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Spectroscopic and biological approach of Ni(II), Cu(II) and Co(II) complexes of 4-methoxy/ethoxybenzaldehyde thiosemicarbazone glyoxime

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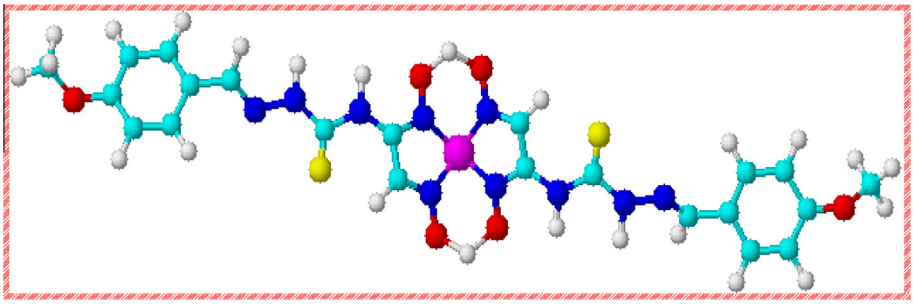
HIGHLIGHTS

- Preparation of novel ligands and complexes.
- Characterization of ligands and complexes.
- ^{1}H NMR, ^{13}C NMR, MS, IR and, UV–VIS. Spectroscopy.
- pH effect.
- Antibacterial activity.

GRAPHICAL ABSTRACT

In this work, novel *vic*-dioxime ligands (L^1H_2 and L^2H_2) containing 4-methoxy or 4-ethoxy thiosemicarbazone moieties and their complexes with Ni(II), Cu(II) and Co(II) ions were synthesized and characterized using ^{1}H NMR, ^{13}C NMR, HMQC, MS, infrared and, UV–VIS. spectroscopy, elemental analysis, and magnetic susceptibility measurements as well as their antimicrobial properties were evaluated.
Among the test compounds attempted, L^1H_2, $[Ni(L^1H)_2]$, $[Cu(L^1H)_2]$, L^2H_2, $[Ni(L^2H)_2]$ and $[Cu(L^1H)_2]$ showed activities against certain Gram-positive bacteria and certain yeasts. Some of them were comparatively higher or equipotent to the antibiotic and antifungal agents in the comparison tests. These compounds appeared to have moderate antibacterial and antifungal activity.



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ABSTRACT

Two novel vicinal dioxime ligands containing (4-methoxybenzaldehyde thiosemicarbazone glyoxime (L^1H_2) or 4-ethoxybenzaldehyde thiosemicarbazone glyoxime (L^2H_2)) thiosemicarbazone units were synthesized and characterized using ^{1}H NMR, ^{13}C NMR, HMQC, MS, infrared and, UV–VIS. spectroscopy, elemental analysis, and magnetic susceptibility measurements. Mononuclear nickel(II), copper(II) and cobalt(II) complexes with a metal:ligand ratio of 1:2 for L^1H_2 and L^2H_2 were also synthesized. The effect of pH and solvent on the absorption spectra of both ligands and complexes was determined. IR spectra show that the ligands act in a bidentate manner and coordinates N_4 donor groups of the ligands to Ni^{II}, Cu^{II} and Co^{II} ions. The detection of H-bonding (O—H···O) in the $[M(LH)_2]$ metal complexes by IR spectra supported the square-planar MN_4 coordination of mononuclear complexes. The antimicrobial activities of compounds L^1H_2, L^2H_2, and their Ni(II), Cu(II) and Co(II) complexes were evaluated using the disc diffusion method against 12 bacteria and 4 yeasts. The minimal inhibitory concentrations (MICs) against 7 bacteria and 3 yeasts were also determined. Among the test compounds attempted, L^1H_2, $[Ni(L^1H)_2]$, $[Cu(L^1H)_2]$, L^2H_2, $[Ni(L^2H)_2]$ and $[Cu(L^2H)_2]$ showed some activities against certain Gram-positive bacteria and some of the yeasts tested.

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Introduction

Nowadays, *vic*-dioximes are appreciated as coordination compounds in lots of usage areas such as analytical, biologically, pigment and medicinal chemistry. Many researchers have studied *vic*-dioximes which have important role of the complexes especially 1,2-dioximes in coordination chemistry [1–3]. Their complexes have been the source, through the decades, of a never-ending series of interesting reports. Owing to their importance as stable MN_4 core-containing coordination compounds, *vic*-dioxime complexes have been much investigated [4].

The exceptional stability and unique electronic properties of these complexes can be attributed to their planar structure, stabilized by hydrogen bonding [5–8].

Metal complexes of Schiff bases have been extensively investigated because of their industrial, antifungal, antibacterial, anticancer and herbicidal applications [9]. It is well known that coordination of metals to Schiff base ligands may enhance their biological activities [10,11]. Many new Schiff bases and their metal complexes reported in the literature have been studied electrochemically, using various electrodes and solvents, with a view to understand the mechanism of their biological activities [12,13].

Thiosemicarbazones, their derivatives and their transition metal complexes have aroused considerable interest in the areas of chemistry and biology. These compounds present a wide variety of biological activity such as antitumoral, fungicidal, bactericidal or antiviral. They have been used for metals analyses, for device applications relative to telecommunications, optical computing, storage and information processing [14].

Although many studies of thiosemicarbazones and their mono- and dioximes have been carried out, no information related to the derivatives of *vic*-dioximes with thiosemicarbazone side groups appears in the literature. In this work, we discuss the synthesis and characterization of *vic*-dioximes containing thiosemicarbazone units (L^1H_2 and L^2H_2) as well as novel mononuclear Ni(II), Cu(II), and Co(II) complexes of these materials and their antimicrobial properties were evaluated. The effects of pH and solvent on the spectroscopic properties of the ligands and complexes are also discussed in detail.

Experimental

Materials and measurements

All reagents used were purchased from Merck. ^{1}H NMR–13C NMR spectra (Bruker 400 MHz), I.R spectra (Varian 900), melting points (Buchi SPM-20) and pH measurements (Orion Expandable Ion Analyzer EA 940) were used to elucidate the structures of the products. The magnetic moments of the complexes were measured by the Gouy method with a Newport type D-104 instrument magnet power supply. Mass spectrometry (MS) spectra were recorded on a Bruker LC/MS/MS-8030 Triple Quadrupole Mass Spectrometer. 4-methoxybenzaldehyde thiosemicarba-zone (Scheme 1, **1a**) and 4-ethoxybenzaldehyde thiosemicarbazone (Scheme 1, 1b) [15] were prepared by literature methods, as was *anti*-chloroglyoxime (Scheme 1, 1c) [16].

Synthesis

Synthesis of (L^1H_2) and (L^2H_2)

A solution of 4-methoxybenzaldehyde thiosemicarbazone (**1a**) (1 mmol) or a solution of 4-ethoxybenzaldehyde thiosemicarbazone (**1b**) in absolute ethanol 30 mL was added dropwise to a solution of *anti*-chloroglyoxime (**1c**) (1 mmol) in absolute ethanol 10 mL for a 30 min period. The reaction mixture was stirred overnight at room temperature. After cooling to 0 °C the pH of the mixture was raised to 5.0–5.5 with treatment with $NaHCO_3$ dissolved in 5 mL distilled water, and stirring was continued for one hour. The solution was poured into 100 mL cold water with stirring. After the end of the period, yellow precipitated solid was filtered, washed thoroughly with distilled water and dried. The chemical reaction and molecular structure are shown in Scheme 1.

