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Synthesis and Characterisation of Novel Palladium(II) Isatin-3-Thiosemicarbazone Complexes with Phosphine and Phenanthroline Ligands: In Vitro Evaluation Against Cancer Cell Lines and Bacterial Strains

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Abstract: In this study, three new palladium (II) complexes with isatin-3-thiosemicarbazone (ITC) were prepared by reacting Pd(II) with ITC and phosphine or diamine ligands. Characterisation was done using CHN analysis, molar conductivity, FTIR spectroscopy, and ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. All analyses confirmed that the complexes exhibit a square planar structure around the Pd^{2+} ion. The ITC ligand displayed a bidentate coordination mode, binding through nitrogen and sulphur atoms. In vitro biological activity studies revealed excellent anti-ovarian cancer potential. Notably, the complex $(Pd(ITC)(Phen))Cl_2$ demonstrated only 5% cell survival at a 400 µM concentration, while the other two complexes, $(Pd(ITC)_2)Cl_2$ and $(Pd(ITC)(PPh_3)Cl)Cl$, did not exceed 10%. These results illustrate the strong ability of these complexes to inhibit cancer cell growth in vitro. Additionally, the three synthesised complexes demonstrated clear antibacterial activity against four bacterial strains: two Gram-positive (*Streptococcus faecalis* and *Staphylococcus aureus*) and two Gram-negative (*E. coli* and *Pseudomonas aeruginosa*). The activity was concentration-dependent, decreasing as the concentration lowered. The complex $(Pd(ITC)(Phen))Cl_2$ exhibited the highest antibacterial activity, particularly against Gram-positive bacteria, followed by $(Pd(ITC)(PPh_3)Cl)Cl$ and $(Pd(ITC)_2)Cl_2$. These findings indicate the possible development of these complexes as therapeutic agents with anticancer and antibacterial properties, particularly in addressing bacterial resistance to conventional antibiotics.

Keywords: Pd(II), (ITC), Cyclic nitrogen, Anti-ovarian cancer activity.

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1. INTRODUCTION

Thiosemicarbazones (TSCs) are significant compounds in coordination chemistry due to their strong metal-chelating capabilities and notable biological activities (1-3), particularly in inhibiting ribonucleotide reductase (RR), an essential enzyme for DNA synthesis (4). These compounds exhibit antiviral and antibacterial properties (5), are utilised in HIV detection (6), and have shown antimalarial effects (7). Their derivatives demonstrate a range of biological activities, including anti-tumour, anti-cancer, and anti-inflammatory effects (8). Thiosemicarbazone (TSC) compounds are among the most prominent ligands used in coordination chemistry. They are typically synthesised as Schiff bases through condensation reactions between thiosemicarbazide and suitable carbonyl compounds and are regarded as effective coordinating agents due to the presence of nitrogen and sulphur donor atoms in their structures (9). The inclusion of a thiol group further classifies them as part of a vital ligand family capable of binding to metals through single, double, or bridging bonds (10,11).

These compounds are recognised for forming stable complexes with transition metals (12). In "isatin-thiosemicarbazone" derivatives, the nitrogen, sulphur, and carbonyl oxygen atoms function as active donor sites. Thiosemicarbazide has also been extensively researched for its bonding capabilities

with various cations via its sulphur or nitrogen atoms (13–16).

Isatin-thiosemicarbazones hold particular significance due to their physiological activity, attributed to the additional oxygen donor atoms from the indole ring, which introduce multiple coordination sites within the molecular framework (17). This structural feature has garnered substantial interest in coordination chemistry by facilitating diverse coordination modes with metal ions (18). Previous studies have reported complexes of these ligands with triphenylphosphines and amines (19), while those involving palladium or mercury have demonstrated promising performance in hydrogen storage applications (20-22).

Additionally, several precursor complexes have been studied to evaluate their potential as anticancer agents and their hydrogen absorption capabilities (23). Based on this, the present study aims to prepare new palladium(II) complexes of isatin-thiosemicarbazone compounds with various coordinating ligands, such as triphenylphosphine (PPh_3) and 1,10-phenanthroline (Phen). The focus is on the formation of stable complexes and their characterisation using different techniques. The study also investigates their effects on two cancer cell lines, MCF-7 and 518A2, as well as on four different bacterial strains: two Gram-positive (*Streptococcus faecalis* and *Staphylococcus aureus*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*).

