

Synthesis, characterization, antioxidant and antimicrobial studies of Cu(II), Co(II), Ni(II) and Mn(II) complexes with a new Schiff base ligand containing a pyrimidine moiety

Hatice Gamze Soğukömeroğulları^{1*}, Mehmet Sönmez¹,
İsmet Berber²

¹Gaziantep University, Faculty of Science and Arts, Chemistry Department, 27310, Gaziantep, Turkey

²Sinop University, Faculty of Science and Arts, Biology Department, 57010, Sinop, Turkey.

Abstract : The new Schiff base ligand derived from 2-hydroxy-5-methoxybenzaldehyde and 1-amino-5-benzoyl-4-phenyl-1H-pyrimidine-2-one and its metal complexes (Cu(II), Co(II), Ni(II) and Mn(II)) have been synthesized. Schiff base ligand and its complexes were characterized by elemental analysis, magnetic measurement, molar conductivity, IR, NMR (for ligand) and Mass spectral studies. All the compounds have encouraged us to study on their antioxidant properties and antimicrobial activities against Gram-positive, Gram-negative bacteria and fungi using microdilution procedure. Cu(II) (**1a**) and Co(II) (**1b**) metallic complexes might be possible as substances to eliminate the free radicals and against the antimicrobial agent.

Keywords: Schiff bases, Metal complexes, antioxidant studies, antimicrobial activity.

Introduction

Schiff bases are quite valuable chemicals that have the usage properties in the area of medicine, chemistry, pharmaceutical chemistry and industry. Especially in recent years, active research fields have included their use in anticancer,¹ antibacterial,^{2,3} antifungal,⁴ anti-inflammation, analgesic,⁵ antiproliferative,⁶ anticonvulsant⁷ and anti-HIV.⁸ According to many reports that after complexation with transition metal ions have shown that an increase in microbial activity.⁹ Metal complexes derived from Schiff base ligands of pyrimidine have been mostly researched in these days on account of their lot of biological activities, which have usually been related to their chelating ability with trace metal ions.⁰

We herein wish to report a newly Schiff base ligand (1-[[1-(2-hydroxy-5-methoxyphenyl) ethylidene]amino]-4-phenyl-5-benzoyl-pyrimidine-2-on) and its complexes (Cu(II), Co(II), Ni(II), Mn(II)) were synthesized. Schiff base ligand and its metal complexes were characterized by elemental, magnetic susceptibility and Mass, NMR, UV-Vis, FT-IR spectral analysis. All the compounds have encouraged us to study on their antioxidant studies and antimicrobial activities against Gram-positive, Gram-negative bacteria and fungi using microdilution procedure.

Experimental

Materials and Methods

Elemental analyses (C, H, N, S) were performed using a Thermo Scientific Flash 2000 elemental analyzer. UV-Vis. spectra were recorded on a PG Instruments T80+UV/Vis. spectrometer. The magnetic moments of the complexes were measured by the Gouy method on a type Sherwood Scientific model Instrument. The IR spectra were recorded in the range 4000–400 cm^{-1} on a PerkinElmer Spectrum 100 FTIR (ATR) model FT-IR spectrometer. Molar conductances of the Schiff base ligand and metal complexes were determined in DMF at room temperature by using Thermo Scientific electron corporation model conductivitymeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker High Performance Digital FT-NMR (400 MHz) spectrometer with the samples dissolved in d_6 -DMSO using TMS as an internal standard. Mass spectra of all the compounds were obtained Atmospheric pressure ionization electrospray mass spectra (API-ES) on a LC/MS/MS AB-Sciex 3200 Q-trap spectrophotometer.

Synthesis of Schiff base ligand (HL) (1)