Synthesis of the Ni(II), Cu(II) and Co(II) Complexes of Ligands

A solution of a metal salt (1 mmol of $NiCl_2{\cdot}6H_2O$, $CoCl_2{\cdot}6H_2O$ and $CuCl_2{\cdot}2H_2O$) in 20 mL of water were added to 2 mmol of the ligand solution (0.590 g L^1H_2 and 0.618 g L^2H_2 in 30 mL of ethanol) with stirring. An initial sharp decrease in the pH of the solution from 5.5 to about 3–3.5 is observed. After raising the pH to 5.0–5.5 using 1% aqueous NaOH solution, the reaction mixture was kept in a hot water bath (60 °C) for 2 h to complete the precipitation. Then the precipitated complex compounds were filtered, washed with water and ethanol, and dried at room temperature in a vacuum oven. The structure of the prepared complexes are shown in Figs. 1a and b.

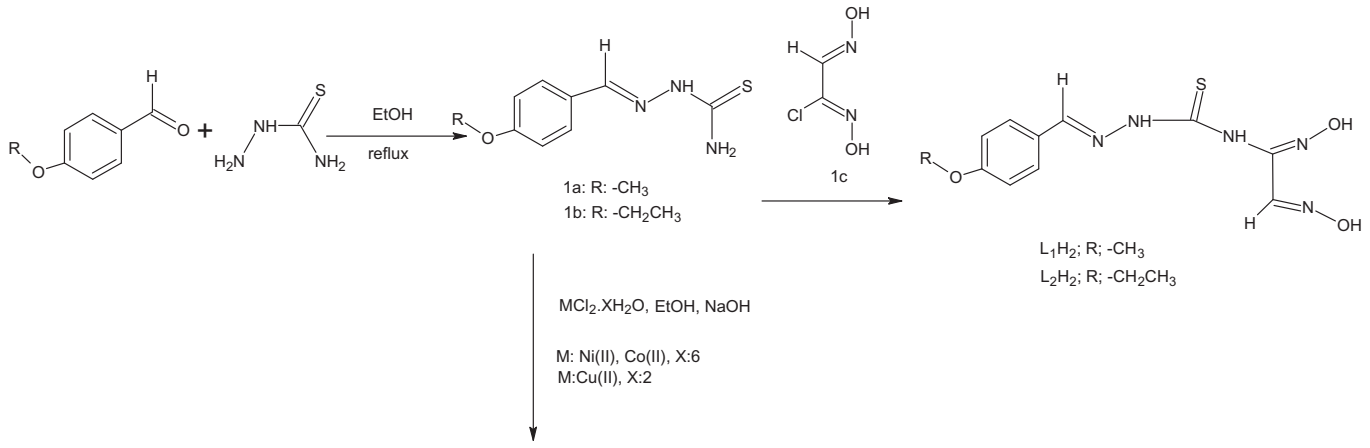
Antimicrobial assays

Twelve bacterial strains and four yeast strain were obtained from the American Type Culture Collection (ATCC, Rockville, MD, USA). Other strains were obtained from Faculty of Medicine, Adnan Menderes University. The Gram-negative (G-) were: *Escherichia coli* ATCC 25922, *Salmonella typhimurium* ATCC 14028, *Proteus vulgaris* ATCC 33420., *Serratia marcescens* ATCC 13880, and the Gram-positive (G+) were: *Micrococcus luteus* ATCC 9341, *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228, *Bacilllus cereus* ATCC 11778, *Bacilllus subtilis* ATCC 6633, *Bacillus thuringiensis*, *Enterococcus faecalis* ATCC 29212, and *Listeria monocytogenes* ATCC 19112. The following four yeast strains, i.e. *Candida utilis* ATCC 9950, *C. albicans* ATCC 10231, *C. tropicalis* and *Saccharomyces cerevisiae* ATCC 9763, were also tested using disc diffusion method [17,18] and the minimum inhibitory concentration (MIC) was determined by broth dilution method [19].

Disc diffusion method

Screening for antibacterial and antifungal activities were carried out using sterile antibiotic discs (6 mm), following the standard procedure of Antimicrobial Disc Susceptibility Tests outlined by the National Committee for Clinical Laboratory Standards-NCCLS [17,18]. Fresh stock solutions (1×10^{-4} M) of the ligands were prepared in DMSO according to the needed concentrations for the experiments. The inoculum suspensions of the tested bacteria and yeasts were prepared from the broth cultures (18–24 h) and the turbidity equivalent adjusted to 0.5 McFarland standard tube to give a concentration of 1×10^8 bacterial cells and 1×10^6 yeast cells/mL. To test the antimicrobial activity of each aromatic hydrazone derivative bearing vic-dioxime group or its complex, a Mueller Hinton agar plate was inoculated with 0.1 mL broth culture of bacteria or yeast. Then a hole of 6 mm in diameter and depth was made on top with a sterile stick and filled with 50 μL of the hydrazone derivative or its complex containing vic-dioxime group.

Plates inoculated with *E. coli* ATCC 25922, *S. typhimurium* ATCC 14028, *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *E. faecalis* ATCC 29212, *L. monocytogenes* ATCC 19112, *P. vulgaris* ATCC 33420 and *S. marcescens* ATCC 13880 were incubated at 37 °C for 24 h and those inoculated with *M. luteus* ATCC 9341, *B. cereus* ATCC 11778, *B. subtilis* ATCC 6633, *B. thuringiensis*, *S. cerevisiae* ATCC 9763, *C. albicans* ATCC 10231, *C. utilis* ATCC 9950 and *C. tropicalis* were incubated at 30 °C for 24 h. The diameter of the inhibition zone was



Scheme 1. Synthesis of the ligands (L^1H_2 and L^2H_2).

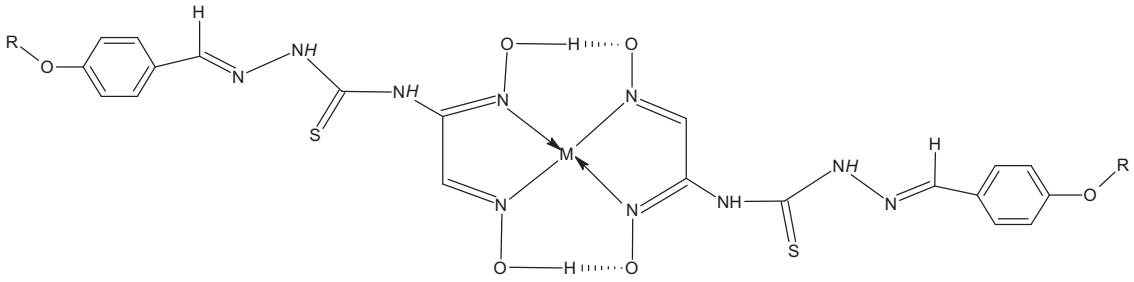


Fig. 1a. *trans*-The suggested structure of metal complexes.

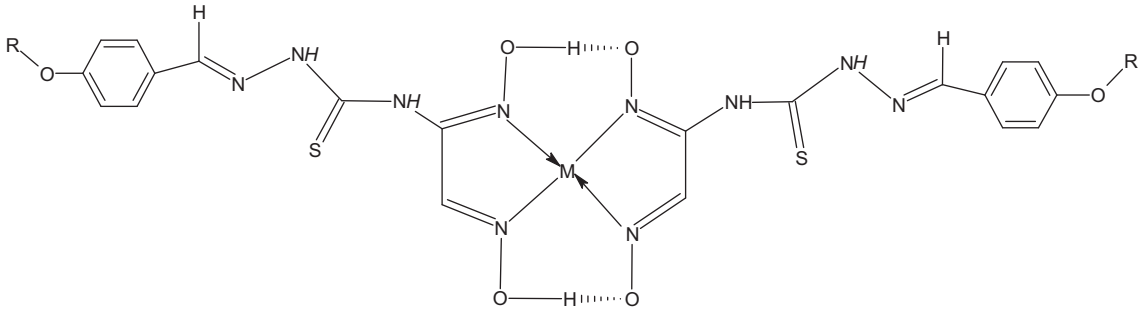


Fig. 1b. *cis*-The suggested structure of metal complexes.

then measured. Discs of Chloramphenicol (C30, Oxoid), Gentamycin (GN10 Oxoid), Tetracycline (TE30), Erytromycine (E15), Ampicillin (AMP10) and Nystatine (NS100) were used as positive controls. The inhibition zones were compared with those of the reference discs.

