



**SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDIES OF
QUINAZOLINE BASED HETEROCYCLIC SCHIFF BASE AND ITS TRANSITION
METAL COMPLEXES**

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Abstract: Cu (II), Co (II), and Ni (II) metal complexes of a new N, N- Bi dentate hetero cyclic Schiff base, which was synthesized by the reaction of 2-chloroquinazolin-4-amine with acetone and characterized on the basis of electronic, IR, and ¹H NMR spectra. It has been found that the Schiff base behaves as a neutral tridentate N, N ligand forming chelates with 1:2 stoichiometry. The complexes of Co(II), Ni(II) and Cu(II) are proposed to have suggested to have octahedral geometry. Schiff base and metal complexes shows good antibacterial activity against *E. Coli*. All the three metal complexes were shown high affinity to words CT-DNA and their binding constants were reported.

Key words: N-hetero cyclic compounds; 2-chloroquinazolin-4-amine; CT-DNA and E.Coli.

I. Introduction

Quinazoline and quinazolinones are the compounds made up of two fused six-member simple aromatic rings, structure of the compound containing benzene fused to pyrimidine. This quinazoline ring system consist a structural fragment of about 150–160 natural alkaloids. The first derivative of quinazoline was prepared in 1869 by Griess as 2-cyano-3,4-dihydro-4-oxoquinazoline. This compound bicyclic called as bicyanoamido benzoyl and obtained by the reaction of cyanogens with anthranilic acid. Many of these derivatives possess broad range of biological properties such as antimalarial, antimicrobial, diuretic, anticancer, antiviral, antifungal, antiprotozoal, anti-inflammatory, muscle relaxant, antitubercular, antidepressant, anticonvulsant, weedicide and many others. Quinazoline and quinazolinone compounds are also useful nucleus in preparation of various functional materials for synthetic chemistry and also present in various drugs molecules.

Quinazoline (1,3-diazaphthalene) is a nitrogen containing heterocyclic compound illustrated by a double-ring structure that contains a benzene ring system fused to pyrimidine at two

adjacent carbon atoms. In 1869, Griess et al., synthesized the first quinazoline derivative 2-cyano-3,4-dihydro-4-oxoquinazoline by condensation process [i,ii]. Bischler and Lang synthesized similar quinazoline analogs by decarboxylation of the 2-carboxy compound [iii]. In 1903, Gabriel and Colman synthesized several quinazoline derivatives and studied its properties in detail^{iv}. The quinazoline compounds may be classified into quinazolin-2(1H)-one and quinazolin-4(3H)-one, depends upon the position of the keto or oxo group, the later ones most dominant, either as intermediates or as natural products in many projected organic synthetic schemes. Quinazolines and its derivatives exemplify one of the most prominent classes of compounds, which possess a wide range of pharmacological activities like analgesic[vi], antioxidant[vii], anti-inflammatory[viii], anti-hypertensive[ix], antitubercular[x], anti-bacterial[xi,xii], anti-viral[xiii,xiv] and anticancer [xvi] activities. The main objective of this review was to collate literature reported by researchers on quinazoline for their various biological activities and also reported recent advancements made on this privileged core. 3-Amino-4(3H)-quinazolinones possess coordinating sites and they were applied to form complexes and bis-complexes with different metal ions. Also, considerable attention has been directed to the chemistry of their Schiff's bases[xvii], where the Schiff's base complexes of 4(3H)-quinazolinones were prepared and characterized. The complexes of metal ions with 2-substituted-3-anilino-4(3H) quinazolinone were prepared. Moreover, the complexes of Cu (II), Co (II), Zn (II) and Cd (II) with 2-methyl-3-hydroxy-4(3H)-quinazolinone and 2-methyl-3-pyridinyl-4(3H)-quinazolinone have been prepared. The analytical and spectral data indicate these ligands act as bidentate and the metal complexes are octahedral, tetragonal, square planar and tetrahedral. Thiosemicarbazones can be reacting with metallic cations to give metal complexes. Thiosemicarbazones as the ligands act as chelating agents which were bonding through the sulfur and azomethine nitrogen atoms. So, when metal salts such as CuCl₂ or ZnCl₂ were treated with the thiosemicarbazone derivatives (0.01 mole) in dioxane the corresponding complexes were obtained in good yield. On the other hand, the corresponding biscomplexes were afforded when a solution of CuCl₂ or ZnCl₂ (0.01 mole) was added to a stirred solution of thiosemicarbazone derivatives (0.02 M) in dioxane at reflux temperature[xviii].