2. EXPERIMENTAL SECTION

2.1. Materials and Instrumentation

All chemicals, reagents, and solvents used to manufacture compounds were supplied and employed without purification.

The melting point of the prepared complexes was recorded using an automatic melting point device (SMP30). The molar conductivity of a freshly prepared 10^{-3} M DMSO solution was noted. The complexes were measured with the Starter 3100c digital conductivity meter. The infrared spectra of the complexes were recorded as KBr tablets using the Shimadzu FTIR 8400s spectrometer (400-4000 cm^{-1}) at the Tikrit University, College of Pure Science in Iraq. Microanalyses for carbon, hydrogen, nitrogen and sulphur were carried out using an Elementar vario El III CHN elemental analyser. Nuclear magnetic resonance spectra were obtained on the Bruker 400 MHz spectrometer using DMSO-d6 as the solvent at the University of Tehran, College of Science.

2.2. Preparation of Ligand (ITC)

The ligand (ITC) was synthesised using a conventional method described in reference (24). Thiosemicarbazide (0.55 g, 7.1 mmol) was dissolved in 10 mL of an appropriate solvent. A solution of isatin (0.99 g, 6 mmol) was prepared in 10 mL of ethanol and added to the mixture, which was then heated in a water bath at 50 °C after adding two to three drops of glacial acetic acid as a catalyst. The reaction mixture was refluxed for one hour and subsequently allowed to cool. The resulting yellow precipitate was separated by filtration, washed with cold ethanol, and dried in a hot-air oven at 90 °C. A yellow crystalline compound with the molecular formula $C_9H_8N_4OS$ was obtained, yielding 1.88 g (83%). Elemental analysis was performed, and the theoretical values for carbon, hydrogen, nitrogen, and sulphur were calculated as follows: C = 49.77%, H = 4.12%, N = 26.00%, S = 14.56%. The experimentally found values were: C = 49.55%, H = 2.960%, N = 26.45%, S = 15.07%.

2.3. Synthesis of $(Pd(ITC)_2)Cl_2$

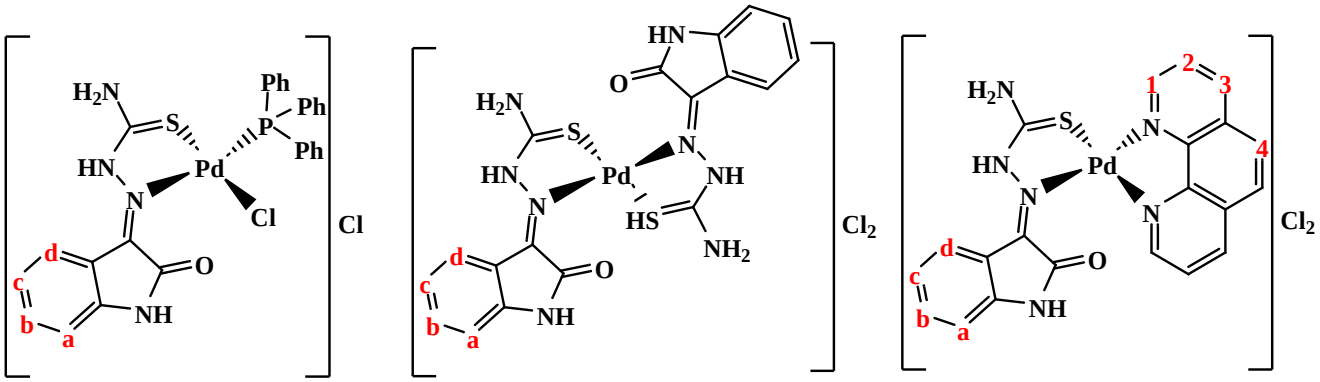
A solution of $PdCl_2$ (1.793 g, 10 mmol) in 99% ethanol (20 mL) was slowly added to a solution of HITC (3.155 g, 10 mmol) in 99% ethanol (20 mL). The mixture was stirred for two hours, resulting in the formation of a yellow suspension. $(Pd(ITC)_2)Cl_2$ (1) appeared as an orange solid with a yield of 0.7272g (90.0% yield). Elemental analysis yielded: C, 33.91; H, 2.64; N, 22.60; S, 12.93; found: C, 34.22; H, 2.97; N, 22.26; S, 12.49. Conductivity measured at 67.3 $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$. IR (KBr, cm-1): 3417s (NH), 3265s (C-H), 3145m (C=S), 1699s (C=O), 1606s (C=N),1344s (C=S),1504s (N-H). 1H-NMR (DMSO-d6): 12.37 (S, 1H, NH isatin), 9.02 (S, 1H, NH2), 8.63 (S, 1H, NH2), 7.64 (d, 1H, Ha), 7.36 (t, 1H, Hc), 7.09 (t, 1H, Hb), 6.91 (d, 1H, Hd). 13C-{1H} NMR: δc, S, 179.3 (C=S), δc, S, 166.1 (C=O), δc, 142.5 (C-NH), δc, 134.2 (C=N), δc, 131.1 -117.2 (Ph-C). Melting point: 262 ℃.

