STUDIES ON TRANSITION METAL COMPLEXES OF DRUG BASED SCHIFF BASES

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Abstract:
The Isoniazide (IZ) reacted with 5-Chlorosalicyladehyde (CSA) and 3,5-dichloro salicylaldehyde (DCSA) yields novel ligands, N'-(5-chloro-2-hydroxy benzylidene) isonicotinohydrazide (CSAIZ) and N'-(3,5-dichloro-2-hydroxy benzylidene) isonicotino hydrazide (DCSAIZ). The transition metal chelates of CSAIZ and DCSAIZ ligands were prepared by using Cu^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+} and Zn^{2+} metal ions. All the CSAIZ and DCSAIZ ligands and its all metal chelates were characterized by elemental content, IR spectroscopic, metal: ligand ratio and magnetic properties. All the CSAIZ and DCSAIZ ligands and its all metal chelates also were monitored for antimicrobial activity.

Keywords: Isoniazide, 5-Chlorosalicyladehyde, 3,5-dichloro salicylaldehyde, Metal Chelates, spectral studies, magnetic properties and antimicrobial activity.

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INTRODUCTION

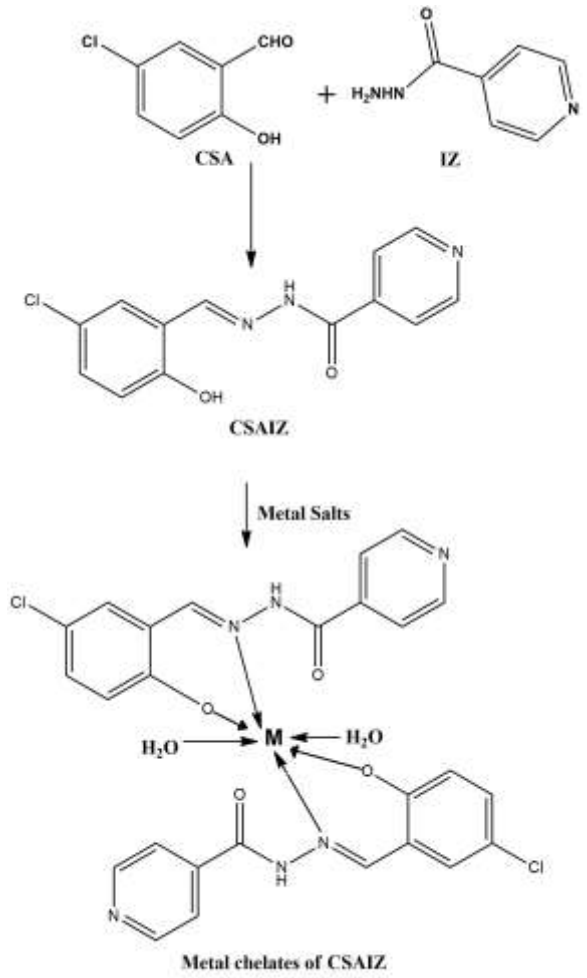
Schiff bases are organic compounds having azomethine group prepared by condensation of aldehydes or ketones with amines. Schiff bases are special type of ligands having remarkable Co-ordination mode towards transition metals [1-3]. The recent report indicate that the investigation of a new category of ligands and their complexes having biomedical applications [4-6]. The Schiff base metal complexes have received too much attention due to their biological applications [7-12]. Numbers of Schiff base-metal complexes have also been found as antimicrobial agents [13-15]. The Schiff's bases based on drugs received more attention towards medicinal applications. The Schiff's bases of sulfa drugs and Isoniazide are the examples reported as excellent pharmaceuticals [16-18]. The Schiff base of Isoniazide and 2-methoxy salicylaldehyde has been reported as antibacterial and antioxidant activity [19]. However, the study on Schiff's base of chloro substituted salicylaldehyde and Isoniazide has not been reported. Thus, the present work comprises the synthesis, Characterization, chelating and microbicidal properties of Schiff's base of chloro substituted salicylaldehyde and Isoniazide. The design of synthesis is shown in scheme 1.

