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A Mini Review: Antibacterial and Antimicrobial application of derivative Dicoumarol metal Complexes in coordination with drugs

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ABSTRACT:

Coumarin and its derivatives like dicumarols exhibits strong medicinal properties. They show anticoagulants, anti-tumor anti-cancer, anti-inflammatory activities. Researchers works are growing over the years to design more effective drug by synthesis of metal (3d metals) complex using coumarin and dicumorl as ligand. Inspite of this work continue to improve the effectiveness of existing drug (like Ofloxacin; Enrofloxacin etc) and reduce of their dose quantity. Co-coordination with metal ligand complex; drug shows enhanced antimicrobial, anti-bacterial activities. In this review article we discussed about the synthesis of heterocyclic metal-complex in coordination with various drugs; several methods used for complex characterization, biological aspect of the drug co-ordinates metal complexes and their applications.

KEY WORDS: Antimicrobial, anti-bacterial, Metal complex, antimicrobial activity, Coumarin, Dicumarol.

1. INTRODUCTION:

Coumarin is exists only in one form. It's biological activity can be enhanced via substitution of different groups in its basic structure [1-4]. In the recent year's research on coumarin has been growing. This is mainly due to the widespread application of its derivatives. Ultimately, a variety of structurally different and novel derivatives of coumarin were discovered that exhibited significant cytotoxic and anti-HIV activities in both vitro and in vivo [2]. The coumarin derivatives segment is widely recognized for its anti-HIV [5-8], pharmaceutical [9,10], anthelmintic [11], anti-inflammatory [12-14] and inhibitory activity [15].

It was also used as an anticoagulant, anticoagulant, antitumor, or plant growth regulator [16]. Coumarin have capability to make complexes with various transition metal ions; it has been studied and repeatedly mentioned in numerous studies [17]. It is hypothesized that metal binding to coumarin fragments can trigger or enhance biological activity [18]. In current scenario, metal ions like cupric (II), ferrous(II), ferric(III) and platinum(II) have shown a wide range of physio-chemical and biological activities like with tumor cells. The recently discovered physio-chemical and biological activity of these conjugates is similar to that of the widely used carboplatin [19]. In addition

to health-promoting, biological and medical uses, coumarin is used as a sweetener, flavor enhancer, food and cosmetic additive, tobacco odor stabilizer, nurse mate, paint and rubber odor mask [20].

Dicoumarol (4-hydroxycoumarin)

Dicoumarol, which is also known as 4-hydroxycoumarin or bishydroxycoumarin, can be synthesized from coumarin by both natural and artificial methods. It is found in Clove. Derivatives of dicoumarol widely used in oral anticoagulant therapy [21-22]. Furano-coumarins (also referred to as psoralens) used in photochemotherapy of disease like psoriasis, alopecia areata, skin diseases like cutaneous T-cell lymphoma, urticaria pigmentosa, atopic dermatitis and lichen planus [23-25]. Xanthotoxin [26], Bergapten are used as alternative for chemotherapy of psoriasis. Clinical efficacy of Bergapten is better than xanthotoxin, although bergapten requires significantly higher doses.

Antibiotics:

Recent studies are mainly focus on the association of dicumarol-metal complex with antibiotics for enhancing the effectivity of antibiotics [27-30]. Effectiveness of many drugs are can be improved via using formation of their metal complex derivatives. Here we discuss about the main drugs which are already reported.

1. Ofloxacin: Ofloxacin is an effective antibiotic which is used in the treatment of various microbial infections. If swallowed or given intravenously, it includes respiratory illness, cellulitis, respiratory infections, congestion, plague, and related types of infectious diarrhea. Some more uses include multi drug-resistant tuberculosis, among other drugs. Eye drops can also be used for superficial infections caused by ophthalmic microbes. Mucus can also be used for otitis media if the eardrum is perforated [29-33].

2. Enrofloxacin: Enrofloxacin is a typical fluoroquinolone carboxylic acid derivative of second-generation. Enrofloxacin have wide range of activity against Gram-negative and Gram-positive bacterial strains. It is a well-known synthetic chemotherapeutic agent as well as antimicrobial drug including those resistant to β-lactam antibiotics and sulfonamides [27]. Enrofloxacin has potential post-antibiotic effect for both Gram-negative and Gram-positive bacterial strains. It is also shows activity for both stationary and growth phases of bacterial replication. Concentration dependent bactericidal activity of enrofloxacin, shows the death of bacteria cell; which occurrs within 20–30 minutes of exposure.

