X-ray diffraction studies of Cu(II) Complexes Based on Levofloxacin and Coumarin derivative with their biological evaluation.

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Abstract
From different coumarin derivative, levofloxacin and transition metal, the Cu(II) complexes were synthesized by classical thermal technique. The structures of the ligands and their cu developments were explored and confirmed by the elemental analysis, FT-IR, ^{1}H-NMR, ^{13}C-NMR, mass spectral and powder X-ray spreading studies respectively. Thermal conduct of newly synthesized mixed ligand Cu(II) complexes were investigated by means of electronic spectra and magnetic dimensions. The assortments were divided for their antimicrobial and antioxidant viewing using serial broth dilution method and Minimum Inhibitory Concentration (MIC) is resolute.

Keywords levofloxacin, MIC, powder XRD.

1. Introduction

Coumarin and its byproducts embody one of the greatest active classes of mixtures holding a wide spectrum of living activity [1-4]. Many of these mixtures have proved to be active as antitumor [5], antibacterial [6], antifungal[7], anticoagulant[8] and antiinflammatory[9]. In addition, these mixtures are cast-off as flavors to food and make-ups[10].dispersed Fluorescent and laser[11]. Various equivalents of 3- Substituted coumarins suchas 3-amino coumarins exhibit antimicrobial activity[12-13]. Recently, coumarin byproducts have been gaged in the behavior of social immune deficiency virus, due to their capacity to inhibit human immune deficiency virus integrase.[14-19]

Transition metal complexes of levofloxacin and its byproducts are of increasing notice since of their versatile roles inmanyfields such as organization chemistry, analytical chemistry and living chemistry.[21] Likewise, study of phenanthroline byproducts has been provoked by current notice in their catalytic, redox, physicochemical, biological belongings and novel supra molecular chemistry.[22–23] In recent years, the schoolwork of cu(II)-Levofloxacin complexes has become gradually more vital owed to their antimicrobial belongings.[24] Furthermore, Cu(II) developments of levofloxacin are talented of cleaving DNA. Copper developments of nitrogen-donor heterocyclic ligands have been used widely to improve nuclease activity.

The aim of this learning was to prepare the ligand based complexes of Cu(II) with levofloxacin by coumarin derivatives and to regulate their assets. In our earlier information, we have cited a series of stuck coumarin products and its transition metal developments.[25] In continuation of our prior effort, we describe here synthesis, description and spectroscopic structures of novel mixed ligand Cu(II) complexes along with antimicrobial and anti-oxidant activities.

2. Experimental

2.1 Materials

All substances were of logical chemical (AR) grade acquired commercially from Spectro chem. Ltd., Mumbai-India and used without further cleansing. Diluters employed were distilled, cleaned and dried by standard techniques earlier to use[26]. levofloxacin was accepted from Chemical, GIDC Rd, Nandesari, Vadodara, Gujarat.. The metallic nitrates secondhand were in hydrated form.

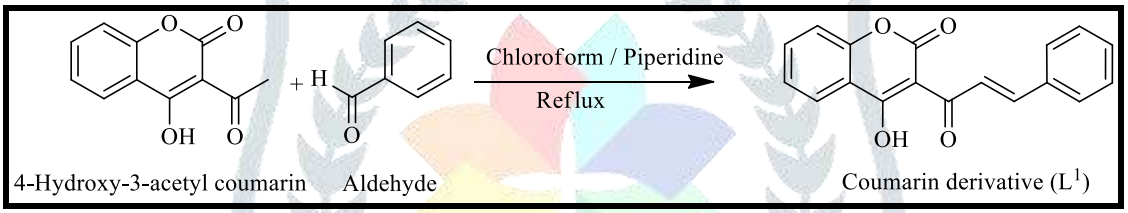
2.2 Physical measurements

All replies were experiential by thin-layer chromatography and finding of the workings were stately under UV light or explore in Iodine chamber. C,H and N were assessed by elemental analyzer PerkinElmer, USA 2400-II CHN analyzer. Metal ion analyses was carry out by the termination of compact multipart in hot concerted nitric acid, additional diluting with distilled water and filtered to reject the advanced instinctive ligands. Residual explanation was opposed with ammonia explanation and the metal ions were titrated by EDTA. ^{1}H and ^{13}C NMR depths were putative out on Advance-II 400 Bruker NMR spectrometer, SAIF, Chandigarh.india The part shifts were measured with detail to TMS which cast-off as inner normal and DMSO-d_6 used as solvent. Infrared spectra of solids were logged in the region 4000-400 cm^{-1} on a Nicolet Impact 400D Fourier-Transform Infrared Spectrophotometer by KBr pellets. M.P. of the ligands and metal developments were stately by open capillary tube system. Hard state magnetic contact measurements were approved out at r.t using a Gouy's magnetic susceptibility balance with mercury tetrathiocyanato cobaltate(II) being second hand as a location normal (g = 16.44×10^{-6} c.g.s. units). Molar defenselessness was adapted using Pascal's constant. The electric spectra were composed using LAMBDA 19 UV/Vis/NIR spectrophotometer in the section 200-1200 nm.

