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Research Article

Synthesis of complexes Co, Cu, Ni and Pd supported by "ONNO" type Schiff base ligand and their DNA cleavage, antioxidant effects and antimicrobial studies

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ABSTRACT

A new Schiff base ligand was synthesized from a reaction of 5-benzoyl-4-hydroxy-2-methyl-6-phenyl-2H-pyridazine-3-one and 1,3-diaminopropane. Schiff base metal complexes were synthesized from a reaction of $Ni(AcO)_2{\cdot}4H_2O$, $Cu(AcO)_2{\cdot}H_2O$, $Co(AcO)_2{\cdot}4H_2O$, $Pd(AcO)_2$ metal salts and ligand, respectively. All compounds were characterized using magnetic susceptibility, elemental analysis, NMR (for ligand), UV-Vis and FT-IR spectroscopic analysis. While octahedral structure has been proposed for Ni(II), Pd(II) and Co(II) complexes, square-planar geometry is suggested for Cu(II) complex. Synthesized compounds were evaluated for their antioxidant effect, DNA cleavage and antimicrobial studies. The DPPH free radical scavenging activity of compounds 1, 2, 3, 4 and 5 on DPPH were found as 38.5%, 32.5%, 36.9%, 35.7% and 45.7% at 200 mg l^{-1}, respectively. The compounds 4 and 5 revealed maximum ferrous chelating activity of 64.5% and 78.1% at 200 mg ml^{-1}, respectively. For all the compounds, DNA cleavage studies showed complete DNA digestion at 100 mg ml^{-1}. Antimicrobial activities of 3 and 4 complexes against *Staphylococcus aureus (*ATTC 6538) were determined to be in 12 mm diameter.

Keywords: Pyridazinone complexes, DNA cleavage, antioxidant effect, antimicrobial studies.

"ONNO" tip Schiff baz ligand destekli Co, Cu, Ni ve Pd komplekslerinin sentezi ve DNA bölünme, antioksidan etkileri ve antimikrobiyal çalışmaları

ÖZ

5-benzoil-4-hidroksi-2-metil-6-fenil-2H-piridazin-3-on ile 1,3-diaminopropan'ın reaksiyonundan yeni bir Schiff baz ligand sentezlendi. Sırasıyla ligand ile $Co(AcO)_2{\cdot}4H_2O$, $Cu(AcO)_2{\cdot}H_2O$, $Ni(AcO)_2{\cdot}4H_2O$, $Pd(AcO)_2$ metal tuzlarının reaksiyonundan Schiff baz metal kompleksleri sentezlendi. Tüm bileşikler elementel analiz, manyetik duyarlılık ile NMR (ligand için), FT-IR ve UV-Vis gibi spektroskopik analiz yöntemleriyle karakterize edildi. Ni(II), Pd(II) ve Co(II) kompleksi için oktahedral geometri önerilirken, bakır kompleksi için kare düzlem geometri önerilmiştir. Sentezlenen bileşiklerin antioksidant etkileri, DNA bölünmesi ve antimikrobiyal özellikleri incelendi. 1, 2, 3, 4 ve 5 bileşiklerinin DPPH üzerinde 200 mg l^{-1}' de DPPH serbest radikallerini çıkarma aktiviteleri sırasıyla % 38.5, % 32.5, % 36.9, % 35.7 ve % 45.7 olarak bulundu. Bileşik 4 ve 5'in 200 mg l^{-1}' de % 64.5 ve % 78.1' lik maksimum demir şelatlama aktivitesi gösterdi. Bütün bileşikler için DNA bölünme çalışmaları 100 mg l^{-1}' de tam DNA parçalanması gösterdi. *Staphylococcus aureus* (ATTC 6538)'e karşı kompleks 3 ve 4' ün antimikrobiyal aktivitelerinin 12 mm çapında olduğu belirlendi.

Anahtar Kelimeler: Piridazinon kompleksleri, DNA bölünmesi, antioksidan etki, antimikrobiyal çalışmalar.

