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Synthesis, Characterization, Antioxidant and Antimicrobial Activities of a Heptadentate N_4O_3-type Schiff Base Ligand and its Metal Complexes

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Abstract

Mo(III), Fe(III), Cd(II), Zn(II), Cu(II) complexes based on Tris[2-salicylaldeneimino)ethyl]amine (H_3saltren) have been successfully synthesized. Newly prepared compounds have been characterized by ^{1}H-NMR, ^{13}C-NMR, IR and UV–VIS spectroscopy techniques. The spectral studies confirmed the ligand coordinates of the metal ion to form complex via the oxygen and nitrogen atoms of the phenolic group and azomethine group. The antioxidant activity of the ligand and its complexes were determined by DPPH (2,2-diphenyl-1-picryl-hydrazyl) method in vitro. The obtained IC_{50} value of the DPPH activity for the copper complex (IC_{50} = 55.30 mg/ml) was higher than other compounds. Furthermore, the antimicrobial effects of the tested compounds have been tested against the bacterial species, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Bacillus cereus by Disc diffusion and Micro-broth dilution methods. It has been found that the Cu complex has more effective against Bacillus cereus and the Cd complex showed the best antibacterial activity against the Staphylococcus aureus.

Key words: Heptadentate, Schiff base, Antibacterial, Antioxidant, DPPH.

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Introduction

Schiff base ligands are very interested in the research field of coordination chemistry because these compounds are potentially capable of forming stable complexes with metal ions [1-5]. Metal complexes have a variety of industrial applications in electrochemistry [6-8], catalysts [9-12] and biological activities [13-19]. A lone pair of electrons of imine nitrogen is of considerable chemical and biological importance. In the last decade, searching for new compounds has increased due to bacterial resistance to antibiotics. Free radicals interact with DNA, lipids and proteins, thus accelerating cancer, aging, inflammation, cardiovascular and neurodegenerative diseases [20-24].

In addition to the biological activity, Macrocyclic Schiff base complexes exhibited interesting antioxidant activities (including hydroxyl radical $OH^{\bullet}$, superoxide anion $O_2^{\bullet-}$, etc.) [25-30]. In the present work, We describe the synthesis and characterization of new Mo(III), Fe(III), Cd(II), Zn(II), Cu(II) complexes of the potentially heptadentate Schiff base ligand (H_3saltren) and we also studied the capability of this ligand and its complexes for in-vitro antibacterial activity against Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Bacillus cereus. In addition, the antioxidant activity Schiff base ligand and its metal complexes have been studied.

Experimental

Materials and spectral measurements

All starting materials were purchased from Aldrich and Merck and were used without further purification. IR spectra were recorded in KBr on a Perkin–Elmer 78 spectrophotometer. UV—VIS spectra were recorded in DMSO on a Shimadzu UV-1601 spectrophotometer. Melting point was obtained on a (Buchi SMP-20 capillary melting point apparatus). NMR spectra (^{1}H, ^{13}C-NMR) were acquired in DMSO–d_6 solution using Brucker AMX 250 MHz spectrometer with tetramethylsilane (TMS) as internal standard for ^{1}H-NMR analysis. Isolates bacteria were purchased from Persian Type Culture Collection (PTCC).

Synthesis of [H_3saltren] ligand (L)

The heptadentate ligand [Tris(2-(salicylaldeneimino)ethyl)amine] was prepared according to the method described by Joy Chakraborty et al [31]. To a solution of salicylaldehyde (0.06 mol, 7.3 g) in absolute ethanol (25 ml) was added tris(2-aminoethyl)amine (0.02 mol, 2.92 g) in absolute ethanol (25 mL). Then the solution was refluxed for 1 h. After evaporation of the solvent, the product (Figure 1) was obtained as a bright yellow precipitate. Yield: 89.12%; mp 191-193 °C; $C_{27}H_{30}N_4O_3$: Anal. Found: C, 70.68; H, 6.63; N, 12.21% Calc.: C, 70.74; H, 6.55; N, 12.22% IR (cm^{-1}): ν_{O-H} 3450, $\nu_{C-H\ (aromatic)}$ 3054, $\nu_{C-H\ (aliphatic)}$ 2939, $\nu_{C=N}$ 1637, $\nu_{C=C}$ 1573 and 1498, ν_{C-N} 1278,

