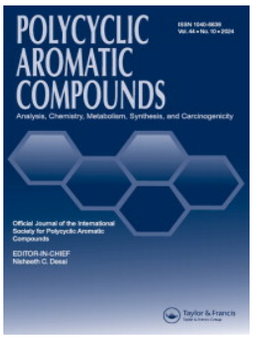

Polycyclic Aromatic Compounds

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Synthesis and *in Vitro* Antimicrobial Evaluation of Novel Potent Bioactive Heterocyclic Compounds

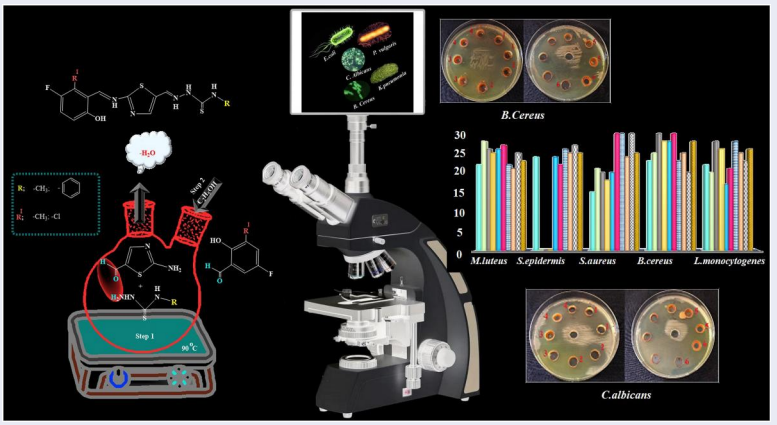
Ahsen Zeynep Macit[a], Elvan Hasanoğlu Özkan[b], Hatice Ogutcu[c], and Dilek Nartop[d]

[a]Department of Chemistry, Graduate School of Natural and Applied Sciences, Düzce University, Düzce, Turkey; [b]Department of Chemistry, Gazi University, Teknikokullar, Turkey; [c]Department of Field Crops, Kırşehir Ahi Evran University, Kırşehir, Turkey; [d]Department of Chemistry, Düzce University, Düzce, Turkey

ABSTRACT

In the present work, the antibacterial and antifungal properties of six new heterocyclic Schiff bases (HSb_1, HSb_2, HSb_3, HSb_4, HSb_5, HSb_6) were evaluated as potential bioactive compounds against the disease-causing pathogenic microorganisms (*S.epidermidis, S.aureus, B.cereus RSKK863, E.aerogenes, P.aeroginosa sp., K. pneumonia, S. type H, P.vulgaris, E. coli* and (*C.albicans Y-1200-NIH*). The well-diffusion-method was used to determine the antimicrobial activity. For this purpose, heterocyclic Schiff bases were synthesized by condensation reaction of aldehyde derivatives and thiosemicarbazide derivatives. Spectral analysis techniques (organic elemental analysis, FT-IR,^{1}H-NMR, HRMS, SEM-EDX) were used to characterize the synthesized compounds. It was determined that all the newly synthesized heterocyclic Schiff bases exhibited sound, high or moderate inhibitory effects on the growth of selected different standard antibiotics.

GRAPHICAL ABSTRACT



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KEYWORDS
heterocyclic compounds; schiff bases; biological activity; pathogenic strains; thiazole

Introduction

Investigation of new bioactive compounds with different molecular structure, conformation, effect mechanisms, solubility, stability, selectivity, and flexibility is extremely important for medicinal chemistry.[1] Heterocyclic compounds containing oxygen, nitrogen, and sulfur are of particular

CONTACT Elvan Hasanoğlu Özkan ehasanoglu@gazi.edu.tr Department of Chemistry, Gazi University, Teknikokullar, Turkey; Dilek Nartop dileknartop@duzce.edu.tr Department of Chemistry, Düzce University, Düzce, Turkey

interest for the development of potential bioactive agents. Due to their structures, these compounds are useful in drug development and design.[2,3] Heterocyclic compounds are essential for their therapeutic, cytotoxic, biological and pharmacological activities.[4–6] They have hypnotic and analgesic effect drug properties.[7,8] Heterocyclic compounds have a broad spectrum of biological activity, such as antibacterial, anti-cancer, anti-inflammatory, antimalarial, anti-tubercular, antifungal, and anti-HIV.[9,10] Heterocyclic compounds bearing thiazole moiety are biologically active compounds as chemotherapeutic agents.[11–13] Some thiazole-based compounds are tyrosine kinase enzyme inhibitors.[14] Thiazole heterocyclics can be used as a pro-apoptotic drug for cancer treatment.[15] Especially, the heterocyclic compounds containing azomethine have important antimicrobial, antitumor, antioxidant activities due to the -CH = N bond. Heterocyclic azomethines, known as heterocyclic Schiff bases, exhibit various physical, chemical, biological, pesticidal, optical, electrochemical, and photochromic properties.[16] Heterocyclic Schiff bases are used in some appications as catalysts, dyes, chemosensors, pigments, and polymer stabilizers.[17–21] Heterocyclic Schiff bases also show corrosion inhibition, DNA cleavage efficiency, fluorescence, and photoluminescence activities.[22,23] Heterocyclic compounds possess impressive biological activity due to aromaticity of the ring.[24,25] They exhibit a broad spectrum of biological activities such as antibacterial, antifungal, anti-inflammatory, antioxidant, anticancer, anti-plasmodial, and anti-depressant activities.[26,27] Developing new bioactive compounds with high potential in pharmaceutical, medicinal, and chemotherapeutic research is extremely important due to the antimicrobial resistance.