2.4. Synthesis of $(Pd(ITC)(Phen))Cl_2$ and $(Pd(ITC)(PPh_3)Cl)Cl$ Complexes

A solution of Na_2PdCl_4 (1.81 mmol, 0.5 g) in 10 mL of absolute ethanol was added to a solution of Phen (1.81 mmol, 0.359 g) in 10 mL of absolute ethanol. The mixture was stirred for an hour at 20°C, resulting in a white precipitate. To this precipitate, a solution of ITC (1.81 mmol, 0.399 g) in 10 mL of absolute ethanol was added. The mixture was stirred for two hours at 20 °C, yielding a light yellow precipitate. The precipitate was filtered, washed with cold ethanol, and dried under reduced pressure, yielding $(Pd(ITC)(Phen))Cl_2$ (2), a pale yellow solid with a yield of 1.231 g (97%). Calculated elemental analysis: C, 38.77; H, 2.00; N, 20.87; S, 7.96; found: C,39.17; H,2.30; N,20.15; S,7.43. Molar conductivity: 76.4 Ω-1.cm^2.$mol^{-1.}$ IR (KBr, cm^{-1}): 3247 m (NH), 3419 w (NH2), 3051 w (=C–H), 1679 s (C=O), 1614 s, 1583 s, 1487 m (C=N), 1346 m (C=S), 854 m. 1H-NMR (DMSO-d_6):11.21 (bs, 1 H, NH), 9.16 (s, 1 H, NH2), 8.86 (s, 1 H, NH2), 9.27 (d, 2 H, H1 phen), 8.97 (d, H3 phen), 8.13 (s, 2 H, H4 phen), 8.18 (m, 2 H, H2 phen), 7.66 (d, 1 H, Ha), 7.37 (t, 1 H, Hc), 7.10 (t, 1 H, Hb), 8.97 (d, 1 H, Hd). 13C-{1H} NMR (DMSO-d6): δ178.98 (C=S), 164.21(C=O), 156.55(C=O)ITC, 141.77 (C1, phen), 139.31(C=N) ITC, 134.68–116.92 (aromatic ITC, phen). Melting point: 285-288 °C.

