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SYNTHESIS, SPECTROSCOPIC CHARACTERIZATION AND BIOLOGICAL STUDIES OF COPPER (II), NICKEL (II), COBALT (II) AND ZINC (II) COMPLEXES DERIVED FROM CURCUMINO – 4 AMINOANTIPYRINE AND TRYPTOPHAN

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ABSTRACT

Neutral tetradentate N_2O_2 donor type Schiff base has been synthesized by condensing curcumino-4-aminoantipyrine and tryptophan in ethanol. Solid metal complexes of the Schiff base with Cu(II), Ni(II), Zn(II) and Co(II) metal ions have been synthesized. All the complexes were characterized by elemental analysis, molar conductivity, magnetic susceptibility data, IR, ^{1}H-NMR, UV-Vis., spectral studies. The physico-chemical studies and spectral data indicates that the ligand act as a divalent tetradentate chelating agent. All the complexes have the general composition [ML] (M= Cu(II), Ni(II), Co(II) and Zn(II); L = Schiff base). The IR, UV-Vis., magnetic susceptibility measurements of the complexes suggests that all the complexes are tetrahedral geometry. The lower conductivity data confirm the non-electrolytic nature of the complexes. The Schiff base and their metal complexes were utilized to test the in vitro antimicrobial activities, which gave good results in the presence of metal ion than the free ligand environment against the different species of microorganisms such Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococci and the fungi Candida albicans.

Keywords: Antimicrobial Studies, Curcumino-4-Aminoantipyrine, IR, Tryptophan,

I. INTRODUCTION

Schiff bases derived from aromatic amines and aromatic aldehydes have a wide variety of applications in biological, inorganic and analytical chemistry. Earlier works, related to the chelating behaviour of β-diketones in metal chelates give more information about the nature of coordination, structural and spectral properties. The coordinating property of 4- aminoantipyrine has been modified into a flexible ligand system by condensation it with β-diketones and amines. In recent years, a number of research articles have been published on transition metal complexes derived from 4-aminoantipyrine derivatives with aza or aza-oxo donor atoms. A search

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through the literature reveals that no work has been done on the transition metal complexes of Schiff bases formed by the condensation of curcumino-4-aminoantipyrine with tryptophan [1-10] We report here in the synthesis, characterization, and biological studies of transition metal complexes containing Schiff base derived from curcumino-4-aminoantipyrine and tryptophan.

II. EXPERIMENTAL

All the reagents, 4-aminoantipyrine, curcumin, tryptophan and the metal salts were purchased from Merck. Melting point of the ligand and complexes were determined on electrochemical capillary apparatus. Elemental analysis was obtained by using a thermal finger- flash CA, 112 series at sophisticated analytical instrumentation facility, IIT, Mumbai. The IR spectra of the samples were recorded on a FT- IR Shimadzu model (8400S) in a KBr pellets and electronic spectra in acetonitrile were recorded using Shimadzu model (1800) spectrophotometer. Conductivity measurements were carried out at room temperature on freshly prepared 10^{-3} M acetonitrile solution was measured using a 305 model systronic conductivity bridge with a dip type cell. ^{1}H NMR spectra of the Schiff base and its zinc complex were recorded in $CDCl_3$ solution on a Brucker 300 MHz FT-NMR spectrometer using TMS as internal standard at Madurai Kamaraj University, Madurai. Magnetic susceptibility of the complexes was measured by Guoy balance using copper sulphate as calibrant. The antimicrobial activities of the ligand and their complexes were carried out by disc diffusion method. Analgesic, antipyretic and CNS activities of curcumino-4-aminoantipyrinyl-tryptophan Schiff base were studied using albino rats. Animals were divided into three groups, each consisting of three animals. Group 1 served as control and group 2 received standard drug. Group 3 received 250 mg/kg Schiff base. For the determination of antipyretic activity, pyrexia was induced by 20% yeast suspension. The analgesic activity was determined by tail immersion method. CNS depressant activity of the compound was measured by placing the rat individually in the actophotometer for 10 min. The results obtained showed that the Schiff base was found to exhibit analgesic, antipyretic and CNS activities.

