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DFT-based prediction of anti-cancer activity of some organo-Pt^{IV} complexes

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Abstracts

Cancer is arguably the most feared of major diseases because of the suffering experienced from diagnosis to end of life. By 2025, the US forecasts 2 million more cases. Various cancer types exhibit different case numbers: 2.5 million lung cancer, 2.3 million breast cancer, 1.9 million colorectal cancer, 1.5 million prostate cancer, and 970,000 stomach cancer cases worldwide. By 2025, the US FDA has approved a spectrum of 300 to 600 anti-cancer medications that encompass surgery, chemotherapy, radiation, targeted therapies, immunotherapies, hormone therapies, monoclonal antibodies, cellular therapy/CART-cells, along with various new agents. The development and investigation of novel anticancer medications are difficult because of significant expenses and time limitations. The synthesis and study of new anticancer drugs are challenging due to high costs and time constraints. To overcome these problems, there is a need to modify existing drugs to enhance their activity with minimal or no adverse effects on human health. The study materials of the study are twenty-three Pt^{IV} complexes, along with four Pt^{II} complexes (cisplatin, carboplatin, oxaliplatin, and nedaplatin). The biological activities of the above-mentioned complexes were measured against human denocarcinoma (HCT116) and ovarian carcinoma (A2780) cells in terms of IC₅₀. This DFT-based study includes thermodynamics (TD) study (transformation of Pt^{IV} prodrugs into active Pt^{II} drugs), pharmacokinetics (PK) study; and prediction of biological activity using TD and PK properties. A comparative study of both models reflected that TD and PK properties have reliability and will give fruitful results if the anticancer activity of newly designed drugs of this group is predicted before their synthesis.

Keywords: Pt^{IV}–prodrugs; Active Pt^{II}–drugs; DFT; Pharmacokinetics; Thermodynamics; Anti-cancer activity

1. Introduction

Exploiting metals for therapeutic gain started by the use of Salvarsan. In fact, the medical application of metals and their complexes are as old as our civilization (*Galib et al., 2011; Bai et al., 2025; Abdolmaleki et al., 2025*). Further, in metallopharmaceuticals, transition metals (TMs) and their complexes (with neutral and (or) negatively charged ligands) gained a lot of attention due to range in oxidation states and coordination number, too (*Crans and, Kostenkova, 2020*). Organometallic complexes made up of organic ligands attached to the central metal gain significance in terms of their relevance to life-living to life-saving applications [5]. Among various TMs, platinum and their complexes have garnered in various areas (*Mudi et al., 2015; Praveen, 2022; Mauro et al., 2014; Albrecht and van Koten, 2001; Yoshida and Kato, 2025; Pedone et al., 2017; Chen, 2010*). The continuous advancement in comprehending the chemistry of platinum and its complexes is linked to their direct or indirect importance to various current concerns related to medicine (*Praveen, 2022*), photochemical biological systems (*Mauro et al., 2014*), materials science (*Albrecht and van Koten, 2001; Yoshida and Kato, 2025*), and nanoscience (*Pedone et al., 2017; Chen, 2010*). This occurs due to its flexible electron transfer pathways. Complex compounds that contain platinum have also been used as drugs to initiate or assist redox reactions (*Belluco, 1974*). Pt drugs dominate medical oncology treatment, with nearly 50% of all cancer treatments being Pt-based (<https://www.cancer.gov/about-cancer/treatment/drugs/cancer-drugs>).

Platinum compounds serve as strong electrophiles that attach directly to DNA, creating cross-links that hinder DNA synthesis and induce apoptosis in cancer cells (*Mukherjee et al., 2017*). The initial Pt-based therapy for cancer was cis-diamminedichloroplatinum(II), represented by the formula cis-[Pt(NH₃)₂Cl₂] and often referred to as cisplatin (*Soni et al., 2025*). Peyrone (1844) first synthesized it in 1844, and later, Rosenberg et al. (1965) inadvertently found the biological effects of this compound. They also found that square planar complexes ([Pt(en)Cl₂]) and octahedral complexes (cis-[Pt(NH₃)₂Cl₄] and [Pt(en)Cl₄]) show antitumor effects against sarcoma-180 (in mice) and murine leukemia (L-1210) cells. Harder and Rosenberg (1970) detailed the specific inhibition of DNA synthesis in vitro by cis-[Pt(NH₃)₂Cl₂] at levels below 5 μM. Cisplatin was first utilized in 1978 as a treatment for cancer and remains in use for managing cancers of the testicles, ovaries, bladder, and neck in individuals (*Helm and States, 2009; Usanova et al., 2010; Jiang et al., 2021; Szturz et al., 2019; Zhang et al., 2022*). Several well-known Pt^{II} complexes utilized for treating various cancer types are cisplatin, carboplatin, oxaliplatin, and nedaplatin, among others (*Zhang et al., 2022*). In the second-generation products, two chloride atoms are replaced by an oxygenated bidentate cyclobutanedicarboxylato group, producing carboplatin, which is easier to give and less toxic than cisplatin. Nonetheless, a comparable anticancer profile to cisplatin is exhibited by carboplatin, and cross-resistance with cisplatin is evident in numerous cancer types (*Wagstaff et al., 2022*). Oxaliplatin is a component of the third generation of platinum-predicated anticancer drugs (*Javier et al., 2026*), where the amine groups in cisplatin are superseded by the 1, 2-diaminocyclohexane (DACH) ligands. Fewer DNA adducts were beaten to be engendered by oxaliplatin, yet more preponderant cytotoxicity was induced compared to cisplatin, and more potent effects in colorectal and other gastrointestinal cancers were exhibited by it, whereas no efficacy is demonstrated by cisplatin and carboplatin. Nedaplatin, a platinum analogue from the second generation, received its initial approval in Japan (*Umemiya et al., 2026*). It is roughly ten times more soluble in water than cisplatin and has reduced toxicity compared to cisplatin. Encouraging outcomes are demonstrated by nedaplatin in conjunction with other therapies. Approval in China was received for lobaplatin (*McKeage, 2001*), a third-generation platinum analog, for the treatment of breast cancer, non-small cell lung cancer (NSCLC), and chronic myelogenous leukemia. Resistance to platinum-based chemotherapy is often developed by patients who initially respond favorably to platinum treatment for a brief period (*Zhou et al., 2020*). The resistance arises from (i) diminished cellular drug uptake, (ii) enhanced detoxification mechanisms, (iii) heightened DNA repair activity, (iv) reduced apoptosis, and (v) autophagy.

The platinum atom can form covalent bonds with the N7 positions of purine bases, creating platinum–DNA adducts (*Harder and Rosenberg, 1970*). Cisplatin can create mono adducts, as well as intra-strand and inter-strand cross-links, with 1,2-intra-strand cross-links representing more than 90%. It is widely recognized that the formation of DNA adducts is the crucial factor for the cytotoxic effects of platinum-based antitumor drugs, as the platinum–DNA complexes affect the configuration of the DNA double helix and nucleosomes. Consequently, it leads to the inhibition of replication and transcription and induces DNA double-strand breaks (DSBs), which are followed by the activation of DNA repair mechanisms. When DNA repair is unsuccessful or inundated with excessive DNA damage, cell death will occur. The enhanced DNA repair mechanism is viewed as the primary feature of platinum resistance (*Zhou et al., 2020*), except for

DNA mismatch repair, where a deficiency leads to resistance to cisplatin/carboplatin, but has a lesser impact on oxaliplatin. Oxaliplatin exhibits stronger cytotoxic effects compared to cisplatin in triggering early secondary DSBs and extensive apoptosis (Lai et al., 2026). Nevertheless, Bruno et al. (2017) indicated that oxaliplatin causes ribosome biogenesis stress instead of DNA damage to eliminate cells. The majority of intra-strand crosslinks are repaired by the nucleotide excision repair (NER) system, which removes damaged nucleotides and synthesizes new DNA to restore genetic integrity, whereas different types of lesions are fixed through intricate combined mechanisms.

Platinum-containing cancer medications, such as cisplatin (Rosenberg et al., 1965), carboplatin (Harder and Rosenberg, 1970), oxaliplatin (Helm and States, 2009), nedaplatin (Usanova et al., 2010), and lobaplatin (Jiang et al., 2021), are extensively utilized in chemotherapy treatments (Rosenberg et al., 1965). Nonetheless, the inherent or developed resistance significantly restricts the clinical use of platinum-based therapies (Szturz et al., 2019). The fundamental processes are exceedingly complex. Several transporters are involved in the active transport of platinum-based antitumor drugs, and any changes in expression levels, localization, or activity may significantly reduce cellular platinum levels. Resistance mechanisms, often heightened in tumor cells, can effectively bind to platinum compounds and inhibit the creation of platinum–DNA adducts (Chen and Holt-Hindle, 2010), yet the generation of these adducts is crucial for the cytotoxic effects of platinum-based antitumor drugs. Even when sufficient adducts are produced, tumor cells continue to survive by enhancing DNA repair mechanisms or raising their apoptosis threshold. Moreover, autophagy significantly affects platinum resistance. This evaluation summarizes the key contributors to platinum resistance mechanisms discussed earlier (Szturz et al., 2019) and emphasizes the most promising therapeutic targets or anticipated markers. By gaining a better insight into the fundamental resistance mechanisms, novel approaches would be developed to significantly broaden the clinical use of platinum-based cancer treatments.

Pt^{IV} complexes (Iova et al., 2025) are substitution-inert and therefore resistant to hydrolysis by gastric acids. The substitution reactions of these complexes occur at a much slower rate than their Pt^{II} counterparts. Tumor tissues with low oxygen levels promote the conversion of Pt^{IV} complexes into Pt^{II} forms (Figure 1). In these states, they execute their cytotoxic functions.

Figure 1. General scheme of the two-electron reduction of Pt^{IV} complexes to Pt^{II} complexes.

Literature analysis shows that designing new ligands that can form complexes with platinum in different oxidation states may lead to the creation of innovative materials (Cheng et al., 2026). These complex compounds can originate from their fundamental compounds or via substitution reactions of already synthesized complex compounds. Creating new molecules and studying their various properties in the lab is difficult due to high costs and lengthy time demands. At present, chemistry, alongside physics and computer science, has shifted from concentrating on the creation of a molecule to identifying which molecule to synthesize, essentially focusing on molecule design.

The growth of computational chemistry and software has introduced a quantitative dimension to the relationship between a molecule, its properties, its synthesis, and thus its numerous applications, bodily functions at a molecular level. Numerous innovative treatment strategies (Zheng et al., 2026; Sahu et al., 2026; <https://www.cancer.gov/about-cancer/treatment/drugs/cancer-drugs>; <https://www.cancer.gov/about-cancer/treatment/side-effects/nutrition>; Kenny et al., 2017) have been investigated to address limitations related to current therapies, including those linked to platinum-based drugs. To utilize various kinds of nanotechnologies for selectively delivering cytotoxic agents, such as Pt^{IV} compounds (Cheng et al., 2026), to tumor cells as investigated by multiple researchers. Pt^{IV}-prodrugs have “magic-bullet-like” characteristics that enable them to experience specific transformations in vivo, leading to the release of active drugs at their site of action. Pt^{IV}-prodrugs present a promising option compared to their Pt^{II} counterparts (Kenny et al., 2017). In this study, twenty-three Pt^{IV} complexes (prodrugs) and four Pt^{II} complexes, depicted in Table 1, were examined.

Table 1. Structure of twenty-three Pt^{IV} complexes along with four Pt^{II} complexes.

The research focuses on thermodynamics followed by pharmacokinetics. To maintain clarity, these studies have been addressed in distinct sections:

2. Materials and Methods

The study materials of the study are twenty-three Pt^{IV} complexes, along with four Pt^{II} complexes listed in Table 1. The biological activities of the above-mentioned complexes were measured against human denocarcinoma (HCT116) and ovarian carcinoma (A2780) cells, in terms of IC₅₀ (Gramatica et al., 2010), as shown in Table 6. The research encompasses: (i) a thermodynamic analysis of the conversion of Pt^{IV} prodrugs (all twenty-three complexes) into active Pt^{II} drugs, by determining three well-known thermodynamic property: Δ_rH , Δ_rS and Δ_rG (Karl, 2012). The redox reaction, which involves the conversion of Pt^{IV} complexes to Pt^{II} complexes, along with associated thermochemical calculations, was conducted using DFT (RPBE1PBE method and SDD basis set) on Gaussian-16 (Kostjukova et al., 2021; Frisch et al., 2016). The work of Buhl et al. on geometries of third-row transition-metal complexes from DFT theory described the selection of various basis sets in DFT-based studies (Buhl et al., 2008). In our previous work on the Pt-metal (a third row transition metal) complex, i.e., cisplatin we utilized the concepts of Buhl et al. (2008) and results obtained were reliable (Soni et al., 2025). Hence, in this study, for the thermodynamic study we followed the same method; (ii) a pharmacokinetics analysis of the complexes based on Lipinski's extended rule of five was made (Sahu et al., 2022). The PK properties were acquired by optimizing the aforementioned complexes with DFT-B88LYP using the DZYP basis (Singhal et al., 2014) set on Fujitsu's CAChe Pro Software (Crouch et al., 1996; Rajamani, 2004), as prior research of our research group utilized this DFT method and yielded significant results (Singhal et al., 2014; Singh and Raja, 2011). The outputs obtained from the two distinct studies were utilized to forecast the anti-cancer efficacy of Pt^{IV} complexes in conjunction with four Pt^{II} complexes. To avoid error and achieve homogeneity in the statistical analysis, all the twenty-seven compounds were optimized by using the same DFT method on the same software. For this, all the compounds were optimized with DFT-B88LYP using the DZYP basis set on Fujitsu's CAChe Pro Software (Singhal et al., 2014) and presented in Table 6. The reason for selection of this DFT method is that in prior research we have utilized this DFT method and significant results were obtained. The methods used for predicting activity are also clearly detailed in our earlier publication along with statistical evaluation, which was conducted on the project leader software linked to CAChe software using leave-out techniques (Singhal et al., 2014).

3. Results and Discussion

Undoubtedly, the domain of medical oncology has grown swiftly, propelled in part by technological advancements that have enabled a more profound comprehension of bodily functions at a molecular level. Numerous innovative treatment strategies (Hammes, 2022; Sabater, 2022; Hill, 2012; Klotz, 2012; Williams and Lemke, 2002) have been investigated to address limitations related to current therapies, including those linked to platinum-based drugs. To utilize various kinds of nanotechnologies for selectively delivering cytotoxic agents, such as Pt^{IV} compounds (Cheng et al., 2026), to tumor cells as investigated by multiple researchers. Pt^{IV}-prodrugs have “magic-bullet-like” characteristics that enable them to experience specific transformations in vivo, leading to the release of active drugs at their site of action. Pt^{IV}-prodrugs present a promising option compared to their Pt^{II} counterparts (Williams and Lemke, 2002). In this study, twenty-three Pt^{IV} complexes (prodrugs) and four Pt^{II} complexes, detailed in Table-1, were examined. The research focuses on thermodynamics followed by pharmacokinetics. To maintain clarity, these studies have been addressed in distinct sections:

3.1. Study Based on Thermodynamics

Here, we studied the general transformation of Pt^{IV} complexes into Pt^{II} complexes (in silico reduction), which in vivo is generally initiated by glutathione (GSH) (Wu et al., 2004), that leads to the release of axial ligands and the formation of the active square planar Pt^{II} species as shown in figure 2, that interacts with DNA, an essential step in the activation of their anticancer prodrugs (Hall et al., 2006).

Figure 2. The general transformation of Pt^{IV} complexes into Pt^{II} complexes by glutathione (GSH).

This conversion is essential for biological function, transmuting the dormant Pt^{IV} into the active Pt^{II} form, frequently accompanied by the concurrent relinquishment of bioactive axial ligands, facilitating double therapeutic effects. Glutathione (GSH) maintains redox balance by acting as an essential cellular antioxidant, converting into oxidized glutathione (GSSG). This cycle is completed by glutathione reductase (GR), which leverages NADPH (obtained from the pentose phosphate pathway) to transform GSSG into GSH, creating a crucial GSH/GSSG ratio that signifies cellular wellness (Owen and Butterfield, 2010). The

transformation of all the twenty-three Pt^{IV} complexes into Pt^{II} complexes presented in Scheme 1 to 3, which explains these transformations along with forming active Pt^{II} drugs.

Scheme 1. Transformation of Pt^{IV}–prodrugs (complex no. 1 to 10) into active Pt^{II}–drug (complex).

Scheme 2. Transformation of Pt^{IV}–prodrugs (complex no. 11 to 16) into active Pt^{II}–drug (complex).

Scheme 3. Transformation of Pt^{IV}–prodrugs (complex no. 17 to 23) into active Pt^{II}–drug (complex).