1-Amino-5-benzoyl-4-phenyl-1H-pyrimidine-2-one (*N*-aminopyrimidine-2-one) was synthesized according to the literature.¹¹ The Schiff bases ligand (1-[[1-(5-methoxy-2-hydroxyphenyl) methyliden] amino]-4-phenyl-5-benzoyl-pyrimidine-2-one) (HL) was synthesized by a condensation method. *N*-aminopyrimidine-2-one (0.291 g, 0.1 mmol) was dissolved in *n*-butanol (40 ml) and was added to a solution of 5-methoxy-2-hydroxybenzaldehyde (0.152 g, 0.1 mmol). The mixture was heated to 100 °C and kept at this temperature for 24 hour. After cooling to room temperature the residue was filtered and the crude product recrystallized in *n*-butanol and dried in a vacuum dessicator (Figure 1). [Yield: 0.316 g, 75 %] Yellow color compound. mp. 198–199 °C. Analysis: Calculated for $\text{C}_{25}\text{H}_{19}\text{N}_3\text{O}_4$ (425.44): C, 70.58; H, 4.50; N, 9.88. Found: C, 70.22; H, 4.71; N, 9.88 %. API-ES in MeOH: m/z 426.66 [HL+1]. IR (ATR) / cm^{-1} : 3160w, 2958w, 1681vs, 1645vs, 1614vs, 1363s (vs, very strong; s, strong; m, medium; w, weak). UV-Vis in DMF [λ_{max} / nm, (Abs)]: 354.72 (0.749), 380 (0.858), 280 (1.515) nm. ^1H NMR (400 MHz, d_6 -DMSO) δ (ppm); s, singlet; d, doublet; m, multiplet: 10.17 (s, 1H, OH proton), 9.41 (s, 1H, H-6), 8.71 (s, 1H, N=C-H), 7.84 (d, 2H, $J=8$ Hz, H-2', H-6'), 7.58 (t, 1H, H-4'), 7.11 (d_d , 1H, H-6'''), 7.48–7.31 (m, 8H, Harm), 6.96 (d, 1H, $J=8.8$ Hz, H-3'''), 3.74 (s, 3H, OCH_3 protons). ^{13}C NMR (d_6 -DMSO, ppm), δ 192.09 ($\text{C}=\text{O}$)_{benzoyl}, 170.99 ($\text{C}=\text{O}$)_{pyrimidine rings}, 163.8 ($\text{C}=\text{N}$), 153.53, 152.65, 151.69, 149.39, 137.36, 133.86, 131.10, 130.20, 129.14, 129.05, 128.68, 122.77, 118.43, 118.34, 116.02, 110.34 (Aromatic carbons), 55.95 (CH_3 -O).

Synthesis of metal complexes

0.213 g (0.5 mmol) (HL) of the ligand was solved in 30 ml THF/MeOH (4:1) mixture, and a solution of 0.25 mmol of the metal salt $\text{Cu}(\text{AcO})_2 \cdot \text{H}_2\text{O}$, $\text{Co}(\text{AcO})_2 \cdot 4\text{H}_2\text{O}$, $\text{Ni}(\text{AcO})_2 \cdot 4\text{H}_2\text{O}$ or $\text{Mn}(\text{AcO})_2 \cdot 2\text{H}_2\text{O}$ in 10 ml methanol was added dropwise with continuous stirring. The mixture was stirred further for 30 minutes at 70 °C. The precipitated solid was then filtered off, washed with cold methanol, and dried in a vacuum dessicator (Figure 1). The characterization data for the complexes are given below.

