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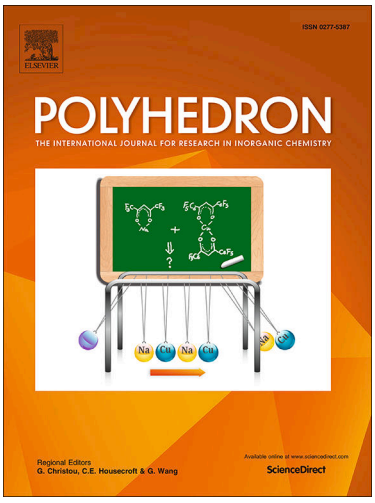


# Antifungal, phyto, cyto,genotoxic and lipophilic properties of three complexes of sulfadimethoxine (HSDM) with Ag(I). Synthesis and characterization of $[Ag_3SDM(SCN)_2]\cdot H_2O$ and $[Ag_2(SDM)_2$ *o*-phenanthroline$]\cdot H_2O$

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# A[illegible]f sulfadimethoxine (HSDM) with Ag(I). Synthesis and characterization of $[Ag_3SDM(SCN)_2]\cdot H_2O$ and $[Ag_2(SDM)_2$*o*-phenanthroline$]\cdot H_2O$

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ABSTRACT

Fungal infections are still a major problem. Some limitations of current antifungals (toxicity, fungal resistance) require the search for new drugs. The interest in metal–sulfanilamide derivatives was stimulated by the successful introduction of a silver-sulfadiazine complex, yet in current use, to prevent microbial infections during burn treatment of both humans and animals. Sulfadimethoxine (HSDM) is used in medicine, most frequently veterinary, to treat many infections, such as respiratory, urinary, etc. In this work we report the synthesis, characterization by elemental analysis, FTIR, $^1$H NMR and $^{13}$C NMR spectra of the heteroleptic complexes $[Ag_3SDM(SCN)_2]\cdot H_2O$ and $[Ag_2(SDM)_2$*o*-phenanthroline$]\cdot H_2O$, named as AgSDM-SCN and AgSDM-phen, respectively, and the biological properties (lipophilicity, antifungal, phyto, cyto and genotoxicity) of AgSDM-SCN, AgSDM-phen and the homoleptic one: AgSDM. $^1$H NMR spectra show that the sulfonamide moiety loses its acidic proton in both complexes, in agreement with the FTIR results. The three complexes showed a moderate antifungal activity, mainly against the yeasts *Candida albicans, C. tropicalis* and *Cryptococcus neoformans*. None of the tested fungi was inhibited by the free ligand. Lipophilicity: log $K_{octanol/water}$ values were 0.80, 0.84, 0.85, 0.94 and 0.43 for HSDM, NaSDM, AgSDM, AgSDM-SCN and AgSDM-phen respectively, similarly to another sulfa-metal complexes. No genotoxicity or cytotoxicity were observed for AgSDM and AgSDM-SCN in the *Allium cepa* test, different from AgSDM-phen. Given these results, the studied complexes could be good candidates for further pharmaceutical studies.

*Keywords:* sulfadrug metal complex; antifungal properties; lipophilicity, *Allium cepa* test

Abbreviations: HSDM: sulfadimethoxine; NaSDM: sulfadimethoxine, sodium salt; AgSDM: complex of Ag(I) with sulfadimetoxine; AgSDM-SCN: complex of Ag(I) with sulfadimetoxine and the thiocyanate group; AgSDM-phen: complex of Ag(I) with sulfadimetoxine and *o*-phenantroline; ATCC: American Type Culture Collection; C: CEREMIC (Centro de Referencia en Micología, Facultad de Ciencias Bioquímicas y Farmacéuticas, Suipacha 531 (2000) Rosario, Argentina); DMSO: dimethylsulfoxide; MIC: minimum inhibitory concentration; MFC: minimum fungicidal concentration; MI: mitotic index; CI: cytotoxic index = MI of the sample/MI of negative control; RL: root length.

**Highlights**

1) Two new silver-sulfadimethoxine complexes were synthesized.

2) Coordination of silver ions occurs through amide and heterocyclic nitrogens.

3) The synthesized complexes showed antifungal activity

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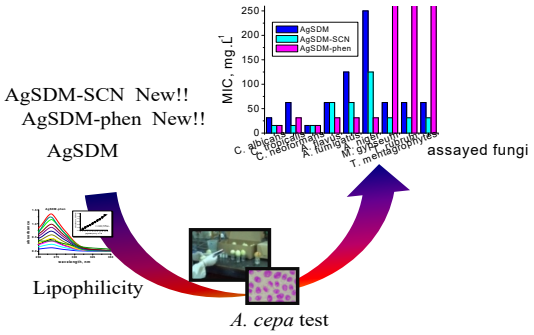


## Synopsis

Fungal infections are still a big problem. Two new heteroleptic complexes between sodium sulfadimethoxine (NaSDM) and the silver(I) ion: AgSDM-SCN and AgSDM-phen, and AgSDM, showed moderate antifungal activity (sulfadimethoxine was inactive), low affinity towards animal fatty tissues and no geno or cytotoxicity in the *Allium cepa* test, except AgSDM-phen, so, these complexes could be good candidates for further pharmaceutical studies.

## 1. Introduction

Fungal infections are still a major problem [1] There are several limitations in current antifungals, including that some of them displayed high toxicity, while others generate fungal resistance. Therefore, there is an urgent need to develop new antifungals [2], and, in a first instance, the evaluation of its cyto and genotoxicity with the *Allium cepa* test might be a good option [3].
Silver is a metal with good antimicrobial properties because of its high toxicity to microorganisms and low toxicity to mammalian cells [4]. The interest in metal–sulfanilamide derivatives has grown in recent years as a result of the successful introduction of the silver-sulfadiazine complex to prevent bacterial infections during burn treatment of both humans and animals, which is still in current use [5].
Sulfadimethoxine (Fig. 1) is a sulfonamide antibiotic employed to treat many infections including treatment of respiratory, urinary tract, enteric, and soft tissue infections. It is most frequently used in veterinary medicine, although it is approved in some countries for human use [6].

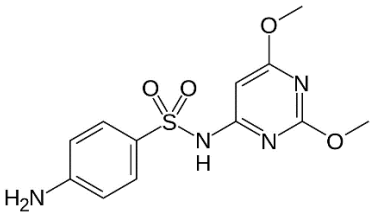

Fig. 1.Sulfadimethoxine (HSDM), IUPAC name: 4-Amino-*N*-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide; formula: $C_{12}H_{14}N_4O_4S$, MW: 310.33 g.mol$^{-1}$

Recently, the crystalline structure of the homoleptic complex of silver with sulfadimethoxine, AgSDM, has been determined, both in aqueous [7,8] and organic medium [9]. The antibacterial properties [7,8] and DNA interaction [9] of AgSDM were determined, but not its antifungal properties.

As a continuation of our studies on silver complexes [10-12], in this work we report the synthesis and characterization of the heteroleptic complexes $[Ag_3SDM(SCN)_2]\cdot H_2O$ and $[Ag_2(SDM)_2$*o*-phenanthroline$]\cdot H_2O$, named as AgSDM-SCN and AgSDM-phen, respectively, and the biological

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the homoleptic one: AgSDM.

## 2. Material and methods

### *2.1. Materials*

Sulfadimethoxine, as sodium salt (NaSDM, FNA grade, Parafarm>99%; MW: 332.3 g.mol$^{-1}$), $AgNO_3$ (FNA grade, Parafarm>99%) and all other chemicals of commercially available reagent grade, were used as received.

### *2.2. Preparative*

In general,experiments were performed by mixing solutions of $AgNO_3$ (aq) with NaSDM (aq) and the second ligand in a 1:1 or 1:1:1 molar ratio, as appropriate, and according to previously reported procedures [10-12]. During all experimental steps, both solutions and precipitates were protected from light. Elemental chemical analyses (C, H, N and S) were performed in a microanalyser Carlo Erba EA1108 (Carlo Erba Reagents S.A., Italy).

*AgSDM*: in a typical experience, 2 mL of aqueous solution of silver nitrate containing 0.1872 g (1 mmol + approximately 10% excess) were added dropwise to 4 mL of stirring aqueous solution containing 0.332 g of NaSDM (1 mmol). Immediately, a white suspension was formed. The mixture was stirred in the absence of light for 20 min. Then, it was left to stand at room temperature, away from light. After 24 h, the mixture was filtered under vacuum, washed several times with water, and dried in the dark [13].

*Elemental analysis* [AgSDM]: (AgSDM) white crystals, calculated MW: 417.19 g.mol$^{-1}$. Anal. Calcd. for $AgC_{12}H_{13}N_4O_4S$ (%): C, 34.5; H, 3.1; N, 13.4; S, 25.9. Experimental (%): C, 34.6; H, 3.2; N, 13.3; S, 26.2. [12]. Yield: 94 %. These data are consistent with those reported by Dubey *et al*, 2018 [7] and Fiori *et al*, 2017 [8].

*AgSDM-SCN*: in a typical experience, 2 mL of aqueous solution of 1.1 mmol of silver nitrate was added dropwise to 4 mL of stirring aqueous solution containing 1 mmol of NaSDM. Immediately, 4 mL of aqueous solution of 0.0987 g (1 mmol) of potassium thiocyanate was incorporated to the white suspension. After stirring the mixture for 20 min in the absence of light, the white precipitate was filtered under vacuum,washed several times with water and dried in the dark at room temperature.

