A theoretical approach and density function theory based to relate the physical and quantum properties of platinum (IV) complex

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Abstract
In this paper, we designed platinum complex drug for used anticancer. The geometry optimized structures and physical properties of platinum complex has been investigated by using the Density Functional Theory DFT/B3LYP/6-31G (d,p) method with basis set SDD via Gaussian 09W program package. This level of calculation was used for physical and quantum features like total energy, HOMO and LUMO orbitals energies, Band gap, electron affinity, Ionization potential, electronegativity, electrophilicity index, Mullikan charge on the atoms in platinum complex. The geometry optimization have been calculated by different methods such as (B3LYP,B3PW91 and CAM B3LYP) also different basis sets (LANL2DZ, LANL2MB and SDD) from total energy of methods and basis sets, they found of the best them are B3LYP/SDD. The calculation of the FT-IR spectra of platinum complex has been recorded in the range 400-4000 cm-1,also fundamental vibrational frequencies and intensity of vibrational bands. In addition, the 1H as well as 13C NMR chemical shifts values of platinum complex in the ground state for DFT/B3LYP/SDD have as well determined by means of Gauge independent atomic orbital (GIAO) technique. The first method includes reduction of prodrug (octahedral) to drug (square planer).the second method involves the binding of drug with nuclear DNA (adenine and guanine).

INTRODUCTION

Cisplatin (CP) stands for extensively given medications for treating patients with cancer (Johnstone, et al.,2016) CP has as well important side effects amongst gastrointestinal symptoms, nephrotoxicity, neuropathy, ototoxicity, and myelosuppression (Kemp, et al., 1996; Gandara,et al., 1995). Today in chemotherapy for platinum complexes are the most promising medications (Lippert, et al., 199). A highly strong antitumor agent (cisplatin) has obtained worldwide authorization and accomplished routine clinical use particularly for testicular and ovarian malignance. It is the effectiveness of cisplatin binding to DNA nucleobases resultant in a in the vicinity of unwound and kinked helix (Loehrer, P. J., & Einhorn, 1984). The cisplatin binding concerning DNA is a somewhat kinetically than thermodynamically controlled procedure. The DNA stands for the foremost organic target for anticancer medications. Correspondingly, a design and formation of DNA targeting metal-based anticancer agents with potential cytotoxicity have gained significance recently. DNA and RNA contain guanine that stands for highly focal purine nucleobases. Cisplatin

stands for highly considered as antitcancer metallodrugs with a foremost target of DNA, both guanine and adenine, cisplatin has a preference with guanine as compared with adenine (Tabrizi, et al., 2020). Several computational papers were given advantageous insights about cisplatin structure, its hydrolysis and comparison of its binding to the purine bases (Burda, et al., 2004; Burda, et al., 2001; Burda, et al., 2003; Baik, et al., 2002; Šebesta, & Burda, 2017).
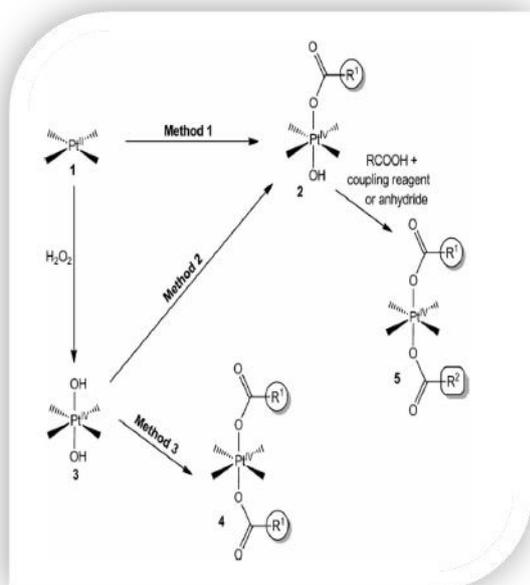
EXPERIMENT

