



SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL STUDIES OF Cu(II), Pd(II), Fe(III) AND Mn(II) COMPLEXES OF TETRADENTATE N₄ LIGAND

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ABSTRACT

1,4-Bis(1-piperidineethyl)piperazine tetradentate N₄ type of ligand synthesized from piperazine and 1-(2-chloroethyl)piperidine HCl. The Cu(II), Pd(II), Fe(III) and Mn(II) complexes of ligand N₄ were synthesized by taking 1:1 ratio of M:N₄. The ligand and complexes have been characterized by elemental analyses, ¹H-NMR, FT-IR, UV-Vis., spectroscopic techniques and mass spectrometric studies. The magnetic moment measurements and conductance measurements were carried out on all the complexes. The elemental analyses shows that the complexes obtained have the composition of [Cu(N₄)](PF₆)₂, [Pd(N₄)](PF₆)₂, [Fe(N₄)Cl₂]PF₆ and [Mn(N₄)Cl₂]. The spectroscopic data revealed, square planar geometries for Cu(II), Pd(II) and octahedral geometries for the Fe(III), Mn(II) complexes and the ligand acts as tetradentate N₄ donor. The ligand and all complexes were screened for their antibacterial activity against bacterial species *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli* as well as fungi *Streptococcus mutans*, *Candida albicans*, *Aspergillus fumigatus*. The activity data revealed that the metal complexes are to be more potent antibacterials in comparison to parent ligand.

KEYWORDS: 1,4-Bis(piperidineethyl)piperazine, N₄ tetradentate ligand, Cu(II), Pd(II), Fe(III) and Mn(II), antimicrobial activity.



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INTRODUCTION

The synthesis of a new ligand is the most important step in the development of metal complexes with unique properties and novel reactivity. The selective complexation of metal ions by tailored ligands has been widely used in creating numerous interesting molecular architectures and correspondingly, new ligand architectures have been designed for selective recognition of metal cations¹. The control of molecular structures and topologies through assembling molecules by using their 'built-in' structural conformation has been the major goal in supra molecular chemistry². Inorganic self-assembly and self-organization involve the spontaneous generation of well-defined metallo-supramolecular architectures from organic ligands and metal ions³. The self-assembled construction of infinite high-dimensional metal-organic frameworks (MOFs) is of current interest in the fields of functional material and crystal engineering, not only because of their potential applications in catalysis, nonlinear optics (NLO), molecular adsorption and magnetic materials, but also because of their intriguing framework topologies⁴⁻⁷. Piperazine is a water soluble cyclic diazine with rigid preorganized cyclohexane conformation⁸. As an amine, piperazine readily undergoes nucleophilic substitution reactions with proper halides. The hexatomic piperazine ring may exhibit a boat or a chair conformation, the latter one is 17.2 kJ mol⁻¹ more stable⁹. The boat conformation is stabilized when the piperazine ring co-ordinates one metal ion through both the nitrogen atoms forming bidentate chelate complexes. However, the structural character of piperazine causes some rigidity. The skeletal ring of piperidine nucleus is often found in the molecular framework of many natural medicaments¹⁰. The piperidine ring is an ubiquitous structural feature of many alkaloid natural products, drug candidates and more interestingly, in many biologically active compounds such as anopterine, pergoline, scopolamine and morphine. Watson et al. asserted that during a recent 10-year period there were thousands of piperidine compounds

mentioned in clinical and preclinical studies¹¹. Recently, in order to enhance oral bioavailability, a series of piperidine-linked aminopyrimidine derivatives were reported with good potency against wild-type and several important resistant mutant strains of HIV-1 in both enzymic and cellular assays^{12,13}. N₄ ligands and their metal complexes have attracted interest among coordination chemists¹⁴. Here we report the detailed study of synthesis, characterization and comparative antimicrobial activities of Cu(II), Pd(II), Fe(III) and Mn(II) complexes of the title ligand.

MATERIALS AND METHODS

All the chemicals used were of AnalaR grade and procured from Sigma-Aldrich. Metal salts were purchased from E. Merck and were used as received.

