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Research Article

Synthesis and *in vitro* Biological Assessments of Novel Thiazole-Based Thiosemicarbazone Complexes

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ABSTRACT

In the present work, novel heterocyclic thiazole-based thiosemicarbazone Ag(I) complexes (**Hc$_1$**, **Hc$_2$**, **Hc$_3$**) were obtained using the template method. The structures of synthesized thiosemicarbazone compounds were determined by some spectroscopic techniques (element analysis, infrared spectra (IR), thermogravimetric analysis (TGA), organic elemental analysis, and magnetic susceptibility measurements). The biological activities of novel heterocyclic thiazole-based thiosemicarbazone Ag(I) complexes were screened *in vitro* against selected disease-causing pathogens (*Micrococcus luteus* ATCC9341, *Staphylococcus epidermidis* ATCC12228, *Bacillus cereus* RSKK863, *Pseudomonas aeroginosa* ATCC27853, *Klebsiella pneumonia* ATCC27853, *Enterobacter aerogenes* ATCC51342, *Salmonella typhi H* NCTC9018394, *Shigella dysenteria* NCTC2966, *Proteus vulgaris* RSKK96026, *Candida albicans* Y-1200-NIH) were as potential antimicrobial agents. It was determined that the thiazole-based thiosemicarbazone Ag(I) complexes exhibited high or moderate antibacterial and antifungal activity.

Keywords: *Ag(I) complex, Thiazole, Thiosemicarbazone, Biological activity*

Yeni Tiyazol Bazlı Tiyosemikarbazon Komplekslerinin Sentezi ve *in vitro* Biyolojik Değerlendirmeleri

ÖZ

Sunulan bu çalışmada, yeni heterosiklik tiyazol bazlı tiyosemikarbazon Ag(I) kompleksleri (**Hc$_1$**, **Hc$_2$**, **Hc$_3$**) template yöntem ile elde edildi. Sentezlenen tiyosemikarbazon bileşiklerinin yapıları bazı spektroskopik teknikler (element analizi, infrared spektra (IR), termogravimetrik analiz (TGA), organic elemental analiz, ve magnetik duyarlılık ölçümleri) ile karakterize edildi. Yeni heterosiklik tiyazol bazlı tiyosemikarbazon Ag(I) komplekslerinin biyolojik aktiviteleri potansiyel antimikrobiyal ajanlar olarak seçilmiş hastalık yapıcı patojenlere (*Micrococcus luteus* ATCC9341, *Staphylococcus epidermidis* ATCC12228, *Bacillus cereus* RSKK863, *Pseudomonas aeroginosa* ATCC27853, *Klebsiella pneumonia* ATCC27853, *Enterobacter aerogenes* ATCC51342, *Salmonella typhi H* NCTC9018394, *Shigella dysenteria* NCTC2966, *Proteus vulgaris* RSKK96026, *Candida albicans* Y-1200-NIH) karşı *in vitro* olarak incelendi.

Anahtar Kelimeler: *Ag(I) kompleksi, Tiyazol, Tiyosemikarbazon, Biyolojik aktivite*

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I. INTRODUCTION

Heterocyclic compounds are defined as cyclic organic compounds containing heteroatoms (nitrogen, oxygen, sulfur, phosphorus, *etc.*) next to carbon atoms [1]. The unique properties of heterocyclic compounds make them an interesting research topic. Among the wide variety of heterocyclic compounds, heterocyclic thiosemicarbazones are an interesting field of study because of their potential biological, physical, chemical, ion sensing, and catalytic properties [2-4].

Heterocyclic thiosemicarbazones are important ligand types due to the containing potent donor atoms and some of their properties such as π delocalization and configuration flexibility [5]. The conjugated N-N-S systems provide important properties such as therapeutic, biological to thiosemicarbazones [6, 7].

Heterocyclic thiosemicarbazones and their metal complexes possess antiviral, antitumor, antimicrobial, anti-inflammatory, antimalarial, antibacterial, antiproliferative, antiplasmodial, antioxidant, and anticancer properties [8-11]. They also demonstrate cytotoxicity activity as antineoplastic agents and are potential therapeutics for cancer and neurodegenerative diseases [12, 13]. Heterocyclic thiosemicarbazone metal complexes are also of great interest in medicinal chemistry due to their interactions with DNA [14, 15].

