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Synthesis, Characterization, and Antibacterial Studies of New Cu(II) and Pd(II) Complexes with 6-Methyl-2-Thiouracil and 6-Propyl-2-Thiouracil

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Abstract: The aim of the present study is to synthesize new metal complexes of 6-methyl-2-thiouracil and 6-propyl-2-thiouracil, elucidate their structures, and investigate their biological properties. All metal complexes were obtained after mixing water solutions of the corresponding metal salts and the ligand dissolved in DMSO and water solutions of NaOH in a metal-to-ligand ratio of 1:4:2. The structures of the new compounds are discussed based on melting point analysis (MP-AES) for Cu and Pd, UV-Vis, IR, ATR, ^{1}H NMR, ^{13}C NMR, and Raman spectroscopy. The interpretation of complex spectra is assisted by the data for 6-methyl-2-thiouracil and 6-propyl-2-thiouracil obtained from ^{1}H-^{1}H COSY, DEPT-135, HMBC and HMQC spectra. In addition, the antimicrobial activity of these complexes and the free ligands are assessed against both Gram-positive and Gram-negative bacteria, as well as yeasts. In general, the addition of metal ions improved the antimicrobial activity of both 6-methyl-2-thiouracil and 6-propyl-2-thiouracil. The Cu(II) complex with 6-methyl-2-thiouracil and the Pd(II) complex with 6-propyl-2-thiouracil exhibited the highest activity against the test microorganisms.

Keywords: antimicrobial activity; copper(II) complexes; 6-methyl-2-thiouracil; palladium(II) complexes; 6-propyl-2-thiouracil

Citation: Marinova, P.; Hristov, M.; Tsoneva, S.; Burdzhiev, N.; Blazheva, D.; Slavchev, A.; Varbanova, E.; Penchev, P. Synthesis, Characterization, and Antibacterial Studies of New Cu(II) and Pd(II) Complexes with 6-Methyl-2-Thiouracil and 6-Propyl-2-Thiouracil. *Appl. Sci.* **2023**, *13*, 13150. https://doi.org/10.3390/app132413150

Academic Editor: Monica Gallo

Received: 23 October 2023
Revised: 7 December 2023
Accepted: 9 December 2023
Published: 11 December 2023

1. Introduction

Pyrimidine derivatives possess a wide range of biological activities, such as antineoplastic [1], antiviral [2], antimicrobial [3], free radical scavenging [4], anti-inflammatory [5], pain-relieving [6], and anxiety-reducing [7] properties. Thionamides, a class of relatively simple molecules, serve as antithyroid drugs, featuring a sulfhydryl group and a thiourea moiety within a heterocyclic framework. In the United States, the antithyroid drugs in use are Propylthiouracil (also known as 6-propyl-2-thiouracil) and Methimazole (also referred to as 1-methyl-2-mercaptoimidazole or Tapazole).

Oladipo and Isola provided a comprehensive review of the coordination possibilities of uracil and the practical applications of some of its complexes [8].

Shaban et al. synthesized metal complexes involving pyrimidine, which encompass Cd- and Zn-barbiturate, as well as Cd- and Hg-thiouracil compounds [9]. The reaction of 5-bromouracil led to the preparation of novel complexes involving Mn(II), Cd(II), Co(II), Ni(II), Cu(II), and Ag(I) [10]. The data obtained demonstrated that these complexes exhibited greater antimicrobial potency compared to the free ligand.

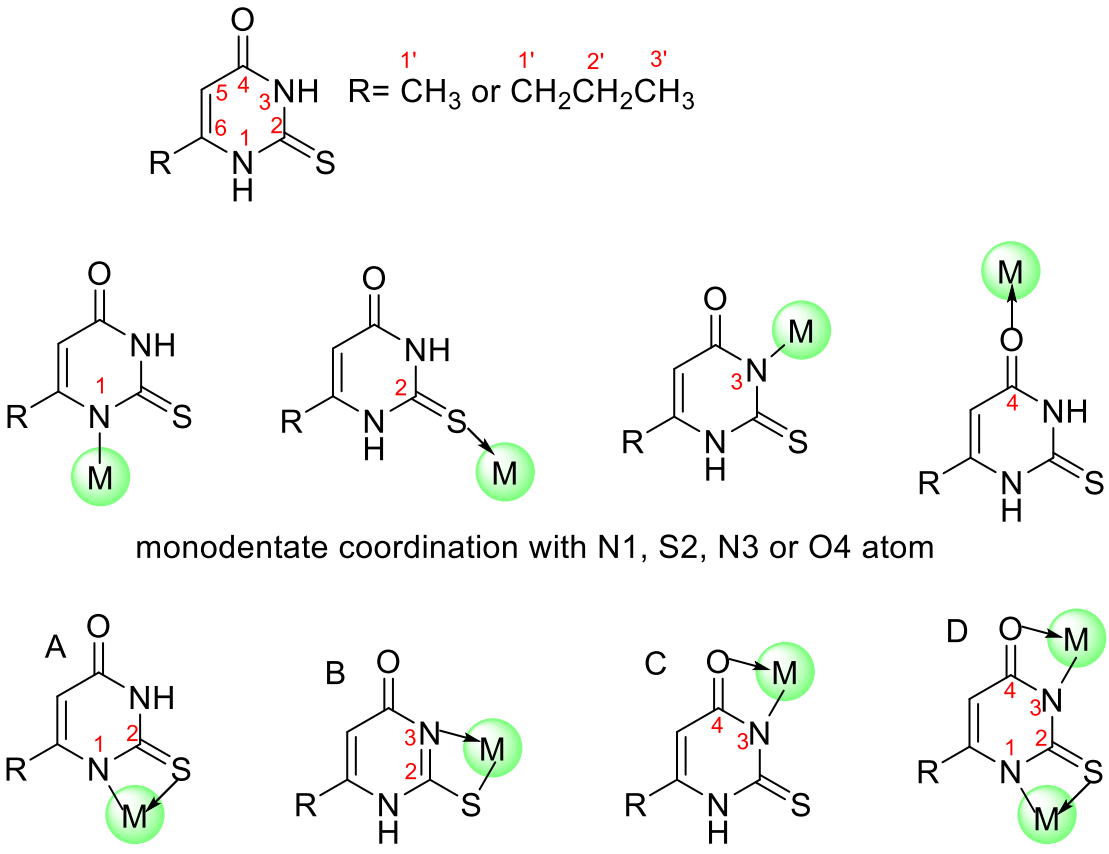
The interest in platinum and palladium complexes stems from their pronounced cytostatic activity. Recently, *cis*-dihalogeno complexes of Pt(II) and Pd(II) were synthesized in conjunction with 6-*tert*-butyl-2-thiouracil [11]. Furthermore, a series of complexes were synthesized using Rh(III), Ir(III), Pt(II), and Pd(II) in combination with the ligand 6-methyl-2-thiouracil [12]. Bomfim et al. conducted a synthesis of Ru(II) complexes involving 6-methyl-2-thiouracil, showing promise for novel antileukemic drug candidates [13]. Paizanos et al. successfully synthesized new Cu(I) complexes featuring the antithyroid drug 6-propyl-thiouracil [14].

To date, a multitude of metal complexes have been synthesized using uracil and thiouracil derivatives, involving various metals such as Cu, Fe, Co, Ni, Zn, Mn, Cd, and V [15–17], as well as Pd, Pt, and Au, with evaluations of their composition and structure [18].

In vitro screening of the antimicrobial activity of numerous metal complexes derived from thiouracil derivatives was conducted against Gram-positive and Gram-negative bacteria, filamentous fungi, and yeast [9,19–21].

Furthermore, the cytotoxic effects of various metal complexes of thiouracil derivatives were investigated against different tumor cell lines [13,22–26].