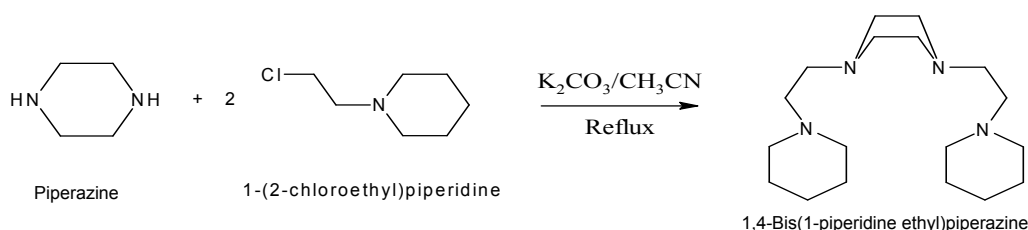
(i) Physical measurements

¹H and ¹³C{¹H}NMR spectra were recorded on Bruker AMX-400 MHz spectrometer operating at 399.6 MHz with TMS as standard. FT-IR spectra were recorded on Perkin-Elmer Spectrum One as KBr pellets in the range 4000-400 cm⁻¹. Elemental analyses were carried out using Flash-2000 Organic Elemental Analyzer. Electronic spectral studies of the compounds were carried out using Shimadzu UV-1800 spectrophotometer. Molar conductance was measured on the ELICO (CM82T) conductivity bridge. Magnetic susceptibility was measured at room temperature on a Gouy balance using CuSO₄·5H₂O as calibrant.

(ii) Synthesis of 1,4-Bis(1-piperidineethyl)piperazine tetradentate ligand (N₄)

To a stirred mixture of piperazine (1.0 g, 0.01 mol) and anhydrous K₂CO₃ (4.8 g, 0.03 mol) in CH₃CN (100 ml), a solution of 1-(2-chloroethyl)piperidine HCl (4.8g, 0.02 mol) in CH₃CN (20 ml) was added under nitrogen atmosphere. The mixture was refluxed for 4-5 h.

After completion of the reaction, by TLC, the reaction mass was cooled and the inorganic residue was filtered. Evaporation of the solvent under vacuum. The product was purified by recrystallization from dichloromethane and N-hexane gave ligand 1,4-Bis(1-piperidine ethyl)piperazine (N_4) as a white solid (Scheme-1).



Scheme-1
Synthesis of tetradentate N_4 ligand

(iii) Synthesis of complexes

(a) Synthesis of $[\text{Cu}(N_4)(\text{PF}_6)_2]$ and $[\text{Pd}(N_4)(\text{PF}_6)_2]$

A mixture of appropriate metal salt ($\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, Na_2PdCl_4) (0.01eq.), Ligand N_4 (0.01eq.) and 0.02 equivalents of NH_4PF_6 in 25 ml of dry methanol was stirred at room temperature for 4-6 h. The resulting precipitate was separated by filtration, washed with diethyl ether, cold methanol, for remove of excess of ligand. The solid dried over P_4O_{10} in *vacuum* to give respective complexes.

$[\text{Cu}(N_4)(\text{PF}_6)_2]$: Yield:68%, Color: Green, MP: 210°C , Anal.: Found (Calculated) in % for $\text{C}_{18}\text{H}_{36}\text{CuN}_4\text{P}_2\text{F}_{12}$; C, 32.45 (32.65); H, 5.38 (5.48); N, 8.35 (8.46). FT-IR (KBr, cm^{-1}): $\nu_{\text{C-H}}$, 2968; $\nu_{\text{C-N}}$, 1275; $\nu_{\text{M-N}}$, 418. UV-Vis.: [λ_{max} (cm^{-1})] 31152, 13020.

$[\text{Pd}(N_4)(\text{PF}_6)_2]$: Yield:73%, Color: Yellow, MP: 249°C , Anal.: Found (Calculated) in % for $\text{C}_{18}\text{H}_{36}\text{PdN}_4\text{P}_2\text{F}_{12}$; C, 30.62 (30.67); H, 5.05 (5.14); N, 7.88 (7.94). FT-IR (KBr, cm^{-1}): $\nu_{\text{C-H}}$, 2939, 2989; $\nu_{\text{C-N}}$, 1280; $\nu_{\text{M-N}}$, 458. UV-Vis.: [λ_{max} (cm^{-1})] 30395, 23584.

