

## Synthesis, Characterization and Antifungal Activity of Metals Complexes having tetrahydro-1,2,4-triazine based Ligands

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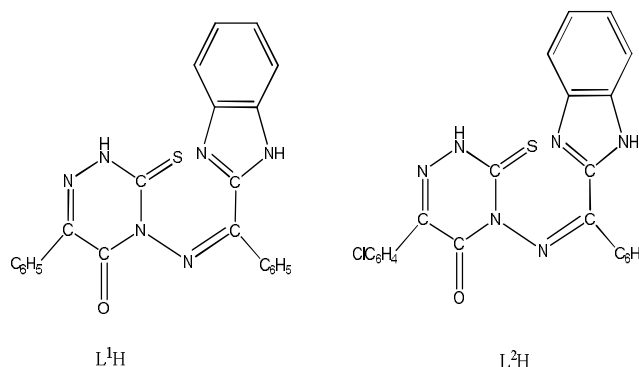
**ABSTRACT:** In present work we have reported the synthesis of some novel metal complexes containing 4- [1E- (1H-benzimidazol-2-yl) phenylmethylideneimino]- 6- aryl-5-oxo-3-thioxo 2,3,4,5- tetrahydro- 1,2,4- triazine (BpartrH) ligands. Synthetic utility was further supported by synthesizing complexes with metals  $ML_2$  ( $M = Mn^{II}, Co^{II}, Ni^{II}, Cu^{II}$  and  $Zn^{II}$ ). All the synthesized complexes were characterized by IR and UV spectra and further supported by elemental analysis. All the synthesized complexes were also evaluated for their antifungal potential and few of prepared complexes exhibited potent antifungal activity. Synthesized complexes were also utilized for magnetic susceptibility measurements and values are reported in tabular form in present article.

**Keywords:** Metal Complexes; Benzimidazole; Chemotherapeutic; Antifungal activity; Medicinal activity; Elemental analyses; Magnetic susceptibility; Triazine and Electrical conductance.

**INTRODUCTION:** Benzimidazole derivatives possess important pharmacophore nuclei and has privileged structure in medicinal chemistry.<sup>1</sup> Their bioactivity is as specific angiotensin II receptor type I selective antagonists<sup>2</sup> as well as hepatitis- C virus NSSB polymerase inhibitors.<sup>3</sup> Furthermore their various pharmacological activity includes antidiabetic,<sup>4</sup> antihistaminic,<sup>4</sup> antiulcer,<sup>5-6</sup> antiviral,<sup>7</sup> antifungal,<sup>8</sup> antiparasitic<sup>9</sup> and chemotherapeutic<sup>10</sup> applications. The wide spectrum of pharmacological and medicinal activity of benzimidazole derivatives and their metal complexes created immense interest to synthesize, characterize and study their microbial properties. In pursuance of our interest to study the coordination complexes of some new benzimidazole derivatives.<sup>11-20</sup> We here report the synthesis, characterization and antifungal activity of some bivalent metal complexes of 4- {1E- (1H-benzimidazol-2-yl) phenylmethylideneimino}- 6- aryl- 5- oxo- 3- thioxo- 2,3,4,5- tetrahydro- 1,2,4- triazine(BpartrH).

The ligand 4- {1E- (1H- benzimidazol-2-yl) phenylmethylideneimino}- 6- aryl-5-oxo-3-thioxo-2,3,4,5-tetrahydro- 1,2,4- triazine (BpartrH) is potent S, N and O donor coordinating molecule and exists in

thione- thiol tautomers (Figure 1). It can coordinate as neutral or mono anionic coordinating molecules.



