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Molecular Modeling Study to Propose a New Model of Cisplatin (IV) Complex as chemotherapy for cancer

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الخلاصة

في هذا البحث تم تصميم مركب بلاتيني جديد (IV) كعلاج للسرطان ودراسته من خلال برنامج Gaussian 09W، ثم تم حساب الخصائص الفيزيائية من خلال نظرية الكثافة الوظيفية DFT في B3LYP مع الأساس (LanL2DZ) مثل الطاقة الإلكترونية الكلية، أعلى مدار جزيئي مشغول بالإلكترونات (HOMO) أدنى مدار جزيئي فارغ من الإلكترونات (LUMO)، فجوة الطاقة وخصائص الطاقة الأخرى. وتشخيص المركب باستخدام طيف الأشعة فوق البنفسجية المرئية (UV) وطيف الأشعة تحت الحمراء (IR)، وكذلك تمت دراسة فعالية المركب والتفاعلات التي يمكن أن تحدث داخل جسم الإنسان، ثم مقارنة ارتباطه بالقواعد النيتروجينية التي تشكل الحمض النووي، ثم استكشاف ارتباطها بجزء صغير من خيط الحمض النووي. أظهرت النتائج أن المركب المقترح حقق صلابة كيميائية مماثلة لربط سيسبلاتين بالحمض النووي تحت نفس الظروف وباستخدام نفس الطريقة ونفس القواعد الأساسية. ومع ذلك، فإن اللكتروفيلية للمركب المقترح المقترحة للمركب كانت أقل من السيسبلاتين، مما يشير إلى فعاليته البيولوجية تجاه تثبيط السرطان وإمكانية عدم مقاومة الخلايا السرطانية له تتمثل فائدة هذه الدراسة في اقتراح عقاقير جديدة أكثر استقرارًا يمكن تناولها عن طريق الفم وتحقيق فعالية أكبر في تثبيط الحمض النووي للخلايا السرطانية.

Abstract

In this paper, a new platinum (IV) complex was designed as a cancer treatment by and study by the Gaussian 09W program, Then the physical properties were calculated by the density functional theory DFT at B3LYP with basis (LanL2DZ) such as the total of the electronic energy, highest occupied molecular orbital (HOMO) lowest unoccupied molecular orbital (LUMO), Energy gap and other energy properties. ultraviolet - visible (UV) spectrum and the infrared (IR) spectrum, have been used, Thus, effectiveness of the complex and the interactions that can take place inside the human body, also have been studied, then comparing its link with the nitrogenous bases that make up the DNA, then exploring its connection with a small section of the DNA strand. The results showed that the proposed compound achieved chemical hardness similar to cisplatin binding with DNA under the same conditions and using the same method and the same basis rules. However, proposed complex's electrophilicity proposed complex's electrophilicity was less than cisplatin, which indicates its biological effectiveness towards cancer inhibition and the possibility of cancer cells not being resistant to it. The benefit of this study is to suggest new, more stable drugs that can be taken orally and achieve greater effectiveness in inhibiting the DNA of cancer cells.

Keywords: Platinum (IV) complex, HOMO, LUMO, electronic density function, theoretical study, the energy gap

