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Synthesis And Pharmacological Evaluation Of Novel Thiazole Derivatives

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ABSTRACT

The design, synthesis, and assessment of novel thiazole derivatives' antibacterial properties are presented here. These compounds showed modest antibacterial activity, according to the in vitro study. Compound 3 had the highest activity, with MIC and MBC ranging from 0.25 to 0.1 and 0.49 to 0.96 mg/mL, respectively. Three compounds (b, c, and d) demonstrated greater potential than the reference medication ampicillin when tested against three resistant strains of P. aeruginosa, E. coli, and methicillin-resistant Staphylococcus aureus. The compounds' antifungal activity was superior, with MIC and MFC falling between 0.07 and 0.49 and 0.12 and 0.96 mg/mL, respectively. Compound I exhibited the highest activity, with a MIC of 0.06–0.25 mg/mL and an MFC of 0.13–0.49 mg/mL. Docking studies suggest that the compounds' antibacterial action may be due to their expected inhibition of the E. coli MurB enzyme, while their antifungal activity is most likely due to their inhibition of 14a-lanosterol demethylase.

Keywords: *Drug, Thiazole, Bacteria, fungi*

1. INTRODUCTION

The need to create novel antibacterial drugs is growing as a result of widespread resistance to traditional antibiotics. Numerous distinct thiazolidine-based compounds have been investigated to assess their pharmacological potential during the past few decades [1,2]. Since one or more nitrogen-based heterocycles are present in 75% of FDA-approved small-molecule medications, nitrogen-containing heterocyclic molecules are crucial to the drug development process. Thiazole, sometimes referred to as 1, 3-thiazole, is a member of the azole group of compounds that contains nitrogen and sulphur atoms in positions 1 and 3, respectively. [3] The thiazole nucleus, one of the most researched heterocycles, is essential to many physiologically active substances. An crucial part of many medication structures is 1,3-thiazole. Products that contain thiazoles

include ritonavir (anti-HIV medication), ravuconazole (antifungal agent), nitazoxanide (antiparasitic agent), fanetizole, meloxicam and fentiazac (anti-inflammatory agents), thiameth, tiazofurin and dasatinib (anti-neoplastic agents), and nizatidine (antiulcer agent). [4, 5]

The thiazole ring is one of these rings. Thiazole is a useful pharmacophore nucleus because of its many medicinal applications. [6] Antioxidant, analgesic, antibacterial, anticancer, antiallergic, antihypertensive, anti-inflammatory, antimalarial, antifungal, and antipsychotic are only a few of the numerous biological properties that its derivatives display. The thiazole scaffold is present in over 18 FDA-approved medications. [8, 9] This thiazole derivative was found to be effective against a range of multi-drug resistant Gram-negative bacteria, including Pseudomonas aeruginosa (P. aeruginosa), when no other choice is available. [10, 11, 12] Taking all of this information into account and based on our previous results, we designed and synthesized new derivatives incorporating thiazole molecule.

2. MATERIALS AND METHODS

Materials: The melting points are uncorrected and were measured using open capillaries on an electrothermal apparatus. On precoated silica-gel 60 F254 (Merck), thin-layer chromatography was carried out, and chemicals were visualised using iodine vapour or UV light at 254 and 365 nm. Using the ATR method, the IR spectra were captured on a Shimadzu FT-IR spectrometer. A Bruker AVANCE III (400 MHz) spectrometer was used to record the 1H and 13C NMR spectra in DMSO-d6. Chemical shifts downfield from Tetra-methylsilane (TMS) are represented in δppm as an internal standard. A direct input probe on a Shimadzu GCMS QP2010 Ultra mass spectrometer was used to record mass spectra. Every reaction was conducted in a natural setting. All reagents were purchased from Loba, Molychem, SRL and CDH and used without further purification.

