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Spectroscopic and molecular modelling studies of Pt(II) complexes of tetrazole-5-thiol ligands and 1,2-Bis(diphenyl phosphino)ethane, and study the anticancer activity against HepG2 Liver cell line

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Abstract

The two mixed ligands of the Pt(II)are "1-methyl-H1-tetrazole-5-thiol (Hmtz) and 1-phenyl-H1-tetrazole-5-thiol (Hptz)" and ,2-Bis(diphenyl phosphino)ethane (dppe) were prepared in one pot method. The prepared complexes were characterized using infrared spectroscopy (FTIR), molar conductivity and nucler magnetic resonance (^{1}H-NMR, and ^{31}P-NMR). The results showed that the thiol ligand pairs through the sulfur atom monodentately and acquired a square planar geometry. The complexes prepared were tested for their ability to inhibitory activity against HepG2 liver cancer and showed good inhibitory activity. Further, the density functional theory (DFT) study was performed for the complexes and ligands using the B3LYP 6-31+G(d, p) functional for the ligands and the LanL2dz functional for complexes. It was found that the [Pt(mtz)$_2$dppe] complex is more stable and chemically efficient than the [Pt(ptz)$_2$dppe] complex through the study of quantum chemical parameters.

Introduction:

Tetrazole thiol ligands are important compounds that contain a five heterocyclic rings containing four nitrogen atoms and one sulfur donor atom, as shown in **Fig** (**1**). They have multiple tautomeric forms in which the sulfur atom can be in the form of a thiol (C-S) or a thione (C=S)[1].

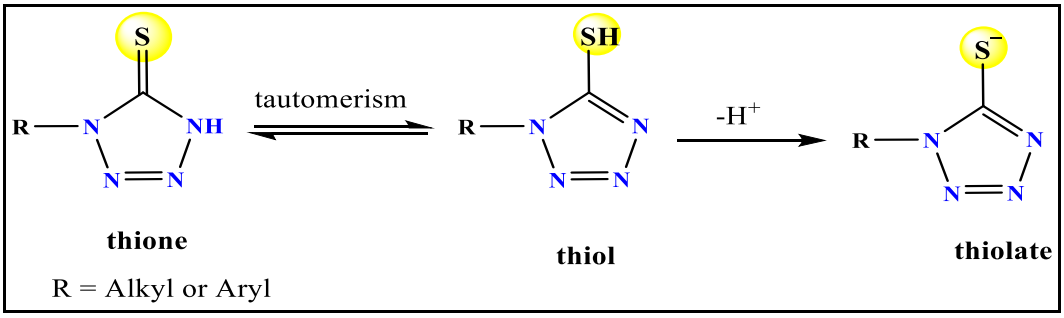

Fig. 1 *Tautomeric forms of the tetrazole thiol ring*

Ligands containing tetrazole rings have attracted great attention from researchers due to their wide applications in the fields of chemistry, medicine[2], and pharmaceuticals[3]. They act as tranquilizers and stimulants for the nervous system, work to lower high blood pressure, fight tumors, and in the agricultural field they act as fungicides that infect plants, and in the industrial field in the manufacture of rocket fuel [4–7]. As part of our interests in sulfur containing ligands[8–15], we herein report synthesis of platinum(II) "mixed ligand complexes of 1-methyl-H1-tetrazole-5-thiol (**Hmtz**) or 1-phenyl-H1-tetrazole-5-thiol (**Hptz**)" and 1,2-bis(diphenylphoshino)ethane (dppe), and characterization by different spectroscopic techniques. Furthermore, computational chemistry is used to compare the two prepared complexes and then evaluate the anti-cancer activity of the prepared complexes against liver cell lines.

Materials and Equipment Used

All chemicals and solvents used in the preparation were used without purification: "1-methyl-H1-tetrazole-5-thiol (**Hmtz**),1-Phenyl-H1-tetrazole-5-thiol(**Hptz**)", potassium tetra chloroplatinate (K_2PtCl_4) and 1,2-bis(diphenylphosphino)ethane (dppe). Melting point apparatus type (Stuarts SMP10) equipped by the British company (STUART), Infrared spectra of the ligands used and the prepared complexes were recorded using a (FTIR-8400S) by SHIMADZU in the region between (400- 4000 cm^{-1}) using KBr discs, The molar conductivity of the prepared complexes was measured using a (10^{-3} mol/L) solution in dimethyl sulfoxide (DMSO) at room temperature (25°C) using a Digital Conductivity meter CD-2005, ^{1}H-NMR and ^{31}P-NMR spectra were measured at the Central Laboratory - College of Education for Pure Sciences - University of Basra - Iraq using a (Bruker Unity Spectrometer 400MHz) using DMSO-d^6 solvent.

Synthesis of Complexes

Synthesis of [Pt(mtz)$_2$dppe]

In round bottom flask (100ml), a colorless solution of (Hmtz) ligand (0.48 mmol, 0.05 g) in ethanol (15 ml) was mixed with a reddish brown solution of potassium tetrachloroplatinate(II) (K_2PtCl_4) (0.24 mmol, 0.10 g) of 10 ml H_2O in a 1:2 (metal :ligand) ratio, respectively. The solution was refluxed for four hours, during which time a weak base of triethylamine (Et_3N) (0.48 mmol, 0.06 ml) was added. A dark orange precipitate formed. Then, a colorless solution of 1,2-Bis(diphenylphosphino) ethane (dppe) ligand (0.24 mmol, 0.09 g) in dichloromethane (15 ml) was added. Upon direct addition, a lemon-yellow solution was formed. The reflux was continued for 9 hours, resulting in the solution turning a light yellow. The solvent was removed from the mixture by evaporation at room temperature. After 4 days, needle-shaped crystals formed. After drying the remaining solvent, a light yellow-orange gum was formed. It was washed with diethyl ether, and then the solvent was removed by applying a vacuum, yielding a light-yellow precipitate (melting point 203 °C, weight 0.16 g, product yield 81%).

