; found: C 58.4%, H 3.01%, N 12.48%, S 9.46%.

*2-Hydroxybenzylidene-4-(4-methylphenyl)-2-amino thiazole L3*: Dark yellow, M.P 161-164, yield 74%. IR (KBr, cm<sup>-1</sup>) v: 3340 (OH), sy16662 asy1608 (C=N), sy1330 (C-N), sy1270 asy1230 (C-O), sy1114 asy1037 (C-S), 3176 (Ar-H), 2924 (CH<sub>3</sub>). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ ppm: 11.58 (s, OH), 9.39 (s, HC=N), 7.01-7.9 (m, 8H, Ar-H + CH thiazole), 2.3 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) δ ppm: 169, 162, 159, 152, 137, 134, 130, 130, 128, 125, 119, 119, 117, 112, and 20.3. MS=m/z 294. Anal. calcd for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>SO: C 69.38%, H 4.76%, N 9.52%, S 10.88%; found: C 68.7%, H 4.31%, N 9.09%, S 10.53%.

*2-Hydroxybenzylidene-4-(4-Methoxyphenyl)-2-amino thiazole L4*: Yellow, M.P 156-158, yield 77%. IR (KBr, cm<sup>-1</sup>) v: 3282 (OH), sy1608 asy1570 (C=N), sy1361 asy1334 (C-N), sy1280 asy1249 (C-O), sy1114 asy1030 (C-S), 3178 (Ar-H), 2935 (CH<sub>3</sub>). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 11.64 (s, OH), 9.2 (s, HC=N), 6.78-7.9 (m, 8H, Ar-H + CH thiazole), 3.8 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) δ ppm: 168, 165, 163, 158, 153, 135, 129, 128, 126, 124, 121, 118, 116, 113, and 54. MS=m/z 310. Anal. calcd for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>SO<sub>2</sub>: C 65.80%, H 4.51%, N 9.03%, S 10.32%; found: C 65.48%, H 3.96%, N 8.64%, S 9.804%.

*2-Hydroxybenzylidene-4-(4-Fluorophenyl) - 2-amino thiazole L5*: Yellow, M.P 154-158, yield

83%. IR (KBr, cm<sup>-1</sup>) v: 3379 (OH), sy1654 asy1604 (C=N), sy1400 asy1330 (C-N), sy1276 asy1230 (C-O), sy1091 asy (C-S), 3163 (Ar-H), 1157 (C-F). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ ppm: 11.64 (s, OH), 9.7 (s, HC=N), 6.8-7.9 (m, 8H, Ar-H + CH thiazole). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) δ: 176, 164, 161, 154, 151, 135, 134, 129.5, 129.2, 129.2, 126, 118, 116, 114. MS=m/z 300. Anal. calcd for C<sub>16</sub>H<sub>11</sub>N<sub>2</sub>SOF: C 64.42%, H 3.69%, N 9.39%, S 10.73%; found: C 63.79%, H 3.08%, N 8.94%, S 10.31%.

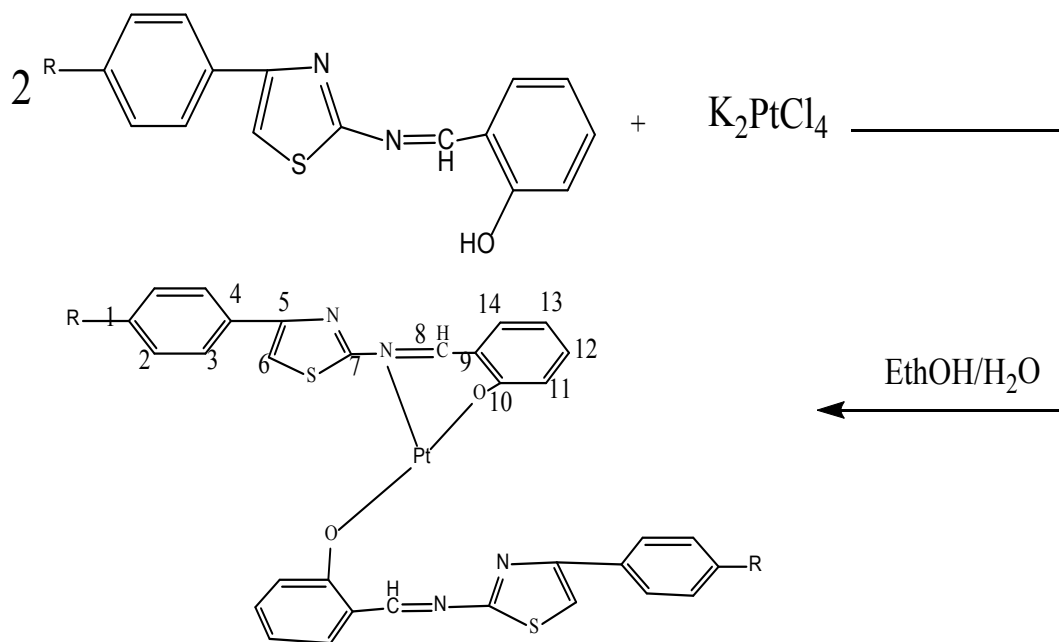
*2-Hydroxybenzylidene-4-(4-chlorophenyl) - 2-amino thiazole L6*: Yellow, M.P 147-150, yield 70%. IR (KBr, cm<sup>-1</sup>) v: 3414 (OH), sy1620 asy1597 (C=N), sy1398 asy1365 (C-N), sy1280 asy1226 (C-O), sy1091 asy1041 (C-S), 3131 (Ar-H), 1153 (C-Cl). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 11.64 (s, OH), 9.7 (s, HC=N), 6.8-7.9 (m, 8H, Ar-H + CH thiazole). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) δ ppm: 170, 169, 162, 159, 146, 142, 142, 131, 129, 128, 127, 119, 114, 110. MS=m/z 314. Anal. calcd for C<sub>16</sub>H<sub>11</sub>N<sub>2</sub>SOCl: C 61.04%, H 3.49%, N 8.90%, S 10.17%; found: C 60.57%, H 3.08%, N 8.58%, S 9.95%.

#### Synthesis of the Schiff Base Metal Complexes:

Solution (2mmol) of ligands in 30ml absolute ethanol was added gradually with stirring to a solution K<sub>2</sub>PtCl<sub>4</sub> (1mmol) in 10ml distilled water with stirring for (2-3) hr. at room temperature. During this period the color changed from yellow to brown. Reflux the resulted mixture was carried out for 1 hr. at 50°C monitoring by TLC technique using (chloroform: methanol) (8:3) eluent. The obtained solid product was filtered, washed with hot water, ethanol and dried at room temperature. The synthesis of the platinum complexes showed in Scheme 2.

[Pt (L1)<sub>2</sub>] **LD1**: Brown, Dec. 310 yield 54%. IR (KBr, cm<sup>-1</sup>) v: 3329 (OH), sy1685 asy1651 (C=N), sy1419 asy1350 (C-N), sy1284 (C-O), sy1107 asy1030 (C-S), 466 (M-N), 582 (M-O). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 9.8 (s, HC=N), 6.82-7.94 (m, 9H, Ar-H + CH thiazole). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) δ: 176, 168, 166, 150, 144, 141, 139, 138, 137, 131, 128, 124, 123, 113, MS=m/z 772. Anal. calcd for C<sub>32</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub>Pt: C 50.85%, H 3.17%, N 7.41%, S 8.47%; found: C 50.36%, H 2.69%, N 6.98%, S 7.94%.

