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Synthesis of novel 1,2,4-triazolodithiocarbamato transition metal complexes as mycocidal agent

Robinpreet Kaur, Anjali Sidhu, Khushbu Gumber and Vineet K Sharma

Abstract
Transition metal complexes of novel 1,2,4-triazolodithiocarbamato ligand system were synthesized and characterized for their antifungal evaluation against various phytopathogenic fungi *viz. Pyricularia grisea, Drechslera oryzae, Fusarium moniliforme and Ustilaginoidea virens*. Some of the complexes, practically insoluble in all the solvents, were converted to their respective nanoemulsions by their *in situ* synthesis in water and rest all were dispersed in water using surfactant, tween 20. Aqua emulsions of all the prepared complexes showed moderate fungitoxic effect in comparison to standard fungicides. The formulated tris (1,2,4-triazole-1-carbodithioato) iron (III) was found to inflict the broad spectrum potential against all the test fungi**.**

Keywords: Sodium1,2,4-triazolodithiocarbamate, metal complexes, antifungal activity.

1. Introduction
The field of bioinorganic chemistry, which deals with the study of role of metal complexes in biological systems, has opened a wide horizon for scientific research [1]. Complexation has immense potential to inflict augmented bioactivities to organic compounds [2, 3]. Biologically relevant metal complexes have several requirements in terms of their synthetic design *viz.* the type of metal ions, its ligands, the relative molar ratio, structure of the compounds, the molecular weight which is responsible for reaching them at the proper target site in the body and solubilisation [4, 5]. Insolubility of complexes, sometimes, marks negative impact on their biological evaluation [6]. Nanotechnology seems to provide solution to this non-favour in terms of reduction of the size of complexes to nanoscale [7]. Furthermore, the size of nanoparticles imparts diversified topological parameter and thus, improved bioactivity than the molecules in bulk, providing additional benefit of greater effectiveness even at low doses [8].
1,2,4-Triazole is a proven lead in the field of antifungal regime, both in agriculture as well pharmaceuticals, with well-known mode of action as 14-alpha demethylase inhibitors [9, 10]. Various 1,2,4-triazole analogues are well in use at commercial level as well as frequently appearing on patent scenario [11]. Carbamodithioates, on the other hand, are another important aza-thio compounds that are most heavily used organic fungicides in terms of tonnage [12] playing a pivotal role as bioactive agents [13-23] and in agriculture [24]. Owing to little resistance developed towards these carbamodithioates, more and more studies are made towards modifying the backbone of DTCs because of their multiple advantages *viz.* low mammalian toxicity, high efficiency in controlling various plant pathogenic fungi, ease of preparation and multisite mode of action [16].
Keeping the above factors in mind and in continuation of our previous work on synthesis of magnesium complexes with the hetero-organic ligand system 1,2,4-triazolocarbodithioate [25], the scope was increased by complexating the ligand system with non-toxic metals *viz.* manganese, iron, cobalt and copper, to see the effect of complexation on the bioactivity of the novel molecules. But, the insolubility of some of the complexes (in all the solvents) prompted us to utilize the power of nano-synthesis for the preparation of nanoemulsions of these complexes. In the present paper, we have reported the synthesis and characterization of transition metal complexes of 1,2,4-triazolodithiocarbamato ligand system along with the preparation, optimization and characterization of nanoemulsions of insoluble complexes. The mycocidal evaluation of all the aqua emulsions and their rationalization in terms of SAR and toxicity analysis is reported in this paper.

