Synthesis and characterization of novel chromone based N₂O ligand and its transition metal(II) complexes: NLO, analgesic and anticonvulsant study

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ABSTRACT: A new series of transition metal complexes of the type[ML.Cl] Where M=Cu(II),Ni(II),Co(II),Zn(II) and L=3-(3(1H-imidazol-1-yl) propylimino) methyl) -2-ethoxy 2H-chromen-4-ol have been designed and synthesized by the condensation of 3-formylchromone and N-(3-aminopropyl)imidazole. Elemental analysis, magnetic susceptibility, molar conductance, IR, UV–Vis, 1H NMR, 13C NMR, and EI-Mass are used to elucidate the structure of the newly prepared metal complexes. The electronic absorption spectra, magnetic susceptibility measurements suggest that tetrahedrally distorted square planar geometry for copper (II) metal complex and distorted tetrahedral geometry for other metal complexes. The ligand and its metal complexes show moderate analgesic activity compared to standard diclofenac sodium. The anticonvulsant activities of the metal complexes were found to be higher than ligand particularly in which copper complex exhibit promising result.

Key words: N-(3-Aminopropyl)imidazole,3-Formylchromone,Analgesic activity, Anticonvulsant activity.

Introduction

Chromone moiety forms an important component of pharmacophores of a number of biologically active molecules of synthetic as well as natural origin. Chromone and their derivatives are found in natural pigments in plant leaves and flowers. They are important for the synthesis of various oxygen heterocycles including xanthones and transition metal chelates [1]. They are widely present in nature and exhibit low toxicity along with a wide variety of useful properties [2]. They are reported to exhibit significant biological activities including anti-inflammatory [3] anti allergic [4] antibacterial [5] neuroprotective [6] anti HIV [7] antioxidant [8] antifungal [9] activities etc. They also display spasmolytic, cardiotonic, antiarrhythmic [10] and also anticancer properties [11]. 3-Formylchromone (4-oxo-4H-1 benzopyran-3-carboxaldehyde) has been frequently used for the synthesis of various heterocyclic derivatives ever since its convenient synthesis was reported by Nohara

et al [12]. Derivatives of 3-formyl chromone are useful synthetic building blocks in both organic and medicinal chemistry [13]. 3-Formylchromone has been chosen for the present study due to the reason that it carries three electron deficient centers viz. unsaturated keto function, a carbonyl group in the form of formyl group at position 3 and a very reactive electrophilic centre at C-2.

The remarkable biological properties of these categories of heterocycles prompted us to undertake the synthesis of schiff base obtained from N-(3-aminopropyl) imidazole and 3-formylchromone. However schiff base of N-(3-aminopropyl) imidazole with 3-formyl chromone and its substituted compounds have not been explored so far. Considering the significance of chromone and its derivatives, we investigate and report that the synthesis, structural elucidation and pharmacological activity of the Co(II), Ni(II), and Cu(II) complexes of schiff base. Non linear optical property of the ligand and its metal complexes also reported in this work.

Experimental

Materials and Methods

All chemicals were obtained from Sigma–Aldrich Chemical & Co. and used without purification. They included O-hydroxyacetophenone, $POCl_3$, N-(3-aminopropyl) imidazole Cu(II)Cl$_2$·2H$_2$O, Co(II)Cl$_2$·6H$_2$O, Ni(II)Cl2·6H2O, ZnCl2·2H2O. The solvents are ethanol petroleum ether (60–80oC), chloroform, DMF and DMSO used after purification by the standard method described in the literature [14, 15].

Physical measurements

Elemental analyses were performed at SAIF, CDRI-Lucknow. Molar conductance of the complexes (10^{-3}M) was measured in DMF at room temperature using a Systronic conductivity bridge type. The UV–Vis spectra of the ligand and metal complexes were recorded using a JASCO V-530 spectrophotometer. The IR spectra in KBr discs were recorded on a SHIMADZU FT-IR 8400S spectrophotometer. The metal contents of the complexes were estimated by incineration method [16]. The chloride ion present in metal complex was estimated by Volhard's method [17]. ^{1}H NMR spectrum was recorded using a Bruker DRX-300 MHz NMR spectrometer. EI-mass spectrum of ligand and metal complexes was recorded by JEOL-GC MATE-2 at IIT, Madras-Chennai. ESR spectrum of Cu(II) complex was recorded by Varian E-112 spectrometer at X-band, using TCNE with 100 kHz modulation frequency and 9.1 GHz microwave frequency at SAIF, IIT Bombay, India. Magnetic susceptibility of the complexes was measured by MSB mark 1 Sherwood UK at Thiagarajar College, Madurai. Effective magnetic moments were calculated using the formula μeff = 2.28(χM^T) 1/2, where χ_M is the corrected molar susceptibility. The SHG efficiency of the ligand and metal complexes were determined by modified version of powder technique at IISc, Bangalore.

Synthesis of ligand

3-Formylchromone was prepared by the Vilsmeier-Haack synthesis [18] followed by a mixture of 3-formyl chromone (1.74 g, 10mmol), and N-(3-aminopropyl) imidazole (1.25g, 10mmol), piperidine (0.05cm^3) in 25 mL of ethanol was added and stirred under reflux for 6 h. The solution was concentrated and the yellow crystalline solid obtained was filtered and recrystallized from ethanol. (Yield: 80%). m.p.128-131oC **(Fig 1.)**.