[Pt (L2)<sub>2</sub>].H<sub>2</sub>O **LD2**: Brown, Dec. >290, yield 51%. IR (KBr, cm<sup>-1</sup>) v: 3321 (OH), sy1600 (C=N), 1404 (C-N), 1284 (C-O), sy1111 asy1018 (C-S), 470 (M-N), 540 (M-O). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ ppm: 9.9 (s, HC=N), 7.1-7.4 (m, 8H, Ar-H + CH thiazole). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) δ ppm: 171, 169, 168, 158, 161, 138, 124, 127, 120, 119, 110, 107, 106, 102. Anal. calcd for C<sub>32</sub>H<sub>23</sub>N<sub>6</sub>O<sub>6</sub>S<sub>2</sub>Pt.H<sub>2</sub>O: C



R= H(LD1), NO<sub>2</sub>(LD2), CH<sub>3</sub>(LD3), OCH<sub>3</sub>(LD4), F(LD5), Cl(LD6)

Scheme 2. synthesis of complexes

44.44%, H 2.79%, N 9.73%, S 7.41%; found: C 44.56%, H 2.14%, N 9.53%, S 7.01%.

[Pt (L<sub>3</sub>)<sub>2</sub>] **LD3**: BrownDec.>240, yield 55%. IR(KBr,cm<sup>-1</sup>) v: 3321(OH), 1604 (C=N), 1350 (C-N), 1240 (C-O), 1075 (C-S), 528(M-N), 595(M-O). <sup>1</sup>HNMR (DMSO-d<sub>6</sub>) δ ppm: 9.44 (s,HC=N), 6.94-7.8 (m, 5H,8H,Ar-H+CH thaizole), 2.3 (s,3H,CH<sub>3</sub>). <sup>13</sup>CNMR(DMSO-d<sub>6</sub>) δ ppm: 177, 166, 164, 160, 155, 151, 147, 144, 136, 132, 131, 128, 121, 115, and 20. Anal.calcd for C<sub>33</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub>Pt: C 52.107%, H 3.57%, N 7.151%, S 8.1%; found: C 51.20%, H 3.12%, N 6.73%, S 7.72%

[Pt (L<sub>4</sub>)<sub>2</sub>] **LD4**: BrownDec.>210, yield 61%. IR(KBr,cm<sup>-1</sup>) v: 3317(OH), 1600 (C=N), 1354 (C-N), 1260 (C-O), sy1111 asy1026 (C-S), 470(M-N), 670(M-O). <sup>1</sup>HNMR (DMSO-d<sub>6</sub>) δ: 9.65 (s,HC=N), 6.78-7.95 (m,8H,Ar-H+CH thaizole), 3.7(s,3H, CH<sub>3</sub>). <sup>13</sup>CNMR(DMSO-d<sub>6</sub>) δ: 177, 170, 166,162, 147, 139, 137,130, 128, 122, 119, 117,113, 101, and 51. MS = m/z 828. Anal.calcd for C<sub>34</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>Pt.H<sub>2</sub>O: C 48.97%, H 3.6%, N 6.7%, S 7.68%; found: C 49.5%, H 2.96%,N 6.47%, S 7.58%.

[Pt (L<sub>5</sub>)<sub>2</sub>] **LD5**: BrownDec.>190, yield 55%, IR(KBr,cm<sup>-1</sup>) v: 3317(OH), 1600 (C=N), sy1405 asy1354 (C-N), 1260 (C-O), 1095 (C-

S), 470(M-N), 641(M-O). <sup>1</sup>HNMR (DMSO-d<sub>6</sub>) δppm : 9.55 (s,HC=N), 6.9-8.05 (m, 8H, Ar-H+CH thaizole). <sup>13</sup>CNMR(DMSO-d<sub>6</sub>) δ ppm: 175,171, 167,165, 163,157,145, 144,137,130, 126, 108, 105, 120. Anal.calcd for C<sub>32</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub>FPt.H<sub>2</sub>O: C 47.46%, H 2.96%, N 6.92%, S 7.91%; found: C 47.14%, H 2.27%,N 6.68%, S 7.63%.

[Pt (L<sub>6</sub>)<sub>2</sub>] **LD6**: BrownDec.>200, yield 56%, IR (KBr,cm<sup>-1</sup>)v: 3321(OH), sy1621 (C=N), sy1392 asy1354 (C-N), sy1230 (C-O), sy1091 asy1041 (C-S), 3178(Ar-H), 1153(C-Cl), 482(M-N), 560 (M-O). <sup>1</sup>HNMR (DMSO-d<sub>6</sub>) δ ppm: 8.9 (s,HC=N), 6.9-7.9 (m,8H, Ar-H+CH thaizole). <sup>13</sup>CNMR(DMSO-d<sub>6</sub>) δ: 170, 165,159, 153, 149, 145, 136, 131, 124, 116, 112, 110, 108, 104. Anal. calcd for C<sub>32</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub>ClPt.H<sub>2</sub>O: C 45.6%, H 2.85%, N 6.65%, S 7.60%; found: C 45.23%, H 2.10%,N 6.53%, S 7.15%.

#### Determination of Antioxidant Activity

The β-Carotene Bleaching Method was followed to determine the antioxidant activities of the prepared Schiff base their own complexes. β- Carotene 1ml (0.2 mg dissolved in 10ml of chloroform) was mixed in a boiling tube together with linoleic acid (20 mg) and Tween- 20 (200 mg), all dissolved in 1 ml of chloroform. The mixture was left overnight in dark to get rid of



the chloroform at room temperature. 50 ml of distilled water were added to the mixture and shaken well. 3.8 ml of the resultant solution was mixed separately with the prepared ligands 0.2 mg, the prepared platinum complexes 0.2 mg, and (BHT butylated hydroxyl toluene) 0.2 mg dissolved in 0.2 ml from DMSO. The control solution was prepared by mixture 3.8 ml of the reaction mixture with 0.2 ml DMSO. Measurements were carried out at the 470 nm wavelength. The test tubes then placed in a 45°C water bath and the spectra were recorded every 15 min. for periods of 105 min. at the same wavelength time. An (absorbance vs. time) plot has been used to compare the antioxidant power activity of BHT versus the prepared compounds depending on the following mathematical equation (2-1): [26].

$$\%AA = \left\{ 1 - \left( \frac{A_j - A_t}{A_{j*} - A_{t*}} \right) \right\} \times 100 \quad \dots \dots (2-1)$$

Where:

%AA: scavenging activity

A<sub>j</sub>: the absorbance of the sample at *t* = 0 min

A<sub>t</sub>: the absorbance of the sample at *t* = 105 min

A<sub>j\*</sub>: the absorbance of the control at *t* = 0 min

A<sub>t\*</sub>: is the absorbance of the control at *t* = 105 min

#### Interaction with DNA

Interaction the Schiff base and their corresponding complexes with DNA were conducted experimentally, using U.v-visible technique with human DNA samples extracted from human blood. The concentration of the use DNA was 0.037 M in 5 mmole Tris-HCl at pH = 7-8. The ratio of absorption at the 260 nm and 280 nm was 1.37 indicating the purity of the DNA used in the experiments. The concentration of the Schiff base ligands and their platinum complexes was 10<sup>-3</sup> M, and the electronic spectra were recorded at (200-330 nm) using a cell width of 1 mm [27].