*Elemental analysis:* $[Ag_3SDM(SCN)_2]\cdot H_2O$: (AgSDM-SCN) white solid, calculated MW: 767.115 g.mol$^{-1}$. Anal. Calcd. for $Ag_3C_{14}H_{15}N_6O_5S_3$(%): C, 21.9; H, 2.0; N, 11.0; S,12.5. Experimental (%): C, 22.9; H, 1.9; N, 11.3; S, 13.0. Yield: 84 %.

*AgSDM-phen*: This heteroleptic silver complex was synthesized following a similar technique, replacing KSCN by *o*-phenantroline (phen, 0.1802 g: 1 mmol), which was dissolved in 1 mL of ethanol. The $AgNO_3$ solution was added dropwise to the NaSDM solution. A white precipitate was obtained, onto which the phen solution was added dropwise under stirring, obtaining a whitish precipitate. A few mL of distilled water was added in order to resuspend the precipitate, which was left to rest for 2 hours, protected from light. After this time, it was filtered under vacuum, washed three times with water and two times with ethanol. The obtained whitish solid was allowed to dry on the same filter, in the air and protected from light.

*Elemental analysis:* $[Ag_2(SDM)_2phen]\cdot H_2O$: (AgSDM-phen) whitish solid, calculated MW: 1032.611 g.mol$^{-1}$. Anal. Calcd. for $Ag_2C_{36}H_{36}N_{10}O_9S_2$ (%): C, 41.9; H, 3.5; N, 13.6; S, 6.2. Experimental (%): C, 42.8; H, 3.3; N, 13.2; S, 6.0. Yield: 80 %.

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IR spectra of powdered samples were measured with a Bruker IFS 66 FTIR-spectrophotometer (Billerica, MA, USA) from 4000 to 400 $cm^{-1}$, using the KBr pellet technique. $^{1}H$ NMR and $^{13}C$ NMR spectra in deuterated dimethylsulfoxide (DMSO-$d_6$) were obtained using a Bruker AC-300 E spectrometer at ambient probe temperature (*ca*. 25ºC), with nominal operating frequencies of 300.1 and 50.3 MHz, respectively.

All chemical shifts (δ) are quoted in parts *per* million (ppm). Chemical shifts (δ) are in ppm relative to the residual DMSO-d6 signals (2.50 and 39.48ppm for $^{1}H$ and $^{13}C$, respectively). Positive values of chemical shifts denote high frequency shifts (less shielded) with respect to standards.

*2.4. Lipophilicity test*

Lipophilicity tests for NaSDM and the three silver complexes were performed in order to determine the partition coefficient between *n*-octanol and water [11]. The concentration of the compound in the original aqueous solutions and after contact with *n*-octanol was determined spectrophotometrically at 268-269nm. UV-Vis spectra of the complexes are presented in Supplementary material, Fig. S1 (A-C).

*2.5. Antifungal assays*

The microorganisms used for assessing antifungal properties were purchased from ATCC, or were clinical isolates from CEREMIC (identified with C). Yeasts: *Candida albicans* ATCC 10231, *C. tropicalis* CCC131, *Saccharomyces cerevisiae* ATCC 9763, *Cryptococcus neoformans* ATCC 32264. Hialohyphomycetes: *Aspergillus fumigatus* ATCC 26934, *A. flavus* ATCC 9170, *A. niger* ATCC 9029. Dermatophytes: *Microsporum gypseum* C 115, *Trichophyton rubrum* C 113, *T. mentagrophytes* ATCC 9972. The fungal strains were grown on Sabouraud-chloramphenicol agar slants for 48 h at 30°C. The strains were maintained on slopes of Sabouraud-dextrose agar (SDA, Oxoid) and subcultured every 15 days to prevent pleomorphic transformations. Spore suspensions were obtained according to reported procedures [14] and adjusted to $1\times10^{3}$ spores with colony forming ability/mL. Assay: Minimum Inhibitory Concentration (MIC) of each compound was determined by using broth microdilution techniques according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI 2008, formerly National Committee for Clinical Laboratory Standards NCCLS) for yeasts (M27-A3) and for filamentous fungi (M38-A2). MIC values were determined in RPMI-1640 (Sigma-Aldrich, St Louis, MO, USA) buffered to pH 7.0 with MOPS. Microtiter trays were incubated at 35°C for yeasts and hialohyphomycetes and at 28-30°C for dermatophyte strains in a moist, dark chamber. For the assay, stock solutions of pure compounds were two-fold diluted with RPMI from 250 to 0.98 $\mu g.mL^{-1}$ (final volume = 100 µL) and a final DMSO concentration ≤ 1%. A volume of 100 µL of inoculum suspension was added to each well with the exception of the sterility control where sterile water was added to the well instead.

Endpoints (MIC) were defined as the lowest concentration of drug resulting in total inhibition of visual growth compared to the growth in the control wells containing no antifungal. They were recorded at 48 h for yeasts (as an example, a photograph of these wells for $AgNO_3$ and AgSDM is presented in Supplementary material, Fig. S2), and at a time according to the control fungus growth, for the rest of fungi.The minimum fungicidal concentration (MFC) was determined by plating by duplicate 5 mL from each clear well of MIC determinations onto a 150 mm SDA plate. After 48 h at 37°C, MFCs were determined as the lowest concentration of each compound showing no growth in the plates. Both MIC and MFC were confirmed by two replicates. Despite the specialized international recommendations [15] a variety of breakpoints is observed in the literature [16], so we decided to take the value of 250 µg/mL as cut-off point for MICs [11,12,17] against all the analyzed fungi: MICs ≤ 250 $\mu g.mL^{-1}$ were considered active. Amphotericin B (Janssen Pharmaceutica, Beerse, Belgium), Ketoconazole (Sigma-Aldrich, St Louis, MO, USA) and Terbinafine (Novartis, Bs. As., Argentina) were used as positive controls.

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For this test, which was performed by following standard procedures [18], equal-sized young bulbs of common *Allium cepa* L. were used. Considering the antifungal MIC values, the experiments covered a 0.250–0.012 $g.L^{-1}$ sulfonamide complex range. Selected yellow onion bulbs were exposed to increasing concentrations of the tested substances (the complexes and the ligands, 7 bulbs/dose). Mother solution ($0.250g.L^{-1}$) and its dilutions (3/4, 1/2, 1/4 and 1/20) were analyzed. In a typical experience, an amount close to 0.125 g of AgSDM was exactly weighed. This quantity was dissolved in 10 mL of DMSO, completing to 500.0 mL with mineral water. Stock solutions of the ligands (NaSDM, phen) and the other silver complexes were prepared in a similar way. Aliquots from these mother solutions were taken out, in order to carry out the experiments. The noninterference of $AgNO_3$ (in distilled water instead of mineral water) and DMSO (until 2.5 % V/V, Fig S3) were checked by dose–response curves. The silver(I) ion concentration released from the complexes was not sufficient for precipitation of AgCl into the mineral water in which the onions were grown. Onion bulbs were kept in mineral water for 48 h, then exposed to the silver complexes and ligand solutions for 24 h, and next, the onions were placed into mineral water for 24 h (recovery time). The roots were then fixed in 1:3 acetic acid/ethanol solution for 24 h and finally stored in 70% ethanol. The roots growing in mineral water were used as a negative control, while the treatment with $K_2Cr_2O_7$ (1–5 $mg.L^{-1}$ in mineral water) represented a positive control. The length of the roots as an index of toxicity and modifications in root consistency and shape (formation of tumors, hookroots, twisted roots) were observed as macroscopic parameters. We follow the technique of measuring the longest root per bulb, already used in previous experiences [11]. The microscopic parameter was the mitotic index (MI). For the MI we evaluated al least five slides, 1000 cells *per* slide, as sum of meta, ana and telophases to evaluate cellular division rate. For the chromosomes preparation and staining, root tips were hydrolyzed in 6 $mol.L^{-1}$HCl at room temperature (25ºC, 10 min) before staining in Schiff's reagent (from Sigma-Aldrich): pararosaniline 1%, sodium metabisulfite 4%, in HCl 0.25M) for 15 min. After the root caps were removed from well stained root tips, 1 mm of the meristematic zones was immersed in a drop of 2% orcein in 45% acetic acid (which carried out the staining of the chromosomes) on a clean slide and squashed into single cells. A Globelight microscope was used with 640× magnification for observations. Photographs of selected preparations were taken with an OLYMPUS BX40 optical microscope coupled to a digital camera (Olympus D-560 Zoom,Tokyo, Japan).
*Statistical analysis*: One-way analysis of variance (ANOVA) was applied, followed by post hoc comparisons with the Student's *t*-test to estimate the significance of the differences between groups. Scatter plots were used to study at first the relationship between the variables, and linear regression to describe it [19]. Data were expressed as mean ± standard deviation (SD). A $p<0.05$ was considered of statistical significance [20].

## 3. Results and discussion

### *3.1. Vibrational Fourier transformed infrared spectra*

Fourier transformed infrared spectra (FTIR) of HSDM, NaSDM and its heteroleptic silver complexes, AgSDM–SCN and AgSDM–phen, are shown in Fig. 2. The FTIR spectrum of the homoleptic complex AgSDM was included for comparison. The assignments of the main vibrational FTIR frequencies are shown in Table 1. In order to obtain a wider insight on the coordination of the metal to the ligand, the experimental infrared spectrum of AgSDM was assigned by comparison with the protonated ligand (HSDM) and its sodium salt. The analysis was performed taking into account previous papers concerning HSDM coordination complexes [21,22] and general articles and books in order to avoid discrepancies in literature [23-27].