Dilution method

Screening for antibacterial and antifungal activities were carried out by preparing a microdilution broth, following the procedure outlined in Manual of Clinical Microbiology [19]. All the bacteria were inoculated in the nutrient broth and incubated at 30–37 °C for 24 h while the yeasts were inoculated in malt extract broth and incubated at 30 °C for 48 h. The compounds were dissolved in DMSO (2 mg mL^{-1}) and then diluted in Mueller Hinton broth. Twofold serial dilution of the compounds were employed to determine the MIC ranging from 256 to 0.125 μg mL^{-1}. Cultures were grown at 30–37 °C (18–20 h) and the final inoculum was approximately 10^6 cfu mL^{-1}. Test cultures were incubated at 37 °C (24 h). The lowest concentration of antimicrobial agent that resulted in complete inhibition of the microorganisms was represented as MIC (μg mL^{-1}). As positive controls, streptomycin (I.E. Ulagay) for bacteria and nystatin (NS100, Oxoid) for yeast were used in the dilution method. In each case, the test was performed in triplicate and the results were expressed as means.

Results and discussion

4-Methoxybenzaldehyde thiosemicarbazone (Scheme 1, **1a**) and 4-ethoxybenzaldehyde thiosemicarbazone (Scheme 1, **1b**) were obtained from the condensation of 4-methoxy benzaldehyde

or 4-ethoxybenzaldehyde with thiosemicarbazide in the presence of alcohol [15]. Subsequently, (1*Z*, 2*E*)-*N*′-hydroxy-2-(hydroxyimino)-*N*-{[(2*E*)-2-(4-methoxybenzylidene) hydrazino]carbonothioyl} ethanimidamide (**2**, L^1H_2) and (1*Z*, 2*E*)-*N*-{[(2*E*)-2-(4-ethoxybenzyl idene)hydrazino]carbonothioyl}-*N*′-hydroxy-2-(hydroxyimino)ethanimidamide (**3**, L^2H_2) were prepared from **1a** and **1b** with *anti*-chloroglyoxime (**1c**) [16] in presence of alcohol.

The mononuclear Ni(II), Cu(II), and Co(II) complexes were prepared from the *vic*-dioxime/thiosemicarbazone derivatives and a stoichiometric amount of $NiCl_2{\cdot}6H_2O$, $CuCl_2{\cdot}2H_2O$ and $CoCl_2{\cdot}6H_2O$ in ethanol (Figs. 1a and b). The metal complexes were characterized using, mass spectrometry, FT-IR, and UV–VIS., spectroscopy, elemental analysis, and magnetic susceptibility measurements. Some physical, elemental, analytical, and magnetic susceptibility data for the ligand and complexes are given in Table 1. FT-IR data of the ligands and their complexes are given in Table 2. ^{1}H NMR and ^{13}C NMR data of the ligands are given in Table 3. Electronic spectral data of the ligands and their metal complexes are given in Table 4.

Antimicrobial activities of the ligands and their metal complexes are given Tables 5 and 6.

IR spectra, mass and magnetic susceptibility

The IR spectra of compounds L^1H_2 and L^2H_2 exhibited —NH (3455 cm^{-1} for L^1H_2 and 3458 cm^{-1} for L^2H_2), —OH (3288 cm^{-1} for L^1H_2 and 3280 cm^{-1} for L^2H_2), —C=N_{oxime} (1652 cm^{-1} for L^1H_2 and 1654 cm^{-1} for L^2H_2), and —NO (930 cm^{-1} for L^1H_2 and 921 cm^{-1} for L^2H_2) stretching vibrations [20]. The C=N and OH stretching vibrations appear similar to other *vic*-dioxime derivatives [16,20–22].

The possibility of thione-thiol tautomerism (Fig. 2, H—N—C=S, C=N—SH) in these ligands was ruled out by the absence of characteristics thiol bands near 2700–2500 cm^{-1} in the infrared spectra [23]. The presence of strong *ν*(C=S) absorption bands near 835 cm^{-1} in the IR spectra of the ligands also suggests that they are in the thione tautomeric form in the solid state. FAB mass spectral analysis indicated molecular ion m/z ratios of 295 for L^1H_2 and 309 for L^2H_2, in agreement with the proposed structures (Fig. 4).

The FT-IR spectra of KBr pellets containing the 4-methoxy and 4-ethoxybenzaldehyde thiosemicarbazone glyoxime complexes of the general formula $M(LH)_2$, in which M is Ni(II), Cu(II), or Co(II)·$2H_2O$, exhibited C=N_{oxime} absorption bands at 1648–1637 cm^{-1}.

Table 2
Characteristic IR bands of the ligands and their metal complexes (cm^{-1}, KBr). (1) L^1H_2 (2) $[Ni(L^1H)_2]$ (3) $[Cu(L^1H)_2]$ (4) $[Co(L^1H)_2(H_2O)_2]$ (5) L^2H_2 (6) $[Ni(L^2H)_2]$ (7) $[Cu(L^2H)_2]$ (8) $[Co(L^2H)_2(H_2O)_2]$.

Compound	NH	—OH/ H_2O	C=S (m)	O—H···O	C=N[a] (s)	C=N[b] (s)	N—O (m)
1	3455b	3288b	832	–	1686	1652	930
2	3464b	–	832	1793w	1690	1644	920
3	3452b	–	832	1774w	1692	1647	931
4	3453b	3280b	832	1796w	1689	1648	928
5	3458b	3280b	832	–	1686	1654	921
6	3456b	–	832	1770w	1690	1637	921
7	3458b	–	833	1739w	1684	1641	921
8	3458b	3290b	833	1847w	1690	1643	921

b: Board s: strong, m: medium, w: weak.
[a] *ν*(C=N): Thiosemicarbazone moiety.
[b] *ν*(C=N): Oxime moiety.

(Fig. S_1 for $[Co(L^2H)_2(H_2O)_2]$ complex in Supplementary Materials). These bands suggest that the ligands are N,N′ coordinated with the metal ion in correspondence with the proposed structures in Figs. 1a and b [23–25]. Intramolecular hydrogen bonding was indicated by a peak appearing between 1847 and 1739 cm^{-1} [26].

FAB mass spectral analysis indicated m/z ratios of 646 $[M-1]^+$ for complex $[Ni(L^1H)_2]$, 652 $[M]^+$ for $[Cu(L^1H)_2]$, 684 $[M+1]^+$, 647 $[M-2H_2O]^+$ for $[Co(L^1H)_2(H_2O)_2]$, 674 $[M-1]^+$ for $[Ni(L^2H)_2]$, 679 $[M-1]^+$ for $[Cu(L^2H)_2]$ (Fig. S_2 for $[Cu(L^2H)_2]$ complex in Supplementary Materials), and 710 $[M-1]^+$, 675 $[M-2H_2O]^+$ for $[Co(L^2H)_2(H_2O)_2]$ (Fig. 4).

The MS-determined metal:ligand ratio was 1:2 for Ni(II), Cu(II) and Co(II) complexes. Elemental analysis data display that the desired compounds are synthesized as well.

Based on IR spectral and magnetic susceptibility data, the complexes have a metal:ligand ratio of 1:2 and square planar or octahedral structures (Figs. 1a and b, 3). The magnetic susceptibility measurements of the Ni(II) complexes indicate that these complexes are diamagnetic. Room temperature magnetic moment measurements indicate that the Co(II) complexes ($[Co(L^1H)_2(H_2O)_2]$ and $[Co(L^2H)_2(H_2O)_2$) are paramagnetic with a magnetic susceptibility of 3.70 B.M. for L^1H_2 and 3.73 B.M. for L^2H_2. The magnetic susceptibilities are within the range of high spin octahedral cobalt(II) complexes (the three-spin value is 3.87 B.M.) [24]. For $[Co(L^1H)_2(H_2O)_2]$ and $[Co(L^2H)_2(H_2O)_2]$, coordinated

Table 1
Physical properties and elemental analyses of the ligands and complexes.

