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***Research Article***

# SCHIFF BASE COMPLEXES DERIVED FROM 2-AMINOBENZOTHIAZOLE AND SUBSTITUTED ACETOPHENONE: SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION

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## ABSTRACT

Chelating ligands having N, S and O as heteroatoms are found to have broad biological activity. Schiff bases formed by condensation of primary amine with an aldehyde or ketone are good chelating agents where carbonyl group is replaced by azomethine group (R-C=N-R'). Further, these ligands bond to metals (act as Lewis acids) in various ways to form metal ligand complexes (Cotton and Wilkinson, 1962) that are proposed to have pharmacological applications. Therepeutic and pharamacological activities of Benzimidazole derivatives have already been reported (Singh and Parle, 2019). Synthesis and antimicrobial studies of Schiff bases derived from imidazole have also been reported (Joseyphus *et al.*, 2015). Similarly, Benzothiazole is a heterocyclic aromatic compound containing Nitrogen and Sulphur heteroatoms. It is a pharmacophore possessing therapeutic activity like antiviral, antifungal, analgesic etc. We emphasized on synthesis of novel schiff base ligand derived from 2-aminobenzothiazole and its complexation with selective metal ions. Further, biological evaluation is done for additional pharmacological activity.

***Keywords**: Azomethine, Benzothiazole, Pharmacophore, Biological evaluation*

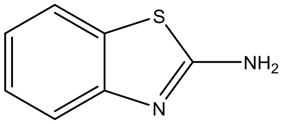
## INTRODUCTION

Benzothiazole is one of the important scaffolds for synthesis and development of new compounds. Benzothiazole ring is an important moiety of various drugs like Ethoxzolomide, Frentizole, Riluzole used as diuretic, antiviral and to treat amyotrophic lateral sclerosis respectively. Derivatives of benzothiazole also have versatile pharmacological applications. In addition, transition metals play a vital role in biological system and co-ordination behaviour of metals is interesting field of research. Our research work aimed to synthesize a novel Schiff base ligand using 2-aminobenzothiazole and 4-methylacetophenone in presence of condensing agent. Schiff base ligand synthesized was allowed to complex with Co(II) and Ni(II) using metal salts. Ligand acts as bidentate with nitrogen and sulphur as donor atoms. Stoichiometry revealed 1:2 metal ligand ratio in synthesized complexes. Both ligand and complexes were characterized by elemental analysis, physicochemical analysis, molar conductance measurement, magnetic moment measurement and various spectral techniques (Silverstein *et al.*, 1981). Biological screening (Barry, 1976) was done against various bacterial and fungal strains and results compared with standard. The complexes of Co(II) and Ni(II) are intensely coloured crystalline solids and stable to air.

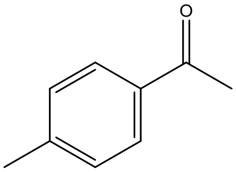
## MATERIALS AND METHODS

All chemicals used were of highest purity and used without further purification. Double distilled water redistilled over alkaline $KMnO_4$ was used for preparation of solutions. Melting points were determined in open capillaries and were uncorrected. Purity of all compounds were checked by TLC using Silica Gel-G plates. All glass apparatus were cleaned, rinsed with alcohol and dried in electric oven, were kept in desiccator to protect from atmospheric moisture.

Chemistry of 2-aminobenzothiazole

| Structure |  |
|---|---|
| IUPAC Name | 1,3-benzothiazol-2-amine |
| Molecular Formula | $C_7H_6N_2S$ |
| Molecular weight | 150.199 g mol $^{-1}$ |
| M.P. | 132°C |
| Solubility | Slightly Soluble in water |

Chemistry of 4-methylacetophenone

| Structure |  |
|---|---|
| IUPAC Name | 1-(4-methylphenyl)ethanone |
| Molecular Formula | $C_9H_{10}O$ |
| Molecular weight | 134.178g/mol |
| M.P. | 24°C |
| B.P. | 226°C |