Design Drug

The design drug include three methods as shown in **Scheme 1**: Reaction paths for forming dual platinum (IV) complexes (symmetric and asymmetric). **Method 1** includes the platinum (II) oxidation with a huge excess of a carboxylic acid and a minor additional appropriate peroxide for generating a monocarboxylate platinum (IV) complex 1. **Method 2** includes using common carbodi-

Scheme 1. Reaction pathways for forming platinum(IV) complexes

Scheme 2. Path way of platinum complex calculation in Gaussian 09W

The zero-point energy

Determination of ZPE for platinum complex from the equation (Rahal, & El Hajbi, 2019).

$$ZPE = \frac{R}{2} \sum_{i=1}^{3N-6} \left(\frac{hc}{k} \right) \nu_i$$

where the sum is valid in the case of 3N-6 normal frequencies (vi) for nonlinear molecule of N atoms, *R* stands for a gas constant, *k* represents the Boltzmann constant, c stands for a light speed, and h stands for Planck constant. Applying this method for large molecules is difficulties because of the presence of overtones and combination frequency in spectra for molecules. The DFT method calculation are used of determine the ZPE of molecules.

RESULTS AND DISCUSSION

Molecular Geometry Optimization

The enhanced geometrical parameters like bond angles, bond lengths and torsion angles of platinum complex gotten by the DFT (Kohn, 1999) and B3LYP approaches (Hanson-Heine, et al., 2013) with LanL2DZ,LanL2MB and SDD) as basis sets, also using DFT and different methods are B3LYP, B3PW91 and CAMB3LYP with SDD basis set are listed in **Tables 1** and **2**. Molecular Geometry optimization has performed to discover the finest atomic structure which creates the molecule more stable (Itte, et al., 2017). Geometry optimization depend on the orbitals configuration in space regarding other throughout the center of atom, in the other band denoted on angles. Torsion angle in the angle between two planes (Razzaq, et al.,2014). **Fig. 1** shows the Enhanced structural parameters like bond angles, bond lengths and dihedral angles of platinum complex by tube form at DFT/B3LYP/SDD level in the gas phase. From **Tables 1** and **2**, the results show that the best method is DFT/ B3LYP method with SDD basis set.

Molecular electrostatic potential

ESP stands for the most advantageous electrostatic property for studying the relationship between structure and activity in biological systems in Nucleophilic and Electrophilic reactions. A negative charge corresponds

imide coupling reagent for generating a monocarboxylate platinum (IV) complex 2, following that a different carboxylate group is inserted in situate using another activated carboxylate for generating a mixed-carboxylate platinum (IV) complex 5. **Method 3** involves using R-group (HOCOCH$_2$CH$_2$CONHOCH$_3$) in the single reaction with an anticipated carboxylate and a platinum (IV) complex 3, for generating a dicarboxylate platinum (IV) complex 4 (Zhang, et al., 2013).

Computational methods

In this paper, calculations have implemented based on Gaussian 09 (Frisch, et al., 2009; Akpor, et al, 2014), and molecular structures have been schemed with the Gauss View program (Becke, 1993). The computations have done with the B3LYP functional density (Belaidi, et al., 2014). Each geometrical optimization has been designed without any symmetry limitations by means of SDD basis set (Hirva, et al., 2008), procedure have determined for verifying the tendencies of Mullikan population analysis. The overall energy and nuclear energies have determined for platinum complex as in LUMO and HOMO orbitals along with their energies. The electronic transition energy of the DOP complex besides a particular point have acquired in accordance with time-dependent density functional theory TD/DFT with B3LYP computations (Baik, et al., 2003). All calculations were completed by using Gaussian09W software, the molecular modeling were carried at DFT/B3LYP method and SDD basis set to investigate geometry optimization, stability and physical properties as shown in **Scheme 2**.