Compounds formula	M.p.(d)[b] (°C)	Yield (%)	Color	μ_{eff} (BM)[a]	Calculated (Found)% of C	H	N	S
L^1H_2	199	65	Yellow	–	44.74 (44.92)	4.44 (4.12)	23.71 (23.75)	10.86 (10.38)
$[Ni(L^1H)_2]$	>400	52	Red	Dia.	40.82 (36.87)	3.74 (3.89)	21.64 (21.31)	9.91 (9.62)
$[Cu(L^1H)_2]$	>400	40	Brown	1.72	40.52 (40.69)	3.71 (3.54)	21.48 (21.78)	9.83 (9.54)
$[Co(L^1H)_2(H_2O)_2]$	210	45	Brown	3.70	38.65 (38.43)	4.13 (4.44)	20.49 (20.86)	9.38 (9.75)
L^2H_2	198	70	Yellow	–	46.59 (46.87)	4.89 (4.45)	22.64 (22.79)	10.37 (10.65)
$[Ni(L^2H)_2]$	>400	60	Red	–	42.68 (42.34)	4.18 (4.53)	20.74 (20.31)	9.50 (9.86)
$[Cu(L^2H)_2]$	>400	45	Brown	1.71	42.38 (42.49)	4.15 (4.45)	20.59 (20.12)	9.43 (9.79)
$[Co(L^2H)_2(H_2O)_2]$	220	50	Brown	3.73	40.51 (40.76)	4.53 (4.86)	19.68 (19.32)	9.01 (9.68)

[a] μ_{eff}: Magnetic moment, Dia.: diamagnetic.
[b] d: Decomposition.

Table 3
^{1}H NMR and ^{13}C NMR spectra of the ligands[a,b] in DMSO-d_6 in δ (ppm).

^{1}H NMR spectra of the ligands							
	—OH[c]	NH[c]	Ar—H	CH=NOH	CH=NNH	CH_3	—CH_2
L^1H_2	11.27–10.05 s, 2H	7.99–7.86 s, 2H	7.61 d, 2H 6.93 d, 2H	6.83 s, 1H	7.77 s, 1H	3.31 s, 3H	–
L^2H_2	11.27–10.05 s, 2H	7.98–7.76 s, 2H	7.60 d, 2H 6.90 d, 2H	6.37 s, 1H	7.70 s, 1H	1.30 t, 3H	4.02 q, 2H
^{13}C NMR spectra of the ligands							
	C=S	HNC=NOH	HC=NOH	HC=NNH	Ar—C	—CH_3	—CH_2
L^1H_2	178.35	157.53	139.93	160.72	129.57–114.74	55.89	–
L^2H_2	178.30	157.52	139.93	160.00	128.70–109.99	15.27	63.83

[a] Chemical shifts (δ) are reported in ppm relative to $SiMe_4$ at 30 °C s: singlet, d: doublet.
[b] In DMSO-d_6.
[c] Disappears on D_2O exchange.

Table 4
Electronic spectral data (nm) of the ligands and their complexes.

Compound	MeOH	MeOH + HCl	MeOH + KOH	DMSO
L^1H_2	306*, 291, 222 ($\log\varepsilon$ = 4.86)	306*, 291, 223 ($\log\varepsilon$ = 4.87)	300*, 288, 222 ($\log\varepsilon$ = 4.93)	322, 298 ($\log\varepsilon$ = 4.15)
$[Ni(L^1H)_2]$	605, 432, 361 309, 296*, 223 ($\log\varepsilon$ = 4.96)	603, 433, 360, 309, 296*, 223 ($\log\varepsilon$ = 4.96)	704, 432, 361, 304*, 292, 221 ($\log\varepsilon$ = 4.75)	544, 370 332, 273 ($\log\varepsilon$ = 4.16)
$[Cu(L^1H)_2]$	604, 432, 361*, 312* 303*, 287, 221 ($\log\varepsilon$ = 4.62)	603, 433, 361*, 312* 301*, 287, 221 ($\log\varepsilon$ = 4.65)	604, 432, 361*, 312* 300*, 288, 221 ($\log\varepsilon$ = 4.54)	544, 452 306, 297, 283 ($\log\varepsilon$ = 4.40)
$[Co(L^1H)_2]$	604, 433, 361*, 335* 303*, 288, 223 ($\log\varepsilon$ = 5.08)	604, 433, 361*, 333* 302*, 289, 222 ($\log\varepsilon$ = 5.08)	626, 433, 360*, 312* 301*, 289, 222 ($\log\varepsilon$ = 5.06)	728, 375 342, 306, 291 ($\log\varepsilon$ = 5.16)
L^2H_2	302*, 291, 223 ($\log\varepsilon$ = 4.69)	302*, 291, 222 ($\log\varepsilon$ = 4.67)	300*, 289, 220 ($\log\varepsilon$ = 4.65)	310, 294 ($\log\varepsilon$ = 4.22)
$[Ni(L^2H)_2]$	593, 432, 334*, 304*, 290, 223 ($\log\varepsilon$ = 4.99)	604, 433, 332* 303*, 290, 223 ($\log\varepsilon$ = 4.98)	604, 432, 334* 299*, 289, 223 ($\log\varepsilon$ = 4.95)	593, 373 322, 293 ($\log\varepsilon$ = 4.29)
$[Cu(L^2H)_2]$	593, 432, 360*, 312* 303*, 289, 222 ($\log\varepsilon$ = 5.09)	603, 432, 361*, 312* 304*, 289, 223 ($\log\varepsilon$ = 5.23)	625, 432, 361*, 312* 303*, 289, 223 ($\log\varepsilon$ = 5.09)	544, 452 320, 308, 293 ($\log\varepsilon$ = 4.92)
$[Co(L^2H)_2]$	592, 433, 367*, 337 304*, 289, 223 ($\log\varepsilon$ = 5.28)	604, 432, 367*, 335 303*, 289, 223 ($\log\varepsilon$ = 5.28)	604, 432, 364*, 312* 302*, 289, 224 ($\log\varepsilon$ = 5.26)	593, 377 344, 308, 291 ($\log\varepsilon$ = 5.15)

* Shoulder.

H_2O molecules were identified by a broad OH absorption band near 3280–3290 cm^{-1} whose intensity remained constant following heating to 110 °C for 24 h [27].

The Cu(II) complexes were also paramagnetic with μ_{eff} = 1.72 for L^1H_2 and 1.71 B.M. for L^2H_2, a close fit for the spin value of 1.73 B.M. Although the magnetic moment is somewhat low, there are likely some diamagnetic contributions from the ligand that ultimately decrease the total paramagnetism of the complexes [27].

NMR spectra

In the ^{1}H NMR spectrum, the proton resonances appear as two low intensity singlets at 11.27 ppm and 10.05 ppm for L^1H_2 and 11.27 ppm and 10.05 ppm for L^2H_2. These two D_2O-exchangeable singlets correspond to two non-equivalent -OH protons and suggest an *anti* configuration for the —OH groups relative to each other [28]. Peaks corresponding to the -NH protons were observed as singlets at 7.99 and 7.86 ppm for L^1H_2 and at 7.98 and 7.76 ppm for L^2H_2. These peaks disappeared upon D_2O exchange. The other evidence of the thion form of the ligands is the appearance of NH signals around 7.76–7.99 ppm in the ^{1}H NMR spectra. Peaks corresponding to the CH=N—OH protons appeared as singlets at 6.83 ppm in L^1H_2 and 6.37 ppm in L^2H_2 (Fig. S_3 for L^2H_2 in Supplementary Materials).

