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Amino methylation, structure and biological activity of the new mannich base derived from Maleic hydrazide and its transition metal complexes

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Abstract
In this study, we report the synthesis of a new Mannich base derived from Maleic hydrazide and its transition metal complexes. Maleic hydrazide was aminomethylated by reacting with formaldehyde and N-methylpiperazine. The so formed base is complexed with transition metals. The structure of the synthesized compounds are confirmed by UV, IR, and ^{1}H NMR spectroscopic techniques. The antibacterial activity of the ligands and the complexes were examined using different bacterias.

Keywords: mannich base, maleic hydrazide, n-methyl piperazine, transition metal complex and antibacterial activity

1. Introduction
Maleic hydrazide is one of the well-known pyridazine derivatives and has been the subject of several theoretical investigations [1]. The pyridazine system act as a potential substitute for aromatic moieties in antithrombotic, antiviral and antitumor agents [2]. Maleic hydrazide was found to be a potent inhibitor of Leukemia [3], its derivatives are used as novel bioactive agents [4]. Mannish N-bases were proved to be pharmacologically more active than maleic hydrazide [5-6]. About twenty Mannich bases were prepared by treating cyclic imides and hydrazides with formaldehyde and secondary amine. The Mannich reaction of Maleic hydrazide and related compounds of Maleic hydrazide are reported in the literature [7]. Based on these facts, we have synthesized a new Mannich base N-Methyl Piperazino Amino Methyl Maleic Hydrazide, its metal complexes and tested for their biological activity. The results are discussed in this report.

2. Materials and Methods
2.1 General
Reagents such as Maleic hydrazide, formaldehyde and N-methylpiperazine were of sigma-Aldrich products and were used as such. The melting point of all the synthesized compounds were determined in open capillaries and is uncorrected. The UV-Vis spectra were recorded in DMSO solvent on Shimadzu UV mini-1240 spectrophotometer, IR spectra were recorded on Agilent FT-IR spectrophotometer using KBr pellets and ^{1}H NMR spectra were recorded with Bruker AMX400 NMR spectrophotometer using DMSO solvent.

2.2 Synthesis of the Mannich Base Ligand
0.05 mol of the N-Methylpiperazine and 0.05 mol of Formaldehyde are dissolved in 50mL of ethanol and taken in a 100mL RB flask. Then 0.05 mol of the Maleic hydrazide dissolved in 20 mL ethanol added in small aliquots to the reaction mixture kept in ice bath and the stirring was continued for about 6hrs.Then the contents of the mixture were refluxed for 5 hours and kept in refrigerator for overnight. The next day, the solvent was recovered from the mixture by distillation. Mannich base, N-Methyl piperazinomethyl maleic hydrazide (NMPMMH), separates out as pale brown coloured precipitate. It is filtered and washed with hot water, recrystallized in alcohol and dried in air-oven at 60°C.

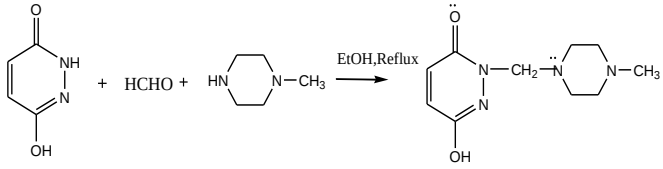


Fig 1: Synthesis of the ligand

2.3 Synthesis of the complexes
Hot ethanolic solution of the ligand (1 equivalent) was slowly mixed with hot ethanolic solution of metal chloride (1 equivalent) under reflux condition with constant stirring. The mixture was refluxed for 3 hours and after that it was cooled and kept in refrigerator for few hours. The colored solid complexes were separated out in each case, it was filtered washed with alcohol and finally dried in air oven.

Table 1: Physical data of the ligand and the complexes

Compound	Yield (%)	Colour	Mp (°C)
NMPMMH Ligand	76	Colorless	257
NMPMMH-Co	78	Pale pink	234
NMPMMH-Ni	70	Pale green	225
NMPMMH-Cu	74	Pale green	242

2.4 Antibacterial activity
For the antibacterial study, nutrient agar was used as the medium. The ligand as well as the complexes were screened for antibacterial activity against certain pathogenic bacteria by

disc diffusion method at concentration of 10µg / ml in DMSO using *Bacillus subtilis*, *Staphaylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. The paper disc containing the compound (10, 20 and 30 µg/disc) was placed on the surface of the nutrient agar plate previously spread with 0.1 mL of sterilized culture of microorganism. After incubating this at 37ºC for 24 hrs, the diameter of inhibition zone around the paper disc was measured.

