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Mathematical Modeling of the Biological Activity of a New Complex Compound Based on Palladium and Mexidol

Burak Tüzün*, Rana Jafarova, Ismail Bagirov, Nigar Magerramova, Tohfa Nasibova

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Abstract

Platinum preparations are widely used in the treatment of cancer patients, as they have an antitumor effect. However, the use of such drugs is limited due to their high toxicity. In this study, the goal was to reveal the anticancer activity of a new complex synthesized compound based on palladium and mexidol (2-ethyl-6-methyl-3-hydroxypyridine ammonium tetrachloropalladic acid), which has low toxicity. The interaction of palladium metal complexes with EGFR kinase protein (PDB ID: 2ITO) and their activity against these proteins were investigated. First, the palladium metal complex and protein have interacted with the HEX program. Afterward, PLIP analysis was performed to examine the interaction of metal complexes with protein in detail. Afterward, a Swiss ADME/T analysis of this palladium complex was performed. According to the Hodge and Sterner toxicity scale, the studied compound belongs to the group of moderately toxic substances that are allowed in medicine. As a result of the conducted calculations, the authors commented on the activity of the Pd metal complex. The interaction of the pd metal complex with the EFGR kinase protein was examined by PLIP analysis and its movements in human metabolism were predicted by ADME analysis of the Pd metal complex.

Keywords: Molecular docking, ADME/T, Anticancer effect, Palladium metal complex

Introduction

The search for new biologically active compounds for use in medical practice remains an important task of medical and pharmaceutical science (Taher *et al*., 2022; Nakagawa *et al*., 2021). Platinum preparations, widely used in the treatment of cancer patients, have shown a significant antitumor effect and prevent the development of metastases. However, their high toxicity limits their use. Thus, the search for new drugs with a similar effect, but less toxic, is carried out among the complex compounds of palladium, a metal from the platinum chemical group. Special attention is paid to structural analogs of cisplatin, as well as palladium compounds with pyridine derivatives (Tanaka *et al*., 2013; Kapdi & Fairlamb, 2014). At present, preparations based on palladium, such as morphosine and others, are recommended for oncological practice.

The search for effective but low-toxic chemotherapeutic agents among metal complexes similar in structure to platinum preparations, in which palladium is the complexing metal, is relevant due to the lower toxicity and equal efficiency of such compounds. A new complex compound based on palladium (Pd(II) and mexidol (ethylmethylhydroxypyridine succinate) was synthesized in the laboratory of the Azerbaijan Medical University, and its physicochemical properties were studied. It was found that the compound has the formula 2-ethyl-6-methyl-3-hydroxypyridine ammonium tetrachloropalladic acid and contains 2-valent palladium, coordinated with the organic core (Anvar & Magerramova, 2019; Jafarova & Magerramova, 2022). Studies also revealed that this compound has low toxicity. LD_{50} for male rats was 430 mg/kg and for white male mice – 355 mg/kg. According to the Hodge and Sterner toxicity scale (1943), it belongs to the group of moderately toxic substances. According to the GOST 12.1.007-76 toxicity classification of chemicals, it qualifies as a compound of the 3rd hazard class allowed for use in medicine (Anvar & Magerramova, 2019). The compound also has a pronounced radioprotective property (Jafarova & Magerramova, 2022).

The purpose of these studies was to identify the anticancer activity of the compound based on a mathematical model.

Materials and Methods

Recent studies showed that theoretical calculations have become an important method used in many processes such as how synthesis takes place and the characterization of molecules and comparison of the activities of molecules (Erdogan *et al*., 2023; Sarkı *et al*., 2023). Many programs can be used for these processes. However, it is one of many important programs used to examine the activities against EGFR kinase protein (Yun *et al*., 2007) using the HEX program (Ritchie & Orpailleur, 2013). Afterward, PLIP analysis (Adasme *et al*., 2021) was performed to examine in detail the interaction between the palladium complex and the protein. ADME/T analysis was then performed using SwissADME (Daina *et al*., 2017) to

Burak Tüzün*
Department of Plant and Animal Production, Technical Sciences Vocational School of Sivas, Sivas Cumhuriyet University, Sivas, Turkey.

Rana Jafarova, Ismail Bagirov, Nigar Magerramova, Tohfa Nasibova
Department of Toxicology, Scientific Research Center, Azerbaijan Medical University, Baku, Azerbaijan.

***E-mail:** theburaktuzun@yahoo.com

predict the effects and responses of the metal complex in human metabolism.