The conversion essentially removes two trans-ligands along the z-axis. As the axial ligands withdraw, the ligands in the (xy) plane draw closer to the metal center. The chemical thermodynamics of the above conversion were studied by enthalpy change of reaction ($\Delta_r H^\circ$), entropy change of reaction ($\Delta_r S^\circ$) and free energy change of reaction ($\Delta_r G^\circ$). The values of the above energy changes were obtained by solving the three equations given below and were tabulated in Tables 2, 3 and 4, respectively.

$$\Delta_r H^\circ = \sum_{products} \Delta_f H^\circ_{prod} - \sum_{reactants} \Delta_f H^\circ_{react} \quad Eq. (i)$$

$$\Delta_r S^\circ = \sum S_{products} - \sum S_{reactants} \quad Eq. (ii)$$

$$\Delta_r G^\circ = \sum G_{products} - \sum G_{reactants} \quad Eq. (iii)$$

3.1.1. Enthalpies of transformation of Pt^{IV}–prodrug to active Pt^{II}–drug

The enthalpy of the conversion of Pt^{IV}–complexes to active Pt^{II}–complexes (Hammes, 2010) was calculated by solving the Eq. (i) and was tabulated in Table 2. A close look at Table 2 shows that the enthalpy's change of transformation Pt^{IV} complexes (1-10, 16 and 18) to Pt^{II} complexes are endothermic and thus taken place with absorption of heat because the total enthalpy of products is more than the total enthalpy of reactant, i.e., $\Sigma H_P > \Sigma H_R$, hence $\Delta_r H^\circ$ are positive. While complexes no. 11-15, 17, and 19-23 (a total of eleven Pt^{IV} complexes) transformed into Pt^{II} active products with evolution of heat and thus exothermic and only exothermic transformations are spontaneous. Compounds no. 17, 18 and 19 have the same parent skeleton but differ in their axial ligands. The axial ligands in these compounds are —OC(O)CH₃, —OC(O)(CH₂)₂CH₃ and —OC(O)(CH₂)₅CH₃, respectively. Further, in axial ligands, the change in number of —(CH₂)_n—moiety changes their anti-cancerous activity 0.49 (n = 0), 0.025 (n = 2) and 0.0009 (n = 5) against A2780, and 171, 0.041 and 0.0014 against HCT116. This abnormal change in their activities is due to change in carbon chain of axial ligands that also changed their thermodynamic properties. The transformation of complex no. 19 has $\Delta_r H^\circ = -127914.87$ kcal/mol, because of the presence of two —OC(O)(CH₂)₅CH₃ moieties as the leaving group. And its active Pt^{II} prodrug showed anti-cancer activity against HCT116 and A2780 of 0.0014 μ M (IC₅₀) and 0.0009 μ M (IC₅₀), respectively. Further, complex no. 11, 12, 13, 14, 15, 17, 20, 21, 22, 23 showed standard enthalpy change of reactions -109.03, -353.19, -748.96, -427.81, -647.95, -357.68, -336.84, -363.43, -596.29 and -796.24 kcal/mol., respectively. And their anticancer activities in terms of IC₅₀ (μ M) against HCT116(A2780) are 116.63(26.63), 143.57(54.18), 161.14(24.63), 130.80(25.43), 23.25(8.04), 1.71(0.49), 0.041(0.025), 23.28(10.01), 2.00(1.05), 0.051(0.02), 0.00165(0.00039), respectively.

Table 2. Enthalpies of reactions of all the twenty-three Pt^{IV} complexes as obtained by solving the equation: $\Delta_r H^\circ = \Sigma \Delta_f H^\circ_{prod} - \Sigma \Delta_f H^\circ_{react}$

3.1.2. Entropies of transformation of Pt^{IV}–prodrug to active Pt^{II}–drug

Whenever a spontaneous process takes place, it is accompanied by an increase in the total entropy of the universe (system/drug + surrounding/ cytoplasm/nucleoplasm, where a reaction is taking place). The entropy change (Sabater, 2022) of the conversion of Pt^{IV} complexes to active Pt^{II} complexes was calculated by solving the Eq. (ii) and was tabulated in Table 3. A close look at Table 3 shows that the entropic change of transformation Pt^{IV} complexes to Pt^{II} complexes are spontaneous as all conversion have positive values of entropy of reaction ($\Delta_r S^\circ$) except complex no. 19, that show a negative value. The Pt^{IV} complex in cancer

cells is converted into an active Pt^{II} complex which is induced by hypoxia condition, and then performs its cytotoxic activity. If we compare the cytotoxic activity of Pt^{IV} complex no. 1-10, with cisplatin then we have found that complex no. 1,2,4,5,6,7,8,9 have better activity against A2780 than cisplatin ($\text{IC}_{50} = 8.74 \mu\text{M}$). Among these eight complexes, five give much better results than cisplatin. These are complex no. 8(0.043/72.982), 9(0.059/115.589), 7(0.191/71.315), 6(1.48/72.595), and 2(1.52/50.290), in bracket are activity/total entropy of the reaction. While against HCL116 ($\text{IC}_{50} = 2.26 \mu\text{M}$), the complexes are 8(0.035/72.982), 9(0.091/115.589), 7(0.298/71.315), and 6(2.05/72.595). Among seven complexes, complex no. 11-16, which on transformation into Pt^{II} give carboplatin as an active drug, five have better activity against A2780 than carboplatin ($\text{IC}_{50} = 50.9 \mu\text{M}$). These are complex no. 15(8.04/42.813), 13(24.63/60.105), 14(25.43/60.444), and 11(26.63/38.092). Among the rest of the seven complexes, the lowest all show reliable activity against both A2780 and HCT116, except compound no. 20(10.1/45.247). The lowest activity is shown by complex no. 23 and 19 as their active Pt^{II} drugs and Pt^{IV} prodrugs have similar structures except a difference that is the free cyclohexane ring attached to nitrogen of the $\text{NH}_2\text{—Pt}^{\text{IV}}$ moiety in compound no. 23 and also in active Pt^{II} drug.

Table 3. Entropies of reactions of all the twenty-three Pt^{IV} complexes as obtained by solving the equation: $\Delta_r S^\circ = \Sigma \Delta_f S^\circ_{\text{prod}} - \Sigma \Delta_f S^\circ_{\text{react}}$

3.1.3. Free energy of transformation of Pt^{IV} –prodrug to active Pt^{II} –drug

Whenever a spontaneous process takes place, it is accompanied by a decrease in the total free energy of the system. The free energy change (*Hill, 2012*) of the conversion of Pt^{IV} –complexes to active Pt^{II} –complexes was calculated by solving the Eq. (iii) and was tabulated in Table 4. A close look at Table 4 shows that all the free energy transformation from Pt^{IV} complexes to Pt^{II} complexes has a negative value of ($-\Delta_r G^\circ$), except complex no. 16 and 18, these have positive values. It means all conversions are spontaneous, except the two. The trend of free energy changes along with activity in increasing order is 9(-235.45/0.059) < 10(-235.40/29.69) < 4(-235.35/5.32) < 8(-235.28/0.043) < 7(-235.18/0.191) < 6(-235.05/1.48) < 5(-234.90/5.93) < 3(-234.77/9.48) < 2(-234.62/1.52) < 1(-234.38/8.11) < 19(-203.85/0.0009) < 13(-1.22/24.63) < 23(-1.19/0.00039) < 15(-1.05/8.04) < 22(-0.98/0.02) < 14(-0.71/25.43) < 21(-0.61/1.05) < 12(-0.59/54.18) < 17(-0.59/0.49) < 20(-0.56/10.01) < 11(-0.19/26.63) < 16(60.63/103.35) < 18(79.03/0.025), here in brackets are free energy changes and activity against A2780. While for HCT166 the trend is 9(-235.45/0.091) < 10(-235.40/183.36) < 4(-235.35/16.2) < 8(-235.28/0.035) < 7(-235.18/0.298) < 6(-235.05/2.05) < 5(-234.90/30.11) < 3(-234.77/33.26) < 2(-234.62/11.87) < 1(-234.38/33.29) < 19(-203.85/0.0014) < 13(-1.22/161.14) < 23(-1.19/0.00165) < 15(-1.05/23.25) < 22(-0.98/0.051) < 14(-0.71/130.8) < 21(-0.61/2.00) < 12(-0.59/143.57) < 17(-0.59/1.71) < 20(-0.56/23.28) < 11(-0.19/116.63) < 16(60.63/111.47) < 18(79.03/0.041). Complex no. 18 has a positive value of free energy change of reaction but has reliable activity in comparison to complex no. 16, which is due to the presence of carboxylic acid moieties in its leaving groups.

Table 4. Free energies of reactions of all the twenty-three Pt^{IV} complexes as obtained by solving the equation: $\Delta_r G^\circ = \Sigma \Delta_f G^\circ_{\text{prod}} - \Sigma \Delta_f G^\circ_{\text{react}}$

3.1.4. Change in total energy (ΔE_T) of transformation of Pt^{IV} –prodrug to active Pt^{II} –drug

The overall energy change, as presented in Table 5, of the above reaction is the total energy absorbed to break bonds and the total energy released when new bonds form. This net difference commands whether the reaction releases heat onto its surroundings or absorbs it. If the overall energy change is negative, then the reaction is exothermic and energy is absorbed from the surrounding, causing the temperature of the immediate environment to drop (photosynthesis). While, if the overall energy change is positive, then the reaction is endothermic and energy (cellular respiration) is transferred to the surrounding environment, causing the temperature of the immediate environment to increase. A close look at Table 5 shows that complexes no. 1-10, 16 and 18 follow an endothermic route, while complexes no. 11-15, 17, 19-23 follow exothermic routes similar to enthalpies energy during the above transformations (*Klotz, 2012*).

Table 5. Change in total energy (ΔE) of products during the transformation of PtIV complex to PtII was obtained by solving the equation: $\Delta E = \Sigma E_{\text{prod}} - \Sigma E_{\text{react}}$

3.2. Study based on pharmacokinetics

A mathematical framework is offered by pharmacokinetics (PK) to evaluate the temporal progression of drugs and their impacts within the body (*Williams and Lemke, 2002*). The quantification of processes such as absorption, distribution, metabolism, excretion, and toxicity is allowed. The concentration of drugs in the body is assessed by these pharmacokinetic processes, commonly called ADMET (*Norinder and Bergstrom, 2006*), when medications are given. A suitable treatment plan for a patient is essential to be created based on a basic comprehension of these factors. In this study, Lipinski's rule of five (RO5) in extended form (*Sahu et al., 2022*), as depicted in figure 3, was initially utilized by us on twenty-seven compounds mentioned above for pharmacokinetic analysis

Molecular Weight (Rule 1)

According to the RO5, it is mentioned that molecular weights above 500 are unhelpful, leading to decreased absorption. Van de Waterbeemd et al. (2001) have likewise proposed a low molecular weight for the compound for oral uptake. The molecular weight for every compound was ascertained through an internal approach relying on the molecular formula. The increasing order of molecular weight is: 300.057 (24) > 303.187 (27) > 334.071 (01) > 337.201 (11) > 370.963 (02) > 371.262 (25) > 397.3 (26) > 418.146 (03) > 421.276 (12) > 444.184 (20) > 446.199 (05) > 449.329 (14) > 474.253 (06) > 498.275 (17) > 500.291 (21) > 502.307 (07) > 526.089 (04) > 529.219 (13) > 530.36 (08) > 533.49 (15) > 534.219 (10) > 537.349 (16) > 554.382 (18) > 558.414 (09) > 638.543 (19) > 640.559 (23). Data shows that compounds numbered 4, 7, 8, 9, 10, 13, 15, 16, 18, 19, 21, 22, and 23 do not meet the criteria of Rule 1. Drug candidates that violate Rule 1 tend to show low solubility and are likely to have difficulty permeating cell membranes [48]. Thus, of the twenty-seven compounds, it is observed that merely fourteen demonstrate consistent solubility and the ability to cross cell membranes.

Log P (Rule 2)

Lipophilicity (the ratio of solubility in octanol compared to solubility in water) was evaluated using log P. The octanol-water partition coefficient is linked to forecasting penetration and permeability across the BBB (*Hansch et al., 1987*). For a medication to be absorbed through the mouth, it generally needs to first pass through lipid bilayers in the intestinal epithelium (a procedure known as trans-cellular transport). For effective transport, the drug must be adequately hydrophobic to blend into the lipid bilayer, but not overly hydrophobic to hinder its release from the bilayer after incorporation. In the same way, the spread of drugs in the body after absorption is greatly affected by hydrophobicity, which in turn influences the speed of their metabolism and elimination. A negative log P value indicates that the compound is more hydrophilic than lipophilic. It tends to remain in blood plasma and extracellular fluids instead of easily moving through cell membranes (lipid bilayer) by passive diffusion. These compounds are typically more readily eliminated by the kidneys. The log P for every compound was calculated using the atom-typing approach of Ghose and Crippen (1986) and is displayed here in increasing order: -2.641(16) < -2.225(12) < -1.791(11) < -1.217(10) < -0.968(14) < -0.922(25) < -0.8(03) < -0.687(24) < -0.485(20) < -0.4(26) < -0.367(01) < -0.002(13) < 0.456(05) < 0.582(02) < 0.774(17) < 1.031(21) < 1.249(06) < 1.41(15) < 1.422(04) < 2.041(07) < 2.823(18) < 2.834(08) < 3.626(09) < 3.873(22) < 5.201(19) < 5.458(23) < 14.91(27). Compounds labeled 1, 3, 10-14, 16, 20, and 24-27 showed a negative log P value, indicating that these medications are mainly administered through intravenous routes to prevent these issues. Compounds 4, 6, 15, and 18 conform to Rule 2, while compounds 19 and 23 exhibit a log P greater than 5 and fail to meet the criteria of Rule 2. Molecules that exhibit moderate lipophilicity are more inclined to reach the receptor site (*Buchwald and Bodor, 1998; Clark, 1999*).

Hydrogen Bonding

The capacity of a drug solute to create hydrogen bonds is now recognized as an important element affecting permeability. Hydrogen bonding, in addition to molecular size and polarity, has been identified as one of the main factors influencing these processes. The importance of hydrogen bonding, in conjunction with lipophilicity (either measured or computed), has been recognized as a contributor to permeability and absorption mechanisms. A robust hydrogen binding ability, either as a donor or acceptor, combined with

considerable steric hindrance, adversely affects effective permeation. Undoubtedly, hydrogen bonding affects membrane transport and the distribution of drugs within the biological system. Increased levels might obstruct permeability across the membrane bilayer. The physicochemical properties (solubility, adsorption, distribution) of a molecule are known to be affected by the number of hydrogen bond donors and acceptors, thus influencing a drug's efficacy. RO5 suggests that to improve permeation and absorption, a ligand should have no more than 5 donors and 10 acceptors (*Raevsky and Schaper, 1998*).

H-bond donors (Rule 3)

The count of hydrogen bond donors in each compound was determined by totaling the NH and OH groups from their structural formula and is presented here in increasing order: 4(18) = 4(19) = 4(20) = 4(26) < 5(21) = 5(22) = 5(23) < 6(02) = 6(03) = 6(04) = 6(05) = 6(06) = 6(07) = 6(08) = 6(12) = 6(13) = 6(14) = 6(15) = 6(17) = 6(24) = 6(25) = 6(27) < 8(01) = 8(09) = 8(10) = 8(11) = 8(16). A mention of this data indicates that it is noted that compounds numbers. Numbers 17, 18, 19, 20, 21, 22, 23, and 26 adhere to Rule 3 and are recognized for their dependable polarity, which enhances permeation and absorption. It is observed that compound numbers 2, 3, 4, 5, 6, 7, 8, 12, 13, 14, 15, 24, 25, and 27 show a small divergence from Rule 3 owing to the existence of an additional hydrogen bond donor (HD = 6). It is observed that compounds numbers. 9, 10, 11, and 16 violate Rule 3 since it is established that their HD is equal to six. It is determined that these four compounds possess greater polarity, which is considered inadequate for permeation and absorption (*Raevsky and Schaper, 1998*).

H-bond acceptors (Rule 4)

The number of hydrogen bond acceptors in each compound was counted by counting the sum of N and O atoms from their molecular formula and is presented here in increasing order: 2(02) = 2(24) < 4(01) < 5(27) < 6(03) = 6(04) = 6(05) = 6(06) = 6(07) = 6(08) = 6(17) = 6(18) = 6(19) = 6(20) = 6(21) = 6(22) = 6(23) = 6(25) = 6(26) < 7(11) < 8(09) < 9(12) = 9(13) = 9(14) = 9(15) < 10(10) < 13(16). It has been revealed by reference to these data that, except for compound no. 16, Rule 4 is followed by all compounds which possess reliable polarity for better permeation and absorption. It is likely believed that compound no. 16 is too polar to pass through the cell membrane (*Sahu et al., 2022; Raevsky and Schaper, 1998*).

Extended RO5

Consequently or naturally, in the spirit of five, it could be considered that the comprehensive sum of H-bond donors and acceptors (HD + HA) limits for drug-like compounds is 12, while it could be considered that the number of rotatable bonds (Rot. Bond) limit for drug-like compounds is 10. It must then be ensured that Lipinski's rule of five is extended to include the comprehensive sum of H-bond donors and acceptors and rotatable bonds, thereby resulting in the establishment of the fifth and sixth rules (*Sahu et al., 2022*).

Sum of H-bond donors and acceptors (Rule 5)

Stenberg et al. discovered that polar surface area is a key factor influencing fraction absorption. The total counts of H-bond donors and acceptors have also been identified as a secondary factor influencing fraction absorption. The total amount of HA + HD in each compound was calculated by adding HD and HA together, and presented here in increasing order: 8(02) = 8(24) < 10(17) = 10(18) = 10(19) = 10(20) = 10(26) < 11(21) = 11(22) = 11(23) = 11(27) < 12(01) = 12(03) = 12(04) = 12(05) = 12(06) = 12(07) = 12(08) = 12(25) < 14(09) < 15(11) = 15(12) = 15(13) = 15(14) = 15(15) < 18(10) < 21(16). A review of these data indicates that compounds 1-8 and 17-27 comply with Rule 5, whereas compounds 10-16 do not comply with Rule 5. Out of the twenty-seven compounds, twenty (1-8, 17-27) demonstrate stable polarity for improved permeation and absorption, while the remaining seven (10-16) show variable polarity which results in insufficient permeation and absorption due to the excessive energy required to separate these compounds for passage through the lipid membrane (*Van de Waterbeemd et al., 2001*).