General Procedure for the Synthesis of (E)-2-Amino-N'-benzylidene-4-methylthiazole-5-Carbohydrazide (3a-t): After stirring and heating to reflux temperature for one hour, a mixture of compound 2 (10 mmol) and substituted benzaldehyde (10 mmol) in 10 mL of MeOH and a catalytic quantity of glacial acetic acid was prepared. Following the completion of the reaction, the reaction mixture was allowed to cool to room temperature before being diluted with HCl and poured into ice-cold water. To obtain crystals (3a-t), the separated solid was filtered, cleaned with water, and refined by recrystallisation from DMF. [13]

General Procedure for the Synthesis of Ethyl (Z) - 3-((5-(2-((E)-arylidene) hydrazine-1-carbonyl)-4 – methylthiazol – 2 - yl) amino) – 2 - cyano-3-(methylthio) acrylate (4a-t): Anhydrous potassium carbonate (10 mmol) and 10 mL of DMF were combined with 3a-t (10 mmol) and ethyl 2-cyano-3,3-bis (methylthio) acrylate (10 mmol), and the mixture was agitated for one hour at room temperature. The reaction mixture was cooled to room temperature and then added to ice-cold water once the reaction was finished. To obtain pure compound (4a-t), the isolated material was filtered, cleaned with water, and refined by recrystallisation from DMF. [14]

General procedure for the synthesis of (Z) - 3 -((5-(2 - ((E) - 4 - arylbenzylidene) hydrazine-1-carbonyl) -4-methylthiazol-2-yl)amino)-2-cyano-3-(methylthio) Acrylic Acid (5a): For six hours, a combination of 10 mmol of 4a and 20 mmol of lithium hydroxide in 10 mL of THF: MeOH: H2O in a 3:1:2:1 ratio was swirled at room temperature. Following the reaction's conclusion, the reaction mixture was allowed to cool to room temperature before being placed in ice-cold water and acidified with diluted HCl. To obtain a pure compound (5a), the separated solid was filtered, cleaned with water, and refined by recrystallisation from DMF. [15, 16, 17]

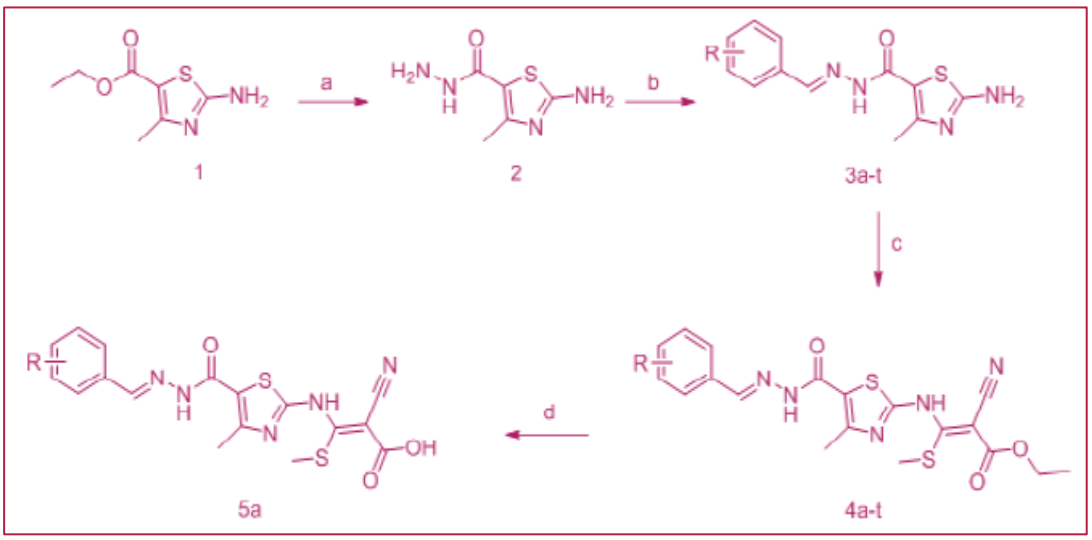
Ethyl (Z) - 3-((5-(2-((Z) – 4 - chlorobenzylidene) hydrazine – 1 - carbonyl) – 4 - methylthiazol- 2-yl) amino) – 2 - cyano -3-(methylthio)acrylate (4b): Yellow Solid, Yield: 67%, mp 211-212 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 12.81 (s, 1H), 9.88 (s, 1H), 7.7 (s, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H), 4.13 (d, J = 7.5 Hz, 2H), 2.54 (s, 3H), 2.33 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d6);184.56, 168.49, 165.73, 161.96, 155.58, 147.32, 136.58, 132.76, 131.93, 129.22, 127.78, 117.22, 95.47, 60.55, 17.34, 16.98, 15.04; MS (m/z): 471 (M+).Anal. Calcd. For $C_{19}H_{18}ClN_5O_3S_2$: C, 47.53; H, 3.56; N, 16.23; Found: C, 47.32; H, 3.49; N, 16.03.

