



SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF TRANSITION METAL COMPLEXES OF 4-[(2-HYDROXY-4-METHOXYPHENYL)METHYLENEAMINO]-2,4-DIHYDRO-3H-1,2,4-TRIAZOLE-3-THIONE

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A novel nitrogen containing 4-[(2-hydroxy-4-methoxyphenyl)methyleneamino]-2,4-dihydro-3H-1,2,4-triazole-3-thione ligand (**H₂L**) was synthesized by using an equimolar ratio of 4-amino-1,2,4-triazole-3-thione and 2-hydroxy-4-methoxybenzaldehyde. A series of Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes was synthesized by using the ligand. The synthesized ligand and transition metal complexes were characterized by IR, ¹H NMR, ¹³C NMR, Mass spectrometry, UV, XRD and TGA investigation methods. Spectral data suggests that the ligand acts as a tridentate SNO donor. Further, the synthesized H₂L ligand and their metal complexes were screened for antimicrobial activity. The results of biological activities showed that the metal complexes have higher antifungal as well as antibacterial activity as compared to the parent H₂L ligand against the tested microbes.

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chelating position of -OH group, which can easily deprotonate and bind to metal ions.

In many cases, triazole moiety containing a ligand having a sulfur, oxygen and nitrogen atoms bind to the metal ion and enhance the biological activity as compared to parent moiety. In the present work, we synthesized tridentate (S,N,O) i. e. 2,4-dihydro-4-[(2-hydroxy-4-methoxyphenyl)methylene]-amino-3H-1,2,4-triazole-3-thione ligand (H₂L) and its transition metal complexes which were screened for antifungal and antibacterial potential.

INTRODUCTION

Schiff base and their metal complexes play an important role in the biological systems due to their ability to bind to biologically active sites. 1,2,4-triazole derivatives show various pharmaceutical potential¹⁻⁶ including antitubercular^{7,8} antimicrobial,⁹ antifungal^{10,11} anticancer,¹² cytotoxic¹³ and antioxidant¹⁴ activities. Due to multidentate nature, they are chelate-forming ligands and can form various transition metal complexes.¹⁵ Various triazole moieties containing drugs such as vorozole, anastrozole and letrozole (Figure 1) are commercially available in the market.¹⁶

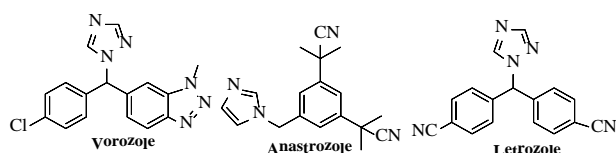


Figure 1. Some commercially marketed azole drugs

Schiff bases derived from vanillin are well-known in the literature for a wide range of biological activities.¹⁷⁻¹⁹ An important benefit of using 2-hydroxy-4-methoxybenzaldehyde instead of vanillin is the availability of

EXPERIMENTAL

All the used chemicals were AR grade and purchased from Spectrochem or SD Fine Ltd. and used without purification. The 4-amino-1,2,4-triazole-3-thione was prepared according to the literature method.²⁰ ¹H and ¹³C NMR spectra were recorded in DMSO-d₆ on Bruker NMR, IR spectra on Perkin IR spectrometer, UV analyses were performed on a Shimadzu UV-VIS instrument and TGA results were obtained on a Shimadzu thermogravimetric analyzer. XRD measurements were done on a Philips Bragg-Brentano parafocusing goniometer (CuK_α) at 298 K.

Synthesis of 4-amino-1, 2, 4-triazole-3-thione (3a)

A thiocarbonylhydrazide (**2**) (20.12g, 0.2 mol) was mixed with 20 mL of 98-100% formic acid (**1**) and the contents were refluxed for 10-20 minutes. The solution was cooled to room temperature to get a white crystalline solid, which was recovered by filtration followed by crystallization from ethanol to afford the pure 4-amino-1, 2, 4-triazole-3-thione (**3a**) (Scheme 1). Yield: 76 %, M. P.= 166 °C.

