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Elvan Hasanoğlu Özkan
Associate Professor, Department of Chemistry, Faculty of Sciences, Gazi University, Teknikokullar, 06500 Ankara, Türkiye

Nurdan Kurnaz Yetim
Associate Professor, Kırklareli University, Faculty of Art and Science, Chemistry Department, 39100, Kırklareli, Türkiye

Hatice Öğütcü
Professor, Department of Field Crops, Faculty of Agriculture, Kırşehir Ahi Evran University, Kırşehir, Türkiye

Dilek Nartop
Professor, Department of Chemistry, Faculty of Arts and Sciences, Düzce University, Düzce, Türkiye

Corresponding Author:
Dilek Nartop
Professor, Department of Chemistry, Faculty of Arts and Sciences, Düzce University, Düzce, Türkiye

Synthesis and biological investigation of novel heterocyclic thiosemicarbazone silver (I) complexes as potent antimicrobial agents

Elvan Hasanoğlu Özkan, Nurdan Kurnaz Yetim, Hatice Öğütcü and Dilek Nartop

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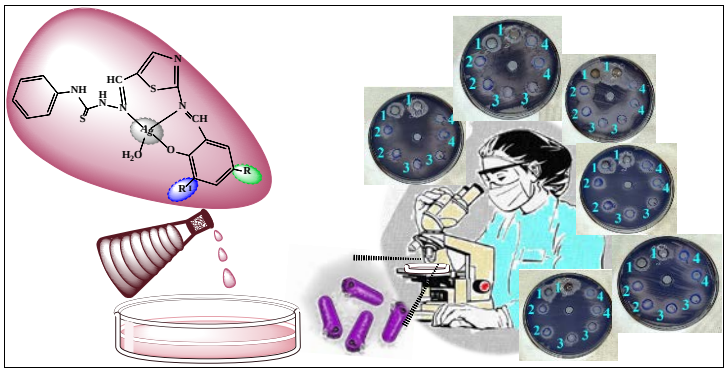
Abstract
Herein, new heterocyclic thiosemicarbazone silver (I) complexes (Tsc_1, Tsc_2, Tsc_3, Tsc_4) were synthesized by the template method, and their structures were determined using some spectral techniques: element analysis, Fourier transform infrared spectra (FT-IR), proton nuclear magnetic resonance (^{1}H-NMR), thermogravimetric analysis (TG-DTA), organic elemental analysis, and magnetic susceptibility measurements. The biological activities of the newly synthesized heterocyclic thiosemicarbazone silver (I) complexes were investigated as potent antimicrobial agents against some disease-causing pathogens. For this purpose, the well-diffusion method was used. The biological activity results demonstrated that all novel heterocyclic thiosemicarbazone silver (I) complexes have high or moderate inhibitory activity of the tested pathogenic strains.

Graphical Abstract



Keywords: Antimicrobial activity, bioactive heterocyclic compounds, disease-causing pathogens, thiosemicarbazones, silver (I) complexes

Introduction
Heterocyclic compounds are the most important cyclic organic compounds that contain heteroatoms (such as nitrogen, oxygen, and sulfur) instead of some carbon atoms (Abbas, 2017) [1]. Heterocyclics are of great interest in drug design and drug discovery because they are biologically active compounds (Majid and Vahideh, 2020) [2]. Heterocyclic thiosemicarbazone compounds are of particular importance in the pharmaceutical industry. Heterocyclic thiosemicarbazones can be attached to a metal atom through various coordination modes (azomethine nitrogen, sulfur atoms, heteroatoms, *etc.*) (Campbell, 1975) [3]. Heterocyclic thiosemicarbazone complexes exhibit various biological activities (such as antibacterial, antitumor, anticarcinogenic, and anticancer *etc.*) depending on their chemical structure (Muralisankar *et al.*, 2016, Aliakbar *et al.*, 2017, Khan *et al.*, 2022) [4-6]. In addition, thiosemicarbazone metal complexes inactivate ribonucleotide reductase, which is an enzyme involved in with cell proliferation and inhibits the growth of various bacteria and moulds (Enrico *et al.*, 2020, Giorgio *et al.*, 2010) [7, 8].

