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Original article

# *N*- and *S*-α-L-Arabinopyranosyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles. First synthesis and biological evaluation

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**Abstract**

First synthesis of *N*- and *S*-α-L-arabinopyranosyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles is described. Antimicrobial screening of two selected regioisomeric compounds against *Aspergillus fumigatus*, *Penicillium italicum*, *Syncephalastrum racemosum*, *Candida albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Escherichia coli* are compared.


*Keywords:* Synthesis; Arabinosidation; 1,2,4-Triazoles; 1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiones; Antimicrobial activity

## 1. Introduction

Nucleoside analogs act as antitumor and antiviral agents [1–14] via inhibition of the enzymes, viz. DNA and RNA polymerases, thymidylate synthetase, adenosine deaminase, adenosine kinase, SAH hydrolase etc. of nucleoside, nucleotide or nucleic acid metabolism of the tumor cells or pathogens.

Arabinosides are known to act as good selective antiviral agents [15] and are probably the most extensively investigated inhibitors of DNA polymerase [16,17]. Though it has been difficult to assign a mechanism for their action, these inhibitors may be said to be rather poor substrates for DNA polymerases, often leading to chain termination during replication. The best-known inhibitor belonging to the arabinoside series is Ara-A or Vidarabin [16–19]. It is an important antiviral and antitumor agent but its activity is restricted by its deamination caused by the enzyme adenosine deaminase [2–5]. Several β-L-nucleosides [20–23] have been synthesized and found to be more active and less toxic than their D-isomers [23,24] against HIV-1 and HBV [25,26] viruses. Biochemically, some L-nucleosides are substrates for cellular kinases [27,28] and have greater stability for catabolizing enzymes such as cytidine and adenosine deaminase [29], thereby providing higher anti HIV and anti HBV activities [20].

Many 1,2,4-triazoles [30–49], their ribosides [50–53], and glucosides [54,55] have been reported to possess antibacterial, antifungal, antiviral, anti-inflammatory, anticonvulsant, antidepressant, antitubercular, antihypertensive, analgesic, hypoglycemic, herbicidal and sedative properties.

1,3,4-Thiadiazoles exhibit broad spectrum of biological activities, possibly due to the presence of toxophoric N–C–S moiety [56]. They find applications as antibacterials, antitumor, anti-inflammatory agents, pesticides, herbicides, dyes, lubricants and analytical reagents [57]. The 1,2,4-triazolo [3,4-*b*][1,3,4]-thiadiazole derivatives obtained by fusing the biolabile 1,2,4-triazole and 1,3,4-thiadiazole rings together, are reported to possess antibacterial, antifungal, anti-inflammatory, CNS depressant, hypocholesteremic, antiviral, analgesic, anthelmintic, herbicidal and plant growth regulatory effects [58].

Recently, we reported a simple base induced regioselective method for the α-arabinopyranosylation of different β-lactams [59], 1,2,4-triazoles [60] and 1,2,4-triazines [61] which resulted in the synthesis of many antimicrobial [59,60] and antitumor [61] α-nucleosides.

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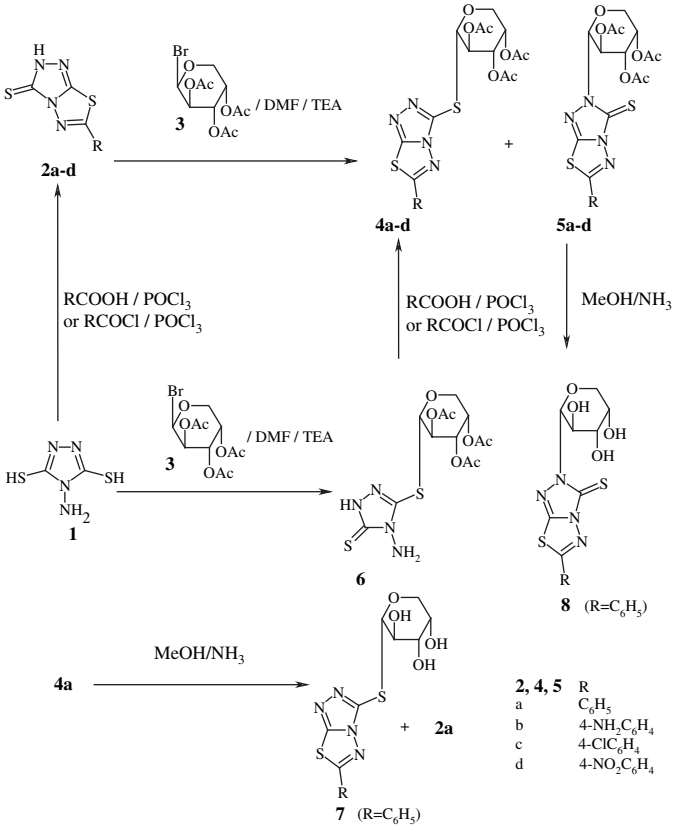
To date there has not been a single report of reactions that produce the α-nucleosides of the 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole ring system. Thus, in this article and in continuation of our ongoing program [54,55,59–68] of research on the synthesis of some biologically active compounds, we report here the first synthesis, antifungal and antibacterial activities of some novel unusual *N*- and *S*-α-L-arabinopyranosyl[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazoles.

