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One pot synthesis of fluorinated carbamodithioato copper complexes as antifungal agents

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Abstract
Novel fluorocarbamodithioa to copper (II) complexes were synthesized by one pot two step reaction protocol by the reaction of fluoroanilines with carbon disulfide followed by the addition of copper chloride, with the aim to evaluate their antifungal potential. The relative evaluation of fluoro and non-fluoro carbamodithioato copper complexes for their *in vitro* antifungal potential against various phytopathogenic fungi *viz. Puccinia hordei, Puccinia striiformis* and *Bipolaris sorokiniana* revealed remarkable potential of non-fluorinated complexes in comparison to fluorinated analogues. Tetraaqua phenyl carbamodithioa to copper (II) chloride (1a) inflicted the highest fungitoxicity in most of the cases.

Keywords: Copper chloride; fluorine moiety; bioactive ligands; mycelial growth; phytopathogens

1. Introduction
Copper (Cu) fungicides *viz.* Burgundy mixture, Bordeaux mixture, copper oxychloride, cupric sulfate, cupric carbonate, cuprous oxide, copper hydroxide, copper zinc chromate etc are used worldwide [1]. The copper ions are generally toxic due to its tendency to alternate between its cuprous Cu (I) and cupric Cu (II) oxidation states [2]. and ultimately get detoxification in nature by sulfidation. Various methodologies are practised to detoxify copper [2]. by its slow release in ionic form. Complexation with thio ligands is a fruitful strategy for control release of copper ion, thereby reducing toxicity [3]. without affecting its biopotential. This is owing to strong affinity of this soft metal ion with soft thio ligands. Moreover, The combination or complexation of copper ions with other bioactive compounds or ligands are reported to have augmented bioactivities [4, 5].
Carbamodithioates have great deal of attention due to their interesting chemistry and wide utility [6-10] These are important synthetic intermediates [11] which are ubiquitously found in a variety of biologically active compounds and exhibit valuable biological effects [12, 13] including antifungal [14-16] antioxidant, [17] antimicrobial activities [18, 19] etc. These are commonly used organic fungicides in terms of tonnage and play pivotal role in agriculture. These are well known to cause pesticidal action due to low mammalian toxicity, high efficiency in controlling various plant pathogenic fungi[16] and multisite mode of action [20]. Till now, there are many carbamodithioates commercially available as fungicides, among them thiram, disulfiram, ziram, and ferbam are some commonly used fungicides.
Carbamodithioates are also versatile ligands [21] capable of forming complexes with most of the transition elements to get stabilized transition metals in a variety of oxidation states. Copper complexes with carbamodithioate ligands have reported literature on synthesis and characterization [22] but there are scanty studies on their derivatization for evaluation against phytopathogenic fungi, [23] which is a pertinent concept needing exploration on agrochemical research front.
Fluorination of organic compounds represents molecular modifications technique in agrochemicals due to positive changes in the physiochemical properties of molecules providing better bioavailability to the plant tissues [24] So, present paper describes the rationale synthesis of fluorocarbamodithioato copper complexes for comparative evaluation with non fluoro analogues on the antifungal evaluation studies against phytopathogenic fungi.

2. Experimental

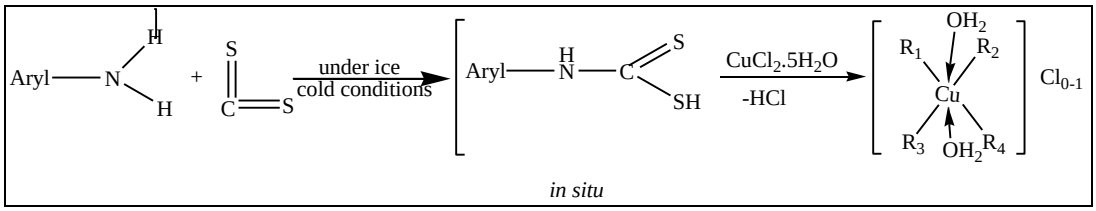
2.1 Materials and measurements

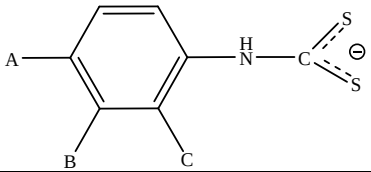
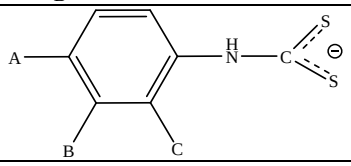
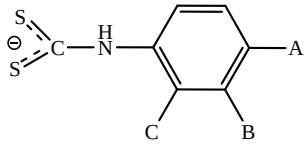
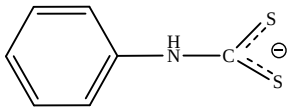
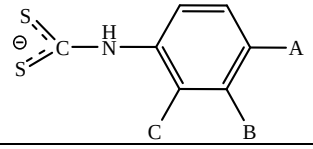
All the chemicals were purchased from Loba Chemie and S.D Fine Chemicals. All the reagents and solvents used were of AR grade and were used as supplied, without further purification. Melting points were taken in open capillaries in an electric melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer with DMSO and $CDCl_3$ as solvents and TMS as internal solvent. IR spectra were recorded on Perkin Elmer FT-IR spectrometer using KBr disc (range 4000–400 cm^{-1}). UV-Visible spectra were recorded with a double beam spectrophotometer, having a path length of 1 cm. CHNS Analysis was made on Thermo Finnigan instrument. Conductivity measurements of 10^{-3} M solutions of the complexes in DMSO were recorded on conductivity bridge type 305 with a cell having constant 1.