Introduction

Cancer is a disease that depends on the development of large numbers of abnormal cells that can divide rapidly and have the ability to infiltrate and destroy normal body tissues [1]. Therefore, new platinum drugs have been proposed that are less toxic than cisplatin, to which cancer cells show resistance. Research has stimulated the development and synthesis of a variety of platinum (IV) complexes. However, no Pt (IV) compound approved for clinical use [2] can act as Pt (IV) complexes. As drugs where the Pt (IV) species are activated by reduction to Pt (II) in physiological conditions, by ascorbic acid, glutathione and sulfhydryl group proteins, which separate the axial ligands of the complex Pt (IV) [3]. Tropical ligands determine the nature and activity of the final complex, while the axial ligands provide an opportunity to modify the properties [4,5]. Nevertheless, the axial ligands can play an essential role in targeting drugs for a specific organ of the body [6,7]. Some are derived from natural sources, and some are the other because some are derived from natural sources, and some are further from synthetic sources. Still, medicines derived from natural products are prevalent "In light of the many side effects associated with current anti-cancer drugs," there is an urgent need for a new drug that is less toxic and more specific to cancer cells [8,9]. The term chemotherapy was started at the beginning of the twentieth century by the famous German physician Paul Ehrlich, who used chemicals to treat cancer [10]. The importance of mineral compounds in chemotherapy are common, such as antimony (anti-parasites), gold (anti-inflammatory), silver (anti-microbial). This study included platinum (anti-cancer testicular, ovarian) [11]. Mineral complex chemotherapy activity has discovered great importance in cancer treatment [12]. First discovery of the anti-cancer effect of cisplatin (cis- [Pt $(NH_3)_2Cl_2$]) [13], cisplatin binds to DNA by forming covalent cross-links. Cisplatin's binding to DNA distorts the helical structure and inhibits DNA replication and transcription and thus cytotoxicity is generated [14]. Platinum ions are covalently linked to DNA, particularly with N7 for both guanine or adenine in the GAG and ACG nucleotide sequences to form crosslinkers between strands [15,16]. The binding of nucleic acid with cisplatin leads to transcription inhibition and stopping the division and proliferation of the cancer cell [17,18] Computational chemical programs play an important and vital role in drug discovery and development to reduce economic values and drug design time [19]. In the past few decades, there has been a remarkable development in computational chemical programs, and with the help of this development, it has become possible to design drugs and discover new drugs [20]. Thus, In the present work. We designed a new complex of platinum complexes as a primary treatment for cancer. We made a diagnosis of the said complex and studied its effectiveness when interacting with DNA.

Theoretical methods

Gauss View 6.0 is program was used to draw and design the complex, while (Gaussian 09W) program was used to complete energy the all calculations of the [dichloro di(4-ethoxy-4-oxobutanoat) diethel ammine platinum(IV)] such as the ultraviolet spectrum and the infrared

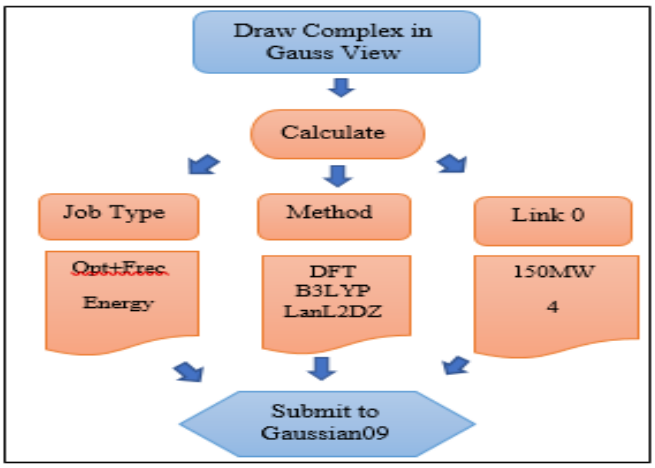
spectrum and this was done through an advanced calculator (Super Computer with the following specifications:

1- Intel Xeon E3-1225 v3.0 (4 core 3.20 GHz)

2- RAM (256 GB)

3- Storage memory (8 TB)

The following scheme can simplify the calculation method:



The energy gap (Egap) is defined as the energy difference between the lowest orbital empty of electrons (LUMO) and the highest orbit occupied with electrons (HOMO) and is calculated according to the following equation:[21].

$$Egap = E_{LUMO} - E_{HOMO} \ldots\ldots\ldots 1$$

It is also possible to calculate the chemical stiffness that shows the stability and reactivity of the compounds through the following equation [22]:

$$\eta = 1/2\ (E_{LUMO} - E_{HOMO}) \ldots\ldots\ldots 2$$

The chemical voltage (μ) and the electronegativity (X) can also be calculated by the following equation, as the electronegativity equals the chemical Potential, but opposite to the sign [23].

$$\mu = -X = 1/2\ (E_{LUMO} + E_{HOMO}) \ldots\ldots 3$$

Electrophilicity (X), which predicts whether compounds have high or low reactivity, is calculated through the following equation based on chemical voltage and chemical stiffness [24].