EXPERIMENTAL

The entire chemicals used for present study were of laboratory grade.

Synthesis of N'-(5-chloro-2-hydroxybenzylidene)isonicotinohydrazide (CSAIZ)

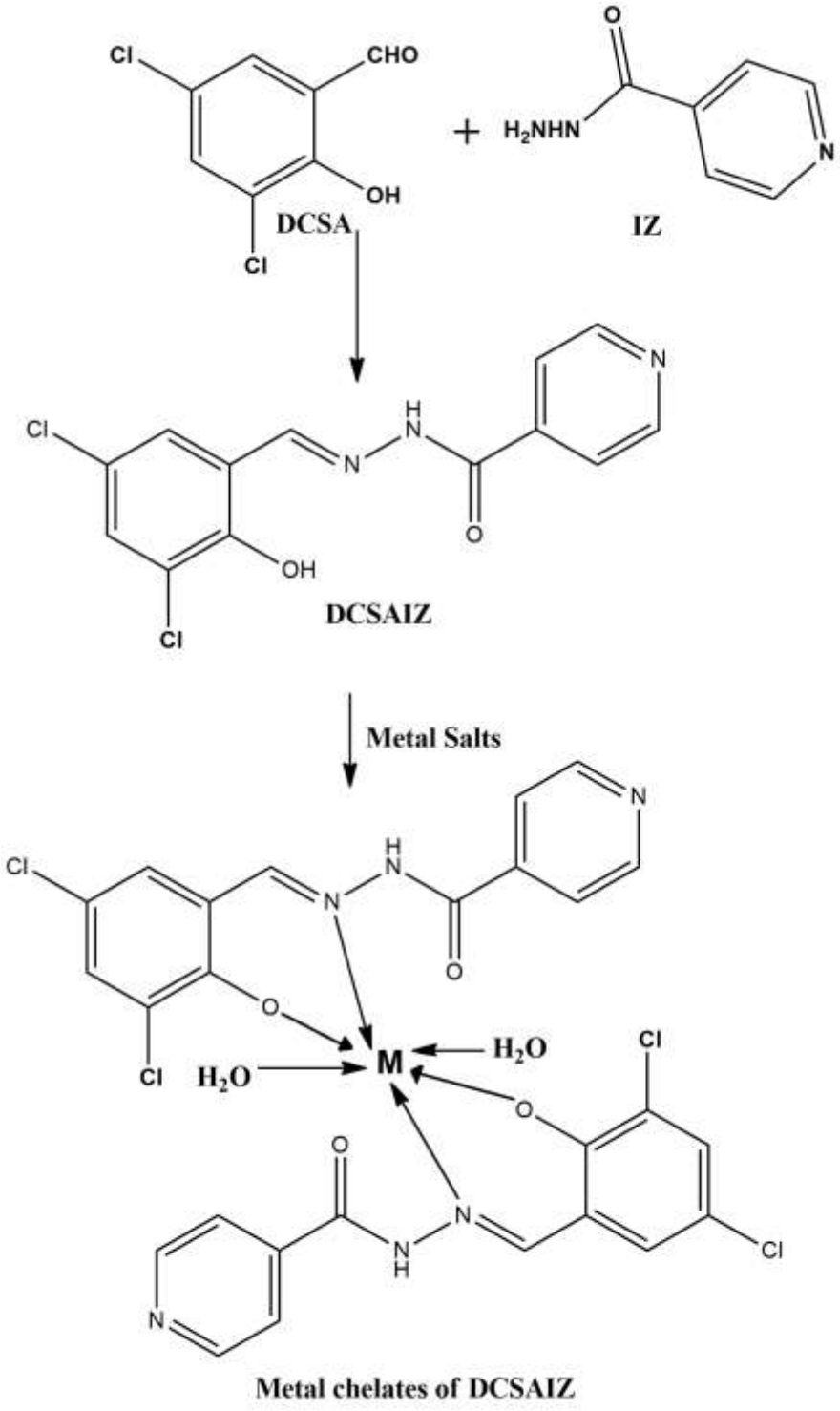
To a solution of Isoniazide (0.01 mol) in absolute alcohol (50ml), 5-chloro salicylaldehyde (0.01 mol) was added. 5 drops of glacial acetic acid was added as catalyst in round bottom flask. The mixture was warmed on the steam bath for 3 hrs. with occasional shaking. The reaction was cooled, filtered, and washed with ethyl acetate. The filtrate was concentrated, the residue was extracted with petroleum ether, and the solution filtered. Concentration of the filtrate gave 77% yield, m.p.156-157° C. Recrystallization from petroleum ether (b.p.60-68°C). Anal. Calcd. for $C_{13}H_{10}N_3O_2Cl$ (275.5): %C, 56.64; %H, 3.66; %N, 15.24;%Cl, 12.86. Found: %C, 56.6; %H, 3.6; %N, 15.2; % Cl, 12.8. IR Spectral Features (cm^{-1}) shows at 3400-3250(NH and OH), 3020, 2850, 1630,1470(C-H),1685(C=O),1590(C=N),1275(C-N),1150(C-O), 750(C-Cl) and NMR Signals (δ ppm) at 5.40 (s,1H,OH), 7.05-8.95(m,9H, Ar-H), 9.20 (1H,s,CH=N) and 8.10 (1H, s,NH). M^+ : 276.4.



