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ANTI-FUNGAL ACTIVITIES OF THIOSEMICARBAZONES AND THEIR COPPER (II) COMPLEXES

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ABSTRACT

Thiosemicarbazones and their metal complexes have numerous biological applications. Most of the studies reported the biological activities of thiosemicarbazones and their metal complexes. But not much reports have been existing about the anti-fungal properties of thiosemicarbazones. In this present study we reported the anti-fungal properties of nine newly synthesized thiosemicarbazones and their copper (II) complexes. For this purpose, we examined the anti-fungal activity of thiosemicarbazones and their copper (II) complexes on *Candida albicans* and *Candida trophicalis*. All the thiosemicarbazones and their metal complexes has taken in four different concentrations. All the results obtained are presented in table and analyzed with the help of graphs.

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Introduction

Thiosemicarbazones had various applications in different fields, such as medical [1-3], pharmaceutical [4-9] and biological [10-12]. In modern days thiosemicarbazones and their complexes are being used in treatments of various diseases. The applications of complexes are not limited to anti-biotic, anti-viral, cytotoxic, etc. These complexes have a wide range of applications in medical field, in the treatment of various drugs. For example, *cis*-platin, a platinum complex is used as anti-cancer to treat a number of cancers, such as testicular, cervical, breast, ovarian and bladder cancers. Gold complexes are used to treat rheumatoid arthritis.

Al-amiery et al. [13] has studied biological activity of (*z*)-2-(pyrrolidine-2-ylidene) hydrazine carbothioamide and its copper complex. The study showed that copper complex exhibit better anti-fungal activity than its parent ligand. Anti-fungal activity of 6-Methtyl-2-formylpyridine 4N-dimethylthiosemi carbazone and their copper complex was reported by Ali et al. [14] This study indicated that free ligands were more effective than their metal complexes. Anti-fungal activity of 2-acetyl-γ-butyrolactone thiosemicarbazone and 2-furan carbaldehyde thiosemicarbazone and their copper complexes was reported by Rodreriguez-Arguelles et al. [15]. This study revealed that copper complexes exhibit better activity than their parent ligands.

Anti-fungal activity of 2-hydroxyacetophenone ^{4}N substituted thiosemicarbazones and their copper complexes against *Aspergillus niger* and *Paecilomyces variotii* was reported by West et al. [16]. They reported that their compounds shows better activity against *P. variotti* than *A. niger*. Recently, few authors also reported the anti-fungal activities of thiosemicarbazones and their metal complexes.

The present study describes the anti-fungal activities of nine thiosemicarbazone ligands, namely 4-(diphenylamino)benzaldehyde-4-methyl-3-thiosemicarbazone(**1**), 4-(bis(4-bromophen -yl)amino)benzaldehyde-4-phenyl-3-thiosemicarbazone(**2**), 4,4′-(4-bromophenylazanediyl) di -benzaldehyde-4-phenyl-3-thiosemicarbazone(**3**), 9H-carbazole-3-carbaldehyde-4-phenyl-3-thio semicarbazone(**4**), 10-hexyl-10H-phenothiazine-3-carbaldehyde-4-phenyl-3-thiosemicarbazone (**5**), 2-thiophenecarboxaldehyde-4-methyl-3-thiosemicarbazone(**6**), 4-methylbenzaldehyde-4-methyl-3-

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thiosemicarbazone**(7)**, 2,3,4-trihydroxybenzaldehyde-4-phenyl-3-thiosemicarbazone (**8**) and 2,3,4-trihydroxybenzaldehyde-4-methyl-3-thiosemicarbazone(**9**) and their copper(II) complexes against *Candida albicans* and *Candida trophicalis*. For this purpose, four different concentrations (25, 50, 75 and 100 µL) of ligands and their copper (II) complexes were used.

Experimental

Experimental procedure for anti-fungal activity

Antifungal activity was screened against two fungal pathogens *Candida albicans* and *Candida trophicalis*. Antifungal activity was determined using the agar well diffusion method. Potato dextrose agar medium was prepared and autoclaved at 121°C and 15lbs pressure for 15 min. The standard drug Amphotericin B was used as negative control and DMSO was used as positive control. Stock solutions of the test compounds and standard drug was prepared in DMSO used as solved control. The sterile medium was poured in to petri plates. The inoculums of *Candida* were taken and spread on agar plate with the help of swabs. The wells were made on agar plate. The chemical compounds were dissolved in DMSO solution. Four different concentrations (25, 50, 75 and 100 µL) are poured into the wells. The plates were incubated at 30°C for 24-48h. After incubation period, the zones were prepared around the wells and the diameter of zones was measured.