2.2 General synthesis of copper complexes

Aniline *viz*. aniline, 3-chloro-4-fluoroaniline, 4-fluoroaniline, 2-fluoroaniline and 3-trifluoromethyl aniline (0.02 mol) was dissolved in 15 ml of ethanol followed by drop-wise addition of 1.52 ml of carbon disulfide (0.02 mol), under ice cold conditions, to afford *in situ* carbamodithioic acid solution. To the same cold reaction mixture, the cupric chloride dissolved in minimum amount of water, was added slowly in different molar ratio (1:1 and 1:2), while continuous stirring to obtain a colored precipitates. The resulting precipitates were then filtered, washed several times with cold water followed by ethanol. It was dried under vacuum to get respective Cu (II) complexes (1a-5a, 1b-5b).

When the mixture of two different anilines (0.01 mol each) was dissolved in 15 ml of ethanol in a flask, CS_2 (0.02 mol, 1.52 ml) was added at low temp. To the same flask, cupric chloride (0.01 mol, 1.70 g) dissolved in 10 ml of water, was added drop-wise, while continuous stirring to obtain respective precipitates. These were separated by filtration and washed with cold water followed by ethanol to get heteroleptic Cu (II) complexes (6-7).



Complexes		R_1	R_2	R_3	R_4
1a	A, B, C= H			OH_2	OH_2
2a	A=F, B=Cl, C=H				
3a	A=F, B=H, C=H				
4a	A=H, B=H, C=F				
5 a	A=H,B=CF_3,C=H				
1b	A, B, C= H				
2b	A=F, B=Cl, C=H				
3b	A=F, B=H, C=H				
4b	A=H, B=H, C=F				
5b	A=H,B=CF_3,C=H				
6	A=F, B=Cl, C=H				
7	A=F, B=H, C=H				

Synthetic strategy of sy nthesis of copper (II) complexes

2.2.1 Tetraaqua phenyl carbamodithioatocopper (II) chloride (1a)

Brownish green solid of $C_7H_{14}ClCuNO_4S_2$ (76% yield); M.P. >300; Elemental analysis: found (calc.): C% 24.55 (24.78), H% 4.03 (4.16), N% 4.00 (4.13), Cu% 18.25 (18.73); ^{1}H NMR (DMSO-d6): δ 6.46-7.01(m, 5H, 5ArH), 4.24 (s, 1H, C-NH Aromatic ring), 10.50 (bs, 2H, coordinated water); Molar conductivity (DMSO): 27 ($Sm^2mol^{-1}\times10^{-6}$).

2.2.2 Tetraaqua - (3-chloro – 4 - fluorophenyl carbamodithioato) copper (II) chloride (2a)

Green solid of $C_7H_{12}Cl_2CuFNO_4S_2$ (79% yield); M.P. >300; Elemental analysis, found (calc.): C% 21.43 (21.46), H% 3.07 (3.09), N% 3.27 (3.58), Cu% 16.05 (16.22); H NMR (DMSO-d6): δ 6.31-6.69 (m, 3H, 3ArH), 4.02 (s, 1H, C-NH Aromatic ring), 10.35 (bs, 2H, coordinated water); Molar conductivity (DMSO): 30 ($Sm^2mol^{-1}\times10^{-6}$).

2.2.3 Tetraaqua-(4-fluorophenylcarbamodithioato) copper (II) chloride (3a)

Dark green solid of $C_7H_{13}ClCuFNO_4S_2$ (78% yield); M.P. >300; Elemental analysis, found (calc.): C% 23.50 (23.53), H% 3.67 (3.82), N% 3.20 (3.92), Cu% 17.65 (17.78); ^{1}H NMR (DMSO-d6): δ 6.43-6.72 (m, 4H, 4ArH), 4.24 (s, 1H, C-NH Aromatic ring), 10.29 (bs, 2H, coordinated water); Molar conductivity (DMSO): 27 ($Sm^2mol^{-1}\times10^{-6}$).