Where M = Cu(II),Mn(II),CO(II),Ni(II) and Zn(II)

Synthesis of N'-(3,5-dichloro-2-hydr oxybenzy lidene)isonicotinohydrazide (DCSAIZ)

This was prepared by similar method for CSAIZ. Instead of 5-chloro salicylaldehyde 3,5-dichloro salicylaldehyde was taken. The yield was 72%. m.p.142-143° C. Recrystallization from petroleum ether (b.p.60-68°C). Anal. Calcd. for $C_{13}H_9N_3O_2Cl_2$ (310): %C, 50.35; %H, 2.92; %N, 13.55;%Cl, 22.86. Found: %C, 50.3; %H, 2.9; %N, 13.5;%Cl, 22.8. IR Spectral Features (cm^{-1}) shows at 3402-3250(NH and OH), 3025, 2852, 1630,1470(C-H), 1680 (C=O), 1590 (C=N),1275(C-N),1150(C-O), 752(C-Cl) and NMR Signals (δ ppm) at 5.40 (s,1H,OH), 7.05 - 8.95(m,8H, Ar-H), 9.20 (1H,s,CH=N) and 8.10 (1H, s,NH). M^+ : 311.9.



Metal chelates of DCSAIZ

Where M = Cu(II),Mn(II),CO(II),Ni(II) and Zn(II)

Scheme-1

Synthesis of metal chelates of CSAIZ and DCSAIZ:

The metal chelates of CSAIZ and DCSAIZ with Cu^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}**,** and Zn^{2+} metal ions were prepared in following general methods. They are according to following two steps:

Step-I Preparation of Ligands solution:

Ligand (0.1 mol) was taken in 500 ml beaker and 1,4-dioxane was added up to complete dissolution. Then dilute to 100 ml. The 20ml of this solution containing 0.02M ligand.

Step-II Synthesis of Ligand-metal-chelates:

In a solution of metal acetate (0.01 mol)in 1,4-dioxane: water (50:50 v/v) mixture (40 ml) the 20 ml of Ligand solution (containing 0.02 M) was

added with vigorous stirring at room temperature. The appropriate pH was adjusted 5-6 by addition of sodium acetate for complete precipitation of metal chelate. The precipitates were digested on a boiling water bath. The precipitates of chelate were filtered off, washed by water and air-dried.

