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Computational assessment of the platinum (II) complex of imidazolidine dioximes substituted with methoxydiglycol units: from activation to DNA binding

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Abstract

To overcome the issue of toxicity inherent in the approved anticancer agents, many cisplatin derivatives continue to be designed and tested today. Recently, we have proposed a new series of platinum complexes with highly potent imidazolidine dioxime ligands, a combination of two active ligands targeting DNA, substituted with aliphatic carbon chains or aromatic moiety. Quantum mechanical calculations have revealed their potential activity, particularly highlighting the potentially enhanced activity of complexes with aliphatic substituents in DNA platination. Here, we extend our previous study with the inclusion of methoxydiglycol unit (2-(2-methoxyethoxy)ethyl substituents) into the imidazolidine dioxime ligands of our previously proposed complexes to possibly enhance the solubility and bioavailability. Our current investigation focuses on modeling the aquation and DNA binding reactions to assess the potential of this modification and the results are compared to cisplatin.

Keywords: *Platinum drugs, anticancer agents, cisplatin derivatives, density functional theory.*

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Metoksidiglikol ile sübstitüe edilmiş imidazolidin dioksimlerinin platin (II) kompleksi üzerine hesapsal bir çalışma: aktivasyondan DNA bağlanmasına

Öz

Onaylanmış antikanser ajanlarının sahip olduğu toksisite sorunlarının üstesinden gelmek amacıyla, günümüzde birçok cisplatin türevi tasarlanmakta ve test edilmektedir. Yakın zamanda, DNA'yı hedef alan iki aktif ligand içeren, alifatik karbon zincirleri veya aromatik yapı ile sübstitüe edilmiş imidazolidin dioksim ligandlarına sahip yeni bir platin kompleks serisi önerdik. Kuantum mekanik hesaplamalar, özellikle alifatik sübstitüentlerin DNA platinasyonu üzerindeki potansiyel aktivitesini vurgulamıştır. Bu çalışmada, çözünürlük ve biyoyararlanımın artırılması amacıyla daha önce önerdiğimiz komplekslere metoksidiglikol (2-(2-metoksietoksi)etil) sübstitüenti dahil edilmiş ve bu modifikasyonun potansiyelini değerlendirmek için yeni önerilen platin kompleksinin hidroliz ve DNA bağlanma reaksiyonları hesapsal olarak çalışılmış ve sonuçlar aktif kullanımda olan cisplatin ile karşılaştırılmıştır.

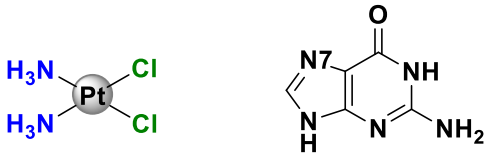
Anahtar kelimeler: *Platin ilaçları, antikanser ajanları, cisplatin türevleri, yoğunluk fonksiyoneli teorisi.*

1. Introduction

Cisplatin, the first Pt(II)-based drug for the treatment of cancer was discovered in the late 1960s and it has been approved by FDA in 1978 for clinical use [1]. However, its efficiency is limited due to its drawbacks including the side effects, low solubility and the acquired drug resistance which encourage researchers to develop improved platinum-based drugs that would be more effective and less toxic [2-4]. Next generation anticancer drugs such as carboplatin and oxaliplatin have been reported and approved for the clinical use [5-6]. These are less toxic than cisplatin, but still, they have side effects. Therefore, drug improvement based on cisplatin and the next-generation platinum drugs are promising to improve the properties of the parent structures.

The mechanism of action of cisplatin is widely recognized, beginning with its hydrolysis to form an aqua species. This occurs as cisplatin, with two coordination sites occupied by labile chloride ligands (Scheme 1), enters the cell, driven by the low concentration of chlorine within the cellular environment. [7]. After hydrolysis, the aqua species binds to DNA resulting in a cross-link with DNA that eventually leads to the cell death. Both hydrolysis and DNA binding reactions are assumed to take place in two steps following an S_N2 reaction mechanism. In the hydrolysis reaction, one nucleophilic water molecule replaces one labile chloride ligand at each step. The platinum (II) water complexes formed exhibit significant electrophilic properties, allowing them to engage in reactions with the purine bases of nucleic acids, which serve as potent nucleophiles at the N7 position [8]. Consequently, cisplatin forms covalent bonds with DNA bases, especially guanine (Scheme 1), resulting in structural distortion that triggers apoptosis. The effectiveness of cisplatin as an anti-cancer compound is partially due to its ability to promote the formation of inter- and intra-strand cross-links in DNA. This process serves

to impede gene transcription and DNA replication, consequently impeding protein synthesis and cell proliferation [9].



