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Synthesis and study of Pd (II), Pt (IV) and Au (III) complexes with amoxicillin and imidazole derivatives heterocycles as biological activity compounds

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ABSTRACT

Amoxicillin was used as the major ligand (L) in the metal condensation reaction to create new mixed metal chloride complexes of palladium (II), platinum (IV), and gold (III) using 2-(4,5-di(4-methoxyphenyl)-2-(4-(methylthio)phenyl).-1H-imidazole-1-yl -5-methylphenol,As a secondary ligand ($L^{/}$). The use of analytical and spectroscopic techniques allowed for the structural characterisation of the compounds. The results of the study demonstrated that amoxicillin's (L) two oxygen atoms caused the coordination sites of the ligands with the metal ions to be diastereomers, whereas derivative imidazole ($L^{/}$) used sulphur and oxygen atoms. The Pt (IV) complex was shown to have an octahedral structure through spectroscopic and analytical studies, whereas the Pd (II) and Au(III) complexes exhibited square planar structures. The ligands and the new compounds were evaluated against strains of bacteria and fungi (E.coli as Gram (-), Staphy. as Gram(+), and Cand.) at three different concentrations (50, 100, and 200) ppm. The results showed that the Au (III) complex was more effective than other compounds. Furthermore, based on the outcomes of the cytotoxic assay, the newly formed complexes were efficiently screened to examine their toxicity as an anticancer drug against MDA cell lines. Specially at high concentrations, these synthetic compounds offer potential as novel candidates for anticancer drugs in the future.

1. Introduction

Recent studies in bioinorganic chemistry and medicine have improved our knowledge of transition metallic ions in coordination chemical reactions with various ligand types [1]. Biologically important ligands can occasionally be more effective in metal complexes than in ligands alone [2]. The kind of ligands employed in complexes determines the solvophilicity, electrical properties of the metal ions, and stability of different oxidation states [3]. Because mixed chelation happens often in biological fluids, mixed ligand complexes are important to biological chemistry [4].

They produce certain structures and are involved in the movement and storage of active ingredients across membranes [5]. The therapeutic benefits of transition metal coordination compounds rely heavily on the latter features. Pharmaceutical companies have therefore thought of ways to stop the spread of drug-resistant microbes that are readily available on the market [6, 7]. One of the most significant classes of antibiotics used as a feed additive in veterinary medicine and medicine is the penicillin group. In many countries, they make up 70% of the antibiotics taken [8,9]. Amoxicillin, ampicillin, bacampicillin, epicillin, and metampicillin are examples of the semi-synthetic penicillin-type antibiotics known as aminopenicillins, which have an additional amine group [10]. Among the most commonly used antibiotics are these. The antibiotic class beta-lactam includes amoxicillin. It has broad-spectrum activity against both positive and gram-negative bacteria. It is used to treat bacterial infections of the skin, gastrointestinal tract, respiratory system, and urinary tract [11]. It works by preventing the bacterial cell wall from being synthesized. Bacteria have become resistant to amoxicillin as a result of its widespread use. Amoxicillin and the salt clavulanic acid are combined to increase the antibiotic's potency. An inhibitor of beta-lactamases is clavulanic acid [12].

A broad range of pharmacological effects, including

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analgesic, anti-tubercular, anti-cancer, anti-fungal, anti-bacterial, anti-inflammatory, antidiabetic, and anti-malarial properties, are displayed by imidazole derivatives [13,14]. Applications for the N-heterocyclic imidazole family are many and span a number of domains, such as dye-sensitized solar cells, optical electronics, and materials chemistry [15,16]. Apart from being employed in the industry for specific purposes as a corrosion inhibitor [17]. Transition metals and imidazole derivatives are also used as photosensitive compounds in photography [18].

Nitrogen-containing heterocycles represent a pivotal class of compounds with wide-ranging applications in medicinal chemistry, catalysis, and materials science [19-23]. A variety of efficient synthetic methodologies—spanning multicomponent reactions, transition-metal-catalyzed processes, and solvent-free green approaches assisted by microwave or ultrasound irradiation—have been established [24-30]. These strategies enable the rapid and high-yield preparation of structurally diverse nitrogen heterocycles with considerable biological and industrial potential.

