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01–30 NOVEMBER 2022 | ONLINE

Silver(I) complexes with clinically used azoles: synthesis, structural characterization and antimicrobial evaluation

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pharmaceuticals MDPI

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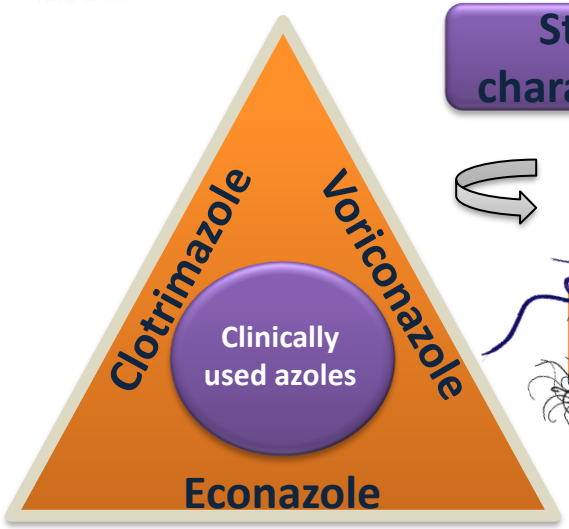
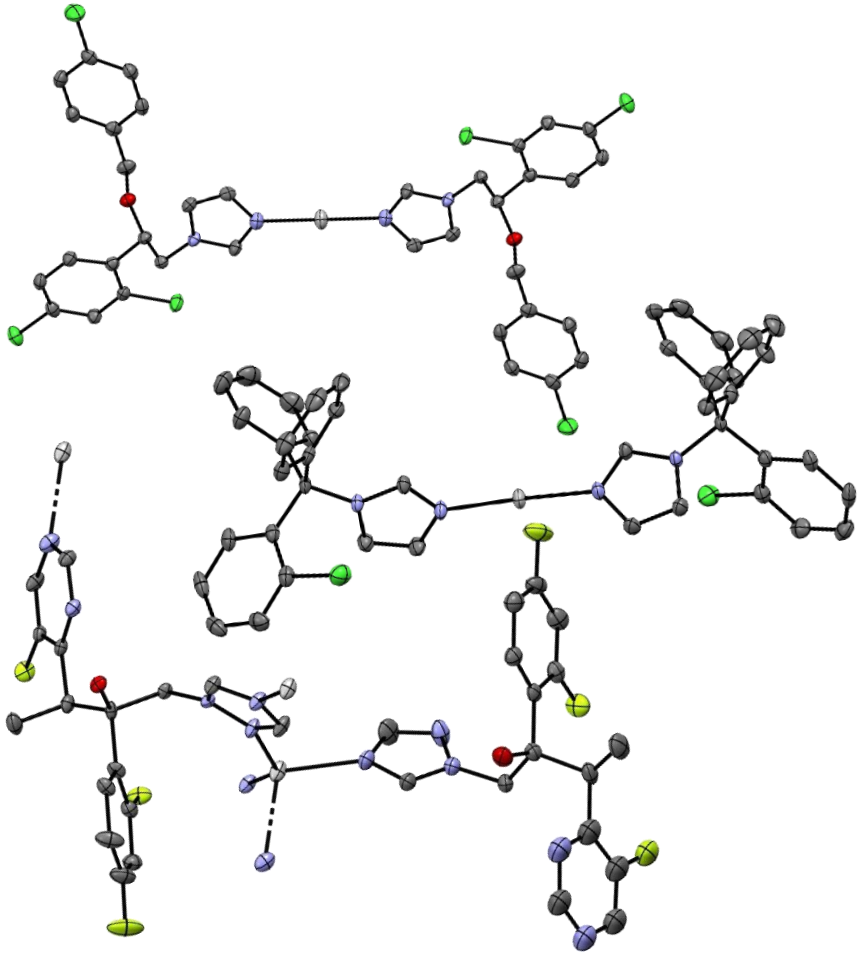
Synthesis

