SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF NEW Ni(II), Co(II) AND Cu(II) COMPLEXES WITH N,N'-DIACYLHYDRAZINES

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Lucrarea prezintă un nou ligand, N'-[4-(4-clorofenilsulfonil)benzoil]-2-oxo-imidazolidin-1-carbohidrazida ***(L)*** *care a fost sintetizat prin reacţia dintre hidrazida acidului 4-(4-clorofenilsulfonil)benzoic şi clorura acidului 2-oxoimidazolidin-1-carboxilic. De asemenea, au fost obţinuţi şi caracterizaţi prin analiză elementală, măsurători de susceptibilitate magnetică, spectre electronice, RES şi IR şi complecşii* $[Cu(L\text{-}H)_2]$, $[Co(L\text{-}H)_2(H_2O)_2]$ *şi* $[Ni(L\text{-}H)_2(H_2O)_2]$.

Aceşti complecşi au fost testaţi pentru acţiunea antibacterială pe culturi de Staphylococcus epidermidis ATCC 14990, Bacillus subtilis ATCC 6633, Bacillus cereus ATCC 14579, Pseudomonas aeruginosa ATCC 9027 şi Escherichia coli ATCC 11775, comparativ cu ligandul necomplexat.

The present paper describes the new ligand, N'-[4-(4-chloro-phenyl-sulfonyl) benzoyl]-2-oxoimidazolidine-1-carbohydrazide ***(L)*** *which has been prepared by the reaction of 4-(4-chlorophenylsulfonyl)benzoic acid hydrazide and 2-oxoimidazolidine-1-carbonyl chloride. Also, the complexes* $[Cu(L\text{-}H)_2]$, $[Co(L\text{-}H)_2(H_2O)_2]$ *and* $[Ni(L\text{-}H)_2(H_2O)_2]$ *have been prepared and characterized by elemental analyses, magnetic susceptibility, electronic, ESR and IR spectral data.*

These complexes were tested for their antibacterial activity (against Staphylococcus epidermidis ATCC 14990, Bacillus subtilis ATCC 6633, Bacillus cereus ATCC 14579, Pseudomonas aeruginosa ATCC 9027 and Escherichia coli ATCC 11775 strains) comparatively with that of free ligand.

Keywords: diacylhydrazines, Cu(II), Co(II) and Ni(II) complexes, spectral data, antibacterial activity

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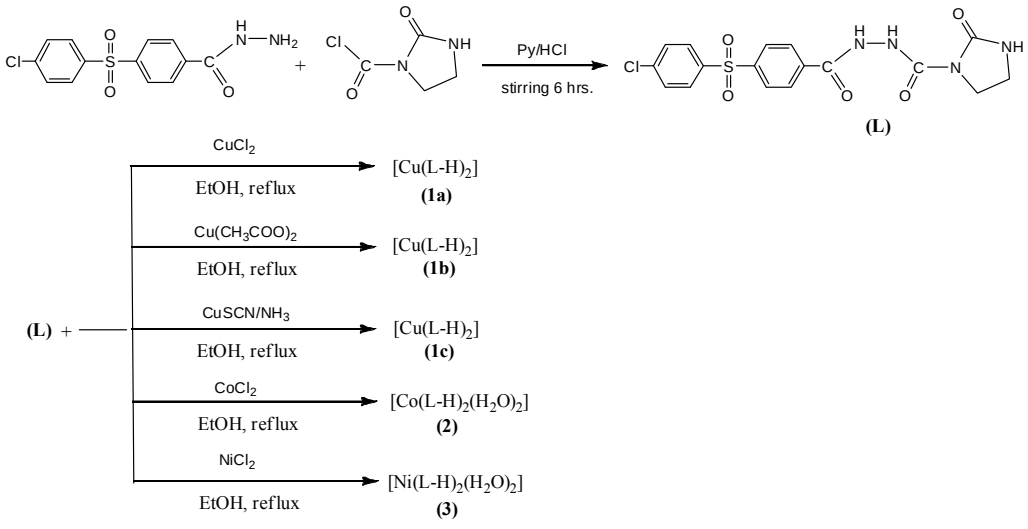
1. Introduction

Aroylhydrazine ligands have recently gained the increasing concern due to their quite interesting chemical properties [1,2]. Most of the studies are focused on unsymmetrical aroylhydrazines, used as ligands for coordination to metal ions, due to the tautomeric effect of the enol form and keto form, several electron-rich donor centers, variable bonding modes, structural diversity and promising biological implications [3-6]. As regards biological implications, complexes with these ligands have been intensively investigated for antitumoral, antimicrobial and anti-inflammatory activities. The inhibitory action is attributed due to their chelating properties [7,8]. In view of our interest in metal complexes with a variety of multidentate acylhydrazines [9], we report here in the synthesis and characterization of N'-[4-(4-chloro-phenylsulfonyl)benzoyl]-2-oxoimidazolidine-1-carbohydrazide **(L)**, which represents a prototype of new of asymmetric ligands, which combine two donor functionalities in one molecule (aroylhydrazine N-acylated and ethylene urea).