This work aims to study the anti-cancer, anti-bacterial and anti-fungal activity of palladium, platinum and gold complexes that contain a mixture of ligands from the imidazole derivative and amoxicillin.

2. Materials and Methods

2.1. Instrumentation

$PdCl_2$, H_2PtCl_6, $HAuCl_4.H_2O$ (analytical grade), amoxicillin with a purity of 99.5%, and the solvents needed for the work were provided by Merck (Schnell Dorf, Germany). The melting points of the produced complexes were measured using the Stuart Melting Point apparatus. Using ethanol as the reference and a quartz cuvette as the absorbance wavelength, the UV-Visible spectrophotometer UV-1601 was utilized. Using an FT-IR 8300 Shimadzu Spectrophotometer, Free ligands and metals complexes' Fourier Transform Infrared (FT-IR) spectra have been measured in the 4000-200 cm-1 range. microelement analysis C.H.N. completed research on the metal complexes listed using the micro analytical unit of the Euro EA3000 elemental analysis. (Atomic Absorption Spectrophotometry AA-6880 Shimadzu) was used to do atomic absorption. The molar conductivities of complexes at 10-3 M in the solution of ethanol complexes at 25°C were determined with the Prof Line Oxi 3205 Instrumentation.The magnetic susceptibility measurements were made at R.T. using a (MSB–MKI) magnetic susceptibility moder balance. The microbiology lab conducted every stage of the antimicrobial test.

2.2. Methods

2.2.1. Synthesis of novel metal complexes

Amoxicillin dissolved in 5ML from ethanol, which is primarily a ligand (L) and 2-(4,5-bis(4-methoxyphenyl)-2-(4-(methylthio)phenyl)-1H-imidazol-1-yl)-5- methylphenol dissolved in 5ML from ethanol as (co-ligand; L/), the preparation in literature [31], the mixture solution of the ligands, were add Slowly to the metal salts of $PdCl_2$, H2PtCl$_6$, and $HAuCl_4$ respectively, dissolved in ethanol by using stoichiometric quantities [(1:1:1) (M:L:L$^/$)]. The mixture was refluxed and heated for two hours. The colour crystalline precipitates were seen, dried in a vacuum, (Scheme 1). Using spectroscopic, analytical, and physical tests, all of the produced complexes were identified, as shown in Table 1.

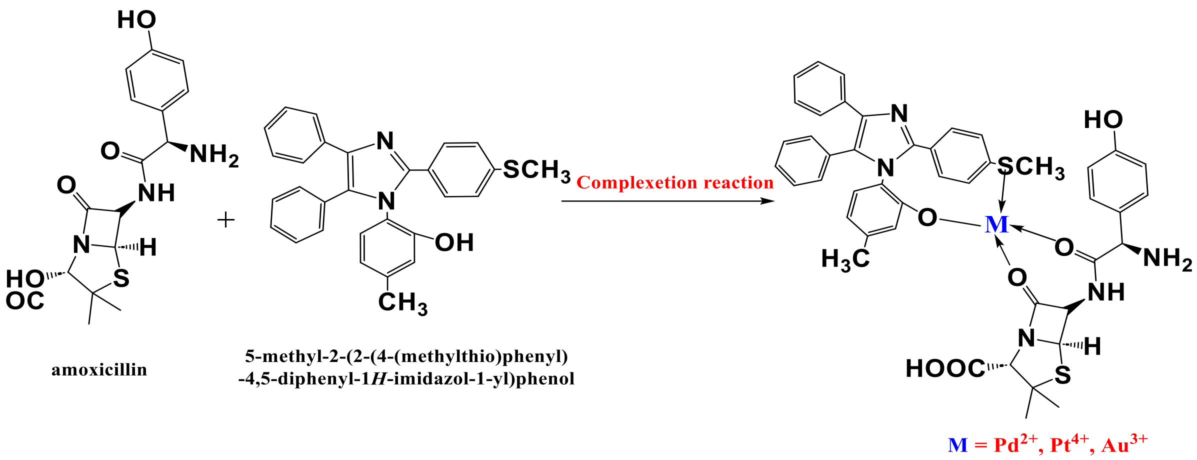
The mixture was then filtered, and the product was purified by recrystallization from ethanol. The physical properties of the obtained compound (A_1) are as follows: Molecular Formula: $C_{13}H_9N_2Br$; Color: Orange; Yield: 83%; Melting Point: 216-218°C [32].