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Ta ), its sodium salt (NaSDM) and its Ag(I) complexes

| HSDM | NaSDM | AgSDM | AgSDM-SCN | AgSDM-phen | Assignments |
|---|---|---|---|---|---|
| 3405 m | 3526 w, 3490 w, 3438 w | 3428 m | broadened by νOH water | broadened by νOH water | $\nu_{as}NH_2$ |
| 3348 m | 3371 m, 3347 sh | 3356 m | broadened by νOH water | broadened by νOH water | $\nu_{s}NH_2$ |
| 3235 s | | | | | ν (NH)(sulfonamide) |
| | 3225 w, 3134 w | 3251 w | 3233 w | 3233 w | |
| 3011 w | 2998 w | 3001 w | 2953 w | 2949 w | $\nu_{as}CH_3$ |
| 2949 w | 2948 w | 2950 w | 2938 w | 2930 w | $\nu_{s}CH_3$ |
| | | | 2086 m | | νC-N, SCN |
| 1646 sh | 1639 sh | 1647 sh | 1627 sh | 1630 sh | $\delta(NH_2)$ |
| 1595 vs | 1602 vs | 1593 vs | 1596 vs | 1596 vs | $\delta(NH_2)$, ν (C=C) |
| | 1549 s | 1544 s | 1544 m | 1540 m | ν (C=C), $\nu_{as}$(C=N)-aromatic rings |
| 1446 m | 1435 s | 1439 s | 1441 m | 1434 m | $\nu_{s}$(C=N)-pyrimidine ring |
| 1386 m | 1396 sh | 1396 sh | 1396 w | 1393 w | δ $(CH_3)$ + $\nu_{ring}$(pyrimidine) + δ (HNC) |
| 1348 vs 1324 m | 1355 vs 1395 sh | 1359 vs | 1354 vs | 1354 vs | $\nu_{as}SO_2$ |
| 1279 sh 1198 vs | 1287 sh, 1247 sh, 1211 vs | 1307 w, 1248 s, 1205 s | 1304 w, 1270 w, 1220 s, 1201 sh | 1311 w, 1263 sh, 1216 s | νCO, CO-aromatic ring |
| 1145 vs | 1131 vs | 1131 vs | 1130 s | 1130 s | $\nu_{s}SO_2$ |
| 1103 s, 1095 s | 1085 m, 1069 m | 1082 m, 1073 m | 1092 m, 1083 m | 1083 m | $\nu_{ip}$ NH |
| 987, 974 w | 983 w | 989 w | 983 w | 988 w | ν(S–N-), νCO, CO-$CH_3$ |
| | | | | 841 m, 721 m | δ(CH) o-phen |
| | | | 754 w | | νC-S |
| | | | 471 w | | δ(NCS) |

Band description: s, strong; m, medium; w, weak; vw, very weak; br, broad; sh, shoulder. FTIR: Fourier transform infrared. AgSDM: [Ag(SDM)]; AgSDM-SCN: $[Ag_3SDM(SCN)_2]\cdot H_2O$; AgSDM-phen: $[Ag_2(SDM)_2phen]\cdot H_2O$



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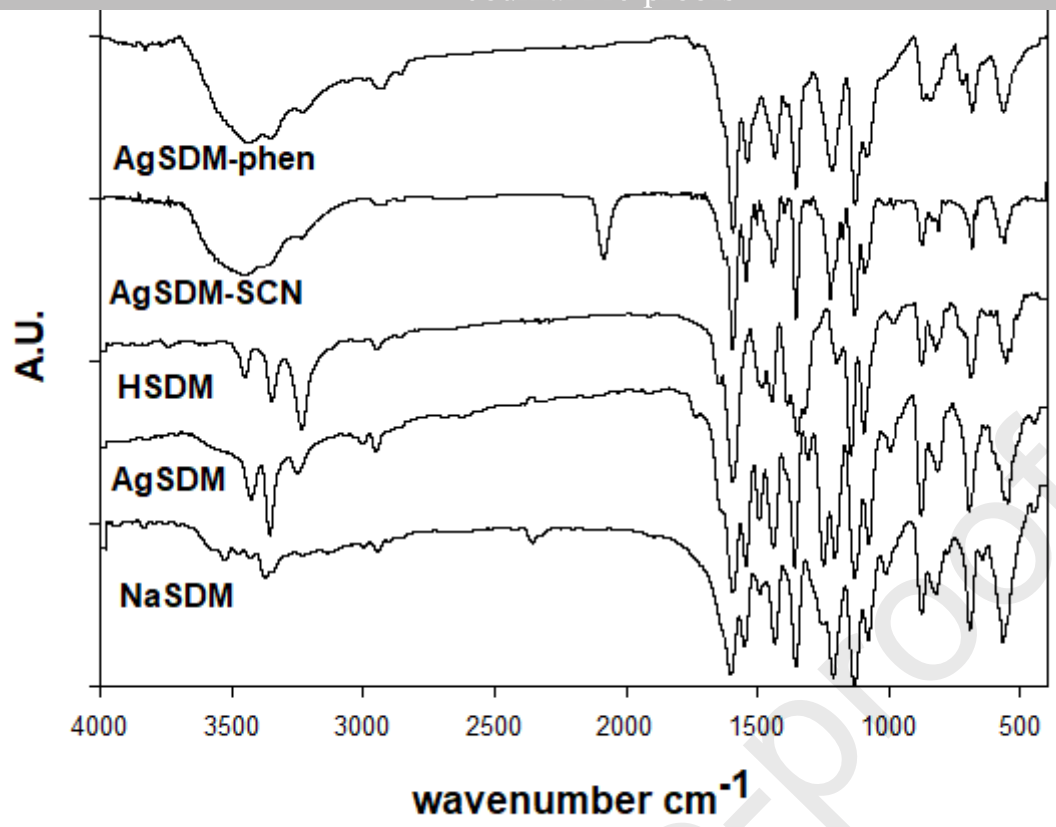


Fig.2. FTIR spectra of sulfadimethoxine (HSDM), its sodium salt (NaSDM) and its Ag(I) complexes (AgSDM, AgSDM–SCN and AgSDM–phen) in the wavenumber range of 4000-400 $cm^{-1}$

As shown in Table 1, the NH stretching of HSDM corresponds to the very strong band located at 3235 $cm^{-1}$ and it is absent in the complexes and in the sodium salt, indicating the presence of the deprotonated ligand in both cases. In addition, the strong band at 1095 $cm^{-1}$ assigned to the in plane stretching NH mode, appeared with low intensities in the complexes.

In spite that in the ca. 1600 $cm^{-1}$ region the intensities of the bands are very strong, the band at 1595 $cm^{-1}$ of HSDM is the most intense band of the compounds (Fig.2). Upon coordination or deprotonation, the intensity of this band is weakened, and new strong bands appeared at ca. 1550 $cm^{-1}$. These bands could be ascribed as vibrations involving the aromatic rings (C=C and C=N groups).

The strong bands related to stretchings of the $SO_2$ group remained unchanged upon deprotonation or coordination. This fact is a demonstration that this group was not involved in the metal-to-ligand bonds.

There are some modifications of the bands related to the CO stretchings of CO-aromatic ring and CO-$CH_3$ moieties in the 1300-1200 $cm^{-1}$ range, of the ternary complexes, both with respect to HSDM and AgSDM. The SCN and phen groups might interact with the SDM ligand by H-bonding.

It has been reported that the structures of silver sulfonamides were found to depend highly on the substituent at the amide nitrogen of the sulfonamide. Silver is coordinated to that nitrogen and the sulfonamide remained in the amido form if no substituent is present or if the substituent is a phenyl, acetyl, or 2-pyrimidyl group. If the substituent is a 2-thiazolyl or 2-pyridinyl group, the sulfonamide is in the imido form and silver coordinates to the nitrogen of the substituent [28]. In the present case, the substituent is 2,6-dimethoxy-4-pyrimidine and it can be deduced from the vibrational analysis that silver interacted with the nitrogen atom of the aromatic ring, generating changes in the methoxy groups vibrations. Besides, it is difficult to determine whether the N atom of the sulfonamide group remained in the anionic form or interacted with the other Ag(I) cation present in the complexes. In the AgSDM-SCN complex, the thiocyanate ion can coordinate to the metal through either the nitrogen or the sulphur atom. These two different modes of coordination are easily distinguishable by the infrared absorption

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and C-N stretching vibrations respectively); these peaks are shifted to 780-860 and 2080-2095 $cm^{-1}$ respectively in the SCN-metal complex and 690-720 and 2100-2125 $cm^{-1}$ respectively in the NCS-metal complex [29]. The thiocyanate group in the complex AgSDM-SCN absorbed at 754 $cm^{-1}$ and 2086 $cm^{-1}$ (as a single band), as would be expected if coordination occurred through the nitrogen atom of the thiocyanate ligand, hence discarding possible S- and bridging coordinations.

The spectra of the ternary complexes themselves differed in minor respects. These differences corresponded to the silver coordination to $SCN^-$ or phenanthroline ligands. While the AgSDM-SCN complex displayed the typical vibrational modes assigned to the SCN group, the AgSDM-phen complex showed the main differences in the 700-900 $cm^{-1}$ region. The C-H deformation bands of phenanthroline around 852 $cm^{-1}$ and 738 $cm^{-1}$ moved to lower frequency 841 $cm^{-1}$ and 721 $cm^{-1}$ in the complex. This red shift is indicative of the coordination of the ligand to the metal center [30].