II. Materials and Methods

II. a. Synthesis of 2-chloroquinazolin-4-amine from 2,4-dichloro quinazoline

A mixture of 0.1 mole of 2,4-dichloroquinazoline (merk) in THF and water (2:1 ratio) was taken and cooled in an ice bath at 0-5^oC. 0.3 mole of Na₂CO₃ and then 20 ml of ammonia solution 0.1 N slowly added to at 5-10^oC. The reaction was allowed to stir at room temperature for 3 hours. Then THF was concentrated under reduced pressure then diluted with water. The solid was dried under vacuum over anhydrous CaCl₂. Reported 75% of yield. Its M.P is 312-315^oC.

Into a 250 cm³ of round bottom flask, 20 cm³ ethanol was taken and 0.05 M of dried compound was dissolved, to this 20 cm³ of acetone was added. The mixture was stirred for 4 hours at 60^oC. The ethanol solution was evaporated under vacuum till remove the solvent after that filtered and washed with several times with ethanol. It was re-crystallized with hot ethanol and the dried. The yellow precipitate was obtained. Its M.P is 312-315^oC. The purity was checked by TLC. These compounds were characterized by UV, IR and NMR spectra,

II. b. Synthesis of metal complexes

Into a clean 250 ml round bottom flask 0.0045 M of dried Schiff base was dissolved in ethanol and mixed with 0.0034 M of Ni(NO₃)₂.6H₂O solution. The mixture was refluxed for 4-6 hours at 70-80^oC. The light green colored complex was formed. It is filtered and dried in vacuum. By following same procedure, we had prepared the cobalt and copper complexes were synthesized with brown color, green-colored complexes with yields of 68%, and 64% respectively, Cobalt and Copper complexes were reported.