2.2.2. The antifungal and antibacterial drugs' biological action

Amoxicillin L and co-ligand 2-(4,5-bis(4-methoxyphenyl)-2-(4-(methylthio) phenyl)-1H-imidazol-1-yl)-5-methylphenol (L$^/$) beside their some metal complexes of Pd (II), Pt (IV) and Au (III) The results were evaluated in vitro using the agar diffusion technique [33] to test the anti-fungi against candida albicaons and the development of two hazardous bacterial isolates, one Gram-positive Staphylococcus aurous and one Gram-negative Escherichia coli. Adjusting the turbidity of the bacterial suspension by comparing it to the standard Macfarland solution, the process comprised dispersing 100μl of (1×109 cells/mL) of bacterial suspension on a petri dish (90 mm diameter) for 24 hours in order to uniformly inoculate the surface of Moller-Hinton agar. Submerge 0.1 mL of prepared ligands and their complexes LL$^/$-Pd (II), LL$^/$-Pt (IV), & LL$^/$-Au (III) that dissolved in DMSO at concentrations of (10, 50, and 200) ppm into the wells (5 mm diameter). After that, leave the plates for 30 minutes. The inhibitory zone (mm) can be used to calculate the antibacterial activity of the plates after they were incubated for 24 hours at 37°.

2.2.3. Cytotoxic assay

The coulometric 3-(4,5-dimethyl thiazole-2-yl)-2,5-biphenyl was used to assess the cytotoxicity of the complexes. The MDA-231 cell lines utilised in this study were acquired from the biotechnology centre at Al-Nahrain University. Cell lines were treated with the complexes at different dosages for 24 hours before being analysed. For every complex, the results of the MTT assay were compared with negative control culture medium at different concentrations (400, 200, 100, 50, 25, and 12.5) μg/mL [34].



Scheme 1. Reaction of mixed ligand complex formation

3. Results and Discussion

3.1 Physical properties of the synthesis compounds

As shown in Table 1, the heavy metal complexes are colored with good percentage yields ranging from 77% to 85% to 88%. L and co-ligand L/, the ligands used in the present study, are pale yellow and white. Regarding light and air, both produced compounds show stability. Several analytical techniques, including C.H.N. elemental analysis, A.A. metal analysis, UV-Vis, FT-IR, magnetic moment measurements, and molar conductivities, were used to investigate the metal complexes. It was observed that there is agreement between the analytical and experimental data results. The results demonstrates that the produced complexes' magnetic susceptibility value and their ionic nature agree with their suggested molecular geometry. Table 1 lists the physiochemical properties of ligands and the metal complexes they form.

3.2. FT-IR spectra of compounds

In the solid state FTIR spectra were measured for all the synthesized ligands (L, L/) and their complexes are reported in Table (2). The sample spectra were measured using potassium bromide in range (4000-400) cm^{-1}. The FTIR spectrum gives information about the diagnostic bands of the various ligands (L, L/) and their behavior in coordination complexes. The characteristic frequencies of free ligands and their metal complexes were readily assigned based on comparison with literature values. FT-IR spectra of compound (Ligand L/) show the following bands at 3224 cm^{-1} ν (OH), 3064 cm^{-1} ν (C–H aromatic), 2964 cm^{-1} ν (C–H aliphatic), 1604 cm^{-1} ν (C=N) and 1517 cm^{-1} ν (C=C) [35,36]. While the compound of the amoxicillin (Ligand L) the appearance of a broad band belonging to ν (OH) phenol and carboxyl groups at 3529 cm^{-1}, (3464-3375) cm^{-1} refers to the symmetry and asymmetry of a group ν (NH_2), the band at (3167) cm^{-1} refers to the group ν (NH), while the bands at (3039 and 2970) cm-1 due (C–H aromatic) and (C–H aliphatic) respectively[37,38], showed sharp and medium characteristic absorption bands at 1778 and 1689 cm-1 due to asymmetric and symmetric ν(COO) stretching respectively, and the band at 1581cm-1 which refer to group ν (C=O)[39], of the ligands as show in Figures (1,2). The IR spectra of the complexes as show in Figures (3-5) the frequency of υ (O-H) phenol and carboxyl group, ν (NH2), ν (N-H), ν (COO) and ν (C=O) and in the complexes (LL/-Pd, LL/-Pt and LL/-Au) groups suffering to shifted towards a lower frequency and changed intensity. The new medium or weak bands that formed at (545, 535, and 610) cm-1, which were attributed to the stretching frequencies of the Pd-O, Pt-O, and Au-O bonds, respectively, provided more evidence for this coordination [40], and for the ν (Pd- SCH_3, Pt- SCH_3 and Au- SCH_3) groups suffering to shifted towards a lower frequency and changed intensity. As a result of these findings, the proposed of complexes exhibit four and six coordination as a square planer and octahedral structure in solid state. Showes the Figures (1-5).

