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Original article

Synthesis, spectroscopic and biological studies on the new symmetric Schiff base derived from 2,6-diformyl-4-methylphenol with N-aminopyrimidine

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ABSTRACT

A phenol based novel Schiff base polydentate symmetric ligand was prepared. The complexes were prepared by reacting ligand and the metal chlorides of Cu (II), Ni(II), Co(II) and Fe(II) in methanol to get a series of mononuclear complexes. The complexes were characterized by elemental analyses, conductivity measurements, magnetic susceptibility data, IR, UV–Vis, NMR and API-ES mass spectral data. The mononuclear structure of the complexes was confirmed on the basis of elemental analyses, magnetic susceptibility and API-ES mass spectral data. The ligand and all the metal complexes were evaluated for their antimicrobial activity against four Gram-positive bacteria (*Staphylococcus aureus* ATCC 6538, *S. aureus* ATCC 25923, *Bacillus cereus* ATCC 7064 and *Micrococcus luteus* ATCC 9345), one Gram-negative bacterium (*Escherichia coli* ATCC 4230), and three yeast (*Candida albicans* ATCC 14053, *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019) strains. Therefore, newly synthesized the ligand and two complexes [(Cu(II) and Co(II)] showed good biological activity against all tested bacteria and yeast strains.

1. Introduction

2,6-Diformyl-4-methylphenol (dfp) is a well-known molecule in coordination chemistry, being employed as a starting material for the synthesis of various compartmental ligands [1–3]. One of the synthetic approaches for obtaining dissymmetric ligands starts from dfp [4]. Many binuclear metal complexes have been studied extensively. First row transition metal Schiff base complexes of dfp with N_2O_2, NON and NOO coordination sites are well characterized. Though many phenoxo bridged acyclic and macrocyclic complexes of dfp are known [5] but symmetric acyclic metal complexes of Schiff base containing both pyrimidine moieties by condensation of dfp are rare [6]. On the other hand, purines and pyrimidines and their derivatives are known for growth factor analogs and they have been used for treatment of bacterial, viral and fungal infections. In recent years, several studies were reported that metal complexes with Schiff bases are extremely important due to their considerable antifungal, antibacterial and antitumor activities [7–9]. A number of previous studies proposed that pyrimidines and their complexes displayed effective and selective antimicrobial activity against bacteria, fungi and virus [10–12].

In view of these observations, we reported synthesis, characterization and biological activity of a novel acyclic symmetric Schiff base ligand obtained by 2 + 1 condensation of dfp with N-aminopyrimidine and its metal complexes.

2. Chemistry

2.1. Materials

All chemicals used in this study were obtained commercially and used without purification. 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one (*N*-AP) [13] and 2,6-diformyl-4-methylphenol [14] were prepared according to the literature method.

2.2. Physical measurements

The Elemental analyses (C, H, N, S) were performed by using Leco CHNS model 932 elemental analyzer. IR spectra were obtained using KBr pellets (4000–400 cm^{-1}) on Bio-Rad-Win-IR Spectrophotometer. The electronic spectra in the 200–900 nm range were recorded in DMF on Unicam UV2-100 UV–Vis spectrophotometer. Magnetic measurements were carried out by Gouy method using $Hg[Co(SCN)_4]$ as a calibrant. Molar conductance of the Schiff base ligand and its transition metal complexes were determined in DMF

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at room temperature by using Jenway model 4070 conductivitymeter. The ^{1}H NMR and ^{13}C NMR spectra of the Schiff base were carried out using Bruker 300 MHz Ultrashield TM NMR instrument. LC/MS-API-ES mass spectra were recorded with Agilent model 1100 MSD mass spectrophotometer.

2.3. Synthesis of the ligand (HL)

The ligand (HL) was prepared by condensation between *N*-aminopyrimidine and dfp. The hot ethanolic solution (25 mL) of dfp (0.164 g, 1 mmol) and *hot* ethanolic solution (25 m*L)* of *N*-aminopyrimidine (0.582 g, 2 mmol) were mixed slowly with a constant stirring. *Then the* mixture was refluxed *for* 3 h. A yellow precipitate *was* formed. The isolated solid precipitate was filtered off, washed with hot ethanol and diethyl ether and then dried in vacuum over P_2O_5.