Vilsmeier-Haack Synthesis

O-Hydroxy acetophenone   3-Formyl chromone

Synthesis of ligand
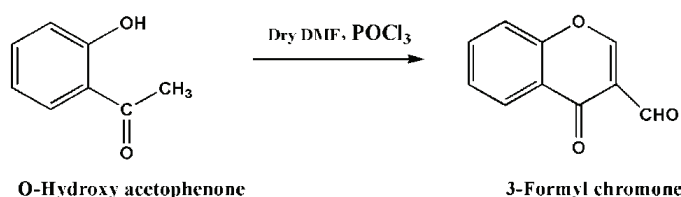
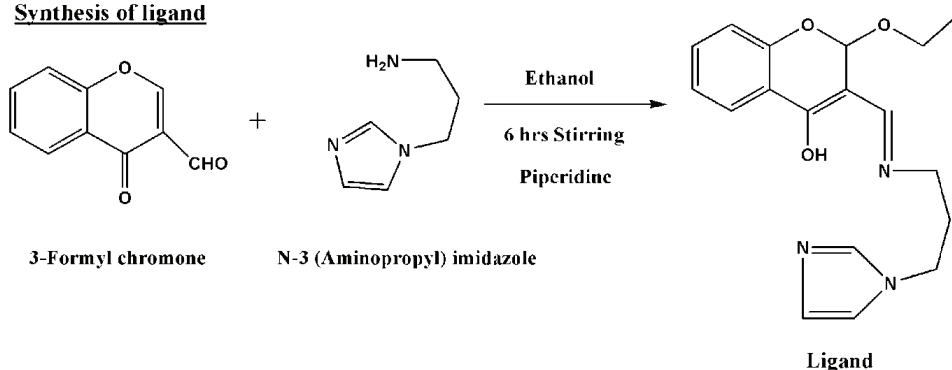3-Formyl chromone   N-3 (Aminopropyl) imidazole   Ligand

Fig 1. Synthesis of ligand

Synthesis of metal(II) complexes

The metal(II) complexes were prepared by the addition of hot ethanolic solution of the appropriate metal(II) chloride (1 mmol) [M =Cu(II), Ni(II), Co(II), and Zn(II)] to the hot ethanolic solution of the ligand (0.327g, 1mmol). The resulting mixture was stirred under reflux for 4 h and the complex precipitated out were collected by filtration, washed thoroughly with ethanol, and dried in vacuum (Yield: 76–78%).

Nonlinear optical property

The SHG (Second Harmonic Generation) efficiency of the schiff base ligand and its metal complexes were determined by the modified version of powder technique developed by Kurtz and Perry [19]. The samples were ground into powder and packed between two transparent glass slides. An Nd: YAG laser beam of wavelength 1064 nm was passed through the sample cell. The transmitted fundamental wave was absorbed by a copper (II) sulphate solution, which removes the incident 1064 nm light & Filter BG-38 removing any residual 1064 nm light. Interference filter band width was 4 nm & for central wavelength of 532 nm. Green light was finally detected by the photomultiplier tube (PMT-Philips Photonics model 8563) and displayed on the oscilloscope. The second harmonic signal was detected by a photomultiplier tube and displayed on a storage oscilloscope. The efficiency of the sample was compared with microcrystalline powder of KDP and urea. The input energy used in this particular setup was 6.5 mJ/pulse.

Pharmacology

The newly synthesized Schiff base ligand and its metal(II) complexes were evaluated for *in vivo* anticonvulsant, and analgesic activities at K.M college of Pharmacy, Madurai. Maximal electroshock method was used for establishing anticonvulsant activity, and acetic acid induced writhing reflux method was used for evaluating analgesic activity of the synthesized compounds.

Analgesic activity

Experimental model used in this study were selected to investigate narcotic analgesic activity of some tested compounds. For this purpose, acetic acid induced writhing reflux in mice to reveal narcotic analgesic activity. Painful reaction in animals may be produced by the chemicals such as phenylquinone, bradykinin etc. Like that, acetic acid induced pain reaction which is characterized as a writhing response. Construction of abdomen, turning of trunk (twist) and extension of hind legs are taken as reaction to chemically induced pain. Analgesics (both narcotic and non-narcotic) inhibit writhing response. In this method, healthy male albino Wister mice weighing from 200-250 g were selected and kept in animal house under standard laboratory conditions. The animals were divided into six groups of six each. The first groups of animals were served as control, received 10 ml/kg normal saline. Second group served as standard which received 10 mg/kg diclofenac sodium through I.P. The newly synthesized ligand and its metal(II) complexes (10 mg/kg) were administered by IP injection to the rest of the four groups. Then after 30 minutes acetic acid induced pain reaction started by administrating 1% acetic acid of volume 1ml to the animals of six groups. Duration of writhing response noted including abdominal contractions, trunk twist and extension of hind limbs. The number of animals protected in each group was recorded and percentage protection was calculated. Then the comparison between the narcotic analgesic activity of the tested compounds and the standard diclofenac sodium carried out followed by weak, moderate and potent analgesic activity were reported.

Anticonvulsant activity

The anticonvulsant activity was studied by Supra maximal electrical shock method. Healthy male albino Wistar mice weighing from 200-250 g were selected and housed in separate cages with 12/12 h light/dark cycle at 21 + 2 °C and fed with balanced diet, water ad libitum. The animals were divided into six groups of six each. The first groups of animals were served as control, received 10 ml/kg normal saline. Second group served as standard which received 10 mg/kg phenytoin sodium. The Schiff base ligand and its metal complexes (10 mg/kg) were administered by IP injection to rest of the four groups. The evaluation was started 30 min after administration of the synthesized compounds and Pinna electrodes with the intensity of 150 mA current were used to deliver the stimuli. The time needed for the development of unequivocal sustained clonic seizure activity involving the limbs was carefully noted. The onset of a general clonus was used as the end point. The general clonus was characterized by forelimb clonus followed by full clonus of the body. The duration of clonic convulsions was also noted. Seizure-free interval in 1 h was considered as protection. The number of animals protected in each group was recorded and percentage protection was calculated.