ν_{C-O} 1068. UV-Vis (nm): 257, 313, and 414. ^{1}H NMR (δ, ppm in dmso-d_6): 2.84 (t, 6H, H-9); 3.59 (t, 6H, H-8), 8.23 (s, 3H, H-7), 6.87 (s, 3H, H-6), 6.74 (t, 3H, H-5), 7.30 (t, 3H, H-4), 6.84 (d, 3H, H-3), 13.65 (s, 3H, OH). ^{13}C NMR (δC, ppm): 55.33 (C-9), 57.39 (C-8), 166.62 (C-7), 116.96, 118.75, 118.84, 131.97, 132.60, 161.33 (C-1 to C-6).

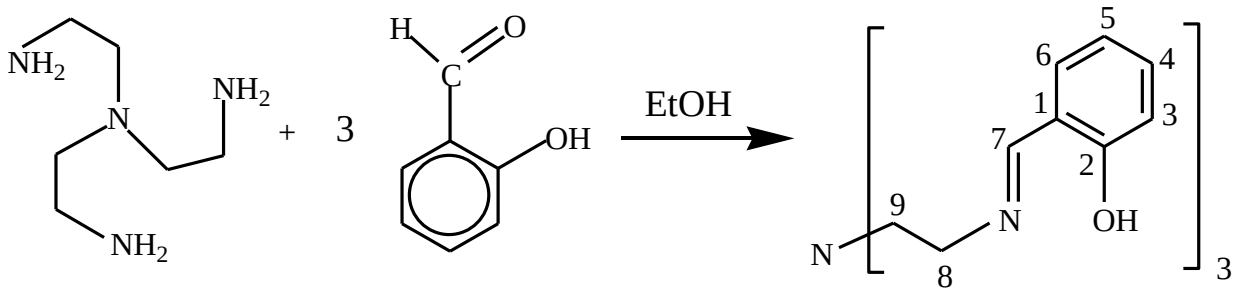

Figure 1. Scheme for synthesis of the ligand.

Preparation of the complexes – general procedures

To a solution of ligand (3 mmol) in 20 mL ethanol was added an aqueous solution of $Cd(NO_3)_2$. $4H_2O$, $Cu(SO_4)$. $5H_2O$, $Zn(NO_3)_2.4H_2O$, $FeCl_3$ and $MoBr_3$ (3 mmol) in 20 ml ethanol. The solution was stirred at room temperature overnight. Then the solution was refluxed for 5 h. The solution was left in Refrigerator overnight. Then the precipitate was filtered off and washed with cold absolute ethanol, and dried in vacuum.

Cd L: The cadmium complex was reported in our previous paper [1]. Yield: 82.25%; mp 141-146 °C. IR (cm^{-1}): $\nu_{C-H\ (aromatic)}$ 3166, $\nu_{C-H\ (aliphatic)}$ 2999, $\nu_{C=N}$ 1606, $\nu_{C=C}$ 1476, ν_{C-N} 1294, ν_{C-O} 1022, ν_{Cd-N} 467, ν_{Cd-O} 430. UV-Vis (nm): 222, 317, 375. ^{1}H NMR (δ, ppm in dmso-d_6): 2.85 (d, 6H, H-9); 3.62 (d, 6H, H-8); 8.23 (s (3H, H-7); 7.12 (d, 3H, H-6); 6.74 (t, 3H, H-5); 7.29 (d, 3H, H-4); 6.85 (d, 3H, H-3). ^{13}C NMR (δC, ppm): 50.61 (C-9), 56.91 (C-8), 166.27 (C-7), 116.61, 118.44, 118.33, 131.63, 132.27, 161.01 (C-1 to C-6).

