1.1 General introduction

Pathogenic microbial infections were threatened to human’s health [1, 2]. The improper usage of antibiotics and increases the growth of pathogenic microbes was identified in worldwide. The increasing drug resistance, intractable pathogenic microorganisms and newly arising pathogens have become an increasingly serious and challenging problem for human health all over the world. The fighting against pathogenic microbes was considered as one of the major public health crisis. Annually, around ∼1 lakh people were died for infectious diseases. The Government of developing countries had spent ∼2 billion USD in healthcare expenses and taken enormous steps to find out new lead molecules for infectious diseases. Researchers have taken world wide effort to attain new antibiotics to combat antimicrobial resistance before 2020. The innovation of structural lead molecules with low economic inputs may attain current status of medicinal research and benefits to human beings.

Among the infectious diseases, tuberculosis (TB) is most vibrant and crucial infectious disease causing death. According to WHO, estimates that around twenty million patients occur annually in the developing countries and the incidence of TB is currently growing day by day [3]. Tuberculosis (TB) is an emerging human health problem in worldwide is due to the poor drug action and development of resistance against the existing drugs that has motivated researchers in the worldwide [4]. Severe side effects were observed for the repeated intake of isoniazid (INH) with different dosage, it is considered and used first line drug for chemotherapy of tuberculosis [5]. There is an emerging need to develop new lead molecules (i.e anti-tuberculosis agents) that allow shorter and more effective therapies [6, 7]. The search for novel lead molecules with different structural features that offers the unique possibilities of different mechanistic action against mycobacterium species.

Inorganic compounds/ complexes is an alternative to heterocyclic organic molecules with unique structural behavior for the design of multiple therapeutic
actions. The introduction of metal ions into the appropriate place in the molecular scaffold of potential drug provides to access various oxidation states of the metal ion and also offer the enhanced pharmacological activities of heterocyclic molecules through its coordination with metal ion.

Bioinorganic research comprises of inorganic chemistry and biology. The synthesis of bioactive lead molecules plays most noteworthy role in the progression of medicinal research. The main aim of the medicinal research is to take part in both synthetic chemist & molecular biologist to enable the development of lead molecules for development and applications towards biomedical fields. To study the structural and biological properties of the lead molecules with different insights were gained into the biomolecular mechanism of complex biological & chemical systems.

Further, researchers have also performed in medicinal chemistry to improve or enhance biopotency, cellular activity, specificity, stability and pharmacological properties of synthesized "lead" compounds in disease affected tissues. A significant challenge is to be addressed in chemical, biology and drug detection due to rapid identification of new, specific and active small molecules as “leads”.

1.2 Metal organic frameworks

Drugs are organic or nature derived bioactive compounds [8]. After the successful innovation and utility of cisplatin, there is enormous interest in metal-containing drugs [8]. The unique emphasis of metal complexes over organic molecules is due to its ability to make changes in coordination number, geometrical arrangements and different redox states [9]. Metal–organic frameworks have attained considerable attention due to their wide applications as dyes, perfume industry etc [10–14]. Multidentate ligands with different coordination sites like N, O and S donor atoms play a key role in the construction of synthetic metal–organic scaffold [5].

1.2.1 Copper

The basic and key role of copper has motivated and its recognition as important bioactive molecules towards medicine for infectious diseases. In vitro and in vivo has stimulated interest in the copper complexes as alternate for platinum complexes in medicine. The broad range of structural and biological information are
available for bioinorganic chemist to open up innovative opportunities in the design and advancement of novel bioactive molecules with lesser side effects may add noteworthy to current clinical research [16].

Due to the biological and medicinal applications of copper complexes and its exclusive redox behavior, plenty of copper complexes have prepared and evaluated for their therapeutic efficiency in infectious diseases [17-20]. The copper carboxylate complexes exhibited different pharmacological activities and may be used as anti-inflammatory agents [17, 21].

Duncan and White (2012) [19] have also investigated the potential of copper complexes to enhance SOD activity, leads the treatment of oxidative stress (neutralization of free radicals). The capability of copper participates in number of redox chemical reactions and to enhance the delivery of copper in the successful compounds.

