Xanthine oxidase inhibitor scaffold diversity and structure-based drug design by transion metal

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Abstract

Schiff base complexes of transition metals are used in a variety of fields, including medicine, agriculture, and industry. For example, [Co(acac2- en)] has been reported to be involved in oxygen metabolism in dimethylformamide, pyridine, and modified pyridines. They're called transition metal complexes, and they're used in the refining of petroleum. Condensed Schiff base derived by the condensation of arylamides with o-hydroxyl or o-methoxy aniline complexes of Co(II), Ni(II), Cu(II), and Zr complexes is a fabrication of the imagination.

Keywords: metal complexes, xanthine oxidase, inhibitors

Introduction

Several key qualities distinguish transition metals from main group metals. Transition metals' capacity to produce coordination compounds is one of their most intriguing properties. Interactions between electron donors and acceptors determine the distance between metal complexes and their ligands. The ligand is a Lewis acid, whereas the metal in the middle is a Lewis base (Battelli *et al.* 2014) [2]. The ligand of the atom's nucleus repels the electron orbitals from the get-go. However, the core atom's positive charge attracts the ligand because of its attraction. Although the ligand has no impact on the spherical-symmetrical s-orbital of the central metal ion, it does have an effect on the d-orbitals. According to the structure, diameter, and charge of the ligand, certain d-orbitals have more energy, while others have less. This means the orbitals are heavier or easier to fill with electrons, depending on the ligand's structure (Brass *et al.* 1991) [5]. Covalent bonds between metal ions and their ligands are formed through the Lewis acid base interaction (L).

The nature of complex bonding has been the subject of several hypotheses. VBA, CFA, MOA, and LFA are some of the most essential methods for determining the structure of atoms and molecules (Chambers 1985) [7]. The crystal field theory may be used to study the impact of repulsion between the ligands' point negative charges and the d-electrons on the metal ions. Many, but not all, of the fundamental physical properties of transition metal complexes have been discussed in this article. Even though Molecular Orbital Theory is more complex than Crystal Field Theory, it provides a more complete description of known physical features (Desco 2002) [9]. Transition metal complex reactions usually entail the substitution of one ligand for another, as well as oxidation or reduction. Two separate variables determine the stability of coordination molecules (metal complexes).

The transition in energy from reactants to products is referred to as thermodynamic stability. Kinetic stability refers to a substance's reactivity, which is usually defined as ligand substitution. Slow reactivity does not indicate high thermodynamic stability. The kinetic stability of the ligand substitution reaction is determined by the activation energy (G) of the reaction; the thermodynamic stability is determined by the free energy change. Complexes may be classified as either inert or labile depending on the pace at which substitution processes take place. Kinetically labile complexes conduct quick ligand substitution processes, while kinetically inert complexes suffer only very slow substitution events. According to the Hunds Rule, the orbitals with the lowest energy are filled first (Dawson and Walters 2006) [8].

Xanthine oxidase is the 290-kDa homodimer of bovine milk XO was previously thought to operate independently of each other. A few years after these findings, Tai and Hwang proved that a substrate binding to one subunit's active site impacts catalytic activity of the other subunit. When we see mixed-type XO inhibition, we may attribute it to this cooperative effect. The enzyme previously had no allosteric site, therefore this could not be explained. Two iron–sulfur clusters, one FAD central domain, and a molybdopterin unit with an 85 kDa molecular mass can be detected in each subunit (Figure 2.1) (Figure 2b, Figure 2c, and Figure 2d) (Malik *et al.* 2017) [25]. 90% of the amino acids in bovine milk XO are the same as those in the human enzyme. Since enzyme inhibitors may be tested in vitro using the bovine milk XO, it is a viable test method.

