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Inhibition of xanthine oxidase by copper-palladium Schiff bases

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Abstract

Gout is a common disease in all the world's population, especially the elderly. This study aims to evaluate the effectiveness of the enzyme xanthine oxidase with some metal complexes Schiff-Base, which contain copper and palladium metal atoms, and to compare these compounds with each other as well as with the drug allopurinol, which is commonly used in this disease. It is worth noting that all the compounds were purchased from Turkey with the industrial enzyme xanthine oxidase (XO). The enzyme activity was measured by a spectrophotometer at a wavelength of 295 nm at a rate of five different concentrations for each compound and the absorbance was transferred at specific times to mathematical equations in Microsoft Excel to draw the inhibition curve, through which we obtain values through which we can calculate (half the inhibitory concentration) IC 50. Cheminformatics was used to predict the associations of these compounds with the protein by drawing the compounds using the Chem Office program in three-dimensional form and saving them in the format (PDB) and loading the protein specific to the enzyme from the site (Protein Data Bank) and performing molecular docking between all compounds and the protein using two programs (PyRx) and (Molegro virtual Docker) and determining the hydrogen bonds with the active site of the protein with the ligands and taking the values of (IC50) and comparing them with the practical side and found that they are highly consistent

Introduction

Gout is the most common disease-causing arthritis and is associated with high levels of serum uric acid (ASU) or high blood uric acid. It is considered the main acid for the development of gout. With an increase in uric acid and exceeding the physiological saturation limit in body fluids, the formation and deposition of small crystals of monosodium uric acid (MSU) crystals occurs in and around the joints [1]. Purine metabolism as a by-product produces hypoxanthine and by the action of the enzyme xanthine oxidase produces xanthine and by the same enzyme (XO) produces uric acid naturally there are benefits to this acid in the body if it is at normal levels which is approximately (3.4-7 mg/DL) as it has an antioxidant role Uric acid can act as a natural antioxidant in the body, helping to protect cells from damage caused by free radicals, which are molecules that can cause inflammation and lead to chronic diseases. Uric acid is part of the defense system that protects cells from oxidation, especially in the brain. It has the ability to protect the nervous system from Alzheimer's and Parkinson's disease [2]. Xanthine oxidase is a flavoprotein enzyme found in bacteria as well as humans and various mammalian tissues that catalyzes the oxidative

hydroxylation of purine substrates at the molybdenum center (reductive half-reaction) and the secondary reduction of oxygen at Flavin centers with the generation of reactive oxygen species (ROS) as for the hydrogen peroxide anion (oxidative half-reaction). Many diseases arise from an increase in uric acid above the normal level so that the kidneys cannot excrete it in the urine.

There is agreement that serum levels of (ROS) increase significantly in various disease states such as hepatitis, ischemia, cancer and aging and that (ROS) produced in the enzymatic process participates in oxidative damage and therefore it has become necessary to inhibit this pathway because it returns to the body [3] It also works to inhibit (XO) reduce oxidative stress on blood vessels [4]. Schiff base metal complexes have been of great interest for many years as biochemical and antimicrobial agents. Many studies have shown that they have anticancer activity [5].

One of the most important substances used for gout is allopurinol, which has many side effects such as skin rash, skin problems, headache, liver and kidney inflammation, and it also remains weak in getting rid of reactive oxygen species. While Schiff bases interact with amino acids present in the active site of the enzyme, which hinders the enzyme's ability to bind to the substrate such as xanthine and hypoxanthine, which is called competitive inhibition [6]. Xanthine oxidase inhibitors with different, non-purine structures have been developed with stronger inhibition than some existing drugs. Schiff bases can be used as potential compounds to inhibit xanthine oxidase. Schiff bases are chemical compounds that contain carbon-nitrogen double bonds (C=N bonds) that are formed by the reaction of the amine group with the carbonyl group [7].

These compounds are known for their biological properties and have been shown to be effective in inhibiting some enzymes, including xanthine oxidase. Schiff bases are known to interact with certain binding sites in enzymes, which may hinder the catalytic activity of xanthine oxidase and prevent the conversion of xanthine to uric acid. Schiff bases can be prepared in different ways to produce compounds with diverse chemical structures, allowing studies to explore their effects as inhibitors. Structural modification of these compounds may improve their ability to inhibit the enzyme and also exhibit antioxidant activity, which may be useful in reducing oxidative stress that may play a role in the aggravation of diseases such as gout. Compounds that inhibit xanthine oxidase and act as antioxidants may be more effective.

This study aims to evaluate the inhibitory activity of xanthine oxidase (XO) using Schiff base metal complexes containing copper and palladium, and compare them with allopurinol. IC_{50} values were calculated experimentally and supported by molecular docking simulations using PyRx and Molegro Virtual Docker. The study also investigates the correlation between in vitro results and in silico predictions.

