SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF NEW SCHIFF BASES 1-(((4,6-DIMETHYLPYRIMIDIN-2-YL)IMINO)METHYL)NAPHTHALEN-2-OL AND THEIR Fe (III) COMPLEXES

D.T. Sakhare, U.G, P.G. & Research Centre, Department of Chemistry, Shivaji, Art's, Comm. & Science College Kannad. Dist. Chhatrapati Sambhajinagar.431103, (M.S.) India.
E-mail- sakharedhondiram@yahoo.com

ABSTRACT
In this present work, the novel heterocyclic Schiff bases ligands derived from 2-amino-4,6-dimethylpyrimidine with 2-hydroxy-1-naphthaldehyde (L_1) was synthesized. These ligand used to synthesis complexes of Fe(III). The synthesized compounds have been characterized by FT-IR, 1H-NMR and UV-Vis techniques for the ligands and FT-IR, UV-Vis, all reactions monitored by TLC, molar conductivity and magnetic susceptibility measurements for the corresponding complexes. General formula of complexes are $[M(L_1)_2]2H_2O$. The complexes are paramagnetic in nature. The results of the molar conductivity measurements indicated that in (DMSO) the complexes $[Fe(L_1)_2]2H_2O$ is electrolyte with a molar ratio (1:1). An octahedral geometry for the complexes. The ligands are bidentate, (L_1) through phenolic (OH) and azomethine nitrogen. The ligand and its complexes were screened for their antifungal and antibacterial activity against Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme and Aspergllus flavus .and Escherichia coli, Salmonella typhi, Staphylococcus aureus, B. subtilis. The result indicated that the complexes exhibited good antifungal and antibacterial activities.
Key-words: Heterocyclic Schiff bases, 2-amino-4,6-dimethypyrimidine, 2-hydroxy-1-naphthaldehyde, Biological Activity.

INTRODUCTION:
The heterocyclic Schiff base ligands with O or N donors and their metal complexes have shown interesting properties and those with pyrimidine and pyridine rings represent a promising group of compounds due to their unique biological and pharmaceutical properties[1]. Pyrimidine and pyridine-based compounds exhibit a wide range of biological activity. Pyrimidines with interesting heterocyclic structures are widely used in drug development due to their antibacterial, antifungal, antiviral and antitumor potential. Many pyridine ring ligands and their transition metal complexes have been synthesized and tested for their biological and therapeutic properties, and sometimes serve as models for the active sites of biomolecules [2]. For example, the importance of 2-benzoylpyridine-metal complexes lies in their ability to facilitate substrate binding and thereby stabilize reactive transition metal intermediates. Copper complexes have recently been the subject of intense research due to their potential as radiopharmaceuticals targeting hypoxic tissues and as an effective drug for the treatment of refractory neuroblastoma in children [3]. Copper is an important trace element for plants and animals and is involved in the formation of mixed-ligand complexes in many biological processes. Many cobalt(II) complexes of Schiff base ligands, including 2-benzoylpyridine, acted as microbial growth inhibitors. Binuclear copper(II) complexes with single-atom bridges, e.g., B. halides, have recently attracted attention due to their structural diversity and interesting catalytic, magnetic and biological properties [4]. Depending on the nature of the ligands, chloride or oxygen-bridged compounds with square planar $Cu(O)_2Cu$ bridging loops have different molecular structures. The crystal structures of these compounds are interesting due to the different nature of the intervening intermolecular forces. Due to the presence of primary amine functional groups in heterocyclic compounds with rings such as pyridine and pyrimidine, researchers have started to synthesize pyridine derivative Schiff bases and their metal complexes. Schiff bases are also susceptible to hydrolysis, which is considered to be a very important reaction in many pharmacological and biological processes, leading to the formation of new species [5] .