$$\omega = \mu 2 / 2\eta \ldots\ldots\ldots\ldots 4$$

there is an approximate possibility of calculate the energy of the IP ionization potential and the electronic spectrum EA, using Koopmans' theorem [25].

$$I = - E_{HOMO} \ldots\ldots\ldots 5$$

$$A = - E_{LUMO} \ldots\ldots\ldots .6$$

The Hartree unit was converted to electron volts with the relationship

1 Hartree energy = 27.2114 electron volts …….7

Results and discussion

The geometric shape of the proposed complex

The geometric shape was calculated to the length of the length of the bonds and the angles between the atoms forming the complex by DFT / B3LYP. For the basis LanL2DZ the results were very close to what was obtained experimentally. As shown In Table (1) and Figure (1)

Table 1: Bonds values computed experimentally and theoretically by DFT in units of A

Bond type	Measured value experimentally	The measured value theoretically
Pt-CL	2.37	2.42
Pt-N	2.09	2.10
Pt-O	2.02	2.03

We note that the obtained results are consistent with what was calculated experimentally using X-ray diffraction (XRD) [25]. It is known that the angles of the octahedral shape are regular, that is, their measurements are 90^0 or very close to this number, but the angles measurements of the designed complex are (CL-Pt-CL) are 96.10, (N-Pt-N) are 92.30, and (O-Pt- O) is 171.890 degrees. Therefore, compound's shape is the deformed shape of an octahedral, because the angles between the atoms are not uniform [27].

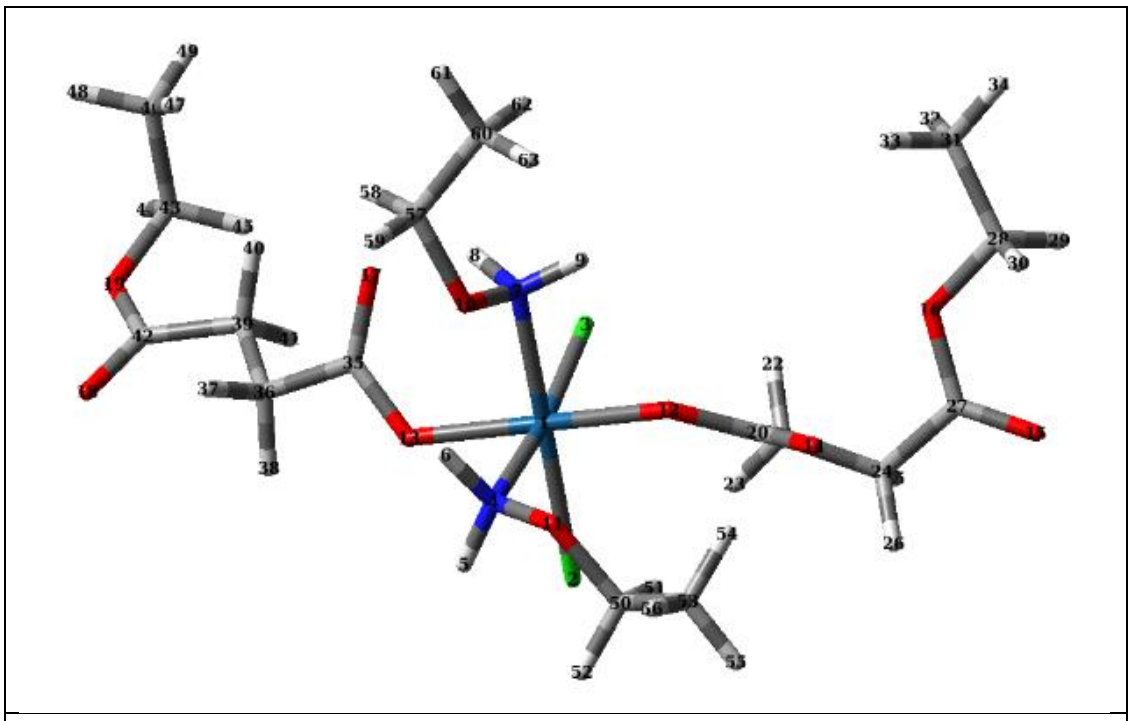


Figure 1: Structural structure of the platinum (IV) complex using DFT

Physical and energy properties of the designed complex

Total density and electrostatic voltage

Figure (2) showed that the red color is a high electron density, Still the green color is the electronic density is low on atoms in the molecular structure, so we notice a high density on (O, N, Cl) atoms, while electronic density of (H, C, Pt) atoms is low.