Table-1: ANALYSIS OF CSAIZ LIGAND AND ITS METAL CHELATES

Empirical Formula (Mol. Wt. gm/mole)	Yield (%)	Elemental Analysis				
		% C	% H	% N	% Cl	%M
		Cald Found	Cald Found	Cald Found	Cald Found	Cald Found
$C_{13}H_{10}N_3O_2Cl$ (275.5)	77	56.64 56.6	3.66 3.6	15.24 15.2	12.86 12.8	-
$C_{26}H_{18}N_6O_4Cl_2Cu.2H_2O$ (648.54)	71	48.11 48.1	3.39 3.3	12.95 12.9	10.95 10.9	9.80 9.7
$C_{26}H_{18}N_6O_4Cl_2Co.2H_2O$ (643.94)	73	48.45 48.4	3.42 3.4	13.04 13.0	11.03 11.0	9.15 9.1
$C_{26}H_{18}N_6O_4Cl_2Ni.2H_2O$ (643.71)	70	48.47 48.4	3.42 3.4	13.05 13.0	11.03 11.0	9.12 9.1
$C_{26}H_{18}N_6O_4Cl_2Mn.2H_2O$ (639.94)	73	48.75 48.7	3.44 3.4	13.13 13.1	11.09 11.0	8.59 8.5
$C_{26}H_{18}N_6O_4Cl_2Zn.2H_2O$ (650.38)	74	47.94 47.9	3.38 3.3	12.92 12.9	10.92 10.9	10.05 10.0

MEASUREMENTS:

The elemental contents were determined by Thermo Finigen Flash1101 EA (Itally) the metals were determined volumetrically by Vogel's method [20].To a 100 mg chelate sample, each 1 ml of HCl, $H_2SO_4$and $HClO_4$ were added and then 1 g of $NaClO_4$ was added. The mixture was evaporated to dryness and the resulting salt was dissolved in double distilled water and diluted to the mark. From this solution the metal content was determined by titration with standard EDTA solution. Infrared spectra of the synthesized compounds were recorded on Nicolet 760 FT-IR spectrometer. NMR spectrum of ligands were recorded on 60 MHz NMR spectrophotometer. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046. Magnetic susceptibility measurement of the synthesized complexes was carried out on Gouy Balance at room temperature. Mercury tetrathio cynato cobalate (II) $Hg[Co(NCS)_4]$ was used as a calibrant. The electronic spectra of complexes in solid were recorded on at room temperature. MgO was used as reference. Antifungal activity of all the samples was monitored against various fungi, following the method reported in literature[21].

Table-2: ANALYSIS OF DCSAIZ LIGAND AND ITS METAL CHELATES

Empirical Formula (Mol. Wt. gm/mole)	Yield (%)	Elemental Analysis				
		% C	% H	% N	% Cl	%M
		Cald Found	Cald Found	Cald Found	Cald Found	Cald Found
$C_{13}H_9N_3O_2Cl_2$ (310)	72	50.35 50.3	2.92 2.9	13.55 13.5	22.86 22.8	-
$C_{26}H_{16}N_6O_4Cl_4Cu.2H_2O$ (717.54)	69	43.48 43.4	2.79 2.7	11.71 11.7	19.79 19.7	8.86 8.8
$C_{26}H_{16}N_6O_4Cl_4Co.2H_2O$ (712.94)	66	43.76 43.7	2.81 2.8	11.78 11.7	19.92 19.9	8.27 8.2
$C_{26}H_{16}N_6O_4Cl_4Ni.2H_2O$ (712.71)	68	43.78 43.7	2.81 2.8	11.79 11.7	19.92 19.3	8.24 8.2
$C_{26}H_{16}N_6O_4Cl_4Mn.2H_2O$ (708.94)	64	44.01 44.0	2.82 2.8	11.85 11.8	20.03 20.0	7.75 7.7
$C_{26}H_{16}N_6O_4Cl_4Zn.2H_2O$ (719.38)	66	43.37 43.3	2.78 2.7	11.68 11.6	19.74 19.7	9.09 9.0

RESULTS AND DISCUSSION:

The synthesis of N'-(5-chloro-2-hydr- oxybenzy lidene)isonicotinohydrazide (CSAIZ) and N'-(3,5-dichloro-2-hydroxy benzylidene) isonicotino hydrazide (DCSAIZ) were preformed by condensation of Isoniazide (IZ) with 5-Chlorosalicyladehyde (CSA) and 5,5-dichloro salicylaldehyde (DCSA). The resulted ligands were an amorphous powder. The C, H, N contents of both ligands (Table-1 and 2) are consistent with the structure predicted (Scheme-1). The IR spectrum of CSAIZ and DCSAIZ comprises the important bands were observed at 1590, 1685, 1150 and 750 cm^{-1}.

The broad band due to –OH and –NH group appeared at 3400-3250 cm^{-1}. The NMR spectrum of CSAIZ and DCSAIZ in DMSO indicates that the singlet of 1H at 9.20 for CH of CH=N. While the singlet at 8.10 δ ppm due to –NH group. The structure of CSAIZ and DCSAIZ are confirmed by LC-MS which is consistent with predicted

structure.Thus the structure of CSAIZ and DCSAIZ are confirmed as shown in Scheme-I.

The metal and C, H, N contents of metal chelates of CSAIZ and DCSAIZ (Table-1 and 2) are also consistent with the predicted structure. The results show that the metal: ligand (M:L) ratio for all divalent metal chelate is 1:2.

The infrared spectra of all the chelates are identical and suggest the formation of the entire metalocyclic compound. The bands are almost at their respectable positions as appeared in the spectrum of parent-ligands. However, the band due to (M-O) band could not be detected as it may appear below the range of instrument used.

TABLE-3: SPECTRAL FEATRUES AND MAGNETIC MOMENT OF CSAIZ METAL CHELATES

Metal Chelates	**μ_{eff} (BM)**	**Electronic spectral data (cm^{-1})**	**Transition**
CSAIZ-Cu^{+2}	2.53	23448 15877	Charge transfer $^2B_{1g}\rightarrow{}^2A_{1g}$
CSAIZ-Ni^{+2}	3.68	22580 15372	$^3A_{1g}\rightarrow{}^3T_{1g}(P)$ $^3A_{1g}\rightarrow{}^3T_{1g}(F)$
CSAIZ-Co^{+2}	4.65	22725 15263 8939	$^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$ $^4T_{1g}(F)\rightarrow{}^4T_{2g}$ $^4T_{1g}(F)\rightarrow{}^4T_{2g}(P)$
CSAIZ-Zn^{+2}	Diamag.	-	-
CSAIZ-Mn^{+2}	5.51	23860 18345 16820	$^6A_{1g}\rightarrow{}^6A_{2g}\,{}^4E_g$ $^6A_{1g}\rightarrow{}^4T_{2g}$ (4G) $^6A_{1g}\rightarrow{}^4T_{1g}$(PG)

The data of electronic transitions and magnetic moments of metal chelates are summarized in Table-3 and 4. The observed μeff values in the range 2.51-5.53 B.M are consistent with the above moiety.The value of magnetic moments and reflectance spectral data of each chelates co-relates with structure assigned as the octahedral geometry. [20-22]

The examination of antibactrial and antifungal activity of CSAIZ and DCSAIZ ligands and their all chelates (Table-5 and 6) reveals that the ligand is moderately toxic against bactria and fungi, while all the chelates are more toxic than ligand. Among all the chelates the Cu^{+2} chelate is more toxic against bactria and fungi.