(0.462 g, 65%); mp: 273 °C. Anal. Calc. for $C_{43}H_{30}N_6O_5$ (710): C, 72.67; H, 4.25; N, 11.82. Found: C, 72.20; H, 4.36; N, 11.66 %. Selected IR data, (ν, cm^{-1}): 3400 (OH), 1687 (–C═O)$_{pyrimidine}$ 1652 (Ph-CO-), 1608 (HC═N); ^{1}H NMR (d6-DMSO, ppm), δ 11.33 (s, 1H, OH), 9.54 (s, 1H, HC═N), 8.85 (s, 1H, C(6)H, 7.31–7.88 (m, 7H, Harm); 2.35 (s, 3H, CH_3); ^{13}C NMR (d6-DMSO, ppm), δ 192.06 (OC-Ar), 179.31 (C═O, pyrimidine), 163.64 (–C6, pyrimidine ring), 157.38 (HC═N), 151.54-116.20 (C, aromatic), 20.22 (CH_3). UV–Vis (in DMF, nm): 276, 302, 347, 363, 396, 483, 549. LC-MS, m/z 711.1 [M + 1].

2.4. Synthesis of the complexes (**1–4**)

0.5 mmol (0.355 g) of the ligand HL was dissolved *in chloroform* and methanol mixture (50 mL; 1:1, v/v) and a solution of 0.5 mmol of $MCl_2 \cdot nH_2O$ in 15 mL methanol was added drop-wise with continuous stirring. The mixture was stirred for 1 h at 60 °C. The precipitated compound was removed by filtration, washed with diethyl ether and cold methanol and dried in vacuum desiccators. The complexes $[CuLCl] \cdot 2H_2O$, $[FeLCl] \cdot 5H_2O$, $[CoL_2] \cdot 4H_2O$ and $[NiL_2] \cdot 2H_2O$ were synthesized by following the above procedure using $CuCl_2 \cdot 2H_2O$ (0.5 mmol, 0.085 g), $FeCl_2 \cdot 4H_2O$ (0.5 mmol, 0.100 g), $CoCl_2 \cdot 6H_2O$ (0.5 mmol, 0.120 g), $NiCl_2 \cdot 6H_2O$ (0.5 mmol, 0.120 g).

2.4.1. Synthesis of $[CuLCl] \cdot 2H_2O$ complex

Cu(II) complex was synthesized according to the procedure as given. Pale green color compound. Yield: 0.290 g (69%); mp: 300 °C. Anal. Calc. for $C_{43}H_{33}ClCuN_6O_7$ (843.93): C, 65.75; H, 4.48; N, 10.46. Found: C, 66.10; H, 4.52; N, 10.40 %. Selected IR data (ν, cm^{-1}): 3332–3400 ν(OH/H_2O), 1659 ν(Ph-CO), 1618 ν(HC═N). μ_{eff}: 1.57 BM. Λ_M (10^{-3} M, in DMF, S cm^2 mol^{-1}): 37. UV–Vis (in DMF, nm): 261, 279, 291, 350, 448, 617. API-ES, m/z: 845.0 [M + $2H_2O$ + 1] (^{64}Cu isotope).

2.4.2. Synthesis of $[FeLCl] \cdot 5H_2O$ complex

Fe(II) complex was synthesized according to the procedure as given. Light brown color compound. Yield: 0.190 g (43%); mp: 225 °C. Anal. Calc. for $C_{43}H_{39}ClFeN_6O_{10}$ (890): C, 57.96; H, 4.41; N, 9.43. Found: C, 58.57; H, 3.93; N, 9.31 %. Selected IR data (ν, cm^{-1}), 3340 ν(OH/H_2O), 1657 ν(Ph-CO), 1617 ν(HC═N). μ_{eff}: 4.60 BM. Λ_M (10^{-3} M, in DMF, S cm^2 mol^{-1}): 46. UV–Vis (in DMF, nm): 236, 285, 330, 372, 407, 526, 652. API-ES, *m/z*: 889 $[M + 5H_2O]^+$ (^{57}Fe isotope).

2.4.3. Synthesis of $[NiL_2] \cdot 2H_2O$ complex

Ni(II) complex was synthesized according to the procedure as given. Red color compound. Yield: 0.997 g (66 %); mp: 145 °C decompose. Anal. Calc. for $C_{86}H_{62}N_{12}NiO_{12}$ (1512.7): C, 68.22; H, 4.10; N, 11.10. Found: C, 68.39; H, 4.34; N, 11.00 %. Selected IR data (ν, cm^{-1}): 3390 ν(OH/H_2O), 1657 ν(Ph-CO), 1602 ν(C═N). μ_{eff}: 1.59 BM. Λ_M (10^{-3} M, in DMF, S cm^2 mol^{-1}): 10.9. UV–Vis (in DMF, nm): 277, 298, 340, 379, 474, 674. API-ES, *m/z*: 1514 [M + $2H_2O$ + 1] (^{58}Ni isotope).