In Scheme 1 (top), the chemical structures of 6-methyl-2-thiouracil and 6-propyl-2-thiouracil are shown. Various metal complexes exhibit a monodentate coordination mode with 2-thiouracil derivatives, binding through different atoms, such as N1 (e.g., Cu(I) complex) [27], N3 (e.g., Pd(II) complex) [28], S (e.g., Ru(II), Cu(I), Sn(IV), Pt(II), and Pd(II) complexes) [11,14,23,29], or O (e.g., Co(II), Ni(II), Mn(II), and Zn(II) complexes) [30–32].



Scheme 1. Structure of 6-methyl-2-thiouracil and 6-propyl-2-thiouracil, including the atoms numbering and representation of coordination binding sites.

At the bottom of Scheme 1, the bidentate coordination modes of these ligands are highlighted. There are at least four potential bidentate coordination possibilities (A–D) for both ligands. Some of these modes were examined by Lusty and colleagues [12], who discussed coordination modes represented in (A) and (B) in the presence of platinum and rhodium centers, respectively. These were the most common coordination modes for this ligand class. Complexes with Pt(II), Pd(II), Ru(II), and Zn(II) also display coordination mode (A) [12,13,28,33], while coordination mode (B) was observed in Cd(II), Hg(II), and Co(II) complexes and peroxo complexes of vanadium [9,34]. To date, possibility (C) has not been observed for thiouracil derivatives, except in an osmium/uracil complex [35] and Mn(II), Co(II), Ni(II), Cu(II), Cd(II), and Ag(I) with 5-bromo-uracil [10] and similar ligand [36]. Coordination mode (D) was observed in a Ru(II) complex with 2,2′-bipyridine (bipy) [37], tin(IV) complexes [38], and Pt(II) with 5,6-diamino-4-hydroxy-2-mercaptopyrimidine [18]. Tridentate coordination mode with the participation of S2, N3, and O4 atoms of the free ligands [9,15,20] was also reported.

Recently, Ahmed et al. reported new 2-thiouracil-5-sulfonamide derivatives and their biological properties [39].

This paper presents the synthesis of novel metal complexes involving 6-methyl-2-thiouracil (L1) and 6-propyl-2-thiouracil (L2). The characterization of these compounds was conducted through various techniques, including melting point determination, UV-Vis, IR, ^{1}H NMR, ^{13}C NMR, and Raman spectroscopy. The assignment of NMR signals of the ligands was obtained from ^{1}H-^{1}H COSY, DEPT-135, HMBC, and HMQC spectra. Furthermore, the antimicrobial activity against both Gram-positive and Gram-negative bacteria, as well as yeasts, is evaluated.

2. Materials and Methods

2.1. Spectra Measurements

The free ligands 6-methyl-2-thiouracil and 6-propyl-2-thiouracil were purchased from Aldrich Chem. The metal salts $Cu(CH_3COO)_2.H_2O$ and $Pd(NO_3)_2.H_2O$ (Aldrich Chem) and solvents used for the synthesis of the complexes had a high purity that was generally equal to A.C.S. grade and were suitable for use in many laboratory and analytical applications. Absorption spectra were registered on a UV-30 SCAN ONDA UV/Vis/NIR Spectrophotometer from 200 to 1000 nm. The IR spectra of L1, L2, and their complexes were registered in KBr pellet on a Bruker FT-IR VERTEX 70 Spectrometer from 4000 cm^{-1} to 400 cm^{-1} at a resolution of 2 cm^{-1} with 25 scans. The stirred crystals were placed in an aluminum disc and the Raman spectra of the compounds were measured on a RAM II (Bruker Optics) with a focused laser beam of Nd:YAG laser (1064 nm) from 4000 to 100 cm^{-1} at a resolution of 2 cm^{-1} with 25 scans. Additionally, ATR spectra of the complexes were measured (MIRacle Single reflection, PIKE technology) to check if the coordination water was present in them. The NMR spectra of the ligand were registered on a Bruker Avance II NMR spectrometer operating at 600.130 and 150.903 MHz for ^{1}H and ^{13}C, respectively, using the standard Bruker software v3.6.3. The NMR spectra of the metal complexes were measured on a Bruker Avance III HD spectrometer operating at 500.130 and 125.76 MHz for ^{1}H and ^{13}C, respectively, using the standard Bruker software v3.6.5. Solid-state NMR spectra were acquired on a Bruker Avance III HD 500 MHz spectrometer equipped with a 2.5 mm Cross-Polarization Magic Angle Spinning (CPMAS) probe head. CP MAS and Cross-Polarization with Polarization Inversion (CPPI) MAS spectra were recorded at a MAS speed of 15 kHz and α-glycine was used as an external reference (α-glycine carbonyl C-176.03 ppm). Measurements were carried out at ambient temperature.

2.2. Microwave Plasma-Atomic Emission Spectrometry (MP-AES) Determination of Cu and Pd in the Complexes

A total of 0.0200 g of sample was weighed on an analytical balance and dissolved with 65% nitric acid, p.a. (Chem-Lab NV, Zedelgem, Belgium) for Cu-complexes, nitric

acid, and 37% hydrochloric acid, and p.a. (Fluka AG, Buchs, Switzerland) for Pd-complexes. Blank solutions were prepared as well. After dilution, the concentration of Cu and Pd was determined via MP-AES 4200 (Agilent technologies, Santa Clara, CA, USA). Calibration standards were prepared from monoelemental standard solutions −1000 mg L^{-1} Cu (Merck, Darmstadt, Germany) and 1000 mg L^{-1} Pd (High-purity standards, Charlestone, UK). Conventional MP-AES operating conditions were used. Analytes were measured on three emission lines for estimation of potential spectral interferences, i.e., 324.754 nm, 327.395 nm, and 510.554 nm for Cu and 340.458 nm, 360.955 nm, and 363.470 nm for Pd. Five replicates and 5 s measurements were applied for all lines.

2.3. General Procedure for the Synthesis of Cu(II) and Pd(II) Complexes of 6-Methyl-2-Thiouracil (L1) and 6-Propyl-2-Thiouracil (L2)

All metal complexes were obtained after mixing water solutions of the corresponding metal salts and the ligands dissolved in DMSO and water solutions of NaOH, in a metal-to-ligand ratio of 1:4:2. Non-charged complexes were formed as precipitates, which were further filtrated, repeatedly washed with water, and dried over $CaCl_2$ for 2 weeks.

2.3.1. Synthesis of CuL1

0.0008 mol $Cu(CH_3COO)_2.H_2O$ (0.1597 g) in 10 mL H_2O;
0.0032 mol (0.4550 g) of 6-methyl-2-thiouracil (L1) in 10 mL DMSO;
0.0016 mol (0.0640 g) NaOH in 5 mL H_2O.

2.3.2. Synthesis of PdL1

0.002 mol (0.4609 g) $Pd(NO_3)_2.H_2O$ in 10 mL H_2O;
0.008 mol (1.1374 g) of 6-methyl-2-thiouracil (L1) in 10 mL DMSO;
0.004 mol (0.1600 g) of NaOH in 5 mL H_2O.

2.3.3. Synthesis of CuL2

0.0008 mol $Cu(CH_3COO)_2.H_2O$ (0.1597 g) in 10 mL H_2O;
0.0032 mol (0.5447 g) of of 6-propyl-2-thiouracil (L2) in 10 mL DMSO;
0.0016 mol (0.0640 g) NaOH in 5 mL H_2O.

2.3.4. Synthesis of PdL2

0.002 mol (0.4609 g) $Pd(NO_3)_2.H_2O$ in 10 mL H_2O;
0.008 mol (1.1318 g) of 6-propyl-2-thiouracil (L2) in 10 mL DMSO;
0.004 mol (0.1600 g) of NaOH in 5 mL H_2O.