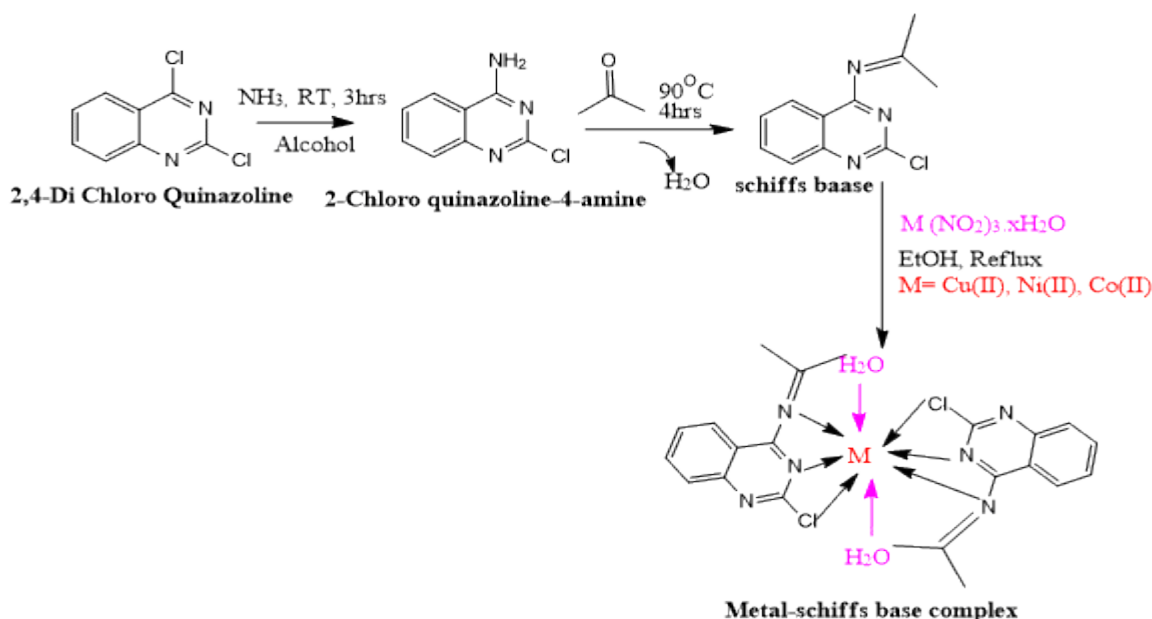


Figure-1 Scheme of preparation of Quinazoline derivative of Schiff base and its complexes

III. Antibacterial screening

Gananamanickam[18] et al., Disc diffusion method of antimicrobial screening was employed for newly synthesized heterocyclic Schiff bases and its Co, Cu and Ni metal complexes were studied against bacteria.

The medium used for testing was nutrient agar medium. The medium was prepared by mixing peptone-5g, Beef extract-3g, NaCl-5gm, agar-15gm in 1 liter of distilled water. The contents were mixed thoroughly. The pH was adjusted to 7.4-7.6. The medium was sterilized in the autoclave at 15 lbs. per Sq. inch pressure for 15 minutes.

The inoculums were prepared by picking up five to ten colonies bacilli and E. Coli with a loop. The colonies were suspended in a nutrient broth and incubated at 37°C for 3 to 4 hours.

Whatman filter paper No.1 was taken and discs of 6mm in diameter were punched with a puncher. The filter paper discs were sterilized in a hot air oven. The sterilized paper discs are soaked in 5 ml of methanol containing known concentration (150 µg/ml) of the samples newly synthesized heterocyclic Schiff bases and its Co, Cu and Ni metal complexes for 2-3 minutes. The discs were allowed to dry for solvent and they get evaporated from the paper discs.

All the required apparatus were sterilized before use and every reasonable precaution was observed to avoid contamination throughout operation.

Sterilized nutrient agar medium 15-20 ml was poured into sterile Petri plates of same size in aseptic conditions. The medium was allowed to solidify the bacterial culture was spreaded uniformly on the surface of nutrient agar medium with sterile cotton swabs. The paper discs soaked with solution of known concentration of the desired Schiff base metal complex and they were placed under aseptic conditions at a particular distance in each petri plate, containing known bacterial suspension. The Petri dishes were labeled with the compound and then incubated at 37°C for 24 hours of incubation. The Petri plate was observed for bacterial growth and the zone of inhibition of bacterial growth in each Petri plate was measured. The discs soaked with the respective solvents of test solutions were used as controls. The zone of inhibition of bacterial growth in the Petri plates under examination was measured. The minimum inhibitory concentration (MIC) was measured by taking 150 µg/ml of the test sample for antibacterial studies.

IV. Results and Discussion

IV. a. Electronic spectral analysis

The UV–Visible data and band assignments are listed in Table. The spectra of the free ligand and its complexes exhibited a high intensity band in the region 300–400 nm, assigning a bp^* ($\text{C}=\text{N}$) of the azomethine groups. Upon complexation, the metal complexes showed a hypsochromic shift (blue shift) to lower wavelengths for both electronic transition bands, likely due to the possible occurrence of a significant amount of p -backbonding from the metal to the ligand, enriching the $\text{C}=\text{N}$ bond with electrons and strengthening it. The peaks attributed to $\text{n}-\text{p}^*$ were observed in the range 330–377 nm. The bands resulted in the UV-visible spectra of the metal complexes are essentially due to $\pi-\pi^*$ and $\text{n}-\pi^*$ electronic transitions. The electronic spectrum of Schiff base shows a broad band at 340 and 380 nm due to $\pi\rightarrow\pi^*$ and $\text{n}\rightarrow\pi^*$ transitions^{xix}. The electronic spectrum of Ni complex shows two absorption bands at 319 and 360 nm suggest at co-ordinate octahedral Ni-complex^{xx}. The electronic transition of Cu-complex shows bands at 325 and 475 nm indicating octahedral Cu-complex. The electronic spectrum of Co-complexes at 356 nm also represents octahedral Co-complexes^{xxi,xxii}.

