



Macrocyclic Metal Complexes of Tetradentate Hydrazone Ligand: Synthesis, Characterization and its Applications

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The condensation reaction between dimethyl tetraphthalate and hydrazine hydrate results in the formation of 4-formylbenzohydrazide, which was refluxed with malonic acid to obtain novel hydrazone ligand (FBH-L). The ligand was further subjected to coordinate with two metal salts *viz.* $ZrCl_4$ and $NiCl_2$ to synthesize respective transition metal(II) complexes. The ligand and its metal complexes were characterized by various spectral and analytical techniques like UV, FTIR, 1H NMR, ^{13}C NMR, mass spectrometry, *etc.* The synthesized complexes were evaluated for their antibacterial and anti-angiogenic properties to determine their impact on microorganisms and the growth of blood cells, respectively and the results obtained were found to be satisfactory. Furthermore, all the metal-complexes demonstrated its efficacy as photocatalyst and also ability to remove metals from real water samples.

Keywords: Hydrazone, Metal complexes, Antimicrobial activity, Anti-angiogenic activity, Photocatalytic activity, Water samples.

INTRODUCTION

The prevailing surge in diseases and mortality rates caused by microbes is a significant and disturbing concern in today's world. The main diseases causing microorganisms are like bacteria, viruses, fungi, yeast, *etc.* The excessive and unrestricted use of antimicrobial agents leads to the development of resistance in microorganisms. Therefore, it is imperative to develop novel antimicrobial drugs that may effectively target and destroy microbes without causing harm to other parts of the body [1,2].

Hydrazones are a class of compounds that are recognized for their exceptional pharmacological capabilities and hence can be used as effective antimicrobials such as antibacterial, antifungal, antiviral along with anti-angiogenic, antidiabetic, anticancer, anti-HIV, *etc.* [3-5]. Despite all these, these compounds are also used in semiconductors, as catalysts, as photocatalytic agents and also to remove impurities in the form of extra metals from water [6,7]. The remarkable pharmacological activity of hydrazone ligands is attributed to the presence of many donor atoms such as oxygen, nitrogen and sulfur in their structure. These ligands form chelates with metal ions, enabling them to exhibit significant biological and pharmacological capabilities. It has been observed that chelation decreases the polarity of

metal ion due to overlapping of orbital of hydrazone ligand and partial positive charge sharing of metal ion [8,9]. Similarly antioxidant activity is also among some tremendous properties of the hydrazone ligands due to their excellent ability for free radical scavenging. They have good ability for free radical scavenging and hence act as a shield against the attack of free radicals [10-12]. The generated free radicals are incriminated as crucial factor in the evolution of oxidative damage diseases such as cancer, cardiovascular diseases, atherosclerosis, diabetes, neurodegenerative, liver cirrhosis, *etc.* [13-15].

Another important application of hydrazone ligands that also been taken into consideration is removal of metals from the wastewater. Many resources of water contain sewage, heavy metals, decaying animal, industrial pollutants, fertilizers and other waste materials. The use of hydrazone ligands which are capable to form stable coordination compounds are found to be effective for removal of heavy metals from wastewater due to presence of coordinating sites. A large number of macrocyclic compounds have been synthesized that are used for this purpose [16]. This article emphasizes on the synthesis and characterization of hydrazone ligand and its metal complexes. Furthermore, all the compounds undergo evaluation for their antioxidant, antibacterial and anti-angiogenic properties. Additionally, their

effectiveness in wastewater remediation by photocatalysis and removal of metals from wastewater is investigated.

EXPERIMENTAL

All the reagents used were of analytical grade, purchased from Sigma-Aldrich and Merck and used as such without any purification. Melting points were determined by using digital melting point apparatus and are uncorrected. Elemental analysis was done on Perkin-Elmer elemental analyzer. FTIR spectra were recorded by using Shimadzu FTIR spectrophotometer in the spectral range 4000–400 cm^{-1} , ^1H NMR and ^{13}C NMR spectra were obtained from Bruker Avance NEO 500 MHz spectrometer. The mass spectra were recorded on WATERS, QTOF MICROMASS (ESI-MS) mass spectrometer.

