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# Synthesis, Characterisation, Antimicrobial studies of Co, Ni, Zn Complexes with Schiff base Ligand derived from 2-thioxo-1,2-dihydropyridine-3-carbaldehyde and 4-phenylpyrimidine-2-carbohydrazide

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## ABSTRACT
New coordination complexes of Co, Ni and Zn with Schiff base bis ((4-phenylpyrimidin-2-yl)(((2-thioxo-1,2-dihydroquinolin-3-yl)methylene)hydrazono)methoxy) have been synthesized and characterized by several techniques using elemental analysis (C, H, N), IR spectra and $^1$HNMR spectra. The new Schiff base has been synthesized by the reaction of 4-phenylpyrimidine-2-carbohydrazide and 2-thioxo-1,2-dihydropyridine-3-carbaldehyde. The Schiff base behaves as tridentate ONS donor ligand and exhibited octahedral geometry. The Schiff base ligand and complexes were tested for their antibacterial activity against Staphylococcus aureus, Escherichia coli and Proteus vulgaris to assess their inhibiting potential. In screening medium was nutrient agar and biological screening were performed by employing cup plate method. Antibacterial activity of the ligand and its metal complexes is compared with the standard drug ciprofloxacin. In this series Co (II) complexes showed high antibacterial activity and the other complexes showed moderate antibacterial activity against different bacteria.

**KEYWORDS:**Schiff base, Metal complexes, antibacterial activity, ciprofloxacin.

## INTRODUCTION
Schiff base ligand are derived by the condensation of active carbonyl group with primary amine containing the azomethine (CH=N) group in which the carbonyl group of aldehyde or ketone is replaced by azomethine group under specific condition and it was named by Hugo Schiff (1864). Schiff base was invented by Hugo Schiff, which is named after him. Basically there are compounds with a functional group those posses a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group, not with hydrogen. In general sense Schiff bases, could be represented as the general formula $R_1R_2C=NR_3$, where R is an organic side chain. Some of them are restricted to the secondary aldimines (like azo-methines as the carbon is attached with a hydrogen atom) with the general formula RCH=NR'[**I-III**].

Carbon-nitrogen double bond provides a significant contribution in various progresses of chemical sciences. Schiff-base compounds have been potentially used as fine chemicals and medical substrates. Number of methods are been applied for synthesis of Schiff base. In traditional method of synthesis also known as organic synthesis, which commonly involve the removal of solvents from the reaction mixture or liquid extraction especially in the case of aprotic dipolar solvent with high boiling point, or product isolation through liquid-liquid extraction [**IV**]. Microwave-assisted reactions have been intensively investigated as mentioned in previous study.Microwave methods have been popularly used in Schiff base synthesis by organic synthesis as it has several benefits like better atom economy, environmental friendly, less hazardous, etc **[V-VIII].**

In general mechanism of synthesis of Schiff base, an aromatic amine reacts with a carbonyl compound by nucleophilic addition. This forms a hemiaminal, followed by a dehydration to produce imines. Schiff bases obtained from aromatic aldehydes and aromatic amines have a shown number of applications in many fields including pharmaceutical, life sciences and chemical science including inorganic and analytical chemistry **[IX-XII]**.

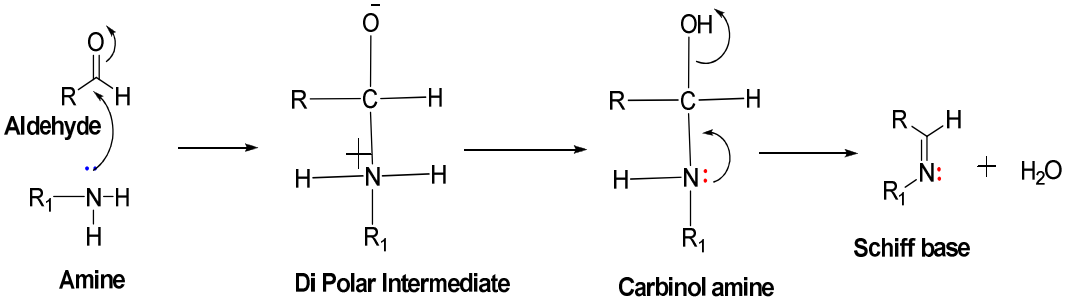



**Figure-1 General reaction mechanism of Schiff base**

The chemistry of coordination compounds with heterocyclic ligands containing oxygen and nitrogen as donor atoms has attracted the attention of chemists in recent years. It is well known that such ligands coordinate to metal atom in different ways in different media. Transition metal complexes with Schiff base have played an important role in much biological system in nature[**XIII-XV**]. The chelating properties of Schiff base display manifold applications in medicine and industry. Pyridine moieties have been reported to possess antimicrobial**[XVI]**, anti-inflammatory**[XVII]** and anticonvulsant**[XVIII]** etc.