The carbon resonances of the oxime groups occurred at 157.53 and 139.93 ppm for L^1H_2 and 157.52 and 139.93 ppm for L^2H_2. The nonequivalence of the hydroxyimino carbon atoms confirms the *anti* structure of L^1H_2 and L^2H_2 [29]. The signals of the $C_{aromatic}$ carbon were observed at 129.57, 128.70, 128.12 and, 114.74 ppm as 4 peaks for L^1H_2 and 128.70, 127.98, 115.17, and 109.09 as 4 peaks for L^2H_2 [30] (Fig. S_4 for L^1H_2 in Supplementary Materials).

UV spectra

The electronic spectra for the ligands recorded in various solvents, CH_3OH and DMSO are given in Table 4. The effect of pH change for absorption spectra was also performed by adding

Table 5
Antimicrobial activities of metal complexes (Inhibition zone mm).

Test microorganisms	Inhibition zones (mm)													
	Metal complexes								Reference antibiotics					
	1	2	3	4	5	6	7	8	C30	CN10	TE30	E15	AMP10	NS100
Escherichia coli ATCC 25922	–	–	–	–	–	–	–	–	24	21	15	11	–	NT
Staphylococcus aureus ATCC 25923	–	–	9	–	9	10	10	–	23	20	22	23	20	NT
Staphylococcus epidermidis ATCC 12228	–	–	9	–	9	9	12	–	22	17	19	11	17	NT
Salmonella typhimirium ATCC 14028	–	–	–	–	–	–	–	–	17	16	15	8	8	NT
Proteus vulgaris ATCC 33420	–	–	–	–	–	–	–	–	19	24	16	22	-	NT
Serratia marcescens ATCC 13880	–	–	–	–	–	8	–	–	23	19	13	–	19	NT
Micrococcus luteus ATCC 9341	–	–	–	–	–	20	21	–	25	15	26	30	28	NT
Listeria monocytogenes ATCC 19112	12	11	7	–	–	11	12	–	19	14	12	–	–	NT
Entereococcus faecalis 29212	–	–	–	–	–	–	–	–	16	11	19	–	14	NT
Bacilllus cereus ATCC 11778	–	–	–	–	–	–	–	–	23	24	25	26	–	NT
Bacilllus subtilis ATCC 6633	–	–	7	–	7	9	8	–	22	20	12	25	–	NT
Bacillus thrungiensis[*]	7	–	–	–	7	7	9	–	26	21	15	28	–	NT
Candida utilis ATCC 9950	–	–	–	–	–	–	–	–	NT	NT	NT	NT	NT	22
Candida albicans ATCC 10231	–	–	–	–	14	15	–	–	NT	NT	NT	NT	NT	23
Candida trophicalis[*]	15	–	12	–	15	13	–	–	NT	NT	NT	NT	NT	18
Saccharomyces cerevisiae ATCC 9763	–	–	–	–	14	13	–	–	NT	NT	NT	NT	NT	19

Note: 1 = L^1H_2, 2 = $[Ni(L^1H)_2]$, 3 = $[Cu(L^1H)_2]$, 4 = $[Co(L^1H)_2(H_2O)_2]$, 5 = L^2H_2, 6 = $[Ni(L^2H)_2]$, 7 = $[Cu(L^2H)_2]$ and 8 = $[Co(L^2H)_2(H_2O)_2]$.
C30 = Chloramphenicol, GN10 = Gentamycin, TE30 = Tetracycline, E15 = Eritromycine, AMP10 = Ampicyline and NS100 = Nystatin.
(–) = No zone, NT = Not tested.
[*] From Faculty of Medicine, Adnan Menderes University.

Table 6
Antimicrobial activities of ligands and their metal complexes (MIC, μg mL^{-1}).

Test microorganisms	1	2	3	5	6	7	Str	NS 100
Micrococcus luteus, ATCC 9341	–	–	–	–	8	8	32	NT
Stapylococcus aureus ATCC 25923	–	–	–	128	64	64	32	NT
Stapylococcus epidermidis ATCC 12228	–	–	128	–	128	64	32	NT
Serratia marcescens ATCC 13880	–	–	–	–	128	–	64	NT
Listeria monocytogenes ATCC 19112	64	64	256	–	64	64	32	NT
Bacillus subtilis ATCC 6633	–	–	256	256	128	128	64	NT
Bacilllus thrungiensis[*]	256	–	–	256	256	128	64	NT
Candida albicans ATCC 10231	–	–	–	32	32	–	NT	64
Candida trophicalis	32	–	64	32	32	–	NT	64
Saccharomyces cerevisiae ATCC 9763	–	–	–	64	32	–	NT	128

Note: 1 = L^1H_2, 2 = $[Ni(L^1H)_2]$, 3 = $[Cu(L^1H)_2]$, 4 = $[Co(L^1H)_2(H_2O)_2]$, 5 = L^2H_2, 6 = $[Ni(L^2H)_2]$, 7 = $[Cu(L^2H)_2]$ and 8 = $[Co(L^2H)_2(H_2O)_2]$.
Compounds 4 and 8 did not show antibacterial activity.
Str = Streptomycin, NS100 = Nystatin.
(–) = No effect.
[*] From Faculty of Medicine, Adnan Menderes University.

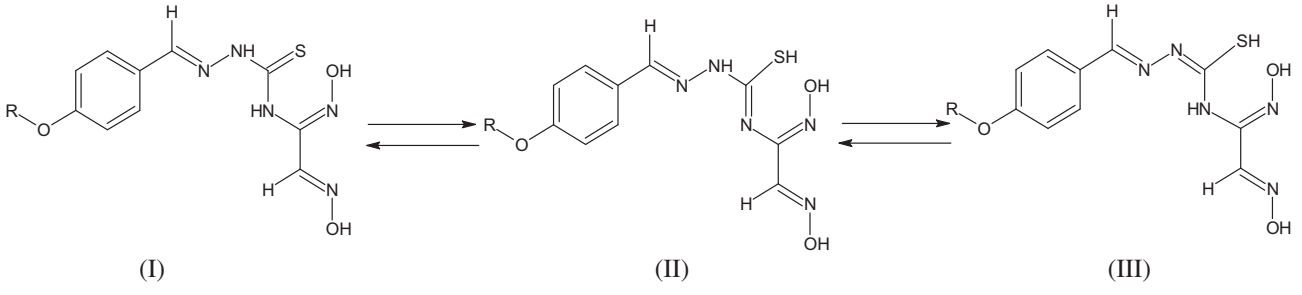


Fig. 2. Thion (I) and thiol (II and III) forms of the ligands (R: —CH_3 for L^1H_2, R: —CH_2CH_3 for L^2H_2).

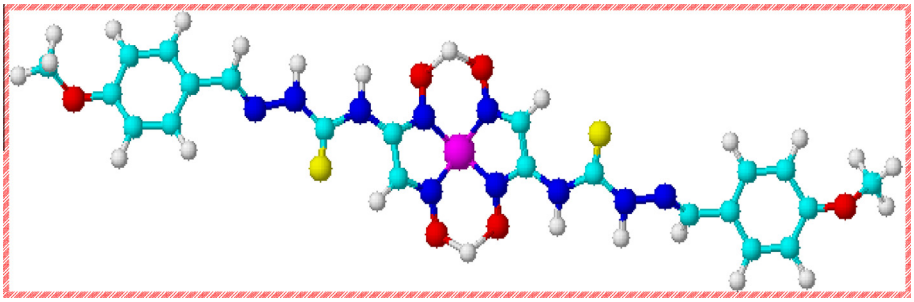


Fig. 3. Conformation of *trans* structure of Ni(II), Cu(II) and Co(II) complexes.