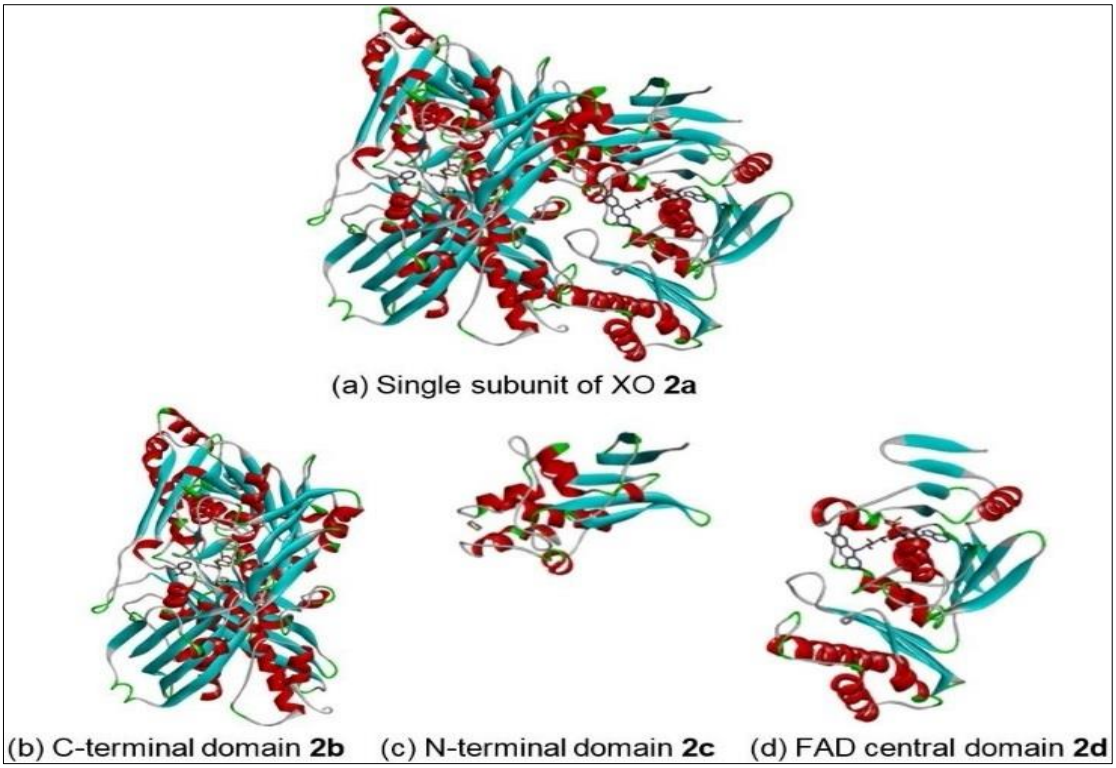

Fig 1: No. 2 (a) Subunit of xanthine oxidase from bovine milk, (b) molybdopterin unit in the C-terminal domain, (c) two iron–sulfur clusters in the N-terminal domain, (d) FAD cofactor in the central domain (Muhammad and Arthur 2018).

Sulfhydryl residues oxidation or proteolysis may swiftly change XDH into an oxidase (XO), which is the first enzyme generated. Ischemic tissue injury is considered to stimulate the conversion of XDH to XO. During the first fall in blood perfusion, ATP synthesis reduces because of the lower quantity of available oxygen. An ATP deficiency results in a decrease in the cell's internal charge, resulting in ion gradient disequilibrium. The increased quantity of calcium ions in the cell causes the protease to convert XDH to XO. Excess AMP is catabolized, resulting in a buildup of hypoxanthine inside the cell since it has not been utilized to make ATP. The XO and hypoxanthine created earlier in the reperfusion process are responsible for the production of reactive oxygen species when oxygen returns to the tissue (ROS). Although XDH and XO have no major structural differences around or within their active sites, the FAD-binding region of each has a distinct conformational shift (Roleira and colleagues 2018) [39]. X-ray diffraction studies of the complex between bovine milk enzyme and hypoxanthine revealed the enzyme-mediated chemical route. Two electrons are transported from the substrate to the molybdopterin unit during substrate oxidation, resulting in the reduction of MoVI to MoIV. XDH transfers the two electrons to NAD+, while XO transfers them to atomic oxygen. This causes the Mo center to be re-oxidized and the enzyme to be re-activated.The aime of this study to using molecular docking to explain changes for xanthine oxidase after effect Schiff base on xanthine oxidase.

Materıals and methods

Suppression of enzymes

First discovered by Falco in the 1950s, xanthine oxidase inhibitors like Allopurinol ([3,4-d]pyrimidin-4-one) have been demonstrated to reduce uric acid levels in both blood and urine (Elion 1993) [11]. A clinical trial of allopurinol in gout was undertaken by Rundles and colleagues in 1963 with great results. In 1966, the FDA gave its approval for the drug. Allopurinol and oxypurinol both inhibit xanthine oxidase, which reduces uric acid synthesis, lowers blood uric acid levels, and increases urine output. According to these findings, medication may be useful in treating gout, a frequent condition for which the treatment is recommended (Saugstad 1996) [41].

Results and discussion

Xanthine oxidase enzyme antioxidant activity *in vitro* evaluation

Hydrogen peroxide radical assays were used to assess the antioxidant properties of newly synthesized substances. Both tests' IC50 values were compared, and the findings are summarized in the table below. Comparing ascorbic acid to the negative control, practically all of the substances showed significant inhibition of xanthine oxidase enzyme Table.3, Table 1, Figure 2. and Figure 3.**.** In the DPPH experiment, the chemical 4-metoksi S1 was discovered to have the highest IC50 value (16,120 M) against oxidative stress caused by free radicals. With an IC50 value of 9,120M, 3-metoksi S2 showed excellent antioxidant capability alongside this chemical Table 2, Table 3, Figure 4. and Figure 5 (Wan *et al.* 2016) [44]. There were two compounds with hydrazine linkages synthesized when the structure-activity connection between these substances was thoroughly examined. Similarly, all compounds with hydrazines substitution demonstrated excellent antioxidant capability in the hydrogen peroxide assay, with IC50 values 16,120 Table 5, Table 6,

Figure 6 and Figure 7. Among all the derivatives, compound metoksi S2 with phenyl thiosemicarbazide substitution demonstrated promising antioxidant activity. metoksi S2, a phenyl hydrazine substituted rutin derivative, similarly demonstrated excellent scavenging activity, with an IC50 of6,601. Studying the connection between these compounds' structure and action revealed that phenyl hydrazine and phenyl thiosemicarbazide were the sources of both of the compounds that contain hydrazine links Table 6, Table 7, Table 8 Figure 8, Figure 9 and Figure 10.