2. Materials and Methods

The reagents and solvents were analytical grade, purchased from CDH Company. Double distilled water was used for preparation of all the solutions. The multiwave ultrasonicator operating at 42 KHz was used for preparation of nano-emulsions. Melting points are checked in open capillaries using electronic melting point apparatus and were uncorrected. Conductivity measurements for the complexes were carried out for 10^{-} [3] M solution in dimethylsulfoxide (DMSO) using digital conductivity meter at room temperature. Elemental analysis was recorded on Thermo Finnigan analyser. Percentage of manganese, iron, cobalt and copper complex was found by complexometric titrations [26]. The IR spectra were recorded on a Perkin Elmer FT-IR spectrometer using KBr disc. A Shimaddzu UV-160 spectrophotometer was used for optical measurements, the sample was placed in quartz cuvette (1 cm path length) using dimethylsulfoxide (DMSO) as a reference solvent [1] H NMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer with DMSO as solvent and TMS as internal solvent. Magnetic measurements were carried out by the Gouy method using Hg [Co(SCN)4] as calibrant. The morphology and Particle size of sample was characterized by using TEM images with a Hitachi Hi-7650 Transmission electron microscope operated at an accelerating voltage of 100 kV in HC mode using water as dispersion medium.

Synthesis of 1,2,4-Triazole-1-carbodithioate derivatives

Synthesis of Sodium 1, 2, 4-triazole-1-carbodithioate (L_1)

0.05 mole of 1, 2, 4 triazole (3.45g) was dissolved in 20 ml of methanol in a clean beaker which was placed in ice bath. To this cold solution 5 ml of sodium hydroxide (10N) solution was added followed by addition of pure carbon disulphide (0.05ml), under constant stirring for about 30 min. Sodium salt of dithiocarbamate so formed was precipitated out using ethyl acetate (Scheme1) and recrystallized to obtain pure crystalline solid.

General preparation for synthesis of metal complexes

A solution of ligand L1 (1.32 g, 5 mmol) dissolved in water (25 ml), was added to the 10 ml aqueous solution of transition metal salt ($MnCl_2$, $FeCl_3$, $CoCl_3$ and $CuCl_2$), in 1:1, 1:2 or 1:3 molar ratios, depending on the basis of relative stoichiometry. The mixture was stirred for 30 minutes. After stirring, the solid obtained was separated out and washed with methanol to obtain metal 1,2,4-triazole-1-carbodithioate complexes to get their pure complexes. Complexes are characterized on the basis of elemental and spectral analysis resulted complexes are presented in Table 1.

Synthesis of nano formulated metal 1,2,4-triazole-1-carbodithioate complexes (1b-5b)

Some of the complexes (Metal: ligand ratio) *viz.* Mn (1:1, 1:2), Fe (1:3) and Cu (1:1, 1:2) being insoluble in most of the organic solvents were formulated as aqua nanoemulsions (1b-5b), by their *in situ* preparation in water.

The aqueous solution of 0.001 mole of metal salts was added with constant stirring to an aqueous solution of required stoichiometric molar amount of L_1, followed by addition of different concentrations of polyvinyl pyrrolidone (PVP) as stabilizer, while sonication. Concentration of PVP required to stabilize the nanoparticles was optimized by repeating the same experiment in triplet with different concentrations of PVP (0.1, 0.3 and 0.5 g). The obtained suspension was allowed to age for 60 min. The exact amount of PVP required was standardized using TEM analysis.

The nano colloids were separated from mother liquor by employing centrifugation at 4000 rpm for 10 min and were re-dispersed in water (20 ml) to get nano 1,2,4-triazole-1-carbodithioato metal complexes (1b-5b).

Toxicity Analysis

Toxtree v 2.6.6 is an open-source software application that places chemicals into categories and predicts various kinds of toxic effect by applying various decision tree approaches [27]. The software is made freely available by ECB as a service to scientific researchers and anyone with an interest in the application of computer-based estimation methods in the assessment of chemical toxicity. The new module with the revised list of SAS includes also structure–activity relationships (SAR) models that enable the toxicity evaluations for a number of chemical classes to be fine-tuned.

In order to find out the toxic hazards of all the synthesized complexes, two dimensional models of the complexes were first converted into its simplified molecular-input line-entry system (SMILES format). Then simply putting the SMILES code into the Chemical identifier row available in the Toxtree software we can easily get the toxic characters on the basis of various decision tree approaches.