The wide interest in pyrimidine-based compounds is mainly due to their applications in different areas such as pharmaceutical, agrochemical, and phytosanitary industries [6]. Pyrimidine is known to be a vital constituent of nucleic acids and employed as a synthetic Precursor of Bioactive molecules. There are a wide spectrum of pharmacological active compounds of pyrimidine, and its use in pharmaceuticals is becoming increasingly broad since the synthetic discovery of its substituted (amino, hydroxyl, fluoro, etc.) derivatives. Pyrimidine derivatives have been reported to exhibit various pharmacological activities such as analgesic, anti-epileptic, antiviral, anti-hypertensive minoxidil, antimycobacterial and potent phosphodiesterase inhibitors [7-10]. In addition, drugs with pyrimidinyl moiety are renowned chemotherapeutic agents and have been used in cancer and tumors treatment. For example, the small molecule multikinase inhibitors (sunitinib and sorafenib) are used for advanced renal-cell carcinoma treatment [11,12]. Also, 5-fluorouracil has been applied as an efficient tumor drug while a combination of 5-fluorouracil with bevacizumab has enhanced the treatment of metastatic colorectal cancer [13]. Furthermore, the pyrimidine derivative which is a potent and selective multi-targeted receptor tyrosine kinase inhibitor drug, pazopanib, (5-(4-[(2,3-dimethyl-2H-indazoyl-6-yl)methylamino]-2-pyrimidinyl]amino-2-ethylbenzenesulfon amide) has successfully passed the pilot phase in clinical trials and the development for use in renal cell cancer treatment [14]. Reportedly, Tyrosine kinases (2HCK) actively participate in the transduction of growth factor signals by catalyzing the phosphorylation of tyrosine residues in proteins. There are usually functional modifications of the proteins and mutations of this kinase can cause cancer [15]. Cryptogein (1LRI) is a small protein that has a sterol carrier activity as it acts as a sterol shuttle that helps the pathogen grow and complete its life cycle [16]. ATPase (2OBM) is a type III secretion system (T3SS) that is involved in the initial stages of selective secretion of specialized T3SS virulence effector proteins from the bacterial cytoplasm to the infected host cell, a process crucial to subsequent pathogenicity. In addition, zidovudine and pyrrolo-pyrimidine nucleoside derivatives are in use as anti-HIV and anti-hepatitis-c drugs [17]. The many therapeutic activities exhibited by pyrimidinyl containing drug/compounds could be attributed to their low toxicity and structural diversity [18].

Pyrimidine bioactive derivatives reportedly form stable Schiff bases which can be used as molecular metal ion chelators [19]. It has also been shown that the efficacy of pyrimidine bioactive molecules is enhanced in its coordination to metal ions [20-22]. Heteroleptic metal complexes of pyrimidinyl Schiff bases bearing hetero (N and O) atoms show high kinetic and thermodynamic stabilities, mixed chelation abilities in biological fluid systems and have the ability to prevent induced cellular oxidative stress damages [23].

Heterocyclic Schiff base ligands containing O- or N-donors and their metal complexes have been shown to exhibit interesting properties [24] and those containing pyrimidine rings represent a promising class of compounds due to their inherent biological and pharmaceutical properties [25]. Pyrimidine based compounds exhibit a broad spectrum of biological activities [26]. Pyrimidine with its interesting heterocyclic structure has extensively been used in drug design due to its potential antimicrobial, antifungal, antiviral and antitumor properties. Many ligands containing the pyrimidine ring and their transition metal complexes have been synthesized and tested for biological and therapeutic properties where they sometimes act as models for the active sites of biomolecules [27]. The importance of 2-benzoylpyridine metal complexes, for example, is due to their ability to facilitate substrate binding thus stabilizing the reactive intermediates of transition metals [28]. Copper complexes have recently been the subject of intense research because of their potentials as radiopharmaceuticals for targeting hypoxic tissues and as effective drugs for the treatment of refractory neuroblastoma in children. Copper is an important trace element for plants and animals and is involved in mixed ligand complex formation in a number of biological processes [29]. Many cobalt(II) complexes of Schiff base ligands containing 2-benzoylpyridine behaved as a growth inhibitor for microorganisms. Binuclear copper(II) complexes with monoatomic bridges, such as halides, have attracted recent attention due to their structural diversity and interesting catalytic,