## 2. Results and discussion

### 2.1. Chemistry

The starting 6-aryl-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiones (**2a–d**) [68] were prepared from 4-amino-4*H*-[1,2,4]triazole-3,5-dithiol (**1**) by its cyclization with the appropriate carboxylic acid or acid chloride in refluxing phosphoryl chloride (Scheme 1). Arabinosidation of compounds **2a–d** with 1.1 mol equiv of 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl bromide (**3**) gave a chromatographically separable mixture (39–55% overall yield) of two products namely, 3-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosylthio)-6-aryl [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**4a–d**) and 2-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)-6-aryl-2*H*-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazole-3-thiones (**5a–d**).




Scheme 1. Synthesis of *N*- and *S*-α-L-arabinosides of 6-aryl[1,2,4]triazolo [3,4,*b*][1,3,4]thiadiazoles.

The *S*-α-L-configuration of compounds **4a–d** and the *N*-α-L-configuration of compounds **5a–d** are supported based on spectroscopic evidences. Thus, the appearance of the anomeric protons of compounds **5a–d** at δ 6.17–6.19 more downfield than those for the *S*-pyranosides **4a–d** which appear at δ 5.64–5.67, consistent with similar reported data for *N*-[54,55,59–65,67–69] and *S*-glycosides [54,55], confirms the *N*-structure of compounds **5a–d** and the *S*-structure compounds **4a–d**. Such downfield shifts in *N*-pyranosyl derivatives is readily explained by the anisotropic deshielding by the C=S (similar downfield shifts of the anomeric proton by an adjacent C=S was reported for pyrimidine [70–72] and 1,2,4-triazole nucleosides [54,55]). The coupling constant values of the anomeric proton of compounds **4a–d** and **5a–d** consistent with similar reported data [54,55,59–65,67–70] proves that the anomeric proton is in a trans position with respect to the proton in position 2 of the L-arabinopyranosyl ring, a fact that assigns their α-configuration.

Compounds **4a–d** were alternatively synthesized in excellent yields (85–90%) via arabinosidation of 4-amino-4*H*-[1,2,4] triazole-3,5-dithiol (**1**) to give 5-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosylthio)-4-amino-2,4-dihydro[1,2,4]triazole-3-thione (**6**) as the sole product followed by its ring closure using the appropriate aromatic acid or acid chloride in the presence of phosphoryl chloride.

Deacetylation of compound **5a** proceeded smoothly via methanolic ammonia treatment to afford the free nucleoside **8**. On the other hand, deacetylation of compound **4a** gave a mixture of the corresponding free nucleoside **7** and 6-phenyl-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thione (**2a**). The $^1$H NMR data of the compounds **7** and **8** revealed the absence of the acetyl protons at δ 1.95–2.22 and the appearance of the $D_2O$ exchangeable OH protons at δ 4.21–5.16. The IR data of compound **8** as a typical example showed

Table 1
Antimicrobial activity as inhibition zones of compounds **4c** and **5c** compared to standard antimicrobial agents

| Test organisms | **4c**[a] | | | **5c**[a] | | | St.[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Concentration (mg/mL) | | | | | | | | |
| | 1 | 2.5 | 5 | 1 | 2.5 | 5 | 1 | 2.5 | 5 |
| *Aspergillus fumigatus* | + | + | + | 0 | 0 | 0 | ++ | +++ | +++ |
| *Penicillium italicum* | 0 | + | + | 0 | 0 | + | ++ | +++ | +++ |
| *Syncephalastrum racemosum* | 0 | + | + | 0 | 0 | 0 | +++ | +++ | +++ |
| *Candida albicans* | 0 | 0 | 0 | 0 | 0 | 0 | ++ | ++ | ++ |
| *Staphylococcus aureus* | + | + | + | 0 | 0 | + | ++ | ++ | ++ |
| *Pseudomonas aeruginosa* | + | + | + | 0 | 0 | 0 | ++ | +++ | +++ |
| *Bacillus subtilis* | + | + | + | 0 | 0 | 0 | ++ | +++ | +++ |
| *Escherichia coli* | 0 | + | + | 0 | 0 | + | ++ | ++ | ++ |

Note: The test was done using the diffusion agar technique. Inhibition values = 0.1–0.5 cm beyond control = +; inhibition values = 0.6–1.0 cm beyond control = ++; inhibition values = 1.0–1.5 cm beyond control = +++; 0 = not detected.

