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Research Article

SYNTHESIS, SPECTROSCOPIC ANALYSIS, AND ANTIBACTERIAL STUDIES OF PT(IV), PT(II), HG(II), AND AU(III) COMPLEXES WITH 5-(4-PYRIDYL)-5-PHENY-2,4-IMIDAZOLIDENEDIONE

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Abstract

A series of Pt(IV), Pt(II), Hg(II), and Au(III) complexes ($PtCl_4L_2$ (**1**), $PtCl_2L_2$ (**2**), HgX_2L_2 (X = Cl^- (**3**), Br^-(**4**), and I^-(**5**), and $Au_2Cl_6L_2$ (**6**)) with 5-(4-Pyridyl)-5-pheny-2,4-imidazolidenedione ligand (**L**) have been synthesized by the reaction of metal salts with **L** in 1:2 (**1**-**5**) and 1:1 (**6**) molar ratios. The binding manner of **L**, and the composition and geometry of the metal complexes were examined by elemental analysis, IR, ^1H, and ^{13}C NMR spectroscopies. The experimental results revealed octahedral (**1**), square-planar (**2** and **6**), and tetrahedral geometry (**3**-**5**) around the metallic center through the pyridine-type nitrogen (N_{py}) and halogen atoms. Antibacterial activity of **L** and the corresponding complexes were evaluated by the agar disc diffusion method against three Gram positive and three Gram negative bacteria. All complexes displayed antibacterial activity against these bacteria, with high levels of inhibitory potency exhibited against the Gram positive species.

Keywords: 2,4-Imidazolidenedione; Pt complex; Hg complex; Au complex; Antibacterial study

1.Introduction

Several classes of antimicrobial compounds are presently available; microorganism's resistance to these drugs constantly emerges. In order to prevent this serious medical problem, the elaboration of new types of antibacterial agents or the expansion of bioactivity of the naturally known bio sensitive compounds is a very interesting research area. The synthesis and characterization of metal complexes with organic bioactive ligands is one of the promising fields for the search. The hydantoin scaffold is a useful structural motif for displaying chemical functionality in biologically active molecules (Swinyard et al., 1954). The profound interest to different hydantoin derivatives stems from the well-established medical applications of some of them as antiepileptic drugs (Butler and Waddell, 1954; Swinyard et al., 1954). Recently, possible application for HIV-1 therapy has also been suggested (Kim et al., 2001a, b). It is well established that the type of the substituents at 5*th* position in the hydantoin ring is of crucial importance for the pharmacological action of the corresponding compounds (Cortes et al., 1985; Dang and Madan, 1994). On the other hand, their ability to form metal complexes with different coordination modes has also been extensively exploited, again with respect to the pharmacological activity of the so-formed complexes (Arrizabalaga et al., 1987; Arrizabalage et al., 1980; Castan, 1981; Castan and Laurent, 1980; Devillanova et al., 1986; Singh et al., 1976).

The biological activities of the metal complexes differ from those of either the ligand or the metal ion. The results obtained thus far have led to the conclusion that structural factors which govern antimicrobial activities are strongly dependent on the central metal ion. Numerous complexes based on platinum(II) and platinum(IV)-ion have been synthesized and their

antimicrobial activities have been documented (Arrizabalaga et al., 1987; Arrizabalage et al., 1980; Castan, 1981; Cortes et al., 1985; Dang and Madan, 1994; Kim et al., 2001a, b). Pt(II) complexes show several restrictions compared with those of Pt(IV) while the later ones are also cytotoxic in nature and have some advantages in comparison to Pt(II) complexes (Castan and Laurent, 1980; Devillanova et al., 1986; Sabounchei et al., 2013; Singh et al., 1976). There is almost no data about mercury complexes of hydantoin derivatives (Abu-Samn et al., 1987; Sabounchei et al., 2013), so we devoted this study to the elucidation of the nature of hydantoin complexes with Hg halides in an attempt to illuminate the potential of these compounds. On the other hand, over the past few years much interest has focused on gold(III) complexes. Au(III) complexes are square-planar d^8, isoelectronic and isostructural to platinum(II) complexes, and therefore they appear to be very good candidates for pharmacological investigations.

In view of the diversified coordination behavior of **L** and biological importance of metal complexes, it has been considered worthwhile to synthesize and characterize some new platinum(IV), platinum(II), Mercury(II), and Gold(III) derivatives of 5-(4-Pyridyl)-5-phenyhydantoin, **1**-**6**, Scheme 1, that could be proved to be antibacterial agents.