### *3.3. $^{1}H$ and $^{13}C$ NMR spectra*

$^{1}H$ NMR spectra of the synthesized compounds and free ligands were collected and analyzed. Chemical shifts (δ) are in ppm relative to the residual DMSO-d6 signals. Assignment of H are showed in Fig. 3.

AgSDM: $\delta_B$ 7.5757 (d, 2H, $^{3}J$ = 8.55 Hz); $\delta_C$ 6.5690 (d, 2H, $^{3}J$ = 8.76 Hz); $\delta_D$ 5.9990 (s, 3H); $\delta_E$ 5.8270 (s, 1H); $\delta_F$ 3.8895 (s, 3H); $\delta_G$ 3.8245 (s, 3H).

AgSDM-SCN: $\delta_B$ 7.5628 (d, 2H, $^{3}J$ = 8.40 Hz); $\delta_C$ 6.5560 (d, 2H, $^{3}J$ = 8.67 Hz); $\delta_D$ 5.9860 (s, 3H); $\delta_E$ 5.8140 (s, 1H); $\delta_F$ 3.8891 (s, 3H); $\delta_G$ 3.8163 (s, 3H).

AgSDM-phen: $\delta_B$ 7.5814 (d, 2H, $^{3}J$ = 8.41 Hz); $\delta_C$ 6.5667 (d, 2H, $^{3}J$ = 8.55 Hz); $\delta_D$ 6.0260 (s, 3H); $\delta_E$ 5.8191 (s, 1H); $\delta_F$ 3.8809 (s, 3H); $\delta_G$ 3.8175 (s, 3H); $\delta_H$ 8.0657 (d, 2H, $^{3}J$ = 8.37 Hz); $\delta_I$ 7.8697 (dd, 2H, $^{3}J$ = 6.81Hz, $^{3}J$ = 13.6 Hz); $\delta_J$ 8.6061 (d, 2H, $^{3}J$ = 7.44Hz); $\delta_K$ 9.0464 (s, 2H).

$^{1}H$ and $^{13}C$ NMR chemical shifts data from the spectra of HDSM, its sodium salt (NaSDM) and its silver complexes, in DMSO-d6, are showed in Tables 2 and 3. The $^{13}C$ NMR spectrum of AgSDM-phen could not be taken due to the poor solubility of this compound in DMSO. Assignment of C are showed in Fig. 3.

Individual spectra (HSDM, NaSDM, its silver complexes, in addition to phen and its silver complex, and comparison of spectra in selected areas, as well as the figure of $\Delta\delta$ (ppm) $= \delta_{compound} - \delta_{HSDM}$ versus type of the sulfonamide hydrogen or carbon atoms are shown as supplementary material (Fig. S3-S5).

Table 2. $^{1}H$ NMR data for HSDM, its sodium salt (NaSDM) and its silver(I) complexes: AgSDM, AgSDM-SCN, AgSDM-phen and the chemical shift differences with respect to the HSDM ones

| | HSDM | NaSDM | | AgSDM | | AgSDM-SCN | | AgSDM-phen | |
|---|---|---|---|---|---|---|---|---|---|
| H | δ | δ | Δδ | δ | Δδ | δ | Δδ | δ | Δδ |
| A | 11.0924 | --- | --- | --- | --- | --- | --- | --- | --- |
| B | 7.5529 | 7.3635 | -0.1894 | 7.5757 | 0.0228 | 7.5628 | 0.0099 | 7.5814 | 0.0285 |
| C | 6.5865 | 6.4693 | -0.1172 | 6.5690 | -0.0175 | 6.5560 | -0.0305 | 6.5667 | -0.0198 |
| D | 6.0847 | 5.5553 | -0.5294 | 5.9990 | -0.0857 | 5.9860 | -0.0987 | 6.0260 | -0.0587 |
| E | 5.9302 | 5.3896 | -0.5406 | 5.8270 | -0.1032 | 5.8140 | -0.1162 | 5.8191 | -0.1111 |
| F | 3.7890 | 3.8794 | 0.0904 | 3.8895 | 0.1005 | 3.8821 | 0.0931 | 3.8809 | 0.0919 |
| G | 3.7811 | 3.8659 | 0.0848 | 3.8245 | 0.0434 | 3.8163 | 0.0352 | 3.8175 | 0.0364 |

Chemical shifts (δ) are in ppm relative to the residual DMSO-d6 signal (2.50 ppm). $\Delta\delta$ (ppm) $= \delta_{compound} - \delta_{HSDM}$

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Ta s:
AgSDM, AgSDM-SCN, and the chemical shift differences with respect to the HSDM ones

| | HSDM | NaSDM | | AgSDM | | AgSDM-SCN | |
|---|---|---|---|---|---|---|---|
| C | δ | δ | Δδ | δ | Δδ | δ | Δδ |
| 1 | 171.5745 | 170.9987 | -0.5758 | 171.8642 | 0.2897 | 171.8642 | 0.2897 |
| 2 | 164.3478 | 160.0075 | -4.3403 | 164.9177 | 0.5699 | 164.9101 | 0.5623 |
| 3 | 160.146 | 155.9647 | -4.1813 | 163.7613 | 3.6153 | 163.7919 | 3.6459 |
| 4 | 153.3222 | 150.5730 | -2.7492 | 152.6026 | -0.7196 | 152.6179 | -0.7043 |
| 5 | 129.3122 | 133.2490 | 3.9368 | 129.3508 | 0.0386 | 129.3508 | 0.0386 |
| 6 | 124.1074 | 128.2479 | 4.1405 | 127.1757 | 3.0683 | 127.1680 | 3.0606 |
| 7 | 112.4025 | 112.5859 | 0.1834 | 113.0224 | 0.6199 | 113.0607 | 0.6582 |
| 8 | 84.1749 | 85.4205 | 1.2456 | 85.6809 | 1.506 | 85.7345 | 1.5596 |
| 9 | 54.3757 | 53.6369 | -0.7388 | 55.4061 | 1.0304 | 55.3984 | 1.0227 |
| 10 | 53.6649 | 53.0089 | -0.656 | 54.5253 | 0.8604 | 54.5253 | 0.8604 |

Chemical shifts (δ) are in ppm relative to the residual DMSO signals (39.48 ppm).Δδ (ppm) $= \delta_{compound} - \delta_{HSDM}$

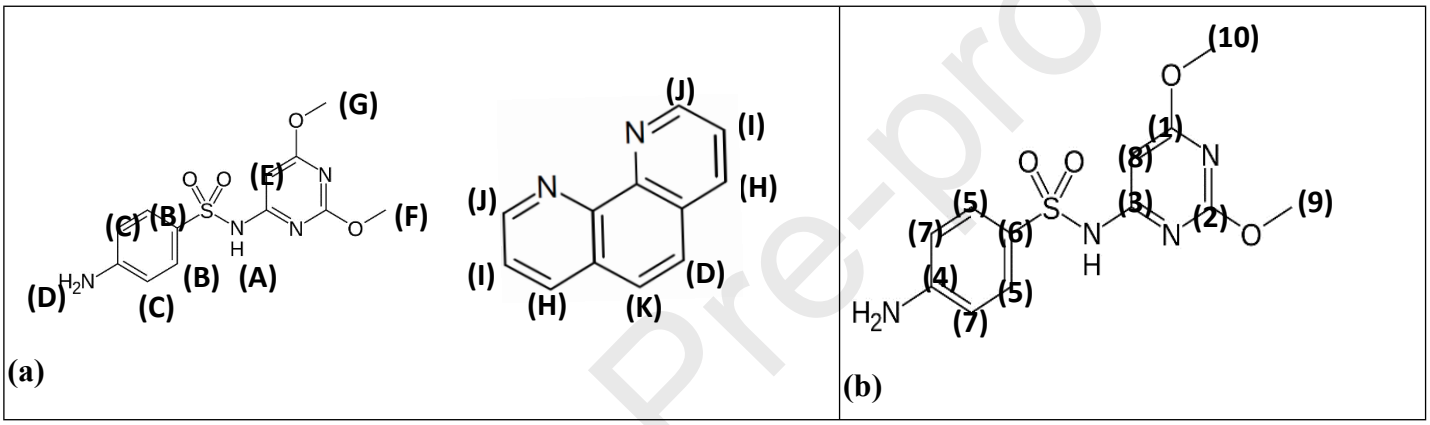


Fig. 3 (a) H labels are indicated for HSDM and phen. (b) C labels are indicated for HSDM

$^{1}$H NMR spectra: the signal of the amide proton [H(A), δ =11.08 ppm in HSDM] is absent in the $^{1}$H NMR spectra of NaSDM and the complexes, which indicates that the sulfa moiety is deprotonated in the complexes [11,12]. The most significant shifts are observed, in the three complexes, with proton "E" (shielded) and the protons of the methoxy groups (deshielded). From these, the most affected were the H atoms of the methoxy group labeled as "F".

$^{13}$C NMR spectra for the assayed silver complexes, the most significant shifts are observed for carbon 6 and those atoms from the pyrimidine ring (C3, C8) and those of the methoxy groups (C9 and C10).

The IR and NMR spectra of the heteroleptic complexes differ very little from each other in relation to the sulfonamide moiety, being similar to the homoleptic one, therefore it could be suggested that the coordination points of the silver cation with the sulfonamide would be the same in the three complexes.