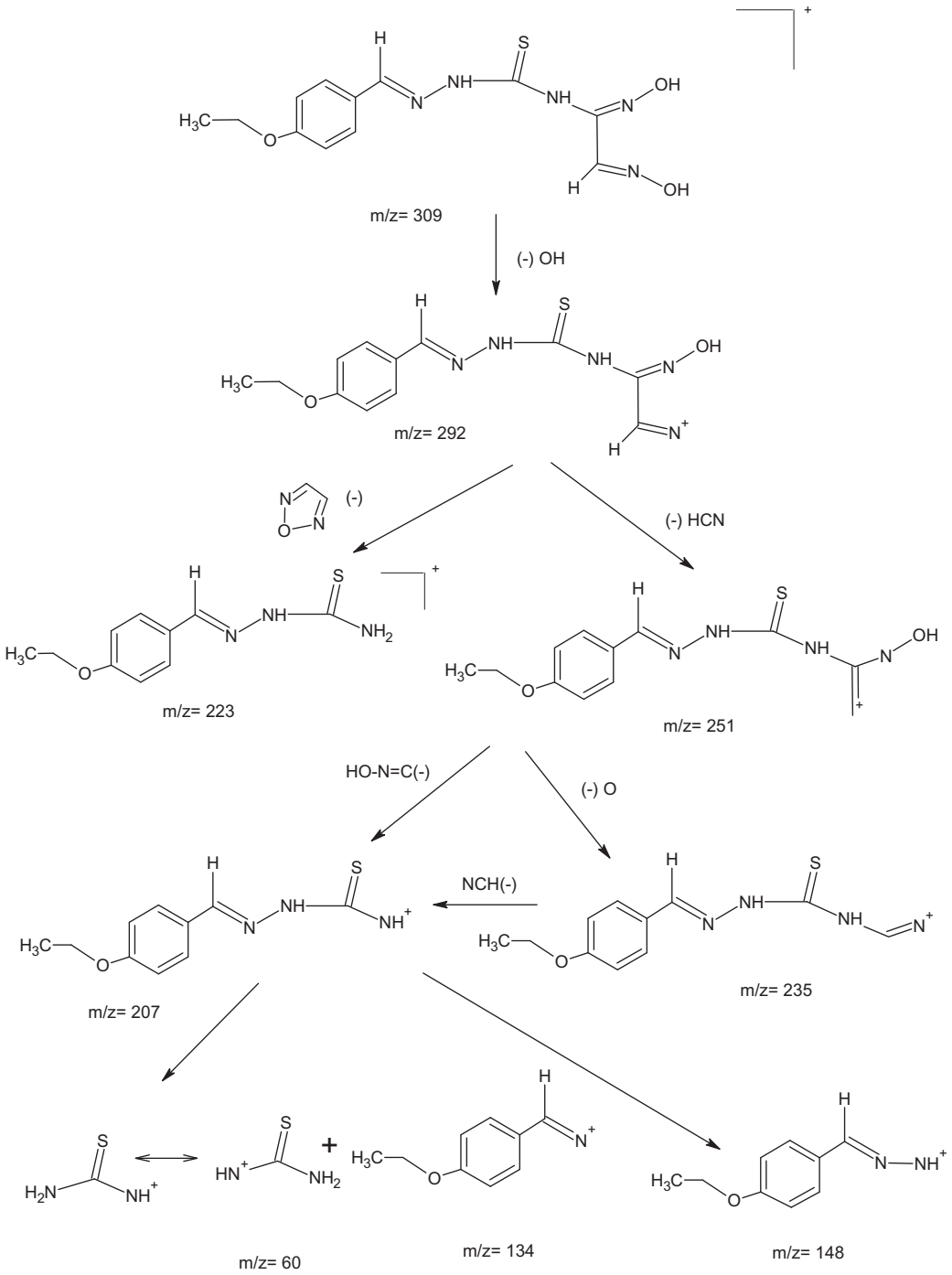


Fig. 4. The proposed fragmentation pattern of L^2H_2.

0.1 M HCl and KOH. The pH value of all solution used was in the range between basic and acidic.

Electronic spectra of the ligands (L^1H_2 and L^2H_2) and their Ni(II), Cu(II), and Co(II) metal complexes were recorded in DMSO and CH_3OH from 200 to 800 nm (Table 4). Both ligands and complexes displayed several intense absorption bands in the visible and ultraviolet region.

The spectra of the ligands and metal complexes contained 2–5 absorption bands between 273 and 728 nm in DMSO and 3–5 absorption bands between 222 and 605 nm in CH_3OH. The wide range of bands seems to be due to $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$, and d–d transitions of C=N and charge transfer transitions arising from π electron interactions between the metal and ligand involving either a metal-to-ligand or ligand-to-metal electron transfer [31].

The absorption bands below 298 nm in DMSO and 291 nm in CH_3OH were practically identical and may be attributed to $\pi \rightarrow \pi*$ transitions in the aromatic ring or azomethine (—C=N) groups. The absorption bands appearing between 344 and 322 nm in DMSO and between 335 and 302 nm in CH_3OH are most probably due to an $n \rightarrow \pi*$ transition of the imine group [32]. The absorption bands between 360 and 452 nm in both DMSO and CH_3OH were assigned to $M \rightarrow L$ charge transfer (MLCT) or $L \rightarrow M$ charge transfer (LMCT) and $^1A_{1g} \rightarrow {}^1B_{1g}$ transitions [33]. Electronic spectra of Co(II) in DMSO or CH_3OH exhibit broadbands between 592 and 728 nm assigned to $^2Eg \rightarrow 2T_{2g}$ transitions, characteristic for octahedral geometry [34a,b]. The Cu(II) complexes show a broad band at 544–625 nm, which can be assigned to a $^2B_{1g} \rightarrow {}^2A_{1g}$ transition [34c]. This, together with the measured μ_{eff} values suggests square-planar geometry. The weak d–d transitions of square planar Ni(II) complexes resulted in peaks between 544 and 605 nm [28].

Solvent effects on electronic spectra of ligands and metal complexes

The electronic absorption spectra of the compounds were examined in CH_3OH and DMSO. The absorption spectra of the *vic*-dioxime derivatives were influenced by changing the solvent (Figs. 5 and 6). The λ_{max} values of the ligands and metal complexes were red-shifted in DMSO. For example, λ_{max} for L^1H_2 was 306 nm in CH_3OH and 322 nm in DMSO (Table 4). An absorption peak near 222 nm was indistinct in DMSO solutions of the ligands and complexes but much more apparent in CH_3OH solutions (Figs. 5 and 6).

Effect of pH on electronic spectra

The effect of pH on the electronic absorption spectra of the compounds was studied in CH_3OH by adding small amounts of 0.1 M HCl or KOH. λ_{max} values of methanolic solutions of the *vic*-dioxime derivatives and metal complexes were not affected by addition of small amounts of 0.1 M HCl. However, addition of 0.1 M KOH in methanolic solution resulted in substantial changes to the absorption spectra. Addition of two drops of 0.1 M KOH to neutral methanolic solutions of these ligands resulted in blue shifts and intensity changes in bands near 304 and 291 nm (Fig. 7. and Table 4).

An isosbestic point was observed at 301 nm in the Ni(II) complexes (Fig. 8), suggesting the presence of two species in the solution. The second species appeared upon addition of KOH and was most likely an ionized form.