TABLE-4: SPECTRAL FEATRUES AND MAGNETIC MOMENT OF DCSAIZ METAL CHELATES

Metal Chelates	**μ_{eff} (BM)**	**Electronic spectral data (cm^{-1})**	**Transition**
DCSAIZ-Cu^{+2}	2.51	23450 15875	Charge transfer $^2B_{1g}\rightarrow{}^2A_{1g}$
DCSAIZ-Ni^{+2}	3.66	22583 15374	$^3A_{1g}\rightarrow{}^3T_{1g}(P)$ $^3A_{1g}\rightarrow{}^3T_{1g}(F)$
DCSAIZ-Co^{+2}	4.63	22726 15264 8942	$^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$ $^4T_{1g}(F)\rightarrow{}^4T_{2g}$ $^4T_{1g}(F)\rightarrow{}^4T_{2g}(P)$
DCSAIZ-Zn^{+2}	Diamag.	-	-
DCSAIZ-Mn^{+2}	5.53	23858 18347 16823	$^6A_{1g}\rightarrow{}^6A_{2g}\,{}^4E_g$ $^6A_{1g}\rightarrow{}^4T_{2g}$ (4G) $^6A_{1g}\rightarrow{}^4T_{1g}$(PG)

TABLE-5: ANTIBACTERIAL ACTIVITY OF LIGANDS AND ITS METAL CHELATES

Compound (Designation)	**Zone of Inhibition (in mm)**			
	Gram positive		**Gram negative**	
	B.megaterium	***S.Aureus***	***E.Coli***	***Ps.Aeruginosa***
CSAIZ	06	07	05	08
CSAIZ-Cu^{+2}	15	16	14	17
CSAIZ-Ni^{+2}	11	10	11	12
CSAIZ-Co^{+2}	13	14	12	15
CSAIZ-Zn^{+2}	12	13	12	14
CSAIZ-Mn^{+2}	09	08	07	10
DCSAIZ	08	08	07	10
DCSAIZ-Cu^{+2}	17	17	16	20

DCSAIZ-Ni^{+2}	12	11	10	14
DCSAIZ-Co^{+2}	15	16	14	18
DCSAIZ-Zn^{+2}	14	14	12	16
DCSAIZ-Mn^{+2}	10	09	08	11
Tetracycline	18	19	18	21