Silver in the +1 oxidation state has been found to adopt a wide variety of coordination geometries [31]. Other factors also showed influence in coordinating the Ag(I) ion, such as the nature and/or the stoichiometry of the ligands [32]. In the AgSDM complex, in the solid state, silver coordinates with the N-sulfonamidic atom, deprotonated, and with the pyrimidine N atom adjacent to the C atom named as 3 [7-9]. This complex also shows an argentophilic interaction, similarly to another silver complexes with sulfonamides [8,11,12]. According to the FTIR spectrum of the AgSDM-SCN complex, the thiocyanate group would be coordinating with silver through the N atom of the SCN group. Some Ag(I) ternary complexes where one of the ligands is phen are curious because of the two different environments that surround the metal centers [10,33-35]. Among these, the heteroleptic silver(I) complex with*N*-(6-methyl-

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geometries around the metal, distorted $\{AgN_2\}$ digonal and $\{AgN_4\}$ tetrahedral, showing a supramolecular structure organized by π,π-stacking and C−H···O interactions [36]. A similar structure could be suggested for the complex $[Ag_2(SDM)_2phen]\cdot H_2O$. Fig. 4 represents, in a tentative and schematic form, the minimum formulas of the complexes, and a possible coordination of silver in each heteroleptic one.

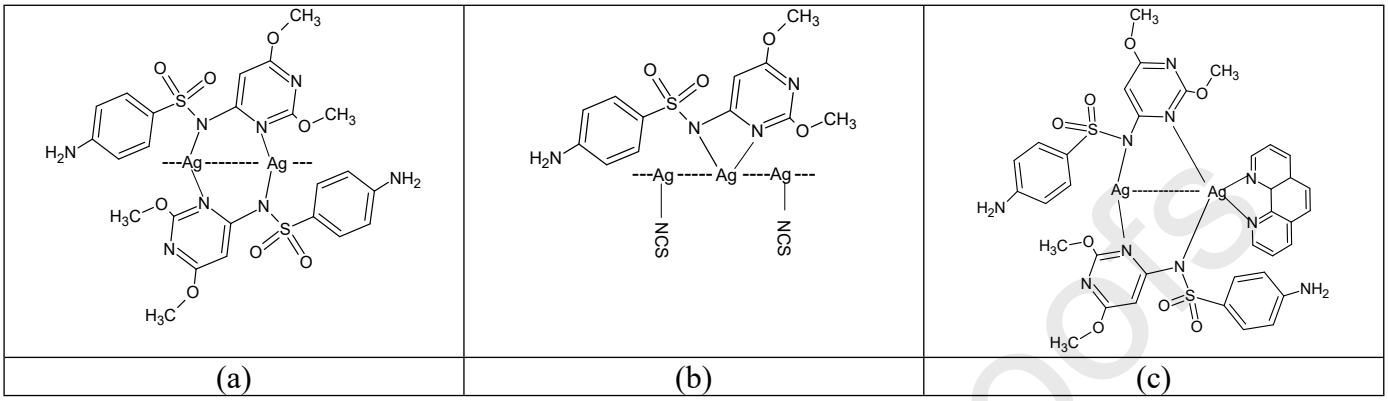


Fig. 4. Schematic form of the minimum formulas of the complexes and a possible coordination of silver in each one: (a) AgSDM [7,8]; (b) AgSDM-SCN; (c) AgSDM-phen

*3.4. Lipophilicity test*

With the aim of determining the lipophilic character of the silver complexes, which can be correlated with biological behavior properties like permeability through lipophilic barriers, partition coefficients (K) between *n*-octanol and water were determined. Log $K_{octanol/water}$ values (log *P*) were 0.85, 0.94 and 0.43 for AgSDM, AgSDM-SCN and AgSDM-phen respectively, which are close to the log *P* of the sulfonamide: 0.80 for HSDM and 0.84 for NaSDM. These values are similar to those of other sulfa-metal complexes [11,37]. The heteroleptic complex AgSDM-phen showed a low log *P* value, although the value of phen is 1.78 [38]. We have observed a fact like this in our laboratory for the Ag(I) complex with sulfamerazine (HSMR) and phen: [Ag(SMR)phen] [39]. Also with the homo and heteroleptic complexes of silver(I) with albendazole, KSCN and phen [10] we have observed similar behavior, since, although albendazole has a Log *P* = 3.5 [40], which indicates high affinity for animal fatty tissues [41], the Log *P* of the complexes were in the range from 0.8 to 1.5 [42], which means from very low to low affinity for animal fatty tissues [41],. This behavior would be probably related to the distribution of polar residues in the compounds after complexation.

The values of the partition coefficient of the complexes of this work indicated a low affinity towards the animal fatty tissues [41], in a similar way to the free sulfonamide and its sodium salt. Although these values were lower than the values considered the optimal partition coefficient for permeating lipophilic membranes [43], this kind of complexes, such as silver sulfadiazine, is generally used topically for prevention and treatment of skin infections [44], so it may be convenient that they do not easily cross lipophilic barriers and remain at the site of the injury.

*3.5. Antifungal properties*

Results of the antifungal assays of sulfadimethoxine and its silver complexes are shown in Table 4 and Fig S6. Examples of some Ag(I)-sulfonamide complexes were included for comparative purposes. In all cases, both silver–sulfadimethoxine complexes showed better antifungal activity than the free ligand, NaSDM, which, like other sulfonamides, was inactive against the tested fungi [11,12,45,46]. The assayed silver–sulfa complexes displayed a moderate activity against the tested fungi. It is important to note the activity against *C. neoformans*, a fact that could be of interest considering that *C. neoformans* has become a major opportunistic fungal pathogen worldwide, whose incidence has considerably increased

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antifungal drugs is high [49]. AgSDM-SCN showed better activity than its analogs against the dermatophytes assayed (Table 4). Silver(I), as $AgNO_3$, showed lower MIC values than the complexes. However, the silver complexes have the advantage of a slow release of silver cation, preventing the inactivation [50] and the cytotoxicity of the free Ag(I) ions [51]. Anyway, it is important to have a drug possessing both antifungal and antibacterial activity [52], as it is the case of these complexes due to the sulfonamide moiety [8,11].

Table 4. MIC/ MFC values in µg/mL of sulfadimethoxine (as sodium salt: NaSDM), its silver(I) complexes: Ag-SDM, Ag-SDM-SCN, Ag-SDM-phen, and, for comparative purposes, MICs of $AgNO_3$, AgSCN, phen, Ag-phen and selected sulfonamide-silver complexes acting against human opportunistic pathogenic fungi

| | Na SDM | AgSDM | AgSDM-SCN | AgSDM-phen | $AgNO_3$ (1) | AgSCN (2) | AgSCP (2) | AgSCP-SCN (2) | AgSMX (3) | AgSMX-SCN (3) | Amp | Ket | Terb |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Yeasts* | | | | | | | | | | | | | |
| *Ca.* | >250 | 31.25/62.5 | **15.6**/62.5 | **15.6**/31.25 | 6.36/12.72 | 31.25/62.5 | 31.25/125.0 | 62.5/125.0 | 31.25/125.0 | 31.25/>250 | 0.78 | 6.25 | 1.56 |
| *Ct.* | >250 | 62.5/62.5 | **15.6**/31.25 | 31.25/62.5 | 12.72/25.44 | 31.25/62.5 | 31.25/125.0 | 62.5/125.0 | 31.25/125.0 | 31.25/>250 | 1.56 | 6.25 | 0.78 |
| *Cn.* | >250 | **15.6**/62.5 | **15.6**/31.25 | **15.6**/ 31.25 | 3.18/12.72 | 15.60/62.5 | **15.6** /31.25 | **15.6** /125.0 | 31.25/62.5 | **15.6**/125.0 | 0.78 | 1.56 | 0.39 |
| *Aspergillus* | | | | | | | | | | | | | |
| *Afl.* | >250 | 62.5/250.0 | 62.5/125.0 | 31.25/125.0 | 12.72/12.72 | 31.25/125 | 31.25/125.0 | 31.25/125.0 | 31.25/ >250 | 31.25/125.0 | 0.78 | 6.25 | 0.78 |
| *Afu.* | >250 | 125.0/>250 | 62.5/250.0 | 31.25/125.0 | 25.44/25.44 | 31.25 62.5 | 31.25/62.5 | 31.25/125.0 | 31.25/ >250 | 31.25/62.5 | 3.12 | 12.5 | 0.78 |
| *Ani.* | >250 | 250.0/>250 | 125.0/ >250 | 31.25/125.0 | 25.44/25.44 | 31.25/125 | 62.5/125.0 | 31.25/125.0 | 31.25/ >250 | 62.5/125.0 | 0.78 | 6.25 | 1.56 |
| *Dermatophytes* | | | | | | | | | | | | | |
| *Mg.* | >250 | 62.5/62.5 | **31.25**/31.25 | >250 | 12.72/12.72 | 62.5/62.5 | 62.5/125.0 | 125.0/125.0 | 125.0/125.0 | >250 | 6.25 | 12.5 | 0.006 |
| *Tr.* | >250 | 62.5/62.5 | **31.25**/62.5 | >250 | 6.36/6.36 | 62.5/62.5 | 62.5/62.5 | 62.5/125.0 | 62.5/62.5 | 125.0/250 | 6.25 | 12.5 | 0.003 |
| *Tm.* | >250 | 62.5/125.0 | **31.25**/31.25 | >250 | 12.72/12.72 | 62.5/62.5 | 62.5/62.5 | 62.5/125.0 | 62.5/62.5 | 250/ >250 | 6.25 | 12.5 | 0.006 |