2.2.4 Tetraaqua - (2-fluorophenylcarbamodithioato) copper (II) chloride (4a)

Green solid of $C_7H_{13}ClCuFNO_4S_2$ (84% yield); M.P. >300; Elemental analysis, found (calc.): C% 25.43 (23.53), H% 3.65 (3.82), N% 3.22 (3.92), Cu% 17.62 (17.78); ^{1}H NMR (DMSO-d6): δ 6.44-6.78 (m, 4H, 4ArH), 4.51 (s, 1H, C-NH Aromatic ring), 10.81 (bs, 2H, coordinated water); Molar conductivity (DMSO): 27 ($Sm^2mol^{-1}\times10^{-6}$).

2.2.5 Tetraaqua - (3-trifluoro methylphenyl carbamodithioato) copper (II) chloride (5a)
Blackish green solid of $C_8H_{13}ClCuF_3NO_4S_2$ (79% yield); M.P. >300; Elemental analysis, found (calc.): C% 23.52 (23.59), H% 3.20 (3.22), N% 3.29 (3.44), Cu% 14.99 (15.12); ^{1}H NMR (DMSO-d6): δ 6.46-7.24 (m, 4H, 4ArH), 4.32 (s, 1H, C-NH Aromatic ring), 10.29 (bs, 2H, coordinated water); Molar conductivity (DMSO): 28 ($Sm^2mol^{-1}\times10^{-6}$).

2.2.6 Diaquabis (phenylcarbamodithioato) copper (II) complex (1b)
Reddish green solid of $C_{14}H_{16}CuN_2O_2S_4$ (80% yield); M.P. 242-244; Elemental analysis, found (calc.): C% 37.92 (38.47), H% 2.98 (3.92), N% 6.21 (6.41), Cu% 14.05 (14.54); ^{1}H NMR (DMSO-d6): δ 7.46-7.01 (m, 10H, 10ArH), 4.24 (s, 1H, C-NH Aromatic ring), 10.50 (bs, 2H, coordinated water); Molar conductivity (DMSO): 13 ($Sm^2mol^{-1}\times10^{-6}$).

2.2.7 Diaquabis (3-chloro-4-fluorophenyl carbamodithioato) copper (II) complex (2b)
Green solid of $C_{14}H_{12}Cl_2CuF_2N_2O_2S_4$ (82% yield); M.P. 245-247; Elemental analysis, found (calc.): C% 31.29 (31.63), H% 2.19 (2.42), N% 5.02 (5.17), Cu% 11.11 (11.72); ^{1}H NMR (DMSO-d6): δ 6.31-6.70 (m, 6H, 6ArH), 4.02 (s, 1H, C-NH Aromatic ring), 10.37 (bs, 2H, coordinated water); Molar conductivity (DMSO): 14 ($Sm^2mol^{-1}\times10^{-6}$).

2.2.8 Diaquabis (4-fluorophenylcarbamodithioato) copper (II) complex (3b)
Dark green solid of $C_{14}H_{14}CuF_2N_2O_2S_4$ (75% yield); M.P. 235-237; Elemental analysis, found (calc.): C% 34.87 (35.54), H% 3.35 (3.20), N% 5.87 (5.92), Cu% 13.07 (13.43); ^{1}H NMR (DMSO-d6): δ 6.43-6.75 (m, 8H, 8ArH), 4.10 (s, 1H, C-NH Aromatic ring), 10.30 (bs, 2H, coordinated water); Molar conductivity (DMSO): 9 ($Sm^2mol^{-1}\times10^{-6}$).

2.2.9 Diaquabis (2-fluorophenylcarbamodithioato) copper (II) complex (4b)
Blackish green solid of $C_{14}H_{14}CuF_2N_2O_2S_{42}$ (77% yield); M.P. 236-238; Elemental analysis, found (calc.): C% 35.12 (35.54), H% 3.01 (3.20), N% 5.15 (5.92), Cu% 12.93 (13.43); ^{1}H NMR (DMSO-d6): δ 6.45-6.76(m, 8H, 8ArH), 4.50 (s, 1H, C-NH Aromatic ring), 10.80 (bs, 2H, coordinated water); Molar conductivity (DMSO): 9 ($Sm^2mol^{-1}\times10^{-6}$).

2.2.10 Diaquabis (3-trifluoromethylphenyl carbamodithioato) copper (II) complex (5b)
Green solid of $C_{16}H_{14}CuF_6N_2O_2S_4$ (88% yield); M.P. 247-249; Elemental analysis, found (calc.): C% 33.35 (33.53), H% 2.43 (2.64), N% 4.19 (4.89), Cu% 10.50 (11.09); ^{1}H NMR (DMSO-d6): δ 6.45-7.21 (m, 8H, 8ArH), 4.32 (s, 1H, C-NH Aromatic ring), 10.29 (bs, 2H, coordinated water); Molar conductivity (DMSO): 8 ($Sm^2mol^{-1}\times10^{-6}$).