2.3 General procedure for the preparation of Coumarine chalcone (L)

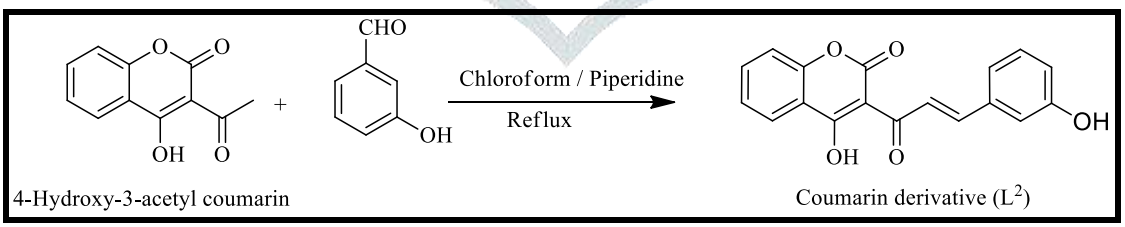
2.3.1 3-cinnamoyl-4-hydroxy-2H-chromen-2-one (L^1):

Yield: 75%, m.p.: 156-158 ℃, Found %: C, 73.13, H, 4.03. $C_{18}H_{12}O_4$ (293.03[M]+) requires %: C, 73.97, H, 4.14. FTIR (KBr. cm^{-1}): 3145 (-OH), 1612 (C=O, *α, β*-unsaturated ketone), 1748 (C=O, lactone carbonyl of coumarin). ^{1}H NMR (ppm): 6.53-7.91 (11H, m, Ar-H), 12.10 (1H, -phenolic proton); ^{13}C NMR (DMSO-d_6 100 MHz): δ:98.54, 113.79,115.32, 122.70, 123.65, 124.05, 128.65, 129.27, 130.05, 133.42, 136.09, 142.44, 152.29 (15C, Ar-C), 158.47 (C=O, lactone carbon of coumarin), 183.05(C-4), 184.32 (C=O, *α, β*-unsaturated ketone);



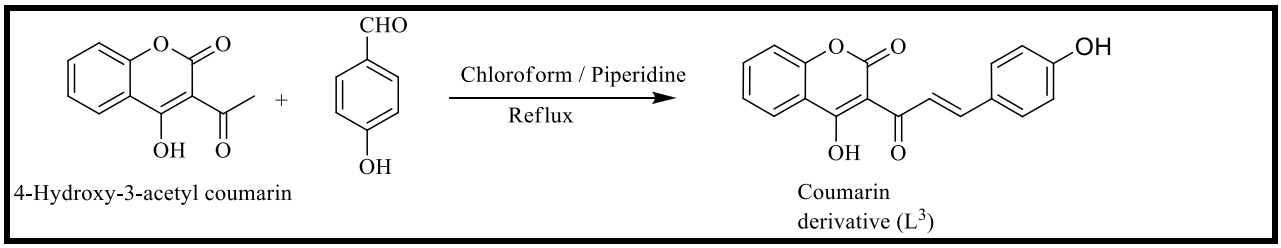
2.3.2 (E)-4-hydroxy-3-(3-(3-hydroxyphenyl)acryloyl)-2H-chromen-2-one (L^2):

Yield: 76%, m.p.: 160-161 ℃, Found %: C, 70.39, H, 4.24, $C_{18}H_{12}O_5$ (308.73[M]+) requires %: C, 70.13, H, 3.92. FTIR (KBr. cm^{-1}): 3150 (-OH), 1602 (C=O, *α, β*-unsaturated ketone), 1741 (C=O, lactone carbonyl of coumarin): ^{1}H NMR (DMSO-d_6 400 MHz): δ: 6.52-8.57 (10H, m, Ar-H), 12.11 (2H, -phenolic proton); ^{13}C NMR (DMSO-d_6 100 MHz): δ:98.32, 115.21, 116.42, 116.95, 117.73, 122.03, 123.51, 124.35, 124.23, 128.20, 133.18, 136.01, 146.28, 153.26, 156.30 (15C, Ar-C), 158.30 (C=O, lactone carbon of coumarin), 183.16(C-4), 184.22 (C=O, *α, β*-unsaturated ketone);