The zone of inhibition was measured in mm and the activity was compared with Gentamycin in 1 µg / disc A comparison of the diameters of inhibition zones of the compounds investigated shows that Cu (II) complex exhibit highest antibacterial activity against all the bacterial species studied. The results are tabulated in Table.2.

Table 2: Antibacterial activity

Samples	Escherichia coli (mm)	Staphylococcus aureus (mm)	Bacillus subtilis (mm)	Pseudomonas aeruginosa (mm)
Ligand (50µl)	1.50±0.09	1.70±0.06	0.70±0.07	1.45±0.07
Co Complex (50µl)	2.70±0.17	1.30±0.11	1.40±0.07	2.15±0.07
Ni Complex (50µl)	2.20±0.05	0.90±0.01	1.20±0.01	1.30±0.02
Cu Complex (50µl)	5.25±0.40	4.10±0.37	3.40±0.23	4.30±0.28
Standard (30µl)	9.60±0.65	8.80±0.61	8.40±0.58	8.70±0.60
Control (Solvent) (30µl)	0	0	0	0

3. Results and Discussion

3.1 ^{1}H NMR Spectra

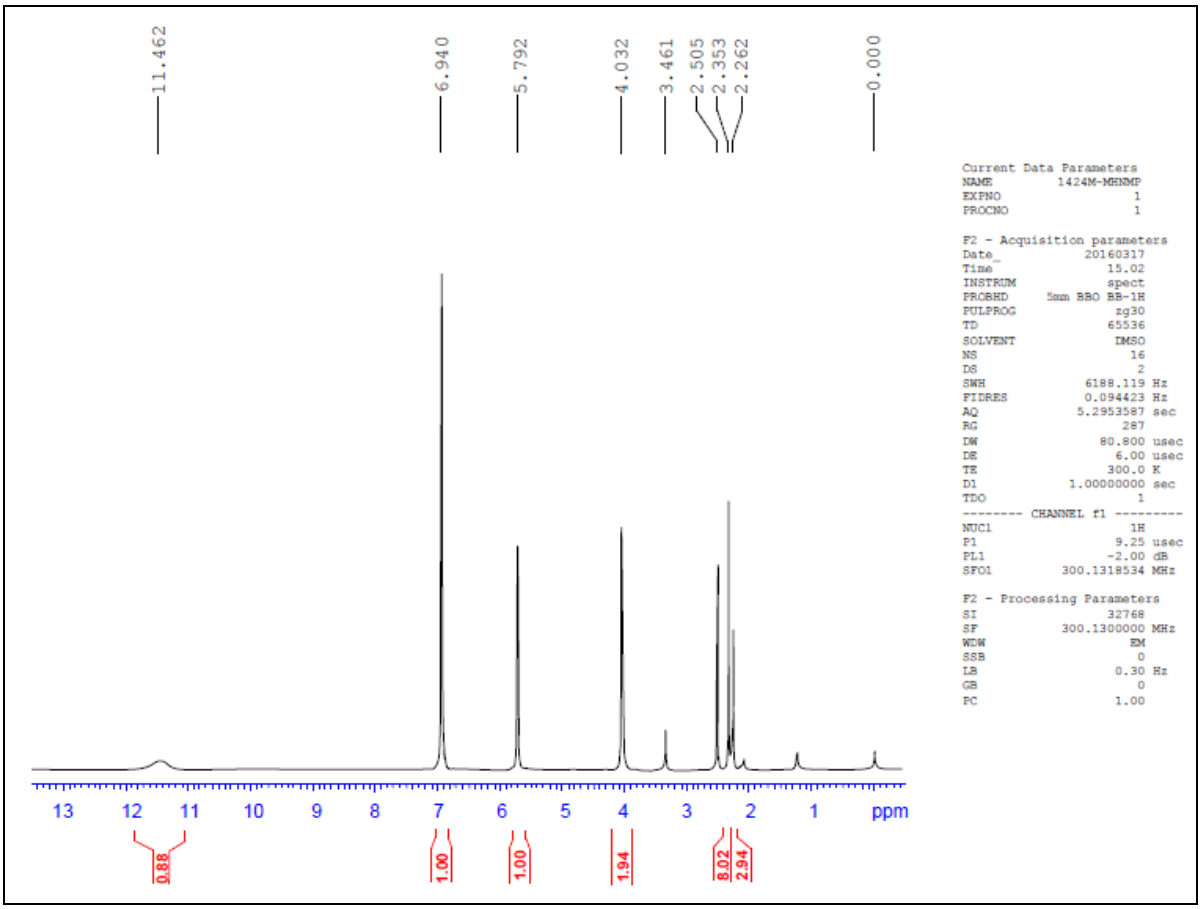


Fig 2: ^{1}H Nmr spectra of the ligand

The ^{1}H NMR spectra of the Mannich base is given in Fig.2.The ligand under study exhibit multiple signals around 2 ppm corresponding to the hydrogens of the piperazine ring. The appearance of peak at 4.3 ppm indicates the methylene hydrogens attached to the nitrogen. Further, the signals at 5.7 and 6.9 ppm corresponds to the ethylenic hydrogens of the pyridazine ring. A peak at 11.4ppm indicates the –OH of the pyridazine ring in the enol form. The formation of the ligand is ascertained by the disappearance of a signal at ~6.5 ppm corresponding to the –NH proton of secondary amine as it was eliminated in the Mannich reaction [8-9].