The biological activities of the complex against cancer proteins were compared. The proteins and metal complexes were studied at HEX 8.0.0 programs. The antibacterial calculations against the crystal structures were performed. The following parameters are used for docking: correlation type shape only, FFT mode: 3D, grid dimension: 0.6, receptor range: 180, ligand range: 180, twist range: 360, distance range: 40. Finally, the Protein-Ligand Interaction Profiler (PLIP) server confirmed the interaction between protein and the metal complex. Afterward, SwissADME was then made for ADME/T analysis of this palladium complex.

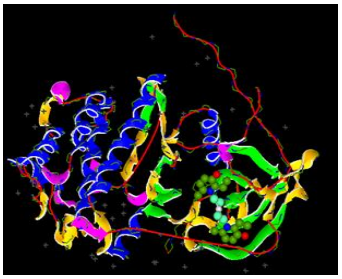
Results and Discussion

The most important thing is to compare their activities against biological materials. It is possible to compare the activities of metal complexes with the molecular docking calculations made for this purpose (Chalkha *et al*., 2023; Daoui *et al*., 2023). In calculations made to compare the activities of molecules and their metal complexes, the most important factor determining the activity of molecules and their metal complexes is the chemical interactions between molecules and proteins, which are hydrogen bonds, polar and hydrophobic interactions, π-π and halogen (Shahzadi *et al*., 2022; Rezaeivala *et al*., 2023). As these interactions increase, it is seen that the activities of the molecules and their metal complexes increase. It was observed that as the interactions of the molecules increased, the activity of the molecules increased because it inhibited the protein more (Alaysuy *et al*., 2022; Tapera *et al*., 2022). Among the parameters obtained in the calculations, the Etotal energy value shows the activity of molecules and their metal complexes. Etotal energy values of studied metal complexes are presented in **Table 1**.

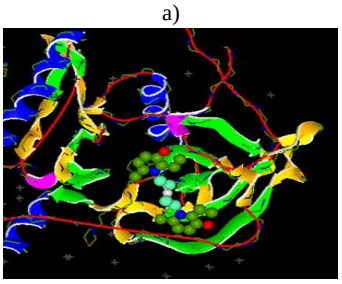
Table 1. E total energy value of complex

Pd metal complex	-352.75

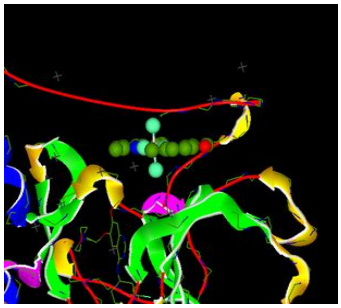
The interactions of the pd metal complex with the EGFR kinase protein are given in **Figure 1**.



a)



b)



c)

Figure 1. Presentation interactions of Pd metal complex with EGFR kinase protein

Chemical interactions between the pd metal complex and EGFR kinase protein were only Hydrophobic Interactions. between which atom and protein these interactions occur is presented in **Table 2**.

Table 2. Hydrophobic Interactions between Pd metal complex and EGFR kinase protein

Index	Residue	AA	Distance	Ligand atom	Protein atom
1	728A	LYS	3.17	3005	313
2	730A	LEU	3.76	3021	332
3	741A	PRO	3.76	3018	439
4	794A	PRO	3.80	3025	928
5	846A	LYS	3.92	3011	1460
6	846A	LYS	3.76	3036	1459
7	1012A	ASP	2.84	3029	2862

PLIP analysis was performed to examine further interactions in more detail. The numerical values of the interactions between the Pd metal complex and the proteins were obtained in **Figure 2**.

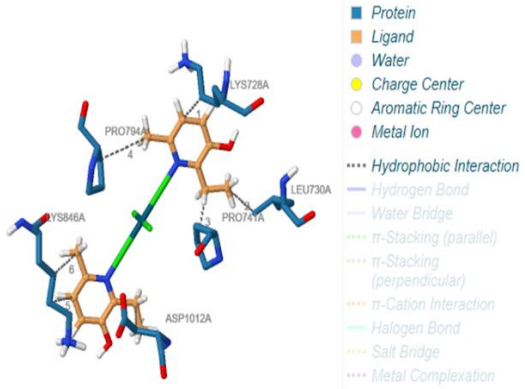


Figure 2. Presentation interactions of Pd metal complex with EGFR kinase protein in PLİP

Swiss-ADME analysis was performed to examine the ADME properties of the Pd metal complex **(Table 3)**. Many pharmacological and pharmacokinetic properties of the Pd metal complex were investigated. **Figure 3** show six physicochemical indexes of the Bioavailability radar, axis lipophilicity, size, polarity, solubility, flexibility, and saturation.