Results and discussion

From the ^{1}H NMR, ^{13}C NMR and elemental analysis, it is observed that the addition of an ethanolate-anion [20] to a molecule of 3-formylchromone in position 4 and this phenomenon is also confirmed by mass spectrum. The tridentate ligand forms stable complex with Cu(II), Ni(II), Co(II) & Zn(II). The complexes have been characterized by IR UV-vis, and ^{1}H NMR, EPR spectra, magnetic susceptibility measurement and molar conductance. The analytical data and physical properties of ligand and metal(II) complexes are summarized in **Table 1**. Elemental analyses of the complexes were in good agreement with calculated values for 1:1 (M: L) ratio. Based on the elemental analyses & mass spectra the stoichiometry type [ML.Cl] was suggested for the metal complexes. The proposed structure of the metal complexes is given in **Fig 2**.
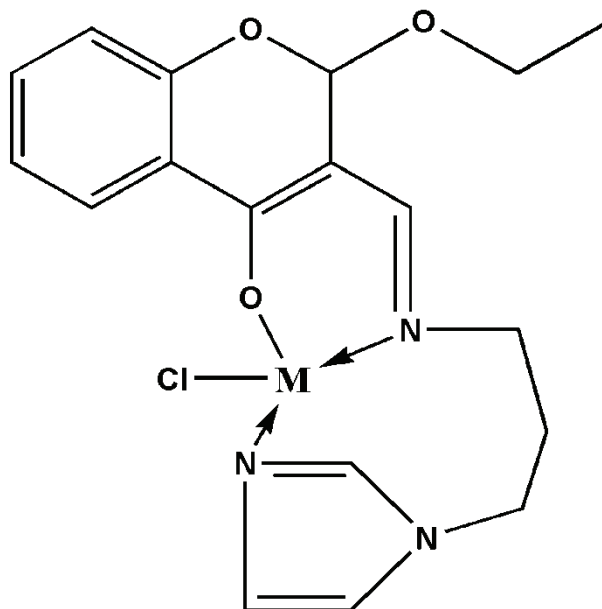

Fig 2. The proposed structure of the metal complexes

Table 1. Analytical and physical data of ligand and its metal (II) complexes

No	Compounds	F.W (gm)	Color	m.pt (°C)	Experimental (Calc) (%)					λ_M [a]
					M	C	H	N	Cl	
1	$C_{18}H_{21}N_3O_3$ (L)	327.15	Yellow	126	-	66.02(66.07)	6.48 (6.47)	12.80(12.83)	-	-
2	$CuC_{18}H_{20}N_3O_3Cl$	425.14	Green	151	14.91(14.94)	50.78(50.84)	4.77(4.74)	9.80(9.87)	8.36(8.33)	11
3	$CoC_{18}H_{20}N_3O_3Cl$	420.52	Green	140	14.04(14.01)	51.37(51.40)	4.71(4.79)	9.92(9.98)	8.39(8.43)	07
4	$NiC_{18}H_{20}N_3O_3Cl$	420.28	Brown	187	13.89(13.96)	51.39(51.43)	4.72(4.79)	9.96(9.99)	8.40(8.43)	14
5	$ZnC_{18}H_{20}N_3O_3Cl$	426.98	Yellow	165	15.33(15.31)	50.67(50.63)	4.69(4.72)	9.79(9.83)	8.36 (8.30)	12

[a] $(\Omega^{-1}cm^{-2}mol^{-1})$

Mass Spectra

The EI mass spectrum of the ligand was compared with the nickel(II) complex to obtain the stoichiometry composition of metal chelates. Mass spectrum of the ligand showed a peak at m/z 328.15 corresponding to the molecular ion peak. The molecular ion peak for the nickel(II) complex observed at m/z 420.51 confirms the stoichiometry of metal(II) complexes as [ML.Cl]. Mass spectra of the ligand and its Nickel (II) complex are shown in **Fig 3.& Fig 4.**

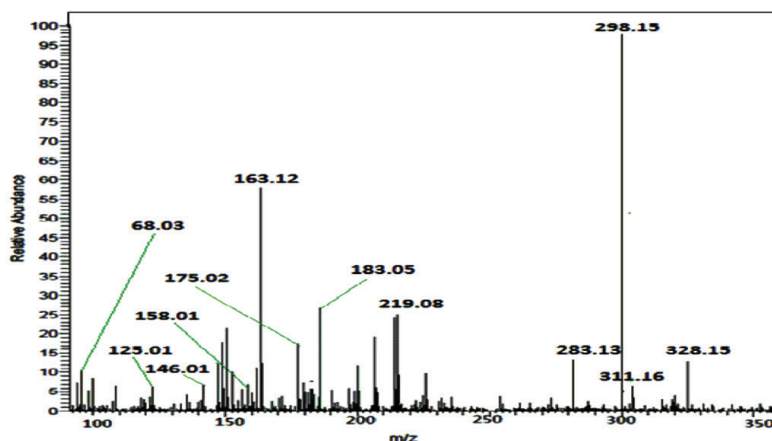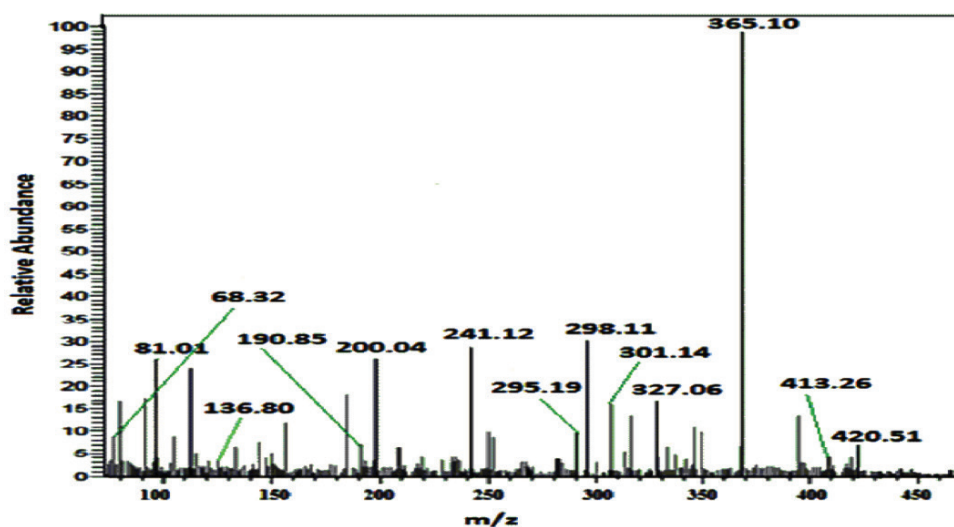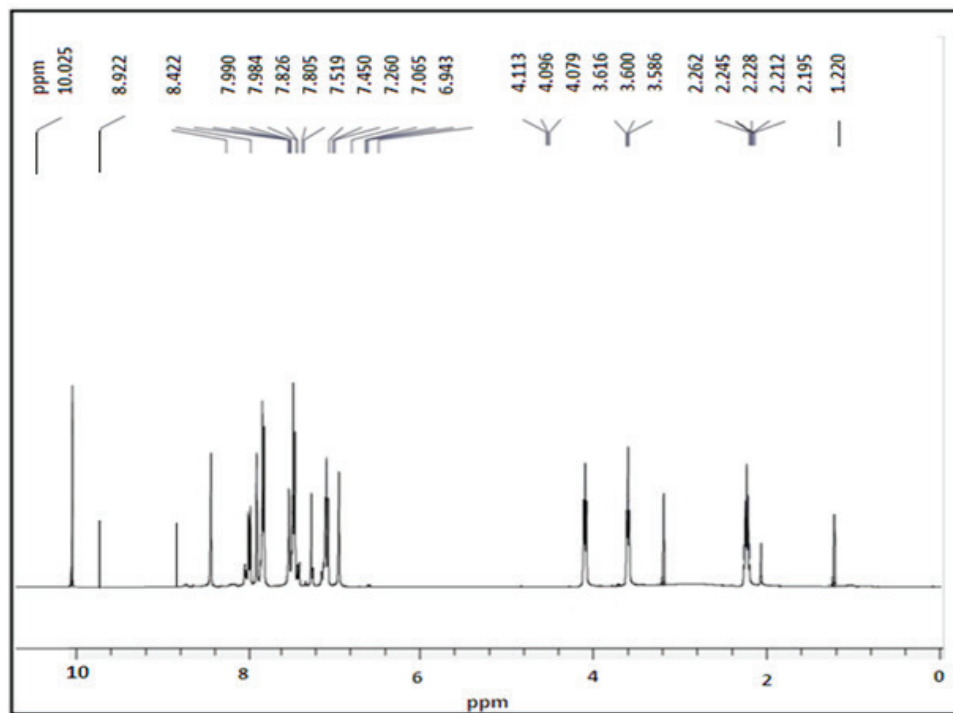**Fig 3.** Mass spectra of the ligand