[Pt(mtz)$_2$dppe] Light yellow: Product yield 81%, chemical formula $C_{30}H_{30}N_8P_2PtS_2$, molar conductivity in DMSO solvent: 2.891 (Ω^{-1} cm^{-1} mol^{-1}). Infrared spectrum (KBr cm^{-1}): (ν C-H Ar) 3055 w, 2955w (ν C-H, P-CH_2), 1481w (ν C=N), 1377m (ν N-N), 1435s 1103m (ν Ph-P), 1311w 1265m (ν –N-N=N), 690 vs (ν C-S), 536 vs (ν P-C). ^{1}H-NMR proton nuclear magnetic resonance

spectrum (400 MHz, DMSO-d^6): δ 7.65 (*m*, 20H, 4Ph ring of dppe), 2.63 (*m*, 4H, 2CH2), 3.43 (*s*, 6H, $2CH_3$) ppm. ^{31}P-{^1H}-NMR (162 MHz, DMSO-d^6): δ47.53 (*s*, $J_{Pt\text{-}P}$ = 3059.4 Hz) ppm.

Synthesis of [Pt(ptz)$_2$dppe]

The method for synthesis the [Pt(mtz)$_2$dppe] complex was the same. It produced a light pink solid precipitation (melting point 219 °C, weight 0.19 g, product yield 83%).

[Pt(ptz)$_2$dppe] Light pink: Product yield 83%, chemical formula $C_{40}H_{34}N_8P_2PtS_2$, molar conductivity in DMSO solvent: 4.27 (Ω^{-1} cm^{-1} mol^{-1}). Infrared spectrum (KBr cm^{-1}): (ν C-H Ar) 3055 w 1500 m, 2947w (ν C-H, P-CH_2), 1485w (ν C=N), 1373m (ν N-N), 1435m 1103s (ν Ph-P) , 1311w 1269w (ν –N-N=N), 690 vs (ν C-S), 536 vs (ν P-C). ^1H-NMR proton nuclear magnetic resonance spectrum (400 MHz, DMSO-d^6): δ 7.68 (*m*, 10H, 2Ph ring of ptz), 7.43 (*m*, 20H, 4Ph ring of dppe), 2.57 (*m*, 4H, $2CH_2$) ppm. ^{31}P-{^1H}-NMR (162 MHz, DMSO-d^6): δ47.19 (*s*, $J_{Pt\text{-}P}$ = 3063.2 Hz) ppm.

Results and Discussion

Synthesis and characterization of the [Pt(mtz)$_2$dppe] and [Pt(ptz)$_2$dppe] complex

The complexes [Pt(mtz)$_2$dppe] and [Pt(ptz)$_2$dppe] were prepared in an one pot method, by the reaction of two moles of 1-methyl-1H-tetrazole-5-thiol or 1-phenyl-1H-tetrazole-5-thiol with one mole of K_2PtCl_4 in the presence of triethylamine (Et_3N) as a base medium using a mixture of distal water, ethanol and dichloromethane solvents. Then the 1,2-Bis (diphenylphosphino)ethane (dppe) ligand was added, to afford a [Pt(mtz)$_2$dppe] complex as light-yellow needle-shaped crystals while the [Pt(ptz)$_2$dppe] as a Light pink powder. The complexes formed are stable when at room temperature and can be dissolved in organic solvents such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), chloroform, and dichloromethane but insoluble in polar solvents such as water and ethanol. The complexes were characterized using Fourier transform infrared spectroscopy (FTIR), proton nuclear magnetic resonance spectroscopy (^1H-NMR) (400 MHz), phosphorus nuclear magnetic resonance spectroscopy (^{31}P NMR) (162 MHz) and molar conductivity .

The results showed the geometry of the [Pt(mtz)$_2$dppe] and [Pt(ptz)$_2$dppe] complexes is a square planar geometry. The phosphine binds bidentate from the phosphorus atom of the phosphine group whereas the thiolate ligands bonded as monodentate through the sulfur atom, as shown in **Fig** (**2**), which is consistent with the literature [16].