[a] Hundered microlitres of each conc. was tested (5, 2.5, and 1.0 mg/mL); well diameter = 0.6 cm.

[b] St. = Reference standard; Chloramphenicol was used as a standard antibacterial agent and Terbinafin was used as a standard antifungal agent.

Table 2
Minimum inhibitory concentrations (MICs) of compounds **4c** and **5c** compared to standard antimicrobial agents

| Test organisms | 4c | 5c | Gentamycin | Griseofulvin |
|---|---|---|---|---|
| *Aspergillus fumigatus* | 25 | – | – | 50 |
| *Penicillium italicum* | 1600 | >1600 | – | 50 |
| *Syncephalastrum racemosum* | 1600 | – | – | 50 |
| *Candida albicans* | – | – | – | 50 |
| *Staphylococcus aureus* | 25 | >1600 | 3.12 | – |
| *Pseudomonas aeruginosa* | 12.5 | – | 12.5 | – |
| *Bacillus subtilis* | 25 | – | 1.56 | – |
| *Escherichia coli* | 1600 | >1600 | 12.5 | – |

also the absence of the acetyl carbonyl function at 1748 $cm^{-1}$ and the appearance of the characteristic OH band at 3380 (br) $cm^{-1}$.

### 2.2. Pharmacology

The in vitro antimicrobial screening of compounds **4c** and **5c** were evaluated against selected two Gram-positive bacteria (*Bacillus subtilis* ATCC 6633 and *Staphylococcus aureus* ATCC 25923), two Gram-negative bacteria (*Pseudomonas aeruginosa* ATCC 10145 and *Escherichia coli* ATCC 23556), one yeast (*Candida albicans* ATCC 14053) and three fungal strains (*Aspergillus fumigatus* ATCC 96918, *Penicillium italicum* ATCC 48114 and *Syncephalastrum racemosum* ATCC 18192). The inhibitory effects of *S*-α-L-arabinoside **4c** was studied in comparison with similar effects due to *N*-α-L-arabinoside **5c** using the diffusion agar technique [73] (Table 1). The broth dilution method [74] was used to determine the minimum inhibitory concentrations (MICs) of the tested compounds (Table 2). Thus, compound **4c** showed higher inhibitory effect against *A. fumigatus*, *P. italicum*, *S. racemosum*, *S. aureus*, *P. aeruginosa*, *B. subtilis* and *E. coli* at MIC values of 12.5–1600 μg/mL, compared to compound **5c**.

## 3. Conclusion

The present work describes the first access to the *N*- and *S*-α-L-arabinosides of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole ring system with potential antimicrobial activities. These compounds could serve as possible starting materials for further synthetic transformations. It also expands the synthesis as well as the utility of both base-modified and sugar-modified nucleosides of possible application in the chemotherapy of cancer and viral infections.

## 4. Experimental

### 4.1. Chemistry

All melting points are uncorrected. IR spectra were recorded on a Perkin–Elmer 1430 spectrometer. NMR spectra were measured with a Varian Mercury 300 spectrometer (300 MHz $^1$H NMR, 75 MHz $^{13}$C NMR). Elemental analyses were carried out at the Micro Analytical Center, Cairo University, Giza, Egypt. The starting 6-substituted-2*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiones (**2a–d**) [68], 4-amino-4*H*-[1,2,4]triazole-3,5-dithiol (**1**) [75] and 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl bromide (**3**) [76] were prepared as reported. TLC was performed on Fluka silica gel 60 $F_{254}$ aluminum sheets, and products were detected using 254 nm light. Fluka silica gel 60 (70–230 mesh) was used for column chromatography.