The metal complexes are used as catalysts in oxidation, transfer hydrogenation, and reduction reactions (Ashraf *et al*., 2023) [9]. Silver compounds are used to treat bacterial infections in burns, skin wounds, and conjunctivitis. Therefore, they are widely used as antibacterial agents (Isabela *et al*., 2013), (Rowan *et al*., 2006) [10, 11]. The complexes demonstrate *in vitro* anti-proliferative activity against some human cells, such as lung cells, breast tumor cells, and colon cancer cells (Bharathi *et al*., 2020, Khir *et al*., 2021) [12, 13]. They are also show antiplasmodial, cytotoxic, antifungal, anti-tuberculosis, and anticancer activity (Syahrina *et al*., 2019, Oliveira *et al*., 2019, Ashiq *et al*., 2020) [14-16].
In order to contribute to the development of chemical biology / medical chemistry, new heterocyclic thiosemicarbazone complexes were synthesized within the scope of this study.

Materials and Methods

All chemicals were provided by Sigma-Aldrich or Merck. Elemental analyses were performed on a Thermo Scientific Flash 2000 model elemental analyzer. ^{1}H-NMR spectra were taken with a Bruker Biospin brand Avance III 400 MHz model device. TGA-DTA analysis were carried out with a Shimadzu DTG 60H-DSC 60 model thermal analyzer. UV-Vis absorption spectra were obtained using a UV-1800 ENG240V, Soft model spectrophotometer. Magnetic measurements were performed with a Sherwood Scientific MKI model *Evans* magnetic susceptibility device.

General procedure for the synthesis of heterocyclic thiosemicarbazone complexes (Tsc_1, Tsc_2, Tsc_3, Tsc_4)

All heterocyclic thiosemicarbazone silver (I) complexes were obtained by condensation reaction by the same general procedure (Figure 1). New heterocyclic thiosemicarbazone complexes (Tsc_1, Tsc_2, Tsc_3, Tsc_4) were synthesized by the reaction of 2-aminothiazole-5-carboxaldehyde, thiosemicarbazide, salicylaldehyde derivatives and metal salt with template method. New heterocyclic thiosemicarbazone silver (I) complexes (Tsc_1, Tsc_2, Tsc_3, Tsc_4) were synthesized by adding 4 mmol of 4-phenylthiosemicarbazide a stirred solution of 2-aminothiazole-5-carboxaldehyde (4 mmol) in ethanol/DMSO and heating for 4 *h* at 80 °C. The pH of the solution was adjusted to 5-5.5 by adding 1 mL of acetic acid. 4 mmol of 5-bromosalicylaldehyde (or 5-chlorosalicylaldehyde or 5-methylsalicylaldehyde or 5-Fluoro-3-methylsalicylaldehyde) in ethanol (50 mL) was added to the solution and was stirred for a further 3 *h* at 80 °C under reflux. A silver acetate in ethanol (5 mL) was then added to the solution and stirred for a further 4 *h* at 70 °C under reflux. The mixture was slowly evaporated at room temperature for a couple of days, and purified, filtered, and colored product was obtained.

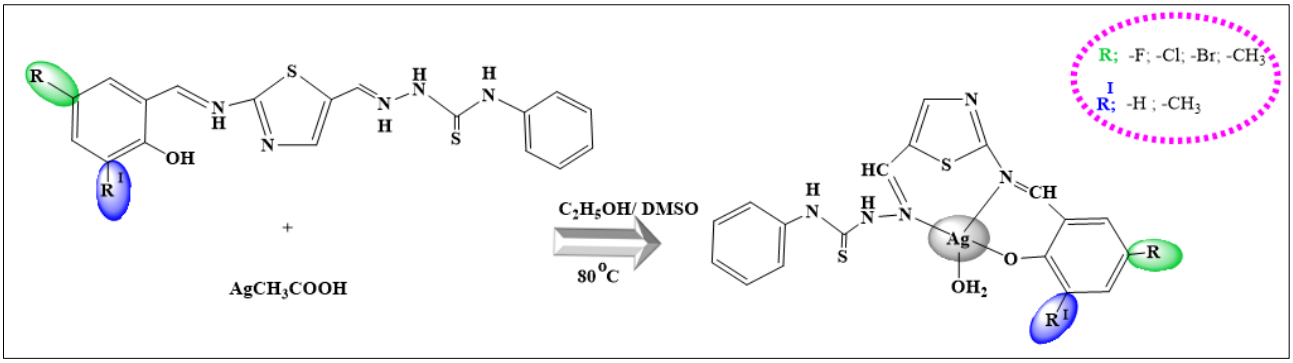


Fig 1: General procedure for thiosemicarbazone complexes (Tsc_1, Tsc_2, Tsc_3, Tsc_4)

All heterocyclic thiosemicarbazone silver (I) complexes were characterized by spectroscopic methods.