Materials and methods

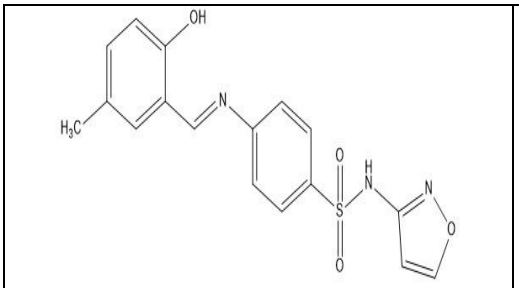
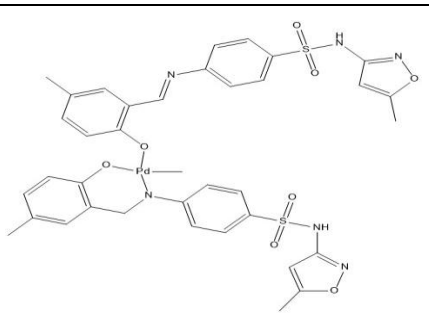
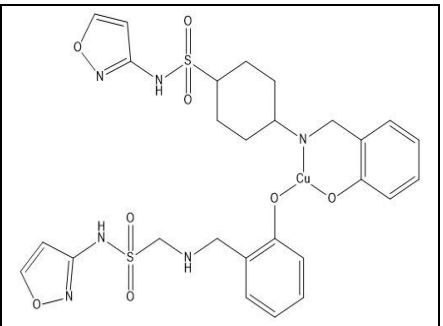
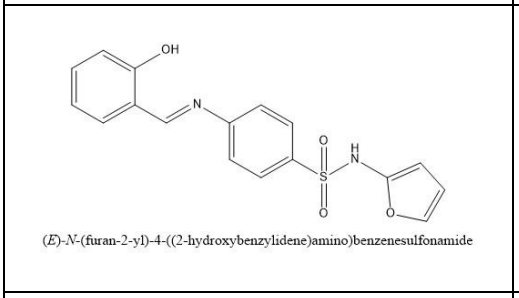
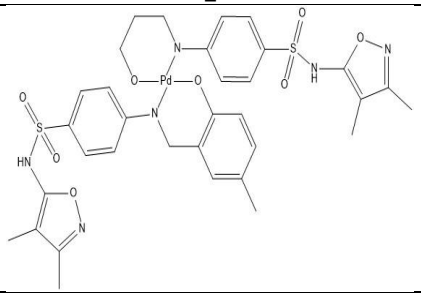
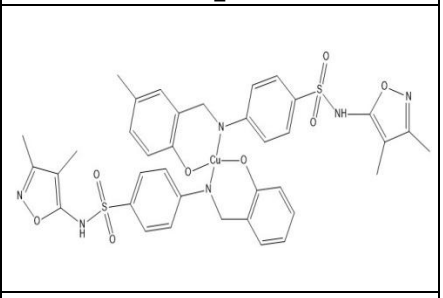
Measurement of enzyme activity

From the protein data bank, xanthine oxidase was downloaded, which carries the symbol (1FIQ), a protein that was uploaded by previous researchers after taking resonance rays for it and was prepared using the Pyrex program in anticipation of a deficiency in its amino acids, as well as completing the protein from water and hydrogen molecules. The 12 compounds, including the drug allopurinol, were purchased from Shandong Look Chemical Co., Ltd in Turkey, and 12 compounds were also drawn in addition to the drug allopurinol using the ChemOffice program table 1. and converting the chemical formula from the second dimension to the third dimension and reducing the energy of the compounds to the minimum to reach the spatial form closest to the real form of

all compounds as it is the appropriate ligand for the protein, where the comparison is made with these ligands so that the larger the number is in the negative value, the better the inhibition, noting that the best inhibition must be higher than -6.

The active sites were determined using two programs, namely PyRx and Molegro Virtual Docker, by specifying the guide box for all proteins and then applying the specified location for all ligands, and the results were as in Table 2

Table 1: All compounds and complexes involved in inhibiting the enzyme (XO)

		
C1	C1_Pd	C1_Cu
		
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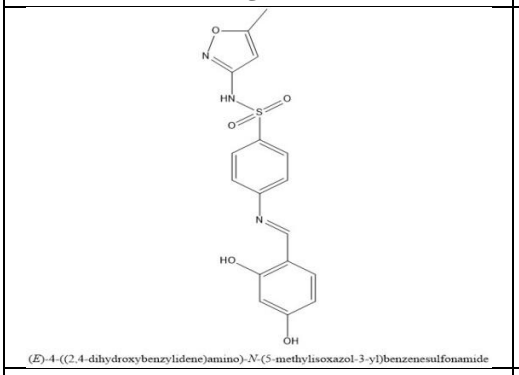
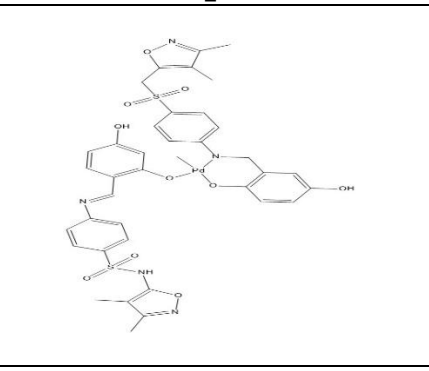
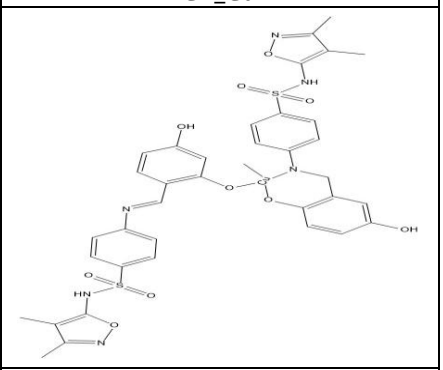
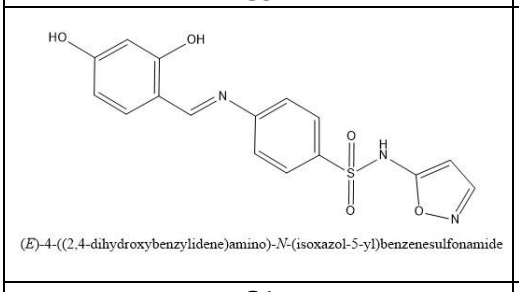
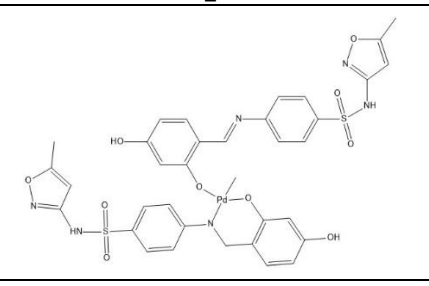
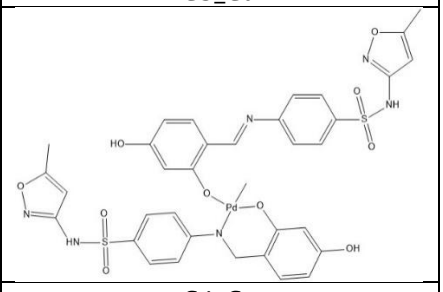
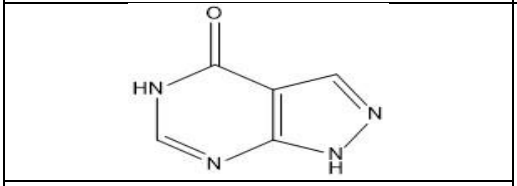
		