Table 1: 3MeOS2M details to explain activity with enzyme

Name of the substance	3MeOS2M	Stock M1	Volume total	Control V1	Absorbance 100	Control 100	Bathtub M 0	Activity 100
Amount taken (mg)	1	0.025	200	30	72	100	0	72
Molecular weight (g)	401.3	0.025	200	50	59	100	3.737851981	59
Dissolved volume (ml)	1	0.025	200	70	51	100	6.229753302	51
Stock Concentration (mM)	2.491901321	0.025	200	90	43	100	8.721654622	43
Dilution coefficient	10	0.025	200	120	33	100	11.21355594	33

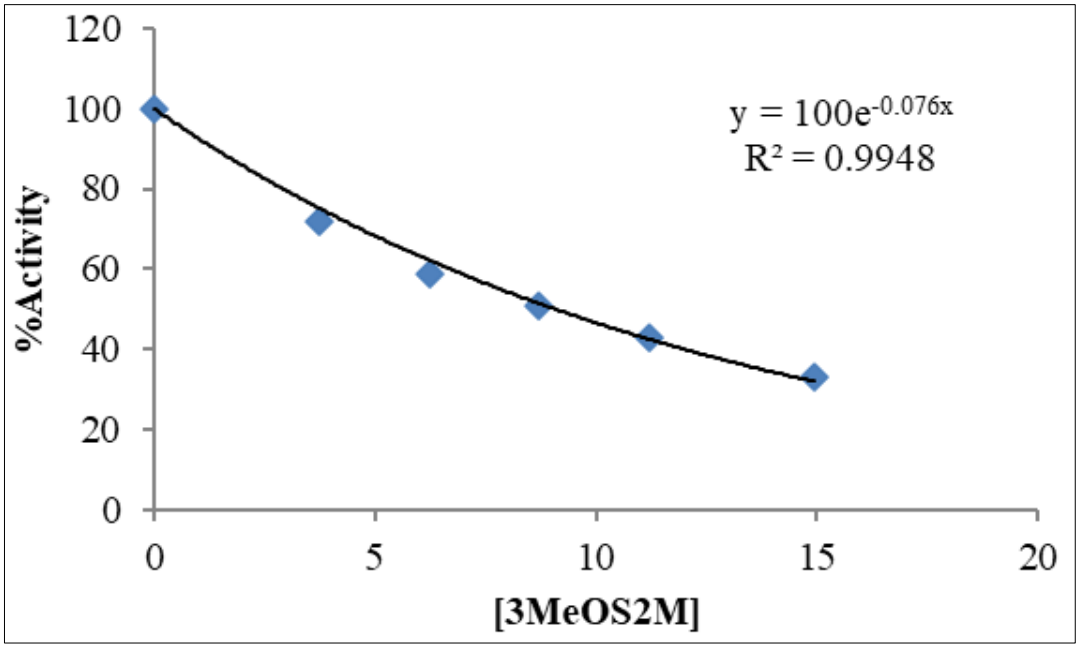

Fig 2: Activity for 3MeOS2M

Tab 2: 4MeOS1M with anther concentration details to explain activity with enzyme

Name of the substance	3MeOS2M	Stock M1	Volume total	Control V1	Absorbance 100	Control 100	Bathtub M 0	Activity 100
Amount taken (mg)	1	0.026	200	50	75	100	6.471654155	75
Molecular weight (g)	386.3	0.026	200	80	65	100	10.35464665	65
Dissolved volume(ml)	1	0.026	200	100	58	100	12.94330831	58
Stock Concentration (mM)	2.588661662	0.026	200	120	50	100	15.53196997	50
Dilution coefficient	10	0.026	200	150	43	100	19.41496246	43