For this reason, synthesis and antimicrobial evaluation of potent bioactive heterocyclic Schiff bases containing thiazole are reported.

Material and methods

Chemicals and devices

All materials were purchased from Sigma&Aldrich or Merck. Infrared spectra (IR) were determined with a Shimadzu IR Prestige-21 spectrophotometer at 400 to 4000 cm^{-1}. Nuclear magnetic resonance spectrophotometer (^{1}H-NMR) spectra were taken with a Bruker Biospin brand Avance III 400 MHz model device. Energy dispersive X-ray (SEM&EDX) images and Scanning electron microscopy were obtained using a Quanta-FEG-250 device. High resolution mass spectrometer (HRMS) analyses were performed with a Waters brand SYNAPT G1 MS model device. Elemental analyses were recorded by a Thermo-Scientific-Flash-2000 model elemental analyzer.

General procedure for synthesis of heterocyclic Schiff bases

The general method used to prepare all the heterocyclic Schiff bases containing thiazole was depicted in Figure 1. Recently, **HSb_1** and **HSb_2** heterocyclic Schiff bases were reported to us.[28] Herein, novel heterocyclic Schiff bases **(HSb_3, HSb_4, HSb_5, HSb_6)** were synthesized from thiazole derivatives, thiosemicarbazide derivatives, and benzaldehyde derivatives by template method. A solution of 2-aminothiazole-5-carboxaldehyde (4 mmol) in ethanol (50 mL) was dissolved, and a solution of 4-methyl-3-thiosemicarbazide/or 4-phenylthiosemicarbazide in ethanol (10 mL) was added to aldehyde solution. The mixture was stirred and heated for 4 *h* under reflux at 90 °C. The pH of the solution was adjusted to 5-5.5 by adding 1 mL of CH_3COOH. A solution of 5-fluro-2-hydroxy-3-methylbenzaldehyde/or 3-chloro-5-fluoro-2-hydroxybenzaldehyde (4 mmol) in ethanol (5 mL) was then added to the mixture and stirred for a further 2 *h* under the reflux. The solution was cooled to room temperature (25 °C), purified, filtered, and colored product was obtained.

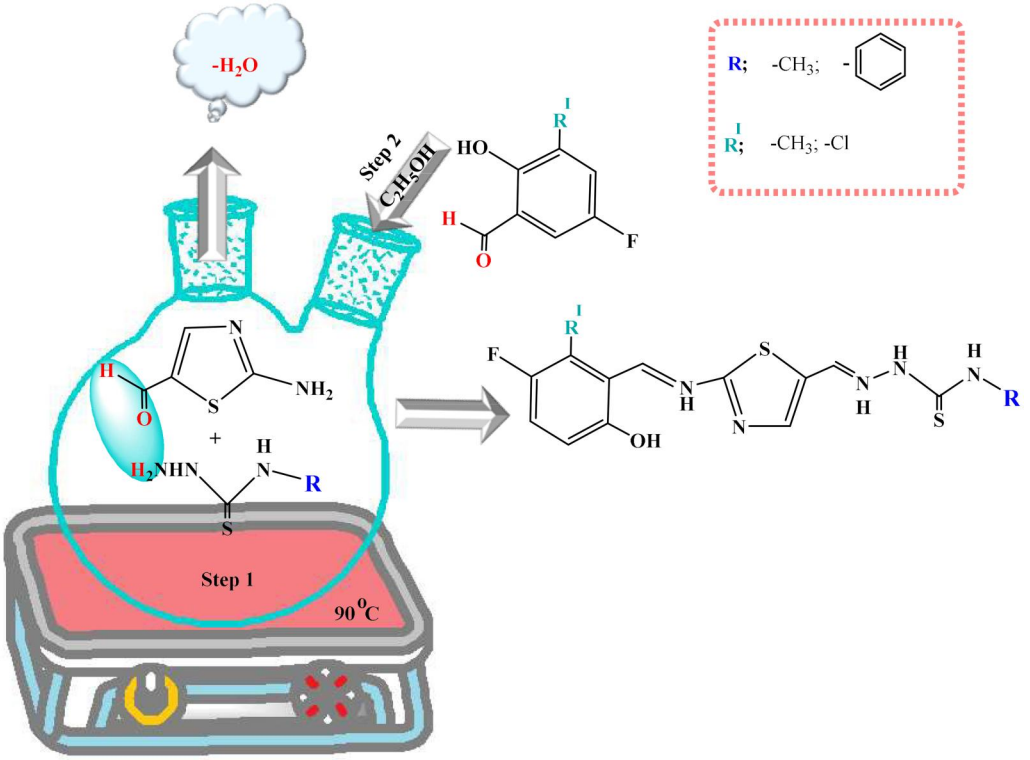

Figure 1. Reaction scheme of heterocyclic Schiff bases (HSb_1, HSb_2, HSb_3, HSb_4).