2.2.11 *Diaqua (3-chloro-4-fluorophenylcarbamodithioato) (phenylcarbamodithioato) copper (II) complex (6)*
Reddish green solid of $C_{14}H_{14}ClCuFN_2O_2S_4$ (76% yield); M.P. 262-264; Elemental analysis, found (calc.): C% 34.07 (34.35), H% 2.85 (3.09), N% 5.12 (5.72), Cu% 12.96 (12.98); ^{1}H NMR (DMSO-d6): δ 6.45-7.05(m, 8H, 8ArH), 4.10 (s, 1H, C-NH Aromatic ring),10.36 (bs, 2H, coordinated water); Molar conductivity (DMSO): 11 ($Sm^2mol^{-1}\times10^{-6}$).

2.2.12 Diaqua (4-fluorophenylcarbamodithioato) (phenylcarbamodithioato) copper (II) complex (7)
Dull green solid of $C_{14}H_{15}CuFN_2O_2S_4$ (87% yield); M.P. 270-272; Elemental analysis, found (calc.): C% 36.53 (36.95), H% 3.19 (3.54), N% 5.94 (6.16), Cu% 13.14 (13.96); ^{1}H NMR (DMSO-d6): δ 6.42-7.21(m, 9H, 9ArH), 4.39 (s, 1H, C-NH Aromatic ring), 10.24 (bs, 2H, coordinated water); Molar conductivity (DMSO): 12 ($Sm^2mol^{-1}\times10^{-6}$).

2.3 Antifungal Evaluation
The spores of *P. striiformis* and *P. hordei* were obtained from stripe rust of wheat and barley respectively from experimental area of PAU (Punjab Agricultural University 2016), Ludhiana. *B. sorokiniana* was cultured on potato dextrose agar (PDA). The culture of *B. sorokiniana* was obtained from seed pathology laboratory of PAU, Ludhiana and the standard propiconazole which served as the positive control were obtained from their respective manufacturers.

2.3.1 Spore germination inhibition technique
The stock solution of 1000 µg/ml were prepared of all the complexes, which were further diluted by adding distilled water. Complexes were insoluble in water, thus the required amount of complex were dissolved in minimum amount of Triton-X 100 and further distilled water was used to complete the volume. Serial dilutions were done to 500, 250, 100, 50, 25 and 10 µg/ml respectively.
Spore suspension was made by adding sterilized distilled water to the fresh spores of respective fungi. Suspension was filtered through three layers of sterilized cheese cloth in order to remove mycelial particles under aseptic conditions. Haemocytometer was used to form standardized spore suspension (1×10^6 spores/ml). Small droplets (0.02 ml) of test solution and spore suspension in equal amount were seeded in the cavity of the cavity slides. These slides were placed in Petri plates lined with moist filter paper and were incubated for 24 hrs at 15 ºC in case of *B. sorokiniana,* for 72-96 hrs at 15 ºC in case of *P. hordei* and *P. striiformis.* The numbers of spores germinated were counted and per cent spore germination inhibition was calculated by the following formula:

$$\%\ \text{spore germination inhibition} = \frac{\text{Spore germination in control} - \text{Spore germination in treatment}}{\text{Spore germination in control}} X100$$

All the tests are performed in triplicate and the reported data is the mean of three replicate tests performed with each antifungal compound. The SPSS statistical software was used for calculation of mean and analysis of the results recorded for antifungal evaluation.

2.3.2 Poisoned food technique
Potato dextrose agar (PDA) medium was prepared by using 250 g peeled potato, 20 g dextrose and 20 g agar in 1 litre water which was then autoclaved for half an hour. 47.5 ml of Potato Dextrose Agar (PDA) media was taken in the volumetric flask to which 2.5ml of stock solution (2000 µg/ml) of the test formulation were added to give the resulting 50 µg/ml of Complex-PDA concentrate. The contents of the

flask were poured aseptically into the Petri plates. Similarly, 50 µg/ml Complex-PDA concentrate of the test solutions were prepared using 1.3 ml of test solution in 48.7 ml of PDA. Similarly, the lower concentrations of PDA were prepared. Test samples, however, were replaced by the equal amount of PDA only in the control set. After solidification of the medium, 3mm culture disc of mycelium, the test fungus was aseptically placed to each Petri plate and were incubated at 25±1 °C. The average diameter of fungal colonies were measured on 7th day after inoculation. The per cent mycelial growth inhibition were recorded using the following formula:

$$\% \text{ mycelial growth inhibition} = \frac{\text{Radial growth of fungal colony in control} - \text{Radial growth of fungal colony in treatment}}{\text{Radial growth of fungal colony in control}} \times 100$$

The antifungal activity was expressed in terms of percent radial growth inhibition. The ED_{50} values (Effective dose at which 50% of inhibition of fungal spores occur) were calculated from per cent mycelial growth inhibition.

3. Results and Discussion

Newly synthesized Cu (II) complexes, obtained were powdered solids except 4a, b and 5a, b which were semisolid in nature and were stable at room temperature. These were insoluble in inorganic solvents like water, partially soluble in $CHCl_3$, however, soluble in organic solvents like DMSO and DMF (Dimethyl sulfoxide and Dimethyl formamide). These were also soluble in Triton X-100, required during antifungal evaluation.