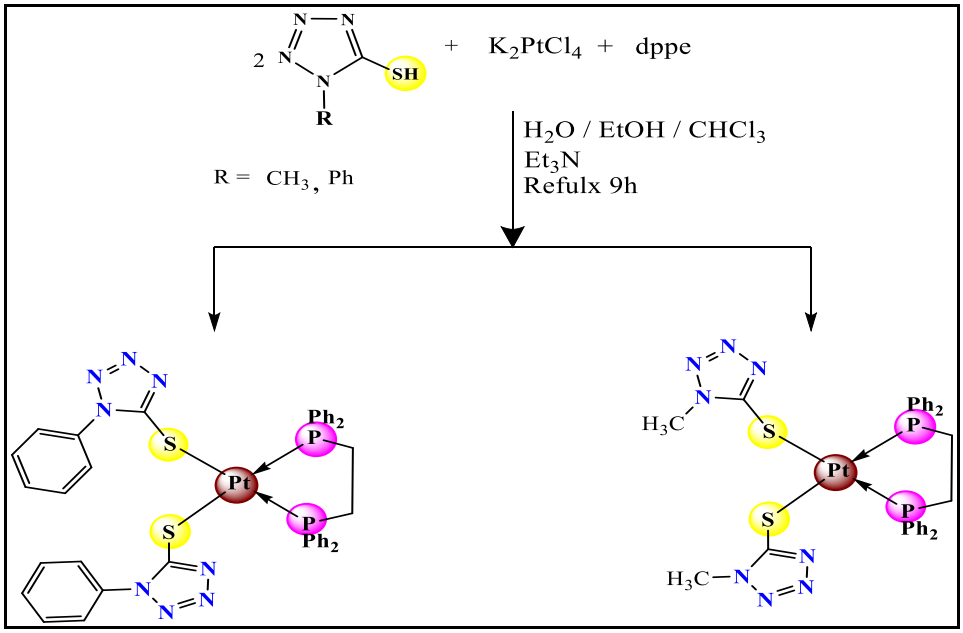

Fig. 2 *Synthesis of complexes [Pt(mtz)₂dppe] and [Pt(ptz)₂dppe]*

The infrared (**FTIR**) spectra (**Figure 3**)of the free Hmtz and Hptz ligands showed a medium- intensity bands at 2607 cm^{-1} and 2546 cm^{-1} respectively, which assigned to the stretching vibration of the thiol group (S-H). This band disappeared after coordinating with the Pt(II) ion, indicating the binding of the Hmtz and Hptz ligands by interacting with the sulfur atom of the thiol group (C-S)[16, 17]. Further evidence for the C-S bonding mode is provided by the shift of the (C-S) stretching vibration band. In the free ligands, this band appeared at 702 cm^{-1} for Hmtz and 752 cm^{-1} for Hptz. Upon coordination with the [Pt(mtz)₂dppe] and [Pt(ptz)₂dppe] complexes, this band shifted to 690 cm^{-1} for both complexes [18]. also showed two medium to strong intensity bands at 1435 cm^{-1} and 1103 cm^{-1}, which are given to the υ(Ph-P) and υ(P-C) stretching vibrations of the phosphine ligand. Additionally, a new strong intensity band appeared at 536 cm^{-1} in the spectra of the compounds, which is designated for the υ(P-C) stretching vibration [19, 20].

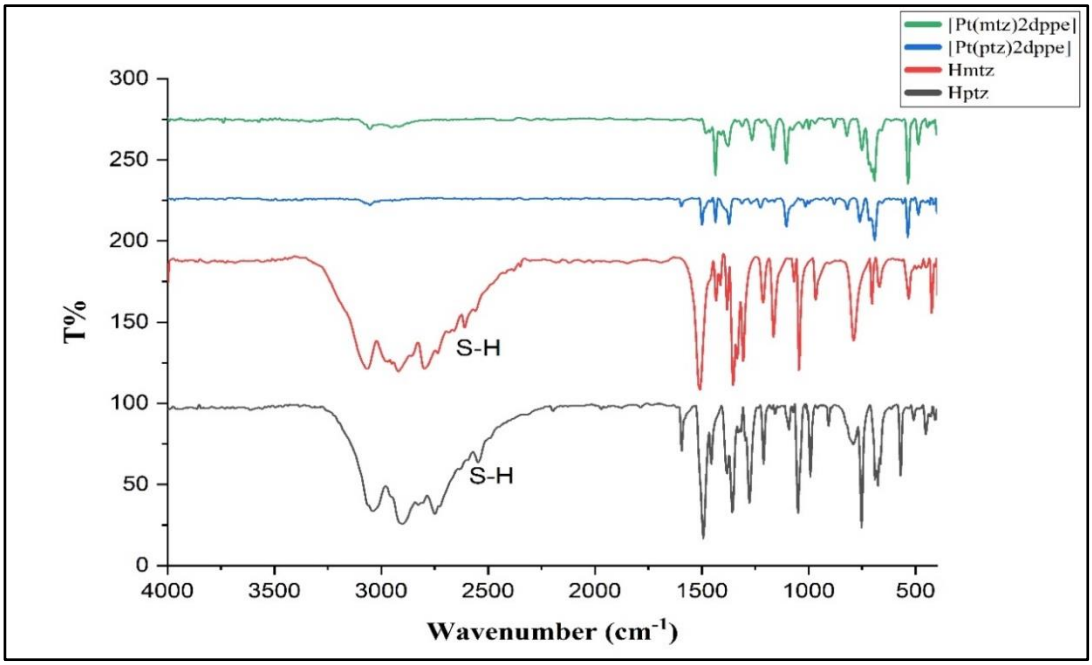

Fig. 3 *Infrared spectrum of the [Pt(mtz)₂dppe] and [Pt(ptz)₂dppe] complexes compared to Hmtz and Hptz Ligands.*

^{1}H-NMR for the complexes [Pt(mtz)$_2$dppe] and [Pt(ptz)$_2$dppe]

The ^{1}H-NMR spectrum of the complex [Pt(mtz)$_2$dppe], measured in the DMSO-d^6 solvent and shown in **Fig(4)**. The spectrum showed a singlet signal at δ^1H =3.68 ppm which was attributed to the methyl protons (2CH$_3$) of the ligand (**mtz-**). According to its integration, it corresponds to 6 protons. A multiplet peak appeared at δ^1H = 2.63 ppm which attributed to the methylene protons of the (P-CH$_2$) group in the ligand (dppe). Its integration indicates that it corresponds to four protons. The phenyl ring protons of the (dppe) ligand appeared as a multiplet signal centered at a chemical shift of δ^1H = 7.65 ppm and according to its integration, it corresponds to 20 protons which is attributed to four phenyl rings [21].