1. INTRODUCTION

Pyridazinone compounds have been the focus of researchers in recent years due to many factors such as analgesic, anti-inflammatory, antipyretic, antihypertensive, antiulcer, antibacterial, antifungal, antituberculous and antitumor effects.[1-10] Synthesis of pharmacologically active pyridazinone derivatives has been rapidly increased, as it has been found that compounds of the pyridazinone ring have positive activity-related contributions to the compounds.[11, 12] In a our previous study, it was observed that pyridazinone-derived ligands and their complexes were synthesized and that these compounds possess antibacterial and antifungal activity.[13]

Antioxidants play a crucial role in the living system in terms of protecting from oxidative stress and other chronic diseases.[14] Recently, many scientists have been working on compounds newly synthesized or acquired from natural originsin order to prevent or decline the effect of oxidative stress on cells. These compounds can be used as free radicals or active oxygen scavengers or metal chelators which reduce agents and also prevent cancer.[15] DNA is the main target molecule for most of antiviral and anticancer therapies. Therefore, DNA cleavage is helpful in molecular biotechnology, genetic engineering and anticancer drug designing.[16] Besides, these compounds can exhibit satisfactory antimicrobial activity.

In this work, a novel pyridazinone derivative ligand and its Co, Cu, Ni and Pd complexes have been synthesized. The structures of these compounds were characterized by elemental analysis, magnetic susceptibility and NMR, FT-IR, UV-Vis by various spectroscopic methods. DNA cleavage, antioxidant effects and antimicrobial activities of these compounds were investigated. The synthesis, characterization and biological activity results of these compounds are presented here for the first time.

2. EXPERIMENTAL

2.1. Materials and methods

All of the reactants and solvents were purchased from Aldrich or Merck and used without further purification (95-99% purity). 5-benzoyl-4-hydroxy-2-methyl-6-phenyl-2H-pyridazine-3-one was prepared according to the procedure in the literature.[17] NMR spectra were measured on Premium Compact NMR (Agilent-600 MHz). Elemental analyses were measured on a Thermo Scientific Flash EA 2000 CHNS analyzer. Infrared spectra were measured on a Perkin-Elmer Spectrum 100 FTIR spectrophotometer with an ATR sampling accessory. Electronic absorption spectra were recorded on a PG Instruments T80 + UV / Vis spectrometer.

2.2. Synthesis of 5,5'-(((propane-1,3 diylbis(azanylylidene))bis(phenylmethanylylidene)bis(4-hydroxy-2-methyl-6-phenylpyridazin-3(2H)-one) ligand (H_2L) (1)