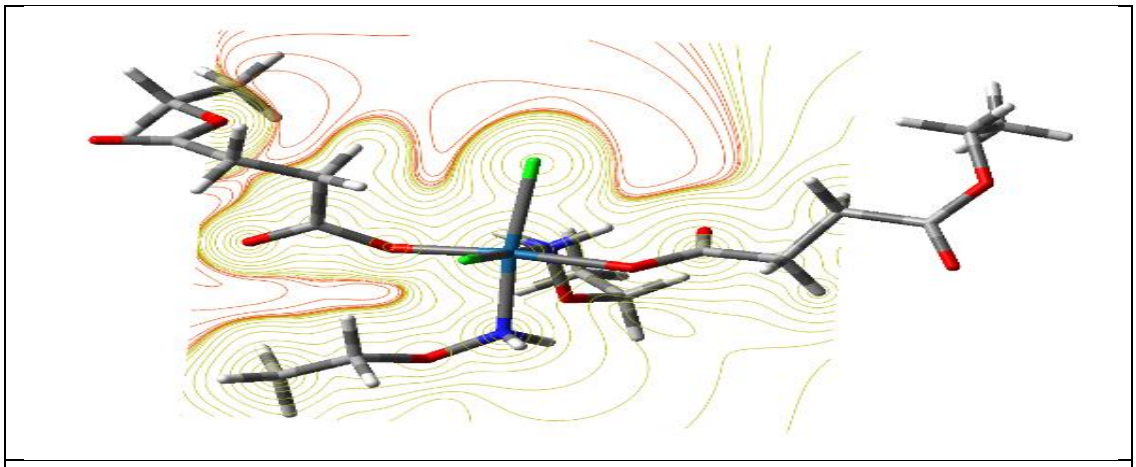


Figure 2: Electronic density of a platinum complex (IV) using DFT

Millikan charge

It is one of the methods of estimating the atomic charges of compounds. There is a complete transfer of electronic charges from one atom to another (charges +1 and -1). In the perfect covalent group, the electron pair is evenly shared (charges = 0) Perfect situations Thus, chemists have tried to develop methods over the years to determine the atomic charge utilizing

quantitative calculations, including the Millikan charge that determines the partial charge. (O and N) as well as notice the hydrogen atom No. (51) carrying the negative charge [28]. shown In Table (2) and Figure (3)

Table 2: Millikan charge values for the platinum complex atoms, using the density function theory

No.	Atoms	values	No.	Atoms	values	No.	Atoms	values
1	Pt	0.095671	22	H	0.263447	43	C	-0.209221
2	**Cl**	-0.126782	23	**H**	0.261955	44	**H**	0.224635
3	**Cl**	-0.130104	24	**C**	-0.438618	45	**H**	0.195926
4	**N**	-0.451465	25	**H**	0.215968	46	**C**	-0.609569
5	**H**	0.382712	26	**H**	0.234236	47	**H**	0.205627
6	**H**	0.417233	27	**C**	0.323322	48	**H**	0.230391
7	**N**	-0.505184	28	**C**	-0.166473	49	**H**	0.205337
8	**H**	0.428038	29	**H**	0.208779	50	**C**	-0.195732
9	**H**	0.402861	30	**H**	0.218809	51	**H**	-0.438894
10	**O**	-0.254737	31	**C**	-0.629883	52	**H**	0.194669
11	**O**	-0.194792	32	**H**	0.213056	53	**C**	-0.630557
12	**O**	-0.442503	33	**H**	0.212063	54	**H**	0.272421
13	**O**	-0.384165	34	**H**	0.193032	55	**H**	0.203332
14	**O**	-0.279412	35	**C**	0.391681	56	**H**	0.203500
15	**O**	-0.288122	36	**C**	-0.454014	57	**C**	-0.216091
16	**O**	-0.325657	37	**H**	0.244779	58	**H**	0.239199
17	**O**	-0.394630	38	**H**	0.257386	59	**H**	0.222380
18	**O**	-0.639374	39	**C**	-0.470147	60	**C**	-0.612905
19	**O**	-0.279285	40	**H**	0.257341	61	**H**	0.220977
20	**C**	0.278353	41	**H**	0.238571	62	**H**	0.207915
21	**C**	-0.405722	42	**C**	0.295183	63	**H**	0.234183