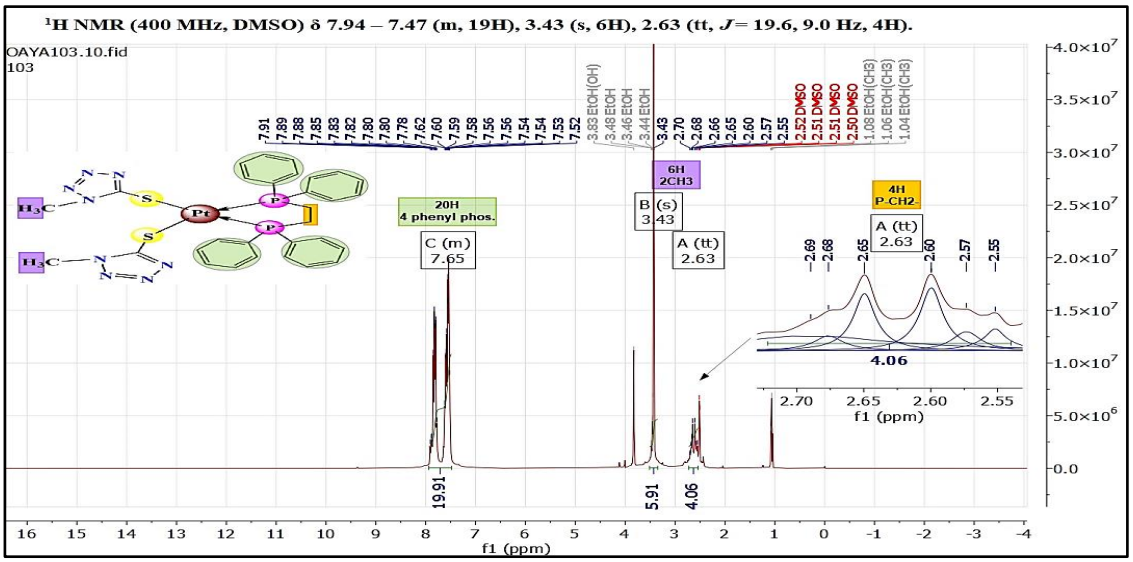

Fig. 4 *^{1}H-NMR Proton Spectrum of [Pt(mtz)$_2$dppe] Complex*

The ^{1}H-NMR spectrum of the complex [Pt(ptz)$_2$dppe] in DMSO-d^6 solvent (Figure **5**) exhibited a multiplet peak at δ^1H = 2.57 ppm, due to the methylene protons of the phosphine (P-CH$_2$) in the (dppe) ligand. Its integration indicates that it corresponds to four protons. The phenyl ring protons of the (dppe) ligand appeared as a multiplet peak centered at a chemical shift of δ^1H = 7.43 ppm and according to its integration, it corresponds to 20 protons for four phenyl rings. Finally, the phenyl ring protons of the (**ptz**-) ligand appeared as a multiplet peak at a chemical shift of δ^1H = 7.68 ppm and according to its integration, it corresponds to 10 protons for two phenyl rings[21].

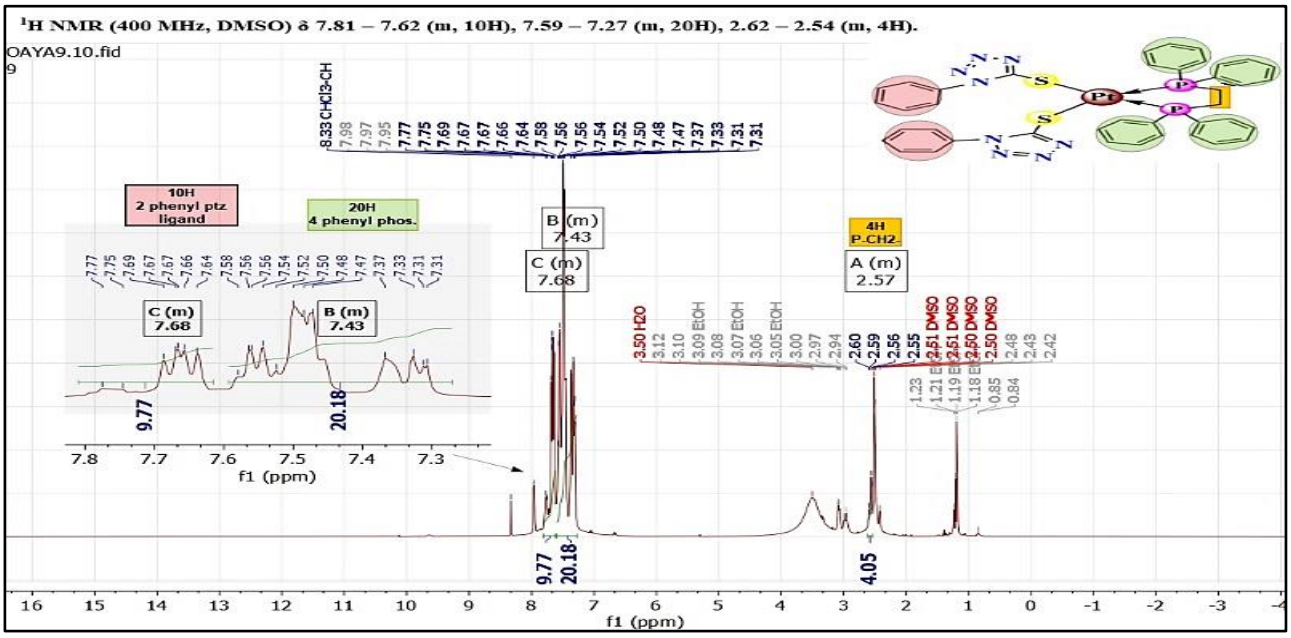

Fig. 5 *¹H-NMR Proton Spectrum of [Pt(ptz)₂dppe] Complex*

^{31}P-{^{1}H} -NMR for the complexes [Pt(mtz)$_2$dppe] and [Pt(ptz)$_2$dppe]