2.1 Synthesis of Schiff base

2.1.1 Synthesis of curcumino- 4- aminoantipyrine

An ethanolic solution (50 ml) of 4-aminoantipyrine (2.03 g, 0.01 mol) and 1, 7-bis(4′ hydroxyl-3′ methoxy phenyl)-1,6-heptadiene-3,5-dione (curcumin) (3.68 g, 0.01 mol) was boiled under reflux on a water bath for 6 hours then concentrated to 10 ml, by heating on a water bath and allowed to cool at 0 ^{o}C for 3 hours. The resulting red orange residue, curcumino- 4- aminoantipyrine obtained was treated with 10 ml of petroleum ether (40-60 ^{o}C) with constant stirring. The separated red orange solid (curcumino-4-aminoantipyrine) was filtered and recrystallized in methanol. The Schiff base derived by the condensation of curcumin and 4-aminoantipyrine is given in the scheme I:

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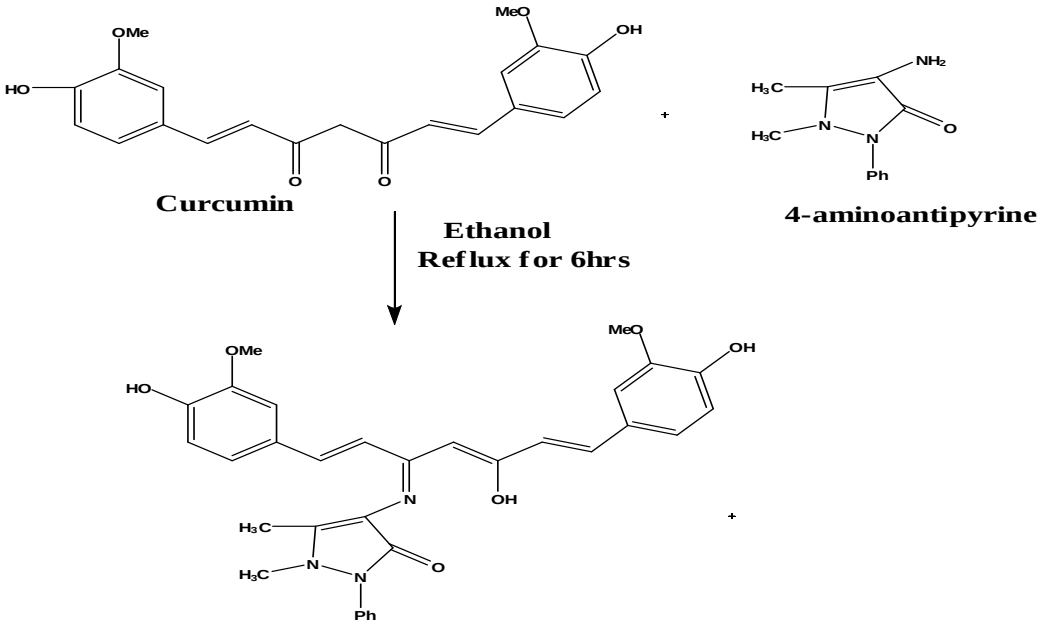
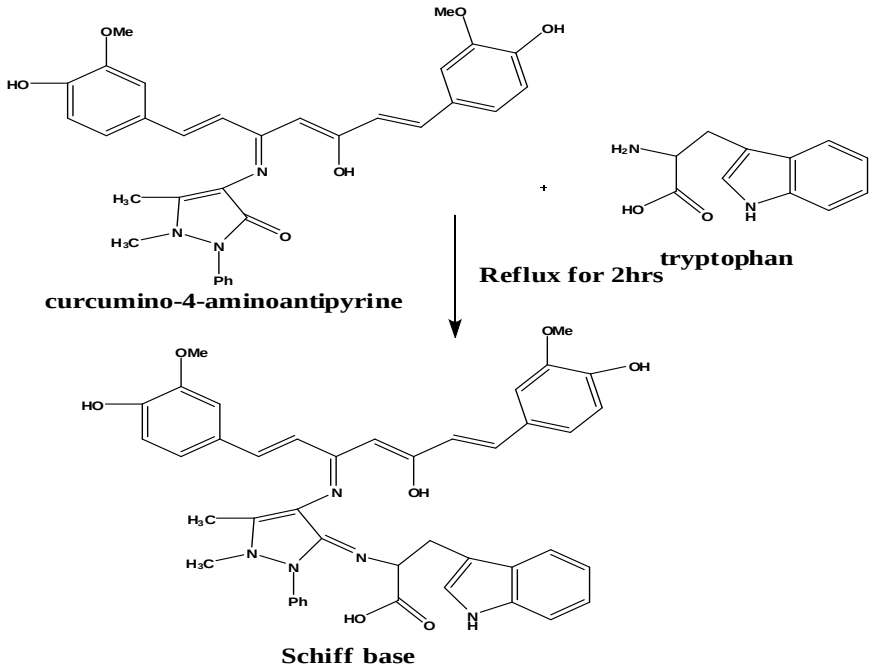
2.1.2 Synthesis of Schiff base