3.1. Molar Conductance

The values of the molar conductance of 10^{-3} M DMSO solutions of the complexes were measured. The values for complexes 1a-5a confirmed that the complexes were in molar ratio 1:1 electrolytes i.e indicating the presence of one chloride ion outside the coordination sphere. The values for complexes 1b-5b, 6, 7 were very low to account for any ionisation, thus indicating the non-electrolytic nature of the complexes. The complexes are hexa coordinated i.e their geometry may be octahedral.

3.2 Elemental and metal analysis

The two different concentrations of the ligands with Cu *viz.* 1:1 and 2:1 were confirmed by elemental analysis of C, H and N that helped to frame general structure of the synthesized complexes. The percentage of Cu was calculated by the estimating the Cu by conductometric titration. Found and theoretical values of percentage of C, H, N and Cu were closed indicated the accuracy of the proposed structure.

3.3 ^{1}H NMR Spectra

The ^{1}HNMR spectra of the complexes were determined in DMSO. It exhibited various peaks corresponding to protons present in the complexes and all the protons responded in the expected region In complexes, the multiplets appeared due to 10 protons in complex1b, 9 protons in complex 7, 8 protons in complex 3b-5b and 6, 6 protons in complex 2b, 5 protons in complex 1a, 4 protons in complexes 3a-5a, 3 protons in complex 2a near δ 6.31–7.21 corresponding to aromatic protons in respective anilines. The proton bonded to nitrogen attached to aromatic ring showed signal near δ 4.02-4.50. The complexation of water molecule with copper ion showed broad signal near δ 10.24-10.81.

3.4 IR Spectra

The IR spectra of the various copper complexes, confirmed the formation of complexes. The bands appeared in the lower region at the range interval 411-469 cm^{-1} which showed the formation of Cu-S bond. A single band in the range 933-997 cm^{-1} indicated the symmetrical coordination through both the sulfur atoms. The sharp bands in the range 1500-1569 cm^{-1} appeared which suggested the presence of >C-N bond. The prominent bands in the range 3137-3240 cm^{-1} corresponded to the N-H stretch in the molecule linked to the aromatic ring of different fluoroaniline moiety. The medium to strong bands in the range 1041-1141 and 817-880 cm^{-1} indicated the C-F and C-Cl bond respectively. The bands near 3120 cm^{-1} indicated the presence of aromatic protons. The broad band showed around 3308-3449 cm^{-1} corresponding to O-H stretching indicated the presence of coordinated water molecules. The various IR frequencies of the complexes are tabulated in Table 1.

Table 1: IR spectral data of copper (II) complexes

No.	Complexes	ν_{Cu-S}	ν_{S-C-S}	ν_{C-N}	ν_{N-H}	ν_{O-H}	ν_{C-F}	ν_{C-Cl}
1a	$[Cu(L_1).4H_2O]Cl$	411	994	1568	3226	3357	-	-
2a	$[Cu(L_2).4H_2O]Cl$	446	997	1561	3199	3448	1141	880
3a	$[Cu(L_3).4H_2O]Cl$	413	960	1509	3239	3308	1093	-
4a	$[Cu(L_4).4H_2O]Cl$	411	980	1500	3219	3312	1090	-
5a	$[Cu(L_5).4H_2O]Cl$	424	933	1569	3235	3315	1130	-
1b	$[Cu(L_1)_2.2H_2O]$	413	933	1560	3219	3355	-	-
2b	$[Cu(L_2)_2.2H_2O]$	418	933	1560	3193	3449	1141	818
3b	$[Cu(L_3)_2.2H_2O]$	416	960	1509	3239	3449	1093	-
4b	$[Cu(L_4)_2.2H_2O]$	413	951	1501	3225	3310	1072	-
5b	$[Cu(L_5)_2.2H_2O]$	433	933	1567	3232	3315	1129	-
6	$[Cu(L_1L_2).2H_2O]$	466	980	1512	3137	3352	1102	880
7	$[Cu(L_1L_3).2H_2O]$	469	951	1567	3240	3337	1041	-

L_1= $C_7H_6NS_2$**, L_2=** $C_7H_4ClFNS_2$**, L_3=** $C_7H_5FNS_2$**, L_4=** $C_7H_5FNS_2$**, L_5=** $C_8H_5F_3NS_2$

3.5 Electronic spectral studies

The electronic spectrum of the copper complexes were recorded in DMSO. It showed a sharp band with λ_{max} around 360 nm i.e due to charge transfer transition. The two bands in the range 262-265 and 319-334 nm corresponding to the π-π^* transitions of N-C-S and S-C-S chromophores respectively. The ligand to metal charge transfer band appeared in the higher region due to π-π^* and n-π^* electron transitions near

360 nm. All the charge-transfer bands were observed below 400 nm. The bands in the higher region corresponding to the d-d metal transitions were less prominent (Table 2).