All the metal complexes were synthesized according to a previously described procedure [40], with a modification in the duration of procedures (24 h for palladium(II) complexes) and/or solvents [9–13].

Figures 1 and 2 demonstrate the synthesis of transition metal complexes with two free ligands.

The synthetic scheme that is shown in Figures 1 and 2 is similar to that reported by other authors [41,42].

2.4. Spectral Data of the Free Ligands and Their Metal Complexes

UV-Vis (DMSO) of L1: λ_{max} = 258, 294 nm.

IR (cm^{-1}) of L1: 3115 (NH), 3080 (NH), 3014 (=CH), 2932 (CH_3), 2890 (CH_3), 2580, 2407, 1920, 1893, 1863, 1754, 1698, 1676 (C=O), 1637, 1560, 1423, 1384, 1349, 1242 (C=S), 1200, 1194, 1167, 1043, 1032, 993, 962, 933, 874, 838, 808, 729, 656, 598, 580, 553, 548, 513, 457, and 416.

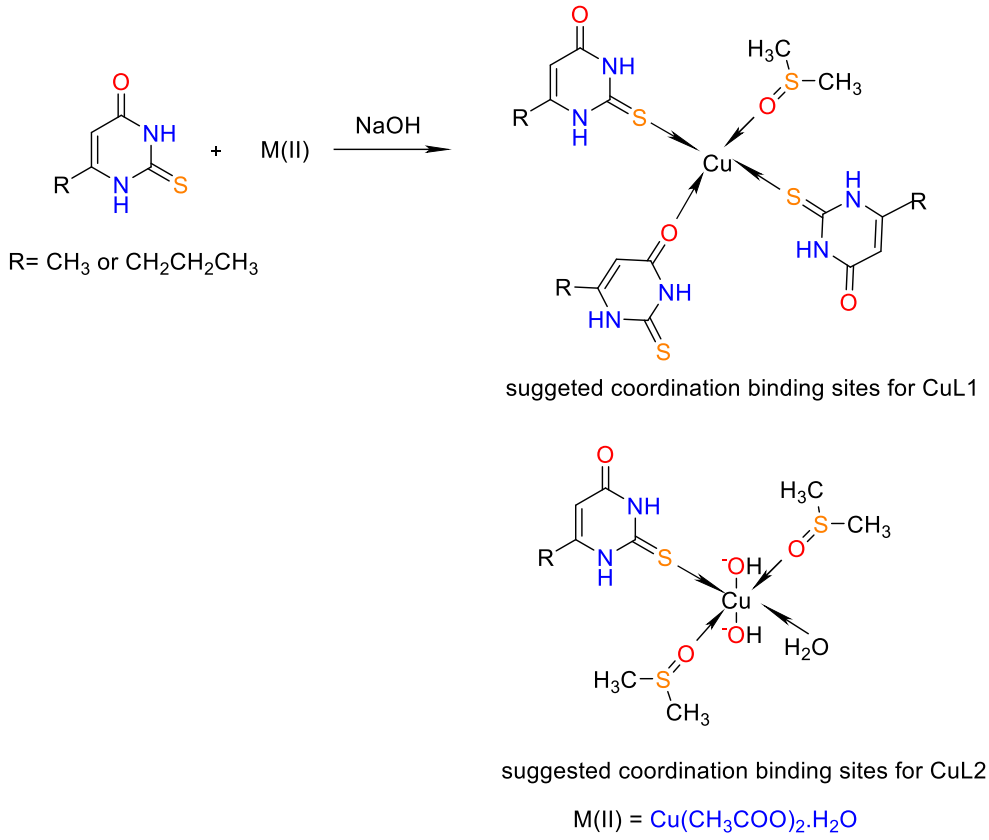


Figure 1. Synthesis of metal complexes of 6-methyl-2-thiouracil (L1) and 6-propyl-2-thiouracil (L2) with Cu(II).

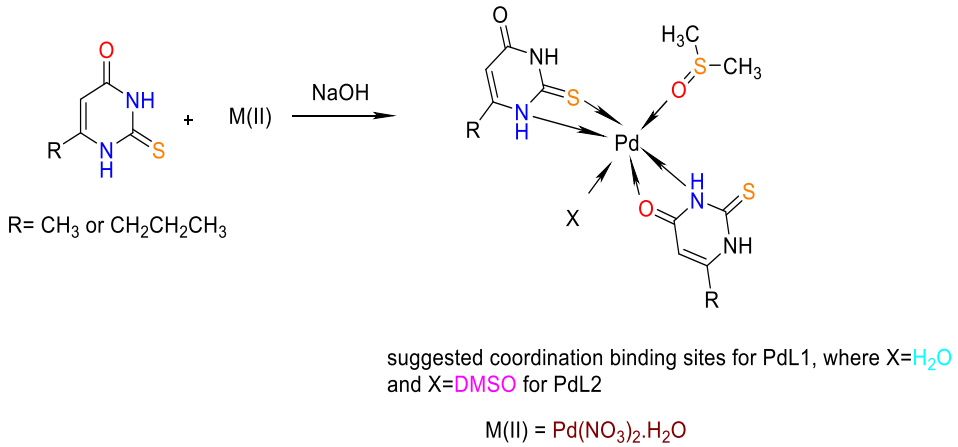


Figure 2. Synthesis of metal complexes of 6-methyl-2-thiouracil (L1) and 6-propyl-2-thiouracil (L2) with Pd(II).

IR (cm^{-1}) of CuL1: 3115 (NH), 3080 (NH), 3003 (=CH), 2931 (CH_3), 2888 (CH_3), 1753, 1637 (C=O), 1578, 1559, 1426, 1385, 1350, 1284, 1241(C=S), 1207, 1199, 1167, 1033, 962, 933, 906, 872, 837, 809, 755, 656, 621, 597, 553, 512, and 457.

ATR (cm^{-1}) of CuL1: 3111 (NH), 3088 (NH), 3001 (=CH), 2934 (CH_3), 2882 (CH_3), 1752, 1699, 1633 (C=O), 1575, 1541, 1424, 1386, 1349, 1283, 1241 (C=S), 1207, 1195, 1164, 1032, 962, 932, 908, 872, 834, 806, 755, 656, 628, and 621.

Raman (cm^{-1}) of L1: 3085 (NH), 2921, 1635 (C=O), 1558, 1419, 1382, 1353, 1245 (C=S), 1199, 1177, 1043, 985, 961, 931, 834, 789, 657, 597, 554, 512, 458, 258, and 214.

Raman (cm^{-1}) of CuL1: 3084 (NH), 2916, 1636 (C=O), 1578, 1549, 1418, 1382, 1281, 1244 (C=S), 1207, 1170, 1043, 986, 961, 650, 622, 596, 573, 553, 512, 473, 456, 257, and 218.

UV-Vis (DMSO) of Pd(II)L1: λ_{max} = 258, 318 nm.

IR (cm^{-1}) of PdL1: 3442 (H_2O), 3111 (NH), 3071 (NH), 3052 (=CH), 2993, 2930 (CH_3), 2892, 2855 (CH_3), 2750, 2697, 1678 (C=O), 1559, 1521, 1466, 1419, 1400, 1366, 1352, 1284, 1244 (C=S), 1193, 1168, 1064, 954, 830, 656, 614, 598, 576, 553, 513, and 459.

ATR (cm^{-1}) of PdL1: 3400 (H_2O), 3105 (NH), 3080 (NH), 3049 (=CH), 2889, 2747, 2694, 1673 (C=O), 1636, 1559, 1515, 1465, 1417, 1399, 1365, 1351, 1285, 1242 (C=S), 1232, 1192, 1166, 1064, 953, 872, 826, 655, and 613.