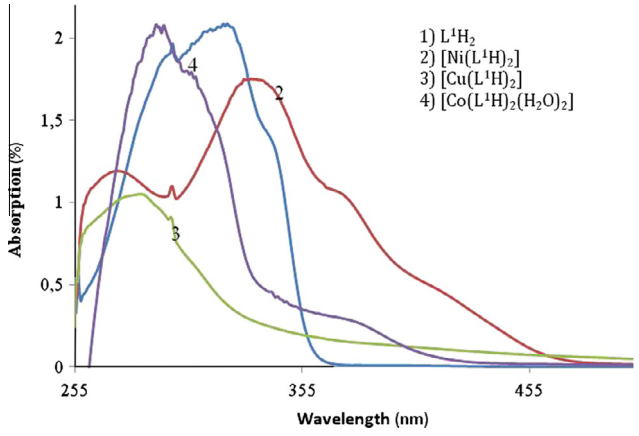


Fig. 5. Absorption spectra of L^1H_2 and its metal complexes in DMSO.

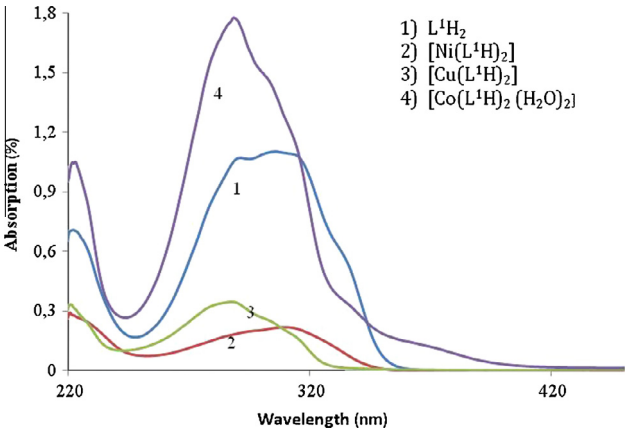


Fig. 6. Absorption spectra of L^1H_2 and its metal complexes in CH_3OH.

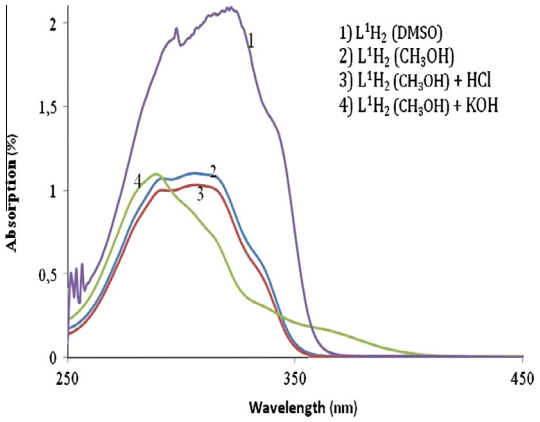


Fig. 7. Absorption spectra of L^1H_2 in DMSO, CH_3OH, CH_3OH + HCl and CH_3OH + KOH.

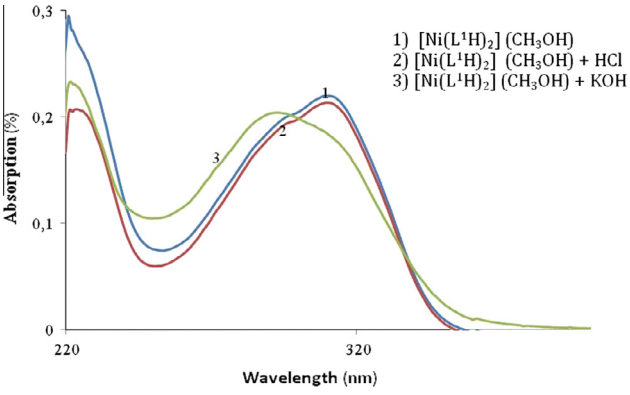


Fig. 8. Absorption spectra of $[Ni(L^1H)_2]$ in (1); MeOH, (2); MeOH + HCl and (3) MeOH + KOH.

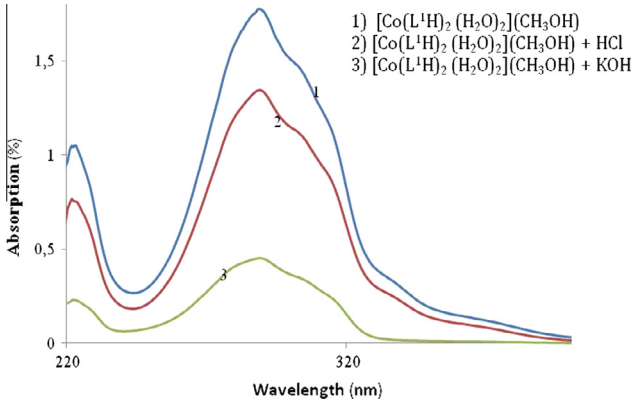


Fig. 9. Absorption spectra of $[Co(L^1H)_2(H_2O)_2]$ in (1); MeOH, (2); MeOH + HCl and (3) MeOH + KOH.

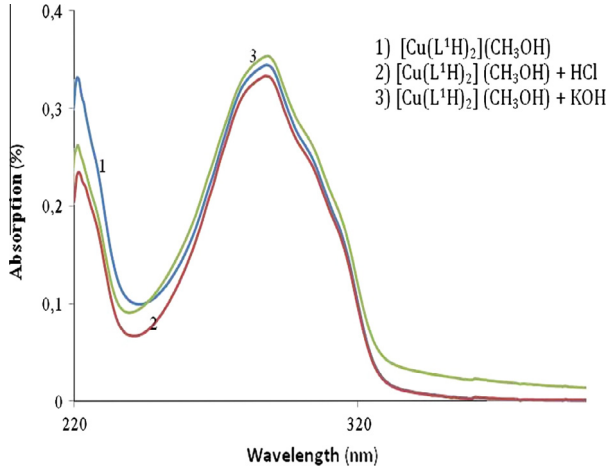


Fig. 10. Absorption spectra of $[Cu(L^1H)_2]$ in (1); MeOH, (2); MeOH + HCl and (3) MeOH + KOH.

Electronic absorption spectra of complexes

The electronic absorption spectra of the $[M(LH)_2]$ complexes were recorded in DMSO and CH_3OH solutions (Table 4). The spectra of the complexes in methanolic solution were not affected by addition of small amounts of 0.1 M HCl. Following addition of two drops of 0.1 M KOH to methanolic solutions of the complexes, the bands appearing near 309 nm in the Ni(II) complexes and 335 nm in the Co(II) complexes were blue shifted (Figs. 8 and 9), while the bands appearing near 600 nm in Ni(II), Cu(II), and Co(II) complexes were red shifted (Table 4). The Cu(II) complexes were not affected by addition of small amounts of 0.1 M HCl or 0.1 M KOH over the range 200–450 nm (Fig. 10). The position of the CT band in all of the complexes exhibited regular variation in DMSO and CH_3OH solvents, with the CT transition bands in DMSO solutions being more blue shifted than those in CH_3OH solutions.

Antimicrobial assays

The two novel vic-dioximes derivatives containing thiosemicarbazone groups and their Ni(II), Cu(II) and Co(II) complexes detemined appreciable antimicrobial activity (Tables 5 and 6).

Among the test compounds essayed, compounds L^1H_2, $[Ni(L^1H)_2]$, $[Cu(L^1H)_2]$, L^2H_2, $[Ni(L^2H)_2]$ and $[Cu(L^2H)_2]$ showed activity against some bacteria and yeasts (Table 5).

According to Table 5, compounds L^1H_2, $[Ni(L^1H)_2]$, $[Ni(L^2H)_2]$, and $[Cu(L^2H)_2]$, displayed stronger activity against using the some bacteria (*Listeria monocytogenes* ATCC 19112, *Micrococcus luteus* ATCC 9341 and *Staphylococcus epidermidis* ATCC 12228. Besides, compounds L^1H_2, $[Cu(L^1H)_2]$, L^2H_2, and $[Ni(L^2H)_2]$ also reflected remarkable activity against using the some yeasts (*Candida albicans* ATCC 10231, *Candida* trophicalis and *Saccharomyces cerevisiae* ATCC 9763). On the other hand, compounds $[Co(L^1H)_2(H_2O)_2]$ and $[Co(L^2H)_2(H_2O)_2]$ had no effect on using the test microorganisms (Table 5). In general, the ligands and their metal complexes have antimicrobial activities against Gram-positive bacteria, especially *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *M. luteus* ATCC 9341, *L. monocytogenes* ATCC 19112, *B. subtilis* ATCC 6633 and *B. thuringiensis*. Although using most compounds have any effect on Gram-negative bacteria, compound $[Ni(L^2H)_2]$ has showed few effect on *S. marcescens* ATCC 13880 from Gram-negative bacteria (Table 5).