Antifungal assay

The *in vitro* antifungal evaluation of all the complexes against various phytopathogenic fungi *viz. Pyricularia grisea*, *Drechslera oryzae, Fusarium* moniliforme and Ustilagnoidea virens was performed by spore germination inhibition technique [28]. Baviston and Tilt were used as standard fungicide for the comparison of the results.

Stock solutions

The L_1 ligand and complexes 3a, 4a, 6a, 7a and 8a were dispersed in water using Tween 20 as surfactant and the prepared concentrations of 10µmol/ml were stored as stock solutions.

Complexes 1a, 2a, 5a, 9a and 10a being insoluble in most of the organic solvents were formulated as nano aqua emulsions (1b-5b), respectively at the concentration of 10 µmol/ml which were used as stock solution. The stock solutions were further diluted as per the requirement on the basis of active ingredient using the mole concept to obtain the required concentration as and when required.

Spore germination inhibition method

Antifungal activity of all formulations against the test phytopathogenic fungi, were done by means of spore germination inhibition technique. Spore suspension was made by adding sterilized distilled water to the small bit of mycelium from infected plate to the sterilized water. Suspension was filtered through three layers of sterilized cheese cloth in order to remove mycelial particles under aseptic conditions. Haemocytometer was used to get spore suspension (1×10 [6] spore/ml). Screening of the test complexes involved floating of fungal spores on the surface of test solution in cavity slides. Small droplets (0·02 ml) of the test solution and spore suspension in equal amount were seeded in the cavity slides. These slides were kept in petriplates lined with moist filter paper and incubated for 24 hrs or 72 hrs at 15 ± 1 °C or 25 ± 1° as per the requirement of the different fungus cultures. The slides were checked for germination and per cent spore germination inhibition was

determined from which EC_{50} values were calculated by probit analysis [29].

3. Results and Discussion

Chemistry

The two step reaction protocol was employed for the synthesis of 1,2,4-triazolodithiocarbamato transition metal complexes. The first step involved the synthesis of ligand by reaction of 1,2,4-triazole with carbon disulfide under basic condition followed by the synthesis of metal complexes in different stoichiometric ratios. The synthesized ligand (L_1) and their complexes were very stable at room temperature in the solid state. Some of the metal complexes *viz.* 3a, 4a, 6a, 7a and 8a are soluble in common organic solvents whereas, the complexes 1a, 2a, 5a, 9a and 10a were insoluble in all the solvents and thus converted to their respective nano-emulsion by their *in situ* synthesis in water. The reaction steps followed for the synthesis is shown in Scheme 1. The prepared ligand and their complexes were analyzed on the basis of their physical parameters, elemental analysis and spectral techniques.

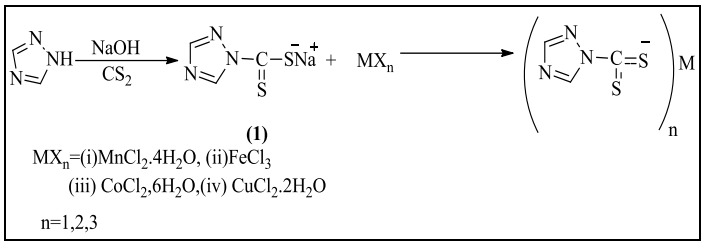


Fig 1

Scheme 1

The elemental analysis of the complexes helped in documenting the percentage of carbon, hydrogen, and nitrogen, which corroborated the structures of the metal complex in coordination with the results of infrared and electronic spectroscopy. The percentages of metals in the complexes were estimated by complexometric titrations. The analytical and physical properties of all the complexes and ligand are shown below in Table 1.

Table 1: Analytical data and some physical properties of ligand (L_1) and their complexes.