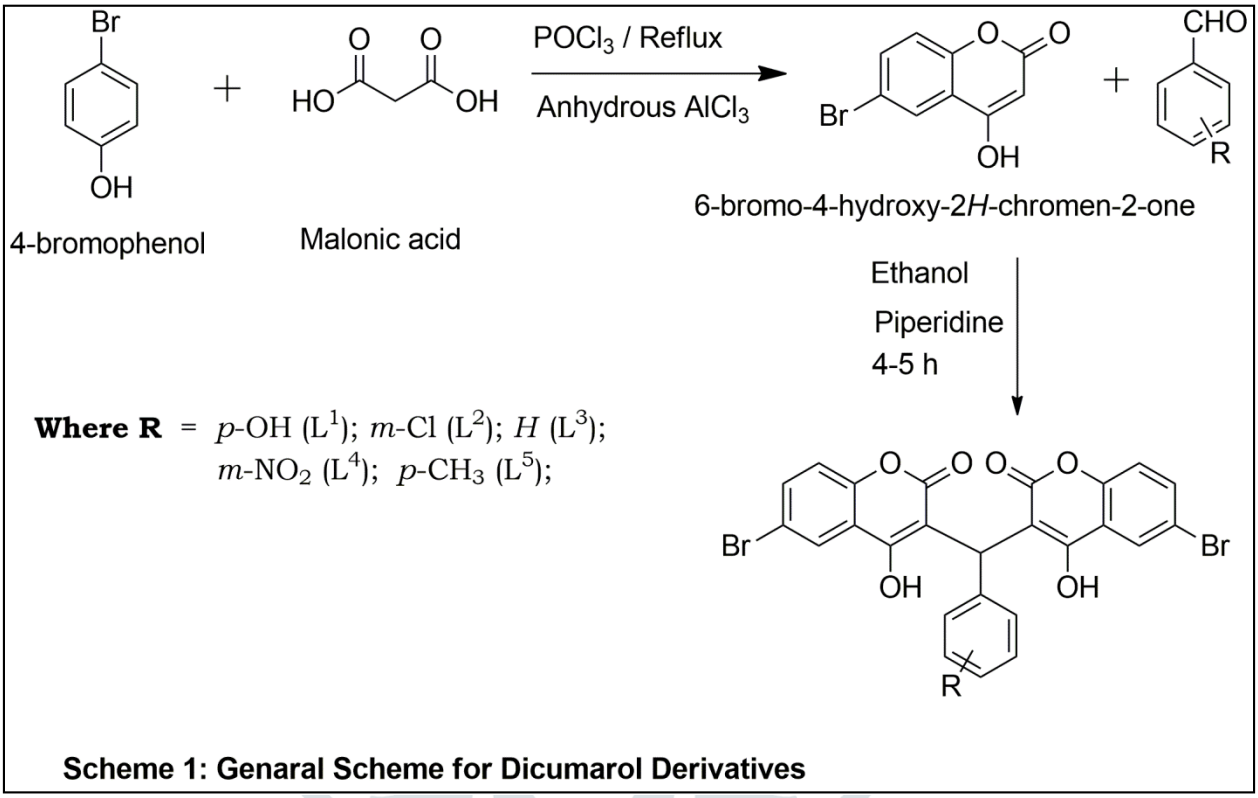
3. Quinolones: The quinolones also known as quinolone carboxylic acids or 4-quinolones are man-made drugs that their effectivity is improved by potently inhibiting DNA replication. They are used sparingly in the treatment of multiple infections [28]. It has a broad spectrum of activity against Gram-positive & negative aerobic, facultative anaerobes, chlamydia, and several related organisms such as mycoplasma and mycobacteria [30-35].

4. Gatifloxacin: Gatifloxacin is third generation fluoroquinolone family member produced by Bristol-Myers Squibb and Allergon, under the brand names Tequin and Zymor. GFL[(±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3- quinoline carboxylic acid] is which also known as 6-fluoro- 8-methoxy quinolone which have important structural modification which expands their spectrum of activity beyond its antibacterial organisms, and reduced adverse effects as compared with earlier fluoroquinolones [36-37].

Review of Literature

2.1 Preparation of 6-Bromo–4-Hydroxy Coumarin:

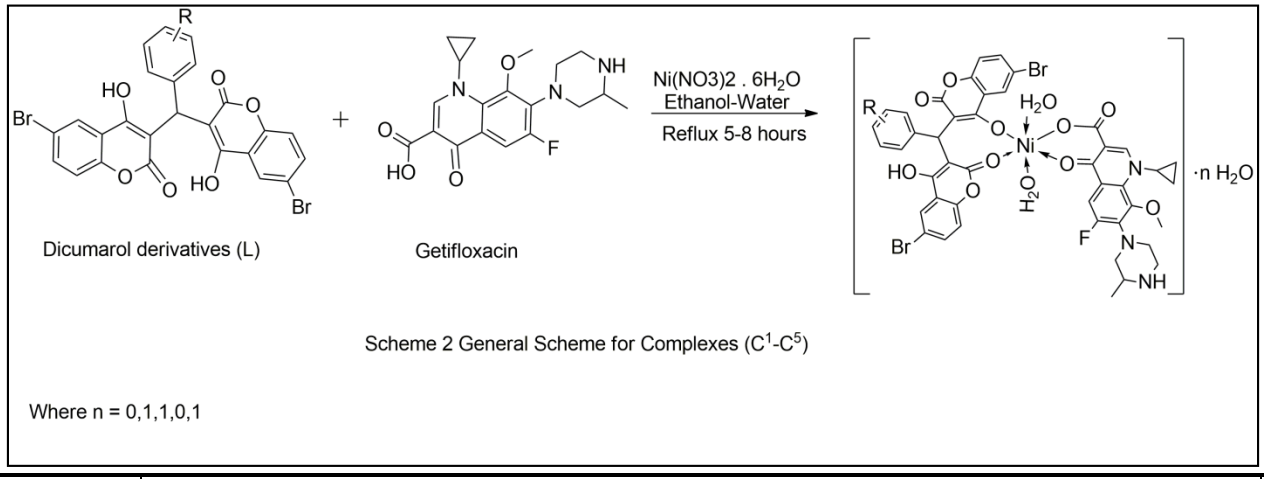
4-bromophenol, malonic acid, anhydrous zinc chloride and phosphorus oxychloride was added to a round bottom flask fitted with a reflux condenser and was Stirred for 35 hours, cooled the yellow colored mixture, decomposed with water and left overnight. The crude solid of 6-bromo-4-hydroxycoumarin was obtained and filtered off, washed with water and dried. The crude product was purified by dissolving in 10% sodium bicarbonate solution, filtered and re-precipitated by adding HCl solution. The product separated as a pale-yellow solid. It was filtered off, washed with water, dried and recrystallized from ethanol-water [38].



Scheme 1: Genaral Scheme for Dicumarol Derivatives

2.2. Preparation of Dicoumarol derivatives:

6-Bromo-4-hydroxycoumarin was dissolved in ethanol and heated in water bath for 4–5 hrs, to obtain a clear solution. ethanolic solution of Aldehyde was added to hot solution and refluxed in presence of H_2SO_4 for 18 hrs. The needle shaped crystals obtained were separated out and were recrystallized from ethanol [39].