Results and Discussion

The newly synthesized thiosemicarbazone ligands (1-9) and their copper (II) complexes (1A-9A) were tested for anti-fungal activity against *Candida albicans* and *Candida trophicalis*. For this purpose, four different concentrations (25, 50, 75 and 100 µL) of ligands and their copper (II) complexes were used. The results obtained in this study is presented in Table 1.

Table 1. Minimal inhibition zones (in mm) of ligands (1-9) and their copper (II) complexes (1A- 9A) against two fungal stains at four different concentrations.

	Candida albicans*				***Candida trophilicalis****			
Conc. (µL)	**25**	**50**	**75**	**100**	**25**	**50**	**75**	**100**
1	-	-	-	-	-	-	-	-
1A	5.0	6.0	6.5	7.0	-	5.0	5.5	6.0
2	-	-	-	-	-	-	-	-
2A	-	-	-	-	-	-	-	-
3	-	-	-	-	-	4.0	6.0	8.0
3A	-	5.0	6.0	7.0	-	-	-	-
4	-	8.0	10.0	15.0	-	-	-	-
4A	5.0	6.0	7.0	7.0	-	4.0	6.0	8.0
5	-	10.0	15.0	20.0	-	-	-	-
5A	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-
6A	-	-	-	-	-	-	6.0	8.0
7	-	-	-	-	-	-	-	-
7A	-	-	-	-	-	-	-	-
8	8.0	10.0	15.0	19.0	5.0	10.0	15.0	17.0
8A	5.0	5.5	6.0	7.0	5.0	6.5	7.0	10.0
9	-	9.0	11.0	15.0	-	8.0	11.0	16.0
9A	-	-	-	-	-	-	-	-

* Minimal inhibition zone values are in mm.

Antifungal activity of ligands (1-9) and their copper(II) complexes (1A-9A) against *Candida albicans*

Activity of ligands (1-9) and their copper(II) complexes (1A-9A) against *C. albicans* is presented in Fig. 1.

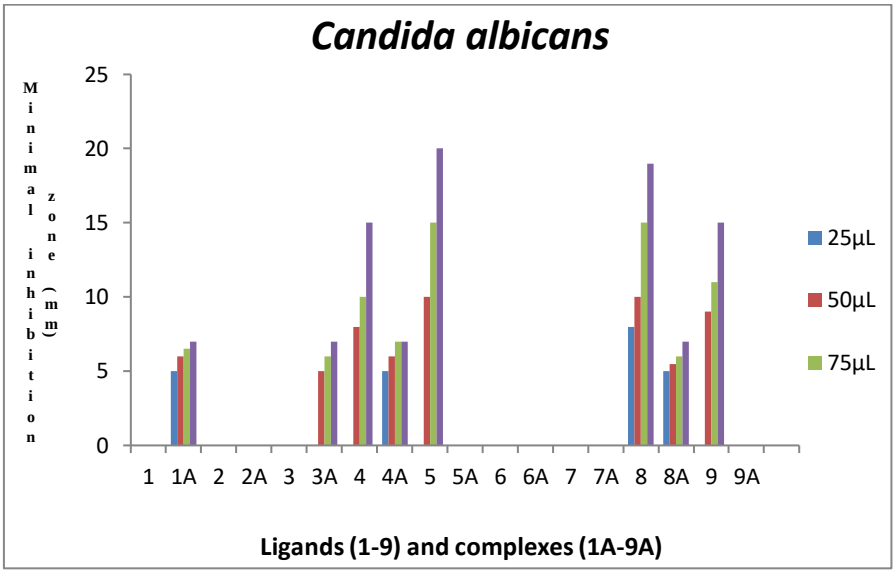

Fig. 1. Minimal inhibition zone values for ligands 91-9) and their copper (II) complexes of (1A- 9A) against *Candida albicans*.