An ethanolic solution curcumino-4-aminoantipyrine and (0.01 mol) and tryptophan.(0.01 mol) was boiled under reflux on a water bath for 3hrs. Then the resulting solution was concentrated to 10ml and stirred with 5ml of ammonia solution. The solid obtained was collected by filtration and recrystalised from ethanol. The Schiff base was derived by the condensation of curcumino – 4aminoantipyrine and tryptophan is given the scheme – II.



scheme I: Curcumino-4-aminoantipyrine



SCHEME II

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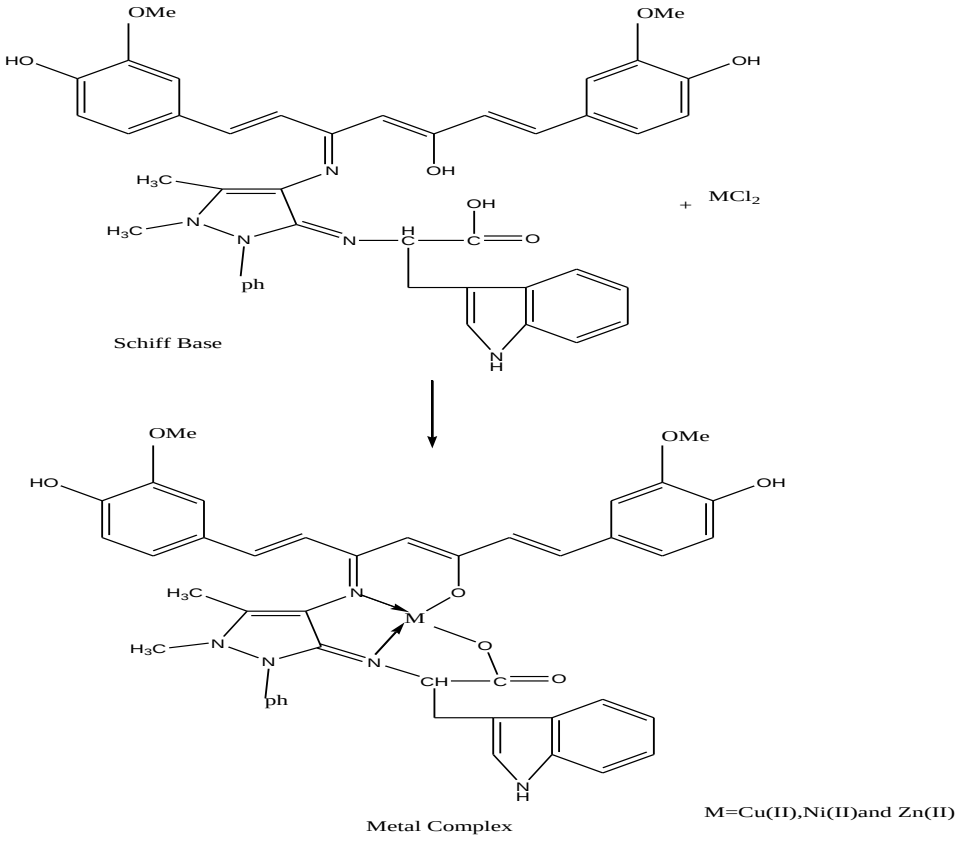
2.2.3 Synthesis of Metal Complexes