IR (cm^{-1}) of L2: 3112 (NH), 3093 (NH), 3042 (=CH), 2958 (CH_3), 2931 (CH_2), 2873, 2607, 1877, 1777, 1703, 1656 (C=O), 1628, 1557, 1445, 1393, 1336, 1314, 1281, 1243 (C=S), 1193, 1165, 1100, 1039, 1014, 965, 940, 888, 821, 790, 743, 641, 558, 538, 508, 465, 422, and 416.

Raman (cm^{-1}) of L2: 3110 (NH), 2929 (CH_2), 2871, 1661 (C=O), 1630, 1548, 1433, 1337, 1243 (C=S), 1184, 1164, 1099, 1039, 1015, 970, 938, 643, 562, 534, 459, 352, 322, 257, and 230.

ATR (cm^{-1}) of L2: 3088 (NH), 3038 (=CH), 2957 (CH_3), 2928 (CH_2), 2872, 1702, 1653 (C=O), 1627, 1554, 1445, 1392, 1336, 1313, 1281, 1242 (C=S), 1191, 1164, 1100, 1039, 1014, 965, 940, 887, 816, 787, 743, and 640.

IR (cm^{-1}) of CuL2: 3451 (OH), 3093 (NH), 3042 (=CH), 2962 (CH_3), 2914 (CH_2), 2873, 1694, 1651 (C=O), 1553, 1497, 1453,1403, 1381, 1346, 1313, 1275, 1232 (C=S), 1210, 1191, 1166, 1008, 1021, 954, 876, 832, 754, 741, 703, 669, 658, 589, 571, 559, 549, 528, 468, 414, and 403.

Raman (cm^{-1}) of CuL2: 3000, 2967, 2914, 2876, 1685, 1660 (C=O), 1631, 1595, 1500, 1438, 1416, 1381, 1276, 1230 (sh., C=S) 1212, 1165, 1089, 1021, 975, 878, 704, 670, 593, 581, 563, 531, 473, 438, 337, 307, 247, and 219.

ATR (cm^{-1}) of CuL2: 3416 (OH), 3093 (NH), 3037 (=CH), 2959 (CH_3), 2913 (CH_2), 2871, 1692, 1642 (C=O), 1551, 1494, 1452, 1401, 1381, 1345, 1310, 1275, 1231 (C=S), 1210, 1190, 1165, 1105, 1015, 966, 953, 875, 831, 787, 754, 738, 703, 657, and 644.

IR (cm^{-1}) of PdL2: 3437 (H_2O), 3200, 3158, 3117 (NH), 3080 (NH), 2962 (CH_3), 2872, 1657 (C=O), 1595, 1545, 1467, 1428, 1379, 1338, 1320, 1261 (C=S), 1202, 1175, 1091, 1023, 972, 916, 882, 832, 789, 748, 697, 643, 606, 548, and 468.

ATR (cm^{-1}) of PdL2: 3402 (H_2O), 3081 (NH), 2944 (CH_3), 2917 (CH_2), 2867, 2829, 1703, 1643 (C=O), 1616, 1564, 1516, 1445, 1425, 1386, 1329, 1286, 1223 (C=S), 1184, 1169, 1100, 997, 965, 908, 887, 860, 819, 787, 763, 745, 680, 643, and 607.

Raman spectra of PdL1 and PdL2 could not be measured; the samples burned at 1 mW.

2.5. Antimicrobial Assay

Antimicrobial activity of 6-methyl-2-thiouracil, 6-propyl-2-thiouracil and their complexes against Gram-positive bacteria—*Enterococcus faecalis* ATCC 19433, *Staphylococcus aureus* ATCC 25923, *Listeria monocytogenes* ATCC 8787, *Bacillus subtilis* ATCC 6633, and *Bacillus cereus* ATCC 11778, Gram-negative bacteria—*Escherichia coli* ATCC 8739, *Salmonella enterica* subsp. *enterica* ser. Enetritidis ATCC 13076, *Pseudomonas aeruginosa* ATCC 9027, *Proteus vulgaris* G, and *Klebsiella pneumoniae* ATCC 13883, and yeasts—*Candida albicans* ATCC 10231 and *Saccharomyces cerevisiae*, was tested using the agar diffusion method. A suspension of each test microorganism (10^6 cfu/cm^3) was spread on the surface of a PCA (Scharlau) nutrient medium for *C. albicans* and the bacteria and Wort agar (Sharlau) was used for *S. cerevisiae*. Wells of 7 mm diameter were made in the inoculated agar medium. Then, 50 µL of the tested substance solution (10 mg/cm^3 in DMSO) was pipetted into the wells. The Petri dishes were incubated at 37 °C (for the bacteria and *C. albicans*) and 30 °C (for *S. cerevisiae*) for 24–48 h. The inhibition zones were measured. Zones with a diameter more than 7 mm were considered as zones of inhibition. Each test was carried out in triplicate, and the data are presented as mean values.

3. Results and Discussion

3.1. Synthesis of the Metal Complexes

The interaction of metal ions with L1 and L2 in a molar ratio of metal:ligand:base (1:4:2) resulted in the formation of the complexes with suggested formulas shown in Table 1. The results of the elemental analysis for the metal ions were determined by Microwave Plasma-Atomic Emission Spectrometry. They can be used to determine the tentative average composition of different complexes.

Table 1. Elemental analysis data for the metal ions of the complexes.

Metal Complex	Composition *	Formula	Molecular Weight	W(M)% Calc./Exp.
CuL1	[3LCu.(DMSO)]	$C_{17}H_{24}N_6O_4S_4Cu$	M = 568.22 g/mol	11.2/11.6 ± 0.6
PdL1	[5LPd.(DMSO)].H_2O	$C_{27}H_{38}N_{10}O_7S_6Pd$	M = 913.46 g/mol	11.6/11.1 ± 0.6
CuL2	[LCu.H_2O.$(OH^-)_2$.$(DMSO)_2$]	$C_{11}H_{26}N_2O_6S_3Cu$	M = 442.07 g/mol	14.4/14.3 ± 0.7
PdL2	[4LPd.$(DMSO)_2$].H_2O	$C_{32}H_{54}N_8O_7S_6Pd$	M = 961.63 g/mol	11.1/11.5 ± 0.5

* Putative average composition of different complexes.

All the complexes were stable in air and moisture and their solubility was limited. We found that the reaction of L1 and L2 with the transition metal ions afforded a 40–72% yield of a stable solid compound. The complexes obtained had a yellow-green or brown color and limited solubility in DMSO and DMF, except CuL2 (soluble in DMSO only); the complexes were insoluble in water, THF, C_2H_5OH, EtOAc, and cyclohexane. The analytical data including the yield percentage of the complexes are presented in Table 2.

Table 2. Analytical and physical characteristics of metal complexes with 6-methyl-2-thiouracil.

Complexes	Color	Yield (%)	Melting Point (°C)	Solubility, * Limited
L1	colorless		330	soluble in DMSO
CuL1	yellow-green	61	>350 °C	soluble in DMSO *, DMF *, C_2H_5OH *, H_2O * and insoluble in THF, EtOAc, and C_6H_{12}.
PdL1	brown	72	>350 °C	soluble in DMSO *, DMF * and insoluble in H_2O, THF, C_2H_5OH, EtOAc, and C_6H_{12}.
L2	colorless		218–220	soluble in DMSO
CuL2	yellow-green	43	260–263 °C	soluble in DMSO * and insoluble in H_2O, THF, C_2H_5OH, EtOAc, and C_6H_{12}.
PdL2	brown	70	255–257 °C	Soluble in DMSO *, DMF * and insoluble in H_2O, THF, C_2H_5OH, EtOAc, and C_6H_{12}.

IR Verification of the structures of the metal complexes can be easily achieved by comparing the IR spectra of the free ligands with that of their metal complexes. The selected experimental data from the IR spectra of the complexes CuL1 and PdL1 and of the free ligand (in cm^{-1}) is shown in Table 3.

