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Design, synthesis, structural elucidation, pharmacological evaluation of metal complexes with pyrazoline derivatives

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ABSTRACT

A bioactive pyrazoline derivatives have been synthesized by the base-catalyzed Claisen–Schmidt condensation of imidazole-2-carboxaldehyde with 1-acetyl-2-hydroxynaphthalene followed by cyclization with phenylhydrazine (L^1)/2,3-dimethylphenylhydrazine (L^2) and 3-nitrophenylhydrazine (L^3). The metal(II) complexes [Ni(II), Co(II), Cu(II) and Zn(II)] were formed by reacting the corresponding metal acetates with the ligands. All complexes were characterized by elemental analyses, electronic, IR, NMR, mass and ESR spectroscopic techniques. The synthesized metal complexes of pyrazoline compounds showed significant antibacterial activity against the organisms *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Salmonella typhii* when compared with the standard antibiotic (Streptomycin). The ligands and their metal complexes were screened for antioxidant activity using DPPH radical scavenging and superoxide radical scavenging assay methods. All the complexes showed good free radical scavenging activity which is comparable to that of the standards. Among the metal complexes, the copper complex has showed higher activity. The results were indicated that 2-pyrazoline (structural core) and copper ion could be responsible for the potential candidate eliciting antioxidant activity. All compounds were evaluated for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis*. The ligands and metal complexes were subjected to fluorescence properties and exhibited that the variable fluorescence emission behavior of complexes. It can be attributed to the combined effect of the substituents and naphthyl structural core present in the ligands.

1. Introduction

The design of new metal-based chemotherapeutic agent is an emerging research area of inorganic medicinal chemistry [1]. It is well known that medicinal inorganic chemistry is a multidisciplinary field comprises of chemistry, pharmacology, toxicology and biochemistry. The medicinal chemists have focused on design and synthesis of new metal-based molecules with improved biological activity, better selectivity, lower toxicity and multiple role of mechanistic action to overcome the clinical problems of existing drugs in the market due to its side effects. The literature survey demonstrated that the metal complexes are growth inhibitors of microbes and have been extensively studied *in vitro* and *in vivo*.

After the discovery of cisplatin [cis-diamminedichloroplatinum(II)] [2], there has been a rapid developments in inorganic research to find out new and more efficacious metal-based chemotherapeutic drugs [3]. The researchers are motivated and search for new metallic species with improved biological applications. Among the metal ions, copper, nickel, cobalt and zinc complexes have proved to be an excellent candidate [4]. Copper complexes have shown remarkable efficiency in antioxidant [5], DNA-binding and anticancer studies [6,7]. There is a great deal of interest in the synthesis and characterization of transition metal chelates of heterocyclic compounds, in particular pyrazoline derivatives.

Pyrazoline derivatives are synthetic structural lead molecules of extreme importance for the researchers because of its wide range of biological and pharmaceutical properties such as analgesic, antipyretic and antiandrogenic activities [8,9]. Pyrazolines have possessed antidepressant, anti-inflammatory and antirheumatic activities [10,11]. After the pioneering work of Fischer and Knoevenagel in the late nineteenth century, the reaction of α,β-unsaturated aldehydes and ketones and then with hydrazines became one of the most popular methods for the preparation of 2-pyrazolines. 2-Pyrazolines have potential antioxidative effects, capable of preventing oxidative damage as well as clastogenic effects [12,13]. As a result, numerous substituted 2-pyrazolines have been synthesized.

In recent years, the success of pyrazole moiety as COX-2 inhibitor [14] has highlighted the importance of this heterocycles in medicinal chemistry. A systematic investigation of this class of compounds revealed that pyrazole containing pharmacophore moiety (imidazole) plays an important role in medicinal chemistry. The dominance of

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pyrazole core in biologically active molecules has stimulated the need for well-designed and efficient ways to make heterocyclic lead for therapeutic purpose.

The interest in compounds of imidazole moiety is due to its unique biological activities [15]. The imidazole ring exists in the histidine and histamine building blocks of proteins, important vitamins (H, B_{12}), alkaloids, and herbicides [16,17]. The imidazole nucleus occurs in several natural compounds and pharmacologically active substances, displaying a broad range of biological activity [18]. In recent years, it is reported that the incorporation of imidazole nucleus could alter the photophysical as well as the biological properties [19].

It is proposed that the combination of both chemical systems (pyrazoline and imidazole) in one molecule which is required for improved biological activities. This structural core may be a breakthrough for the development of novel lead molecule for antioxidant and antitubercular research work. The various literature reports of pyrazolines [20] and in continuation of our search for new biologically active pyrazoline derivatives [21], we have developed a systematic synthetic approach for the generation of imidazole substituted 2-pyrazoline derivatives.

Structural modifications have been made in the top and bottom of pyrazoline moiety (Fig. 1) towards the developing of more potent and safer antituberculosis agents. They were carried out in the head and tail portions *via* substitutions like imidazole and naphthyl moiety. Many of these modified compounds have displayed interesting biological activity, showing that modifications at either site could modulate the activity.