Compound Tsc_1

Yield, 64%; Dark brown solid; FT-IR (KBr, ν, cm^{-1}): 3351 (H_2O), 3044 $(CH)_{aro.}$, 1612 (CH=N), 1519 $(CH=N)_{tyz.}$, 1471 (C=C), 1205, 818 (C=S), 742 (C-S-C), 1011 (N-N), 3276 (N-H), 555 (M-O), 475 (M-N); ^{1}H-NMR (400 MHz, DMSO-d6, ppm): 11.16 (1H, s, N-NH), 8.95 (1H, s, CH=N), 6.95-7.91 (5H, m, Ar-H); Elemental analysis, calcd. (found): C_{18} H_{15} $AgBrN_5$ S_2 O_2, C: 36.94 (36.03), H: 2.58 (2.05), N: 11.97 (11.15), S: 10.96 (11.03). UV-Vis (DMSO, λmax, nm): 269, 328, 376.

Compound Tsc_2

Yield, 60%; Dark brown solid; FT-IR (KBr, ν, cm^{-1}): 3321 (H_2O), 3033 $(CH)_{aro.}$, 1610 (CH=N), 1520 $(CH=N)_{tyz.}$, 1476 (C=C), 1203, 823 (C=S), 740 (C-S-C), 1014 (N-N), 3273 (N-H); ^{1}H-NMR (400 MHz, DMSO-d6, ppm): 11.48 (1H, s, N-NH), 8.91 (1H, s, CH=N), 6.99-7.79 (5H, m, Ar-H); Elemental analysis, calcd. (found): $C_{18}H_{15}AgClN_5S_2O_2$, C: 39.98 (39.33), H: 2.58 (2.87), N: 12.95 (12.55), S: 11.86 (11.39). UV-Vis (DMSO, λmax, nm): 262, 327, 371.

Compound Tsc_3

Yield, 65%; Dark brown solid; FT-IR (KBr, ν, cm^{-1}): 3315 (H_2O), 3043 $(CH)_{aro.}$, 1611 (CH=N), 1519 $(CH=N)_{tyz.}$, 1485 (C=C), 1206, 824 (C=S), 743 (C-S-C), 1016 (N-N), 3281 (N-H); ^{1}H-NMR (400 MHz, DMSO-d6, ppm): 10.91 (1H, s, N-NH), 8.94 (1H, s, CH=N), 6.87-7.50 (5H, m, Ar-H), 2.39 (3H, s, Ar-CH_3); Elemental analysis, calcd. (found), $C_{19}H_{18}AgN_5S_2O_2$, C: 43.85 (43.88), H:3.49 (3.57), N: 13.46 (13.48), S: 12.32 (12.58). UV-Vis (DMSO, λmax, nm): 260, 325, 372.

Compound Tsc_4

Yield, 61%; Dark brown solid; FT-IR (KBr, ν, cm^{-1}): 3311 (H_2O), 3049 $(CH)_{aro.}$, 1622 (CH=N), 1513 $(CH=N)_{tyz.}$, 1469 (C=C), 1196, 853 (C=S), 737 (C-S-C), 1036 (N-N), 3277 (N-H); ^{1}H-NMR (400 MHz, DMSO-d6, ppm): 11.30 (1H, s, N-NH), 9.03 (1H, s, CH=N), 7.25-7.33 (5H, m, Ar-H); Elemental analysis, calcd. (found), $C_{19}H_{17}AgFN_5S_2O_2$, C: 42.39 (43.01), H: 3.18 (3.11), N: 13.01 (13.40), S: 11.91 (12.05). UV-Vis (DMSO, λmax, nm): 263, 326, 376.