(b) Synthesis of $[\text{Fe}(N_4)\text{Cl}_2](\text{PF}_6)_2$:

A mixture of anhydrous FeCl_3 (0.01eq), ligand N_4 (0.01eq) and NH_4PF_6 (0.02eq) in 25 ml of

N_4 : Yield: 2.8g, 80%, MP: 90°C , Anal.: Found (Calculated) in % for $\text{C}_{18}\text{H}_{36}\text{N}_4$, C, 69.95 (70.07); H, 11.58 (11.76); N, 18.01 (18.16). FT-IR (KBr, cm^{-1}): $\nu_{\text{C-H}}$, 2930, 2830; $\nu_{\text{C-N}}$, 1108. LC-MS (crude): m/z, 309.3 (93%). $^1\text{H-NMR}$: 1.38 (1.0, m), 2.06 (2.06, m), 2.33 (5.40, m).

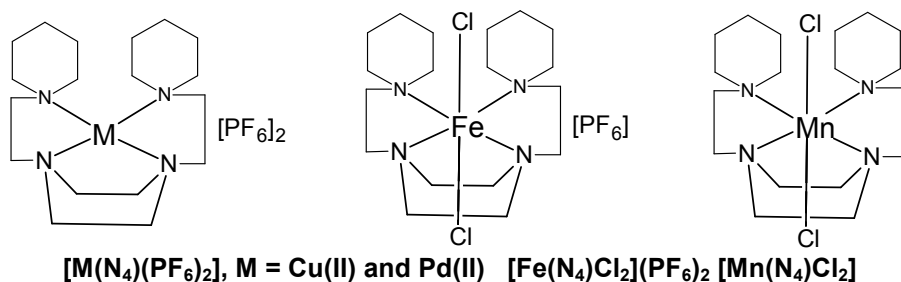
dry methanol was stirred at room temperature for 4-5 h. The resulting reddish yellow precipitate was separated by filtration, washed with diethyl ether cold methanol for remove of excess of ligand. The solid dried over P_4O_{10} in *vacuum* to give respective complexes.

$[\text{Fe}(N_4)\text{Cl}_2](\text{PF}_6)_2$: Yield:58%, MP: 272°C , Anal.: Found (Calculated) in % for $\text{C}_{18}\text{H}_{36}\text{FeN}_4\text{Cl}_2\text{PF}_6$; C, 37.19 (37.26), H, 6.23 (6.25), N, 9.64 (9.69). FT-IR (KBr, cm^{-1}): $\nu_{\text{C-H}}$, 2972; $\nu_{\text{C-N}}$, 1261; $\nu_{\text{M-N}}$, 442; $\nu_{\text{M-Cl}}$, 358. UV-Vis.: [λ_{max} (cm^{-1})] 29850, 16393.

(c) Synthesis of $[\text{Mn}(N_4)\text{Cl}_2]$:

A mixture of $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ (0.01eq) and ligand N_4 (0.01eq) in 25 ml of dry methanol was stirred at room temperature for 4h. The resulting brown precipitate was separated by filtration, washed with, diethyl ether, cold methanol for remove of excess of ligand. The solid dried over P_4O_{10} in *vacuum* to give respective complexes.

$[\text{Mn}(N_4)\text{Cl}_2]$: Yield:65%, MP: 255°C , Anal.: Found (Calculated) in % for $\text{C}_{18}\text{H}_{36}\text{MnN}_4\text{P}_2\text{F}_{12}$; C, 33.01 (33.08), H, 5.44 (5.55), N, 8.49 (8.57). FT-IR (KBr, cm^{-1}): $\nu_{\text{C-H}}$, 2941, 3015; $\nu_{\text{C-N}}$, 1271; $\nu_{\text{M-N}}$, 460; $\nu_{\text{M-Cl}}$, 360. UV-Vis.: [λ_{max} (cm^{-1})] 31526, 24826, 18742, 3150.