Complex	λ_{max}	Band assignment
Ni-complex	340nm	${}^3\text{A}_{2\text{g}}(\text{F})\rightarrow{}^3\text{T}_{1\text{g}}(\text{F})$
	380nm	${}^3\text{A}_{2\text{g}}(\text{F})\rightarrow{}^3\text{T}_{1\text{g}}(\text{p})$
Cu-complex	325nm	${}^2\text{E}_{\text{g}}\rightarrow{}^2\text{F}_{2\text{g}}(\text{F})$
	375nm	${}^2\text{E}_{\text{g}}\rightarrow{}^2\text{F}_{2\text{g}}(\text{p})$
Co-complex	356nm	${}^4\text{T}_{1\text{g}}(\text{F})\rightarrow{}^4\text{T}_{1\text{g}}(\text{p})$

Table:1. Results of electronic spectra of Schiff base metal complexes

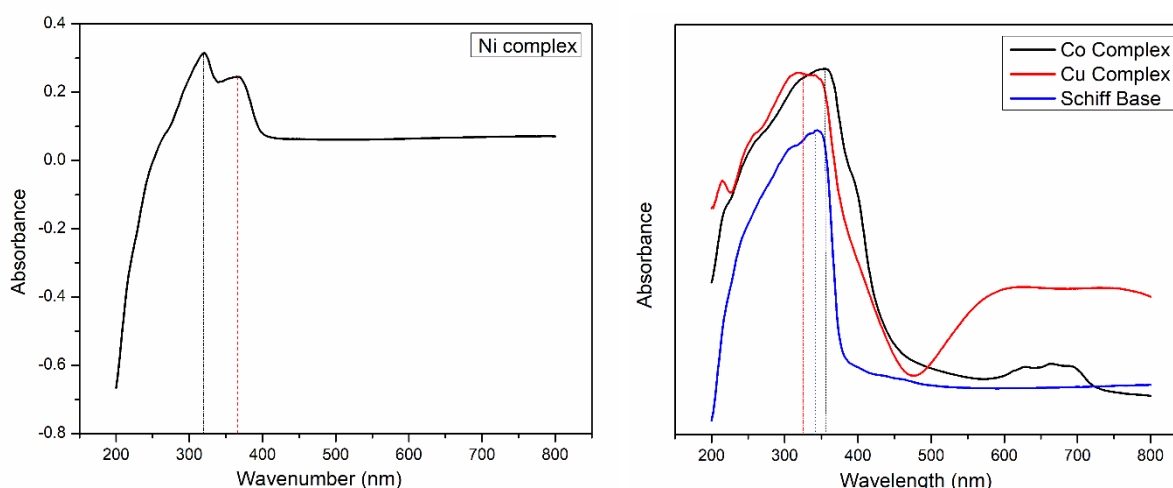


Figure:1. Electronic spectra's of Schiff base ligand and Co, Cu and Ni metal complexes

IV. b. Infra-red spectral analysis

The major absorption frequencies that can be observed in the IR spectra of Schiff base ligand and metal complexes were $\nu(\text{N-H})$, $\nu(\text{C}=\text{N})$, $\nu(\text{M-N})$, $\nu(\text{C-H})$, $\nu(\text{M-O})$ [xxiii,xxiv]. The IR spectrum of Schiff base ligand shows a broad peak at 3378cm^{-1} can be attributed to N-H vibration. A peak in the range of $1600-1650\text{cm}^{-1}$ may be due to $\text{C}=\text{N}$ stretching vibration [xxv,xxvi]. In the spectrum other strong band at 1041cm^{-1} due to C-H stretching vibration. Metal complexes Co(II) , Ni(II) , Cu(II) exhibits $\nu(\text{M-N})$ bonds at 624cm^{-1} , 528cm^{-1} , 609cm^{-1} respectively [xxvii,xxviii]. The lower frequency is observed in the spectrum M-N at $550-$

650 cm^{-1} and metal complexes exhibits $\nu(\text{M-O})$ bonds at 430-500 cm^{-1} $\nu(\text{M-O})$ bonds are due to coordination of water molecules[xxviii-xxxv].