Ethyl (Z) - 3-((5-(2-((Z) – 4 - bromobenzylidene) hydrazine – 1 - carbonyl) – 4 – methylthiazol - 2-yl) amino) - 2-cyano – 3 -(methylthio)acrylate (4c): Yellow Solid, Yield: 78%, mp 221-223 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.76 (s, 1H), 10.18 (s, 1H), 7.62 (s, 1H), 7.56 – 7.65 (m, 4H), 4.12 (d, J = 8.1 Hz, 2H), 2.54 (s, 3H), 2.33 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6); 112.32, 184.55, 165.13, 165.39, 143.75, 154.89, 154.21, 163.21, 132.98, 131.82, 128.91, 121.54, 95.50, 54.39, 15.44; MS (m/z): 511 (M+). Anal. Calcd. For C_{19}H18Br$N_5O_3S_2$: C, 45.67; H, 4.11; N, 12.33; Found: C, 44.32; H, 3.54; N, 13.64.

Ethyl (Z) – 2 – cyano – 3 - ((5-(2-((Z)-4-methoxybenzylidene) hydrazine -1-carbonyl)-4 methylthiazol-2-yl) amino) – 3 - (methylthio) acrylate (4d): Yellowish White Solid, Yield: 79%, mp 233-235°C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.65 (s, 1H), 11.12 (s, 1H), 7.67 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.3 Hz, 2H), 4.12 (s, 2H), 3.17 (s, 3H), 2.76 (s, 3H), 2.33 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6); 184.63, 167.11, 154.43, 149.98, 146.97, 135.32, 131.18, 129.54, 125.66, 119.11, 95.51, 76.55, 17.02, 11.54; MS (m/z): 463 (M+). Anal. Calcd. For $C_{20}H_{21}N_5O_4S_2$: C, 53.53; H, 5.53; N, 17.24; Found: C, 52.87; H, 4.87; N, 15.65.

Ethyl (Z) – 2 – cyano – 3 - ((4-methyl – 5 - (2-((Z)-4-nitrobenzylidene) hydrazine-1-carbonyl) thiazol-2-yl) amino)-3-(methylthio)acrylate (4h): Yellow Solid, Yield: 87%, mp 234-237 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.79 (s, 1H), 11.54 (s, 1H), 8.27 (d, J = 8.4 Hz, 2H), 8.11 (s, 1H), 8.65 (d, J = 8.3 Hz, 2H), 4.12 (d, J = 8.1 Hz, 2H), 2.75 (s, 3H), 2.63 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6); 187.63, 173.76, 165.43, 155.85, 149.654, 135.32, 135.18, 125.66, 95.51, 76.55, 35.64, 17.02, 15.55; MS (m/z): 475 (M^{+}).Anal. Calcd. For $C_{19}H_{18}N_6O_5S_2$: C, 48.09; H, 3.82; N, 17.71; Found: C, 48.01; H, 3.62; N, 17.60.

(Z) – 3 - ((5 - (2-((E) – 4 - chlorobenzylidene) hydrazine-1-carbonyl) – 4 – methylthiazol - 2-yl) amino) - 2 -cyano-3-(methylthio) acrylic acid (4i): White Solid, Yield: 62%, mp 256-257°C; 1H NMR (400 MHz, DMSO-d6) δ 12.22 (s, 1H), 12.80 (s, 1H), 11.88 (s, 1H),), 7.80 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 4.13 (d, J = 7.5 Hz, 2H), 2.54 (s, 3H), 2.33 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d6); 184.55, 183.13, 182.39, 174.75, 169.89, 167.21, 153.21, 129.68, 131.82, 128.91, 121.54, 95.50, 36.65, 11.76; MS (m/z): 435 (M+); Anal. Calcd. For $C_{17}H_{14}ClN_5O_3S_2$: C, 47.65; H, 4.85; N, 16.86; Found: C, 46.56; H, 4.65; N, 15.46.