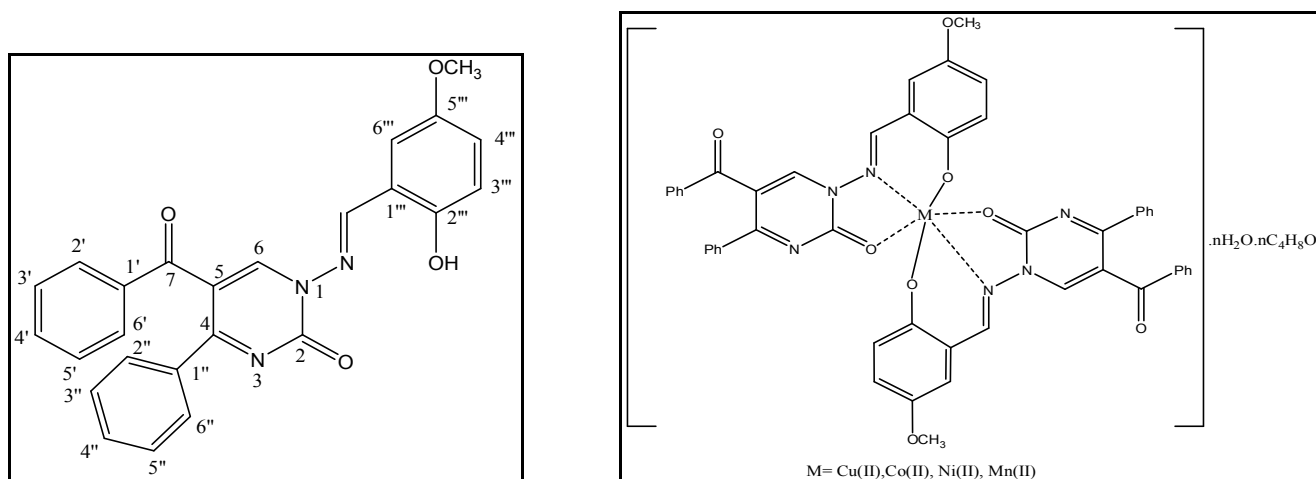


Figure 1. Structure of the Schiff base ligand (HL) and its metal complexes

[CuL₂]·H₂O·C₄H₈O (1a): [Yield: 0.218 g, 48%] Brown color compound. 179 °C decompose. Analysis: Calculated for C₅₄H₄₆CuN₆O₁₀ (1002.5) : C, 64.69; H, 4.62; N, 8.38. Found: C, 64.23; H, 4.60; N, 8.44 %. API-ES in MeOH: m/z 1002.1 [Cu+2L+H₂O+ C₄H₈O]⁺. IR (ATR) / cm⁻¹: 2997w, 1709m, 1655vs, 1607vs, 1363vs, 530m, 436m. UV-Vis in DMF [λ_{max} / nm, (Abs)]: 463.20 (0.076), 437.09 (0.120), 380 (0.357), 275 (0.927), 255.73 (0.322), nm. μ_{eff} : 1.81 BM. Conductivity in 10⁻³ M DMF (Λ_{M}): 1.00 $\mu\text{S}/\text{cm}$.

[CoL₂]·2H₂O (1b): [Yield: 0.240 g, 53%] Red-Brown color compound. 220 °C decompose. Analysis: Calculated for C₅₀H₄₀CoN₆O₁₀ (943.82) : C, 63.63; H, 4.27; N, 8.90. Found: C, 63.63; H, 4.39; N, 9.28 %. API-ES in MeOH: m/z 944.1 [Co + 2L+2H₂O]⁺. IR (ATR) / cm⁻¹: 3060w, 2831w, 1657vs, 1614vs, 1394vs, 539m, 445m. UV-Vis in DMF [λ_{max} / nm, (Abs)]: 426.04 (0.110), 386.87 (0.265), 350.00 (0.312), 270.00 (0.819) nm. μ_{eff} : 3.75 BM. Conductivity in 10⁻³ M DMF (Λ_{M}): 1.07 $\mu\text{S}/\text{cm}$.

[NiL₂]·2H₂O (1c): [Yield: 0.220 g, 49%] Claret red color compound. 150 °C decompose. Analysis: Calculated for C₅₀H₄₀NiN₆O₁₀ (943,6) : C, 63.64; H, 4.27; N, 8.91. Found: C, 63.39; H, 4.69; N, 8.79 %. API-ES in MeOH: m/z 943.2 [Ni+2L+2H₂O]⁺. IR (ATR) / cm⁻¹: 3058w, 2936w, 1636s, 1615vs, 1336vs, 536m, 434m. UV-Vis in DMF [λ_{max} / nm, (Abs)]: 524.47 (0.153), 465 (0.166), 345 (0.405), 270 (0.998) nm. μ_{eff} : 2.61 BM. Conductivity in 10⁻³ M DMF (Λ_{M}): 2.36 $\mu\text{S}/\text{cm}$.

[MnL₂]·C₄H₈O (1d): [Yield: 0.256 g, 57%] Dark claret red color compound. 87 °C decompose. Analysis: Calculated for C₅₄H₄₄MnN₆O₉ (975,9) : C, 66.46; H, 4.54; N, 8.61. Found: C, 67.89; H, 5.10; N, 9.26 %. API-ES in MeOH: m/z 976 [Mn + 2L+ C₄H₈O]⁺. IR (ATR) / cm⁻¹: 3060w, 2957w, 1680vs, 1645vs, 1612vs, 1363s, 532m 433m. UV-Vis in DMF [λ_{max} / nm, (Abs)]: 505.30 (0.046), 375.82 (0.574), 355 (0.545), 275 (1.206) nm. μ_{eff} : 2.44 BM. Conductivity in 10⁻³ M DMF (Λ_{M}): 1.14 $\mu\text{S}/\text{cm}$.