Fig 4. Mass spectra of the Nickel complex

^{1}H NMR Spectra

The ^{1}H NMR spectrum of the ligand recorded in CDCl$_3$ is assigned as follows: azomethine proton as singlet (s, 8.92 δ), hydroxyl proton as singlet (s, 10.02 δ), imidazole proton as singlet (s, 8.42 δ), aromatic proton as multiplet at 6.94-7.99 δ, -OCH$_2$ proton as quartet at 3.60-3.61 δ, -CH$_3$ as triplet at 1.22 δ, CH$_2$-CH$_2$-**CH$_2$**-N at 4.07- 4.11 δ (2H, t), CH$_2$-**CH$_2$**-CH$_2$-N at 2.19-2.26 δ (2H, m), **CH$_2$**-CH$_2$-CH$_2$-N at 3.58 δ (2H, t) [21].

^{1}H NMR spectrum of Zn(II) complex have the azomethine and imidazole proton signal shifted downfield at 9.321δ & 8.832δ respectively, compared to the free ligand suggesting coordination via azomethine nitrogen and imidazole nitrogen. The absence of OH proton signal in the zinc(II) complex indicates that deprotonation of the ligand takes place and coordination through the enolic oxygen. ^{1}H NMR spectra of the ligand and its Zinc(II)complex are shown in **Fig 5 & Fig 6**.
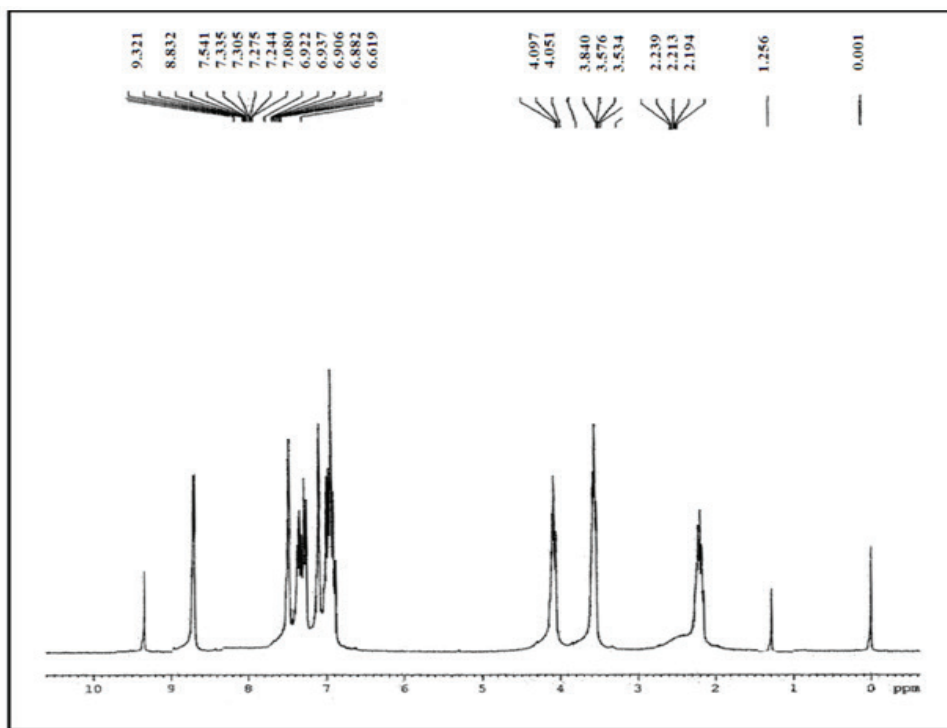

