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ORIGINAL ARTICLE

Metal complexes of Schiff base: Preparation, characterization and antibacterial activity

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Abstract A total of five new metal complex derivatives of 2N-salicylidene-5-(*p*-nitro phenyl)-1,3,4-thiadiazole, HL with the metal ions Vo(II), Co(II), Rh(III), Pd(II) and Au(III) have been successfully prepared in alcoholic medium. The complexes obtained are characterized quantitatively and qualitatively by using micro elemental analysis, FTIR spectroscopy, UV–Vis spectroscopy, mass spectroscopy, ^{1}H & ^{13}C NMR, magnetic susceptibility and conductivity measurements. From the spectral study, all the complexes obtained as monomeric structure and the metals center moieties are four-coordinated with square planar geometry except VO(II) and Co complexes which existed as a square pyramidal and tetrahedral geometry respectively. The preliminary *in vitro* antibacterial screening activity revealed that complexes **1–5** showed moderate activity against tested bacterial strains and slightly higher compared to the ligand, HL.

1. Introduction

Schiff bases derived from an amino and carbonyl compound are an important class of ligands that coordinate to metal ions via azomethine nitrogen and have been studied extensively. In azomethine derivatives, the C═N linkage is essential for biological activity, several azomethine have been reported to possess remarkable antibacterial, antifungal, anticancer and antimalarial activities (Annapoorani and Krishnan, 2013).

1,3,4-Thiadiazole derivatives possess interesting biological activity probably conferred to them by the strong aromaticity of this ring system, which leads to great in vivo stability and generally, a lack of toxicity for higher vertebrates, including humans. When diverse functional groups that interact with biological receptors are attached to this ring, compounds possessing outstanding properties are obtained. Except for some antibacterial sulfonamides (albucid and globucid), no longer used clinically, but which possessed historical importance, the most interesting examples are constituted by

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5-amino-l,3,4-thiadiazole-derivatives (Kornis et al., 1984). In addition, the chemistry and the applications of these new Schiff base thiadiazole derivatives could be extensively studied by coordinating to various metal ion moieties. As a result, the structural-activity relationship study of 1,3,4-thiadiazoles could be expanded in the near future (Elzahany et al., 2008; Gaber et al., 2001; Hadizadeh and Vosoogh, 2008; Jarrahpour et al., 2007; Taggi et al., 2002; Salimon et al., 2010).

As the continuation interest of our study of transition metal complexes (Yousif et al., 2010a,b; Majeed et al., 2010; Ibraheem et al., 2010), here we present the synthesis and characterization of new complex derivatives of 2N-salicylidene-5-(*p*-nitro phenyl)-1,3,4-thiadiazole. Moreover, the preliminary *in vitro* antibacterial screening activities of the complexes obtained are carried out and the results are reported herein.

2. Experimental

2.1. General and instrumental

All the reagents, starting materials as well as solvents were purchased commercially and used without any further purification. The melting points were recorded on a hot stage Gallen Kamp melting point apparatus. Elemental C, H, N and S analysis were carried out on a Fison EA 1108 analyzer. The Infrared (FTIR) spectra were recorded by using FTIR.8300 Shimadzu Spectrophotometer by using CsI disc in the frequency range of 4000–200 cm^{-1}. The ultraviolet–visible (UV–Vis) spectra were recorded by using a Shimadzu Uv–vis. 160 A-Ultra-violet Spectrophotometer in the range of 200–1100 nm. The magnetic susceptibility values were obtained at room temperature using Magnetic Susceptibility Balance Bruke Magnet B.M.6. Conductivity measurements were carried out by using a WTW conductivity meter, atomic absorption measurements were obtained by using Shimadzu 680 cc-flame. The spectra of ^{1}H and ^{13}C NMR spectra were recorded on a Jeol 400 MHz spectrometer using deuterated d_6-DMSO as the solvent and tetramethylsilane, TMS as the internal standard. Mass spectra were recorded on a Micromass UK PLATFORM II LC-MS spectrometer.