C3	C3_Pd	C3_Cu
		
C4	C4_Pd	C4_Cu
		
Allopurinol		

Table 2: Results of XO enzyme inhibition

Compounds	IC50 µM	MolDock Score	HBond	RMSD
C1	188.982	-144.628	-4.8	7.920
C1_Pd	0.834726	-215.155	-9.7	4.447
C1_Cu	1.044281	-215.142	-8.8	1.688
C2	200.0526	-125.989	-2.5	2.725
C2_Pd	30.6152	-215.841	-	3.004
C2_Cu	0.210211	-215.845	-10.2	3.571
C3	139.1842	-137.491	-5.2	4.363
C3_Pd	14.1289	-200.861	-4.5	2.177
C3_Cu	0.25386	-200.854	-10.8	2.360
C4	72.1027	-128.059	-3.1	2.078
C4_Pd	43.2015	-202.749	-10.2	2.757
C4_Cu	0.348531	-202.658	-11.2	2.078
Allopurinol	0.368987	-220.426	-6.6	1.562

Buffer was prepared by dissolving 68.043 g of potassium dihydrogen phosphate in distilled water and making up the volume to 1000 ml with the same solvent, titrating the solution with 2 M sodium hydroxide solution on a pH meter to obtain a pH of 5.7.

Dissolving 4 mg of synthetic hypoxanthine per 9 ml of distilled water and making up the volume with phosphate buffer to 10 ml, 60 microliters of which were used. In the same way and concentrations, synthetic xanthine was prepared and 10 microliters were taken from it. These volumes were placed in a 100 ml volumetric flask, adding 50 ml of phosphate buffer and making up the volume with distilled water.

The ligands were prepared at several concentrations 10-20-50-60-80 µ liter also using phosphate buffer and distilled water in the same volumes used in the preparation of the protein and were applied to all ligands including allopurinol. The device was zeroed on the solvent and then readings were taken for each concentration after 30 seconds. The readings were taken and entered into an equation on the Excel program to obtain the inhibition curve.

The device reading is taken first for the protein at the beginning and is called control, then the rest of the readings are taken according to the time mentioned above 30 Sec. and the absorbance of each concentration is recorded to draw the curve.

$$curve = \frac{absorbance}{control} * 100$$

By entering the absorbance of five concentrations in addition to the absorbance of the control, which is 100, we obtain the 6 points through which the inhibition curve will pass which I get the exponential value

y = 100 e-0,xxxxx

From the equation below, get the value of ic50.

$$IC50 = Ln2/-0.xxxxx$$

IC50 stands for "Inhibitory Concentration 50%", a measure of the inhibitory effectiveness of a compound against an enzyme or biological pathway. It refers to the concentration of an inhibitory substance that reduces the target biological activity such as the activity of a specific enzyme by

50%.

Different concentrations of the inhibitor the substance whose ability to inhibit the enzyme is to be tested are used and the enzyme activity is recorded at each concentration. Then, a dose-response curve is drawn, where the X-axis represents the different concentrations of the inhibitor, and the Y-axis represents the percentage of enzyme activity remaining. The IC50 is the concentration that causes a 50% reduction in activity and is the point on the curve where the horizontal line crosses at 50%. The IC50 is an important measure in drug discovery and development, as it is used to evaluate the effectiveness of inhibitory drugs or other chemical compounds against specific targets such as enzymes or receptors [8].

Molecular modeling

The three-dimensional crystal structure of the enzyme protein xanthine oxidase (1FIQ) was downloaded from the Protein Data Bank website (PDB) and hydrogen atoms were added and water molecules and the old ligand were removed from the protein using Pyrex and Molcro programs, then a two-dimensional structure was built for all complexes and also for the drug allopurinol on the ChemOffice program and converted to three dimensions and reduced the energy of the bonds to the minimum. The best site for the complexes was determined by doing a comprehensive way for the protein by specifying it with the guidebox of the Pyrex program

Results and Discussion

The A chain of the 1FIQ protein was targeted due to the presence of a ligand, including allopurinol, identified in the PDB. The ligands were removed, and the complexes specific to the study were introduced. Additionally, the programs used in the study (PyRx and Molegro Virtual Docker) contain a guided box feature, and the entire 1FIQ protein was identified to determine the optimal location for the enzyme's active site.

Figure 1 shows the xanthine oxidase enzyme protein and its ligand binding site, taken from Cheminformatics using the PyMOL program.

PyMOL is a powerful molecular visualization tool commonly used in structural biology. It allows users to generate high-quality 3D representations of macromolecules such as proteins and nucleic acids, as well as visualize molecular interactions, like ligand binding sites. In this study, PyMOL was used to analyze and display the binding interactions between the enzyme and its ligand, providing a detailed view of the molecular structure

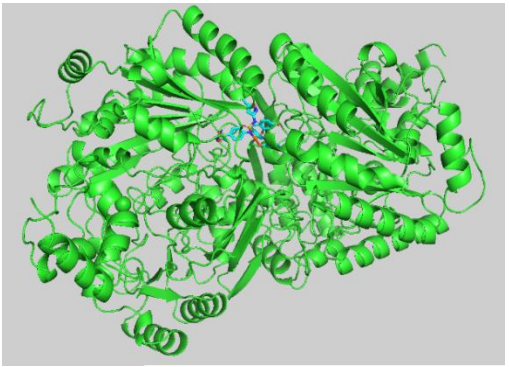


Fig. 1. *Location of the ligand in the active site of the enzyme*

Table 2 compares the original compound (C1) with the metal complexes (C1_Pd and C1_Cu). After adding Pd and Cu, there is a significant improvement in the compounds' activity:

C50 µM: IC50 values decrease dramatically (from 188.982 µM for C1 to 0.834726 µM for C1_Pd and 1.044281 µM for C1_Cu), indicating increased potency.