Schiff base metal complexes based research works have been widely carried out from 1930 because of their biological and industrial application**[XIX-XXII]**, In organic chemistry Schiff bases are most widely used as pigments and dyes, catalysts, intermediate in organic synthesis, and as a polymer stabilizer **[XXIII]**. Schiff bases and their metal complexes are also well known to have pronounced biological activity **[XXIV-XXV]** and form an important class of compounds in medicine and pharmaceutical field also showed some degree of antibacterial ,antifungal, antitumor, anticancer and anti-inflammatory activity **[XXVI-XXXIV]** ,the azo-methine linkage are responsible for the biological activity of Schiff bases.

Heterocyclic compounds are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, and antibiotics [**XXXV, XXXVI**]. Hence, they have attracted considerable attention in the design of biologically active molecules [**XXXVII, XXXVIII**] and advanced organic chemistry [**XXXIX,XL**]. Also in the family of heterocyclic compounds nitrogen containing heterocyclesare an important class of compounds in the medicinal chemistry and also

contributed to the society from biological and industrial point which helps to understand life processes

[**XL1**]. A totally unsaturated six membered -ring containing nitrogen is known as azine [**XLII**] or pyridine (1); with two nitrogen atoms it is known as diazine [**XLIII**]. and with a nitrogen at 1,2-position, it is known as pyridazine, at 1,3-position as Pyrimidine and at 1,4-position as pyrazine (**Figure2**). However, the current review focus on the significance of Pyrimidines class of antimicrobial agents along with clinical and in vitro applications of pyrimidine derivatives to facilitate the development of more potent as well as effective antimicrobial agents.


**Fig 2 Structures of Pyridazine, Pyrimidine, Pyrazine**

Pyrimidines [**XLIV**] are the heterocyclic aromatic compounds similar to benzene and pyridine containing two nitrogen atoms at positions 1 and 3 of the six membered rings. Heterocycles containing pyrimidine moiety are of great interest because they constitute an important class of natural and non natural products, many of which exhibit useful biological activities and clinical applications [**XLV, XLVI**]. Substituted purines and pyrimidines occur very widely in living organisms and were some of the first compounds studied by the organic chemists [**XLVII**].

The aim of this study was to make Schiff bases of 4-phenyl pyrimidine-2-carbohydrazide and their complexes, followed by characterization and antimicrobial activity determination of the schiff bases and metal complexes.

In view of these findings we have synthesized some metal complexes with a new Schiff base bis ((4-phenylpyrimidin-2-yl)(((2-thioxo-1,2-dihydroquinolin-3-yl)methylene)hydrazono)methoxy) which was prepared by the reaction between 4-phenyl pyrimidine-2-carbohydrazide and 2-thioxo-1,2-dihydroquinoline-3carbaldehyde.

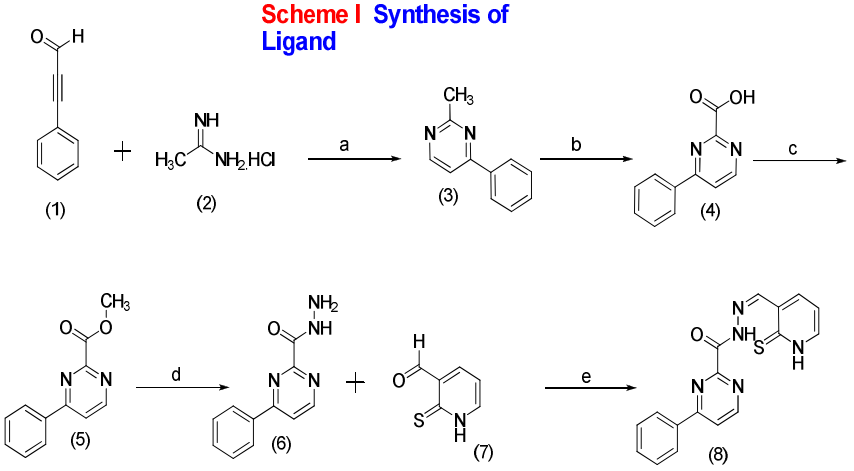
**MATERIALS AND METHODS**

All the chemicals used were of analytical grade and were used without further purification.