Number of rotatable bonds (Rule 6)

This straightforward topological parameter assesses the flexibility of molecules. It has proven to be an excellent indicator of the oral bioavailability of medications. The bioavailability refers to the proportion of the dose that enters the bloodstream. A rotatable bond is characterized as any single non-ring bond attached to a non-terminal heavy atom (i.e., not hydrogen). Amide C-N bonds are excluded due to their elevated rotational energy barrier. The number of rotatable bond for each compound is presented here: 0(26)

$< 2(02) = 2(24) = 2(25) = 2(27) < 4(01) = 4(11) < 6(03) = 6(04) = 6(17) = 6(20) < 8(05) = 8(12) = 8(13) < 9(21) < 10(06) = 10(14) = 10(18) < 14(07) = 14(10) = 14(16) < 15(22) < 16(08) = 16(15) = 16(19) < 18(09) = 18(23)$. A look at these data shows that compounds no. 1-6, 11-14, 17, 18, 20, 21, 24-27 adhere to Rule 6, whereas compounds 7-10, 15, 16, 19, and 23 violate Rule 6. Therefore, among twenty-seven eight compounds, six violate Rule 6 as the Rot. Bond exceeds the boundaries. Consequently, all these substances exhibit low oral bioavailability of medications (Kola and Landis, 2010).

3.3. Prediction of activity

In the foregoing sections, first we studied the thermodynamics of conversion of twenty-three Pt^{IV} prodrugs into active Pt^{II} drugs (in silico) and the results obtained ($\Delta_r H$, $\Delta_r S$, $\Delta_r G$) were used to explain the above conversion, their feasibility and its impact on experimental activity. Secondly, we studied the pharmacokinetics of twenty-three Pt^{IV} complexes along with four Pt^{II} complexes. Thus, a total of twenty-seven complexes were explain here with their absorption, distribution, metabolism, excretion and toxicity based on the Lipinski rule of five in extended form. The results obtained from both the ongoing studies catalyzed us to develop a statistical model to correlate the anti-cancer activity of twenty-seven Pt-complexes against TD and PK properties. The TD properties of the complexes selected here are enthalpy (H), entropy (S), free energy (G), total energy (E_T) and heat capacity (C). These are general thermodynamic properties used to study the thermochemistry of a compound. In the case of PK, the properties are the same as we studied in section 3.2. To explain well, the prediction of activity is studied into two subsections.

3.3.1. Prediction of activity based on TD property

The TD properties: total energy, enthalpy, entropy, free energy and heat capacity selected for the prediction of anticancer activity of the above Pt^{IV} complexes were defined by the equations (Eq. iv to Eq. xii) and applied to all the twenty-seven complexes. For the sake of simplicity, each TD property with respect to the above complexes was well-defined and described separately as given below.

Total Energy (TD-1)

Total energy (E_T) of a molecular system (Klotz, 2012) is the sum of the total electronic energy, E_{ee} , and the energy of internuclear repulsion, E_{nr} . The total electronic energy and the energy of internuclear repulsion of the system is given by

$$E_T = E_{ee} + E_{nr} \quad \text{Eq. (iv)}$$

$$E_{ee} = \frac{1}{2} P(H + F) \quad \text{Eq. (v)}$$

$$E_{nr} = V_{rep} = \frac{Z_1 Z_2 e^2}{4\pi\epsilon_0 r} \quad \text{Eq. (vi)}$$

where P is the density matrix and H is the one electron matrix, F is the fock matrix, V_{rep} is the electrostatic potential energy between positive charged nuclei of two atoms, Z_1 and Z_2 are atomic numbers of two interacting particles, e is the elementary charge of a proton/electron (1.602×10^{-19}), ϵ_0 is the permittivity of free space (8.854×10^{12} F/m), r is the distance of separation between the centers of the two charges. Total energy is the absolute energy of a molecule or crystal in a specific arrangement; the most stable structure has the lowest E_T . The total energy is presented here in increasing order: $-2028.27(04) < -1995.57(19) < -1980.13(02) < -1972.95(23) < -1889.7(10) < -1854.53(22) < -1834.27(18) < -1792.23(09) < -1733.19(08) < -1698.95(17) < -1686.79(07) < -1677.77(21) < -1554.67(06) < -1548.26(05) < -1533.28(20) < -1477.44(03) < -1398.28(13) < -1266.55(16) < -1211.43(01) < -1113.49(15) < -1059.8(24) < -913.299(14) < -842.744(12) < -691.552(26) < -631.774(25) < -560.128(11) < -414.853(27)$

Enthalpy (TD-2)

Enthalpy (H) is a thermodynamic property that measures the total heat content of a system (Hammes, 2000).

$$H = E_{int} + H_{trans} + H_{rot} + H_{vib} \quad \text{Eq. (vii)}$$

where E_{int} is the internal energy of the reactant (the total QM or MM energy), H_{trans} is the translational enthalpy, which is $2.5RT$ for any molecule (where R is the gas constant and T is the absolute temperature).

H_{rot} is the rotational enthalpy, which is RT for linear molecule, $1.5RT$ for linear molecule, and vanishes for atom. H_{vib} is the vibrational enthalpy, which depends on the $3N - 5$ (linear molecule) or $3N - 6$ (non-linear molecule). In other words, it is the sum of the system's internal energy (U) and the product of its pressure (P) and volume (V), as given below.

$$H = U + PV \quad \text{Eq. (viii)}$$

The enthalpy is presented here in increasing order: $-1238266(02) < -757065(01) < -662582(24) < 6.929(27) < 8.932(25) < 9.671(11) < 9.778(26) < 12.504(03) < 12.66(20) < 12.7(05) < 13.661(12) < 14.054(04) < 14.296(17) < 15.363(14) < 15.464(06) < 16.099(21) < 16.235(13) < 16.68(08) < 17.42(07) < 17.982(10) < 18.198(18) < 18.382(15) < 19.019(16) < 19.165(09) < 21.291(22) < 22.849(19) < 24.253(23)$.

Entropy (TD-3)

Like enthalpy, entropy (S) (Sabater, 2022) is given by

$$S = S_{trans} + S_{rot} + S_{vib} \quad \text{Eq. (ix)}$$

where S_{trans} is the translational entropy, which depends on the molar mass of the molecule, S_{rot} is the rotational entropy depends on the symmetry number and the moments of inertia of the molecule, and S_{vib} is vibrational entropy depending on the vibrational frequencies. Throughout the article, all entropies are discussed in energy terms, $T\Delta S$ at $T = 298.15$ K. The entropy is presented here in increasing order: $75.375(02) < 75.475(24) < 77.642(01) < 103.303(27) < 116.882(25) < 121.513(11) < 122.206(26) < 141.569(03) < 143.151(05) < 144.805(20) < 154.992(12) < 156.019(04) < 158.03(17) < 167.374(06) < 170.679(14) < 174.63(21) < 175.899(08) < 178.065(13) < 188.09(15) < 189.288(07) < 191.999(18) < 194.832(09) < 197.287(10) < 205.927(16) < 220.017(22) < 229.542(19) < 244.153(23)$.

Free Energy (TD-4)

The free energy (Hill, 2012) is calculated from

$$G = H - TS \quad \text{Eq. (x)}$$

where H is the enthalpy, T is the absolute temperature, and S is the entropy. A compound is most stable when its Gibbs free energy is at its lowest possible value for given conditions (temperature, pressure). The free energy is presented here in increasing order: $-1238289(02) < -757088(01) < -662605(24) < -606.05(13) < -530.072(16) < -526.551(04) < -456.538(10) < -382.752(15) < -361.272(23) < -345.197(14) < -345.193(19) < -331.971(12) < -327.259(22) < -324.846(09) < -308.336(08) < -302.618(07) < -301.476(18) < -285.943(21) < -284.17(06) < -272.03(17) < -266.034(05) < -257.133(03) < -248.534(20) < -213.561(11) < -194.924(26) < -184.01(25) < -138.206(27)$.

Heat Capacity (TD-5)

The change in heat capacity (Klotz, 2012) is obtained without resorting to the calculation of ΔG : at constant pressure, in fact, we have

$$\Delta C_p = \left(\frac{\partial E}{\partial T} \right)_p \quad \text{Eq. (xii)}$$

Heat capacity is presented here in increasing order: $0.014(02) < 0.017(24) < 0.018(01) < 0.036(27) < 0.051(11) < 0.051(25) < 0.058(26) < 0.065(03) < 0.068(20) < 0.069(05) < 0.073(12) < 0.075(04) < 0.081(17) < 0.083(06) < 0.083(14) < 0.087(13) < 0.088(21) < 0.093(07) < 0.094(10) < 0.095(08) < 0.102(18) < 0.103(16) < 0.105(15) < 0.106(09) < 0.118(22) < 0.13(19) < 0.136(23)$.

For QSAR analysis, the biological activities (IC₅₀ data of the compounds against (i) HCT116 human adenocarcinoma and (ii) A2780 ovarian carcinoma cells) were used as dependent variables and the above TD properties as independent. A huge number of models were developed but only top five models were selected and presented here. Equations 1–5 were selected for predicting anticancer activity of (i) human adenocarcinoma (HCT116), while equations 6–10 for (ii) ovarian carcinoma cells (A2780). These equations

were, screened in on the basis of correlation coefficient (r^2), cross-validated correlation coefficient (r^2_{CV}) followed by the number of descriptors (k).

(i) Five reliable models for human adenocarcinoma (HCT116):

$$IC_{50} (HCT116) = 0.119 \times E_T - 0.892 \times \Delta G^\circ + 0.891 \times \Delta H^\circ - 56.901$$

$$r^2_{CV} = 0.686, r^2 = 0.796, k = 3 \quad \text{Eq.1}$$

$$IC_{50} (HCT116) = -1.064 \times \Delta G^\circ + 1.063 \times \Delta H^\circ - 3017.16 \times C - 29.018$$

$$r^2_{CV} = 0.696, r^2 = 0.787, k = 3 \quad \text{Eq.2}$$

$$IC_{50} (HCT116) = 0.078 \times E_T - 1.208 \times \Delta G^\circ + 1.208 \times \Delta H^\circ - 1.337 \times \Delta S^\circ + 9.075$$

$$r^2_{CV} = 0.844, r^2 = 0.915, k = 4 \quad \text{Eq.3}$$

$$IC_{50} (HCT116) = 0.0746 \times E_T - 1.123 \times \Delta G^\circ + 1.123 \times \Delta H^\circ - 1833.9 \times C - 41.048$$

$$r^2_{CV} = 0.876, r^2 = 0.923, k = 4 \quad \text{Eq.4}$$

$$IC_{50} (HCT116) = 0.0752 \times E_T - 1.131 \times \Delta G^\circ + 1.131 \times \Delta H^\circ - 0.107 \times \Delta S^\circ - 1696.39 \times H - 36.953$$

$$r^2_{CV} = 0.839, r^2 = 0.923, k = 5 \quad \text{Eq.5}$$

(ii) Five reliable models for ovarian carcinoma cells (A2780):

$$IC_{50} (A2780) = -0.441 \times \Delta G^\circ + 0.441 \times \Delta H^\circ - 1342.08 \times C - 10.212$$

$$r^2_{CV} = 0.744, r^2 = 0.875, k = 3 \quad \text{Eq.6}$$

$$IC_{50} (A2780) = 0.027 \times E_T - 0.393 \times \Delta G^\circ + 0.393 \times \Delta H^\circ - 0.459 \times \Delta S^\circ + 6.08$$

$$r^2_{CV} = 0.6421, r^2 = 0.902, k = 4 \quad \text{Eq.7}$$

$$IC_{50} (A2780) = 0.021 \times E_T - 0.392 \times \Delta G^\circ + 0.392 \times \Delta H^\circ - 795.999 \times C - 11.599$$

$$r^2_{CV} = 0.715, r^2 = 0.913, k = 4 \quad \text{Eq.8}$$

$$IC_{50} (A2780) = -0.419 \times \Delta G^\circ + 0.419 \times \Delta H^\circ + 0.451 \times \Delta S^\circ - 1938.38 \times C - 29.098$$

$$r^2_{CV} = 0.7388, r^2 = 0.880, k = 4 \quad \text{Eq.9}$$

$$IC_{50} (A2780) = 0.020 \times E_T - 0.385 \times \Delta G^\circ + 0.385 \times \Delta H^\circ + 0.192 \times \Delta S^\circ - 1070.15 \times C - 19.603$$

$$r^2_{CV} = 0.704, r^2 = 0.914, k = 5 \quad \text{Eq.10}$$

The predicted activities of the above models are also tabulated in Table 6. A fine comparison between observed and predicted activities (IC_{50}), as calculated from Eq. 1-5 and Eq. 6-10, a graphs with respect to colon carcinoma (HCT116) and also with respect to ovarian carcinoma (A2780) were depicted into figure 4 and figure 5, respectively.

Figure 4. Graphical representation of observed and predicted activity (TD- IC_{50} extracted from Eq.4) of colon carcinoma (HCT116).

Figure 5. Graphical representation of observed and predicted activity (TD-IC₅₀ extracted from Eq.8) of ovarian carcinoma (A2780).

A close look at these figures shows a resemblance between experimental activities and predicted activities with respect to the concerned model. Among the top five reliable models of human adenocarcinoma (HCT116), Eq. 4 is the best as it has $r^2_{CV}=0.876$, $r^2=0.923$, and $k=4$. The descriptors of this model are also total energy, free energy, enthalpy and heat capacity. The coefficient of total energy and enthalpy has positive signs that show a direct relationship with activity. Whereas the coefficient of free energy and heat capacity have negative signs that show an indirect relationship with activity. The reliable model of ovarian carcinoma (A2780) is Eq. 8, as it has $r^2_{CV}=0.715$, $r^2=0.913$, and $k=4$. The descriptors of this model are also total energy, free energy, enthalpy and heat capacity. The coefficients of total energy and enthalpy also have positive signs that show a direct relationship with activity. Whereas the coefficients of free energy and heat capacity have negative signs that show an indirect relationship with activity.

Table 6. Compounds, thermodynamics and pharmacokinetics descriptors, biological activities and predicted activities.

3.3.2. Prediction of activity based on PK property

Here, we have used PK properties (studied in section 3.2) as descriptors to predict the activity of all compounds listed in Table 6. To do this, the biological activities (IC₅₀ data of the compounds against (i) HCT116 human adenocarcinoma and (ii) A2780 ovarian carcinoma cells) [55] were used as dependent variables and the above PK properties as independent. Equations 11–15 were developed for predicting anticancer activity of (i) human adenocarcinoma (HCT116), while equations 16–20 for (ii) ovarian carcinoma cells (A2780). These equations were the top five models among numerous QSAR models, screened in on the basis of correlation coefficient (r^2), cross-validated correlation coefficient (r^2_{CV}) followed by the number of descriptors (k).

(i) Five reliable models for human adenocarcinoma (HCT116):

$$\begin{aligned} \text{IC}_{50}(\text{HCT116}) = & 22.142 \times \text{HD} + \text{HA} - 220.202 \\ & r^2_{CV}=0.799 \quad r^2=0.853, \quad k=1 \end{aligned} \quad \text{Eq.11}$$

$$\begin{aligned} \text{IC}_{50}(\text{HCT116}) = & -6.205 \times \log P + 20.086 \times \text{HD} + \text{HA} - 195.013 \\ & r^2_{CV}=0.823 \quad r^2=0.891, \quad k=2 \end{aligned} \quad \text{Eq.12}$$

$$\begin{aligned} \text{IC}_{50}(\text{HCT116}) = & -31.876 \times \log P + 0.614 \times \text{MW} + 22.176 \times \text{HD} - \\ & 350.028 \\ & r^2_{CV}=0.724 \quad r^2=0.839, \quad k=3 \end{aligned} \quad \text{Eq.13}$$

$$\begin{aligned} \text{IC}_{50}(\text{HCT116}) = & -10.774 \times \log P + 0.0983 \times \text{MW} + 18.287 \times \text{HD} + \\ & \text{HA} - 216.282 \\ & r^2_{CV}=0.808 \quad r^2=0.896, \quad k=3 \end{aligned} \quad \text{Eq.14}$$

$$\begin{aligned} \text{IC}_{50}(\text{HCT116}) = & -9.294 \times \log P + 0.058 \times \text{MW} + 17.534 \times \text{HD} \\ & + 19.682 \times \text{HA} - 203.201 \\ & r^2_{CV}=0.773 \quad r^2=0.896, \quad k=4 \end{aligned} \quad \text{Eq.15}$$

(ii) Five reliable models for ovarian carcinoma cells (A2780):

$$\begin{aligned} \text{IC}_{50}(\text{A2780}) = & -5.313 \times \log P + 6.522 \times \text{HD} + \text{HA} - 63.04 \\ & r^2_{CV}=0.703 \quad r^2=0.865, \quad k=2 \end{aligned} \quad \text{Eq.16}$$

$$\begin{aligned} \text{IC}_{50}(\text{A2780}) = & -15.064 \times \log P + 0.251 \times \text{MW} + 7.276 \times \text{HD} - \\ & 136.668 \end{aligned} \quad \text{Eq.17}$$

$$r^2_{CV}=0.813 \quad r^2=0.918, \quad k = 3$$

$$\begin{aligned} \text{IC}_{50} (\text{A2780}) = & -9.07766 \times \log P + 0.101829 \times \text{MW} + 4.58251 \times \text{HD} \\ & + \text{HA} - 84.0045 \end{aligned} \quad \text{Eq.18}$$

$$r^2_{CV}=0.749 \quad r^2=0.889, \quad k = 3$$

$$\begin{aligned} \text{IC}_{50} (\text{A2780}) = & 7.685 \times \text{HD} + 9.806 \times \text{HA} - 1.774 \times \text{nroth} - 77.153 \end{aligned} \quad \text{Eq.19}$$

$$r^2_{CV}=0.601 \quad r^2=0.841, \quad k = 3$$

$$\begin{aligned} \text{IC}_{50} (\text{A2780}) = & -17.81 \times \log P + 0.319 \times \text{MW} + 7.828 \times \text{HD} - 2.066 \times \\ & \text{HA} - 156.754 \end{aligned} \quad \text{Eq.20}$$

$$r^2_{CV}=0.810 \quad r^2=0.921, \quad k = 4$$

The predicted activities of the above models are also tabulated in Table 6. A fine comparison between observed and predicted activities (IC_{50}), as calculated from Eq. 11-15 and Eq. 16-20, a graphs with respect to colon carcinoma (HCT116) and also with respect to ovarian carcinoma (A2780) were depicted into figure 6 and figure 7, respectively.