Fig 5. ^{1}H NMR spectra of the ligand

Fig 6. ¹H NMR spectra of the Zinc complex

¹³C NMR Spectrum

The **¹³C** NMR (DMSO, δ, ppm) spectrum of the ligand has following signals. δ = 15.02 (CH$_3$); δ = 64.53 (CH$_2$); δ = 118- 136 (aromatic carbons); δ = 164 (CH=N); δ = 176 (C=N imidazole ring); δ = 151 (Carbon bearing hydroxyl group) [22]. The ¹³C NMR spectrum of the ligand is shown in **Fig 7**.
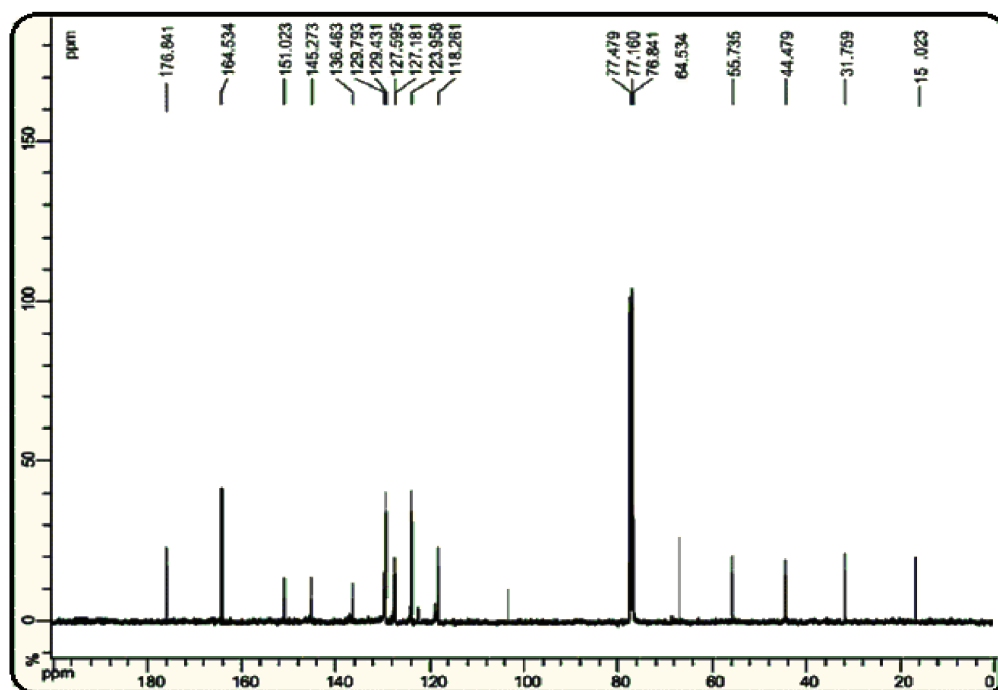

Fig 7. ¹³C NMR spectrum of the ligand

Electronic absorption spectra and magnetic susceptibility

The electronic spectra were recorded in chloroform and are presented in **Table 2**. The absorption spectra of the ligand show strong peaks at 26,315 and 33,670 cm^{-1} arising from π-π* and n-π* transitions. The cobalt(II) complex exhibits two peaks at 14,556 and 16,528 cm^{-1} which are closer and it can be assigned tentatively to $^4A_2(F) \rightarrow {}^4T_1(P)$ transition for the tetrahedral geometry [23]. The magnetic susceptibility value 4.20 B.M. also confirms the above geometry [24].

Nickel(II) complex exhibits absorption bands at 12,820 and 15,151 cm^{-1} due to $^3T_1(F) \rightarrow {}^3T_1(P)$ transition characteristic of tetrahedral geometry [25].The observed magnetic moment is 2.92 B.M. which is in the normal range (2.9–3.9 B.M.) for tetrahedral nickel(II) complex[26]. The copper(II) complex shows band at 13,513 cm^{-1} which can be tentatively assigned to the $^2B_{1g} \rightarrow {}^2A_{1g}$ transition of tetrahedrally distorted square planar [27] and the magnetic moment value of 1.71 B.M falls within the range normally observed for square planar copper(II) complexes [28].

Table 2. Magnetic moment and electronic spectral data of metal(II) complexes

No	Compound	λ_{max} (cm^{-1})	Transition	Geometry	μ_{eff} (B.M)
1	$C_{18}H_{21}N_3O_3$ (L)	26,315 33,670	ILCT[a] ILCT	-	-
2	$C_{18}H_{20}N_3O_3CuCl$	13,513	$^2B_{1g} \rightarrow {}^2A_{1g}$	tetrahedrally distorted Square planar	1.71
3	$C_{18}H_{20}N_3O_3CoCl$	14,556 16,528	$^4A_2(F) \rightarrow {}^4T_1(P)$	distorted tetrahedral	4.20
4	$C_{18}H_{20}N_3O_3NiCl$	12,820 15,151	$^3T_1(F) \rightarrow {}^3T_1(P)$	distorted tetrahedral	2.92

[a]Intra ligand charge transfer.

Table 3. IR spectral data of the ligand and its metal(II) complexes(cm^{-1})

No	Compounds	Vibrational Frequencies (cm^{-1})						
		v (OH)	v (C=N)	v (C=N) of Imidazole ring	v (C-O)	v (M-N)	v (M-O)	v (M-Cl)
1	$C_{18}H_{21}N_3O_3$ (L)	3380	1635	1620	1261	-	-	-
2	$C_{18}H_{20}N_3O_3CuCl$	-	1630	1610	1271	462	560	342
3	$C_{18}H_{20}N_3O_3CoCl$	-	1619	1605	1275	452	562	351
4	$C_{18}H_{20}N_3O_3NiCl$	-	1612	1595	1280	461	550	358
5	$C_{18}H_{20}N_3O_3ZnCl$	-	1618	1590	1267	478	565	368