Scheme 2

Proposed Structures of Cu(II), Pd(II), Fe(III) and Mn(II) complexes:

(iv) Antimicrobial activity

Peptone (5 g), sodium chloride (5 g), beef extract (1.5 g) were suspended in 1000 mL distilled water and boiled to dissolve all the ingredients. The pH of the solution at 25 °C was adjusted to 7.4 ± 0.2 and sterilized by autoclaving at 15 lb pressure (121 °C) for 15 min. One day prior to the test, bacterial and fungal strains were made in the sterile nutrient broth and incubated at 37 °C overnight. Sample solutions were prepared by dissolving 1 mg of sample in 10 mL of 2% DMSO to give the concentration of 100 µg/ml. The standard solutions of Ciprofloxacin (antibacterial drug) and Ketoconazole (antifungal drug) were prepared in 2% DMSO to give a concentration of 100 µg/ml. Serial broth microdilution was adopted as a reference method. Serial dilutions of test compounds were made in broth, after which a standardized microorganism suspension was added (10 test tubes). Quantities of test compounds were serially diluted to attain the final concentrations of 100–0.2 µg/ml. One of the test tubes was kept as

control. Each of the 10 test tubes was inoculated with a suspension of microorganism to be tested and incubated at 35 °C for 18 h. At the end of the incubation period, the tubes were visually examined for the turbidity. Cloudiness in the test tubes indicated that microorganism growth has not inhibited by the antibiotic contained in the medium at the test concentration. The tests were run in triplicate.

RESULTS AND DISCUSSION

The N₄ tetradentate ligand was synthesized from piperazine and 1-(2-chloroethyl)piperidine HCl. It is characterized by ¹H-NMR (show in fig:-1), LC-MS (show in fig:-2) and FT-IR. Its metal complexes obtained by substitution reaction of metal halides with N₄ tetradentate ligand, 1:1 ratio. Metal complexes are characterized by FT-IR, UV-Vis., Melting point, Magnetic moment and Molar conductivity measurements.