Antimicrobial assessment

The antifungal and antibacterial activities of the heterocyclic Schiff bases were screened against pathogenic bacterial strains (*Proteus vulgaris* RSKK96026, *Staphylococcus epidermidis* ATCC12228, *Micrococcus luteus-ATCC9341*, *Bacillus cereus* RSKK863, *Listeria monocytogenes* ATCC19115, *Staphylococcus aureus* ATCC25923, *Klebsiella pneumonia* ATCC27853, *Salmonella typhi H*-NCTC9018394, *Pseudomonas aeroginosa* ATCC27853) and fungal strain (*Candida albicans* Y-1200-NIH) by the well-diffusion-method.[29] In this method, DMF (dimethylformamide) was used as solvent control, and was detected that it had no antimicrobial activity against any of the tested organisms. All the thiazole-based thiosemicarbazones were dissolved (3.5 µg/mL) in DMF. Pathogenic microorganisms were incubated in Nutrient Broth Agar (10^6CFU/mL) for 24 *h* at 37 °C. Afterwards, these cultures were homogenized by adding to Mueller-Hinton Agar (MHA) cooled to 45 °C and poured into sterile-petri-dishes. The thiazole-based thiosemicarbazones were then introduced after 6 mm diameter wells in these agars were punctured. The zones of inhibition for each chemical were assessed after the plates had been incubated in the oven for 24 *h* at 37 °C, and the average of the activity levels obtained after two repeats were taken.

In addition, pathogenic bacteria cultures and yeast were compared with standard antibiotics: SXT25 (Sulphamethoxazole), AMP10 (Ampicillin), AMC30 (Amoxicillin), K30 (Kanamycin) and NYS100 (Nystatin). Gram (+) and Gram (-) bacteria were compared with AMP10, SXT25, AMC30, K30 antibiotics, and yeast was compared with NYS100 antibiotic.

Table 1. Elemental analyses, some analytical and physical data and of heterocyclic Schiff bases.

			Elemental analysis (calc.) %			
Compound	Chemical Formula	Color / Yield (%)	C	H	N	S
HSb_1	$C_{14}H_{14}N_5S_2OF$ (351)	Cinnamon color / 75%	48.92 (49.14)	3.05 (3.02)	20.94 (21.28)	17.23 (16.89)
HSb_2	$C_{13}H_{11}N_5S_2OFCl$ (372)	Burgundy / 91%	39.87 (39.71)	3.96 (3.89)	16.82 (16.95)	19.20 (19.38)
HSb_3	$C_{19}H_{16}N_5S_2OF$ (413)	Dark gold / 94%	54.13 (54.04)	3.88 (3.11)	17.95 (18.97)	17.50 (17.37)
HSb_4	$C_{18}H_{13}N_5S_2OFCl$ (434)	Mustard color / 87%	51.63 (52.23)	4.00 (4.51)	17.13 (17.54)	16.75 (16.92)

Table 2. FTIR Vibration frequencies (cm^{-1}) of heterocyclic Schiff bases.

Compound	ν(OH)	$\nu(CH)_{aro.}$	$\nu(CH=N)/\nu(CH=N)_{tyz..}$	$\nu(C=C)$	$\nu(C=S)$	ν(C-S-C)	ν(N–N)/ ν(N–H)
HSb_1	3370	3003	1552	1502	1253	777	1042
			1530		868		3146
HSb_2	3387	2986	1553	1504	1258	768	1098
			1535		862		3129
HSb_3	3337	2976	1595	1518	1261	777	1040
			1546		851		3140
HSb_4	3339	2974	1595	1517	1203	748	1082
			1549		856		3138

Results and discussion

Characterization of heterocyclic Schiff bases (HSb_1, HSb_2, HSb_3, HSb_4)

Some analytical findings and elemental analysis results of heterocyclic Schiff bases containing thiazole are given in Table 1. It was seen that the elemental analyses and the chemical formulas of the compounds were compatible.

The importance FT-IR spectrum data for heterocyclic Schiff bases containing thiazole are shown in Table 2 and Figure 2. For all heterocyclic compounds, stretching vibrations of the azomethine ($\nu CH=N$) groups formed by the condensation of aldehydes and amines appeared in the 1552–1595 cm^{-1} and 1530–1549 cm^{-1} ranges, respectively. First $\nu CH=N$) absorption bands appeared in the 1552–1595 cm^{-1} ranges, resulting from adding 2-aminothiazole-5-carboxaldehyde to thiosemicarbazides. The second $\nu CH=N)_{tyz.}$ bands in the 1530–1549 cm^{-1} ranges were formed by the condensation of benzaldehydes and thiosemicarbazones. The bands detected in the region of 748-777 cm^{-1} were assigned to the stretching vibrations of ν(C-S-C) belonging to the thiazole groups. ν(OH), ν(CH), and $\nu(C=C)$ absorption bands belonging to the aromatic ring were observed in the 3337–3387 cm^{-1}, 2974-3003cm^{-1} and 1502–1518cm^{-1} ranges, respectively. The stretching vibrations of ν(N-N) and ν(N-H) occurred in the regions 1040–1098 cm^{-1} and 3129–3146 cm^{-1}, respectively. Also, $\nu(C=S)$ vibrations obtained in the range of 851–868 cm^{-1} and 1203–1261 cm^{-1}, respectively.[30,31]