IR Spectra

The spectral data for ligand and its complexes are presented in **Table 3**. In the infrared spectrum of the ligand the formation of condensation product was observed by the absence of parent bands at 1740 and 3340,3450cm^{-1} originally attributed to (C=O) of aldehyde and the (NH$_2$)

group of 3-formylchromone and N (3-aminopropyl) imidazole, respectively. The spectrum of the ligand shows a band at 3380 cm^{-1} which is assigned to (OH) stretching vibration. A strong new band appeared at 1635cm^{-1} confirming the azomethine linkage [29]. Also the ligand shows a band at 1620 cm^{-1} which is attributed

to ʋ (CH= N) of the imidazole ring. The phenyl group shows ʋ (CH) at 3052 cm⁻¹ and ʋ(C=C) at 1545 cm⁻¹. The band at 1261cm⁻¹ is assigned to ʋ(C–O) of the enolic OH group [30]. The ligand as well as their coordinating complexes show peaks at 2886 and 2944 cm⁻¹ due to C–H stretching in CH_2 group of N (3–aminopropyl) imidazole molecule. Considering the IR spectra of the ligand is compared with that of its metal(II) complexes in which ʋ (CH= N) due to azomethine vibration is shifted to a lower frequency (10–19 cm⁻¹) indicating the coordination of azomethine nitrogen to the metal(II) ion [31]. A shift in the band at 1620 cm⁻¹ of the imidazole ring (1605–1590cm⁻¹) in complexes suggesting the coordination via imidazole nitrogen (N⟶M) [32]. The participation of deprotanated OH group is confirmed by the blue shift (1267–1280 cm⁻¹) of ʋ(C–O) in the complexes. In addition, the IR spectra of complexes show new nonligand bands at 452–478 cm⁻¹ and 550–565 cm⁻¹ assigned to ʋ(M–N) and ʋ(M–O) modes respectively [33,34]. Furthermore, the IR spectra of the all complexes showed another band at 342–368 cm⁻¹which may be due to ʋ (M–Cl) vibrations [35].Therefore, the above arguments together with the elemental analyses indicated that ligand behaves as a monobasic tridentate ligand coordinated to the metal(II) ions via the azomethine nitrogen, imidazole nitrogen enolic oxygen and chlorine.

NLO study

From the experimental data, the ligand exhibits second harmonic efficiency 0.3times less than urea and 1.1times more than KDP. The metal complexes exhibits second harmonic efficiency 0.4 times less than urea and 1.6 times higher than KDP.The SHG (second harmonic generation) efficiency of the ligand and its metal complexes is presented in **Table 4**.Thus from the NLO table values we concluded that the ligand and its metal(II) complexes are NLO active with respect to KDP and NLO inactive with respect to urea. In general a molecule with delocalized π-electron system can have large nonlinear polarizabilities [36] and it has is generally understood that the molecular nonlinearity can be enhanced by systems with strong donor and acceptor groups [37]. From the analysis of electronic transitions and molecular orbital involved, ligand orbital can improve the NLO properties.

Table 4. SHG parameters of the ligand and its metal(II) complexes

Compound	Measured SHG Efficiency (mV)	SHG Efficiency of KDP (mV)	SHG Efficiency with respect KDP	SHG Efficiency of urea (mV)	SHG Efficiency with respect to Urea
$C_{18}H_{21}N_3O_3$ (L)	33	29	1.1	115	0.3
$C_{18}H_{20}N_3O_3CuCl$	47	31	1.5	117	0.4
$C_{18}H_{20}N_3O_3NiCl$	49	31	1.6	117	0.4

ESR Spectra

ESR spectrum of the Cu (II) complex was recorded at room temperature and liquid nitrogen temperature and it provide important information for studying the metal ion environment (**Fig 8.**). The spin Hamiltonian parameters calculated for the copper complex are given in **Table 5**. The spectrum of the copper complex at room temperature shows one intense absorption in the high field and is isotropic due to tumbling of the molecules. However, this complex in frozen state shows four well-resolved peaks at low field. The trend g‖(2.311) > $g_⊥$ 2.031) > g_e(2.002) shows that the unpaired electron localized in the d_x^2-d_y^2orbital, characteristic of tetrahedrally distorted square planar geometry in Cu(II) complex [38]. The fact g‖ ((2.311) > $g_⊥$(2.031) suggests that the complex is square planar. The unpaired electron lies predominately in the d_x^2-d_y^2 orbital is supported by exchange interaction term G estimated from the expression;

$$G = (g‖ - 2.0023) / g_⊥ - 2.0023)$$

If G > 4.0, the local axes are aligned parallel or only slightly misaligned. If G < 4.0 significant exchange coupling is present and the misalignment is appreciable. The observed value for the exchange interaction parameter for the copper complex (G > 4.0) suggest that the local tetragonal axes are aligned parallel or slightly misaligned and the unpaired electron is in d_x^2-d_y^2orbital [39-42].Kivelson and Neiman showed that for an ionic environment g‖ is normally 2.3 or larger, but for a covalent environment g‖ are less than 2.3. The g‖ value for the Cu(II) complex is 2.311 consequently the environment is ionic. The g‖ /A ‖ ratio can be used as an empirical convenient of distortion from square-planar structure [43]. The value of the g‖ / A ‖ ratio for Cu complex is 161cm indicate nearly square-planar environments with tetrahedral distortion [44]. The orbital reduction factors

K∥ and K⊥ were calculated and reported that for pure σ bonding K∥ ≈ K⊥ ≈ 0.77, for in-plane π bonding K∥ < K⊥, and for out-of-plane π bonding K∥ > K⊥. The K∥, K⊥ value in complex is in agreement with the relation K∥ > K⊥ which indicates the presence of out-of plane π bonding.