2.Materials and Methods

2.1. Chemicals and reagents

All necessary chemicals were of analytical grade obtained from commercial suppliers and were used without further purification.

2.2. Synthesis and Characterization

2.2.1. 5-(4-Pyridyl)-5-phenylhydantoin (L)

This ligand was prepared by a previously published method (Chu and Teague, 1958; Eknoian et al., 1999). For comparative purposes, a spectroscopic characterization of **L** was performed.

2.2.2.Tetrachloro-bis(5-(4-Pyridyl)-5-pheny lhydantoin) platinum(IV) (1)

$K_2[PtCl_6]$ (0.2429 g, 0.5 mmol) in 15 cm^3 water, dissolved on a steam bath within 50 min, was added to a solution of **L** (0.2532 g, 1 mmol) in 8 cm^3 50% water-ethanol and the resulting yellow solution was stirred at 600 rpm and 50 °C for 1 week in N_2 atmosphere. The solid product was precipitated from the reaction mixture by solvent evaporation. The stable complex was filtered off, washed with cold water, and dried under vacuum. The purity was checked up by thin layer chromatography with the eluent $CH_3COOC_2H_5/C_2H_5OH$ = 2:1. The substance is soluble in DMSO. Yield: 0.3033 g (71.2%). M.P. = 288-289 ºC. Anal. Calcd. For $PtCl_4C_{28}H_{22}N_6O_4$: C, 39.87; H, 3.63; N, 9.96. Found C, 40.33; H, 3.22; N, 9.49.

2.2.3. Dichloro-bis(5-(4-Pyridyl)-5-phenylhydantoin) platinum(II) (2)

$K_2[PtCl_4]$ (0.2075 g, 0.5 mmol) in 5 cm^3 water was added to a solution of **L** (0.2532 g, 1 mmol) in 5 cm^3 50% water-ethanol and the resulting solution was stirred at 600 rpm and 50 °C for 1 week in N_2 atmosphere. The solid product precipitated from the reaction mixture. The stable complex was filtered off, washed with cold water, and dried under vacuum. The purity was checked up by thin layer chromatography with the eluent $CH_3COOC_2H_5/C_2H_5OH$ = 2:1. The substance is soluble in DMSO. Yield: 0.2960 g (76.6%). M.P. = 267< D, Anal. Calcd. For $PtCl_2C_{28}H_{22}N_6O_4$: C, 43.53; H, 2.87; N, 10.88. Found C, 43.85; H, 3.26; N, 10.54.

2.2.4.Dichloro-bis(5-(4-Pyridyl)-5-phenylhydantoin) mercury (II) (3)

$HgCl_2$ (0.1357 g, 0.5 mmol) in 5 cm^3 methanol was added to a solution of **L** (0.2532 g, 1 mmol) in 5 cm^3 methanol. The resulting solution was stirred at 600 rpm and room temperature for 1 week The purity was checked up by thin layer chromatography with the eluent $CH_3COOC_2H_5/C_6H_{12}$ = 1:2. The separated solid was filtered and washed with cold methanol and dried under vacuum. The substance is soluble in DMSO. Yield: 0.2903 g (74.7%). M.P. = 308-309 ºC. Anal. Calcd. For $HgCl_2C_{28}H_{22}N_6O_4$: C, 43.23; H, 2.85; N, 10.80. Found C, 43.75; H, 3.00; N, 10.28.

2.2.5. Dibromo-bis(5-(4-Pyridyl)-5-phenylhydantoin) mercury(II) (4)

$HgBr_2$ (0.1801 g, 0.5 mmol) in 5 cm^3 methanol was added to a solution of **L** (0.2532 g, 1 mmol) in 5 cm^3 methanol. The resulting solution was stirred at 600 rpm and room temperature for 1 week. The purity was checked up by thin layer chromatography with the eluent $CH_3COOC_2H_5/C_6H_{12}$ = 1:2. The separated solid was filtered and washed with cold methanol and dried under vacuum. The substance is soluble in DMSO. Yield: 0.3560 g (82.2%). M.P. = 301-300 ºC. Anal. Calcd. For $HgBr_2C_{28}H_{22}N_6O_4$: C, 38.79; H, 2.56; N, 9.69. Found C, 39.10; H, 3.00; N, 10.02.