2.4.4. Synthesis of $[CoL_2] \cdot 4H_2O$ complex

Co(II) complex was synthesized according to the procedure as given. Red-brown color compound. Yield: 0.880 g (57%); mp: 186 °C decompose. Anal. Calc. for $C_{86}H_{66}CoN_{12}O_{14}$ (1549): C, 66.62; H, 4.26; N, 10.84. Found: C, 66.27; H, 4.32; N, 10.52. %. Selected IR data (ν, cm^{-1}): 3320 (OH/H_2O), 1654 ν(Ph-CO), 1618 ν(C═N). μ_{eff}:: 3.35 BM. Λ_M (10^{-3} M, in DMF, S cm^2 mol^{-1}): 7.5. UV–Vis (in DMF, nm): 203, 281, 356, 464, 677. API-ES, *m/z*: 1550 [M + $4H_2O$ + 1] (^{59}Co isotope).

3. Biological assay

3.1. Compounds

Test compounds were dissolved in DMSO (12.5%) at an initial concentration 1280 $\mu g\,mL^{-1}$ and then were serially diluted in culture medium.

3.2. Cells

Bacterial strains were supplied from American Types Culture Collection. *Candida* strains were obtained from Refik Saydam Hifsisihha Research Institute, Ankara, Turkey.

3.3. Antibacterial assay

Newly synthesized compounds were screened for their antibacterial activity against four 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 described by the guidelines in NCCLS approved standard document M7-A4 using the microdilution broth procedure [15]. Ampicillin trihydrate was used as reference antibacterial agent. Solutions of the compounds and reference drug were dissolved in DMSO at a concentration of 2560 $\mu g\,mL^{-1}$. The two-fold dilution of compounds and reference drug were prepared (1280, 640, 320, 160, 80, 40, 20, 10, $5 > \mu g\,mL^{-1}$). Antibacterial activities of the new synthesized compounds were performed in Mueller-Hinton broth (Difco) medium at pH 7.2 with an inoculum of $(1–2) \times 10^3$ cells mL^{-1} by spectrophotometric method and an aliquot of 100 µL was added to each tube of serial dilution. The chemical compounds-broth medium serial tube dilutions inoculated with each bacterium were incubated on a rotary shaker at 37 °C for 18 h at 150 rpm. The minimum inhibitory concentrations (MICs) of each chemical compounds were recorded as the lowest concentration of each chemical compounds in the tubes with no growth (i.e. no turbidity) of inoculated bacteria.

3.4. Antifungal assay

The antifungal activities of newly synthesized compounds were tested against three 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 [16]. Fluconazole was used as reference antifungal agent. Solution of the test compounds and reference drug were dissolved in DMSO at a concentration of 2560 $\mu g\,mL^{-1}$. The two-fold dilution of the compounds and reference drug were prepared (1280, 640, 320, 160, 80, 40, 20, 10,

$5 > \mu g\,mL^{-1}$). Antifungal activities of the yeast strains were performed in RPMI 1640 Medium (Sigma) which buffered to pH 7.0 with 0.165 M morpholinopropanesulfonic acid (Sigma) as outlined in document M27-A. The stock yeast inoculum suspensions were adjusted to concentration of $(0.5–2.5) \times 10^3$ cells ml^{-1} by spectrophotometric method and aliquot of 100 μL was added to each tube of the serial dilution. The synthesized compound-broth medium serial tube dilutions inoculated with yeast were incubated on a rotary shaker at 37 °C for 18 h at 150 rpm. The minimum inhibitory concentrations (MICs) of each synthesized compounds were recorded as the lowest concentration of each chemical compounds in the tubes with no growth (i.e. no turbidity) of inoculated yeast.

4. Result and discussion

4.1. Synthesis of the ligand and metal complexes

The ligand and complexes were synthesized and characterized by elemental analysis, IR, ^1H and ^{13}C NMR data, electronic spectra, mass spectra, magnetic susceptibility measurements and molar conductivity. The antimicrobial efficient of all the compounds was investigated and reported. The newly synthesized mononuclear Schiff base complexes were very stable at room temperature in the solid state. The metal complexes were generally soluble in DMF and DMSO. The corresponding data for the ligand and complexes were presented in the experimental section.