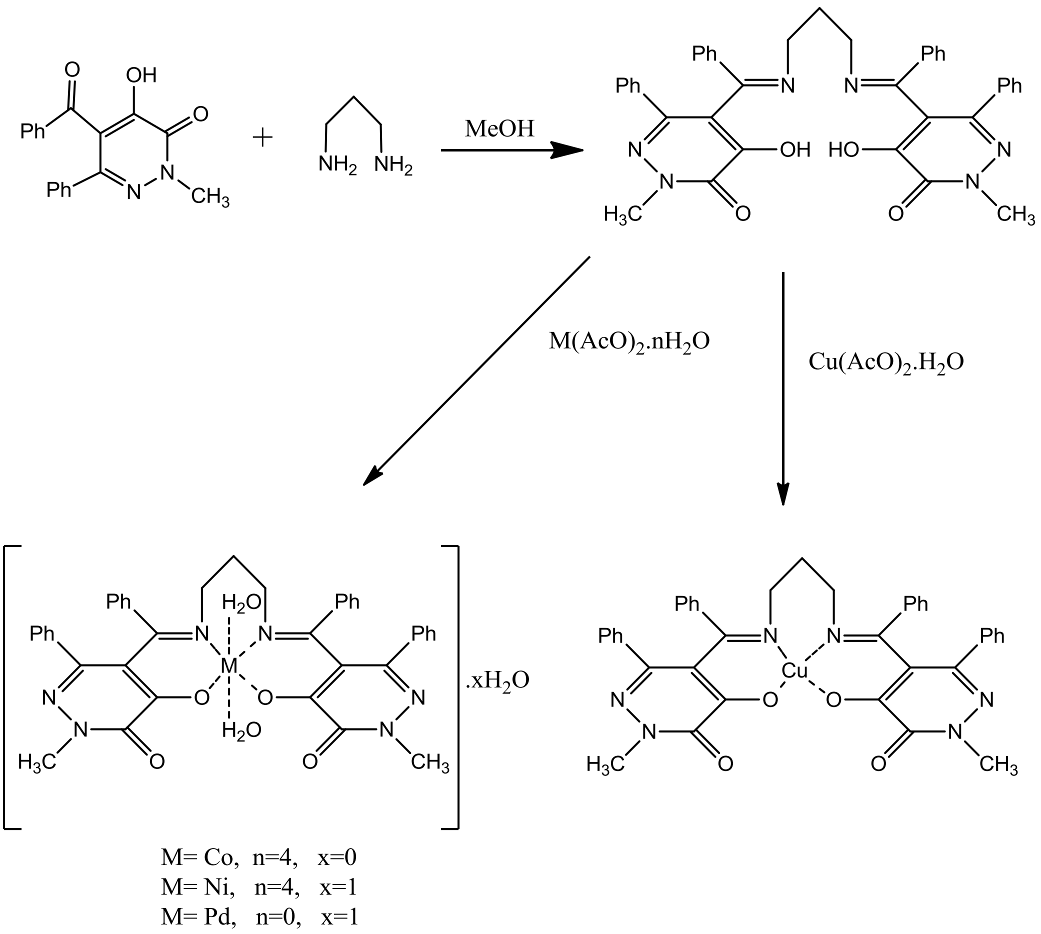
The ligand (H_2L) was prepared by heating a solution of 5– benzoyl - 4 – hydroxyl – 2 – methyl – 6 - phenyl-2H-pyridazine-3-one (0.153 g, 0.5 mmol) and *o*-aminophenol (0.055 g, 0.5 mmol) in 20 ml methanol to 65°C for 1 h. (Scheme 1) After cooling to room temperature, the solid in the reaction medium was filtered. The product was washed in diethylether and was purified slowly with vapor diffusion of Et_2O with a ethanol/chloroform (1:1) solution of ligand and then dried in vacuo. Yellow. Yield 0.150 g (46 %); 239-240°C. IR, (ATR) ν, cm^{-1}: 3524 (O-H); 3089 (C-H)$_{arom.}$; 1638 (C=O); 1597, 1579 (C=N); 1340 (C-O); 1525 (C=C). UV-Vis (DMF, λ_{max} nm, (Abs.)): 390 (0.155), 294 (0.760), 270 (0.880) nm. ^{1}H NMR (600 MHz, d$_6$-DMSO) δ (ppm); s, singlet; m, multiplet; p, pentet: 8.22 (s, 2H, O-H protons), 7.75-7.16 (m, 20H, Harm), 3.59 (s, 6H, CH_3 protons), 2.77 (t, 4H, CH_2 protons), 1.74 (p, 2H, CH_2 protons). ^{13}C NMR (600 MHz, d$_6$-DMSO) δ (ppm); δ 197.18 (C-O)$_{pyridazine}$, 164.25, 162.85 (C=N), 148.25, 139.24, 138.94, 132.58, 129.46, 128.69, 128.05, 128.37, 127.76, 116.20 (Aromatic carbons), 36.62 (CH_3), 25.87 (CH_2). Anal. Calc. $C_{39}H_{34}N_6O_4$ (650.73): C, 71.98, H, 5.27, N, 12.91 Found: C, 71.83, H, 5.51, N, 12.60%.

2.3. General synthesis method of the complexes *(2-5)*

A methanolic solution (10 ml) of metal acetate ($Co(AcO)_2\cdot 4H_2O$ (0.062 g), $Cu(AcO)_2\cdot H_2O$ (0.050 g), $Ni(AcO)_2\cdot 4H_2O$ (0.062 g), $Pd(AcO)_2$ (0.056 g), 0.25 mmol) was mixed with a solution of ligand (H_2L) (0.163 g, 0.25 mmol) in 20 ml of ethanol/chloroform (1:1). The reaction mixture was stirred for 30 minutes at 65-70°C, the precipitate was filtered off, it was washed with cold MeOH-H_2O (1:1) and Et_2O, the complex was purified slowly with vapor diffusion of Et_2O with a THF solution of complex and then dried in vacuo.