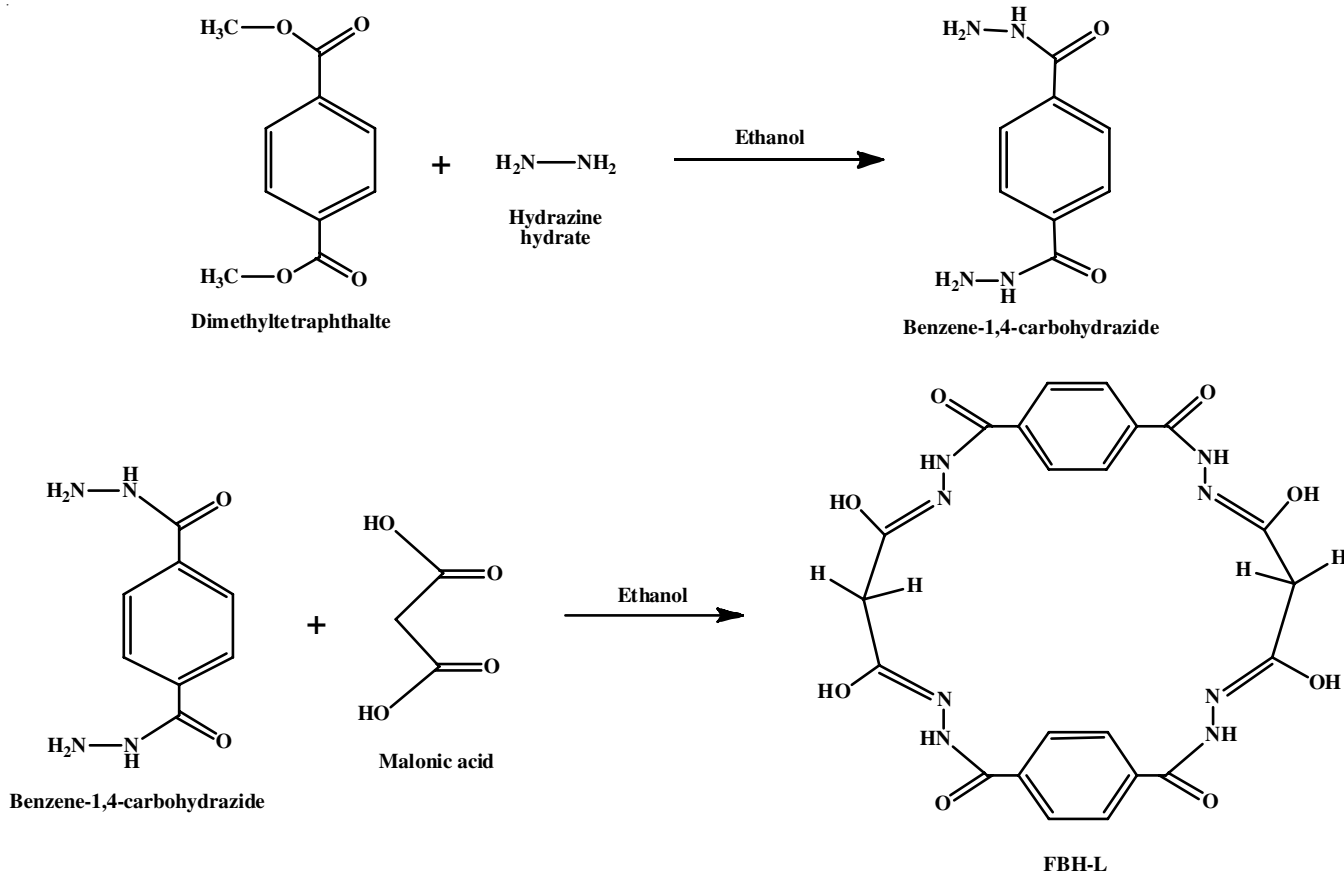
Synthesis of benzene-1,4-carbohydrazide: Dimethyl tetraphthalate (1 mol) dissolved in 20 mL of ethanol was mixed with hydrazine hydrate (2 mol) and the solution was stirred for 3 h on a heating mantle by using a water condenser. After that the reaction mixture was allowed to cool at room temperature and then poured into ice cold water. A white coloured precipitate appeared were filtered, recrystallized with ethanol and then dried in desiccator (**Scheme-I**).