Figure 6. Graphical representation of observed and predicted activity (PK- IC_{50} as extracted from Eq.12) of colon carcinoma (HCT116).

Figure 7. Graphical representation of observed and predicted activity (PK- IC_{50} as extracted from Eq.16) of ovarian carcinoma (A2780).

A close look at these figures shows a resemblance between experimental activities and predicted activities with respect to the concerned model. Among the top five reliable models of human adenocarcinoma (HCT116), Eq. 12 is the much reliable as it has $r^2_{CV}=0.823$, $r^2=0.891$, and $k = 2$. The descriptors of this model are $\log P$ and sum of H-bond donor and acceptor ($\text{HD} + \text{HA}$). The coefficient of $\log P$ has a negative sign that shows an inverse relationship with activity. That also supports Rule 2 because as $\log P$ increases from its optimal value (5), the activity of drugs decreases. Whereas the reliable model of ovarian carcinoma (A2780) Eq. 16, as it has $r^2_{CV}=0.813$, $r^2=0.918$, and $k = 3$. The descriptors of this model are $\log P$, molecular weight (MW), and H-bond donor. The coefficients of $\log P$, MW and HD are negative, positive, and positive, respectively.

4. Conclusion:

The study included (i) thermodynamics (transformation of Pt^{IV} complexes (prodrugs) into Pt^{II} complexes (drugs) based on $\Delta_r H$, $\Delta_r S$ and $\Delta_r G$; followed by (ii) pharmacokinetics of the complexes; and (iii) prediction of biological activity using TD and PK properties as descriptors. The results of the study concluded that:

- i. The thermodynamic characteristics— $\Delta_r H$, $\Delta_r S$, and $\Delta_r G$ —adequately clarified the transformation of Pt^{IV} prodrugs into active Pt^{II} drugs along with their effectiveness.
- ii. Pharmacokinetic analyses of the twenty-seven complexes effectively clarify the rationale for their absorption, distribution, metabolism, excretion, and toxicity/side effects.
- iii. Thermodynamics properties also provide reliable correlation with experimental activities of $\text{Pt}^{\text{(IV)}}$ complexes. Eq. 4 is a reliable model of human adenocarcinoma (HCT116). The descriptors of this model are total energy, free energy, enthalpy and heat capacity. The coefficient of total energy and enthalpy has positive signs that show a direct relationship with activity. Whereas the coefficient of free energy and heat capacity have negative signs that show an indirect relationship with activity. The reliable model of ovarian carcinoma (A2780) is Eq. 8. The descriptors of this model are also total energy, free energy, enthalpy and heat capacity. The coefficients of total energy and enthalpy also have positive signs that show a direct relationship with activity. Whereas the coefficients of free energy and heat capacity have negative signs that show an indirect relationship with activity.
- iv. Pharmacokinetics studies provide reliable correlation with experimental activities of $\text{Pt}^{\text{(IV)}}$ complexes. The best model as obtained from pharmacokinetics properties for HCT116 is Eq. 12.

The descriptors of the model are log P and sum of H-bond donor and acceptor (HD + HA). The coefficient of log P has a negative sign that shows an inverse relationship with activity. That also supports Rule 2 because as log P increases from its optimal value (5), the activity of drugs decreases. Whereas the reliable model of ovarian carcinoma (A2780) Eq. 16. The descriptors of this model are log P, molecular weight (MW), and H-bond donor. The coefficients of log P, MW and HD are negative, positive, and positive, respectively.

- v. A comparative study of both models reflected that TD and PK properties have reliability and will give fruitful results if the anticancer activity of newly designed drugs is predicted before their synthesis.

5. Future perspectives

The synthesis and study of new anticancer drugs are challenging due to high costs and time constraints. Nowadays, computational tools have been employed either independently or in combination with experimental methodologies to investigate and develop small molecules to corresponding targets (Wender *et al.*, 2008; Nair and Jain, 2026; Chang *et al.*, 2025; Naji *et al.*, 2026; Shahrukh *et al.*, 2026; Singh *et al.*, 2026). The future of anticancer drugs, their design and development will be decided by a combo of AI (artificial intelligence) and NI (natural intelligence). By appropriate diets, lifestyle and environment (within the body and around the body), we can live long without cancer or with cancer (sleeping form) as studied by us and write in our editorial article (Sahu *et al.*, 2026). Hence, cancer medications and their fruitful results should also be correlated on the above-said routine.

References

1. Abdolmaleki S, Aliabadi A, Khaksar S. Bridging the gap between theory and treatment: Transition metal complexes as successful candidates in medicine. *Coordination Chemistry Reviews*, 2025, 531, 216477.
2. Albrecht M, van Koten G. Platinum group organometallics based on “pincer” complexes: sensors, switches, and catalysts. *Angewandte Chemie International Edition*. 2001, 40(20), 3750-3781.
3. Bai D, Nowak M, Lu D, et al. The outcast of medicine: metals in medicine--from traditional mineral medicine to metallodrugs. *Front Pharmacol*. 2025, 16, 1542560. doi:10.3389/fphar.2025.1542560.
4. Belluco U. Organometallic and Coordination Chemistry of Platinum, *Academic Press, London*, 1974, 44.
5. Bodor N, Buchwald P. Molecular size based approach to estimate partition properties for organic solutes. *J. Phys Chem. B*, 1997, 101(17), 3404-3412. DOI: 10.1021/jp9638503.
6. Bruno, P, Liu, Y, Park, G. *et al.* A subset of platinum-containing chemotherapeutic agents kills cells by inducing ribosome biogenesis stress. *Nat. Med.* 2017, 23, 461–471. <https://doi.org/10.1038/nm.4291>
7. Buchwald P, Bodor N. Octanol-water partition: searching for predicting models. *Curr. Med. Chem.* 1998, 5, 353-380. ISSN: 0929-8673.
8. Bühl M, Reimann C, Pantazis DA, Bredow T, Neese F. Geometries of Third-Row Transition-Metal Complexes from Density-Functional Theory. *J. Chem. Theory Comput.* 2008, 4 (9), 1449–1459.
9. Chang L, Wang M, Zhang H, Li Z, Song Z, Zhao L, Jiang F, Wang J, Quan Y. Synthesis and Clinical Application of Small-Molecule Drugs Approved by FDA in 2025. *Medicinal Research Reviews*. 2026. <https://doi.org/10.1002/med.70064>
10. Chen A, Holt-Hindle P. Platinum-based nanostructured materials: synthesis, properties, and applications. *Chemical reviews*. 2010, 110(6), 3767-3804.
11. Cheng, Y., Mou, Y., Wang, H. *et al.* Platinum-based functional nanomaterials: mechanisms and therapeutic strategies in cancer radiotherapy sensitization. *Mol. Cancer*. 2026, 25, 18. <https://doi.org/10.1186/s12943-025-02421-8>
12. Clark DE. Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena. 1. Prediction of intestinal absorption. *J. Pharm. Sci.*, 1999, 88(8), 807-814. DOI: 10.1021/js9804011.
13. Crans DC, Kostenkova K. Open questions on the biological roles of first-row transition metals. *Commun Chem*. 2020, 3(1), 104. doi:10.1038/s42004-020-00341-w.

14. Crouch RD, Holden MS, Samet C. CAChe Molecular Modeling: A Visualization Tool Early in the Undergraduate Chemistry Curriculum. *J. Chem. Educ.* 1996, 73 (10), 916. <https://doi.org/10.1021/ed073p916>.
15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian 16, Revision C.01, 2016.
16. Galib, Barve M, Mashru M, Jagtap C, Patgiri BJ, Prajapati PK. Therapeutic potentials of metals in ancient India: A review through Charaka Samhita. *J. Ayurveda Integr. Med.* 2011, 2(2), 55-63. doi:10.4103/0975-9476.82523.
17. Ghose AK, Crippen GM. Atomic physicochemical parameters for 3-dimensional structure-directed quantitative structure-activity-relationships. 1. partition-coefficients as a measure of hydrophobicity. *J. Comput. Chem.* 1986, 7, 565-577. DOI: 10.1002/jcc.540070419.
18. Gramatica P, Papa E, Luini M, Monti E, Gariboldi MB, Ravera M, Gabano E, Gaviglio L, Osella D. Antiproliferative Pt (IV) complexes: synthesis, biological activity, and quantitative structure-activity relationship modeling. *Journal of Biological Inorganic Chemistry.* 2010, 15(7), 1157-69.
19. Hall MD, Alderden RA, Zhang M, Beale PJ, Cai Z, Lai B, Hambley TW. The fate of platinum (II) and platinum (IV) anti-cancer agents in cancer cells and tumours. *Journal of structural biology*, 2006, 155(1), 38-44.
20. Hammes GG. Thermodynamics and kinetics for the biological sciences. 2000, John Wiley & Sons.
21. Hansch C, Björkroth JP, Leo A. Hydrophobicity and central nervous system agents: On the principle of minimal hydrophobicity in drug design. *J. Pharm. Sci.*, 1987, 76, 663-687. <https://doi.org/10.1002/jps.2600760902>.
22. Harder HC, Rosenberg B. Inhibitory Effects of Anti-Tumor Platinum Compounds on DNA, RNA and Protein Syntheses in Mammalian Cells *in Vitro*. *International Journal of Cancer*, 1970, 6, 207-216.
23. Helm CW, States JC. Enhancing the Efficacy of Cisplatin in Ovarian Cancer Treatment—Could Arsenic Have a Role. *Journal of Ovarian Research*, 2009, 2, 2.
24. Hill T. Free energy transduction in biology: the steady-state kinetic and thermodynamic formalism. 2012, Elsevier.
25. Iova, V., Tincu, R. C., Scrobota, I., & Tudosie, M. S. Pt (IV) Complexes as Anticancer Drugs and Their Relationship with Oxidative Stress. *Biomedicines*, 2025, 13(4), 981.
26. Javier Soto Alsar et al. Efficacy data of oxaliplatin retreatment in patients with metastatic colorectal cancer in a real-world setting. *J. Clin. Oncol.* 2026, 44, 167-167. DOI:10.1200/JCO.2026.44.2_suppl.167
27. Jiang DM, Gupta S, Kitchlu A, Meraz-Munoz A, North SA, Alimohamed NS, et al. Defining Cisplatin Eligibility in Patients with Muscle-Invasive Bladder Cancer. *Nature Reviews Urology*, 2021, 18, 104-114.
28. Karl F. A Free Energy Principle for Biological Systems. *Entropy (Basel)*. 2012, 14(11), 2100-2121. doi:10.3390/e14112100
29. Kenny RG, Chuah SW, Crawford A, Marmion CJ. Platinum (IV) prodrugs—a step closer to Ehrlich's vision? *European Journal of Inorganic Chemistry.* 2017, 12, 1596-612.
30. Klotz, I. (Ed.). Energy changes in biochemical reactions. 2012, Elsevier.
31. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat Rev. Drug Discov.* 2010, 3, 711-715. DOI: 10.1038/nrd1470.

32. Kostjukova LO, Leontieva SV, Kostjukov VV. Vibronic absorption spectrum and electronic properties of methylene blue in aqueous solution: TD-DFT study. *Journal of Molecular Liquids*. 2021, 336, 116369
33. Lai, Y., Qiu, G., Zheng, Z. *et al.* Platinum accumulation in chemotherapy: toxicity mechanisms, challenges, and mitigation strategies. *Biometals*, 2026. <https://doi.org/10.1007/s10534-026-00812-y>.
34. Mauro M, Aliprandi A, Septiadi D, Kehr NS, De Cola L. When self-assembly meets biology: luminescent platinum complexes for imaging applications. *Chemical Society Reviews*. 2014, 43(12), 4144-4166.
35. McKeage MJ. Lobaplatin: a new antitumour platinum drug. *Expert opinion on investigational drugs*, 2001, 10(1), 119-128.
36. Mudi SY, Usman MT, Ibrahim S. Clinical and industrial application of organometallic compounds and complexes: a review. *American Journal of Chemistry and Applications*, 2015, 2(6), 151-158.
37. Mukherjee S, Mitra I, Fouzder C, Mukherjee S, Ghosh S, Chatterji U, Moi SC. Effect of Pt (II) complexes on cancer and normal cells compared to clinically used anticancer drugs: cell cycle analysis, apoptosis and DNA/BSA binding study. *Journal of Molecular Liquids*. 2017, 247, 126-140.
38. Nair SG, Jain NA. Analysis of Novel Drug Approvals in 2024–2025: Chemical Attributes, Biological Mechanisms, and Advances in Synthesis. *Medicinal and Medical Chemistry*. 2026, 3(1), 27-35.
39. Naji HA, Naser ST, Jawad HA, Al-Akkam EJ, Al-Karagoly H, ALdujaili SL. Green Chemistry in Pharmaceutical Industry: Sustainable Approaches to Drug Synthesis. *Current Pharmacology Reports*. 2026, 12(1), 12.
40. National Cancer Institute. A to Z List of Cancer Drugs. United States: National Cancer Institute; Available from: <https://www.cancer.gov/about-cancer/treatment/drugs/cancer-drugs>.
41. National Cancer Institute. A to Z List of Cancer Drugs. United States: National Cancer Institute; Available from: <https://www.cancer.gov/about-cancer/treatment/drugs/cancer-drugs>.
42. National Cancer Institute. Nutrition During Cancer Treatment. United States: National Cancer Institute; 2024. Available from: <https://www.cancer.gov/about-cancer/treatment/side-effects/nutrition>.
43. Norinder U, Bergstrom CAS. Prediction of ADMET Properties. *Chem. Med. Chem.*, 2006, 1, 920 – 937. DOI: 10.1002/cmdc.200600155.
44. Owen JB, Butterfield DA. Measurement of oxidized/reduced glutathione ratio. In *Protein misfolding and cellular stress in disease and aging: concepts and protocols*. 2010, 269-277, Totowa, NJ: Humana Press.
45. Parveen S. Platinum-based cancer chemotherapeutics: Recent trends and future perspectives. *Current Chinese Science*. 2022, 2(4), 275-293.
46. Pedone D, Moglianetti M, De Luca E, Bardi G, Pompa PP. Platinum nanoparticles in nanobiomedicine. *Chemical Society Reviews*. 2017, 46(16), 4951-4975.
47. Raevsky OA, Schaper KJ. Quantitative estimation of hydrogen bond contribution to permeability and absorption processes of some chemicals and drugs. *Eur. J. Med. Chem.*, 1998, 33 (10), 799-807. DOI: 10.1016/S0223-5234(99)80031-2.
48. Rajamani R. CAChe 6.1 WorkSystem Pro plus Active Site Add-On. CAChe Group, Fujitsu America, Inc., 15244 Greenbriar Parkway, Beaverton, OR 97006. <http://www.cachesoftware.com/>. Contact CAChe group for pricing information. *Journal American Chemical Society*. 2004, 126 (28), 8856–8857. <https://doi.org/10.1021/ja033646a>
49. Rosenberg B, Van Camp L, Krigas T. Inhibition of Cell Division in *Escherichia coli* by Electrolysis Products from a Platinum Electrode. *Nature*, 1965, 205, 698-699.
50. Sabater B. Entropy perspectives of molecular and evolutionary biology. *International journal of molecular sciences*, 2022, 23(8), 4098.
51. Sahu VK, Singh RK, Singh PP. Extended Rule of Five and Prediction of Biological Activity of peptidic HIV-1-PR Inhibitors. *Universal Journal of Pharmacy and Pharmacology*, 2022, 1(1), 20-42. <https://doi.org/10.31586/ujpp.2022.403>.
52. Sahu VK, Swati, Soni AK. Cancer: disease, drugs and diets – an opinion. *Arch Clin Toxicol*. 2026, 8(1):11-13.