**Figure 1: Structure of Ligands ( $L^1H$ , aryl= Phenyl,  $L^2H$ , aryl= p-chlorophenyl).**

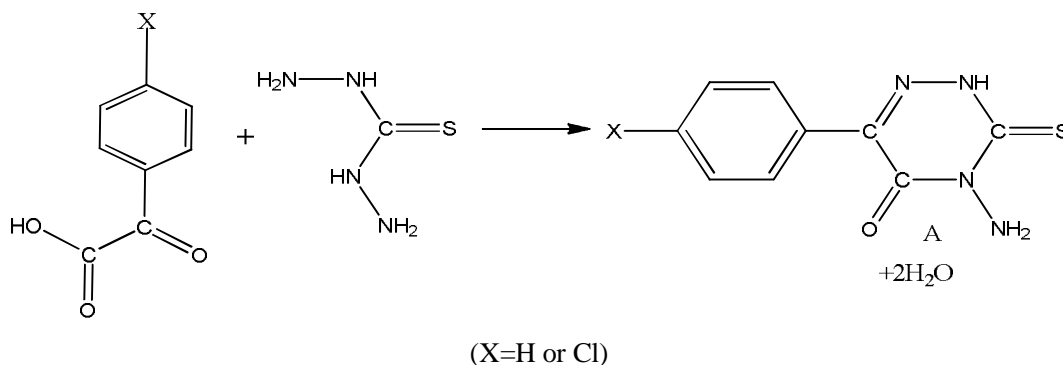
**MATERIAL AND METHODS:** Metal salts and solvents used were extra pure reagent of E. Merck or Anal-R Grade chemical of B.D.H. The ligands were prepared by known procedure<sup>8</sup>. The metal content of complexes were determined by standard procedure. The elemental analyses were performed as reported earlier.<sup>8</sup> The results of IR and UV were obtained from I.I.T, Patna and C.D.R.I. Lucknow.

**Preparation of ligand:** These ligands were prepared in two steps. The first part was preparation of ligand by condensing phenyl pyruvic acid ( $C_6H_5CO-COOH$ ) or p- chlorophenyl pyruvic acid ( $p-Cl-C_6H_4-CO-COOH$ ) with thiocarbohydrazide in aqueous ethanol at reflux temperature to give 4-amino-6-aryl-5-oxo-3-thioxo-2,3,4,5- tetrahydro- 1,2,4- triazine(A).

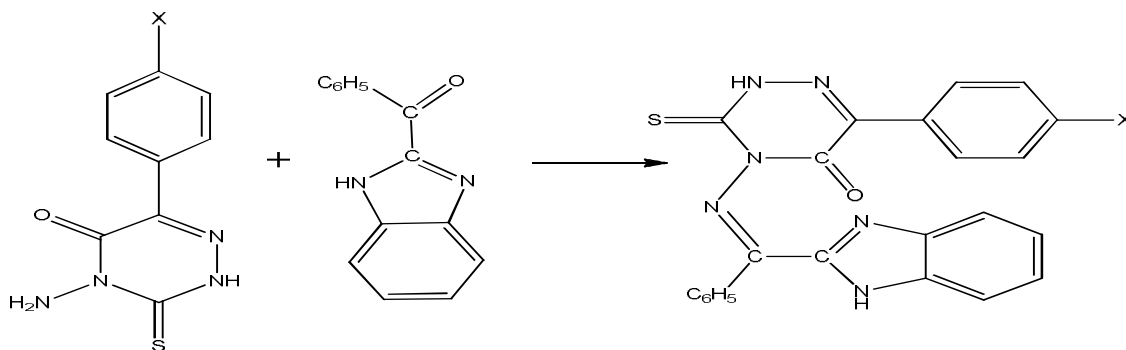
Second step: In second step the product 'A' was refluxed with 2- benzoyl- (1H- benzimidazole) leading to the formation of 4- {1E- (1H- benzimidazol- 2-yl)}

phenylmethylideneimino}-6- aryl- 5-oxo-3-thioxo-2,3,4,5- tetrahydro- 1,2,4 triazine ( $HL^1 =$  aryl group is  $C_6H_5$  and  $HL^2 =$  aryl group is p-chlorobenzene).

$HL^1 =$  4- {1E-(1H-benzimidazol-2-yl)-phenylmethylideneimino}-6-phenyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4- triazine and  $HL^2 =$  4- {1E-(1H-benzimidazol-2-yl)- phenylmethylideneimino}-6-p-chlorophenyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine (A).



**Scheme 1: Synthesis of 4-amino-6-aryl-5-oxo-3-thioxo-2,3,4,5- tetrahydro- 1,2,4- triazine.**



**Scheme 2: Synthesis of tetrahydro triazine derivative.**

These ligands were crystallized with (1:1) ethanol dioxane medium as cream coloured crystalline precipitate, M.P. of  $H_2L^1 = 227-228$  and those of  $H_2L^2 = 231-232$ .