An ethanolic solution of $CuCl_2$/ $NiCl_2$/Zn $(OAc)_2$ / $CoCl_2$(5 mmol) salts and (10 mmol) of Schiff base was stirred for 4hrs and then concentrated to 10ml. The mixture was cooled at room temperature and the precipitated complex was filtered, washed with ethanol and dried in vacuo and then recrystalised from ethanol. The metal complex derived from Schiff base and metal chloride is given the scheme - III



Scheme III

III. RESULT AND DISCUSSION

3.1 UV-Visible Spectroscopy

The spectra of transition metal complexes depend on the transition of unpaired electrons from the ground state to an excited state. Transition may occur between the split d-levels of the central atom, giving rise to the d-d or ligand field spectra. The spectra regio were these bands occur spans the near infrared, visible and UV. Most of the transition metal complexes are colored due to d-d transitions in the visible region. The atomic overlap in metal- ligand bands allowed d electrons to penetrate from the central atom to the ligand and vice-versa. The transitions are affected by the effect of ligands on the energies of the d-orbital of the metal ions.

The electronic spectrum of the Schiff base in MeCN shows a predominant band at nm region, which is assigned as intra ligand charge transfer (INCT) band. The electronic spectra can often provide quick and reliable

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information about the ligand arrangement in transition metal complexes. The electronic absorption spectra of the Schiif base and its Cu(II) and Ni(II) complexes, recorded at 300 K in MeCN solution .

The electronic spectrum of the ligand in MeCN shows two predominant bands in the regions 23752 cm^{-1} and 39683 cm^{-1}, which are assigned as intra ligand charge transfer (INCT) bands. The copper complex shows a broad band at ca. 10953 cm^{-1}, which is assigned as $^2B_1g \rightarrow {}^2A_1g$ d-d transitions. The broadness of the band can be taken as an indication of distortion from perfect planar symmetry. This complex also shows a well defined shoulder at 17657 cm^{-1}, which is characteristic $^2B_1g \rightarrow {}^2B_2g$ transition of square planar copper complex. Absence of any band below 10,000 cm^{-1} eliminates the possibility of a tetrahedral or pseudo-tetrahedral environment in this complex. This is further supported by the magnetic susceptibility value (1.76 BM).

The electronic spectrum of nickel complex in acetonitrile shows three predominant bands at 30803 cm^{-1}, 21276 cm^{-1} and 14492 cm^{-1}. A comparison of the spectrum with that of the free ligand origin, first two bands is assignable to INCT transitions and the remaining one occurring at 14492 cm^{-1} is due to the $^1A_{1g} \rightarrow {}^1B_{1g}$ transition which confirms the square-planar geometry of the nickel complex. The observed zero magnetic moment also confirms the square planar environment for the nickel (II) complex, in conformity with the fact that all known square planar

3.2 Infrared Spectroscopy

The infrared spectrum of the Schiff base shows a merged strong band at 2789 cm^{-1} and 3446 cm^{-1} region which are assigned to enolic –OH group of Curcumin and –COOH group of Tryptophan moiety. Disappearance of these bands indicates the deprotonation of these groups upon co-ordination. IR spectrum of the complexes shows a new strong band at 3371 cm^{-1} region which are assigned to cyclic –NH group of Tryptophan moiety and the same peak is also appeared in the IR spectrum of Schiff base as a weak node due to merging of –OH group. In the IR spectrum of the Schiff bases, the strong bands at 1653 cm^{-1} region are attributable to –C=N groups. On chelation due to possible drift of lone pair electron density towards the metal ion, the -C=N bond is expected to absorb at lower frequency in the complex.

