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In Vitro Evaluation of Antimicrobial Properties of Some Newly Synthesized S-Triazole Thioglycosides

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ABSTRACT

Backgrounds: Nowadays, the need for replacement of new drug structures is felt more than ever due to the spread of microbial resistance. S-triazoles are significant five-membered heterocyclic scaffolds due to their wide range of biological activities.

Materials & Methods: A new series of Schiff bases (5a-f) were synthesized by the reaction of 4-amino-S-triazoles (3a-c) with furan and benzaldehyde 4(d-e). Then a novel series of triazole thioglycosides (7a-f) were synthesized by the reaction of Schiff bases (5a-f) and T-O-acetyle-α-D-glucopyranosyle-Br in the presence of potassium carbonate as a weak base in acetone. The structure of the products was confirmed by FT-IR, H-NMR, and C-NMR assays. The antimicrobial properties of the newly synthesized compounds were studied against four bacterial strains, including *Bacillus cereus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*, and two fungal strains, including *Aspergillus niger* and *Candida albicans*.

Findings: The synthesized compounds exhibited better antifungal activity than antibacterial activity, espetially 7d. Among all the compounds, the compound 7d was found to have the highest activity against *C. albicans* with IZ=18±0.7 mm, MIC=250 mg/mL, and MFC= 250 mg/mL.

Conclusion: The present study results indicated that compounds containing S-triazole had the potential to be used in a wide variety of new antifungal formulations.

Keywords: Triazoles, Candida albicans, Drug resistance.

CITATION LINKS

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Introduction

Nowadays, there is a long list of drug-resistant microbes, including sulfonamide-resistant, penicillin-resistant, methicillin-resistant, macrolide - resistant, multicellular, and vancomycin-resistant microbes [1]. As a result, treatment of drug-resistant bacterial diseases requires large amounts of drugs and sedative treatments for a long time, which eventually leads to incremented mortality. In addition, the widespread and aimless use of powerful antibiotics in recent decades has led to the emergence of a large number of microbial resistances, which are currently considered as one of the most important concerns and serious threats to global public health [2]. In general, the classification of antibiotics is based on their mechanism of action, for example, interference with cell wall synthesis, interference with the cell proliferation cycle, and disruption of the cell cycle [3]. Considering the advances in recent decades, especially in the science of synthesis of pharmaceutical structures, it seems the main strategy against microbial resistance is to develop new drug structures. Nowadays, S-triazole core is considered as a significant moiety in the design and synthesis of bioactive compounds possessing many biological properties, including anti-microbial [4-5], antibacterial [6], antifungal [7], anti-HIV [8], anti-inflammatory [9], analgesic [10] and anticancer activities[11]. Fungal and bacterial infections have become a major challenge and an important cause of fatality. Based on these observations, S-triazole derivatives may be considered as possible candidates for use as safe antimicrobial agents. Thus, there is a need to prospect these pharmacophores for the extension of modern molecules with several activities. [12]. Schiff bases have attracted much interest due to their synthetic availability along with antibacterial [13-15] and antitumor [16] properties. The synthesis and verification of the biological activity of S-triazole glycosides have been motivated by the detection of Ribavirin [17]. It has been reported that coupling of carbohydrate derivatives to the S-triazole nucleus through a thioglycosidic linkage enhances its biological activities. Some novel S-β-D-glucosides of 5-aryl-S-triazole-3-thiones derivatives have been shown to exhibite biological activities [18].

Objectives: Due to mentioned findings, this study aimed to design potent antibacterial agents with S-triazole moieties, to synthesis some new substituted thioglycosides via the reaction of α-D- aceto- bromo- glucose with 4- amino- 5- alkyl- 4H- S-triazole- 3-thiol Schiff bases (5a-f), and to investigate the newly synthesized hybrid compounds (7a-f) in terms of biological activities such as antibacterial and antifungal effects.

Materials and Methods

This research was conducted in the chemical laboratories of Urmia University in collaboration with the Microbiology Laboratory of the Islamic Azad University, Tehran Branch in 2020. Starting materials, solvents, and culture environments (nutrient agar/broth, sabouraud dextroseand agar/broth) were obtained from Merck, Germany and used without any more filtration. FT-IR, as well as H-NMR and C-NMR spectra were recorded on Thermo Nicolet Nexus-670 and Bruker Avance-300MHz spectrometers, respectively. Thin layer chromatography (TLC) analyses were carried out on silica gel plates. All chemicals were purchased from Merck (Germany) and used according to standard procedures. Newly distilled solvents were used throughout the study, and anhydrous solvents were dried according to the method reported by Perrin and Armarego (1988) [19]. All bacterial and fungal strains were prepared f rom the Iranian Industrial Microorganisms Collection Center (Lyophilized). Microbio logical tests were performed using a Memmert- INC153T2T3