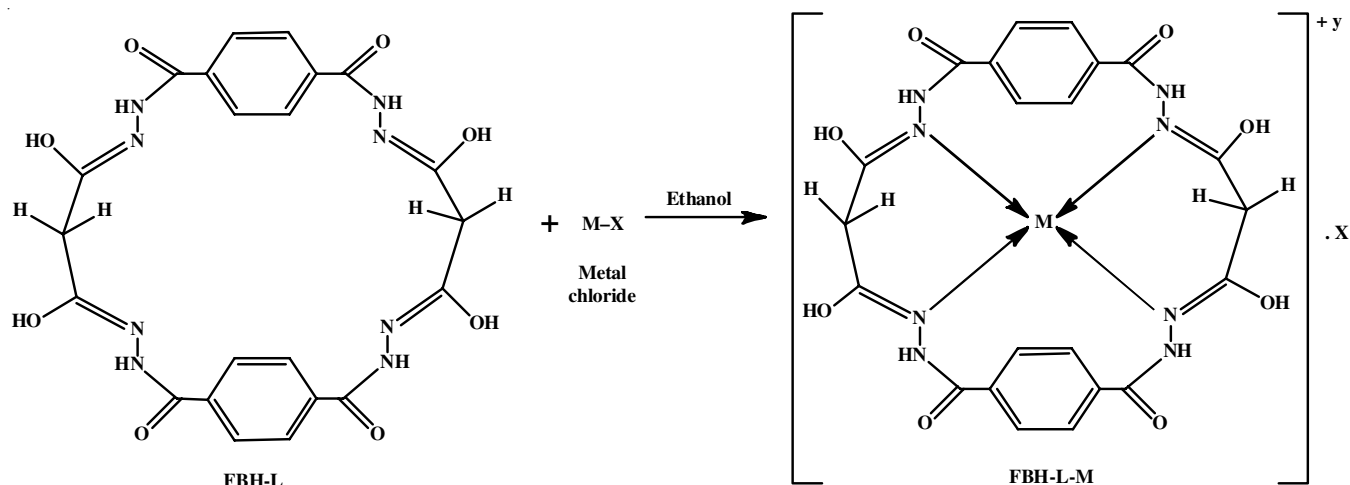
Synthesis of hydrazone ligand (FBH-L): A hot ethanolic solution of malonic acid (2 mmol) was mixed with benzene-1,4-carbohydrazide (2 mmol) dissolved in 20 mL ethanolic solution along with few drops of sulphuric acid. The content was refluxed on heating mantle at 75–80 $^{\circ}\text{C}$ for 4 h using a

water condenser. Then the solution was allowed to cool at room temperature and poured into ice cold water. Off white coloured precipitate obtained was filtered, recrystallized and dried in a vacuum desiccator overnight to obtain ligand FBH-L (**Scheme-I**). Elemental analysis: calcd. (found) % of $\text{C}_{22}\text{H}_{20}\text{N}_8\text{O}_8$: C, 50.38 (50.36); H, 3.82 (3.81); N, 21.37 (21.38); O, 24.42 (24.40). IR (KBr, ν_{max} , cm^{-1}): 3214 (-OH, br), 2940 (N-H, str.), 1695 (C=O, str.), 1590 (-C=N), 1085 (C-N str.). ^1H NMR (600 MHz, DMSO- d_6) δ ppm: 10.975 (s, 1H, O-H), 8.254 (s, 1H, N-H), 7.514–6.616 (m, aromatic H), 1.256 (s, 2H, - CH_2). ^{13}C NMR (δ ppm): 52.40 (C- H_2), 77.28–76.77 (C-OH), 166.25 (C=O), 133.90 and 129.53 (aromatic). GC-MS (m/z): calcd. (found) m/z 524.00 (524.125).

Synthesis of metal complexes: Zr(II) and Ni(II) complexes of ligands were synthesized by dissolving 1 mmol of oxozirconium(IV) chloride or nickel chloride in 20 mL ethanol followed by slow addition of 1 mmol of ethanolic solution of ligand. The content was refluxed for 3 h on water bath and on cooling, the crystals was filtered, washed with methanol and then air dried in vacuum overnight. The complexes were purified by recrystallization from the same solvent (**Scheme-II**). The purity of the compounds was determined by TLC with silica gel as adsorbent.

Zirconium complex: Elemental anal. calcd. (found) % of $\text{C}_{22}\text{H}_{20}\text{N}_8\text{O}_8\text{Cl}_4\text{Zr}$: C, 34.87 (34.84); H, 2.64 (2.61); N, 14.79 (14.74); O, 16.91 (16.88); Cl, 18.76 (18.73); Zr, 12.05 (12.06). IR (KBr, ν_{max} , cm^{-1}): 3069 (-OH, br), 2727 (N-H, str.), 1517 (C=O, str.), 1420 (-C=N), 906 (C-N str.), 610 (N-Zr str.). ^1H NMR





Scheme-II: Synthetic route of metal complexes of tetradentate hydrazone ligand

(600 MHz, DMSO- d_6) δ ppm: 11.247 (s, 1H, O-H), 8.295 (s, 1H, N-H), 7.762-6.754 (m, aromatic H), 1.331 (s, 2H, $-CH_2$). GC-MS: calcd. (found) m/z 757.224 (757.525).