MolDock Score: The MolDock scores become more negative (-144.628 for C1 to -215.155 for C1_Pd and -215.142 for C1_Cu), showing stronger binding affinity.

HBond: The number of hydrogen bonds increases (from 4.8 for C1 to 9.7 for C1_Pd and 8.8 for C1_Cu), suggesting more stable interactions.

RMSD: RMSD decreases (from 7.920 for C1 to 4.447 for C1_Pd and 1.688 for C1_Cu), indicating better binding alignment.

Figure 3 suggests that the metal complexes enhance the compound's inhibitory activity, making them more potent inhibitors of the enzyme. Additionally, Figure 2 shows that the ligand is linked to the protein by two hydrogen bonds with the amino acids MET 270 and ARG 269.

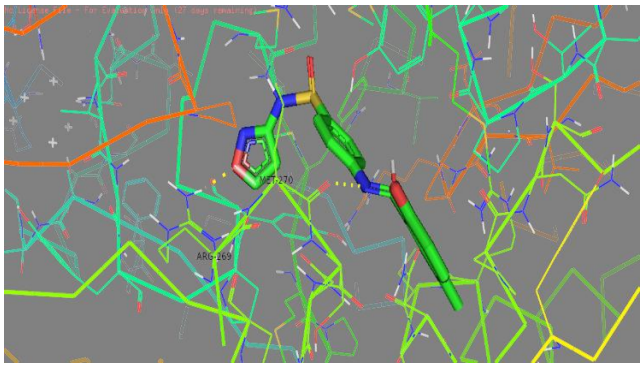


Fig. 2. *Activity of compound C1 in the enzyme (XO)*

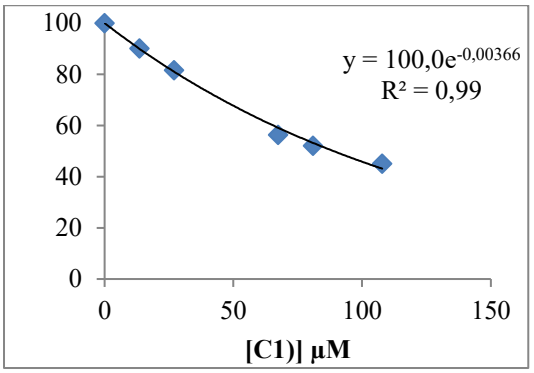


Fig.3. *Inhibition curve of compound C1*

In the complex (C1_Pd) result of the MolDock Score was (-215.155) as in the figure (4) the ligand has been linked to the protein with three hydrogen bonds with the amino acids ARG433, GLU177 and PRO 174 and the value of the HBond (-9.7) and the IC 50 is (0.834726) figure (5) which means that this complex has the ability to inhibit in an acceptable way but not the best.

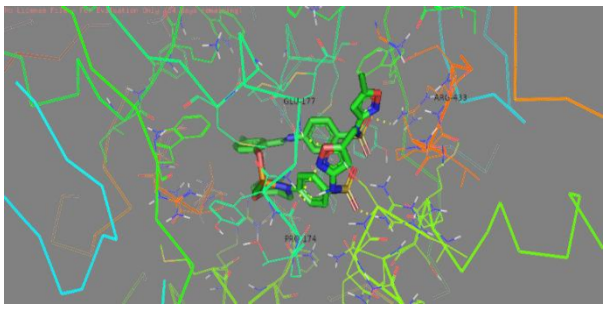


Fig. 4. *Activity of complex C1_Pd in the enzyme (XO)*

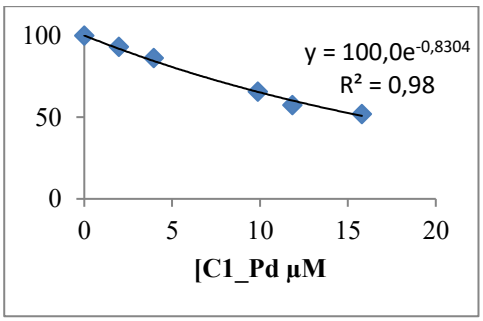


Fig. 5. *Inhibition curve of complex C1_Pd*

In the complex (C1_Cu) result of the MolDock Score was (-215.142) as in the figure 6 the ligand

has been linked to the protein with tow hydrogen bonds with the amino acids ARG433 and GLU177 the value of the HBond (-8.8) and the IC 50 is (1.044281) figure 7 which means that this complex has the ability to inhibit in an acceptable way but not the best.

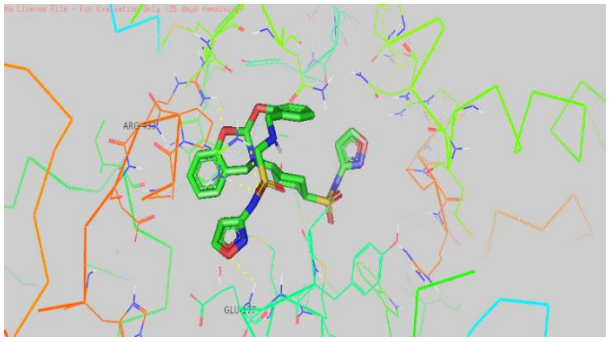


Fig. 6. *Activity of complex C1_Cu in the enzyme (XO)*

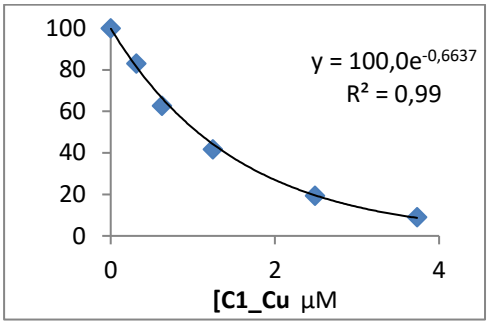


Fig. 7. *Inhibition curve of complex C1_Cu*

The compound (C2) the result of the MolDock Score was (-125.989) We notice in the figure 8 the ligand is linked to the protein by hydrogen bonds with the amino acids only ARG 433 only and the result of the HBond is (-2.5) and the result of ic50 is (200.0526) Figure 9 which means that this compound does not have the ability to inhibit the enzyme well and this is logical because the compound does not contain any metal atoms.