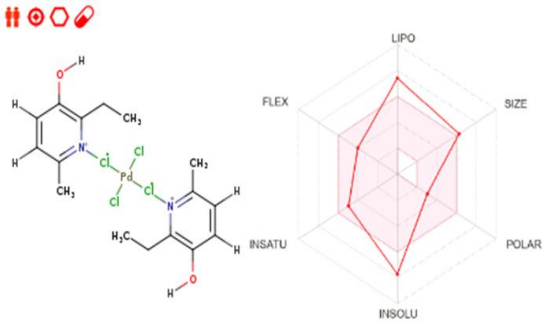


Figure 3. Drug likeness parameters of Pd metal complex

It is given as the value of the Log P o/w of the molecules as the partition coefficient factor between octane and water solvents through the pharmacokinetic route, which is the classical indicator of lipophilicity (Alkandahri *et al*., 2021; Yusuf *et al*., 2021). Apart from these, it is very important to examine the behavior of the studied metal complexes against certain pharmacokinetic proteins such as P-glycoprotein (P-gp) and cytochromes P450 (CYP) (Tapera *et al*., 2022). It should be well known that the most important task of P-gp is to keep the central nervous system away from xenobiotics, on the other hand, this protein is secreted in some tumor cells and leads to drug-resistant cancers (Ukibayev *et al*., 2021; Lalthanpuii *et al*., 2022). It is also pharmacologically very important to understand how these compounds interact with cytochrome P450 (CYP) (Alaysuy *et al*., 2022; Bakchi *et al*., 2022). This group of iso-enzymes metabolically plays an important role in drug clearance, it has been suggested that CYP and P-gp may work together to metabolize small compounds synergistically to promote tissue and organism protection (AlRuwaili *et al*., 2022).

Table 3. ADME properties of metal complex

Physicochemical Properties		**Druglikeness**	
Formula	$C_{16}H_{22}Cl_4N_2O_2Pd$	Lipinski	Yes; 1 violation: MW>500
Molecular weight	522.59 g/mol	Ghose	No; 1 violation: MW>480
Num. heavy atoms	25	Veber	Yes
Num. arom. heavy atoms	12	Egan	Yes
Fraction Csp3	0.38	Muegge	No; 1 violation: XLOGP3>5
Num. rotatable bonds	6	Bioavailability Score	0.55
Num. H-bond acceptors	2	**Water Solubility**	
Num. H-bond donors	2	Log *S* (ESOL)	-7.73
Molar Refractivity	105.27	Solubility	9.86 10^{-06} mg/ml; 1.88 10^{-08} mol/l
TPSA	48.22 Å²	Class	Poorly soluble
Lipophilicity		Log S (Ali)	-8.28
Log $P_{o/w}$ (iLOGP)	0.00	Solubility	2.72 10^{-06} mg/ml; 5.20 10^{-09} mol/l
Log $P_{o/w}$ (XLOGP3)	7.44	Class	Poorly soluble
Log $P_{o/w}$ (WLOGP)	4.48	Log *S* (SILICOS-IT)	-6.38
Log $P_{o/w}$ (MLOGP)	2.81	Solubility	2.20 10^{-04} mg/ml; 4.21 10^{-07} mol/l
Log $P_{o/w}$ (SILICOS-IT)	3.46	Class	Poorly soluble
Consensus Log$P_{o/w}$	3.64	**Medicinal Chemistry**	
Pharmacokinetics		PAINS	0 alert
GI absorption	High	Brenk	0 alert
BBB permeant	Yes		
P-gp substrate	No		
CYP1A2 inhibitor	Yes	Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
CYP2C19 inhibitor	No	Synthetic accessibility	3.31
CYP2C9 inhibitor	No		
CYP2D6 inhibitor	Yes		
CYP3A4 inhibitor	No		
Log Kp (skin permeation)	-4.21 cm/s		

Conclusion

As a result of the theoretical calculations made, it was tried to comment on the activity of the Pd metal complex. The interaction of the pd metal complex with the EFGR kinase protein was examined by PLIP analysis. However, its movements in human metabolism were predicted by ADME analysis of the Pd metal complex.

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Conflict of interest: None

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Ethics statement: The study was conducted in accordance with international ethical standards.

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