## Results and Discussion

### Infrared spectra

The IR spectra of the prepared Schiff base showed asymmetrical bands in the range (1689-1654) cm<sup>-1</sup> and symmetrical in the range (1616-1570) cm<sup>-1</sup> due to the azomethine group ν(C=N) [28]. Broad bands in the range (3379-3286) cm<sup>-1</sup> for the ν(OH) [29]. Moreover the Schiff base spectrum display bands at region (1400-1330) cm<sup>-1</sup>, (1284-1230) cm<sup>-1</sup>, (1114-1020) cm<sup>-1</sup>, due to

ν(C-N), ν(C-O) and ν(C-S) respectively; as shown in Fig. 1a.

Comparison of the IR spectra of platinum complexes to those of the Schiff bases, show that the symmetrical ν(C=N) band at (1685-1600) cm<sup>-1</sup> is shifted to lower values, and the ν(C-N) band (1419-1350) cm<sup>-1</sup> is changeable either to lower or higher. Thus, this phenomenon appears to be due to the coordination of azomethine nitrogen to the metal ion [30]. The ν(OH) band (3329-3317) cm<sup>-1</sup> and the ν(C-O) band (1284-1240) cm<sup>-1</sup> in this spectral of the complexes is shift to lower or higher frequencies [31], while the stretching band ν(C-S) of thiophene remain almost unchanged relatively to ν(OH). Also, the ring's nitrogen doesn't show any sign of involvement in coordination. The coordination through the azomethine nitrogen and phenolic ν(OH) as shown in Fig. 1b. Further supported by the occurrence of new bands at (466-528) and (540-670) cm<sup>-1</sup> in the spectra of the complexes, which may be assigned to ν(Pt-N) and ν(Pt-O), respectively [32].

### <sup>1</sup>H NMR Spectra

The <sup>1</sup>H NMR spectra of all Schiff bases display signals at δ(11.58-11.66) ppm owing to the δ(OH) group<sup>30</sup>, while the azomethine proton of the Schiff base δ(HC=N) resonated at δ(9.20-9.70) ppm as sharp singlet [33]. They, also, exhibit a singlet at δ (7.10-7.90) ppm due to the proton δ (H-C) ring thiazole [34]. The aromatic ring protons signals are posed within the range δ (8.20-6.78) ppm [35], as shown in Fig. 2a. Compounds (L3, L4) show a peak at δ (2.5-3.8) ppm, which belongs to the methyl δ (CH<sub>3</sub>) and methoxy δ (OCH<sub>3</sub>) groups [36,37].

Comparison of the <sup>1</sup>H NMR spectra of the prepared Schiff bases to those of their corresponding complexes leads to the following conclusions: first, disappearance of the hydroxyl's proton resonating signal in the complexes spectra, which appears in the ligands spectra at δ (11.58-11.66) ppm indicate, evidently the deprotonation of the hydroxyl group and its coordination to the metal ion. Second, on complexation the azomethine proton signals δ(9.20- 9.39 ) ppm undergo a significant shift ranged to downfield ( 0.06 – 0.45 ) ppm and to upfield [(-0.15) - (-0.8)] ppm. Thus, this shift gives good evidence that the azomethine group is linked to platinum ion via a dative bond, as shown in Fig. 2b. Third, unexplained findings that the unsubstituted (L1/LD1) compounds show highest downfield shift