In the IR spectra of the free ligand L1, the bands at 3115 cm^{-1} and 3080 cm^{-1} were observed, which may refer to the stretching vibrations of N-H groups. In the spectrum of the Cu(II) complex, the same bands were observed at the same frequencies. In the IR spectrum of the Pd(II)L1, these bands were shifted to the lower frequencies compared to the free ligand bands with 4 cm^{-1} and 9 cm^{-1}, respectively. This shows that the two N-H groups of the ligand participate in the coordination of the palladium complex. The L1 IR bands at 1676 and 1242 cm^{-1} can be attributed to the stretching vibration of C^4=O and C^2=S groups, respectively. The stretching vibration of C^4=O in the CuL1 complex was shifted to the lower frequency with 39 cm^{-1} compared to this stretching in the free ligand. The same bands in the IR spectrum of the PdL1 complex did not change. In the ATR spectrum

of PdL1 complex, the band at 3400 cm^{-1} may refer to the stretching vibrations of molecular H_2O. This band was missing in the spectrum of the CuL1 complex.

Table 3. Selected experimental IR data (in KBr, wavenumber in cm^{-1}) for 6-methyl-2-thiouracil and its complexes.

Assignment	L1	CuL1	PdL1
ν(OH)	-	-	3442
ν(NH)	3115 sh	3115	3111
ν(NH)	3080	3080	3071
ν(=CH)	3014	3003	3052
ν(C=O)	1676 m	1637	1678
	1560 w	1559	1559
ν(C=S)	1242	1242	1244
	1167 s	1167	1168

In the IR spectrum of the free ligand L2, the bands at 3112 cm^{-1} and 3093 cm^{-1} were observed, which may refer to the stretching vibrations of N-H groups. In the spectrum of the copper complex, the same bands were observed at the same frequencies. In the IR spectrum of the PdL2 complex, these bands were shifted; the first with +5 cm^{-1} and the second with −13 cm^{-1} compared to those in the free ligand spectrum. This shows that the two N-H groups of the ligand participate in the coordination of PdL2. In the IR spectrum of L2, the bands at 1656 and 1243 cm^{-1} can be attributed to the stretching vibrations of C^4=O and C^2=S groups, respectively. The band for the C^2=S group was shifted to the lower frequencies compared to the free ligand spectrum with 11 cm^{-1} and to the higher frequencies with 18 cm^{-1} for the CuL2 and PdL2 complexes, respectively. The band at 3451 and 3437 cm^{-1} in the IR spectrum of the two complexes may refer to the stretching vibrations of OH^- (CuL2) and molecular H_2O (PdL2), shown in Table 4. The solid-state ATR spectra confirm these findings.

The stretching vibrations of C^4=O and C^2=S appear at 1635 and 1245 cm^{-1} in the Raman spectrum of 6-metyl-2-thiouracil and 1661 and 1243 cm^{-1} in that of 6-propyl-2-thiouracil, respectively. In the Raman spectrum of the CuL2, the band for the C=S group was shifted by 13 cm^{-1} to the lower frequency.

The ^{1}H NMR spectrum of 6-metyl-2-thiouracil (L1) showed four signals: a singlet at 12.29 ppm for H-1 and H-3 (overlap resonances) and the olefin proton at 5.68 ppm (H-5) and 2.06 ppm for H-1′. These assignments were confirmed by ^{1}H-^{1}H COSY, ^{1}H-broadband decoupled ^{13}C-NMR, DEPT-135, and HMBC spectra and are shown in Table 5.

Table 4. Selected experimental IR data (in KBr, wavenumber in cm^{-1}) for 6-propyl-2-thiouracil and its complexes.

Assignment	L2	CuL2	PdL2
ν(OH)	-	3451	3437
ν(NH)	3112	-	3117
ν(NH)	3093	3093	3080
ν(=CH)	3042	3042	
ν(C=O)	1656	1651	1657
	1557	1553	1545
ν(C=S)	1243	1232	1261
	1165	1166	1175

Table 5. ^{1}H and ^{13}C NMR spectral data and ^{1}H-^{1}H COSY and HMBC correlations for **6-methyl-2-thiouracil** [600.13 MHz (^{1}H) and 150.903 MHz (^{13}C)] [a].

Atom	δ (^{13}C) ppm	DEPT-135	δ (^{1}H) ppm	Multiplicity (*J*, Hz)	^{1}H-^{1}H COSY	HMBC
1 (NH)			12.29	s		
2 (C=S)	175.87	C				
3 (NH)			12.29	s		
4 (C=O)	161.06	C				
5	103.72	CH	5.68	d (0.9)	7	4 [b], 6, 7
6	153.20	C				
1′	18.11	CH_3	2.06	d (0.7)	5	5, 6

[a] In DMSO-*d6* solution. All these assignments were in agreement with COSY, HMQC, and HMBC spectra. [b] These correlations are weak.

The ^{1}H NMR and ^{13}C NMR spectral data of the Cu(II) and Pd(II) complexes are presented in Tables 6 and 7, respectively.

Table 6. ^{1}H NMR spectral data (in ppm) for complexes of 6-methyl-2-thiouracil with Cu(II) and Pd(II).

Atom	L1 (6-Methyl-2-Thiouracil)	CuL1 Multiplicity (*J*, Hz)	PdL1 Multiplicity (*J*, Hz)
1 (NH)	12.29 s	12.24 s	12.24 s and 10.80
2 (C=S)	-	-	-
3 (NH)	12.29 s	12.29 s	12.30 s and 10.86
4 (C=O)	-	-	-
5	5.68	5.68 s	5.68 s and 5.31
6	-	-	-
1′	2.06	2.07	2.07 and 2.01
DMSO-$_{H6}$		2.54 s	2.54 s

Table 7. ^{13}C NMR spectral data (in ppm) for complexes of 6-methyl-2-thiouracil with Cu(II) and Pd(II).

Atom	δ (^{13}C) ppm, L1	CuL1	PdL1
1 (NH)	-	-	-
2 (C=S)	175.87	175.86	175.86/?
3 (NH)	-	-	-
4 (C=O)	161.06	161.01	161.01/?
5	103.72	103.69	103.69 and 98.71
6	153.20	153.12	153.12/?
1′	18.11	18.06	18.06 and 18.20

The ^{1}H NMR and ^{13}C NMR spectra in the DMSO-d6 solution of CuL1 had the same values of chemical shift as those of L1, but the solid-state NMR differentiated between them (see Tables 6–8 and Figure 3). The ^{13}C NMR spectrum of the L1 registered with the cross-polarization (CP) experiment showed five signals. Two of them were observed for the C=S and C=O groups at 174.6 and 163.0 ppm, respectively.

In the ^{13}C NMR solid-state spectrum of CuL1, the two couples at 171.7/174.8 ppm and 162.9/169.5 ppm were observed for the C=S and C=O groups, respectively. This

means that the resonance for C=S was upfield shifted by 2.9 ppm, and the signal for C=O was downfield shifted by 6.5 ppm, respectively. This shows that the C=S and C=O groups of the ligand participated in the coordination with the copper. The two couples at 104.7/105.4 ppm and 154.0/156.4 ppm (Table 8), were observed for the carbon atom in positions 5 and 6, respectively.

Table 8. ^{13}C NMR spectral data (in ppm) for L1, L2, and some of the complexes acquired with cross-polarization experiments, calibrated with the external reference α-glycine carbonyl C (176.03 ppm).