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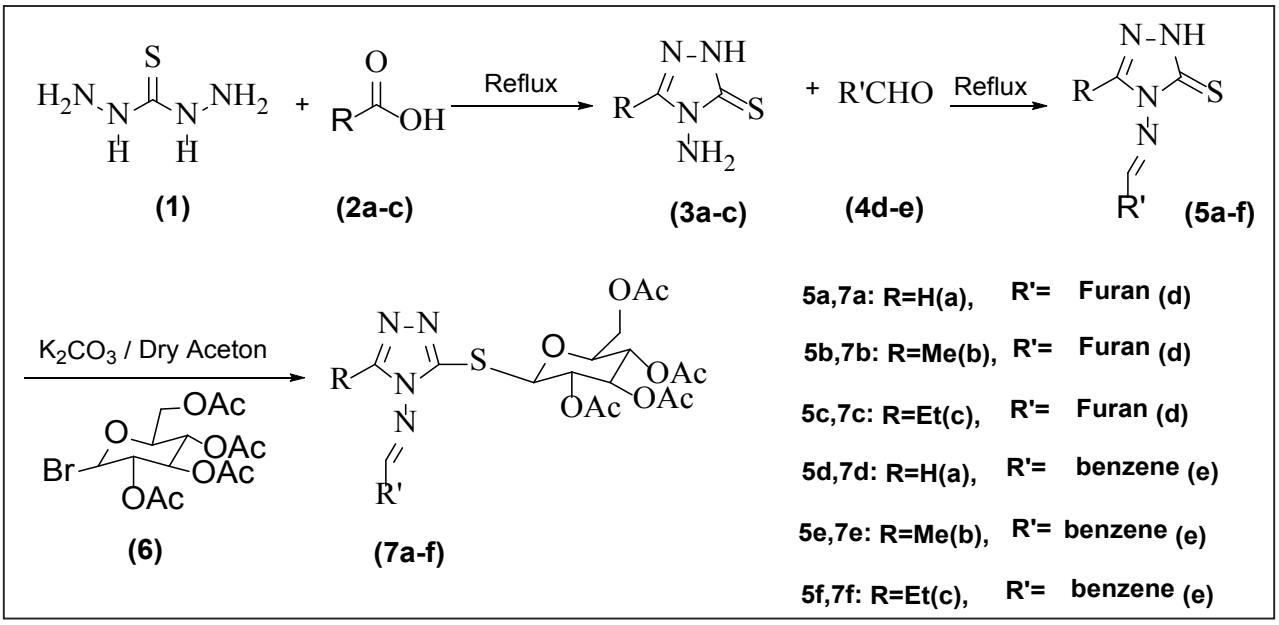


Scheme1) Synthesis of S-β-Dglycosides-4-arylideneamino-5- alkyl-S-triazole-3-thione

incubator.

Chemistry: 1. General synthesis of 4-amino- 5- alkyl- 4H- S-triazole- 3- thiol (3a-c): At first, carboxylic acid (0.01 mol) was added to thiocarbohydrazide (0.01 mol) at 150 °C for 15 min and then refluxed for 40 min. After cooling, the obtained product was treated with a sodium bicarbonate solution. The compound was then washed with water and collected by filtration. The solid product was recrystallized from instiled water (Scheme1) [20].

2. General synthesis of Schiff bases of (E)-5- alkyl- 4- ((benzyliden/ furfuraldyn) amino) Alkyl- 2, 3-dihydro- 4H- S-triazole-3-thione (5a-f): At first, substituted amino mercapto triazole (0.1 mol) (3a-c) in ethanol (1 mL) was added to aryl carboxaldehyde (4d-e) (0.1 mol). Then sulfuric acid was added to the previous solution and heated for 6 hrs.

The precipitated solid was filtered off and recrystallized in ethanol (Scheme1)[21].

3. General synthesis of 2, 3, 4, 6-tetra- O-acetyl- α- D-glucopyranosyl bromid (6): It was also prepared according to the literature procedure (Scheme1) [22].

4. General synthesis of 3- S- β- D-glucosides-4- arylideneamino- 5- alkyl- S-triazoles (7a-f): At first, compound (5a-f) (1 mmol) was added to potassium carbonate (1 mmol) in dry acetone (25 mL) along with 2 drops of Dimethylformamide and stirred for 1 hrs, then glycosyl bromid (1.2 mmol) was added, stirred for 12 hrs, and heated under reflux for 2-4 hrs. After cooling, the mixture was filtered, then the precipitate of the compound was submitted to column chromatography (Scheme1) [23].

Preparation of compound concentrations: Dimethyl sulfoxide (99%) (DMSO) was used to dissolve all compounds. Initially, a concentration of 0.5 mg/mL was prepared from the powders of synthesized compounds (1:9 ratios). Afterwards, they were kept at -18˚C in sterile test tubes until the tests were performed.

Antimicrobial Activity: Agar well diffusion (inhibition zone), MIC (minimum inhibitory concentration), and MBC (minimum bactericidal concentration)/ MFC (minimum fungicidal concentration) methods were used to evaluated the antibacterial and antifungal properties of the newly synthesized compounds.