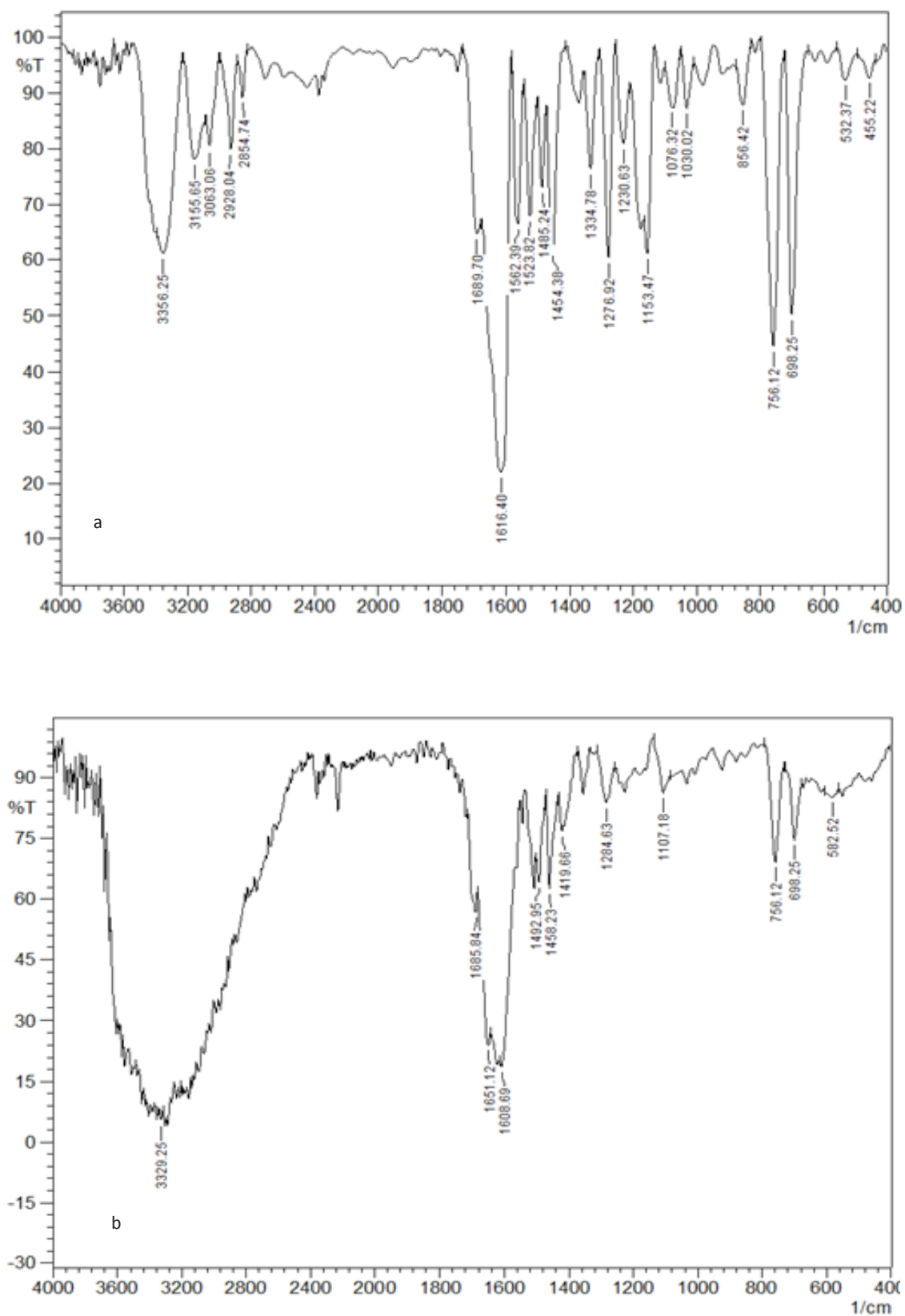
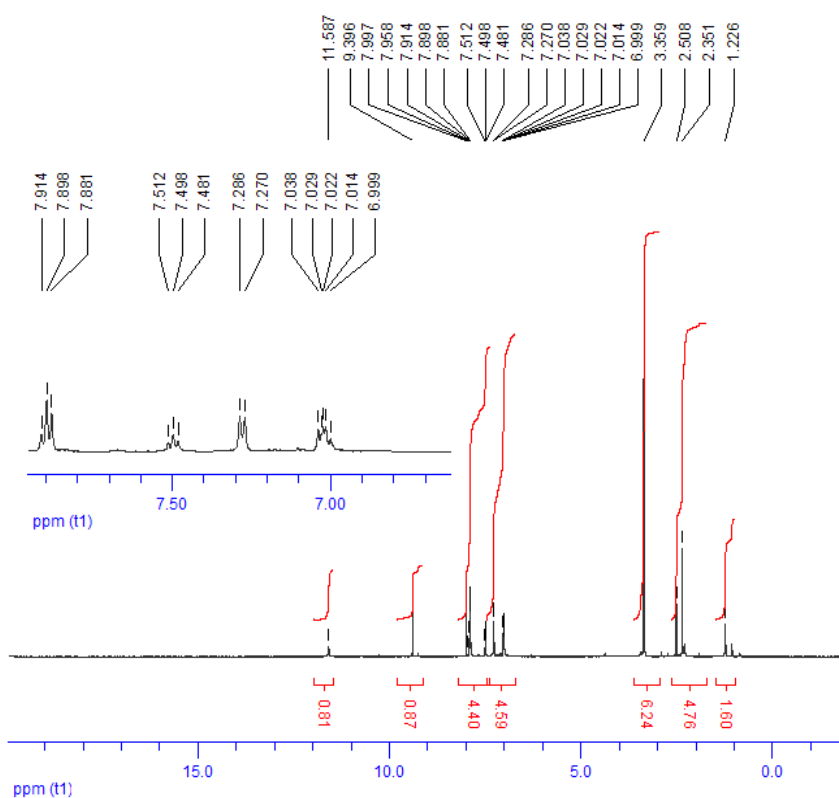
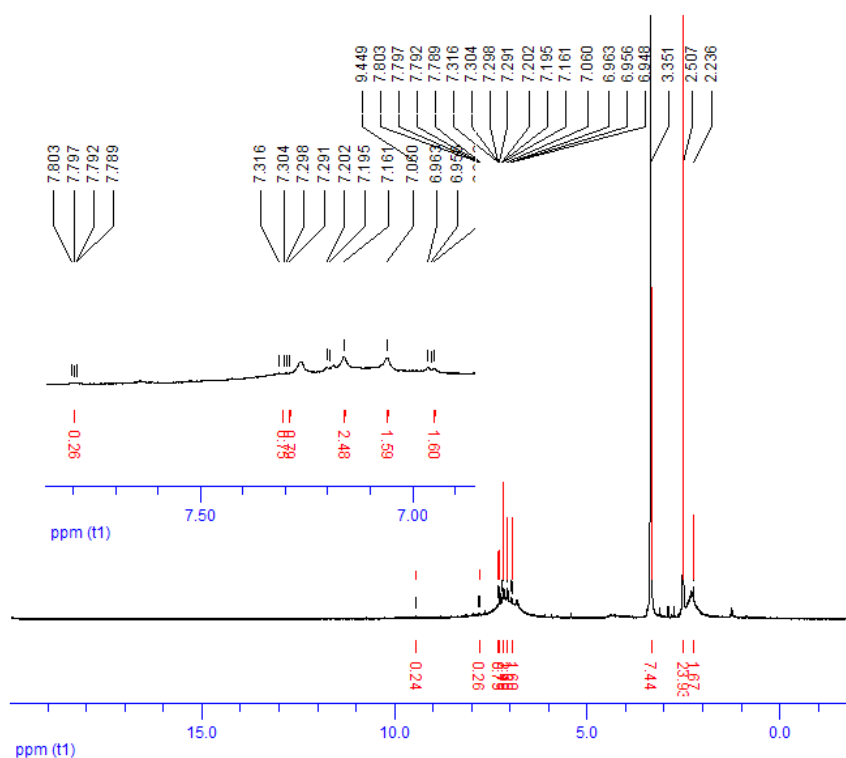


Fig. 1. IR Spectra of a-Ligand L1 and b-Complex LD1.



Date:  
7 Jan 2019  
Document's Title:  
1  
Spectrum Title:  
2M 1HNMR in DMSO  
at 298k 1397/10/12  
Frequency (MHz):  
(f1) 500.130  
Original Points Count:  
(f1) 32768  
Actual Points Count:  
(f1) 32768  
Acquisition Time (sec):  
(f1) 2.9884  
Spectral Width (ppm):  
(f1) 21.924  
Pulse Program:  
Unknown

a



Date:  
24 Jan 2019  
Document's Title:  
3M 1H  
Spectrum Title:  
3M 1HNMR in DMSO  
at 298k 1397/10/12  
Frequency (MHz):  
(f1) 500.130  
Original Points Count:  
(f1) 32768  
Actual Points Count:  
(f1) 32768  
Acquisition Time (sec):  
(f1) 2.9884  
Spectral Width (ppm):  
(f1) 21.924  
Pulse Program:  
Unknown

b

Fig. 2. <sup>1</sup>H NMR Spectra of a-Ligand L3 and b-Complex LD3.

(+ 0.28) ppm, while the Cl derivative (L6/LD6) explores the highest upfield shift (- 0.800) ppm.

#### <sup>13</sup>CNMR Spectra

The spectra of substituted phenyl thiazole Schiff bases (L1 – L6) display a single peak within the range  $\delta$ (113-169) ppm attributed to the aromatic ring including C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>9</sub>, C<sub>10</sub>, C<sub>11</sub>, C<sub>12</sub>, C<sub>13</sub> and C<sub>14</sub> atoms. While the carbon of the thiazole ring exhibits a signal at the region  $\delta$  (107-173) ppm due to C<sub>5</sub>, C<sub>6</sub> and C<sub>7</sub>. The Schiff bases compounds exhibit a peak at  $\delta$  (153-163) ppm due to the azomethine carbon, C<sub>8</sub> [38-40].