Atom	L1	L2	CuL1	CuL2	PdL2
1 (NH)					
2 (C=S)	174.6	175.5	171.7/174.8	168.3/175.4	172.3/172.9/174.0
3 (NH)					
4 (C=O)	163.0	164.8	162.9/169.5	164.9/166.1	160.3/166.4/167.0
5 (CH)	104.7	103.8/104.6	104.7/105.4	103.8/104.6/105.4/107.2	95.8/103.1/105.0
6 (C)	156.2	159.9	154.0/156.4	159.9/161.3	153.0/156.0/159.7
1′	20.2	32.7	20.1	32.7/39.3/39.6/40.9	33.4/34.2/38.6
2′		19.6/20.2		18.2/19.7/20.2/24.4	18.2/19.3/19.7
3′		13.1/14.7		13.1/13.6/14.7/15.7	12.9/15.4
DMSO				40.3	

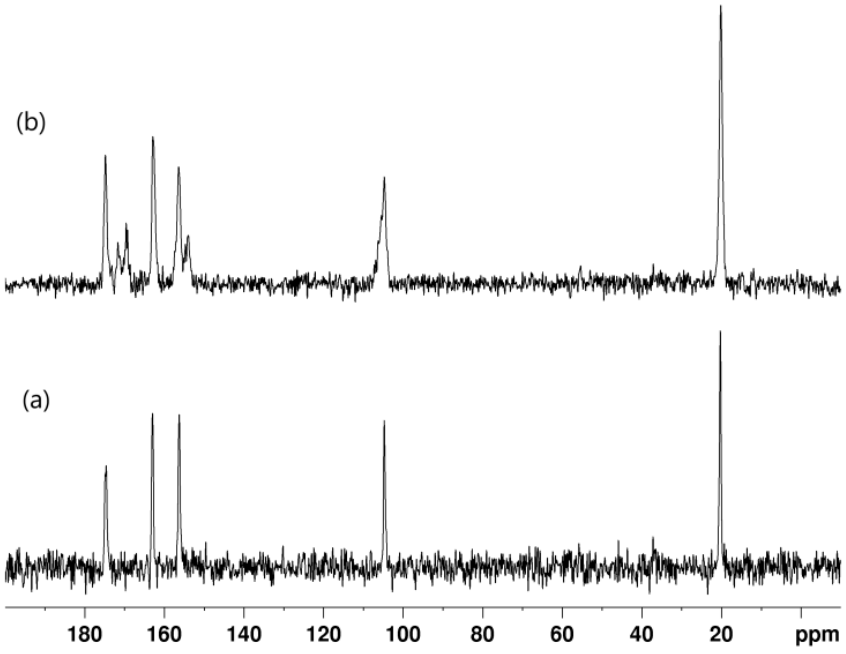


Figure 3. Solid-state CP MAS ^{13}C NMR of the ligand L1 (**a**) and its complex with copper (**b**).

The ^{1}H NMR solution spectrum of PdL1 showed that the signals for the two amine protons (H-1 and H-3) were upfield shifted by 1.49 and 1.43 ppm. Also, all resonances of the free ligand are present in excess; this could be from the remaining reagent L1 or from the decomposition of PdL1 in the solution. In the ^{13}C NMR solution spectrum of PdL1, only methyl and olefin resonances of the coordinated ligand can be seen; the others are indistinguishable from the noise. This once again shows the limited solubility of the complexes.

The ^{1}H NMR spectrum of 6-propyl-2-thiouracil (L2) showed six signals: two broad singlets at 12.20 ppm (H-1) and 12.31 ppm (H-3) and the olefin proton at 5.67 ppm (H-5)

and 2.32 ppm for H-1′, 1.54 ppm for H-2′, and 0.87 ppm for H-3′. These assignments were confirmed by ^{1}H-^{1}H COSY, ^{1}H-broadband decoupled ^{13}C-NMR, and DEPT-135 spectra and are shown in Table 9.

Table 9. ^{1}H and ^{13}C NMR spectral data and ^{1}H-^{1}H COSY and HMBC correlations for 6-propyl-2-thiouracil [500.13 MHz (^{1}H) and 150.903 MHz (^{13}C)] [a].

Atom	δ (^{13}C) ppm	DEPT -135	δ (^{1}H) ppm	Multiplicity (*J*, Hz)	^{1}H-^{1}H COSY
1 (NH)	-	-	12.20	s	
2 (C=S)	176.08	C	-		
3 (NH)	-	-	12.31	s	
4 (C=O)	161.22	C	-		
5	103.06	CH	5.67	s	
6	156.74	C			
1′	33.21	CH_2	2.32	t(7.5)	2′
2′	20.58	CH_2	1.54	sx(7.4)	1′, 3′
3′	13.26	CH_3	0.87	t(7.4)	2′

[a] In DMSO-*d6* solution. All these assignments were in agreement with COSY spectra.

The characterization of the CuL2 complex in solution was obstructed by its low solubility in various solvents including DMSO. In the ^{1}H NMR and ^{13}C NMR solution spectra of CuL2, only the free ligand resonances were present. In the solid-state ^{13}C NMR spectrum, there were resonances for both free and coordinated ligands. In the proton spectrum of CuL2 in DMSO-d6, a singlet at 2.54 ppm was observed for DMSO-h6 that was coordinated to Cu(II) during synthesis. The data about L2 and CuL2 are summarized and shown in Tables 10 and 11 and Figure 4a–c.

Table 10. ^{1}H NMR spectral data (in ppm) for complexes of 6-propyl-2-thiouracil with Cu(II) and Pd(II).

Atom	L2 (6-Propyl-2-Thiouracil)	CuL2 Multiplicity (*J*, Hz)	PdL2 Multiplicity (*J*, Hz)
1 (NH)	12.20 s	12.20 s	12.20 and 10.77 s
2 (C=S)	-	-	-
3 (NH)	12.31 s	12.31 s	12.32 and 10.87 s
4 (C=O)	-	-	-
5	5.67 s	5.67 s	5.68 and 5.31 s and t(1.8)
6	-	-	-
1′	2.32 t(7.5)	2.32 t(7.4)	2.32 and 2.25 t(7.3) and t(7.3)
2′	1.54 sx(7.4)	1.54 sx(7.5)	1.54 and 1.48 sx(7.6) and m
3′	0.87 t(7.4)	0.88 t(7.3)	0.87 and 0.82 t(7.3) and m
DMSO	-	2.54 s	2.54 s

In DMSO-*d6* solution.

The ^{13}C NMR spectrum of the L2 registered with the cross-polarization experiment showed seven signals. The two signals at 175.5 and 164.8 ppm were observed for the C=S and C=O groups, respectively. In the ^{13}C NMR spectrum with the cross-polarization experiment of CuL2, the signal for C=S was upfield shifted by 7.2 ppm. This showed that the C=S group of the ligand participated in the coordination with the copper. Also, a signal at 40.3 ppm was observed, confirming the coordination of DMSO-h6 to Cu(II).

Table 11. ^{13}C NMR spectral data (in ppm) for complexes of 6-propyl-2-thiouracil with Cu(II) and Pd(II).

Atom	δ (^{13}C) ppm, L2	CuL2	PdL2
1 (NH)	-	-	-
2 (C=S)	176.08		176.02
3 (NH)	-	-	-
4 (C=O)	161.22		164.19 and 161.09
5	103.06		98.03
6	156.74		156.61 and 156.33 and 151.71
1′	33.21	33.24	33.56 and 33.14
2′	20.58	20.55	20.50 and 20.24
3′	13.26	13.25	13.20

In DMSO-*d*6 solution.