Synthesis of 4-[(2-hydroxy-4-methoxyphenyl)methyleneamino]-2,4-dihydro-3H-1,2,4-triazole-3-thione, ligand (H₂L) (5a)

An equimolar mixture of 2-hydroxy-4-methoxy benzaldehyde (**4**) (0.116g, 0.001 mol) and 4-amino-1,2,4-triazole-3-thione (**3a**) (0.152g, 0.001 mole) in 3 mL glacial acetic acid was refluxed for 3 hours. After completion of reaction, the reaction mass was poured on crushed ice and filtered off to get 2,4-Dihydro-4-[(2-hydroxy-4-methoxyphenyl)methyleneamino]-3H-1,2,4-triazole-3-thione as a yellow coloured solid which was crystallized from absolute ethanol (Scheme 2).

The physical and analytical data of the synthesized compound are reported in Table 1.

Spectral data of ligand (H₂L)

Yield: 80 %, M. P.: 259-260 °C; IR (KBr): cm⁻¹ 1608.52 ν (HC=N), 2758ν (-SH), 3232ν (-OH); ¹H NMR (200 MHz, DMSO-*d*₆) δ ppm 3.39 (s, 3H, -OCH₃); 5.98 - 6.17 (m, 2H, Ar-H); 6.92 (d, *J* = 8.08 Hz, 1H, Ar-H); 7.92 (s, 1H, -N=CH-N); 9.13 (d, *J* = 2.53 Hz, 1H, Ar-H); 10.26 (s, 1H, -OH); 13.29 (br. s, 1H, SH); ¹³C NMR (125 MHz, DMSO-*d*₆): δ ppm 164.16 (s, quat, Ar), 162.71 (s, quat, Ar), 160.46 (s, quat, triazole), 158.94 (-HC=N), 137.58 (s, triazole), 130.91 (s, Ar), 110.81 (s, Ar), 107.37 (s, Ar), 101.13 (s, Ar), 55.52 (s, OCH₃); LCMS: *m/z* (%): 251.1 (M+H).

General procedure for preparation of metal complexes (6a-6f)

A methanolic solution of metal salt was added dropwise to a boiling methanolic solution of ligand H₂L in an equimolar ratio (1:1) with constant stirring. The pH of the reaction mixture was adjusted to 7.5 to 8.5 by adding 10 % ethanolic ammonia solution and the contents were refluxed for about 7-8 hr.

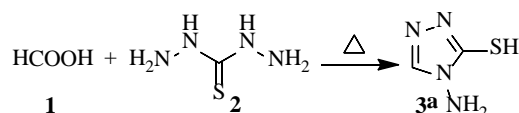
Table 1. Physical and analytical data of the synthesized compounds

Compounds	Mol. Formula (Formula weight)	Melting point, °C	Color	Elemental analysis found (calculated)%				
				% C	% H	% N	% S	% M
Ligand (H ₂ L) (5a)	C ₁₀ H ₁₀ N ₄ O ₂ S (250.05)	259-260	Pale yellow	47.87 (47.99)	4.09 (4.03)	22.44 (22.39)	12.79 (12.81)	-
[Mn(L)(H ₂ O) ₃] (6a)	C ₁₀ H ₁₄ MnN ₄ O ₅ S (357.24)	dec	Bright yellow	33.75 (33.62)	3.99 (3.95)	15.59 (15.68)	8.92 (8.98)	15.31 (15.38)
[Co(L)(H ₂ O) ₃] (6b)	C ₁₀ H ₁₄ CoN ₄ O ₅ S (361.24)	dec	Brown	33.16 (33.25)	3.80 (3.91)	15.64 (15.51)	8.79 (8.88)	16.22 (16.31)
[Ni(L)(H ₂ O) ₃] (6c)	C ₁₀ H ₁₄ N ₄ NiO ₅ S (360.00)	dec	Brownish	33.26 (33.27)	3.80 (3.91)	15.59 (15.52)	8.79 (8.88)	16.40 (16.26)
[Cu(L)(H ₂ O)] (6d)	C ₁₀ H ₁₀ CuN ₄ O ₃ S (329.82)	dec	Light green	36.49 (36.42)	3.10 (3.06)	16.80 (16.99)	9.80 (9.72)	19.15 (19.27)
[Zn(L)(H ₂ O)] (6e)	C ₁₀ H ₁₀ N ₄ O ₃ SZn (330.00)	dec	Yellow	36.29 (36.21)	3.15 (3.04)	16.81 (16.89)	9.55 (9.67)	19.60 (19.72)
[Cd(L)(H ₂ O) ₃] (6f)	C ₁₀ H ₁₄ CdN ₄ O ₅ S (414.71)	dec	Cream yellow	28.89 (28.96)	3.52 (3.40)	13.42 (13.51)	7.65 (7.73)	27.20 (27.11)

The precipitated solid metal complex was filtered and washed several times with absolute methanol and dried (Scheme 3).