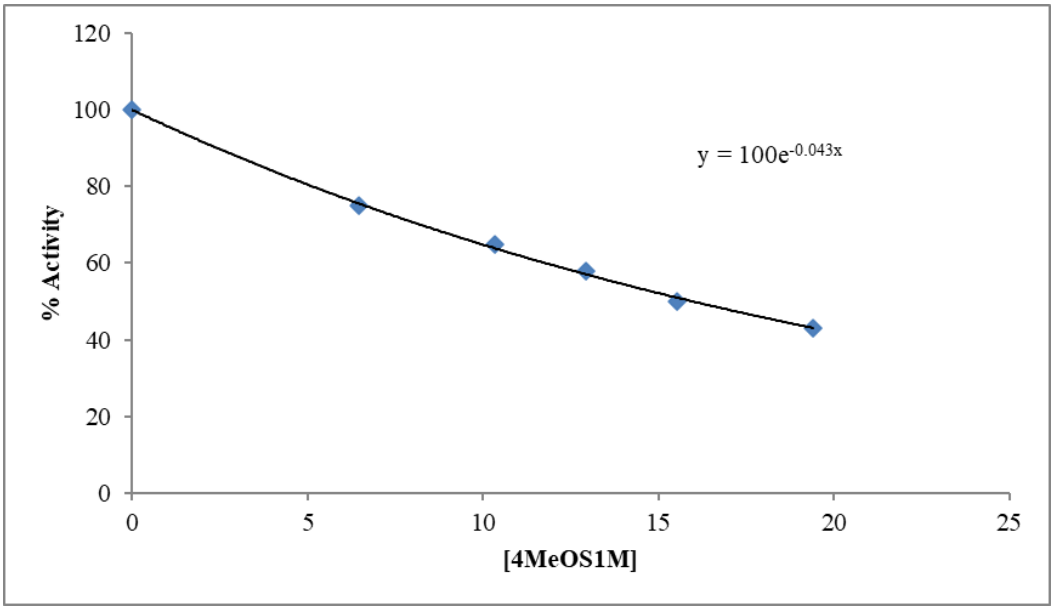

Fig 3: Activity for anther 4MeOS1M

Table 3: 4MeOS2M with 0.025 concentration details to explain activity with enzyme

Name of the substance	3MeOS2M	Stock	Volume	Control	Absorbance	Control	Bathtub M	Activity
		M1	total	V1	100	100	0	100
Amount taken (mg)	1	0.025	200	30	80	100	3.737851981	80
Molecular weight (g)	401.3	0.025	200	50	65	100	6.229753302	65
Dissolved volume (ml)	1	0.025	200	70	55	100	8.721654622	55
Stock Concentration (mM)	2.491901321	0.025	200	90	45	100	11.21355594	45
Dilution coefficient	10	0.025	200	120	33	100	14.95140792	33

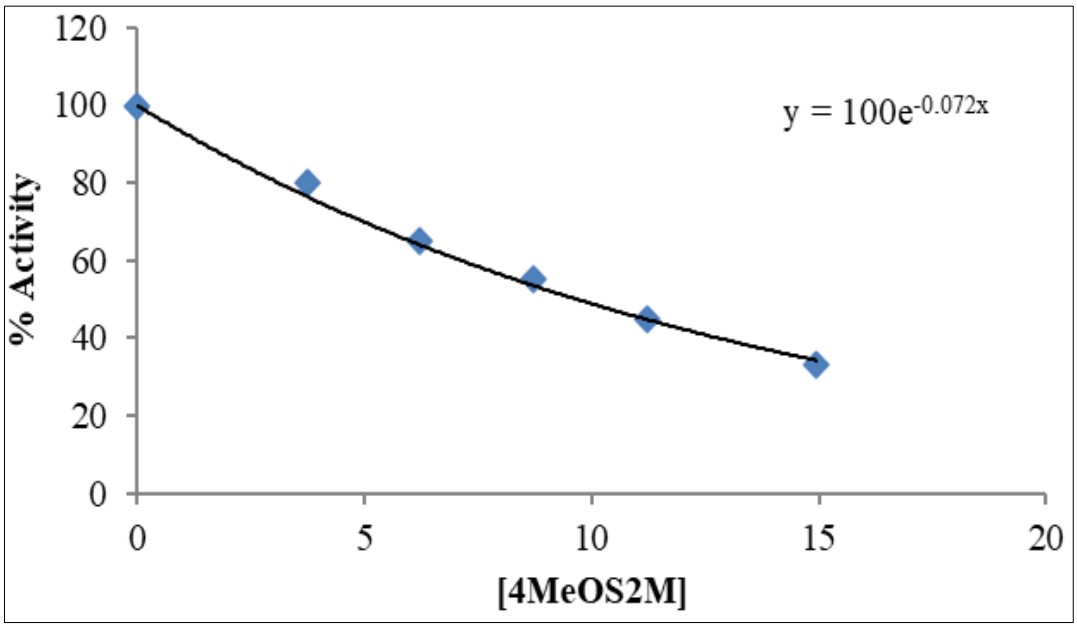

Fig 4: Activity for 0.025 4MeOS2M

Table 4: Pd(3MeOS2M) with details to explain activity with enzyme

Name of the substance	Pd(3MeOS2M)	Stock	Volume	Control	Absorbance	Control	Bathtub M	Activity
		M1	total	V1	100	100	0	100
Amount taken (mg)	1	0.011	200	30	82	100	1.65012871	82
Molecular weight (g)	909.02	0.011	200	50	75	100	2.750214517	75
Dissolved volume (ml)	1	0.011	200	70	66	100	3.850300323	66
Stock Concentration (mM)	1.100085807	0.011	200	90	60	100	4.95038613	60
Dilution coefficient	10	0.011	200	120	50	100	6.60051484	50