Scheme 1. Structures of cisplatin (left) and guanine (right).

It is important to understand the basic chemistry of platinum compounds, as well as to focus on enhancing the clinical delivery of these drugs. Cisplatin, carboplatin, and oxaliplatin are all administered exclusively as intravenous (IV) infusions. If the solubility of platinum drugs could be improved, clinicians could administer these drugs as injections rather than infusions [4].

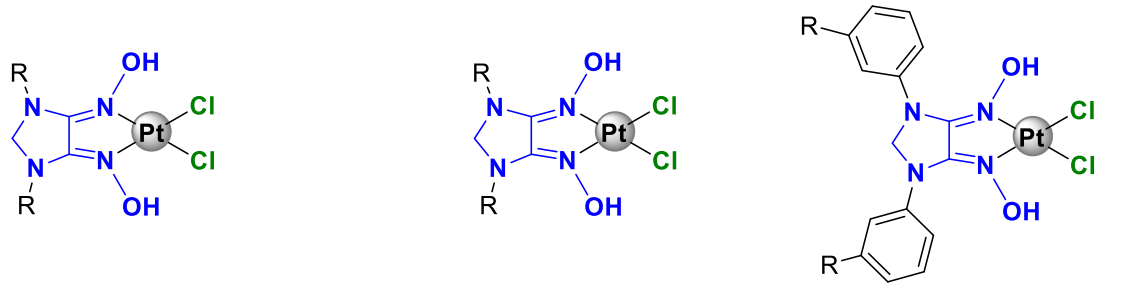
Oximes exhibit important biological activity through their interaction with DNA, and their complexes with platinum demonstrate significant cytotoxicity along with high DNA platination [10-13]. Recently, Pt(II) complexes of oxime ligands with aniline groups have been synthesized and these platinum complexes were shown to exhibit anticancer activity [14]. On the other hand, imidazolidine ring is a biologically important structure which is considered as a chemotherapeutic agent. Thus, oximes and imidazolidines represent two distinct families of compounds recognized for their biological activity through interaction with DNA; nevertheless, dioxime derivatives of imidazolidines [15-16].

We have recently proposed a new series of platinum complexes with highly potent imidazolidine dioxime ligands substituted with aliphatic carbon chains or aromatic unit and their fluorine analogues (Scheme 2) [17]. We have investigated the hydrolysis and DNA binding of these platinum complexes with quantum mechanical calculations to evaluate their potency as anticancer agents in comparison to the widely used anticancer agent, cisplatin. Our results indicated that these platinum complexes, particularly substituted with aliphatic carbon chains, might display enhanced activity due to their better DNA platination profile. Based on these promising results, we have extended our study with the utilization of 2-(2-methoxyethoxy)ethyl substituent resembling polyethylene glycol (PEG) which would confer greater solubility on this potent imidazolidine dioxime ligand of the platinum complex.

The modification of biological molecules with PEG, known as PEGylation, is used as a strategy to improve the pharmacokinetic behavior of the drug molecules [18]. Here, we have studied the hydrolysis and DNA binding of this platinum complex, **1a**, (Scheme 2) by using density functional theory to evaluate its activity compared to cisplatin.

This study

Previous study



Scheme 2. Structures of platinum complexes investigated in this study and in the previous study [17].

2. Computational methods

All calculations have been carried out with the Gaussian 16 program package [19]. Geometry optimizations were performed using density functional B3LYP. The dispersion effects were included using Grimme's D3 approach [20]. For platinum, the effective core potential (SDD) [21], and for the rest of the atoms the 6-31+G (d, p) basis set were used. This is the methodology we have applied in our previous study [17]. All calculations were performed with the SMD polarizable continuum model using water as a solvent [22]. Atomic charges were calculated using the NPA approach at the same level of theory [23].