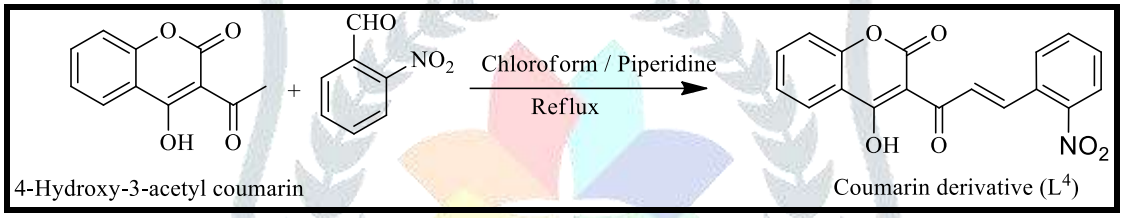
2.3.3 (E)-4-hydroxy-3-(3-(4-hydroxyphenyl)acryloyl)-2H-chromen-2-one (L^3):

Yield: 74%, m.p.: 165-166 ℃, Found %: C, 70.04, H, 4.09. $C_{18}H_{12}O_5$ (309.02[M]+) requires %: C, 70.13, H, 3.92. : FTIR (KBr. cm^{-1}): 3143 (-OH), 1604 (C=O, *α, β*-unsaturated ketone), 1737 (C=O, lactone carbonyl of coumarin): ^{1}H NMR (DMSO-d_6 400 MHz): δ: 6.36-8.69 (10H, m, Ar-H), 12.25 (2H, -phenolic proton); ^{13}C NMR (DMSO-d_6 100 MHz): δ:97.50, 115.29, 116.02, 116.87, 123.70, 124.15, 124.95, 128.35, 132.12, 136.37, 146.40, 153.19, 155.06 (15C, Ar-C), 158.47 (C=O, lactone carbon of coumarin), 183.05(C-4), 184.32 (C=O, *α, β*-unsaturated ketone);



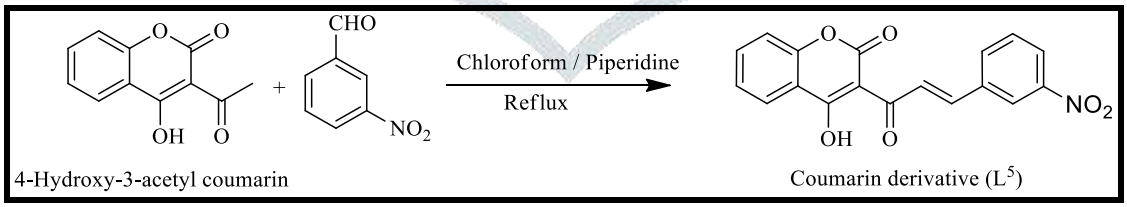
2.3.4. (E)-4-hydroxy-3-(3-(2-nitrophenyl)acryloyl)-2H-chromen-2-one (L^4):

Yield: 63%, m.p.: 170-171 ℃, Found %: C, 64.38, H, 3.51, N, 4.28. $C_{18}H_{11}O_6$ (337.64[M]+) requires %: C, 64.10, H, 3.29, N, 4.15. FTIR (KBr. cm^{-1}): 3158 (-OH), 1612 (C=O, *α, β*-unsaturated ketone), 1720(C=O, lactone carbonyl of coumarin), 1513 (Ar-NO_2, asymmetric), 1352 (Ar-NO_2, symmetric).). ^{1}H NMR (DMSO-d_6 400 MHz): δ: 6.72-8.57 (10H, m, Ar-H), 12.04 (1H, -phenolic proton); ^{13}C NMR (DMSO-d_6 100 MHz): δ:97.43, 113.82, 116.49, 121.16, 123.25, 124.18, 124.17, 126.52, 130.28, 136.20, 136.79, 138.70, 142.38, 150. 22, 153.03 (15C, Ar-C), 158.64 (C=O, lactone carbon of coumarin), 183.20(C-4), 184.28 (C=O, *α, β*-unsaturated ketone);



2.3.5. (E)-4-hydroxy-3-(3-(3-nitrophenyl)acryloyl)-2H-chromen-2-one (L^5):