Scheme 1: Thiazole derivatives

Antimicrobial activity

Antibacterial Action: Gram-positive bacteria Listeria monocytogenes (NCTC 432), Bacillus cereus (clinical isolate), Staphylococcus aureus (ATCC 3875), and Gram-negative bacteria Salmonella Typhimurium (ATCC 153411), Escherichia coli (ATCC 67510), and Enterobacter cloacae (clinical isolate) were employed. As previously mentioned, the minimal inhibitory and bactericidal (MIC/MBC) concentrations were established. [18, 19]

Antifungal Activity: Penicillium funiculosum (ATCC 83659), Trichoderma viride (IAM 6321), Aspergillus niger (ATCC 7065), Aspergillus fumigatus (ATCC 2532), Aspergillus versicolour (ATCC 10755), and Penicillium verrucosum var. cyclopium (food isolate) were the strains that were analysed. Every experiment was carried out three times. [20-22]

Inhibition of Biofilm Formation: The assays were carried out as previously mentioned. In short, a resistant strain of P. aeruginosa was cultured for 24 hours at 37 °C with the MIC and subMIC of the drugs under test in tryptic soy broth enhanced with 2% glucose. Following two rounds of washing with sterile PBS (pH 7.4), each well was fixed with methanol for ten minutes. After removing the methanol, the plate was allowed to air dry. 0.1% crystal violet (Bio-Merieux, France) was used to stain the biofilm for 30 minutes. After being cleaned with water and allowed to air dry, the wells were coloured using 96% ethanol (Zorka, Serbia). Thermo Scientific's Multiskan FC Microplate Photometer was used to detect the absorbance at 620 nm. [23-30]

3. RESULTS AND DISCUSSION

In an effort to identify new heterocyclic compounds, we present recently synthesised compounds using thiazole as their primary structural component. According to the molecules' 1H-NMR graph, the methyl proton of the ester was visible as a triplet peak at t 1.16-1.19 ppm (CH3), whereas the thiomethyl protons were visible as a singlet peak at s 2.33 ppm (SCH3). Ester methylene protons were observed at t 4.12-4.14 ppm (CH3), which were triplet peaks, while thiazole methyl protons were found at s 2.54-2.55 ppm (CH3) as a singlet. There was an aromatic area between 7.58 and 8.82 ppm. The solitary proton was indicated by a singlet peak observed at s 7.94-8.24 ppm (CH). Acetamide protons were detected as a singlet at s 12.79-12.83 ppm (NH), while thiazole NH protons were detected at s 11.71-11.91 ppm (NH). Downfield, acid hydrogen of

5a was found at 13.33 ppm (COOH). Several bases, including anhydrous potassium carbonate and triethylamine, were employed in various solvents, including methanol, ethanol, tetrahydrofuran, and acetonitrile, in order to enhance the experimental conditions for the production of molecules 4a-t. As a result, we discovered that using potassium carbonate with DMF accelerated the reaction of 3a-t with ethyl 2-cyano-3,3-bis(methylthio) acrylate and produced thiazole derivatives 4a-t with a good yield. **Antibacterial Activity:** Using a microdilution method to determine the minimal inhibitory and minimal bactericidal concentrations (MIC and MBC, respectively), synthesised compounds were evaluated for their antibacterial activity against a panel of six microorganisms. According to Table 1, the investigated compounds' antibacterial activity ranged from moderate to good, with MICs between 0.17 and >3.75 mg/mL and MBCs between 0.25 and >3.75 mg/mL. The following is a presentation of the activity order: c > b > i > d > e > g > h > a > f. Compound C had the highest action, with MIC and MBC of 0.23–0.70 mg/mL and 0.47–0.94 mg/mL, respectively.

It seemed that E. coli was the most resistant bacterium, whereas B. cereus was the most sensitive. With a MIC/MBC of 0.17/0.25 mg/mL, compound d demonstrated the highest activity among the compounds tested against E. coli, whereas compound I shown similarly strong activity against B. cereus and S. Typhimurium. In vitro, compounds a and h demonstrated action against E. cloacae with MIC and MBC of 0.25/0.49 mg/mL, compounds c and e against E. coli, while compound 3 demonstrated good activity against S. Typhimurium. These substances generally exhibited moderate to low activity.

Methicillin-resistant Staphylococcus aureus (MRSA), P. aeruginosa, and E. coli were the three resistant strains against which the three most active compounds (b, c, and d) were tested. The results showed that all three compounds were more effective against MRSA than ampicillin and streptomycin, which did not exhibit a bactericidal effect. No compound outperformed the reference medication against E. coli, although compound d appears to be more effective than ampicillin against P. aeruginosa strains (Table 2). The compounds' capacity to prevent the formation of biofilms was also assessed. Regretfully, no chemical exhibited strong action.