All stationary points have been characterized by a frequency analysis at the same theory level as the geometry optimizations. All the energies reported in the manuscript are free energies (kcal mol^{-1}). CYLview was used to generate three-dimensional molecular images [24].

3. Results and discussion

A new platinum(II) complex of imidazolidine dioxime ligand substituted with 2-(2-methoxyethoxy)ethyl (**1a**) has been subject to a computational investigation to identify its potency as an anticancer agent in terms of its hydrolysis and DNA binding. Prior to calculations on the reaction mechanisms, charge analysis has been carried out for the neutral complex with two labile chloride ligands (Figure 1, left) and the fully hydrolyzed complex with 2+ charge (Figure 1, right) to explore their reactivity for hydrolysis and guanine binding reactions respectively. According to the NPA charge analysis (Figure 1), the Pt atom in both the neutral and fully hydrolyzed complexes possesses a larger positive charge relative to cisplatin. An increased positive charge on the Pt atom enhances the metal site's efficacy as an electrophilic center for nucleophilic substitution reactions during hydrolysis and guanine binding. Next, the aquation of **1a** and its binding to DNA (binding to guanine, as model of a purine base site of DNA) have been explored theoretically and the calculated energy profiles are shown in Figures 2 and 3 respectively.

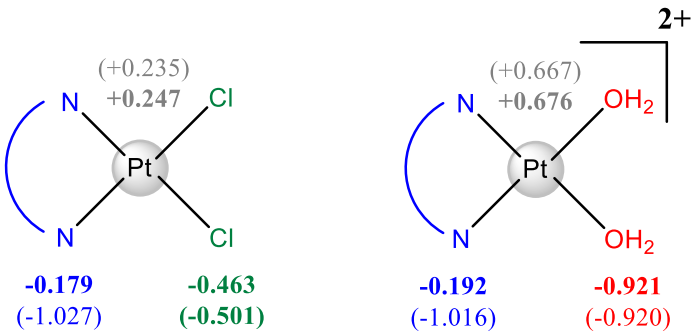


Figure 1. Natural charges of Pt, N, Cl and O atoms of the complex (**1a**, left) and its fully hydrolyzed form (right). The values in the parentheses are for cisplatin as a comparison from our previous study [17].

The initial reaction of cisplatin prior to DNA binding involves the substitution of chlorine atoms with water molecules in cellular environments characterized by low Cl^- concentration. In the hydrolysis reaction, the platinum complex is activated as its labile chloride ligands dissociate through a two-step S_N2 mechanism, with each step involving the replacement of a chloride by a water molecule as widely reported throughout in the literature (Figure 2). The reaction starts with a prereactive complex (**PRC$_{hyd}$**), where two water molecules form hydrogen bonds with the chloride ligand and the nitrogen atom of the oxime. In the first transition state, **TS1$_{hyd}$**, the Pt-Cl bond elongates from 2.37 Å to 2.86 Å, resulting in the dissociation of one chloride anion and the formation of an intermediate (**INT$_{hyd}$**) that is 7.5 kcal mol^{-1} of energy higher than **PRC$_{hyd}$**. This step requires 21.8 kcal mol^{-1} of energy. In **TS1$_{hyd}$**, the leaving chloride anion is stabilized by the hydroxyl of the oxime. The intermediate, **INT$_{hyd}$**, subsequently undergoes a second S_N2 reaction, with a lower energy barrier of 18.6 kcal mol^{-1}, leading to the fully aquated product, **PRO$_{hyd}$**. In the second transition state, **TS2$_{hyd}$**, the leaving chloride ion is stabilized by hydrogen bonding interactions with the oxime of the carrier ligand and the approaching nucleophile, water. Both transition states exhibit a pseudo-trigonal bipyramidal structure with the metal, the approaching water molecule and the leaving chloride anion lie in the same equatorial plane. The energy barriers for cisplatin are 22.8 and 24.0 kcal mol^{-1} for the first and second substitution reactions of hydrolysis. The overall hydrolysis of cisplatin is endergonic by 12.9 kcal mol^{-1}. For compound **1a**, the barrier for the first step of the hydrolysis is comparable to that of cisplatin, however the second step is 5.4 kcal mol^{-1} lower than that of cisplatin. The first step is the rate-determining step, in contrast to the hydrolysis of cisplatin. The overall hydrolysis of compound **1a** is endergonic by 10.7 kcal mol^{-1}. These results confirm the viability of aquation for compound **1a**.