In addition, the <sup>13</sup>CNMR Spectra of L3, L4 compounds show single peaks at 20, 54 ppm respectively due to methyl and methoxy groups that represent as C<sub>15</sub> as shown in Fig. 3a. When the Schiff bases spectra compare to their corresponding complexes, one can explore the following categories: first, the ligand carbon C<sub>10</sub> resonating at (163.7 – 169) ppm undergoes a downfield shift [(+4)–(+ 7.3)] ppm as it appears at (165 – 171) ppm on complexation.

Thus, this shift suggests the coordination of the bases to platinum ion through the deprotonated hydroxyl group. This suggestion is backed up by both the <sup>1</sup>H NMR and IR spectroscopy as mentioned previously. Secondly, the resonance signal obtained for azomethine carbon, C<sub>8</sub>, of the bases at (153 – 163) ppm shifted to either downfield by [(+3) – (+13)] ppm or up field by (-3) ppm in complexes where appeared at 159 – 168 ppm, indicating the coordination of the ligand to Pt (II) ion via the azomethine moiety. Thus, this prediction is coincided with inference drawn from both proton NMR and IR tools. Thirdly, the highest downfield shift is observed that of the unsubstituted species (L1/LD1), which is around (+13) ppm, while the (Cl) derivatives (L6 /LD6) show up field shift (-3) ppm. As shown in Fig. 3b.

#### SEM Analysis

The surface morphology of the prepared bases and their own complexes were examined by SEM (Scanning Electron Microscopic) technical analysis. The averages of particle size were estimated using Image-J program. Figure 6 presents the micrographs of ligand (L4) and their Pt(II) complexes (Pt(L1)<sub>2</sub>). Micrographs on the low magnification explore the rough and pitted surfaces of ligands and complexes. On comparison of the two sets of micrographs, one can observe the differences in surface morphology between each ligand and its corresponding complex. Thus,

this significant change many due to the metal coordination to the bases. On high magnification, these micrographs show the morphological nature of spherical- shaped appearance such as Pt(L1)<sub>2</sub>, Pt(L3)<sub>2</sub>-Pt(L6)<sub>2</sub>. The estimated values of the average particle size of each species, Table 1 reveals that all bases L1-L6 have micro scale size 112.6-132.2 nm, while their corresponding complexes, except Pt(L3)<sub>2</sub>, are displayed a nano scale 81.9-100nm. The nitro-derivatives Pt(L4)<sub>2</sub> has the most probable nano characters.

#### Biological Activity

##### Antioxidant Activity

The series of substituted phenyl thiazole Schiff bases (L1-L6) showed different scavenging activities due to the substituents electron donating or electron withdrawing groups, that scavenging activity of L4 is 95% and the L3 gives 75%. Thus, these compounds are containing electron donating groups which increase the stability of the aromatic ring, while those with electron withdrawing moieties i.e. L2 (67%) and both L5 and L6 (63%) explored less activities. The unsubstituted L1 has recorded activity of 42%. Therefore, the following sequence can be established compared to the BHT activity:



The mechanism of this process involves oxidation of the linoleic acid to form linoleic acid hydroperoxide which attacks the unsaturated  $\beta$ -carotene molecules at their double bonds leading to oxidation of the compound as it begins to lose its orange color[41]. The presence of phenolic compounds as antioxidants may, then, accomplish the termination of the  $\beta$ -carotene chain reaction by easily giving the hydrogen atom from the hydroxyl group. The freeness of the system, and the stability of the phenox radical by the phenomenon of delocalization or by words The resonance phenomenon is the non-uniformity of the electrons (non-duplex) around the loop aromatic[42].

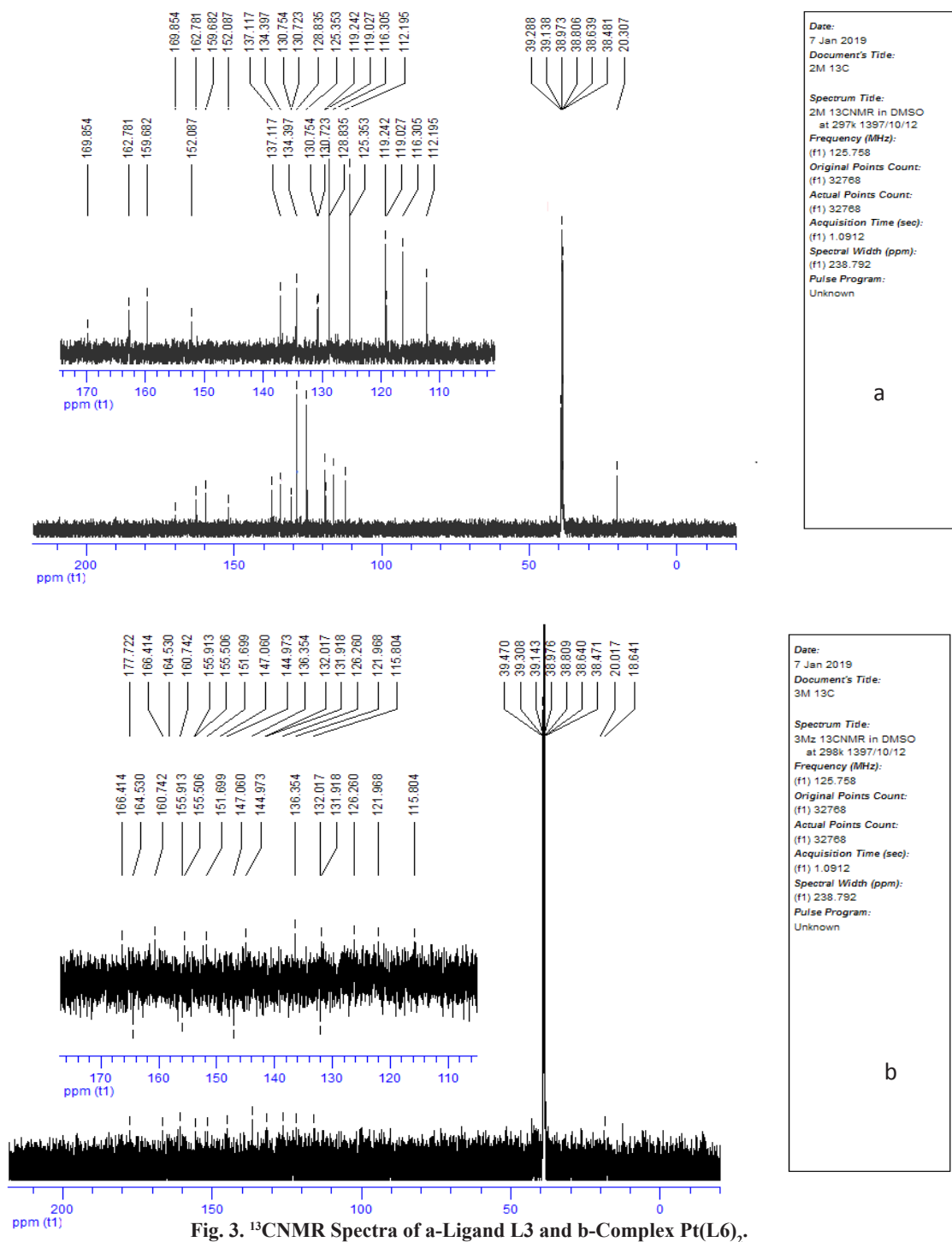
Comparison of the antioxidant activity of the Schiff bases with their own complexes found that the platinum complexes have more distinguished activity than their corresponding substituted Schiff bases. Thus, it is believed that the platinum metal may increase the stability of the resultant radicals electronically, as It is known that the process of anti-oxidation involves the transference of proton or electron from the antioxidant compound to the free radical and produces a stable composite composition and then the formation of neutral compounds ending the propagation of the free