#### 4.1.1. Synthesis of 5-(2,3,4-tri-O-acetyl-α-L-arabinopyranosylthio)-4-amino-2,4-dihydro[1,2,4]triazole-3-thione (6)

To a solution of compound **1** (500 mg, 3.4 mmol) in *N*,*N*-dimethylformamide (3.0 mL) and triethylamine (1 mL, 7.2 mmol) was added 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl bromide (**3**) (900 mg, 2.6 mmol) and the reaction mixture was stirred overnight. The next day, the reaction mixture was diluted with ice–water mixture and the formed precipitate was collected by filtration, washed several times with water and dried at room temperature. The precipitate was extracted with dichloromethane, the solution was concentrated and the residue subjected to silica gel (70–230 mesh) column chromatography. Compound **6** was eluted with 60% ethyl acetate/petroleum ether (bp 40–60 °C) → 80% ethyl acetate/petroleum ether (bp 40–60 °C) and recrystallised from ethanol to give 586 mg (42% based on **1**) of colorless crystals, mp 228–230 °C ($R_f = 0.70$, determined on TLC aluminum sheets using ethyl acetate/petroleum ether (bp 40–60 °C) [60:40, v/v] as a developing system). IR: 3308, 3227, 3156, 2994, 2936, 2798, 1744, 1617, 1510, 1451, 1375, 1299, 1249, 1223, 1161, 1103, 1085, 1059, 1024, 947, 916, 883, 802, 724, 656, 600, 549, 496, 463; $^1$H NMR (DMSO-$d_6$) $\delta$ 2.01, 2.06, 2.08 (3s, 3H each, $CH_3CO$), 3.88 (dd, 1H, $J_{H\text{-}5'-H\text{-}4'} = 2.2$ Hz, $J_{H\text{-}5'-H\text{-}5''} = 12.7$ Hz, H-5′), 3.95 (dd, 1H, $J_{H\text{-}5''-H\text{-}4'} = 3.7$ Hz, $J_{H\text{-}5''-H\text{-}5'} = 12.9$ Hz, H-5″), 5.12 (t, 1H, $J_{H\text{-}2'-H\text{-}1'} = 8.1$ Hz, $J_{H\text{-}2'-H\text{-}3'} = 8.4$ Hz, H-2′), 5.18 (m, 1H, H-4′), 5.26 (dd, 1H, $J_{H\text{-}3'-H\text{-}4'} = 3.4$ Hz, $J_{H\text{-}3'-H\text{-}2'} = 8.4$ Hz, H-3′), 5.57 (d, 1H, $J_{H\text{-}1'-H\text{-}2'} = 8.1$ Hz, H-1′), 5.62 (s, 2H, $D_2O$ exchangeable $NH_2$). Anal. Calcd for $C_{13}H_{18}N_4O_7S_2$ (406.4): C, 38.42; H, 4.46; N, 13.78; S, 15.78. Found: C, 38.33; H, 4.41; N, 13.68; S, 15.84.

#### 4.1.2. General procedures for the synthesis of compounds 4a–d and 5a–d

(A) To a solution of each of compounds **2a–d** (2.1 mmol) in *N*,*N*-dimethylformamide (2.5 mL) and triethylamine (0.36 mL, 2.6 mmol) was added 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl bromide (**3**) (780 mg, 2.3 mmol) and the reaction mixture was stirred overnight. The next day, the reaction mixture was diluted with ice–water mixture and the formed precipitate was collected by filtration, washed several times with water and dried at room temperature. The precipitate was extracted with dichloromethane, the solution was concentrated and the residue subjected to silica gel (70–230 mesh) column chromatography. Compounds **5a–d** were eluted first with 50% ethyl acetate/petroleum ether (bp 40–60 °C) → 70% ethyl acetate/petroleum ether (bp 40–60 °C), followed by compounds **4a–d** with 80% ethyl acetate/petroleum ether (bp 40–60 °C) → 10% methanol/ethyl acetate. The

chromatographically separated crude products were recrystallised from dichloromethane/petroleum ether (bp 40–60 °C). $R_f$ values of the latter compounds were determined on TLC aluminum sheets using ethyl acetate/petroleum ether (bp 40–60 °C) [60:40, v/v] as a developing system.

(B) A mixture of compound **6** (406 mg, 1.0 mmol) and the appropriate carboxylic acid (1 mmol; for the synthesis of compounds **4a**, **b** and **d**) or acyl chloride (1 mmol for the synthesis of compound **4c**) in phosphoryl chloride (2 mL) was heated at reflux temperature in an oil bath for 8 h. The excess of phosphoryl chloride was removed under reduced pressure and the formed residue was extracted with dichloromethane, washed with KOH solution (0.1 M, $2 \times 100$ mL) then water ($4 \times 100$ mL) and dried ($Na_2SO_4$). The solvent was then removed under reduced pressure and the formed residue was recrystallised from dichloromethane/petroleum ether (bp 40–60 °C). $R_f$ values of the latter compounds were determined on TLC aluminum sheets using ethyl acetate/petroleum ether (bp 40–60 °C) [60:40, v/v] as a developing system.