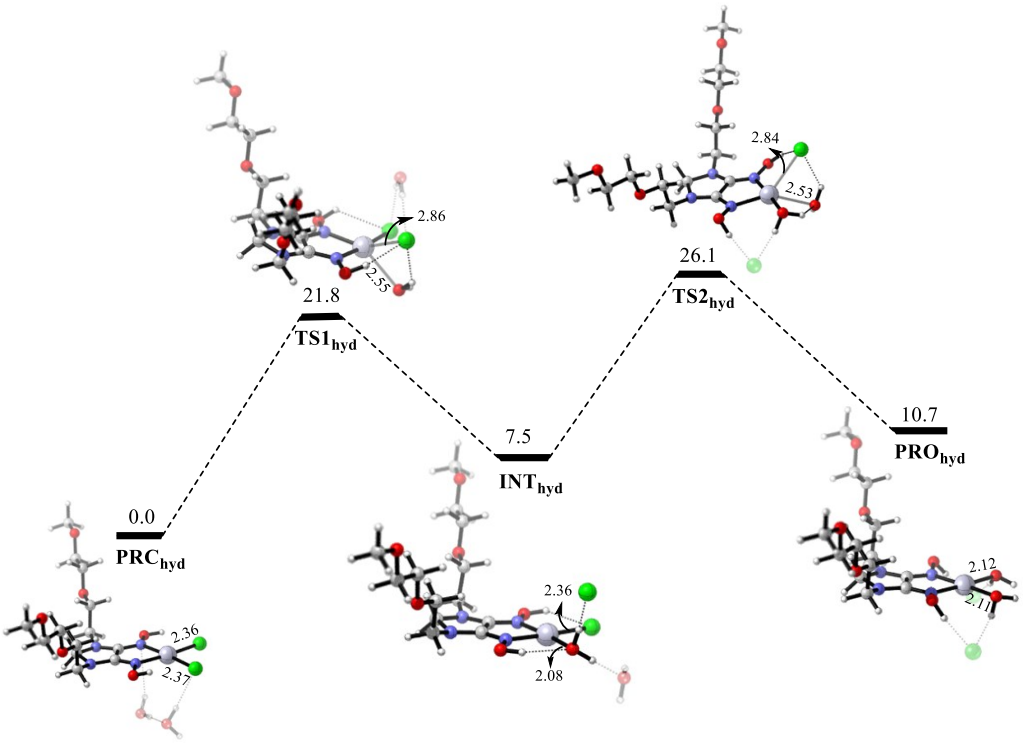


Figure 2. Energy profile for the hydrolysis of complex **1a**.

The positively charged and hydrolyzed complexes of classical platinum drugs exhibit electrostatic attraction to DNA. This interaction leads to binding with purine bases, ultimately causing DNA damage. Thus, the aquation reaction is followed by the displacement of the water molecule due to the interaction with DNA bases. Therefore, the interaction of the aquated form of compound **1a** with a purine base of DNA has been computationally investigated utilizing guanine as a model system (Figure 3).

