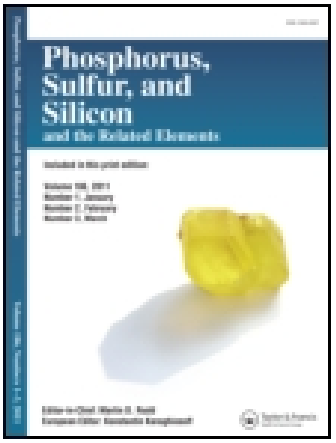

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Synthesis of New 1,2,4-Triazole-5-Thiones and Their Thioglycoside Derivatives as Potential Antibacterial Agents

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SYNTHESIS OF NEW 1,2,4-TRIAZOLE-5-THIONES AND THEIR THIOGLYCOSIDE DERIVATIVES AS POTENTIAL ANTIBACTERIAL AGENTS

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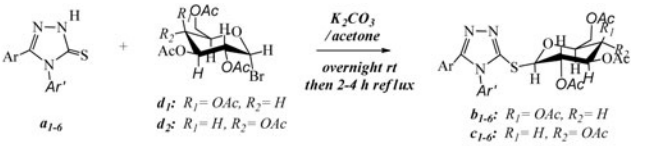
GRAPHICAL ABSTRACT



1: *Ar=Ph, Ar'=Ph* **2:** *Ar=m-PhNO$_2$, Ar'=Ph* **3:** *Ar=2-furyl, Ar'=Ph*
4: *Ar=Ph, Ar'=p-PhBr* **5:** *Ar=m-PhNO$_2$, Ar'=p-PhBr* **6:** *Ar=2-furyl, Ar'=p-PhBr*

Abstract *Abstract The glycosylation of 1,2,4-triazole-5-thiones has been performed with per-acetylated β-pyranosyl bromide in the presence of potassium carbonate. The synthesized compounds were tested for their antimicrobial activity against bacterial (Gram-negative and Gram-positive) and yeasts strains in vitro. The synthetic compounds showed different inhibition zones against tested bacterial and yeasts strains. Among them, compounds which possessed 2-furyl and p-bromophenyl moieties showed the best results against Acinetobacter calcoaceticus ATCC 23055.*

Keywords 1,2,4-Triazole-thione; β-pyranosyl; thioglycoside; antimicrobial; yeasts strain; in vitro

INTRODUCTION

The majority of carbohydrates found in nature or biological systems exist as glycoconjugates in which the monosaccharide units are joined via *O*-, *N*-, or *S*-glycosidic

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bonds. Thioglycosides have received considerable attention, because they are widely employed as biological inhibitors,[1–4] inducers,[5,6] and ligands[7,8] for affinity chromatography of carbohydrate-processing enzymes and proteins. They have excellent chemoselectivity in glycosylation processes as both donors and acceptors[9] particularly via reaction processes that involve active and latent glycosylation protocols.[10] The thioglycosyl heterocycles are sufficiently stable under a variety of reaction conditions and have the ability to be readily converted into a variety of other functionalities.[11,12]

Multivalent display of carbohydrates is frequently used as a method to increase affinities[13,14] in various contexts such as the binding of bacteria,[15–18] bacterial toxins,[19–21] galectins,[22,23] and other lectins.[24,25] These properties may affect medicinal effect of antibiotic agents.

On the other hand, the 1,2,4-triazole nucleus is found in many drug structures such as anastrozole, estazolam, ribavirin, and triazolam. In addition, these compounds show antiseptic, analgesic, and anticonvulsant properties.[26–28] Moreover, sulfur-containing heterocycles represent an important group of sulfur compounds that are promising for use in practical applications. Among these heterocycles, thione-substituted 1,2,4-triazole ring systems have been well studied and so far a variety of biological activities have been reported for a large number of their derivatives, such as antibacterial,[29,30] antifungal,[31,32] antitubercular,[33] antimycobacterial,[34] anticancer,[35,36] diuretic,[37,38] and hypoglycemic[39] properties.

Therefore, it is interesting to report the synthesis of a new series of compounds in which the glycosyl moieties have been used as carriers for the heterocycles having the triazole ring.

In our previous work,[40] we reported the synthesis of new series of antimycobacterial agents with heterocyclic nucleus, whereas in the present work, we report the synthesis of new groups of antibacterial agents in which the heterocyclic moiety is coupled to monosaccharide units.