2.2. Preparation of 2N-salicylidene-5-(p-nitro phenyl)-1,3,4-thiadiazole, HL

A mixture of 4-nitrobenzoic acid (0.01 mole), thiosemicarbazide (0.01 mole) and phosphorus oxychloride (5 mL) was heated under reflux for 3 h. Upon cooling, distilled water (50 mL) was added to the mixture and the heating under reflux was carried out for another 4 h. The obtained filtrate was neutralized with potassium hydroxide. Then, the precipitate was filtered and washed with cold distilled water and finally recrystallized by using ethanol-water solvent mixture to obtain 5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine. In the next reaction, 5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (0.01 mole) and salicylaldehyde (0.01 mole) were heated under reflux for 3 h to obtained the yellow precipitate. The precipitate obtained was filtered and crystallized from ethanol to give the respective 2N-salicylidene-5-(*p*-nitro phenyl)-1,3,4-thiadiazole, HL ligand for the further complexation with metal ion. The stepwise preparation of the ligand, HL is shown in Fig. 1.

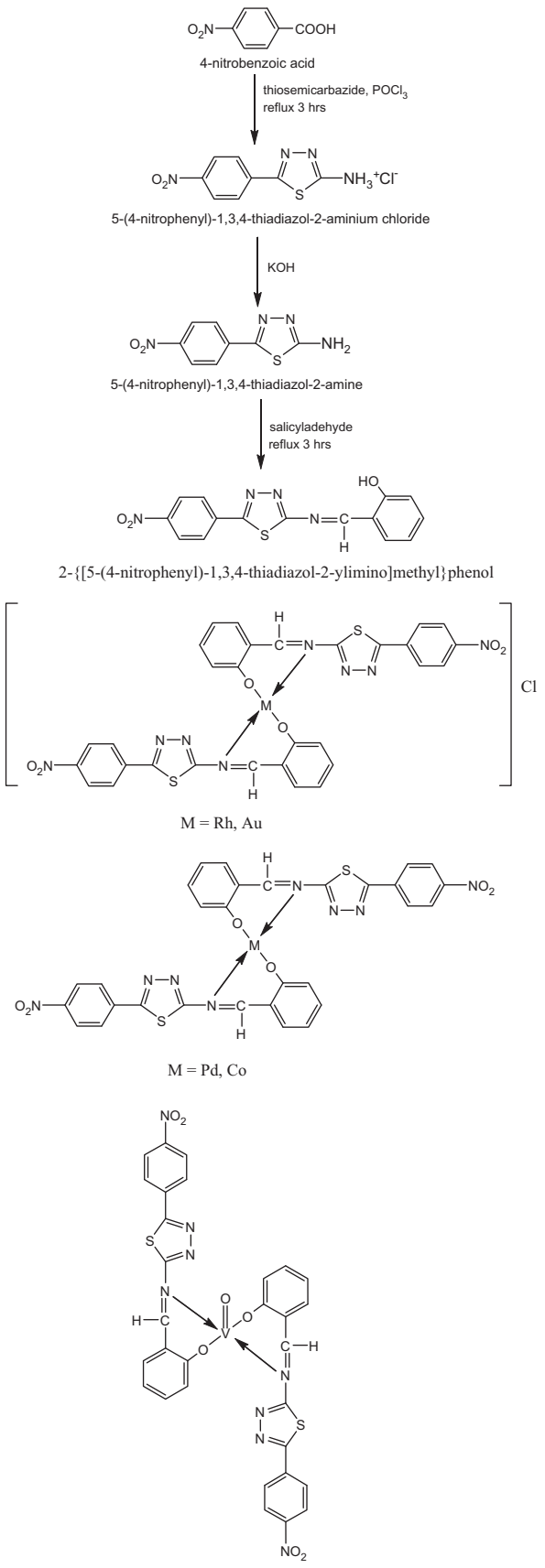

Figure 1 The structure of HL and the proposed structure of complexes **1**–**5** (M = metal).

2.3. Preparation of complexes

An ethanol solution of the metal ions [VO(II)$SO_4 \cdot H_2O$, $CoCl_2 \cdot 6H_2O$, $RhCl_3 \cdot XH_2O$, $PdCl_2$ and $HAuCl_3 \cdot H_2O$] was added to ethanol solution of 2N-salicylidene-5-(*p*-nitro phenyl)-1,3,4-thiadiazole, HL in 1:2 (metal:ligand) molar ratio. Then, the mixture was heated under reflux for half an hour and coloured precipitates were obtained. Later, the precipitates were filtered out, washed with distilled water and finally recrystallized from ethanol.