The reactions of the synthesis of the ligand and its complexes could be represented as follows.

$$2(N-AP) + dfp \xrightarrow{\text{methanole/chloroform}} [HL] + 2H_2O$$

$$HL + MCl_2 \cdot nH_2O \xrightarrow{\text{methanole/chloroform}} [MLCl]mH_2O + xH_2O$$

$$2HL + M'Cl_2 \cdot nH_2O \xrightarrow{\text{methanole/chloroform}} [M'(L)_2]mH_2O + xH_2O$$

$$HL = C_{43}H_{30}N_6O_5$$

M	Cu(II)	–	Fe(II)	–
M′	–	Co(II)	–	Ni(II)
n	2	6	4	6
m	2	4	5	2
x	–	2	1	4

The metal-to-ligand ratio of pentadentate Cu(II) and Fe(II) complexes was found to be 1:1 and in addition to this, the one chloride ligand was coordinated to metal ions. On the other hand, the metal-to-ligand ratio of Ni(II) and Co(II) complexes was found to be 2:1. All the complexes had two or more additional water of crystallization. This Schiff base had donor sites with the ONONO sequence and varied coordination abilities. This nature of the Schiff base attracted our attention and aroused our interest in elucidating the structure of Co(II), Ni(II) and Cu(II) complexes. These compounds were evaluated for their antibacterial and antifungal activities against various pathogenic bacterial and fungal microorganisms by using broth microdilution procedures (Tables 1 and 2).

Table 2
MICs[a] of the ligand (HL) and its metal complexes [Cu(II), Ni(II), Co(II) and Fe(II)] against fungal strains.

Compounds	*Candida albicans*	*Candida parapsilosis*	*Candida krusei*
	ATCC 14053	ATCC 22019	ATCC 6258
M (Cu)	20	20	20
M (Ni)	160	160	160
M (Co)	80	80	40
M $(Fe)_2$	160	160	160
HL	40	40	40
Fluconazole	5	5	10

[a] The MICs values were determined as μg ml^{-1} active compounds in medium.

4.2. IR spectra

The IR spectrum of the ligand showed a ν(C=N) peak *at* 1608 cm^{-1} and the absence of a ν(C=O) and ν(NH_2) peaks around 3250-3350 and 1681 cm^{-1} is indicative of Schiff base condensation. The IR spectra of Schiff base ligand showed a broad band *at* the 3435 cm^{-1} due to ν(OH). The free ν(OH) *was* generally observed between 3500 and 3650 cm^{-1} [17,18].

The intense band at 1288 cm^{-1} in the IR spectrum of the Schiff base ligand might be assigned to phenolic (C–O) stretching mode, according to the previous assignments. The pyrimidine ring showed characteristic stretching absorption bands at the 3060 cm^{-1}. The phenyl group showed C–H stretching at 3030 cm^{-1} and C=C stretching at 1550 cm^{-1}. The bands at 1583 cm^{-1} could be very safely assigned to ν(C=N) (pyrimidine) [18,19]. The strong bands at l687, 1652 cm^{-1} and 1608 cm^{-1} in the IR spectra of the free ligand assigned to ν(C=O) and ν(C=N) [20–22] were changed by ±10–30 cm^{-1} in the spectra of complexes, indicating coordination through azomethine nitrogen, phenolic oxygen and carbonyl oxygen of Schiff base (Fig. 1). In the spectra of the Cu(II), Ni(II), Co(II) and Fe(II) complexes, the bands observed in the 445–470 and 420–426 cm^{-1} region might be due to ν(M-N) and ν(M-O), respectively [20,23]. The IR spectra of the complexes was characterized by the appearance of a broad band in the region 3240–3350 cm^{-1} due to the υ(O–H) frequency of water of crystallization. This water was also identified by the elemental analyses. Broad bands of all the complexes in the 3240–3350 cm^{-1} region were assigned to the ν(OH) vibration of the water molecules [17,20,21].

Table 1
MICs[a] of the ligand (HL) and its metal complexes [Cu(II), Ni(II), Co(II) and Fe(II)] against Gram-negative and Gram-positive bacterial strains.

Compounds	*Bacillus cereus*	*Staphylococcus aureus*	*Staphylococcus aureus*	*Escherichia coli*	*Micrococcus luteus*
	ATCC 7064	ATCC 6538	ATCC 25923	ATCC 4230	ATCC 9345
M (Cu)	20	40	20	40	20
M (Ni)	80	40	40	80	40
M (Co)	80	40	40	40	80
M $(Fe)_2$	320	320	320	160	160
HL	80	20	20	40	20
Ampicillin	5	5	10	20	10

[a] The MICs values were determined as μg ml^{-1} active compounds in medium.

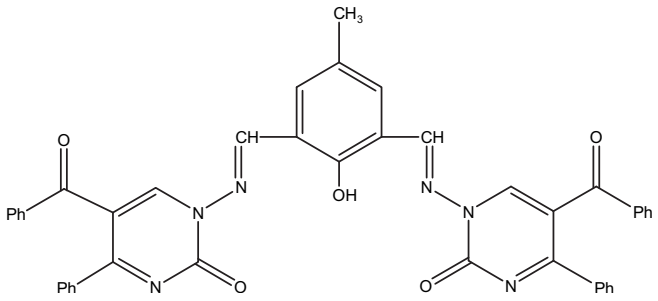

Fig. 1. Chemical structure of the Schiff base ligand (HL).