magnetic and biological properties [30]. The crystalline architectures of these compounds are found to be interesting due to variations in the nature of intervening intermolecular forces.
In the present work, we report a synthesis, characterization, antibacterial and antifungal studies of a Schiff base derived from 2-amino-4,6-dimethylpyrimidine and 2-hydroxy-1-naphthaldehyde and its iron (III) complexes.Also, the structure of prepared ligands were checked by FT-IR, ^{1}H- NMR, UV-Vis techniques and prepared complexes were characterized by FT-IR, UV-Vis, molar conductivity and magnetic susceptibility measurements.

EXPERIMENTAL SECTION:

Materials:

Chemicals and reagents used in this work: 2-amino-4,6-dimethylpyrimidine, 2-hydroxy-1-naphthaldehyde, $Fe(NO_3)_2.2H_2O$, were obtained from Sigma-Aldrich Chemical Company.

INSTRUMENTATION:

IR spectra were recorded on FTIR (ATR)-BRUKER-TENSOR37 spectrometer using KBr pellets in the range of 4000-400 cm-1. 1H- NMR (Varian mercury 300MHZ) spectra of ligand were measured in DMSO using TMS as internal standard. X-RD was recorded on BRUKER D8 Advance. TGA-DTA was recorded on Shimadzu. The carbon, hydrogen and nitrogen contents were determined on Elemental model vario SHIMADZU spectrometer. Molar conductance of complexeswas measured on Elico CM 180 conductivity meter using 10-4 M solution in DMSO. Magnetic susceptibility measurements of the metal chelates were done on a Guoy balance at roomtemperature using $Hg[Co(SCN)_4]$ as a calibrant.

PROCEDURES:

Synthesis of schiff base ligand (L_1):

The ligand as illustrated in Fig.6was prepared by a modification of the reported methods [31]. The Schiff base ligand has been synthesized by refluxing a mixture of 0.01 mol (1.2015g) of 2-hydroxy-1-naphthaldehyde, and 0.01 mol (1.2710 g) of 2-amino-4,6-dimethylpyrimidine, in 50 ml super dry ethanol refluxed for about 4h. Schiff base thus formed was cooled to room temperature and collected by filtration, followed by recrystallization in ethanol and dried in vacuo over anhydrous calcium chloride (Yield:70%).

Synthesis of metal complexes[$M(L_1)_2$]:

To a hot ethanol solution (25ml) of the ligand (2 mol) and (25ml) of metal Nitrate (1mol) was added with constant stirring. The pH of reaction mixture was adjusted to 7-8 by adding 10% alcoholic ammonia solution and refluxed for about 3 h. The precipitated solid metal complex was filtered off in hot condition and washed with hot ethanol and dried over calcium chloride in vacuum desiccators. (Yield: 65%) [32].

RESULTS AND DISCUSSION:

Some of physical properties of Schiff bases ligands and their metal complexes are given in (Table 1).

Table 1: Physical properties of Schiff base ligands (L_1) and their metal complexes.

Compound Molecular formula	Mol.Wt.	M.P. Decomp temp. 0C	Colour	Molar Conduc. Mho. Cm^2mol^{-1}
L_1	227	86	Yellow	---
Fe-L_1	477	>300	Dark Yellow	19.27

Table: 2. Elemental Analysis of Fe(III) Complex

Compound	% Found (Calculated)			
	C	H	N	M
L_1	51.54 (53.21)	3.57 (3.85)	16.64 (16.89)	----
Fe-L_1	44.43 (44.35)	3.37 (3.29)	14.17 (14.15)	9.90 (9.88)

^{1}H-NMR spectra of ligand:

The ^{1}H-NMR. Spectra of free ligand at room temperature show the following signals. 5.9 δ (s, 2H, Phenolic (OH) hydrogen of pyrimidine ring), 6.66 δ(s, 1H, Hydrogen bonded to pyrimidine ring), 7.94 δ (s, 1H, hydrogen bonded to azomethine carbon), 7.69-7.28 δ (D,4H, Aromatic Ha, Hb, protons of phenyl ring).