RESULTS AND DISCUSSION

A general approach to the synthesis of thioglycosides may proceed via the direct introduction of the heterocyclic thiol part, either by an S_N1 or S_N2 displacement reaction of an anomeric leaving group, in a manner similar to *O*-glycosylation reactions. Alternatively, two (or more) step procedures may be employed in which a thiol group is primarily introduced on the anomeric center and then its reaction with an electrophile will lead to the target thioglycoside. The anomeric halide group in a glycosyl donor can be efficiently displaced by a thiol group linked to a heterocycle under the influence of a basic catalyst.

In our attempt to obtain 1-bromide sugars, at the first step D-galactose and D-glucose were treated with acetic anhydride in pyridine at room temperature and gave 1,2,3,4,6-penta-*O*-acetyl-β-galactose and 1,2,3,4,6-penta-*O*-acetyl-β-glucose, respectively. The anomeric bromination of these compounds with hydrogen bromide in acetic acid gave 2,3,4,6-tetra-*O*-acetyl-α-galactopyrnosyl bromide (**d_1**) and 2,3,4,6-tetra-*O*-acetyl-α-glucopyranosyl bromide (**d_2**), respectively.

The reaction of aryl carboxylic acid hydrazides with aryl isothiocyanate in ethanol gave the corresponding thiosemicarbazides which were cyclized in alkaline media to yield 1,2,4-triazole-5-thiones (**$a_{1–6}$**). Thioglycosyl triazoles (**$b_{1–6}$**, **$c_{1–6}$**) were synthesized by the S_N2 reaction of 1,2,4-triazole-5-thiones (**$a_{1–6}$**) and the peracetylated β-pyranosyl bromides (**$d_{1,2}$**) in the presence of potassium carbonate as a weak base in dry acetone.

The structure of thioglycosyl triazoles was confirmed by appropriate spectroscopic methods such as ^{1}H NMR, ^{13}C NMR, and high resolution mass spectroscopy (HRMS). The anomeric protons of compounds (**b$_{1–6}$**, **c$_{1–6}$**) were assigned to the doublet at 5.63–6.41 ppm with $J_{1,2} = 8.4$–9.6 Hz, confirming the β-configuration.

The in vitro antibacterial activity of the synthesized compounds in DMSO against some of most important Gram-positive and Gram-negative infectious agents is shown in Tables S1–S3 (Supplemental Materials available online).

The synthetic compounds showed different inhibition zones against tested bacterial and yeasts strains. *Pseudomonas aeruginosa* and *E. coli* (Gram-negative) and *Enterococcus faecalis* (Gram-positive) were resistant ("R") to all prepared compounds. On the other hand, *Acinetobacter calcoaceticus* was sensitive to compounds of the **a** set, especially **a$_4$** and **a$_6$** as well as the **b** group, especially **b$_4$**, **b$_5$**, and **b$_6$**, and compounds from the **c** series, especially **c$_1$** and **c$_6$** (Tables S1–S3). As shown in the tables, these compounds showed high antibacterial effects in comparison with different kinds of antibiotics such as Ampicillin and Trimethoprim/Sulfamethoxazole which are normally used for treating such infections.

Staphylococcus aureus (Gram-positive, relatively resistant to antimicrobials) showed limited sensitivity to only **a$_6$** (with low antibacterial effects in comparison with Erythromycin and Cephalothin*)*. On the other hand, *S. aureus* was resistant to all compounds from the **a**, **b,** and **c** series (Tables S1–S3, Supplemental Materials available online).

Only compound **a$_6$** of the **a** set exerted comparable activity to reference antimicrobial Nystatin against *Candida albicans* and its activity in comparison with Fluconazole was just slightly weaker (Table S1, Supplemental Materials available online). Also, all compounds from the **b** and **c** series showed limited activity against this microorganism (Tables S2 and S3).

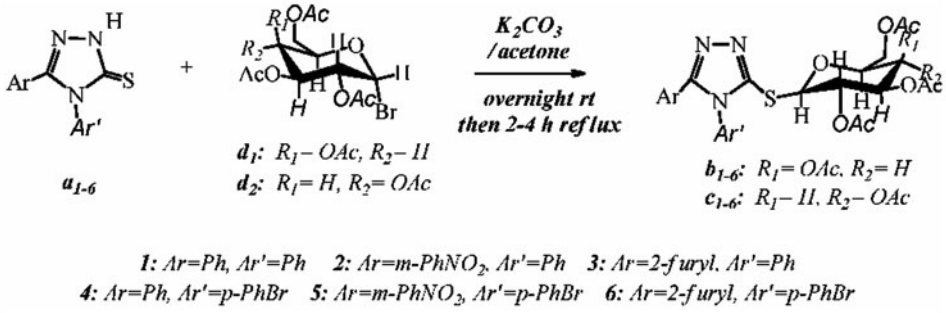
Candida tropicalis was resistant to all synthetic compounds of the **c** and **b** series, and in the **a** set only **a$_6$** exhibited a low activity which was not comparable to the standard compounds of Fluconazole and Nystatin (Table S 1).