The ^{31}P-{^{1}H}-NMR spectra of the [Pt(mtz)$_2$dppe] and [Pt(ptz)$_2$dppe] complexes (Figures **6** and **7**) showed a singlet peak at δ^{31}P = 47.53 ppm and δ^{31}P = 47.19 ppm, respectively, indicating the presence of a single isomer. Additionally, the low coupling constant values ***J*(Pt-P)** = 3059.4 Hz and ***J*(Pt-P)** = 3063.2 Hz support the binding of the (**mtz**-) and (**ptz**-) ligands to platinum by the sulfur atom of a thiol group[21, 22].

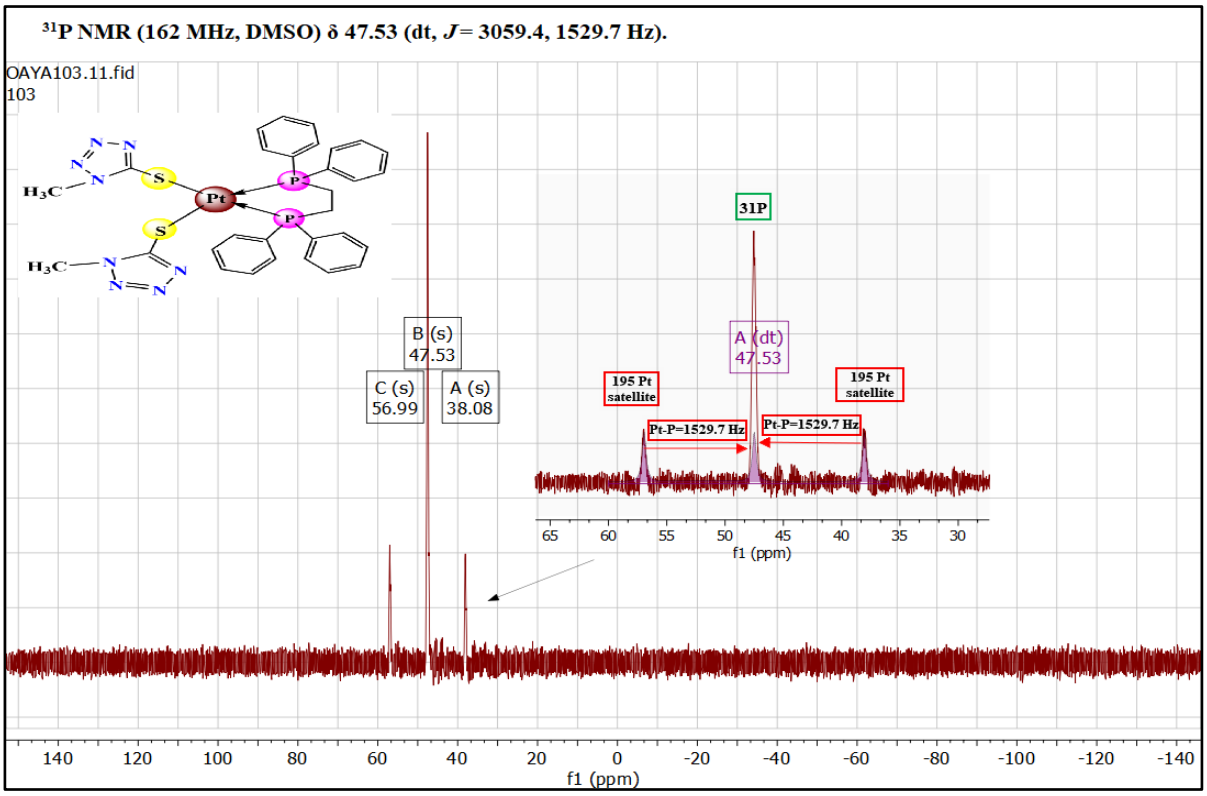

Fig. 6 *^{31}P-{^{1}H} NMR Phosphorus Spectrum of [Pt(mtz)$_2$dppe] Complex*

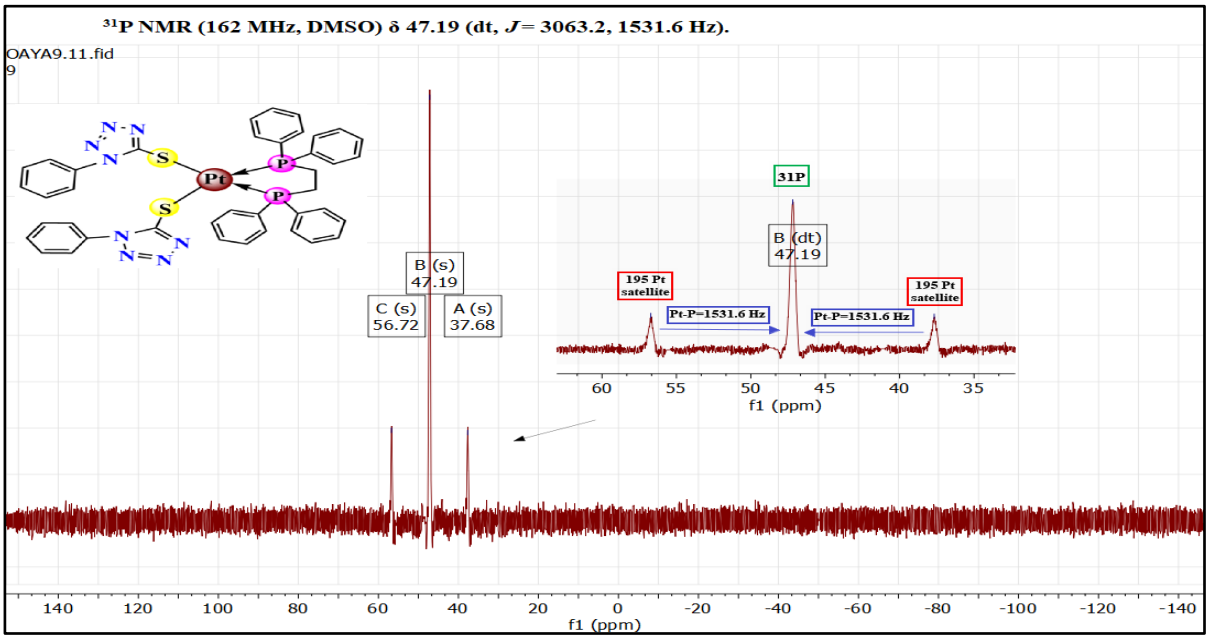

Fig. 7 *^{31}P-{^{1}H} NMR Phosphorus Spectrum of [Pt(ptz)$_2$dppe] Complex*

Density functional theory (DFT) study

Geometry optimization and vibrational analysis calculations were performed for the [Pt(mtz)$_2$dppe] and [Pt(ptz)$_2$dppe] complexes using the Gaussian 16 Linux program and Gauss View 6.0 program for all calculations[23]. The ligands and their complexes were optimized using the density functional theory (DFT) with the B3LYP [24]Becke, 3-parameter, Lee–Yang–Parr functional, 6-31+G(d, p) for the ligand atoms and (LanL2dz) Los Alamos National Laboratory Double Zeta for the central metal ion.

\The energy levels of the lowest unoccupied molecular orbital (ELUMO) and the highest occupied molecular orbital (EHOMO) were found using DFT calculations (Figure 8).
Chemical reactions were also observed to exhibit the energy gap(ΔEgap). The two important molecular orbitals are the filled molecular orbital (HOMO) and the lowest empty molecular orbital (LUMO). The energy difference between the HOMO and LUMO orbitals, also identified as the HOMO-LUMO gap, It indicates the reactivity of molecules at the levels of chemistry and biology. A lower energy gap indicates polarity and greater reactivity in chemical and biological systems. To evaluate the stability and chemical behavior of the thiol ligand and its corresponding metal complex, different quantum chemical properties were computed, including energies of "HOMO and LUMO electronegativity index (χ) electrophilicity index (ω) chemical hardness (η) softness (σ) chemical potential (μ) and energy gap ΔEgap". These values were derived from calculations based on HOMO and LUMO energies using equations. The resulting data is presented