	Mol. Formula	Color	Mol. Weight	Yield (%)	M.P (ºC)	Calculated (found)			
						C (%)	H (%)	N (%)	Metal
L_1	$C_3H_2N_3NaS_2$ (L_1)	Off white	167	65	215	21.54 (21.55)	1.19 (1.21)	24.14 (24.13)	-
1a	$[Mn(L_1)_1.2H_2O]Cl$	Pink	269.9	69	>500	13.29 (13.31)	2.20 (2.23)	15.51 (15.53)	20.28 (20.30)
2a	$[Mn(L_1)_2]$	Light pink	342.9	72	>500	20.97 (20.99)	1.15 (1.17)	24.45 (24.48)	15.58 (16.00)
3a	$[Fe(L_1)_1.4H_2O]Cl_2$	Red	341.9	64	>500	10.49 (10.50)	2.95 (2.94)	12.33 (12.25)	16.25 (16.28)
4a	$[Fe(L_1)_2.2H_2O]Cl^-$	Red	414.9	77	>500	17.32 (17.33)	1.92 (1.94)	20.19 (20.22)	13.40 (13.43)
5a	$[Fe(L_1)_3]$	Red	487.8	80	>500	22.11 (22.13)	1.23 (1.24)	25.79 (25.81)	11.42 (11.43)
6a	$[Co(L_1)_1.4H_2O]2Cl^-$	Pink	309.9	64	>500	11.58 (11.60)	3.23 (3.24)	13.52 (13.53)	18.95 (18.97)
7a	$[Co(L_1)_2.2H_2O]Cl^-$	Pink	382.9	75	>500	18.78 (18.80)	2.08 (2.10)	21.89 (21.92)	15.35 (15.37)
8a	$[Co(L_1)_3]$	Pink	490.8	79	>500	21.97 (21.99)	1.19 (1.23)	25.62 (25.65)	11.96 (11.99)
9a	$[Cu(L_1)_1.2H_2O]Cl^-$	Blue	277.9	64	>500	12.86 (12.90)	2.15 (2.17)	15.03 (15.05)	22.75 (22.76)
10a	$[Cu(L_1)_2]$	Sky blue	350.9	80	>500	20.47 (20.48)	1.13 (1.15)	23.85 (23.88)	18.03 (18.06)

Table 2: Molar conductance of complexes

Complex no.	Molecular formula	Molar conductance
(3a)	$[Fe(L_1)_1.4H_2O]Cl_2$	42.6
(4a)	$[Fe(L_1)_2.2H_2O]Cl^-$	23
(6a)	$[Co(L_1)_1.4H_2O]Cl^-$	20
(7a)	$[Co(L_1)_2.2H_2O]$	17
(8a)	$[Co(L_1)_3]$	16

^{1}H NMR spectra

The synthesized complexes were intense coloured, thermally stable, non-hygroscopic and soluble in DMSO and DMF, only. The molar conductance of the complexes soluble in DMSO *viz.* 3a, 4a, 6a, 7a and 8a has been recorded in 10^{-} [3] M DMSO solution at room temperature. The values for 3a, 4a, 6a and 7a indicated that these complexes are 1:1, 1:2 or 1:3 electrolytes; consequently one, two or three chloride ion is present outside the coordination sphere leading to its higher molar conductance. On the other hand, in complex 8a, the molar conductance (Λ_M) values are too low to account for an ionic complex; therefore, these complexes were considered to be neutral. The values of molar conductance in DMSO are compiled in Table 2.

The ^{1}H NMR spectrum of the ligand (L_1) show characteristic signals due to the aromatic protons appearing at 8.27 and 8.29 ppm may be assigned to the (–CH) protons of 1,2,4-triazole. In all the complexes, the protons resonated in the expected regions. On complexation, the bands due to CH of triazole rings showed a downfield shift with values ranging between 8.31 and 8.40 ppm in all the complexes.