In view of the urgent need of potent and safe antimycobacterial agents and in continuation of our earlier interest in this field, here it was planned to synthesize new derivatives by introducing imidazole and naphthyl ring systems at bottom and top of pyrazoline.

According to a literature survey, it was noted that little research work has been carried out on pyrazolines carrying naphthyl/substituted naphthyl groups. Till now, there are no reports on the development of pyrazoline based ligands (incorporation of imidazole and naphthyl moieties) and their transition metal complexes as antituberculosis agents. In view of these facts, we herein described the synthesis and characterization of a pyrazoline based ligands and their copper(II), nickel(II), cobalt(II) and zinc(II) complexes. Further, the ligands and their metal complexes were subjected to antioxidant and antitubercular activities.

2. Experimental

All the solvents and chemicals used in the synthesis were purchased from commercial suppliers and purified when necessary. The completion of the reaction was monitored by thin layer chromatography and performed on Merck precoated silica gel plates. Silica gel (60–120 mesh size, Merck) was used for column chromatography for purification purpose.

Carbon, hydrogen and nitrogen were estimated by using Elemental Analyzer Carlo Erba EA1108 analyzer. The IR spectrum of synthesized compounds was recorded on a Shimadzu FTIR Affinity-1 Spectrophotometer in the 4000–400 cm^{-1} region in KBr disc. The electronic spectra of the complexes were recorded in HPLC grade DMSO on a Systronics UV–Visible spectrophotometer in the region of 200–1100 nm. The ^1H NMR spectrum of the ligand was recorded in DMSO-d_6 on a BRUKER 300 MHz spectrometer at room temperature using TMS as an internal reference. FAB-Mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer/data system using Argon/Xenon (6 kV, 10 A) as the FAB gas. The accelerating voltage was 10 kV and the spectra were recorded at room temperature and *m*-nitrobenzyl alcohol was used as the matrix. Molar conductivity measurements were recorded on Remi Conductivity Bridge with a cell (Cell constant: 1) and magnetic moment was carried out using Gouy balance. The electrochemical behavior of the metal complexes was investigated with CH Instruments, U.S.A (Model CH604D-Electrochemical analyzer) in DMSO containing n-Bu_4NClO_4 as supporting electrolyte with three electrode system.

2.1. Synthesis of Ligand (L)

A solution of 1-acetyl-2-hydroxynapthalene (0.01 M) and imidazole-2-carboxaldehyde (0.01 M) in 40 ml methanolic NaOH (10% methanolic solution) was stirred well for 6 h at room temperature. The solid precipitate was washed with ice-cold water and then rectified spirit, dried. It was recrystallized from ethanol. A mixture of chalcone (0.01 M), phenylhydrazine (0.01 M) L^1/2,3-dimethylphenylhydrazine L^2 & 3-nitrophenylhydrazine L^3 and NaOH (0.02 M) was refluxed in 40 mL of methanol for 8 h. The solution was poured into ice water which resulted into the precipitation of the ligand (L). The precipitate was filtered and recrystallized from methanol. The recrystallized ligand was dried in a vacuum desiccator over fused calcium chloride.

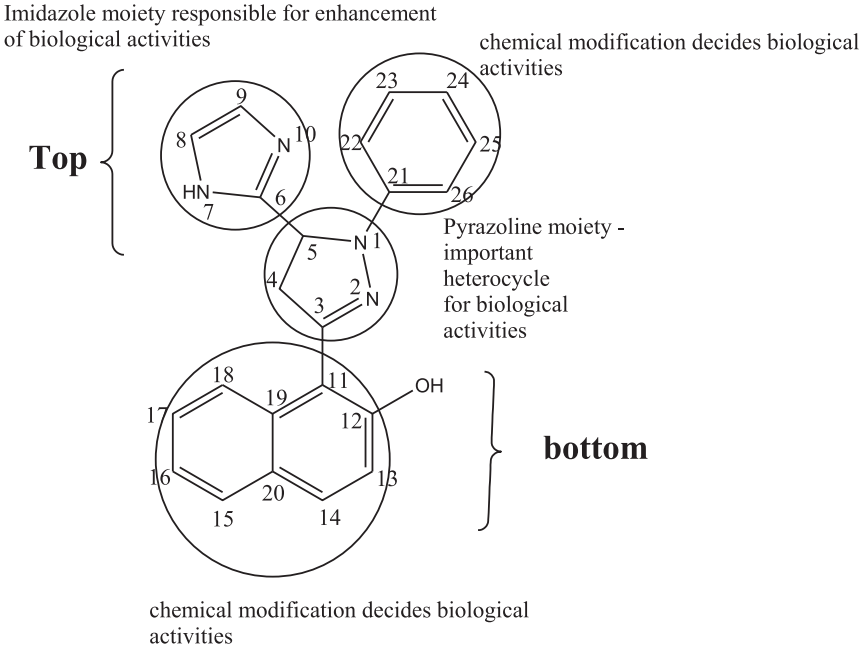

Fig. 1. Structural modification to obtain bioactive lead molecules.