The solution of (Na_2PdCl_4) (2.302 mmol, 0.0474g) in 10 mL of chloroform was slowly added to the solution of (ITC) (2.302 mmol, 0.0507 g) in 10 mL of chloroform, and the mixture was allowed to ascend for two hours, resulting in the formation of a white precipitate. A solution of a (20 mmol) equivalent of PPh_3 in chloroform (51 mL) was then added to the previous mixture and refluxed for three more hours. The pale yellow or white precipitate was collected and dried at room temperature. $(Pd(ITC)(PPh_3))Cl_2$ (3) Orange solid, yield (2.817 g, 80%). Calculated

elemental analysis: C, 48.27; H, 3.35; N, 9.79; S, 5.60; found: C, 48.70; H, 3.69; N, 9.65; S, 5.48. Molar conductivity (30.8 $\Omega^{-1}.cm^2.mol^{-1}$). IR (KBr, cm^{-1}): 3417 m (NH2), 3272 m (NH), 3049 m (=C–H), 2977 w (C–H); 1677 s (C=O), 1614 s (C=N), 1429 s (P–Ph), 1477 m (Ph-Ph), 1344 w (C-S), 1095 m (P–C), 690 s. ^{1}H-NMR (δ ppm, J Hz, DMSO-d_6): 11.20 (s, 1H, NH), 9.04 (s, 1H, NH2), 8.69 (s, 1H, NH2), (7.68–7.50) (m, 15H, PPh_3), 7.67 (d, 1H, Ha), 7.36 (t, 1H, Hc), 7.10 (t, 1H, Hb), 6.940 (d, 1H, Hd). ^{31}P-{^{1}H}NMR (δ ppm, JHz, DMSO-d_6): 30.62. Melting point: 279–282 ◦C.



(3) (1) (2)

Figure 1: The prepared complexes.

2.5. Evaluation of the Bacterial Activity of the Prepared Complexes

The bacterial (biological) activity of the prepared complexes was evaluated on four types of bacteria: two Gram-positive and two Gram-negative strains, using the agar well diffusion method. (25) The bacterial isolates were identified by the Department of Life Sciences at the College of Science, Tikrit University, and they are: *Pseudomonas aeruginosa* (Gram-negative), *Escherichia coli* (Gram-negative), *Staphylococcus aureus* (Gram-positive), and *Streptococcus faecalis* (Gram-positive).

The complex solutions were prepared using DMSO solvent at concentrations of (10^{-1}, 10^{-3}, 10^{-5} x 1 M). Next, the culture medium was prepared by dissolving 38 grams of nutrient agar in 1 litre of distilled water and placing it in a conical flask. The mixture was stirred thoroughly and heated until the agar (a gelatinous substance used as a medium for bacterial growth) was completely dissolved. Afterwards, the medium was sterilized in an autoclave at 121 °C and 15 bars for 15 minutes. After sterilisation, the medium was poured into Petri dishes and left to solidify.

Subsequently, 3 to 5 bacterial swabs were placed on the prepared medium and incubated for 24 hours at 37 °C. For evaluating biological activity, a second medium was prepared by dissolving 53.5 grams of Mueller-Hinton agar in 1 litre of distilled water. The medium was sterilised in an autoclave at 121 °C and 15 bars for 15 minutes.

After sterilisation, the medium was poured into Petri dishes and allowed to solidify. A quantity of activated bacteria was collected using a swab and spread evenly over the solidified Mueller-Hinton agar. The plate was left for 30 minutes to facilitate absorption, and then wells were created using a sterile 5 mm diameter punching tool. Four wells were formed, and 1 mL of each prepared compound solution at varying concentrations was added to the wells. All Petri dishes were incubated for 24 hours. The inhibition zones were measured to assess the effectiveness of the compounds in inhibiting bacterial growth (26).

3. RESULTS AND DISCUSSION

Molar conductivity of the complexes exhibited molar conductivity values in DMSO at (25 °C, 10^{-3} M) within the range of (67.3 - 76.4 $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$) for $(Pd(ITC)_2)Cl_2$ and $(Pd(ITC)(Phen))Cl_2$ respectively, indicating that the solutions of these complexes are 1:2 electrolytes. On the other hand, the complex $(Pd(ITC)PPh_3)Cl)Cl$ (3) showed a value of (30.8 $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$), suggesting that the solution of this complex is a 1:1 electrolyte (27,28).