4.3. NMR spectra

DMSO-d_6 was used as a solvent to measure the ^1H, ^{13}C-NMR spectra (Fig. 2) of the ligand (Fig. 1). The ^1H NMR spectrum of the ligand showed signal at 2.35 ppm corresponding to the signals of CH_3. The sharp singlet observed at about δ 11.33 ppm due to phenolic proton of the ligand [22]. The singlet at δ 9.54 ppm and 8.85 ppm were due to azomethine proton and pyrimidine ring (C–H) proton in the spectrum of the ligand, respectively. The multi-signals corresponding aromatic protons appeared between at δ 7.31–7.88 ppm.

^{13}C NMR spectra displayed characteristic signals at 192.06, 179.31 and 163.64 ppm due to the (OC-Ar), (C=O, pyrimidine) and (-C6, pyrimidine ring) of the Schiff base ligand, respectively. The singlet peaks at 157.38 and 20.22 ppm were due to azomethine carbon and methyl carbon of the ligand [23]. On the other hand, the spectrum of the ligand showed peaks in the region δ 151.54–116.20 ppm, due to aromatic carbons.

4.4. Electronic spectra

The electronic absorption spectral data for the complexes, which were dissolved in DMF, was shown in the experimental section. In the UV-Vis region, the complexes showed bands at approximately 290 nm and in the range 340–410 nm as the weaker bands. The weak bands were attributed to intramolecular charge transfer transition [24] from the pπ orbital on the phenolate oxygen to the empty d orbitals of the metal.

The magnetic moment value (1.57 B.M.) for $[CuLCl]\cdot 2H_2O$ as well as the broad band in its electronic spectrum centered at 617 nm suggested a octahedral geometry [25] around the copper (II) ion. The observed band was due to the $^2B_{1g} \rightarrow {}^2E_{1g}$ and $^2B_{1g} \rightarrow {}^2A_{1g}$ transitions in the octahedral geometry. However, the band observed at 448 nm was probably due to a ligand-copper(II) ion charge transfer.

The electronic spectrum of the Ni(II) complex showed two d–d transitions at 474 and 674 nm assignable to the $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ (ν_2) and $^3A_{2g} \rightarrow {}^3T_{1g}(P)$ (ν_2) transitions, respectively, which indicated an octahedral environment around the metal ion [25] (Fig. 3a). The observed magnetic moment of the Ni(II) complex was 1.59 B.M.

The measured magnetic moment value (3.35 B.M.) of the Co(II) complex was lower than spin-only value (3.87 B.M.) and also lower than the values reported for complexes having octahedral. [26]. The electronic spectrum of $[CoL_2]\cdot 4H_2O$ in DMF solution showed two broad bands at 667 and 464 nm assignable to the $^4T_{1g} \rightarrow {}^4A_{2g}$ and $^4T_{1g} \rightarrow {}^4T_{1g}(P)$ transitions, respectively, in around the cobalt(II) ion.

The electronic spectrum of the Fe(II) complex consisted of a pair of low intensity bands at 526 and 652 nm, arising from a $^5T_{2g} \rightarrow {}^5E_g$ transition, similar to those found for distorted octahedral complexes. The doublet was attributed to Jahn–Teller distortion in