Nickel complex: Elemental anal. calcd. (found) % of $C_{22}H_{20}N_8O_8Cl_2Ni$: C, 40.37 (40.35); H, 3.05 (3.02); N, 17.12 (17.14); O, 19.57 (19.55); Cl, 10.84 (10.82); Ni, 8.97 (8.95). IR (KBr, ν_{max} , cm^{-1}): 3083 ($-OH$, br), 2724 (N-H, *str.*), 1528 (C=O, *str.*), 1424 ($-C=N$), 918 (C-N *str.*), 510 (N-Zr *str.*). 1H NMR (600 MHz, DMSO- d_6) δ ppm: 11.512 (s, 1H, O-H), 8.305 (s, 1H, N-H), 7.985-6.645 (m, aromatic H), 1.312 (s, 2H, $-CH_2$). GC-MS: calcd. (found) m/z 653.599 (654.245).

RESULTS AND DISCUSSION

FTIR studies: The FTIR spectrum of ligand was compared with the metal(II) complexes that were recorded in the range 4000-400 cm^{-1} . All the characteristic peaks of ligand and its complexes along with their assignments are described in Fig. 1. In FBH-L ligand, a broad absorption band at 3214 cm^{-1} is due to $-OH$ stretching vibrations. Appearance of same peak at 3069 and 3083 cm^{-1} in the synthesized metal complexes indicate the non-involvement of hydroxyl oxygen in coordination with metals [17]. A sharp peak with weak intensity at 2940 cm^{-1} in ligand and at 2727 cm^{-1} in zirconium and at 2724 cm^{-1} in nickel complex corresponds to the $-N-H$ vibrations.

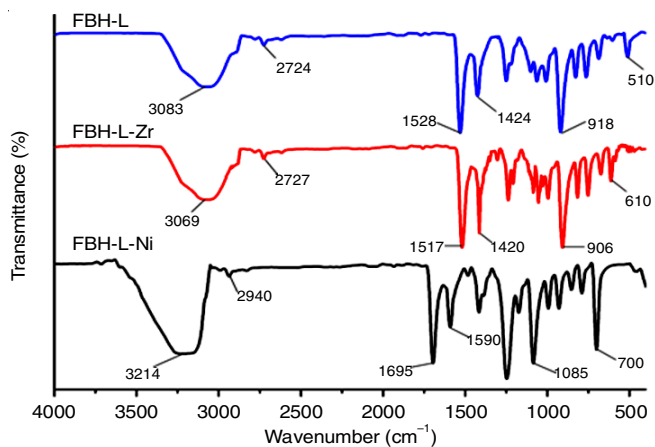


Fig. 1. IR spectra of FBH-L, FBH-L-Zr and FBH-L-Ni

The non-participation of the carbonyl group in the formation of the metal and oxygen bond is shown by the presence of distinct peaks at slightly lower frequencies compared to the ligand. Specifically, the ligand exhibited strong peaks at 1695 cm^{-1} [18], whereas their respective metal complexes had sharp peaks at 1517 and 1528 cm^{-1} . In IR spectra of ligands, a sharp and strong band at 1590 cm^{-1} confirmed the formation of characteristic $-C=N-$ linkage [19], which shifted to the lower value in case of metal complexes hence gives an indication for metal coordination to $-C=N-$ moiety. A sharp band at 1085 cm^{-1} for ligand might suggest the presence of $-N-H$ moiety. Thus, it can be concluded that the ligand acts as tetradentate where metal atom coordinated with four nitrogen atoms. The newly appeared bands at 610 cm^{-1} and 510 cm^{-1} in metal complexes of FBH-L attribute the linkage between Zr and Ni [20] with imine group, respectively.

1H NMR studies: The 1H NMR spectra of the synthesized ligand and their metal complexes were recorded in DMSO- d_6 solution using TMS as an internal standard. The 1H NMR spectrum for ligand *i.e.* FBH-L show multiplet in the region between 6.616-7.514 ppm, which may be assigned to four protons of aromatic rings [21]. Appearance of singlet at δ 1.256 ppm has been assigned to $-C-H$ proton (Fig. 2). Similarly, the band