Cu L: Dark green precipitate; Yield: 74.64%; mp 298-300 °C. IR (cm^{-1}): $\nu_{C-H\ (aromatic)}$ 3062, $\nu_{C-H\ (aliphatic)}$ 2885, $\nu_{C=N}$ 1599, $\nu_{C=C}$ 1524 and 1446, ν_{C-O} 1074, ν_{C-N} 1291, ν_{Cu-N} 544, ν_{Cu-O} 418; UV-Vis (nm): 219, 311 and 369. ^{1}H and ^{13}C NMR data were not obtained because the complex was paramagnetic.

Zn L: Yellow precipitate; Yield: 80.34%; mp 244-246 °C. IR (cm^{-1}): $\nu_{C-H\ (aromatic)}$ 3055, $\nu_{C-H\ (aliphatic)}$ 2939, $\nu_{C=N}$ 1635, $\nu_{C=C}$ 1577 and 1498, ν_{C-O} 1067, ν_{C-N} 1278, ν_{Zn-N} 495, ν_{Zn-O} 461. UV-Vis (nm): 210, 270 and 369. ^{1}H NMR (δ, ppm in dmso-d_6): 2.68 (t, 6H, 9-H), 2.80 (d, 6H, 8-H), 8.45 (s, 3H, 7-H), 6.38-7.14 (m, 4H, aromatic ring). ^{13}C NMR (δC, ppm): 51.86 (C-9), 52.36 (C-8), 166.02 (C-7), 112.56, 118.67, 119.52, 130.53, 131.48, 161.06 (C-1 to C-6).

Fe L: Dark Brown precipitate; Yield: 76.61%; mp 303-305 °C. IR (cm^{-1}): $\nu_{C-H\ (aromatic)}$ 3062, $\nu_{C-H\ (aliphatic)}$ 2948, $\nu_{C=N}$ 1597, $\nu_{C=C}$ 1524 and 1461, ν_{C-O} 1074, ν_{C-N} 1290, ν_{Fe-N} 498, ν_{Fe-O} 418. UV-Vis (nm): 230, 261 and 380. ^{1}H and ^{13}C NMR data were not obtained because the complex was paramagnetic.

Mo L: Dark red precipitate, Yield: 83%; mp 339-341 °C. IR (cm^{-1}): $\nu_{C-H\ (aromatic)}$ 3007, $\nu_{C-H\ (aliphatic)}$ 2885, $\nu_{C=N}$ 1594, $\nu_{C=C}$ 1469 and 1546, ν_{C-N} 1274, ν_{C-O} 1019, ν_{M-N} 430, ν_{M-O} 418. UV-Vis (nm): 260, 310, 430. ^{1}H NMR (δ, ppm in dmso-d_6): 2.08 (s, 6H, H-9), 2.76 (t, 6H, H-8), 8.23 (s, 3H, H-7), 6.85 (d, 3H, H-6), 6.75 (d, 3H, H-5), 7.30 (t, 3H, H-4), 7.11 (s, 3H, H-3). ^{13}C NMR data (δC, ppm): 48.50 (C-9), 50.974 (C-8), 162.27(C-7), 112.61, 114.33, 115.57, 128.27, 132.46, 157.33 (C-1 to C-6).

Antimicrobial activity - Bacterial species

In this study, four bacteria were used (2 gram-negative and 2 gram-positive). The standard strains of the following microorganisms were used as test organisms S. aureus (PTCC 1112), E. coli (PTCC 1330), P. aeruginosa (PTCC 1074) and B. cereus (PTCC 1015).

Preparation of cultures for antimicrobial susceptibilities

Bacterial isolates were grown in 5 mL aliquots of Mueller-Hinton broth medium for 24 h at 37 °C. The inoculums density of each bacterial isolate was standardized with 0.5 McFarland turbidity standards. The suspension had final inoculums of 5×10^{8} cfu mL^{-1} (colony-forming unit). We used two ways for Antimicrobial activity Disc diffusion and Micro-broth dilution methods.