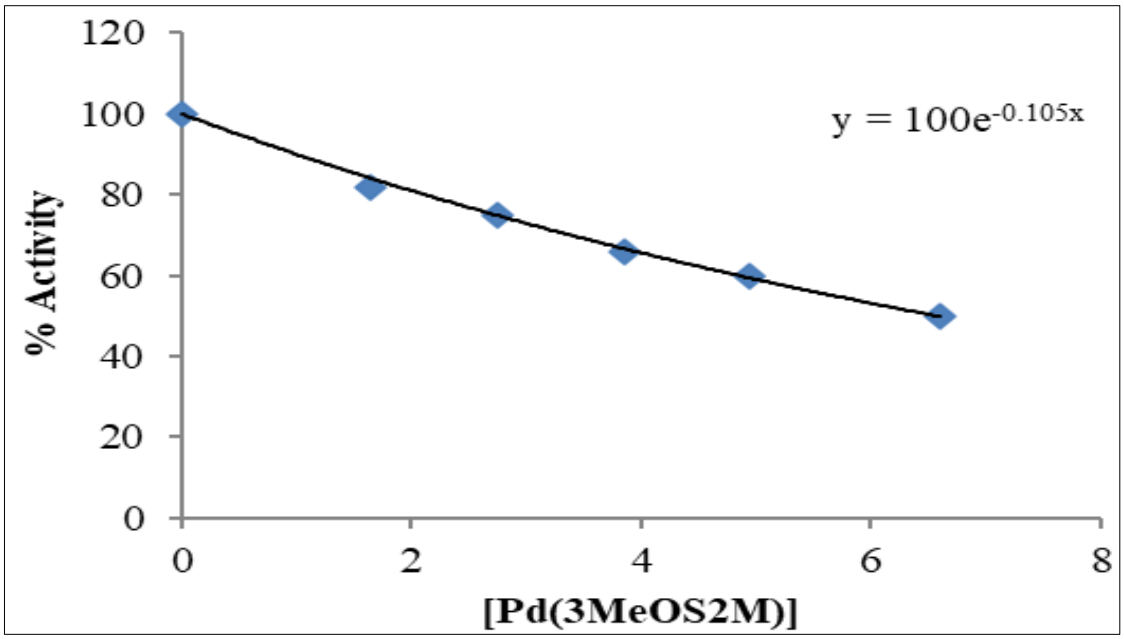

Fig 5: Pd(3MeOS2M) activity

Table 5: Pd(4MeOS1M) with 0.011 details to explain activity with enzyme

Name of the substance	Pd(3MeOS2M)	Stock	Volume	Control	Absorbance	Control	Bathtub M	Activity
		M1	total	V1	100	100	0	100
Amount taken (mg)	1	0.011	200	30	85	100	1.65012871	85
Molecular weight (g)	909.02	0.011	200	50	72	100	2.750214517	72
Dissolved volume (ml)	1	0.011	200	70	61	100	3.850300323	61
Stock Concentration (mM)	1.100085807	0.011	200	90	53	100	4.95038613	53
Dilution coefficient	10	0.011	200	120	43	100	6.60051484	43