Due to the increase in microbiological resistance, there has been a need for the discovery of new antimicrobial agents in recent years. For this reason, due to the biological, therapeutic, and pharmacological potential of silver complexes, novel heterocyclic thiazole-based thiosemicarbazone Ag(I) complexes were synthesized and characterized here.

II. MATERIALS AND METHODS

All materials were provided by Sigma-Aldrich or Merck. Elemental analyses were recorded on a Thermo Scientific Flash 2000 model elemental analyzer. ^{1}H-NMR spectra were determined with a Bruker Biospin brand Avance III 400 MHz model device. TGA measurements were obtained using a Shimadzu-DTG 60H DSC 60 model thermal analyzer. UV-Vis absorption spectra were collected using a UV-1800 ENG-240V, Soft type spectrophotometer. Magnetic susceptibility measurements were carried out using a Sherwood - Scientific-MKI type Evans magnetic susceptibility device.

A. GENERAL PROCEDURE FOR THE SYNTHESIS OF THIAZOLE-BASED THIOSEMICARBAZONE Ag(I) COMPLEXES (Hc_1, Hc_2, Hc_3)

All thiazole-based thiosemicarbazone Ag(I) complexes (**Hc_1**, **Hc_2**, **Hc_3**) were synthesized by condensation reaction by the general procedure (Figure 1). New thiosemicarbazone Ag(I) complexes were obtained by the reaction of 2-aminothiazole-5-carboxaldehyde, 4-methyl-3-thiosemicarbazide, salicylaldehyde derivatives, and silver(I) acetate with template method. New thiosemicarbazone Ag(I) complexes were synthesized by adding 4 mmol of 4-methyl-3-thiosemicarbazide, a stirred solution of 2-aminothiazole-5-carboxaldehyde (4 mmol) in ethyl alcohol/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-fluorosalicylaldehyde (or 5-Fluoro-3-methylsalicylaldehyde or 3-chloro-5-fluorosalicylaldehyde) in ethyl alcohol (50mL)was added to the solution and was stirred for a further 3 *h* at 80 °Cunder reflux. A silver(I) acetate in ethyl alcohol (5mL) 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.