Biological assay

All chemical compounds and standard drugs were dissolved in DMSO (12.5%) at an initial concentration 1280 $\mu\text{g mL}^{-1}$ and then the two-fold serial dilutions of the compounds were prepared in culture medium. Bacterial strains were obtained from American Types Culture Collection. *Candida* strains were provided from Refik Saydam Hifsisihha Research Institute, Ankara, Turkey.

The synthesized ligand and 4 metallic complexes were screened for their antibacterial efficiency against 4 Gram-positive (*Staphylococcus aureus* ATCC 6538, *S. aureus* ATCC 25923, *Bacillus cereus* ATCC 7064 and *Micrococcus luteus* ATCC 9345) and one Gram-negative (*Escherichia coli* ATCC 4230) bacteria as mentioned by the guidelines in NCCLS approved standard document M7-A6 using the microdilution broth procedure.¹² Ampicillin was used as antibacterial drug. The antifungal activities of the compounds were tested against 3 yeast (*Candida albicans* ATCC 14053, *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019) strains according to the guidelines in NCCLS approved standard document M27-A2 using the microdilution broth procedure.¹³ Fluconazole was anti-yeast agent. All compounds were prepared to achieve the final concentrations (1280, 640, 320, 160, 80, 40, 20, 10, 5 > $\mu\text{g mL}^{-1}$) with two-fold serial dilutions in DMSO as mentioned above. The last two tubes were selected as the positive and the negative controls, respectively. Antibacterial activities of the chemicals were performed in Mueller-Hinton broth (Difco) medium at pH 7.2 with an inoculum of (1-2) x 10³ cells mL⁻¹ by the spectrophotometric method. All serial dilutions inoculated with each bacterium were cultivated on a rotary shaker at 37 °C for 18 h at 150 rpm. Antifungal activity against *Candida* strains was determined in RPMI 1640 Medium (Sigma) buffered to pH 7.0 with 0.165 M morpholinopropanesulfonic acid (Sigma), as described in document M27-A2. The stock yeast inoculum suspensions were adjusted to concentration of (1-2) x 10³ cells mL⁻¹ by spectrophotometric method same as before. The minimum inhibitory concentrations (MICs) of each chemical compounds were recorded as lowest concentration of each compounds, comparing to negative controls.

The antioxidant activities assay of the synthesized compounds was evaluated by using the DPPH method as described according to the literature.¹⁴ For this purpose, the stock solutions of the ligand and 4 metallic complexes were prepared by dissolving in DMSO (0.001 g/mL), and different concentrations (1000, 500, 250, 125 and 62.5 $\mu\text{g}/\text{mL}$) of each stock solution were make up to 3 mL with ethanol. One mL of a stock solution of DPPH (0.0001 mol) in ethanol was added to each serial dilution solutions containing chemical compounds, and the mixture was stirred vigorously. Then, the each solution was incubated for 30 min at room temperature, and free radical scavenging activity was measured at 517 nm. Ascorbic acid was used as a

standard. Not contained compound/standard was used as the negative control, and all experiments were run in the triplicate. DPPH free radical scavenging effect (%) was calculated by using the following equation:

$$\text{DPPH scavenging effect (\%)} = [(A_c - A_b/A_c) \times 100]$$

where A_c is the absorbance of the negative control, and A_b is the absorbance of the sample or the standard. Ascorbic acid was used as a standard or positive control. Not contained compound/standard was used as the negative control. Free radical scavenging activity was expressed as IC_{50} , which represent the concentration of the extract (mg ml^{-1}) required to inhibit 50% of the free radical scavenging activity.

Result and Discussion

Chemistry

A new Schiff bases ligand (HL) was prepared by the condensation of one mole of 5-methoxy-2-hydroxybenzaldehyde with one mole N-aminopyrimidine-2-on, as given experimental section. The addition of Cu(II), Co(II), Ni(II) and Mn(II) acetate dissolved in methanol to a THF solution of the ligand gave colored complexes. The newly synthesized metal complexes are very stable at room temperature in the solid state. We have estimated from the elemental analysis results that the metal complexes general formula is $[ML_2]$ where L is the anion of HL. The molar conductance measured for 10^{-3} M solutions in DMF of these complexes fall in the range 1.00-2.36 $\mu\text{S/cm}$ indicating their non-electrolytic behavior.⁹