Copper is redox active in the copper complexes with bioactive heterocyclic ligands have been synthesized and evaluated for SOD activity [22] (Anacona et al., 2004). Copper complexes with imines have deserved much attention because of their ability to participate in DNA binding and exhibit different mechanistic action through different redox states [23, 24].

1.2.2 Zinc

In 1869, Raulin has identified that Zinc is necessary for increased growth of *Aspergillus niger*. Zinc has also been demonstrated that it is essential for the growth of plants, animals etc (Vallee 1986) [25]. In the human body, zinc is the second most essential metal. The carbonic anhydrase enzyme containing zinc was discovered by Keilin and Mann in 1940. Therefore, zinc is an essential element for biological functions particularly metalloenzymes. The biological function of zinc is versatile and observed in many tissues [26].

In general, the zinc having d^{10} configuration and does not participate in redox chemical reactions. The lack of redox potential make Zn^{2+} is a stable species in the biological system. Due to filled 3d orbitals, its field stabilization energy is zero (Huheey et al. 1993) and hence no geometry is naturally more stable than another
Zinc is found in many proteins and participates in chemical catalysis and stability. Therefore, the zinc ion may behave as Lewis acid [26].

In 1961, it was identified that zinc deficiency may occur in man and microorganism and confirmed in 1963. It is essential for growth factor in man and organism. It was clearly indicated that zinc ion is one of the principal cofactor for nutrition. It was found that the deficiency of zinc not only for nutrition and also complicated diseases [27].

A wide range of enzymatic and metabolic processes have been identified and studied for different biological activities [28]. The nature and flexibility of ligands and coordination behavior leads to diverse Zn(II) binding sites in zinc-metalloenzymes and exhibiting wide range of biological roles [29, 30].

1.2.3 Cobalt

In plants, animals and humans, the cobalt is one of the essential trace metals. In the vitamin B\textsubscript{12} (cobalamin), cobalt plays a number of essential roles in many biological systems. Cobalamin is essential for DNA synthesis, formation of red blood cells, maintenance of nervous system, growth and development of children. The cobalt complexes were structurally characterized and studied for DNA cleavage property. They have exhibited antitumor, anti-proliferative, antimicrobial, antifungal, antiviral and antioxidant activities. The Co(III) Schiff base complex (Doxovir) has successfully completed phase II clinical trials for the treatment of herpes simplex virus [31].

1.2.4 Nickel

Nickel has been exhibited different coordination behavior and redox characteristics. The nickel was observed in the redox states (Ni\textsuperscript{2+}, Ni\textsuperscript{2+}, Ni\textsuperscript{3+}) during electrolysis or catalytic process. The observed nickel complexes contains nickel centre vary from mononuclear to metal clusters. It may catalyze hydrolytic to multistep redox reactions. The nickel sites in metalloenzymes exhibited flexibility in nickel coordination. The nickel centre in SOD is able to proceed with different redox processes. The nickel complexes have shown different pharmacological activities [32-34].
Nickel contains 10 d-electrons in zero oxidation state and can exist in a variety of oxidation states Ni(0)–Ni(IV). In the Ni(II) oxidation state, a variety of coordination geometries can be observed [35, 36]. The most commonly observed geometries adopted by Ni(II) are square planar and octahedral arrangements.

1.3 Claisen Schmidt condensation reaction

In Carbonyl chemistry, Claisen Schmidt reaction is one of the most efficient and elegant strategies to build carbon-carbon bonds. In the literature, the base catalyzed organic transformations are Aldol [37], Knoevenagel [38], Henry [39], and Michael [40] reactions. In past few decades, several synthetic attempts have been made to develop carbon-carbon bond-forming reaction [41-46] and it’s utility towards medicinal important precursor molecule, Chalcone. The ‘chalcone’ is an α,β-unsaturated ketone, whereby an aryl group is present on either end of the enone (Figure 1.3). The condensation reaction of benzaldehyde and acetophenone yielded as chalcone. It was first reported in 1881 by Schmidt [47] and Claisen [48].