Table 1. Bond lengths, bond angles and torsion angle for platinum complex by DFT/SDD basis set with different methods

| Bond lengths(A°) | | | | Bond angles(Degree) | | | | Torsion angle | | | |
| B3LYPE | | B3PW91 | CAMB3LYP | B3LYPE | | B3PW91 | CAMB3LYP | B3LYPE | | B3PW91 | CAMB3LYP |
Bond	Value	Value	Value	Bond	Value	Value	Value	Bond	Value	Value	Value
$R(Pt_1-Cl_2)$	1.325	2.393	2.389	A $(Cl_2-Pt_1-Cl_3)$	96.618	95.018	94.79	$D(Pt_1-Cl_2-Cl_3-N_4)$	102.507	-178.88	-178.59
$R(Pt_1-Cl_3)$	1.3189	2.395	2.389	A $(N_7-Pt_1-N_4)$	96.313	93.554	92.96	$D(Pt_1-Cl_2-Cl_3-O_{12})$	102.232	-89.304	-89.57
$R(Pt_1-N_4)$	1.087	2.079	2.061	A $(N_4-Pt_1-Cl_3)$	178.396	85.84	86.13	$D(Pt_1-Cl_2-Cl_3-O_{13})$	22.658	24.886	26.054
$R(Pt_1-N_7)$	1.0781	2.076	2.068	A $(N_7-Pt_1-O_{12})$	95.854	93.98	93.775				
$R(Pt_1-O_{12})$	1.0728	2.048	2.033								
$R(Pt_1-O_{13})$	1.0347	2.027	2.012								
Total energy	-2254.78	-2254.25	-2254.173								

Table 2. Bond lengths, bond angles and torsion angle for platinum complex by DFT/B3LYP method with different basis set

| Bond lengths(A°) | | | | Bond angles(Degree) | | | | Torsion angle | | | |
| SDD | | LanL2DZ | LanL2MB | SDD | | LanL2DZ | LanL2MB | SDD | | LanL2DZ | LanL2MB |
Bond	Value	Value	Value	Bond	Value	Value	Value	Bond	Value	Value	Value
$R(Pt_1-Cl_2)$	1.325	2.325	2.527	A $(Cl_2-Pt_1-Cl_3)$	96.618	96.62	99.04	$D(Pt_1-Cl_2-Cl_3-N_4)$	102.507	102.51	176.28
$R(Pt_1-Cl_3)$	1.3189	2.319	2.56	A $(N_7-Pt_1-N_4)$	96.313	96.312	95.60	$D(Pt_1-Cl_2-Cl_3-O_{12})$	102.232	102.232	-86.62
$R(Pt_1-N_4)$	1.087	2.087	2.09	A $(N_4-Pt_1-Cl_3)$	178.396	178.39	83.75	$D(Pt_1-Cl_2-Cl_3-O_{13})$	22.658	22.657	170.95
$R(Pt_1-N_7)$	1.0781	2.078	2.112	A $(N_7-Pt_1-O_{12})$	95.854	95.853	87.95				
$R(Pt_1-O_{12})$	1.0728	2.073	2.18								
$R(Pt_1-O_{13})$	1.0347	2.035	2.082								
Total energy a.u	-2254.787	-1363.65	-1348.18								