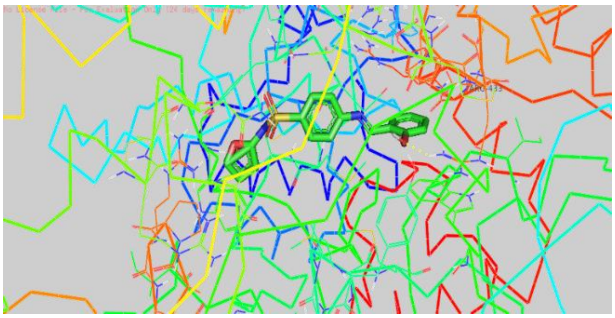


Fig. 8. *Activity of complex C2 in the enzyme (XO)*

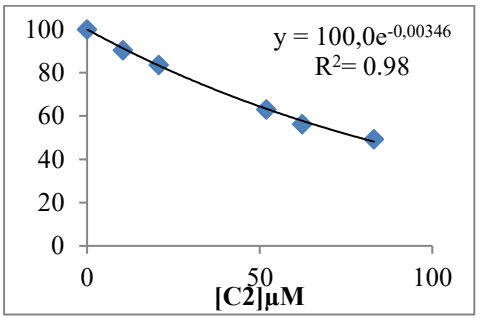
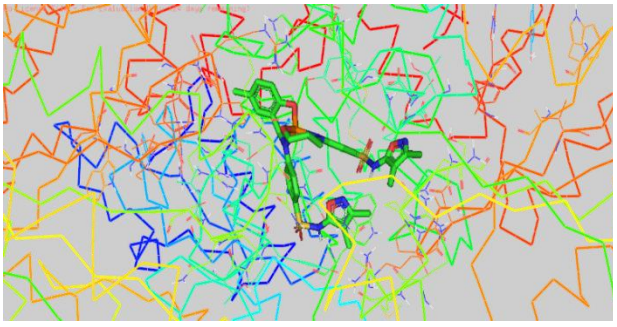


Fig. 9. *Inhibition curve of complex C2*

In the complex (C2_Pd) the MolDock Score result was (-215.841) as in Figure 10 and the result of IC50 (30.6152) Figure 11 showed that there is good inhibition of the enzyme despite the absence of any hydrogen bond between the ligand and the protein. This indicates that the complex is linked by non-hydrogen bonds, especially with hydrophobic acids such as valine, leucine and phenylalanine, in addition to van der Waals interactions.



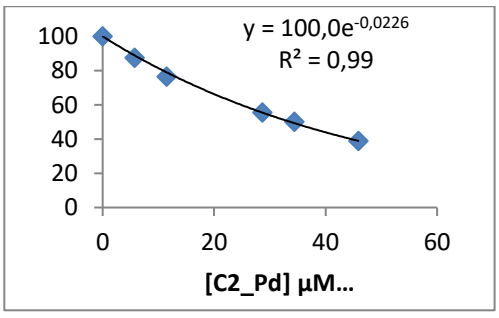
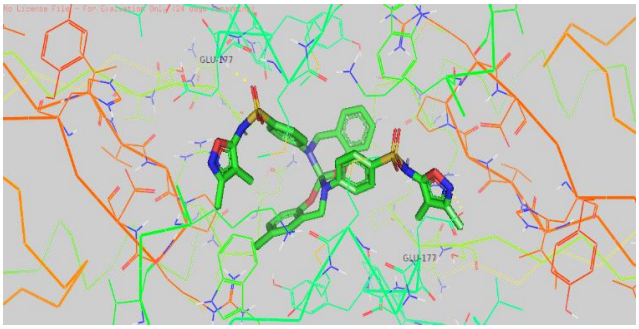


Fig. 10. *Activity of complex C1_Pd in the enzyme (XO)*

Fig. 11. *Inhibition curve of complex C1_Pd*

In the complex (C2_Cu) result of the MolDock Score was (-215.845) as in the figure 12 the ligand has been linked to the protein with tow hydrogen bonds with the amino acids GLU177 and GLU177 the value of the HBond (-10.2) and the IC 50(0.248531) figure 13 This means that this chemical complex has the ability to inhibit the enzyme with high efficiency



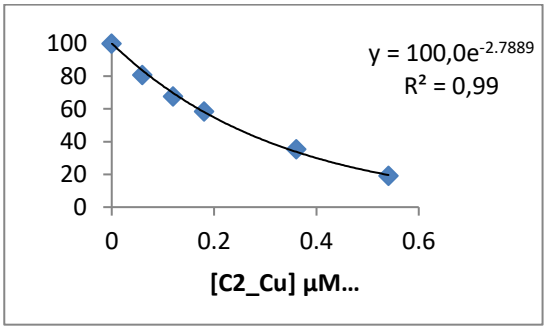
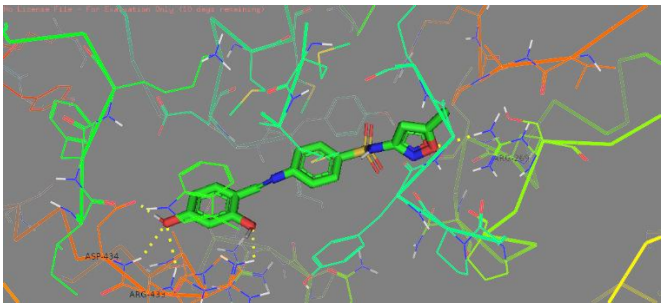


Fig 12. Activity of complex C2_Cu in the enzyme (XO)

Fig 13. Inhibition curve of complex C2_Cu

The compound (C3) the result of the MolDock Score was (-137.491) We notice in the figure 14 the ligand is linked to the protein by hydrogen bonds with three amino acids GLY329, THR173 and GLU177 the result of the HBond is (-5.2) and the result of IC50 is (139.1842) figure 15 which means that this compound does not have the ability to inhibit the enzyme well and this is logical because the compound does not contain any metal atoms.