3.3. Electronic spectra, Magnetic susceptibility and Conductivity measurements:

The Brown Pd(II) complex's UV-Vis spectrum shows two bands. As seen in Figure (8), the two absorption bands occurred at 42000 cm-1 and the first absorption band at 33120 cm-1. The transition $^1A_1g \rightarrow$ 1B1g, represented by 10Dq, has been assigned to these absorption bands, the transition $^1A_1g \rightarrow {}^1Eg$ Which represents the second absorption for spin- parried d8 square planar configuration [41,42]. The magnetic moment of the crystalline complex was found to be (Zero B.M.). The conductance behaviour suggests that this compound has an electrolyte. Figure (9) displays the electronic spectra of the produced Yellow Pt(IV) complex, with absorption bands corresponding to the transition at 26416 and 36910 cm^{-1}. $^1T_2g \rightarrow {}^1A_1g$, $^1A_1g \rightarrow$

^1T_1g. The band that was observed at 9925 cm^{-1} is associated with spin-forbidden transitions. $^1A_1g \rightarrow {}^3T_1g$, ^3T_2g. These, in accordance with accounts, suggested an octahedral geometry [43,44]. This result was related to $t_2g^6eg^0$ configuration spin pair octahedral stereochemistry. The magnetic moment of the crystalline complex was found to be (Zero B.M.). The conductance behaviour suggests that this compound has an electrolyte. The orang Au(III) complex spectrum. The electronic spectra of this complex are depicted in Figure (10), with two main bands at 23825 and 35744 cm^{-1}, corresponding to the $^1A_1g \rightarrow {}^1B_1g$ and $^1A_1g \rightarrow {}^1Eg$ transitions, and another peak appearing at 44060 cm^{-1}, which is attributed to charge transfer in a square planar geometry [45] and zero magnetic moment. This chemical appears to have an electrolyte based on its conductivity behaviour.

Moreover, the proposed square planar geometry for these Pd(II) and Au(III) complexes was validated by data analysis and spectroscopy techniques. However, this Pt(IV) complex was proposed to have an octahedral shape. as displayed in Table 3 and Scheme 2.

3.4. Antimicrobial activity

Amoxicillin, co-ligand, LL$^/$-Pd, LL$^/$-Pt, and LL$^/$-Au were investigated for their antimicrobial activity against fungi and two bacterial strains: one gram-positive and one gram-negative. Table 4 displays the ligands' and inclusion complexes' inhibitory zones. In the great majority of the plates, zones of bacterial growth suppression surrounding the impregnated paper discs were detected during the anti-biological activity test conducted against the microorganisms in conjunction with the ligands and their heavy metal complexes. Conclusion: Amoxicillin and its inclusion complexes have strong antibacterial action, particularly at high concentrations. When compared to their parent ligands, the own metal complexes have more activity. The influence of metal ions on the normal cell membrane could be the cause of the activity of compounds with metal ions, as shown in Figure (11). It is commonly recognized that metal chelates combine their polar and non-polar properties, which allows them to easily pass through cell walls. On the other hand, salt metal ions increase the lipophilicity of their complexes, which facilitates their penetration of cell walls and alteration of the cell environment. Apart from the previously mentioned aspects, the way the compounds behaved towards the microorganisms under investigation can be explained by the following: the type of metal ions, the geometric structure of these complexes, the way the ligands were arranged around the metal ion, the chelation effect of the organic molecules used as ligands, the kind of atoms that coordinate with metals, and the kind and oxidation state of the metals [46]. The complexes inhibit bacteria from synthesizing proteins. This activity also hinders peptide translocation and ribosome disassembly. Due to its unique structure and mode of action, there is little cross-resistance with other recognized antibiotics.