Preparation of bacterial and fungal suspension: The lipophilic ampoules containing *Bacillus cereus*, *Staphylococcus*

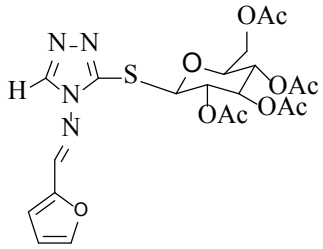
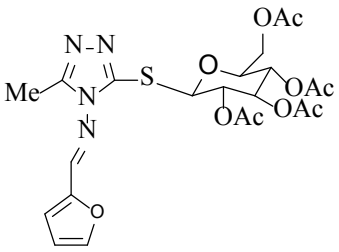
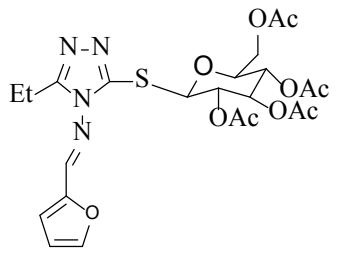
<table>
<tr><td colspan="2">Compound(7a): 4- (furfuraldehyde amino) -2 –yl -3- (2, 3, 4, 6-tetra-O- acetyl-β-D-gluco pyranosyl Sulfonyl) -S-triazole (light yellow crystals), (yield% = 73) (0.70 g), (m.p:160-163)</td></tr>
<tr><td rowspan="3">  </td><td>FT-IR (KBr, υ cm^{-1}): 2975 (C- H), 1749 (C= O), 1620 (HC= N), 1376 (CH_3), 1232, 1042 (C- O)</td></tr>
<tr><td>^{1}H-NMR (300 MHz,$CDCl_3$): δ (ppm), 1.93 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.09 (s, 3H, OAc), 3.98-4.01 (m, 1H, H-5), 4.14 - 4.19 (m, 1H, H- 6a), 4.28 - 4.33 (m, 1H, H- 6b), 5.25 (t, J=9 Hz, 1H, H- 2), 5.42 (t, J=9.6 Hz, 1H, H- 4) 5.76 (t, J=9 Hz, 1H, H- 3), 6.19 (d, J=9.3 Hz, 1H, H- 1), 6.60 - 6.61 (d, J=1.8 Hz, 1H, Furyl), 7.06 - 7.07 (d, J=3.3 Hz, 1H, Furyl), 7.68 (s, 1H, Furyl), 8.07 (s, 1H, H- C triazole), 10.48 (s, 1H, HC= N).</td></tr>
<tr><td>^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm), 20.43, 67.09, 68.39, 73.77, 75.39, 76.62, 80.31, 112.6, 118.9, 141.54, 145.77, 163.72, 168.85, 169.35, 170.14, 170.60. Found: C, 48.12; H, 4.51; N, 10.88; S, 6.25 %.</td></tr>
<tr><td colspan="2">Compound(7b): 4- (furfuraldehyde amino)- 5- methyl- 2- yl- 3- (2, 3, 4, 6-tetra-O-acetyl-β-D-gluco pyranosyl-Sulfonyl) -S-triazole (light yellow crystals), (yield% = 79) (0.81 g), (m.p :130-132 °C)</td></tr>
<tr><td rowspan="3">  </td><td>FT-IR (KBr, υ cm^{-1}): 2961 (C- H), 1751 (C= O), 1607 (HC= N), 1376 (CH_3), 1235, 1044 (C- O)</td></tr>
<tr><td>^{1}H-NMR (300 MHz,$CDCl_3$): δ (ppm), 1.93 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.45 (s, 3H, CH_3), 3.96 - 3.99 (m, 1H, H- 5), 4.13 - 4.18 (m, 1H, H- 6a), 4.28 - 4.34 (m, 1H, H- 6b), 5.25 (t, J=9.6 Hz, 1H, H- 2), 5.41 (t, J=9.3 Hz, 1H, H- 4) 5.73 (t, J=9.3 Hz, 1H, H- 3), 6.207 (d, J=9.3 Hz, 1H, H- 1), 6.60 - 6.61 (d, J=1.5 Hz, 1H, Furyl), 7.06 - 7.07 (d, J=3 Hz, 1H, Furyl), 7.68 (s, 1H, Furyl), 10.32 (s, 1H, HC= N)</td></tr>
<tr><td>^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm), 11.13, 20.33, 61.55, 66.34, 68.49, 73.63, 76.63, 80.01, 111.52, 11363, 145.65, 149.17, 163.79, 168.89, 169.33, 170.15, 170.20. Found: C, 49.11; H, 4.77; N, 10.48; S, 5.87 %.</td></tr>
<tr><td colspan="2">Compound(7c): 4- (furfuraldehyde amino)-5- etyl- 2- yl- 3- (2, 3, 4, 6-tetra- O- acetyl- β- D-gluco pyranosyl Sulfonyl) -S-triazole (light brown crystals), (yield% = 78) (0.72 g), (m.p: 87 - 89 °C)</td></tr>
<tr><td rowspan="3">  </td><td>FT-IR (KBr, υ cm^{-1}): 2951 (C- H), 1753 (C= O), 1608 (HC= N), 1373 (CH_3), 1230, 1043 (C- O)</td></tr>
<tr><td>^{1}H-NMR (300 MHz,$CDCl_3$): δ (ppm), 1.25 - 1.34 (t, J=7.5 Hz, 3H, CH_3), 1.91 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.73 - 2.86 (q, J=7.5 Hz, 2H, CH_2), 3.97 - 4.00 (m, 1H, H- 5), 4.14 - 4.18 (m, 1H, H- 6a), 4.27 - 4.33 (m, 1H, H- 6b), 5.25 (t, J=9.9 Hz, 1H, H- 2), 5.40 (t, J=9.6 Hz, 1H, H- 4) 5.78 (t, J=9.3 Hz, 1H, H- 3), 6.16 (d, J=9.3 Hz, 1H, H- 1), 6.59 - 6.59 (d, J=1.5 Hz, 1H, Furyl), 7.04 - 7.05 (d, J=3.3 Hz, 1H, Furyl), 7.67 (s, 1H, Furyl), 10.29 (s, 1H, HC= N)</td></tr>
<tr><td>^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm), 20.22, 62.65, 66.42, 67.17, 73.59, 76.61, 80.85, 153.07, 153.02, 150.08, 111.63, 113.76, 148.52, 149.16, 163.93. Found: C, 50.19; H, 5.21; N, 10.01; S, 5.70 %.</td></tr>
</table>