Importance ^{1}H-NMR spectrum data for heterocyclic Schiff bases containing thiazole are shown in Table 3 and Figure 3. Asymmetric azomethine ($CH=N$) bands obtained by the condensation reaction of aldehydes and amines were observed in the range of 8.18–9.52 and 9.50–9.68 ppm, respectively. Due to the different chemical environments of NH protons, the ^{1}H-NMR spectra of all heterocyclic Schiff bases displayed two signals. For HSb_1 and HSb_2, (N-NH and Me-NH) peaks were observed in the 11.24–11.72 and 10.68–11.43 ppm ranges, respectively. For HSb_3 and HSb_4, (N-NH and Ph-NH) peaks appeared in the range of 11.63–11.95 and 10.63–10.68 ppm, respectively. The phenolic protons (Ar-OH) and aromatic protons (Ar-H) were observed in the regions 10.05–10.16 and 7.00–8.55 ppm, respectively. Additionally, the bands at 1.91 ppm belonging to

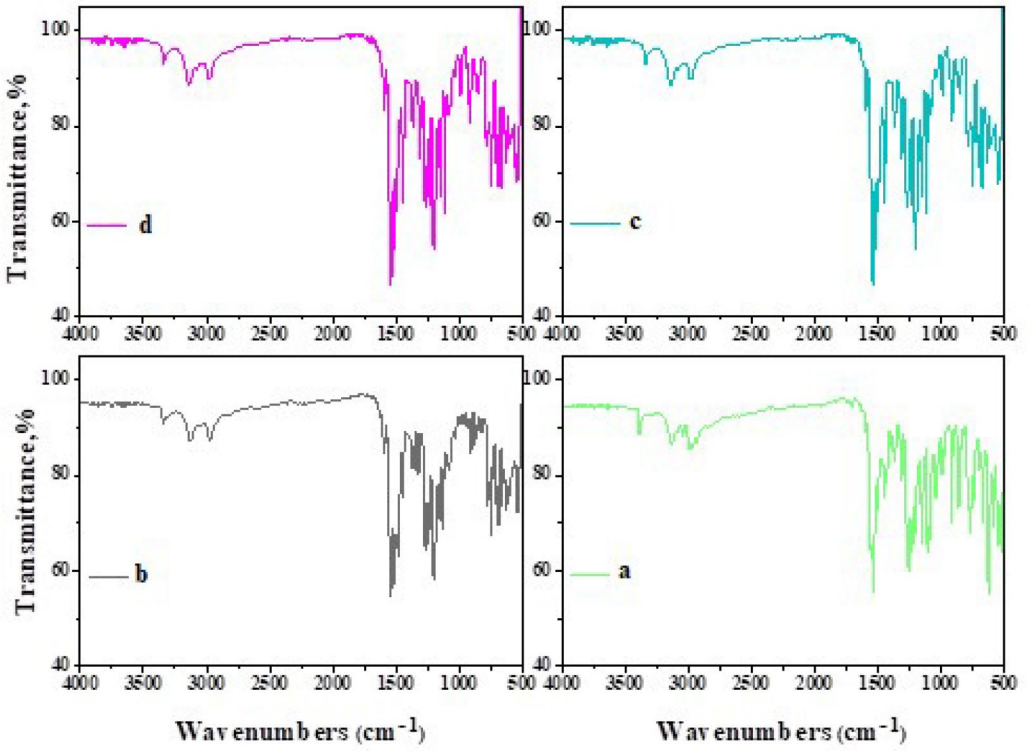

Figure 2. FTIR spectrums of heterocyclic Schiff bases (a) HSb_1 (b) HSb_2 (c) HSb_3 (d) HSb_4.

Table 3. ^{1}H-NMR chemical shift (ppm) of heterocyclic Schiff bases.

Compound	N-NH	Me-NH	Ph-NH	Ar-OH	CH = N	Ar-H	HN-CH_3/ Ar-CH_3
HSb_1	11.24	10.68	–	10.05	9.50, 9.00	7.00–8.55	1.91 / 1.06
HSb_2	11.72	11.43	–	10.16	9.68, 9.52	7.31–8.42	1.91 / -
HSb_3	11.63	–	10.68	10.06	9.59, 8.18	7.10–7.68	- / 2.09
HSb_4	11.95	–	11.63	10.16	9.58, 8.18	7.16–7.80	- / -

methyl protons (HN-CH_3) were detected for HSb_1 and HSb_2. The methyl proton (Ar-CH_3) was also determined at 1.06 and 2.09 ppm for HSb_1 and HSb_3.[32,33]

SEM-EDX analysis data for heterocyclic Schiff bases containing thiazole are given in Figure 4. It was determined that the heterocyclic Schiff bases have a crystal structure (such as rod-shaped, cluster-shaped, cloud-shaped, or porous) in small particles with the SEM image, which gives information about the morphology. Also, the EDX analysis data supported the chemical composition of the heterocyclic Schiff bases (C, N, O, F, S, Cl)