There are six couples of signals in the ^{1}H NMR spectrum of Pd(II) complex with 6-propyl-2-thiouracil. In each couple, one of the resonances was observed for the free ligand (the L2) and the other for the coordinated L2. The couples at 12.20/10.77 ppm and 12.32/10.87 ppm were observed for NH at the first and third positions. The couple at 5.68/5.31 ppm was observed for olefin proton 5. The three couples at 2.32 ppm (t,7.3)/2.25 (t,7.3) ppm, 1.54 ppm (sx, 7.6)/1.48 ppm (m), and 0.87 ppm (t, 7.3)/0.82 ppm (m) were observed for propyl protons (H-1′), (H-2′), and (H-3′), respectively. A singlet at 2.54 ppm was observed, which corresponds to DMSO-h6. It is interesting to note that all resonances were shifted for coordinated L2 compared to the free L2 but the shifts were higher for NHs. In PdL2, the singlets for NH-1 and NH-3 were upfield shifted by 1.43 and 1.44 ppm, respectively.

The ^{13}C NMR solution spectrum of PdL2 showed seven groups of signals. The two signals with the highest chemical shift, at 176.02 ppm and 164.19 ppm, were for the C=S and C=O groups in PdL2, respectively. There was also a resonance at 161.09 ppm (free ligand), i.e., there was downfield shift of 2.97 ppm. This shows that the C=O group of the ligand participated in the coordination with Pd(II).

In the CP NMR spectrum of PdL2, the signal for C=S was upfield shifted by 3.2 and 2.6 ppm. In the same spectrum, there were three signals for C=O, shown in Table 8. One was upfield shifted by 4.5 ppm and the other was downfield shifted by 2.2 ppm. This shows that the C=S and C=O groups of the ligand participated in the coordination with the palladium in two different ways.

The ATR spectra of CuL2 and PdL2 showed the presence of H_2O and/or OH^-.

According to the solid-state NMR, clear shifts in the signals of the carbon atoms were observed in the complex of Cu(II) with L1, indicating the presence of the complex. There were also signals corresponding to the starting ligand L1, which may or may not be included in the second coordination sphere.

In the case of ligand L2, the ligand itself showed doubled signals for the carbon atoms C-5, C-2′, and C-3′, possibly due to a different spatial arrangement of these atoms in the crystalline lattice of the ligand (Figure 4a). In the case of the Cu(II)L2 complex, the ligand signals could still be observed, accompanied by the complex signals. However, in this case, the DMSO in the complex was present as a ligand. Despite the presence of many C-1′ signals around it in the CP spectrum (Figure 4b), the DMSO signal could be easily identified in the CPPI spectrum (Figure 4c).

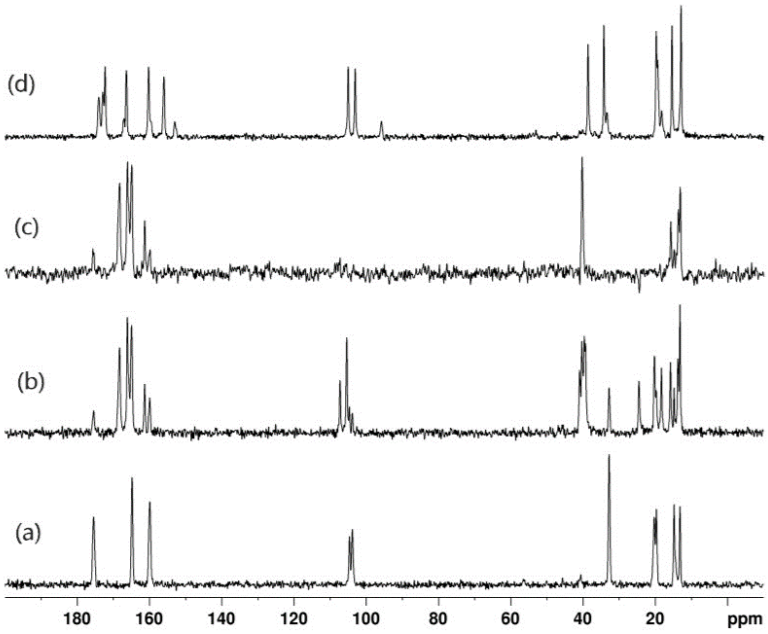


Figure 4. Solid-state ^{13}C NMR of the ligand L2 and its complexes: (**a**) ^{13}C CP spectrum of L2, (**b**) ^{13}C CP spectrum of Cu(II)L2, (**c**) ^{13}C CPPI spectrum of Cu(II)L2, and (**d**) ^{13}C CP spectrum of Pd(II)L2.

The ^{13}C spectrum of PdL2 obtained by cross-polarization (Figure 4d) showed unexpected results. There were multiple signals for each type of carbon atom in the ligand, indicating the presence of more than one palladium complex or a palladium complex with two ligands in the coordination sphere simultaneously.

The representation of coordination binding sites for 6-metyl-2-thiouracil and 6-propyl-2-thiouracil with copper and palladium ions is shown in Figure 5.

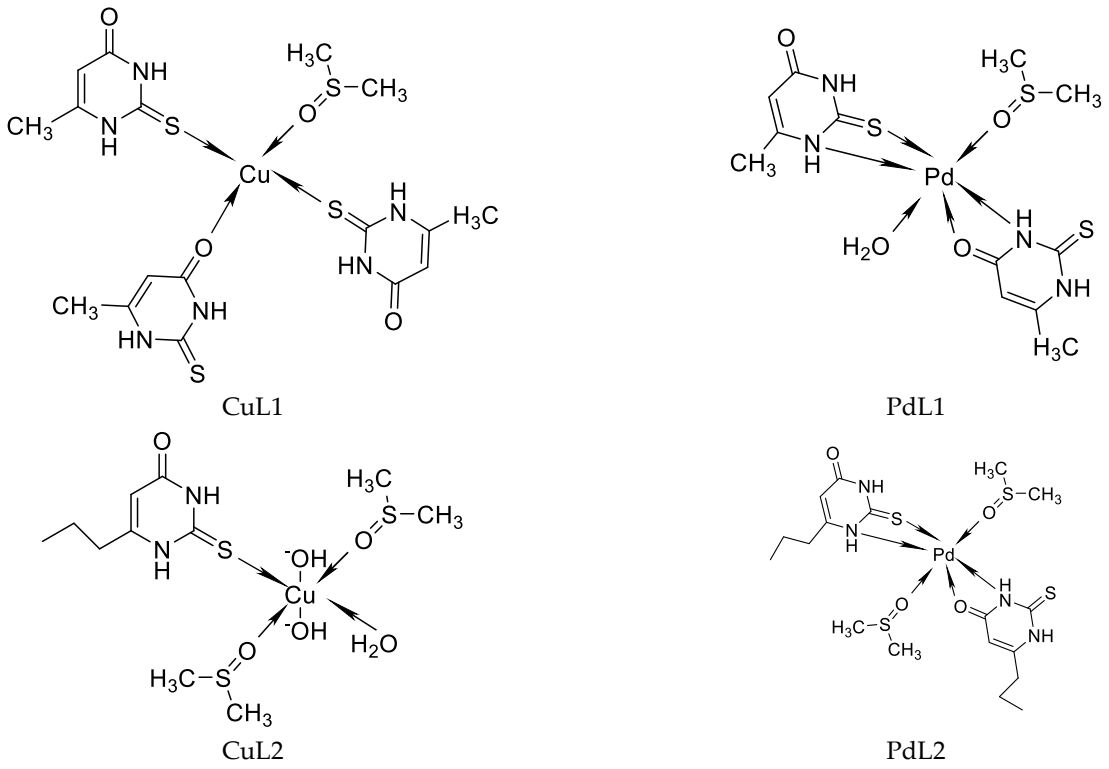


Figure 5. The representation of suggested coordination binding sites for 6-metyl-2-thiouracil and 6-propyl-2-thiouracil.