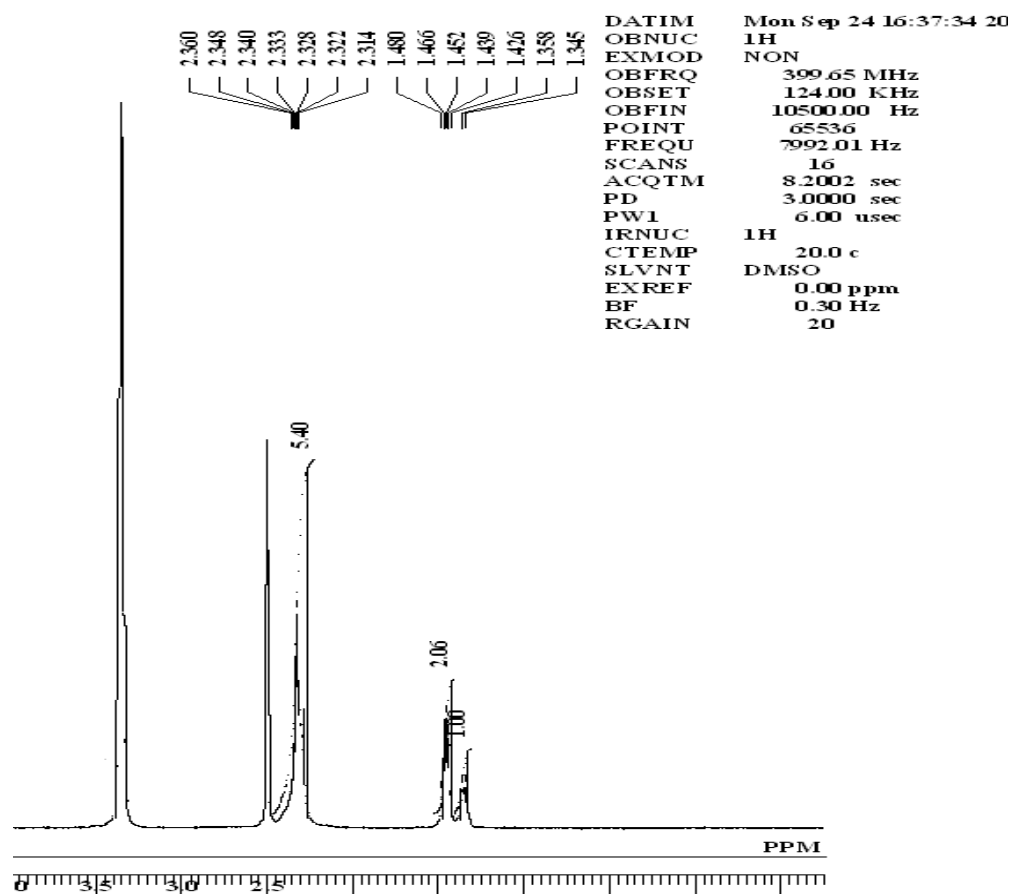


Figure 1
1H-NMR; 1,4-Bis(1-piperidineethyl)piperazine

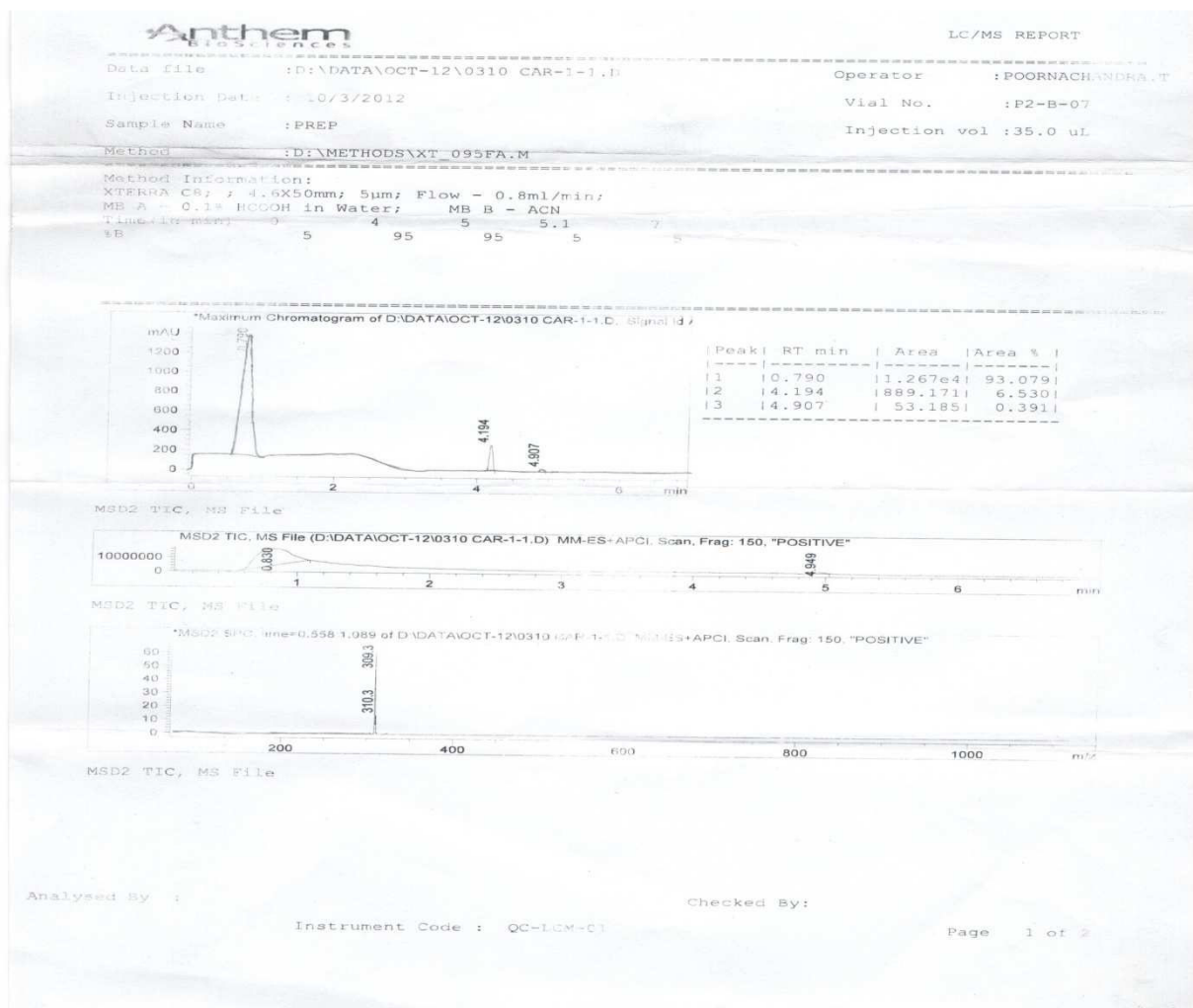


Figure 2
LC-MS; 1,4-Bis(1-piperidineethyl)piperazine

1. Molar conductivity measurements

The compounds were dissolved in DMF and the molar conductivities of 10^{-3} M of their solutions at 25 °C were measured. The conductivity data of $[\text{Cu}(\text{N}_4)(\text{PF}_6)_2]$ 245, $[\text{Pd}(\text{N}_4)(\text{PF}_6)_2]$ 267 ($\Omega^1 \text{cm}^2 \text{mol}^{-1}$) showed them to be 1:2 electrolytes. The conductivity data of $[[\text{Fe}(\text{N}_4)\text{Cl}_2](\text{PF}_6)]$ 145 ($\Omega^1 \text{cm}^2 \text{mol}^{-1}$) showed them to be 1:1 electrolytes. The conductivity data of $[\text{Mn}(\text{N}_4)\text{Cl}_2]$ 13 ($\Omega^1 \text{cm}^2 \text{mol}^{-1}$) showed them to be non-electrolytes,¹⁵⁻¹⁶ (Table-2)

2. Magnetic moments

At room temperature Cu(II), Fe(III) and Mn(II) complexes show magnetic moment 1.82, 5.75 and 5.89 BM corresponding to one, five and five unpaired electrons, respectively¹⁷. While the Pd(II) complexes are diamagnetic as expected for low spin, square planar geometry^{18,19} (Table-2).

Table 1
Analytical data and physical properties of the complexes.