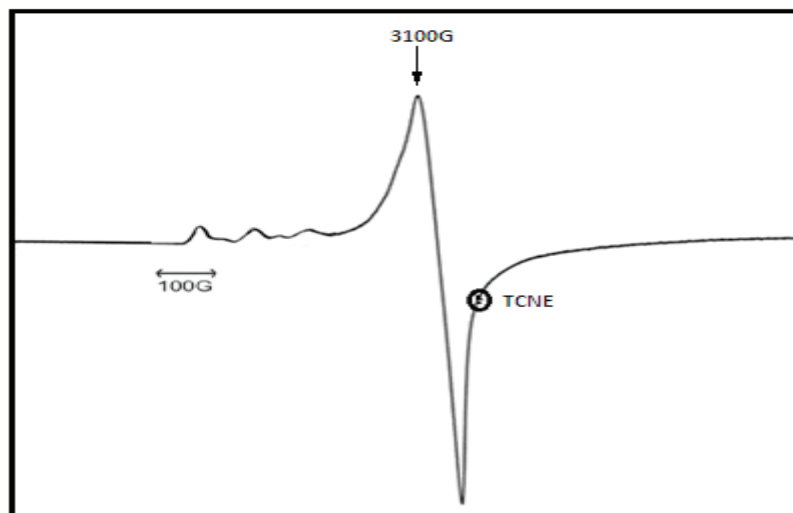**Fig 8.** ESR spectrum of the Cu (II) complex

Table 5. The spin Hamiltonian parameter of the Copper complex at 77K in DMSO

Complex	g∥	g⊥	A∥ (10⁻⁴ cm⁻¹)	A⊥	α^2	β^2	K∥	K⊥
Cu Complex	2.311	2.031	143	20.11	0.811	0.982	0.792	0.661

Scanning electron microscopy

The surface morphology and particle size of the synthesized ligand and its copper complex have been studied by using scanning electron microscopy (**Fig 9a. and 9b.**) depicts the SEM photograph of the synthesized ligand and its copper complex of schiff base . In the pictograph of ligand we noted that there is a rigid like morphological structure and few micro crystallites are in agglomerated form. Porous region also found. The particle size of the ligand was found to be 2μm in size. However in the pictograph of copper complex particles are found to be grain like morphological structure and the particle size was 1μm. It is inferred from scanning electron microscopy that both the synthesized ligand and its copper complex have different particle size due to the influence of metal ions and dealing with homogeneous phase material.
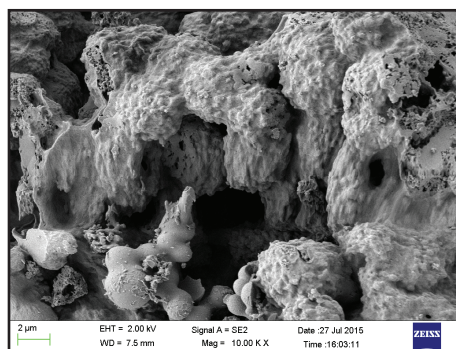

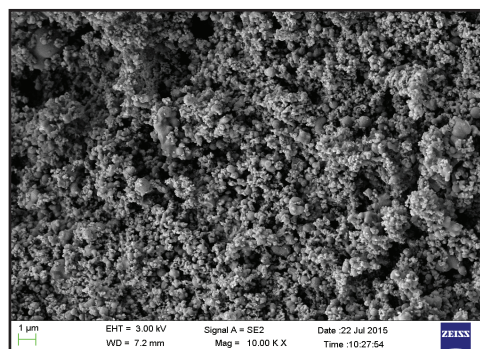**Fig 9a.** SEM images of ligand

Fig 9b. SEM images of copper complex

Analgesic activity

Analgesic activity is one of the most important therapeutic effects as pain is a part of nearly every disease. Secondly, analgesic activity is usually associated with large number of other important pharmacological actions. Thus, positive result offers valuable lead for other important pharmacological studies. Most of the analgesic drugs act either as opioids or as NSAIDs so if a compound is shown to possess opioid analgesia it may also have sedative anti-tussive and anti diarrhoeal activity. Whereas, possession of aspirin-like analgesia is likely to be associated with anti-inflammatory and anti-pyretic activity, therefore, analgesic activity was chosen and carried out for synthesized ligand and its metal(II) complexes **Fig 10**.The mechanism of

action of diclofenac sodium as analgesic standard seems to be the same that as anticonvulsant. Diclofenac sodium appears to act on areas of the limbic system, thalamus, and hypothalamus. Its actions are due to the enhancement of GABA activity. Diclofenac sodium increases the inhibitory processes in the cerebral cortex. From the **Table 6.** it is found that the newly synthesized schiff base ligand its metal complexes possess moderate analgesic activity compared to the standard diclofenac sodium. Among all the metal complexes, the percentage inhibition shown by the copper complex was 61 % and it was significant and comparable with the standard drug diclofenac sodium 83 %. The enhanced analgesic activity of the complexes may be explained on the basis of enhanced penetration through cellular membranes due to complexation [45].
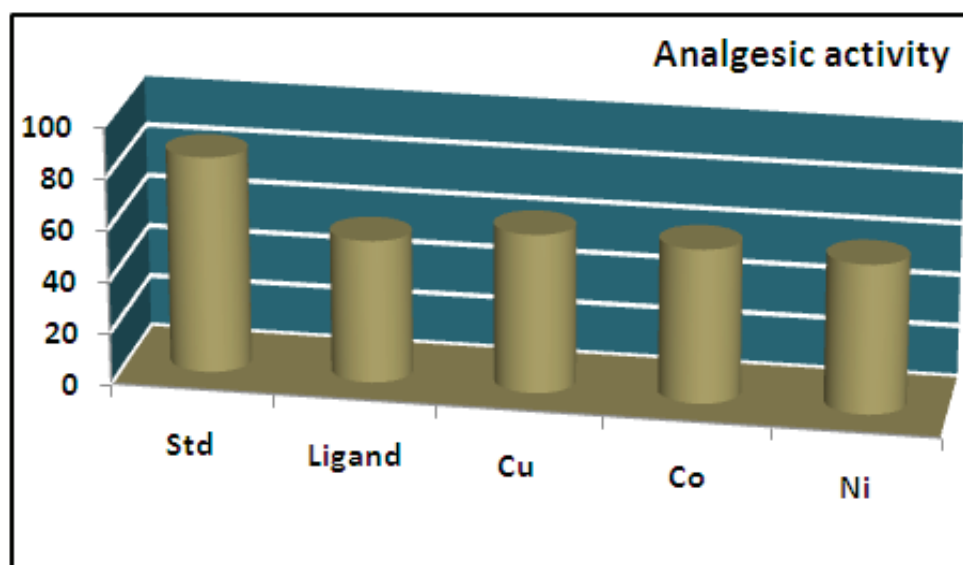