Structural characterization

Antimicrobial activity





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Abstract:

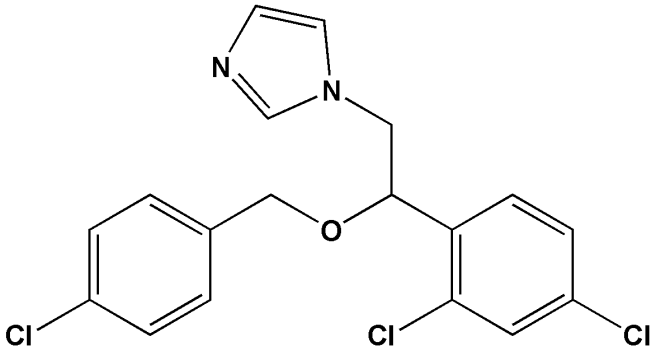
Recently, we synthesized silver(I) complex with the antifungal agent itraconazole, which showed improved anti-*Candida* potential and therapeutic safety in comparison to itraconazole and rescued the zebrafish embryos of lethal *C. albicans* infection at safe doses.[1] Inspired by these results, in the present study, three new silver(I) complexes with clinically used azoles, econazole (ecz), clotrimazole (ctz) and voriconazole (vcz), $[Ag(ecz)_2]SbF_6$ (**Ag1**), $[Ag(ctz)_2]SbF_6$ (**Ag2**) and $\{[Ag(vcz)_2]SbF_6\}_n$ (**Ag3**) were synthesized and structurally characterized by elemental microanalysis, mass spectrometry, spectroscopy (^{1}H NMR, IR and UV-Vis), cyclic voltammetry, molar conductivity measurements and single crystal X-ray diffraction analysis.[2] The spectroscopic and crystallographic results revealed that, in the synthesized silver(I) complexes, azole ligands are monodentately coordinated to the Ag(I) ion through the nitrogen atom forming $[Ag(azole)_2]^+$ complex cation. The antimicrobial effect of complexes and azole ligands was evaluated against different *Candida* species, as well as Gram-positive and Gram-negative bacteria. The synthesized complexes **Ag1 – 3** exhibited good to moderate antimicrobial activity being, in most cases, more active than the corresponding azole ligands. Complexes **Ag2** and **Ag3** also showed strong inhibitory activity against *C. albicans* biofilm formation and strong inhibition of *C. albicans* filamentation at subinhibitory concentrations.

Keywords: Silver(I) complexes; Antifungal azoles; Antimicrobials; Biofilms.

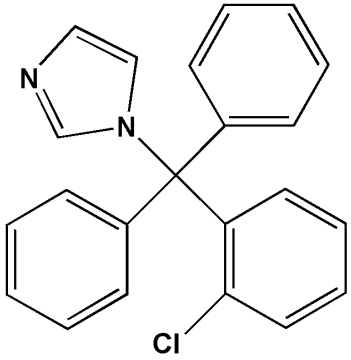
1. N. Lj. Stevanović, B. Đ. Glišić, S. Vojnovic, H. Wadepohl, T. P. Andrejević, S. Ž. Đurić, N. D. Savić, J. Nikodinovic-Runic, M. I. Djuran, A. Pavic, *J. Mol. Struct*. 1232 (2021) 130006.
2. N. Lj. Stevanović, J. Kljun, M. Stankovic, S. Skaro-Bogojevic, J. Lazic, I. Turel, M. I. Djuran, B. Đ. Glišić, *Manuscript in preparation* .