In order to further investigate the coordination modes of **(L)** with transition metals and to study the chemistry of its complexes, we synthesized and characterized and their Cu(II), Co(II) and Ni(II) complexes (Scheme 1). These studies have been mainly directed towards identifying the groups directly attached to the metal site and establishing the structure of the coordination compounds thus formed. More, these complexes were also tested for their antibacterial activity comparatively with that of free ligand.



Scheme 1. Route of synthesis for **(L)** and the corresponding Cu(II), Co(II) and Ni(II) complexes

2. Experimental

2.1. Physical measurements

The reagents used in this work were commercial products (Merck or Chimopar Bucharest). Chemical elemental analyses were done with Carlo-Erba La-118 micro dosimeter (for C, H and N) and an AAS-1N Carl-Zeiss-Jena spectrometer (for metallic ions). Melting points were determined with Boetius apparatus and are uncorrected.

The NMR spectra were registered on a Varian Gemini 300 BB apparatus working at 300 MHz for a ^{1}H and 75 MHz for ^{13}C using TMS as internal standard. The mass spectra were registered with a triple quadrupole mass spectrometer Varian 1200 L/MS/MS coupled with a high performance liquid chromatograph with Varian ProStar 240 pump and a Varian ProStar 410 automatic injector. For the ionisation of the sample was used an electro-spray interface (ESI) or an atmospheric pressure chemical ionization (APCI). The solvent used was DMSO.

Molar conductivities of the complexes were measured in DMSO (3.10^{-3}M), at room temperature using OK-102/1 Radelkis conductivity instrument. Electronic spectra were recorded using a Jasco V-550 spectrophotometer, in diffuse reflectance mode, using MgO dilution matrices. IR spectra (KBr pellets) were recorded in the 4000-400 cm-1 region with BioRad FTS 135, spectrophotometer. ESR spectra were registered on an ART-6-IFIN type spectrophotometer, equipped with a field modulation unit at 100 kHz. The measurements were done in the X band, on micro-crystalline powder at room temperature using DPPH as standard.

2.2. Synthesis of ligand (L)

4-(4-chloro-phenylsulfonyl)benzohydrazida (20 mmol) was dissolved in 50 ml pyridine. The solution was mixed with 2-oxo-1-imidazolidine-carbonyl chloride (20 mmol), in the presence of few drops of concentrated HCl and stirring constant for 6 hours. The resulting mixture was cooled to 5^{0}C for ten hours and solid obtained was filtered, washed with water to neutral pH and recrystallized from chloroform:petroleum ether 1:1 (v:v).

Yield: 80%; m.p.264-267 ºC; Anal. calcd. for $C_{17}H_{15}ClN_4O_5S$ (422.84 g/mol): C, 48.14, H, 3.50, N, 13.18%. Found: C, 48.29, H, 3.58, N, 13.25%;

IR (KBr, cm^{-1}): 3410m (NH-imidazolidinone), 3262m, 3186m (N^2H, N^1H-hydrazine), 3060m (C-H stretching of aromatic ring), 2929w (CH_2 ^{as}), 2868s (CH ^{sym}), 1710i (C=O cyclic urea), 1692i, 1652m (C=O of diacylated hydrazine), 1326ws, 1157s ($SO_2^{sym, as}$), 764ws (Ar-Cl)

UV-Vis (MgO) (λ_{max} / nm): 248, 343

^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 10.74 (s, 1H, N^1H), 9.75 (s, 1H, N^2H), 6.92 (s, 1H, NH-imidazolidinone), 8.13 (d, 2H, aromatic, J = 8.6 Hz), 8.09 (d, 2H, aromatic, J = 8.6 Hz), 8.02 (d, 2H, aromatic, J = 8.7 Hz), 7.72 (d, 2H, aromatic, J = 8.7 Hz), 3.79 (t, 2H, imidazolidinone, J = 6.4 Hz), 3.42 (t, 2H, imidazolidinone, J = 6.4 Hz)