The observed band at 1591 cm^{-1} region indicates the co-ordination of azomethine nitrogen to the metal. The bands observe at 1600 cm^{-1} in the free ligands are assigned to υ (C=O) stretching frequency. These bands are shifted to higher wave number 1656 cm^{-1} in the Schiff base complexes. IR spectra of the complexes also show a new peak at 464 cm^{-1} and 615 cm^{-1} region due to the formation of υ (M-O) and υ (M-N) bond respectively.

3.3 ^{1}H-NMR SPECTRUM

The ^{1}H-NMR spectrum of Schiff base in DMSO-d_6 shows the following signals: C_6H_5 as at 6.4 -7.6 ppm, =C-CH_3 at 2.7 ppm,-N-CH_3 at 3.2 ppm and azomethine proton at 8.9 ppm.The peaks at 10.2 ppm and 12.3 ppm are attributable to the COOH group present in Tryptophan and enolic –OH group present in the curcumin moiety respectively.

The absence of this two peaks in the zinc complex, favours the loss of enolic -OH and Tryptophan -COOH proton due to coordination with zinc ion. A slight downfield shift was noted in all other signals of the complex.

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They confirm the structure of Schiff base and its zinc complex. The peaks at 6.21 and 6.92 ppm in Schiff base and the complex are assignable to two phenolic – OH group in the curcumin moiety which suggested that they are not involved in the coordination