The coordination binding sites in the CuL2 complex proposed in this study was similar to that reported by Golubyatnikova et al. for Pt(II) and Pd(II) complexes with 6-*tert*-butyl-2-thiouracil [11]. These results demonstrated the bonding of ligand through sulfur in all complexes [11]. Our suggested coordination binding site for 6-propyl-2-thiouracil in CuL2 was similar to that presented by Paizanos et al. for Cu(I) complexes [14]. Various metal complexes exhibited a monodentate coordination mode with 2-thiouracil derivatives, binding through an S atom (Ru(II), Cu(I), Sn(IV), Pt(II), and Pd(II) complexes) [11,14,23,29] (see Scheme 1, middle). For the Cu(II)L1 complex, we proposed monodentate coordination through an S atom and/or monodentate coordination through an O atom. The coordination binding sites of the abovementioned complex are a combination of structures shown in Scheme 1 (middle). The coordination geometry of Cu(II)L1 and CuL2 complexes is tetrahedral/planar square and octahedral, respectively.

The coordination binding sites of PdL1 and PdL2 complexes proposed here are consistent with the data reported by Khan et al. [43] for Pd(II) complexes with sodium 4-(2-methoxyphenyl)piperazine-1-carbodithioate and diphenyl-p-tolylphosphine or tri-p-tolylphosphine. The S-containing ligands acted as a bidentate ligand, coordinating with the metal ion through the two sulfur atoms [43]. In our study, we proposed that one of the ligands participate in coordination via N1 and S2 atoms, and that the other ligand participates in coordination via N3 and O4 atoms. The coordination binding sites of PdL1 and PdL2 complexes are likely a combination of structures A and C shown in Scheme 1. Complexes with Pt(II), Pd(II), Ru(II), and Zn(II) display coordination mode (A) in which the ligand acted as a bidentate chelate through an N1 atom and a S2 atom as it is described [12,13,28,33].

3.2. Antimicrobial Activity

Table 12 shows the results of the antimicrobial assay of 6-methyl-2-thiouracil and its complexes.

Table 12. Antimicrobial activity of 6-methyl-2-thiouracil and its complexes.

Test Microorganisms	Complexes		
	6-Methyl-2-Thiouracil	CuL1	PdL1
	Inhibition Zone, mm		
Staphylococcus aureus ATCC 25923	-	8	-
Escherichia coli ATCC 8739	-	11 *	10 *
Eterococcus faecalis ATCC 19433	11	13	-
Salmonella enterica ssp. *enterica* ser. Enetritidis ATCC 13076	-	13	8
Pseudomonas aeruginosa ATCC 9027	9	12	9
Proteus vulgaris G	9 *	11 *	9 *
Bacillus subtilis ATCC 6633	9 *	9	10 *
Bacillus cereus ATCC 11778	9 *	8	9 *
Listeria monocytogenes ATCC 8787	9 *	11	8
Klebsiella pneumoniae ATCC 13883	9 *	13 *	11 *
Candida albicans ATCC 10231	11	11	9/10 *
Saccharomyces cerevisiae	-	9	-

Well diameter—7 mm, * Inhibition zone with single cell colonies.

The highest antimicrobial activity was exhibited by the CuL1 complex. It was active against all the test-microorganisms. The Pd(II)L1 complex did not inhibit the growth of

S. aureus, *E. faecalis*, and *S. cerevisiae*. 6-methyl-2-thiouracil showed the smallest antimicrobial specter; it was not active against *S. aureus*, *E. coli*, *S. enterica*, and *S. cerevisiae*. The addition of Cu(II) improved the antimicrobial activity of 6-methyl-2-thiouracil against all of the test microorganisms, except *B. cereus*. However, there were single cell colonies in the inhibition zones (IZ) against *E. coli*, *P. vulgaris*, and *K. pneumoniae*. This is indicative of different levels of resistance in the microbial population. The addition of Pd(II) on the other hand, led to a loss of activity against *E. faecalis* and lower activity against *L. monocytogenes* and *C. albicans.*

The inhibition zone diameters for 6-propyl-2-thiouracil are presented in Table 13.

Table 13. Antimicrobial activity of 6-propyl-2-thiouracil and its complexes.

Test Microorganisms	Complexes		
	6-Propyl-2-Thiouracil	CuL2	PdL2
	Inhibition Zone, mm		
Staphylococcus aureus ATCC 25923	-	8	11/16 *
Escherichia coli ATCC 8739	-	10 *	-
Eterococcus faecalis ATCC 19433	-	12	15
Salmonella enterica ssp. *enterica* ser. Enetritidis ATCC 13076	8	12	15
Pseudomonas aeruginosa ATCC 9027	8	12	14
Proteus vulgaris G	10	9 *	-
Bacillus subtilis ATCC 6633	8	12 *	12
Bacillus cereus ATCC 11778	10 *	8	11/15 *
Listeria monocytogenes ATCC 8787	8	9	14
Klebsiella pneumoniae ATCC 13883	11 *	12 *	12 *
Candida albicans ATCC 10231	12	11	11
Saccharomyces cerevisiae	11 *	9	8

Well diameter—7 mm, * Inhibition zone with single cell colonies.

It showed higher antimicrobial activity against *P. vulgaris* and both yeasts strains in comparison to the complexes with Cu(II) and Pd(II). The Cu(II) complex inhibited the growth of all test microorganisms to a different degree; the best results were obtained against *E. faecalis, S. enterica*, and *P. aueruginosa*. *P. vulgaris* was resistant to the tested concentration of the Pd(II) complex (unlike against 6-propyl-2-thiouracil), but all other test microorganisms were more sensitive towards its action in comparison to 6-propyl-2-thiouracil. This pattern was also observed in comparison to the Cu(II) complex, except for *E. coli, P. vulgaris*, and *S. cerevisiae*. Similar to 6-methyl-2-thiouracil and its complexes, there were single cells in some inhibition zones (e.g., 6-propyl-2-thiouracil against *B. cereus, K. pneumonia*, and *S. cerevisiae*). There were two distinct inhibition zones of the Pd(II) complex against *S. aureus* and *B. cereus*: a smaller clear zone and an additional larger zone with single cell colonies within. A more concentrated sample would probably completely inhibit the growth of these microorganisms and significantly increase the antimicrobial activity of the complex.

Generally, the presence of Cu(II) and Pd(II) ions in the complexes increased the antimicrobial activity of the tested substances, which is in line with the work of other authors [44].

4. Conclusions

This paper presents the synthesis of four novel complexes of 6-methyl-2-thiouracil and 6-propyl-2-thiouracil. The structures of the new complexes are discussed based on melting point analysis (MP-AES) for Cu and Pd, UV-Vis, IR, ATR, solution and solid-state NMR, and Raman spectroscopy. Based on the spectral data, we proposed the coordination

binding site of the ligands. We assume that polymer complexes are formed, as shown by their low solubility in different polarity organic solvents.

The antimicrobial activity of the ligands and their complexes against Gram-positive and Gram-negative bacteria and yeasts was investigated. In general, addition of metal ions improved the antimicrobial activity of both 6-methyl-2-thiouracil and 6-propyl-2-thiouracil. The complex of Cu(II) with 6-methyl-2-thiouracil and Pd(II) with 6-propyl-2-thiouracil demonstrated the highest activity against the test microorganisms.

Author Contributions: Conceptualization, P.M. and P.P.; methodology, P.M. and M.H.; formal analysis, P.P., N.B., S.T. and E.V.; investigation, S.T., N.B., D.B., A.S. and E.V.; resources, N.B.; data curation, P.M.; writing—original draft preparation, P.M., N.B., D.B., A.S. and P.P.; writing—review and editing, P.M., P.P. and N.B.; supervision, P.M.; project administration, S.T.; funding acquisition, P.P. All authors have read and agreed to the published version of the manuscript.

Funding: We acknowledge the financial support from the Fund for Scientific Research of the Plovdiv University, project СП 23-Хф-006.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data is contained within the article.

Conflicts of Interest: The authors declare no conflict of interest.

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