The MIC values in Table 6 also pointed out that some of the compounds tested presented noteworthy antimicrobial activity on the tested microorganisms. According to data, L^1H_2, $[Ni(L^1H)_2]$, $[Ni(L^2H)_2]$, and $[Cu(L^2H)_2]$ compounds have exposed considerable effect against *M. luteus* ATCC 9341, *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228 and *L. monocytogenes* ATCC 19112. For example, *M. luteus* ATCC 9341 (compounds $[Ni(L^2H)_2]$ and $[Cu(L^2H)_2] = 8\ \mu g\ mL^{-1}$, *S. aureus* ATCC 25923 (compounds $[Ni(L^2H)_2]$ and $[Cu(L^2H)_2] = 64\ \mu g\ mL^{-1}$), *S. epidermidis* ATCC 12228 (compound $[Cu(L^2H)_2] = 64\ \mu g\ mL^{-1}$) and *L. monocytogenes* ATCC 19112 (compounds L^1H_2 and $[Ni(L^1H)_2] = 64\ \mu g\ mL^{-1}$).

However, compounds L^1H_2, $[Cu(L^1H)_2]$, L^2H_2, $[Ni(L^2H)_2]$ and $[Cu(L^2H)_2]$ showed low effect against *B. subtilis* ATCC 6633 and *B. thuringiensis* such as compounds $L^2H_2 = 256\ \mu g\ mL^{-1}$, $[Cu(L^2H)_2] = 128\ \mu g\ mL^{-1}$, $[Ni(L^2H)_2] = 128\ \mu g\ mL^{-1}$ and $256\ \mu g\ mL^{-1}$, respectively.

Compounds L^1H_2, $[Cu(L^1H)_2]$, L^2H_2 and $[Ni(L^2H)_2]$ demonstrated strong activity on using three yeast cultures such as *C. albicans* ATCC 10231 (compounds L^2H_2 and $[Ni(L^2H)_2] = 32\ \mu g\ mL^{-1}$), *C. trophicalis* (compounds L^1H_2, L^2H_2 and $[Ni(L^2H)_2] = 32\ \mu g\ mL^{-1}$, compound $[Cu(L^1H)_2] = 64\ \mu g\ mL^{-1}$), *S. cerevisiae* ATCC 9763 (compound $L^2H_2 = 64\ \mu g\ mL^{-1}$ and compound $[Ni(L^2H)_2] = 32\ \mu g\ mL^{-1}$).

Micrococcus luteus doesn't regard as a pathogen bacteria but, in individual with a decreased immune system such as newborn infants or patients with AIDS, it can cause skin infections. The skin infections, or chronic cutaneous infections, result in pruritic eruptions of the skin in some areas as well as scattered papule lesions with or without central ulcerations [35]. Recently, this organism was recognized as an opportunistic pathogen and has been implicated in recurrent bacteremia, septic shock, septic arthritis, endocarditis, meningitis, intracranial suppuration, and cavitating pneumonia in immunosuppressed patients [36].

Staphylococcus aureus brings about for many infections. It can infect tissues when the skin or mucosal membrane have been injured [37]. This can conduct to many different types of infections including fruncles. In infants, *S. aureus* infection can cause a dangerous disease [38].

Listeria monocytogenes is the bacterium that causes the infection listeriosis. This bacterium results in septicemia, meningitis, encephalitis, corneal ulser, pneumonia [39].

S. marcescens is commonly detected in bathrooms especially on tile grout, shower corners, toilet water line, and basin [40]. *S. marcescens* brings about infection in many localite, including the urinary tract, respiratory tract, wounds, and the eye, where it may cause conjuctivities and keratitis infections [41].

Candida is a member of normal flora of skin, mouth, vagina, and stool. Infections caused by *Candida* spp. are in general referred to as candidiasis. Candidiasis embraces infections that range from external such as oral trush and vaginitis, to potentially life-threatening diseases. Candida infections of the latter category are also assigned as candidemia and are usually restricted entirely immunocompromised persons, such as cancer, transplant, and AIDS patients, as well as nontrauma emergency surgery patients [42].

Suggestions are made that the negative inductive effect plays a significant role. Dimerisation of oxime involves the formation of a pair of H bonds [30c,43]. This feature causes a decrease in electronic density of oximes compared with phenylhydrazones, thereby facilitating entry of the oxime into the cell. This is likely to increase the antibacterial potency [30c,43].

A comparative study of the ligands and their complexes as antibacterial agents indicates that the metal complexes are more active than the free ligands [30c,43]. Such increased activity of the metal chelates can be explained by the reduced polarity of the ligand due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with electron releasing groups. It is obvious that reducing the total electron density on free ligands makes the diffusion proceed faster through the bacterial cells [44].

It is generally observed that metal chelates have higher antibacterial activity than the free ligand due to an increase in cell permeability. The lipid membrane which surrounds the cell favors only the passage of lipid soluble materials and it is known that liposolubility is an important factor controlling antimicrobial activity [45–47]. Such screening of various organic compounds and identifying the active agents are essential because the successful prediction of a lead molecule and the drug-like properties at the onset of drug design will pay off later in drug development.

Conclusions

Novel *vic*-dioxime ligands (L^1H_2 and L^2H_2) containing 4-methoxy or 4-ethoxy thiosemicarbazone moieties and their mononuclear Ni(II), Cu(II), and Co(II) complexes were synthesized and characterized. Reaction of L^1H_2 and L^2H_2 with metal(II) salts yielded mononuclear complexes corresponding to the general formulas $[M(LH)_2]$ (M: Ni(II), Cu(II), or $Co(II)\cdot 2H_2O$).

Both oxime moieties were in the E configuration, and the complexes underwent intramolecular hydrogen bonding. Strong ν(C=S) absorption bands near 835 cm^{-1} in the IR spectra indicated that the ligands are in the thione tautomeric form in the solid state. Other evidence for the presence of the thione form of the ligands included the appearance of NH signals near 7.79–8.00 ppm in the ^1H NMR spectra.

The effect of pH and solvent on the electronic absorption spectra was also examined. In basic solutions, *vic*-dioximes derived from thiosemicarbazones underwent a considerable blue shift for peaks between 200 and 450 nm and a red shift for peaks between 450 and 750 nm, while addition of acid did not affect the absorption spectra. The λ_{max} values of the compounds were considerably affected by the choice of solvent.

The antimicrobial activities of compounds (L^1H_2, L^2H_2, and their Ni(II), Cu(II) and Co(II) complexes) were evaluated using disc diffusion method against 12 bacteria and 4 yeasts. Minimal inhibitory concentration (MIC) dilution against 7 bacteria and 3 yeasts were also determined. Among the test compounds attempted, L^1H_2, $[Ni(L^1H)_2]$, $[Cu(L^1H)_2]$, L^2H_2, $[Ni(L^2H)_2]$ and $[Cu(L^1H)_2]$ showed activities against certain Gram-positive bacteria and certain yeasts. Some of them were comparatively higher or equipotent to the antibiotic and antifungal agents in the comparison tests. These compounds appeared to have moderate antibacterial and antifungal activity. However, compounds $[Co(L^1H)_2(H_2O)_2]$ and $[Co(L^2H)_2(H_2O)_2]$ have any effect using microorganisms.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.saa.2013.10.040.

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