**Preparation of complexes  $[ML_2]$  ( $M = Co^{II}, Mn^{II}, Ni^{II}, Cu^{II},$  and  $Zn^{II}$   $HL = HL^1$  and  $HL^2$ ):** About 20 millimole of ligand dissolved in hot 1:1 dioxane-ethanol mixture 30-40ml was treated with ethanol solution of 10 millimole of metal chloride. The mixed solution was heated upto reflux temperature and pH was raised by adding aqueous solution of sodium acetate under stirring for 7-8 hrs. Gradually separation was observed by formation of colored complexes and precipitation was completed by adding equal volume of water. The separated precipitate was digested on steam bath and collected on Buchner funnel and washed with cold methanol. The precipitate were

dried over  $CaCl_2$  and finally at  $50-60^\circ C$  in an air over. The dried products were analyzed and their analytical results are shown in Table 1. The E.P.R spectra of complexes were recorded on Varian EPR (E-112) Spectrophotometer in micro crystalline form at LNT. The Magnetic susceptibility was determined by Gouy's method making Diamagnetic correction using Pascal's constants.

**RESULTS AND DISCUSSION:** The elemental analysis of complexes formed by both ligands  $L^1H$  and  $L^2H$  corresponds to compositions  $ML_2$  ( $M = Mn^{II}, Co^{II}, Ni^{II}, Cu^{II}$  and  $Zn^{II}$ ,  $LH = L^1H$  or  $L^2H$ ). The dried complexes are almost insoluble in water but dissolved slightly in ethanol, methanol and acetone but soluble in dimethyl sulfoxide and dimethylformamide (DMF). The DMF solution of complexes exhibited negligible

electrical conductance value (6-10 ohm<sup>-1</sup>mol<sup>-1</sup>cm<sup>2</sup>) indicating that complexes are nonelectrolyte.<sup>21</sup> Zinc(II) Complexes ZnL<sub>2</sub> (HL= HL<sup>1</sup> or HL<sup>2</sup>) are diamagnetic while Mn<sup>II</sup>, Co<sup>II</sup>, Ni<sup>II</sup> and Cu<sup>II</sup> complexes are Paramagnetic (Table 2) and magnetic moment values were found in the range of high spin octahedral complexes.<sup>22</sup>

The electronic absorption spectra (qualitative) of Co<sup>II</sup> complexes shows strong absorption below 390 nm probably charge transfer type and two weak bands at 450-460 and 520-535 nm assignable to <sup>4</sup>T<sub>1g</sub> → <sup>4</sup>T<sub>2g</sub> and <sup>4</sup>T<sub>1g</sub> → <sup>4</sup>A<sub>2g</sub> transitions in octahedral field<sup>23</sup>.

Mn(II) Complexes do not show electronic absorption bands of appreciable intensity as Mn(II) complexes show only spin forbidden transition.<sup>24</sup> Ni(II) Complexes NiL<sub>2</sub> (HL= HL<sup>1</sup> or HL<sup>2</sup>) show strong absorption below 400 nm one weak band at 580-590 nm in the instrumental range 200-850 nm. The band is assigned to <sup>3</sup>A<sub>2g</sub>- <sup>4</sup>T<sub>1g</sub>(f) transition similar to high spin octahedral Ni(II) complexes.<sup>23-24</sup> Cu (II) complexes also show charge transfer strong absorption below 420 nm and a broad asymmetric band between 640-655 nm assignable to <sup>2</sup>B<sub>1g</sub> → <sup>2</sup>B<sub>2g</sub>, <sup>2</sup>E<sub>g</sub> transition similar to distorted octahedral copper (II) Complexes.<sup>25</sup>