Determination of antimicrobial activity

The antibacterial and antifungal activities of the heterocyclic

thiosemicarbazone silver (I) complexes were examined using the well-diffusion method against some disease-causing pathogenic microorganisms. Herein, Gram-positive bacteria (*Micrococcus luteus ATCC9341*, *Staphylococcus epidermidis* ATCC12228, *Bacillus cereus* RSKK863) and Gram-negative bacteria (*Pseudomonas aeroginosa* ATCC27853, *Klebsiella pneumonia* ATCC27853, *Enterobacter aerogenes ATCC51342*, *Salmonella typhi H* NCTC9018394, *Shigella dysenteria* NCTC2966, *Proteus vulgaris* RSKK96026,) and yeast (*Candida albicans* Y-1200-NIH) were used. In the well-diffusion method, dimethylsulfoxide(DMSO) was used as solvent control, and it was detected that it had no antimicrobial activity against any of the tested organisms. All the heterocyclic thiosemicarbazone compounds were dissolved (3.5 µg/mL) in DMSO. Pathogenic strains were incubated in Nutrient Broth agar (10^6 CFU/mL) for 24 *h* at 37 ^oC. Then, these cultures were homogenized by adding to Mueller-Hinton Agar (MHA) cooled to 45 ^oC and were poured into sterile petri dishes and were cooled. Afterwards, wells of 6 mm diameter were pierced in these agars, and the heterocyclic thiosemicarbazone compounds were added. The plates were incubated in an oven at 37 °C for 24 *h*, and the zone of inhibition was then measured for each compound and the average of the activity values performed with two repetitions was taken (Ülke *et al*., 2022) [17]. In addition, ampicillin (AMP10), sulphamethoxazole (SXT25), amoxicillin (AMC30), kanamycin (K30), and nystatin (NYS100) standard antibiotics were used. Pathogenic Gram (+) and Gram (-) bacteria were compared with AMP10, SXT25, AMC30, K30 antibiotics, and yeast was compared with NYS100 antibiotic.

Results and Discussion

Chemistry

Elemental analysis results and some analytical data of the heterocyclic thiosemicarbazone silver (I) complexes are presented in Table 1. For all heterocyclic thiosemicarbazone compounds, it was determined that the elemental analyses and the chemical formulas of the compounds were compatible.

Table 1: Analytical, electromagnetic spectra and thermal data of thiosemicarbazone complexes.

Compound	Chemical Formula	Colour μ_{eff} / $\mu_{S/cm}$	Step	T_i (°C)	T_f (°C)	Residue mass at 800 °C (wt %)	Charge transfer transition (nm)
Tsc_1	$C_{18}H_{15}AgBrN_5S_2O_2$ (585)	Dark brown - / 15.3	1st 2nd 3rd	255.44 429.07 547.73	310.74 509.91 639.57	21.42	376
Tsc_2	$C_{18}H_{15}AgClN_5S_2O_2$ (541)	Dark brown - / 15.7	1st 2nd 3rd	260.97 468.35 584.67	315.36 489.98 656.52	22.66	371
Tsc_3	$C_{19}H_{18}AgN_5S_2O_2$ (520)	Dark brown - / 25.7	1st 2nd	225.83 456.82	386.58 663.03	17.77	372
Tsc_4	$C_{19}H_{17}AgFN_5S_2O_2$ (538)	Dark brown - / 35.9	1st 2nd 3rd	224.01 467.51 530.85	324.13 495.65 640.44	30.12	376

Characteristic FT-IR spectrum data for the heterocyclic thiosemicarbazone silver (I) complexes are presented in Table 2 and are shown in Figure 2. The ν(CH=N) absorption bands of azomethine groups appeared in the 1610-1622 cm^{-1} and 1513-1520 cm^{-1} ranges, respectively. The ν(C-S-C) stretching vibrations of thiazole groups were observed in the region of 737-743 cm^{-1}. ν(CH) and ν(C=C) absorption bands of the aromatic ring appeared in the 3033-3049 cm^{-1} and 1469-1485 cm^{-1} regions, respectively. The ν(N-N) and ν(N-H) stretching vibrations were determined in the ranges 1011-1036 cm^{-1} and 3273-3281 cm^{-1}, respectively. The ν(C=S) absorption bands were occurred in the range of 818-853 cm^{-1} and 1196-1205 cm^{-1}, respectively (Obasi *et al*., 2011) [18]. The ν(H_2O) stretching vibrations were determined in the ranges 3331-3351 cm^{-1}. Additionally, the (νM-O) and (νM-N) absorption bands were appeared in the range of 535-555 cm^{-1} and 454-471 cm^{-1}. These weak stretching vibrations are predicted as an indication of the coordination of Ag(I) ions with the azomethine groups (Sundaram *et al*., 2019) [19]. Further, the ν(Ar-OH) stretching vibrations were not observed in the spectra of the complexes, indicating the coordination of oxygen atoms with Ag(I).