*Ca.: C. albicans* ATCC 10231; *Ct.: C. tropicalis*C 131; *Cn.: C. neoformans* ATCC 32264; *Afl.: A. flavus* ATCC 9170; *Afu.: A. fumigatus* ATCC 26934; *Ani.: A. niger* ATCC 9029; *Mg.: M. gypseum* C 115; *Tr.: T. rubrum* C 113; *Tm.: T. mentagrophytes* ATCC 9972 SCP: sulfachloropyridazine; SMX: sulfamoxole. MIC: Minimal Inhibitory Concentration; MFC: Minimal Fungicidal Concentration; Amp: Amphotericin B; Ket: Ketoconazole; Terb, Terbinafine (MIC´s in µg/mL). ATCC: American Type Culture Collection (Rockville, MD, USA); C: CEREMIC, Centro de Referencia Micológica, Facultad de Ciencias Bioquímicas y Farmacéuticas, Suipacha 531-(2000)-Rosario, Argentina.Remarkable results fort hecomplexes are in bold. (1): [58]; (2): [12]; (3): [11]

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*3.6. Plant Genotoxicity Test (Allium cepa Test)*

The *A. cepa* test, which is considered an efficient tool to evaluate toxic effects of different chemicals, currently in use [3] was selected to assess the potential cytogenotoxic effects of the evaluated silver-sulfadimethoxine complexes. *A .cepa* test has a long history in scientific literature i.e. developed and described by Levan [53], later modified for environmental monitoring [54] and optimization of the technique [55]. *A. cepa* species have been frequently used to determine the cytotoxic and genotoxic effects of several substances, being considered a standard organism for quick tests, since it shows a high correlation with mammal test systems [3 d)], although it cannot replace other studies such as mammalian cell cultures. Another advantage of this test system is the presence of an oxidase enzyme system, which is useful for promutagen evaluations [56], fact that we checked in our laboratory with the promutagen 2-aminofluorene [57]. The results of phytotoxicity (as change of root length –RL–, expressed as % from the RL of the negative control) and cytotoxicity, expressed as the cytotoxic index (CI) calculated as: MI‰ of the sample/MI‰ of the negative control, of NaSDM and its silver complexes, evaluated with the *A. cepa* test are shown in Tables 5 and 6, and Fig. 4 (supplementary material Fig. S8).

Table 5. Phytotoxicity (as % of the change of root length, RL, respect to the negative control: Δ± SD) of sodium sulfadimethoxine (NaSDM) and its silver(I) complexes, evaluated with the *A. cepa* test

| sulfa drug conc. (a) | sulfa drug; concentration of each mother solutions, $mg.L^{-1}$ | | | |
|---|---|---|---|---|
| | NaSDM; 252$mg.L^{-1}$ | AgSDM; 255.0 $mg.L^{-1}$ | AgSDM- SCN; 251.6 $mg.L^{-1}$ | AgSDM-phen; 258.6 $mg.L^{-1}$ |
| 0 (b) | (2.91± 0.76) cm; % RL: 100.0 ± 25.94 | | | (2.10 ± 0.39) cm; % RL: 100.0 ± 18.56 |
| 1/20 | 100.1 ± 14.62 | 65.77 ± 33.79 | 54.90 ± 27.79 | 65.08 ± 52.24 |
| 1/4 | 99.51 ± 37.51 | 41.75 ± 12.91 | 21.73 ± 15.14 | 14.29 ± 7.78 |
| 1/2 | 85.78 ± 23.07 | 21.96 ± 9.89 | 28.02 ± 22.49 | 19.64 ± 9.20 |
| 3/4 | 67.48 ± 25.83 | 11.44 ± 9.12 | 10.87 ± 12.16 | 21.43 ± 22.16 |
| 1 | 92.65 ± 15.19 | 8.58 ± 14.19 | 15.44 ± 14.84 | 8.33 ± 8.13 |
| Linear Regression (c) | y = 98.52 – 0.050x r: -0.53; p: 0.28 | y = 62.24 – 0.257x r: -0.87; p: 0.022 | y= 53.44 – 0.195x r:-0.71 p: 0.12 (d) | y = 25.26 –0.065x r: -0.46; p: 0.36 (d) |

Δ: [RL substance (mean, cm)/RL negative control, mean, cm]×100; SD: standard deviation.r: Pearson's correlation coefficient. (a): dilution from mother solution. (b): negative control (mineral water). (c): y = a + bx; weight given by data sd error bars. p-value ≤ 0.05 was considered as statistically significant [20]. (d): Mean significantly different from the negative control mean (Student's t-test post ANOVA at the 0.05 level)

Table 6. Cytotoxic Index (C.I.) for sodium sulfadimethoxine (NaSDM) and its silver(I) complexes, evaluated with the *A.cepa* test

| sulfa drug conc. (a) | sulfa drug; concentration of each mother solutions, $mg.L^{-1}$ | | | |
|---|---|---|---|---|
| | NaSDM; 252 $mg.L^{-1}$ | AgSDM; 255.0 $mg.L^{-1}$ | AgSDM-SCN; 251.6 $mg.L^{-1}$ | Ag-SDM-phen; 258.6$mg.L^{-1}$ |
| 0 (b) | C. I.: 1.0 ± 0.21 (M.I.: 27.5 ± 5.86) | | | C.I.: 1.0 ± 0.15 (M.I.: 30.6 ± 4.67) |
| 1/20 | 1.14 ± 0.15 | 1.76 ± 0.28 | 1.31 ± 0.23 | 0.97± 0.50 |
| 1/4 | 0.94 ± 0.18 | 0.99 ± 0.26 | 1.18 ± 0.17 | without observable mitotic figures |
| 1/2 | 1.11 ± 0.05 | 1.00 ± 0.26 | 1.26 ± 0.13 | |
| 3/4 | 1.15 ± 0.28 | 0.81 ± 0.17 | 0.74 ± 0.16 | |
| 1 | 1.10 ± 0.39 | 1.03 ± 0.39 | 1.20 ± 0.34 | |
| Linear Regression (c) | y = 1.05 + 3.82E-4x r: 0.37; p: 0.47 | y = 1.23 – 0.0018x r: -0.56; p: 0.25 | y = 1.23 – 0.00115x r: -0.40; p: 0.44 | it was not possible to analyze statistically |

C.I.: MI sample/MI negative control; MI mitotic index: Nº dividing cells/1000 cells. r: Pearson's correlation coefficient; (a) dilution from mother solution; (b): negative control (mineral water); (c): y = a + bx; weight given by data sd error bars. p-value ≤ 0.05 was considered as statistically significant [20].

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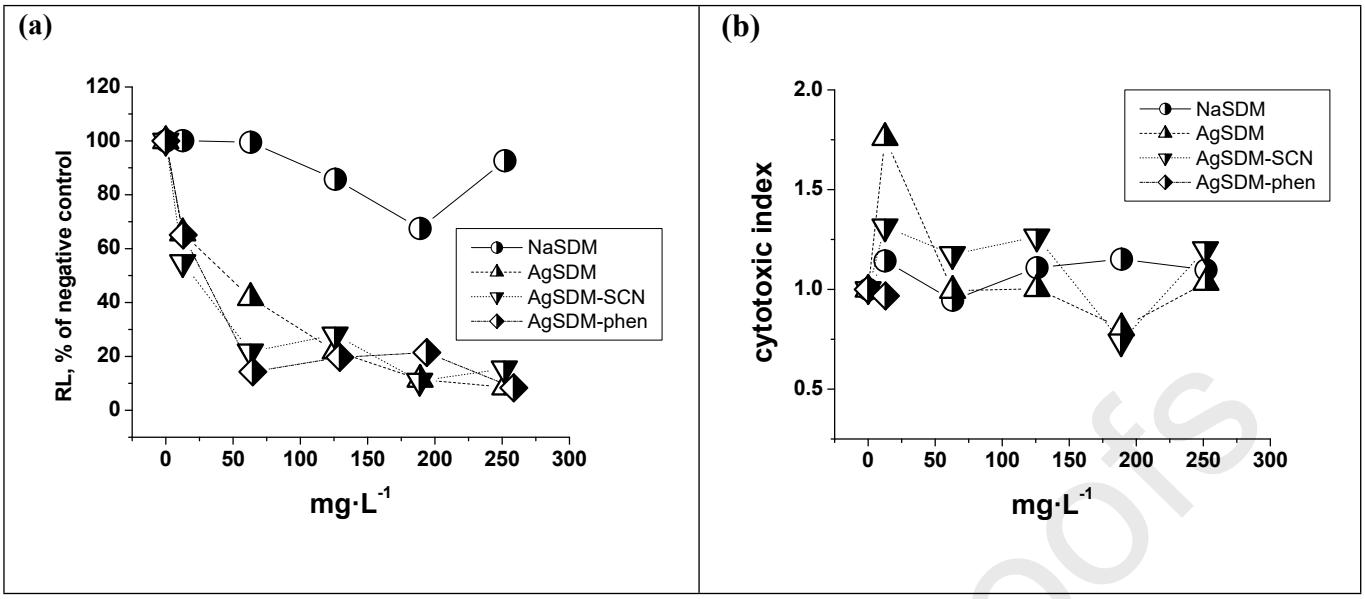


Fig. 5. Influence of the concentration of NaSDM and its silver complexes (a) on the root elongation and (b) on the cytotoxic index (Mitotic index of the sample/mitotic index of negative control) of *A. cepa* L.

