



Synthesis, Spectral and Antibacterial Studies of 4-Aminoantipyrene Based Tetradentate Ligand and Its Cu(II), Ni(II) and Co(II) Metal Complexes

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Four Schiff base metal complexes of Cu(II), Ni(II), Co(II) have been synthesized from a new tetradentate ligand, 2-((E)-1,5-dimethyl-2-phenyl-3-((E)-quinolin-8-methyl)-2,3-dihydro-1H-pyrazol-4-ylimino)methyl)phenol. The ligand and its metal complexes have been characterized on the basis of elemental analysis, electronic, infrared, ¹H NMR and ¹³C NMR spectral studies. On the basis of electronic spectral studies, for Cu(II) complex, deformed tetrahedral, Co(II) complex, tetrahedral and Ni(II) complex octahedral geometry has been proposed. The *in vitro* antimicrobial activity of the investigated compounds was tested against the bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae* and fungi-*Candida albicans* and *Rhizopus stolonifer*. The data indicate that most of the metal complexes have higher antimicrobial activity than the free ligand.

Key Words: 4-Aminoantipyrene, Metal complexes, Antibacterial nature, Amoxicillin.

INTRODUCTION

N-Phenyl-3-substituted 5-pyrazolone derivatives are used as intermediate for the development of various anti-inflammatory agents and allergy inhibitors in pharmaceuticals¹.

4-Aminoantipyrene (N-phenyl-2,3-dimethyl-4-pyrazolin-5-one) is an active moiety in the class of non-steroidal, anti-inflammatory agents used in the treatment of arthritis and other musculoskeletal and joint disorders. Some 4-aminoantipyrene derivatives are reported to exhibit analgesic and anti-inflammatory effects², antiviral³ and antibacterial activities⁴.

The 4-aminoantipyrene molecule due to the presence of free -NH₂ and -C=O group can be modified into a flexible ligand system by condensation with a variety of reagents like aldehyde, ketone, *etc.* and the presence of these electron donor sites this molecule also exhibit its coordination behaviour with the metal ions which contain partially filled *d* and *f*-orbital⁵⁻⁹.

In this arena, metal complexes derived from N-heterocyclic ligands, based on 4-aminoantipyrene and derivatives of aromatic amines, play an important role in pharmaceutical, clinical and analytical applications and their complexes with platinum(II) and cobalt(II) ions have been shown to act as antitumor substances¹⁰.

Herein we report the synthesis of a novel Schiff base ligand, 2-((E)-1,5-dimethyl-2-phenyl-3-((E)-quinolin-8-methyl)-2,3-dihydro-1H-pyrazol-4-ylimino)methyl)phenol (DPQDPP) derived from 4-aminoantipyrene, salicylaldehyde and 8-amino-quinoline and its Cu(II), Co(II) and Ni(II) complexes. Their spectral properties and antibacterial nature were investigated against bacteria as *E. coli*, *S. aureus* and *K. pneumoniae* and fungi as *C. albicans* and *R. stolonifer*.

EXPERIMENTAL

All reagents and solvents used were BDH, AnalaR or Merck products. The organic Schiff base ligands and 2,3-dimethyl-1-phenyl-4-salicyclidene-3-pyrazolin-5-one was reported earlier¹¹.

Synthesis of ligand: Salicylidene-4-aminoantipyrene Schiff base was prepared as reported in the literature¹²⁻¹⁴. The ethanolic solution of salicylidene-4-aminoantipyrene (10 mM) was refluxed with 8-amino-quinoline (10 mM) for 10 h in presence of K₂CO₃. After refluxing, the volume of the solution was reduced to one third. On cooling, a dark brown solid was separated, filtered and recrystallized from ethanol.

Synthesis of metal complexes: An ethanolic solution of the ligand (DPQDPP) (10 mM) was refluxed with (10 mM) metal chloride [(Co(II), Cu(II) and Ni(II) for *ca.* 4 h. The mixture was kept at 0 °C for *ca.* 12 h. The solid product so

TABLE-1
MICROANALYSIS OF LIGAND AND METAL COMPLEXES

| Ligand / Metal complexes | Elemental analysis (%): Calcd. (Found) | | | | Molar conductivity (ohm ⁻¹ cm ² mol ⁻¹) | μ_{eff} (BM) |
|---|--|-------------|---------------|---------------|--|-------------------------|
| | C | H | N | M | | |
| C ₃₀ H ₃₀ N ₅ O (DPQDPP) | 75.60 (75.55) | 6.34 (6.35) | 14.69 (14.59) | – | – | – |
| [Cu(DPQDPP)] | 66.83 (66.85) | 5.42 (5.40) | 12.99 (12.85) | 11.79 (11.85) | 8 | 4.95 |
| [Co(DPQDPP)] | 67.41 (67.48) | 5.47 (5.49) | 13.10 (13.05) | 11.03 (11.00) | 7 | 3.52 |
| [Ni(DPQDPP)] | 67.44 (67.88) | 5.47 (5.40) | 13.11 (13.05) | 10.99 (11.93) | 5 | 1.91 |

formed was separated by filtration and washed thoroughly with hot ethanol and then dried *in vacuo* (Yield: 60 %).