***Methods of analysis***

Elemental analysis of carbon and hydrogen were done by **Liebig's** method, nitrogen by **Kjeldahl's** method, sulphur by **Messenger's** method, chloride by **Gravimetric** determination and Cobalt(II) and Nickel(II) by **EDTA** (Vogel, 1962) method. Molecular weights were determined by **Rast** method. For calculation of molar conductance of complex, first specific conductance (K) was measured in DMSO by Systronics Direct Reading Conductivity Meter-304 using glass cell (cell constant = 1.0 cm$^{-1}$) at room temperature.

$$\Lambda_M = \frac{K \times 1000}{M}$$

$\Lambda_M$ = Molar conductance
K = Specific conductance
M = Molarity of solution

For magnetic moment measurement Gouy's Balance Model no: HO-ED-EM-08 was used. Electronic absorption spectra measurements (Lever, 1984) were made on spectro scan UV-2600 double beam spectrophotometer at room temperature. FTIR spectra measurements (Kemp, 1991) of ligand and complex were recorded on model SHIMADZU-JAPAN 8400S FTIR spectrophotometer in region 4000-

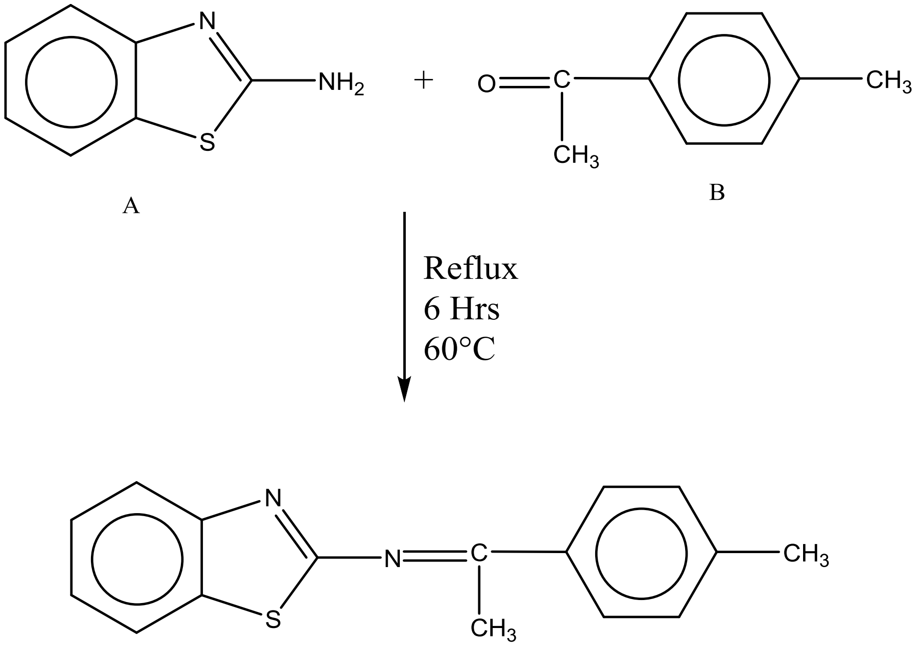
400 $cm^{-1}$. $^1$HNMR spectra (Duddeck and Dietrich, 1992) was recorded on a Hitachi Perkin Elmer Spectrometer in DMSO-$d_6$ using TMS as internal standard.

**[A] Synthesis of ligand L´:** 2-N-(4-methyl phenyl ethanimine) benzothiazole (MPEIBT)
Equimolar solutions were prepared as below:

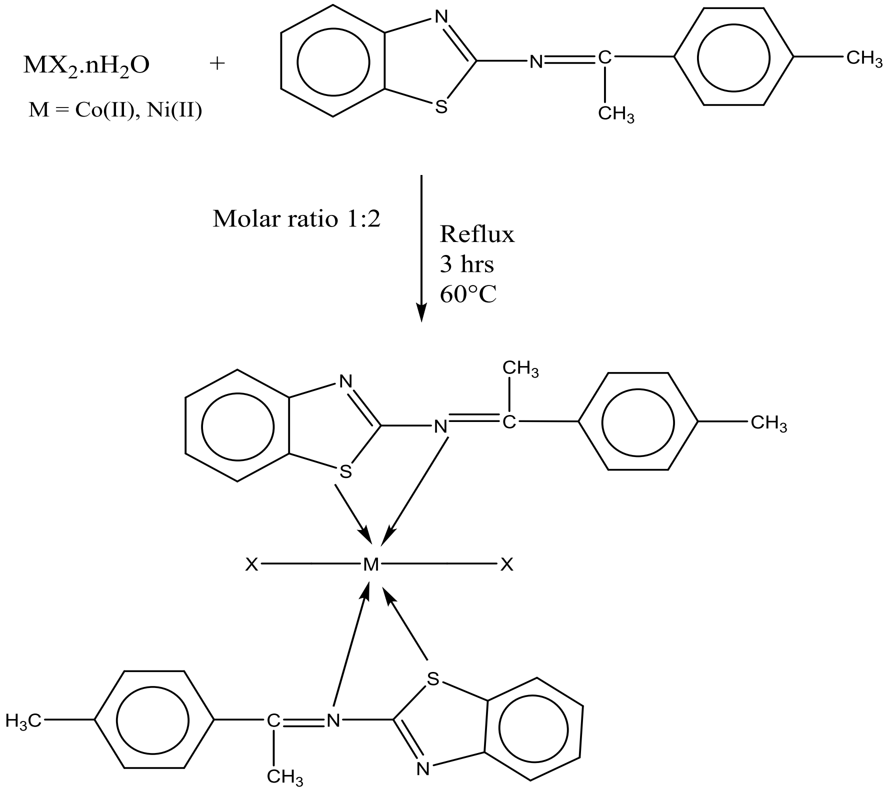
**Solution A-** Aqueous ethanolic solution of 2-Aminobenzothiazole (1.50g, 10mmol).
**Soluion B-** Aqueous ethanolic solution of 4-Methyl acetophenone (1.34g, 10mmol).

**Methodology:** 5mL of solution A was added to 5mL of solution B with constant stirring in presence of condensing agent. The reaction mixture was stirred continuously for approximately 20 minutes. No precipitation was observed. Then the contents of reaction mixture poured in a 250mL round bottom flask fitted with reflux water condenser. Then the reaction mixture was refluxed for 6 hours on heating mental maintaining temperature at 60°C. After reflux the solution was cooled at room temperature. Solid product started to appear and it was kept overnight. Further the product was filtered, washed, recrystallised and dried properly. Pale yellow coloured crystals were obtained with Yield (55.63%), m.p. 248.2 °C.
Proposed scheme for above synthesis [ Scheme – I]

**[B] Synthesis of complex [ML´$_2$X$_2$] :** Common procedure was carried out for preparation of complexes. 10mL ethanolic solution of synthesized ligand L´ (20mmol) was added to 10mL aqueous solution of $MX_2.nH_2O$ (10mmol) with constant stirring. No precipitate was observed. The reaction mixture was refluxed for 3 hours until the reaction was complete (monitored by TLC) and further concentrated and cooled at room temperature. Solid products obtained were filtered, washed, recrystallised and dried properly.
Proposed scheme for above synthesis [Scheme – II]



**Scheme -I**



**Scheme-II**

### *Antimicrobial Activity*

Biological activity of both ligand and complexes was done ***in vitro*** for growth inhibiting potential against selective bacterial and fungal strains using **Cup-Plate** method. For bacterial study, ***in vitro***, gram positive bacteria ***Staphylococcus aureus*** (MTCC-96), gram negative bacteria ***Pseudomonas aeruginosa*** (MTCC-424) and fungal strain ***Candida albicans*** (MTCC-227) were evaluated. For bacterial studies, **Nutrient agar** was employed whereas **Malt Yeast agar** was used as culture media for antifungal study. **Norfloxacin** and **Clotrimazole** were used as standard drug for antibacterial and antifungal studies respectively. Sterilization of culture medias, petridishes and other glasswares done by autoclave. For antibacterial study, incubation was carried out at 37± $2^o$ C for 48 hours. For antifungal study, incubation period for ***Candida albicans*** was 72 hours at 25± $2^o$ C. Solutions of test compounds (100µg/ml, 50µg/ml) were prepared by dissolving the test compounds in DMF and definite concentration is employed. Zone of inhibition (mm) was measured for different strains after incubation and results are tabulated in **Table-4**.