HRMS spectrum results for heterocyclic Schiff bases containing thiazole are given in Table 4. The values of the molecular ion peaks and the fragmentation products are compatible with the heterocyclic Schiff base structures that have been postulated. The molecular ion peaks were obtained at the predicted values of m/z: 352.07 $[M+H]^+$, 372.02 $[M]^+$, 414.09 $[M+H]^+$, and 432.02 $[M\text{-}2H]^+$ for HSb_1, HSb_2, HSb_3 and HSb_4, respectively. The fragmentation peaks at m/z; 341.31 (HSb_1), m/z; 353.27 (HSb_2), m/z; 381.30 (HSb_3), and m/z; 418.98 (HSb_4), were attributed to the loss of the $[M\text{-}(CH_3)+4H]^+$, $[M\text{-}(CH_3)\text{-}4H]^+$, $[M\text{-}(CH_4O)]^+$, $[M\text{-}(OH)+2H]^+$.

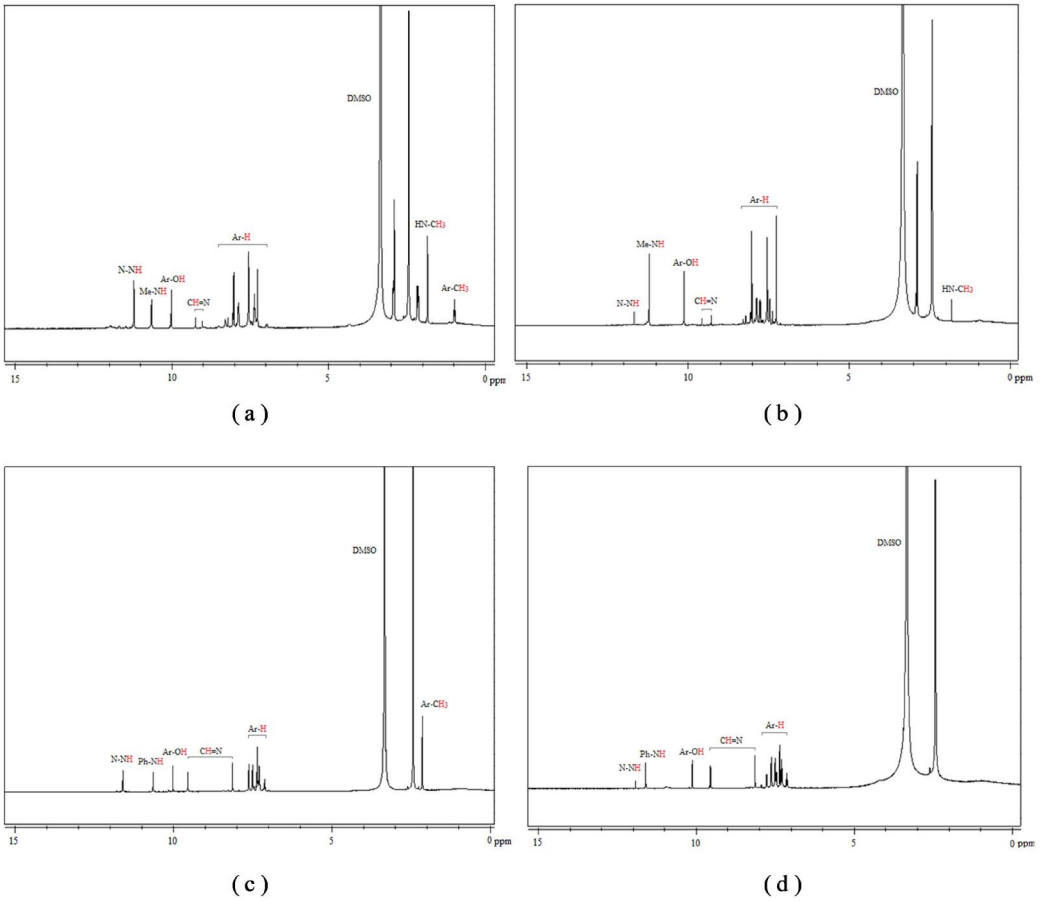

Figure 3. ^{1}H-NMR spectrums of heterocyclic Schiff bases (a) HSb_1 (b) HSb_2 (c) HSb_3 (d) HSb_4.

The photographs of inhibition regions of pathogenic bacteria for the biological activity of heterocyclic Schiff bases containing thiazole are shown in Figure 5. The graphical illustration of pathogenic bacteria for the biological activity of heterocyclic Schiff bases containing thiazole are shown in Figures 6 and 7. The antibacterial effectiveness of the heterocyclic compounds against several pathogenic strains that cause disease was examined *in vitro*. The results of antibacterial screening indicated that the heterocyclic Schiff base compounds showed varying degrees of efficacy in inhibiting the activities of the tested pathogenic strains. HSb_2 (30 mm), HSb_3 (28 mm), HSb_4 (30 mm) and HSb_6 (28 mm) exhibited the highest antibacterial activity against *B. cereus* in Gram-positive bacteria. *B. Cereus* is a bacterium that causes diarrhea, vomiting, and eye infections.[34] HSb_4 (30 mm) also showed a high inhibitory effect against *S. aureus,* another Gram-positive bacteria. *S. aureus* is a pathogen responsible for bacterial infections such as pulmonary and urinary tract infections.[35] HSb1 (28 mm), and HSb_5 (24 mm), exhibited the highest activity against *M. luteus* and *S. Epidermis*, respectively. *M. luteus* is an opportunistic pathogen that causes infections such as skin and fungi in patients with compromised immune systems.[36] *S. epidermis* is an opportunistic microorganism that causes infections, especially in patients with an intravascular device.[37] HSb_1, HSb_2, and HSb_6 did not show inhibitory effect against *S. epidermis* in Gram-positive bacteria. HSb_1 (30 mm) showed the highest inhibition activity against *K. pneumonia* in Gram-negative bacteria. *K. pneumonia* is responsible for causing some diseases such as biliary tract infections, gastrointestinal tract, and urinary infections.[38] HSb_2 (31 mm) and HSb_5 (28 mm)