Fig 10. Analgesic activities of ligand and its metal complexes

Table 6. Analgesic activity of the ligand and its metal(II) complexes

Compound	Dose (mg/kg)	Duration of writhing (Minutes)	% of inhibition
Control	10	45.00±1.46	-
Diclofenac Sodium	10	7.33±0.33	83.71
$C_{18}H_{21}N_3O_3$ (L)	10	20.16±0.47	55.20
$C_{18}H_{20}N_3O_3CuCl$	10	17.33±0.49	61.48
$C_{18}H_{20}N_3O_3CoCl$	10	18.16±0.30	59.64
$C_{18}H_{20}N_3O_3NiCl$	10	19.00±0.63	57.77

Data are given as mean ± S.E.M (n = 6).

Anticonvulsant activity

Anticonvulsant activity data of the schiff base ligand and its metal complexes are presented in **Table 7** and the graphical representation is shown in **Fig. 11**. The results were statistically analyzed by one-way ANOVA followed by Newman keul's multiple range tests and expressed as mean ± SEM (n=6). The results of the schiff base ligand and its metal(II) complexes are satisfactory on comparison with that of phenytoin sodium which is used asthe standard anticonvulsant drug. It has been reported that the existence of a hydrophobic unit, an electron donor group, and hydrogen bonding domain are essential for anticonvulsant activity. As evidenced by the active drugs, such as carbamazepine and lamotrigine. The synthesized

Schiff base fulfills these demands. The percentage of inhibition shown by

ligand was 68%. All the synthesized metal(II) complexes showed higher anticonvulsant activity on animals for a longer duration when compared to schiff base ligand. Among all the metal complexes, the percentage inhibition shown by the copper complex was 70 % and it was significant and comparable with the standard drug diclofenac sodium 83 %. Such increased activity of the metal complexes is of tremendous importance in pharmaceutical field [46]. Procedures employed for evaluation of anticonvulsant and analgesic activity were reviewed and approved by the Institutional Animal Ethical Committee (IAEC).
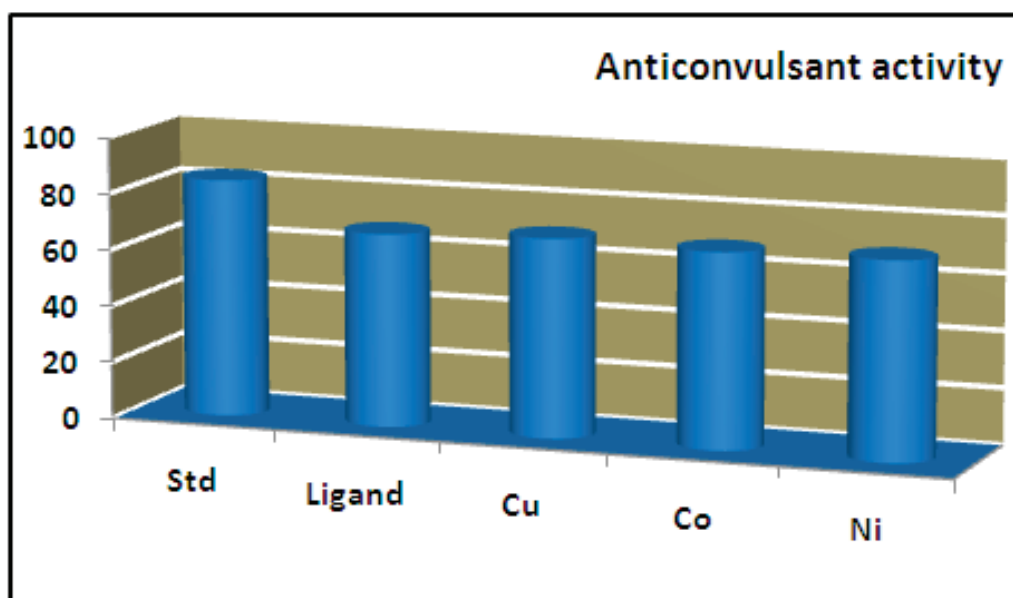

Fig 11. Anticonvulsant activities of ligand and its metal complexes

Table 7. Anticonvulsant activity of the ligand and its metal(II) complexes

Compound	Dose (mg/kg)	Duration of seizure	% inhibition of extension phase
Control	10	13.05 ± 2.20	-
Phenytoin Sodium	10	2.10 ± 0.32	83.90
$C_{18}H_{21}N_3O_3$ (L)	10	5.15 ± 0.96	60.53
$C_{18}H_{20}N_3O_3CuCl$	10	3.80 ± 0.08	70.88
$C_{18}H_{20}N_3O_3CoCl$	10	4.65 ± 0.90	64.36
$C_{18}H_{20}N_3O_3NiCl$	10	4.91 ± 0.70	62.37

Data are given as mean ± S.E.M (n = 6).

Conclusion

Transition metal complexes of ML.Cl type of novel chromone based ligand 3-(3(1H-imidazol-1-yl) propylimino)methyl)-2-ethoxy 2H-chromen-4-ol have been synthesized and characterized by spectral and analytical methods. Based on the analytical and spectral data, it is concluded that the ligand act as tridentate forming tetrahedrally distorted square planar geometry with Cu(II) ion and distorted tetrahedral geometry with Co(II),Ni(II), and Zn(II). The metal(II) complexes of the ligand are exhibit excellent NLO property. The synthesized compounds exhibit promising *in vivo* anticonvulsant, and analgesic activity. Our finding suggests that the synthesized compounds may be utilized for further investigations to be formulated as a useful drug.

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