Infrared spectroscopy analysis

The important IR frequencies of sodium 1, 2, 4-triazole-1-carbodithioate and its metal complexes (1a-10a) are presented in Table 3. The main regions of interest in dithiocarbamate complexes: the 1580-1450 associated with the stretching of the C-N of NCS_2^-; the 1060-940 cm^{-} [1] region, associated with

υ(-CSS); and the 500-300 cm^{-1} region which is associated with υ (M-S).

Table 3: IR frequencies

No.	Complexes	υ OH	υC-N	υC=S, υC-S	υM-S
L_1	$C_3H_2N_3NaS_2$ (L_1)	-	1487	992, 980	-
1a	$[Mn(L_1)_1.2H_2O]Cl$	3392	1501	989	448
2a	$[Mn(L_1)_2]$	-	1510	992	464
3a	$[Fe(L_1)_1.4H_2O]Cl_2$	3400	1492	965	452
4a	$[Fe(L_1)_2.2H_2O]Cl^-$	3389	1494	970	479
5a	$[Fe(L_1)_3]$	-	1496	976	483
6a	$[Co(L_1)_1.4H_2O]Cl^-$	3412	1483	940	465
7a	$[Co(L_1)_2.2H_2O]$	3412	1493	958	471
8a	$[Co(L_1)_3]$		1496	985	480
9a	$[Cu(L_1)_1.2H_2O]Cl^-$	3392	1512	980	466
10a	$[Cu(L_1)_2]$	-	1515	995	470

The strong band in range of 1483-1515 cm^{-1} in all the complexes was attributed to the υ(C-N) stretching vibration. This band is observed at a lower frequency in the free ligand (1402 cm^{-1}) and indicates an increase of the carbon-nitrogen double bond character, caused by electron delocalization toward the metal centre upon coordination to metal atoms. It is found that the coordination mode of 1,2,4-triazole-1-carbodithioate ligand with transition metals is bidentate by the sulfur atoms. The $υ(CS_2)_{assy}$ and $υ(CS)_{sym}$ which appear at 992 cm^{-1} and 980 cm^{-1} in the ligand are replaced by strong singlet at about 1000 cm^{-1} in all the complexes indicating that dithiocarbamate moiety is symmetrically coordinated to the metal ions[30]. It has been shown that presence of only one band in the 1000 + 70 cm^{-1} region is characteristic of a bidentate nature for the dithiocarbamate moiety, while the splitting of the same band within a difference of 20 cm^{-1} in the same region is due to the monodentate binding of dithiocarbamate ligand. The broad band around 3369-3412 cm^{-1} corresponding to ν(O-H str) indicates the presence of coordinated water molecules and appearance of a new bands in the region 448-487 cm^{-1} were in favour of the formation of M-S bond.

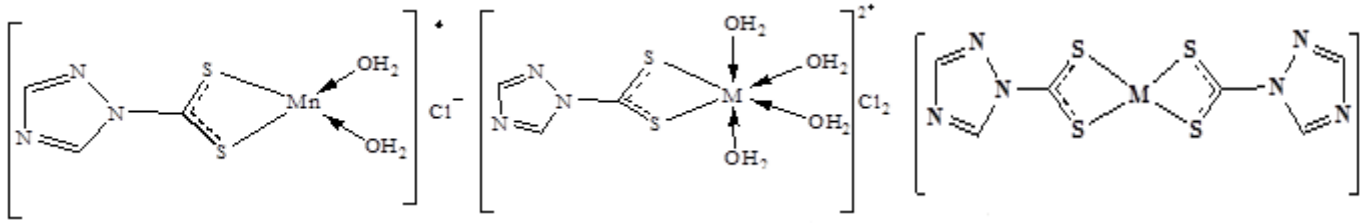
Electronic spectral studies

The electronic spectra of the ligand and complexes display the absorption bands listed in Table 4. The ligand showed bands at 248 and 259 nm which were assigned to π- π* and n- π* transition, respectively. The electronic spectrum of metal complex showed band due to π→π* between 263-277 & 275-320 nm corresponding to N-C-S and S-C-S chromophore, respectively and an additional charge transfer band around 403-430 nm. Electronic spectra of the complexes (1a, 2a, 5a, 9a, 10a) could not be obtained due to insolubility of complexes while their nano complexes show band in the region (253-277, 305-330) due to π-π* transition of (S-C-N) and (S-C-S) chromophore. An additional band in case of metal complexes appeared in the region 360-415 nm which was assigned to charge transfer transition whereas, a weak band in higher visible region due to d-d transition is less pronounced [31].