The FTIR spectrum of the free ligand HITC exhibited vibrational bands at 3419, 3265/3174, 1679, 1614, and 1346 cm^{-1}, corresponding to ν(N-H), ν(NH_2), ν(C=O), ν(C=N), and ν(C=S) respectively (28,29). The bands associated with the NH_2 groups in the prepared complexes were slightly shifted from their positions in the free ligand, indicating no coordination of the NH_2 nitrogen groups with the metal ions. Additionally, NH group bands in the prepared complexes appeared in the range of 8-9, along with a shift of the ν(CS) group bands to lower values, within the range of 1313-1334 cm^{-1}, confirming the coordination of the ligand through the sulphur atom of the thionate group. All prepared complexes exhibited sharp and strong bands in the range of 1658-1697 cm^{-1}, attributed to ν(C=O), while the bands in the range of 1512-1583 cm^{-1} were assigned to the vibration of the ν(C=N) group (28,29).

The ^{1}H-NMR spectrum of the ITC ligand revealed a singlet at (δH=13.93 ppm, 1H) and (δH=11.37 ppm, 1H), corresponding to the NH protons in the isatin and hydrazone groups, respectively. Two doublet signals appeared at (δH=7.88ppm, 2H, 3JH-H = 7.70 Hz) and (δH=7.67ppm, 1H, ^{3}JH-H = 7.59 Hz), which were attributed to the He and Ha protons, respectively. A triplet signal was observed at

(δH=7.60ppm, 3H, 3JH-H = 7.92 Hz), corresponding to the Hf and Hg protons. Additionally, two triplet signals appeared at (δH=7.38 ppm, 1H, ^{3}JH-H =7.13 Hz) and (δH=7.10 ppm, 1H, ^{3}JH-H =7.68 Hz), assigned to the Hc and Hb protons, respectively. A doublet signal was observed at (δH=6.95ppm, 1H, ^{3}JH-H = 7.88 Hz) for the Hd proton (28,30).

The ^{13}C-NMR spectrum of ITC showed signals at (δC=200.70 ppm) and (δC=175.95 ppm), corresponding to the (C=O) carbons in the benzoyl and isatin groups, respectively. Signals were also observed in the range of (δC=158.05-159.02 ppm) for the atoms (C7, C1, C8, and C11) in sequence and (δC=142.92 ppm) assigned to the (C5) carbon.

The ^{1}H-NMR spectrum of the complex $(Pd(ITC)_2)Cl_2$ showed a singlet at (δH = 12.37ppm) with an integration of one proton corresponding to the NH group of thiosemicarbazone. The spectrum also showed a singlet at (δH = 11.23 ppm) with an integration of one proton corresponding to the NH group of isatin. Two singlets appeared at (δH=9.02 ppm) and (δH=8.63 ppm) for the NH_2 group, indicating unequal protonation of the amine group, with one proton for each. A doublet signal appeared at (δH=7.64 ppm) for the Ha proton, integrating one proton, and a triplet at (δH=7.36 ppm) integrating one proton for the Hc proton. The spectrum showed a triplet at (δH=7.09 ppm) integrating one proton for the Hb proton. A doublet signal also appeared at (δH=6.92 ppm) integrating one proton for the Hd proton (28,30).

The ^{1}H-NMR spectrum of complex (**1**) showed a singlet at (δH=12.54 ppm) with a one proton integration for the NH group of thiosemicarbazone. A singlet at (δH=11.21 ppm) with a one proton integration corresponded to the NH group of isatin. Two singlets at (δH=9.16 ppm) and (δH=8.86 ppm) were assigned to the NH_2 group, indicating unequal protonation of the amine group, with one proton for each. The spectrum also showed a signal for the ligand (Phen), with a doublet at (δH=9.27 ppm) for the H1 proton, integrating two protons, and another doublet at (δH=8.97 ppm) for the H3 proton, integrating two protons. The spectrum also showed a singlet at (δH=8.31 ppm) for the H4 proton, integrating two protons, and a multiplet at (δH=8.18 ppm) for the H2 proton, integrating two protons. A doublet appeared at (δH=7.66 ppm) for the Ha proton, integrating one proton, and a triplet at (δH=7.37 ppm) for the Hc proton, integrating one proton. A triplet at (δH=7.10 ppm) for the Hb proton, integrating one proton, and a doublet at (δH=6.93 ppm) for the Hd proton, integrating one proton, were also observed.