From the above figure it is found that the ligands 1, 2, 4, 6 and 7 are inactive against *C. albicans* even at high concentrations (100 µL). Complexation with copper(II) of nine ligands gave mixed results. In case of ligands 1 and 3, complexation increases the activity, while in case of ligands 4, 8 and 9 complexation decreases the activity. In case of ligands 2, 6 and 7 there is no effect of complexation on their activity against *C. albicans*. Only 1A, 3A, 4, 4A, 5, 8, 8A and 9 compounds are active against *C. albicans* among all of the 18 compounds tested. Among the active compounds, the activity at high concentration (100µL) follows the order 5>8>4=9>1A=3A=4A=8A. The images of activity of ligands and complexes against *C. albicans* is presented in Fig. 2 and Fig.3, respectively.

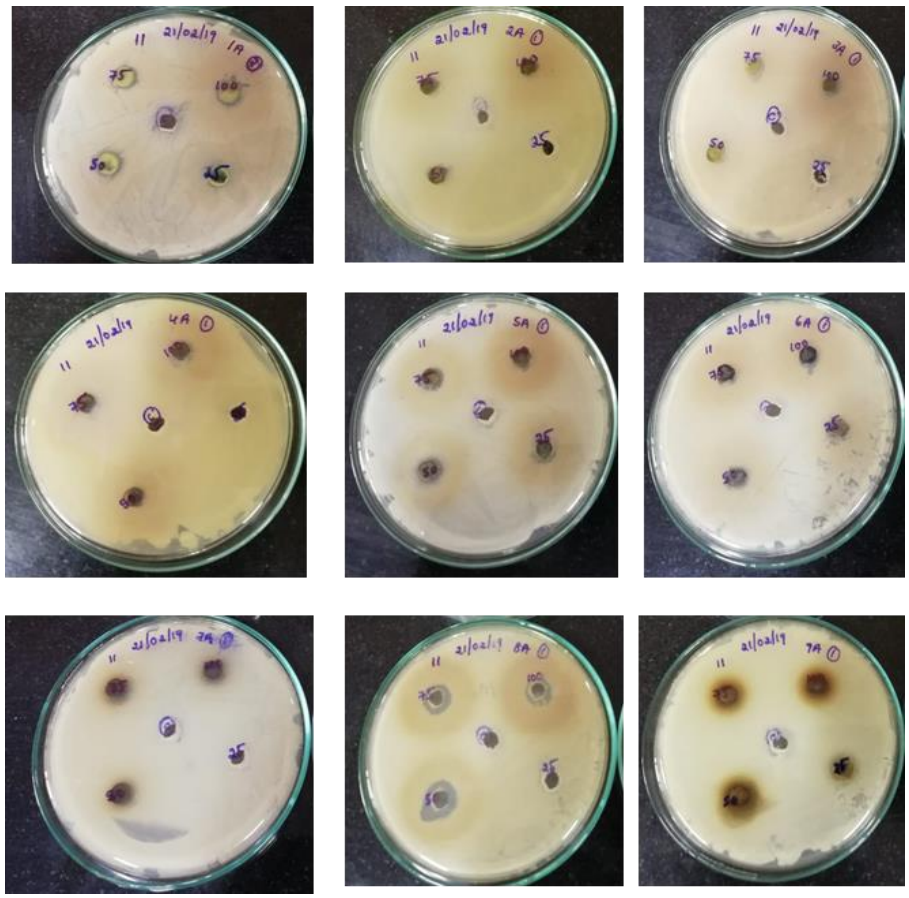

Fig. 2 Activity of ligands against *C. albicans*.