^{13}C-NMR (75 MHz, $CDCl_3$, δ / ppm): 165.80 (C=O near aryl), 158.90 (C=O heterocycle), 153.83 (C=O near imidazolidinone), 144.36, 140.35, 138.21, 130.10 (aromatic quaternary-C), 131.13, 130.62, 130.0, 128.85 (CH aryl), 42.81, 37.57 (CH_2 imidazolidinone)
ESI-MS: *m/z* (%) $[M+H]^+$ 422 (100, isotopic contribution ^{35}Cl), $[M+H]^+$ 444 (33, isotopic contribution ^{37}Cl)

2.3. Synthesis of the complexes

(1a), (1b), (2) and (3) complexes

Complexes were prepared with $CuCl_2$, $Cu(CH_3COO)_2 \cdot H_2O$, CuSCN, $CoCl_2 \cdot 6H_2O$ and $NiCl_2 \cdot 6H_2O$ salts. The ethanolic solution of metallic ion salt (1 mmol/5 mL ethanol) was mixed with stirring with a hot clear ethanolic solution of the ligand **(L)** (2 mmol/20 mL ethanol). After refluxing the solution for 2 hrs. Na_2CO_3 was added until the pH=8-8.5 and after cooling the contents, colored complex separated out in each case. It was filtered, washed successively with water, hot ethanol, cold ethanol and diethylether and finally dried under vacuum.

(1c) complex

A blue solution of CuSCN (1 mmol CuSCN in 5ml NH_3) was mixed by stirring with a hot clear ethanolic solution of the ligand **(L)** (2 mmol/20 mL ethanol). The obtained mixture was refluxed 2,5-3 hrs. and the obtained precipitate was filtered, washed successively with water, hot ethanol, cold ethanol and diethylether and finally dried under vacuum.

2.4. Antibacterial activity

The synthesized compounds were tested for their in vitro antibacterial activity against the Gram-positive and the Gram-negative bacteria: *Staphylococcus epidermidis (Se)* ATCC 14990; *Bacillus subtilis (Bs)* ATCC 6633; *Bacillus cereus (Bc)* ATCC 14579; *Pseudomonas aeruginosa (Pa)* ATCC 9027*; Escherichia coli (Ec)* ATCC 11775, comparative with free-ligands.

Qualitative determination of antimicrobial activity was done using the disk diffusion method [10]. Suspensions in sterile peptone water from 24 h cultures of microorganisms were adjusted to 0.5 McFarland. Muller-Hinton Petri dishes of 90 mm were inoculated using these suspensions. Paper disks (6 mm in diameter) containing 10μL of the substance to be tested (at a concentration of 2048 μg/mL in DMSO) were placed in a circular pattern in each inoculated plate. Incubation of the plates was done at 37°C for 18-24 hours. Reading of the results was done by measuring the diameters of the inhibition zones generated by the tested substances using a ruler.

Determination of MIC was done using the serial dilutions in liquid broth method [11,12]. The materials used were 96-well plates, suspensions of microorganism (0.5 McFarland), Muller-Hinton broth (Merck) and solutions of the substances to be tested (2048 μg/mL in DMSO). The following concentrations of the substances to be tested were obtained in the 96-well plates: 1024; 512; 256;

128; 64; 32; 16; 8; 4; 2 μg/mL. After incubation at 37°C for 18-24 hours, the MIC for each tested substance was determined by macroscopic observation of microbial growth. It corresponds to the well with the lowest concentration of the tested substance where microbial growth was clearly inhibited. Chloramphenicol was used as control drug.

3. Results and discussions

All synthesized complex compounds have melting points higher than 300°C. The elemental analyses data (which confirm M:L= 1:2 molar ratio) along with some physical properties of the complexes are reported in Table 1. All the solid complexes are stable in air, soluble in DMF and DMSO, but insoluble in other organic solvents. The molar conductivity values ($\Omega^{-1}cm^2mol^{-1}$) in DMSO (10^{-3} M) are too low to account for any dissociation, therefore the complexes are considered to be no electrolytes [13,14].