[$CoL(H_2O)_2$] complex (**2**): Brown. Yield 0.043 g (23 %); 220°C decompose. IR, (ATR)ν, cm^{-1}: 3300 (O-H); 3060 (C-H)$_{arom.}$; 1661 (C=O); 1592 (C=N); 1356 (C-O); 1542 (C=C); 508 (M-O); 540 (M-N). μ_{eff}: 4.99. UV-Vis (DMF, λ_{max} nm, (Abs.)): 405 (0.057), 345 (0.341), 284 (1.143) nm. Anal. Calc. $C_{39}H_{36}CoN_6O_6$ (743.20): C, 62.99, H, 4.88, N, 11.30 Found: C, 62.82, H, 4.96, N, 10.85%.

[CuL] complex (**3**): Green. Yield 0.077 g (43 %); 245°C decompose. IR, (ATR)ν, cm^{-1}: 3058 (C-H)$_{arom.}$; 1655 (C=O); 1594 (C=N); 1364 (C-O); 1538 (C=C); 507 (M-O); 536 (M-N). μ_{eff}: 1.56. UV-Vis (DMF, λ_{max} nm, (Abs.)): 405 (0.033), 327 (0.510), 284 (1.452), 270 (1.985) nm. Anal. Calc. $C_{39}H_{32}CuN_6O_4$ (712.26): C, 65.77, H, 4.53, N, 11.80 Found: C, 65.56, H, 4.20, N, 10.78%.



Scheme 1. Synthesis of Schiff base ligand and its metal complexes.

[NiL(H$_2$O)$_2$]·H$_2$O complex (**4**): Green. Yield 0.084 g (44 %); 250 °C decompose. IR, (ATR)*v*, cm^{-1}: 3350 (O-H); 3058 (C-H)$_{arom.}$; 1659 (C=O); 1589 (C=N); 1355 (C-O); 1538 (C=C); 508 (M-O); 542 (M-N). μ_{eff}: 3.08. UV-Vis (DMF, λ_{max} nm, (Abs.)): 400 (0.110), 350 (0.437), 286 (1.426), 270 (1.638) nm. Anal. Calc. $C_{39}H_{38}N_6NiO_7$ (761.45): C, 61.52, H, 5.03, N, 11.04 Found: C, 60.66, H, 4.88, N, 10.41%.

[PdL(H$_2$O)$_2$]·H$_2$O complex (**5**): Brown. Yield 0.047 g (23 %); 135 °C decompose. IR, (ATR) *v*, cm^{-1}: 3400 (O-H); 3060 (C-H)$_{arom.}$; 1642 (C=O); 1578 (C=N); 1338 (C-O); 1538 (C=C); 503 (M-O); 527 (M-N). μ_{eff}: diamagnetic. UV-Vis (DMF, λ_{max} nm, (Abs.)): 420 (0.158), 381 (0.313), 286 (1.508), 270 (1.786) nm. Anal. Calc. $C_{39}H_{38}N_6O_7Pd$ (809.18): C, 57.89, H, 4.73, N, 10.39 Found: C, 57.18, H, 4.84, N, 10.73%.

2.4. DPPH radical scavenging assay

Different solutions (10, 25, 50,100 and 200 mg l^{-1}) (0.5 ml) in dimethyl formamide (DMF) of compounds and 2 ml of 2,2- diphenyl-1-picrylhydrazyl radical (DPPH) (0.004%) solution were incubated at 25°C in the dark for half an hour.[18] The absorbance was measured at 517 nm. DMF solution was used as the blank control. The DPPH scavenging activity was calculated as follows: DPPH scavenging activity (%) = [1- ($A_{517\text{ nm, sample}}$ / $A_{517\text{ nm,control}}$)] x 100 Trolox and Ascorbic Acid were used as standards in order to compare with the results.

2.5. Ferrous ion chelating activity

Metal chelating ability on ferrous ions examined by the compounds were applied as recorded by Hsu et al.[19] Metal chelating effect was calculated as follows: Metal chelating ability (%) = [($A_{562\text{ nm, control}}$ - $A_{562\text{ nm, sample}}$) / $A_{562\text{ nm, control}}$] x 100 Ethylenediaminetetraacetic acid (EDTA) was used as the positive control.