## RESULTS AND DISCUSSIONS

Physiochemical data, elemental analysis with molar conductance and magnetic moments of synthesized ligand/ complexes were determined using common procedure and tabulated in **Table-1**. FTIR and $^1$HNMR spectral data are tabulated in **Table-2** and **Table-3** respectively. Antimicrobial activity results are tabulated in **Table-4**.

**Table 1: Physical Proprieties and Elemental Analysis of Synthesized Compounds**

| Compound (ligand/complex)<br>Empirical Formula | Colour/ M.P. | Mol. wt. Anal. Calcd. (Found) | % Elemental Analysis Anal. Calcd. (Found) | | | | | | Molar cond. (ohm$^{-1}$ cm$^2$ mol$^{-1}$) | $\mu_{eff}$ (BM) Appr. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | S | Cl | M | | |
| L´ (MPEIBT)<br>$C_{16}H_{14}N_2S$ | Pale Yellow/ 248.2 $^{O}$C | 266.3 (266.1) | 72.1 (72.2) | 5.3 (5.1) | 10.5 (10.4) | 12.0 (12.2) | - | - | - | - |
| CoL´$_2$Cl$_2$<br>$C_{32}H_{28}N_4S_2Cl_2Co$ | Purple Pink/ 275.6 $^{O}$C | 662.5 (661.4) | 58.0 (58.1) | 4.2 (4.0) | 4.2 (4.1) | 9.6 (9.4) | 10.7 (10.5) | 8.8 (8.7) | 11.20 | 4.89 |
| NiL´$_2$Cl$_2$<br>$C_{32}H_{28}N_4S_2\,Cl_2Ni$ | Yellow-ish Green 263.2 $^{O}$C | 662.3 (660.9) | 58.0 (58.3) | 4.2 (4.1) | 4.2 (4.3) | 9.6 (9.3) | 10.7 (10.2) | 8.8 (8.6) | 12.04 | 3.39 |

**Table 2: Selected FTIR spectral data ν (cm$^{-1}$) of ligand and complexes**

| Compound | ν (C=N) | ν (C=C) | ν (C-S) | ν (M-N) | ν (M-S) |
|---|---|---|---|---|---|
| L´ (MPEIBT) | 1570 | 1440 | 660 | - | - |
| CoL´$_2$Cl$_2$ | 1560 | 1435 | 637 | 486 | 520 |
| NiL´$_2$Cl$_2$ | 1558 | 1436 | 628 | 474 | 524 |

**Table 3: Important $^1$HNMR spectral data δ (ppm) of ligand and complexes**

| Compound | Ar-H | CH$_3$ (Azomethine) | CH$_3$ (Ar-CH$_3$) |
|---|---|---|---|
| L´ (MPEIBT) | 7.6 | 1.8 | 2.2 |
| CoL´$_2$Cl$_2$ | 7.8 | 1.9 | 2.3 |
| NiL´$_2$Cl$_2$ | 8.0 | 2.0 | 2.3 |

**Table 4: Antimicrobial Activity of Synthesized Compounds using Cup-Plate Method**

| Compound | Conc. (μg/ml) | Zone of inhibition (mm) | | |
|---|---|---|---|---|
| | | Antibacterial Activity | | Antifungal Activity |
| | | *S.aureus* | *P.aeruginosa* | *C.albicans* |
| L´ (MPEIBT) | 100 | 28 | 25 | 19 |
| | 50 | 17 | 16 | 15 |
| CoL´$_2$Cl$_2$ | 100 | 31 | 33 | 23 |
| | 50 | 22 | 26 | 15 |
| NiL´$_2$Cl$_2$ | 100 | 35 | 40 | 26 |
| | 50 | 26 | 28 | 21 |
| Norfloxacin (for antibacterial) | 50 | 23 | 21 | NT |
| Clotrimazole (for antifungal) | 50 | NT | NT | 15 |