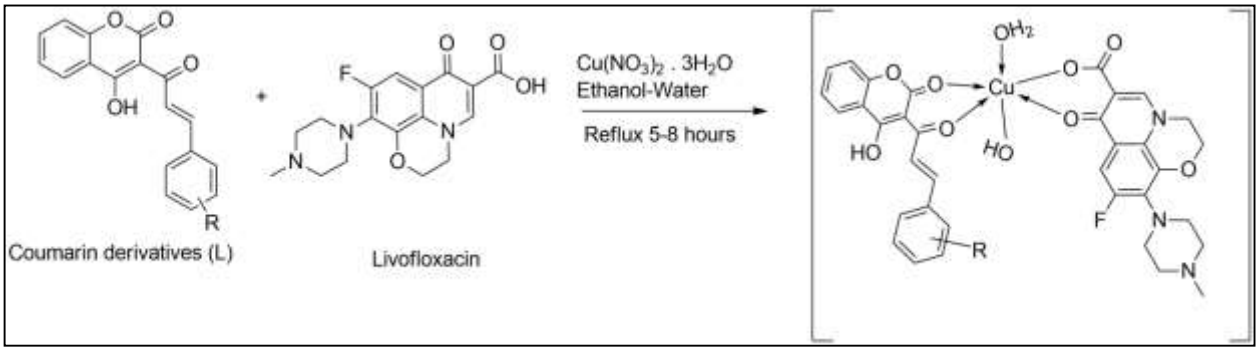
Yield: 75%, m.p.: 180-181 ℃, Found %: C, 64.47, H, 3.45, N, 4.03. $C_{18}H_{11}O_6$ (338.05[M]+) requires %: C, 64.10, H, 3.29, N, 4.15 FTIR (KBr. cm^{-1}): 3148 (-OH), 1603 (C=O, *α, β*-unsaturated ketone), 1728 (C=O, lactone carbonyl of coumarin), 1517 (Ar-NO_2, asymmetric), 1351 (Ar-NO_2, symmetric). ^{1}H NMR (DMSO-d_6 400 MHz): δ: 6.69-8.75 (10H, m, Ar-H), 12.16 (1H, -phenolic proton); ^{13}C NMR (DMSO-d_6 100 MHz): δ:97.57, 114.96, 116.39, 121.77, 123.60, 124.06, 124.87, 126.63, 130.15, 136.02, 136.89, 138.57, 142.48, 150. 07, 152.29 (15C, Ar-C), 158.24 (C=O, lactone carbon of coumarin), 183.14(C-4), 184.13 (C=O, *α, β*-unsaturated ketone);



2.4 Synthesis of metal complexes: [M(L)(PH)(H_2O)$_2$](C)

An aqueous solution of $M(NO_3)_2$•$3H_2O$ salt (10 mmol) was added into ethanolic solution of ligand (L) (10 mmol) and subsequently an ethanolic solution of levofloxacin (10 mmol) was added with continuous stirring. Then the pH was adjusted in between 4.5-6.0 by addition of diluted NH_4OH solution. The resultant solution was refluxed for 5 h and then heated over a steam bath to vaporize up to half of the volume. The reaction combination was reserved overnight at room temperature. A fine coloured clear product was attained. The obtained creation was washed with ether and dried over vacuum desiccators.

Complexes C^2-C^4 was prepared allowing to same process and their physicochemical parameters are shortened in Table 1. The synthetic protocol of complexes is shown in Scheme 2, while FT-IR spectrum of C^1 is given in the figure 2.



Scheme 2. Synthesis of Metal complexes (C)

2.5 Antimicrobial activity

All the ATCC nation was collected from society of bacterial skill, Bangalore. 2% Luria broth explanation was settled in distilled water while, pH of the Fluid was habituated to 7.4±0.2 at room temperature and purified by autoclaving at 15 lb pressure for 25 minute. The established bacterial and fungal strains were prepared in the luria broth and gestated at 37 °C and 200 rpm in an orbital incubator for instant. Example solutions were ready in DMSO for concentration 200, 150, 100, 50, 25, 12 and 6µg/mL. The usual drug key of Streptomycin (antibacterial drug) and Nystatin (anti fungal drug) were fortified in DMSO. Serial broth micro thinning was espoused as a reference process. 10 µl solution of test composite was inoculated in 5 mL luria broth for each concentration respectively and moreover one test tubes was reserved as control. Each of the test tubes was immunized with a interruption of standard microorganism to be tested and incubated at 35 °C for 24 h. At the end of the incubation period, the tubes were inspected for the turbidity. Turbidity in the test tubes specified that microorganism growth has not repressed by the antibiotic contained in the medium at the test concentration. The antimicrobial action tests were run in triplicate.

2.6 Antioxidant studies

Ferric reducing antioxidant power (FRAP) was regulate by an adapted technique [27]. The antioxidant abilities of the mixtures were observe by their dipping authority of the TPTZ-Fe(III) complex to TPTZ-Fe(II) complex for the total antioxidant volume of tested samples, This process was employed because of its simple, fast and also outcomes can be attain was reproducible. Initially subsequent solutions were organized, A) acetate buffer, 300 mM pH 3.6 (3.1g sodium acetate trihydrate and 16 ml conc. acetic acid per L of buffer solution), B) 10 mM 2,4,6-tripyridyl-s-triazine in 40 mM HCl, C) 20 mM $FeCl_3$•$6H_2O$ in distilled water, D) 1mM of ascorbic acid dissolved in 100 mL distilled water. FRAP occupied answer was ready by mixing the above (A), (B) and (C) keys in the ratio of 10:1:1 correspondingly. A mixture of 40.0 µL, 0.5 mM example solution and 1.2 mL FRAP substance was hatched at 37 ℃ for 15 min. The working solution was essential to usage as newly prepared. The ascorbic acid was used as a typical antioxidant compound and fallouts were uttered with associated towards ascorbic acid.