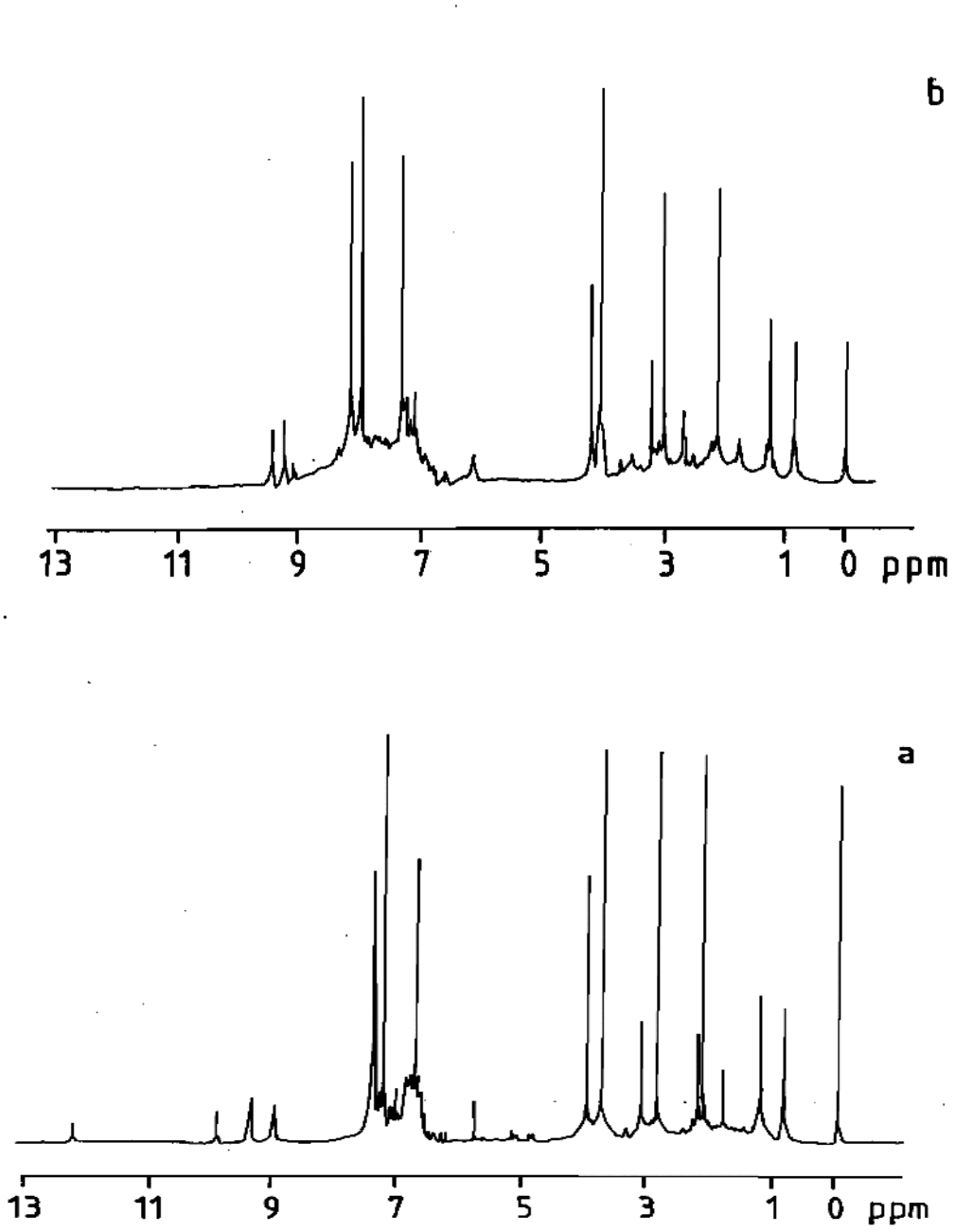

Fig 1- ^{1}H-NMR spectra of Schiff base (a) and Zinc complex (b) complex in DMSO solution.

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IV. BIOLOGICAL SCREENING ACTIVITY

4.1 Analgesic Activity

Analgesic activity of Schiff base by tail immersion method in rats was given in Table1

Table- 4.1 Effect of Schiff base on reaction time (in sec) in albino rats

Treatment	Dose	Mean time (sec) ± SEM			
		1 hrs	2hrs	3hrs	4 hrs
Control	Saline	1.75±0.288	2.25±0.288	2.25±0.552	2.33±0.40
Paracetamol	100mg/kg	3.5±0.571 50%	5.0±0 55%	5.75±0.288 60.8%	6.5±0.333 64%
Schiff base	250mg/kg	3.5±0.333 50%	4.25±0.288 47%	4.75±0.288 52.6%	5.0±0 53.4%
One way Anova					
F		7.736	20.78	27.52	44.6
DF		(2,9)	(2,9)	(2,9)	(2,9)
P		0.01109	0.000423	0.000146	0.000128

Data are expressed as Mean±SEM, n=3 in each group, statistical analysis done by one way ANOVA followed by Dunnett's test. The value in the parenthesis indicates the percentage of analgesic activity. Schiff base of 250 mg/kg has shows higher Analgesic activity at 4 hrs and it probability of < 0.001 after the drug administration.

4.2 Antipyretic Activity

Antipyretic activity of Schiff base on rectal temperature in rats is given in table. The following results were observed for different Schiff bases as given in Table 2

Table 4. 2 Effect of Schiff bases on rectal temperature (^{o}C) in albino rats.

Drug Treatment	Dose (mg/kg)	Rectal temperature after yeast administration(^{o}C)		Rectal temperature after administration of drug(^{o}C)				Reduction in temperature(^{o}C)
		Normal	18 hrs	1 hrs	2 hrs	3 hrs	4 hrs	---
Control	1ml/ kg saline	37.43± 0.7222	37.9± 0.5338	37.8±0 .6014	37.9± 0.6377	37.9± 0.481	37.96± 0.6377	
paracetamol	33mg/kg	37.17± 0.2033	38.13± 0.1630	37.66± 0.1473	37.40± 0.1870	37.3± 0.2121	37.23± 0.600	0.9
Schiff base	250mg/kg	37.23± 0.2857	38.33± 0.1079	37.86± 0.1079	37.6± 0.2121	37.43± 0.2272	37.43± 0.2272	0.9

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The reduction in temperature from 38.13 ^{o}C to 37.23 ^{o}C for 33 mg/kg for paracetamol, 38.33 ^{o}C to 37.43 ^{o}C for 250 mg/kg of Schiff base were observed. The reduction in temperature of Schiff base is (0.9 ^{o}C) was found to possessed equal antipyretic activity to that of the standard (0.9 ^{o}C).