2.6. DNA cleavage activity

The DNA cleavage studies were carried out by using agarose gel electrophoresis. pBR 322 plasmid DNA (0.1 mg ml^{-1}), Tris–HCI and NaCI (pH 7.4) and ligands and metal complexes (100 mg l^{-1}) were mixed and incubated in an incubator at 37 °C for 90 min. Then, the loading buffer was added and the reaction mixture was electrophoresed for 1.5 hour at 80 V by. Tris-boric acid-EDTA was used as an electrophoresis buffer. The electrophoresis bands were visualized by UV-A light.

2.7. Antimicrobial activity

Enterococcus hirae (ATCC 10541), *Bacillus cereus*, *Staphylococcus aureus* (ATCC 6538), *Escherichia coli* (ATCC 10536), *Legionella pneumophila* subsp. *pneumophila* (ATCC 33152), *Pseudomonas aeruginosa* (ATCC 9027) and *Candida albicans* were used as test microorganisms. Antimicrobial activity of compounds was evaluated by using disk-diffusion method.[20]

3. RESULTS AND DISCUSSION

The Schiff base ligand (H_2L) was synthesized from a reaction of 5-benzoyl-4-hydroxy-2-methyl-6-phenyl-2H-pyridazine-3-one and *o*-aminophenol in methanol. The complexes were synthesized from the reaction of (1:1) ligand with cobalt(II), copper(II), nickel(II) and palladium(II) acetate salts, respectively. The structures of compounds were characterized by NMR (for ligand), UV-Vis, FT-IR, magnetic susceptibility and elemental analysis. All of the complexes are air-stable at room temperature in the solid state, soluble in DMF, THF and insoluble in water. The structure of the copper complex appears to be [CuL], while the structure of the other complexes appears to be $[ML(H_2O)_2]\cdot nH_2O$. According to the magnetic susceptibility measurements, the copper complex is square plane geometry while the other complexes are octahedral geometry.

3.1. FT-IR spectra

When the FT-IR spectra of Schiff base ligand (1) and its metal complexes (2-5) are examined, it is found that (C=N) imine group is between 1594 cm^{-1} and 1589 cm^{-1}. These values are quite compatible with the literature.[21-23] While the C=N stretching band of the Schiff base ligand is 1597 cm^{-1}, this value is shifted 3-8 cm^{-1} down in the complexes. This suggests that the complexes are linked to the metal via the imine group. It has been observed that the carbonyl (C=O) stretching bands in all the synthesized compounds are in the range of 1661-1638 cm^{-1}.[24] Metal-N and metal-O bands in the metal complexes are 542-527 cm^{-1} and 508-503 cm^{-1}, respectively.[21-23]

3.2. Electronic spectra and magnetic measurements

The UV-Vis spectra of the synthesized compounds were recorded in the range of 190-1100 nm, at a concentration of 2 x 10^{-5} M and in DMF. The n-π* transitions of the azomethine group were observed at 390 nm in the ligand, while the values of the complexes were observed at 345, 327, 350, 381 nm, respectively. Transitions observed 270 nm and between 294-284 nm in the complexes are the n-π* and π-π* transitions of the phenyl and pyridazine rings. It is believed that the transition observed in the complexes between 400-420 nm is due to the weak charge-transfer transition. In the complexes, d-d transition was not observed clearly. For this reason, it is considered that the other transitions mask the d-d transition. In addition, the magnetic susceptibility value of the Cu (II) complex is 1.56 BM. This indicates that the copper complexes have square plane geometry and partial anti-ferromagnetic.[25] The magnetic susceptibility value of the cobalt (II) complex is 4.99 BM. This value is above the octahedral geometry values (4.2-4.6 BM) in the literature. This result shows that Co (II) complex has octahedral geometry and partial ferromagnetic properties.[26] The magnetic susceptibility value of the Ni (II) complex is 3.08 BM. This value is consistent with octahedral geometry values (2.8-3.1 BM) in the literature. The complex of Pd (II) is diamagnetic. The complex is thought to have octahedral geometry.