Table 1. Antibacterial activity of the compounds (MIC/MBC in mg/mL).

Compounds		***S.A.***	***B.C.***	***L.M.***	***E.C.***	***S.T.***	***E.C.***
a	MIC	0.71 ± 0.1	0.36 ± 0.03	0.36 ± 0.01	>3.75	>3.75	0.24 ± 0.01
	MBC	0.95 ± 0.23	0.48 ± 0.02	0.47 ± 0.01	>3.75	>3.75	0.49 ± 0.01
b	MIC	0.95 ± 0.23	0.48 ± 0.02	0.71 ± 0.03	0.37 ± 0.01	0.38 ± 0.01	0.37 ± 0.01
	MBC	1.91 ± 0.02	0.96 ± 0.01	0.96 ± 0.01	0.49 ± 0.01	0.49 ± 0.01	0.49 ± 0.01
c	MIC	0.71 ± 0.01	0.25 ± 0.01	0.71 ± 0.01	0.25 ± 0.01	0.25 ± 0.01	0.71 ± 0.03
	MBC	0.96 ± 0.02	0.49 ± 0.01	0.96 ± 0.01	0.49 ± 0.02	0.49 ± 0.01	0.96 ± 0.01
d	MIC	1.42 ± 0.04	0.71 ± 0.01	0.71 ± 0.02	0.19 ± 0.02	0.71 ± 0.06	0.72 ± 0.05
	MBC	1.90 ± 0.01	0.95 ± 0.02	0.95 ± 0.01	0.25 ± 0.01	0.96 ± 0.02	0.96 ± 0.03
e	MIC	1.43 ± 0.12	0.72 ± 0.03	0.72 ± 0.02	0.25 ± 0.01	0.49 ± 0.02	0.71 ± 0.01
	MBC	1.90 ± 0.02	0.96 ± 0.03	0.97 ± 0.02	0.48 ± 0.04	0.96 ± 0.02	0.94 ± 0.30
f	MIC	2.54 ± 0.32	1.43 ± 0.03	0.72 ± 0.09	0.71± 0.03	0.73 ± 0.3	0.73 ± 0.76
	MBC	3.54 ± 0.01	1.92 ± 0.02	0.96 ± 0.01	>3.75	0.96 ± 0.02	0.96 ± 0.02

g	MIC	1.42 ± 0.03	0.71 ± 0.01	0.71 ± 0.01	0.37 ± 0.01	0.71 ± 0.02	0.71 ± 0.02
	MBC	1.90 ± 0.23	0.96 ± 0.03	0.96 ± 0.04	0.49 ± 0.86	0.95 ± 0.05	0.96 ± 0.87
h	MIC	1.41 ± 0.38	0.47 ± 0.00	0.35 ± 0.09	0.75± 0.86	0.36 ± 0.09	0.25 ± 0.01
	MBC	1.91 ± 0.04	0.96 ± 0.02	0.49 ± 0.01	>3.75	0.49 ± 0.02	0.49 ± 0.02
i	MIC	0.96 ± 0.02	0.19 ± 0.02	0.38 ± 0.02	0.71 ± 0.23	0.32 ± 0.11	0.72 ± 0.03
	MBC	1.91 ± 0.02	0.25 ± 0.02	0.47 ± 0.02	0.96 ± 0.01	0.25 ± 0.02	0.96 ± 0.01
Streptomycin	MIC	0.25 ± 0.05	0.12 ± 0.01	0.15 ± 0.01	0.16 ± 0.01	0.19 ± 0.02	0.06 ± 0.01
	MBC	0.21 ± 0.01	0.07 ± 0.00	0.35 ± 0.01	0.28 ± 0.00	0.23 ± 0.01	0.09 ± 0.00
Ampicillin	MIC	0.12 ± 0.00	0.12 ± 0.00	0.15 ± 0.00	0.16 ± 0.00	0.18 ± 0.00	0.11 ± 0.00
	MBC	0.15 ± 0.00	0.11 ± 0.00	0.35 ± 0.02	0.27 ± 0.01	0.25 ± 0.00	0.12 ± 0.01