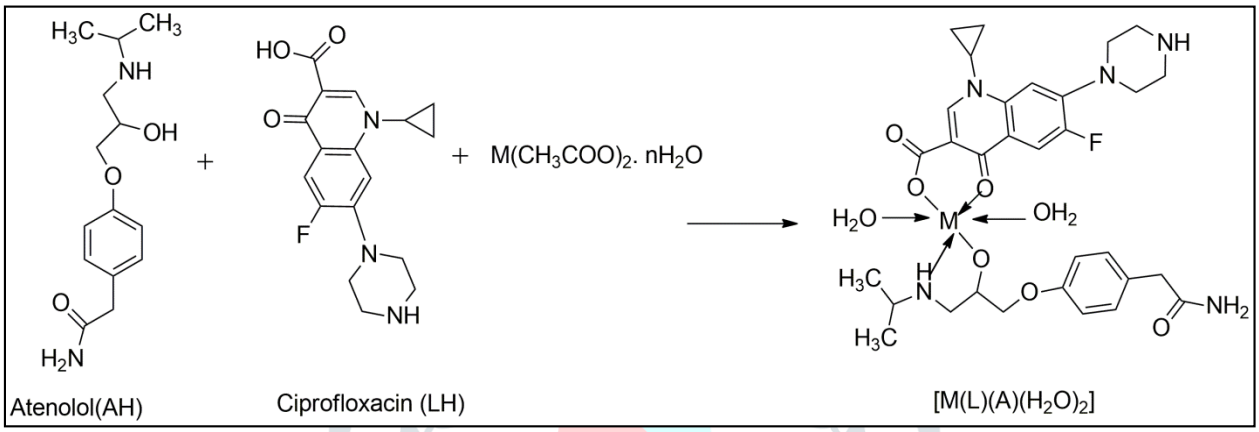


Scheme 2 General Scheme for Complexes (C^1-C^5)

Where n = 0,1,1,0,1

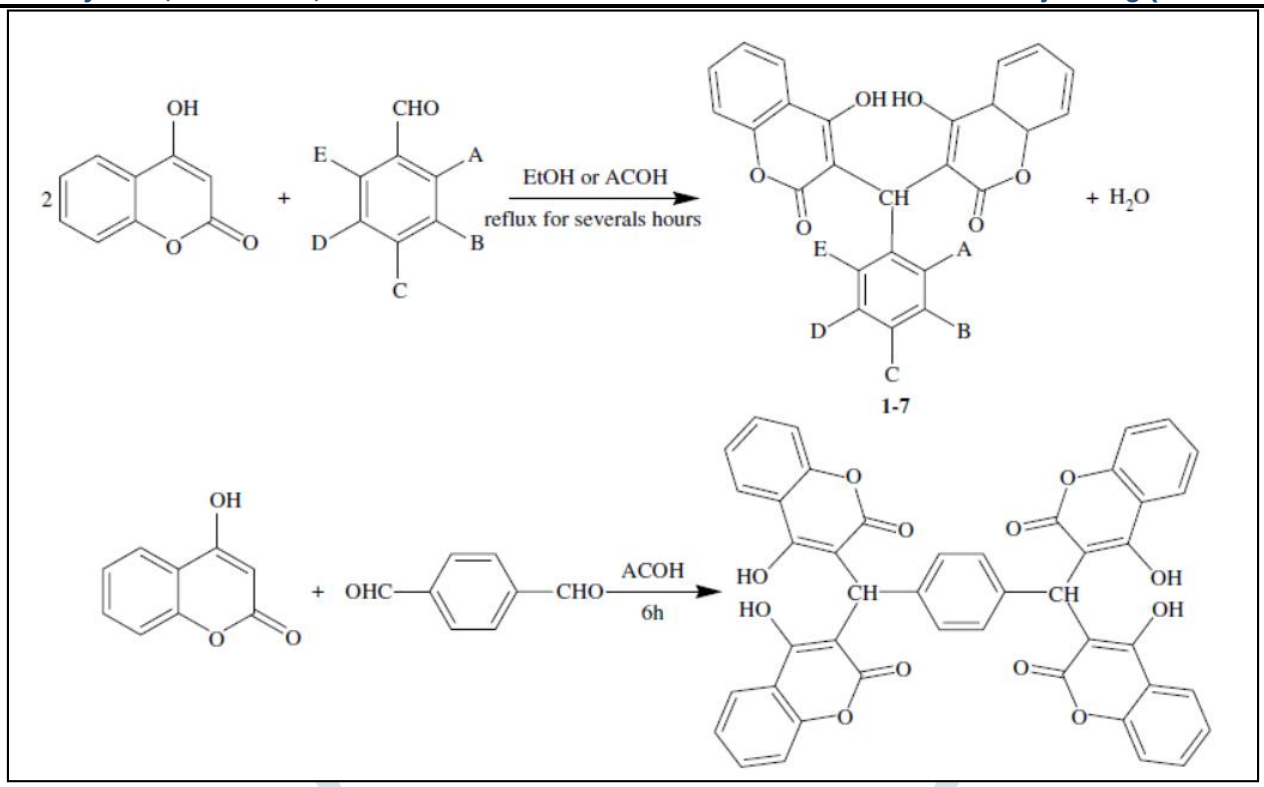
2.3 Preparation of $[M(L)(A)(H_2O)_2]$:

The preparation of $[M(L)(A)(H_2O)_2]$ (where, M= Cu(II), Ni(II), Co(II), Zn(II), Cd(II), and Mn(II)) was carried out by mixing an aqueous solution of metal acetate and an aqueous solution of ciprofloxacin (LH) hydrochloride followed by addition of an acetonitrile solution of atenolol (AH) in 1:1:1 mole ratio. The mixed ligand complex was formed by heating in a water bath for 3 – 4 h at 50°C temperature with continuous stirring. The mixture was kept overnight at room temperature. A fine-colored product was obtained. The obtained crystals were collected by filtration, washed with water and ether, and dried in air [40].