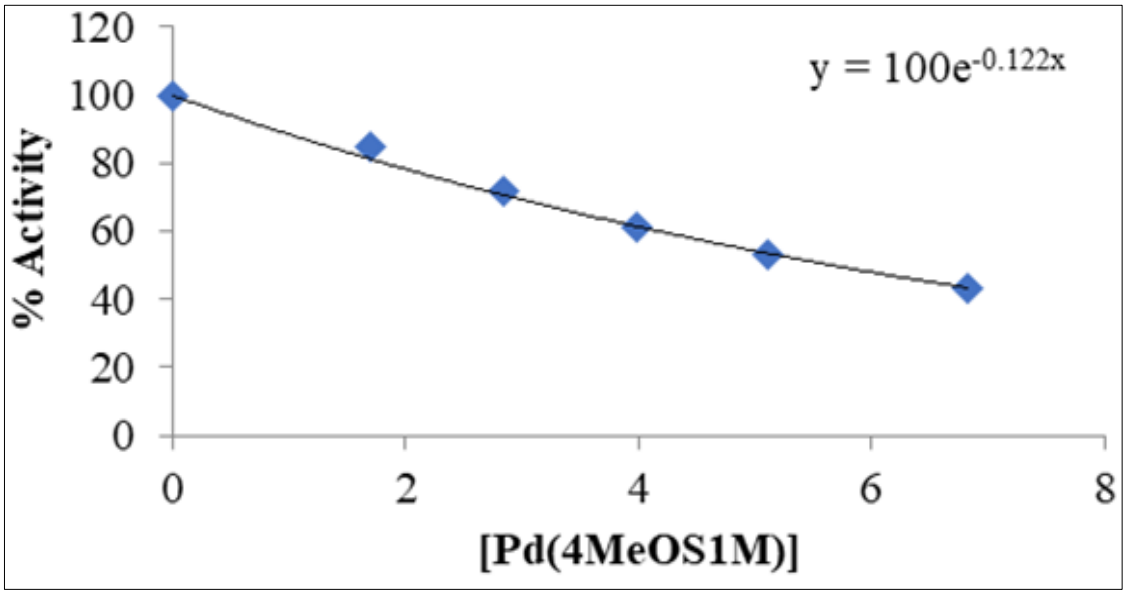

Fig 6: Pd(4MeOS1M) activity

Table 6: Pd(4MeOS2M) details to explain activity with enzyme

Name of the substance	Pd(3MeOS2M)	Stock	Volume	Control	Absorbance	Control	Bathtub M	Activity
		M1	total	V1	100	100	0	100
Amount taken (mg)	1	0.011	200	30	85	100	1.65012871	85
Molecular weight (g)	909.02	0.011	200	50	72	100	2.750214517	72
Dissolved volume (ml)	1	0.011	200	70	61	100	3.850300323	61
Stock Concentration (mM)	1.100085807	0.011	200	90	53	100	4.95038613	53
Dilution coefficient	10	0.011	200	120	43	100	6.60051484	43

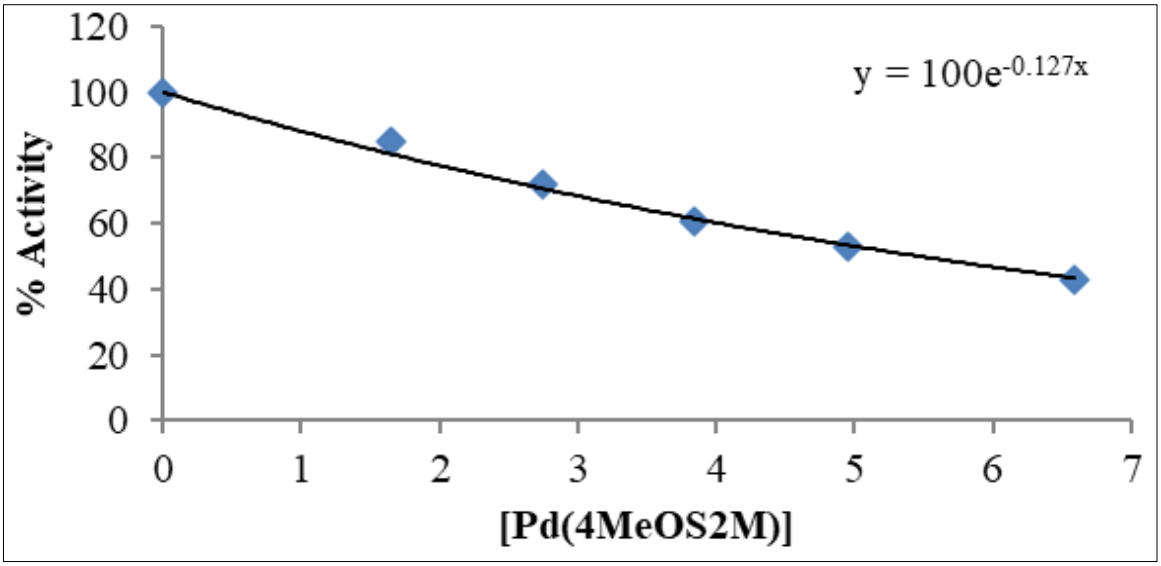

Fig 7: Pd(4MeOS2M) activity

Table 7: Cu(3MeOS2M) details to explain activity with enzyme

Name of the substance	Cu(3MeOS2M)	Stock	Volume	Control	Absorbance	Control	Bathtub M	Activity
		M1	total	V1	100	100	0	100
Amount taken (mg)	1	0.011	200	5	74	100	0.288636941	74
Molecular weight (g)	909.02	0.011	200	10	58	100	0.577273882	58
Dissolved volume (ml)	1	0.011	200	20	35	100	1.154547764	35
Stock Concentration (mM)	1.100085807	0.011	200	30	20	100	1.731821645	20
Dilution coefficient	10	0.011	200	40	13	100	2.309095527	13