Disc diffusion method

Mueller Hinton agar medium (38 g Mueller Hinton agar and 3 g agar in 1000 ml of distilled water) was prepared and sterilized. A small amount of each bacterium was placed on the side of the plate. A sterile loop was used to spread the bacteria in one direction from the initial site of inoculation. The plates were incubated for 24 hours at 37 °C for bacteria growth. A bit of each bacteria was

dissolved in a sterile distilled water tube similar to 0.5 McFarland turbidity standard (The suspension had a final inoculum of 1.5×10^8 cfu/ml). The plates (with respect to the number of samples) were inoculated with bacteria by two sterile cotton swabs. 0.02 g of the substance was dissolved in 1 ml of DMSO. The sterile blank discs (Whitman No.1 filter paper, 5 mm diameter) were dipped in 0.1 ml of each sample. The discs were placed on plates at specified intervals by sterile forceps. After an incubation period of 24 h at 37 °C, the diameter of each zone of inhibition was measured with a ruler (mm). Cephradine (30 μg/disc), Ampicillin (10 μg/disc), Imipeneme (10 μg/disc) and Chloramphenicol (30 μg/disc) were chosen as a standard for the antibacterial activity measurements. To clarify any participating role of DMSO in the biological screening, separate study was carried out with the solution of DMSO alone and it showed no activity against any bacterial strains. The test results are presented in Table 1. These results were confirmed by repeating it three times using the same procedure conditions.

Table 1. Inhibition zones (mm) of complexes and ligand against bacterial strains.

Compound	Bacteria(D[a])			
	Pseudomonas aeruginosa	**Escherichia coli**	**Bacillus cereus**	**Staphylococcus aureus**
Ligand (L)	7	10	12	9
Cu L	17	17	25	20
Fe L	10	11	17	18
Zn L	12	15	20	15
Cd L	15	15	20	30
Mo L	12	22	22	18
Choloramphenicol	8	15	-	14
Imipeneme	-	25	20	20
Cephradine	-	-	-	8
Ampicilin	-	11	-	14
Dimethyl sulfoxide	-	-	-	-

[a]D = Diameter inhibition zone (mm)

Micro-broth dilution minimum inhibition concentration

The MIC is the lowest concentration of the test compound. MICs were determined with micro-broth dilution. 13 sterile tubes containing 1 ml solution Mueller nutrient broth medium were prepared and sterilized for each substance. 0.02 g of each substance was dissolved in 1 mL of DMSO. Then the first tube was filled with 1 ml of sample. After pipetting, 1 ml of the solution from the first tube was added to the second tube. Then, 1 ml of the solution from the second tube was added to the third tube. This process was repeated for all 12 tubes. As a result, the concentration of each tube was half of the previous tube. The extra solution (1 ml) from the twelfth tube was discarded. Thus, the thirteenth tube acted as control bacteria. After an incubation of 24 h at 37 °C, a bit of one bacterium was dissolved in a sterile distilled water tube similar to 0.5 McFarland turbidity standards. A specified amount of a type of bacteria suspension was added in all tubes except tube 12 (as a control

sample) until the concentration of all the tubes was 5×10^5 cfu/ml. The tubes were placed in an incubator at 37 °C. After 24 h, MIC values of the substances were determined by the control tubes. MIC values of Schiff base and its complexes are indicated in Table 2.

Table 2. Minimum inhibition concentration (mg/mL).

Compound	Bacteria			
	Pseudomonas aeruginosa	**Escherichia coli**	**Bacillus cereus**	**Staphylococcus aureus**
Ligand (L)	1.250	0.625	1.250	0.625
Cu L	0.156	0.156	0.156	0.078
Fe L	1.250	0.625	0.312	0.312
Zn L	1.250	0.625	0.156	0.156
Mo L	0.312	0.312	0.078	0.031
Cd L	0.312	0.156	0.078	0.009