Phytotoxicity: The analysis by linear regression and/or the Student´s *t*-test performed post ANOVA showed significant influence of the concentration of the silver complexes on the change of root length of *A. cepa* L. We have observed similar influence of $AgNO_3$ (in distilled water) in a range of up to 200 $mg.L^{-1}$ [58]. On the other hand, we did not observe any influence of NaSDM and DMSO (Fig. S3) with respect to the negative control (mineral water).
Mitotic index (MI): Inhibition of mitotic activities is often used for tracking cytotoxic substances. A MI decrease below 22% of the control causes lethal effects on test organisms, while a decrease below 50% (cytotoxic limit value) usually has sub-lethal effects [59]. Moreover, the inhibition of division without the observation of chromosome aberrations may be a promising result for anticancer therapy, as it leads first to block the development of cancer [60]. NaSDM and the complexes AgSDM and AgSDM-SCN did not modify the MI in the range of experimented concentrations. On the contrary, the AgSDM-phen complex showed significant inhibition of the MI, probably due to the phenanthroline moiety of the compound [61]. Similar behavior presented other silver complexes with phenanthroline derivatives, also with antifungal properties, which they showed anticancer properties [62].

## 4. Conclusion

Fungal infections are still a big problem. Two new heteroleptic synthesized complexes between sodium sulfadimethoxine (NaSDM) and the silver(I) ion: AgSDM-SCN and AgSDM-phen, and the homoleptic one, AgSDM, showed moderate antifungal activity (NaSDM was inactive), low affinity towards animal fatty tissues and no genotoxicity or cytotoxicity in the *A. cepa* test, except AgSDM-phen. Given these results, the analyzed complexes might be good candidates for further pharmaceutical studies.

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**References**


[1] B. Pathakumari, G. Liang, W. Liu, Biomedicine & Pharmacotherapy 130 (2020) 110550.
[2] Y. Qin, P. Li. Z. Guo, Carbohydrate Polymers 236 (2020) 116002.
[3] a) P. Debnath, A. Mondal, K. Sen, D. Mishra, N. K. Mondal, Science of The Total Environment 713 (2020) 136592; b) Y. M. Heikal, N.A.Şuţan, M.Rizwan, A.Elsayed, Chemosphere 243 (2020) 125430; c) R. Liman, A. N. Kursunlu, İ. H. Ciğerci, M. Ozmen, Y. Acikbas, Ecotoxicology and Environmental Safety 192 (2020) 110328; d) L. Bellani, S. Muccifora, F. Barbieri, E. Tassi, M. Ruffini Castiglione, L. Giorgetti, Mutation Research/Genetic Toxicology and Environmental Mutagenesis 849 (2020) 503142; d) I. S. Khan, Md. N. Ali, R. Hamid, S. A. Ganie, Toxicology Reports 7 (2020) 370–375.
[4] P. Kleyi, R. S. Walmsley, M. A. Fernandes, N. Torto, Z. R. Tshentu, Polyhedron. 41(2012) 25–29.
[5] https://medlineplus.gov/druginfo/meds/a682598.html consulted November 2020.
[6] https://www.drugbank.ca/drugs/DB06150 consulted November 2020.
[7] R. P. Dubey, U. H. Patel, B. D. Patel, Inorg. and Nano-Metal Chem., 48 (2018) 110-119.
[8] A. T. M Fiori, D. H. Nakahata, A. Cuin, W. R. Lustri, P. P. Corbi, Polyhedron 121 (2017) 172–179.
[9] B. N.Socha, U. H.Patel, S. B.Pandya, B. R.Chavda, K. P.Chaudhary, B. D.Patel, R.H. Patel, N. J.Patel, B.S.Bhatt, Polyhedron 188 (2020) 114696.
[10] C. Giulidori, N. Mosconi, B. Toplikar, M. Vega, P.A.M. Williams, L. Svetaz, M. Raimondi, M. Rizzotto, J. Phys. Org. Chem. 29 (2016) 656–664.
[11] F. Velluti, N. Mosconi, A. Acevedo, G. Borthagaray, J. Castiglioni, R. Faccio, D. Back, G. Moyna, M. Rizzotto, M.H. Torre, J. Inorg. Biochem. 141 (2014) 58–69.
[12] N. Mosconi, C. Giulidori, F. Velluti, E. Hure, A. Postigo, G.Borthagaray, D. Back, M.H. Torre, M. Rizzotto, ChemMedChem 9 (2014) 1211-1220
[13] L. Monti., degree thesis, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario (UNR), Argentina, unpublished results. 2009.
[14] Wright, L.; E. Scott, S. Gorman, J. Antimicrob. Chemother. 12 (1983) 317–327.
[15] a) J. Rex, M. Pfaller, J. Galgiani, M. Bartlett, A. Espinel-Ingroff, M. Ghannoum, M. Lancaster, F. Odds, M. Rinaldi, T. Walsh, A. Barry, Subcommittee on Antifungal Susceptibility Testing of the National Committee for Clinical Laboratory Standards, Clin. Infect. Dis. 24 (1997) 235–247; b) M. A. Pfaller, J. H. Rex, M. G. Rinaldi, Clin Infect Dis. 24 (1997) 776–784; c) M. A. Pfaller, D. J. Diekem, J. Clin. microbiology, (2012) 2846–2856.
[16] I. Özdemir, S. D., S. Günal, I. Özdemir, C. Arıcı, D. Ülkü, Inorg. Chim.Acta. 363 (2010) 3803–3808.
[17] L. Monti, A. Pontoriero, N.Mosconi, C. Giulidori, E. Hure, P. A.M.Williams, M. V. Rodríguez, G. Feresin, D. Campagnoli, M. Rizzotto, Biometals. 2010, 23, 1015–1028.
[18] M. I. Nieva Moreno, I. C. Zampini, R. M. Ord_Cez, G. S. Jaime, M. A. Vattuone, M. I. Isla, J. Agric. FoodChem., 53(2005) 8957– 8962.
[19] L. Orellana. Regresión Lineal Simple, Estadística para Química, UBA, Buenos Aires, 2008.
[20] G. Bourke, L. Daly, J. McGilvray, Interpretation and Uses of Medical Statistics, Bourke, G. Blackwell Scientific Publications, Oxford, 1985.
[21] M. H.Torre, G. Facchin , E. Kremer , E.E. Castellano, O.E. Piro, E. J. Baran, J. Inorg. Biochem. 94 (2003) 200-204.
[22] T. Ulusoy, A.Topagli, S. Ide, Pharm. ActaHelv. 72 (1998) 295-300.
[23] B. Smith. Infrared Spectral Interpretation: a systematic approach, CRC Press, New York, 1999.
[24] A. Gómez-Zavaglia, I.D. Reva, L. Frija, M.L.S. Cristiano, R. Fausto, J. Photochem. Photobiol. A: Chemistry 180 (2006) 175-183.
[25] K.C. Medhi. Bull. Chem Soc. Jpn. 57 (1984) 261-266.
[26] M.M. Habeeb, A.S. AL-Attas, M.T. Basha, J. Mol. Liq. 150 (2009) 56-61.
[27] E.E. Chufán, J.C. Pedregosa, S. Ferrer, J. Borrás, Vibrat. Spectrosc. 20 (1999) 35-45.
[28] A. Bult, H.B. Klasen, J. Pharm. Sci. 67 (1978) 284-287.
[29] J. F. Duncan, K. F. Mok, J. Auet, J. Chem., 19 (1966) 701-703.
[30] T.P. Gerasimova, S.A. Katsyuba, Dalton Trans. 42 (2013) 1787–1797.
[31] A. G. Young, L. R. Hanton, Coord. Chem. Rev. 252 (2008) 1346–1386.
[32] A. Kaeser, B. Delavaux-Nicot, C. Duhayon, Y. Coppel, J.-F. Nierengarten, Inorg. Chem., 52 (2013) 14343–14354.