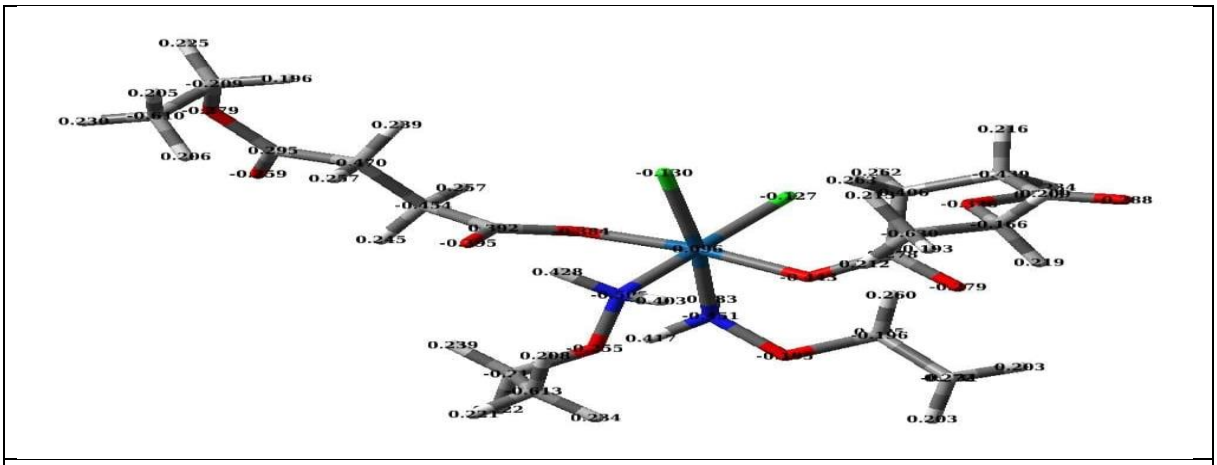


Figure 3: The Millikan charge values of the platinum complex (IV) using DFT

The energy of molecular orbitals

Molecular orbital energy levels such as EHOMO, ELUMO and Egap were calculated by DFT using B3LYP / Lanl2DZ. EHOMO energy is related to electron transmissibility, while ELUMO energy is related to the acceptability of electrons. The designed complex Egap appears relatively high and the chemical stiffness value (η) is high and electrophilic.(ω) Low and this indicates the stability of the structure of this complex and has low reactivity, meaning that it is inert in the direction of chemical reactions that may affect its structural as the chemical voltage (μ) and electrical negativity (x) were calculated. The results are shown in Figure (4). and Table (3).

Table 3: Energy Values of Platinum (IV) Complex Using DFT

EHOMO (ev)	ELUMO (ev)	Egap (ev)	μ (ev)	x (ev)	ω (ev)	η (ev)	I (ev)	A (ev)
-7.074	-3.646	3.428	-5.35	4.955	5.018	2.446	7.074	3.646