**Table 1: Results of Elemental analysis of Ligands and Complexes.**

L <sup>1</sup> H	CuL <sub>2</sub> <sup>1</sup>	NiL <sub>2</sub> <sup>1</sup>	MnL <sub>2</sub> <sup>1</sup>	ZnL <sub>2</sub> <sup>1</sup>	CoL <sub>2</sub> <sup>1</sup>	L <sup>1</sup> H Found (Calculated)
% Metal	7.13(6.98)	6.31(6.49)	5.63(5.78)	7.02(7.17)	6.59(6.50)	-----
% Carbon	60.43(60.68)	60.81(61.00)	61.31(61.46)	60.41(60.56)	60.72(60.99)	64.78(65.09)
% Hydrogen	3.22(3.29)	3.21(3.31)	3.46(3.34)	3.43(3.29)	3.46(3.31)	3.89(3.77)
% Nitrogen	18.41(18.46)	18.43(18.56)	18.62(18.70)	18.38(18.43)	18.41(18.56)	19.70(19.81)
% Sulphur	7.21(7.03)	6.93(7.07)	7.01(7.12)	7.11(7.02)	6.93(7.07)	7.39(7.54)
L <sup>2</sup> H	CuL <sub>2</sub> <sup>2</sup>	NiL <sub>2</sub> <sup>2</sup>	MnL <sub>2</sub> <sup>2</sup>	ZnL <sub>2</sub> <sup>2</sup>	CoL <sub>2</sub> <sup>2</sup>	L <sup>2</sup> H Found (Calc)
% Metal	6.21(6.49)	5.92(6.03)	5.16(5.38)	6.61(6.67)	5.91(6.04)	-----
% Carbon	56.21(56.41)	56.48(56.68)	57.01(57.14)	56.27(56.30)	56.43(56.67)	60.21(60.06)
% Hydrogen	3.11(3.06)	3.21(3.08)	3.21(3.10)	3.31(3.05)	3.21(3.08)	3.63(3.48)
% Nitrogen	17.01(17.16)	17.13(17.25)	17.21(17.39)	17.01(17.13)	17.03(17.24)	18.12(18.28)
% Sulphur	6.42(6.54)	6.51(6.57)	6.48(6.62)	6.43(6.52)	6.41(6.57)	6.71(6.96)

**Table 2: Analytical result and Physical data of complexes.**

Compound	%Analytical result found (Calculated)					Magnetic moment values at 30 ±1°C in BM	Electrical conductance in ohm <sup>-1</sup> mol <sup>-1</sup> cm <sup>2</sup>
	Metal	Carbon	Hydrogen	Nitrogen	Sulphur		
L <sup>1</sup> H	-----	64.78(65.09)	3.89(3.77)	19.70(19.81)	7.39(7.54)	-----	-----
L <sup>2</sup> H	-----	60.21(60.06)	3.63(3.48)	18.12(18.28)	6.71(6.96)	-----	-----
CuL <sub>2</sub> <sup>1</sup>	7.13(6.98)	60.43(60.68)	3.22(3.29)	18.41(18.46)	7.21(7.03)	1.89	7
CuL <sub>2</sub> <sup>2</sup>	6.21(6.49)	56.21(56.41)	3.11(3.06)	17.01(17.16)	6.42(6.54)	1.86	6
MnL <sub>2</sub> <sup>1</sup>	5.63(5.78)	61.31(61.46)	3.46(3.34)	18.62(18.70)	7.01(7.12)	5.92	8
MnL <sub>2</sub> <sup>2</sup>	5.16(5.38)	57.01(57.14)	3.21(3.10)	17.21(17.39)	6.48(6.62)	5.94	5
NiL <sub>2</sub> <sup>1</sup>	6.31(6.49)	60.81(61.00)	3.21(3.31)	18.43(18.56)	6.98(7.07)	3.08	5
NiL <sub>2</sub> <sup>2</sup>	5.92(6.03)	56.48(56.68)	3.21(3.08)	17.13(17.25)	6.51(6.57)	3.21	7
ZnL <sub>2</sub> <sup>1</sup>	7.02(7.17)	60.41(60.56)	3.43(3.29)	18.38(18.43)	7.11(7.02)	Diamagnetic	6
ZnL <sub>2</sub> <sup>2</sup>	6.61(6.67)	56.27(56.30)	3.31(3.05)	17.01(17.13)	6.43(6.52)	Diamagnetic	5
CoL <sub>2</sub> <sup>1</sup>	6.59(6.50)	60.72(60.99)	3.46(3.31)	18.41(18.56)	6.93(7.07)	5.12	8
CoL <sub>2</sub> <sup>2</sup>	5.91(6.04)	56.43(56.67)	3.21(3.08)	17.03(17.24)	6.41(6.57)	5.03	7