Introduction

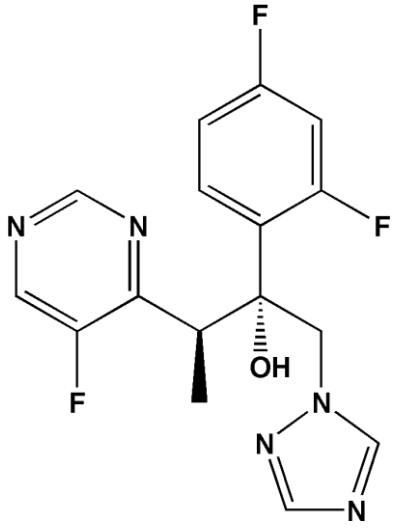
- ✓ Fungal infections represent a serious problem for modern-day healthcare
- ✓ Antifungal agents inhibit the enzymes (cytochrome P450), included in the synthesis of ergosterol, which is a component of the fungal cell membrane
- ✓ Azoles are of particular importance as potent broad-spectrum agents used as first-line therapy for the treatment of many invasive fungal infections associated with significant morbidity and mortality worldwide



Econazole (ecz)



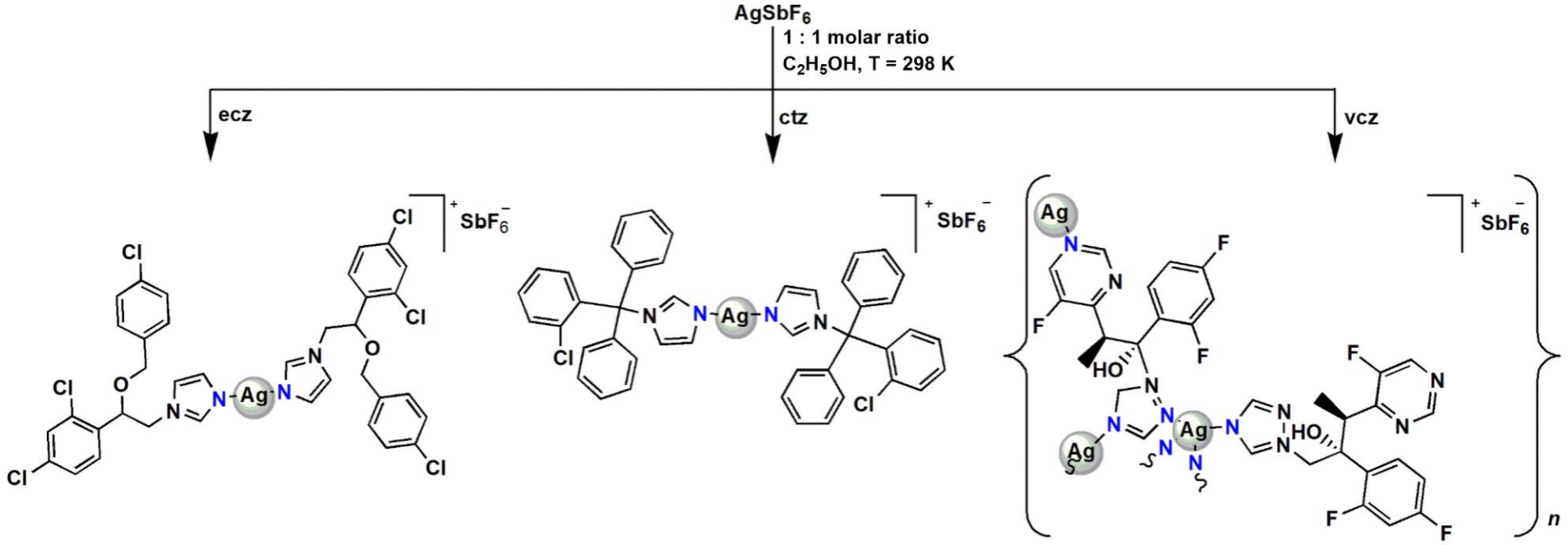
Clotrimazole (ctz)



Voriconazole (vcz)