3. Result and Discussion

The produced Cu(II) developments were categorized by elemental examination, FTIR spectra, The metal ion in their complexes were resolute after mineralization. The metal content in chemical study was projected by complex metrically[28], while geometry of the complexes was complete from electronic spectra and magnetic moment.

3.1 Elemental analysis

The logical and physiochemical statistics of the developments are summarized in Table 1. The experimental data were in very good agreement with the calculated ones. The complexes were colored, insoluble in water and commonly organic solvents while soluble in DMSO as well as stable in air. The structure of the complexes is assumed according to the chemical reaction as shown below;

Table 1 Analytical and physical parameters of complexes.

Comp	Elemental analyses, % found (required)				M.p. (°C)	Yield (%)	Molecular weight	μ_{eff}/B. M.
	C	H	N	Cu(II)				
C^1	61.84(61.93)	4.35(4.49)	4.65(4.81)	10.55(10.71)	>350	71	602.09	1.83
C^2	56.88(56.99)	4.16(4.29)	4.28(4.41)	9.71(9.93)	>350	72	654.55	1.85
C^3	58.49(58.64)	3.96(4.10)	4.40(4.56)	9.98(10.09)	>300	66	636.54	1.78
C^4	59.58(59.69)	4.22(4.35)	6.51(6.65)	9.25(9.39)	>350	74	645.12	1.84
C^5	59.55(59.66)	4.24(4.39)	6.54(6.62)	9.23(9.37)	>350	71	645.12	1.82

3.2 FT-IR spectra

The study of the FT-IR spectra of together ligands and compound delivered evidence on the coordination manner between the ligands and the metal ion *IR* Spectra. The IR spectral facts are shortened in Table 2. The infrared spectra of fluoroquinolones are fairly complex owing to the presence of the numerous functional groups in the molecules, therefore their interpretation is based on the most typical vibrations being the most important region in the IR spectra of fluoroquinolones between ~1810 and ~1320 cm^{-1} [28]. Spectra of the mixed-ligand Cu(II) complexes reveals that a broad band in the region ~3430-3450 cm^{-1} due to stretching vibration of OH group. The ν(C=O) stretching vibration band seems at ~1704 cm^{-1} in the spectra of ciprofloxacin, and the developments display this band at ~1628 cm^{-1}; this band lifted near lower energy, suggesting that coordination occurs through the pyridone oxygen atom [29]. The strong absorption bands obtained at ~1620 and ~1385 cm^{-1} in ciprofloxacin are observed at ~1580-1590 and ~1355-1385 cm^{-1} for $\nu(COO)_a$ and $\nu(COO)_s$ in the complexes, respectively; in the present case the separation frequency $\Delta\nu > 210$ cm^{-1} ($\Delta\nu = \nu$COO a - νCOO s), suggesting unidentate binding of the carboxylato group [30]. The IR spectra of the coumarin derivatives shows ~1615 and ~1755 cm^{-1} bands corresponding to *α, β*-unsaturated ketone and lactone carbonyl ketone respectively, on complexation these peaks shifted to a lower frequency ~1610 and ~1745 cm^{-1} due to complex formation. In all the complexes, a new band is seen in the ~ 535-545 cm^{-1} region, which is probably due to the formation of the weak band observed in the ~ 440-465 cm^{-1} range can be attributed to ν(M-O) [30]. (Fig.2)