Table 1. physiochemical details of the three heavy metals complexes and both the primary and secondary ligands.

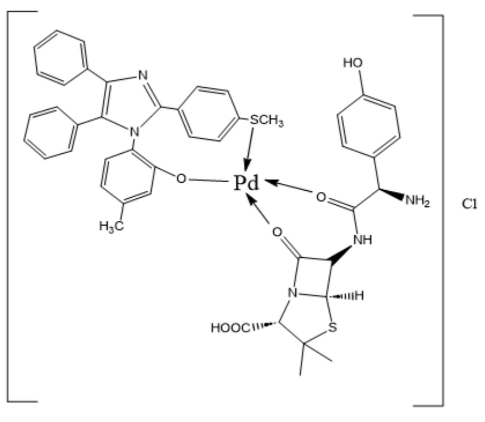
Comp.	Colour	Molecular weight g/mole	mp (ºC)	Yield (%)	C.H.N analysis Found (calc.)			%Metal found (calc.)	Suggested Molecular formula
					%C	%H	%N		
L	Pale yellow	448.58	263-265		77.12 (77.65)	5.34 (5.39)	6.09 (6.24)	-	$C_{29}H_{24}N_2OS$
L$^/$	White	365.40	192-194		52.22 (52.59)	5.13 (5.24)	11.40 (11.50)	-	$C_{16}H_{19}N_3O_5S$
Pd-LL$^/$	Dark brown	954.85	235-237	77	56.52 (56.61)	4.12 (4.43)	7.02 (7.33)	11.06 (11.15)	$C_{45}H_{42}PdClN_5O_6S_2$
Pt-LL$^/$	Yellowish orang	1150.44	244-246	85	46.24 (46.98)	3.82 (4.03)	5.97 (6.09)	16.48 (16.96)	$C_{45}H_{46}PtCl_3N_5O_8S_2$
Au-LL$^/$	orang	1080.85	252-255	88	49.11 (50.01)	3.23 (3.92)	6.03 (6.48)	18.12 (18.22)	$C_{46}H_{45}AuClN_5O_6S_2$

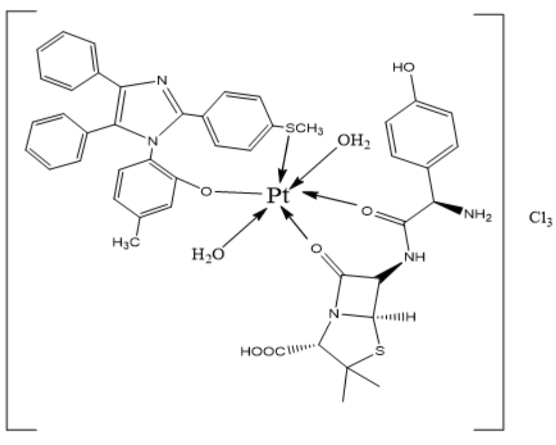
Table 2. FT-IR bands of absorption of particular mix ligands complexes in (cm^{-1})

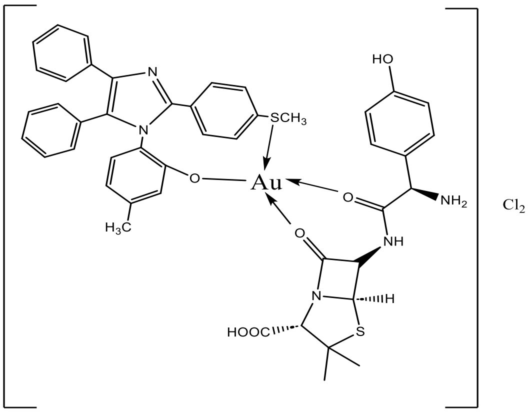
Comp.	ν (OH)	ν (NH_2)	ν (NH)	ν (COO)	ν (C=O)	ν (SCH_3)	ν (M-O)
L	3224	---	---	---	---	2887	---
L/	3529	3464-3375	3167	1778 1689-	1581	---	---
Pd-LL/	---	3317-3263	3066	1685-1735	1516	2638	545
Pt-LL/	---	3255-3225	3075	1685-1735	1516	2623	535
Au-LL/	---	3186-3232	3070	1635-1716	1516	2739	610