Bacterial culture: The strains of bacteria used were *E. coli*, *S. aureus* and *K. pneumoniae* and fungi *C. albicans* and *R. stolonifer*. All strains were isolated from patients in L.L.R. Medical College Hospital, Meerut, India. The identity of all strains was confirmed. A bacterial pension was prepared and added to the sterilized medium before solidification. The media with bacteria was poured in to sterilized Petri dishes under aseptic condition. 5 mg weights of Schiff base and Co(II), Ni(II) and Cu(II) complexes of Schiff base complexes were placed on the surface of the culture and incubated at 37 °C for 24 h. After incubation the inhibition (mm) and average of inhibition zones recorded.

RESULTS AND DISCUSSION

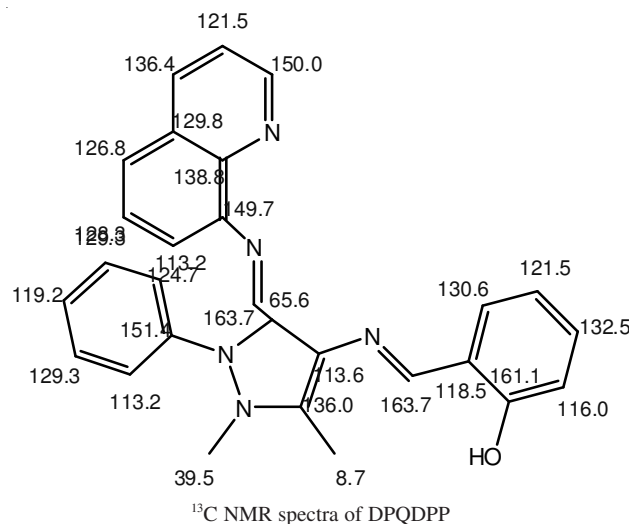
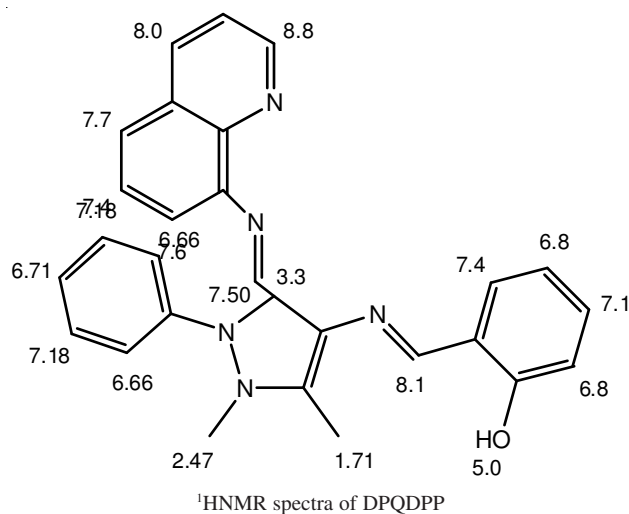
All the complexes are air stable. They were identified by their physical and analytical data. The monomeric nature of the complexes was evidenced from their magnetic susceptibility values (Table-1). Study of magnetic and electronic spectral data is quite informative in characterizing the geometry of the complexes. These complexes were non-electrolytic due to the low conductivity values¹⁵.

Electronic absorption spectra: The electronic absorption spectra of the ligand and its complexes were recorded at 300 K in DMSO solution¹⁶. Electronic spectra of Cu(II) complex present two type of $d \rightarrow d$ transition $xy \rightarrow xz$, yz and $xy \rightarrow z^2$, x^2-y^2 at 14650 cm⁻¹ whose values are characteristics of a deformed tetrahedral geometry¹⁷. The Co(II) complex also exhibit $d \rightarrow d$ transition $xy \rightarrow xz$, yz at 9746 cm⁻¹ and $xy \rightarrow z^2$, x^2-y^2 at 15247 cm⁻¹ and characteristics of a tetragonal geometry¹⁸. The absorption spectra of Ni(II) complex display three $d \rightarrow d$ transitions $z^2 \rightarrow x^2-y^2$, $xy \rightarrow x^2-y^2$ and $xy, yz \rightarrow x^2-y^2$ in the range of 11135-121081, 8621-19416 and 21413-27322 cm⁻¹ proposed octahedral geometry¹⁹.