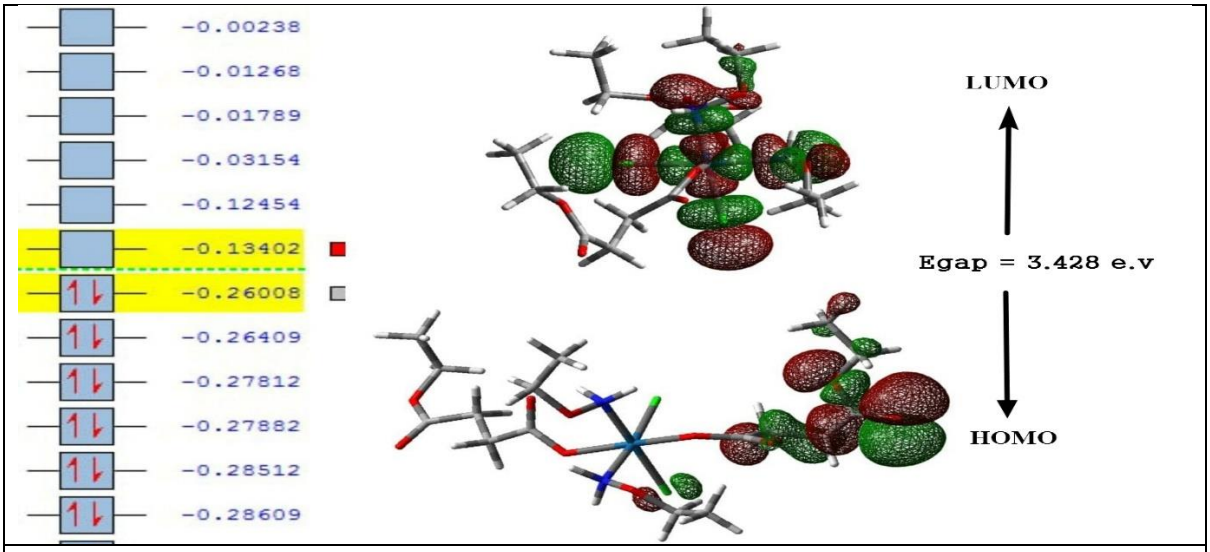


Figure 4: 3D Structure of Platinum Complex (IV) Molecular Orbitals Using DFT

Spectral properties

UV-Visible Spectrum

The UV-Visible spectrum is located in the area bounded between (100-800 nm) of the spectrum, and the range of the UV spectrum is small, as it is in the region (100-380 nm). The visible area (380-800 nm) from our theoretical calculation of the complex shows the absorption spectrum. The electron complex (VI) has two bands. The first band occurs at a

wavelength of 430 nm, indicating the (n – π*) transition, which transfers non-contact electrons in nitrogen, to the amine group. The second band appears at 450 nm and the third band at 455 nm, shown in Fig (5). However, the last two bands can be ignored due to the weak absorption band [29]. It appears that the maximum wavelength of absorption is (430 nm), as it is located within the visible region of the spectrum, and from this. we conclude that this complex is colored.