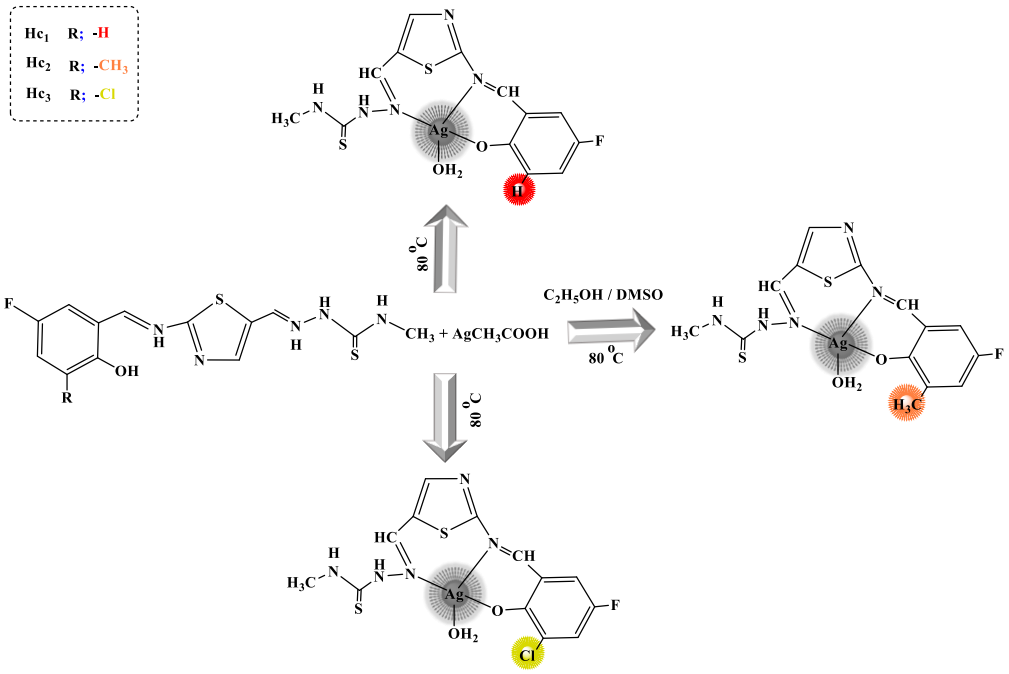


Figure 1. *General procedure for the thiazole-based thiosemicarbazone Ag(I) complexes (**Hc₁**, **Hc₂**, **Hc₃**)*

B. BIOLOGICAL ASSESSMENTS

The antimicrobial activities of the thiazole-based thiosemicarbazone Ag(I) complexes (**Hc$_1$**, **Hc$_2$**, **Hc$_3$**) were investigated *in vitro* against some disease-causing pathogenic microorganisms. For this purpose, the well-diffusion method was used. In the method, dimethylsulfoxide (DMSO) was used as solvent control. It had no antimicrobial activity against any of the tested organisms. All of the thiosemicarbazone Ag(I) complexes were dissolved in DMSO (3.5 g/mL). Pathogens were cultured for 24*h* at 37°C in Nutrient Broth Agar (10^6 CFU/mL). The cultures were homogenized by adding Mueller-Hinton Agar (MHA), then chilled to 45 °C and put into sterile petri dishes. The thiosemicarbazone Ag(I) complexes were then introduced to wells 6 mm in diameter in the agars. The plates were incubated in an oven at 37 °C for 24*h* before measuring the zone of inhibition for each complex and taking the average of the activity values done twice [16].

Furthermore, ampicillin (AMP10), sulphamethoxazole (SXT25), amoxicillin (AMC30), kanamycin (K30), and nystatin (NYS100) were used as standard antibiotics. Pathogenic bacteria were compared with AMP10, SXT25, AMC30, and K30 antibiotics. The yeast was compared only with the NYS100 antibiotic.

III. RESULTS AND DISCUSSION

A. CHEMISTRY

Elemental analysis results, analytical, electromagnetic spectra, and thermal data of the thiazole-based thiosemicarbazone Ag(I) complexes (**Hc$_1$**, **Hc$_2$**, **Hc$_3$**) are presented in Table 1. For all thiosemicarbazone Ag(I) complexes, it was seen that the elemental analysis and the chemical formulas of the complexes were compatible. Elemental analysis, calcd. (found): $C_{13}H_{13}FN_5O_2S_2Ag$, C: 33.78 (34.02), H: 2.83 (3.01), N: 15.15 (14.79), S: 13.87 (13.95) for **Hc$_1$**; $C_{14}H_{15}FN_5O_2S_2Ag$, C: 35.30 (35.27), H: 3.17 (3.26), N: 14.70 (14.64), S: 13.46 (13.37) for **Hc$_2$**; $C_{13}H_{12}FClN_5O_2S_2Ag$, C: 31.44 (31.50), H: 2.44 (2.41), N: 14.10 (14.13), S: 12.91 (13.04) for **Hc$_3$**.

Table 1.*TGA, UV-vis and analytical data of the thiazole-based thiosemicarbazone Ag(I)complexes(nm, ε×10^{-4}M)*

Compound	Chemical Formula	Colour / μ_{eff} ($\mu_{S/cm}$)		T_i (°C)	T_f (°C)	Residue mass at 800 °C (wt %)	Charge transfer transition
Hc$_1$	$C_{13}H_{13}FN_5O_2S_2Ag$ (462)	Dark brown / 40.5	1st 2nd	400.39 584.71	541.63 684.71	11.51	363
Hc$_2$	$C_{14}H_{15}FN_5O_2S_2Ag$ (476)	Brown / 5.9	1st 2nd	453.21 590.70	560.73 687.74	12.87	361
Hc$_3$	$C_{13}H_{12}FClN_5O_2S_2Ag$ (497)	Dark brown / 71.4	1st 2nd 3rd 4th	111.95 244.23 414.99 576.80	241.63 329.80 548.77 647.42	43.45	359