Table 2: Electronic and mass spectral data of copper (II) complexes

Complex No.	ƛmax (nm)		
	N-C-S	S-C-S	Charge Transfer
1a	262	330	365
2a	264	333	360
3a	267	319	364
4a	263	334	362
5a	263	326	364
1b	264	322	370
2b	264	343	368
3b	262	329	360
4b	264	335	360
5b	262	327	365
6	263	328	362
7	265	329	368

3. 6 Antifungal activity

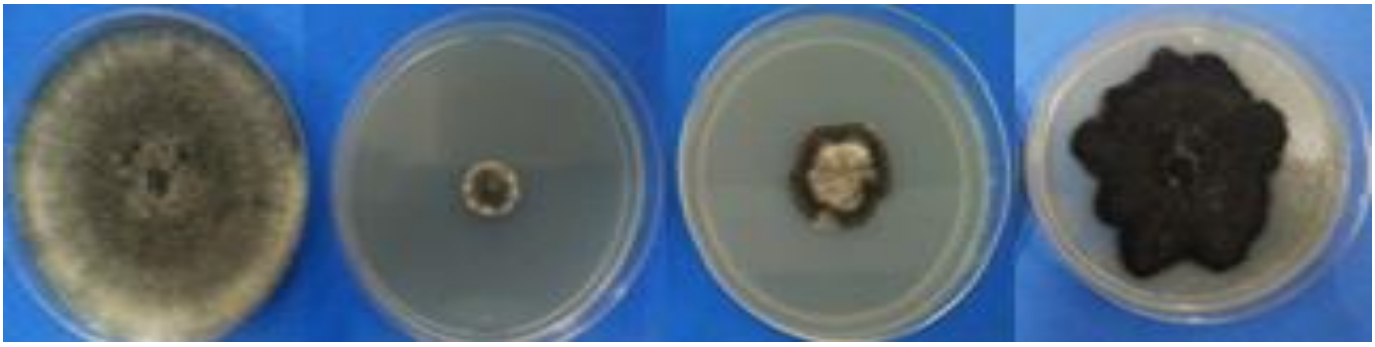
Trends of antifungal activity against *P. hordei* and *P. striiformis* were quite similar. Here the complex 1a with ED_{50} value near 76 µg/ml showed the best inhibition of germination of fungal spores followed by complexes 1b and complex 2a with ED_{50} value near 79 µg/ml. The ED_{50} values of the test complexes against *B. sorokiniana* clearly implicated the higher bioactivity which were comparable to the standard fungicide (propiconazole) used. The non-fluorinated complexes 1a and 1b were found to be more active than the complexes with the fluorine moiety. The complex 1a showed the best inhibition of germination of mycelial growth with ED_{50} value 21 µg/ml. The radial growth inhibition of the test complex 1a at 100, 50 and 20 µg/ml are shown in Fig 1. The 90-95% of the inhibition was observed at 100 µg/ml, 70-75% at 50 µg/ml and 50% of inhibition was observed between 50-20 µg/ml.

The mono-carbamodithioato complexes showed better activity than the bis-carbamodithioato complexes. The pictorial diagram (Fig 2) of relative effect of complexes 1a and 1b on the radial growth gave clear inference of better activity of 1a. Among the fluorinated copper complexes, the complexes 2a and 2b i.e 3-chloro-4-fluoro carbamodithioato copper complexes showed better activity than the complexes containing only fluorine moiety (Fig 3). All the treatments were significantly different from each other as well as the standard at 5% level of significance. The relative stoichiometry was an important concept and the decrease in the stoichiometric concentration of bioactive ligand was found to affect the antifungal potential in augmented manner.

Table 3: Antifungal potential of Cu complexes of carbamodithioates (1a, 1b) and fluorinated carbamodithioates ED_{50} values (µg/ml)

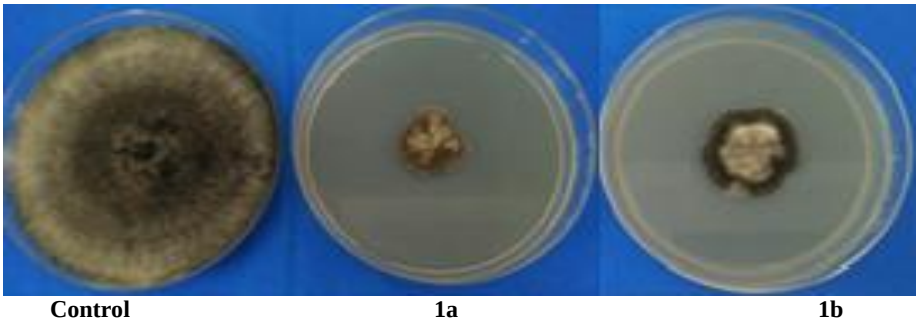
Complex no.	*P. hordei*	*P. striiformis*	*B. sorokiniana*
1a	75	77	21
2a	78	80	23
3a	85	89	26
4a	86	89	26
5a	82	86	25
1b	79	80	22
2b	81	87	25
3b	89	97	28
4b	92	100	27
5b	83	95	28
6	87	90	28
7	92	100	30
* Propiconazole	36	34	30