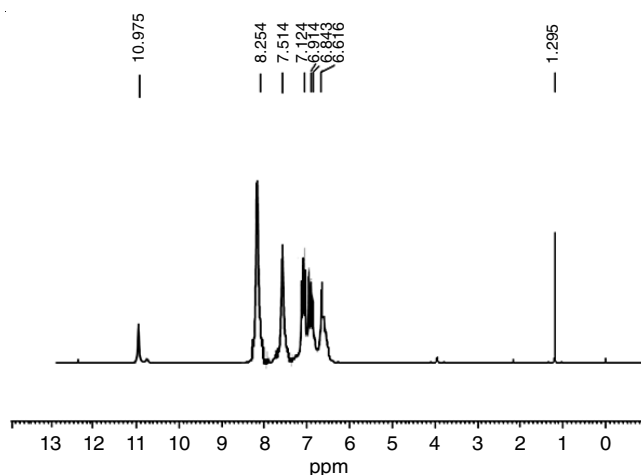


Fig. 2. 1H NMR spectra of FBH-L

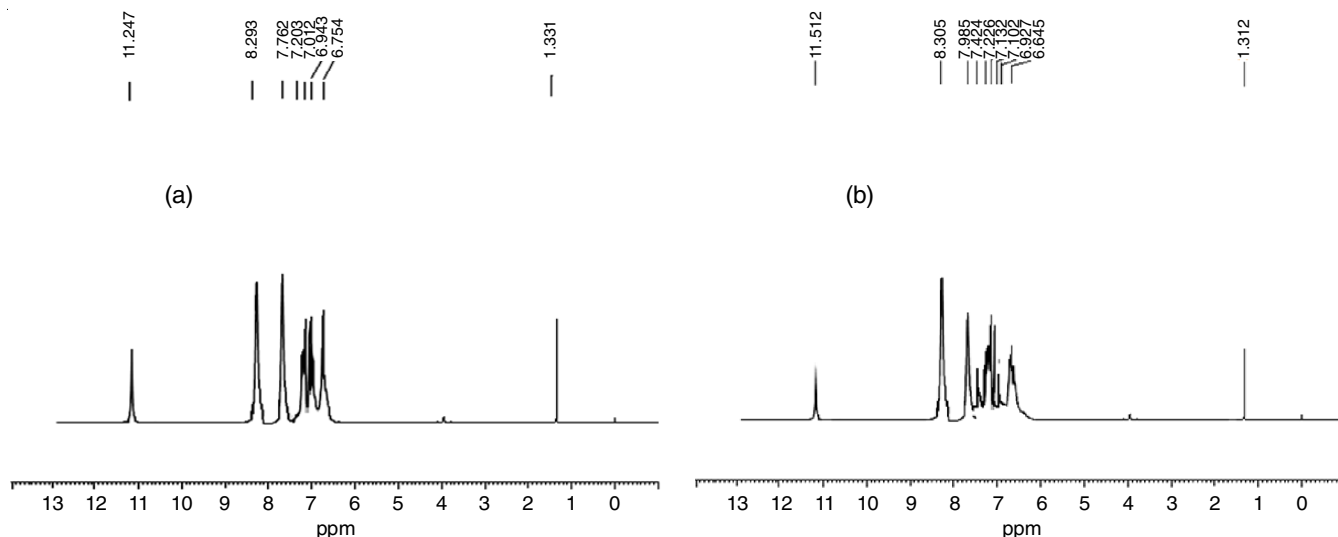


Fig. 3. ^1H NMR spectra of (a) FBH-L-Zr and (b) FBH-L-Ni

position at δ 8.254 ppm shows the presence of $-\text{N-H}$ moiety and singlet at 10.975 ppm $-\text{OH}$ proton in the ligand. A slight shifts in the metal complexes show contribution of metals in the formation of coordination bond (Fig. 3). The presence of the $-\text{OH}$ band [22] in both metal complexes indicates that there is no formation of an oxygen-metal bond.

^{13}C NMR studies: The ^{13}C NMR spectra confirmed the presence of $-\text{CH}_2$ carbon at δ 52.40 ppm and the C-OH carbon between δ 77.30-76.79 ppm. The peaks of carbonyl carbon appeared at downfield with value δ 166.25 ppm [23,24] while peaks for two dissimilar carbons of aromatic ring exhibited at δ 133.90 and 129.53 ppm, respectively [25]. All these peaks indicate the presence of five magnetically different carbons in the compound confirmed the proposed structure of the ligand (Fig. 4).

Mass spectral studies: The mass spectra of ligand and its Zr and Ni complexes were also characterized. The mass

spectra of ligand showed a clear and well defined peak at m/z 524 that exactly coincide with its calculated molecular mass and hence give evidence for proposed molecular formula *i.e.* $[\text{C}_{22}\text{H}_{20}\text{N}_8\text{O}_8]$. Moreover, the spectra of Zr(IV) and Ni(II) complexes indicates molecular ion peak at m/z at 654 and 758 that corresponds to the molecular formula $[\text{C}_{22}\text{H}_{20}\text{N}_8\text{O}_8\text{Cl}_4\text{Zr}]$ and $[\text{C}_{22}\text{H}_{20}\text{N}_8\text{O}_8\text{Cl}_2\text{Ni}]$, respectively. Similarly some major peaks at m/z 321, 218 and 165 are also found which identify the various stable fragments in ligand. However, upon careful examination of the mass spectra of Zr(IV) and Ni(II), it is evident that a peak at m/z 524, indicating the formation of a ligand fragment. This data is found in good agreement with the proposed molecular formula of ligand and its complexes.