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[33] M. Devheny, R. M. Ferullo, O. V. Quinzani, S. D. Mandolesi, N. Castellani, M. Jennings, Polyhedron. 27 (2008) 2243–2250.
[34] B. Liu, M. Liu, H. Wu, W. Chen, J. Organometallic Chem. 772–773 (2014) 113–121.
[35] L. Thornton, V. Dixit, L. Assad, T. Ribeiro, D. Queiroz, A. Kellett, A. Casey, J. Colleran, M. Pereira, G. Rochford, M. McCann, D. O'Shea, R. Dempsey, S. McClean, A. Kia, M. Walsh, B. Creaven, O. Howe, M. Devereux, J. Inorg. Biochem. 159 (2016) 120–132.
[36] I. Beloso, J. Castro, J. A. García-Vázquez, P. Pérez-Lourido, J. Romero, A. Sousa, Inorg. Chem.44 (2005) 336–351.
[37] E. Kremer, G. Facchin, E. Estévez, P. Alborés, E.J. Baran, J. Ellena, M.H. Torre, J. Inorg. Biochem. 100 (2006) 1167–1175
[38] https://www.drugbank.ca/drugs/DB02365, consulted November 2020
[39] E. Hure, N. Mosconi, G. Camí, M. Rizzotto, in: Ciencia&Tecnología: CyTXII, Rosario, Argentina, Editorial de la UNR, pp 151-156, ISBN 978-987-702-366-4. 2019.
[40] S. S. Bharate, V. Kumar, R.A.Vishwakarma, Comb Chem High Throughput Screen 19 (2016) 461-469
[41] S. K. Bhal Advanced Chemistry Development, Inc. Toronto, ON, Canada https://www.acdlabs.com/download/app/physchem/making_sense.pdf consulted November 2020.
[42] N. Mosconi, C. Giulidori, M. Vega, B. Toplikar, M. Rizzotto, *5º* Enaqui Congress (2017) Montevideo, Uruguay.
[43] A. R. Gennaro, Remington Farmacia, Editorial Médica Panamericana, Buenos Aires, 2003.
[44] https://www.drugs.com/mtm_esp/silvadene.html, consulted November 2020
[45] X.;Wang, K. Wan, C. Zhou, Eur. J. Med. Chem. 45 (2010) 4631–4639.
[46] C. MacDougall, Cap. 56, in: Goodman&Gilman: Las Bases Farmacológicas De La Terapéutica, 13ed, España, 2019.
[47] Negroni, R. Clin. Dermatol. 30 (2012) 599–609.
[48] M. Andreou, M. Cogliati, F. Kolonitsiou, C. Stroumpos,V.Stamouli, P. Ravazoula, D.Siagris, H. Papadogeorgaki, M. Christofidou, A. Lekkou, Medical Mycology Case Reports 27 (2020) 1–3.
[49] J. R. Perfect, G. M. Cox, Drug Resistance Updates, 2 (1999) 259-269.
[50] L. Kyros, C.N. Banti, N. Kourkoumelis, M. Kubicki, I. Sainis, S.K. Hadjikakou, J. Biol. Inorg. Chem. 19 (2014) 449–464.
[51] B.S. Atiyeh, M. Costagliola, S.N. Hayek, S.A. Dibo, Burns 33 (2007) 139–148.
[52] A. Acar, F. Uygur, H. Diktaş, R. Evinç, E. Ülkür,O.Öncül, L. Görenek, Burns 37 (2011) 882–885.
[53] A. Levan,Hereditas 24 (1938) 471–486.
[54] G. Fiskesjö, Hereditas 102 (1985) 99–112.
[55] J. Rank, Ekologija 1 (2003) 38–42.
[56] D. MoraisLeme, M. Marin-Morales, Mutat. Res. 682 (2009) 71–81.
[57] M. Vega, N. Mosconi, B. Toplikar, M. Rizzotto, ALDEQ N° XXXIII, (2018 – 2019) 38-43. ISSN: 0328-087X
[58] N. Mosconi, degree thesis, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario (UNR), Argentina, 2013.
[59] H. Migid, Y. Azab, W. Ibrahim, Ecotox. Environm. Saf. 66 (2007) 57–64.
[60] M. Kuras, J. Nowakowska, E. Sliwinska, R. Pilarski, R. Ilasz, T. Tykarska, A. Zobel, K. J. Gulewicz, Ethnopharmacol. 107 (2006) 211–221.
[61] R. Bastão de Souza, C. Pereira de Souza, O. Correa Bueno, C. S. Fontanetti, Chemosphere 168 (2017) 1093-1099.
[62] S. Ž. Đurić, M. Mojicevic, S. Vojnovic, H. Wadepohl, T. P. Andrejević, N. Lj. Stevanović, J. Nikodinovic-Runic, M. I. Djuran, B. Đ. Glišić, Inorganica Chimica Acta 502 (2020) 119357.

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Fig. 1. Sulfadimethoxine (HSDM), IUPAC name: 4-Amino-*N*-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide; formula: $C_{12}H_{14}N_4O_4S$, MW: 310.33 g.mol$^{-1}$

Fig.2. FTIR spectra of sulfadimethoxine (HSDM), its sodium salt (NaSDM) and its Ag(I) complexes (AgSDM, AgSDM–SCN and AgSDM–phen) in the wavenumber range of 4000-400 cm$^{-1}$

Fig. 3 (a) H labels are indicated for HSDM and phen. (b) C labels are indicated for HSDM

Fig. 4. Schematic form of the minimum formulas of the complexes and a possible coordination of silver in each one: a) AgSDM [7,8]; b) AgSDM-SCN; c) AgSDM-phen

Fig. 5. Influence of the concentration of NaSDM and its silver complexes (a) on the root elongation and (b) on the cytotoxic index (Mitotic index of the sample/mitotic index of negative control) of *A. cepa* L.

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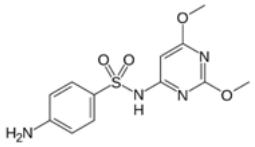

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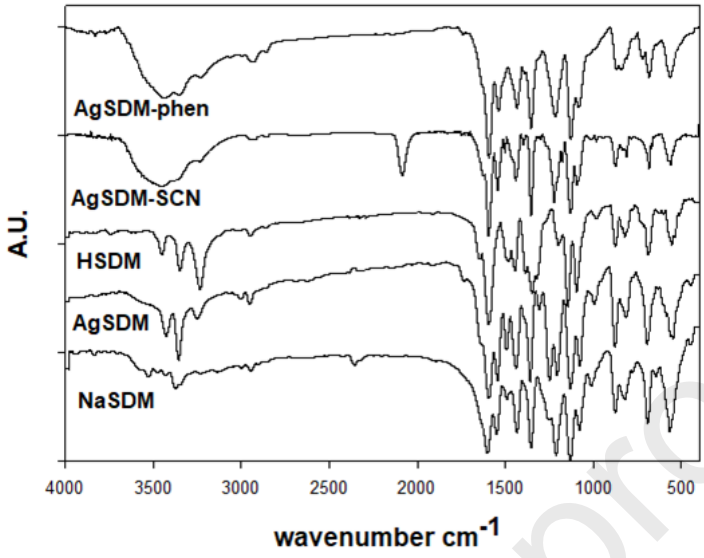


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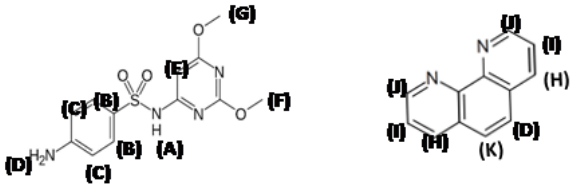


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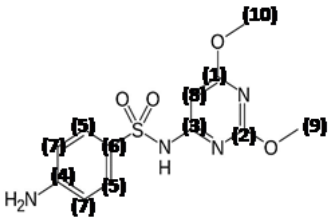


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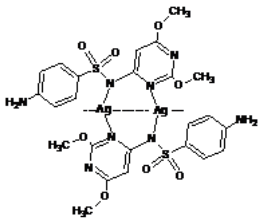

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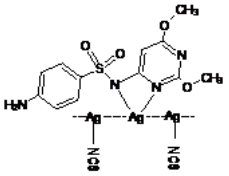

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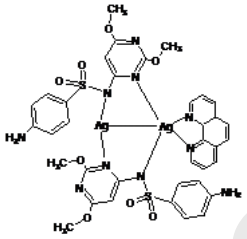

(c)



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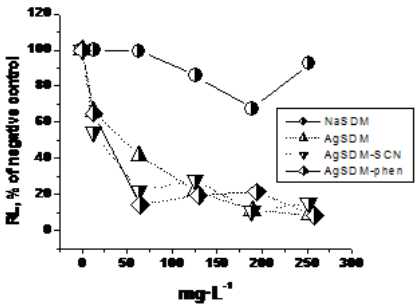


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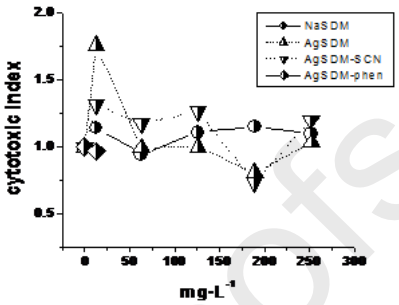


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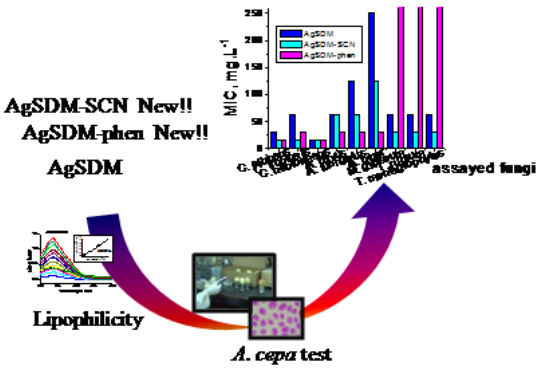


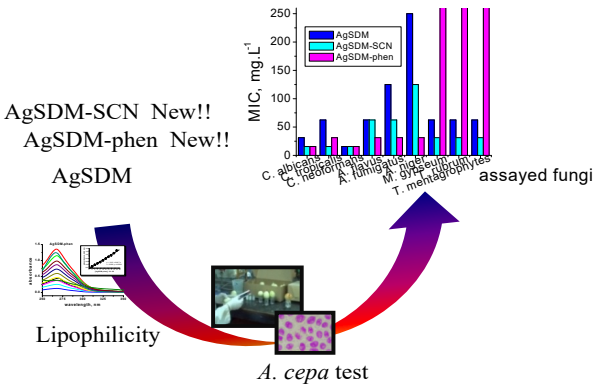

Highlights

1) Two new silver-sulfadimethoxine complexes were synthesized.

2) Coordination of silver ions occurs through amide and heterocyclic nitrogens.

3) The synthesized complexes showed antifungal activity

Graphical Abstract




Synopsis

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Fungal infections are still a big problem. Two new heteroleptic complexes between sodium sulfadimethoxine (NaSDM) and the silver(I) ion: AgSDM-SCN and AgSDM-phen, and AgSDM, showed moderate antifungal activity **(**sulfadimethoxine was inactive), low affinity towards animal fatty tissues and no geno or cytotoxicity in the *Allium cepa* test, except AgSDM-phen, so, these complexes could be good candidates for further pharmaceutical studies.



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