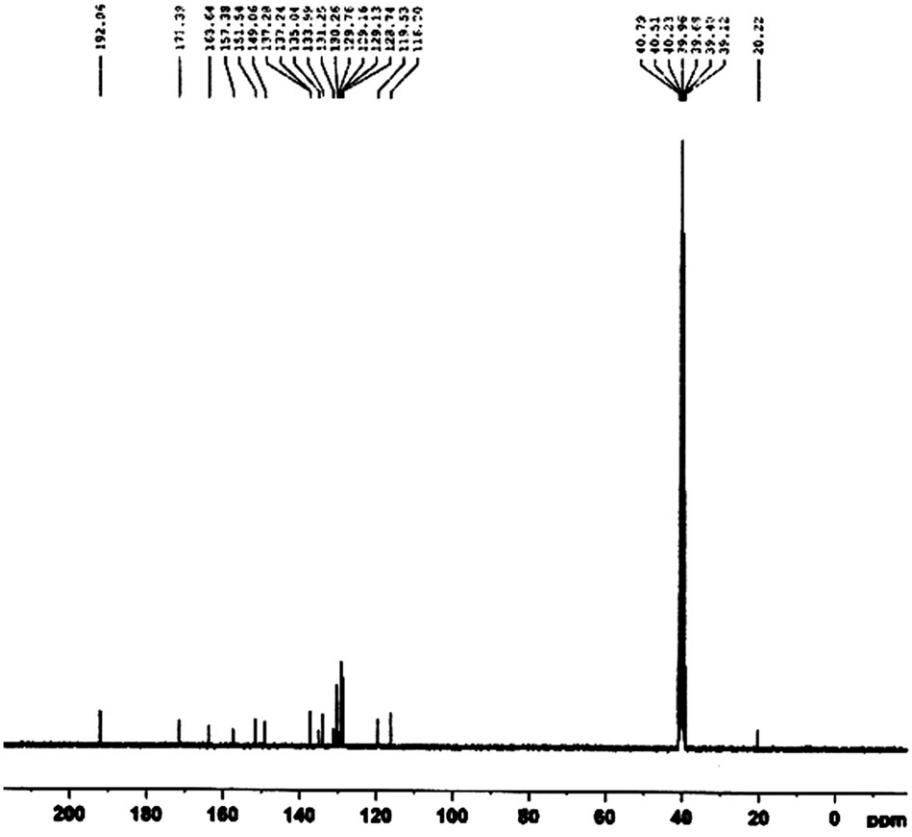

Fig. 2. ^{13}C NMR spectrum of the Schiff base ligand (in d_6-DMSO).

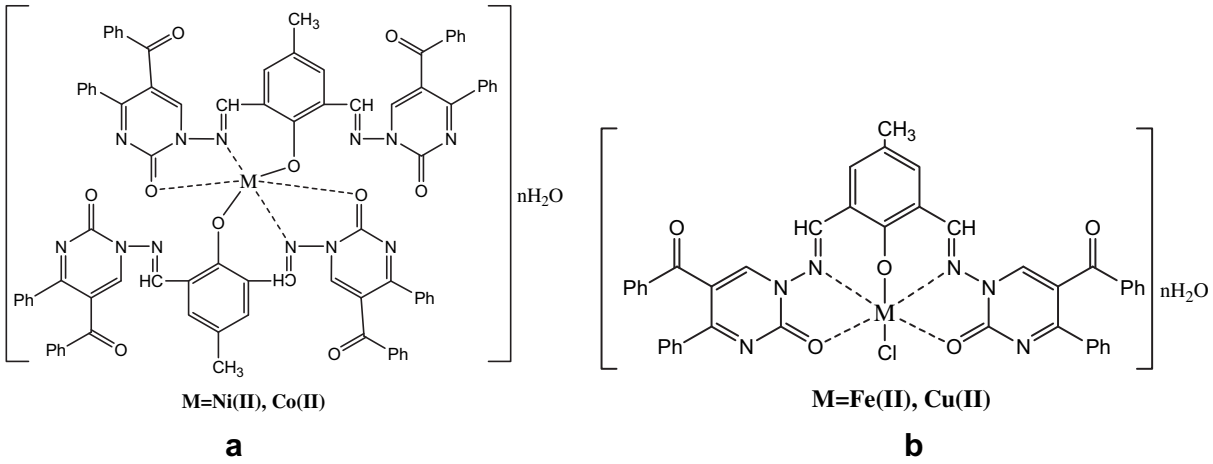

Fig. 3. Suggested structures of the Schiff base metal complexes.

the excited state [25]. At the room temperature, the magnetic moment (5.50 BM) corresponded to octahedral symmetry (Fig. 3b).

4.5. Mass spectra

In the mass spectra of the ligand and its metal complexes, peaks were attributable to the molecular ions; *m/z*: 711.1 [LH + 1], *m/z*: 845.0 [CuCl + L + $2H_2O$ + 1], *m/z*: 889.0 [FeCl + L+$5H_2O$]$^+$, *m/z*: 1514 [Ni + 2L + $2H_2O$ + 1], *m/z*: 1550 [Co + 2L + $4H_2O$ + 1]. The spectrum of the Schiff base ligand and Ni(II) complex were shown in Figs. 4 and 5, respectively.

4.6. Biological results

Biological activity of the ligand and a series of its metal complexes [Cu(II), Ni(II), Co(II) and Fe(II)] were screened for antibacterial activity 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 procedures. Ampicillin trihydrate for bacteria and fluconazole for yeast were used as reference drugs. The results of antimicrobial activity of the ligand and its metal complexes against all the bacterial and fungal strains were shown in Tables 1 and 2. As presented in tables, all compounds inhibited the growth of bacteria (Gram-negative and Gram-positive) with MIC values in the range of 20–320 μg mL^{-1} as well as exhibited antifungal activity with MICs between 20–160 μg mL^{-1}. However, they had similar or much less active against the tested organisms, compared with the standard drug.