in Table 1. These properties serve as indicators of reactivity according to Koopmans theory for compounds with closed shell configurations. The hardness parameter η gauges how difficult it is to alter the electron cloud distribution, around a molecule, which reflects the arrangement of electrons surrounding the nucleus. It is a theoretical description of computational chemistry calculations directly related to the energy gap. The softness σ is a measure of ease in changing the shape of the electron cloud around a molecule and is inversely related to hardness. The electrophilicity index ω is a theoretical description in chemistry that measures the ability of a molecule to accept electrons

(electrophilicity) and indicates the probability of a molecule attracting and forming a bond with an electron-donating molecule (nucleophile)[25, 26].

Table 1: Calculated data from HOMO and LUMO energies for the complexes [Pt(mtz)$_2$dppe] and [Pt(ptz)$_2$dppe] compared with the ligands Hmtz and Hptz

Compounds	EHOMO (eV)	ELUMO (eV)	ΔE gap (eV)	η (eV)	σ (eV)	Dipole moment (debye)	μ (eV)	χ (eV)	ω (eV)	total energy kcal/mol
Hmtz	-7.59	-1.22	6.37	3.18	0.157	6.29	-4.40	4.40	3.04	-436596
Hptz	-7.28	-1.64	5.64	2.82	0.177	13.07	-4.46	4.46	3.52	-556925
Pt(mtz)$_2$dppe]	-5.79	-2.07	3.72	1.86	0.26	12.07	-3.93	3.93	4.15	-1098970
[Pt(ptz)$_2$dppe]	-5.63	-2.08	3.55	1.77	0.28	14.07	-3.85	3.85	4.18	-1339559

$$\Delta Egap = E_{LUMO} - E_{HOMO} \qquad \eta = \frac{(\Delta E)}{2} \qquad \sigma = \frac{1}{(2\eta)} \qquad \omega = \frac{(\mu)^2}{2\eta} \qquad \chi = -\mu$$

The stability of the complexes is indicated by the negative EHOMO and ELUMO values. However large negative values may result in the weakening of the high coordination bonds. The chemical hardness η and softness σ indices are interrelated measures that Explain the stability and function of molecules. Softness index correlates inversely with chemical hardness, so a balance between stability and reactivity must be achieved in the design of complexes; the study showed higher electrophilicity values for both complexes [Pt(mtz)$_2$dppe] and [Pt(ptz)$_2$dppe] which are (4.18,4.15) eV respectively compared to the ligands **Hmtz** and **Hptz**, indicating a more substantial binding and a faster reaction rate between the ligand and the central metal [27].