53. Shahrukh A, Batool S, Sarfraz M, Hawsawi MB, Choudhary MI, Saleem RS. Natural Products, Synthesis, and Biological Activities of Quinolines (2020-2024). *Mini-Reviews in Medicinal Chemistry*. 2026, 26(10), 706-742.
54. Singh J, Singh NK, Dubey S, Jaiswal G, Srivastava A, Telang SP, Srivastava SK. Novel Molecules and Materials for Drug Discovery. *In Experimental and Computational Advances in Materials*. 2026, 439-472. Singapore: Springer Nature Singapore.
55. Singh RK, Raja AD. DFT Based QSAR Studies of Derivatives of Benzene Sulphonamide Using Quantum Chemical Descriptors. *J Adv Scient Res*, 2011, 2(9), 87-92. ISSN: 0976-9595.
56. Singhal K, Sahu VK, Singh P, Raj P. DFT-based prediction of antifungal and insecticidal activities of perfluorophenyl antimony(III) and antimony(V) chlorides. *Med Chem Res*, 2014, 23, 1758–1767.
57. Soni AK, Azim I, Swati VK. Cisplatin at Atomic, Molecular and Electronic Level: A DFT Based Study. *Open Journal of Applied Sciences*. 2025, 15(5):1429-41.
58. Szturcz P, Cristina V, Herrera Gómez RG, Bourhis J, Simon C, Vermorken JB. Cisplatin Eligibility Issues and Alternative Regimens in Locoregionally Advanced Head and Neck Cancer: Recommendations for Clinical Practice. *Frontiers in Oncology*, 2019, 9, 464.
59. Umemiya, M., Kou, K., Inayama, Y. *et al.* Comparison of nedaplatin and cisplatin in concurrent chemoradiotherapy for cervical cancer: a systematic review and meta-analysis. *Int. J. Clin. Oncol.* 2026, 31, 537–547.
60. Usanova S, Piée-Staffa A, Sied U, Thomale J, Schneider A, Kaina B, *et al.* Cisplatin Sensitivity of Testis Tumour Cells Is Due to Deficiency in Interstrand-Crosslink Repair and Low ERCC1-XPF Expression. *Molecular Cancer*, 2010, 9, 248.
61. Van de Waterbeemd H, Smith DA, Beaumont K, Walker DK. Property-based design: optimization of drug absorption and pharmacokinetics. *J. Med. Chem.*, 2001, 44 (9), 1313-1333. DOI: 10.1021/jm000407e.
62. Wagstaff AJ, Ward A, Benfield P, Heel RC. Carboplatin: A Preliminary Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Efficacy in the Treatment of Cancer. *Drugs*, 1989, 37, 162–190. <https://doi.org/10.2165/00003495-198937020-00005>.
63. Wender PA, Verma VA, Paxton TJ, Pillow TH. Function-oriented synthesis, step economy, and drug design. *Accounts of chemical research*. 2008, 41(1), 40-49.
64. Williams DA, Lemke TL. Physicochemical and Biopharmaceutical Properties of Drug Substances and Pharmacokinetics; chapter 7, Principles of Drug Discovery; part 1, Foye's Principles of Medicinal Chemistry, 2002, 5th edn. pp 115-142, ISBN: 978-0-683-30737-5.
65. Wu G, Lupton JR, Turner ND, Fang YZ, Yang S. Glutathione metabolism and its implications for health. *The Journal of nutrition*. 2004, 134(3), 489-92.
66. Yoshida M, Kato M. Control of Pt··· Pt interactions in Pt (II) complex crystals as luminescence sensors for the detection of external stimuli: recent achievements and perspectives: M. Yoshida, M. Kato. *Analytical Sciences*. 2025, 41(8), 1233-1249.
67. Zhang C, Xu C, Gao X, Yao Q. Platinum-based drugs for cancer therapy and anti-tumor strategies. *Theranostics*. 2022, 12(5), 2115-2132. Published 2022 Feb 7. doi:10.7150/thno.69424.
68. Zheng L, Serin D, Metges JP, Oncologie Editorial Office. Advancing multidisciplinary oncology: reflections on 2025 and perspectives for the future. *Oncologie*. 2026 Jan 21(0).
69. Zhou J, Kang Y, Chen L, Wang H, Liu J, Zeng S, Yu L. The Drug-Resistance Mechanisms of Five Platinum-Based Antitumor Agents. *Front. Pharmacol*. 2020, 11, 343. doi: 10.3389/fphar.2020.00343.

Vishnu Kumar Sahu ^{1,3*} and Swati ²

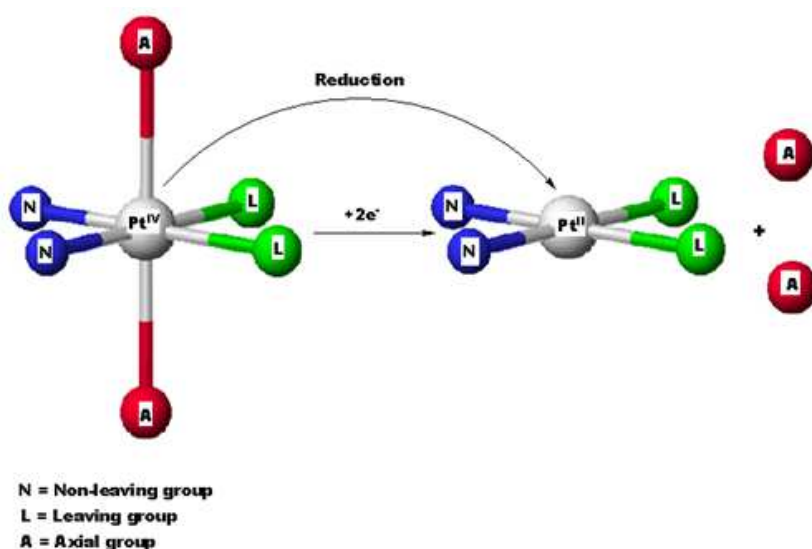
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Graphical Abstracts:



Tumor tissues with low oxygen levels promote the conversion of Pt^{IV} complexes into Pt^{II} forms. In these states, they execute their cytotoxic functions.

Keywords: Pt^{IV}–prodrugs, Active Pt^{II}–drugs, DFT, Pharmacokinetics, Thermodynamics, Anti-cancer activity

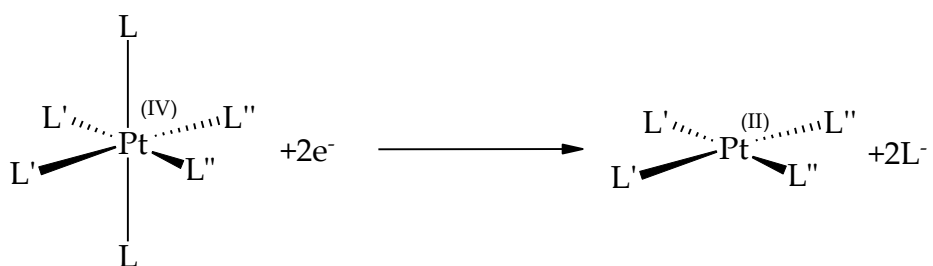


Figure 1. General scheme of the two-electron reduction of Pt^{IV} complexes to Pt^{II} complexes.

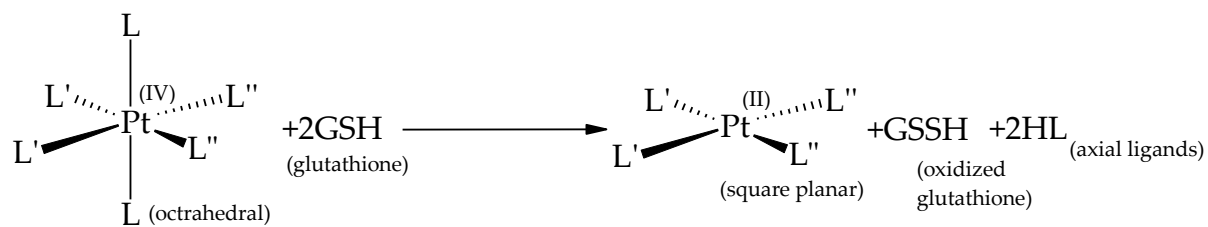


Figure 2. The general transformation of Pt^{IV} complexes into Pt^{II} complexes by glutathione (GSH).

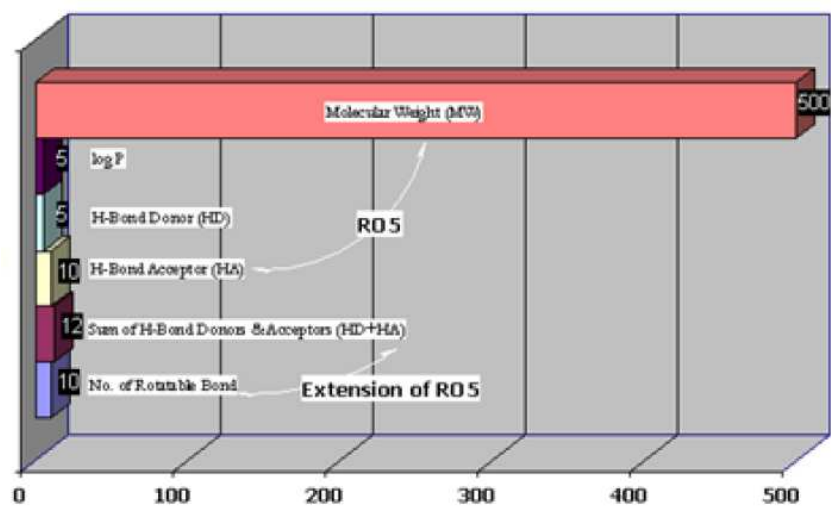


Figure 3. Graphical representation of RO5 in extended form (reproduced from the reference no. 46).

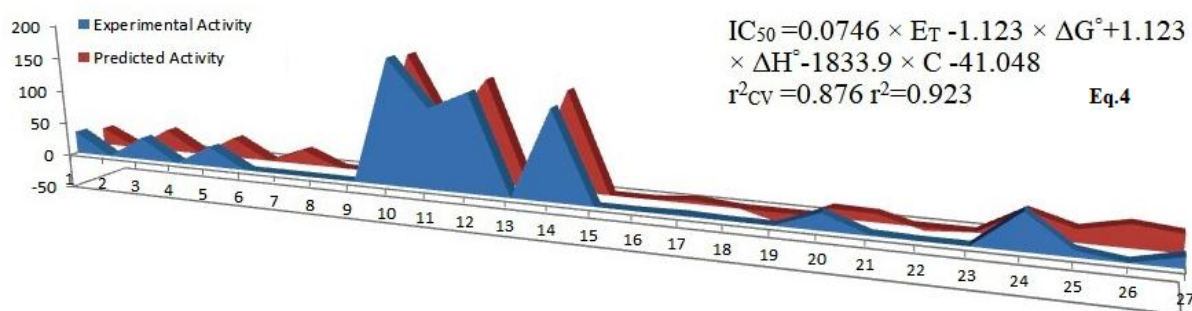


Figure 4. Graphical representation of observed and predicted activity (TD- IC_{50} extracted from Eq.4) of colon carcinoma (HCT116).

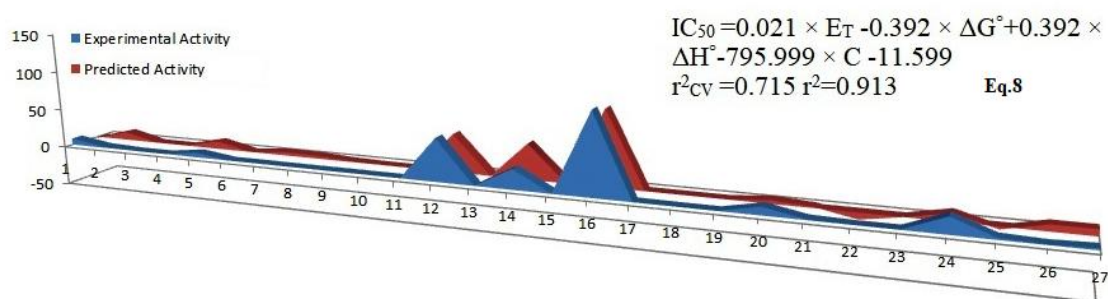


Figure 5. Graphical representation of observed and predicted activity (TD- IC_{50} extracted from Eq.8) of ovarian carcinoma (A2780).

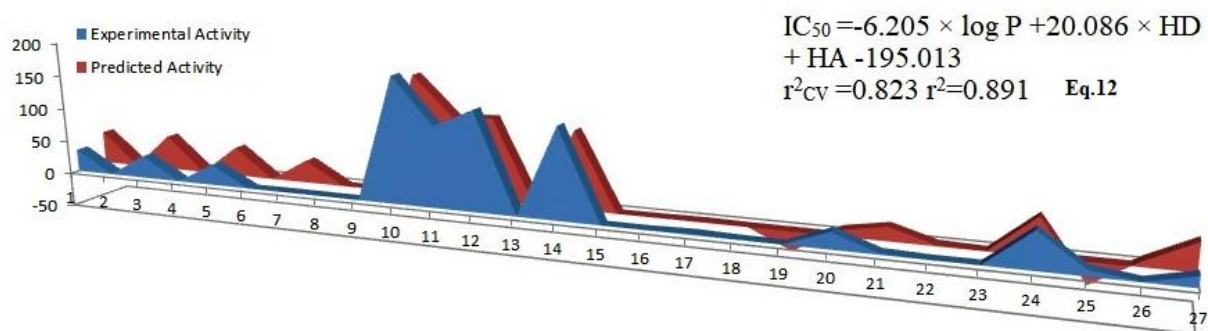


Figure 6. Graphical representation of observed and predicted activity (PK- IC_{50} as extracted from Eq.12) of colon carcinoma (HCT116).

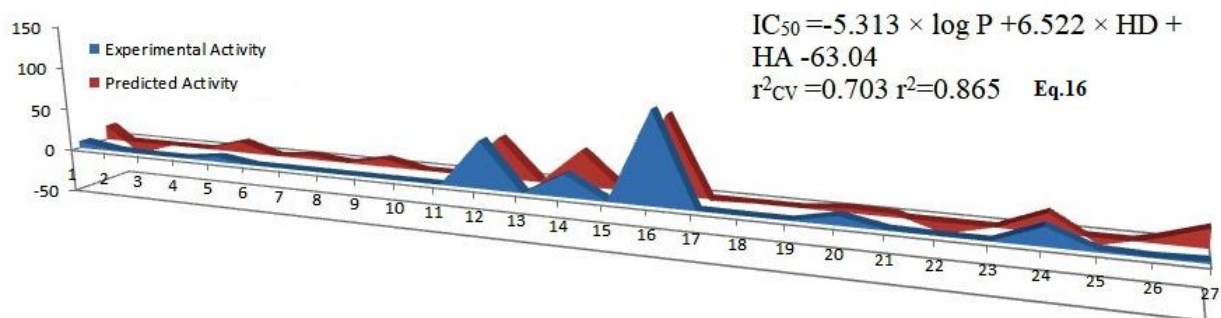
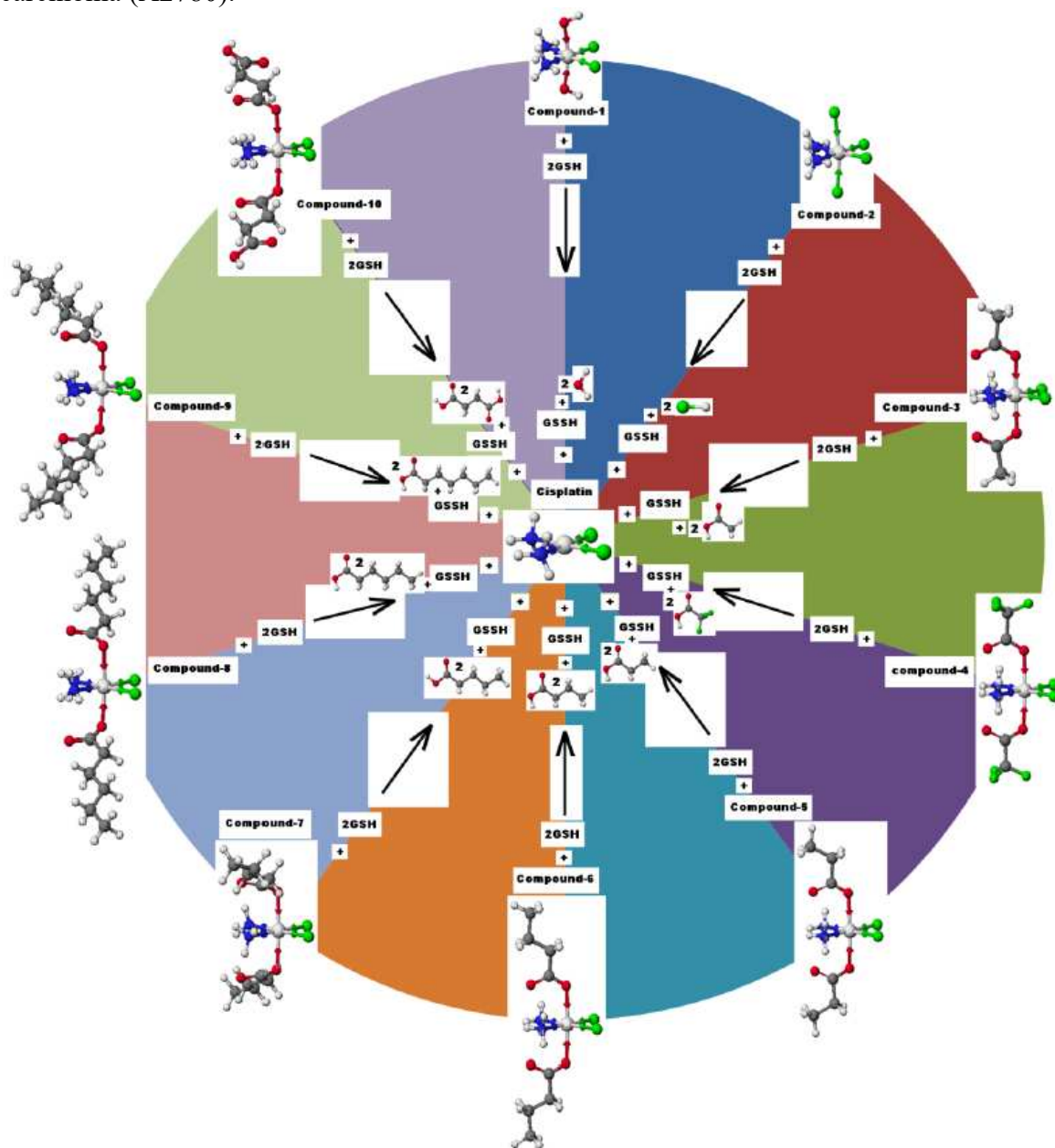
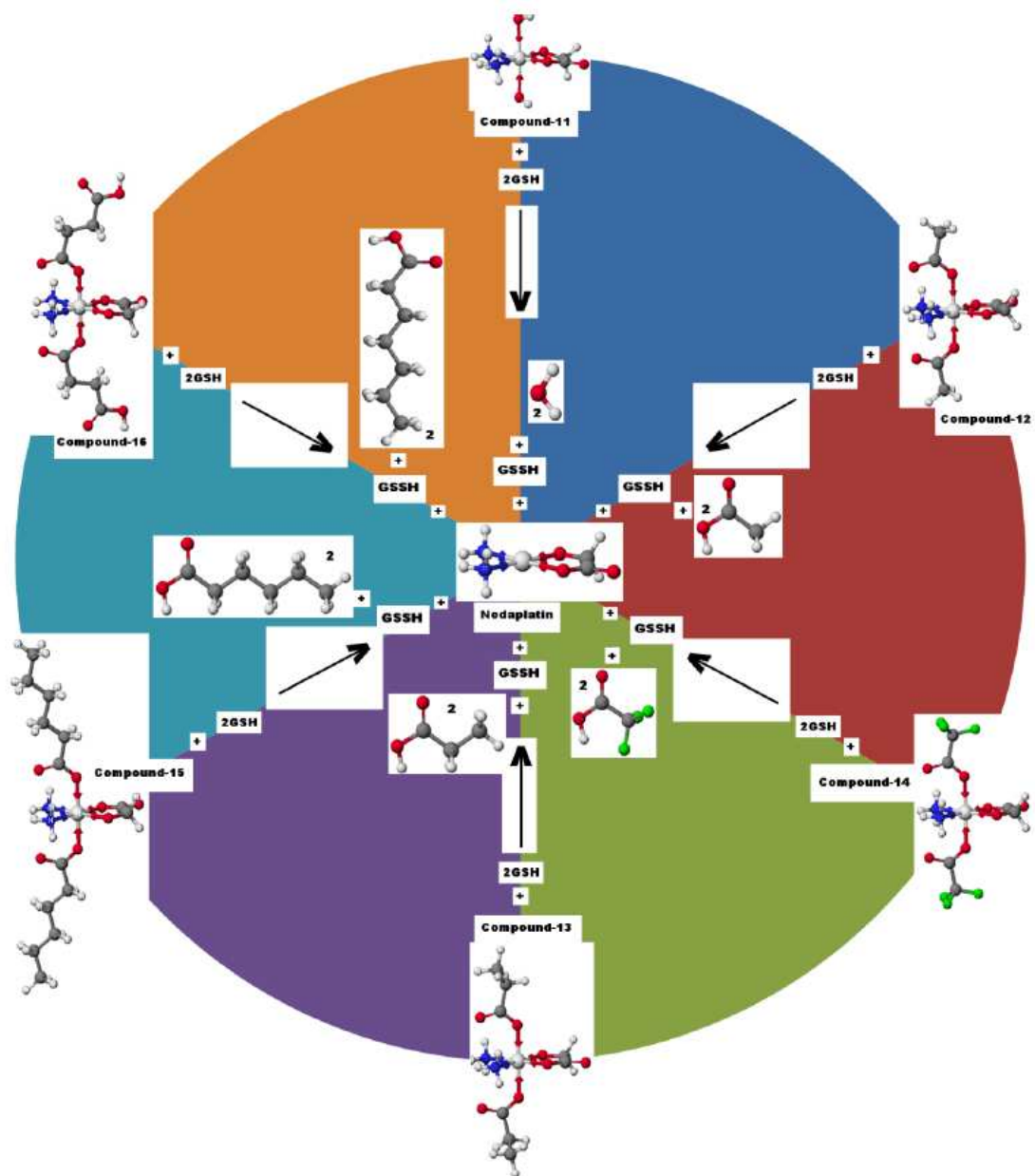