Antioxidant activity

In vitro antioxidant activities were measured against DPPH (2,2-diphenyl-1-picryl-hydrazyl) [32]. A quantitative kinetic study of the antioxidant activities of the compounds toward DPPH at 25 °C was performed in methanol by UV–VIS spectroscopy. DPPH has a strong absorption band at 517 nm. So, the absorbance of test solutions was measured at 517 nm. The IC_{50} (Inhibitory Concentration 50%) value denotes the concentration of sample required to scavenge 50% of the DPPH free radicals. The IC_{50} of butylated hydroxyanisole (BHA) was also determined for comparison (Table 3). 25, 50, 75 and 100 mg/ml of the test compounds in 1 mL DMSO were taken in different test tubes. Then, 5 mL methanolic solution of DPPH (0.1 mM) was added to these tubes. After that, the tubes were incubated at 37 °C for 30 min in the dark. The absorbance of test solutions and a blank solution of DPPH (as a control) was measured at 517 nm. The reduction of DPPH was calculated relative to the measured absorbance of the control. The DPPH radical scavenging activities for the compounds are shown in Figure 2. These results were confirmed by repeating it three times using the same procedure conditions and the results were averaged. The percent of inhibition (I %) of free radical production from DPPH was calculated by using the following equation:

$$(\%)\ \text{Inhibition} = \frac{\text{Abs}_{\text{control}} - \text{Abs}_{\text{sample}}}{\text{Abs}_{\text{control}}} \times 100$$

where $\text{Abs}_{\text{control}}$ is the absorbance of the blank and $\text{Abs}_{\text{sample}}$ is the absorbance of the samples/standard.

Table 3. DPPH scavenging activities of compounds.

Compounds	IC_{50} (mg/ml)
Ligand (L)	90.55
Cu L	55.30
Fe L	73.94
Zn L	68.93
Mo L	90.55
Cd L	89.28
butylated hydroxyanisole	42.04

Results and discussion

Synthesis and characterization

The prepared macrocyclic ligand was synthesized by condensation of salicylaldehyde and tris(2-aminoethyl)amine in ethanol. The reaction proceeded smoothly, producing the corresponding Schiff base ligand in a good yield. The ligand is soluble in common organic solvents. All the complexes are stable at room temperature and insoluble in water, but soluble in dimethyl sulfoxide (DMSO). The purity of the Schiff base ligand and its complexes were checked by thin-layer chromatography (TLC).

The IR spectrum of the free ligand show the characteristic C=N band in the 1637 cm^{-1} region which is shifted to lower frequencies in the spectra of the metal complexes (1635–1594 cm^{-1}), indicating the bonding of nitrogen of the azomethine group to the metal ion which can be explained by the donation of electrons from nitrogen to the empty orbital of the metal ion. The band observed at 1573 cm^{-1} is due to the C=C stretching of the aromatic ring system. The ligand spectrum showed band at 3450 cm^{-1} due to the stretching and deformation of the phenolic OH. These are absent in the spectra of the complexes, indicating the deprotonation of the hydroxyl group and coordination through oxygen. Phenolic $\nu_{(C-O)}$ stretching vibrations appeared at 1068 cm^{-1} in the Schiff base ligand; however, the signal was shifted in the complexes. This shift confirms the participation of oxygen in the C-O-M bond. The observed new high intensity bands at 418-461 cm^{-1} are ascribed to $\nu_{(M-O)}$, suggesting the involvement of the oxygen atoms in the bonding with the metals centers. Proof of the coordination to the N atom is provided by the occurrence of the new absorption bands at 430-544 cm^{-1} in the complexes.

The electronic spectra of the Schiff base ligand and its complexes were recorded in DMSO as a solvent. The Salicylaldimines exhibit interesting electronic properties due to close proximity of the hydroxyl and imine groups. The absorption bands of the ligand (in the UV region) at 257, 313 and 414 nm are attributed to transitions $\pi\rightarrow\pi^*$ (aromatic ring) and $n\rightarrow\pi^*$ (C-O) and $n\rightarrow\pi^*$ (C=N) respectively. In the metal complexes, these bonds were shifted to some extent, because the imine nitrogen is involved in coordination with the metal ion. The first band in the complexes were observed in the range of 210-260 nm, can be ascribed to the $\pi\rightarrow\pi^*$ transitions of the benzenoid

system chromophores. Another absorptions were observed in the range of 261-317 and 369-430 nm can be related to n→π* electronic transition that involves the nonbonding electrons of the azomethine nitrogen (C=N) and keto oxygen (C–O) atoms.