Table 2: FT-IR vibration frequencies (cm^{-1}) of thiosemicarbazone complexes.

Compound	N (H_2O)	N $(CH)_{aro.}$ /ν(C=C)	ν(CH=N)/ν $(CH=N)_{tyz.}$	ν(C=S)	ν(C-S-C)	ν(N-N) /ν(N-H)	ν(M-O) /ν(M-N)
Tsc_1	3351	3044 1471	1612 1519	1205 818	742	1011 3276	555 475
Tsc_2	3321	3033 1476	1610 1520	1203 823	740	1014 3273	535 -
Tsc_3	3315	3043 1485	1611 1519	1206 824	743	1016 3281	536 454
Tsc_4	3311	3049 1469	1622 1513	1196 853	737	1036 3277	547 461

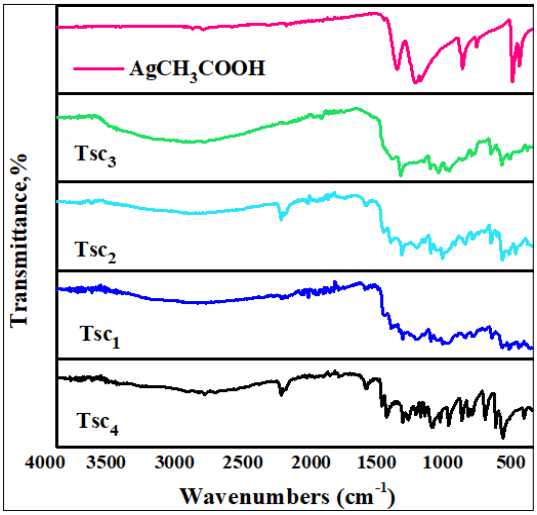


Fig 2: FT-IR spectrums of thiosemicarbazone complexes

Characteristic ^{1}H-NMR spectrum data for the heterocyclic thiosemicarbazone silver (I) complexes are presented in Table 3 and are shown in Figure 3. Two unsymmetric imine (CH=N) bands obtained by the condensation of aldehydes and amines were observed in the range of 8.91-9.03 ppm. NH protons (N-NH) were appeared in the 10.91-11.48 ppm ranges. The aromatic protons (Ar-H) were appeared in the ranges 6.87-7.91 ppm. Additionally, the methyl proton (Ar-CH_3) were determined at 2.25 ppm and 2.39 ppm for **Tsc$_3$** and Tsc$_4$ (Silverstein and Webster, 1998) [20].

Table 3: ^{1}H-NMR chemical shift (ppm) of thiosemicarbazone complexes.

sCompound	N-NH	CH=N	Ar-H	Ar -CH_3
Tsc$_1$	11.16	8.95	6.95-7.91	-
Tsc$_2$	11.48	8.91	6.99-7.79	-
Tsc$_3$	10.91	8.94	6.87-7.50	2.39
Tsc$_4$	11.30	9.03	7.25-7.33	2.25