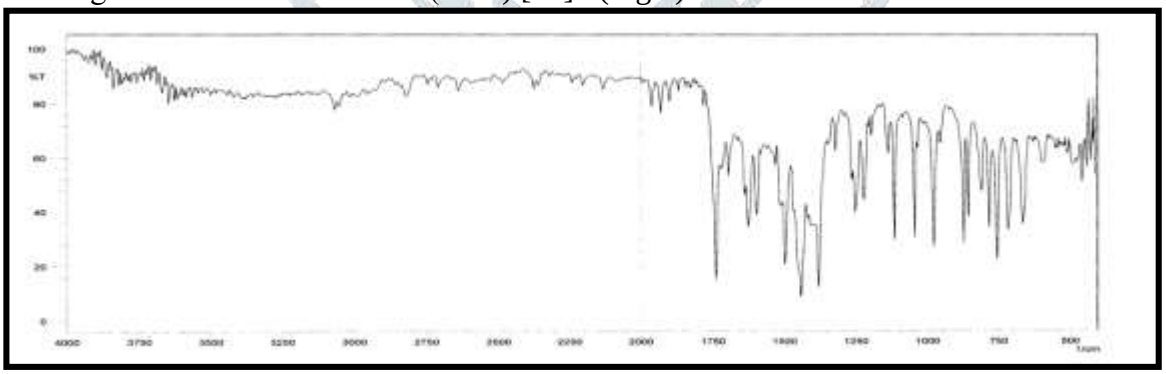


Fig.1 FT-IR spectrum of L2

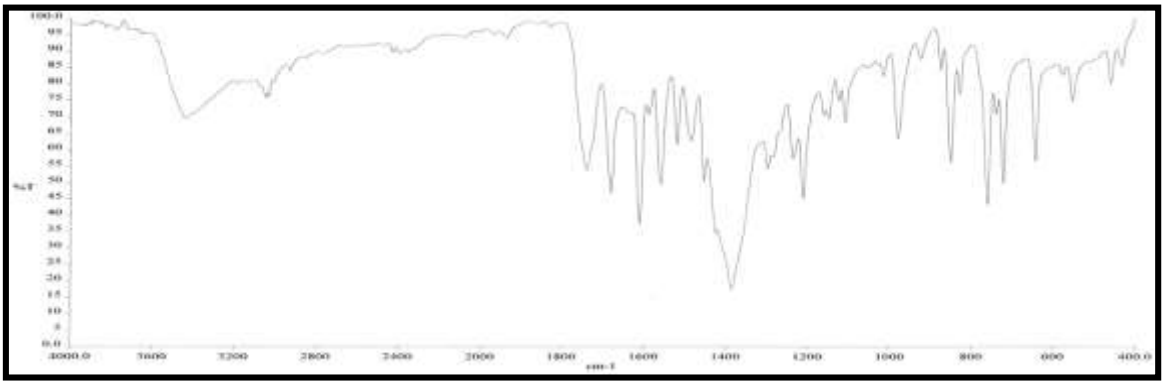


Fig.2. FT-IR spectrum of complex C2

Table 2 FT-IR data of synssthesized compounds

Complexes	ν(OH/H_2O)^{br} cm^{-1}	ν(C=N^{w} cm^{-1}	α, β-unsaturated ν(C=O) ^{s} cm^{-1}	lactone carbonyl ν(C=O) ^{s} cm^{-1}	ν(Ni-O)^{w} cm^{-1}	ν(Ni-N) ^{w} cm^{-1}
C1	3437	1545	1605	1700	461	562
C2	3422	1548	1612	1708	471	572
C3	3424	1547	1602	1721	466	558
C4	3435	1550	1606	1710	469	579
C5	3419	1540	1601	1715	468	561

s = strong, **w** = weak, **br** = broad

3.3 Electronic spectra and magnetic measurement

The Cu(II), Cu(II), Co(II), and Mn(II) complexes show magnetic moments of 1.82. 3.15, 3.86 and 5.90 B.M. respectively which is characteristic of mononuclear, Cu(II) (d^9, 1 unpaired electron) octahedral, Cu(II) (d^8, 2 unpaired electrons), Co(II) (d^7, 3 unpaired electrons), and Mn(II) (d^5, 5 unpaired electrons) complexes.[31].

The electronic spectral data of the complexes in DMF are shown in Table 3. The Cu(II) complexes display three prominent bands. Low intensity broad band in the region 16,920-17,930 cm^{-1} was assigned as 10 Dq band corresponding to $^2E_g \rightarrow {}^2T_{2g}$ transition [32]. In addition, there was a high intensity band in the region 22,900-27,100 cm^{-1}. This band is due to symmetry forbidden ligand → metal charge transfer transition [33]. The band above 27,100 cm^{-1} was assigned as ligand band. Therefore distorted octahedral geometry around Cu(II) ion was suggested on the basis of electronic spectra [34]. (Fig. 3).

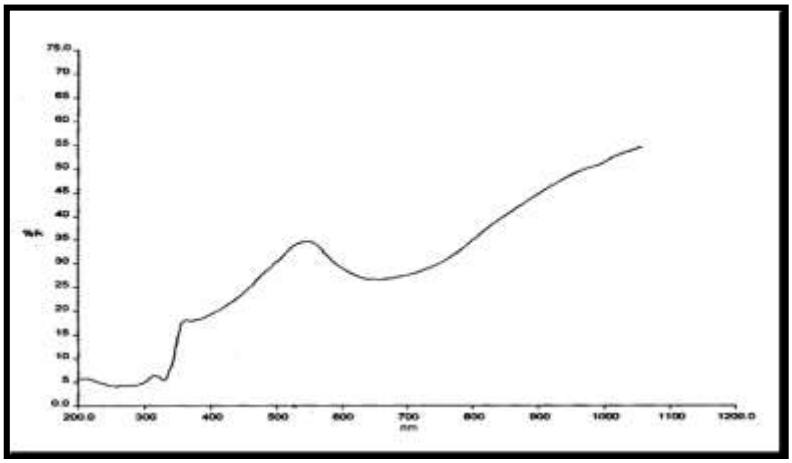


Fig.3. Electronics Spectrum of complex Cu(II)