The ^{1}H-NMR spectrum of the ligand showed a peak at 13.65 ppm for phenolic OH group which disappeared in the complexes. That indicates the coordination bond formation between metal ions with oxygen due to deprotonation. The azomethine proton of the ligand was seen at 8.23 ppm (singlet). The formations of the complexes were confirmed from characteristic peak of the imine hydrogen in the region of 8.23-8.45 ppm. In the ^{13}C-NMR spectrum of the ligand, the phenolic C-OH observed at 161.33 ppm which in the complexes shifted and was appeared in the range of 157.33-161.01 ppm. The signal due to the azomethine carbon atom of the ligand appeared at 166.62 ppm while in the complexes were seen in the range of 162.27-166.27 ppm. In the NMR spectra of the complexes were observed similar signals for phenyl protons and carbons.

However, our attempts to isolate single crystals suitable for X-ray crystal structure determination were not successful for the Mo(III), Fe(III), Zn(II), Cu(II) complexes, but spectral study and X-ray structure analysis of the Cd complex [1] provide strong evidence for the complexation of the ligand.

Biological activity

In this study, different metal complexes with the same ligand have been used to detect antibacterial activities against the same microorganisms. According to the results in Table 1, it can be concluded that the Schiff base and complexes had antibacterial activity against the investigated bacterial strains. The Cu complex showed the best antibacterial activity against Bacillus cereus and the Cd complex showed the best antibacterial activity against the Staphylococcus aureus, on the other hand, the Fe complex showed the least activity against the Pseudomonas aeruginosa. A comparative study of the ligand and their complexes (Inhibition zones' values (mm)) indicates that complexes exhibit higher antimicrobial activity than the free ligand. The results show that the compound's effect on gram-positive bacteria is more than gram-negative bacteria.

The results reveal that the functional groups are critical factors for the observation of antibacterial activity. Ismail et al. reported antipyrine (N-heterocyclic compound) and its derivatives exhibit a wide range of biological activities and applications [3]. Antipyrine is a marker in the study of transfer and biotransformations of drugs in the human body [33] and antipyrine metabolites are reported to show a positive correlation with plasma fibronectin level in monitoring patients with chronic liver illness (HBC, HCV and alcohol-related disease) [34]. Copper complexes with imines have deserved much attention, probably because of their ability to intercalate between the bases of

DNA and to participate in catalytic cycles with usual reducing and oxidizing agents in biological medium [35].

According to the results in Table 2, the Cu, Cd and Mo complexes showed the lowest MIC against Staphylococcus aureus, and the highest MIC was detected by all the complexes against Pseudomonas aeruginosa. A comparative study of MIC values of ligand and the complexes indicated that metal complexes exhibited higher antibacterial activity than the free ligand. It suggests that the complexes possess antibacterial activity inhibiting multiplication process of the microbes by blocking their active sites. On the basis of the Chelation theory [36]; with interaction of the ligand orbitals with the metal, the polarity of the metal ion is decreased and increased the delocalization of π-electrons over the whole chelating. These factors increase the interaction between complex and lipid cells, which increase the penetration of complex into the cell. The Schiff base can penetrate the bacterial cell membrane by the coordination of the metal ion through oxygen or nitrogen donor atom to lipopolysaccharide which leads to the damage of the outer cell membrane and inhibits growth of the bacteria. So, the synthesized Schiff base ligand has moderate inhibitory effects on the growth of tested microorganisms.

The increased activity of the complexes may also be explained on the basis of their high solubility, fitness of the particles, size of the metal ion and the presence of the bulkier organic moieties. Presumably, the different lipophilic behaviour of the aromatic residues such as salicylaldehyde, antipyrine, aniline and furfuryl is involved in the biological activity mechanisms [37].