In general, compounds from the **b** set showed more antimicrobial activity than two other series. Thioglycoside derivatives of 1,2,4-triazole-5-thiones (series **b** and **c**) were more active against *Acinetobacter calcoaceticus ATCC 23055* than "parent" 1,2,4-triazole-5-thiones (**a** set), this consideration confirmed the relation between glyco-conjugation and increasing of antiproliferative activity of antibiotic agents.

The best results in the tables belonged to **a$_6$** that showed high activity against *A. calcoaceticus (24 mm) a*s well as *Candida albicans* (20 mm). Also, its glycoconjugates (**b$_6$** and **c$_6$**) possessed this property only against *A. calcoaceticus*. Among them, **c$_6$** was the best choice (25 mm) for *A. calcoaceticus* as an antibacterial agent.

Thioglyco conjugation of 1,2,4-triazole-5-thiones (**a** group) increased (except **a$_6$**) the antifungal property of the corresponding compounds from the **b** and **c** groups, whereas that was only limited activity against *C. albicans* (Tables S1–S3, Supplemental Materials available online). As shown in the tables, galactose was more effective than glucose in mentioned increasing for thioglycosides from the **b** and **c** sets (except for glycoconjugates of **a$_1$** and **a$_2$**).

Likewise, **a$_6$**, **b$_6$**, and **c$_6$**, compounds **a$_1$**, **a$_4$** and sugar-coupled of them showed high activity against *A. calcoaceticus* too. Going over the structure of these synthetic compounds confirmed that the existence of 2-furyl or phenyl instead of a *m*-nitrophenyl group as Ar and p-bromophenyl instead of a phenyl group as Ar′ (Scheme 1) increased their antibacterial activity against *A. calcoaceticus*. We realized this by comparing the structures of **a$_3$**, **a$_6$** and



Scheme 1 General synthetic pathway for the synthesis of thioglycosyl triazoles.

their thioglycosides with the values of their antibacterial activity in vitro as well as $\mathbf{a_1}$ and $\mathbf{a_4}$ or $\mathbf{a_2}$ and $\mathbf{a_5}$. The presence of a *m*-nitrophenyl group as Ar in structures of $\mathbf{a_2}$, $\mathbf{a_5}$ and their corresponding sugar derivatives decreased their antibacterial activity in comparison with the rest of the synthetic compounds.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE-300 spectrometer at 300 and 75 MHz, respectively in $CDCl_3$ using TMS as the internal standard. High-resolution mass spectra were obtained with a HPLC-Q-TOF system equipped with Q-TOF micro mass spectrometer (dual ESI). Melting points were measured on a Philip Harris C4954718 apparatus without calibration. Optically active samples were analyzed by EHARTNACK apparatus (Paris, France) at 20°C in dichloromethane. Thin layer chromatography (TLC) analyses were carried out on silica gel plates. All chemicals were purchased from Merck and used as received.

1,2,4-Triazole-5-thiones ($\mathbf{a_{1–6}}$) were synthesized according to the literature procedure.[41] Peracetylated α-pyranosyl bromides ($\mathbf{d_{1,2}}$) were prepared according to the published methods.[42,43]

Synthesis of Thioglycosyl Triazoles ($\mathbf{b_{1–6}}$ and $\mathbf{c_{1–6}}$)

A mixture of compound $\mathbf{a_{1–6}}$ (1 mmol) and K_2CO_3 (2 mmol, 0.276 g) in dry acetone (25 mL) and 5 drops of DMF were stirred for 1 h, then glycosyl bromide $\mathbf{d_{1,2}}$ (2.2 mmol) was added. Stirring was continued overnight, and then the reaction mixture was heated under reflux for 2–4 h. After cooling, the mixture was filtered, the solids were washed with acetone, the filtrate was evaporated under reduced pressure, and the crude product was recrystallized from ethanol.

We report herein the spectroscopic data of compounds $\mathbf{b_1}$ and $\mathbf{c_1}$, but the rest of compounds were unambiguously characterized by similar spectroscopic methods. Characterization data are presented in the online Supplemental Materials.