2.2.6.Diiodo-bis(5-(4-Pyridyl)-5-phenylhydantoin) mercury(II) (5)

HgI_2 (0.2272 g, 0.5 mmol) in 5 cm^3 methanol was added to a solution of **L** (0.2532 g, 1 mmol) in 5 cm^3 methanol.

The resulting solution was stirred at 600 rpm and room temperature for 1 week. The purity was checked up by thin layer chromatography with the eluent $CH_3COOC_2H_5/C_6H_{12}$ = 1:2. The separated solid was filtered and washed with cold methanol and dried under vacuum. The substance is soluble in DMSO. Yield: 0.2993 g (62.2%). M.P. = 253-254 ºC. Anal. Calcd. For $HgI_2C_{28}H_{22}N_6O_4$: C, 35.00; H, 2.31; N, 8.75. Found C, 35.30; H, 2.70; N, 8.15.

2.2.7.Dichloro-bis(5-(4-Pyridyl)-5-phenylhydantoin) gold(III) tetrachloroaurate(III) (6)

$H[AuCl_4]\cdot xH_2O$ (0.3397 g, 1 mmol) in 3 cm^3 water was added to a solution of the ligand (0.2532 g, 1 mmol) in 3 cm^3 water-ethanol 50% and the resulting solution was stirred at 600 rpm and room temperature for 1 week. The solid product was precipitated from the reaction mixture. The stable complex was filtered off, washed with cold water and dried under vacuum. The purity was checked up by thin layer chromatography with the eluent $CH_3COOC_2H_5/C_2H_5OH$ = 2:1. The substance is soluble in DMSO. Yield: 0.3820 g (68.8%). M.P. = 216-217 ºC. Anal. Calcd. For $Au_2Cl_6C_{28}H_{22}N_6O_4$: C, 30.21; H, 1.99; N, 7.55. Found C, 30.80; H, 2.40; N, 7.40.

2.3. Antibacterial study

The potential antibacterial effects of the compounds were investigated by agar disc diffusion method against three gram positive bacteria, *Staphylicoccus aureus* (Wild), *Bacillus thuringiensis* (Wild), and *Bacillus megaterium* (PTCC 1017), and three gram negative bacteria, *Serratia marcescens* (PTCC 1111), *Entrabacter aerogenesis* (PTCC 1221), and *Salmonella enterica* (PTCC 1236). The compounds were dissolved in DMSO to a final concentration of 1 $mg.ml^{-1}$ and then sterilized by filtration using 0.45 μm Millipore. All tests were carried out using 10 ml of suspension containing 1.5×10^8 bacteria per ml and spread on nutrient agar medium. Negative controls were prepared by using DMSO. Gentamycine, penicillin, neomycin and nitroflantoin were used as positive reference standards. The diameters of inhibition zones generated by the compounds were measured.

2.4. Instrumentation

Carbon, nitrogen, and hydrogen contents of the compounds were determined by elemental analysis carried out on a 'Vario EL III' elemental analyzer. IR spectra were recorded on Perkin-Elmer FT-IR spectrophotometer in the range of 4000-400 cm^{-1} as KBr cells. NMR spectra were obtained on a 400 MHz Bruker spectrometers in DMSO-d_6 as solvent. Melting points were determined using a SMP_3 apparatus.