3.3. Proton and carbon nuclear magnetic resonance spectra

^{1}H-NMR and ^{13}C-NMR spectrums of the Schiff base ligand (**1**) were recorded in d_6-DMSO as a deuterated solvent. The ^{1}H-NMR spectra of the Schiff base ligand (**1**) exhibits signals due to OH protons as singlet at δ 8.22 ppm (2H), protons of pyridazine and phenyl rings as multiplet at δ 7.75-7.16 ppm (20 H), CH_3 protons as singlet at δ 3.59 ppm (6H), CH_2 protons as triplet at δ 2.77 ppm (4H), CH_2 protons as pentet at δ 1.74 ppm (2H) (Figure 1). Since there are many aromatic rings in the structure of Ligand (1), the aromatic region is complicated in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectra of the Schiff base ligand (**1**) exhibits signals due to of pyridazine ring (C=O) carbon at 197.18 ppm, azomethine carbons at 162.85 and 164.25 ppm, aromatic carbons at 148.25-116.20 ppm, CH_3 carbon at 36.62 ppm and CH_2 carbon at 25.87 ppm (Figure 2). Since the Pd complex does not have good solubility in solvents such as DMSO and chloroform, the NMR can't be obtained.

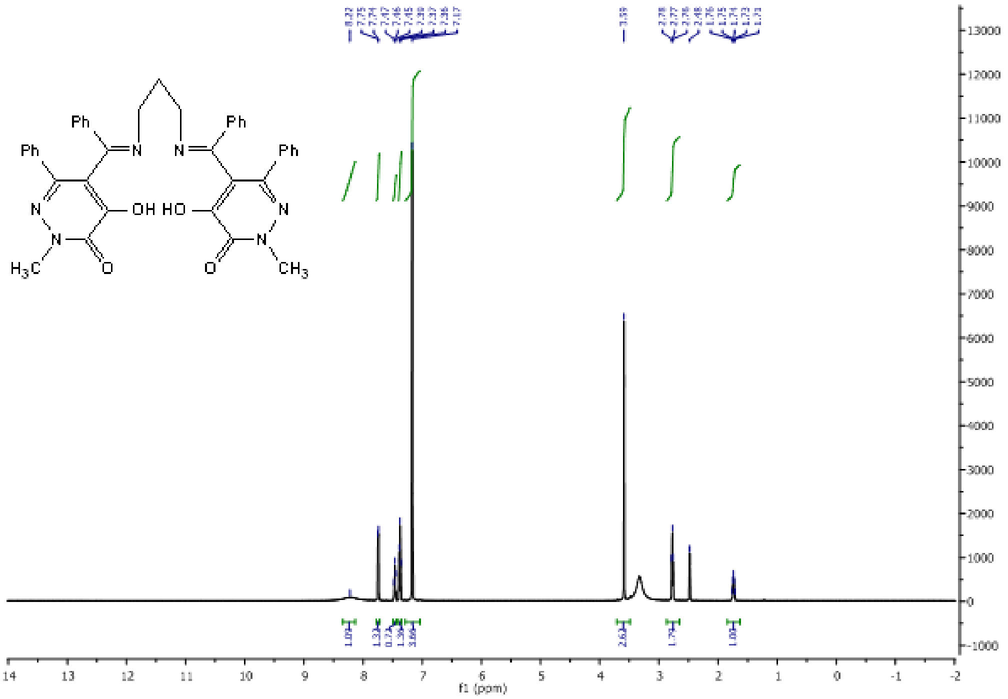


Figure 1. ^{1}H-NMR spectrum of ligand.