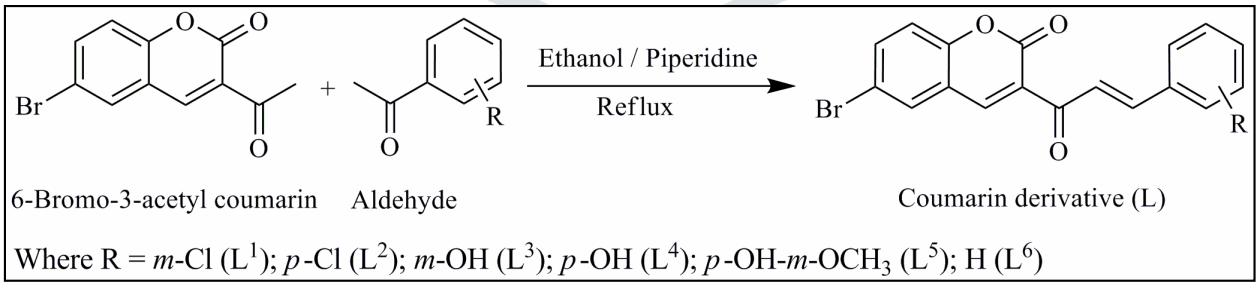
2.4 Preparation of some dicumarol derivative:

4-Hydroxycoumarin and the respective aromatic aldehyde at a molar ratio in ethanol or glacial acetic acid were mixed under stirring and heated at reflux until the appearance of an insoluble product. After cooling the product was filtered and recrystallized with the appropriate solvent. The following 3,30-arylidenebis-(4-hydroxy-2H-1-benzopyran-2-ones) or tetrakis- 4-hydroxycoumarin derivatives were synthesized according to this procedure [41].



2.5 Preparation of cumarin derivative:

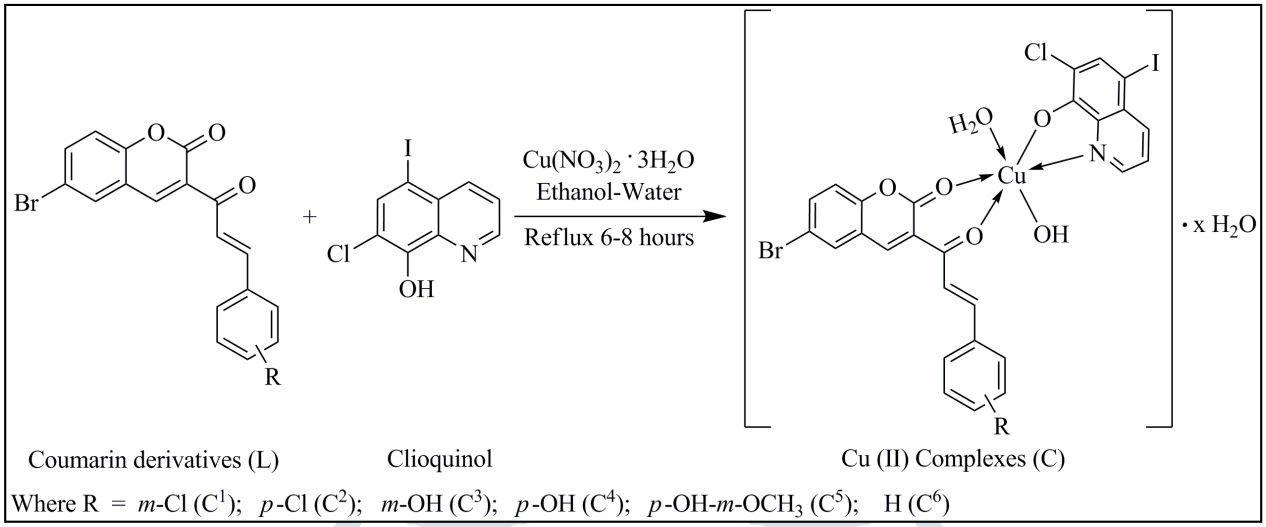
In a round bottom flask 6-Bromo 3-acetyl coumarin and 3-chloro benzaldehyde were taken in pyridine. Catalytic amount of piperidine was added and the reaction mixture was stirred for 10 min at room temperature. After clear solution obtained, the reaction mixture was refluxed on oil bath. Completion of reaction was checked by TLC using mobile phase Ethyl acetate:Hexane (7:3). After the completion of reaction, subsequently it was allowed to room temperature. Afterwards it was pour into ice-cold water and adjusts the pH 4-5 using diluted HCl. A solid product separated out was filtered off, later on washed with cold ethanol and dried in air. It was recrystallized from ethanol [42].