IR Spectra:

The IR spectrum in Fig.2 & 3 of free ligands shows characteristic bands at 3325, 1638, 1487,1207 and 1089 cm-1 assignable to υOH (intramolecular hydrogen bonded), υ C=N (azomethine), υ C=C(aromatic), υ C-N (aryl azomethine) and υ C-O (Enolic) stretching modes respectively [3324] The absence of a weak broad band in the 3200-3400 cm-1 region, in the spectra of the metal complexes suggests deprotonation of the intermolecular hydrogen bonded OH group on complexation and subsequent coordination of phenolic oxygen to the metal ion. This is further supported by downward shift in υ C-O (phenolic) [34] with respect to free ligand. On complexation, the υ (C=N) [35] band is shifted to lower wave number with respect to free ligand, denoting that the nitrogen of azomethine group is coordinated to the metal ion. The υ C-N band is shifted to lower wave number with respect to free ligand, The IR spectra of metal chelates showed new bands in between the 500-600 and 400-500 cm-1 regions which can be assigned to υ M-O and M-N [36] vibrations respectively The IR spectra of Fe(III) show a strong band in the 3050-3600 cm-1 region, suggesting the presence of coordinated water in these metal complexes. The presence of coordinated water is further confirmed by the appearance of non-ligand band in 830-840 cm-1 region, assignable to the rocking mode of water. The presence of coordinated water is also established and supported by TG/DTA analysis of these complexes. Hence it is concluded that the coordination takes place via phenolic oxygen and azomethine nitrogen of ligand molecule in below Table 3.

Table: 3 Salient features of IR spectral data of ligands & Metal complex

Bond vibrational modes	O-H Free Stretching(□)	C = N AzomethineStretching(□)	C = C Aromatic ring stretching(□)	C -- N Aryl azomethine stretch (□)	C -- O Enolic stretching (□)	M--O	M--N
L	3325	1638	1487	1207	1089	--	--
Fe-L	1625.55	1433.23	1351.21	1190.22	1210.31	501.30	451.23

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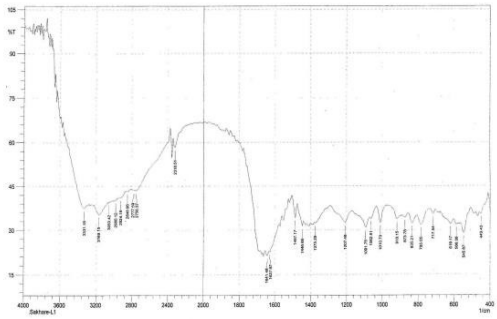

Fig. 2 Infrared Spectra of Ligand L

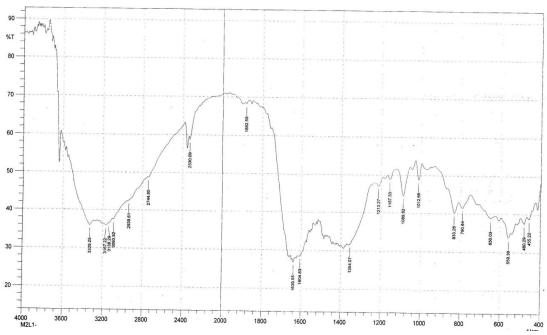

Fig. 3 Infrared Spectra of Fe(III) Complex of Ligand L

Molar conductance measurements:

The conductivity measurements of the complexes were recorded for (10^{-3} M), the solution of the samples was in (DMso) at room temperature. The molar conductance values of the complexes showed in (Table 4). We concluded from the results that the Ni(II) complexes of the ligand (L_1) have a molar conductivity values in the range (10.5 - 72.4 Ω-1 mol^{-1} cm^2). Which indicates that complexes are non-ionic therefore, they are considered as non-electrolytes[37].