3. Results and discussion

In general, the complexes were obtained by heating under reflux of respective metal salts with ligand, HL in 1:2 molar ratio. The purity of the ligand, HL and complexes **1–5** obtained were checked by TLC using silica gel-G as adsorbent. Complexes **1–5** gave a sharp melting point indicating the isolation of fairly pure complexes. The micro-elemental analysis for C, H, N and S as well as the molecular weight of the complexes obtained were in agreement with the predicted formula for complexes **1–5**. An outline of the proposed structure for complexes **1–5** and ligand, HL is depicted in Fig. 1. The melting point, micro-elemental analysis and *m*/*z* data are given in Table 1.

The infrared spectrum of ligand, HL showed some characteristic stretching bands at 1635 and 1116 cm^{-1} assigned to υ (C═N) and υ (C–O) respectively which could be found in complexes **1–5**. The exceptional case is that the υ (C═N) of complexes **1–5** were found to be shifted to a lower wavelength number compared to the ligand, HL signifying that the coordination took place via the nitrogen atom of the ligand, HL (Sliverstein et al., 2005). In addition, the stretching of metal–oxygen and metal–nitrogen bands of the complexes appeared in the lower wavelength region in the range of 556–500 and 488–432 cm^{-1} also signifying the complexation through nitrogen and oxygen atoms from the ligand (Nakamoto, 1997). The important infrared data of the ligand, HL and complexes **1–5** are given in Table 2.

The ultraviolet visible electronic spectrum of the ligand, HL and complexes **1–5** in ethanol solution are given in Table 3. The ligand showed three bands at 47,620, 39,370 and 28,901 cm^{-1} attributed to $\pi \rightarrow \pi^*$, $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transitions respectively. For all complexes it showed the similar electronic transition as observed in the ligand and it also showed the electronic transitions of the metal *d* orbitals (*d-d* electronic transition) observed located in the visible region as an extra information. In VO(II), *d-d* electronic transition appeared at 23,800 cm^{-1} assigned to the $^2B_2 \rightarrow {}^2A_1$ transition, and for Co(II), the band appeared at 6,265, 9,346 and 15,665 cm^{-1} which was attributed to $^4A_2 \rightarrow {}^4T_2^{(F)}$, $^4A_2 \rightarrow {}^4T_1^{(F)}$, $^4A_2 \rightarrow {}^4T_1^{(P)}$ transition respectively (Green-Wood and Earnshow, 2002). For Rh(III), the bands appearing at 23,200 and 26,333 cm^{-1} were attributed to the $^1A_1g \rightarrow 1B_1g$ and L (ligand) → Rh (charge transfer, C.T.). Pd(II) complex gave three band at 22,121, 24,500 and 31,100 cm^{-1} which were assigned to $^1A_1g \rightarrow 1B_1g$, $^1A_1g \rightarrow 1Eg$, $L \rightarrow Pd$ (C.T.), respectively.

The last complex of Au(III) also gave three bands in the visible region at 16,500, 24,012 and 30,550 cm^{-1} which were attributed to $^1A_1g \rightarrow 3B_1g$, $^1A_1g \rightarrow 1B_1g$, $^1A_1g \rightarrow 1Eg$ (Figgis, 2000; Jorgensen, 2004).

The ^1H NMR spectra of complexes **1–5** gave an additional support for the formation of the complexation. In the ^1H NMR spectra of ligand, HL showed a sharp peak, δ(OH) at 9.90 ppm which was absent in the spectra of the complexes **1–5** indicating deprotonation and complexation of ligand anion to metal ions. The ^1H NMR spectra of complexes **1–5** exhibited some similarities to the ligand, HL with the occurrence of –N═CH– and aromatic protons signals centering at $\delta \approx 7.36$ ppm and in the range of 8.24–9.21 ppm, respectively (Salimon et al., 2009). From the ^{13}C NMR study, all the com-

Table 2 Selected infrared data of HL and complexes **1–5**.

Compounds	Wavelength (cm^{-1})			
	υ (C═N)	υ (C–O)	υ (M–O)	υ (M–N)
HL	1635	1115	–	–
$VO(L)_2$, 1	1605	1124	509	486
$Co(L)_2$, 2	1602	1120	508	480
$Rh(L)_2$, 3	168	1110	504	488
$Pd(L)_2$, 4	1610	1110	508	485
$Au(L)_2$, 5	1611	1122	511	481

Table 1 Melting points, elemental analytical data (%) and *m*/*z* value of HL and complexes **1–5**.