Table 1

Elemental analysis data and some physical characteristics of the complexes (1)-(3)

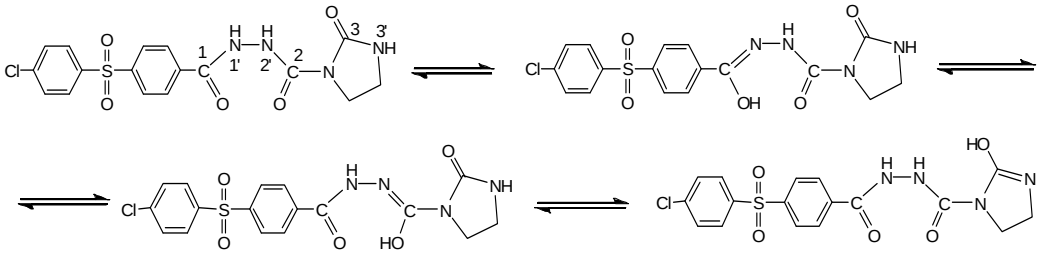
Comp	Molecular formula (M, g/mol)	Color	η (%)	Elemental analyses calc. (found) (%)				Λ
				C	H	N	Cu	
(1a) (1b) (1c)	$C_{34}H_{28}Cl_2CuN_8O_8S_2$ (907.22)	kaki	75	45.01 (45.10)	3.11 (3.16)	12.35 (12.41)	7.00 (6.93)	3.90 4.80 5.85
(2)	$C_{34}H_{32}Cl_2CoN_8O_{12}S_2$ (938.63)	dark-brown	77	43.51 (43.58)	3.44 (3.51)	11.94 (12.01)	6.28 (6.19)	3.60
(3)	$C_{34}H_{32}Cl_2NiN_8O_{12}S_2$ (938.39)	yellow-green	69	43.52 (43.61)	3.44 (3.52)	11.94 (12.04)	6.25 (6.17)	6.80

3.1. Infrared spectra

The IR spectra of all the complexes were recorded and compared with that of the ligand to study the structural changes in the ligand upon complexation. The IR spectra for the ligand shows three bands at 1710, 1692 and 1652 cm^{-1} due to the three different carbonyl group and three bands at 3410, 3262, 3186 cm^{-1} which are assigned to the different NH groups [15]. We expect to show any changes after complexation in these regions, because the ligand contains many potential donor sites visible by keto-enol tautomerism (Scheme 2): (i) the enolic oxygen; (ii) the hydrazinic nitrogen; (iii) the cyclic nitrogen; (iv) the carbonyl oxygen; (v) the azomethine nitrogen which appears after tautomerisation.

The C=O (cyclic) band arising from imidazolidine moiety appears at 1692 cm^{-1} and does not show any appreciable change in their position in the complexes (Table 2). Instead, the C^2=O peak (1652 cm^{-1}) disappears and the band corresponding to C^1=O group (1710 cm^{-1}) is found to shift to lower wave numbers and overlaps the C=O (cyclic band). The three ν(NH) bands in the free ligand, became only two bands on complexation, indicating conversion of the $C^2ON^{2'}H$

group to $C^{2}(OH)=N^{2'}$ which is strongly involved in the structural chemistry of the complexes (in all the complexes IR spectra appear new bands in the 1569-1585 cm^{-1} range assignable to C=N group).



Scheme 2. Keto-enol forms of the ligand **(L)**

The coordination of the carbonyl ($C^{1}=O$) via enolisation followed by deprotonation is unfavorable due to the presence of the bulky phenyl ring attached to it and therefore, the enol form of the ligand are obtained by deprotonation of $N^{2'}H$. More appearance of new bands characteristic of ν(C-O) in the 1453-1491 cm^{-1} range, further supports the enolic oxygen coordination [16]. So is concluded that the ligand acts as a monobasic bidentate manner in all the complexes. The type of bonding sites are the $N^{1'}H$ nitrogen and $C^{2}=O$ oxygen atom in enol form.

The IR spectra of the complexes **(2)** and **(3)** exhibit a broad band centered at 3440 cm^{-1} due to the symmetric and asymmetric stretching modes of coordinated H_2O. The H-O-H bending modes occur in the 1550–1610 cm^{-1} range. These H-O-H bending and stretching bands obscure the C=N stretching and bending vibrations which occur in the same regions. Weak bands in the 900–940, 750–760 and 640–660 cm^{-1} ranges represent the wagging, twisting and rocking modes of coordinated water [17]. The nature of the metal-ligand bonding is confirmed by the newly formed bands in the region 498-527 cm^{-1} and 415-417 cm^{-1} in the spectra of complexes, which is tentatively assigned to M-O and M-N vibrations [18].