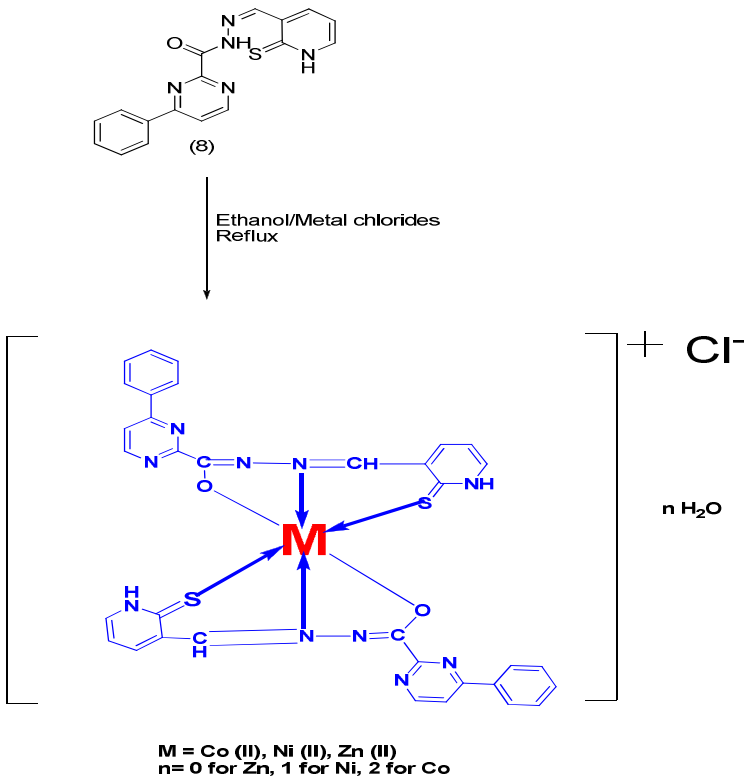
**EXPERIMENTAL Section:**

All reagents and solvents used in this work were analytical grade and used directly. Themelting points were determined in open glass capillaries tubes. Purity of the compounds was checked by thin layer chromatography (TLC) on silica gel G plates and spots were located by using iodine chamber. Elemental analysis (C, H, N) of all the synthesized compounds were determined by perkin-Elmer 2400 elemental analyzer. The IR spectra were recorded on a Beckman Acculab-10 spectrometer (ν max in $cm^{-1}$) and the $^1H$ NMR spectra were recorded by Brucker DPX300 MHz using $CDCl_3$ as solvent.

**Scheme I Synthesis of Ligand**




**Scheme II Synthesis of Metal Complexes**




M = Co (II), Ni (II), Zn (II)
n= 0 for Zn, 1 for Ni, 2 for Co

**Reagents and Reaction conditions: (a)** *Microwave reaction,$Na_2CO_3$, Aceto Nitrile, $90^OC$,1hr* (b) *$SeO_2$, pyridine, reflux, 24 hrs* (c) *Methanol , $H_2SO_4$, Reflux, 12hrs (d)Hydrazine hydrate, Ethanol, Reflux, 6 hrs (e) Ethanol, Acetic acid(catalytic).*

**Synthesis:**

**Synthesis of 2-methyl-4-phenylpyrimidine(3):**

A mixture of 3-phenylpropiolaldehyde (0.01 mol) and acetimidine hydro chloride (0.01 mol) was stirred in dry aceto nitrile(10 ml) and dry $Na_2CO_3$ (0.02mol) was added to it. The stirring was continued for 0.5 hr under Micro Wave conditions at $90^Oc$ .Reaction progress was

monitored by TLC.After completion of reaction cool to RT. Then concentrated under reduced pressure by using rota evaporator & Purified by column chromatography(100-200 mesh size silica) with elution of 10% Ethyl acetate to get pure yellow solid yield:47 % mp: $130^{O}$c-$132^{O}$c.

**Synthesis of 4-phenylpyrimidine-2-carboxylic acid (4):**

A mixture of compound (3) (0.01 mol), selenium di oxide (0.05 mol), and pyridine (10 ml) was refluxed for 2 hours. Reaction progress was monitored by TLC. after completion of compound 3, concentrated under reduced pressure, then added water (10 ml),acidified with Conc.HCl, white solid was formed, filter off, dried, to get 75 % yield. M.P.: 187-189$^{O}$C.

