



## RESEARCH ARTICLE

# Synthesis, characterization and biological studies of metal complexes with Quinoxaline derivatives

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## Abstract

Metal complexes with quinoxaline derivatives were synthesized by the condensation of quinoxaline-2-carboxaldehyde with substituted 5-aminoflavones. The synthesized metal complexes were characterized by elemental analysis, IR, <sup>1</sup>H-NMR, UV-Vis., molar conductance, magnetic moment and electrochemical studies. Based on the magnetic moment and electronic spectral data, square planar geometry has been proposed for all the complexes. The antimicrobial screening of the ligands and their metal complexes suggested that for the complexes showed higher activities than the free ligands. The DNA binding behavior of complexes with CT DNA has been studied using electronic absorption spectra and cyclic voltammetry techniques. The DNA binding constants indicated that all metal complexes interacted with DNA through intercalation binding mode. Superoxide dismutase activity of the metal complexes were performed and discussed in detail.

## Keywords

Aminoflavone  
Binding  
SOD  
Screening

## Introduction

Quinoxalines are also termed as benzopyrazines, they belong to the category of heterocyclic molecules, containing fused benzene and pyrazine rings. The applications of quinoxaline and its derivatives have been extensively reported in the field of photochemical,

electrical, dyes and pharmaceuticals. Many antibiotics viz., levomycin, actinoleutin and echinomycin consist of quinoxaline molecules are induced to reduce the growth of microorganisms. Many synthetic protocols are available for the synthesis of quinoxalines and its derivatives. Almost many of the quinoxalines are synthesized from aromatic 1,2-dicarbonyl compounds and 1,2-diamines. A familiar method used to synthesize quinoxalines is the reaction of a 1,2-dicarbonyl compound with o-phenylenediamine [1]. Using Suzuki–Miyaura coupling reaction

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Heravi *et al.* synthesised 2,3-disubstituted quinoxalines [2]. In 1974, Ovchinnikov and co-workers pointed out the mode of coordination of metal ions with heterocycles. The five armed heterocyclic compounds employed as a model in proteins for cation receptors [3, 4]. For more than half a century, quinoxalines have been utilized effectively in two dimensional network metal complexes as a building block [5]. Quinoxaline Schiff bases coordinate well with metal halides and produces exciting coordination polymers. Further, quinoxaline derivatives, which can undergo coordination with metal ions easily, produces new three-dimensional network structures, have been prepared. Due to the availability of quinoxaline heterocycles in biological and natural systems, it attracted more research interest [6, 7]. Several quinoxaline derivatives exhibit high selectivity for the treatment of tumour against the cancer cells having multi drug resistivity. The synthetic value and pharmacological significance of these complexes have encouraged many scientists to design new complexes of quinoxaline derivatives [8, 9]. The present study was focused on the synthesis and characterization of quinoxaline derivatives and their metal complexes. They were subjected to DNA binding and SOD activity studies.

## Experimental

### Material

All chemicals and solvents were analar grade and were purchased from Merck. Calf thymus DNA purchased from Genie Biolab, Bangalore, India.

### Instrumentation

The amount of metal present in the complex was estimated using ammonium oxalate method. Elemental analysis of ligands and their copper complexes were carried out using Elementar Vario EL III. Molar conductance of the complex was measured using a coronation digital conductivity meter. The  $^1\text{H-NMR}$  spectra of the ligands were recorded using TMS as internal standard. Chemical shifts are expressed in units of parts per million relative to TMS. The IR spectra of the ligands and their metal complexes were recorded on a Perkin-Elmer 783 spectrophotometer in 4000-200  $\text{cm}^{-1}$  range using KBr disc. Electronic spectra were recorded in a Systronics 2201 Double beam UV-Vis., spectrophotometer within the range of 200-800 nm regions. Magnetic moments were measured by Guoy method and corrected for diamagnetism of the component using Pascal's constants. Cyclic voltammetry was performed on a CHI 604D

electrochemical analyzer with three electrode system of glassy carbon as the working electrode, a platinum wire as auxiliary electrode and Ag/AgCl as the reference electrode. Tetrabutylammoniumperchlorate (TBAP) was used as the supporting electrolyte. Solutions were deoxygenated by eradication with  $\text{N}_2$  previous to measurements. The interactions between metal complexes and DNA were studied using electrochemical and electronic absorption techniques.

### Synthesis of Schiff base ligands

Hot ethanolic solutions of 5-aminoflavone (1 M) was added drop wise to one mole of 40 ml of ethanolic solution of quinoxaline-2-carboxaldehyde. Then the mixture was refluxed by using anhydrous potassium carbonate as a catalyst. The obtained product was set aside in a refrigerator for 12 h. The course of reaction was observed by TLC. The precipitate obtained after the complete reaction was filtered and recrystallized from ethanol.

### Synthesis of metal complexes

Ethanolic solutions of quinoxaline-2-methylenyl-5-aminoflavone and its derivatives (1 M) and metal acetate(s) (1 M) were refluxed for about 6 h at room temperature. The course of reaction was observed by TLC upto the formation of product. Then the solution was poured on crushed ice. Thus obtained solid compound was filtered and recrystallized from ethanol.