Physiochemical analysis of ligand and complexes compared and it is observed that complexes are coloured with sharp melting points and soluble in ethanol, DMSO, DMF and THF. Elemental analysis revealed that observed values are in good agreement with calculated values. Molar conductance of complexes at concentration 0.001 M in DMSO were measured at room temperature. For complexes i.e. $CoL'_2Cl_2$ and $NiL'_2Cl_2$, molar conductance is ~ 11.20 $\Omega^{-1}cm^2mol^{-1}$ and ~12.04 $\Omega^{-1}cm^2mol^{-1}$ respectively indicating that complexes are non-electrolytic in nature. Magnetic moment measurements ($\mu_{eff}$ values) for $CoL'_2Cl_2$ is found ~ 4.89 BM and for $NiL'_2Cl_2$ it is found ~ 3.39 BM which support octahedral geometries for both complexes and their paramagnetic nature.

**FTIR Spectra** provide valuable information regarding nature of azomethine group (C=N-) attached to metal ions. Synthesized metal complexes exhibit strong absorption frequencies at 1560 $cm^{-1}$ and 1558 $cm^{-1}$ as compared to that of free ligand L´(MPEIBT) which appears at 1570 $cm^{-1}$. This shifting of ν(C=N) to lower frequency in the metal ligand complexes support the coordination of the azomethine - N of these ligands to the central metal ion. Absorption bands for C–S bond appear at 637 $cm^{-1}$ and 628 $cm^{-1}$ in complexes as compared to that of free ligand which appears at 660 $cm^{-1}$. In metal ligand complexes absorption frequencies for C=C observed at 1435 $cm^{-1}$, 1436 $cm^{-1}$ which show shift towards lower frequency as compared to that of free ligand which appears at 1440 $cm^{-1}$. New absorption bands appeared at 486 $cm^{-1}$, 474 $cm^{-1}$ correspond to M-N bond and 520 $cm^{-1}$, 524 $cm^{-1}$ correspond to M-S bond.

**$^1$HNMR** spectra of synthesized compounds recorded in $CDCl_3$ and chemical shift expressed in δ values (ppm) downfield to TMS. Observed peaks at δ (8.0-7.6 ppm) show the presence of aromatic protons but above peaks in complexes compared to ligand were found to be shifted to lower field after complex formation takes place. Methyl protons attached to C=N observed at δ 1.8 ppm in ligand that shows shift to downfield in complexes. In addition, methyl protons attached to phenyl ring observed at 2.2 ppm that also show shift to downfield in complexes.

The peaks in electronic spectrum of each complex in DMF solution was studied. The absorption spectrum of free ligand appears at 345 nm which is assigned to $\pi$-$\pi^*$ transition but in complexes, intense bands observed at 382 nm and 385 nm for Co(II) and Ni(II) complexes respectively. The shift of absorbance indicates the complexation behaviour of ligand towards metal ions. Electronic spectra of Co(II) exhibits two additional bands whereas Ni(II) complex shows three additional bands indicating octahedral geometries for both complexes.

On the basis of spectroscopic (FTIR, $^1$HNMR, electronic) evidences a six coordinated behaviour is expected for complexes with no water molecules either coordinated or lattice held. Magnetic moment measurements concide with spin only formula with slight orbital contribution.

Biological screening results ***in vitro*** for selective bacterial and fungal strains report enhanced zone of inhibition for complexes as compared to parent ligand in most of the cases. This may be due to coordination of ligand to metal ions. Synthesized complexes are found to have remarkable antimicrobial activities and are more potent.

## CONCLUSIONS

An octahedral geometry has been proposed for synthesized complexes. The complexes are non-electrolytic in nature with paramagnetic behaviour. In FTIR spectra of complexes shifting of ν(C-S) and ν(C=N) to lower frequency supports coordination of (C=N) group and (C-S) bond to metal. No coordinated water molecules are present in complexes because there is no FTIR band related to water in their FTIR spectra.

The present work that involves synthesis, characterization and biological activity of ligand and metal chelates reveals that efficiency of metal ions in biological system is increased on complexation with biologically active ligands. The compounds may act either by killing the microbe or by blocking their active sites. Further, nature of microorganism plays important role to decide the potency of test compounds. The complexes were found to exhibit remarkable antibacterial and antifungal activity as compared to respective ligand.

## CONFLICT OF INTEREST

There is no conflict of interest.

## ACKNOWLEDGEMENT

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