Figure 1) Structural and spectral information of newly synthesized derivatives

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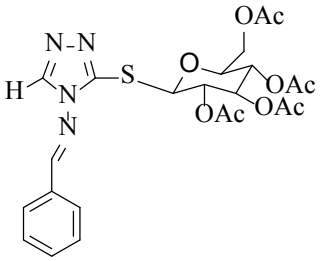
[DOI: 10.52547/iem.7.2.109]

Compound(7d): 4- (benzylidene amino)- 2- yl- 3- (2, 3, 4, 6- tetra- O- acetyl- β- D- gluco pyranosyl Sulfonyl) -S-triazole (white crystals), (yield% = 71) (0.61 g), (m.p: 162-164 °C)

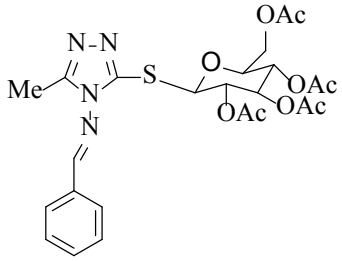


FT-IR (KBr, υ cm^{-1}): 2937 (C- H), 1748 (C= O), 1368 (CH_3), 1045, 1233 (C- O)

^{1}H-NMR (300 MHz,$CDCl_3$): δ (ppm), 1.95 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.09 (s, 3H, OAc), 3.98 - 4.03 (m, 1H, H- 5), 4.15 - 4.19 (m, 1H, H- 6a), 4.28 - 4.34 (m, 1H, H- 6b), 5.26 (t, J=9 Hz, 1H, H- 2), 5.43 (t, J=9.6 Hz, 1H, H- 4) 5.78 (t, J=9.3 Hz, 1H, H- 3), 6.23 (d, J=9.3 Hz, 1H, H- 1), 7.46-7.56 (m, 3H, Ar), 7.84 - 7.87 (m, 2H, Ar), 8.07 (s, 1H, H- C triazole), 10.37 (s, 1H, HC= N)

^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm), 20.57, 73.67, 75.40, 77.07, 77.49, 80.17, 80.41, 127.74, 129.75, 129.87, 130.12, 161.68, 168.94, 169.39, 170.13, 170.49. Found: C, 51.78; H, 4.80; N, 10.58; S, 6.19 %.

Compound(7e): 4- (benzylidene amino)- 5- methyl- 2- yl- 3- (2, 3, 4, 6-tetra-O-acetyl-β-D-gluco pyranosyl Sulfonyl) -S-triazole (light yellow crystals), (yield% = 70), (0.51 g), (m.p: 110 - 112 °C)

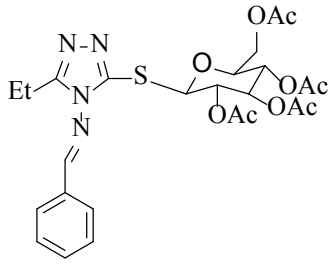


FT-IR (KBr, υ cm^{-1}): 2961 (C- H), 1752 (C= O), 1605 (HC= N), 1370 (CH_3), 1045, 1230 (C- O)

^{1}H-NMR (300 MHz,$CDCl_3$): δ (ppm), 1.95 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.47 (s, 3H, CH_3), 3.97 - 4.01 (m, 1H, H- 5), 4.14 - 4.18 (m, 1H, H- 6a), 4.27 - 4.35 (m, 1H, H- 6b), 5.26 (t, J=9.6 Hz, 1H, H- 2), 5.43 (t, J=9.3 Hz, 1H, H- 4) 5.76 (t, J=9.3 Hz, 1H, H- 3), 6.23 (d, J=9.3 Hz, 1H, H- 1), 7.47 - 7.56 (m, 3H, Ar), 7.85 - 7.88 (m, 2H, Ar), 10.40 (s, 1H, HC= N)

^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm), 11.27, 20.60, 66.96, 67.12, 69.70, 76.64, 77.07, 80.34, 127.65, 127.93, 129.77, 130.10, 160.56, 163.94, 168.95, 169.34, 169.37. Found: C, 52.65; H, 5.28; N, 10.10; S, 5.79 %.