Biological activities

Antimicrobial activity: The antimicrobial activity of ligand and its metal complexes has been evaluated against two pathogens *E. coli* (Gram-negative bacteria) and *A. niger* (fungus). The ligand and its metal complexes were tested at concentrations of 100, 150, 200 and 250 ppm to determine the degree of antibacterial activity. The antimicrobial activity shown by these compounds was also compared with standard antibacterial drug *i.e.* neomycin and antifungal drug *i.e.* fluconazole. Table-1 shows that antibacterial activity increases from ligand to metal complexes. Moreover, the nickel complex is found to inhibit the microbes more strongly as compare to zirconium complex. The improved antibacterial action can be attributed to the increased lipophilic activity of metal complexes, which allows them to more effectively penetrate the cell membranes of microorganisms, as compared to the ligand alone [26,27].

Anti-angiogenic activity: *Ex-vivo* chorioallantoic membrane assay (CAM) was used to evaluate the anti-angiogenic activity of the ligand and its metal complexes. The scoring method was utilized to evaluate the degree of anti-angiogenesis of all the compounds by quantifying the total number of blood vessels in terms of branch points on the CAM. A significant difference was observed when comparing treated samples with untreated control samples (Fig. 5).

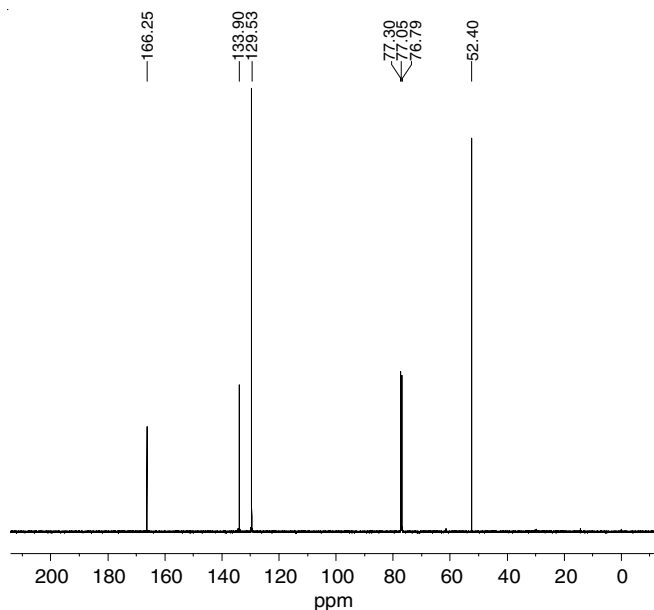


Fig. 4. ^{13}C NMR spectra of FBH-L

TABLE-1
ANTIMICROBIAL ACTIVITY DATA OF TETRADENTATE HYDRAZONE LIGAND (FBH-L) AND ITS METAL COMPLEXES

	<i>Escherichia coli</i> (ppm)				<i>A. niger</i> (ppm)			
	100 ppm	150 ppm	200 ppm	250 ppm	100 ppm	150 ppm	200 ppm	250 ppm
FBH-L	8 ($\pm 0.5-0.7$)	10 ($\pm 0.5-0.7$)	15 ($\pm 0.5-0.7$)	23 ($\pm 0.5-0.7$)	10 ($\pm 0.5-0.7$)	14 ($\pm 0.5-0.7$)	18 ($\pm 0.5-0.7$)	22 ($\pm 0.5-0.7$)
FBH-L-Zr	10 ($\pm 0.5-0.7$)	14 ($\pm 0.5-0.7$)	17 ($\pm 0.5-0.7$)	25 ($\pm 0.5-0.7$)	13 ($\pm 0.5-0.7$)	16 ($\pm 0.5-0.7$)	22 ($\pm 0.5-0.7$)	25 ($\pm 0.5-0.7$)
FBH-L-Ni	13 ($\pm 0.5-0.7$)	16 ($\pm 0.5-0.7$)	21 ($\pm 0.5-0.7$)	24 ($\pm 0.5-0.7$)	16 ($\pm 0.5-0.7$)	17 ($\pm 0.5-0.7$)	21 ($\pm 0.5-0.7$)	24 ($\pm 0.5-0.7$)
Standard	23 mm: (Neomycin, 250 ppm)				24 mm: (Fluconazole, 250 ppm)			