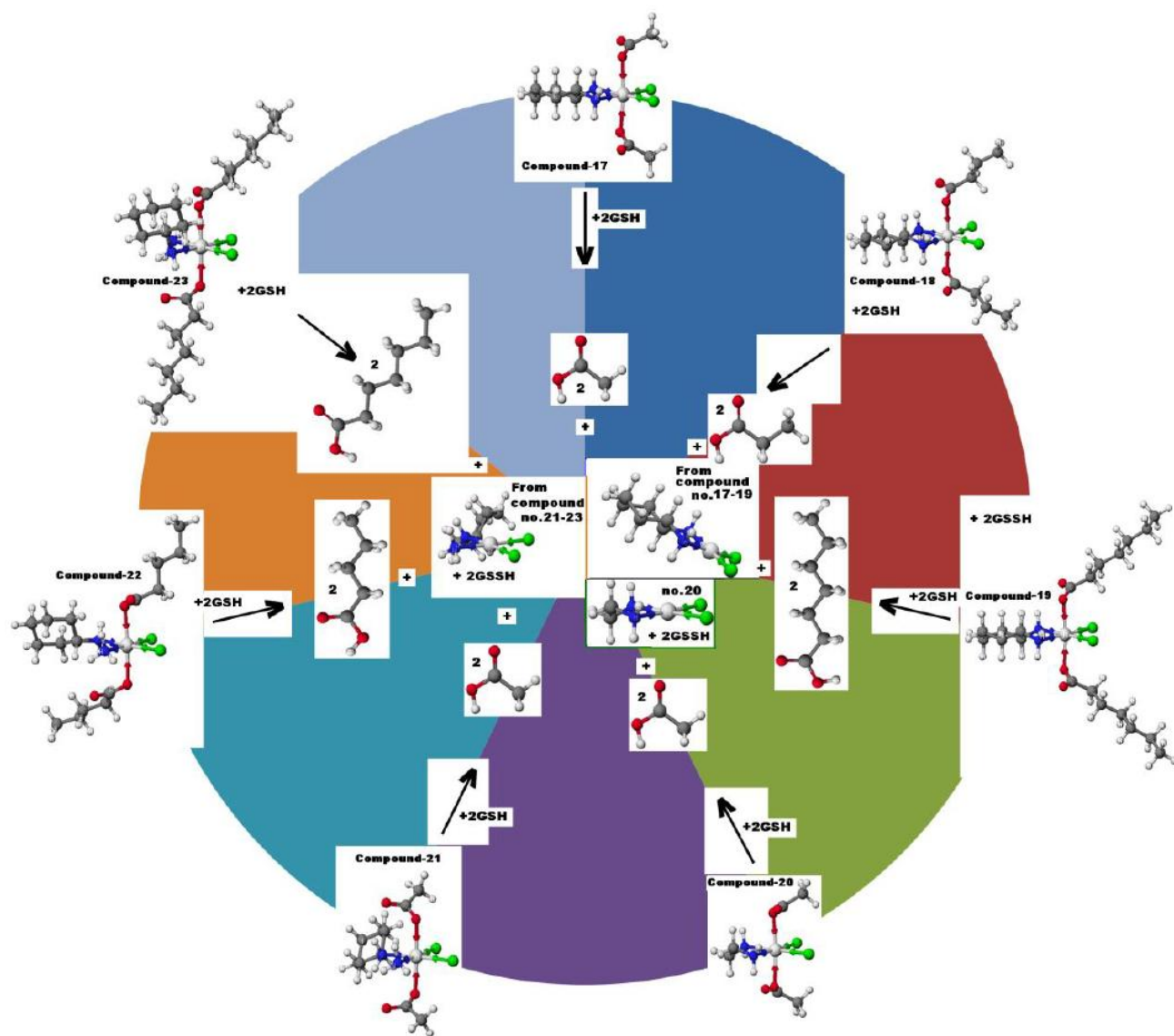
Figure 7. Graphical representation of observed and predicted activity (PK- IC_{50} as extracted from Eq.16) of ovarian carcinoma (A2780).



Scheme 1. Transformation of Pt^{IV} -prodrugs (complex no. 1 to 10) into active Pt^{II} -drug (complex).

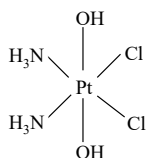


Scheme 2. Transformation of Pt^{IV}-prodrugs (complex no. 11 to 16) into active Pt^{II}-drug (complex).

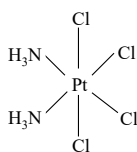


Scheme 3. Transformation of Pt^{IV}-prodrugs (complex no. 17 to 23) into active Pt^{II}-drug (complex).

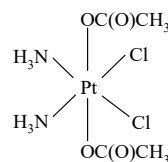
Table 1. Structure of twenty-three Pt^{IV} complexes along with four Pt^{II} complexes.



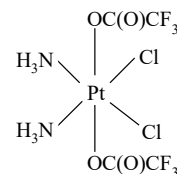
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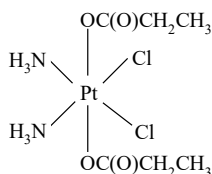
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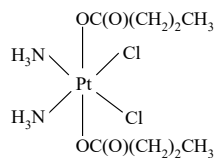
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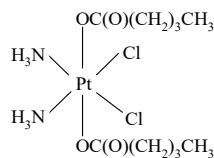
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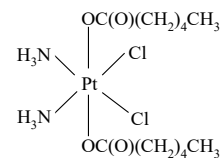
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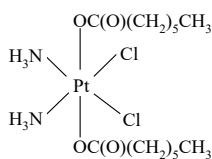
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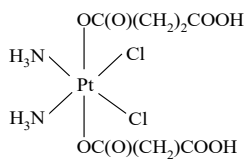
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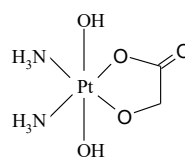
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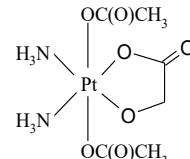
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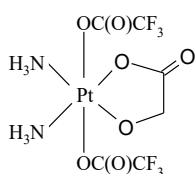
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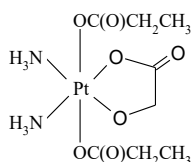
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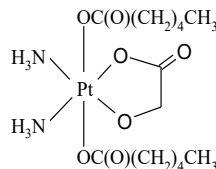
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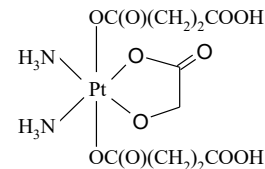
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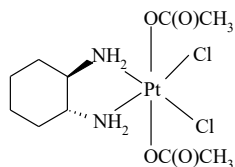
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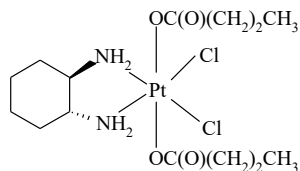
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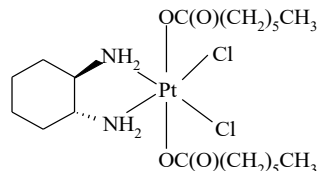
Compound no. 16



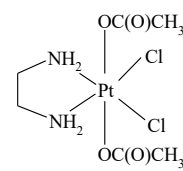
Compound no. 17



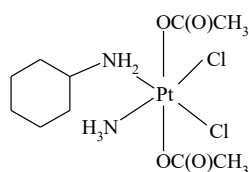
Compound no. 18



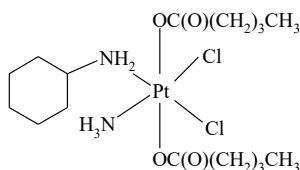
Compound no. 19



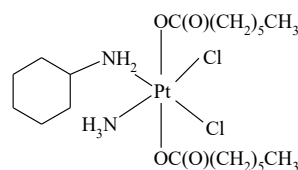
Compound no. 20



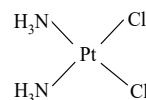
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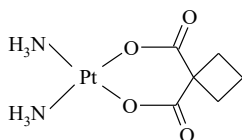
Compound no. 22



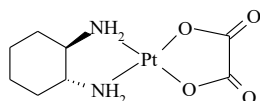
Compound no. 23



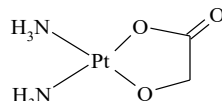
Compound no. 24



Compound no. 25



Compound no. 26



Compound no. 27

Table 2. Enthalpies of reactions of all the twenty-three Pt^{IV} complexes as obtained by solving the equation: $\Delta_r H^\circ = \Sigma \Delta_f H^\circ \text{prod} - \Sigma \Delta_f H^\circ \text{react}$

S.No.	Reactant-1	2Reactant-2	→	Product-1	Product-2	2Product-3	$\Delta_r H^\circ$ (Reaction) (Hartree)	$IC_{50}(\mu M)$	
	$\Delta_f H^\circ$ (Hartree)	$\Delta_f H^\circ$ (Hartree)		$\Delta_f H^\circ$ (Hartree)	$\Delta_f H^\circ$ (Hartree)	$\Delta_f H^\circ$ (Hartree)		A2780	HCT116
1	-1303.84	-2731.19	→	-764.68	-2730.01	2087573.24	243198.53	8.11	33.29
2	-2072.40	-2731.19	→	-764.68	-2730.01	2087573.24	243050.90	1.52	11.87
3	-1608.74	-2731.19	→	-764.68	-2730.01	2087573.24	242961.77	9.48	33.26
4	-2203.71	-2731.19	→	-764.68	-2730.01	2087573.24	242593.88	5.32	16.2
5	-1687.18	-2731.19	→	-764.68	-2730.01	2087573.24	242881.08	5.93	30.11
6	-1765.61	-2731.19	→	-764.68	-2730.01	2087573.24	242788.17	1.48	2.05
7	-1844.07	-2731.19	→	-764.68	-2730.01	2087573.24	242703.02	0.191	0.298
8	-1922.53	-2731.19	→	-764.68	-2730.01	2087573.24	242640.10	0.043	0.035
9	-2000.96	-2731.19	→	-764.68	-2730.01	2087573.24	242486.02	0.059	0.091
10	-2063.81	-2731.19	→	-764.68	-2730.01	2087573.24	242566.25	29.69	183.36
11	-686.41	-2731.19	→	-534.98	-2730.01	1460492.66	-109.03	26.63	116.63
12	-991.29	-2731.19	→	-534.98	-2730.01	1460492.66	-353.19	54.18	143.57
13	-1586.22	-2731.19	→	-534.98	-2730.01	1460492.66	-748.96	24.63	161.14
14	-1069.75	-2731.19	→	-534.98	-2730.01	1460492.66	-427.81	25.43	130.8
15	-1305.12	-2731.19	→	-534.98	-2730.01	1460492.66	-647.95	8.04	23.25
16	-1445.40	-2731.19	→	-534.98	-2730.01	1460492.66	38010.21	103.35	111.47
17	-1841.72	-2731.19	→	-1385.41	-2730.01	3782181.50	-357.68	0.49	1.71
18	-1999.91	-2731.19	→	-1385.41	-2730.01	3782181.50	49600.30	0.025	0.041
19	-2234.00	-2731.19	→	-1385.41	-2730.01	3782181.50	-127914.87	0.0009	0.0014
20	-1685.99	-2731.19	→	-1229.66	-2730.01	3356968.40	-336.84	10.01	23.28
21	-1842.89	-2731.19	→	-1386.59	-2730.01	3785411.57	-363.43	1.05	2
22	-2078.26	-2731.19	→	-1386.59	-2730.01	3785411.57	-596.29	0.02	0.051
23	-2235.18	-2731.19	→	-1386.59	-2730.01	3785411.57	-796.24	0.00039	0.00165

Table 3. Entropies of reactions of all the twenty-three Pt^{IV} complexes as obtained by solving the equation: $\Delta_r S^\circ = \Sigma \Delta_f S^\circ_{\text{prod}} - \Sigma \Delta_f S^\circ_{\text{react}}$

S.No.	Reactant-1	+2Reactant-	→	Product-1	+Product-2	+2Product-3	$\Delta_r S^\circ$ (Reaction)	IC ₅₀ (μ M)	
	S°(Cal/Mol-Kelvin)	S°(Cal/Mol-Kelvin)	→	S°(Cal/Mol-Kelvin)	S°(Cal/Mol-Kelvin)	S°(Cal/Mol-Kelvin)	(Cal/Mol-Kelvin)	A2780	HCT116
1	113.087	334.238	→	118.080	290.430	92.988	54.173	8.11	33.29
2	113.188	334.238	→	118.080	290.430	89.206	50.290	1.52	11.87
3	144.852	334.238	→	118.080	290.430	137.890	67.310	9.48	33.26
4	170.695	334.238	→	118.080	290.430	164.440	68.017	5.32	16.2
5	158.720	334.238	→	118.080	290.430	151.978	67.530	5.93	30.11
6	169.387	334.238	→	118.080	290.430	167.710	72.595	1.48	2.05
7	184.451	334.238	→	118.080	290.430	181.494	71.315	0.191	0.298
8	198.648	334.238	→	118.080	290.430	197.358	72.982	0.043	0.035
9	170.539	334.238	→	118.080	290.430	211.856	115.589	0.059	0.091
10	166.398	334.238	→	118.080	290.430	173.384	81.258	29.69	183.36
11	107.996	334.238	→	96.908	290.430	92.988	38.092	26.63	116.63
12	133.191	334.238	→	96.908	290.430	137.890	57.799	54.18	143.57
13	157.435	334.238	→	96.908	290.430	164.440	60.105	24.63	161.14
14	144.634	334.238	→	96.908	290.430	151.978	60.444	25.43	130.8
15	207.645	334.238	→	96.908	290.430	197.358	42.813	8.04	23.25
16	169.437	334.238	→	96.908	290.430	211.856	95.519	103.35	111.47
17	158.034	334.238	→	112.745	290.430	137.890	48.793	0.49	1.71
18	190.249	334.238	→	112.745	290.430	151.978	30.666	0.025	0.041
19	233.469	334.238	→	112.745	290.430	164.440	-0.092	0.0009	0.0014
20	144.502	334.238	→	95.667	290.430	137.890	45.247	10.01	23.28
21	153.254	334.238	→	123.065	290.430	137.890	63.893	1.05	2
22	206.134	334.238	→	123.065	290.430	181.494	54.617	0.02	0.051
23	239.259	334.238	→	123.065	290.430	211.856	51.854	0.00039	0.00165