The ^{1}H-NMR spectra of complexes (2-5) showed various signals for both the ligand (ITC) and the corresponding phosphine. A singlet at (δH=12.49 ppm) with one proton integration corresponded to the NH group of thiosemicarbazone. The spectrum also showed a singlet at (δH=11.20 ppm) with one proton integration for the NH group of isatin, and two singlets at (δH=9.04 ppm) and (δH=8.69 ppm) for the NH_2 group, indicating unequal protonation of the amine group, with one proton for each. In the spectra of complex (2), two multiplets appeared at (δH=7.62 ppm) and (δH=7.50 ppm), integrating 15 protons, attributed to the phenyl rings of (PPh_3). In the spectra of complex (3), two multiplets appeared at (δH=7.69 ppm) and (δH=7.56 ppm), integrating approximately 11 protons corresponding to the phenyl rings of dppe, with proton Ha among them (28,30).

3.1. Anti-Cancer Activity of $(Pd(ITC)(PPh_3)Cl_2)$

The cytotoxic activity of the complex $(Pd(ITC)(PPh_3)Cl_2)$ was evaluated using the MTT assay against two human cancer cell lines: MCF-7 (breast adenocarcinoma) and 518A2 (melanoma), at a concentration of 0.01 µm. The results showed that the complex exhibited significant inhibitory effects against both cell lines (31,32).

Against the MCF-7 cell line, $(Pd(ITC)(PPh_3)Cl_2)$ demonstrated an IC_{50} value of 15.43 µM, indicating good cytotoxic potential, although it was less effective than cis-platin (IC_{50} = 4.45 ± 0.04 µM).

Similarly, against the 518A2 cell line, the same complex exhibited an IC_{50} value of 16.93 µM, compared to cis-platin with an IC_{50} of 1.45 ± 0.04 µm.

These findings suggest that $(Pd(ITC)(PPh_3)Cl_2)$ possesses promising anticancer activity, particularly among the tested Pd(II) complexes, though it remains less potent than cis-platin (33).

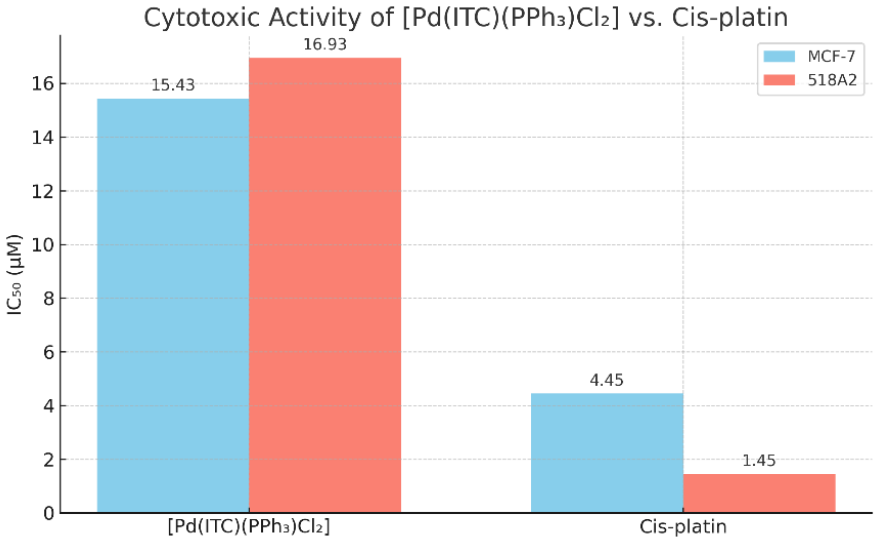


Figure 2: Comparison of IC_{50} Values for $(Pd(ITC)(PPh_3)Cl_2)$ and Cisplatin Against MCF-7 and 518A2 Cell Lines.