Characteristic FT-IR spectrum data for the thiazole-based thiosemicarbazone Ag(I) complexes (**Hc$_1$**, **Hc$_2$**, **Hc$_3$**) are presented in Table 2 and are shown in Figure 2. The ν(CH=N) stretching vibrations of azomethine groups were observed in the 1620-1633 cm^{-1} and 1515-1517 cm^{-1} ranges, respectively. The ν(C-S-C) absorption bands of thiazole groups appeared in the region of 735-743 cm^{-1}. ν(CH) and ν(C=C) stretching vibrations of the aromatic ring were determined in the 3012-3022 cm^{-1} and 1480-1488 cm^{-1} regions, respectively. The ν(N-N) and ν(N-H) absorption bands appeared in 1011-1018 cm^{-1} and 3272-3287 cm^{-1}, respectively. The ν(C=S) absorption bands occurred between 851-865 cm^{-1} and 1208-1211 cm^{-1}, respectively [17]. The stretching vibrations of ν(H_2O) were determined in the ranges 3316-3318 cm^{-1}. Additionally, the absorption bands of ν(M-O) and ν(M-N) were observed in the range of 533-544 cm^{-1} and 460-469 cm^{-1}. The weak stretching vibrations are predicted to indicate the coordination of Ag(I) ions with the azomethine groups [18]. Further, the ν(Ar-OH) absorption bands did not appear in the spectra of the complexes, indicating the coordination of oxygen atoms with Ag(I).

Table 2. *FTIR - vibration frequencies(cm^{-1}) of the thiazole-based thiosemicarbazone Ag(I) complexes*

Compound	ν(H_2O)	ν(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)
Hc$_1$	3316	3022 1486	1620 1515	1210 865	743	1018 3280	534 / 462
Hc$_2$	3318	3013 1480	1630 1516	1208 851	743	1011 3272	533 / 460
Hc$_3$	3317	3012 1488	1633 1517	1211 854	735	1016 3287	544 / 469

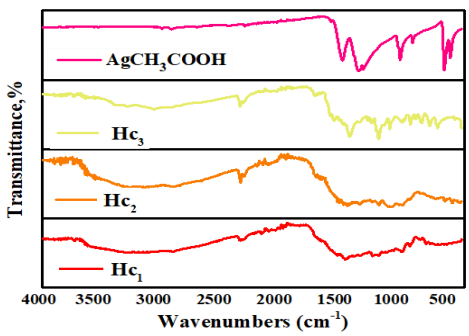


Figure 2. *FT-IR vibration frequencies the thiazole-based thiosemicarbazone Ag(I) complexes (**Hc$_1$**, **Hc$_2$**, **Hc$_3$**)*

TGA data for the thiazole-based thiosemicarbazone Ag(I) complexes (**Hc_1**, **Hc_2**, **Hc_3**) are presented in Table 1 and are shown in Figure 3. The thermal degradation curves show that **Hc_1** exhibited two-step weights. In the first step, the values T_i and T_f were observed at 400.39 and 541.63 ℃, respectively. In the second step, the values T_i and T_f were determined at 584.71 and 684.71 ℃, respectively. The thermal degradation curves show that **Hc_2** exhibited two-step weights. In the first step, the values T_i and T_f were observed at 453.21 and 560.73 ℃, respectively. In the second step, the values T_i and T_f were determined at 590.70 and 687.74 ℃, respectively. **Hc_3** exhibited four-step weights. In the first step, T_i and T_f were observed at 111.95 and 241.63 ℃, respectively. In the second step, T_i and T_f were determined at 244.23 and 329.80 ℃, respectively. In the third step, the values T_i and T_f values were observed at 414.99 and 548.77 ℃, respectively. In the fourth step, the values T_i and T_f were determined at 576.80 and 647.42 ℃, respectively. In addition, the percentage of residue mass in all thiosemicarbazone Ag(I) complexes at final temperature was determined to be 11.51-43.45 %, indicating AgO.