to nucleophilic sites are remarked by red color and distribute on the oxygen, chloride and nitrogen(electron rich centers)n atoms Similarly, the positive charge based on the electrophilic sites (electron deficient centers) are remarked by the green color and distribute on the carbon and hydrogen atoms (Govindarajan, et al. 2013; Munoz-Caro, 2000). The electrostatic potential (ESP) has determined by DFT/B3LYP/SDD with SCF density matrix. **Figs. 2** and **3** represented Mullikan charge, electron density respectively (Itte, et al., 2017).
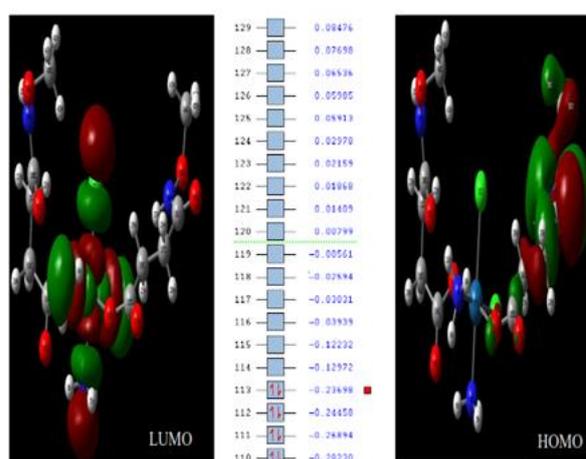
Mulliken charge distribution

Mulliken populations represent the straightforward depictions of charge distribution. Mulliken charges make available net atomic populations in a molecule while electrostatic potentials yield the electric field outside a molecule created through an internal charge distribution. Mulliken charge distribution can be measured based on DFT/B3LYP and SDD basis sets. A charge distribution of the compound from **Table 2** and **Fig. 2** depicts that carbon atom C14 attached with oxygen atoms take positive charges and it has the maximum Mulliken charge than other C atoms. Each hydrogen atoms has

Table 3. Mulliken charges distribution of platinum complex by DFT/B3LYP/SDD levels

Numbers of atoms	Atoms	values	Numbers of atoms	Atoms	values
1	Pt	-0.010931	25	H	0.256058
2	Cl	-0.124499	26	H	0.284506
3	Cl	-0.089902	27	C	-0.450715
4	N	-0.855988	28	H	0.237925
5	H	0.408928	29	H	0.228394
6	H	0.425747	30	C	0.325175
7	N	-0.838828	31	C	0.223043
8	H	0.422019	32	O	-0.309360
9	H	0.409222	33	O	-0.242965
10	H	0.400809	34	N	-0.297443
11	H	0.432971	35	H	0.320104
12	O	-0.312931	36	N	-0.290758
13	O	-0.471682	37	H	0.330217
14	C	0.390486	38	O	-0.251300
15	C	0.263518	39	O	-0.239894
16	O	-0.368074	40	C	-0.427042
17	O	-0.224084	41	H	0.211740
18	C	-0.463758	42	H	0.217699
19	H	0.243994	43	H	0.234332
20	H	0.219423	44	C	-0.457563
21	C	-0.493901	45	H	0.250800
22	H	0.282208	46	H	0.215697
23	H	0.216342	47	H	0.194480
24	C	-0.424219			
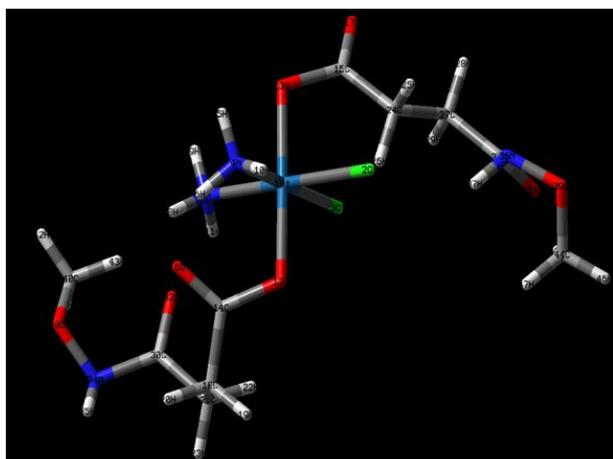
Fig. 1. Geometry optimization of platinum complex by DFT/B3LYP/SDD levels
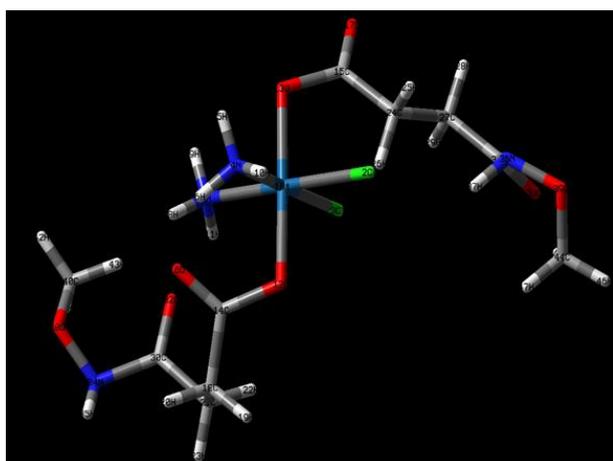
Fig. 2. Geometry optimization of platinum complex by DFT/B3LYP/SDD levels