3. Results and Discussion

3.1. Synthesis

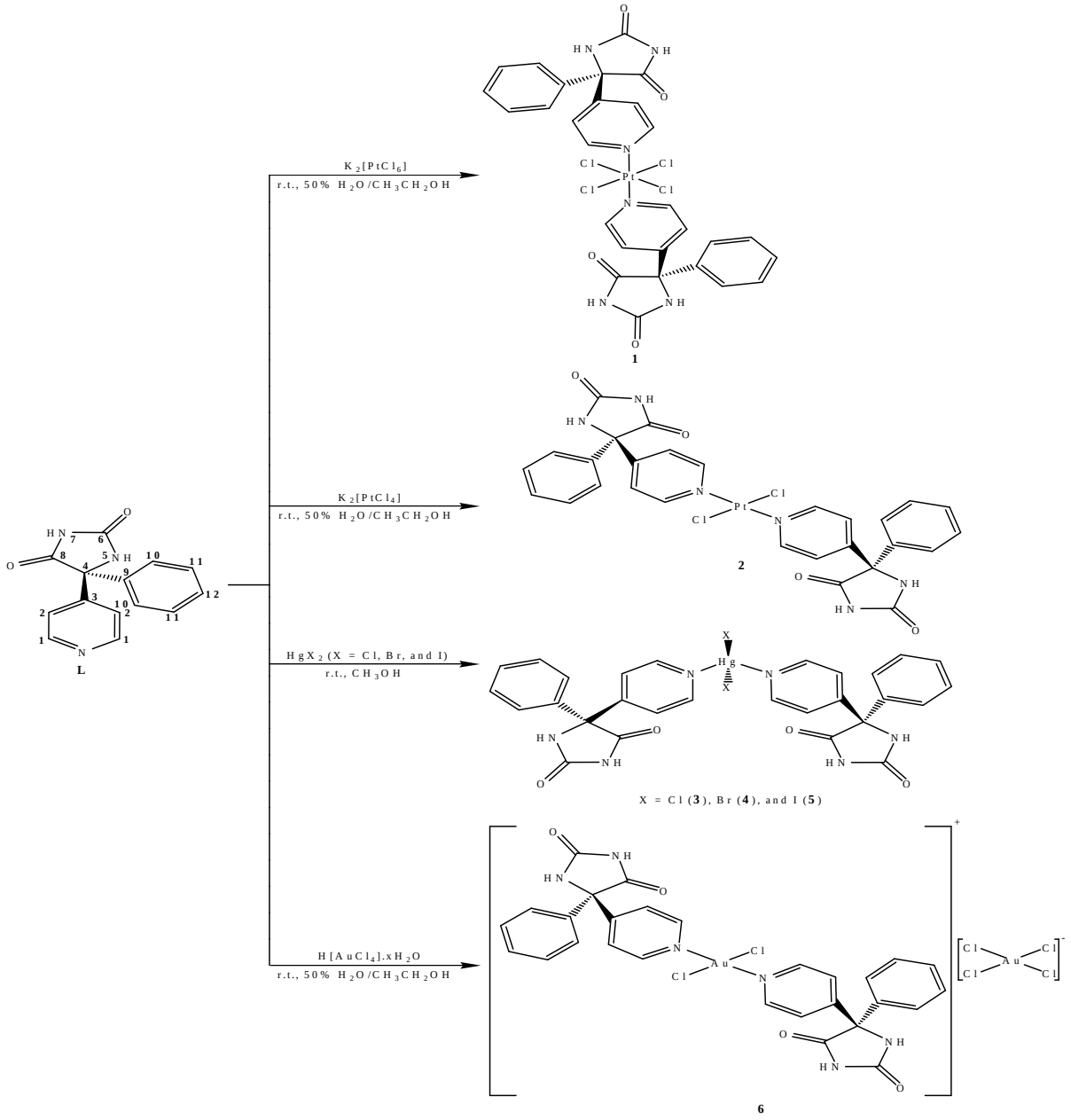
Room temperature reactions of $K_2[PtCl_6]$, $K_2[PtCl_4]$, HgX_2 (X = Cl, Br and I), and $H[AuCl_4].xH_2O$ with **L** gave the complexes **1**-**6** (Scheme 1). The results of elemental analysis showed 1:2 and 1:1 metal/ligand stoichiometry for the complexes **1**-**5** and **6**, respectively. The analytical results were in good agreement with those required by the general formula $Pt(C_{14}H_{11}N_3O_2)_2Cl_4$ (**1**), $Pt(C_{14}H_{11}N_3O_2)_2Cl_2$ (**2**), $Hg(C_{14}H_{11}N_3O_2)_2Cl_2$ (**3**), $Hg(C_{14}H_{11}N_3O_2)_2Br_2$ (**4**), $Hg(C_{14}H_{11}N_3O_2)_2I_2$ (**5**), and $Au(C_{14}H_{11}N_3O_2)_2Cl_6$ (**6**). Binuclear complex **6** has $[AuCl_4]^-$ as a counter-ion (Sabounchei et al., 2014; Segapelo et al., 2009; Shi et al., 2006). Crystals of these complexes could not be grown therefore X-ray crystal determination was not possible. The compounds were characterized on the basis of the following studies (Scheme 1).