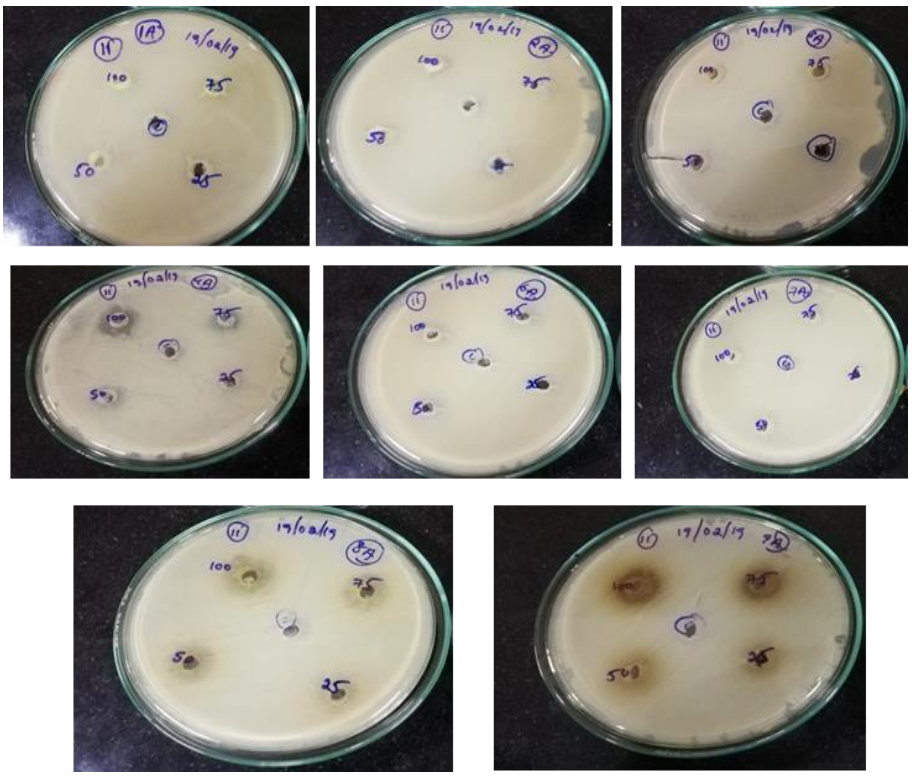

Fig. 3. Activity of complexes against *C. albicans*.

Antifungal activity of ligands (1-9) and their copper(II) complexes (1A-9A) against *Candida trophicalis*

Activity of ligands (1-9) and their copper(II) complexes (1A-9A) against *C. trophicalis* is presented in Fig. 4.

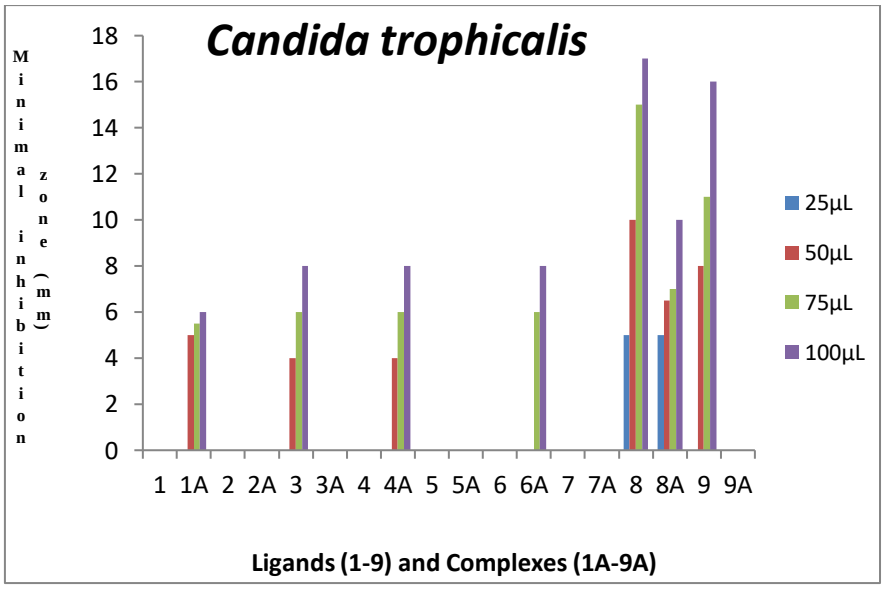

Fig. 4. Minimal inhibition zone values for ligands (1-9) and their copper (II) complexes (1A- 9A) against *Candida trophicalis*

From the above figure it is found that the ligands 1, 2, 4, 6, 7 and 9 are inactive against *C. trophicalis* even at high concentrations (100µL). Complexation with copper(II) of nine ligands gave mixed results. In case of ligands 1, 4 and 6 complexation increases the activity while in case of ligands 3, 8 and 9 complexation decreases the activity. In case of ligands 2, 5 and 7 there is no effect of complexation on their activity against *C. trophicalis*. Only 1A, 3, 4A, 6A,8, 8A and 9 compounds are active against *C. trophicalis* among all of the 18 compounds tested. Among the active compounds the activity at high concentration (100µL) follows the order 8>9>8A>3=4A=6A>1A. The images of activity of ligands and complexes against *C. trophicalis* is presented in Fig. 5 and Fig. 6, respectively.