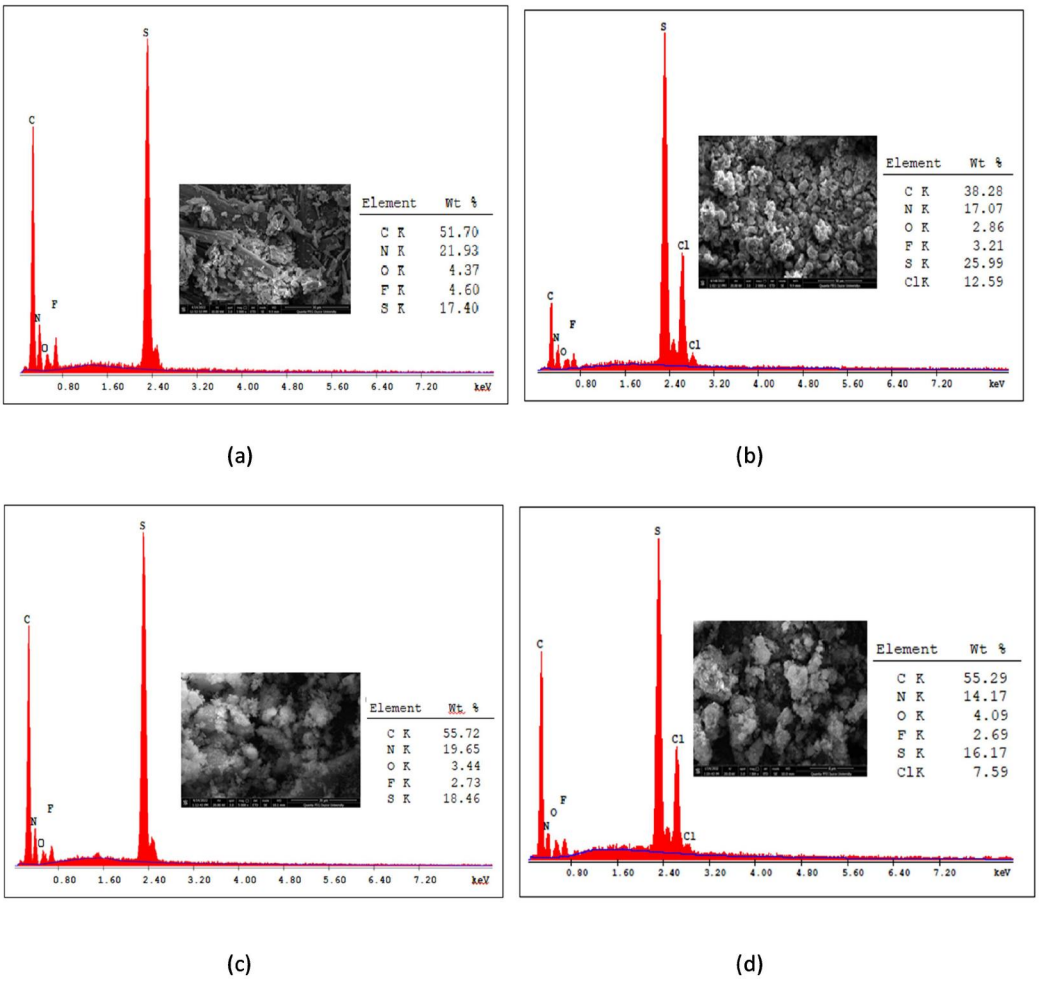

Figure 4. SEM-EDX analysis data for heterocyclic Schiff bases (a) HSb_1 (b) HSb_2 (c) HSb_3 (d) HSb_4.

Table 4. HRMS spectral data for heterocyclic Schiff bases.