3.2. Molar conductivity studies

Molar conductance values of 10^{-3} M solutions for the complexes **1**-**6** were measured in DMSO. The low conductance values for complexes **1**-**5** (16.93, 9.57, 11.2, 11.84, and 23.63 Ω^{-1} cm^2 mol^{-1}) suggested that replacement of two halide ligands by two **L** had occurred to give a neutral and non-electrolytic complexes (Geary, 1971). In the complexe **6**, the molar conductivity value, 58.73 Ω^{-1} cm^2 mol^{-1} is in the range for 1:1 electrolytes in this solvent (Geary, 1971). This may be taken as an evidence for the presence of $[AuCl_4]^-$ as a counterion, indicating the electrolytic nature of this complex.

Table 1 shows the most important vibrations in the ligand and the corresponding complexes, for the numbering of the atoms see Scheme 1 (to see the spectra refer to Figs. A.1-A.21, ESI†).

Comparative analysis of the IR spectra of the complexes and of the free ligand revealed that the characteristic absorption bands for the stretching vibrations of –C=N– from the pyridine ring shifted towards higher frequencies in the complexes. This indicates the nitrogen atom from the pyridine ring participates in the coordination to the metal ion. The other characteristic bands of the pyridine ring of the free ligand also shifted to higher frequencies upon complexation



Scheme 1. Synthesis of complexes **1**-**6**

3.3. Spectroscopy

The bands related to the stretching vibrations of the hydantoin ring (carbonyl groups and more acidic NH group (7-N–H)), and phenyl ring remained almost unchanged in the all complexes. This fact is evidence that these groups are not involved in the complex formation. However, coordination of pyridine ring to the metal ions has had some impact on these bonds. On the other hand, as the nitrogen atom of the pyridine ring only participates in the coordination, the stretching vibrations of 5-N–H group are shifted to higher frequencies. This change in the stretching frequency of this group can be due to their proximity to the coordination site.

Table 1. IR selected bands (υ_{max}/cm^{-1}) of the ligand and complexes (**1**-**6**), for the numbering of the atoms, see Scheme 1

Compound	$\upsilon_{5\text{-}N\text{–}H}$	$\upsilon_{7\text{-}N\text{–}H}$	$\upsilon_{6\text{-}C=O}$	$\upsilon_{8\text{-}C=O}$	$\upsilon_{(C=N)}$	$\upsilon_{(C=C)}$
L	3130	3060	1726	1775	1599	1448
1	3192	3061	1728	1766	1618	1448
2	3244	3055	1736	1783	1617	1447
3	3183	3060	1717	1771	1605	1439
4	3185	3060	1718	1771	1605	1436
5	3184	3057	1716	1770	1603	1436
6	3212	3062	1693	1737	1618	1443

The chemical shifts from the NMR spectra of the ligand and complexes are shown in Table 2. Assignment of the NMR peaks was performed according to the Scheme 1. In the ^{1}H NMR spectra of the complexes, the signals of the protons from the pyridine ring are shifted to lower frequencies compared to the spectra of the ligands. There are noticeable differences between the proton chemical shifts of the ligands and the corresponding complexes (especially in **1**, **2**, and **6**). These show that in these complexes, the most probable bonding of the ligand with the metal ions is realized through the nitrogen atom of the pyridine ring. The reduction in coupling constants $J_{1,2}$ in the complexes compared with the ligand indicates that electronic density on the C–H bonds of the pyridine ring decreases upon complexation. The signals for the protons and the NH groups of the phenyl and hydantoin rings, respectively, are slightly shifted. This fact indicates these atoms are not involved in the coordination. The impressive changes in the chemical shifts related to the carbon atoms of the pyridine ring also confirm the participation of this ring in the bonding with the metal ion. The signals of the two C=O groups from the hydantoin ring in both complexes are slightly changed. 8-C=O group show greater shifts toward higher frequencies than 6-C=O which could be because these groups are nearer to the coordination site. These findings are an indication that in theses complexes, the phenyl and hydantoin rings do not participate in the coordination.