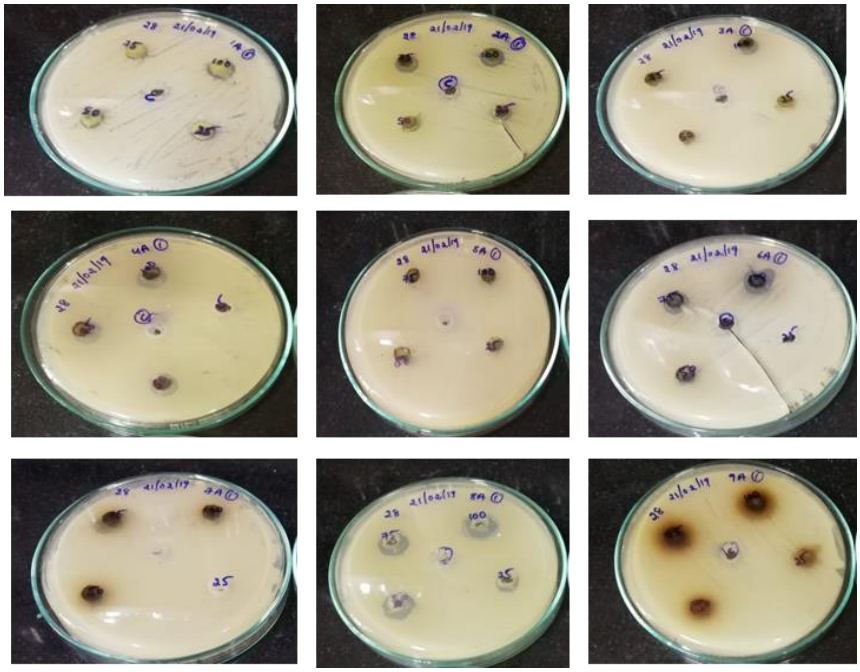

Fig. 5. Activity of ligands against *C. trophicalis*.