**Synthesis of Schiff base (8):**

The Schiff base (ligand) was prepared by the reaction of 4-phenylpyrimidine-2-carbohydrazide (0.6gm, 0.00280 mol) and 2-thioxo-1,2-dihydropyridine-3-carbaldehyde (0.390gm, 0.0028 mol) in the presence of catalytic of glacial acetic acid (1-3 drops) under reflux for 7-8 h on the water bath. The reaction mixture was cooled at room temperature. The precipitate was then removed from the reaction mixture by filtration, washed with ethanol, dried and recrystallized from appropriate solvent. The synthesis of Schiff base have been shown in scheme 1

**Synthesis of complexes**

Schiff base (Z)-4-phenyl-N'-((2-thioxo-1,2-dihydropyridin-3-yl)methylene)pyrimidine-2-carbohydrazide (0.67 gm, 0.002 mol) in ethanol (30 ml) and stirred gently for one hour to give homogeneous solution and added Ethanolic solution (10 ml) of respective metal chlorides (0.002 mol). The resulting solution was refluxed for 5 h on steam bath and then sodium acetate (0.5 gm) was added to it and refluxed for 2 h. It was poured into distilled water. The solid complexes were collected by filtration, washed with distilled water and dried in a vaccum over anhydrous calcium chloride in a desicater. The synthesis of metal complexes is given in scheme 2 and physical analytical data of ligand and its complexes are given in table 1.

**IR, $^{1}$HNMR Spectra of Ligand**

The IR spectrum of ligand showed peak at 1635 $cm^{-1}$ due to imine group and three absorption band at 3115 and 3060 $cm^{-1}$ due to amide NH and NH of quinolone moiety. The bands observed at 1635, 1562 and 1161 $cm^{-1}$ are due to carbonyl C=O, azomethene C=N and C=S function at 2-position of quinoline moiety respectively. The $^{1}$HNMR spectra of the Schiff base in $d_6$ DMSO at room temperature showed signal at δ 9.6 (s,1H, quinoline NH), δ 11.4 (s, 1H, CONH), δ 8.82 (s, 1H, N=CH) and δ 7.40-7.94 (m, 10H, Ar-H) due to protons of benzene ring aromatic protons, 8.4(1H,d),8.86(1H,d)due to protons of Pyrimidine ring protons, 6.92-7.16(8H,m) due to protons of quinoline ring protons respectively.

**IR Spectral data of the complexes of ligand**

IR spectral data of ligand. and its complexes are given in table 2. The IR spectrum of ligand was compared with those of the complexes of metal ions Co (II), Ni (II) and Zn (II) in order to study the binding mode of schiff base to the metal ions. In the IR spectra of ligand the band appeared at 1635 $cm^{-1}$ assigned to carbonyl group (C=O) has disappeared in its complexes the above metal ions suggesting the involvement of carbonyl oxygen atom in coordination by the deprotonation after its enolization. All the complexes except Zn (II) complex of the ligand under the present study displayed broad bands in the region 34253410 $cm^{-1}$ indicating the presence of lattice or coordinated water molecules. The peak observed at 3060 $cm^{-1}$ due to quinolone NH has appeared at about the same region 3020-3075 $cm^{-1}$ in all the complexes indicates the non-involvement of quinolone NH in complexation. Absorption band at 1562 $cm^{-1}$ in case of ligand due to C=N of azomethine function has been found to be shifted towards the lower frequency side 1536-1515 cm-1 in allthe complexes indicates the metal

ions have coordinated to azomethine nitrogen. A band at of all the complexes indicating the coordination of metal ions with sulfur of C=S function. The bands of weak intensity in the region 545-505 $cm^{-1}$ in case of all the complexes of the ligand are assigned M-O vibrations and the bands in the region 457-410 cm-1 to M-N vibration.

**Table 1: Physical and analytical data of ligand and its complexes:**

| **Compounds** | **Molecular formula** | **Mol.wt** | **M.P.($^{O}$C)** | **Elemental analysis (%) Calculated (Found)** | | | |
|---|---|---|---|---|---|---|---|
| | | | | M | C | H | N |
| Ligand | $C_{21}H_{15}N_5OS$ | 335.442 | 212-214 | --- | 60.44 | 3.92 | 20.87 |
| Co-complex | $Co[C_{42}H_{26}N_8O_2S_2]2H_2O$ | 762.285 | 264-266 | 7.72 (7.80) | 53.40 (53.35) | 3.13 (3.17) | 18.31 (18.36) |
| Ni-complex | $Ni[C_{42}H_{30}N_{10}O_2S_2]H_2O$ | 762.591 | 370-372 | 780 (7.78) | 53.53 (53.34) | 3.17 (3.21) | 18.36 (18.32) |
| Zn-complex | $Zn[C_{34}H_{28}N_8O_2S_2]$ | 767.113 | 346-349 | 19.04 (19.02) | 53.07 (53.05) | 3.18 (3.15) | 18.29 (18.24) |