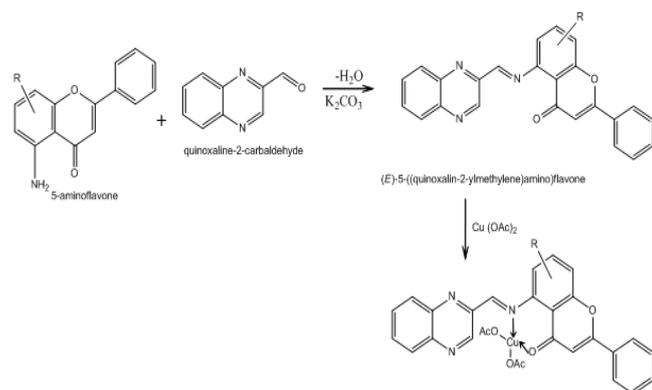
### Superoxide dismutase activity (SOD)

The superoxide dismutase activity (SOD) of the copper complexes were evaluated using alkaline DMSO as source of superoxide radicals ( $\text{O}_2^{\cdot-}$ ) generating system in association with nitro blue tetrazolium chloride (NBT) as a scavenger of superoxide. Add 2.1 ml of 0.2 M potassium phosphate buffer (pH 8.6) and 1 ml of 56  $\mu\text{l}$  of NBT solutions to the different concentration of copper complex solution. The mixtures were kept in ice for 15 min and then 1.5 ml of alkaline DMSO solution was added while stirring. The absorbance was monitored at 540 nm against a sample prepared under similar condition except NaOH was absent in DMSO.

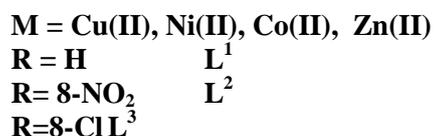
### Results and Discussions

The metal complexes are soluble in  $\text{CHCl}_3$ , DMSO,

DMF and insoluble in water. The elemental analysis data of the Schiff bases and their metal complexes are equivalent with the calculated results from the empirical formula of each compound. The Cu(II) complexes were dissolved in DMSO and the molar conductivities of  $10^{-3}$  M of their solution at room temperature were measured. The lower molar conductivity values of copper complexes were found in the range of (8.4-14.2)  $\text{ohm}^{-1} \text{cm}^2 \text{mol}^{-1}$  suggesting them to be non-electrolytes [10] which is evidenced the presence of acetate ions in coordination sphere. The analytical data are in a good agreement with the proposed stoichiometry  $[\text{ML}(\text{OAc})_2]$  of all the complexes.



#### Where



#### Scheme 1. Schematic route for the synthesis of ligands and their metal complexes

#### FT-IR

The characteristic IR bands for the synthesized ligands and copper complexes are discussed. The ligand  $\text{L}^2$  exhibits two IR bands assigned to azomethine  $\nu(\text{C}=\text{N})$  groups of quinoxaline moiety at  $1642 \text{ cm}^{-1}$  is shifted to a lower frequency of  $1621 \text{ cm}^{-1}$  after complexation [11]. The carbonyl stretching vibration is observed at  $1706 \text{ cm}^{-1}$  is also shifted to lower wave number ( $1682 \text{ cm}^{-1}$ ) due to complexation with copper ion. Also, the new IR bands [26] were seen at  $435 \text{ cm}^{-1}$  and  $505 \text{ cm}^{-1}$  assigned to (M-N) and  $\nu(\text{M}-\text{O})$  groups respectively. It was reported that the copper complexes were behaved as bidentate and coordinate through azomethine nitrogen and carbonyl oxygen atoms. The IR Spectral features were reinforced the conclusion drawn from conductance measurements [12].

#### Electronic Spectral features

The electronic absorption spectra of the ligands and

their copper complexes in DMSO solvent were recorded at room temperature. The band positions of the absorption maxima; band assignments and the proposed geometry mentioned in Table 2. The absorption spectrum for ligand  $\text{L}^1$  showed a band at 270 nm attributed to  $n-\pi^*$  transitions within the Schiff base molecule. The electronic spectrum of the corresponding complex  $[\text{CuL}^1(\text{OAc})_2]$  in DMSO reveals a broad band at 427 nm assigned to  ${}^2\text{B}_{1g} \rightarrow {}^2\text{A}_{1g}$  transition which is characteristic of square planar environment around the copper(II) ion. Similar spectral features were observed for other metal complexes [13].

#### Mass Spectra

The FAB mass spectra of the Schiff bases and their corresponding copper complexes were recorded and compared with their stoichiometry compositions. The  $[\text{CuL}^1(\text{OAc})_2]$  complex shows the molecular ion peak at  $m/z$  757. This molecular ion further by losing two acetate ions gave a fragment ion peak at  $m/z$  638 and these undergo demetallation to form the species  $[\text{L}]^+$  gave fragment ion peak at  $m/z$  575.

#### SOD activity

Superoxide anions have a very short half life and produced continuously. In this colorimetric based assay, Inhibition of the reduction of NBT to formazan (F) by the reported metal(II) complexes was used for detection of the SOD mimetic catalytic activity of these chelates in the phosphate buffer under similar biological conditions. Among the synthesized metal complexes, the copper complexes exhibited higher activities may be attributed to the flexible ligands, which are able to accommodate the geometrical change from  $\text{Cu}^{\text{II}}$  to  $\text{Cu}^{\text{I}}$  and to convert superoxide ion into hydrogen peroxide which is similar mechanism proposed for native enzyme.

#### Conclusions

In the present study of metal complexes with quinoxaline scaffold were designed for free radical dismutation activity. The ligands were synthesized from quinoxaline carboxaldehyde and substituted 5-aminoflavone. The cobalt, nickel, copper and zinc complexes of the synthesized ligands were also synthesized (scheme 1). The low molar conductance values of the complexes which corresponds to non-electrolytic nature. The higher SOD potencies of copper complexes with quinoxaline derivatives reported here to open up new opportunities for synthesizing different derivatives around 'quinoxaline'

scaffold as free radical quenching agents. On the basis of the above observations, modification will be done to improve pharmacological activities.

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