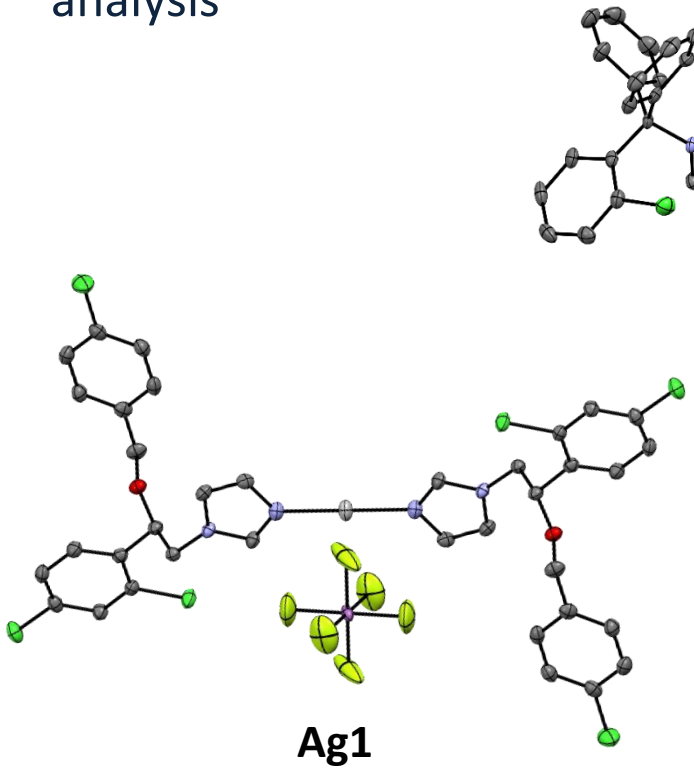
Results and discussion

✓ Silver(I) complexes were synthesized according to the presented procedure

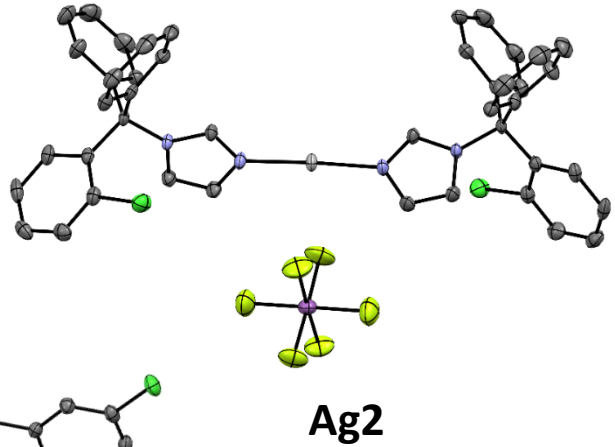


Structural characterization

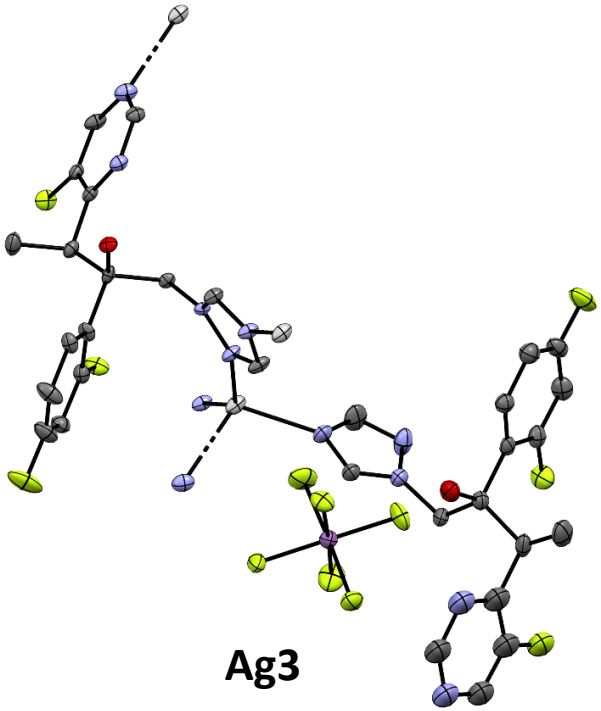
- ✓ The synthesized complexes were characterized by elemental analysis, UV-Vis, IR and ^{1}H NMR spectroscopy, mass spectrometry and cyclic voltammetry, while their structure was determined by a single-crystal X-ray diffraction analysis