4.3 CNS depressant activity

The dose dependent depression in the locomotor activity was measured for caffeine, chlorpromazine and all Schiff bases are shown in Table4. 3

Table 4. 3 Effect of Schiff bases on locomotor activity (in min) in albino rats.

Drug treatment	Dose (mg/kg)	Before treatment	After treatment	% change in activity
Caffeine	3 mg/kg(i.p)	23.66 ± 0.4080	40.33 ± 1.080	70.45
Chlorpromazine	3 mg/kg(p.o.)	18.66 ± 0.4080	5.00 ± 1.414	73.20
Schiff base	250mg/kg(p.o)	18.33 ± 0.8163	9.00 ± 1.4142	50.90

The result obtain for the Schiff base showed that the dose dependent depression in the locomotor activity was 5.00 ±1.414 for standard chlorpromazine and 9.00 ± 1.4142 for Schiff base. Lower CNS depressant activity was observed for the compound with a percentage of 50.90 with probability <0.001.

4.4 Antimicrobial Activity

The *in vitro* biological screening effects of the investigated compounds were tested against the various bacteria such as *Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococci and the fungi Candida albicans* by disc diffusion method. The minimum inhibition concentration values of the compounds against the growth microorganisms are summarized the Table 4.4.

The MIC (Minimum Inhibitory Concentration) values of the free ligand and its complexes indicate that all the metal chelates have higher antimicrobial activity than the free ligand. Such increased activity of the metal chelates can be explained on the basis of overtone's concept and the Tweedy's chelation theory. According to overtones concept of cell permeability, the lipid membrane that surrounds the cell favours the passage of only lipid soluble material due to which lipophilicity is an important factor which controls the antimicrobial activity. On chelation, the polarity of the metal ion will be reduced to a great extent due to overlap of the ligand orbital and partial sharing of the positive charge of the metal ion which donor groups. Further, it increases the delocalisation of the π-electrons over the whole chelate ring and enhances the lipophilicity of the complex.[11-14]

This increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocks the metal binding sites in the enzymes of microorganisms. These complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restrict further growth of the organism. Furthermore, the

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mode of action the compounds may involve the formation of a hydrogen bond through the azomethine group with the active centers of cell constituents, resulting in interference with the normal cell process. Comparatively zinc complex shows higher activity than all other complex which is due to its higher lipid solubility.

Table 4.4 Antimicrobial activities of Schiff base and their metal complexes (MIC in mg)

Compound	*Escherichia coli*	*Salmonella typhi*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Streptococci*	*Aspergillus niger*	*Candida albicans*
Schiff base	53	60	55	60	73	64	99
Cu complexes	51	40	50	50	60	50	61
Ni complexes	44	45	50	40	49	54	43
Co complexes	33	40	65	35	45	60	50
Zn complexes	35	30	40	30	35	30	40

V. CONCLUSION

A Schiff base curcumino-4-aminoantipyrine with tryptophan and their metal complexes of Cu(II), Ni(II), Co(II) and Zn(II) were synthesized and structure was characterized using spectroscopic techniques. The metal complexes formed were non electrolytic in nature. Schiff base behaves as a tetra dentate ligand and is coordinated to the central metal ion through the azomethine. The metal complexes Cu(II), Ni(II), Co(II) and Zn(II) were square planar geometry. The biological activity of the metal complexes is higher than the free Schiff base.

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