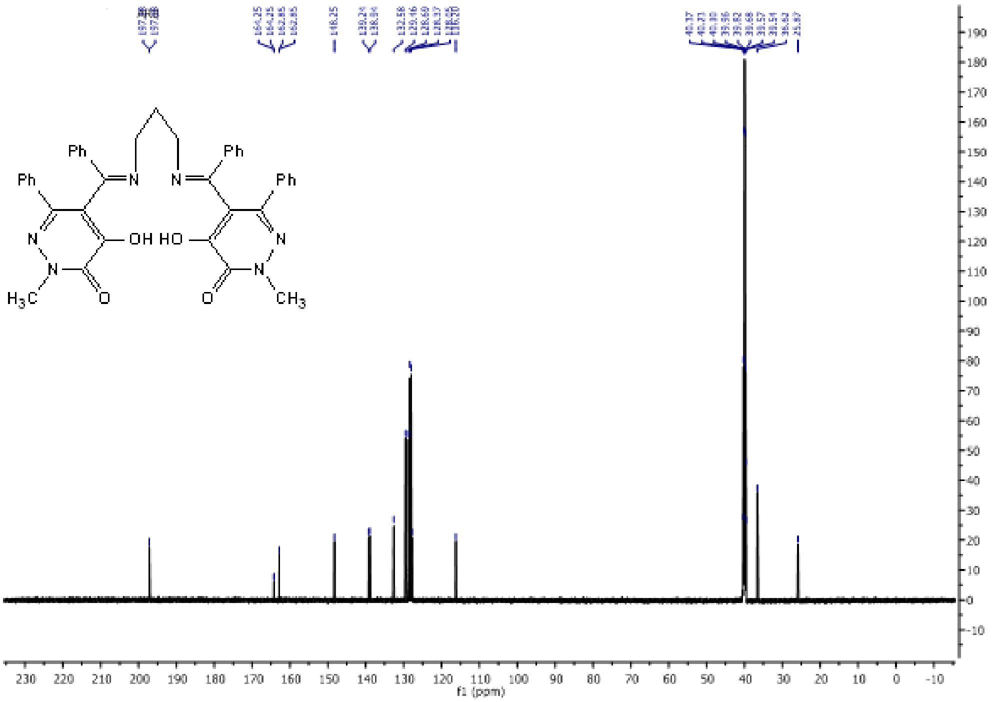


Figure 2. ^{13}C-NMR spectrum of ligand.

3.4. Antioxidant studies

3.4.1. DPPH scavenging activity

The scavenging ability on DPPH radicals test was widely carried out as a screening process for testing the antiradical ability of compounds.[27,28] Various concentrations of compounds were investigated in order to determine DPPH scavenging activity by comparing with standard Ascorbic acid and Trolox. The obtained results are given in Figure 3. The DPPH scavenging activity of five compounds increased with concentration. The lowest and highest free radical scavenging activity was observed as 8.5% for compound 2 at the concentration of 10 mg/L and 45.7% for compound 5 at the concentration of 200 mg l^{-1}, respectively. Similar results were reported for compound 8 by Ağırtas et al. (2013).[29]

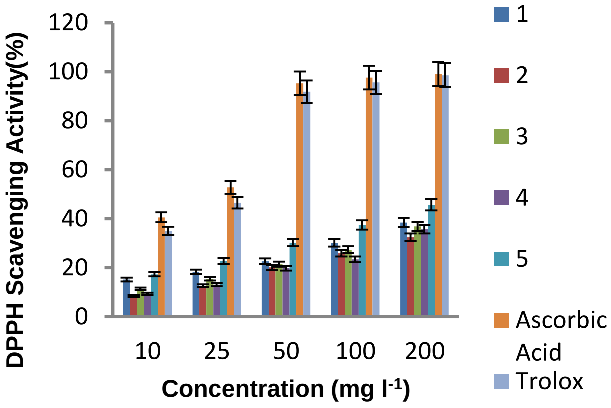


Figure 3. Free radical scavenging activities of the compounds on DPPH radicals.

3.4.2. Metal chelating activity

The metal chelating activity of tested compounds is presented in Figure 4. The chelating activity increased with concentration. The chelating activity of compounds at 200 mg/L concentration was 78.1% for compound 5, 64.5% for compound 4, 54.7% for compound 1, 51.8% for compound 3 and 44.9% for compound 2. EDTA exhibited great activity (90.18–100%) for all concentrations studied. Our results showed greater metal chelating activity than Baykara at al. (2013).[30]

3.5. DNA cleavage studies

In order to detect the DNA cleavage, the activities of the newly synthesized compounds were studied by supercoiled plasmid DNA as a substrate in a medium of 50 mM Tris–HCl and NaCl buffer (pH 7.4). It is known that one pair of DNA strands was broken by the metal compounds.[31]

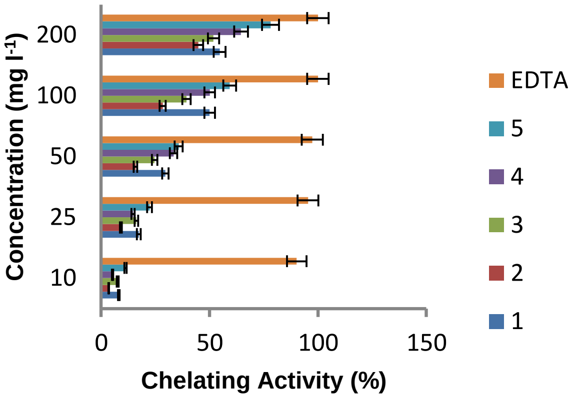


Figure 4. Metal chelating activities of compounds.