IR spectra

The infrared spectra of the ligand observed a broad band at 3160 cm^{-1} free $\nu(\text{OH})$ stretching frequencies which was disappeared in all complexes. The FT-IR spectra of HL exhibits frequencies due to $\nu(\text{C}=\text{N})$ as sharp band at 1614 cm^{-1} which in the all metal complexes this band was shifted to lower or upper ($1-7\text{ cm}^{-1}$) wavenumbers indicating the involvement of azomethine nitrogen in the coordination to metal ion.¹⁵ Moreover, the absorption due to $\nu(\text{C}=\text{O})$ of the ligand at 1681 and 1645 cm^{-1} is shifted to $1709-1655\text{ cm}^{-1}$ in complexes indicating that the other coordination is through oxygen atom belong to pyrimidine rings.¹⁶ Moreover, new band in the complexes at $539-530\text{ cm}^{-1}$ and $433-445\text{ cm}^{-1}$ are predicated to the $\nu(\text{M}-\text{N})$ and $\nu(\text{M}-\text{O})$ vibrations, respectively.^{17,18}

Mass Spectra

In the mass spectra of the Schiff base ligand and its metal complexes, peaks were attributable to the molecular ions: m/z : 426.66 $[\text{HL}^+ + 1]$, m/z : 1002.1 $[\text{Cu} + 2\text{L} + \text{H}_2\text{O} + \text{C}_4\text{H}_8\text{O}]^+$, m/z : 944.1 $[\text{Co} + 2\text{L} + 2\text{H}_2\text{O}]^+$, m/z : 943.2 $[\text{Ni} + 2\text{L} + 2\text{H}_2\text{O}]^+$, m/z : 976 $[\text{Mn} + 2\text{L} + \text{C}_4\text{H}_8\text{O}]^+$.

Electronic Spectra and Magnetic Measurements

$[\text{Cu}(\text{L}_2)] \cdot \text{H}_2\text{O} \cdot \text{C}_4\text{H}_8\text{O}$, $[\text{Co}(\text{L}_2)] \cdot 2\text{H}_2\text{O}$, $[\text{Ni}(\text{L}_2)] \cdot 2\text{H}_2\text{O}$ and $[\text{Mn}(\text{L}_2)] \cdot \text{C}_4\text{H}_8\text{O}$ complexes exhibit brown, red-brown, claret and dark claret-red in DMF or aqueous solutions, respectively. Electronic spectra of the all compounds were recorded in the range 190-1100 nm. The absorption spectrum of the free ligand observes absorption at 354, 380 and 280 nm, which can be attributed to $\pi-\pi^*$ and $n \rightarrow \pi^*$ transitions of the Schiff base ligand.¹⁹ Magnetic susceptibility measurements show paramagnetism for Cu(II), Co(II), Ni(II) and Mn(II) complexes at room temperature. The observed magnetic moment for the Cu(II) complex is 1.81 B.M., which is owing to the octahedral geometry.²⁰ The measured magnetic moment value of the Co(II) complex was found at 3.75 B.M. which this value complies with values reported for octahedral complexes.^{21,22} The valence electron configuration of Mn^{2+} is $3d^5$. Also, the theoretical magnetic moment for Mn^{2+} is predicted to be 5.92 B.M, but the reached value in our calculations is about 2.44 B.M, which is due to the antiferromagnetic coupling of Mn^{2+} ions.²³ The magnetic moment value of 2.61 B.M. for the Ni(II) complex suggest an octahedral structure.²⁴

Proton and Carbon Nuclear Magnetic Resonance Spectra

^1H -NMR and ^{13}C -NMR spectrums of the ligand (HL) were recorded in d_6 -DMSO as a deuterated solvent. The ^1H -NMR spectra of HL exhibits signals due to phenolic proton as singlet at δ 10.17 ppm (1H), H-6 proton of pyrimidine ring as singlet at δ 9.41 ppm (1H), $-\text{CH}=\text{N}$ proton as singlet at δ 8.71 ppm (1H), H-2' and

H-6' protons as doublet at 7.84 ppm (2H, J=8 Hz), H-4' proton as triplet at 7.58 ppm (1H), aromatic protons as multiplet at 7.48-7.31 ppm (8H), H-6''' proton as double doublet at 7.11 ppm (1H), H-3''' proton as doublet at 6.96 ppm (1H, J=8.8 Hz) and O-CH₃ protons as singlet at 3.74 ppm (3H) (Figure 1 and Figure 2).^{9, 25} The ¹³C-NMR spectra of HL exhibits signals due to of benzoyl carbonyl carbon at 192.09 ppm, pyrimidine ring carbonyl carbon 170.99 ppm, azomethine carbon at 163.8 ppm, aromatic carbons at 153.5-110.34 ppm and O-CH₃ carbon at 55.95 ppm (Figure 2).⁹