Compound	m/z	Peak
HSb_1	352.07	$[M+H]^+$
HSb_2	372.02	$[M]^+$
HSb_3	414.09	$[M+H]^+$
HSb_4	432.02	$[M\text{-}2H]^+$

exhibited the highest antibacterial effect against *S. typhi*. It is a pathogen that causes enteric fever (typhoid).[29] HSb_3 (25 mm) showed the highest inhibitory effect against *P. vulgaris*. It is a bacterium responsible for some infections (burns, abscesses, diarrhea, meningitis) seen in people with compromised immune systems.[39] HSb_4 (29 mm) and HSb_6 (32 mm) exhibited the highest activity against *P. aeruginosa*. It is a pathogen associated with otitis media, urinary tract infections, burn infections, and bloodstream infections.[40] In all compounds, HSb_6 showed the highest inhibitory effect against gram-negative bacteria *P. aeroginosa*. The effects of all heterocyclic Schiff base compounds against yeast *C. albicans* were compared with standard antibiotic nystatin. All heterocyclic compounds were more effective than nystatin. HSb_2 (31 mm) showed the highest antifungal

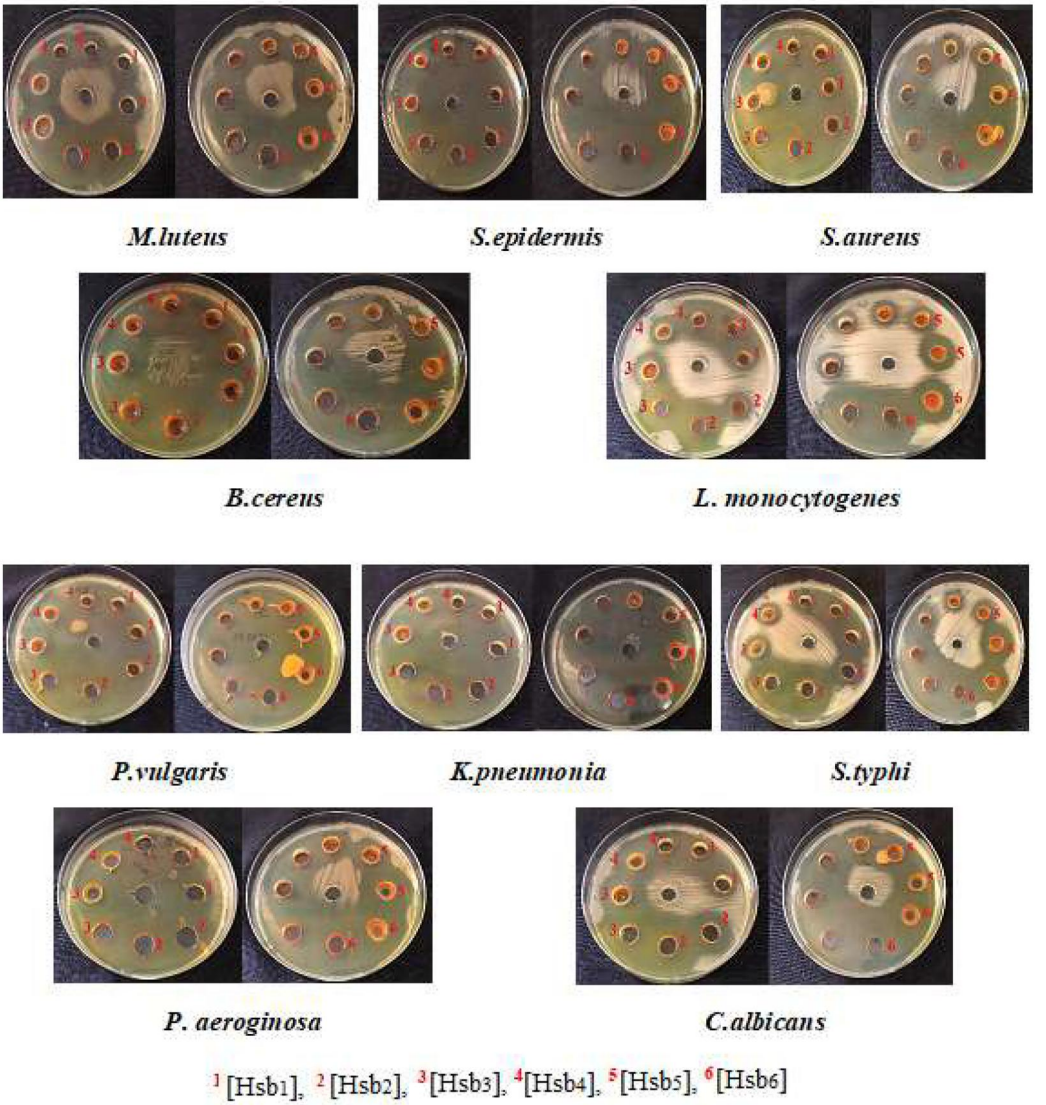

Figure 5. Photographs of inhibition zones (mm) of some Gram (+) and Gram (-) bacteria.

activity among them. *C. albicans* is an opportunistic pathogen that causes nosocomial bloodstream infections.[41]

According to the results, it was determined that all heterocyclic Schiff base compounds exhibited good antifungal and antibacterial activity against selected disease-causing pathogenic microorganisms. All heterocyclic compounds were found to be more effective against gram-negative bacteria than gram-positive bacteria. Compared to standard antibiotics, the highest inhibition effect was observed against Gram (-) bacteria *P. aeruginosa*, *P. vulgaris,* and Gram (+) bacteria *M. luteus.* It was seen that the antifungal and antibacterial activities of thiosemicarbazone compounds are associated with their structures, functional groups, and substituent types (electron withdrawing/or electron-donating). Based on the findings, it can be said that synthesized heterocyclic Schiff bases could be used as drugs for potential application in pharmacological and medicinal.