Table 2. Antibacterial activity and inhibition of biofilm formation against resistant strains (MIC/MBC in mg/mL)

Compound		***MRSA***	***P.A.***	***EC***	**MIC**	**0% MIC**
b	MIC	0.96 ± 0.01	0.25 ± 0.02	0.96 ± 0.01	15.64	8.23
	MBC	1.90 ± 0.01	0.49 ± 0.01	1.90 ± 0.01		
c	MIC	0.49 ± 0.02	0.25 ± 0.01	0.49 ± 0.01	21.43	9.56
	MBC	0.96 ± 0.01	0.49 ± 0.01	0.96 ± 0.01		
d	MIC	0.96 ± 0.01	0.25 ± 0.01	0.96 ± 0.01	6.23	-
	MBC	1.90 ± 0.02	0.49 ± 0.01	1.9 ± 0.01		
Strept	MIC	0.12 ± 0.01	0.07 ± 0.01	0.12 ± 0.01	72.21	57.65
	MBC	-	0.12 ± 0.02	0.28 ± 0.01		
Ampi	MIC	-	0.27 ± 0.01	0.28 ± 0.02	68.68	32.56
	MBC	-	-	-		

Antifungal Activity: The antifungal activity of synthesised thiazolyl derivatives (4a–4i) was assessed. The microdilution method was employed to determine the least inhibitory/fungicidal activity. Table 3 presents the results of the compounds' good antifungal efficacy. The following is a presentation of the synthetic chemicals' antifungal potency: h > i > a > c > e > b > d > f > g. With a minimum fungicidal concentration (MFC) of 0.11–0.49 mg/mL and a minimum fungicidal concentration (MIC) of 0.08–0.25 mg/mL, compound h exhibits the best antifungal activity, whereas compound g exhibits the lowest activity, with MFC of 0.49–0.96 mg/mL and MIC of 0.25–0.49 mg/mL.

Thus, the sensitivity of the most resistant strain, Aspergillus fumigatus, toward the compounds tested is c > e = h = i > a = b > d = f = g, while for the most susceptible one, which is Trichoderma viride, the susceptibility can be presented as i > h >

a = c > e= f > b = d > g. At MIC 0.2–1.0 mg/mL and MFC 0.3–1.5 mg/mL, respectively, ketoconazole shown antifungal potential, whereas bifonazole had MIC at 0.1–0.2 and MFC at 0.2–0.25 mg/mL, respectively. In addition to being nearly four times more effective than bifonazole and 29 times more effective than ketoconazole against T. viride, compounds h and i also demonstrated excellent activity against A. niger, A. versicolour, P. funiculosum, and P. cyclpoium var. verucosum, with MIC/MFC of 0.08/0.11 mg/mL and 0.11/0.25 mg/mL, respectively. Additionally, compounds a and c, as well as compounds b, e, and f, had good action against T. viride, with MIC and MFC of 0.11 mg/mL and 0.25 mg/mL, respectively, and MIC/MFC of 0.17/0.25 mg/mL, respectively. When it came to A. niger, compounds c, e, and h all had good efficacy; compound h was particularly effective against P. cyclpoium var. verucosum. With the exception of compounds d and g, it was found that practically all of the compounds showed more effectiveness against T. viride than ketoconazole. With the exception of P.v.c., where only three compounds (a, h, and i) were more active than ketoconazole, the majority of the compounds seemed to be more effective than ketoconazole against all fungi. It should be noted that the synthetic chemicals' antifungal activity is far superior to their antibacterial activity.

Table 3. Antifungal activity of thiazole derivatives. (MIC and MBC in mg/mL).