According to the results of the antibacterial activity, the free ligand and its Cu(II), Ni(II) and Co(II) complexes possessed effective and selective antibacterial activity against one Gram-negative bacterium (*E. coli* ATCC 4230) and five Gram-positive bacteria (*B. cereus* ATCC 7064, *S. aureus* ATCC 6538, *S. aureus* ATCC 25923 and *M. luteus* ATCC 9345) with MIC values in the range of 20–80 μg mL^{-1} (Table 1). Additionally, Cu(II) complex was the most effective compound toward tested Gram-positive bacterial strains (MIC values 20–40 μg mL^{-1}). But, the Fe(II) complex had weak antibacterial activity against all Gram positive and Gram-negative bacteria with MICs between 160 and 320 μg mL^{-1}. Our findings also indicated that all prepared compounds displayed similar antibacterial efficiency against Gram-negative and Gram-positive bacteria.

Table 2 summarized antifungal activities of the free ligand and the complexes compounds against 3 yeast strains (*C. albicans* ATCC 14053, *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019). According to antifungal studies, the ligand and Cu(II) and Co(II) complex compounds displayed good anti-yeast efficiency against the fungal species (MICs, 20–40 μg mL^{-1}). However, Ni(II) and Fe(II) complexes exhibited weakly antifungal activity (MIC, 160 μg mL^{-1}).

The results of this investigation revealed that the ligand, Cu(II), Ni(II) and Co(II) complexes possessed higher antimicrobial activity, although it was generally reported that free ligands shown lower activity than complexes [7–9,27,28]. Additionally, when all the antimicrobial MIC values were compared, the ligand and Cu(II) complex displayed the highest antimicrobial efficacy with MIC values ranging between 20–40 μg mL^{-1}. Accordingly, the data obtained from this investigation were in good agreement with the previous studies that expressed the metal complexes with Schiff bases have greater activity toward microorganisms [7–9]. Finally, it suggested that the reason for this higher antimicrobial efficacy can be related to the inhibition several structural enzymes, which play a key role in vital metabolic pathways of the microorganisms.

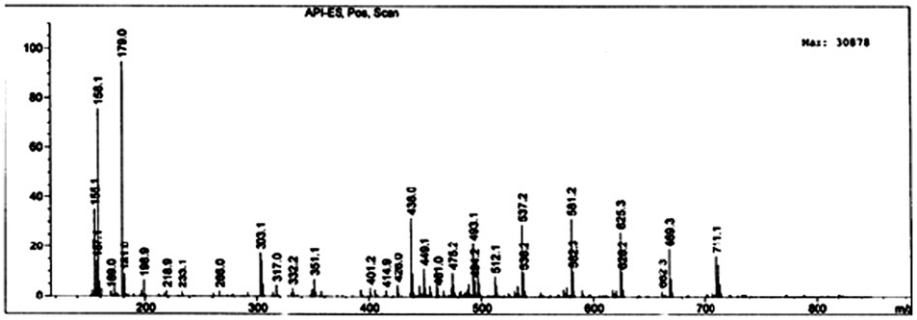

Fig. 4. API-ES spectrum of the Schiff base ligand.

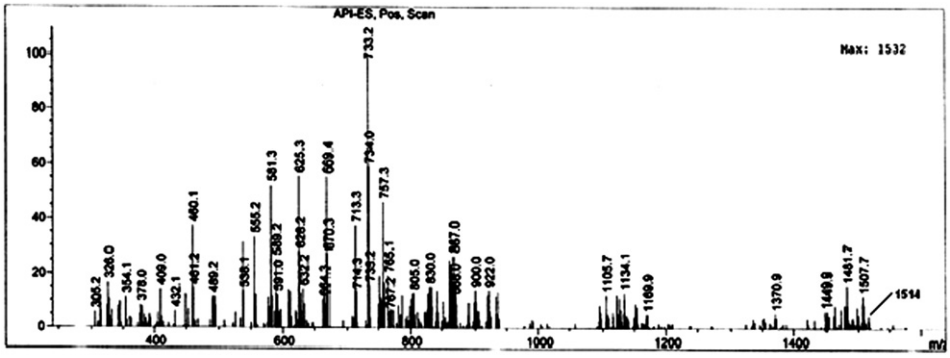

Fig. 5. API-ES spectrum of the $[NiL_2]\cdot 2H_2O$ complex.

5. Conclusion

We have evaluated in vitro the antibacterial and the antifungal activities of newly synthesized polydentate symmetric Schiff base and mononuclear Cu(II), Fe(II), Co(II) and Ni(II) complexes of the types $[MLCl]\cdot nH_2O$ and $[ML_2]\cdot nH_2O$. The results obtained from this research demonstrated that newly synthesized all compounds had good antibacterial activity against the bacterial strains, except for Fe(II) complex. Besides, the ligand, Cu(II) and Co(II) complexes exhibited selective and effective activity against *Candida* species. Multi-drug resistant microorganisms pose a serious challenge to the medical community and there is therefore an urgent need to develop new agents. In this sense, we think that the ligand and two metal complexes [Cu(II) and Co(II)] might be effective as antimicrobial agents bacteria and fungi.