Compound	Empirical formula	Color	MP (°C)	Yield (%)	Elemental analysis, % Found (Calculated)		
					C	H	N
Tetradentate N ₄	[C ₁₈ H ₃₆ N ₄]	White	90	80	69.95 (70.07)	11.58 (11.76)	18.01 (18.16)
[Cu (N ₄)(PF ₆) ₂]	[C ₁₈ H ₃₆ CuN ₄ P ₂ F ₁₂]	Green	210	68	32.45 (32.65)	5.38 (5.48)	8.35 (8.46)
[Pd(N ₄)(PF ₆) ₂]	[C ₁₈ H ₃₆ PdN ₄ P ₂ F ₁₂]	Yellow	249	73	30.62 (30.67)	5.05 (5.14)	9.64 (9.69)
[[Fe(N ₄)Cl ₂](PF ₆)]	[C ₁₈ H ₃₆ FeN ₄ Cl ₂ PF ₆]	Reddish-yellow	272	58	37.19 (37.26)	6.23 (6.25)	7.88 (7.94)
[Mn(N ₄)Cl ₂]	[C ₁₈ H ₃₆ MnN ₄]	Brown	255	65	33.01 (33.08)	5.44 (5.55)	8.49 (8.57)

3. FT-IR spectra

The FT-IR spectrum of the ligand exhibit band corresponding to the ν_{C-H} 2930, 2830; ν_{C-N} , 1286 cm^{-1} . The bands appear in the spectrum of the complex in the regions 2926, 2931, 2919, 2922 cm^{-1} are assignable to ν_{C-H} of metal complexes, respectively. The bands appear in the spectrum of the complex in the regions 1275, 1280, 1261, 1271 cm^{-1} are assignable to ν_{C-N} of metal complexes, respectively. On complex formation some new bands at 418–460 cm^{-1} and 358–320 cm^{-1} may be attributed to ν_{M-N} and ν_{M-Cl} vibrations, respectively²⁰⁻²³. (Table-2).

