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ORIGINAL ARTICLE

Evaluation of Nano-formulated Heteroleptic metal complexes as potential Antifungals against *Fusarium oxysporum*

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ABSTRACT
The established antifungal moieties viz. 1,2,4-triazole, dithiocarbamate and phosphorous were brought in a single molecule to give a series of metal complexes ofcobalt, copper and iron. The synthesized derivatives were further improvised with an essence of nanotechnology for the better application of the non-soluble molecules to get nano-sized dispersion in water. The formulated target compounds were evaluated for their fungicidal potential against Fusarium oxysporum, by poisoned food technique. The overwhelming results were indicated by compound ***5*** *(EC_{50} value 4.80 ppm).*
Keywords*: Antifungal, Fusarium oxysporum, nano-formulation, triazole, dithiocarbamate, triphenyl phosphine, heteroleptic, metal complexes*

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INTRODUCTION

1,2,4-Triazole, dithiocarbamates and organophosphorus are the established bioactive moieties, dominating all over the agrochemical market [1-3]. The heterorganic leads among them were also found to have the moderate toxicity [4, 5]whereas, the third phosphor compoundsotherwise forms a widely used class of pesticides needed at the time of sudden and severe outbreak of diseases. The toxicity and tendency of these organophosphorus to develop resistance, demands their redesigning, so as to use them as resistance measure as and when required [6, 7]. Additionally, complexation of heterorganic ligands with bioactive metals has an immense potential to portray an augmented bioactivities to them, which is further influenced by the design and bioactivities of the ligands along with the type of the metal ions used [8].

Furthermore, it is found that most of the organic and inorganic molecules fail to reach the target site due to their poor solubility leading to the poor applicability[9]. This drawback can be overcome by essence of nanotechnology, i.e. preparing the nano-formulations of the bioactive molecules. The nano-formulations also impart diversified topological parameters which are responsible for improved bioactivity than the molecules in bulk providing additional benefits with greater effectiveness at low doses [10].

In the multi-component regime for the synthesis of bioactive molecules, we endeavoured to design complexes of Cu (II), Co (II) and Fe (III) with heteroleptic ligands *viz.* 1,2,4-triazole-dithiocarbamate, triphenyl phosphine and isothiocyanate, in variable ratios. The synthesized complexes were converted to nano aqua formulations for evaluation of their antifungal potential against the test fungi *Fusarium oxysporum,* using Tilt (Propiconazole) as positive control.

MATERIALS AND METHODS

All the reagents and solvents were commercially available, analytical grade materials and were used as supplied, without further purification. Deionized water was used for preparation of all the aqua formulations. The antifungal activity of the nano-dispersions was checked by established method against the phytopathogenic fungus of rice,*Fusarium oxysporum.*

Synthesis of Heteroleptic Metal Complexes(1-12) and their Nano-formulations

The established method was employed for the synthesis of heteroleptic metal complexes [11].

The synthesized metal complexes (**1-12**) were finely grounded using a pestle mortar. Different amounts *viz.* 1.0, 0.5, 0.2and 0.1 g of the metal complexes were mixed with 0.2 g of PVP and the mixture was slowly