2.6 Preparation of Cu(II) Complexes:

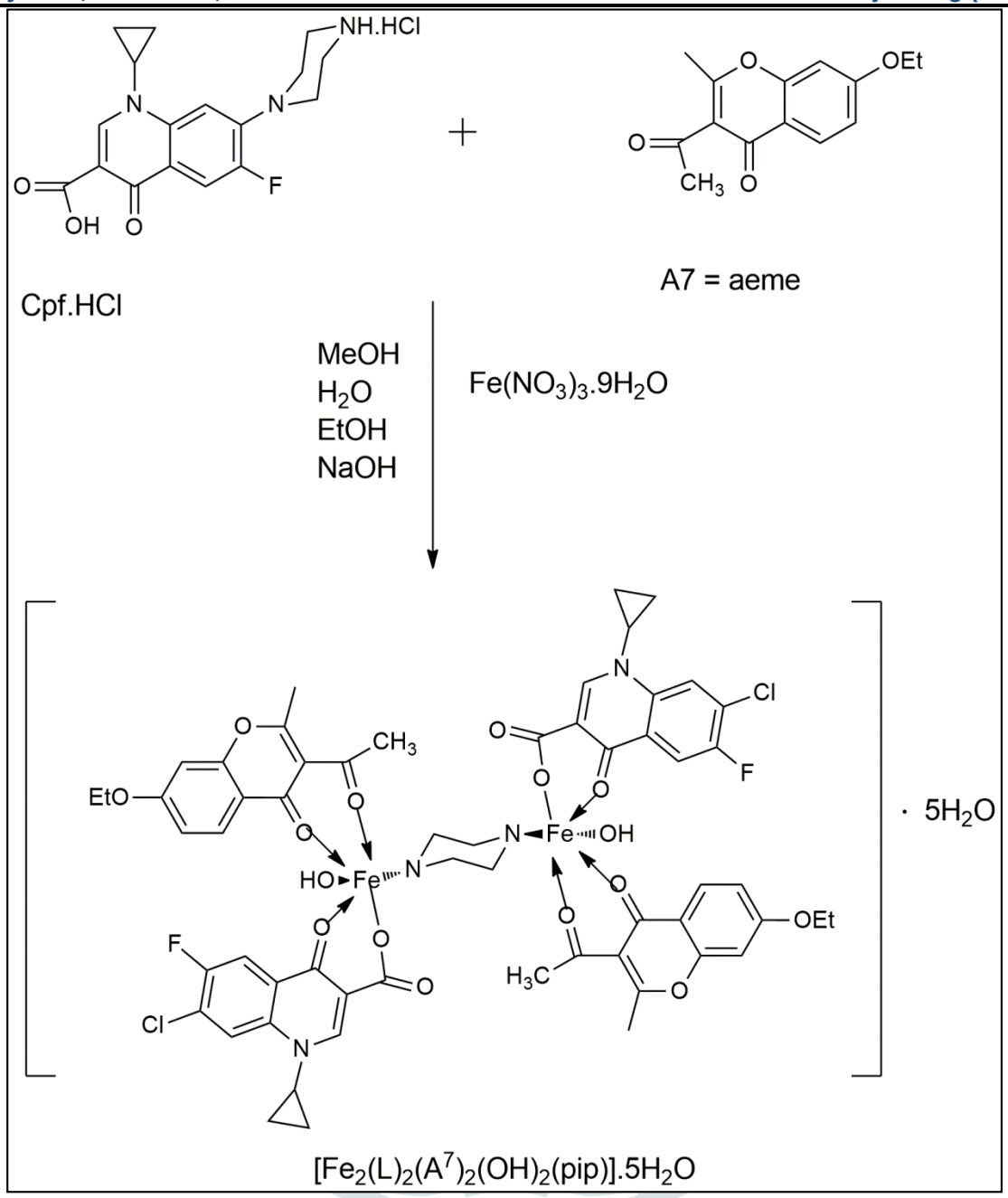
An aqueous solution of $Cu(NO_3)_2 \cdot 3H_2O$ salt was added into ethanolic solution of ligand (L^1) and subsequently an ethanolic solution of Clioqunol was added with continuous stirring. Then the pH was adjusted in between addition of diluted NH_4OH solution. The resulting solution was refluxed for 5 h and then heated over a steam bath to evaporate upto half of the volume. The reaction mixture was kept overnight at room temperature. A fine

coloured crystalline product was obtained. The obtained product was washed with ether and dried over vacuum desiccators. Complexes C^2-C^6 was prepared according to same method [43].



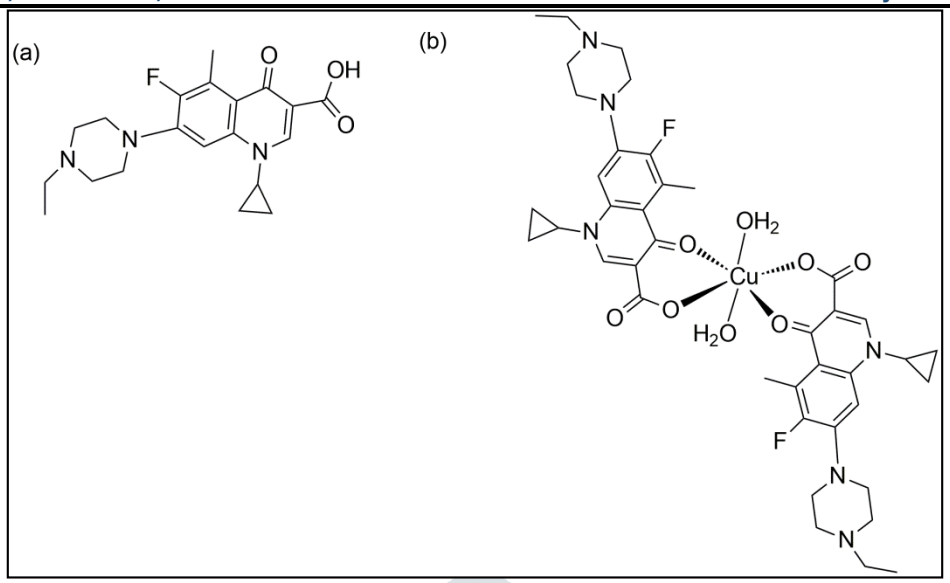
2.7 Preparation of Fe(II) Complexes:

A methanolic solution of Fe(N03h ·9H_20 was added to in ethilnolic solution oemc (A7) (2.329, , followed by accumulation of a previously primed solution of Cpf· HCI in water; the pH was adjusted to 5.0 - 6.0 pH with dilute NaOH solution. The resulting redd ish brown solution was refluxed for 7 h, and then heated on a steam bath to evaporate up to half the volume. The reaction mixture was kept overnight at room temperature. A fine colored product was obtained. The obtained product was washed with ether and dried over a vacuum desiccator [44].