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References

[1] S. Broker, D.J. de Geest, G.S. Dunber, Inorg. Chim. Acta 282 (1998) 222.
[2] B.H.M. Mruthyunjayaswamy, Omkar B. Ijore, Y. Jadegoud, J. Braz. Chem. Soc. 16 (4) (2005) 783.
[3] H. Okawa, I. Ando, S. Kida, Bul. Chem. Soc. Jap. 47 (12) (1974) 3041.
[4] P. Akilan, M. Thirumavalavan, M. Kandaswamy, Polyhedron 2 (2003) 3483.
[5] P. Guerriero, S. Tamburini, P.A. Vigato, Coord. Chem. Rev. 139 (1995) 17.
[6] G. Bandoli, A. Dolmella, F. Tisato, M. Porchia, F. Refosco, Coord. Chem. Rev. 253 (2009) 56.
[7] K.V. Sharma, V. Sharma, U.N. Tripathi, J. Coord. Chem. 62 (3) (2009) 506–518.
[8] H. Arslan, N. Duran, G. Borekci, C.K. Ozer, C. Akbay, Molecules 14 (2009) 519–527.
[9] A. Abdou, M. Mahmoud, Z. Yasser, Phosphorus Sulfur Silicon Relat. Elem. 183 (7) (2008) 1746–1754.
[10] H. Francisco, A. Nuria, N. Miguel, M. Jose, J. Maria, J. Inorg. Biochem. 94 (2003) 326.
[11] M.T. Madigan, J.M. Martinko, J. Parker, Brock Biology of Microorganisms, eighth ed. Prentice-Hall, Inc. Upper Saddle River, New Jersey, USA, 1997.
[12] R. Hilal, Z.M. Zaky, S.A.K. Elroby, Spectrochim. Acta A 63 (2006) 740.
[13] Y. Akçamur, B. Altural, E. Sarıpınar, G. Kollenz, O. Kappe, K. . Peters, E. Peters, H. Schering, J. Heterocylic Chem. 25 (1988) 1419.
[14] R.R. Gagne, C.L. Spiro, T.J. Smith, C.A. Hamann, W.R. Thies, A.K. Shiemke, J. Am. Chem. Soc. 103 (1981) 4073.
[15] National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, Approved Standard M7-A4. NCCLS: Villanova, PA, USA, (1997).
[16] National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of yeasts, Approved Standard M27-A2. NCCLS: Wayne, PA, USA, (2002).
[17] K. Nakamoto, Infrared and Raman Spectra of Inorganic and Coordination Compounds. Wiley, New York, 1986.
[18] M. Sönmez, A. Levent, M. Şekerci, Synth. React. Inorg. Met-Org. Chem. 33 (10) (2003) 1747–1761.
[19] M. Sönmez, Synth. React. Inorg. Met-Org. Chem. 34 (4) (2004) 733–741.
[20] N.R. Mohamed, M.M.T. El-Saidi, Y.M. Ali, M.H. Elnagdi, Bioorg. Med. Chem. 15 (2007) 6227.
[21] G. Asgedom, A. Streedhara, J. Kivikoski, E. Kolehmainen, C.P. Rao, J. Chem. Soc. Dalton Trans. (1996) 93.
[22] P.G. Avaji, C.H.V. Kumar, S.A. Patil, K.N. Shivananda, C. Nagaraju, Eur. J. Med. Chem. 44 (2009) 3552–3559.
[23] M. Tümer, N. Deligönül, A. Gölcü, E. Akgün, M. Dolaz, H. Demirelli, M. Dığrak, Trans. Met. Chem. 31 (2006) 1–12.
[24] G. Ferguson, J.N. Low, M. Quirós-Olozábal, J.M. Salas-Peregrin, F. Hueso-Urena, M.N. Moreno-Carretero, Polyhedron 15 (19) (1996) 3233–3239.
[25] A.B.P. Lever, Inorganic Electronic Spectroscopy, second ed. Elsevier, Amsterdam, 1984.
[26] M. Nath, A. Kumar, S. Vashistha, Synth. React. Inorg. Met.-Org. Chem. 28 (6) (1998) 893–906.
[27] X.Y. Xu, J. Gao, M.Y. Wang, W.X. Ma, H.B. Song, K.P. Wainwright, J. Coord. Chem. 58 (2005) 669–676.
[28] A.A. Massoud, V. Langer, L. Öhrstrom, M.A.M. Abu-Youssef, J. Coord. Chem. 62 (2009) 519–530.