Fig. 3. Electrostatic potential of 2D for platinum complex by DFT/B3LYP/SDD levels

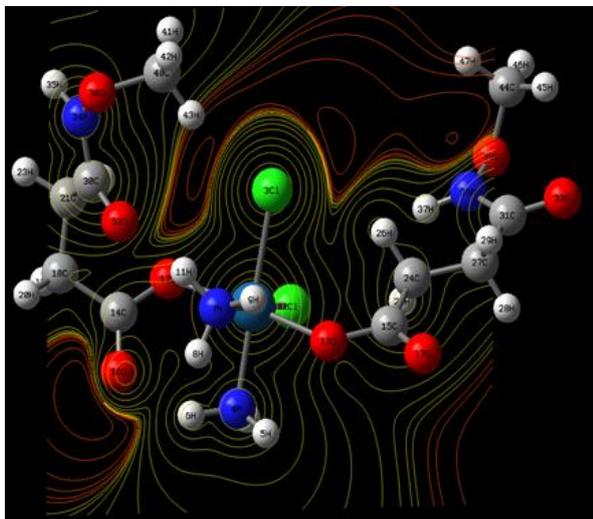positive Mulliken charges and the hydrogen atom H11 attached to Nitrogen (N7) has the uppermost positive charge (Yuan, & Zhang, 2020). The Pt1 bears negative Mulliken charge and stands for the uppermost as B3LYP/SDD method is applied (Khan, et al., 2016).

Frontier molecular orbitals and physical properties

The electronic properties are represented by HOMO in addition to LUMO energies. The HOMO denotes high occupied molecular orbital. Nonetheless, LUMO refers to low vacant molecular orbitals. Also, we indicate a difference between HOMO and LUMO as the energy gap (Egap) (Omar, et al., 2017). The dual arbitrary colors (green and red) represent the positive and negative isosurface. The energy gap between HOMO is -0.23698 ev and LUMO is 0.00799 ev. The low energy gap candidates this molecule to be a noble semiconductor and solar material with more polarizable and great chemical activity and low stability. Consequently, it stands for soft molecule. The high binding of platinum

Table 4. HOMO,LUMO and Egap for platinum complex

System	HOMO	LUMO	Egap
complex	-0.23698	0.00799	0.24497

Fig. 4. Frontal molecular orbital's of 3D for platinum complex by DFT/ B3LYP/SDD at Level of theory

Table 5. Calculation of quantum parameters chemical values of studied compound obtained DFT/B3LYP/SDD levels

values	μ(ev)	X(ev)	η(ev)	I(ev)	A(ev)	ω (ev)	$\omega^-(ev)$	$\omega^+(ev)$
Platinum complex	0.1225	-0.125	0.245	0.237	-0.0080	0.0307	0.1261	0.0116

The calculation from equation as shown (Pritchard, & Skinner, 1955).

$$-χ = μ$$

The fraction of electrons (ΔN) according to Lekovic's (Lukovits, et al., 2001), quantifies the transfer of electrons from complex(IV) to DNA if ΔN > 0, and from DNA to complex(IV) if ΔN < 0,the results show the increasing electron donating complex(IV) to donate electron to DNA in **Table 4**. It has defined by equation [35]:

$$ΔN = -\frac{μ}{η}$$

The electron affinity (A) is amount of energy change when the species take the electron. Electron affinity (A) is the capability of an atom to gain electrons. The A values for platinum complexe is small, it is easier for an atom to gains electrons, the defined by equation (Mutlak, et al., 2016)

$$A = -E_{LUMO}$$

Where E_{LUMO} is the low unoccupied molecular orbital.