radical chain reaction[43]. Data in Table 2 show that the  $Pt(L3)_2$  gives activity closed to that of BHT (86%), while both  $Pt(L2)_2$  and  $Pt(L6)_2$  give 89% which exceeds the BHT value. The complex  $Pt(L4)_2$  recorded 78% while the unsubstituted  $Pt(L1)_2$  reached the lowest value of 51%. The highest AA% value in the series, that obtained for L4 (95.58%), which indicates that this Schiff base

potentially possesses a considerable antioxidant ability exceeds the value of the standard BHT.

The attempt to know the behavior of platinum complexes as antioxidants, particularly cisplatin, remains unclear, although there is an impact on the ability of nanotubes to behave as an antagonist<sup>44</sup>, mechanisms may be related to the ability of platinum (electronically). Figure 4 effect of L3,



**TABLE 1. Result from the SEM of Schiff Bases and their Corresponding Complexes.**

Sym.	Particle size nm	Average	Sym.	Particle size nm	Average
L1	98, 147, 161, 119	131.25	LD1	93, 99, 71, 74, 86, 118, 121	94.57
L2	108, 101, 141, 117, 123, 129	119.8	LD2	58, 92, 86, 98, 123, 138	99.16
L3	111, 147, 144, 127	132.2	LD3	98.7, 92, 111, 123	106.0
L4	130, 108, 111, 126	118.75	LD4	58.6, 92, 83, 89, 104, 70, 77	81.94
L5	98, 117, 123	112.6	LD5	86, 80.7, 118, 114	99.68
L6	102, 114, 121, 111, 133, 127	118.0	LD6	65, 98, 119, 118	100.0

**TABLE 2. The measured absorbance and the percentage of efficacy of the model as an antioxidant for Schiff Base (L1-L6) and Their Corresponding Complexes (LD1-LD6) Compared with BHT**

Sym.	A <sub>j</sub>	A <sub>t</sub>	A <sub>j</sub> *	A <sub>t</sub> *	AA%
BHT	0.529	0.520	0.262	0.194	86.7647
L1	0.393	0.354	0.262	0.194	42.6
Pt(L1) <sub>2</sub>	0.776	0.743	0.262	0.194	51.47
L2	0.968	0.946	0.262	0.194	67
Pt(L2) <sub>2</sub>	1.245	1.238	0.262	0.194	89.7
L3	0.664	0.647	0.262	0.194	75
Pt(L3) <sub>2</sub>	0.718	0.709	0.262	0.194	86.76
L4	0.831	0.828	0.262	0.194	95.58
Pt(L4) <sub>2</sub>	0.958	0.943	0.262	0.194	77.9
L5	0.291	0.266	0.262	0.194	63.23529
Pt(L5) <sub>2</sub>	0.319	0.301	0.262	0.194	73.529
L6	0.794	0.769	0.262	0.194	63.23529
Pt(L6) <sub>2</sub>	0.805	0.798	0.262	0.194	89.7058

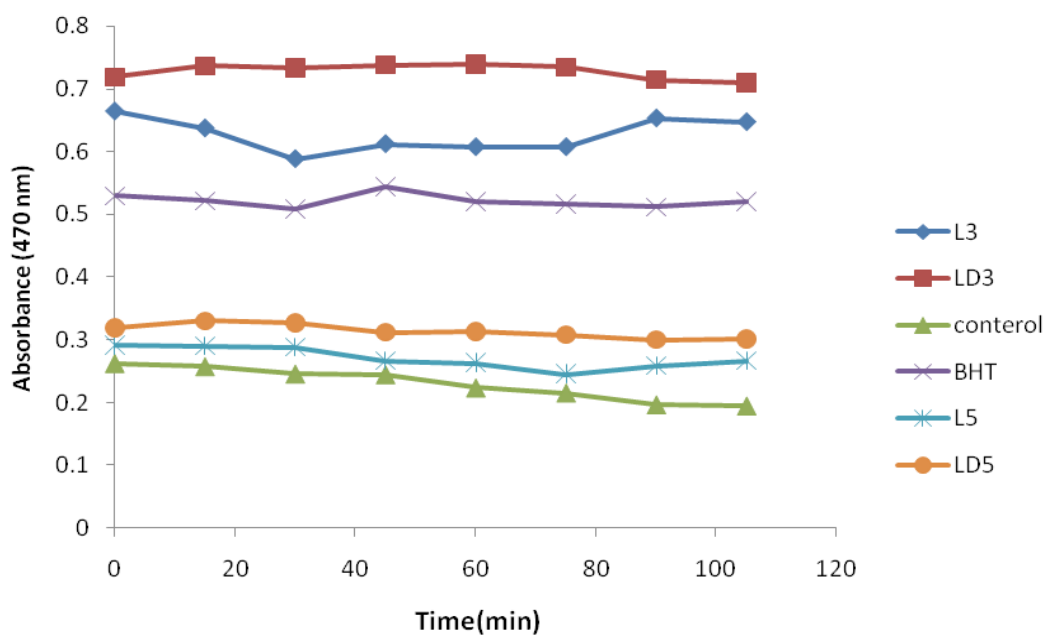


Fig. 4. Effect of L3, LD3 and L5, LD5 as Antioxidant.

LD3 and L5, LD5 as antioxidant.

#### DNA interaction

Interactions of the prepared Schiff bases and their corresponding complexes have been monitored by U.v.-visible spectroscopy as the strength of this interaction can be measured relatively to the variation in the absorption intensity of the DNA spectrum. Thus, both decreasing (hypochromism) and increasing (hyperchromism) in intensity indicate, evidently the interaction among the complexes and the DNA strands. The absorption ratios show an increase (hyperchromic) and a decrease in absorbance (hypochromic) in absorption for each Schiff bases and their platinum complexes as shown in Table 3. From these ratios, it can be concluded that there is a considerable interference among the prepared compounds and DNA.

In general, there are many concepts explain the type of interference depending on structure, type and geometry of the ligand, also it is possible to have an overlap between the ligand and DNA. Thus, what so called Intercalation, include forming hydrogen bonds or through van der Waals forces with the main and non-

main grooves. There is another mechanism of this electrostatically interfering which occurs between the positive metal ion and the acid-negative phosphate group [27]. The table below, shows that on comparison the Schiff bases to their platinum complexes evidently there is a slight change in the spectral properties of the complexes, giving a clear evidence that the interference is achieved through Schiff bases ligand rather than metal ion, such mechanism is called Intercalation.