The experiment showed that the supercoiled form I cleaved by to varying extent all tested compounds. Form I (supercoiled DNA) was converted to form II (nicked circular DNA) and form III (linear DNA) at 100 μg ml^{-1} concentrations of all complexes. Figure 5 presents the results of the agarose gel electrophoresis separations of plasmid DNA from form I to form II and III by the compounds. Control experiments clearly revealed that plasmid DNA and DNA in %3 DMF did not show any cleavage. These experimental studies revealed that ligands and metal compounds were cleavage active. These DNA cleavage findings are better than the study of Keypour et al. (2015). [32]

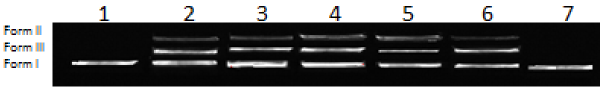


Figure 5. DNA Cleavage of ligand and its metal complexes. Lane 1, pBR 322 DNA; Lane 2, pBR 322 DNA + 100 μg ml^{-1} of **1**; Lane 3, pBR 322 DNA + 100 μg ml^{-1} of **2**; Lane 4, pBR 322 DNA + 100 μg ml^{-1} of **3**; Lane 5, pBR 322 DNA + 100 μg ml^{-1} of **4**; Lane 6, pBR 322 DNA + 100 μg ml^{-1} of **5**; Lane 7, pBR 322 DNA + 3% **DMF.**

3.6. Antimicrobial activity

The antimicrobial activities of the five newly synthesized compounds were investigated for *E. hirae* (ATCC 10541), *B. cereus*, *S. aureus* (ATCC 6538), *L. pneumophila* subsp. *pneumophila* (ATCC 33152), *P. aeruginosa* (ATCC 9027), *E. coli* (ATCC 10536), and *C. albicans*. In this study, only *S. aureus* was inhibited by all compounds and antimicrobial activity was in order of 3 = 4 > 2 > 1 > 5. Compound 2 inhibited all microorganisms and showed the highest antimicrobial activity against *E. coli* with inhibition zone value equal to 12 mm (Figure 6).

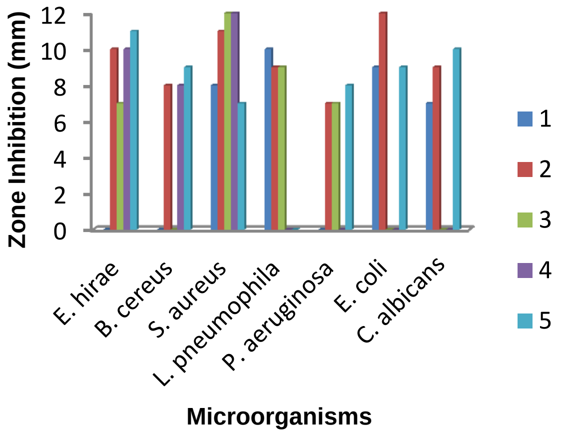


Figure 6. Antimicrobial activities of compounds.

4. CONCLUSION

In this work, new Schiff base ligand and its complexes of Co (II), Cu (II), Ni (II) and Pd (II) were synthesized. The synthesized compounds were characterized by elemental analysis, magnetic susceptibility, NMR, FT-IR and UV-Vis spectroscopy. The synthesized copper (II) complex has square plane geometry, while others have octahedral geometry. The antioxidant activities of the newly synthesized compounds on scavenging of DPPH and metal chelating activity varied depending on the concentration. These compounds showed modest scavenging of DPPH activity when compared with the standards. Also Ni (**4**) and Pd (**5**) demonstrated significant metal chelating activity. According to the DNA cleavage studies all compounds were active in cleavage. The obtained results of the antimicrobial studies for compound Co (**2**) inhibited all tested microorganisms and showed the highest antimicrobial activity against *E. coli*.

Conflict of interest

Authors declare that there is no a conflict of interest with any person, institute, company, etc.

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