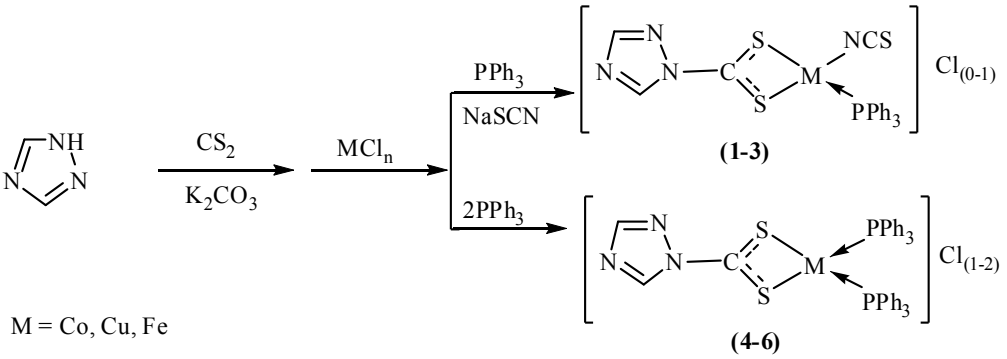
dispersed in 100 ml of distilled water containing 0.2 g of SDS, while ultrasonication. The sonication was continued for 20 minutes and the nano-dispersion was allowed to age for 1 hour. The formulation with clear appearance containing maximum amount of solid complex by weight were analysed by TEM micrographs to get the optimum amount required to prepare 100 ml of nano-formulation. All the other nano-formulations were prepared by the same standard method and were diluted to 500 ppm on active ingredient basis, and stored as stock solution for antifungal evaluation [12].

Antifungal Assay

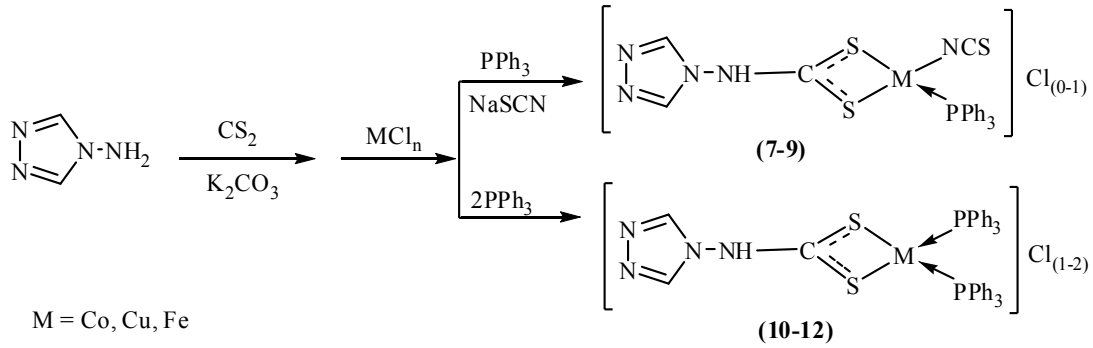
The *in vitro* antifungal activity of all the compounds were performed by Poisoned food technique [13, 14] against phytopathogenic fungi,*Fusarium oxysporum* in comparison with the standard fungicidesTilt (1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole). The isolates of phytopathogenic fungi were provided by the Plant Pathology Department of the Punjab Agricultural University and the standards, which served as the positive control was obtained from their respective manufacturers.

RESULTS AND DISCUSSION

The heteroleptic complexes were prepared according to the established synthetic procedure as described in Scheme 1 and Scheme 2. The complexes formed were stable but insoluble in most of the solvents leading to its poor applicability as antifungal agent. Thus, the essence of nanotechnology was added to make the biologically active molecules water dispersible with help of surfactant SDS and stabilizing agent PVP.



Scheme 1: Synthesis of metal complexes of 1,2,4-Triazole



Scheme 2: Synthesis of metal complexes of 4-Amino-1,2,4-triazole

Antifungal Assay of the test compounds

As shown in Table 1, many of the title compounds showed good control efficacy against *Fusarium oxysporum,* tested at variable concentration*viz.* 500, 250, 100, 50, 25 and 10µg/ml. Most of the test formulations inflicted the excellent fungitoxicity with EC_{50} values less than 60 µg/ml with some of the complexes (2, 3, 4, 5, 6 & 9) overpowering the existing triazole standard, Tilt (EC_{50} value, 10.79 µg/ml) against the test fungi. Notably, the comparison between the 1,2,4-triazole and 4-amino-1,2,4-triazole analogues showed the edge of the former over the latter. The presence of triphenyl phosphine in higher molar ratio in the complex molecules also inflicted the synergistic results. For example, compound **4** and **5** displayed excellent inhibition with EC_{50} values better than the standard Tilt.The strong potential of the nanoformulations was attributed to the variable ligand system attached to the different metal centre and the nanosization of the metal complexes [12, 15]. The edge of copper and iron complexes in comparison

to the cobalt analogues was supported by the earlier reported work on the excellent fungitoxicity of the iron complexes with the polydentate dithiocarbamates ligand against *Phomopsis viticola* [16].