Ag1



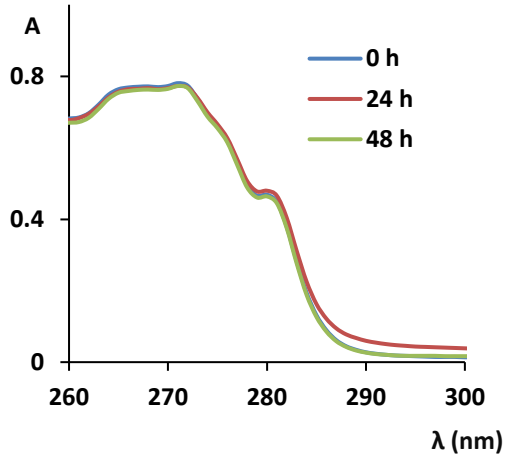
Ag2



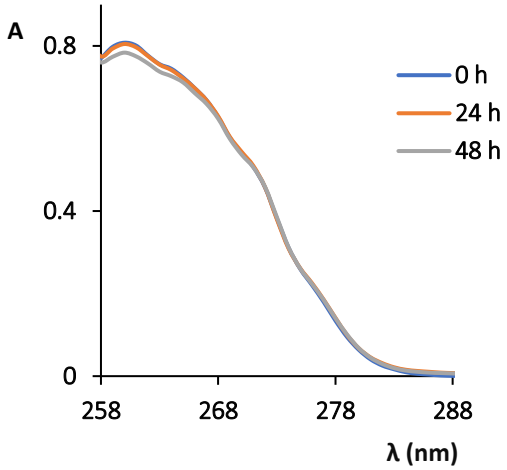
Ag3

UV-Vis stability

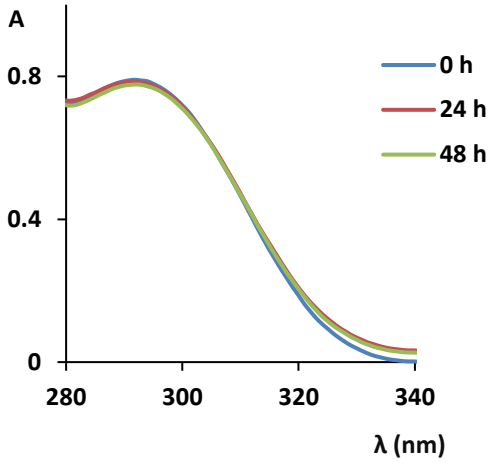
DMSO solvent
c (Ag1) = 6.4×10^{-4} M
c (Ag2) = 4.8×10^{-4} M
c (Ag3) = 7.4×10^{-4} M
t = 25 °C