4,5-Diphenyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-1-thio-galactopyranose)-1,2,4-triazole ($\mathbf{b_1}$)

White powder, Yield: 42%; mp. 201–203 °C; $[\alpha]_D^{20} = -1°$ (c = 1.0, CH_2Cl_2). ^{1}H NMR: 1.98 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.06 (s, 3H, OAc), 4.03–4.35

(m, 3H, H-6a, H-6b, H-5), 5.23–5.35 (m, 1H, H-2), 5.45–5.60 (m, 1H, H-4), 5.94 (t, 1H, $J_{2,3} = J_{3,4} = 9.6$, H-3), 6.30 (d, 1H, $J_{1,2} = 8.4$, H-1), 7.20–7.68 (m, 10H, ArH); ^{13}C NMR: 20.57, 20.72, 20.78, 20.83 (4 × OCO$\underline{C}$H$_3$), 61.32 (C-6), 66.97 (C-4), 67.57 (C-2), 71.51 (C-3), 73.63 (C-5), 83.27 (C-1), 124.99, 128.23, 128.57, 128.66, 129.73, 129.93, 130.84, 134.69, 150.56 (Triazole), 169.18 (C−S), 169.90, 170.34, 170.41, 171.35 (4 × O$\underline{C}$OCH$_3$); HRMS (ESI), *m*/*z*: Calculated, 584.1703. $C_{28}H_{29}N_3O_9S$ $[M+H]^+$. Found, 584.1785.

4,5-Diphenyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-1-thio-glucopyranose)-1,2,4-triazole (c_1)

White powder, Yield: 77%; mp. 261–262 °C; $[\alpha]_D^{20} = 2°$ ($c = 1.0$, CH_2Cl_2). ^{1}H NMR: 1.97 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.09 (s, 3H, OAc), 3.95–4.10 (m, 1H, H-6a), 4.11–4.26 (m, 1H, H-6b), 4.27–4.41 (m, 1H, H-5), 5.29 (t, 1H, $J_{1,2} = J_{2,3} = 9.3$, H-2), 5.46 (t, 1H, $J_{2,3} = J_{3,4} = 9.3$, H-4), 5.86 (t, 1H, $J_{2,3} = J_{3,4} = 9.3$, H-3), 6.33 (d, 1H, $J_{1,2} = 9$, H-1), 7.20–7.67 (m, 10H, ArH); ^{13}C NMR: 20.61 (2C), 20.71, 20.79 (4 × OCO$\underline{C}$H$_3$), 61.70 (C-6), 67.71 (C-4), 69.79 (C-2), 73.48 (C-3), 74.61 (C-5), 82.73 (C-1), 124.88, 128.20, 128.50, 128.62, 129.75, 129.97, 130.89, 134.63, 150.42 (Triazole), 169.07 (C−S), 169.44, 170.09, 170.69, 171.44 (4 × O$\underline{C}$OCH$_3$); HRMS (ESI), *m*/*z*: Calculated, 584.1703. $C_{28}H_{29}N_3O_9S$ $[M+H]^+$. Found, 584.1787.

Bacterial Strains

The antibacterial activity of the compounds was tested against Gram-positive and Gram-negative bacterial strains including *Enterococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 25923, as well as Gram-negative strains covering *Acinetobacter calcoaceticus* ATCC 23055, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853 and yeast strains including one clinical isolate of *Candida albicans* and one isolate of *Candida tropicalis*.

Preparation of Test Compounds and Antibacterial Activity Assays

The antibacterial activity of the compounds was assayed with the method of Parekh et al.[44] with some modifications. In brief, solutions with 10 μg/μL concentrations of each compound in DMSO (Merck) were being prepared. A loop full of defined strain was inoculated in 25 mL of Nutrient Broth medium (BBL) and was incubated for 24 h in 37°C. Mueller Hinton Agar (MHA) (Merck) plates were prepared according to the manufacturer's recommendations by dissolving 34 g of the medium in 1000 mL of distilled water. Thirty milliliters of autoclaved media were added into a 10 cm plate. Inoculation of each strain was done by the pour-plate method. Two hundred microliter of the activated strain was added into the MHA medium in 45°C and after proper homogenization was distributed into a Petri-dish. The complete microbiological procedures were performed in a laminar airflow to maintain aseptic conditions. After solidification of the media, a well was made in the MHA with a sterile glass tube (6 mm) and 50 μL of drug compound was added into the well. Fifty microliter of DMSO was inoculated into another well as negative control. The antibacterial activities of drug compounds were determined by measuring the inhibition zone formed around each well against defined bacterial strain. Erythromycin and Cephalothin

were used as standard drugs for antibacterial effects against Gram-positive bacteria, Ampicillin and Trimethoprim/ sulfamethoxazole were used as standards for Gram-negative bacteria, and Fluconazole and Nystatin were used as standard drugs for antibacterial effects against yeasts. All strains were resistant to DMSO (negative control).

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