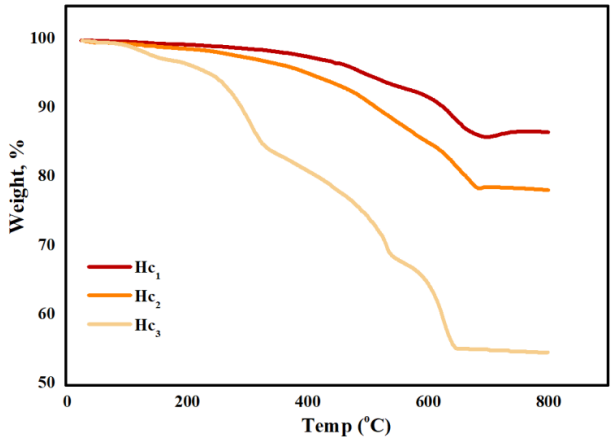


Figure 3. *TGA curves of the thiazole-based thiosemicarbazone Ag(I) complexes (**Hc_1**, **Hc_2**, **Hc_3**)*

UV-Vis data for the thiazole-based thiosemicarbazone Ag(I) complexes (**Hc_1**, **Hc_2**, **Hc_3**) are presented in Table 1 and are shown in Figure 4. For all thiosemicarbazone Ag(I) complexes, the π→π* transitions belonging to the aromatic ring appeared in the ranges 259-263 nm. The n→π* transitions belonging to the imine group were observed in the ranges 338-345 nm. For all thiosemicarbazone Ag(I) complexes, the absorption bands appeared in the ranges 359-363 nm, which is assigned to charge transfer transitions [19,20]. The absence of absorption bands in the visible region due to the d^{10} configuration is an indication of the tetrahedral geometry [18]. According to magnetic susceptibility measurement, all thiosemicarbazone complexes showed diamagnetic properties. These results indicate that the thiazole-based thiosemicarbazone Ag(I) complexes have tetrahedral geometry [21].

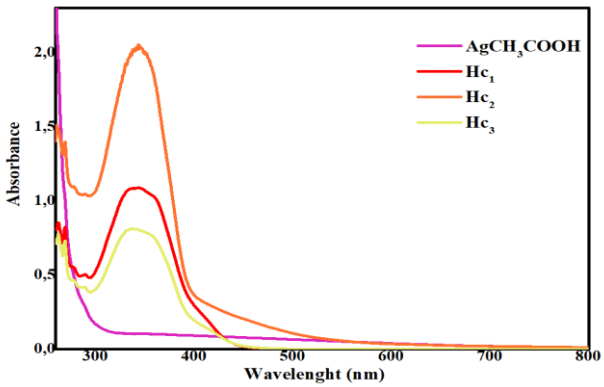


Figure 4. *UV-Vis spectra of the thiazole-based thiosemicarbazone Ag(I) complexes (**Hc_1**, **Hc_2**, **Hc_3**)*

B. BIOLOGICAL EVALUATION

The antimicrobial activity data for the thiazole-based thiosemicarbazone Ag(I) complexes (**Hc_1**, **Hc_2**, **Hc_3**) are presented in Table 3 and are shown in Figure 5. The thiosemicarbazone Ag(I) complexes were evaluated *in vitro* for the antifungal and antibacterial activities against selected disease-causing pathogenic strains. In the well-diffusion method, *Micrococcus luteus ATCC9341*, *Staphylococcus epidermidis* ATCC12228, and *Bacillus cereus* RSKK863 were used as Gram (+) bacteria. *Pseudomonas aeroginosa* ATCC27853, *Klebsiella pneumonia* ATCC27853, *Enterobacter aerogenes* ATCC51342, *Salmonella typhi H* NCTC9018394, *Shigella dysenteria* NCTC2966, and *Proteus vulgaris* RSKK96026 were used as Gram (-) bacteria. *C. albicans* was used as yeast. Additionally, pathogenic microorganisms and yeast were compared with standard antibiotics (Ampicillin, Kanamycin, Sulphamethoxazole, Amoxicillin) and anticandidal (Nystatin).