Compound(7f): 4- (benzylidene amino)- 5- ethyl- 2- yl- 3- (2, 3, 4, 6- tetra-O-acetyl-β-D-gluco pyranosyl Sulfonyl) -S-triazole (white crystals), (yield% = 79) (0.61 g), (m.p: 131 – 133 °C)



FT-IR (KBr, υ cm^{-1}): 2955 (C- H), 1756 (C= O), 1593 (HC= N), 1369 (CH_3), 1039, 1231 (C- O)

^{1}H-NMR (300 MHz,$CDCl_3$): δ (ppm), 1.26 - 1.34 (t, J=7.5 Hz, 3H, CH_3), 1.93 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.81 - 2.88 (q, J=7.2 Hz, 2H, CH_2), 3.98 - 4.00 (m, 1H, H- 5), 4.09 - 4.19 (m, 1H, H- 6a), 4.29 - 4.33 (m, 1H, H- 6b), 5.27 (t, J=9.3 Hz, 1H, H- 2), 5.42 (t, J=9.3 Hz, 1H, H- 4) 5.81 (t, J=9.6 Hz, 1H, H- 3), 6.20 (d, J=9.3 Hz, 1H, H- 1), 7.48 - 7.55 (m, 3H, Ar), 7.85 - 7.87 (m, 2H, Ar), 10.39 (s, 1H, HC= N)

^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm), 10.11, 18.93, 20.73, 73.58, 75.32, 77.05, 77.47, 81.46, 81.66, 160.48, 168.77, 169.39, 170.12, 127.62, 127.75, 128.08, 130.01. Found: C, 53.49; H, 5.48; N, 9.90; S, 5.60 %.

Figure 1) Structural and spectral information of newly synthesized derivatives

Table 1) Antibacterial activity of the synthesized derivatives (0.5 mg.mL)

Compounds	Microorganism											
	E. Coli PTCC1769			*P. aeruginosa* PTCC1690			*S. aureus* PTCC1917			*B. Cereus* PTCC1015		
	MBC	MIC	IZ	MBC	MIC	IZ	MBC	MIC	IZ	MBC	MIC	IZ
5a	-	-	-	-	-	-	-	-	6 ± 0.7	-	-	6 ± 0.5
7a	1000	1000	7 ± 0.2	1000	500	7 ± 0.2	-	-	8 ± 0.9	-	-	9 ± 0.8
5b	-	-	-	-	-	-	-	-	6 ± 0.8	-	-	6 ± 0.1
7b	-	-	6 ± 0.3	1000	1000	7 ± 0.1	1000	1000	9 ± 0.5	-	-	9 ± 0.1
5c	-	-	-	-	-	-	-	-	8 ± 0.7	-	-	9 ± 0.1
7c	-	-	7 ± 0.8	-	-	6 ± 0.5	500	500	14 ± 0.3	500	250	16 ± 0.1
5d	-	-	-	-	-	-	-	-	8 ± 0.7	-	-	7 ± 0.9
7d	1000	1000	7 ± 0.6	-	-	-	1000	500	13 ± 0.1	1000	500	15 ± 0.3
5e	-	-	-	-	-	-	-	-	8 ± 0.1	-	-	7 ± 0.2
7e	-	-	7 ± 0.1	-	-	-	1000	1000	11 ± 0.1	1000	500	12 ± 0.1
5f	-	-	NA	-	-	-	-	-	-	-	-	8 ± 0.1
7f	-	-	6 ± 0.2	-	-	6 ± 0.5	NA	NA	8 ± 0.7	1000	500	11 ± 0.2
G	1000	500	23 ± 0.4	500	250	27 ± 0.3	250	125	28 ± 0.5	125	62.50	31 ± 0.6

IZ: Inhibition Zone.
MIC: Minimum Inhibitory Concentration.
MBC: Minimum Bactericidal Concentration.
7c: 4- (furfuraldehyde amino)-5- etyl- 2- yl- 3- (2, 3, 4, 6-tetra- O- acetyl- β- D-gluco pyranosyl Sulfonyl) -S-triazol.
7d: 4- (benzylidene amino)- 2- yl- 3- (2, 3, 4, 6- tetra- O- acetyl- β- D- gluco pyranosyl Sulfonyl) -S-triazol.
±: Averaged three times.
-: No activity.
G: Penicillin G.

aureus, *Pseudomonas aeruginosa*, and *Escherichia coli* strains were first opened under sterile conditions and transferred to the nutrient broth (NB) culture medium and incubated at 37 ˚C for 24 hours. Also, for fungi samples, ampouls containing *Aspergillus niger* and *Candida albicans* strains were first opened under sterile conditions and transferred to the sabouraud dextrose broth (SDB) and incubated at 37˚C for 24 hours. Using a sampler, 1 mL of the 24 hour culture of microbial suspension was transferred to a tube containing sterile nutrient broth, and then the turbidity of the microbial suspension was visually compared to the McFarland standard set with a spectrophotometer at 625 nm and absorption rate of 1.5 × 10^9 CFU/mL. For bacterial strains, the nutrient agar culture medium was used for agar well diffusion test, and the nutrient broth culture medium was used to test the dilution in the tubes. For fungal strains, the sabouraud dextrose agar (SDA) culture medium was used for agar well diffusion test, and SDB culture medium was used to test the dilution in the tubes. All environments were prepared according to the manufacturer's instructions and sterilized using an autoclave [24].

Agar well diffusion method: The agar disc diffusion method was used to determine antimicrobial activity of the compounds using a previously described standard method [24].

Broth dilution method: The MIC, MBC and MFC values of the compounds were determined using a previously described standard method [24].