Table 4: Electronic spectral studies of complexes (1a-5a)

Complex No.	Complexes	$λ_{max}$ (nm) N-C-S	S-C-S	Charge Transfer
1	$C_3H_2N_3NaS_2$ (L_1)	248	259	-
(3a)	$[Fe(L_1)_1.4H_2O]Cl_2$	263	320	403
(4a)	$[Fe(L_1)_2.2H_2O]Cl^-$	265	326	410
(6a)	$[Co(L_1)_1.4H_2O]Cl^-$	265	275	420
(7a)	$[Co(L_1)_2.2H_2O]$	269	285	425
(8a)	$[Co(L_1)_3]$	270	320	430
(1b)	$[Mn(L_1)_1.2H_2O]Cl^-$	253	305	360
(2b)	$[Mn(L_1)_2]$	255	310	365
(3b)	$[Fe(L_1)_3]$	267	332	415
(4b)	$[Cu(L_1)_1.2H_2O]Cl^-$	275	325	360
(5b)	$[Cu(L_1)_2]$	277	330	365

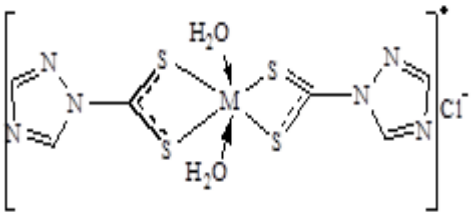
On the basis of all the analysis the proposed structures of the complexes are as shown below:



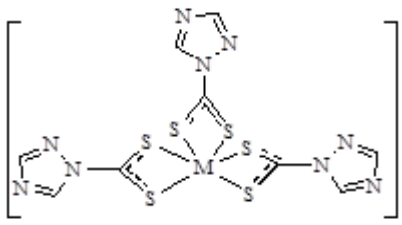
M =Mn (II), Cu(II) 1:1Metal DTC Comlex

M=Fe(III), Co (II) 1:1Metal DTC complex N=1.2

M=Cu(II), Mn(II) 1:2 Metal DTC Complex



M=Fe(III), Co(II) 1:2 Metal DTC Complex N=0



M=Fe(III), Co(II) 1:3 Metal DTC Complex

Fig 2: Proposed Structures of Complexes

Transmission electron microscopy (TEM)

Transmission electron microscopy (TEM) was used to measure the nanoparticles core dimensions. The samples prepared without PVP were unstable which get aggregated after some time. The amount of PVP added for the stabilization was standardized by repeating the experiment with different amount of PVP in the solution. Comparison of figure 1, 2 and 3 revealed that the particle size was more in case when 0.1 g of PVP was added to the sample in comparison to the one containing 0.3 g of PVP. The surface-capped 1,2,4-triazole-1-carbodithioatomaganese(II) chloride nanoparticles appeared uniformly spherical, with average particle diameter within a range of 50−100 nm (Figure 4). There was no obvious aggregating phenomenon even after six months, revealed good particle size stability. PVP had been observed to get adsorbed on the surface of the nanoparticles, thus reducing their surface energy and preventing them efficiently from aggregation giving a nano aqua emulsion with well controlled particle size and improved dispersion capability in water. Addition of higher amount of PVP revealed the excess of PVP with no observed reduction in particle size as shown in figure 5. Thus, 0.3 g of PVP was the optimum concentration for capping of 10 ml of 0.05 molar of diaqua-1,2,4-triazole-1-carbodithioato complexes. The results for all the five nano-formulated metal complexes with optimum concentration of PVP are compiled in Table 5.