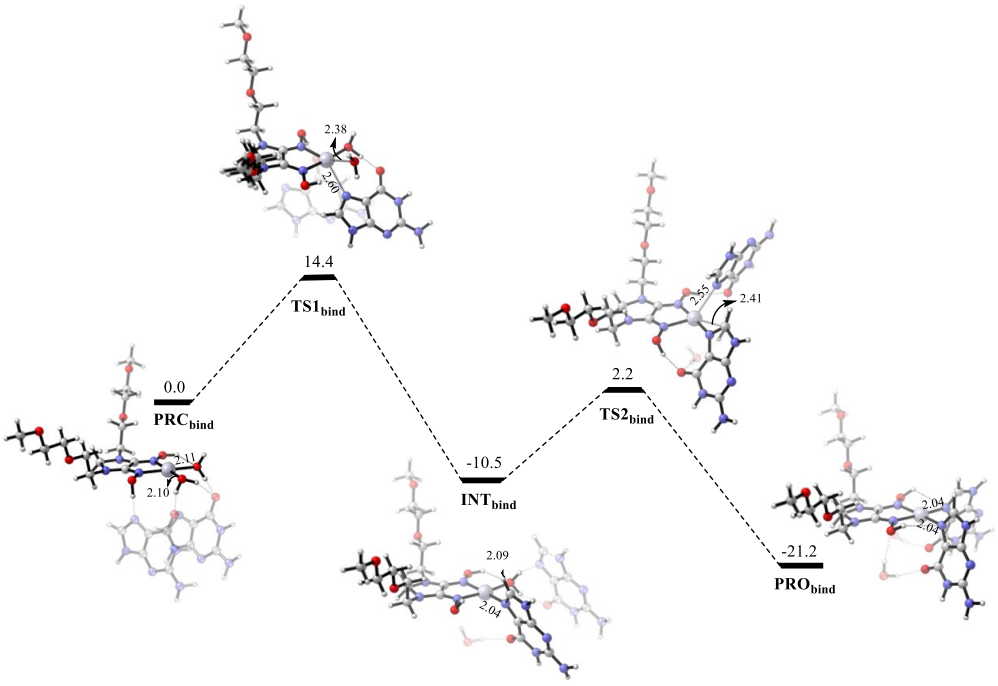


Figure 3. Energy profile for the binding of complex **1a** to guanine.

Guanine binding reaction is modeled from the prereactive complex, **PRC$_{bind}$**, where the oxygen atoms of guanine molecules establish hydrogen bonds with the water molecules (Figure 3). Additionally, the hydroxyl group of the oxime of the carrier ligand interacts with the N7 position of guanine. The initial step demands an energy input of 14.4 kcal mol^{-1} to surmount the barrier and form the intermediate, **INT$_{bind}$**. This intermediate has a lower energy than the prereactive complex, **PRC$_{bind}$**, by 10.5 kcal mol^{-1}. In the first transition state, **TS1$_{bind}$**, the approaching distance for the incoming guanine molecule is 2.60 Å, while the distance for the leaving water molecule elongates from 2.10 Å to 2.38 Å. IRC calculations have verified that **TS1$_{bind}$** connects the intermediate to the preractive complex. In the **INT$_{bind}$**, guanine forms a covalent bond with Pt with 2.04 Å and the free water molecule forms a hydrogen bond with the oxygen atom of the guanine molecule. The second step requires 12.7 kcal mol^{-1} of energy and through **TS2$_{bind}$** substitution leads to the final product, **PRO$_{bind}$**. In **TS2$_{bind}$**, the nucleophilic guanine molecule approaches the electrophilic metal center with a distance of 2.55 Å and the distance for the leaving water molecule elongates from 2.09 Å to 2.41 Å. The binding of the complex to guanine proceeds through a trigonal pyramidal transition state like hydrolysis. The overall process is highly exergonic by 21.2 kcal mol^{-1}. For compound **1a**, both energy barriers are similar, with the first step being the rate determining step. The binding of cisplatin to guanine occurs in two steps that require energies of 11.9 and 19.2 kcal mol^{-1}, respectively. While the first step has a lower energy requirement, the second step is significantly higher in energy and ultimately determines the rate of the overall reaction for cisplatin. The overall binding of guanine by cisplatin is highly exergonic, similar to that of compound **1a**.

The relative free energies of the intermediates, products and the transition states of all complexes investigated in this study (**1a**), as well as in our previous study (**1b-c**, **2a-b**) and cisplatin for the hydrolysis and guanine binding reactions are summarized in Table 1. Overall, the energy values for the proposed complexes are comparable to each other and are also lower than that of cisplatin.

Table 1. The relative free energies of the intermediates, products and the transition states for hydrolysis and guanine binding of **1a-c**, **2a-b** and cisplatin with respect to the corresponding pre-reactive complexes.