Compound	$\nu(\text{N-H})$	$\nu(\text{C=N})$	$\nu(\text{C-H})$	$\nu(\text{M-N})$	$\nu(\text{M-O})$
Schiffbase(L)	3378	1643	1041	--
Co-complex	3324	1627	1037	624	478
Ni-complex	3158	1619	1072	528	485
Cu-complex	3124	1670	1083	609	435

Table;2, Results of selected infra-red spectra of Schiff base metal complexes

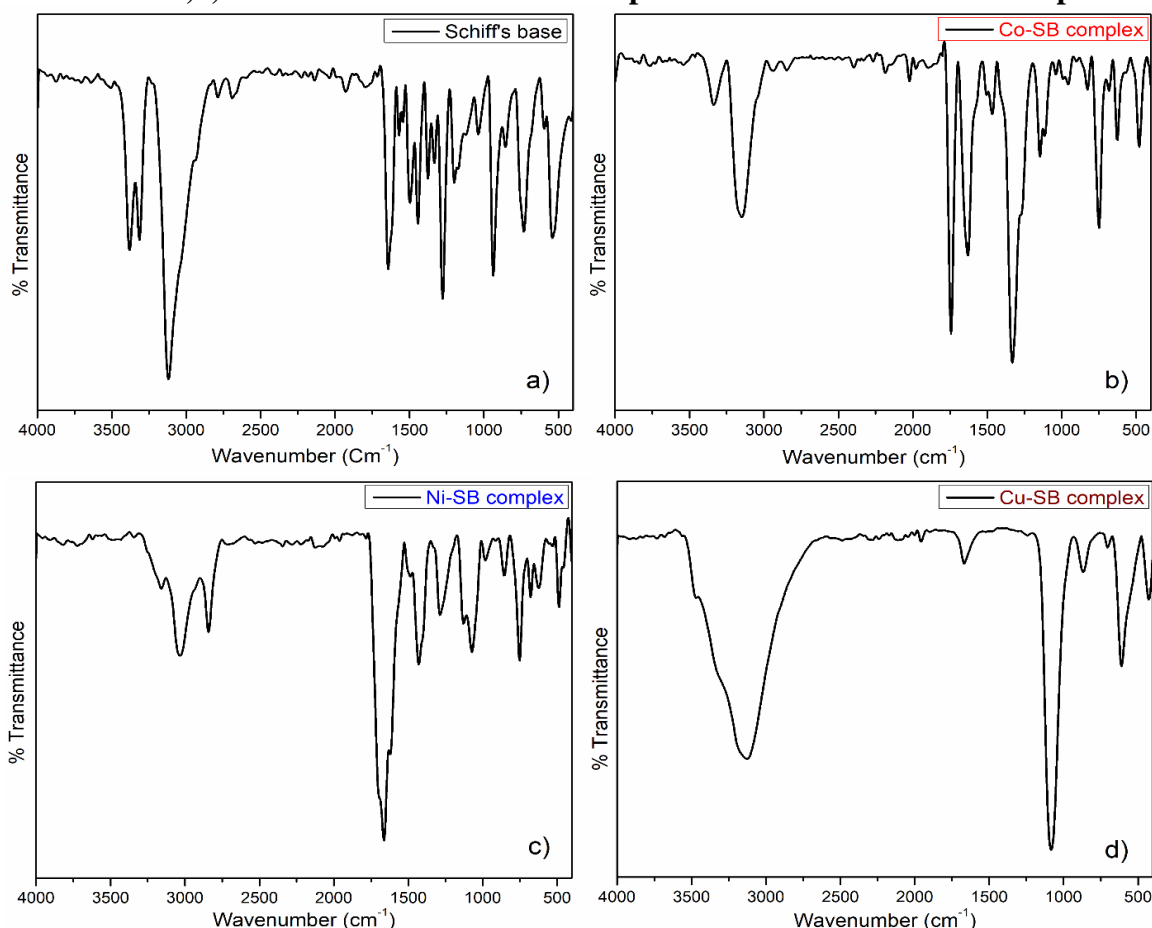


Figure:2. Infrared spectra s of Schiff base and its metal complexes

IV. c. Nuclear Magnetic resonance spectral analysis

The proton NMR spectrum of Schiff base ligand recorded in CDCl_3 is showing figure and their values are tabulated below. Two triplets at 2.5 and 3.4 ppm corresponds to the methyl groups present on imine linkage. A set of our peaks in the aromatic region ranging from 7.5 to 8.5 ppm corresponds to phenyl ring protons in quinazoline ring. In cobalt metal complex chemical shift present at 3.4 and mingled with 2.5. this will conform the double bond nature of imine was decreased and indicating the formation of M-N bond, In the same metal complexes of Copper and Nickel also lose their peak at their respected methyl group position. all the above data conforms the bonding of metal with nitrogen of quinazoline.