Table 3 Electronic spectral data of the complexes

Compounds	Transition band observed (cm^{-1})		μ_{eff} B.M	Geometry
C1	17,355	25,240	1.78	Octahedral
C2	17,260	25,230	1.85	Octahedral
C3	17,290	25,295	1.84	Octahedral
C4	17,280	25,245	1.82	Octahedral
C5	17,250	25,210	1.83	Octahedral

3.4 Antimicrobial bioassay

The ligand and its metal complexes were screened for their antibacterial and antifungal activities according to the respective literature protocol [35] and the results obtained are presented in Table 4. The results were compared with those of the standard drug. All the metal complexes were more potent bactericides and fungicides than the ligand. C1 and C2 complexes were much less bacterial activity than the C4 and C5 complex while C3 complex shows superior antifungal activity compare to other complexes. From Table 4,

3.5 Antioxidant studies

A capacity to transfer a single electron i.e. the antioxidant power of all compounds was determined by a FRAP assay. The FRAP value was expressed as an equivalent of standard antioxidant ascorbic acid (mmol/100 g of dried compound). FRAP values indicate that all the compounds have a ferric reducing antioxidant power. The compounds C1 and C2 showed relatively high antioxidant activity while compound C3, C5 and C4 shows poor antioxidant power (Table 4).

Table 4 Antimicrobial, Anti-tubercular and antioxidant results of compounds

Antimicrobial Activity (Minimal Inhibition Concentration, in µg/mL)							Antioxidant Activity
Entry	Gram negative bacteria		Gram positive bacteria		Fungus		FRAP value(mmol/100 g)
	E. coli	*P. aeruginosa*	*S. pyogenes*	*B. subtilis*	*C. albicans*	*A. niger*	
L_1	400	400	400	>600	400	200	NT
L_2	100	100	100	200	200	200	NT
L_3	100	200	100	200	200	200	NT
L_4	400	200	200	600	200	200	NT
L_5	200	200	400	400	200	400	NT
C_1	100	100	100	200	100	100	54.05
C_2	70	100	100	100	100	100	63.92
C_3	40	70	40	40	100	100	82.44
C_4	100	100	100	100	200	100	75.76
C_5	70	100	70	100	100	100	86.32
Levofloxacin	NT	NT	NT	NT	10	10	NT
Nystatin	NT	NT	NT	NT	100	100	NT

E. Coli= ATCC25922; *P. aeruginosa*= ATCC25619; *S. pyogenes*= ATCC12384 ; *B. subtilis*= ATCC11774 ; *C.albicans*= ATCC 66027; *A.niger*= ATCC 64958
NT= Not tested

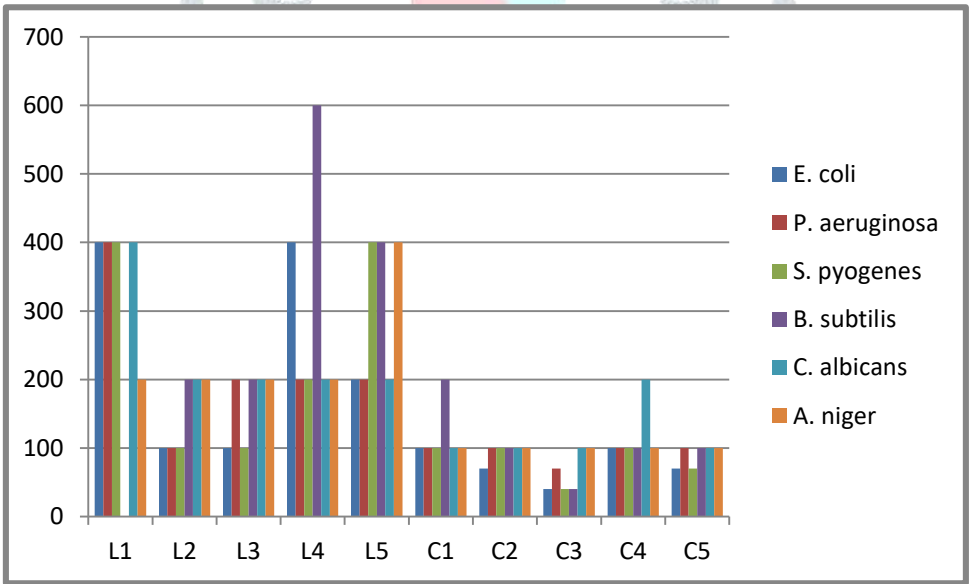


Fig. 4. Statistical representation for biological activity of ligand and its complexes.