Infrared spectral studies: The spectrum of the ligand shows a weak broad band in the region 3200-3000 cm⁻¹ assignable to intra-molecular hydrogen bonded -OH groups²⁰. The absence of this band, noted in the spectra of the complexes, indicates the deprotonation of the -OH group on complexation. The spectra of the ligand shows a characteristic -C=N bands in the region 1610 cm⁻¹ which are also shifted to lower frequencies in the spectra of the complexes (1580 cm⁻¹). The bands in the ligand spectrum at 1560 and 1410 cm⁻¹ are ascribed to C=N and C=C of quinoline ring²¹⁻²⁴, but there is no appreciable change in the complex spectrum which indicates that quinolinic nitrogen atom does not involve in the coordination. The IR spectra of the metal chelates also show some new bands in the region 460-450 and 400-380 cm⁻¹ which are assigned

due to the formation of (M-O) and (M-N) bonds respectively. All complexes show specific band $\nu(\text{C}=\text{O})$ band (cyclic keto group present in the pyrazole ring at 1615, 1596 cm⁻¹) moves towards lower wave length (1589, 1580 cm⁻¹) suggesting the coordination of the ligands to the metallic ion *via* carbonyl group²⁵.

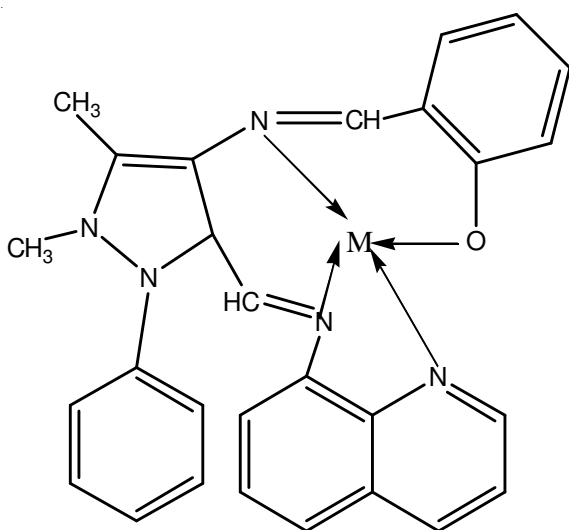
¹H NMR studies: The ¹H-NMR spectrum of the ligand in DMSO-*d*₆ shows the following signals; C₆H₅ as a multiplet around 6.8-7.4 δ , -C-CH₃ at 1.71 δ , -N-CH₃ at 2.47. The spectra of ligand show singlet at δ 8.5 due to azomethine proton at 8.5 δ . The peak at 6.66-8.8 δ is attributed to quinoline moiety. The peaks at δ 5.0 are attributed to the phenolic -OH group present in the salicylaldehyde moiety and This peak is absent in the metal complexes confirming the loss of -OH protons due to complexation²⁶⁻²⁸.



¹³C NMR studies: The spectra display the signals corresponding to different nonequivalent carbon atom at δ 8.8 ppm ($-C-CH_3$), 39.6 ($-N-CH_3$) corresponding to carbon atom of methyl group at *ca.* δ 150 ppm ($C=N$) due to carbon atom of azomethine group and δ 150, 121.5, 136.4, 129.0, 126.8, 138.8, 129.8, 126.8, 138.8, 149.7 due to aromatic carbon atom of quinolonic ring²⁹⁻³¹.

Antimicrobial activity: The *in vitro* antimicrobial activity of the investigated compounds was tested against the bacteria such as *S. aureus*, *E. coli*, *K. pneumoniae* and also fungi *C. albicans* and *R. stolonifer* by the serial dilution method. The minimum inhibitory concentration (MIC) values of the compounds against the growth of microorganisms are summarized in Table-2. A comparative study of the ligand and its metal complexes (MIC values) indicates that the complexes exhibit slightly higher antimicrobial activity than the free ligand. Such increased activity of the complexes can be explained on the basis of Overtones concept and Tweedys Chelation theory³². According to Overtones concept of cell permeability, the lipid membrane that surrounds the cell favours the passage of only the lipid-soluble materials due to which liposolubility is an important factor, which controls the antimicrobial activity. On chelation, the polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of π -electrons over the whole chelate ring and enhances the lipophilicity of the complexes³³⁻³⁵. This increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms. These complexes also disturb the respiration process of the cell and thus block the synthesis of the proteins that restricts further growth of the organism. Furthermore, the mode of action of the compound may involve formation of a hydrogen bond through the azomethine group with the active centre of cell constituents, resulting in interference with normal cell process^{36,37}.

The following structure of metal complexes are proposed.



where M = Cu(II), Co (II) and Ni(II)

TABLE-2
ANTIMICROBIAL STUDY OF THE
INVESTIGATED COMPOUNDS (MIC $\times 10^{-2}$ M)

| Compound | EC | SA | KP | CA | RS |
|--------------|-----|-----|-----|-----|-----|
| DPQDPP | 4.8 | 4.2 | 5.6 | 3.8 | 5.9 |
| [Cu(DPQDPP)] | 3.2 | 2.5 | 3.2 | 2.9 | 4.4 |
| [Co(DPQDPP)] | 4.1 | 3.2 | 4.9 | 2.1 | 5.1 |
| [Ni(DPQDPP)] | 2.8 | 2.9 | 3.5 | 3.1 | 3.9 |
| Amoxicillin | 2.1 | 4.0 | 4.9 | 3.0 | 5.2 |

EC = *E. coli*; SA = *S. aureus*; KP = *K. pneumoniae*; CA = *C. albicans*; RS = *R. stolonifer*

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