Compounds		***AF***	***AN***	***AV***	***PF***	***TV***	***PVC***
a	MIC	0.37 ± 0.03	0.09 ± 0.03	0.25 ± 0.02	0.19 ± 0.02	0.13 ± 0.01	0.19 ± 0.01
	MBC	0.49 ± 0.02	0.13 ± 0.01	0.49 ± 0.01	0.25 ± 0.01	0.25 ± 0.01	0.25 ± 0.01
b	MIC	0.37 ± 0.02	0.25 ± 0.00	0.37 ± 0.03	0.25 ± 0.00	0.17 ± 0.00	0.37 ± 0.03
	MBC	0.49 ± 0.02	0.49 ± 0.02	0.49 ± 0.02	0.49 ± 0.02	0.25 ± 0.00	0.49 ± 0.02
c	MIC	0.18 ± 0.00	0.12 ± 0.00	0.25 ± 0.00	0.25 ± 0.00	0.13 ± 0.00	0.37 ± 0.03
	MBC	0.25 ± 0.01	0.25 ± 0.01	0.47 ± 0.00	0.47 ± 0.00	0.25 ± 0.01	0.47 ± 0.00
d	MIC	0.49 ± 0.02	0.49 ± 0.02	0.25 ± 0.01	0.37 ± 0.03	0.25 ± 0.01	0.25 ± 0.01
	MBC	0.96 ± 0.01	0.96 ± 0.01	0.49 ± 0.02	0.49 ± 0.02	0.49 ± 0.02	0.49 ± 0.02
e	MIC	0.25 ± 0.01	0.06 ± 0.00	0.25 ± 0.01	0.25 ± 0.01	0.18 ± 0.01	0.18 ± 0.02
	MBC	0.49 ± 0.02	0.11 ± 0.00	0.49 ± 0.02	0.49 ± 0.02	0.25 ± 0.01	0.25 ± 0.01
f	MIC	0.49 ± 0.02	0.25 ± 0.01	0.49 ± 0.02	0.25 ± 0.01	0.17 ± 0.00	0.49 ± 0.02
	MBC	0.94 ± 0.00	0.49 ± 0.02	0.94 ± 0.00	0.49 ± 0.02	0.25 ± 0.01	0.94 ± 0.00
g	MIC	0.49 ± 0.02	0.25 ± 0.01	0.25 ± 0.01	0.49 ± 0.02	0.49 ± 0.02	0.25 ± 0.01
	MBC	0.96 ± 0.01	0.49 ± 0.02	0.49 ± 0.02	0.96 ± 0.01	0.94 ± 0.00	0.47 ± 0.00
h	MIC	0.25 ± 0.01	0.11 ± 0.00	0.11 ± 0.00	0.17 ± 0.00	0.08 ± 0.00	0.11 ± 0.00
	MBC	0.49 ± 0.02	0.25 ± 0.01	0.25 ± 0.01	0.25 ± 0.01	0.11 ± 0.00	0.25 ± 0.01

i	MIC	0.25 ± 0.01	0.17 ± 0.00	0.17 ± 0.00	0.17 ± 0.00	0.06 ± 0.00	0.17 ± 0.00
	MBC	0.49 ± 0.02	0.25 ± 0.01	0.25 ± 0.01	0.25 ± 0.01	0.11 ± 0.00	0.25 ± 0.01
Streptomycin	MIC	0.17 ± 0.00	0.17 ± 0.00	0.12 ± 0.00	0.22 ± 0.00	0.17 ± 0.00	0.12 ± 0.00
	MBC	0.20 ± 0.00	0.20 ± 0.00	0.22 ± 0.00	0.25 ± 0.00	0.22 ± 0.00	0.22 ± 0.00
Ampicillin	MIC	0.22 ± 0.00	0.22 ± 0.00	0.22 ± 0.00	0.22 ± 0.00	1.02 ± 0.01	0.22 ± 0.00
	MBC	0.52 ± 0.00	0.52 ± 0.00	0.52 ± 0.00	0.52 ± 0.00	1.52 ± 0.00	0.32± 0.01

4. CONCLUSION

This study synthesised three structural series of novel thiazole derivatives and assessed their antifungal and antibacterial properties against a range of bacterial and fungal diseases. The studied compounds have moderate to good antibacterial activity, with MICs ranging from 0.25 to >3.75 mg/mL and MBCs ranging from 0.35 to >3.75 mg/mL. With MIC/MBC values of 0.18/0.25 mg/mL, compounds d and i showed the strongest activity among the investigated compounds against E. coli and B. cereus and S. Typhimurium, respectively. When tested against three resistant strains of MRSA, E. coli, and P. artuginosa, the three most active compounds (b, c, and d) showed superior performance to the reference medications against MRSA, while compound d was also effective against P. aeruginosa. All of the compounds are active, according to the antifungal activity data, while compound h showed the highest activity, with MIC and MFC ranging from 0.08 to 0.25 and 0.11 to 0.49 mg/mL, respectively.

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