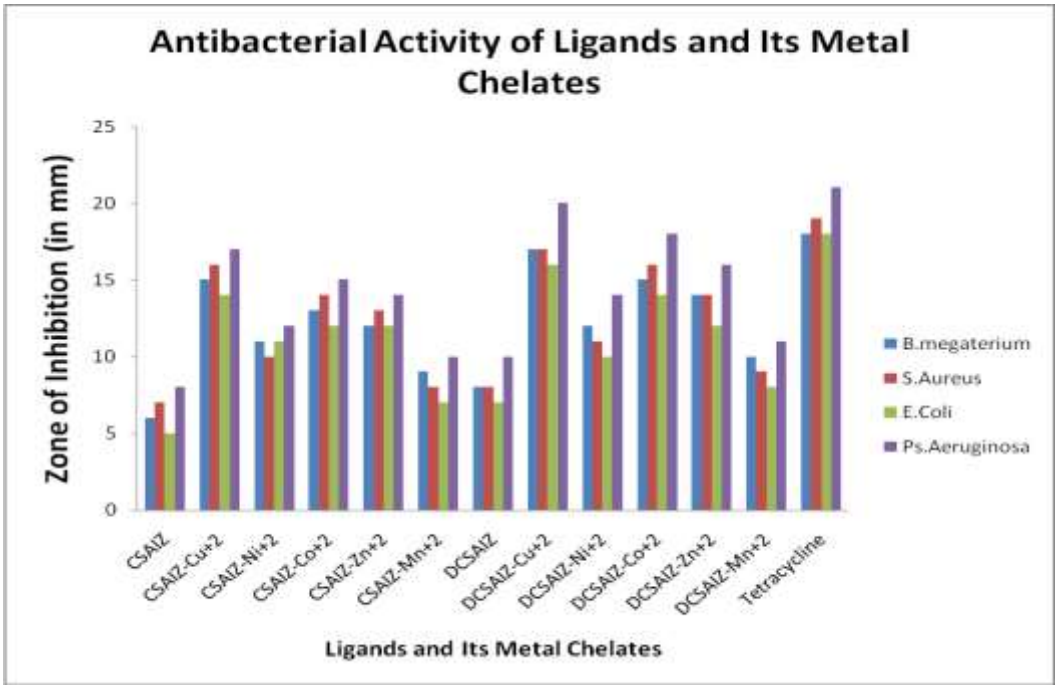


Fig-2. Histogram of antibacterial activity of ligands and its metal chelates

TABLE-6: ANTIFUNGAL ACTIVITY OF LIGANDS AND ITS METAL CHELATES

Sample	**Zone of inhibition of fungus at 1000 ppm (%)**			
	Aspergillus Niger	***Botrydepladia Thiobromine***	***Nigrospora Sp.***	***Fusarium oxyporium***
CSAIZ	62	64	61	66
CSAIZ-Cu^{+2}	78	81	76	79
CSAIZ-Ni^{+2}	76	76	71	75
CSAIZ-Co^{+2}	75	78	74	77
CSAIZ-Zn^{+2}	74	74	75	77
CSAIZ-Mn^{+2}	72	75	76	78
DCSAIZ	67	67	66	68
DCSAIZ-Cu^{+2}	83	84	81	81
DCSAIZ-Ni^{+2}	81	79	76	77
DCSAIZ-Co^{+2}	80	81	79	79
DCSAIZ-Zn^{+2}	79	77	80	79
DCSAIZ-Mn^{+2}	77	78	81	80

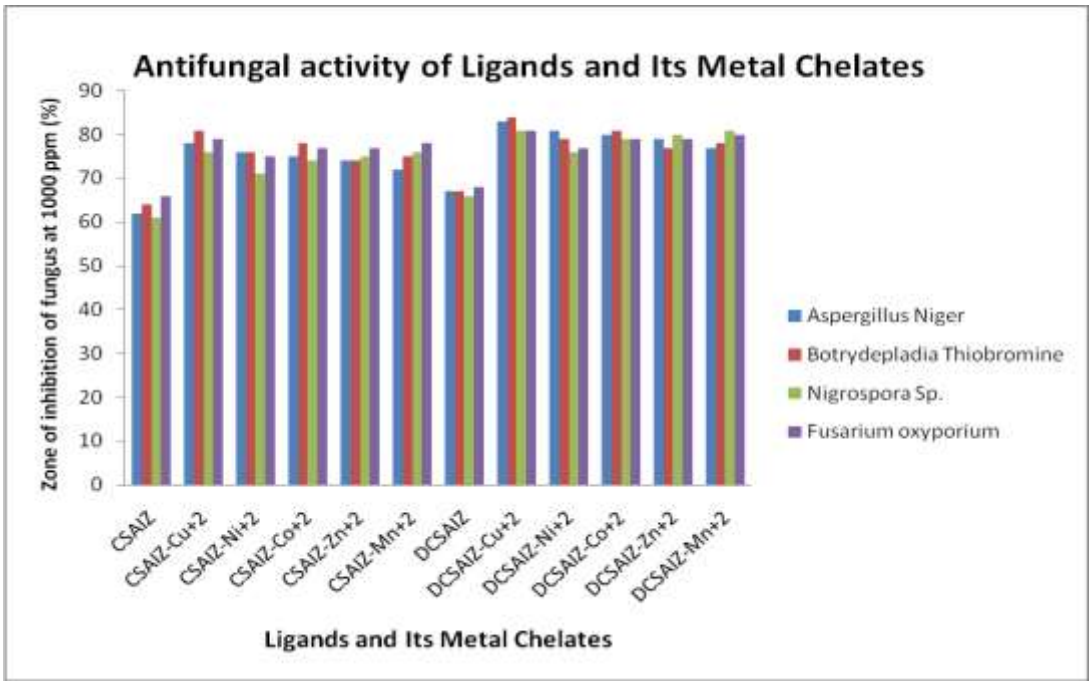


Fig-3. Histogram of antifungal activity of ligands and its metal chelates

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