*Standard fungicide



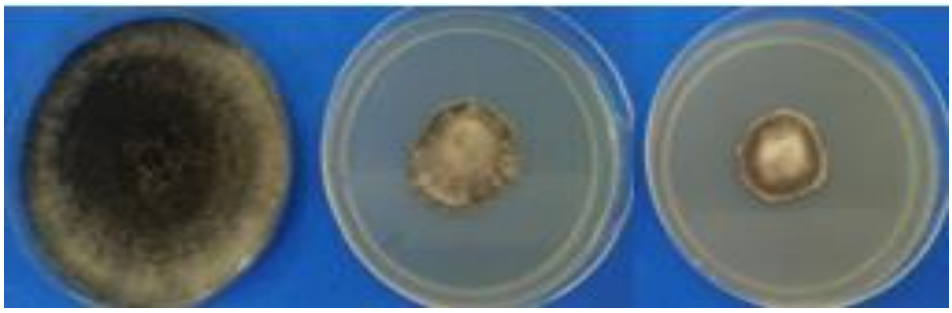
Control **100 µg/ml** **50µg/ml** **20µg/ml**

Fig 1: Inhibition zone of complex 1a at different concentration against *B. sorokiniana*



Control **1a** **1b**

Fig 2: Inhibition zone of mono and bis-carbamodithioato complexes (1a and 1b) respectively against *B. sorokiniana*



Control **2a** **3a**

Fig 3: Inhibition zone of fluorinated carbamodithioato complexes (2a and 3a) respectively against *B. sorokiniana*

Synthetic studies indicated the chemically privileged nature of flouro carbamodithioato copper (II) complexes owing to their ease of preparation, in a single pot and in the absence of any catalyst. The one pot synthesis of complexes was performed owing to non-separation of fluorinated ligands from the solvent systems used.

All the prepared complexes showed inhibition of fungal growth better than the control. There is indication of the use of $CuSO_4$ for fungicidal activity carrying the effective activity at concentration as low as 0.8mg/L [25] But $CuSO_4$ has lost its indispensability in agriculture worldwide in free form. Free form of Cu ions show extensive disruption of membrane integrity and loss of cell viability [26] The mancozeb (Standard DTC used) has its ED_{50} value at 45ppm [27] No doubt that the activity of prepared complexes of copper were moderate than copper ions but better than the carbamodithioates alone, which are in agreement with results of biological activity of the eugenol-copper complex [28] But the results are still commendable in comparison to standard carbamodithioates used and propiconazole (commercial standard) against *B. sorokiniana*. The further exploration is recommended in agriculture as resistance measure against standard commercial fungicides.

4. Conclusion

In summary, the copper complexes of fluorinated carbamodithioates were synthesized using one pot two step reaction protocol. Attempts to isolate the free ligand were unsuccessful. Therefore, a one pot approach was implemented to obtain metal complexes. The reactions were performed without the use of sodium hydroxide, which made the work-up conditions easier. Various spectral data recorded were in conformity with the proposed structure of the complexes. Better fungitoxicity activity of the non-fluorinated carbamodithioato complexes showed the negative influence of the fluorine moiety in the rest of the complexes. Against *B. sorokiniana,* the complexes were found to be more bioactive even than the standard fungicide used (propiconazole).