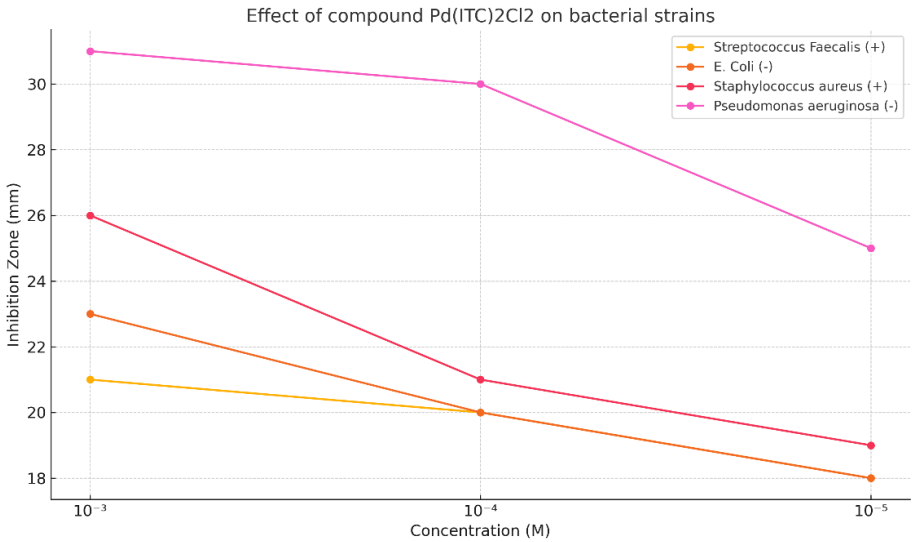
3.2. Biological Study

The antibacterial activity of three synthesised complexes $(Pd(ITC)_2)Cl_2$, $(Pd(ITC)(Phen))Cl_2$, and $(Pd(ITC)(PPh_3)Cl)Cl$ was assessed against four bacterial strains: two Gram-positive (*Streptococcus faecalis* and *Staphylococcus aureus*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*). This evaluation utilised the disc diffusion method at various concentrations (10^{-3}, 10^{-4}, and 10^{-5} g/mol) for each complex, with DMSO serving as the solvent. The findings indicated that the antibacterial effectiveness of these complexes was distinctly concentration-dependent; inhibition zones decreased as the concentration lowered, and no activity was noted at the lowest concentration (10^{-5} g/mol).

The complex $(Pd(ITC)_2)Cl_2$ exhibited moderate activity against all tested bacterial strains at the highest concentration (10^{-3} g/mol), showing inhibition zones from 21 mm for Gram-positive bacteria up to 31 mm for Gram-negative bacteria. However, this activity dropped significantly at lower concentrations. In contrast, $(Pd(ITC)(Phen))Cl_2$ displayed the highest antibacterial activity among the tested complexes, particularly against Gram-positive bacteria, achieving an inhibition zone of 36 mm against *S. aureus* at the maximum concentration. It also revealed considerable effectiveness against Gram-negative bacteria. The complex $(Pd(ITC)(PPh_3)Cl)Cl$ demonstrated consistent effectiveness against all examined strains, with inhibition zones ranging from 27 mm to 32 mm at the highest concentration, followed by a gradual reduction at lower concentrations.

This may be attributed to the rigid and planar structure of Phen, which may allow better interaction with cellular structures compared to the structure of PPh_3, where the phenyl rings increase steric hindrance (23).

These results indicate that the synthesised complexes exhibit promising biological activity as antibacterial agents, particularly at higher concentrations. This suggests their potential for future development as pharmaceutical compounds, especially in light of the growing bacterial resistance to conventional antibiotics (34-36).