Table 2
FT-IR, Molar conductivity measurements, Magnetic moment

Compounds	ν_{C-H}	ν_{C-N}	ν_{M-N}	ν_{M-Cl}	Molarcond. ($\Omega^{-1} \text{cm}^2 \text{mol}^{-1}$)	$\mu_{\text{eff}}(\text{BM})$
Tetradentate N ₄	2930	1286	–	–	–	–
[Cu (N ₄)(PF ₆) ₂]	2926	1275	418	–	245	1.82
[Pd(N ₄)(PF ₆) ₂]	2931	1280	458	–	267	Diamagnetic
[[Fe(N ₄)Cl ₂](PF ₆)]	2919	1261	442	358	145	5.75
[Mn(N ₄)Cl ₂]	2922	1271	460	320	13	5.89

4. Electronic spectra

The electronic absorption spectra of complexes obtained in DMSO solution in the 250–600 nm. The UV-Vis spectra of the free Tetradentate N₄ ligand nearly 33890 cm^{-1} exhibit, which can be attributed to $n \rightarrow \sigma^*$. The UV-Vis spectra of the complexes 29100–31500 cm^{-1} due to charge transfer spectra of LMCT/MLCT. The UV-Vis spectrum of Cu (II) shows a broad absorption in the range 1300–1600 cm^{-1} due to d–d transition for Cu (II) complex. Such a feature is expected for a square planar geometry in accordance with earlier reports²⁴⁻²⁶. For the square planar complexes with $d_{x^2-y^2}$ ground state, three spin allowed transitions are possible

viz., ${}^2B_{1g} \rightarrow {}^2A_{1g}$ ($d_{x^2-y^2} \rightarrow d_{z^2}$), ${}^2B_{1g} \rightarrow {}^2B_{2g}$ ($d_{x^2-y^2} \rightarrow d_{xy}$) and ${}^2B_{1g} \rightarrow {}^2E_g$ ($d_{x^2-y^2} \rightarrow d_{xz}, dyz$) and it is difficult to resolve it into three bands. The four lower orbitals are often so close together in energy that individual transfer there from to the upper d level cannot be distinguished and hence the single absorption band. Palladium(II) complexes have d→d bands in the range 23584 cm^{-1} , which assigned to $d_{z^2}, d_{x^2-y^2}$ transition, for which three spin-allowed d–d transitions are expected, corresponding to transitions from the three lower lying d-levels to the empty $d_{x^2-y^2}$ orbitals. All these point toward the low spin complex of d⁸ system with square planar symmetry²⁷⁻²⁹. Electronic spectra of iron

(III) complexes have $d \rightarrow d$ bands in the range 16393 cm^{-1} . The positions and nature of the observed ligand field bands for the complexes suggest a high-spin ground state configurations of the metal ions i.e., $\text{Fe}^{3+} (t_{2g}^3 e_g^2)$, with ${}^6A_{1g}$, ground energy level, respectively, in the hexacoordinate environment of the ligands

³⁰. The electronic spectrum of the Mn(II) complex displays weak absorption bands at 13150 , 18742 , 24826 and 31526 cm^{-1} . These bands can be assigned to the transitions: ${}^6A_{1g} \rightarrow {}^4T_{1g}$, ${}^6A_g \rightarrow {}^4E_g$, ${}^4A_{1g} \rightarrow ({}^4G)$, ${}^6A_g \rightarrow {}^4E_g$ and ${}^6A_{1g} \rightarrow {}^4T_{1g}$ respectively. It shows octahedral geometry ³¹.