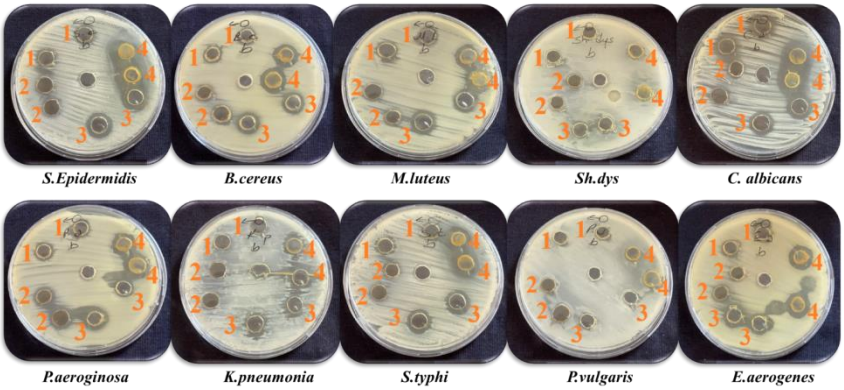
The thiazole-based thiosemicarbazone Ag(I) complexes (**Hc_1**, **Hc_2**, **Hc_3**) exhibited different antibacterial and antifungal activity. All Ag(I) complexes, **Hc_1** (15 mm), **Hc_2** (16 mm), and **Hc_3** (20 mm) exhibited the highest antibacterial activity against *P. aeroginosa* than all standard antibiotics (AMP10, SXT25, AMC30, K30). *P. aeroginosa* is an opportunistic pathogen responsible for burn injuries, urinary tract infections [22-24]. Among gram (-) bacteria, **Hc_3** (20 mm) showed the highest inhibitory effect against *P. aeroginosa.* Among gram (+) bacteria, **Hc_3** (18 mm) showed the highest inhibitory effect against *S. epidermidis.* It is a pathogen that causes some infections (septicemia, endocarditis, *etc.*) [25]. **Hc_1** (16 mm) also exhibited the highest antibacterial activity against *M. Luteus*. It is a bacteria that causes bloodstream infections [26]. **Hc_1** (20 mm) showed the highest antifungal activity against *C. albicans.* The complex exhibited as much antifungal activity as standard antibiotic NYS10. *C. albicans* is a fungus that causes infections in the gastrointestinal tract and bloodstream [27].

Table 3. *Antimicrobial activities of the thiazole-based thiosemicarbazone Ag(I) complexes (diameter of zone of inhibition (mm)).*

Microorganisms	**Compounds**			**Positive control**			
	Hc_1	**Hc_2**	**Hc_3**	AMP10	SXT25	AMC30	K30
M. luteus	16	13	16	22	21	25	23
S. epidermidis	15	11	18	26	25	27	25
B. cereus	13	12	15	23	25	20	28
P. aeroginosa	15	16	20	8	18	15	14
K. pneumonia	11	-	16	21	20	21	23
E. aerogenes	15	12	18	21	19	20	24
S. typhi H	13	12	15	11	17	19	20
S. dysenteria	10	10	11	10	18	14	25
P. vulgaris	10	10	11	17	19	20	21
				NYS10			
C. albicans	20	11	16	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.

According to the biological evaluation results, it was determined that thiazole-based thiosemicarbazone Ag(I) complexes had high or moderate antibacterial and antifungal effects. Based on these results, it can be said that newly synthesized thiosemicarbazone Ag(I) complexes can be used as powerful antimicrobial agents in various biomedical applications.



[1][Hc_1], [2][Hc_2], [3][Hc_3], [4][$AgCH_3COOH$]

Figure 5. *Photographs of inhibition zones (mm) of some Gram (+) and Gram (-) bacteria and yeast*

IV. CONCLUSION

In the work, novel heterocyclic thiazole-based thiosemicarbazone Ag(I) complexes were synthesized to investigated their *in vitro* antibacterial and antifungal efficacy. The synthesized thiosemicarbazone Ag(I) complexes were characterized by various spectroscopic techniques. Biological assessments were performed using the well-diffusion method against pathogenic strains. The results demonstrated that the thiosemicarbazone Ag(I) complexes had high/or moderate antimicrobial efficacy. In conclusion, novel thiazole-based thiosemicarbazone Ag(I) complexes can be suggested as potential agents to be evaluated in relevant fields (such as pharmaceuticals, medicinal chemistry, biology, *etc.*) due to their biological activities.

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