3.5 X-ray diffraction studies

The feasible lattice dynamics of the finely powdered compound $[Cu(L^2)(LF(H_2O)OH]\bullet xH_2O$ structure was presumed on the basis of X-ray powder diffraction studies. The experiential inter planar arrangement values i.e. *d*-spacing were stately from the diffract gram of the compound. Furthermore, the Miller directories *h*, *k* and *l* were allocated to each *d* worth along with 2-Theta angles are specified in Table 5. The consequences show that the composite fits to hexagonal crystal organization having unit cell parameters as a = 4.9168, b = 4.9168, c = 5.4089, maximum deviation of 2-Theta = 0.025 and Alpha = 90, Beta = 90, Gama = 120 at the wavelength =

1.540598. We have tried to insulate single crystal of Cu(II) composite for correct X-ray crystal study but could not prosper to improve single crystal, it might be due to polycrystalline environment of complex. Conversely, the structural evidence on the popular of inorganic metal complexes is not obtainable because of the powder or polycrystalline environment of these materials. Normally it is often trying to grow good superiority single crystals of these inorganic developments. In such cases, the powder X-ray diffraction lessons might be valuable. Even with some inherent margins, this process yield respected evidence about the features of the crystal w3x. Moreover, Singh *et al*. [36] were newly stated the X-ray powder diffraction lessons for structure of hexa-coordinated Tin(IV) complex in which the ligand espouses the most stereo-chemically satisfactory alignment. On the basis of the above conversation, ensuing structures shown in Fig. 5 and Fig. 6 were suggested for the complexes.

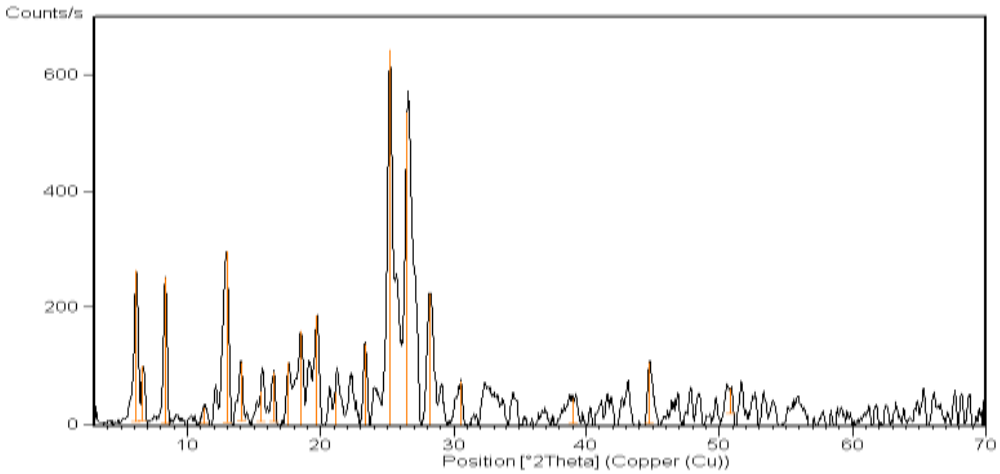


Fig. 5. X-ray patterns of complex C2 powder samples

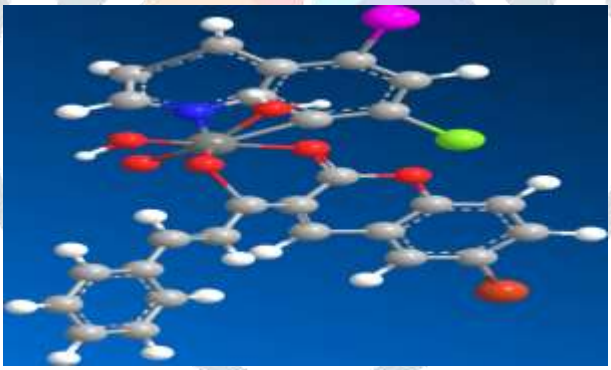


Fig. 6. 3D Molecular structures of C2

4. Conclusions

Here elucidate the synthesis of biological active coumarin derivatives and their Cu(II) complexes (C^1-C^5). Octahedral geometry were allocate for Cu(II) complexes on the basis of electronic spectra and magnetic moment. X-ray diffraction results show that the compound belongs to hexagonal crystal system with polycrystalline nature of complex which was further conformed octahydral geometry. Complexes shows momentous effective antioxidant activities compared to their ligand employed for complexation. *In vitro* antimicrobial activity of all synthesized compounds show good results with an enhancement of activity on complexation with metal ions. This enhancement in the activity may be attributed to increased lipophilicity of the complexes. The structures of the ligands were investigated and confirmed by the elemental analysis, FT-IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral studies.

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Reference:

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