3.2. Electronic spectra and magnetic studies

The electronic spectra of Cu(II) complexes **(1)** (Table 3) displays a broad band at 11,254-12,553 cm^{-1} and a well-define shoulder in region 21,000-23,645 cm^{-1}, attributable to $^{2}A_{1g}\leftarrow{}^{2}B_{1g}$ and $^{2}B_{2g}\leftarrow{}^{2}B_{1g}$ transitions which strongly favor tetrahedral geometry around metal ion [19,20]. The broadness of the band can be taken as indication of distortion from perfect symmetry. This is further supported by the magnetic susceptibility values (1.87-1.95 BM) [21,22].

The UV-Visible spectra of Co(II) complex **(2)** showed two bands observed at 14,477 and 18,561 cm^{-1} which may be assigned to $^{4}A_{2g}\leftarrow{}^{4}T_{1g}(F)$ and $^{4}T_{1g}(P)\leftarrow{}^{4}T_{1g}(F)$ transitions corresponding to high-spin cobalt(II) octahedral complexes [23,24]. The measured value of the magnetic moment, μ_{eff}, was 5.08 BM, which lie in the range (4.80–5.20 BM) of the octahedral compounds [25].

Table 2

Important infrared spectral bands (cm^{-1}) and their assignments

Comp	υ OH	$\upsilon_{NH-cycl}$	υ $N^{2'}H$	υ $N^{1'}H$	υ_{CH} (aril)	υ C=O	υ C-O	υ C=N	υ SO_2	υ C-Cl	υ_{M-O}, υ_{M-N}
L	-	3410	3262	3186	3060	1710 1692 1652	-	-	1326 1157	764	-
(1a)	-	3347	- -	3154	3089	1690	1491	1569	1320 1154	768	527 417
(1b)	-	3350	-	3176	3093	1680	1479	1585	1321 1159	762	515 417
(1c)	-	3435		3190	3091	1681	1480	1572	1322 1159	764	520 412
(2)	3440	3331	-	3175	3089	1684	1483	1575	1320 1157	756	498 415
(3)	3438	3363	-	3145	3046	1681	1452	1579	1323 1158	760	499 417

The electronic spectra of Ni (II) complex **(3)** display three absorption bands at 9845, 15869 and 20242 cm^{-1}, which may be assigned to three spin-allowed transitions: $^3T_{2g}(F) \leftarrow {}^3A_{2g}(F)$ (ν_1), $^3T_{1g}(F) \leftarrow {}^3A_{2g}(F)$($\nu_2$), and $^3T_{1g}(P) \leftarrow {}^3A_{2g}(F)$ (ν_3), respectively and indicating an octahedral nickel(II) complex [26,27]. The position of bands indicates that the complex has six coordinated octahedral geometry [18]. The υ_2/υ_1 ratio for the complex (1.61) and the magnetic moment (3.30 BM) shows two unpaired electrons per Ni(II) ion and suggesting a distorted octahedral geometry for the nickel(II) complex [28-30].

Table 3

Electronic spectral bands (cm^{-1}) and their assignments

Comp.	Band (cm^{-1})	Assignment	Geometry	μ_{ef} (BM)
(1a) **(1b)** **(1c)**	12,553; 21,000 12,200; 23,645 11,254; 22,456	$d_{xy} \rightarrow d_{xz}, d_{yz}$, charge transfer $d_{xy} \rightarrow d_{xz}, d_{yz}$, charge transfer $d_{xy} \rightarrow d_{xz}, d_{yz}$, charge transfer	pseudo-tetrahedral	1.95 1.87 1.90
(2)	14,477 18,561	$^4A_{2g} \leftarrow {}^4T_{1g}(F)$ $^4T_{1g}(P) \leftarrow {}^4T_{1g}(F)$	distorted octahedral (D_{4h})	5.08
(3)	9,845 15,869 20,242	$^3T_{2g}(F) \leftarrow {}^3A_{2g}(F)$ (ν_1) $^3T_{1g}(F) \leftarrow {}^3A_{2g}(F)$($\nu_2$) $^3T_{1g}(P) \leftarrow {}^3A_{2g}(F)$	distorted octahedral (D_{4h})	3.30

3.4. Electronic paramagnetic spectra

The paramagnetic spectra in X-band of the copper complexes were recorded on crystalline powder, at room temperature and exhibits an isotropic signal, with g_{iso}=2.087 **(1a)**; 2.105 **(1b)** and 2.107 **(1c)**. The shape of the spectra are consistent with the tetrahedral geometry around the Cu(II) environment in the

complexes **(1)** [31,32]. Correlating the experimental data we can propose the general structures for the prepared metal complexes (Fig. 1).