**Table 2: IR data of ligand and its complexes**

| **Compound** | **$\nu_{H2O}$** | **Amide NH** | **Quinoline NH** | **$\nu_{C=O}$** | **$\nu_{C=S}$** | **$\nu_{C=N}$** | **$\nu_{M-O}$** | **$\nu_{M-N}$** |
|---|---|---|---|---|---|---|---|---|
| Ligand | --- | 3112 | 3045 | 1655 | 1160 | 1562 | --- | --- |
| Co-complex | 3410 | --- | 3020 | --- | 1135 | 1536 | 515 | 467 |
| Ni-complex | 3425 | ---- | 3028 | --- | 1145 | 1542 | 526 | 465 |
| Zn-complex | --- | --- | 3075 | --- | 1164 | 1515 | 534 | 430 |

**Pharmacological Studies**

**Antibacterial Activity**

All the newly synthesized metal complexes were tested for their antibacterial activity. Antibacterial activity was determined by agar cup plate method **[XLVIII]** against the following organism- Staphylococcus aureus, Escherichia coli and Proteus vulgaris. The zone of inhibition of each strain was recorded. Antibacterial activity of the ligand and its metal complexes was compared with the standard drug ciprofloxacin. The variation in the activity of different metal complexes against different micro-organism depends on their impermeability of the cell or the differences in ribosomes in microbial cell. The lipid membrane surrounding the cell favours the passage of any lipid soluble materials and it is knows that lipo solubility is an important factor controlling antibacterial activity.

**Table 3: Antibacterial activity of ligand and its complexes:**

| **Compounds** | **Bacterial inhibition zone/mm** | | |
|---|---|---|---|
| | **S. aureus** | **E. coli** | **P. vulgaris** |
| Ligand | 13 | 16 | 14 |
| Co- complex | 19 | 20 | 19 |
| Ni- complex | 14 | 13 | 18 |
| Zn- complex | 12 | 18 | 19 |
| Ciprofloxacin | 20 | 22 | 20 |

## RESULTS AND DISCUSSION

### Synthesis:

2-Methyl-4-phenyl pyrimidine (3) was synthesized according to the reported procedure [**XLIX**]. The reaction of 2-methyl- 4-phenyl pyrimidine with selenium di oxide in pyridine to afford the corresponding 4-phenyl pyrimidine-2carboxylic acid(4) as per the reported procedure**[L],** which was reacted with methanol as per the reported procedure[**LI**] to afford methyl 4-phenylpyrimidine-2-carboxylate (5), which was reacted with hydrazine hydrate in Ethanol as per the reported procedure[**LXI**] to afford 4-phenylpyrimidine-2-carbohydrazide (6).Compound (6) reacts with 2-thioxo-1,2-dihydroquinoline-3-carbaldehyde (6) to form (Z)-4-phenyl-N'-((2-thioxo-1,2-dihydroquinolin-3-yl)methylene)pyrimidine-2-carbohydrazide [Schiff base ] (8) as per the reported procedure [**LXII**].

The results showed (table-3) that ligand exhibits moderate activity against all tested bacteria. Co (II) complex showed high antibacterial activity against S. aureus, E. coli and P. vulgaris. Ni complex exhibited moderate activity against S. aureus and E. coli but highly effective against P. vulgaris. Zn complex exhibited moderate activity against S. aureus but showed good activity against E. coli and P. vulgaris microorganism. Antibacterial activity of the ligand and its metal complexes is compared with the standard drug ciprofloxacin. The variation in the activity of different metal complexes against different micro-organism depends on their impermeability of the cell.

### Conclusion :

Based on overall study it was concluded that metal complexes of schiff bases are more efficient antimicrobial agent than its native form. However the antimicrobial potentiality is of metal complex is highly dependent in the metal ion used for formation of metal complex.A new ligand (Z)-4-phenyl-N'-((2-thioxo-1,2-dihydroquinolin-3-yl)methylene)pyrimidine-2-carbohydrazide and its complexes have been synthesized and characterized by IR and $^{1}$HNMR spectral data which includes that all the complexes exhibited octahedral geometry. Some of these complexes have exhibited good antibacterial activity.

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