Table 5: Average particle size and stability of nanoparticles at different polymer concentration

S.No.	Complex	Diameter (nanometers)
1b	$[Mn(L_1)_1.2H_2O]Cl^-$	50-60 nm
2b	$[Mn(L_1)_2]$	45-60 nm
3b	$[Fe(L_1)_3]$	55-70 nm
4b	$[Cu(L_1)_1.2H_2O]Cl^-$	60-75 nm
5b	$[Cu(L_1)_2]$	70 -75nm

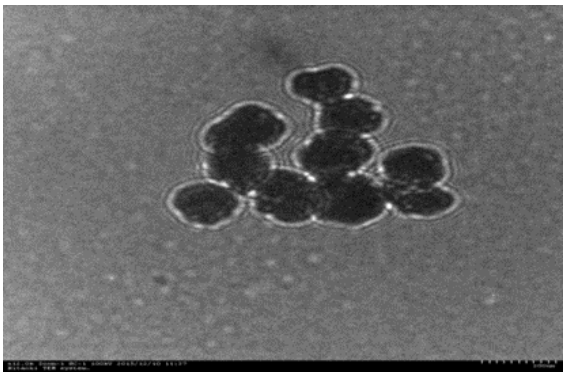


Fig 3: TEM micrograph of complex 1b (0.1 g PVP)

Toxicity analysis

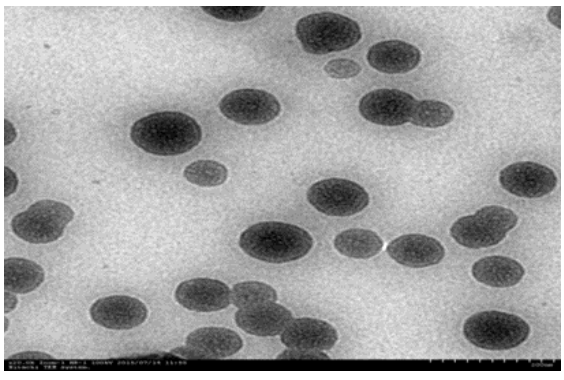


Fig 4: TEM micrograph of complex 1b (0.2 g PVP)

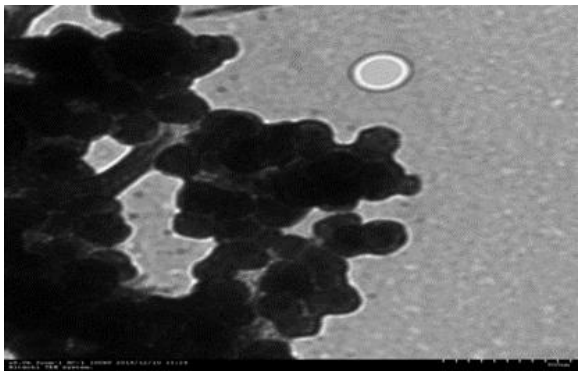


Fig. 5 TEM micrograph of complex 1b (0.3 g PVP)

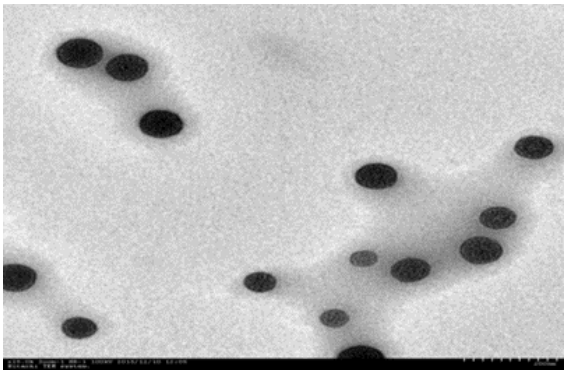


Fig. 6 TEM micrograph of complex 2b (0.3 g PVP)

Estimation of toxic hazards by Cramer rules was carried out using Toxtree v.2.6.6 software, showed that complexes belong to class III level of toxicity, which was same as that of the toxicity level of standards fungicides used.