Table 3. Conductivity tests, magnetic moments, proposed synthesis complex form, and the electronic spectra of two ligands and their metal complexes are likely to be assigned.

Com.	Abs. cm^{-1}	Assignments	μeff B.M	μs. cm^{-1}	Suggested geometry
L	42476 35720	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	----	----	-----
L/	45439 42321 36147	$\pi \rightarrow \pi^*$ $\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	----	-----	------
LL/-Pd	33120 42000	$^1A_1g \rightarrow {}^1B_1g$ $^1A_1g \rightarrow {}^1Eg$	0.00	77.8	Square planer
LL/-Pt	26416 36910 9925	$^1A^1g \rightarrow {}^1T_2g$ $^1A_1g \rightarrow {}^1T_1g$ $^1A_1g \rightarrow {}^3T_1g, {}^3T_2g$	0.00	300.2	Octahedral
LL/-Au	23825 35744 44060	$^1A_1g \rightarrow {}^1B_1g$ $^1A_1g \rightarrow {}^1Eg$ Au →LCT	0.00	275.5	Square planer







Scheme 2. Geometry suggestions for newly synthesised compounds

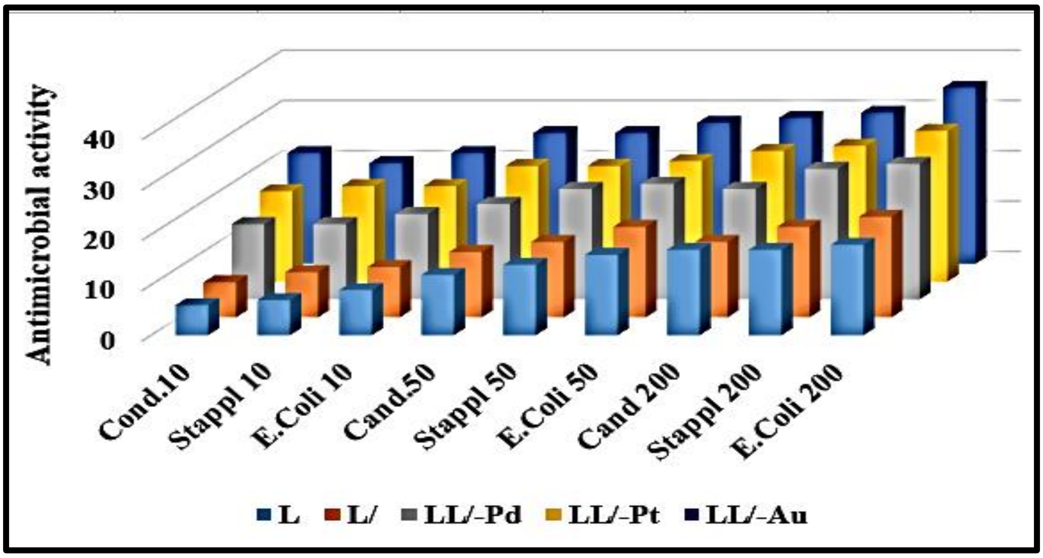


Figure 11. The generated compounds and their ligands' biological activities

3.5. Assay for cytotoxicity

Breast cancer represents the most prevalent form of cancer in women globally, making up around 25% of all malignant tumours in women, most of which have spread widely. Moreover, 28 nations—even developed nations—show a low response to treatment even after numerous new drugs have been introduced to the market. Therefore, the need to create more potent anticancer agents is urgent. The majority of research teams are working on drugs 29 in an effort to create a useful anticancer drug that can be used successfully to treat cancer in people. This research provides? Evidence that the artificial compounds are effective against breast cancer MDA-MB-231 (in vitro) cell lines. Following a 24-hour treatment with varying concentrations (12.5, 25, 50, 100, 200, and 400) µg/mL of freshly produced compounds, the MTT test was utilised to evaluate the cytotoxicity and viability of the MDA-MB-231 cell lines (Fig. 12). The results of the MTT experiment demonstrated a significant rate of inhibition for metal complexes as compared to the negative control cells