Magnetic susceptibility:

The values of effective magnetic moment of metal complexes were summarized in (Table 1), which were measured at room temperature. The complexes [Fe(L_1)] have (μ*eff*) in the range (2.81-2.97 B.M) this value is within the range of octahedral geometry[38].

Thermogravimetric analysis:

Thermal decomposition studies of complex have been carried out as to corroborate the information obtained from the IR spectral studies to know the presence of water molecule in these complexes as well as to know their decomposition pattern. The simultaneous TGA/DTA analysis of Fe(III) was studied from ambienttemperature to 1000^0C in nitrogen atmosphere using α-Al_2O_3 as reference. An analysis of the thermogram of thecomplexes indicated that Fe(III) complexes Fig. 4 shows two step decomposition. The first weight loss 6.66 0%, in between temp. 55-230^0C could be correlated with the loss of two coordinated water (calculated 6.01 %). The anhydrous compound does not remain stable at higher temperature; it undergoes rapid decomposition in the range 230-650°C with 79.72 % mass loss corresponds to decomposition of the complex (calcd. 80.70%) in second step.

The decomposition is completed leading to the formation of stable residue of metal oxide Fe_2O_3 obs. 13.12 % (calcd. 13.28 %). The kinetic and thermodynamic viz the energy of activation (Ea), frequency factor (Z), entropy change (-ΔS) and free energy change (ΔG) for the non-isothermal decomposition of complexes have been determined by employing Horowitz-Metzger method [39] values are given in Table 3. The Calculated values of the given activation energy of the complexes are relatively low, indicating the autocatalysis effect of metal ion on the thermal decomposition of the complex. The negative value of activation entropy indicates that the activated complexes were more ordered than the reaction was slow. The more ordered nature may be due to the polarization of bonds in the activated state, which might occur through charge transfer transitions [40].

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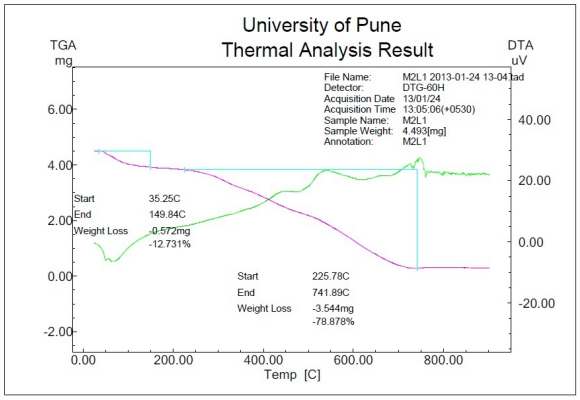

Fig. 4 TGA-DTA Curve of Fe (III) Complex of Ligand L_1

Electronic Spectra:

The electronic spectra of Schiff base ligand (L_1) show absorption bands at (42553cm^{-1} and 27027cm^{-1}) which are attributed to ($\pi \rightarrow \pi^*$) and ($n \rightarrow \pi^*$) transitions respectively, the complex of Ni(II) shows band at (42553cm^{-1}) which due to ($\pi \rightarrow \pi^*$) transition, the band at (23255cm^{-1}) is due to charge transfer (C.T), the band at (14814cm^{-1}) is due to the transition $^3A_{2g} \rightarrow {}^3T_{2g}$the complexes are octahedral geometry[41].

X – Ray Diffraction Studies of Metal Complexes:

The Fe(III) complexes of ligand L_1 was selected for X-ray powder diffraction studies (Fig.5). X-ray powder data of all the main peaks have been indexed independently by trial and error method. The unit cell data crystal lattice parameters and the data obtained after indexing the powder data is presented in Table 4