Table 2. Experimental ^{1}H and ^{13}C NMR (400 MHz; DMSO; Me_4Si) chemical shifts/ppm for the ligand and corresponding complexes, for the numbering of the atoms, see Scheme 1

Compound	^{1}HNMR									
	1-H	2-H & 10-H–12-H		5-NH	7-NH					
L	8.67 (d) $^{1}J_{1,2}$ = 6.24	7.34-7.54		9.57	11.36					
1	8.81-9.02 (m)	7.35-8.08		9.64	11.50					
2	8.81-9.16 (m)	7.34-7.78		9.59	11.46					
3	8.62 (d) $^{1}J_{1,2}$ = 5.53	7.32-7.44		9.48	11.29					
4	8.63 (s)	7.33-7.47		9.50	11.31					
5	8.62 (d) $^{1}J_{1,2}$ = 5.69	7.32-7.44		9.48	11.29					
6	8.84 (d) $^{1}J_{1,2}$ = 5.36	7.32-7.89		9.61	11.44					
	^{13}CNMR									
	1-C	2-C	3-C	4-C	6-C	8-C	9-C	10-C	11-C	12-C

L	148.55	121.95	149.63	69.42	155.78	173.47	138.62	128.80	126.34	128.46
1	151.84	124.72	149.92	69.32	155.62	172.64	138.06	129.07	126.38	128.81
2	150.25	122.53	152.48	-	154.19	-	133.68	129.84	128.80	128.96
3	149.85	121.43	148.20	69.34	155.80	173.64	138.70	128.74	126.30	128.37
4	149.64	121.71	148.69	69.38	155.81	173.58	136.66	128.77	126.33	128.41
5	149.82	121.46	148.23	69.34	155.80	173.64	138.70	128.74	126.31	128.37
6	146.04	123.07	144.30	-	155.69	173.01	138.31	128.95	126.34	128.68

It is noticeable that both the IR and NMR spectra of mercury complexes (**3**-**5**) are almost identical with the ligand and the signals for the pyridine ring shifted only slightly. This fact illustrate that the local environment is structurally similar in the ligand and the corresponding complexes (Sabounchei et al., 2013).

3.4. Antibacterial studies

Results from the antibacterial assessment of the chemicals, antibiotics (for positive controls), and DMSO (for negative control) are shown in Table 3. All prepared chemicals inhibited the growth of bacterial strains producing a zone diameter of inhibition from 8 to 30 mm, depending on susceptibility of tested bacteria. The results indicate that the complexes show more activity and the ligand does not have any activity against same microorganisms under identical experimental conditions. This would be suggested the strong chelation could facilitate the ability of a complex to cross a cell membrane and can be explained by Tweedy's chelation theory (Tweedy, 1964). Chelation considerably reduces the polarity of the metal ion because of partial sharing of its positive charge with donor groups and possible electron delocalization over the whole chelate ring. Such a chelation can enhance the lipophilic character of the central metal atom, which subsequently favors its permeation through the lipid layer of the cell membrane (Tümer et al., 2007). As can be seen in Table 3, these chemical compounds displayed antibacterial activity against most of bacteria tested specially Gram positive ones. When antimicrobial activities of the tested samples were compared with some reference antibiotics, the inhibitory potency of the tested compounds (especially **6**) was found to be remarkable.

Table 3. Antibacterial activity of chemicals, antibiotics (for positive controls), and DMSO (for negative control) as inhibition zones (mm)

Bacterial strains	Inhibition zones											
	Chemical compounds							positive control				negative control
	L	**1**	**2**	**3**	**4**	**5**	**6**	Gentamicine	Penicillin	Nitroflantoin	Neomycin	DMSO
Gram positive bacteria												
Staphylicoccus aureus	-	-	-	-	15	-	-	16	-	9	15	-
Bacillus thuringiensis	-	10	16	-	14	11	30	16	-	12	13	-
Bacillus megaterium	-	10	9	10	17	19	25	12	-	15	11	-
Gram negative bacteria												
Serratia marcescens	-	11	14	9	17	15	16	12	17	10	14	-
Entrabacter aerogenesis	-	-	-	8	14	21	28	17	-	14	16	-
Salmonella enterica	-	-	-	-	-	-	-	13	16	12	13	-

4. Conclusions

The present study describes the synthesis and characterization of six new complexes (**1**-**6**) with 5-methyl-5-(4-pyridyl)hydantoin, **L**. Although none of the complexes has been obtained in the crystalline state, on the basis of the physico-chemical and spectroscopic data is clear that **L** exhibit monodentate N-coordination to the metal center, $N_{pyridine\ ring}$ as the coordination site. Complexes **1**-**5** and **6** were obtained with 2:1 and 1:1 ligand-metal ratio in a substitution reaction, respectively. In **6**, $[AuCl_4]^-$ acts as a counter-ion. Results from the antibacterial studies demonstrate that the chemicals have moderate to strong activity against tested bacterial strains than reference antibiotics.

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