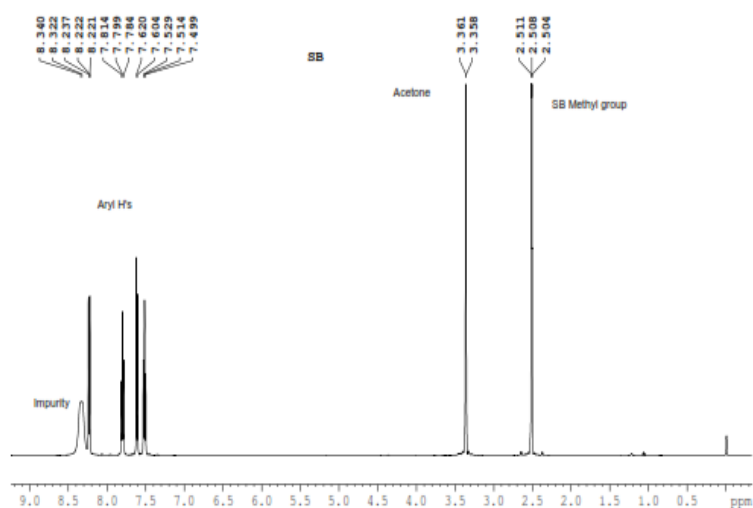


Fig.4 Proton NMR spectrum of Schiff base in CDCl₃

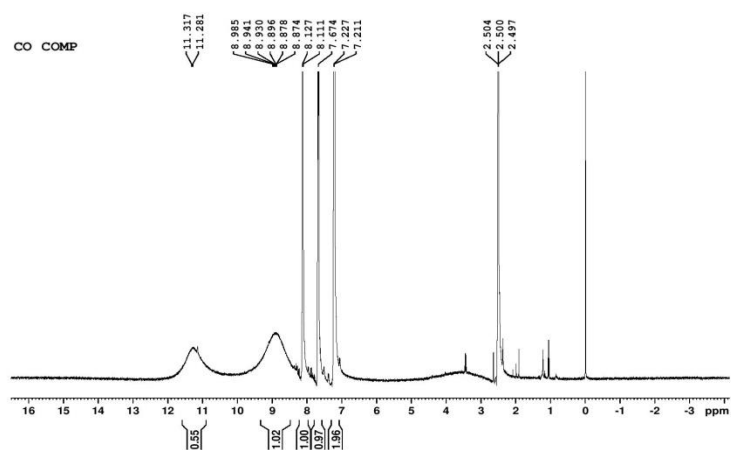


Figure:5. Proton NMR spectrum of Co- Schiff base metal complex

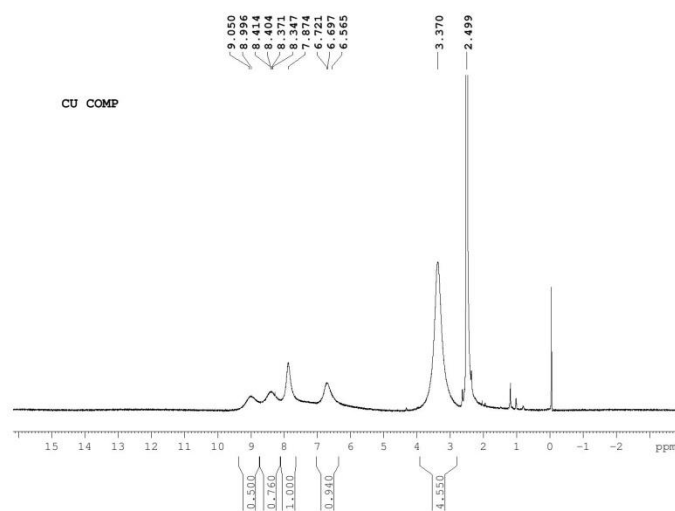


Figure :6. Proton NMR spectrum of Cu- Schiff base metal complex

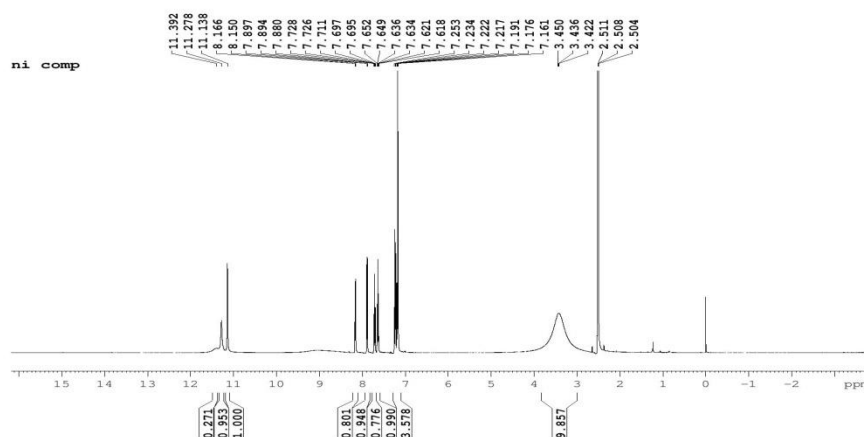


Figure:7. Proton NMR spectrum of Ni- Schiff base metal complex.

IV. d. Antibacterial activity

The antibacterial studies were carried out using the chloramphenicol as reference standard. The results pertaining to