Also, it can be observed that compound L5 showed the highest hypochromic change at 230nm and 260nm 3.010, 2.391 respectively and the compounds L2, Pt(L2)<sub>2</sub>, L3, Pt(L3)<sub>2</sub>, L6, Pt(L6)<sub>2</sub> showed a hyperchromic effect.

Either the Schiff base L1 and its complexes Pt(L1)<sub>2</sub> explore a different variation at 230nm. The base L1 gives a hyperchromic ratio of 0.274, while Pt(L1)<sub>2</sub> shows a hypochromic 2.301 in the mean time both of them show hypochromic effect at 260nm. Also, both L4 and Pt(L4)<sub>2</sub> show hypochromic at 230nm and hyperchromic at 260nm. Figure 5 shows interaction of L2 and LD2 with DNA.

TABLE 3. The absorbances of DNA, DNA+Schiff Bases and DNA+Schiff Bases+Complexes at 230nm and 260nm

Sym.	Absorbance			Type of Variation
	DNA. $A_1^*$	DNA+Com. $A_2^{**}$	$A_1/A_2$	
L1	0.587a	0.214	0.274	Hyperchromic Hypochromic
	0.373b	0.184	2.027	
Pt(L1) <sub>2</sub>	0.587	0.255	2.301	Hypochromic Hypochromic
	0.373	0.195	1.912	
L2	0.587	1.209	0.485	Hyperchromic Hyperchromic
	0.373	2.311	0.245	
Pt(L2) <sub>2</sub>	0.587	2.187	0.268	Hyperchromic Hyperchromic
	0.373	1.571	0.161	
L3	0.587	1.203	0.487	Hyperchromic Hyperchromic
	0.373	2.483	0.153	
Pt(L3) <sub>2</sub>	0.587	1.619	0.362	Hyperchromic Hyperchromic
	0.373	1.448	0.257	
L4	0.587	0.454	1.292	Hypochromic Hyperchromic
	0.373	0.387	0.963	
Pt(L4) <sub>2</sub>	0.587	0.402	1.460	Hypochromic Hyperchromic
	0.373	0.496	0.752	
L5	0.587	0.195	3.010	Hypochromic Hypochromic
	0.373	0.156	2.391	
Pt(L5) <sub>2</sub>	0.587	0.296	1.983	Hypochromic Hypochromic
	0.373	0.224	1.665	
L6	0.587	1.634	0.359	Hyperchromic Hyperchromic
	0.373	1.302	0.286	
Pt(L6) <sub>2</sub>	0.587	1.888	0.310	Hyperchromic Hyperchromic
	0.373	1.232	0.302	

\* a= absorbance at 230nm, b=absorbance at 260.

\*\* the first reading at 230nm, the second at 260.

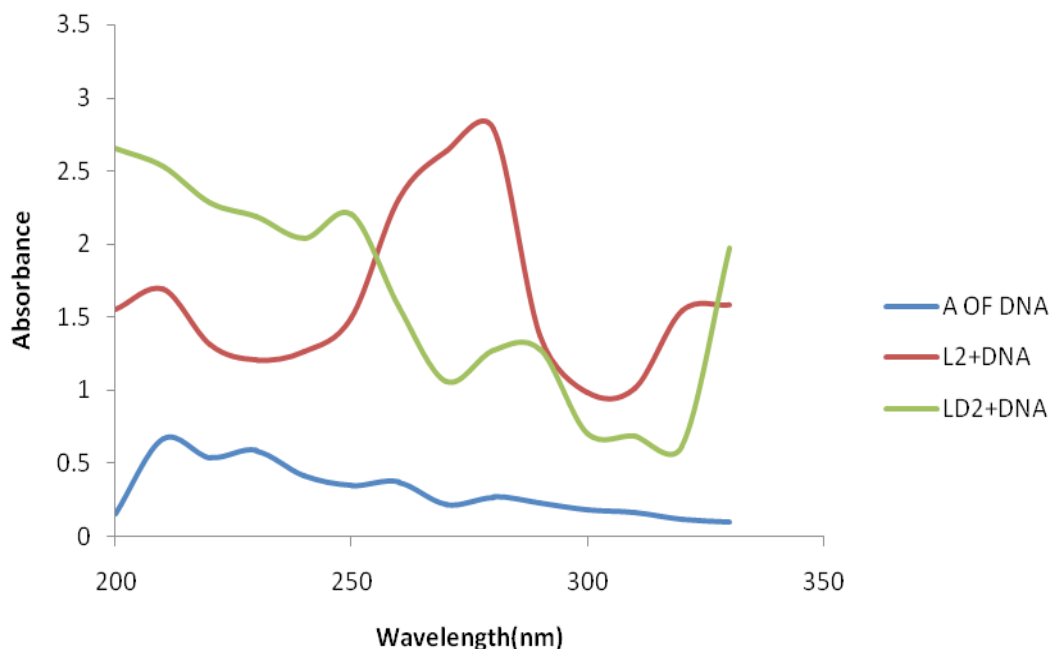


Fig. 5. Ultraviolet-visible Spectrophotometer of L2 and LD2 with DNA.