3.2 IR Spectra

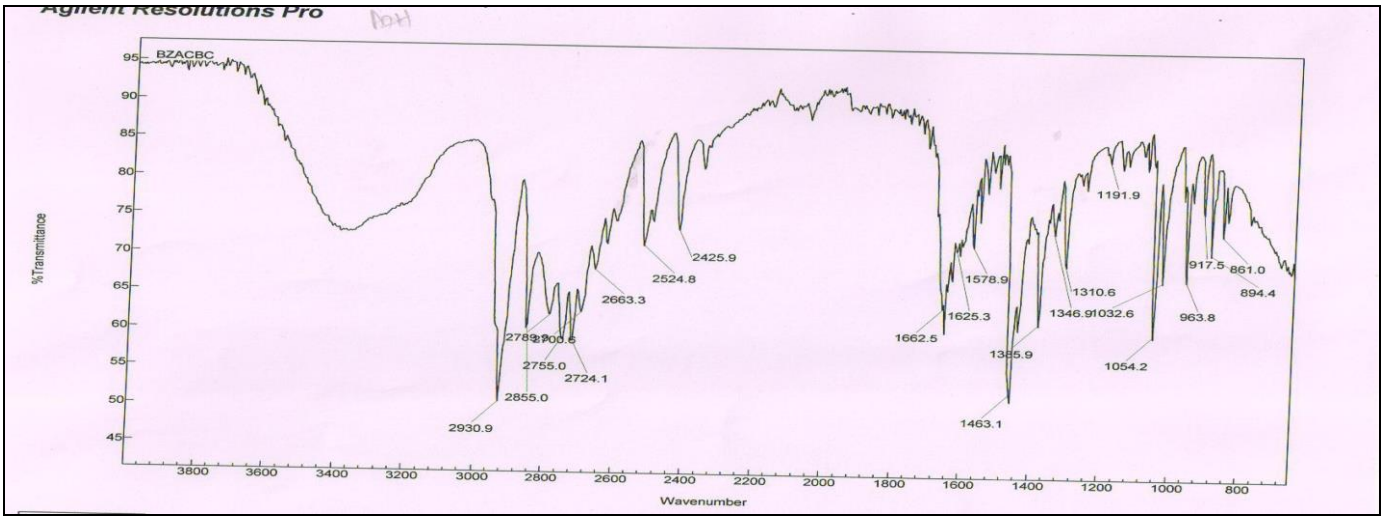


Fig 3: IR Spectra of the ligand NMPMMH

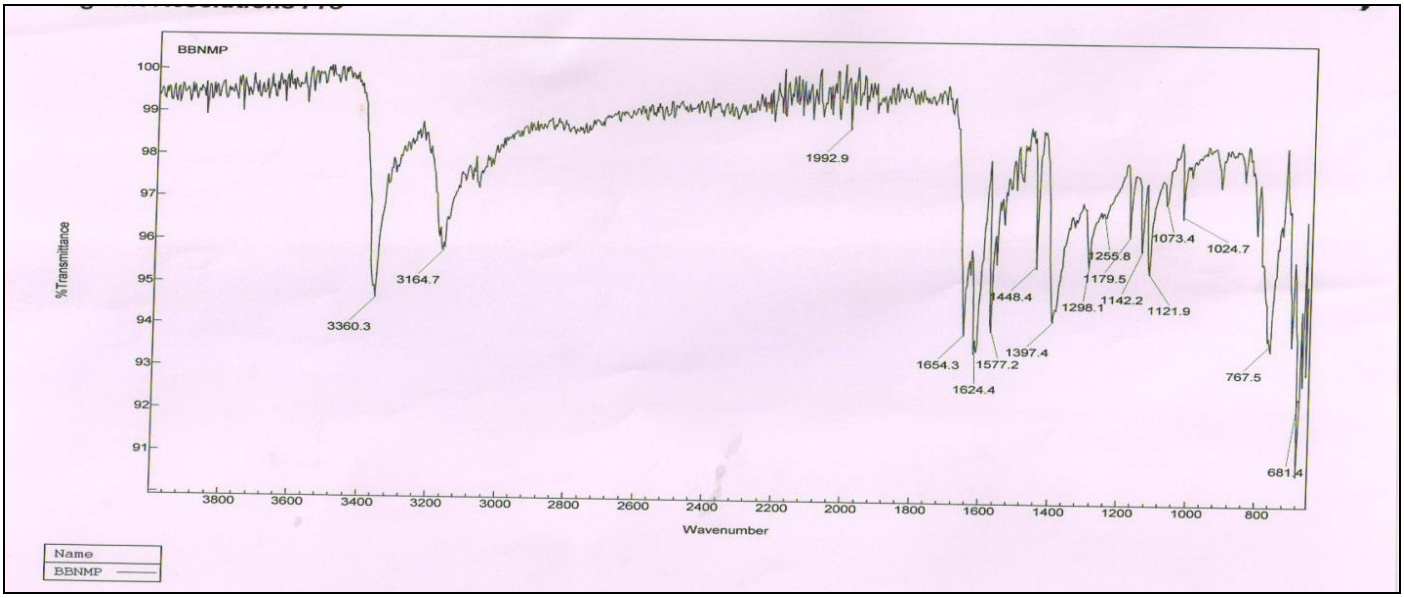


Fig 4: IR Spectra of the metal complex

Table 3: IR Spectral data of the ligand and the complexes

Compound	Vibrational frequency of various functional groups (in cm-1)				
	-OH	-C=O	CNC	M-N	M-Cl
NMPMMH	2930	1662	1191	----	----
NMPMMH-Co	3363	1655	1142	767	681
NMPMMH-Ni	3391	1654	1141	765	682
NMPMMH-Cu	3391	1654	1142	767	681

The IR spectra of the ligand and the metal complexes are shown in Fig 3and Fig.4 respectively. The important observation is the presence of an intense band at ~ 1662 cm^{-1} which is due to νC=O carbonyl group. The most notable change in the IR spectra is the disappearance of the – NH stretching vibration and appearance of an intense band at 1191cm^{-1} due to νC-N-C stretching which is formed due to the amino methylation [10-11]. The absence of band at 3300 cm^{-1} due to amino -NH disappears implying its condensation after deprotonation. These results confirms the formation of the Mannich base. In all the complexes, band due to νC=O and νC-N shifted towards lower frequency clearly indicating the nitrogen and carbonyl oxygen are involved in coordination with metal ions. Further, the appearance of new bands around 767cm^{-1} corresponding to M-O bond and a signal at 681 cm^{-1} corresponding to M-Cl bond confirms the formation of the metal complex.