The energy gaps (ΔE $_{gap}$)of the [Pt(mtz)$_2$dppe] complex are higher than the [Pt(ptz)$_2$dppe] complex. This indicates that the [Pt(mtz)$_2$dppe] complex is less chemically active and more stable. This is because it is more difficult for electrons to transition and be excited from the HOMO orbital energy to the LUMO orbital energy. Therefore, higher energy is required for electron transfer. The [Pt(mtz)$_2$dppe] complex also showed a higher chemical hardness η than the [Pt(ptz)$_2$dppe] complex, reaching (1.87) eV, which makes it more difficult for electrons to transfer and the shape of the molecule's electron cloud to change, making the complex more stable [28]

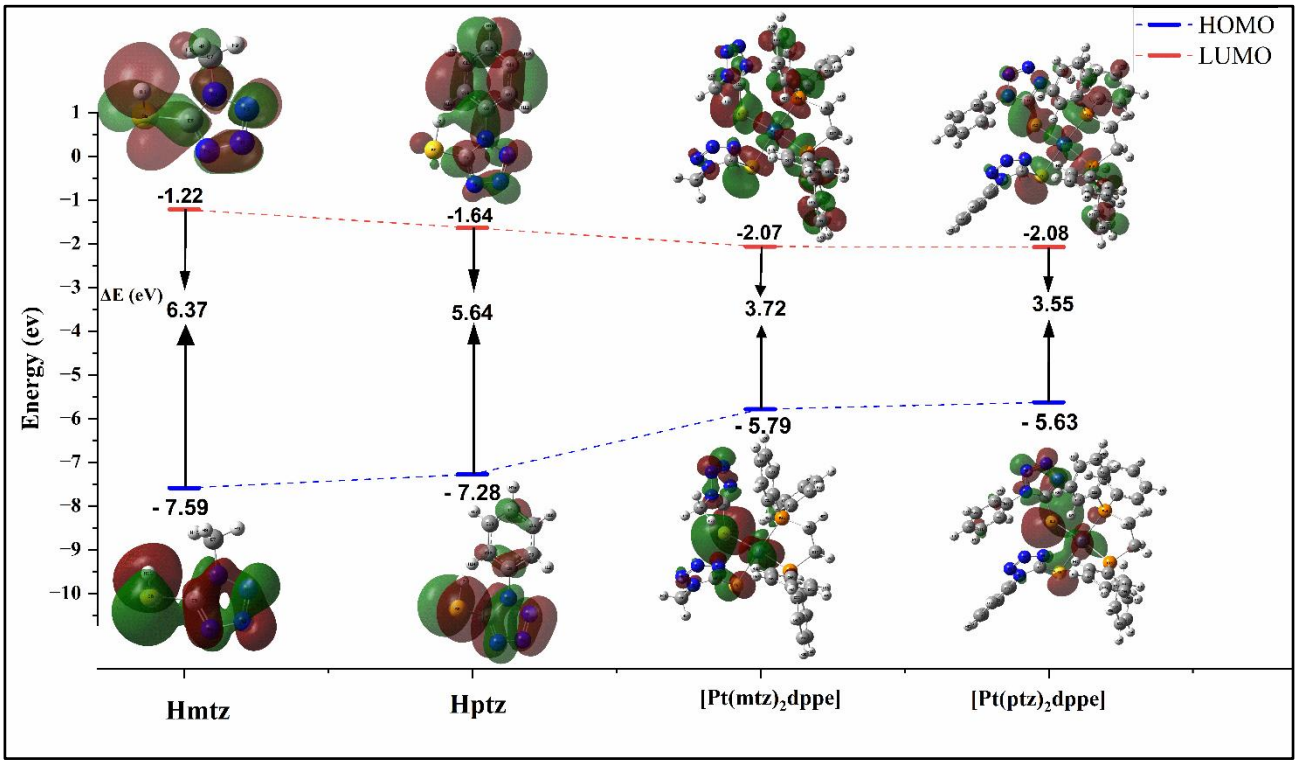

Figure 8 *Optimized Geometries of [Pt(mtz)₂dppe] and [Pt(ptz)₂dppe] Complexes and HMtz and Hptz Ligands with HOMO, LUMO, and ΔEgap*

Anti-Hepatocellular carcinoma (HepG2) inhibitory activity

The complexes [Pt(mtz)₂dppe] and [Pt(ptz)₂dppe] were tested in vitro for their antiproliferative activity against the human liver cancer cell line HepG2, in comparison with *cis*-platin as control. HepG2 cells were treated with the prepared complexes, and their growth was analyzed after 24 hours. Cell viability and growth were determined by measuring the number of metabolically active cells[29, 30]. MTT {3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-2H-tetrazolium bromide } was then added as a colorimetric assay reagent to each test plate. The calculated inhibition rate (%) is included in **Table 2** and the IC_{50} values in **Table 3** and **Figure9**.