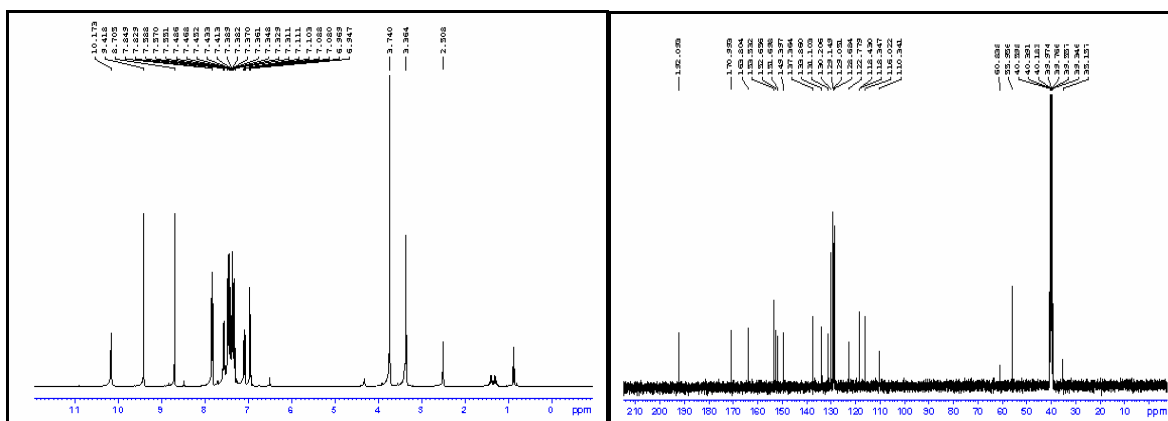


Figure 2. ¹H-NMR and ¹³C-NMR spectrum of the ligand

Antimicrobial Studies

Antimicrobial activity of the ligand and 4 metallic complexes (1a, 1b, 1c and 1d) were evaluated for antibacterial efficiency against *S. aureus* ATCC 6538, *S. aureus* ATCC 25923, *B. cereus* ATCC 7064, *M. luteus* ATCC 9345 and *E. coli* ATCC 4230 and for antifungal activity against *C. albicans* ATCC 14053, *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 by using broth microdilution procedure. Ampicillin and fluconazole were used as standard drugs. The antimicrobial activities of all chemical compounds against tested bacterial and fungal strains are given in Tables 1 and 2. According to the results, all compounds inhibited the growth of bacteria with MIC values in the range of 40-160 µg mL⁻¹ as well as displayed antifungal activity with MICs between 40-320 µg mL⁻¹.

Table 1. The MICs* of the ligand and its metal complexes against bacterial strains.

Compounds	<i>Bacillus cereus</i> ATCC 7064	<i>Staphylococcus aureus</i> ATCC 6538	<i>Staphylococcus aureus</i> ATCC 25923	<i>Escherichia coli</i> ATCC 4230	<i>Micrococcus luteus</i> ATCC 9345
HL	80	80	80	80	80
[CuL ₂]·H ₂ O·C ₄ H ₈ O	40	40	40	40	40
[CoL ₂]·2H ₂ O	80	40	80	80	40
[NiL ₂]·2H ₂ O	80	80	80	80	80
[MnL ₂]·C ₄ H ₈ O	160	80	80	160	80
Ampicillin	5	5	10	10	10

*The MICs values were determined as µg mL⁻¹ active compounds in medium.

The results of the antibacterial activity indicated that the complex called by Cu(II) (1a) had high antibacterial activity against the tested bacteria and yeast with MIC value 40 µg mL⁻¹. However, the other chemical compounds showed different levels antimicrobial activity against bacterial and fungal strains with MIC values in the range of 40-320 µg mL⁻¹. Finally, the results of antimicrobial assays suggested that the Cu(II) complex had good antimicrobial activity against all tested microorganisms. But, the antimicrobial efficacy of all tested compounds was lower than standard drugs.