Ag1



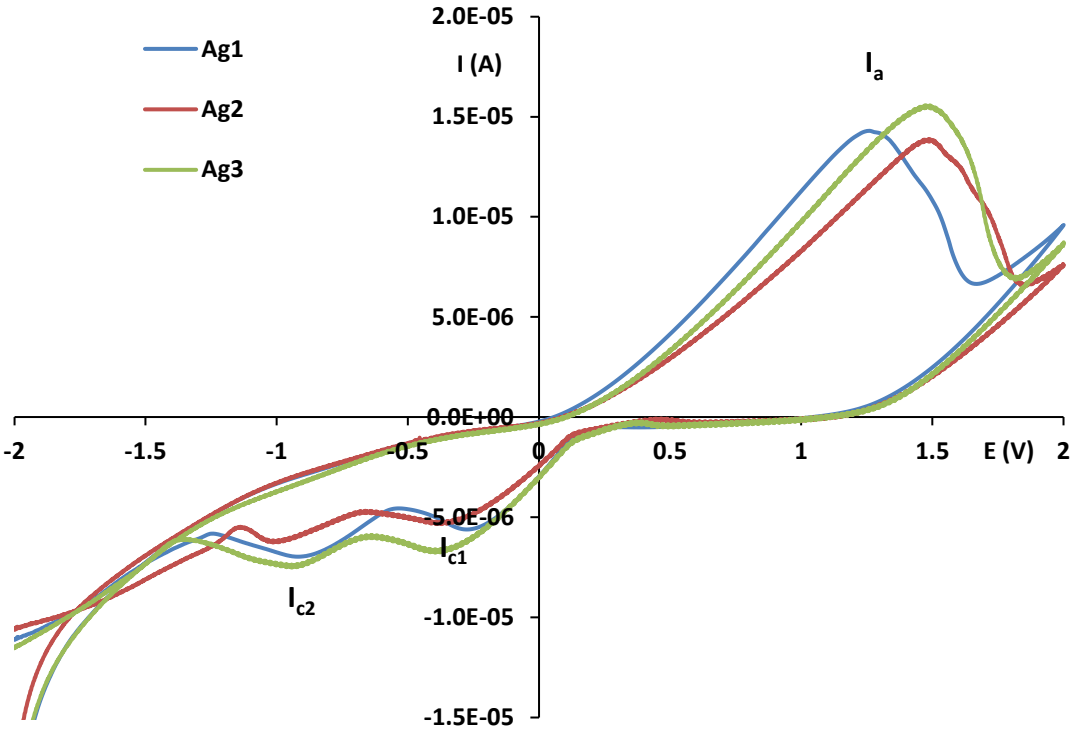
Ag2



Ag3

✓ The intensity and the position of the absorption maxima of **Ag1 – 3** and the shape of spectra remained unmodified during the investigated time, being in accordance with the stability of these complexes in solution

Electrochemical characterization



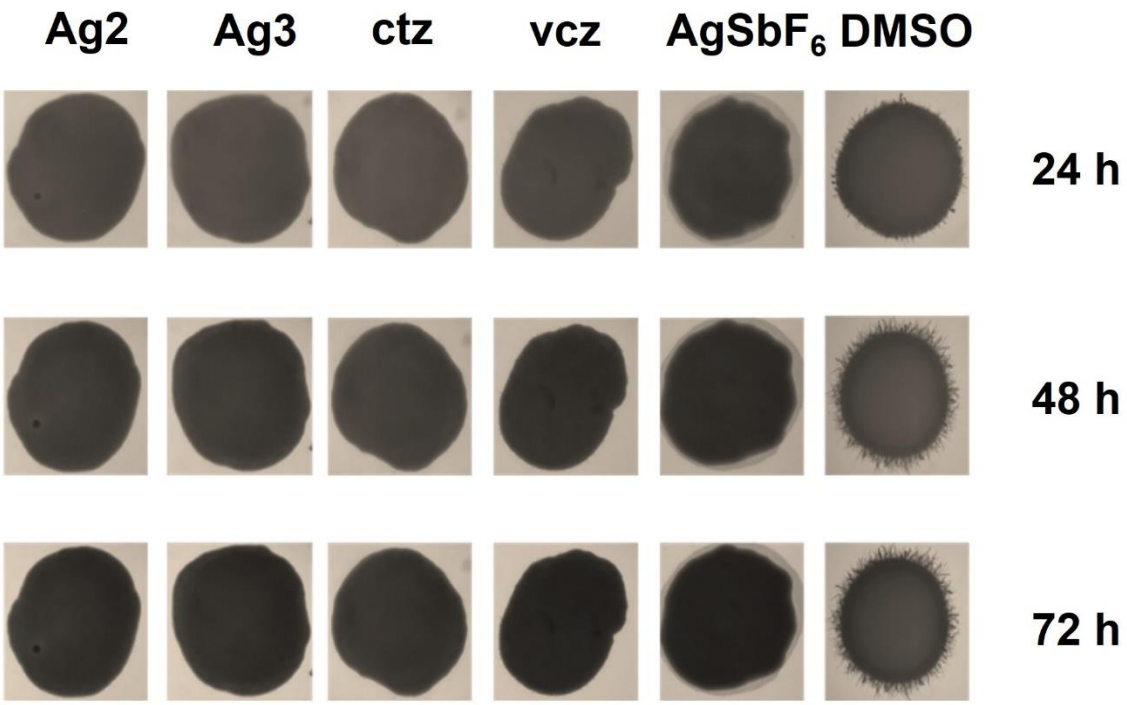
✓ Cyclic voltammograms of complexes **Ag1 – 3** recorded at the GC electrode in DMSO and 0.1 M tetrabutylammonium hexafluorophosphate (TBAHP) as a supporting electrolyte at a scan rate of 50 mV/s. The conditions are given as follows: E_{begin} = −2.0 V, E_{end} = 2.0 V and E_{step} = 0.002 V