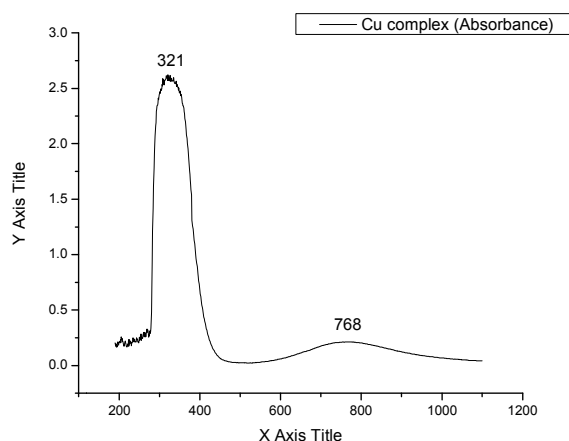


Figure 3
Electronic Spectra for $[\text{Cu}(\text{N}_4)](\text{PF}_6)_2$

5. Antimicrobial activity

All the synthesized compounds were screened for their *in vitro* antimicrobial activity against two Gram-positive, two Gram-negative bacterial strains and two fungal strains. A comparative study of MIC (Minimum Inhibitory Concentrations) values of the Tetradentate N_4 and its complexes (Table-3) indicates that the metal complexes generally have a better activity than the free ligand. The increase in biological activity of the metal chelates may be due to the effect of the metal ion on the normal cell process. A possible mode of toxicity increase may be considered in the light of Tweedy's chelation theory ³²⁻³⁵. Chelation considerably reduces the polarity of the metal ion because of partial sharing of its positive charge with the donor group and possible π -electron delocalization within the whole chelate ring system that is formed during coordination. Such chelation could enhance the lipophilic character of the central metal atom and hence increase the hydrophobic character and liposolubility of

the complex favoring its permeation through the lipid layers of the cell membrane. This enhances the rate of uptake/entrance and thus the antimicrobial activity of the testing compounds. Accordingly, the antimicrobial activity of the complexes present in this investigation can be referred to the increase of their lipophilic character which in turn deactivates enzymes responsible for respiration processes and probably other cellular enzymes, which play a vital role in various metabolic pathways of the tested micro-organisms. The antimicrobial results evidently show that the activity of the Tetradentate N_4 has enhanced on coordination to the metal ions.

The tested complexes were more active against Gram-positive than Gram-negative bacteria, it may be concluded that the antimicrobial activity of the compounds is related to cell wall structure of the bacteria. It is possible because the cell wall is essential to the survival of bacteria and some antibiotics are able to kill bacteria by inhibiting a step in the

synthesis of peptidoglycan. The bacterium, *Staphylococcus aureus* (SA) is found to be most susceptible one while against all the compounds. Similarly, *Candida albicans* (CA) is most susceptible among the fungal strains.

From the *in vitro* antimicrobial assay, it is thus found that the tested compounds possess excellent antimicrobial activities even when compared with the standards used.

Table 3
In vitro antimicrobial and anti-tubercular activities of the compounds.

Compound	MIC(μ M)					
	Bacteria				Fungi	
	Gram Positive		Gram Negative		CA	AF
EF	SA	EC	SM			
Tetradentate N ₄	5.2	5.7	38.4	11.6	21.3	1.1
[Cu(N ₄)(PF ₆) ₂]	0.4	3.8	4.0	0.8	0.4	7.3
[Pd(N ₄)(PF ₆) ₂]	0.5	1.5	0.9	27.9	1.4	31.0
[[Fe(N ₄)Cl ₂](PF ₆)]	0.6	4.3	16.3	25.6	0.6	5.5
[Mn(N ₄)Cl ₂]	0.9	2.2	1.1	0.5	4.0	2.0
Ciprofloxacin	0.7	9.4	1.2	0.7		
Ketoconazole					0.7	0.4

EF, *Enterococcus faecalis*; SA, *Staphylococcus aureus*; EC, *Escherichia coli*; SM, *Streptococcus mutans*; CA, *Candida albicans*; AF, *Aspergillus fumigatus*.

CONCLUSION

The analytical and physico-chemical analysis confirmed the composition and structure of the newly synthesized complexes. The IR, electronic spectra and magnetic moment data lead to the conclusion that the metal ions take different geometries. These studies revealed, square planar geometries for Cu(II), Pd(II) and octahedral geometries for the Fe(III), Mn(II) complexes. In all complexes, the N₄ tetradentate ligand around metallic ion, coordinating through nitrogen. The N₄ tetradentate ligand and their complexes were

evaluated for their antimicrobial activity against a panel of Gram-positive and Gram-negative bacteria, as well as fungal strains. The activity of metal complexes are comparable with the standard used and have shown comparatively good activity against Gram-positive bacteria. From the results, it must be emphasized that the studied metal complexes were more active than the free ligand. The difference in activity among the tested compounds may be attributed to the electrostatic nature of ligand and central metal ion and the lipophilicity of compounds.

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