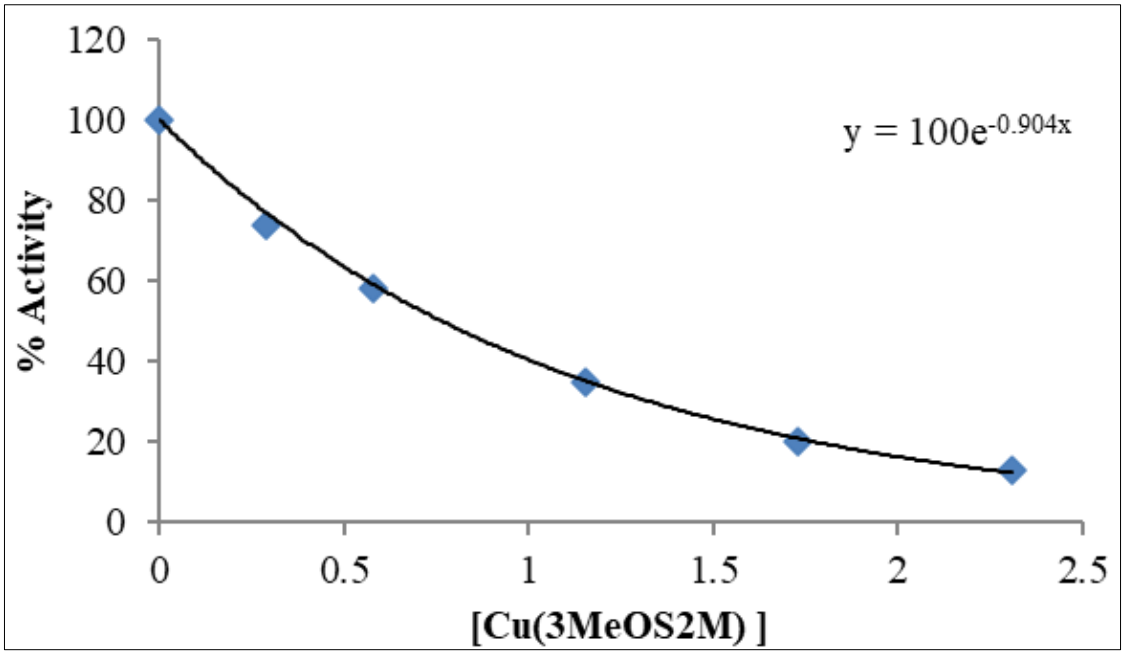

Fig 8: Cu(3MeOS2M) activity

Table 8: Cu(4MeOS1M) details to explain activity with enzyme

Name of the substance	Cu(3MeOS2M)	Stock	Volume	Control	Absorbance	Control	Bathtub M	Activity
		M1	total	V1	100	100	0	100
Amount taken (mg)	1	0.011	200	5	80	100	0.288636941	80
Molecular weight (g)	909.02	0.011	200	10	62	100	0.577273882	62
Dissolved volume (ml)	1	0.011	200	20	40	100	1.154547764	40
Stock Concentration (mM)	1.100085807	0.011	200	30	26	100	1.731821645	26
Dilution coefficient	10	0.011	200	40	18	100	2.309095527	18