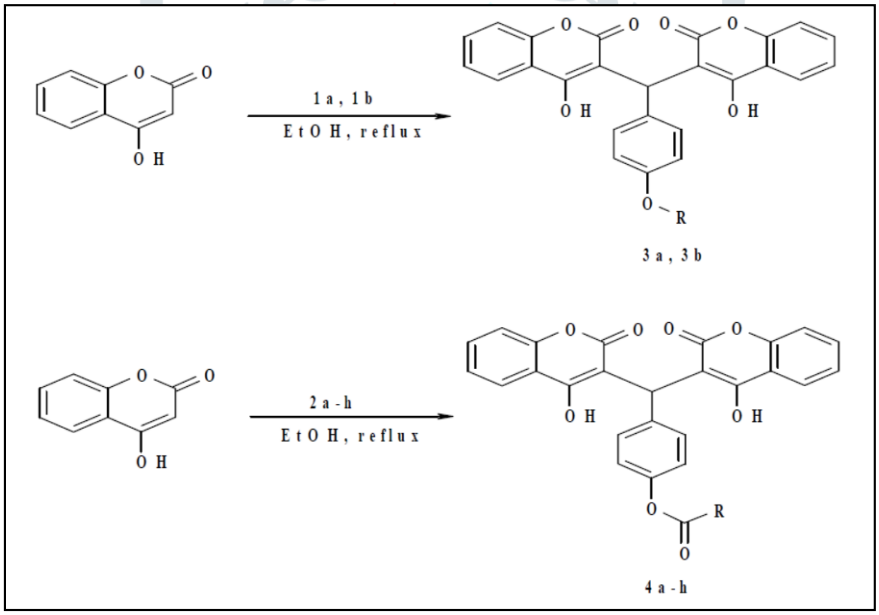
2.8 Preparation of [Cu(erx)$_2$(H$_2$O)$_2$] complex:

The structure of [Cu(erx)$_2$(H$_2$O)$_2$] complex was assessed using copper K-edge X-ray absorption spectroscopy (XAS) through X-ray absorption near edge structure (XANES) and extended X-ray absorption fine structure (EXAFS) combined with EPR spectroscopy. A Jahn–Teller distorted octahedra was evidenced for Cu^{2+} geometry. Four equatorial oxygen atoms from two enrofloxacin ligands were found with Cu–Oeq distances of 1.93 Å. The coordination was completed by two water molecules in axial position at an average distance of 2.11 Å [45].



2.9 Preparation of the coumarin dimmers:

The p-hydroxy- modified benzaldehyde with two equivalent of 4-hydroxycoumarin under reflux. The target compounds were screened for their antibacterial activity against Escherichia coli (E.*coli*), Staphylococcus aureus (SA), Pseudomonas aeruginosa (PA), Enterococcus species (Esp.), Streptococcus pyogenes (SP), and Streptococcus pneumoniae (SPn). Certain compounds showed good or moderate antimicrobial activity on SA and SP [46].

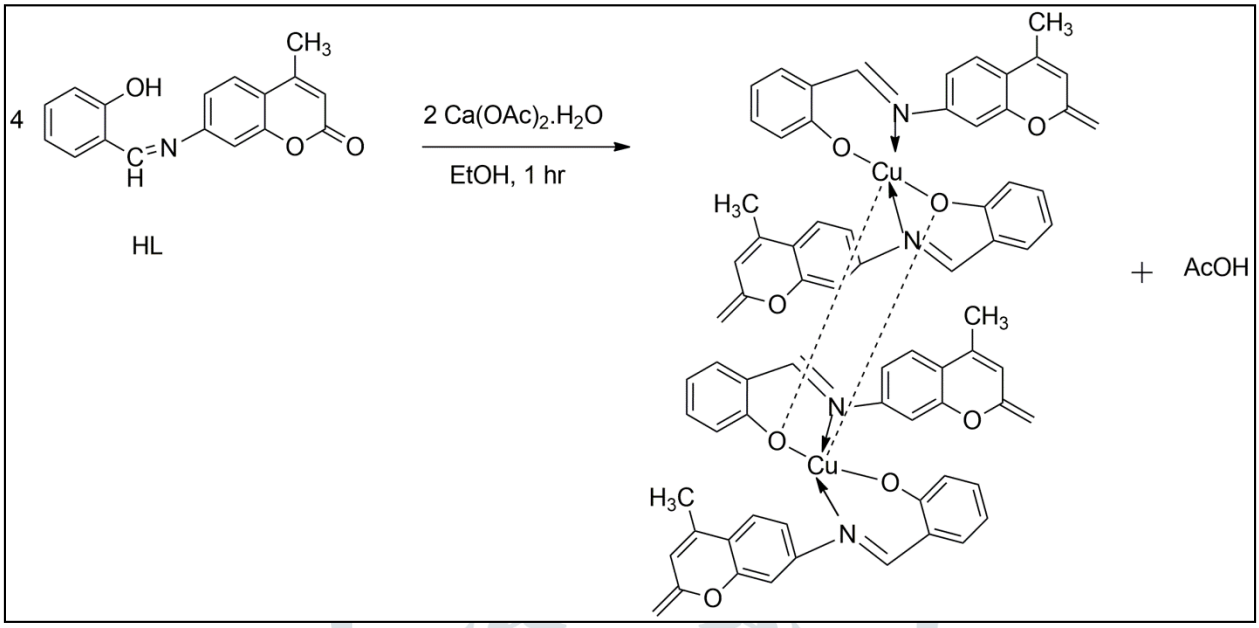


2.10 Preparation of binuclear copper complex [{Cu(L)2}2:

A binuclear copper complex [{Cu(L)2}2], C68H48Cu2N4O12C (where L is 4-methyl-7-(salicylideneamino)coumarin), has been synthesized and characterized using elemental analysis, molar conductance measurements, and infrared, ultraviolet and ESR spectrosopy.