Antioxidant activity

The compounds were screened for free radical scavenging activity by the DPPH method. The DPPH radical reacts with any compound that releases a hydrogen atom or an electron, resulting in a color change from purple to yellow. It can be seen from Figure 2, that the inhibitory effects of the tested compounds against the DPPH radical are observed with an increasing dosedependent manner, and the suppression ratio increases with increasing concentrations. As the results supported, all the metal complexes showed comparable or slight less activity to the standard (BHA) and The DPPH scavenging activity of Schiff base metal complexes is significantly higher than that of free ligand. On the other hand, the Cu(II) complex obviously displays a better DPPH radical scavenging activity than ligand and other complexes with IC_{50} of 55.30 mg/ml. The trend observed in the antioxidant activity with IC_{50} values for the compounds, BHT > Cu(Ⅱ) > Zn(Ⅱ) > Mo(III) > Fe(III) > Cd(Ⅱ) > L.

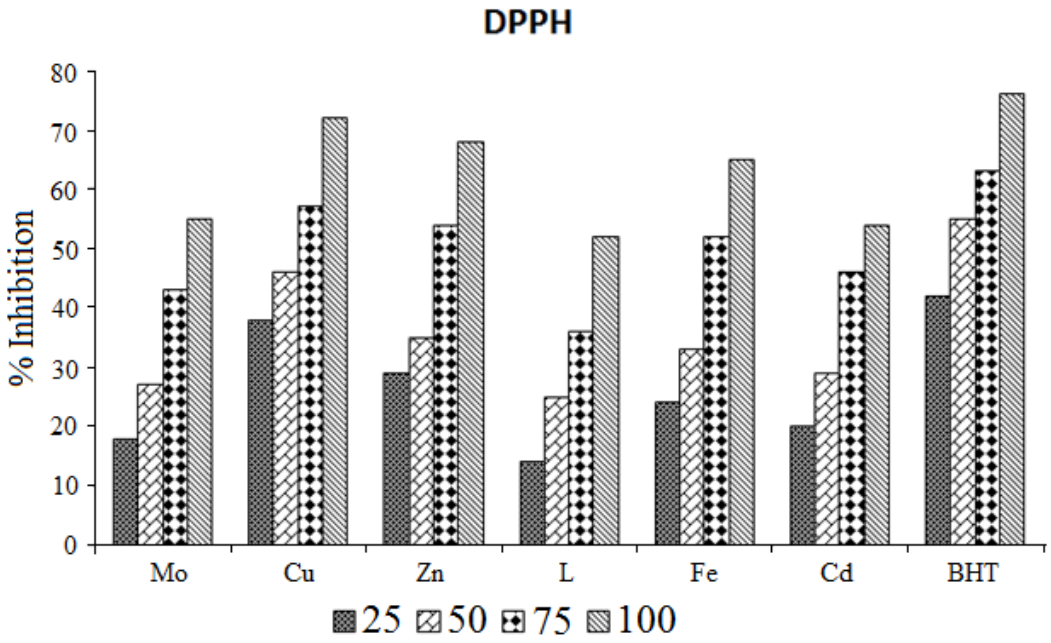

Figure 2. DPPH inhibition effects of ligand and Mo(III), Fe(III), Cd(II), Zn(II) and Cu(II) complexes.

Conclusion

In the present study, the potentially heptadentate Schiff base ligand (H_3saltren) and its Mo(III), Fe(III), Cd(II), Zn(II), Cu(II) complexes have been synthesized. The analytical data show that, the complexes are surrounded by imine nitrogen and phenolic oxygen atoms. To the best knowledge of the researchers, this is the first study which investigates the antioxidant and antibacterial activity of heptadentate Schiff base ligand complexes. The in vitro biological evaluation of complexes against various pathogenic bacterial strains reveals that the metal complexes exhibited higher antimicrobial activity than the free ligand. Additionally, the antioxidant activity revealed that all the tested compounds have good antioxidant activity and the complexes show stronger scavenging effects than the ligand.

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