***In Vitro* antifungal studies**

In the current study, synthesized complexes were tested against phytopathogenic fungal strains such as *P. grisea, D. oryzae, F. moniliforme* and *U. virens.* Bavistin and Tilt were used as reference drug for fungi. The effective concentration at which 50% inhibition takes place (EC_{50}) was noted by spore germination inhibition technique. All the complex molecules were found to show moderate toxicity against the test fungi in comparison to the commercial standards but the water bases formulations were considered to be eco-friendly solution to the menace of resistance and environmental toxicity.

For the comparison of the results, the EC_{50} values less than 1.00 µmol/ml were taken as best while the values ranging from 1.00-1.50 µmol/ml were taken as moderate for the fungi. The compounds with higher EC_{50} values were taken as mild against the test fungi.

On the basis of the demarcation, complex 4a, 4b and 5b were found to be moderately active against *P. grisea.* In case of *D. oryzae,* compound 4a, 8a, 3b and 5b were found to inflict high fungitoxicity followed by complex 3a, 7a and 6b. It is found that the metal complexes have higher antifungal activity against all the fungi as compared to the free ligand. Against *F. moniliforme,* the moderate toxicity was inflicted by most of the compounds whereas the results of complex 3b and 5b were found to be quite effective against *U. hordei.* All the results are compiled in terms of EC_{50} values in Table 5.

Overall results indicated that the complexation increases the antifungal activity. Nano aqua formulation of tris (1,2,4-triazole-1-carbodithioato)iron (III) (3b**)** was found to be most active against all the test fungi though its EC_{50} value was

much higher than standard fungicides used. In comparison to other organic fungicidal formulation, the nanoemulsions of 3b have a favourable edge of being dispersed in non-toxic aqua emulsions having no genotoxicity, mutagenicity, carcinogenicity and are ecofriendly. According to Cramer rules[32], the complexes belong to class III level of toxicity, which was same as that of the toxicity level of standards fungicides used. The other advantage of using this is the presence of iron which could be easily assimilated in plants keeping the risk of metal residual effect at bay. So, they can be further derivitized to make better dithiocarbamate.

4. Conclusion

Our study endorsed the use of iron in the derivatization as antifungals and negated cobalt and manganese metals for the same. The relative stoichiometry was an important concept and the increase in the stoichiometric concentration of bioactive ligand was found to affect the antifungal potential in augmented manner. The most potent complex 3a (1:3 iron: ligand) complex showed fungitoxic potential better than 1:1 and 1:2 analogues.

The above study also revealed the power of nano-application methodologies which made the insoluble materials to come into the solution form for their antifungal assays. These nanoemulsions prepared in water were more eco-friendly than usual formulations which are prepared in toxic organic solvents. So, our study had an edge of eco-friendly nature and non-toxicity.

Table 5: *In Vitro* Antifungal Potential of complexes (1a-5a)

EC_{50} values (µmol/ml)				
Compd No.	***P. grisea***	***D. oryzae***	***F. moniliforme***	***U. virens***
L_1	2.93	2.75	2.99	2.84
3a	2.04	1.02	2.92	1.90
4a	1.45	0.72	2.16	1.20
6a	3.38	2.42	4.03	2.43
7a	2.48	1.61	2.61	1.82
8a	1.52	0.98	1.78	1.32
1b	4.13	2.72	4.81	3.70
2b	2.62	2.04	1.74	1.45
3b	10.82	0.51	1.02	0.70
4b	1.24	1.32	1.97	1.25
5b	1.28	0.91	1.56	0.85
Bavistin*	-	-	0.78	-
Tilt**	0.20	0.15	-	0.18

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