Antimicrobial potential

Test organism: / Ligand/ Complex	*C. albicans*	*C. parapsilosis*	*C. krusei*	*C. glabrata*	*P. aerugonosa*	*E. coli*	*S. aureus*	*L. monocytogenes*	*MRC-5*
Econazole (ecz)	7.00	3.90	14.10	56.20	>500	>500	225	>500	10 ± 1.0
Clotrimazole (ctz)	2.60	10.2	1.40	9.10	>500	>500	290	>500	8.7 ± 0.4
Voriconazole (vcz)	35.80	0.30	1.40	572	>500	>500	>500	>500	859 ± 5.0
Ag1	2.25	2.25	27.10	11.29	22.6	11.30	2.70	22.60	10 ± 1.0
Ag2	0.12	0.01	0.03	0.97	12.10	12.10	2.61	12.10	16 ± 0.9
Ag3	0.48	0.01	0.01	0.06	11.90	23.90	47.90	47.90	36 ± 1.5

✓ Antimicrobial activity of silver(I) complexes and the corresponding azole expressed as MIC (μM) in comparison to their cytotoxicity against healthy human fibroblasts MRC-5 (IC_{50}, μM)

Filamentation test on *C. albicans*



✓ Filamentation of *C. albicans* ATCC 10231 in the presence of subinhibitory (0.5 × MIC value) concentrations of complexes **Ag2** and **Ag3**

Inhibition of *C. albicans* biofilm formation

Compounds	Ag2	Ag3	ctz	vcz
Biofilm formation inhibition [%]	86 ± 1.3	87 ± 0.4	79 ± 3.9	62 ± 6.3

Inhibition of *P. aeruginosa* biofilm formation

Compounds	Ag2	Ag3	ctz	vcz
Biofilm formation inhibition [%]	14 ± 1.4	3 ± 1.4	19 ± 1.1	4 ± 1.1

✓ Effect of complexes **Ag2**, **Ag3** and azoles on biofilm formation of *C. albicans* and *P. aeruginosa*. Tested concentration for biofilm inhibition was 0.5 × MIC

Conclusions

- ✓ Three new silver(I) complexes with clinically used azoles, econazole (ecz), clotrimazole (ctz) and voriconazole (vcz), $[Ag(ecz)_2]SbF_6$ (**Ag1**), $[Ag(ctz)_2]SbF_6$ (**Ag2**) and $\{[Ag(vcz)_2]SbF_6\}_n$ (**Ag3**) were synthesized and structurally characterized

- ✓ Azole ligands are coordinated to the Ag(I) ion through the nitrogen atom, leading to the formation of $[Ag(azole)_2]^+$ complex cation

- ✓ The synthesized complexes **Ag1 – 3** have shown good to moderate antimicrobial activity being, in most cases, more active than the corresponding azoles

- ✓ Two most active complexes, **Ag2** and **Ag3**, have shown strong inhibitory activity against *C. albicans* biofilm formation and strong inhibition of *C. albicans* filamentation at subinhibitory concentrations

Acknowledgments

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МИНИСТАРСТВО ПРОСВЕТЕ,
НАУКЕ И ТЕХНОЛОШКОГ РАЗВОЈА