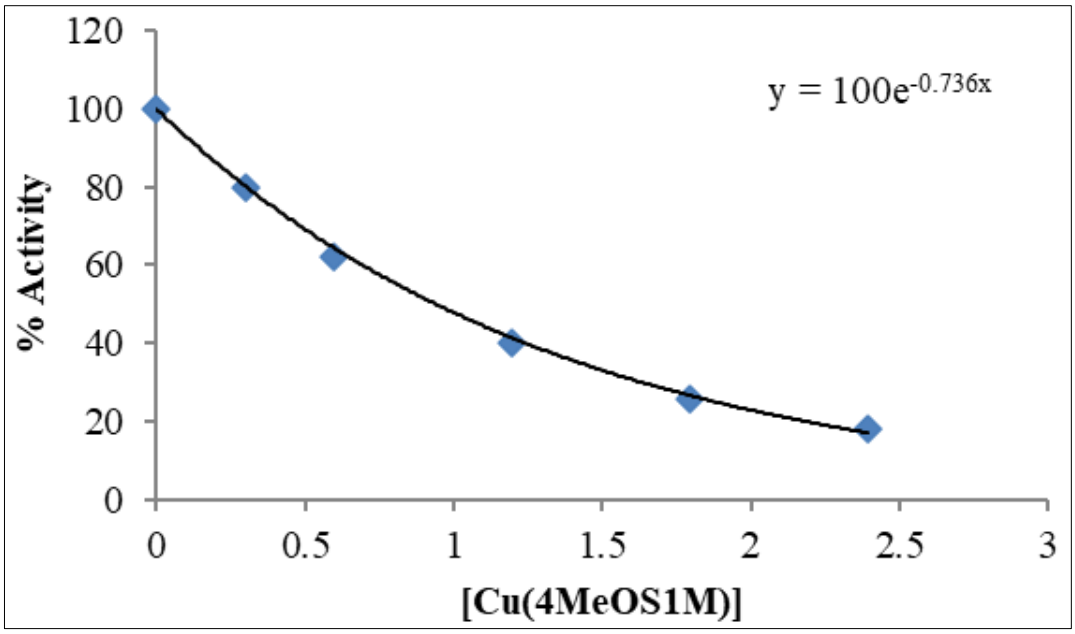

Fig 9: Cu(4MeOS1M) activity

Table 9: Cu(4MeOS1M) details to explain activity with enzyme

		Stock	Volume	Control	Absorbance	Control	Bathtub M	Activity
Name of the substance	Cu(3MeOS2M)	M1	total	V1	100	100	0	100
Amount taken (mg)	1	0.011	200	5	62	100	0.288636941	62
Molecular weight (g)	909.02	0.011	200	10	46	100	0.577273882	46
Dissolved volume (ml)	1	0.011	200	20	22	100	1.154547764	22
Stock Concentration (mM)	1.100085807	0.011	200	30	11	100	1.731821645	11
Dilution coefficient	10	0.011	200	40	5	100	2.309095527	5

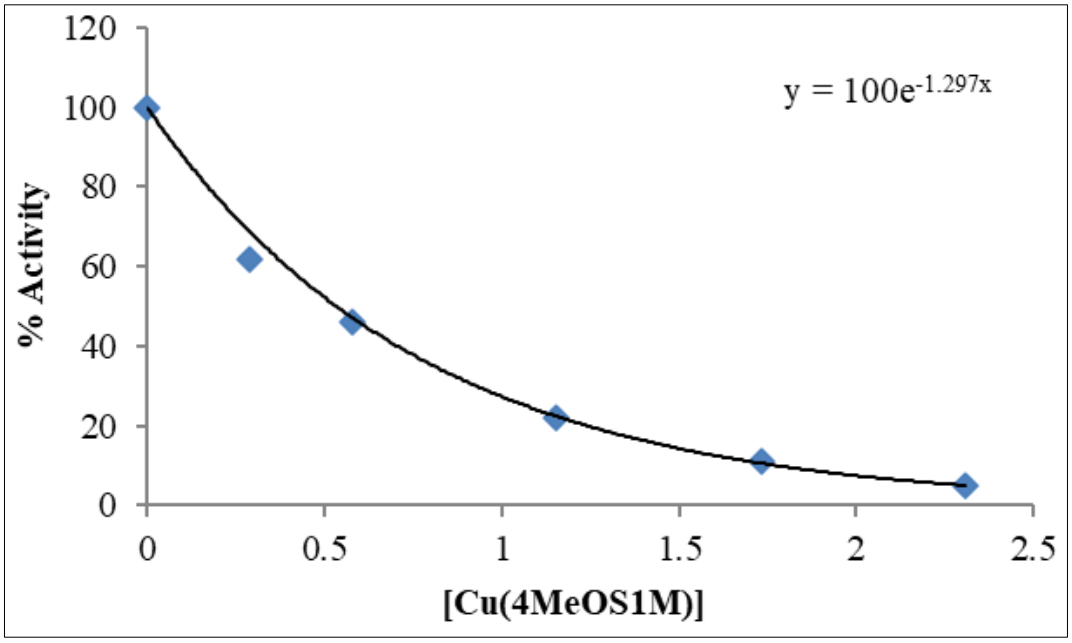

Fig 10: Cu(4MeOS1M) activity

Aldehyde and ketone condensation with primery amine was first described by Hugo Schiff, who is responsible for the term "Schiff bases" (Inkster *et al.* 2007) [16]. In the case of aldimines, the carbonyl group of an aldehyde is responsible for forming them, whereas the carbonyl group of a ketone is responsible for forming them. In these compounds, the azomethine group, which has the general formula RHC=N-R1, is a structural feature that may be substituted in many ways with alkyl, aryl, cycloalkyl, or heterocyclic groups. These chemicals are referred to as anils, imines, and azomethines by their different names. Chemically and biologically significant, according to various studies, is the presence of a pair of electrons in an SP2 hybridized orbital occupied only by the nitrogen atom in the azomethine group the imines produced in (Figure 2.6) often breakdown or polymerize unless at least one aryl group is connected to the

nitrogen or carbon atoms (Sagor *et al.* 2015) [40]. This huge chemical universe has been opened up by the production of several Schiff base metal complexes (both acyclic and cyclic). For example, Schiff base metal-ion conjugates are of interest because of the multiple ways in which they may be coupled to metal ions (such as N,O,S, and others). Especially when functional groups like –OH or –SH are nearby the azomethine group, Schiff bases are excellent chelating agents because the metal ion may join the functional group in a five- or six-member ring.

The synthesis and characterisation of transition metal complexes using Schiff bases as ligands have seen a rise in attention in recent years due to their potential as catalysts in several processes (Quach and Galen 2018) [37]. Schiff base complexes may be classified as mononuclear, binuclear, or poly-nuclear, as well as monodentate, bidentate, or polydentate, depending on the number of metal ions or atoms they contain.

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