Table 2: Inhibition rate (%) of [Pt(mtz)₂dppe] and [Pt(ptz)₂dppe] complexes showed greater effectiveness in inhibiting HepG2 cell growth compared to *cis*-platin

100% inhibition rate		
Concentration µg/ml	**[Pt(mtz)₂dppe]**	**[Pt(ptz)₂dppe]**
12.5	22.43	16.43
25	25.00	27.17
50	55.86	39.54
75	78.06	59.83
100	89.10	79.30
12.5	22.43	16.43

Table 3: IC_{50} values of [Pt(mtz)$_2$dppe] and [Pt(ptz)$_2$dppe] complexes showed greater effectiveness in inhibiting HepG2 cell growth compared to *cis*-platin

complexes	IC_{50} (µg/ml) of HepG2	M.wt g/mole	IC_{50} (µM)
[Pt(mtz)$_2$dppe]	39.52 ±1.91	823.77	47.975 ±1.91
[Pt(ptz)$_2$dppe]	53.27 ±1.45	947.92	56.197 ±1.45
***cis*-platin**	5.41 ± 0.34	300.04	18.031 ± 0.34

IC_{50} (µM) =(IC_{50} (µg/ml) / M.wt (g/mole)) * 1000

The prepared complexes showed a good to moderate activity compared to the reference standard. The complex [Pt(mtz)$_2$dppe] showed the greatest level of activity with an IC_{50} value of 47.975 ± 1.91 µM compared to the complex [Pt(ptz)$_2$dppe] having a value of IC_{50} at 56.197 ± 1.45 µM.

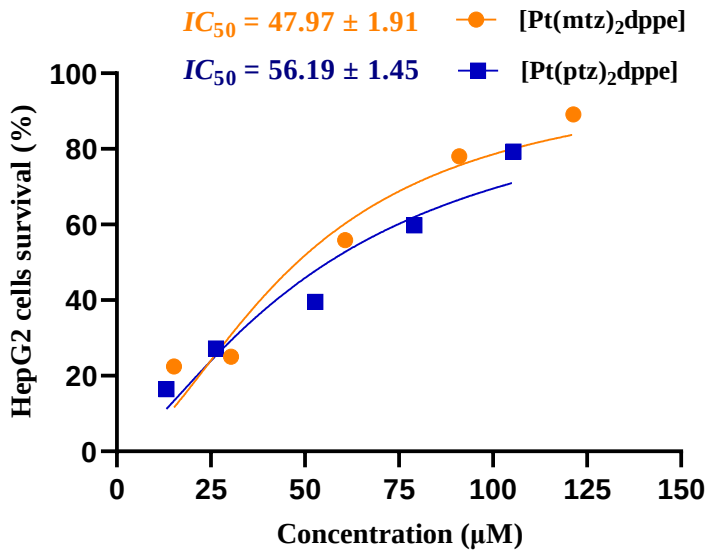

Fig. 9 *The inhibitory activity of [Pt(mtz)$_2$dppe] and [Pt(ptz)$_2$dppe] complexes against HepG2 cells lines using the MTT colorimetric method.*

Conclusions

[Pt(mtz)$_2$dppe] and [Pt(ptz)$_2$dppe] complexes were prepared and characterized, and the results showed the geometry is square planar, and the thiol ligands were coordinated through the sulfur atom of the thiolate group. Also, The thiol ligand and its metal complex were evaluated for their chemical properties and stability, with multiple quantum chemical expressions were calculated. The complexes that were prepared were evaluated in vitro for their ability to inhibit the growth of HepG2 cells. The results showed good to moderate activity compared to the reference standard. The complex [Pt(mtz)$_2$dppe] exhibited the greatest level of activity amongst an IC_{50} value of 47.975 ± 1.91 µM, whereas the complex [Pt(ptz)$_2$dppe] has an IC_{50} value of 56.197 ± 1.45 µM.

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دراسة طيفية ونمذجة جزيئية لمعقدات Pt(II) الحاوية على ليكاندات تيترازول-5-ثايول و 1،2--بس(ثنائي فينيل فوسفينو)ايثان ودراسة الفعالية المضادة للسرطان تجاه خلايا سرطان كبد HepG2

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الخلاصة:

حُضر معقدين للبلاتين (II) الحاوية على مزيج ليكاند 1-مثيل-H1-تترازول-5-ثايول (**Hmtz**)، أو ليكاند 1-فينيل-H1-تترازول-5-ثايول (**Hptz**) مع ليكاند 1,2-بس (ثنائي فنيل فوسفين) ايثان (**dppe**) باستخدام طريقة الخطوة الواحدة، وشخصت المعقدات المحضرة باستخدام مطيافية الاشعة تحت الحمراء (**FTIR**) ، التوصيلية المولارية الكهربائي، طيف الرنين النووي المغناطيسي للبروتون والفسفور وقد أظهرت النتائج ان ليكاندات الثايون ترتبط بشكل احادي السن من خلال كبريت مجموعة الثايوليت لتعطي معقدات ذات شكل مربع مستوي واجري للمعقدات المحضرة تقيم الفعالية التثبيطية لسرطان الكبد HepG2 واعطت فعالية تثبيطية جيدة وكذلك أجريت للمعقدات والليكاند دراسة دالة الكثافة الوظيفية (DFT) باستخدام الوظيفة B3LYP 6-31+G(d,p) لليكاندات والوظيفة LanL2dz للمعقدات حيث وجد ان المعقد $[Pt(mtz)_2dppe]$ يكون اكثر استقراراً وكفاءة كيميائية من المعقد $[Pt(ptz)_2dppe]$ من خلال دراسة المحددات الكيميائية الكمية ومقارنتها مع الليكاندات.