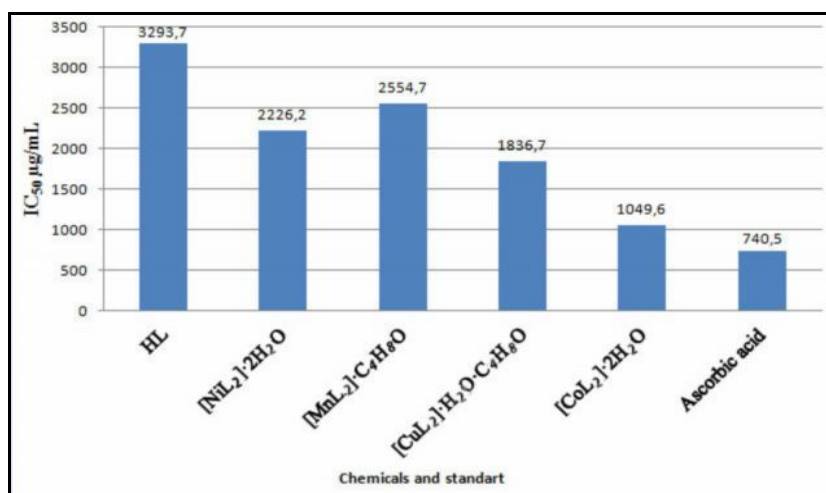
Table 2. The MICs* of the ligand and its metal complexes against fungal strains.

Compounds	<i>Candidaalbicans</i> ATCC 14053	<i>Candidaparapsilosis</i> ATCC 22019	<i>Candidakrusei</i> ATCC 6258
HL	80	80	80
[CuL ₂].H ₂ O.C ₄ H ₈ O	40	40	40
[CoL ₂].2H ₂ O	80	80	40
[NiL ₂].2H ₂ O	80	80	80
[MnL ₂].C ₄ H ₈ O	320	160	160
Fluconazole	5	5	10

*The MICs values were determined as $\mu\text{g mL}^{-1}$ active compounds in medium.

Antioxidant Studies

Free radical scavenging activity of new synthesized ligand, 4 metal complexes and ascorbic acid was evaluated for reduction of DPPH. Free radical scavenging ability (%) of ligand (HL), 4 metallic complexes (1a, 1b, 1c and 1d), and ascorbic acid against DPPH are given in figure 3. The complex called by Co(II) (1b) displayed good antioxidant activity with IC_{50} value $1049.6 \mu\text{g mL}^{-1}$, according to other complexes. However, this compound had not higher antioxidant efficiency than ascorbic acid used as standard. In addition, the Cu(II) (1a) and Ni(II) (1c) complexes showed moderate antioxidant activity with IC_{50} values $1836.7 \mu\text{g mL}^{-1}$ and $2226.2 \mu\text{g mL}^{-1}$, respectively, whereas ligand and Mn(II) (1d) complex had the least free radical scavenging activity with IC_{50} values ranging from 2554.7 – $3293.7 \mu\text{g mL}^{-1}$ (Figure 3).


Figure 3. IC_{50} values ($\mu\text{g/mL}$) of ligand, metal complexes and ascorbic acid

Cytosolic free radicals have adverse effects in living organisms for promoting aging, autoimmune disorders and tumor forming effects.^{26, 27} Hence, several natural and synthetic antioxidants have been used to protect from adverse effects of free radicals in pharmaceutical and medical studies.²⁸ It is well known that aromatic ring containing phenolic compounds are displayed good free radical scavenging activity. According to our findings, it can be suggested the antioxidant activity of the Co(II) complex was high when compared to ligand and other complexes. This case may be ascribed to standard reduction and oxidation potential of the Co(II) complex, the presence of methyl groups, and at position of methyl groups in aromatic ring.

Conclusion

In summary, pyrimidine derivative new Schiff base and its Cu(II), Co(II), Ni(II) and Mn(II) metal complexes were synthesized. All compounds were characterized NMR (for ligand), mass, UV-vis, FT-IR, elemental analyses and magnetic susceptibility. According to magnetic susceptibility and others data, all complexes showed octahedral geometry. The conductive values showed nonelectrolytic behavior of the

complexes. Schiff base and its metal complexes were screened for in vitro antioxidant studies and antimicrobial activities against bacteria and fungi.

Consequently, the findings of our findings suggested that two metal complexes (Cu(II) and Co(II)) had good biological efficiency in terms of antioxidant and antimicrobial. Finally, the Cu(II) and Co(II) metallic complexes might be possible as substances to eliminate the free radicals and against the antimicrobial agent.

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