The Fe(III) complex of ligand L_1 showed fourteen reflections with maxima at 2θ = 9.77° corresponding to d value 4.54Å. The unit cell values of lattice constants are a = 6.8760 Å, b = 9.2456 Å, c = 24.234 Å, α = β = 90° γ= 120° and unit cell volume V = 1334.21763 (Å) 3. The Ni(II) complex of ligand L5 showed nine reflections with maxima at 2θ = 6.49° corresponding to d value 6.80Å. The unit cell values of lattice constants are a = 8.765 Å, b = 11.234 Å, c = 15.345 Å, α = β =90^0 γ= 120° and unit cell volume V = 1308.53064 (Å) ^{3}

Table: 4Indexed X-ray Diffraction Data of Fe(III) Complex of Ligand L_1

Peak No.	2θ (observed)	2θ (calculated)	d (observed)	d (calculated)	Miller indices of Planes			Relative intensities (%)
					h	k	l	
1	6.63463	6.62449	6.66864	6.67725	0	1	1	100.00
2	12.59236	12.57585	3.5337	3.53783	0	2	1	1.54
3	16.31655	16.32083	2.74208	2.74113	1	0	6	9.21
4	18.26175	18.2811	2.4584	2.45569	-1	3	3	2.83
5	19.79914	19.79243	2.27429	2.27486	-3	2	5	2.77
6	20.72674	20.72733	2.17669	2.17647	3	1	1	1.60
7	22.3461	22.35721	2.02617	2.02508	-2	4	2	2.42
8	24.40686	24.41306	1.86428	1.86372	2	2	5	3.64
9	25.43005	25.42349	1.79396	1.79429	-5	3	2	3.37
10	28.15861	28.16861	1.63237	1.63175	-5	4	3	1.98
11	29.1444	29.12894	1.58176	1.58245	1	3	7	4.99
12	30.22681	30.2306	1.53019	1.52995	-6	3	2	3.11
13	30.98353	30.96346	1.4964	1.49721	-5	5	2	2.49

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Unit cell data and crystal lattice parameter

a (A^0) = 9.345	Volume(V) = 1178.91101 $(A^0)^3$
b (A^0) = 8.345	Density(obs.) = 1.0504 gcm^{-3}
c (A^0) = 17.456	Density(cal.) = 1.0394 gcm^{-3}
α = 90.00	Z = 1
β = 90.00	Crystal system = Monoclinic
γ = 120.00	
Standard deviation (%) = 0.050	Porosity = 1.05%

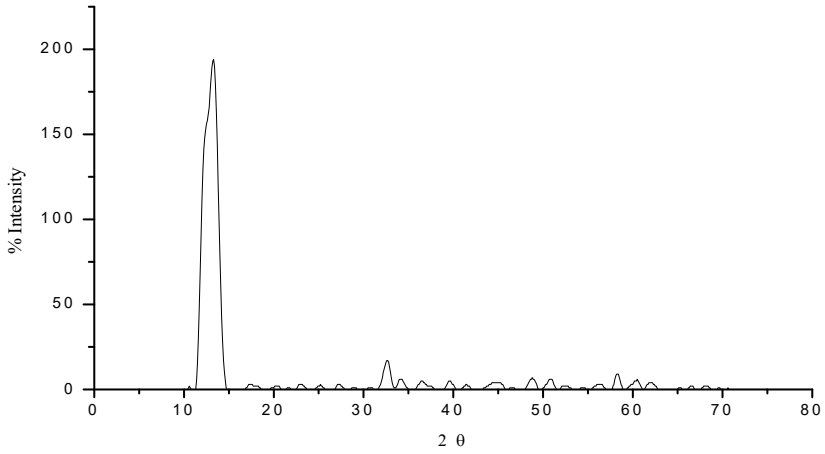

Fig. 5 X-ray Diffractogram of Fe(III) complex of L_1

BIOLOGICAL ACTIVITY :

Antibacterial activity & Antifungal Activity:

Antifungal activity and Antibacterial activity of ligand and metal complexes were tested in vitro against fungal such as *Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme, Aspergillus flavus* and bacteria such as *E. Coli, B.Subtilis, Staphylococcus aureus and Bacillus subtlis* by paper disc plate method [42] The compounds were tested at the concentrations 1% and 2% in DMSO and compared with known antibiotics viz *Griseofulvin* and *Penicillin*. (Table 5 and 6). From Table 5 and 6, it is clear that the inhibition by metal chelates is higher than that of a ligand and results are in good agreement with previous findings with respect to comparative activity of free ligand and its complexes [43] Such enhanced activity of metal chelates is due to the increased lipophilic nature of the metal ions in complexes. The increase in activity with concentration is due to the effect of metal ions on the normal cellprocess. The action of compounds may involve the formation of hydrogen bond with the active centre of cell constituents, resulting in interference with the normal cell process.