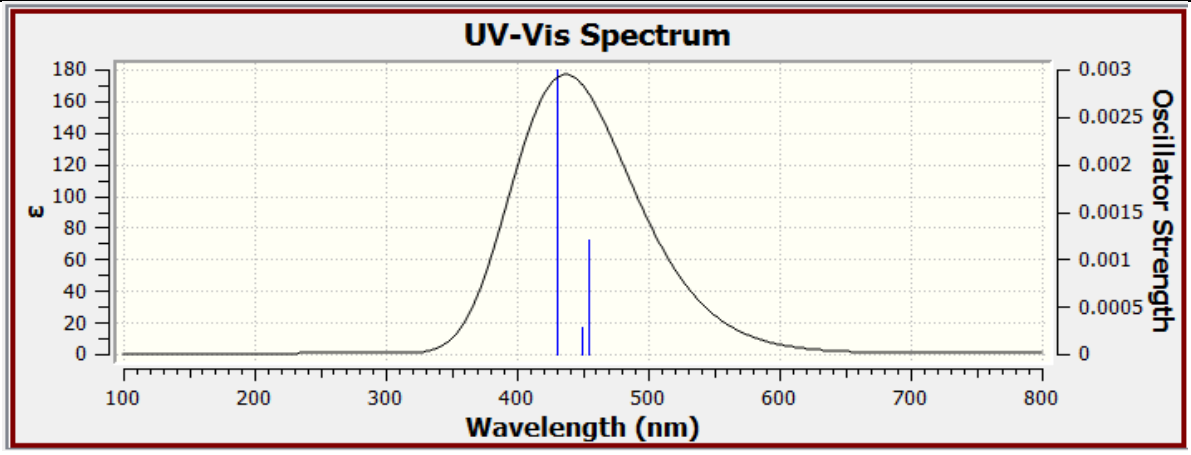


Figure 5: spectrum UV - visible to the platinum complex using DFT

Infrared (IR) spectrum

The theoretical vibration spectrum of the platinum complex is shown in Fig. (6) cm^{-1} 3050 indicating the expansion of the (C - H) aliphatic vibrations and the expansion of (NH), the secondary amine vibration computed at cm^{-1} 3484 and the frequency of υ (C = O) 1603 cm^{-1} refers to the carboxyl group in axial bonding, the υ (CO) vibration expansion at 1205 cm^{-1}. Whereas, the expansion υ (Pt-Cl) was shown in cm^{-1} 328 of the chlorine ligand and the vibration expansion (Pt-N) υ was at cm^{-1} 468 [30, 31]. The emergence of a new low-frequency band υ (Pt-O) at cm^{-1} 694 [32].

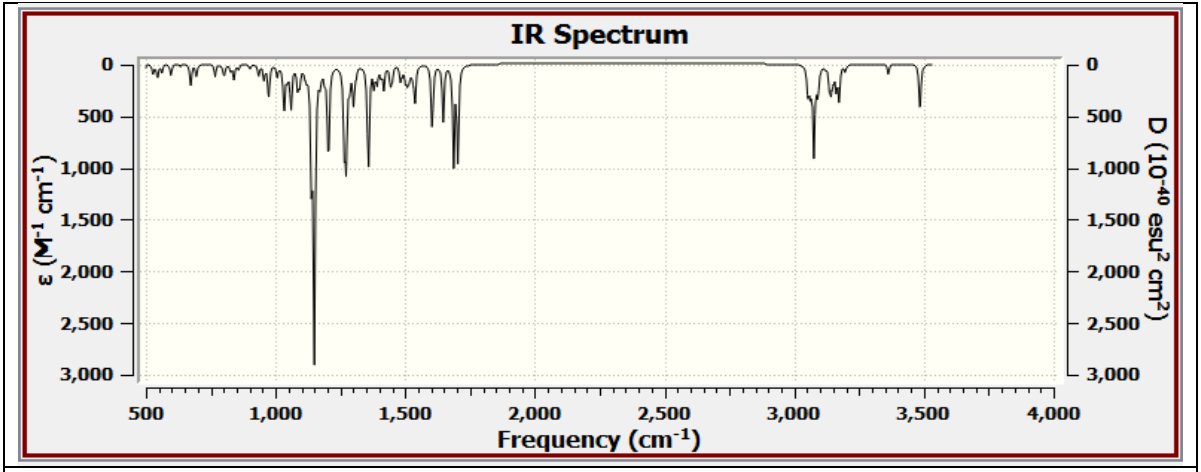


Figure 6: Infrared spectrum of the platinum complex using DFT

The effectiveness of the complex with DNA methylation

Platinum (IV) complexes are considered stable and inert in the direction of interaction with DNA [33], so they are reduced inside the body to platinum (II) complexes by glutathione or ascorbic acid (vitamin C) where the axial bonds separate [34], when the complex reaches The blood does not dissociate the chloride ions because their concentration is relatively high in the blood (about 100 mM). But upon entering the (II) complex into the cell, we will find that the chloride ion concentration decreases to (about 4 mM) [36,35] and then the complex gets hydrolysis because the chlorine ions are considered good leaving groups in the presence of water. We performed theoretical calculations of the effectiveness of the complex produced after hydrolysis with adenine and alkaline once and with human DNA again, and compared the interaction of the designed complex with the known anti-cancer drug cisplatin. By selecting three nucleotides in a G-G-T shape sequence, the connection was through the nitrogen atom N7 in both Guanine and adenine [37]. The results related to the interaction of the complex with the laws showed an advantage over its interaction with the adenine, through the calculations of Egap, in which the exchange of the Guanine has been greater than the adenine, and this means a greater stability of the Guanine bonding than the two adenines. On the other hand, the results of the comparison shown in Table (3) and Figure (7) were that Egap. The chemical stiffness [38] of the designer complex and cisplatin are equal. This indicates that the designed complex has stability by binding to DNA similar to that of cisplatin, but the complex's electrophilicity

was less than that of cisplatin. This indicates that it has proven that cisplatin has the direction of side reactions and it may address the effects of cell resistance to cisplatin. shown In Table (4) and Figure (7)