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Table 2) Antifungal activity of the synthesized derivatives (0.5 mg.mL)

Compounds	Microorganism					
	C. Albicans PTCC5027			*A. Niger PTCC5162*		
	MFC	MIC	IZ	MFC	MIC	IZ
5a	-	-	6 ± 0.9	-	-	7 ± 0.1
7a	1000	1000	12 ± 0.1	1000	1000	11 ± 0.3
5b	-	-	7 ± 0.2	-	-	7 ± 0.1
7b	1000	1000	11 ± 0.3	1000	1000	11 ± 0.1
5c	-	-	8 ± 0.5	-	-	9 ± 0.1
7c	250	125	16 ± 0.1	250	125	16 ± 0.2
5d	-	-	9 ± 0.1	-	-	8 ± 0.7
7d	250	125	18 ± 0.7	500	250	14 ± 0.5
5e	-	-	8 ± 0.7	-	-	8 ± 0.1
7e	1000	500	12 ± 0.4	1000	500	12 ± 0.1
5f	-	-	6 ± 0.5	-	-	7 ± 0.3
7f	1000	1000	12 ± 0.7	1000	1000	11 ± 0.5
N	125	62.50	26 ± 0.8	250	125	22 ± 0.6

IZ: Inhibition Zone.
MIC: Minimum Inhibitory Concentration.
MFC: Minimum Fungicidal Concentration.
7c: 4- (furfuraldehyde amino)-5- etyl- 2- yl- 3- (2, 3, 4, 6-tetra- O- acetyl- β- D-gluco pyranosyl Sulfonyl) -S-triazol.
7d: 4- (benzylidene amino)- 2- yl- 3- (2, 3, 4, 6- tetra- O- acetyl- β- D- gluco pyranosyl Sulfonyl) -S-triazol.
±: Averaged three times.
-: No activity.
N: Nystatin.

Statistical methods: All diameter results obtained from three repetitions were reported as mean ± standard deviation. SPSS statistical software Version 22 was used for data analysis.

Findings

Chemistry: FT-IR, H-NMR, and C-NMR spectra of all the compounds were obtained (Figure 1). 4-amino-5-alkyl-4H-S-triazole-3-thiol 3(a-c) were prepared by condensing aliphatic carboxylic acids (2a-c) with thiocarbohydrazide. This reaction is the selective method for the preparation of 4-amino-5- alkyl-4H-S-triazole-3-thiol (Scheme 1). Schiff bases (5a-f) were synthesized by the reaction of 3-alkyl-4-amino-S-triazole-5-thione (3a-c) with furan and benzene aldehydes (4d-e) in absolute ethanol as a solvent in the presence of glacial acetic acid as a catalyst. The ^{1}H-NMR spectra showed a singlet signal at about 10 ppm due to CH=N and the lack of chemical shift of 4-NH_2 in the spectra of 3(a-c), proving that the intended Schiff bases (5a-f) were formed. In an attempt to obtain *α*-aceto-bromo-glucose, D-glucose was first treated with acetic anhydride in pyridin at room temperature, resulting in the produciton of 1,2,3,4,6-penta-*O*-acetyl-*β*-glucose, then anomeric bromination of this compound with hydrogen bromide in acetic acid resulted in 2,3,4,6-tetra-*O*-acetyl-*α*-gluco-pyranosyl-bromide production. The presence of thiol-thione tautomerism is known for the compounds 3(a–c), and generally one form is predominant [25-27]. Thioglycosides of S-triazoles (7a-f) were synthesized by the reaction of 3-alkyl-4-

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amino-S-triazole-5-thione Schiff bases (5a-f) with the peracetylated *β*-pyranosyl-bromide [6] in the presence of potassium carbonate as a weak base in dry acetone (Scheme 1). Anomeric β-configurations of the *S*-linked glycosides (7a-f) were supported by their ^{1}H-NMR data. The chemical shifts of the anomeric proton signals of thioglycosides were revealed around δ (6.20) with a large coupling constant $J_{1,2}$ values of 9.3 Hz, consistent with the reported data for S-β-D glycosides.

Determination of *in Vitro* Antimicrobial Activity: According to the results, all the compounds had lesser activity than corresponding standard compounds, and the target compounds exhibited better antifungal activity than antibacterial activity. However, the antibacterial activity results showed that compound 7c with IZ=16 ± 0.1mm, compound 7d with IZ= 15 ± 0.3mm, andcompound 7e with IZ=12 ± 0.1mm had antibacterial properties against *B. Cereus*; also, compound 7c with IZ=14 ± 0.3 mm and compound 7d with IZ= 13 ± 0.1mm had antibacterial properties against *S. aureus*. It should be noted that the synthesized compounds did not show antibacterial properties against Gram-negative bacteria (Table 1). The antifungal study results revealed that compound 7c with IZ=16 ± 0.2mm and compound 7d with IZ= 14 ± 0.5mm showed antifungal properties against *A. Niger*; also, compound 7c with IZ=16 ± 0.1mm and compound 7d with IZ= 18 ± 0.7mm showed antifungal properties against *C. albicans*. It was found that compound 7c had the highest activity against *B. Cereus,* and compound 7d had the highest activity against *C. albicans* among all the tested compounds (Table 2).