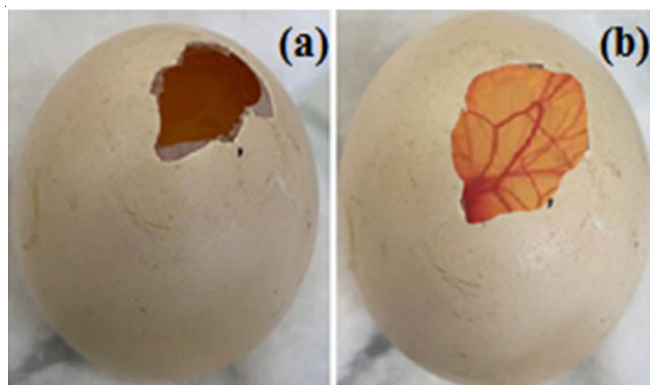


Fig. 5. (a) Maximum inhibition on blood cells shown by FBH-L-Zr, (b) Minimum inhibition on blood cells shown by blank solution (control)

The capability of ligand FBH-L to inhibit the blood vessels has been shown in Fig. 6. The activity was measured at various concentrations of the ligand and its complexes (1 and 10 μg), and it was found that the inhibitory activity of metal complexes was greater than the ligand at 10 μg concentration [28]. The results indicated that ligand and its both metal complexes have significant ability to inhibit the formation of blood vessels (Fig. 6).

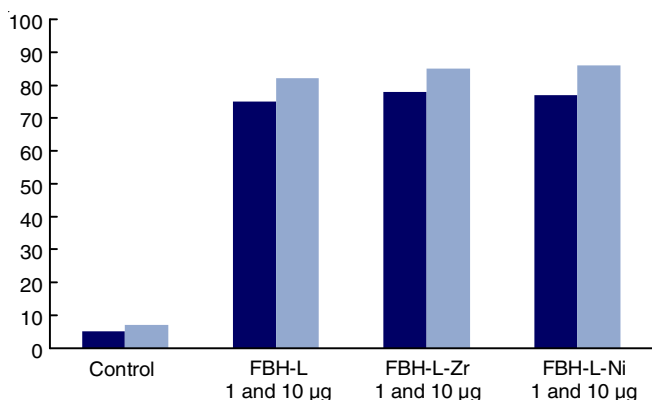


Fig. 6. Anti-angiogenic activity shown by FBH-L, FBH-L-Zr and FBH-L-Ni at different concentrations

Photocatalytic activity: Photocatalytic activity of ligand and its both metal complexes was analyzed by methylene blue degradation in absence and presence of sun light. The solutions of methylene blue, ligand and its metal complexes were prepared and subjected to UV-visible spectrophotometer. A 5 to 20 ppm solution of the ligand and its metal complexes were used as catalyst to find the extent of degradation of methylene blue. After that the same solution was kept in dark room and reading

was recorded again. There were no recognizable changes in the absorption and colour of the solution after and before placing the solution in dark. The absorption maxima for methylene blue (MB) was found at 632 nm, which is attributed due to $n \rightarrow \pi^*$ transition [29]. An appreciable change in colour and gradual decline in absorbance intensities was found after keeping all these solutions in sunlight. The degradation process is indicated by the fact that the absorbance intensity decreases as the concentration of compounds in the solution increases (Fig. 7). The results indicated that Zr and Ni complex degrade the methylene blue dye more efficiently than ligand alone [30]. The ligand had a degradation efficiency of approximately 70%, whereas its metal complexes were found to have degradation efficiencies ranging from 90% to 95%.

Spectrophotometric determination to Fe(III) ions in different natural water samples: Water samples were taken from different sources, were subjected to analyze the recovery of Fe(III) by using the synthesized ligand to ensure its ability of complexation. A definite concentration of Fe(III) was added to ligand, FBH-L with little adjustment of pH using either nitric acid or sodium hydroxide. The determination was done on UV-vis spectrophotometer at 250-900 nm wavelength at an interval of 1 nm with 1 s per wavelength measuring time [31,32]. The maximum absorbance was found at 310 nm. Various recovery methods were implemented for to study the recovery of iron complex with ligand.

The optimum recovery was found at 25 $^{\circ}\text{C}$, pH = 3 and 1:1 metal ligand ratio for 30 min. Table-2 shows the satisfactory recovery of Fe(III) from various natural water samples. Moreover, the standard deviation was also examined which shows that this method had a amazing degree of precision and accuracy. Hence synthesis of ligands like this generate the era where purification of water can be done easily.