![Figure 1.1 Structure of chalcone](image)

Chalcones are the main substrate for the synthesis of many therapeutic molecules [49]. As look into the literature, the chalcone showed wide range of biological activities like anticancer [50, 51], anti-inflammatory etc. Many synthetic protocols are available for the preparation of chalcones and widely used in medicinal fields. It was prepared by the base-catalyzed reaction in which the condensation of ketone with aldehyde was carried out in the presence of aq. NaOH [52], KOH [53], Ba(OH)₂ [54, 55], hydrotalcites [56], LiHDMS [57], and calcined NaNO₃/natural phosphates [58]. The acid catalyzed methodologies include the use of AlCl₃ [59], dry HCl [60], Zn(bpy)(OAc)₂ [61], TiCl₄ [62], CpZrH₂/NiCl₂ [63], Zeolites [64], RuCl₃ [65] and Selectfluor [66].
1.4 Pyrazoline

Nitrogen containing heterocycles play an important role in diverse biological activities. Pyrazoles and pyrazolines are well known nitrogen heterocycles. The various synthetic procedures have been adopted for their preparation [67]. Pyrazolines (Figure 1.2) are five-membered heterocycles and constitute numerous therapeutic molecules exhibiting wide range of pharmacological activities. In the late nineteenth century, the reaction of $\alpha,\beta$-unsaturated aldehyde and ketones with hydrazines became one of the most popular method for the preparation of 2-pyrazolines.

![2-Pyrazoline](image)

2-Pyrazoline

Figure 1.2 Structure of 2-Pyrazoline

In the past few decades, 2-Pyrazoline ring system has attracted researchers towards therapeutic agents [68]. Scaffolds containing the 2-pyrazoline (4,5-dihydropyrazole) heterocyclic have demonstrated a wide range of biological activity viz. anti-inflammatory activity [69, 70], anticancer activity [71], antidepressant [72] and antidiabetic [73, 74].

1.5 Incorporation of imidazole nucleus

The introduction of imidazole nucleus is an important synthetic strategy in drug discovery process. Imidazoles are present in many natural products and pharmacologically active molecules. The therapeutic properties of the imidazole analogs have encouraged the synthetic chemist to synthesize novel series of imidazole derivatives. They have broadened aim towards clinical medicines and alternative for existing drug molecules. The interest in compounds of imidazole moiety is due to its unique biological activities [75]. The imidazole ring exists in the histidine and histamine building blocks of proteins, important vitamins (H, B$_{12}$), alkaloids, and herbicides [76, 77]. In recent years, it is reported that the incorporation of imidazole nucleus could alter the reaction as well as the biological properties [78].
Imidazole, benzimidazole and their derivatives are important class of N-heterocycles which may be used as excellent ligands to generate various metal complexes upon coordination [79–89].

1.6 Literature Review

In the literature reviews, nitrogenated heterocyclic derivatives have been described with wide range of structural, biological properties. The azole derivatives, namely pyrroles [90–93], imidazoles [94], pyrazoles [95, 97] and pyrazolines showed remarkable biological activities [98, 99]. The biological evaluation of molecules containing pyrazoline nucleus is vital for the designing of future promising antimicrobial agents [100–101].

Pyrazolines are the class of five membered heterocycles and comprise of wide range of pharmacological activities. Comprehensive literatures survey have presented that pyrazoline derivatives exhibited various pharmacological activities includes antibacterial, antifungal, and anticancer [102–105] etc.

Pyrazolines have received considerable interest in recent years due to its potential applications [106-109]. Metal complexes of organic ligands with pyrazoline motifs have gained considerable interest not only due to their extensive coordination chemistry but due to their catalytic and biological properties [110, 111]. Moreover, in the recent years, tremendous growth in synthesizing and screening copper(II) and nickel(II) complexes for antifungal activities led to the identification of novel promising antifungals [112-116].

Literature survey revealed that many pyrazoline derivatives have found their clinical application as NSAIDS. Antipyrine (a) was the first pyrazoline derivative used in the treatment of pain and inflammation. Phenyl butazone (b) and its potent metabolite celocoxib (c), a prototype of pyrazolinedione NSAIDs, are potent anti-inflammatory agents. The continuous intake of these drugs became restricted due to their side effects [117]. The pyrazoline derivatives (d) and (e) are also reported in literature as potent anti-inflammatory activity [118, 119].
Amir Azam et al [120] synthesized Pd(II) complexes of substituted 2-pyrazoline derivatives by cyclization process. The structure of ligand and its Pd(II) complexes were structurally characterized by analytical and spectral studies. The antiamoebic activity of compounds was performed using strain of *Entamoeba histolytica* and Metronidazole as reference drug. Authors have also studied cytotoxicity using MTT assay method and indicated that the compounds are less toxic to epithelial cell line.