**Table 3: Antifungal activity of ligands and some complexes at 30 ± 1 °C.**

Fungi	Conc. in ppm	L <sup>1</sup> H	L <sup>2</sup> H	CuL <sub>2</sub> <sup>1</sup>	CuL <sub>2</sub> <sup>2</sup>	ZnL <sub>1</sub> <sup>2</sup>	ZnL <sub>2</sub> <sup>2</sup>	CoL <sub>1</sub> <sup>2</sup>	CoL <sub>2</sub> <sup>2</sup>	Ref
A. Flavus	50	35	37	65	68	48	50	47	50	85
	100	48	52	82	85	60	65	61	63	96
A. Niger	50	36	38	63	66	55	60	58	62	82
	100	46	54	81	86	68	76	73	80	97
R. phaseoli	50	30	35	58	62	52	58	56	60	79
	100	44	49	80	87	69	78	72	75	97
F. oxysporum	50	42	42	68	70	50	60	48	53	81
	100	52	55	85	88	62	72	63	68	98

The reference used for antifungal activity was Mycostatin.

The IR spectra of ligand HL<sup>1</sup> and HL<sup>2</sup> both display NH stretching band of benzimidazole<sup>26</sup> and triazine ring NH vibrations are observed at 3185 and 3235 cm<sup>-1</sup>. The ligand exist in thione form in solid state as the free ligands HL<sup>1</sup> and HL<sup>2</sup> show (>C=S) stretch as strong band at 965 and 972 respectively.<sup>27</sup> The out of plane bending band of (CH), phenyl ring, triazine and imidazole ring were observed at 905, 868, 745, 692.

The (C=O) group stretching vibration of HL<sup>1</sup> is observed as strong band at 1721 and for HL<sup>2</sup> at 1728 cm<sup>-1</sup> and these vibrations are retained in their metal complexes suggesting that oxo group of CO oxygen is not involved in coordination<sup>28</sup>. The imidazole ring δ (NH) vibration and triazine ring δ (NH) band was assigned to IR band located at 1505-1512 cm<sup>-1</sup>. The ν (C=N) of free ligand was observed at 1630 cm<sup>-1</sup>. The phenyl and triazine ring skeletal vibrations were located at 1605, 1555, 1445, 1365, 1245 and 1120 cm<sup>-1</sup> and these vibrations are retained in complexes with slight chain in band position and intensity due to coordination of ligands. The ν (C=N) vibration of ligands were found to be shifted at lower position by 20-25 in complexes suggesting that (C=N) tertiary nitrogen of benzimidazole is involved in bonding.<sup>29</sup> The thione group (C=S) stretch at 965 and 972 cm<sup>-1</sup> disappear and new bands for (C-S) group is observed at 720 ± 12 cm<sup>-1</sup> suggesting that coordination of (C=S) sulphur has taken place by deprotonation of thiol tautomers of both HL<sup>1</sup> and HL<sup>2</sup>. The aldimine >C=N stretch of HL<sup>1</sup> assigned to a medium band at 1605 ± 2 cm<sup>-1</sup> which has been found to be shifted to lower frequency and observed at 1990 ± 5 cm<sup>-1</sup> due to coordination of aldimine (C=N) nitrogen.<sup>30-33</sup> Thus both the ligand HL<sup>1</sup> and HL<sup>2</sup> are suggested to coordinate as tridentate (NNS) ligand.

Antifungal activity of ligand HL<sup>1</sup> and HL<sup>2</sup> and some of their complexes were screened by radial growth

method<sup>31</sup>. The screening medium of compositions 20g starch, 20g agar agar, 20g glucose dissolved in 1 litre distilled water were made. To this medium 50 and 100 ppm concentration of ligands and Cu(II), Zn(II) and Co(II) complexes were made in DMF.

The medium were poured in petri plate and shown in Table 3. It was found that Cu(II) complexes of both HL<sup>1</sup> and HL<sup>2</sup> display larger antifungal activity than those of Zn(II) and Co(II) complexes. The chlorobenzyl derivative L<sup>2</sup>H complexes show much activity compared to benzyl derivative L<sup>1</sup>H.

**CONCLUSION:** In summary we have reported here a suitable and facile method for preparation of some novel metal complexes having benzimidazole and triazine based ligands. All the prepared complexes were evaluated for antifungal potential and few of them were found to be potent antifungal agents. All the characterization data and elemental analysis results were in good agreement with illustrated structures of metal complexes. Magnetic susceptibility results were also in support of synthesized metal complexes. Our present study is very useful from synthetic as well as medicinal perspective. Our work may open new doors in antifungal drug discovery research and metal complex synthesis.

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