Discussion

The emergence of antibiotic-resistant organisms is a global problem in various societies [1]. At present, the response of nosocomial infections to standard antibiotic treatment has changed, and the prevalence of antibiotic resistance in many hospitals has reached dangerous levels [2-3]. According to some studies results, about 50 to 60% of nosocomial infections are caused by antibiotic-resistant strains [28]. One of the most important factors contributing to the development of antibiotic resistance is the history of arbitrary use of antibiotics. Antibiotic resistance increases the incidence of complications, mortality, and treatment costs in patients. According to some studies, the per capita consumption of antibiotics has increased significantly in recent years worldwide, which could be due to non-compliance with standard principles of prescribing antibiotics to patients by physicians or could be due to arbitrary consumption of antibiotics by individuals in the community [2]. In any case, the mentioned cases have caused the pattern of microbial resistance to change and the prevalence of strains resistant to the first line and even the second line treatment to increase. In the meantime, there is a need to introduce and explore new drug structures that could be used in the synthesis of various drug formulations [29]. In this study, novel structures of S-triazoles (7a-f) were synthesized, and their antimicrobial properties were investigated. According to the antibacterial activity results of the compounds, compounds 7c and 7d had an acceptable effect on Gram-positive bacteria. It was thought that the presence of these compounds along with the structure of triazole increased the antibacterial properties of the derivatives. In this regard, El Ashry et al. (2021) synthesized some new derivatives of 5- phenyl- 2, 4-dihydro- 3H-S-triazole as a combination with V-triazole and studied their antibacterial properties, the antibacterial activity of some compounds was the highest against *E. coli* and *S. aureus* [30]. In the present study, the greatest effect of the compounds was against *C. albicans*, so that both 7c and 7d compounds exhibited significant effects. In a study by

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Revanasiddappa et al. (2017), the best effect of these compounds was reported to be against *A. fumigatus* [31], which is consistent with the present study result. Godeau et al. (2021) stated that Difenoconazole is a triazole fungicide widely used in agriculture to protect various crops [32]. According to the results of this study and similar studies, triazole-based compounds could be considered as a good candidate for use in the development of common antifungal drugs that are commonly used today.

Conclusion

A series of new thioglycoside derivatives of S-triazoles (7a-f) were synthesized. The triazoles (3a-c) were produced via the reaction of thiocarbohydrazide with aliphatic carboxylic acids. The Schiff bases (5a-f) were produced through the reaction of 4-amino-5-alkyl-S-triazole-3-thione with appropriate aryl aldehydes (furan and benzne) and then heated under reflux in ethanol and in the presence of glacial acetic acid. S-glycosilytion of Schiff bases was performed by aceto bromo glucose in acetone in the presence of potassium carbonate. The structures of the target compounds were characterized by ^{1}H NMR, ^{13}C NMR, and FT-IR. All the newly synthesized compounds were evaluated for their antimicrobial activities in vitro against two Gram-positive bacteria, two Gram-negative bacteria, and two fungi. These compounds exhibited better antifungal activity than antibacterial activity. Though compound 7c was found to have the highest activity against *B. Cereus*, and compound 7d was found to have the highest activity against *C. albicans* among all the tested compounds.

Supplementary materials

(5a)= 4- ((furan- 2- yl- methylen) amino)- 2, 4-dihydro- 3H- S-triazol- 3-thion: (Light Yellow crystals) (Yield% =75) (0.52 g) m.p: 173 - 175 °C. FT-IR (KBr, υ cm^{-1}): 3108, 3068, 2995 (N- H), 1546 (C= N), 1480 (C= S), 1275 (C- C). ^{1}H-NMR (300 MHz, DMSO): δ (ppm), 6.72 (s, 1H, Furyl), 7.30 - 7.31 (d, J=3 Hz, 1H, Furyl), 8.20 (s, 1H, Furyl), 8.41 (s, 1H, C- H), 9.78 (s, 1H, HC= N) , 13.64 (s, 1H, N- H). ^{13}C-NMR (75 MHz, $CDCl_3$): Found: C, 43.15; H, 3.39; N, 28.60; S, 16.63.

(5b)= 4- ((furan- 2- yl- methylene) amino)- 5- methyl- 2, 4-dihydro- 3H- S-triazol- 3-thion: (Light Yellow crystals) (Yield% = 77) (0.80 g), m.p: 167 - 169°C. FT-IR (KBr, υ cm^{-1}): 3118, 2940 (N- H), 1600 (C= N), 1488 (C= S), 1266 (C- C), ^{1}H-NMR (300 MHz, DMSO): δ (ppm), 2.28 (s, 3H, CH3), 6.74 (s, 1H, Furyl), 7.29 - 7.30 (d, J=3 Hz, 1H, Furyl), 8.00 (s, 1H, Furyl), 9.75 (s, 1H, HC= N), 13.75 (s, 1H, N- H). ^{13}C-NMR (75 MHz, $CDCl_3$): Found: C, 45.19; H, 3.95; N, 24.99; S, 15.32.

(5c)= 5- ethyl- 4- ((furan- 2- yl- methylene) amino)-2 ,4- dihydro- 3H- S-triazol- 3-thion: (Light Brown crystals), (Yield% = 86) (0.6g), m.p: 177 - 179 °C. FT-IR (KBr, υ cm^{-1}): 3112, 3076, 2945 (N- H), 1594 (C= N), 1484 (C= S), 1280 (C- C). ^{1}H-NMR (300 MHz, DMSO): δ (ppm), δ 1.19 (t, J=7.5 Hz, 3H, CH3), 2.68 (q, J=7.5 Hz, 2H, CH2), 6.75 (s, 1H, Furyl), 7.31 (d, J=3.3 Hz, 1H, Furyl), 8.04 (s, 1H, Furyl), 9.87 (s, 1H, HC= N), 13.73 (s, 1H, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): Found: C, 48.58; H, 4.40; N, 25.41; S, 14.60.