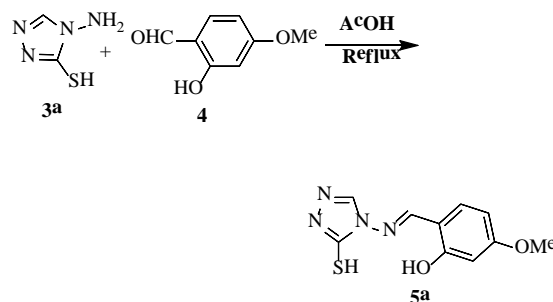
RESULTS AND DISCUSSIONS

Synthesis of triazole ring was performed by reacting thiocarbonylhydrazide (**2**) with 98-100% formic acid (**1**) under reflux for 10-20 minutes. The yield of 4-amino-1, 2, 4-triazole-3-thione (**3a**) (Scheme 1) was found to be 76 %.



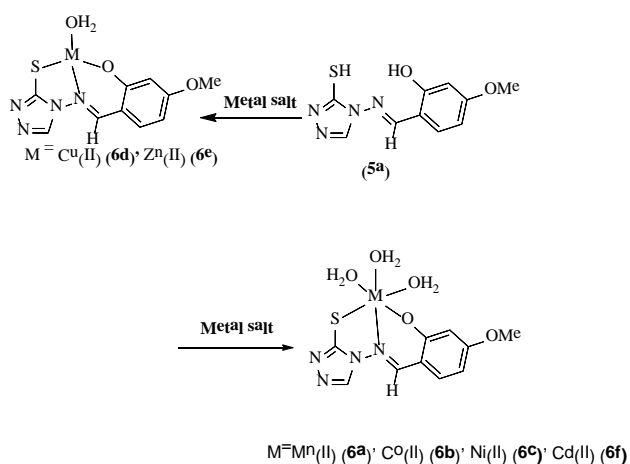
Scheme 1. Synthesis of 4-amino-1,2,4-triazole-3-thione

An equimolar mixture of 2-hydroxy-4-methoxy benzaldehyde (**4**) and 4-amino-1,2,4-triazole-3-thione (**3a**) in acetic acid under 3 h reflux resulted in 4-[(2-hydroxy-4-methoxyphenyl)methyleneamino]-2,4-dihydro-3H-1,2,4-triazole-3-thione as yellow solid (Scheme 2). The physical and analytical data of the synthesized ligand is reported in Table 1.



Scheme 2. Synthesis of Schiff base ligand H₂L

Refluxing methanolic solutions of the metal salt and ligand H₂L in an equimolar ratio (1:1) for 7-8 h followed by adjusting the pH of the reaction mixture to 7.5-8.5 by adding 10 % ethanolic ammonia solution resulted in solid metal complexes (Scheme 3).



Scheme 3. Synthesis of metal complexes (6a-6f)

Physical and analytical data of the synthesized metal complexes is given in Table 1. The analogous reaction with iron(II) salts resulted in a complex mixture containing an iron(II) and two iron(III) complexes as detected by Mössbauer. Efforts to grow single crystals were unsuccessful. The synthesized complexes were proved to be X-ray amorphous except Mn(II), Zn(II) and Cd(II) complexes. These complexes look like to be monoclinic, and the lattice constants could not be determined exactly because of small particle size and wide bands of compounds.

¹H NMR spectra

In the ¹H NMR spectrum of the ligand, the azomethine (-CH=N-) proton appearing as a singlet at 9.14 δ ppm was shifted to δ 9.18 ppm in Zn complex. The signal for azomethine proton in zinc complex was observed slightly downfield, which is due to the transfer of electrons from azomethine nitrogen to zinc metal. There is formation of a coordination bond between azomethine nitrogen and zinc (Zn←N) [21]. The characteristic proton signal of triazole (-SH) and phenolic (-OH) disappeared in Zn complex, indicating that -S⁻, -O⁻ bindings form during complex formation. The coordinated water peak appeared at δ 3.04 ppm in the spectrum of Zn complex.