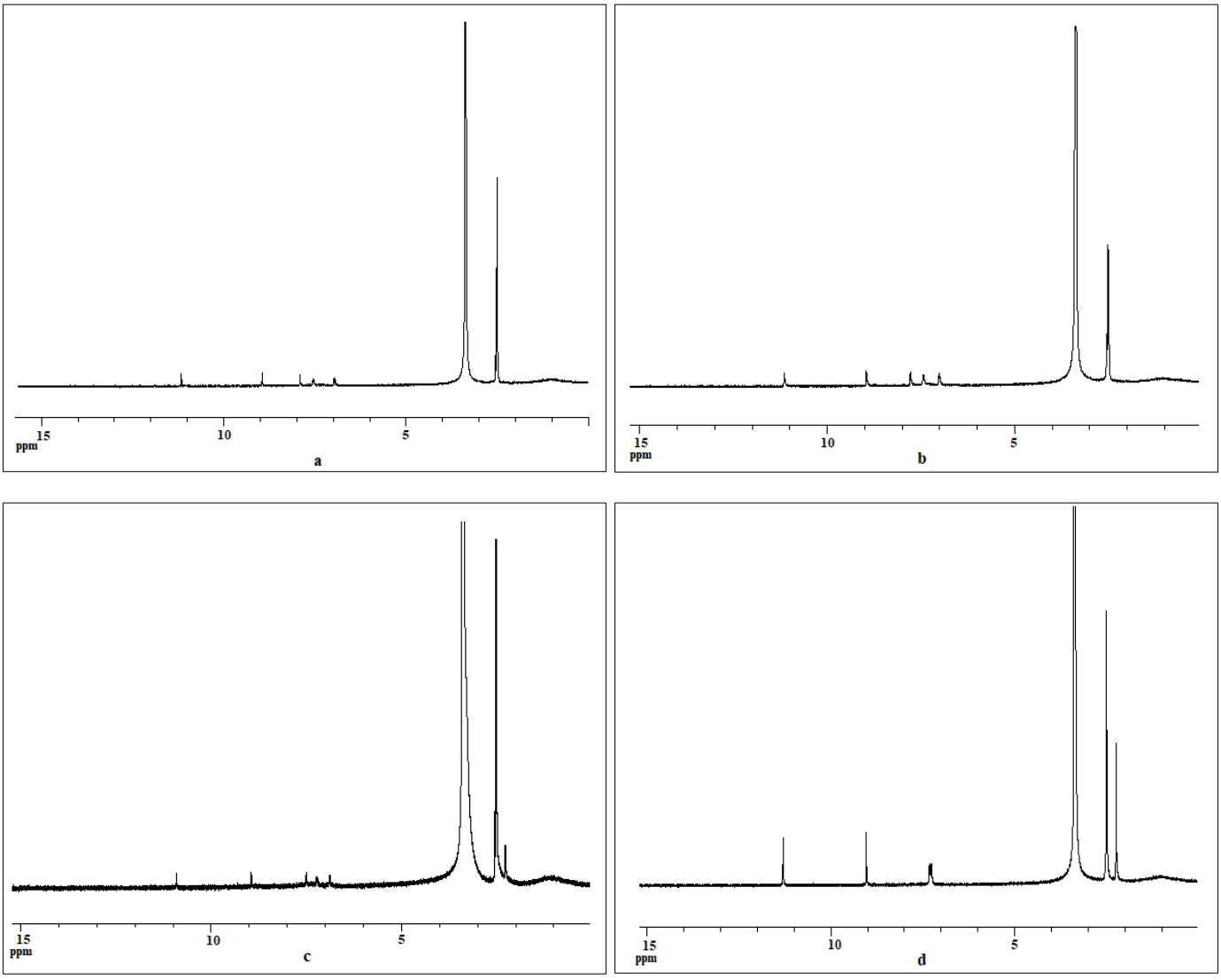


Fig 3: ^{1}H-NMR spectrum of thiosemicarbazone complexes (a) Tsc$_1$ (b) Tsc$_2$ (c) Tsc$_3$ (d) Tsc$_4$

TGA-DTA data for the heterocyclic thiosemicarbazone silver (I) complexes are presented in Table 1 and are shown in Figure 4. The thermal degradation curves show that Tsc$_1$, Tsc$_2$, and Tsc$_4$ exhibited three-step weights. In the first step, the values T_i and T_f were observed in the ranges 224.01-260.97 °C and 310.74-324.13 °C, respectively. In the second step, the values T_i and T_f were determined in the ranges 429.07-468.35°C and 489.98-509.91 °C, respectively. In the third step, the values T_i and T_f were determined in the ranges 530.85-584.67 °C and 639.57-656.52 °C, respectively. Tsc$_3$ exhibited one-step weight In the first step, T_i and T_f were observed at 225.83 and 386.58 °C. In the second step, T_i and T_f were determined in the ranges 456.82-663.03 °C. Additionally, the percentage of residue mass in all heterocyclic thiosemicarbazones at final temperature was determined to be in the range 17.17-30.12%, indicating AgO.