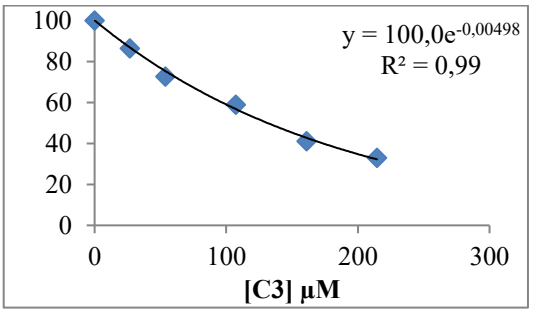


Fig. 14. Activity of complex C3 in the enzyme (XO)

Fig. 15. Inhibition curve of complex C3_Pd

In the complex (C3_Pd) result of the MolDock Score was (-200.861) as in the figure 16 the ligand has been linked to the protein with three hydrogen bonds with the amino acids GLY329, THR173 and GLU 177 and the value of the HBond (-4.5) and the IC 50(14.1289) figure 17. This means that this complex does not have the ability to inhibit the enzyme.

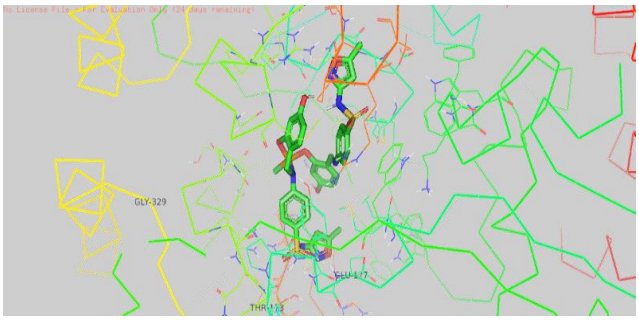


Fig 16. Activity of complex C3_Pd in the enzyme (XO)

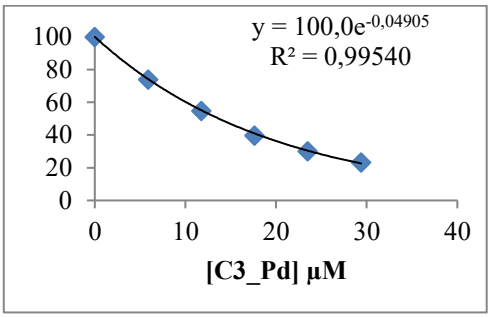


Fig 17. Inhibition curve of complex C3_Pd

In the complex (C3_Cu) result of the MolDock Score was (-200.854) as in the figure 18 the ligand has been linked to the protein with three hydrogen bonds with the amino acids PRO275, GLY176 and GLU177 the value of the HBond (-10.8) and the IC 50(0.25386) figure 19. This means that this complex has the ability to inhibit the enzyme efficiently.

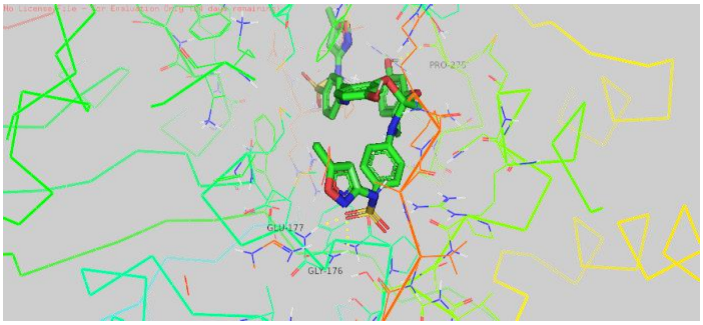


Fig. 18. *Activity of complex C3_Cu in the enzyme (XO)*

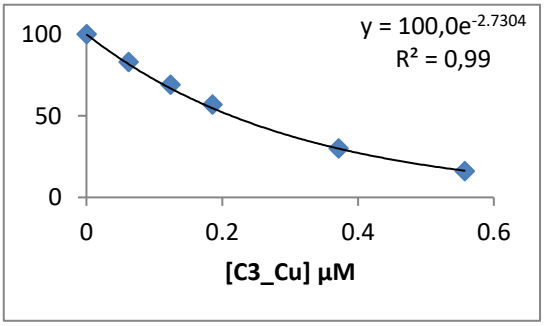


Fig. 19. *Inhibition curve of complex C3_Pd*

the compound (C4) the result of the MolDock Score was (-128.059) We notice in the figure 20 the ligand is linked to the protein by hydrogen bonds with the amino acids ARG 433 ,ASP434, GLU177 and PRO 174 the result of the HBond is (-3.1) and the result of IC 50 is (200.0526) figure 21 which means that this compound does not have the ability to inhibit the enzyme well and this is logical because the compound does not contain any metal atoms.