3.3 UV-Visible spectra

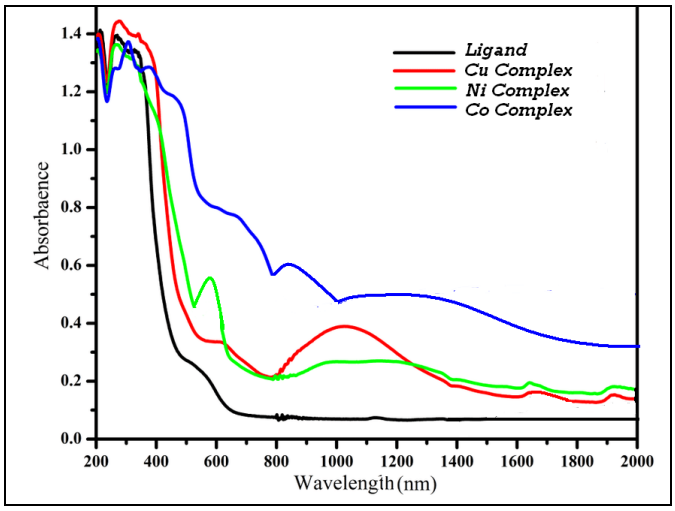
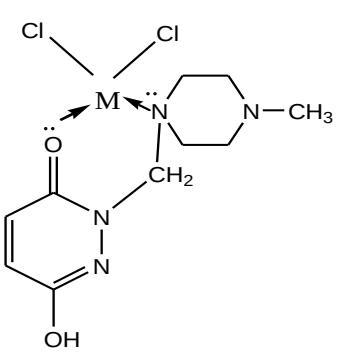
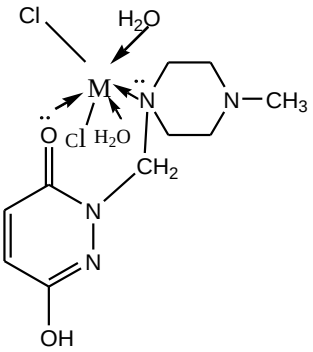


Fig 5: UV Spectra of the ligand and the complexes

The electronic absorption spectra of the ligand and their metal complexes were carried using DMSO solvent is as shown in figure 5. The electronic spectrum of Ni complex showed a weak band at 6072cm^{-1} due to the transition $^3T_1(F) \rightarrow {}^3T_2(F)$ (ν_1). A broad band at 9695 cm^{-1}is assigned to the $^3T_1(F) \rightarrow {}^3A_2(F)$ (ν_2) transition and a weak shoulder like band occur at 15382 cm-1is due to the transition $^3T_1(F) \rightarrow {}^3T_1(P)$ (ν_3). The spectral data indicate that the complex have tetrahedral geometry. The Co complex spectrum showed a weak band at 5154 cm^{-1} which is assigned to the transition $^4A_2 \rightarrow {}^4T_2(F)$ and a band at 8765 cm^{-1}is assigned to the transition $^4A2 \rightarrow 4T_1(F)$ and another transition occur at 16675 cm-1 is due $^4A_2 \rightarrow {}^4T_2$ (P) transition. Based on the spectral results, it can be suggested that the Co (II) complex possess tetrahedral geometry. The Cu (II) complex results a broad absorption but split band at 12490 and 14250 cm^{-1}were assigned to the transitions from $^2E_g \rightarrow {}^2T_{2g}$ respectively. The split in band may due to John-Teller distortion normally occur in copper (II) complexes, thus Cu complex is proposed to have distorted octahedral geometry.



Where M-Co or Ni



where M-Cu

3.4 Antimicrobial activity

The ligand as well as the complexes were screened for antibacterial activity against certain gram positive and gram negative bacterias by disc diffusion method at a concentration of 10µg / ml in DMSO using *Bascillus subtilis, Staphaylococcus aureus, Escherichia coli and Pseudomonas aeruginosa.* The zone of inhibition was measured in mm and the activity was compared with Gentamycin in 1 µg / disc. The results showed that the chelating tends to make the ligand act as more potent bactericidal agents, thus destroying more bacteria than the free ligand. Such increased activity of metal chelates can be explained on the basis of overtone concept and chelation theory. According to the overtone concept of cell permeability, the lipid membrane that surrounds the cell favours the passage of only lipid-soluble materials in which lip solubility is an important factor that controls the anti-microbial activity. On chelation it increases the delocalization of π-electrons over the whole chelate ring and enhances the lipophilicity of complexes. This lipophilicity enhances the penetration of complexes into the lipid membranes and blocks the metal binding sites in enzymes of microorganisms. These complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organism.

4. Conclusion

It may be concluded that the newly synthesized N- Methyl Piperazine methyl Maleic hydrazide thro Mannich reaction, behaves as a good bidentate chelating agent thro the Oxygen and Nitrogen donor atoms and the spectroscopic data is in support of our proposed structure. The antimicrobial property of the complexes were better than that of the free ligand.

5. References

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