Table 1: Antifungal Assay of nano-formulated Metal complexes at different concentrations against *F. oxysporum*

S.No.	Concentration/Percentage inhibition							EC_{50} (µg/ml)
	500	250	100	50	25	10	5	
1	80.25	72.50	56.45	48.63	43.92	35.45	24.25	38.57 (20.00-66.85)
2	95.63	88.75	77.45	72.49	67.85	60.25	50.35	6.21 (2.45-11.17)
3	94.35	82.50	77.50	73.28	65.45	56.25	48.75	7.12 (2.61-13.19)
4	95.68	90.65	83.75	77.84	68.42	59.35	52.75	5.48 (3.24-8.13)
5	97.50	90.90	80.25	75.25	70.46	62.45	55.45	4.80 (1.69-9.03)
6	86.25	80.05	75.45	69.45	62.15	52.50	40.65	9.76 (5.78-14.53)
7	83.75	75.15	62.50	45.25	28.65	20.45	10.56	57.77 (41.89-71.02)
8	95.24	86.25	80.25	74.65	68.42	45.35	35.43	11.71 (8.41-15.40)
9	100	90.45	77.50	69.25	63.85	56.25	48.95	8.28 (2.83-15.50)
10	92.25	77.50	53.25	45.25	38.45	32.68	25.20	38.95 (19.65-69.86)
11	90.24	73.75	56.25	45.80	36.42	25.85	15.26	48.82 (32.24-72.19)
12	95.24	90.20	76.25	67.25	58.42	45.35	32.50	15.17 (11.41-19.36)
Tilt	100	100	100	100	90.35	45.62	10.23	10.79 (9.72-11.97)

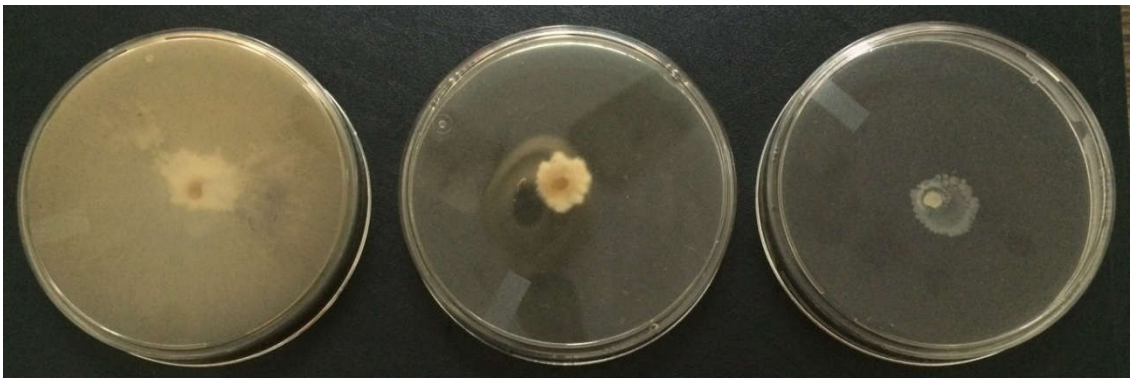


Figure 7: Zone of inhibition for complex 5 at 100 and 50 ppm along with the control set against *F. oxysporum*

CONCLUSION

The nanoformulated heteroleptic metal complexes can be considered as a better alternative due to lower toxicity and water dispersibility. Further modification of the effective moieties is recommended to get more effective and eco-friendly solutions. Studies are currently underwayto optimize and enhance the activity of the complex derivatives.

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