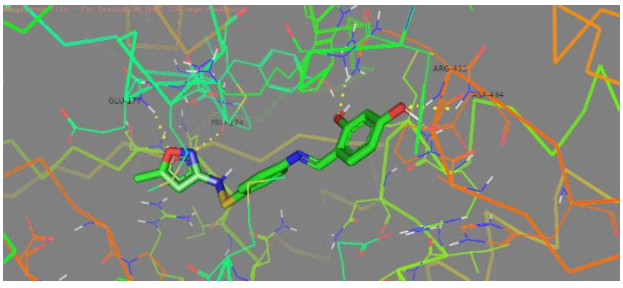


Fig.20. *Activity of complex C4 in the enzyme (XO)*

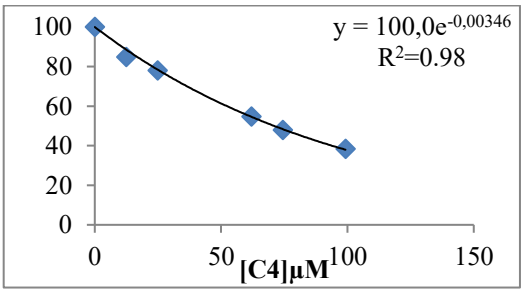
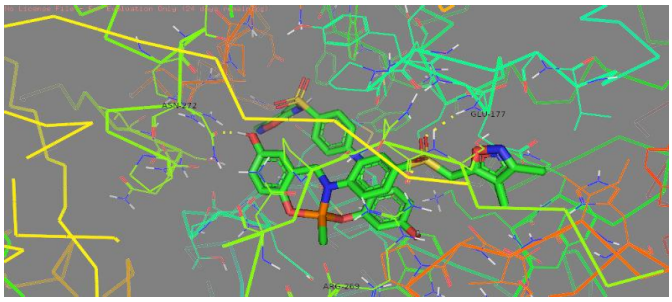


Fig. 21. Inhibition curve of complex C4

In the complex (C4_Pd) result of the MolDock Score was (-202.749) as in the figure 22 the ligand has been linked to the protein with three hydrogen bonds with the amino acids GLU177, ARG269 and ASN272 and the value of the HBond (-10.2) and the IC 50 (0.24879) figure 23. This

means that this complex also has the ability to inhibit the enzyme efficiently.



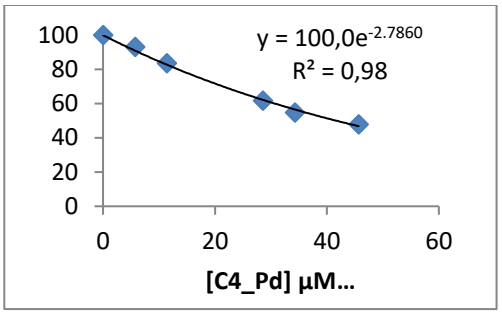
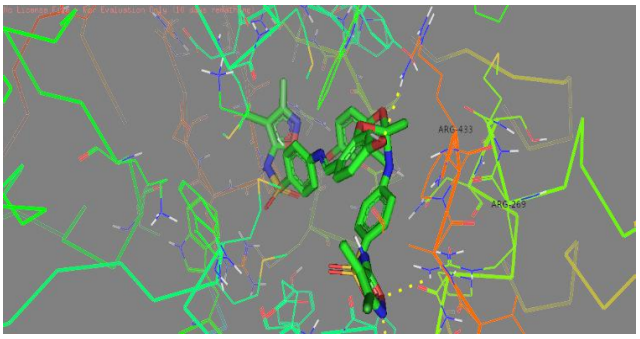


Fig 22. *Activity of complex C4_Pd in the enzyme (XO)*

Fig 23. *Inhibition curve of complex C4_Pd*

In the complex (C4_Cu) result of the MolDock Score was (-202.658) as in the figure 24 the ligand has been linked to the protein with three hydrogen bonds with the amino acids GLU177, ARG269 and ASN272 and the value of the HBond (-11.2) and the IC 50 (0.210211) figure 25. This means that this complex is considered one of the best compounds in inhibiting the xanthine enzyme, with an efficiency that exceeds all compounds, including allopurinol.



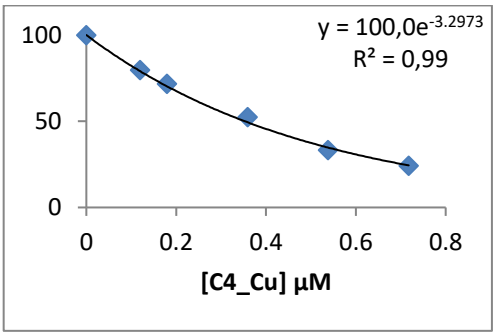
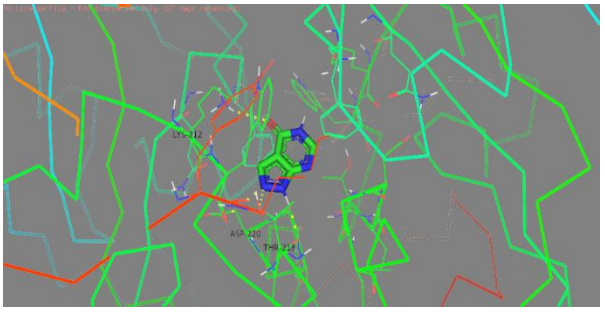


Fig. 24. *Activity of complex C4_Cu in the enzyme (XO)*

Fig. 25. *Inhibition curve of complex C4_Cu*

The compound (Allopurinol) the result of the MolDock Score was (-220.426) We notice in the figure 26 the ligand is linked to the protein by hydrogen bonds with the amino acids LYS212 ,ASP220 and THR218 the result of the HBond is (-6.6) and the result of ic50 is (0.368987) figure 27 which means that this compound does not have the ability to inhibit the enzyme well



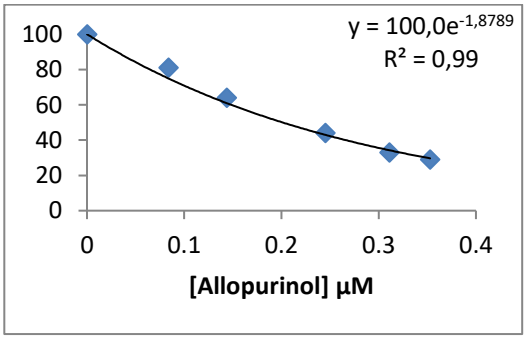


Fig. 26.: *Activity of allopurinol in the enzyme (XO)*

Fig. 27. *Inhibition curve of complex allopurinol*

In metal complexes, copper ions frequently interact with the amine group (-NH_2) of amino acids [9]. Copper particularly coordinates with oxygen of the carboxyl group (COOH) of amino acids [10]. This relationship enables copper to stabilize the complex by forming coordination bonds

with the nitrogen or oxygen atoms of the amino acid side chains (e.g. histidine (His) or cysteine (Cys)) The hydroxyl group dot been suggested also, that copper complexes can create hydrogen bonds or carboxyla groups of amino acids such as serine (Ser), threonine (Thr), aspartate (Asp), and glutamate (Glu), arguably contributing to structure stabilization in the enzyme's active site.