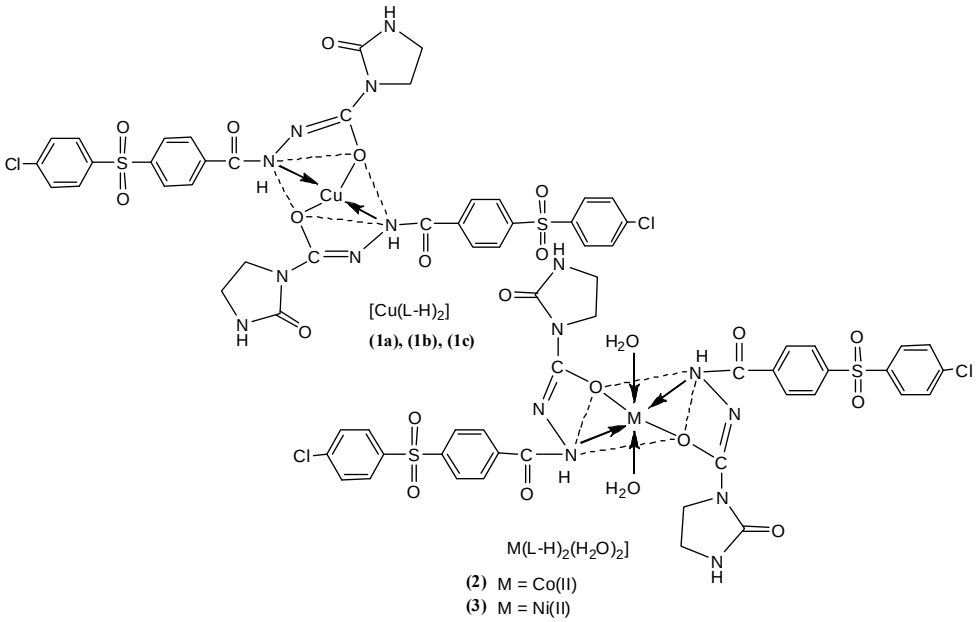


Fig. 1. Proposed structures of the complexes **(1-3)**

4. Antibacterial activity

The results of antibacterial screening of **(L)** and its complexes against *Staphylococcus epidermidis* ATCC 14990 (Se)*, Bacillus subtilis* ATCC 6633 (Bs)*, Bacillus cereus ATCC* 14579 (Bc)*, Pseudomonas aeruginosa* ATCC 9027 (Pa) *and Escherichia coli* ATCC 11775 (Ec) strains are shown in Table 4.

Table 4

Antibacterial activities of compounds (1a,b,c), (2) and (3) as MIC values (µg/mL)

Compound	Gram-positive bacteria			Gram-negative bacteria	
	Se	***Bs***	***Bc***	***Pa***	***Ec***
(L)	1024	512	1024	1024	1024
(1a)	512	512	512	512	512
(1b)	512	512	512	512	512
(1c)	512	512	512	512	512
(2)	128	128	256	256	128
(3)	128	64	1024	1024	512
Chloramphenicol	64	64	128	64	128

It may be observed that the ligand are inactive against all of the nine bacteria, but their potency was enhanced upon coordination with the metal ions. The Co(II) and Ni(II) complexes of **(L)** showed moderate activities against tested bacteria, comparative with Cu(II) complexes probably due to the less bulkiness of

the metal ion. Moreover, coordination reduces the polarity [33,34] of the metal ion mainly because of the partial sharing of its positive charge with the donor groups within the chelate ring system, which is mainly formed during chelation. This process, in turn, increases the lipophilic nature of the central metal atom, which favors its permeation more efficiently through the lipoid layer of the microorganism [35,36].

5. Conclusions

Six metal complexes with the new N'-[4-(4-chlorophenylsulfonyl)benzoyl]-2-oxoimidazolidine-1-carbohydrazide **(L)** based ligand were prepared and characterized by elemental analysis, magnetic susceptibility, electronic, ESR and IR spectral data. The similarities observed in the IR spectra are indicative of a similar behavior of the ligand in all the complexes, thus suggesting a four-coordinated copper (pseudo-tetrahedral) and six-coordinated cobalt and nickel (distorted octahedral) derivatives. The ligand acts in a monobasic bidentate manner in all the complexes by the carbonyl/enolic oxygen (C^2=O) and the hydrazinic N^1H nitrogen. The results of antibacterial screening showed that the ligand is inactive against all of the nine tested bacteria, but his potency was enhanced upon coordination with the metal ions.

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