Table 4: The energy values for the interaction of platinum (II) and cisplatin complex with DNA

Complex type	μ (ev)	E gap (ev)	η (ev)	ω (ev)	Electronic energy
CEP	-8.19	4.23	2.115	15.89	-3886.7
Cisplatin	-8.31	4.23	2.115	16.28	-3579.2

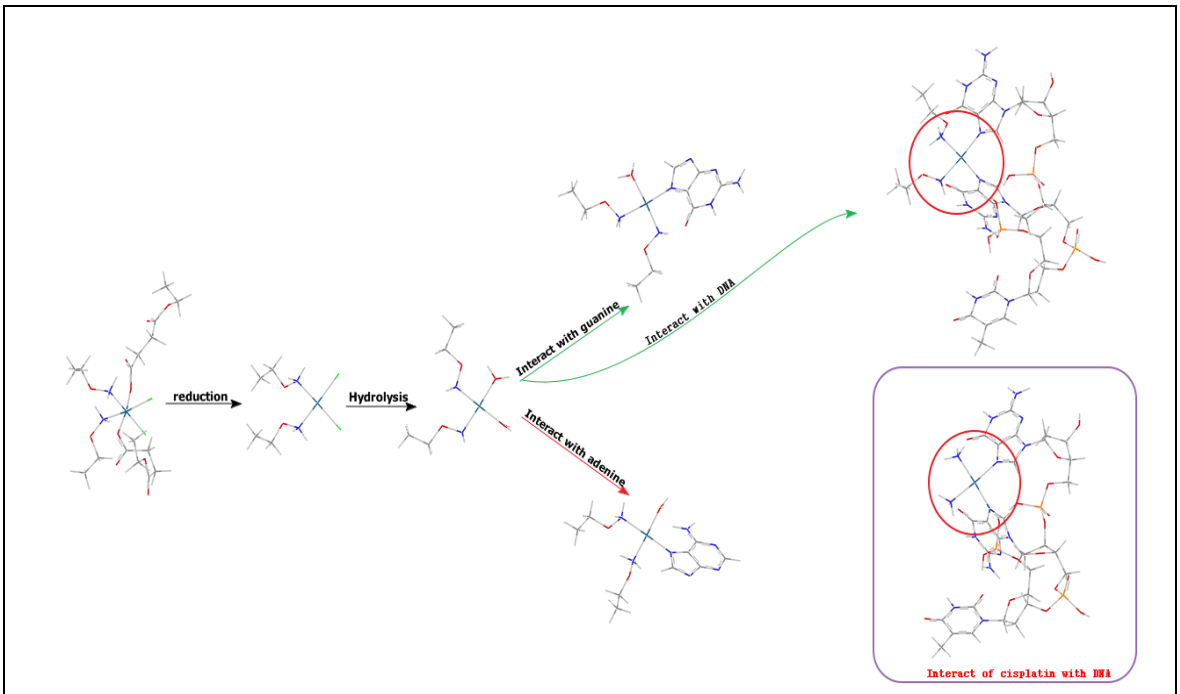


Figure 7: In-body designer complex interactions, theoretically using DFT

Conclusions

1- Theoretical calculations of a new Pt (IV) compound were performed using DFT / B3LYP / LanL2DZ and studied as a possible primary cancer drug, The results were compared. It was found that the designer compound may gain an advantage over the resistance of cancer cells to cisplatin due to the stability of its molecular structure

upon interaction with DNA. This study contributes to the proposal and development of a drug that can be taken orally for both clinical and pharmacological purposes.
2- The relatively high value of the energy gap is evidence of high complex stability.
3-The lengths of the bonds between the platinum atom and the other atoms, O, N, and Cl are very important for the transport of shipments between the donor and the receiver.

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