Copper resident in an aqueous phase used may also couple to aromatic amino acids through π − π interactions as seen on tryptophan (Trp), phenylalanine (Phe), and tyrosine (Tyr). The resultant complex displays some level of inductive stability, which is apparent by the ability of the complex to inhibit the enzyme. The oxidation and reduction reactions that copper can induce also affect the reactive oxygen species (ROS) balance, reducing their harmful effects [11].

In contrast, palladium ions in metal complexes act differently by coordinating with amino acids via the amine moiety (-NH_2) in a different way [12]. The palladium will often establish links to the oxygen in the carboxyl group (-COOH) on the amino acids that modifies the total construction of an enzyme. In addition, Palladium interacts with amino acid side chains at nitrogen or oxygen atoms and is able to form hydrogen bonds with amino acids causing hydrogen bonding with serine (Ser), thesine (Thr), and glutamic (Glu) acids [13].

These interactions stabilize palladium-derived complexes in the active site of the enzyme. Palladium complexes also can have π-π interactions with aromatic amino acids like tryptophan (Trp), phenylalanine (Phe), and tyrosine (Tyr) and ionic interactions with charged side chains like lysine (Lys) and arginine (Arg). Hydrophobic interactions between palladium complexes and residues Leu/Ile have also been reported. Despite these interactions, palladium's influence on the enzyme's activity and its ability to inhibit the enzyme may differ from that of copper, but both metal complexes ultimately act as enzyme inhibitors [14].

Conclusions

The study demonstrates that Schiff-Base metal complexes, particularly those containing copper (Cu) and palladium (Pd), show significant enhancement in the inhibition of the xanthine oxidase (XO) enzyme, compared to the original compound (C1). The introduction of metal atoms led to a dramatic reduction in IC50 values, indicating a higher potency of these metal complexes as inhibitors of XO. For example, C1_Pd and C1_Cu exhibited IC50 values of 0.834726 μM and 1.044281 μM, respectively, compared to 188.982 μM for C1. This suggests that the metal complexes can be more effective alternatives to conventional treatments like allopurinol (IC50 = 0.368987 μM).

The molecular docking results further support the observed increased potency. The more negative MolDock scores (-215.155 for C1_Pd and -215.142 for C1_Cu compared to -144.628 for C1) indicate stronger binding affinities of the metal complexes to the XO enzyme. Additionally, the increase in the number of hydrogen bonds (from 4.8 for C1 to 9.7 for C1_Pd and 8.8 for C1_Cu) and the reduction in RMSD values (from 7.920 for C1 to 4.447 for C1_Pd and 1.688 for C1_Cu) suggest that the metal complexes form more stable and well-aligned interactions with the enzyme's active site.

The consistency experimental IC50 values and computational predictions underscores the

reliability of the cheminformatics approach in predicting the inhibitory potential of these compounds.

Furthermore, the molecular modeling results, visualized through the PyMOL program, show that the ligand binding involves interactions with the active site of the enzyme, including hydrogen bonds with the amino acids MET 270 and ARG 269.

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دراسة تأثير معقدات النحاس والبلاديوم لبعض قواعد شيف على نشاط انزيم أكسيديز الزانثين

معلومات البحث:

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تاريخ التعديل: 2024/02/25
تاريخ القبــول: 2025/03/03
تاريخ الـنشر: 2025/09/30

الكلمات المفتاحية:

Molegro Virtual Docker, Cheminformatics, PyRx, Xanthine Oxidase inhibition METADISE

معلومات المؤلف

الايميل:
الموبايل:

الخلاصة:

النقرس مرض شائع لدى كافة سكان العالم وخاصة كبار السن، وتهدف هذه الدراسة إلى تقييم فعالية إنزيم أوكسيديز الزانثين (XO) مع بعض معقدات فلزات شيف بيز والتي تحتوي على ذرات معدنية من النحاس والبلاديوم، ومقارنة هذه المركبات مع بعضها البعض وكذلك مع عقار الوبيورينول والذي يستخدم عادة في هذا المرض، والجدير بالذكر أن جميع المركبات تم شراؤها من تركيا مع إنزيم أوكسيديز الزانثين الصناعي (XO). تم قياس نشاط الانزيم (XO) بواسطة جهاز مطياف ضوئي بطول موجي 295 نانومتر بمعدل خمسة تركيزات مختلفة لكل مركب وتم نقل الامتصاصية في اوقات محددة الى معادلات رياضية في برنامج مايكروسوفت اكسل لرسم منحنى التثبيط والذي من خلاله نحصل على قيم نستطيع من خلالها حساب (نصف التركيز المثبط) IC 50 وتم استخدام علم الكيمياء المعلوماتية للتنبؤ بارتباطات هذه المركبات بالبروتين وذلك برسم المركبات باستخدام برنامج ChemOffice بشكل ثلاثي الابعاد وحفظها بصيغة (PDB) وتحميل البروتين الخاص بالانزيم من موقع (Protein Data Bank) واجراء الالتحام الجزيئي بين جميع المركبات والبروتين باستخدام برنامجين (PyRx) و(Molegro virtual Docker) وتحديد الروابط الهيدروجينية بالموقع النشط للبروتين مع الربائط واخذ قيم (IC50) ومقارنتها بالجانب العملي ووجد انها متناسقة بدرجة عالية