that were left untreated. At high concentrations of 400µg/ml for each of LL/-Pd, LL/-Pt, and LL/-Au in sequential order, the metal complexes demonstrated high toxicity and recorded high inhibition rates (77, 84, and 90%). Gradually, the inhibition rates decreased from high to low concentrations. The pharmacological effects of these complexes can be traced back to a number of situations. For example, synthetic derivatives can limit the growth and activity of breast cancer cells by following apoptotic and autophagic pathways, just like natural material can [47].

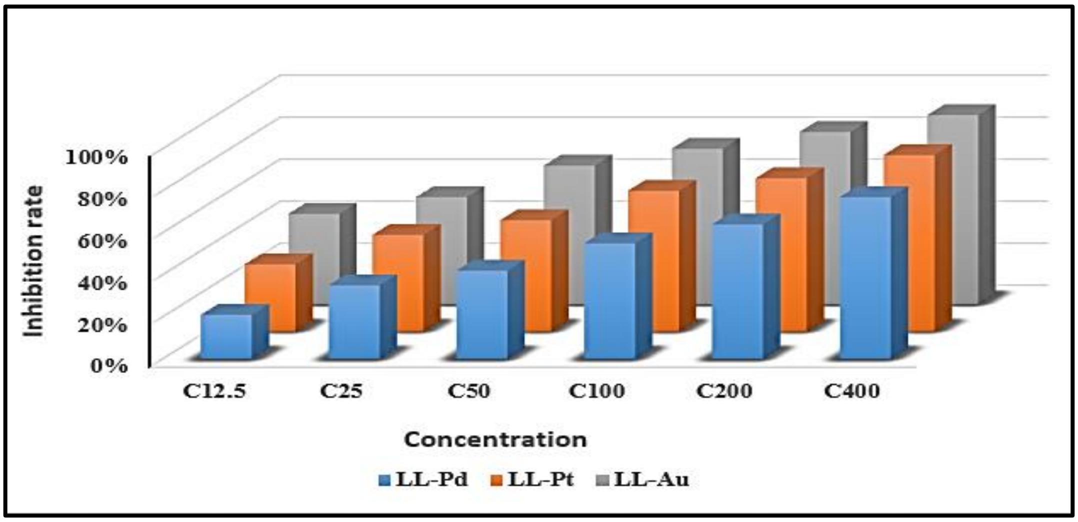


Figure 12. The MDA cell line's inhibition rate as a percentage following a 24-hour exposure to prepared compounds

4. Conclusion

Amoxicillin (L) and 2-(4,5-bis(4- methoxyphenyl)-2-(4-(methylthio)phenyl)-1H-imidazol-1-yl)-5-methylphenol($L^/$) mixed ligands. Three selected heavy metal complexes, Pd(II), Pt(IV), and Au(III), were successfully used to synthesize. Chemical and physical methods were used to diagnose the complexes in order to ascertain their mechanism of bonding and overall structure. A square planner structure for Pd(II) and Au(III) complexes and an octahedral geometry for Pt(IV) complex are suggested by the physicochemical and spectroscopic data, which further suggest that Pd(II), Pt(IV), Au(III), and the ligands are brought together with a rigid configuration and that two ligands behave as a bidentate, one by oxygen atoms (L) and another by oxygen atom and Sulphur atom ($L^/$). These addition metal complexes' free ligands biological activity was examined in vitro against three different bacteria at three different concentrations. The results demonstrated good biological activity, particularly for the gold complex. These compounds were tested against the anticancer MDA cell line, and it was shown that the more concentrated they are, the more effective they are against cancer cells. Compared to these complexes, the synergistic impact of the Au(III) complex has a higher biological activity.

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