antibacterial activity of Schiff base and Co, Ni and Cu metal complexes against *E. coli* bacteria was presented in the **Table-3** and the zone of inhibition of azomethines was demonstrated in **Plate-1** [xxxvi-xl]

Table:3. Anti-bacterial activity of Schiff base and metal complexes against *E.coli*

S.No	Samples	Zone of Inhibition in (mm) <i>against E.coli</i>
1	Schiff base	07
2	Co-Sb	09
3	Cu-Sb	10
4	Ni-Sb	09
5	Chloramphenicol	11

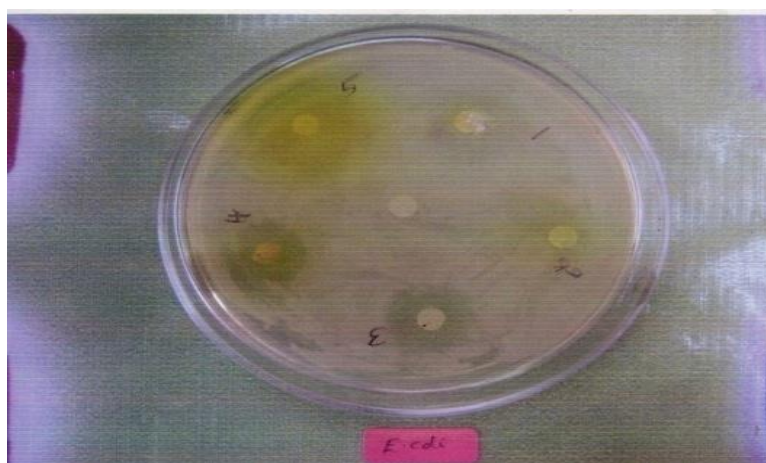


Plate :1 Anti bacterial screening of Heterocyclic schiff base and its metal complexes.