Table 5. Antifungal activity of ligands

Test Compound	Antifungal Growth							
	Aspergillus niger		***Penicilliumchrysogenum***		***Fusarium moneliforme***		***Aspergillus flavus***	
	1%	**2%**	**1%**	**2%**	**1%**	**2%**	**1%**	**2%**
L_1	**-ve**	**RG**	**-ve**	**-ve**	**-ve**	**-ve**	**-ve**	**-ve**

Ni-L_1	**-ve**	**-ve**	**-ve**	**-ve**	**-ve**	**-ve**	**RG**	**+ve**
+ve control	**+ve**	**+ve**	**+ve**	**+ve**	**+ve**	**+ve**	**+ve**	**+ve**
-ve control (Griseofulvin)	**-ve**	**-ve**	**-ve**	**-ve**	**-ve**	**-ve**	**-ve**	**-ve**

Ligand& Metal : +ve – Growth (Antifungal Activity absent)
-ve - Growth (Antifungal Activity present)
RG - Reduced Growth (More than 50% reduction in growth observed)

Table 6. Antibacterial activity of ligands and their metal complexes

Test Compound	**Diameter of inhibition zone (mm)**							
	E. coli		***Salmonella typhi***		***Staphylococcu saureus***		***Bacillus subtlis***	
	1%	**2%**	**1%**	**2%**	**1%**	**2%**	**1%**	**2%**
L	**-ve**	**12mm**	**-ve**	**14mm**	**-ve**	**18mm**	**-ve**	**19mm**
Ni-L	**12mm**	**14mm**	**13mm**	**15mm**	**18mm**	**21mm**	**11mm**	**14mm**
DMSO	**-ve**	**-ve**	**-ve**	**-ve**	**-ve**	**-ve**	**-ve**	**-ve**
Penicillin	**14mm**	**14mm**	**18mm**	**18mm**	**31mm**	**31mm**	**19mm**	**19mm**

Ligand & Metal: - ve - No Antibacterial Activity
Zone of inhibition - --mm

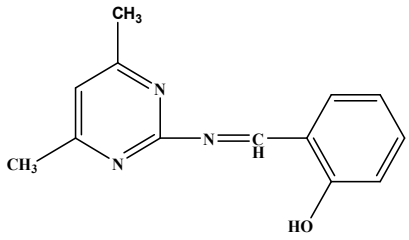

Fig. 6 Structure of Schiff Base Ligand L_1

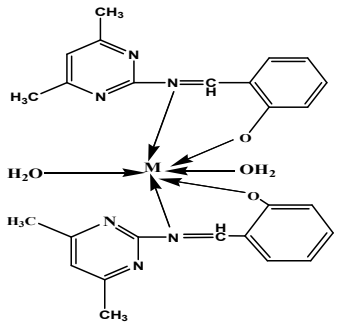

Fig. 7. The proposed Structure of the Metal complexes. [When M= Fe(III)]

CONCLUSION:

In the light of above discussion we have proposed octahedral geometry for Fe(III) complexes. On the basis of the physico-chemical and spectral data discussed above, one can assume that the ligand behave as dibasic, NO bidentate, coordinating via phenolic oxygen and imino nitrogen as illustrated in Fig.7. The complexes are biologically active and show enhanced antimicrobial activities compared

to free ligand. Thermal study reveals thermal stability of complexes. The X-ray study suggests monoclinic crystal system for Fe(III) complexes.

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