	TS1$_{hyd}$	**INT$_{hyd}$**	**TS2$_{hyd}$**	**PRO$_{hyd}$**	**TS1$_{bind}$**	**INT$_{bind}$**	**TS2$_{bind}$**	**PRO$_{bind}$**
1a*	21.8	7.5	26.1	10.7	14.4	-10.5	2.2	-21.2
1b**	22.5	10.4	30.8	12.1	12.8	-13.7	2.5	-22.8
1c**	21.8	7.7	27.3	11.1	11.6	-13.1	1.9	-25.2
2a**	21.7	8.5	28.3	11.9	15.5	-7.4	5.5	-17.4
2b**	21.8	8.9	27.6	11.1	16.7	-7.7	5.1	-16.4
CisPt**	22.8	5.1	29.1	12.9	11.9	−16.4	2.8	−25.3

*this study ** values taken from our previous study [17]

4. Conclusions

In this study, we conducted a quantum mechanical investigation of the cytotoxic potential of a platinum (II) complex comprising imidazolidine dioxime ligands, two active components that target DNA, with 2-(2-methoxyethoxy)ethyl substituent as an extension of our previous study. In our previous study we have studied the cytotoxic activity of platinum (II) complexes of imidazolidine dioxime ligands substituted with aliphatic

carbon chains or aromatic unit and their fluorine analogues and concluded that newly proposed platinum complexes might display an improved activity particularly in terms of DNA platination compared to the clinically used anticancer agent, cisplatin. Based on these promising results, we have extended our study with the inclusion of 2-(2-methoxyethoxy)ethyl substituent so that their solubility could be improved and then this may open up new clinical avenues for their delivery.

The reactivity of the proposed platinum complex **1a** was elucidated regarding their performance in hydrolysis and guanine binding reactions. The calculated barrier height for the hydrolysis reaction was found to be generally similar to the previously proposed complexes, **1b-c** and **2a-b**, albeit marginally lower than that of cisplatin. In the guanine binding reaction, the complex showed significantly lower calculated activation barriers compared to cisplatin, and even lower barriers than the previously proposed platinum complexes of imidazolidine dioxime ligands substituted with aliphatic carbon chains (**1b-c**), indicating an enhanced reactivity. These insights will inform forthcoming experimental endeavors focused on the synthesis of the proposed complexes and the subsequent evaluation of their in-vitro cytotoxic activity.

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References

[1] Rozencweig, M., von Hoff, D.D., Slavik, M. and Muggia, F.M., Cis-diamminedichloroplatinum (II). A new anticancer drug, **Annals of Internal Medicine,** 86, 6, 803–812, (1977).

[2] Oun, R., Moussa, Y. E. and Wheate, N. J., The side effects of platinum-based chemotherapy drugs: a review for chemists, **Dalton Transactions**, 47, 19, 6645–6653, (2018).

[3] Stordal, B. and Davey, M., Understanding cisplatin resistance using cellular models, **IUBMB Life**, 59, 11, 696–699, (2007).

[4] Alassadi, S., Pisani, M.J. and Wheate, N.J., A chemical perspective on the clinical use of platinum-based anticancer drugs, **Dalton Transactions**, 51, 29, 10835–10846, (2022).

[5] Yarbro, C. H., Carboplatin: A clinical review, **Seminars in Oncology Nursing**, 5, 2, 63–69, (1989).

[6] Stein, A. and Arnold, D., Oxaliplatin: a review of approved uses, **Expert Opinion on Pharmacotherapy**, 13, 1, 125–137, (2012).

[7] El-Khateeb, M., Appleton, T.G., Gahan, L.R., Charles, B.G., Berners-Price, S.J. and Bolton, A.M., Reactions of cisplatin hydrolytes with methionine, cysteine, and plasma ultrafiltrate studied by a combination of HPLC and NMR techniques, **Journal of Inorganic Biochemistry**, 77, 13–21, (1999).

[8] Pinto, A. L. and Lippard, S. J., Binding of the antitumor drug c/s-diamminedichloroplatinum(II) (cisplatin) to DNA, **Biochimica et Biophysica Acta**, 780, 167–180, (1985).

[9] Dasari, S. and Bernard Tchounwou, P., Cisplatin in cancer therapy: Molecular mechanisms of action, **European Journal of Pharmacology**, 740, 364–378, (2014).

[10] Schepetkin, I. A., Plotnikov, M. B., Khlebnikov, A. I., Plotnikova, T. M. and Quinn, M. T., Oximes: Novel Therapeutics with Anticancer and Anti-Inflammatory Potential, **Biomolecules**, 11, 6, 777, (2021).