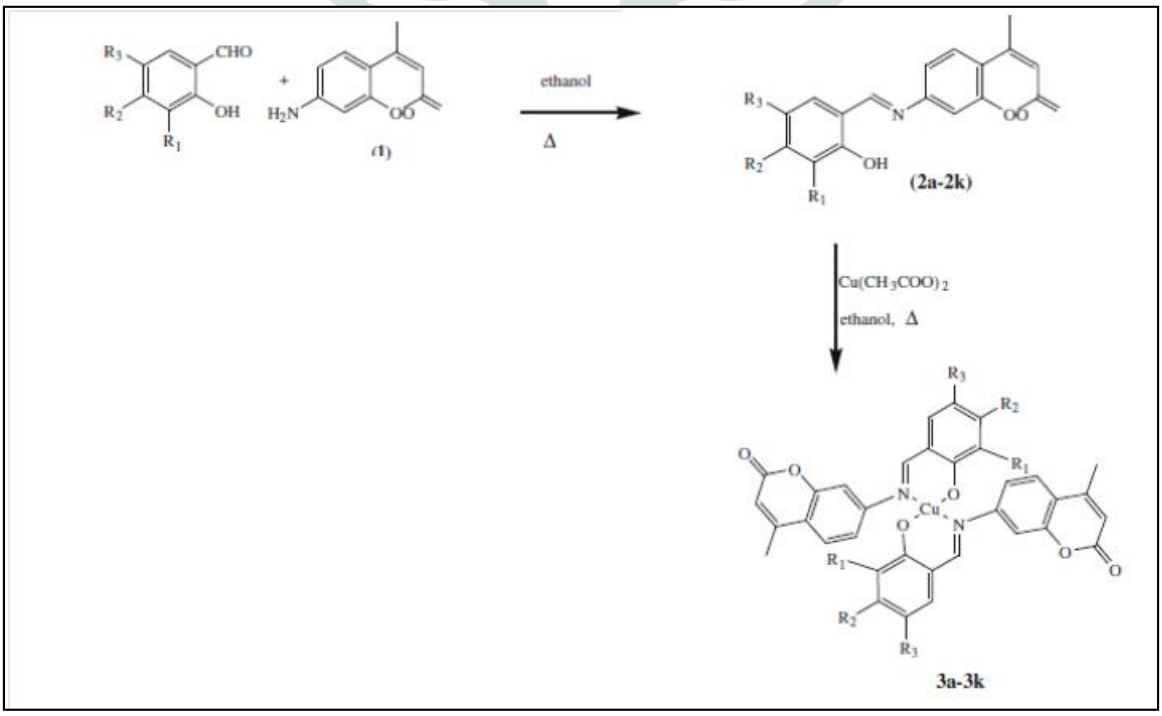
The molecular structure of title compound, determined by single-crystal X-ray diffraction studies, reveals that the two symmetric Cu(L)2 units are associated into a dimer by rather long Cu...O bonds. The Cu(II) ions are bridged *via*

the phenolic oxygen of one of the monomers and have distorted trigonal bipyramidal conformation geometry. Within each monomer the two methylsubstituted coumarin skeletons are trans to one another, but adopt a parallel arrangement with respect to the other monomer. Only half of the complex molecule can be found in the asymmetric unit, Z' = 0.5, the other half is generated by the symmetry centre [47].



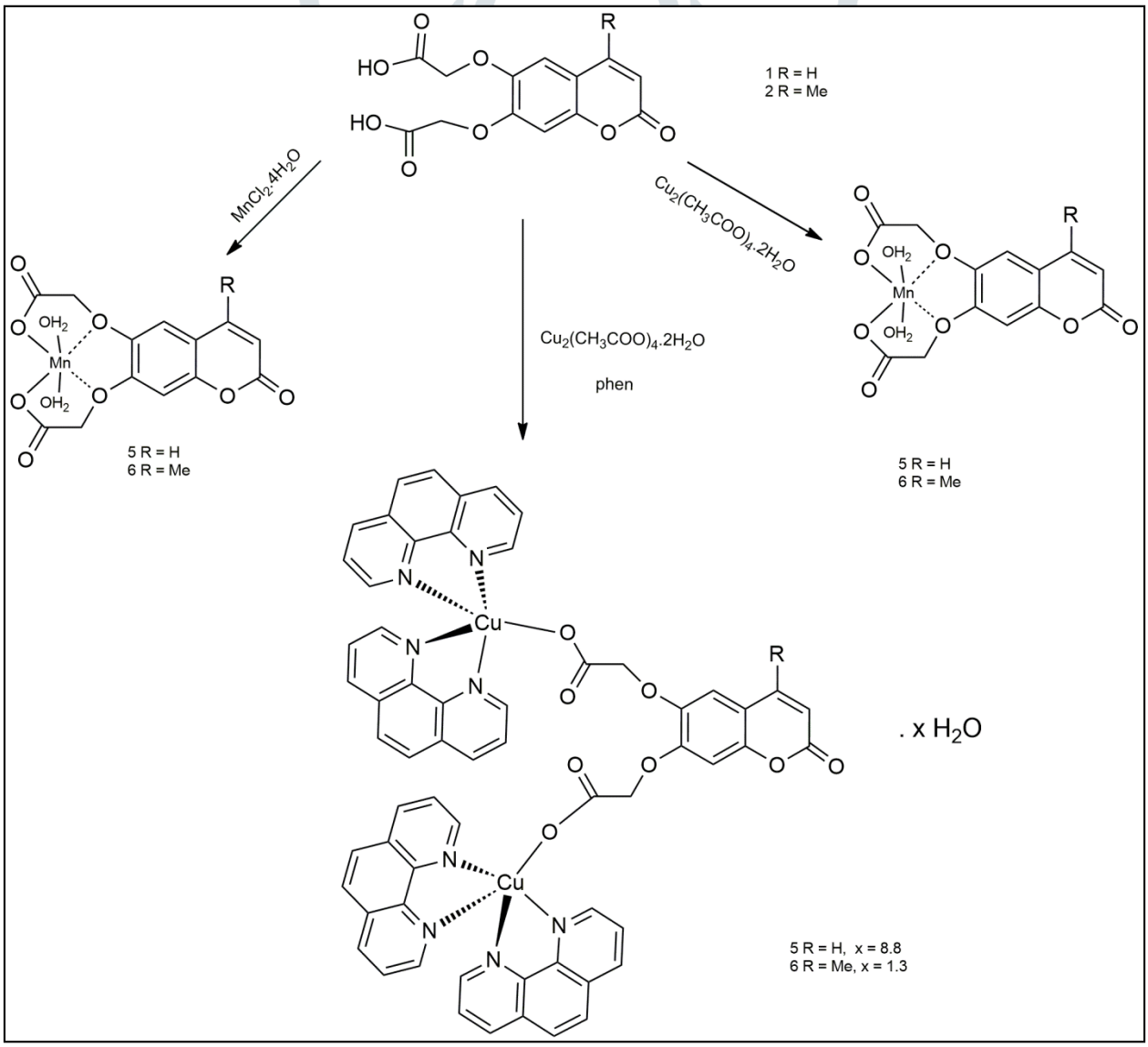
2.11 Preparation of 7-amino-4-methyl-coumarin based complexes:

The condensation of 7-amino-4-methyl-coumarin with a number of substituted salicylaldehydes yielded a series of Schiff bases (2a–2k) in good yields. Subsequent reaction of these ligands with copper(II) acetate yielded Cu(II) complexes (3a–3k) and some were characterised using X-ray crystallography. All of the free ligands and their metal complexes were tested for their anti-Candida activity. A number of the ligands and complexes exhibited anti-Candida activity comparable to that of the commercially available antifungal drugs, ketoconazole and Amphotericin B [48].



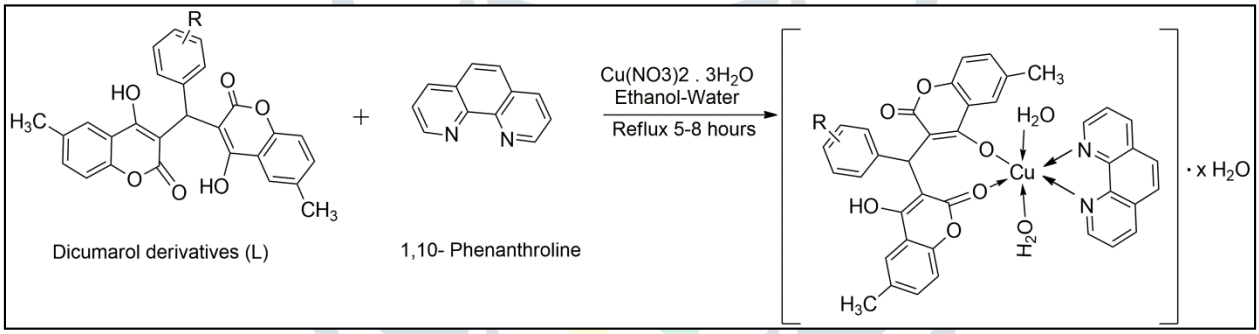
2.12 Preparation of novel coumarin-based ligands and its complexes:

Two novel coumarin-based ligands, coumarin-6,7-dioxyacetic acid (cdoaH2) and 4-methylcoumarin-6,7-dioxyacetic acid (4- MecdoaH2), were reacted with copper(II) and manganese(II) salts to give [Cu(cdoa)(H2O)2] Æ 1.5H2O (3), [Cu(4-Mecdoa)(H2O)2] (4), [Mn(cdoa)(H2O)2] (5) and [Mn(4-Mecdoa)(H2O)2]. The metal complexes, 3–6, were characterised by elemental analysis, IR and UV–Vis spectroscopy, and magnetic susceptibility measurements and were assigned a polymeric structure. 1 and 2 react with Cu(II) in the presence of excess 1,10-phenanthroline (phen) giving [Cu(cdoa)(phen)2] Æ 8.8H2O (7) and [Cu(4-Mecdoa)(phen)2] Æ 13H2O (8), respectively. The X-ray crystal structures of 7 and 8 confirmed trigonal bipyramidal geometries, with the metals bonded to the four nitrogen atoms of the two chelating phen molecules and to a single carboxylate oxygen of the dicarboxylate ligand. The complexes were screened for their antimicrobial activity against a number of microbial species, including methicillin-resistant Staphylococcus aureus (MRSA), Escherichia coli and Candida albicans. The metal-free ligands 1 and 2 were active against all of the microbes. Complexes 3– 6 demonstrated no significant activity whilst the phen adducts 7 and 8 were active against MRSA (MIC80 = 12.1 lM), E. coli (MIC80 = 14.9 lM) and Patonea agglumerans (MIC80 = 12.6 lM). Complex 7 also demonstrated anti-Candida activity (MIC80 = 22 lM) comparable to that of the commercially available antifungal agent ketoconazole (MIC80 = 25 lM) [49].



2.13 A series of Cu(II) complexes containing dicoumarol derivatives:

A series of Cu(II) complexes containing dicoumarol derivatives and 1, 10-phenanthroline have been synthesized. Structural and spectroscopic properties of ligands were studied on the basis of mass spectra, NMR (1H and 13C) spectra, FT-IR spectrophotometry and elemental analysis, while physico-chemical, spectroscopic and thermal properties of mixed ligand complexes have been studied on the basis of infrared spectra, mass spectra, electronic spectra, powder X-ray diffraction, elemental analysis and thermogravimetric analysis. X-ray diffraction study suggested the suitable octahedral geometry for hexacoordinated state. The kinetic parameters such as order of reaction (n), energy of activation (Ea), entropy (S_), pre-exponential factor (A), enthalpy (H_) and Gibbs free energy (G_) have been calculated using Freeman– Carroll method. Ferric-reducing antioxidant power (FRAP) of all complexes were measured. All the compounds were screened for their antibacterial activity against Escherichia coli, Pseudomonas aeruginosa, Streptococcus pyogenes and Bacillus subtilis, while antifungal activity against Candida albicans and Aspergillus niger have been carried out. Also compounds against Mycobacterium tuberculosis shows clear enhancement in the anti-tubercular activity upon copper complexation [50].



Conclusion:

Here we describe the synthesis of biologically active coumarin derivatives and their Ni(II) and Cu(II) complexes. An octahedral geometry was assigned to the Ni(II) and Cu(II) complexes based on thermogravimetric analysis and magnetic moment. The conjugate exhibits fairly potent antioxidant activity compared to the ligands used to form the conjugate. The in vitro antibacterial activity of all synthetic compounds shows good results with increased activity upon complexation with metal ions. This increased activity could be attributed to the increased lipophilicity of the complex. The structures of the ligands were examined and confirmed by elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral studies.

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