Mass spectra

The LCMS spectrum of ligand (H₂L) showed a peak at 251.1 amu corresponding to M+H confirming the suggested formula (C₁₀H₁₀N₄O₂S). The mass spectrum of metal complexes displayed peaks at 361.0 and 331.2 amu for nickel(II) and zinc(II) complexes, respectively, corresponding to the molecular ion peak (M+H). The molecular ion peaks of metal complexes confirm the proposed molecular formula C₁₀H₁₄N₄NiO₅S for nickel and C₁₀H₁₀N₄O₃SZn for zinc complex. The mass spectra of

metal complexes reveal the evidence of equimolar ratio of metal and ligand (1:1) as presented in Scheme 3.

UV-Visible spectra

Electronic spectra of the synthesized metal complexes were recorded in DMSO solvent at room temperature. The results can be seen in Table 3. The bands found for d¹⁰ metal-containing complexes (Zn(II), Cd(II)) may contain only CT and ligand n→π* bands, while ligand absorptions may correspond to n→π* and π→π* transitions.²³⁻²⁵

Table 3. UV data for the synthesized metal complexes

Sample	Absorption maxima, λ _{max} , nm
Ligand (H ₂ L) (5a)	400, 325
[Mn(L)(H ₂ O) ₃] (6a)	406, 279
[Co(L)(H ₂ O) ₃] (6b)	552, 404
[Ni(L)(H ₂ O) ₃] (6c)	800, 613, 394
[Cu(L)(H ₂ O)] (6d)	612, 432
[Zn(L)(H ₂ O)] (6e)	402
[Cd(L)(H ₂ O) ₃] (6f)	516, 389

As can be seen from Table 3, the geometry around Zn(II) and Cd(II) might be different, probably due to the difference in coordination numbers of central ions in these complexes. The UV-Vis intensities of octahedral Mn(II) complexes are very low as a consequence of their doubly forbidden nature and easily be masked by the bands of the organic ligand. Over the ligand bands, the d-d bands of octahedral Co(II) and Ni(II) complexes could be detected (Table 3). The visible range bands at 552 for Co(II) and at 800 and 613 for Ni(II) probably belongs to the ⁴T_{1g}→⁴T_{1g}(P) and the ³A_{2g}→¹E_g and ³A_{2g}→³T_{1g} transitions, respectively. As usual, the distorted tetrahedral Cu(II) complex has only one broadband in the visible region.

IR spectra and bonding modes

Infrared spectroscopy gives information regarding the type of functional groups (-SH, -OH, -N=CH-) attached to the corresponding metal ions. IR spectrum of ligand displays a band corresponding to -N=CH- linkage at 1598 cm⁻¹, which confirms the formation of Schiff base. Similarly, the band observed around 1608 cm⁻¹ corresponds to the same -N=CH- linkage coordinated to the metals.²⁶⁻²⁸ It is supported by the appearance of metal-nitrogen ν(M-N) bands between 441 and 466 cm⁻¹. In the IR spectra of ligand and complexes, a broad band at 2758 and 1109 cm⁻¹ arise due the ν(S-H) and ν(C=S), respectively, while in the complexes, an ionic nature C-S band appears at 720 cm⁻¹.²⁷

The broad band in the spectra of complexes in the 3310-3330 cm⁻¹ region indicates the presence of coordinated water. The broad band observed at 3232 cm⁻¹ corresponds to -O-H stretching mode in the ligand, which disappears in the complexes indicating deprotonation of phenolic-OH during the complex formation. In IR spectra, -S-H stretching vibration was absent in metal complex due to deprotonation of thiol group and thiol sulfur coordinated to the metal ion.²⁹ Some selected IR spectral data are summarized in Table 4.

Table 4. Important IR spectral bands and their assignment

Compound	$\nu(\text{HC}=\text{N})$	$\nu(-\text{OH})$	$\nu(\text{M}-\text{N})$	$\nu(\text{M}-\text{O})$
5a	1609	3237	-	-
6a	1592	3390 (br.)	435	490
6b	1594	3345 (br.)	470	580
6c	1597	3361 (br.)	451	550
6d	1595	3450 (br.)	460	530
6e	1594	3370	447	569
6f	1592	3300 (br.)	490	553

From the IR data of the ligand and the corresponding metal complexes, it is clear that the ligand acts as a

tridentate ligand. The coordinating atoms are the azomethine nitrogen, the thiol-sulfur and phenolate oxygen.