Compounds	Physical appearance	Melting point (°C)	Elemental (%)					*m*/*z*
			C	H	N	S	M (metal)	
HL	Yellow	113–115	55.44 (55.04)	3.33 (3.36)	17.32 (17.12)	9.99 (9.78)	–	327.0
$VO(L)_2$, 1	Green	218–220	50.33 (50.07)	3.00 (3.06)	15.55 (15.57)	9.03 (8.92)	9.23 (9.31)	718.94
$Co(L)_2$, 2	Blue	98–100	50.70 (50.63)	3.22 (3.10)	15.67 (15.80)	8.96 (9.03)	8.22 (8.28)	710.93
$Rh(L)_2$, 3	Deep Orange	198–200	45.44 (45.55)	2.65 (2.78)	14.12 (14.17)	8.00 (8.10)	13.16 (13.02)	790.35
$Pd(L)_2$, 4	Brown	195–197	23.12 (47.47)	1.32 (2.90)	7.55 (14.76)	4.33 (8.44)	14.00 (14.03)	758.42
$Au(L)_2$, 5	Pale Yellow	212–214	40.65 (40.70)	2.50 (2.49)	12.12 (12.66)	7.21 (7.23)	22.12 (22.27)	884.41

Calculated values are given in parentheses.

Table 3 Electronic spectral data of HL and complexes **1–5** in ethanol.

Compounds	Absorption bands (cm^{-1})	Assigned transition
HL	47,620, 39,370, 28,901	$\pi \rightarrow \pi^*$, $\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$
$VO(L)_2$, 1	40,816, 28,653	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$,
	23,800	$^2B_2 \rightarrow {}^2A_1$
$Co(L)_2$, 2	39,680, 28,650	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$
	6,265, 9,346, 15,665	$^4A_2 \rightarrow {}^4T_2^{(F)}$, $^4A_2 \rightarrow {}^4T_1^{(F)}$, $^4A_2 \rightarrow {}^4T_1^{(P)}$
$Rh(L)_2$, 3	39,683, 28,666	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$
	23,200, 26,333	$^1A_1g \rightarrow {}^1B_1g$, L $\rightarrow$ Rh (C.T.)
$Pd(L)_2$, 4	39,677, 28,570	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$
	22,121, 24,500, 31,100	$^1A_1g \rightarrow {}^1B_1g$, $^1A_1g \rightarrow {}^1Eg$, L $\rightarrow$ Pd (C.T.)
$Au(L)_2$, 5	42,015, 30,959	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$
	16,500, 24,012, 30,550	$^1A_1g \rightarrow {}^3B_1g$, $^1A_1g \rightarrow {}^1B_1g$, $^1A_1g \rightarrow {}^1Eg$
	35,600	L $\rightarrow$ Au (C.T.)

plexes obtained also exhibited some similarities to the ligand, HL with the occurrence of –N=CH– carbon signals centering at $\delta \approx 111.00$ ppm and thiadiazole carbons signals centering at $\delta \approx 87.61$ and 90.79 ppm, respectively. Moreover, the aromatic carbons signals of both complexes **1–5** and ligand, HL were located at the downfield region in the range of 125.42–132.61 ppm. Generally, there is no uncharacterized peak in the ^1H and ^{13}C NMR spectra of ligand, HL and complexes **1–5** signify the purity of the samples obtained. The ^1H and ^{13}C NMR spectra data of ligand, HL and complexes **1–5** are given in Table 4.

Magnetic moment measurements are widely used in studying transition metal complexes and the magnetic moment and conductivity measurements of complexes **1–5** are given in Table 5. The magnetic properties are due to the presence of unpaired electrons in the partially filled *d*-orbital in the outer shell of these elements. These magnetic measurements give an outline about the electronic state of the metal ion in the complexes. The magnetic moment value of complex **1** was approximately 1.68 B.M. and referred as paramagnetic and the geometry of Vanadyl(II) metal center was square pyramidal. Conductivity measurements show the complex to be non-electrolyte. Complex **2** showed the magnetic moment value at 0.85 B.M. and believed that the Cobalt(II) metal moiety exhibited tetrahedral geometry (Win et al., 2011), the molar conductivity measurements in DMF show that the complex was non-electrolyte. The magnetic moment for Complexes **3** is 150 which showed a higher (d-orbital) contribution, and conductivity measurement in DMF showed that the complex was conducting. The measured magnetic moment for complex **4** is 0.55 B.M which showed the complex to be with low spin. Conductivity measurement in DMF showed that the complex was non-ionic. The complex **5** was diamagnetic and conductivity measurement in DMF showed that the complex was conducting.