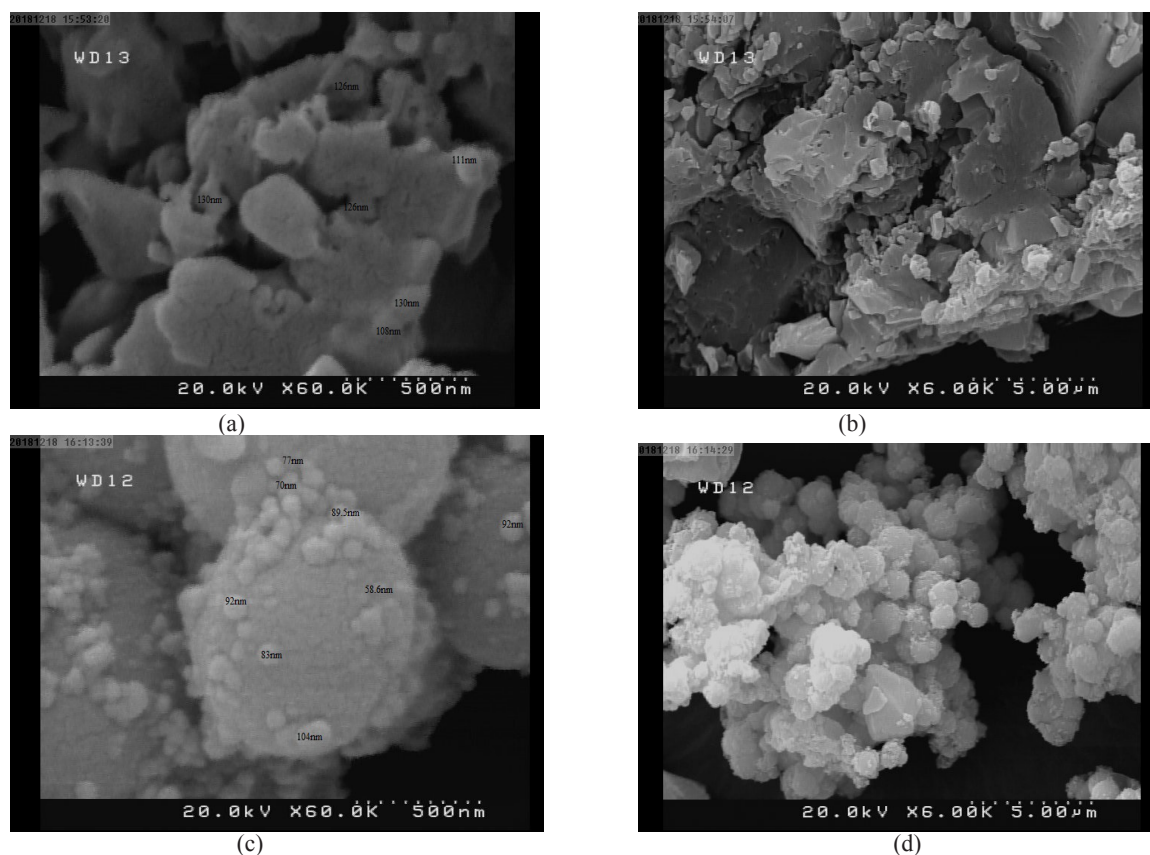
*Cytotoxicity Activity*

The dependable standards for judging the efficacy of any anticancer drug are a prolongation of lifespan, improving the clinical, hematological, biochemical profile, and reduction in possible tumor cellular member inside the host[45]. In order to evaluate the biological results of the phenyl thiazole Schiff base(L4, L5) and their platinum complexes (Pt(L4)<sub>2</sub>, Pt(L5)<sub>2</sub>) on cancer cells, we used the compounds to deal with MCF-7 human breast cancer cell line at the concentrations 50, 150 and 250 µm/l for 48h and 72h. Cell growth inhibition was evaluated by MTT assay (MTT is a yellow water soluble tetrazolium salt [(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)]. Succinate-dehydrogenase, a mitochondrial enzyme in living cells cleaves the tetrazolium ring, converting the

MTT to an insoluble purple formazan) and the results have shown different values at 48h and 72h as shown in Table 4. The phenyl thiazole Schiff base (L4) showed higher activity against MCF-7 cell at 72h the results appeared value of viability 52.1 at 250µg/l for L4 compound and the L5 compound showed values of viability Convergedat 72h with constrictions different the high viability of this compound 78.4 at 250µg/l. And at 48h the L4 the viability at 50µg/l was 48.1 this means that the inhibition ratio is high. Compared the Schiff base with their platinum complex (Pt(L4)<sub>2</sub>, Pt(L5)<sub>2</sub>) the results showed value viability high this means it gave vitality to the exposed cells. Further, the IC<sub>50</sub> value of compounds L4 and L5 at 72h was determined by using Graph Pad Prism software 11.15 and 11.44 respectively.

**TABLE 4. Cytotoxicity Activity (% Viability) of Phenyl Thiazole Schiff Base and their Corresponding Complexes at 48h. and 72h.**

Sym.	Viability at 48h			Viability at 72h		
	50µg/l	150µg/l	250µg/l	50µg/l	150µg/l	250µg/l
L4	52.38	54.8	55.5	52.1	70.5	80
L5	48.1	71.5	74.4	78.4	79.6	103.8
Pt(L4) <sub>2</sub>	129.5	107.6	122.2	119.4	164.2	185.7
Pt(L5) <sub>2</sub>	77.2	79.1	93.75	137.5	146.1	191.9



**Fig. 6. SEM a,b of L4 and c,d of LD4.**



## Conclusions

This study reports the synthesis of heterocyclic Schiff bases compounds containing 4-substituted phenyl thiazole ring and their platinum complexes. The elemental analysis data and spectral of the Schiff bases compounds are in agreement with the structure of the compounds and the bases are bonded to platinum ion via both hydroxyl group of aromatic ring and imine group Schiff bases to suggest a square planar of newly platinum complexes. The study showed that activities of these Schiff bases and their platinum complexes as antioxidants are comparable to that of BHT. On comparison, one can discern that the activity of platinum complexes is higher than their corresponding bases which mean that platinum metal supports strongly the activity of the Schiff bases. The obtained results indicate that there are expected interactions among extracted human DNA with the Schiff bases and their platinum complexes. The conducted experiments showed that the type of the interference is intracalation. Measurements of cytotoxicity activity on cancer cell MCF-7 of some Schiff bases (L4, L5) and their corresponding platinum complexes (LD4, LD5) showed results that the prepared bases possess  $IC_{50}$  more than those recorded for their corresponding Pt (II) complexes.

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## -هيدروكسي بنزايلايدين-4-(4-معوض فنيل)-2-امينو ثيازول ومعداتها مع البلاتين: تحضير وتشخيصها بالطرق الطيفية ودراسة نشاطها البيولوجي

زهراء داود خلف الدلفي، زكي عصمان ناصر الشمخاتي، محمد جاسم بدر الاسدي  
قسم الكيمياء – كلية العلوم – جامعة البصرة – العراق.

تضمنت الدراسة الحالية تحضير وتشخيص ودراسة بايولوجية لمركبات قواعد شف المشتقة من الثيازول ومعداتها مع البلاتين , حيث تم تحضير قواعد شيف  
2-هيدروكسي بنزايلايدين-4-(4-معوض فنيل)-2-امينو ثيازول بوجود معوضات مختلفة ومعداتها المقابلة  
من البلاتين [ L1-L6 = H, NO<sub>2</sub>, CH<sub>3</sub>, OCH<sub>3</sub>, F, Cl ]  
[Pt(L1)-Pt(L6) ] حيث تم تشخيص قواعد شف ومعداتها من البلاتين باستخدام تحليل العناصر الدقيق CHNS  
ومطيافية الأشعة تحت الحمراء FTIR ومطيافية الرنين النووي المغناطيسي NMR بالإضافة الى استخدام مطيافية  
الكتلة MS وايضا جهاز المجهر الالكتروني الماسح SEM.  
من خلال التشخيص تبين ان التناسق بين قواعد شف ومعداتها البلاتين تم عن طريق مجموعة الايمين المجموعة الفعالة  
لقواعد شف ومجموعة الهيدروكسيل في الحلقة الاروماتية ويكون الارتباط مع جزيئين من مركب قاعدة شف مما يشير  
الى الشكل الهندسي للمعدد يكون مربع مستوي.  
اشتملت الدراسة على تداخل المركبات (قواعد شيف ومعداتها) مع الحامض النووي البشري طبيياً ووجد ان نوع  
التداخل يكون عن طريق الليكاند, كذلك تم قياس النشاط المضاد للاكسدة لكلاً من الليكاندات ومعداتها من البلاتين  
عن طريق حامض اللينوليك بطريقة مسح الجذور الحرة ووجد ان المعوض L4=OCH<sub>3</sub> الميثوكسي الاكثر نشاطاً  
بالنسبة الى BHT وتسلسل نشاط المركبات يكون حسب الترتيب التالي:  
L4>L3>L2>L5=L6>L1  
درست سمية بعض مركبات قواعد شف ومعداتها على نوع من الخلايا السرطانية MCF-7 بتركيز مختلفة و خلال  
اوقات مختلفة باستخدام فحص MTT.