5. References

1. Rusjan D. Copper in horticulture, in: D Dhanasekaran (Ed.), Fungicides for Plant and Animal Diseases. University of Ljubljana, Slovenia, 2012, 257-278.
2. Santra S. Silica based antibacterial and antifungal nanoformulation. U.S. Patent 8632811 B1, 2014.
3. Wang Z, Bussche AVD, Kabadi PK, Kane AB, Hurt RH. Biological and environmental transformation of copper-based nanomaterials. ACS Nano. 2013; 7(10):8715-8727.
4. Stevenson FJ. Organic matter-micronutrient reactions in soil, in: Cox F R, Shuman L M and Welch R M (Ed.). Soil Science Society of America, Madison, 1991, 145-186.
5. Shobha G, Moses V, Ananda S. Biological synthesis of copper nanoparticles and its impact- a review. Int. J Pharma. Sci. Inv. 2014; 3(8):28-38.
6. Han C, Porco A. Synthesis of carbamates and ureas Zr (IV) catalyzed exchange processes. J Org. Lett. 2007; 9(8):1517-1520.
7. Rafin C, Veignie E, Sancholle M, Postal D, Len C, Villa P. *et al.* Synthesis and antifungal activity of novel bisdithiocarbamate derivatives of carbohydrates against *Fusarium oxysporum* f. sp. Lini. J Agric. Food. Chem. 2000; 48(11):5283-5287.
8. Greene TW, Wuts PGM. Protecting group in organic synthesis. Wiley Intersci. 1999; 3:484.
9. Chaturvedi D, Ray S. An efficient one-pot synthesis of dithiocarbamates from the corresponding alcohols using Mitsunobu's reagent. Tetrahedron Lett. 2006; 47(8):1307-1309.
10. Crich D, Quintero L. Radical chemistry associated with thiocarbonyl group. Chem. Rev. 1989; 89(7):1413-1432.
11. Boas U, Gertz H, Christensen JB, Heegaard PMH. Facile synthesis of aliphatic isothiocyanates and thioureas on solid phase using peptide coupling reagents. Tetrahedron Lett. 2004; 45(2):269-272.
12. Mamba SM, Mishra AK, Mamba BB, Njobeh PB, Dutton MF, Fosso-Kankeu F. Spectral, thermal and *in vitro* antimicrobial studies of cyclohexylamine-N-dithiocarbamate transition metal complexes. Spectrochim. Acta Mol. Biomol. Spectrosc. 2010; 77(3):579-587.
13. Awang N, Baba I, Yamin BM, Othman MS, Halim AA. Synthesis, characterization and crystal structure of triphenyltin (IV)N-alkyl-N-cyclohexyldithiocarbamate compound. World App. Sci J. 2011; 12(5):630-635.
14. Shahnaz M. Synthesis, characterization of N,N-disubstituted dithiocarbamates derivatives and evaluation of antifungal activity. J. Drug Deliv. Th. 2013; 3(5):110-114.
15. Mujawar S, Utture S, Fonseca E, Matarrita J, Banerjee K. Validation of a GC–MS method for the estimation of dithiocarbamate fungicide residues and safety evaluation of mancozeb in fruits and vegetables. Food Chem. 2014; 150:175-181.
16. Qin Y, Liu S, Xing R, Yu H, Li K, Meng X *et al.* Synthesis and characterization of dithiocarbamate chitosan derivatives with enhanced antifungal activity. Carbohydr. Polym. 2012; 89(2):388-393.
17. Schreck R, Meier B, Mannel DN, Droge W, Baeuerle PA. Dithiocarbamates as potent inhibitors of nuclear factor kappa B activation in intact cell. J Exp. Med. 1992; 175(5):1181-1194.
18. Basirah A, Hasan MFA, Norliawati MS, Khairul WM, Noraznawati I. Synthesis, characterization and

antimicrobial activity of organotin (IV) complexes featuring bis-2-methoxyethyl dithiocarbamate as ligand. J App. Sci. Res. 2013; 9(10):5562-5567.
19. Palanisamy JR, Subbiah T. Synthesis, characterization, cytotoxicity and antimicrobial studies on bis(N-furfuryl-N-(2-phenylethyl)dithiocarbamato-S,S0)zinc(II) and its nitrogen donor adducts. Eur. J Med. Chem. 2013; 62:139-147.
20. Charles JD. Coping with resistance to plant disease. Plant Dis. 1980; 64:652-657.
21. Al-Hasani TJ, Al-Taie MK. Synthesis, Structural and antibacterial study of some metal ion dithiocarbamate-azo complexes. JNUS. 2015; 18(4):1-12.
22. Al-Fahdawi AS, Al-kafajy HA, Al-Jeboori MJ, Potgieter H. Synthesis, spectral and structural studies of neutral Co(II), Ni(II) and Cu(II) macrocyclic dithiocarbamate-based complexes formed via one pot reaction. Irq. Nat. J Chem. 2013; 52:414-429.
23. Kaur R, Sidhu A, Gumber K, Sharma VK. Synthesis of novel 1, 2, 4-triazolodithiocarbamato transition metal complexes as mycocidal agent. Int. J Chem. Studies. 2017; 5(2):460-466.
24. Purser S, Swallow S, Gouvemeur V, Moore PR. Flourine in medicinal chemistry. Chem. Soc. Rev. 2008; 37(2):320-330.
25. Oziengbe EO, Osazee JO. Antifungal activity of copper sulphate against *colletotrichum gloeosporioides.* J asian sci. res. 2(12):835-839.
26. Kumbhar AS, Padhye SB, Saraf AP, Mahajan HB, Chopade BA, West DX. Novel broad-spectrum metal-based antifungal agents. Correlations amongst the structural and biological properties of copper 2-acetylpyridine N4dialkylthiosemicarbazones. Biology of metals. 1991; 4:3141-3143.
27. Leka Z, Bulatovic D, Latinovic N. Antifungal activity of newly synthesized dithiocarbamates on the fungus *Phomopsis viticola sacc*, University of Montenegro, 2013, 495-500.
28. Upadhyaya S, Behara J, Tewari SN. Synthesis and biological activity of eugenol-copper complex. Chem. Sci. Trans. 2014; 3(1):213-220.