1,3,5-trisubstituted pyrazoline derivatives of Ru(III) complexes have been synthesized and characterized by elemental and spectral techniques. On the basis of EPR and electronic spectral studies, an octahedral geometry around ruthenium has arrived. All the prepared Ru(III) complexes have been also evaluated for their *in vitro* antimalarial activity against *Plasmodium falciparum* strain [121].
Pyrazoline derivatives containing acyl moiety exhibited good chelating and extractants. Based on this importance, Maurelia et al [122] synthesized substituted l-phenylpyrazoles and their copper and nickel complexes. The pyrazole analogs and their complexes were characterized using analytical and spectral studies. The analytical and spectroscopic studies have agreed with square planar structure around metal center.

Jayaprakash et al [123] prepared the substituted pyrazolines were screened for their MAO inhibitory and antidepressant activities. It was found that pyrazoline analog (Figure 1.5) suggested that the selective inhibitor of MAO-B.

![Figure 1.5 Structure of pyrazoline analog [123]](image)

Keleke et al [124] synthesized 4, 5-dihydro-(1H)-pyrazole derivatives and evaluated for in vivo anti-inflammatory activity using carrageenan-induced edema in mice. Further, the analgesic and ulcerogenic studies were also evaluated. The in vivo animal model anti-inflammatory values exhibited that compound (Figure 1.6) anti-inflammatory activity with no ulcerogenic effects as comparable to that of indomethacin (positive control).

![Figure 1.6 Structure of 4, 5-dihydro-(1H)-pyrazole derivative](image)

Complexes of copper (II) and cobalt(II) with pyrazoline derivatives in ethanol were prepared. The observed ligands and their complexes were characterized using analytical, molar conductance and FTIR studies. Hexa coordinated octahedral
structures were arrived from analytical and spectral data for these complexes by R.C.Maurya et al [125].

Basawaraj et al [126] synthesized pyrazolines containing benzofuran (Figure 1.7). They were screened for antibacterial activity against *S. aureus* and *E. coli*. Authors have observed that high to moderate activity for the pyrazoline derivatives and may be behave as better antimicrobial agents.

![Figure 1.7 Structure of pyrazolines containing benzofuran](image)

Desai et al [127] synthesized some pyrazolines, phenylpyrazolines, flavanones and related compounds (Figure 1.8) and evaluated for their antimicrobial activities against gram +ve bacteria. They exhibited that higher activity against Gram +ve bacteria.

![Figure 1.8 Structure of sterically hindered pyrazoline derivative](image)

Jamode et al [128] synthesized 1-Isonicotinoyl/Carboxamido-2-pyrazolines (Figure 1.9) and evaluated their antimicrobial properties against *S. aureus, E. coli, Proteus mirabilis, and Pseudomonas aeruginosa.*
Shenoy et al [129] prepared 1,3,5-trisubstituted-2-pyrazolines (Figure 1.10) and evaluated their antimicrobial activity. The compound (Figure 1.10) has exhibited higher antitubercular activity.

Mamolo et al [130] synthesized 5-Aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4, 5-dihydro-1H-pyrazole derivatives. They were screened for their in vitro antimycobacterial activity. The compound (Figure 1.11) showed an interesting activity against a strain of *M. tuberculosis* and a human strain of *M. tuberculosis* H4.
Ozdemir et al [131] synthesized a 1-[(N, N-disubstituted thiocarbamoylthio) acetyl]-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives (Figure 1.12) and evaluated for \textit{in vitro} antimycobacterial activity against \textit{M. tuberculosis} H\textsubscript{37}Rv.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1}
\caption{Structure of 1-[(N, N-disubstituted thiocarbamoylthio) acetyl]-3-(2-thienyl)-5-aryl-2-pyrazoline derivative}
\end{figure}

R.C. Maurya et al [132] have prepared a series of mixed-ligand cyanonitrosyl complexes of chromium with ligand, L=4-methyl-2-pyrazoline-5-one, 2,3-dimethyl-1-phenyl-3-pyrazoline-5-one or 4-dimethylamino-2,3-dimethyl-1-phenyl-3-pyrazoline-5-one. They were characterized by elemental analysis, molar conductances and spectral techniques. On the basis of spectral evidences, octahedral structure has been arrived for chromium complexes.