All the complexes obtained were studied in ethanol solution to determine the M/L ratio in the complex by Job's Method (Harris, 2010). A series of solutions were prepared with a constant concentration (10^{-3} M) of the metal ion and ligand, HL. The M/L ratio was determined from the relationship between the absorption of the absorbed light and the mole ratio of M/L. The study showed that the metal to ligand, HL ratio was 1/2 for complexes **1–5** and found to be similar to the solid state. Based on the spectral study, complex **1** exhibited square pyramidal geometry, complex **2** is a tetrahedral geometry and the last three complexes are square planar. The proposed structures of complexes **1–5** are depicted in Fig. 1.

Microorganisms have existed on the earth for more than 3.8 billion years and exhibit the greatest genetic and metabolic diversity. They are an essential component of the biosphere and serve an important role in the maintenance and sustainability of ecosystems. It is believed that they compose about 50% of the living biomass. In order to survive, they have evolved mechanisms that enable them to respond to selective pressure exerted by various environments and competitive challenges. The disease-causing microorganisms have particularly been vulnerable to man's selfishness for survival who has sought to deprive them of their habitat using antimicrobial agents. These microorganisms have responded by developing resistance mechanisms to fight off this offensive. Currently

Table 4 ^1H and ^{13}C NMR data of HL and complexes **1–5** in d_6-DMSO.

Chemical Shift, δ (ppm)						
^1H NMR				^{13}C NMR		
Compounds	–N=CH–	Aromatic	OH	–N=CH–	Thiadiazole	Aromatic
HL	7.41 (s)	8.24–9.06 (m)	9.90	111.12	87.71, 90.79	125.43–132.54
$VO(L)_2$, 1	7.36 (s)	8.34–9.17 (m)	–	112.68	87.67, 90.78	125.58–132.52
$Co(L)_2$, 2	7.35 (s)	8.30–9.18 (m)	–	110.86	87.67, 90.81	125.53–132.62
$Rh(L)_2$, 3	7.38 (s)	8.41–9.21 (m)	–	111.50	87.65, 90.79	125.43–132.53
$Pd(L)_2$, 4	7.36 (s)	8.29–9.20 (m)	–	112.35	87.62, 90.76	125.53–132.62
$Au(L)_2$, 5	7.39 (s)	8.32–9.18 (m)	–	110.57	87.67, 90.79	125.43–132.55

s = Singlet, m = multiplet.

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Table 5 Conductivity measurements and magnetic moment of HL and complexes **1–5** in DMF.

Compounds	Conductivity (μS/cm)	Magnetic moment (B.M.)	Proposed structure
HL	–	–	–
$VO(L)_2$, 1	20	1.68	Square pyramidal
$Co(L)_2$, 2	17	0.85	Tetrahedral
$Rh(L)_2$, 3	150	2.55	Square planar
$Pd(L)_2$, 4	15	0.55	Square planar
$Au(L)_2$, 5	165	0.77	Square planar

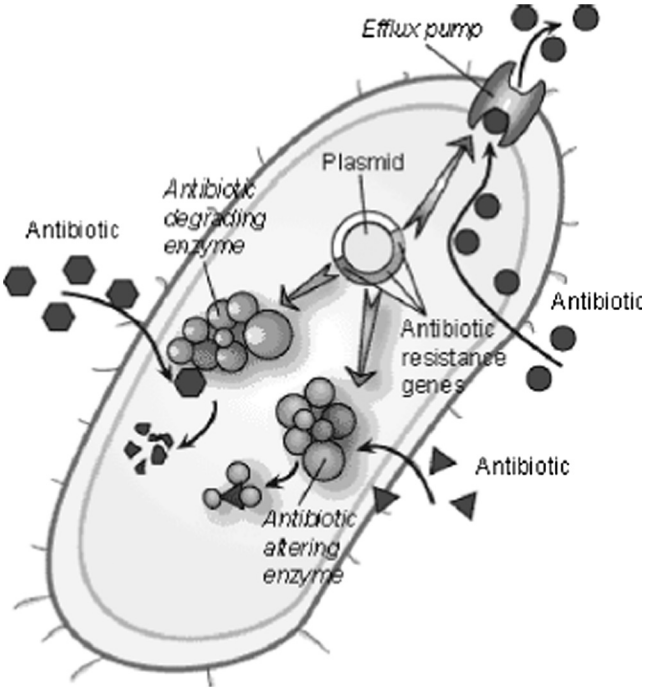

Figure 2 Illustration of how some antimicrobial agents are rendered ineffective (Fluit et al., 2001).

antimicrobial resistance among bacteria, viruses, parasites, and other disease-causing organisms is a serious threat to infectious disease management globally (Dun, 1999).