IV. e. DNAbinding studies

In this present investigation DNA interaction of newly synthesised Heterocyclic schiff base metal complexes (Cu,Ni&Co) were studied by using spectrophotometric titration. Disodium salt of calf thymus DNA was stored at 4⁰C. Solution of DNA in buffer 50mM (pH 7.1) in water with ratio of 1:9 gave absorptions at 260nm and 280nm conforms DNA is sufficiently free from protein. Concentrated stock solutions of metal complexes were prepared by dissolving in DMSO and also diluted with suitably buffer solution. Absorption spectra of metal complexes were compared in presence and absence of CT-DNA. The complexes showed a strong decrease in absorption hypochromicity in intensity with shift in absorption maxima towards higher wavelengths (Red shift). The hychromisam and red shift are due to staking interaction aromatic moiety of ligand with DNA base pairs. binding constants K_b were calculated shown in table-4. Electronic spectral data of complexes in presence of CT-DNA and their binding constants K_b were shown in table-4. from te data it was evident that these complexes bind with DNA with high affinities and binding constants were estimated in the range of 10^{-5} - $10^{-6}M^{-1}$.

Table:4. DNA binding constants of metal complexes

S.N O	Complex	λ_{max} metal complex (nm)		$\Delta\lambda_{max}$	H %	Binding constant (K_b)
		free	bound			
1	Cu-sb	350	360	5	14.64	7.46×10^{-5}
2	Ni-sb	361	366	5	15.72	7.86×10^{-5}
3	Co-sb	330	334	4	11.45	5.15×10^{-5}

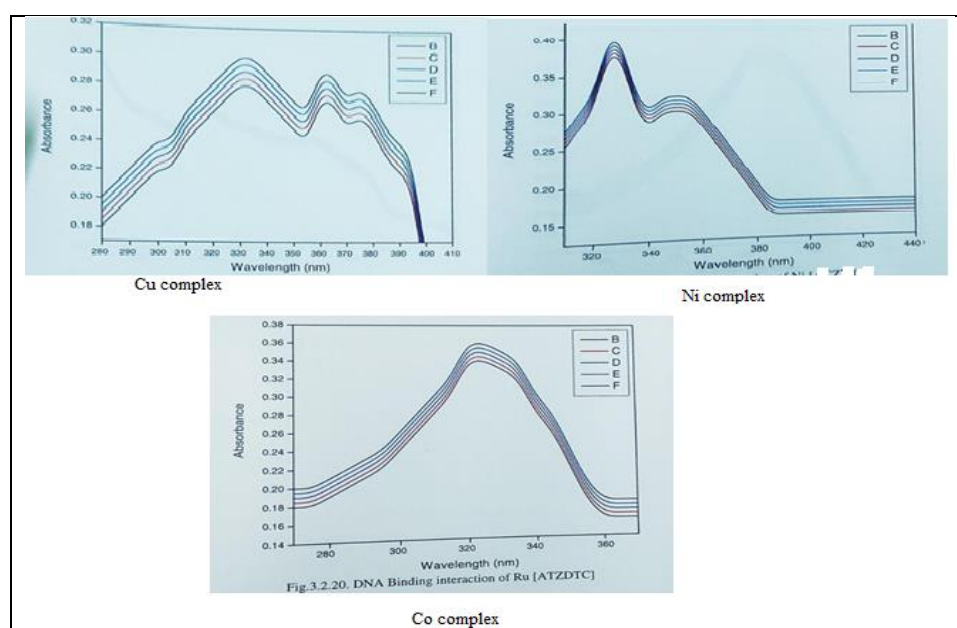


Fig:8. Graphs showing DNA binding interaction of Cu,Ni & Co Metal Complexes

V. CONCLUSIONS

Newly synthesized Schiff base and its metal complexes were new addition to literature, These metal complexes and Schiff base under present investigations exhibit good antibacterial activity. As the quinazoline ring was present in the complex increases the antibacterial activity against E.coli. We hope that this present investigation is more helpful to invention of the new drugs against bacteria.

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