(5d)= 4- (benzylidene- amino)- 2, 4-dihydro- 3H- S-triazol- 3-thion: (White crystals), (Yield% = 74) (0.5 g), m.p: 158 - 160 °C, FT-IR (KBr, υ cm^{-1}): 3104, 3073, 3000 (N- H), 2870 (C- H), 1552 (C= N), 1488 (C= S). ^{1}H-NMR (300 MHz, DMSO): δ (ppm), 7.53 - 7.57 (m, 3H, Ar), 7.86 - 7.88 (m, 2H, Ar), 9.85 (s, 1H, HC= N) 9.83 (s, 1H, HC= N), 13.58 (s, 1H, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): Found: C, 52.79; H, 3.90; N, 27.62; S, 15.81.

(5e)= 4- (benzylidene- amino)- 5- methyl- 2, 4-dihydro- 3H- S-triazol- 3-thion: (Light Yellow crystals), (Yield% = 85) (0.8 g), m.p: 188 - 190 °C, FT-IR (KBr, υ cm^{-1}): 3066, 2930 (N- H), 1584 (C= N), 1493 (C= S). ^{1}H-NMR (300 MHz, DMSO): δ (ppm), 2.32 (s, 3H, CH3), 7.53 - 7.57 (m, 3H, Ar), 7.86 - 7.88 (m, 2H, Ar), 9.85 (s, 1H, HC= N), 13.65 (s, 1H, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): Found: C,

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52.79; H, 3.90; N, 27.62; S, 15.81.
(5f)= 4- (benzylidene- amino)- 5- ethyl- 2, 4-dihydro- 3H- S-triazol- 3-thion: (White crystals), (Yield% = 76) (0.5 g), m.p:160-162°C, FT-IR (KBr, υ cm^{-1}): 3100, 3060, 2934 (NH), 1577 (C= N), 1493 (C= S). ^{1}H-NMR (300 MHz, DMSO): δ (ppm), 1.17 - 1.22 (t, J= 7.5 Hz, 3H, CH3), 2.67 - 2.75 (q, J= 7.5 Hz, 2H, CH2), 7.54 - 7.61 (m, 3H, Ar), 7.86 - 7.89 (m, 2H, Ar), 9.86 (s, 1H, CH), 13.69 (s, 1H, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): Found: C, 56.93; H, 5.14; N, 24.35; S, 13.70.
Synthesis of 1, 2, 3, 4, 6-penta-O-acetyl-β-D-glucopyranose: (White precipitate), (Yield% = 68) (7.5 g), FT-IR (KBr, υ cm^{-1}): 1748, 1374, 1227, ^{1}H-NMR (300 MHz, CDCl3): δ (ppm), 2.01 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.18 (s, 3H, OAc), 3.82 - 3.85 (m, 1H, H-5), 4.08 - 4.12 (m, 1H, H- 6a), 4.26 - 4.32 (m, 1H, H- 6b), 5.09 - 5.28 (m, 3H, H- 2, H- 4, H- 3), 5.71 (d, 1H, J1, 2 = 8.4, H- 1). ^{13}C-NMR (75 MHz, CDCl3): δ (ppm), 20.55 (3C), 20.69, 20.80 (5OCOCH3), 61.41 (C-6), 67.70 (C- 4), 70.18 (C- 2), 72.69 (C- 3), 72.75 (C- 5), 91.66 (C- 1), 168.94, 169.23, 169.37, 170.08, 170.59 (5 OCOCH3). Calcd: C, 52.58; H, 6.23 %; Found: C, 52.68; H, 6.11; O %.
Synthesis of 2, 3, 4, 6-tetra- O- acetyl-*α-D-glucopyranosyl bromide*: (White precipitate),(Yield% = 57) (1.2 g), FT-IR (KBr, υ cm^{-1}): 1745, 1377, 1236, 607, ^{1}H-NMR (300 MHz, CDCl3): δ (ppm), 2.03 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.10 (s, 6H, OAc), 4.12 (d, 1H, H-6a), 4.28 - 4.36 (m, 2H, H-6b, H-5), 4.81 - 4.86 (dd, 1H, J1,2 = 3.9, J2,3 = 9.9, H- 2), 5.16 (t, 1H, J = 9.9, H- 4), 5.56 (t, 1H, J = 9.9,H- 3), 6.61 (d, 1H, J1,2 = 3.9, H- 1). ^{13}C-NMR (75 MHz, CDCl3): δ (ppm), 20.53, 20.60 (2C), 20.63 (4OCOCH3), 60.93 (C- 6), 67.15 (C- 4), 70.14 (C- 2), 70.58 (C-3), 72.12 (C- 5), 86.54 (C^{-1}), 169.44, 169.77, 169.82, 170.48 (4OCOCH3). Calcd: C, 44.03; H, 5.17 %; Found: C, 43.19; H, 5.09 %.

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Authors' contribution: Conceptualization: KA,ZD; Data curation and formal analysis: KA,ZD,YS,KA; Investigation: KA,ZD,YS,KA; Methodology and project administration: KA,ZD,YS; Supervision: KA,ZD; Validation: KA,ZD,YS; Writing of original draft: KA,YS; Writing, reviewing, and editing: KA,YS.

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