The electrophilicity index that has been proposed by parr etal (Parr, et al., 1999) as the measure of the electrophilic power of a molecule. The defined by equation:

$$ω = \frac{μ}{2η}$$

The power of electron donating($ω^-$) and electron($ω^+$) were determined by (Glossman-Mitnik,:2013):

$$ω^- = \frac{(3I + A)^2}{16(I - A)}$$

$$ω^+ = \frac{(I + 3A)^2}{16(I - A)}$$

Therefore the high value of $ω^-$ corresponds a better acceptability of the charge, but the low value of $ω^+$ makes it a better electronic donor (Dikmen, & Hür, 2019).

Spectroscopy properties

Infrared spectroscopy

The harmonic vibrational frequencies were examined for Pt(IV)complex, at ground state, B3LYP, SDD basis sets shown in **Fig. 6**. There have been dual kinds of stretching deviations including symmetric besides asymmetric variations. The symmetric stretching has occurred as the identical atoms vibrate in a same phase, and the asymmetric stretching has occurred as the bonds vibrate in dissimilar phases. The aliphatic υ(C–H) stretching vibrations are observed as multiple bands in the region3050 cm⁻¹ (Rastogi, et al., 2006). The υ (N-H)aminde and υ (N-H)amine stretching vibration of the complex calculated at 3625,3178 cm⁻¹ respectively.A new band appears υ (C-O), υ (C=O), υ (N-O) and υ (C-

complex with DNA strand from define low Egap value, therefore prevents DNA division and it inhibits cancer. The other hand in low value of Egap, there is easy flow of electrons to high energy state making it softer and more reactive (Kumer, et al., 2018). The calculation of Egap from equation as shown (Ammouchi, et al., 2020).

ΔEgap = ELUMO – EHOMO

To know of stability and reactivity for platinum complex (IV) through using quantum mechanic calculation method. The absolute hardness (η) (Miranda, & Bueno, 2019) as follows:

$$μ = -X = \frac{1}{2}(E_{LUMO} + E_{HOMO})$$

The absolute hardness (η) is measure the stability and reactivity for platinum complex(IV).The fundamentally hardness on resistant to deformation or the polarization of the electron cloud of the atoms, ions or molecular down small perturbation reaction (Rajendran, et al, 2016). The ionization potential (I) is important properties of the chemical reactivity of atoms and molecules, The I values of platinum complexes are bigger, that specify the capability to lose electrons more straightforwardly. From **Table 4**, the low value of ionization energy indicates is high binding of platinum complex with binding DNA fragment. The equation as shown (Mutlak, et al., 2016):

$$I = -E_{HOMO}$$

Where E_{HOMO} is the high occupied molecular orbital.