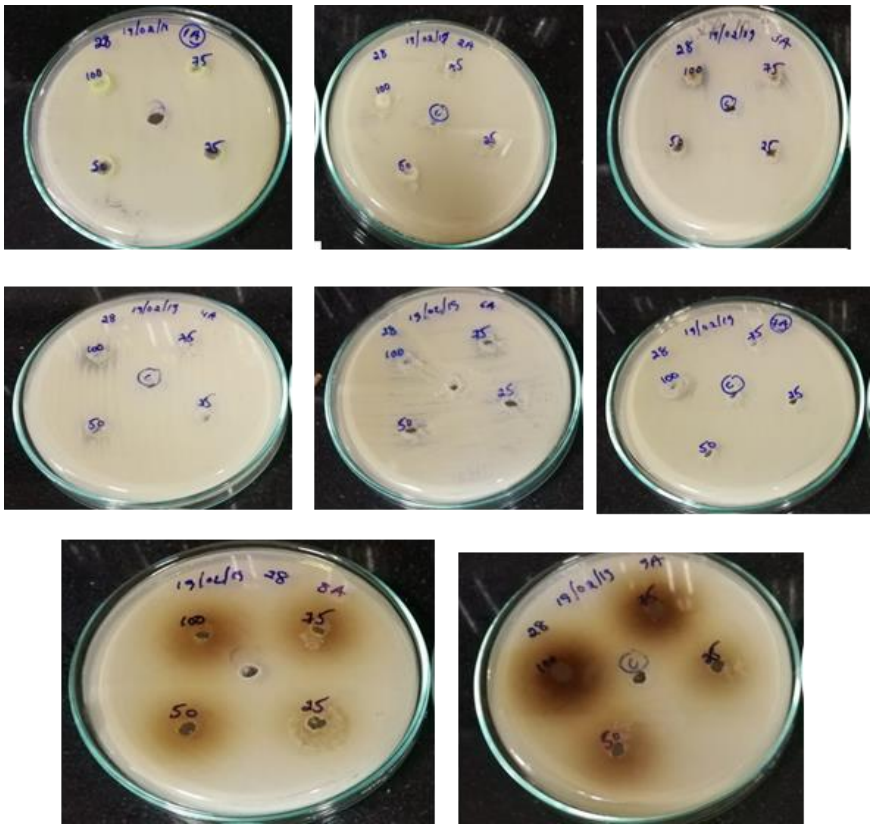

Fig. 6. Activity of complexes against *C. trophicalis*

Antifungal activity of ligands (1-9) and their copper(II) complexes (1A-9A) against two fungal species *C. albicans* and *C. trophicalis*

Activity of ligands (1-9) and their copper(II) complexes (1A-9A) against *C. albicans* and *C. trophicalis* is presented in Fig. 7.

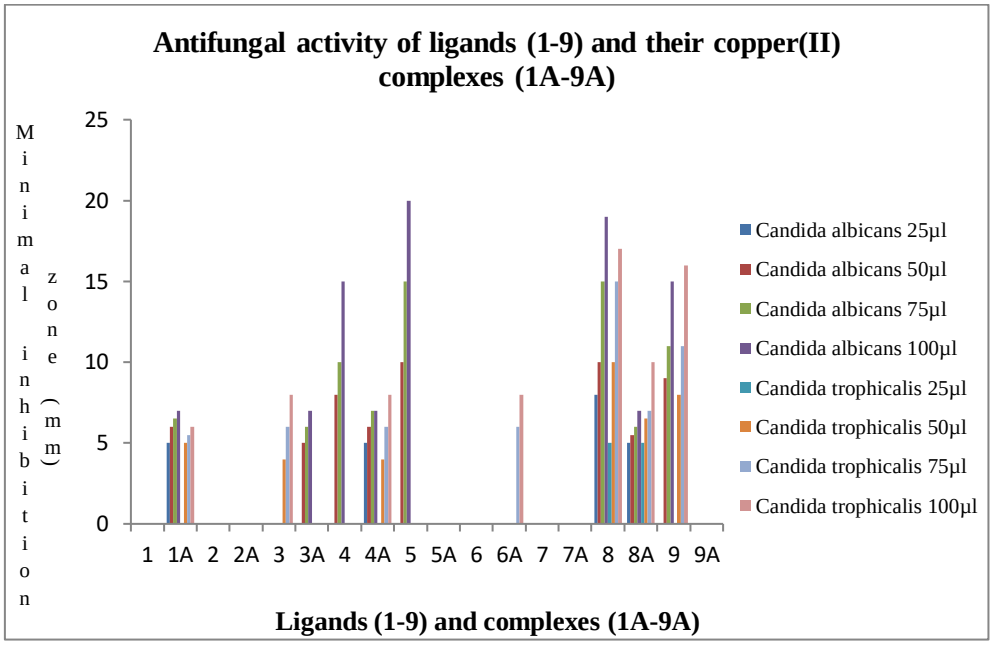

Fig. 7. Minimal inhibition zone values for ligands (1-9) and their copper (II) complexes of (1A- 9A) against *Candida albicans* and *Candida trophicalis*

From the above figure, it is observed that ligands 1, 2 and 7 and complexes 2A, 5A, 7A and 9A are inactive against both fungi. Ligand 3 and complex 6A are inactive against *C. albicans* and active against *C. trophicalis* while ligands 4, 5 and complex 3A are inactive against *C. trophicalis* and active against *C. albicans*. Among all 18 compounds tested, only 1A, 4A, 8, 8A and 9 are active against both fungi.

Conclusions

From the above discussion, it is clear that the activity of all eighteen compounds against *C. albicans* at high concentration (100µL) follows the order 5>8>4=9>1A=3A=4A=8A. The activity against *C. trophicalis* at high concentration (100µL) follows the order 8>9>8A> 3=4A=6A>1A. The ligands 1.2,4,6, and 7 are inactive against both fungi and among the complexes 1A, 4A, 8, 8A are inactive against both fungi.

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