In order to appreciate the mechanisms of resistance, it is important to understand how antimicrobial agents act. Antimicrobial agents act selectively on vital microbial functions with minimal effects or without affecting host functions. Different antimicrobial agents act in different ways. The understanding of these mechanisms as well as the chemical nature of the antimicrobial agents is crucial in the understanding of the ways how resistance against them develops. However, the mechanism of action of antimicrobial agents can be categorized further based on the structure of the bacteria or the function that is affected by the agents. These include generally the following:

- Inhibition of the cell wall synthesis.
- Inhibition of ribosome function.
- Inhibition of nucleic acid synthesis.
- Inhibition of folate metabolism.
- Inhibition of cell membrane function.

Microorganisms were increasingly becoming resistant to ensure their survival against the arsenal of antimicrobial agents to which they were being bombarded. They achieved this through different means but primarily based on the chemical structure of the antimicrobial agent and the mechanisms through which the agents acted. The resistance mechanisms therefore depend on which specific pathways are inhibited by the drugs and the alternative ways available for those pathways that the organisms can modify to get a way around in order to survive (Yeaman and Yount, 2003). Resistance can be described in two ways:

a) intrinsic or natural whereby microorganisms naturally do not posses target sites for the drugs and therefore the drug does not affect them or they naturally have low permeability to those agents because of the differences in the chemical nature of the drug and the microbial membrane structures especially for those that require entry into the microbial cell in order to effect their action or
b) acquired resistance whereby a naturally susceptible microorganism acquires ways of not being affected by the drug.

Table 6 Preliminary *in vitro* antibacterial screening activity of HL and complexes **1–5**.

Compounds	Inhibition Zone (mm)					
	Staphylococcus aureus		*Salmonella typhi*		*Escherichia coli*	
	100 μg	200 μg	100 μg	200 μg	100 μg	200 μg
HL	-	+	+	+	+	+
$VO(L)_2$, 1	+	+	+	+ +	+	+ +
$Co(L)_2$, 2	+ +	+ +	+	+	+ +	+ +
$Rh(L)_2$, 3	-	+	+	+ +	+ +	+ +
$Pd(L)_2$, 4	+ +	+	+ +	+	+ +	+ +
$Au(L)_2$, 5	+ +	+ +	+ + +	+ +	+ +	+ +

+ = 5–10 mm, + + = 11–20 mm, + + + = larger than 20 mm, - = no inhibition.

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Acquired resistance mechanisms can occur through various ways, Fig. 2.

The preliminary *in vitro* antibacterial screening activity of ligand, HL and complexes **1–5** are given in Table 6. The synthesized complexes and ligand, HL were screened for their *in vitro* antibacterial activity against *Staphylococcus aureus, Salmonella typhi* and *Escherishia coli* bacterial strains by Inhibition zone method using agar diffusion method (Yousif et al., 2009; Frankle et al., 1970) In this method a standard 6.35 mm diameter sterilized filter paper disc impregnated with the compound (200 and 100 μg/ml in DMSO) was placed on an agar plate seeded with the test bacterial strains. The plates were incubated for 24 hours at 37 °C. The activity was determined by measuring the diameter of the inhibition zone (in mm) and streptomycin was used as the standard control. The preliminary screening results revealed that complexes **1–5** showed a significant activity compared to the ligand, HL. Overall, the activities of all the complexes obtained were found to be moderate even though higher concentrations were applied. This may be due to the bulkiness of the molecule with a complicated structure which in turn restricts their mobility to the target cell or active site although all the complexes were obtained as a monomeric and four-coordinated metal(II) and metal(III) moieties.

4. Conclusions

The ligand 2N-salicylidene-5-(*p*-nitro phenyl)-1,3,4-thiadiazole was successfully synthesized. The ligand, HL was coordinated to five different metal ions via oxygen and nitrogen atoms to afford the corresponding complexes. All the complexes were four-coordinated and exhibited square planar geometry except complex **1** and complex **2** which are square pyramidal and tetrahedral in shape respectively. Preliminary *in vitro* antibacterial study indicated that all the complexes obtained showed a moderate activity against the tested bacterial strains and a slightly higher activity compared to the ligand, HL.

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