Talal A.K. Al-Allaf et al., [133] had synthesized platinum(II) complexes of 3-aryl-5,5-dimethyl-2-pyrazolines. The \textsuperscript{1}H and \textsuperscript{13}C-NMR and IR spectral data for the complexes were discussed. The analytical and spectral data were supported the molecular structure of complexes.

Ni(II) and Cu(II) metal ions with ligand, L = (1E)-N-((5-((E)-(2,3-dimethyl-1-phenyl-4-pyrazolineimino) methyl) thiophen-2-yl) methylene)-2,3-dimethyl-1-phenyl-4-pyrazoline amine have been synthesized and characterized. They were structurally characterized by analytical and spectral studies. On the basis of spectral data, nickel(II) complexes were found to have octahedral geometry, whereas the copper(II) complexes were of tetragonal geometry. They were screened for antimicrobial activity in terms of minimum inhibitory concentration (MIC) of the ligand and its metal complexes by the serial dilution method [134].
1.7 **Scope of the present work**

A significant progress has been made in the treatment/prevention of bacterial infections. Now, it is a human health problem due to the rapid growth of pathogenic microbial resistance against the existing drug molecules. In order to overcome the antimicrobial battle against resistance, the researchers have motivated to design and develop novel heterocyclic molecules with different mechanistic drug action than that of existing mode of action [135].

Inorganic coordination compounds or metallodrugs has received considerable attention due to its electron transfer properties (redox characteristics) in designing novel molecules with different therapeutic action. Several metal complexes are well known and shown antimicrobial, antiviral, anticancer activities etc. The transition metal ions are accountable for the proper utilization of different proteins and enzymes. Nitrogen bases (pyridine, pyrimidine and pyrazine) and amines (histamine, and different vitamins) are act as bio-ligands in complex formation. Metal complexes of phenolates could enhance membrane permeability and exploited as antimalarial agents.

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 highlighted the importance of pyrazolines in biological fields [136], the present study has adopted a systematic synthetic approach for the generation of imidazole bearing 2-pyrazoline derivatives and their metal complexes.

Structural modifications have been made in the top and bottom approach of pyrazine moiety towards the developing of more potent and safer antituberculosis agents. Researchers have much interested to combine imidazole and substituted naphthyl moieties to produce bioactive pyrazoline derivatives. The structurally modified compounds have shown interesting biological activities [137]. In view of the vital need of potent, less expensive and less toxic antituberculosis molecule and it is planned to synthesize novel series of pyrazoline derivatives having imidazole and naphthyl ring moieties.
Based on the literature reviews, it was observed that there is no research work has been performed on pyrazolines bearing substituted naphthyl moiety [138]. In view of these importance, the present study focused on the synthesis and structural elucidation of pyrazoline derivatives bearing imidazole moiety and their Copper(II), Nickel(II), Cobalt(II) and Zinc(II) complexes. Further, the pyrazoline derivatives as ligands and their metal complexes were subjected to antioxidant and antitubercular activities.

The main objectives of the present investigations are,

a) To prepare some novel, non-toxic and stable metal complexes with pyrazoline derivatives containing imidazole moiety

b) To characterize the synthesized pyrazolines and their complexes by analytical and spectroscopic methods

c) To study the antimicrobial and antioxidant activities of the synthesized compounds and compare the activities with known standards

d) To find out the effect of structural modification by designing various suitably substituted ligands and their complexes on the above biological activities

e) To find out the efficiency of DNA binding by different metal complexes and develop as new therapeutic molecules

f) To study the antioxidant activity of the synthesised compounds using catalase enzyme by standard assay methods and cyclic voltammetric techniques

g) To evaluate the antimycobacterial activities of the synthesized pyrazolines and their metal complexes and compare the activities with standards

h) To study the catalytic activity of the synthesized complexes to convert benzyl alcohol to benaldehyde

i) To study the photochemical behavior of the synthesized complexes