An electronegativity is an capability of a molecule for attracting electrons to itself in covalent bond. The results shown in high electronegativity value rapidly influences equalization and therefore low reactivity that predicts lower binding of platinum complex with DNA in **Table 4**.
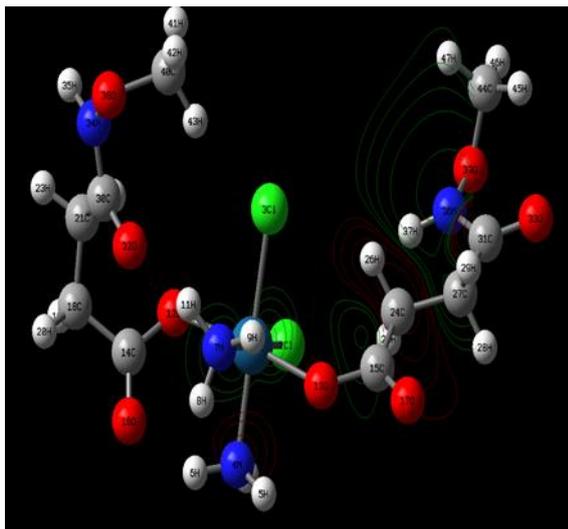
Fig. 5. Frontal molecular orbital's of 2D for platinum complex by DFT/ B3LYP/SDD at Level of theory
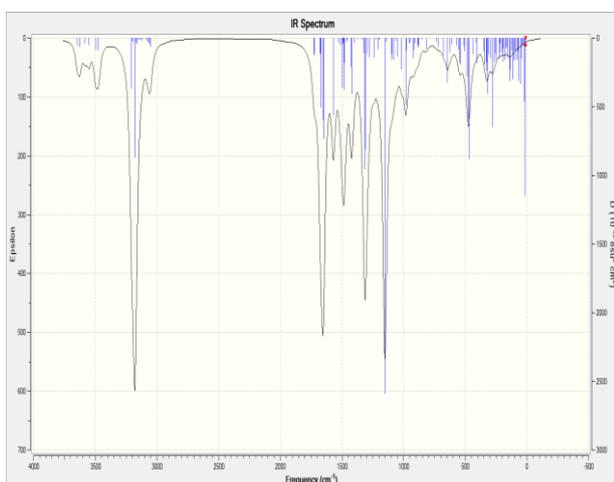

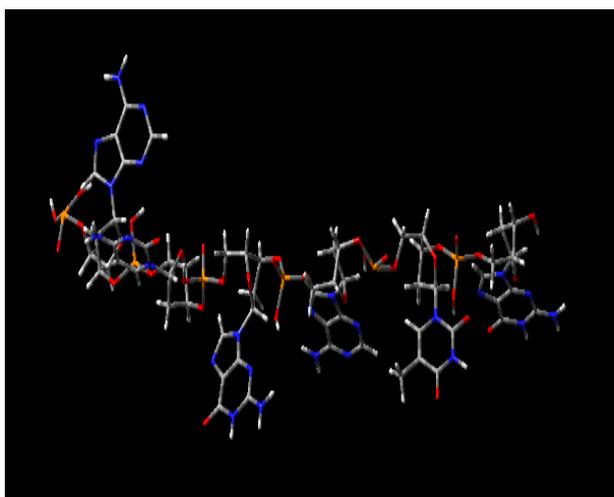**Fig. 6.** Infrared spectroscopy of platinum complex by DFT/ B3LYP/SDD at Level of theory

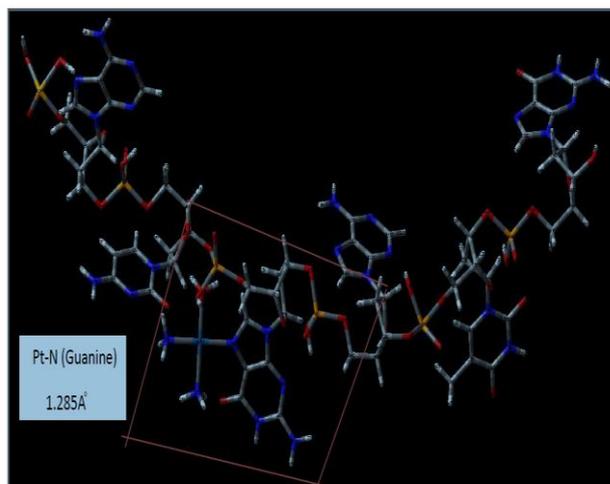**Fig. 7.** The infected fragment of DNA by Malignant cancer

Fig. 8. Binding platinum complex(II) with N-base for Guanine formations calculated by DFT/ B3LYP/SDD at Level of theory

generally appears in 322cm^{-1} in complex containing a chlorine atom [37,36].The υ (Pt-O) at 677cm^{-1} and υ (Pt-N) band appear is 508cm^{-1} (Booth,. 1992). The calculations of the theoretical vibrational decomposition of the platinum complex was performed using a Gussain09 program.