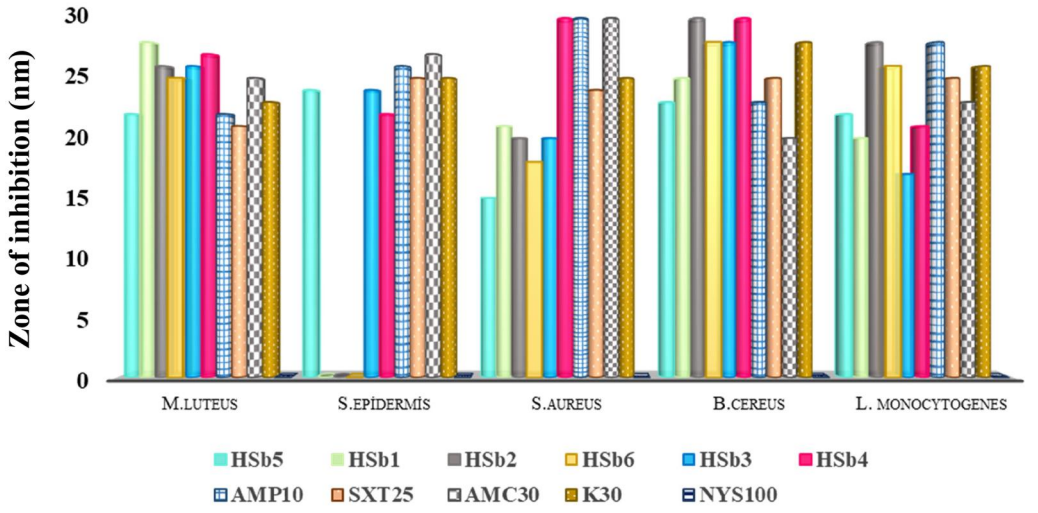

Figure 6. Graphical illustration of Gram (+) pathogenic bacteria and standard antibiotics.

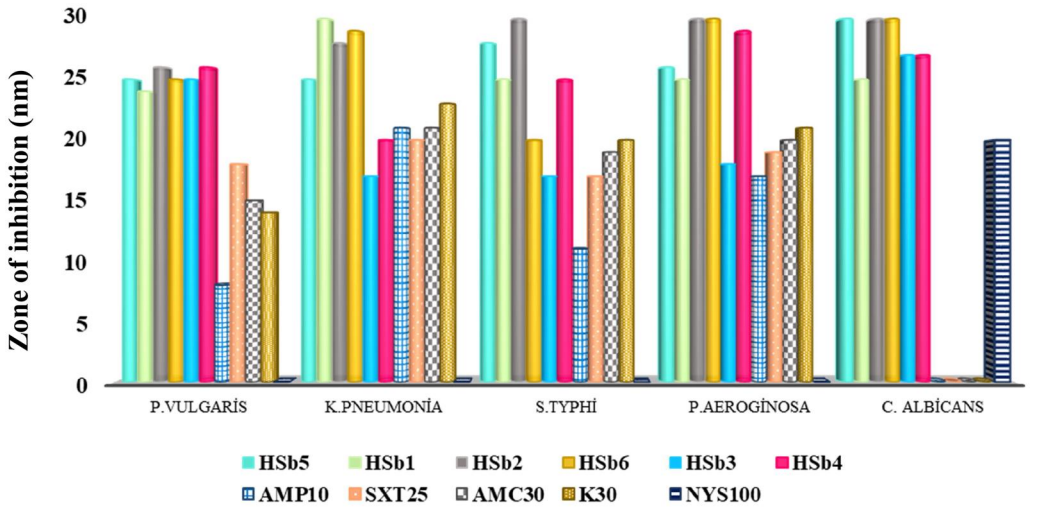

Figure 7. Graphical illustration of Gram (-) pathogenic bacteria and standard antibiotics.

Conclusions

The need for more effective and new antibiotics is increasing due to disease-causing pathogenic microorganisms becoming resistant to existing antibiotics over time. It has become important to search for new bioactive compounds with properties such as different molecular structure, efficacy, solubility, stability, selectivity. In this study, heterocyclic Schiff bases containing thiazole by condensation reaction were prepared and characterized by spectral analysis techniques to develop new bioactive compounds. The antimicrobial activity of synthesized heterocyclic compounds was examined using the well-diffusion method against selected pathogenic strains. It was determined that all the synthesized heterocyclic Schiff bases were more effective against disease-causing pathogenic microorganisms than standard antibiotics. The heterocyclic Schiff bases exhibited high or moderate antifungal and antibacterial activity. The results indicate that all the heterocyclic compounds can be recommended potential bioactive agents for biological, pharmacological, and medicinal applications.

Ethical approval

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

Authors' contributions

D. NARTOP designed the experiments and contributed to the interpretation of the results. A. Zeynep MACİT carried out the experiments depending on synthesis. D. NARTOP and E. HASANOĞLU ÖZKAN performed visualization, formal analysis, writing-original draft, writing-review & editing, H.OGUTCU carried out the antimicrobial assessment. The each author contributed to the final manuscript and discussed the findings.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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