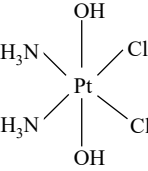
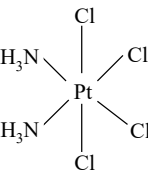
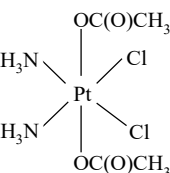
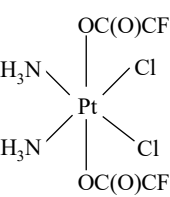
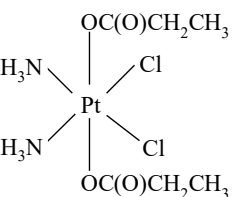
Table 4. Free energies of reactions of all the twenty-three Pt^{IV} complexes as obtained by solving the equation: $\Delta_r G^\circ = \Sigma \Delta_f G^\circ_{\text{prod}} - \Sigma \Delta_f G^\circ_{\text{react}}$

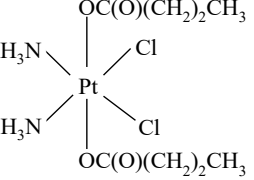
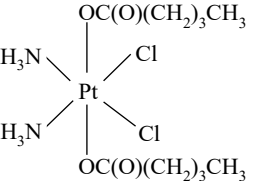
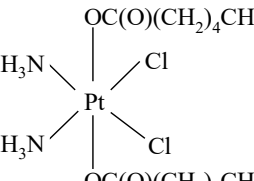
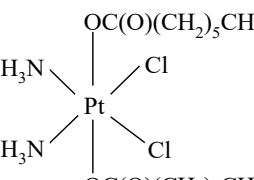
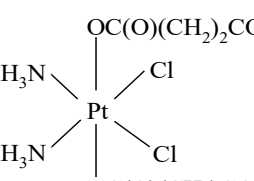
S.No.	Reactant-1	+2Reactant-2	→	Product-1	+Product-2	+2Product-3	$\Delta_r G^\circ$ (Reaction) (Hartree)	IC ₅₀ (μ M)	
	G°(Hartree)	G°(Hartree)		G°(Hartree)	G°(Hartree)	G°(Hartree)		A2780	HCT116
1	-1303.90	-2731.35	→	-1386.65	-2730.14	-152.83	-234.38	8.11	33.29
2	-2072.46	-2731.35	→	-1386.65	-2730.14	-921.62	-234.62	1.52	11.87
3	-1608.81	-2731.35	→	-1386.65	-2730.14	-458.12	-234.77	9.48	33.26
4	-2203.79	-2731.35	→	-1386.65	-2730.14	-1053.70	-235.35	5.32	16.2
5	-1687.26	-2731.35	→	-1386.65	-2730.14	-536.71	-234.90	5.93	30.11
6	-1765.69	-2731.35	→	-1386.65	-2730.14	-615.29	-235.05	1.48	2.05
7	-1844.16	-2731.35	→	-1386.65	-2730.14	-693.89	-235.18	0.191	0.298
8	-1922.62	-2731.35	→	-1386.65	-2730.14	-772.46	-235.28	0.043	0.035
9	-2001.04	-2731.35	→	-1386.65	-2730.14	-851.04	-235.45	0.059	0.091
10	-2063.89	-2731.35	→	-1386.65	-2730.14	-913.84	-235.40	29.69	183.36
11	-686.46	-2731.35	→	-535.02	-2730.14	-152.83	-0.19	26.63	116.63
12	-991.35	-2731.35	→	-535.02	-2730.14	-458.12	-0.59	54.18	143.57
13	-1586.30	-2731.35	→	-535.02	-2730.14	-1053.70	-1.22	24.63	161.14
14	-1069.82	-2731.35	→	-535.02	-2730.14	-536.71	-0.71	25.43	130.8
15	-1305.22	-2731.35	→	-535.02	-2730.14	-772.46	-1.05	8.04	23.25
16	-1445.49	-2731.35	→	-535.02	-2730.14	-851.04	60.63	103.35	111.47
17	-1841.79	-2731.35	→	-1385.47	-2730.14	-458.12	-0.59	0.49	1.71
18	-2000.00	-2731.35	→	-1385.47	-2730.14	-536.71	79.03	0.025	0.041
19	-2234.12	-2731.35	→	-1385.47	-2730.14	-1053.70	-203.85	0.0009	0.0014
20	-1686.06	-2731.35	→	-1229.70	-2730.14	-458.12	-0.56	10.01	23.28
21	-1842.96	-2731.35	→	-1386.65	-2730.14	-458.12	-0.61	1.05	2.00
22	-2078.36	-2731.35	→	-1386.65	-2730.14	-693.89	-0.98	0.02	0.051
23	-2235.29	-2731.35	→	-1386.65	-2730.14	-851.04	-1.19	0.00039	0.00165

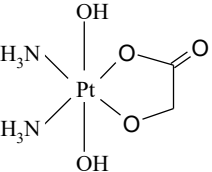
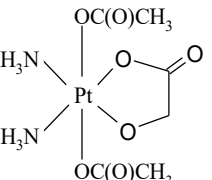
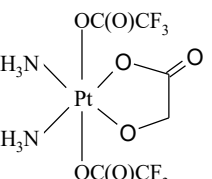
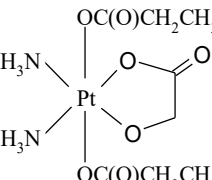
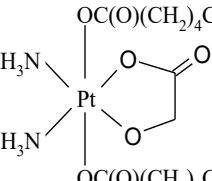
Table 5. Change in total energy (ΔE) of products during the transformation of PtIV complex to PtII was obtained by solving the equation: $\Delta E = \Sigma E_{\text{prod}} - \Sigma E_{\text{react}}$.

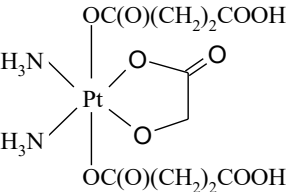
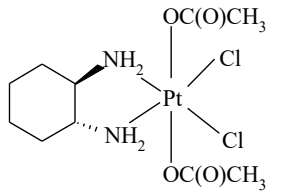
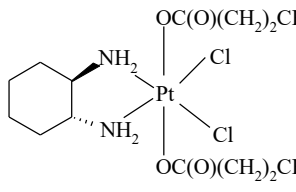
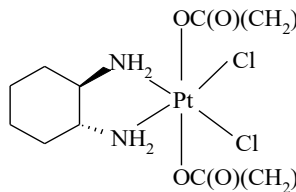
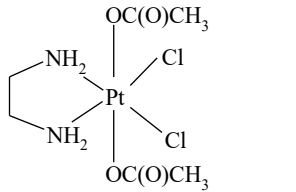
S.No.	Reactant-1	2Reactant-2	→	Product-1	Product-2	2Product-3	ΔE_T (Reaction) (Hartree)	IC ₅₀ (μ M)	
	E _T (Hartree)	E _T (Hartree)		E _T (Hartree)	E _T (Hartree)	E _T (Hartree)		A2780	HCT116
1	-1303.84	-2731.19	→	-764.68	-2730.01	-152.79	387.56	8.11	33.29
2	-2072.40	-2731.19	→	-764.68	-2730.01	-921.58	387.33	1.52	11.87
3	-1608.74	-2731.19	→	-764.68	-2730.01	-458.06	387.18	9.48	33.26
4	-2203.71	-2731.19	→	-764.68	-2730.01	-1053.62	386.60	5.32	16.2
5	-1687.19	-2731.19	→	-764.68	-2730.01	-536.64	387.06	5.93	30.11
6	-1765.61	-2731.19	→	-764.68	-2730.01	-615.21	386.91	1.48	2.05
7	-1844.07	-2731.19	→	-764.68	-2730.01	-693.81	386.77	0.191	0.298
8	-1922.53	-2731.19	→	-764.68	-2730.01	-772.36	386.67	0.043	0.035
9	-2000.96	-2731.19	→	-764.68	-2730.01	-850.94	386.53	0.059	0.091
10	-2063.81	-2731.19	→	-764.68	-2730.01	-913.76	386.55	29.69	183.36
11	-686.41	-2731.19	→	-534.98	-2730.01	-152.79	-0.17	26.63	116.63
12	-991.29	-2731.19	→	-534.98	-2730.01	-458.06	-0.56	54.18	143.57
13	-1586.22	-2731.19	→	-534.98	-2730.01	-1053.62	-1.19	24.63	161.14
14	-1069.75	-2731.19	→	-534.98	-2730.01	-536.64	-0.68	25.43	130.8
15	-1305.12	-2731.19	→	-534.98	-2730.01	-772.36	-1.03	8.04	23.25
16	-1445.41	-2731.19	→	-534.98	-2730.01	-850.94	60.67	103.35	111.47
17	-1841.72	-2731.19	→	-1385.41	-2730.01	-458.06	-0.57	0.49	1.71
18	-1999.91	-2731.19	→	-1385.41	-2730.01	-536.64	79.04	0.025	0.041
19	-2234.01	-2731.19	→	-1385.41	-2730.01	-1053.62	-203.85	0.0009	0.0014
20	-1686.00	-2731.19	→	-1229.66	-2730.01	-458.06	-0.54	10.01	23.28
21	-1842.89	-2731.19	→	-1386.60	-2730.01	-458.06	-0.58	1.05	2
22	-2078.27	-2731.19	→	-1386.60	-2730.01	-693.81	-0.95	0.02	0.051
23	-2235.18	-2731.19	→	-1386.60	-2730.01	-850.94	-1.17	0.00039	0.00165

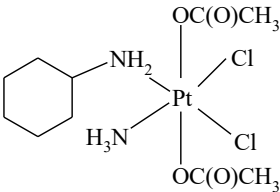
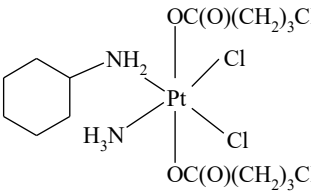
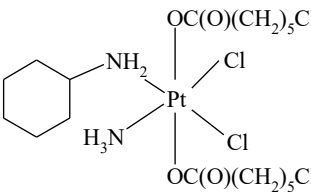
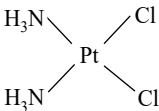
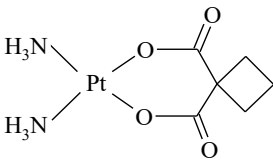
Table 6. Compounds, thermodynamics and pharmacokinetics descriptors, biological activities and predicted activities.

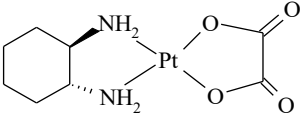
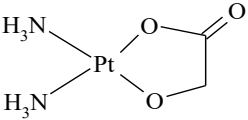
S.No.	Structure of Compound	Thermodynamics			Pharmacokinetics		
		Parameters	HCT116 (μM)	A2780 (μM)	Parameters	HCT116 (μM)	A2780 (μM)
1		-1211.43(E_T) -757088(G) -757065(H) 77.642(S) 0.018(C)	33.29(IC ₅₀) 25.678(Eq.1) 25.651(Eq.2) 26.236(Eq.3) 25.581(Eq.4) 25.633(Eq.5)	8.11(IC ₅₀) -4.291(Eq.6) -1.89(Eq.7) -1.88(Eq.8) -3.701(Eq.9) -1.715(Eq.10)	-0.367(log P) 334.071(MW) 8(HD) 4(HA) 12(HD+HA) 4(nrobt.)	33.29(IC ₅₀) 45.504(Eq.11) 48.293(Eq.12) 44.316(Eq.13) 39.938(Eq.14) 38.699(Eq.15)	8.11(IC ₅₀) 17.178(Eq.16) 11.043(Eq.17) 8.335(Eq.18) 16.456(Eq.19) 10.83(Eq.20)
2		-1980.13(E_T) -1238289(G) -1238266(H) 75.375(S) 0.014(C)	11.87(IC ₅₀) ^a 64.519(Eq.1) 90.52(Eq.2) 87.544(Eq.3) 78.962(Eq.4) 79.723(Eq.5)	1.52(IC ₅₀) 13.365(Eq.6) 10.689(Eq.7) 10.544(Eq.8) 12.598(Eq.9) 10.319(Eq.10)	0.582(log P) 370.963(MW) 6(HD) 2(HA) 8(HD+HA) 2(nrobt.)	11.87(IC ₅₀) ^a -43.065(Eq.11) -37.939(Eq.12) -7.624(Eq.13) -39.81(Eq.14) -42.402(Eq.15)	1.52(IC ₅₀) -13.953(Eq.16) -8.53(Eq.17) -14.853(Eq.18) -14.978(Eq.19) -5.815(Eq.20)
3		-1477.44(E_T) -257.133(G) 12.504(H) 141.569(S) 0.065(C)	33.26(IC ₅₀) 6.803(Eq.1) 61.631(Eq.2) 30.932(Eq.3) 32.207(Eq.4) 32.234(Eq.5)	9.48(IC ₅₀) ^a 21.492(Eq.6) 7.773(Eq.7) 11.153(Eq.8) 21.813(Eq.9) 11.666(Eq.10)	-0.8(log P) 418.146(MW) 6(HD) 6(HA) 12(HD+HA) 6(nrobt.)	33.26(IC ₅₀) 45.504(Eq.11) 50.983(Eq.12) 65.428(Eq.13) 52.868(Eq.14) 51.928(Eq.15)	9.48(IC ₅₀) ^a 19.481(Eq.16) 24.154(Eq.17) 20.831(Eq.18) 17.149(Eq.19) 25.61(Eq.20)
4		-2028.27(E_T) -526.551(G) 14.054(H) 156.019(S) 0.075(C)	16.20(IC ₅₀) ^a 182.496(Eq.1) 319.642(Eq.2) 296.284(Eq.3) 276.984(Eq.4) 279.011(Eq.5)	5.32(IC ₅₀) ^a 127.597(Eq.6) 92.905(Eq.7) 97.819(Eq.8) 122.555(Eq.9) 96.75(Eq.10)	1.422(log P) 526.089(MW) 6(HD) 6(HA) 12(HD+HA) 6(nrobt.)	16.20(IC ₅₀) ^a 45.504(Eq.11) 37.191(Eq.12) 60.894(Eq.13) 39.526(Eq.14) 37.568(Eq.15)	5.32(IC ₅₀) ^a 7.673(Eq.16) 17.807(Eq.17) 11.647(Eq.18) 17.149(Eq.19) 20.497(Eq.20)
5		-1548.26(E_T) -266.034(G) 12.7(H) 143.151(S) 0.069(C)	30.11(IC ₅₀) 6.445(Eq.1) 59.238(Eq.2) 34.312(Eq.3) 29.799(Eq.4) 30.28(Eq.5)	5.93(IC ₅₀) 20.136(Eq.6) 8.74(Eq.7) 10.039(Eq.8) 18.587(Eq.9) 9.745(Eq.10)	0.456(log P) 446.199(MW) 6(HD) 6(HA) 12(HD+HA) 8(nrobt.)	30.11(IC ₅₀) 45.504(Eq.11) 43.186(Eq.12) 42.614(Eq.13) 42.087(Eq.14) 41.888(Eq.15)	5.93(IC ₅₀) 12.806(Eq.16) 12.28(Eq.17) 12.282(Eq.18) 13.601(Eq.19) 12.192(Eq.20)