[11] Kaya, Y., Icsel, C., Yilmaz, V. T. and Buyukgungor, O., Palladium(II) and platinum(II) complexes of a new imineoxime ligand – Structural, spectroscopic and DFT/time-dependent (TD) DFT studies, **Journal of Organometallic Chemistry**, 752, 83–90, (2014).

[12] Sayin, K. and Karakaş, D., Computational investigations of trans-platinum(II) oxime complexes used as anticancer drug, **Spectrochimica Acta, Part A: Molecular and Biomolecular Spectroscopy**, 188, 537–546, (2018).

[13] Alinaghi, M. Karami, K., Shahpiri, A., Nasab, A.K., Momtazi-Borojeni, A.A., Abdollahi, E. and Lipkowsk, J., A Pd(II) complex derived from pyridine-2-carbaldehyde oxime ligand: Synthesis, characterization, DNA and BSA interaction studies and in vitro anticancer activity, **Journal of Molecular Structure**, 1219, 128479, (2020).

[14] Eroğlu Gülümsek, Ö., Erciyas Baykal, E., Küçükpolat, C., Önal, E., Balcik-Ercin, P., Yagci, T., Ahsen, V., and Gürek, A.G., Bis[N,N′-bis(anilino)glioximato]platinum(II) complex: synthesis, characterization and biological activity, **Journal of Coordination Chemistry**, 75, 197–210, (2022).

[15] Caterina, M.C., Perillo, I.A., Boiani, L., Pezaroglo, H., Cerecetto, H., González, M. and Salerno, A., Imidazolidines as new anti-Trypanosoma cruzi agents: Biological evaluation and structure–activity relationships, **Bioorganic & Medicinal Chemistry**, 16, 5, 2226–2234, (2008).

[16] Gürses, C., Aktaş, A., Balcıoğlu, S., Fadhilah, A., Gök, Y. and Ateş, B., Synthesis, characterization, DNA binding and anticancer activities of the imidazolidine-functionalized (NHC)Ru(II) complexes, **Journal of Molecular Structure**, 1247, 131350, (2022).

[17] Emirik, Ö.F., Şanlı, C., Ahsen, V., Gürek, A.G. and Dedeoglu, B., Theoretical investigation of the hydrolysis and DNA binding of platinum (II) complexes of imidazolidine dioximes, **Molecular Physics**, 121, 22, e2236244.

[18] Veronese, F.M. and Mero, A., The impact of PEGylation on biological therapies, Drug Development, **BioDrugs**, 22, 315-329 (2008).

[19] Frisch, M.J., Trucks, G.W., Fox, D.J., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G.A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H.P., Izmaylov, A.F., Bloino, J., Zheng, G., Sonnenberg, J.L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery Jr., J.A., Peralta, J.E., Ogliaro, F., Bearpark, M., Heyd, J.J., Brothers, E., Kudin, K.N., Staroverov, V.N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J.C., Iyengar, S.S., Tomasi, J., Cossi, M.,

Rega, N., Millam, J.M., Klene, M., Knox, J.E., Cross, J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J.W., Martin, R.L., Morokuma, K., Zakrzewski, V.G., Voth, G.A., Salvador, P., Dannenberg, J.J., Dapprich, S., Daniels, A.D., Farkas, Ö., Foresman, J.B., Ortiz, J.v., Cioslowski, J. and Fox, D.J., Gaussian Inc., Wallingford, Wallingford CT, 2013.

[20] Grimme, S., Antony, J., Ehrlich, S. and Krieg, H., **The Journal of Chemical Physics**, 132, 154104, (2010).

[21] Grimme, S., Semiempirical hybrid density functional with perturbative second-order correlation, **The Journal of Chemical Physics**, 124, 3, 34108, (2006).

[22] Marenich, A.V., Cramer, J.C. and Truhlar, D.G., Performance of SM6, SM8, and SMD on the SAMPL1 Test Set for the Prediction of Small-Molecule Solvation Free Energies, **Journal of Physical Chemistry B**, 113, 14, 4538–4543, (2009).

[23] Reed, A.E., Weinstock, R.B. and Weinhold, F., **The Journal of Chemical Physics**, 83, 735–746 (1985).

[24] C.Y. Legault, CYLviewsoftware [Online]. Available: http://www.cylview.org.