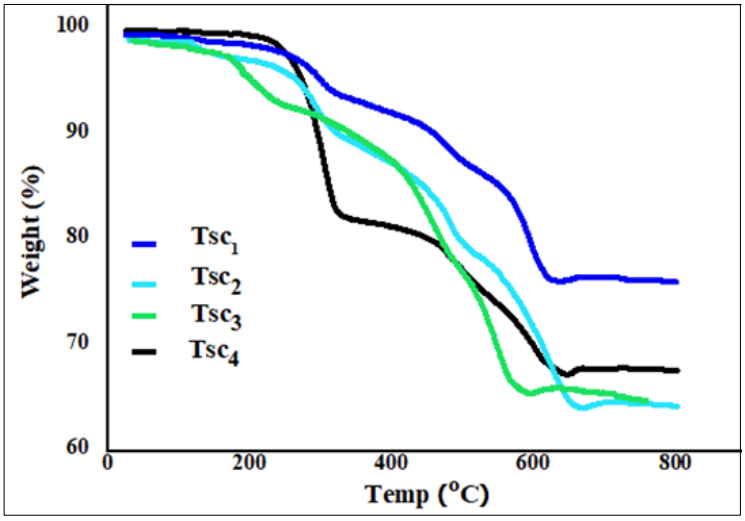


Fig 4: TGA-DTA curves of thiosemicarbazone complexes

UV-Vis data for the heterocyclic thiosemicarbazone silver (I) complexes are presented in Table 1 and are shown in Figure 5. For all heterocyclic compounds, the $\pi \rightarrow \pi^*$ transitions belonging to the aromatic ring and the $n \rightarrow \pi^*$ transitions belonging to the imine group appeared in the ranges 260-269 nm and 325-328 nm, respectively. For all heterocyclic thiosemicarbazone-Ag(I) complexes, the absorption bands which is assigned to charge transfer transitions appeared in the ranges 371-376 nm (Vinod *et al*., 2014), (Suman *et al*., 2011) [21,22]. The absence of absorption bands in the visible region due to the d^{10} configuration is an indication of tetrahedral geometry (Sundaram *et al*., 2020) [19]. Additionally, according to the magnetic susceptibility measurement, all heterocyclic thiosemicarbazone-Ag (I) complexes showed diamagnetic properties, indicating tetrahedral geometry (Jan *et al*., 2022) [23].