The comparison for binding Pt(IV) complex with N-bases

Cisplatin is platinum (II) complex containing two groups is Cis-chloride ligands and two ammine ligands. Pt-N(amine) bonds have been kinetically inert and thermodynamically stable. On the other hand, Pt-Cl bonds have been semi-labile and Pt-OH$_2$ are highly reactive (Zhang, et al., 2015). The chloride ligands can be slowly substituted by water (aquation) or by other nucleophiles as follow **Fig. 7**. Platinum stands for a soft metal. Based on the HSAB (hard soft acid base) theory, it has a greater affinity toward softer ligands which swiftly form strong bonds with the Pt(II) center. In this present, work of geometry optimization of DNA strand as fragment(A-C-G-A-T-G) in **Fig. 8** and binding with platinum complex for inhibition tumor. The binding to the DNA the non-amine ligands have exchanged through N7 atoms of dual adjacent guanines and adenine on the same DNA strand. The DNA stand is contained nucleobases (adenine or guanine) in the intrastrand cross-link as was the asymmetric platinum complex. The stability of structure through a formation of intra molecular covalent bond 1.285A,1.390A between platinum atom with Adenine and Guanine in DAN strand from low value of bond length indicate more stable. Also the minimum binding energies of platinum complex with Guanine compare Adenine refers to target of platinum complex to Guanine **Figs. 8** and **9**, from minimum binding energies gives greater cancer inhibition (Li, et al., 2017). **Figs. 8** and **9** indicate of the lowest value of binding energy is - 3512.75 Kcal.mol^{-1} of Guanine while
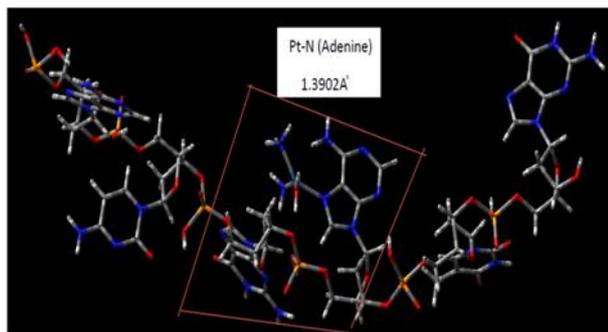
N) at1152cm^{-1}, 1650cm^{-1}, 1077 cm^{-1} and 1495 cm^{-1} respectively.The υ (Pt-Cl) stretching wavenumber

Fig. 9. Binding platinum complex(II) with N-base for Adenine formations calculated by DFT/ B3LYP/SDD at Level of theory

-5234.45 Kcal.mol^{-1} of Adenine. The enthalpy of reaction computed by DFT has a negative value which means the reaction is exothermic, but the spontaneous of Gibbs free energy for binding Platinum complex with DNA, indicate more reactive of Pt(II) complex for binding with DNA nucleobases: Adenine (A), Guanine (G).

CONCLUSION

In the study, the geometry molecular structural parameters have been similar in terms of bond angle, dihedral angle, bond length and vibrational frequencies of essential modes of enhanced geometry. They have been measured from DFT with diverse methods B3LYP, B3PW91 and CAMB3LYP, also the different basis set are Lan2DZ, LanL2MB and SDD. The HOMO-LUMO and energy gap was determined for getting the worldwide reactivity descriptors of platinum complex. The considered molecular features have potential perception of stability and activity of platinum complex and binding with DNA fragment.

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