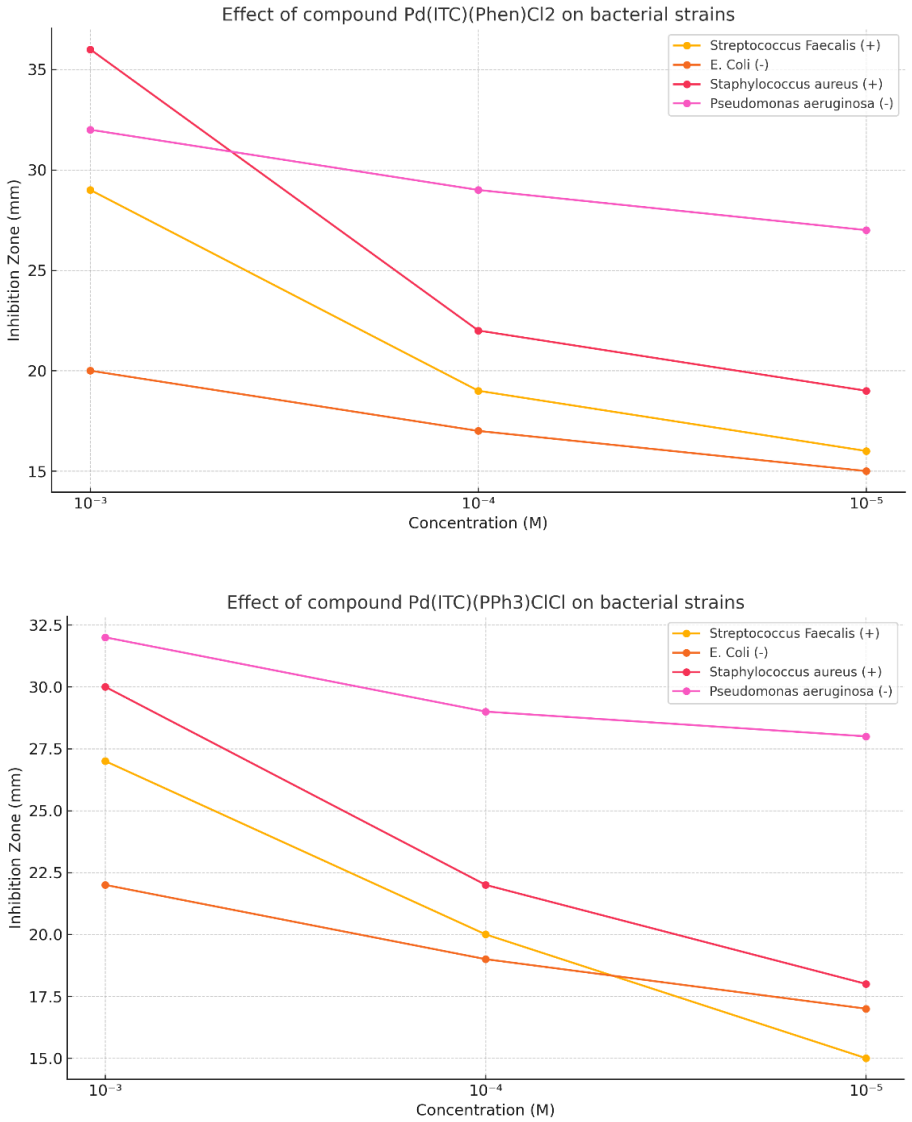


Figure 3: Antibacterial Activity of Palladium(II) Isothiocyanate Complexes Against Various Bacterial Strains at Different Concentrations.

3.3. Future Implications

These findings further explore the action mechanisms of such compounds and their efficacy for cell lines of other tumours. Furthermore, some studies by (36) allow us to suggest that treating certain diseases with palladium(II) complexes combined with other therapeutic agents can enhance effectiveness with reduced toxicity, which could be investigated in future studies involving our synthesised compounds.

These results have therefore unravelled the potential of such complexes in developing novel therapeutic agents. Further preclinical studies, including toxicity profiling, mechanistic studies, and pharmacokinetics, could help refine and optimise compounds for clinical applications. In this respect, the high anti-ovarian cancer activity suggests that this compound is a good candidate for targeted synthesis as a chemotherapeutic drug, playing a significant role in improving cancer treatment outcomes.

4. CONCLUSION

Because most cancers are preventable, it is possible to create new and suitable pharmacological compounds in this study. The biological and antioxidant activity of the produced compounds was good. The preparation was done effortlessly and confidently due to the favourable proportion of the compounds, as revealed in the research.

5. CONFLICT OF INTEREST

The authors declare no conflict of interest to declare.

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