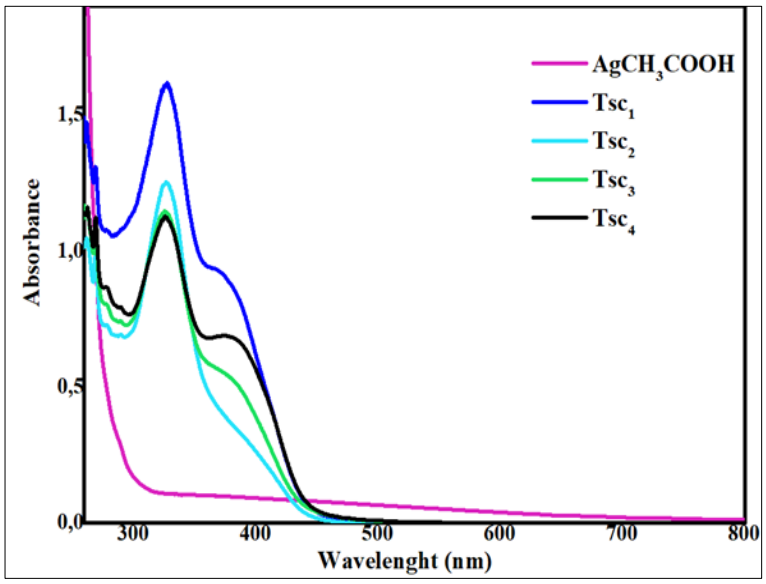


Fig 5: UV-Vis spectra of thiosemicarbazone complexes

The antifungal and antibacterial activity data for the heterocyclic thiosemicarbazone silver (I) complexes are presented in Table 4 and are shown in Figure 6. The heterocyclic complexes were screened for antimicrobial activities against some disease-causing pathogens (*M. luteus, S. epidermidis, B. cereus, P. aeroginosa, K. pneumonia, E. aerogenes, S. typhi H, S. dysenteria, P. vulgaris)* and yeast (*C. albicans*) by the well-diffusion method. Further, pathogenic bacteria strains and yeast were compared with standard antibiotics (Ampicillin, kanamycin, sulphamethoxazole, amoxicillin) and anticandidal (Nystatin). The results demonstrated that the heterocyclic thiosemicarbazone silver (I) complexes showed different antibacterial and antifungal activity. The thiosemicarbazone silver (I) complexes (Tsc_1, Tsc_2, and Tsc_4), except Tsc_3, showed higher antibacterial activity than all standard antibiotics against *S. Typhi H.* It is a pathogen that causes typhoid and paratyphoid (Nartop *et al*., 2020) [24]. Among gram (-) bacteria, Tsc_1 (24 mm) exhibited the highest antibacterial activity against *S. typhi H.* Among gram (+) bacteria, Tsc_2 (25 mm) showed the highest antibacterial activity against *S. epidermidis.* It is a pathogen that causes endocarditis and septicemia infections (Georg *et al*., 1990) [25]. Tsc_3 (20 mm) exhibited the highest inhibitory effect against *S. dysenteria.* It is a bacteria that causes bacillary dysentery or shigellosis (Sophie *et al*., 2015) [26]. Tsc_4 (19 mm) demonstrated the highest antibacterial activity against *S. epidermidis.* Tsc_3 (25 mm) exhibited the highest antifungal activity against *C. Albicans.* Tsc_2 (20 mm) showed as much antifungal activity as standard antibiotic Nystatin. *C. albicans* is a fungus responsible for the gastrointestinal tract and bloodstream infections (Carolus *et al*., 2019) [27].

Table 4: Antibacterial and antifungal activities of thiosemicarbazone complexes (diameter of zone of inhibition (mm)).

Microorganisms	Compounds Positive control							
	Tsc_1	Tsc_2	Tsc_3	Tsc_4	AMP10	SXT25	AMC30	K30
M. luteus	16	15	17	18	22	21	25	23
S. epidermidis	21	25	18	19	26	25	27	25
B. cereus	13	14	15	17	23	25	20	28
P. aeroginosa	15	13	16	17	8	18	15	14
K. pneumonia	16	13	16	18	21	20	21	23
E. aerogenes	15	15	16	18	21	19	20	24
S. typhi H	24	20	-	17	11	17	19	20
S. dysenteria	13	12	20	10	10	18	14	25
P. vulgaris	11	12	13	13	17	19	20	21
					NYS10			
C. albicans	18	20	25	18	20			
DMSO (Solvent control)	-	-	-	-				

Standard reagents: K30 Kanamycin, 30 µg; SXT25 sulfamethoxazol, 25 µg; AMP10 Ampicillin, 10 µg; AMC30 Amoxycillin, 30 µg; NYS100 Nystatin, 100 µg.

As a result, it can be said that the heterocyclic thiosemicarbazone silver (I) complexes with high or moderate antifungal and antibacterial efficacy can be used as potent antimicrobial agents in various biomedical applications.

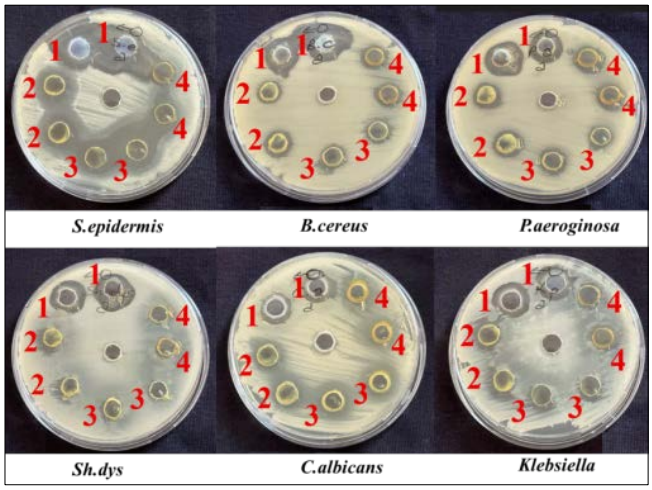


Fig 6: Photographs of inhibition zones (mm) of some Gram (+) and Gram (-) bacteria and yeast

Conclusions

Within the scope of this study, new examples of heterocyclic thiosemicarbazone complexes, which are of particular interest due to their wide biological applications, were synthesized and characterized by various spectroscopic methods. The antibacterial and antifungal activities of the synthesized heterocyclic thiosemicarbazone complexes were determined *in vitro* against selected disease-causing pathogenic strains using the well-diffusion method. The results showed that the heterocyclic thiosemicarbazone complexes had high / or moderate antibacterial and antifungal efficacy. In conclusion, it can be said that novel heterocyclic thiosemicarbazone complexes can be suggested as potential antimicrobial agents for use in pharmacy, biology, medicine, and biomedical applications.

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Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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