TABLE-2
DETERMINATION TO Fe(III) IONS IN DIFFERENT NATURAL WATER SAMPLES BY SPECTROSCOPIC METHOD

Water sample	Fe(III) spiked (mg L^{-1})	Fe(III) recovered (mg L^{-1})	Recovery (%)	Standard deviation
Distilled water	4.62	4.628	99.82	0.08
	8.41	8.412	99.97	
Tap water	4.63	4.635	99.89	0.04
	8.41	8.413	99.96	
Underground water	4.64	4.647	99.84	0.04
	8.42	8.426	99.92	
Well water	4.63	4.631	99.97	0.03
	8.40	8.407	99.91	
River water	4.62	4.625	99.89	0.04
	8.41	8.413	99.96	

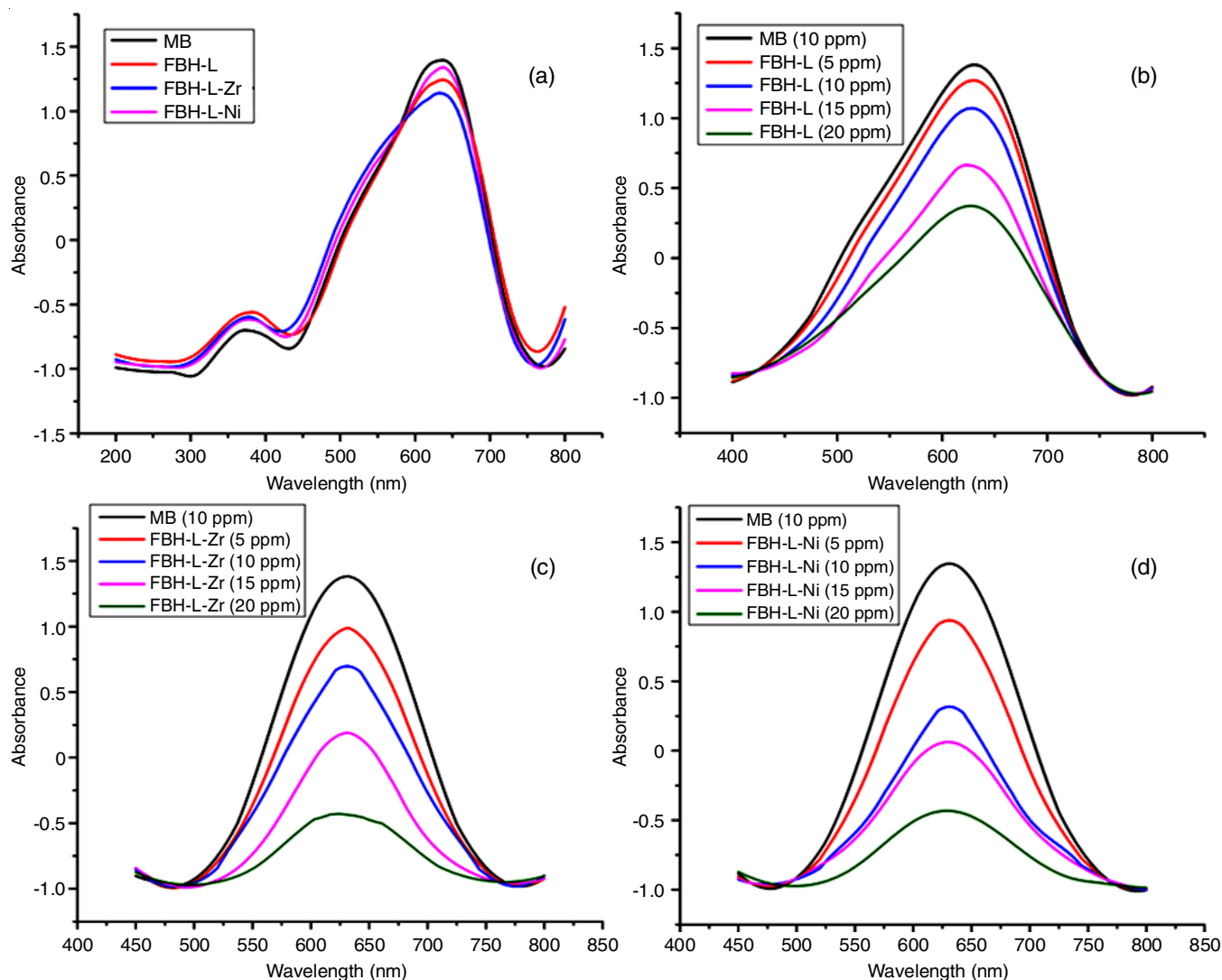


Fig. 7. Photocatalytic activity shown by methylene blue, FBH-L, FBH-L-Zr and FBH-L-Ni in- (a) absence of sun light (b) by FBH-L in sun light at different concentrations (c) by FBH-L-Zr in sun light at different concentrations and (d) by FBH-L-Ni in sun light at different concentrations

Conclusion

Present work reported the synthesis of novel hydrazone ligand and its two metal complexes which were identified by different spectral and analytical techniques. The prepared compounds were recognized as effective biological agents as they showed excellent antimicrobial and anti-angiogenic activities as well they have a tendency to remove metal ions in water samples and act as a photocatalyst for the degradation of methylene blue dye.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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