6		-1554.67(E _T)	2.05(IC ₅₀) ^a	1.48(IC ₅₀) ^a	1.249(log P)	2.05(IC ₅₀) ^a	1.48(IC ₅₀) ^a
		-284.17(G)	24.309(Eq.1)	10.566(Eq.6)	474.253(MW)	45.504(Eq.11)	8.595(Eq.16)
		15.464(H)	39.225(Eq.2)	5.657(Eq.7)	6(HD)	38.268(Eq.12)	7.392(Eq.17)
		167.374(S)	26.683(Eq.3)	6.957(Eq.8)	6(HA)	34.583(Eq.13)	7.944(Eq.18)
		0.083(C)	27.111(Eq.4)	11.138(Eq.9)	12(HD+HA)	36.304(Eq.14)	10.053(Eq.19)
			27.091(Eq.5)	7.332(Eq.10)	10(nrotb.)	36.158(Eq.15)	7.035(Eq.20)
7		-1686.79(E _T)	0.298(IC ₅₀)	0.191(IC ₅₀)	2.041(log P)	0.298(IC ₅₀)	0.191(IC ₅₀)
		-302.618(G)	26.7(Eq.1)	6.146(Eq.6)	502.307(MW)	45.504(Eq.11)	4.384(Eq.16)
		17.42(H)	30.753(Eq.2)	0.106(Eq.7)	6(HD)	33.35(Eq.12)	2.504(Eq.17)
		189.288(S)	11.785(Eq.3)	4.204(Eq.8)	6(HA)	26.553(Eq.13)	3.606(Eq.18)
		0.093(C)	21.819(Eq.4)	10.194(Eq.9)	12(HD+HA)	30.52(Eq.14)	2.956(Eq.19)
			20.991(Eq.5)	6.001(Eq.10)	14(nrotb.)	30.428(Eq.15)	1.878(Eq.20)
8		-1733.19(E _T)	0.035(IC ₅₀) ^a	0.043(IC ₅₀)	2.834(log P)	0.035(IC ₅₀) ^a	0.043(IC ₅₀)
		-308.336(G)	25.59(Eq.1)	5.657(Eq.6)	530.36(MW)	45.504(Eq.11)	0.174(Eq.16)
		16.68(H)	30.013(Eq.2)	6.974(Eq.7)	6(HD)	28.432(Eq.12)	-2.383(Eq.17)
		175.899(S)	32.099(Eq.3)	3.582(Eq.8)	6(HA)	18.522(Eq.13)	-0.732(Eq.18)
		0.095(C)	20.277(Eq.4)	2.365(Eq.9)	12(HD+HA)	24.737(Eq.14)	-0.592(Eq.19)
			21.197(Eq.5)	2.254(Eq.10)	16(nrotb.)	24.699(Eq.15)	-3.28(Eq.20)
9		-1792.23(E _T)	0.091(IC ₅₀) ^a	0.059(IC ₅₀)	3.626(log P)	0.091(IC ₅₀) ^a	0.059(IC ₅₀)
		-324.846(G)	35.462(Eq.1)	-0.727(Eq.6)	558.414(MW)	89.789(Eq.11)	9.008(Eq.16)
		19.165(H)	17.026(Eq.2)	4.176(Eq.7)	8(HD)	63.685(Eq.12)	7.281(Eq.17)
		194.832(S)	25.155(Eq.3)	1.027(Eq.8)	6(HA)	54.844(Eq.13)	4.094(Eq.18)
		0.106(C)	17.023(Eq.4)	-2.453(Eq.9)	14(HD+HA)	55.527(Eq.14)	11.23(Eq.19)
			17.581(Eq.5)	0.227(Eq.10)	18(nrotb.)	54.037(Eq.15)	7.219(Eq.20)
10		-1889.7(E _T)	183.36(IC ₅₀)	29.69(IC ₅₀) ^a	-1.217(log P)	183.36(IC ₅₀)	29.69(IC ₅₀) ^a
		-456.538(G)	140.152(Eq.1)	72.947(Eq.6)	534.219(MW)	178.357(Eq.11)	60.826(Eq.16)
		17.982(H)	192.032(Eq.2)	51.698(Eq.7)	8(HD)	174.08(Eq.12)	74.152(Eq.17)
		197.287(S)	172.012(Eq.3)	59.707(Eq.8)	10(HA)	194.357(Eq.13)	63.924(Eq.18)
		0.094(C)	178.285(Eq.4)	76.633(Eq.9)	18(HD+HA)	178.478(Eq.14)	57.55(Eq.19)
			177.977(Eq.5)	61.759(Eq.10)	14(nrotb.)	176.365(Eq.15)	77.483(Eq.20)

11		-560.128(E _T)	116.63(IC ₅₀)	26.63(IC ₅₀) ^a	-1.791(log P)	116.63(IC ₅₀)	26.63(IC ₅₀) ^a
		-213.561(G)	75.122(Eq.1)	19.811(Eq.6)	337.201(MW)	111.931(Eq.11)	44.312(Eq.16)
		9.671(H)	54.519(Eq.2)	23.091(Eq.7)	8(HD)	117.389(Eq.12)	33.285(Eq.7)
		121.513(S)	72.883(Eq.3)	23.51(Eq.8)	7(HA)	91.64(Eq.13)	35.331(Eq.18)
		0.051(C)	74.248(Eq.4)	20.448(Eq.9)	15(HD+HA)	110.452(Eq.14)	45.873(Eq.19)
			74.134(Eq.5)	23.647(Eq.10)	4(nroth.)	111.166(Eq.15)	30.999(Eq.20)
12		-842.744(E _T)	143.57(IC ₅₀)	54.18(IC ₅₀)	-2.225(log P)	143.57(IC ₅₀)	54.18(IC ₅₀)
		-331.971(G)	150.443(Eq.1)	44.277(Eq.6)	421.276(MW)	111.931(Eq.11)	46.615(Eq.16)
		13.661(H)	118.317(Eq.2)	48.281(Eq.7)	6(HD)	120.078(Eq.12)	46.396(Eq.17)
		154.992(S)	154.089(Eq.3)	48.026(Eq.8)	9(HA)	112.753(Eq.13)	47.826(Eq.18)
		0.073(C)	150.232(Eq.4)	44.223(Eq.9)	15(HD+HA)	123.382(Eq.14)	43.018(Eq.19)
			150.54(Eq.5)	47.867(Eq.10)	8(nroth.)	124.395(Eq.15)	45.779(Eq.20)
13		-1398.28(E _T)	161.14(IC ₅₀) ^a	24.63(IC ₅₀) ^a	-0.002(log P)	161.14(IC ₅₀) ^a	24.63(IC ₅₀) ^a
		-606.05(G)	330.64(Eq.1)	147.521(Eq.6)	529.219(MW)	111.931(Eq.11)	34.807(Eq.16)
		16.235(H)	370.304(Eq.2)	131.562(Eq.7)	6(HD)	106.286(Eq.12)	40.049(Eq.17)
		178.065(S)	414.417(Eq.3)	133.638(Eq.8)	9(HA)	108.219(Eq.13)	38.642(Eq.18)
		0.087(C)	393.705(Eq.4)	143.484(Eq.9)	15(HD+HA)	110.04(Eq.14)	43.018(Eq.19)
			395.685(Eq.5)	132.42(Eq.10)	8(nroth.)	110.035(Eq.15)	40.666(Eq.20)
14		-913.299(E _T)	130.8(IC ₅₀)	25.43(IC ₅₀)	-0.968(log P)	130.8(IC ₅₀)	25.43(IC ₅₀)
		-345.197(G)	155.313(Eq.1)	37.441(Eq.6)	449.329(MW)	111.931(Eq.11)	39.94(Eq.16)
		15.363(H)	104.021(Eq.2)	45.07(Eq.7)	6(HD)	112.282(Eq.12)	34.522(Eq.17)
		170.679(S)	145.677(Eq.3)	44.428(Eq.8)	9(HA)	89.938(Eq.13)	39.278(Eq.18)
		0.083(C)	143.387(Eq.4)	38.173(Eq.9)	15(HD+HA)	112.601(Eq.14)	39.47(Eq.19)
			143.509(Eq.5)	44.487(Eq.10)	10(nroth.)	114.355(Eq.15)	32.361(Eq.20)
15		-1113.49(E _T)	23.25(IC ₅₀) ^a	8.04(IC ₅₀) ^a	1.41(log P)	23.25(IC ₅₀) ^a	8.04(IC ₅₀) ^a
		-382.752(G)	167.546(Eq.1)	25.813(Eq.6)	533.49(MW)	111.931(Eq.11)	27.308(Eq.16)
		18.382(H)	80.795(Eq.2)	47.698(Eq.7)	6(HD)	97.527(Eq.12)	19.859(Eq.17)
		188.09(S)	155.887(Eq.3)	38.594(Eq.8)	9(HA)	65.846(Eq.13)	26.263(Eq.18)
		0.105(C)	133.653(Eq.4)	20.394(Eq.9)	15(HD+HA)	95.251(Eq.14)	28.826(Eq.19)
			135.261(Eq.5)	35.818(Eq.10)	16(nroth.)	97.166(Eq.15)	16.889(Eq.20)

16		-1266.55(E _T) -530.072(G) 19.019(H) 205.927(S) 0.103(C)	111.47(IC ₅₀) ^a 281.141(Eq.1) 244.186(Eq.2) 298.946(Eq.3) 292.015(Eq.4) 292.626(Eq.5)	103.35(IC ₅₀) 93.762(Eq.6) 93.536(Eq.7) 94.98(Eq.8) 94.35(Eq.9) 95.187(Eq.10)	-2.641(log P) 537.349(MW) 8(HD) 13(HA) 21(HD+HA) 14(nrobtb.)	111.47(IC ₅₀) ^a 244.784(Eq.11) 243.176(Eq.12) 241.681(Eq.13) 248.992(Eq.14) 248.832(Eq.15)	103.35(IC ₅₀) 87.96(Eq.16) 96.394(Eq.17) 90.919(Eq.18) 86.967(Eq.19) 97.652(Eq.20)
17		-1698.95(E _T) -272.03(G) 14.296(H) 158.03(S) 0.081(C)	1.71(IC ₅₀) -4.806(Eq.1) 31.106(Eq.2) 11.895(Eq.3) 5.069(Eq.4) 5.666(Eq.5)	0.49(IC ₅₀) 7.38(Eq.6) 0.894(Eq.7) 0.275(Eq.8) 5.221(Eq.9) -0.387(Eq.10)	0.774(log P) 498.275(MW) 4(HD) 6(HA) 10(HD+HA) 6(nrobtb.)	1.71(IC ₅₀) 1.22(Eq.11) 1.04(Eq.12) 20.11(Eq.13) 7.202(Eq.14) 6.9(Eq.15)	0.49(IC ₅₀) -1.929(Eq.16) 6.025(Eq.17) 5.532(Eq.18) 1.779(Eq.19) 7.499(Eq.20)
18		-1834.27(E _T) -301.476(G) 18.198(H) 191.999(S) 0.102(C)	0.041(IC ₅₀) ^a 8.741(Eq.1) 3.212(Eq.2) -3.728(Eq.3) -6.102(Eq.4) -5.988(Eq.5)	0.025(IC ₅₀) ^a -6.094(Eq.6) -5.193(Eq.7) -6.224(Eq.8) -6.181(Eq.9) -6.257(Eq.10)	2.823(log P) 554.382(MW) 4(HD) 6(HA) 10(HD+HA) 10(nrobtb.)	0.041(IC ₅₀) ^a 1.22(Eq.11) -11.674(Eq.12) -10.735(Eq.13) -9.363(Eq.14) -8.87(Eq.15)	0.025(IC ₅₀) ^a -12.815(Eq.16) -10.737(Eq.17) -7.355(Eq.18) -5.318(Eq.19) -11.076(Eq.20)
19		-1995.57(E _T) -345.193(G) 22.849(H) 229.542(S) 0.13(C)	0.0014(IC ₅₀) 32.57(Eq.1) -29.829(Eq.2) -7.998(Eq.3) -15.187(Eq.4) -14.855(Eq.5)	0.0009(IC ₅₀) ^a -22.336(Eq.6) -7.714(Eq.7) -12.955(Eq.8) -23.243(Eq.9) - 13.682(Eq.10)	5.201(log P) 638.543(MW) 4(HD) 6(HA) 10(HD+HA) 16(nrobtb.)	0.0014(IC ₅₀) 1.22(Eq.11) -26.429(Eq.12) -34.827(Eq.13) -26.713(Eq.14) -26.059(Eq.15)	0.0009(IC ₅₀) ^a -25.447(Eq.16) -25.4(Eq.17) -20.37(Eq.18) -15.962(Eq.19) -26.548(Eq.20)
20		-1533.28(E _T) -248.534(G) 12.66(H) 144.805(S) 0.068(C)	23.28(IC ₅₀) -7.4(Eq.1) 43.601(Eq.2) 12.069(Eq.3) 13.058(Eq.4) 13.083(Eq.5)	10.01(IC ₅₀) ^a 13.741(Eq.6) 1.492(Eq.7) 4.272(Eq.8) 13.918(Eq.9) 4.691(Eq.10)	-0.485(log P) 444.184(MW) 4(HD) 6(HA) 10(HD+HA) 6(nrobtb.)	23.28(IC ₅₀) 1.22(Eq.11) 8.855(Eq.12) 27.025(Eq.13) 15.456(Eq.14) 15.45(Eq.15)	10.01(IC ₅₀) ^a 4.761(Eq.16) 11.399(Eq.17) 11.456(Eq.18) 1.779(Eq.19) 12.655(Eq.20)

21		-1677.77(E _T) -285.943(G) 16.099(H) 174.63(S) 0.088(C)	2(IC ₅₀) 11.736(Eq.1) 26.7(Eq.2) 10.336(Eq.3) 11.457(Eq.4) 11.366(Eq.5)	1.05(IC ₅₀) 4.918(Eq.6) 0.007(Eq.7) 1.316(Eq.8) 5.729(Eq.9) 1.793(Eq.10)	1.031(log P) 500.291(MW) 5(HD) 6(HA) 11(HD+HA) 9(nrothb.)	2(IC ₅₀) 23.362(Eq.11) 19.531(Eq.12) 35.333(Eq.13) 22.917(Eq.14) 22.163(Eq.15)	1.05(IC ₅₀) 3.228(Eq.16) 9.936(Eq.17) 7.987(Eq.18) 4.142(Eq.19) 11.394(Eq.20)
22		-1854.53(E _T) -327.259(G) 21.291(H) 220.017(S) 0.118(C)	0.051(IC ₅₀) 32.059(Eq.1) -14.353(Eq.2) -7.867(Eq.3) -4.537(Eq.4) -4.991(Eq.5)	0.02(IC ₅₀) -14.83(Eq.6) -7.253(Eq.7) -8.063(Eq.8) -12.451(Eq.9) -7.294(Eq.10)	3.873(log P) 584.452(MW) 5(HD) 6(HA) 11(HD+HA) 15(nrothb.)	0.051(IC ₅₀) 23.362(Eq.11) 1.899(Eq.12) -3.543(Eq.13) 0.57(Eq.14) 0.664(Eq.15)	0.02(IC ₅₀) -11.869(Eq.16) -11.713(Eq.17) -9.238(Eq.18) -6.503(Eq.19) -12.338(Eq.20)
23		-1972.95(E _T) -361.272(G) 24.253(H) 244.153(S) 0.136(C)	0.00165(IC ₅₀) ^a 50.859(Eq.1) -29.338(Eq.2) -4.65(Eq.3) -4.874(Eq.4) -5.14(Eq.5)	0.00039(IC ₅₀) ^a -22.677(Eq.6) -6.956(Eq.7) -10.395(Eq.8) -20.953(Eq.9) - 10.105(Eq.10)	5.458(log P) 640.559(MW) 5(HD) 6(HA) 11(HD+HA) 18(nrothb.)	0.00165(IC ₅₀) ^a 23.362(Eq.11) -7.938(Eq.12) -19.604(Eq.13) -10.997(Eq.14) -10.796(Eq.15)	0.00039(IC ₅₀) ^a -20.29(Eq.16) -21.489(Eq.17) -17.915(Eq.18) -11.825(Eq.19) -22.653(Eq.20)
24		-1059.8(E _T) -662605(G) -662582(H) 75.475(S) 0.017(C)	8.74(IC ₅₀) 17.438(Eq.1) 17.469(Eq.2) 16.8(Eq.3) 17.548(Eq.4) 17.489(Eq.5)	2.26(IC ₅₀) -5.707(Eq.6) -3.45(Eq.7) -3.19(Eq.8) -4.947(Eq.9) -2.957(Eq.10)	-0.687(log P) 300.057(MW) 6(HD) 2(HA) 8(HD+HA) 2(nrothb.)	8.74(IC ₅₀) -43.065(Eq.11) -30.064(Eq.12) -10.733(Eq.13) -33.104(Eq.14) -34.744(Eq.15)	2.26(IC ₅₀) -7.211(Eq.16) -7.238(Eq.17) -10.553(Eq.18) -14.978(Eq.19) -5.858(Eq.20)
25		-631.774(E _T) -184.01(G) 8.932(H) 116.882(S) 0.051(C)	50.9(IC ₅₀) 39.553(Eq.1) 22.305(Eq.2) 36.911(Eq.3) 34.892(Eq.4) 35.03(Eq.5)	19.95(IC ₅₀) 6.45(Eq.6) 11.425(Eq.7) 10.113(Eq.8) 5.659(Eq.9) 9.642(Eq.10)	-0.922(log P) 371.262(MW) 6(HD) 6(HA) 12(HD+HA) 2(nrothb.)	50.9(IC ₅₀) 45.504(Eq.11) 51.739(Eq.12) 40.511(Eq.13) 49.575(Eq.14) 50.326(Eq.15)	19.95(IC ₅₀) 20.128(Eq.16) 14.205(Eq.17) 17.163(Eq.18) 24.245(Eq.19) 12.809(Eq.20)

26		-691.552(E _T)	0.66(IC ₅₀)	0.63(IC ₅₀)	-0.4(log P)	0.66(IC ₅₀)	0.63(IC ₅₀)
		-194.924(G)	42.889(Eq.1)	2.243(Eq.6)	397.3(MW)	1.22(Eq.11)	4.309(Eq.16)
		9.778(H)	13.692(Eq.2)	12.013(Eq.7)	4(HD)	8.327(Eq.12)	-1.67(Eq.17)
		122.206(S)	39.363(Eq.3)	7.888(Eq.8)	6(HA)	-4.494(Eq.13)	5.908(Eq.18)
		0.058(C)	30.797(Eq.4)	-0.577(Eq.9)	10(HD+HA)	9.932(Eq.14)	12.423(Eq.19)
			31.421(Eq.5)	6.48(Eq.10)	0(nroth.)	11.923(Eq.15)	-3.835(Eq.20)
27		-414.853(E _T)	14.91(IC ₅₀)	2.23(IC ₅₀)	-2.111(log P)	14.91(IC ₅₀)	2.23(IC ₅₀)
		-138.206(G)	22.874(Eq.1)	5.493(Eq.6)	303.187(MW)	23.362(Eq.11)	19.923(Eq.16)
		6.929(H)	16.719(Eq.2)	4.643(Eq.7)	6(HD)	39.031(Eq.12)	15.004(Eq.17)
		103.303(S)	14.136(Eq.3)	7.892(Eq.8)	5(HA)	36.591(Eq.13)	16.442(Eq.18)
		0.036(C)	24.917(Eq.4)	8.566(Eq.9)	11(HD+HA)	37.41(Eq.14)	14.439(Eq.19)
			24.064(Eq.5)	9.116(Eq.10)	2(nroth.)	37.723(Eq.15)	14.311(Eq.20)

^a Data points not included in the deriving regression equation