On the basis of the above spectral observations, we conclude that the ligand coordinates dinegative and tridentate around the metal ions.

Thermogravimetric analysis

Thermal data was recorded in the temperature range between 25-1000 °C under N₂ and the results are summarized in Table 5. The primary decomposition intermediates were proved to be X-ray amorphous, based on the mass loss, these are expected to be the appropriate oxides of the central metal ions.

Table 5. Thermogravimetric analysis of the synthesized complexes

Sample	Temperature range, °C (Peak temp.)	Mass loss, %
Mn(II) 6a	54-150	7.11
	350-400	17.13
	575-600	18.66
Co(II) 6b	60-150	9
	310-350	27.23
	440-535	12
Ni(II) 6c	67-150	11
	323-385	51
Cu(II) 6d	60-155	6.37
	232-250	11
	332-350	10
Zn(II) 6e	200-212	4.53 (5.42)
	339-382	29.82
	457-660	35.26
Cd(II) 6f	71-170	11
	335-370	22
	423-500	18

Antimicrobial study

The synthesized compounds (ligand and metal complexes) were explored for antifungal and antibacterial activities. These activities were performed on Petri-plate containing 30 mL potato dextrose agar and nutrient agar medium. The plates were incubated for 24-48 h and 20-24 h culture of fungal and bacterial strains, respectively and the results were measured in terms of zone of inhibition in mm. Two fungal (*Aspergillus niger*, *Alternaria alternata*) and one bacterial (*S. Aureus*) species at 250 ppm concentration were used for studying antimicrobial activities. Results were compared with the standard drug i. e. carbendazim for fungal and streptomycin for bacterial as positive control reference drugs (Table 6).

The results of antifungal activity suggested that among the tested compounds, only the cobalt complex was active against *Aspergillus niger* and copper, cadmium complexes against *Alternaria alternata* comparable with the standard drug.

Table 6. Results of antimicrobial activity of the synthesized compounds

Compounds	Zone of Inhibition Diameter in mm		
	Antifungal		Antibacterial
	<i>A. Niger</i>	<i>Alternaria A.</i>	<i>S. Aureus</i>
Ligand (H ₂ L)	17	5	10
6a	13	12	15
6b	21	15	15
6c	14	11	16
6d	17	40	17
6e	14	25	15
6f	13	45	20
*AF	24	26	-
*AB	-	-	40

*AF = Carbendazim, *AB = Streptomycin

The antibacterial screening performed against *Streptococcus Aureus* indicates that all complexes were less potent than the standard drug - streptomycin. Selected images for the antimicrobial activity are shown in Figure 5.

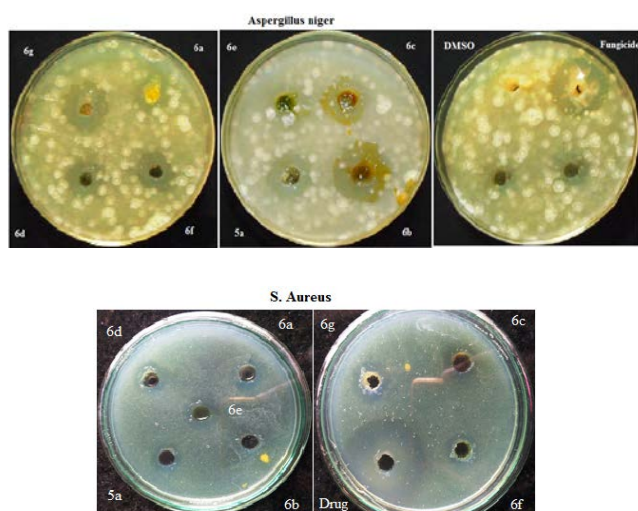


Figure 5. Selected images for the antimicrobial activity

CONCLUSION

The synthesized ligand acts as tridentate around the central metal(II) ions. On the basis of different techniques, the complexes of Mn(II), Co(II), Ni(II) and Cd(II) showed octahedral geometry, but Cu(II) complex exhibits square planar and Zn(II) form tetrahedral geometry. Results of antimicrobial activity indicate that the metal complexes show greater activity than the parent ligand. The ligand and metal complexes showed very less activity against *S. aureus*, which could be due to azomethine linkage and hetero atoms present in these compounds.

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