*4.1.2.1. 3-(2,3,4-Tri-O-acetyl-α-L-arabinopyranosylthio)-6-phenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**4a**).* Yield 114 mg (11%, A), 428 mg (87%, B); yellow crystals, mp 206–208 °C ($R_f = 0.77$). $^1$H NMR ($CDCl_3$) δ, 2.11, 2.15, 2.17 (3s, 3H each, $CH_3CO$), 3.75 (dd, 1H, $J_{H\text{-}5'-H\text{-}4'} = 3.3$ Hz, $J_{H\text{-}5'-H\text{-}5''} = 12.3$ Hz, H-5′), 4.25 (dd, 1H, $J_{H\text{-}5''-H\text{-}4'} = 6.3$ Hz, $J_{H\text{-}5''-H\text{-}5'} = 12.3$ Hz, H-5″), 5.24 (dd, 1H, $J_{H\text{-}3'-H\text{-}4'} = 3.3$ Hz, $J_{H\text{-}3'-H\text{-}2'} = 6.9$ Hz, H-3′), 5.30 (dd, 1H, $J_{H\text{-}4'-H\text{-}3'} = 3.3$ Hz, $J_{H\text{-}4'-H\text{-}5''} = 6.3$ Hz, H-4′), 5.37 (t, 1H, $J_{H\text{-}2'-H\text{-}1'} = 6.0$ Hz, $J_{H\text{-}2'-H\text{-}3'} = 6.9$ Hz, H-2′), 5.67 (d, 1H, $J_{H\text{-}1'-H\text{-}2'} = 6.0$ Hz, H-1′), 7.52–7.61 (m, 3H, ArH), 7.88–7.97 (m, 2H, ArH). Anal. Calcd for $C_{20}H_{20}N_4O_7S_2$ (492.5): C, 48.77; H, 4.09; N, 11.38; S, 13.02. Found: C, 48.58; H, 4.00; N, 11.46; S, 12.99.

*4.1.2.2. 3-(2,3,4-Tri-O-acetyl-α-L-arabinopyranosylthio)-6-(4-aminophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**4b**).* Yield 149 mg (14%, A), 447 mg (88%, B); yellow crystals, mp 132–134 °C ($R_f = 0.42$). $^1$H NMR ($CDCl_3$) δ 2.07, 2.10, 2.12 (3s, 3H each, $CH_3CO$), 3.72 (dd, 1H, $J_{H\text{-}5'-H\text{-}4'} = 7.2$ Hz, $J_{H\text{-}5'-H\text{-}5''} = 14.1$ Hz, H-5′), 4.23 (dd, 1H, $J_{H\text{-}5''-H\text{-}4'} = 6.0$ Hz, $J_{H\text{-}5''-H\text{-}5'} = 14.1$ Hz, H-5″), 5.22 (dd, 1H, $J_{H\text{-}3'-H\text{-}4'} = 3.1$ Hz, $J_{H\text{-}3'-H\text{-}2'} = 6.6$ Hz, H-3′), 5.28 (m, 1H, H-4′), 5.35 (t, 1H, $J_{H\text{-}2'-H\text{-}1'} = 5.7$ Hz, $J_{H\text{-}2'-H\text{-}3'} = 6.6$ Hz, H-2′), 5.20–5.50 (br s, 2H, $D_2O$ exchangeable $NH_2$), 5.64 (d, 1H, $J_{H\text{-}1'-H\text{-}2'} = 5.7$ Hz, H-1′), 6.73 (d, 2H, $J = 8.7$ Hz, ArH), 7.68 (d, 2H, $J = 8.7$ Hz, ArH). Anal. Calcd for $C_{20}H_{21}N_5O_7S_2$ (507.5): C, 47.33; H, 4.17; N, 13.80; S, 12.63. Found: C, 47.22; H, 4.12; N, 13.77; S, 12.76.

*4.1.2.3. 3-(2,3,4-Tri-O-acetyl-α-L-arabinopyranosylthio)-6-(4-chlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**4c**).* Yield 509 mg (46%, A), 448 mg (85%, B); pale yellow crystals, mp 186–188 °C ($R_f = 0.53$). IR: 3062, 3027, 2989, 2934, 2911, 2853, 1747, 1595, 1545, 1521, 1483, 1372, 1223, 1090, 1009, 933, 830, 754, 681, 600, 471; $^1$H NMR ($CDCl_3$) δ 2.07, 2.10, 2.12 (3s, 3H each, $CH_3CO$), 3.72 (dd, 1H, $J_{H\text{-}5'-H\text{-}4'} = 3.0$ Hz, $J_{H\text{-}5'-H\text{-}5''} = 12.3$ Hz, H-5′), 4.21 (dd, 1H, $J_{H\text{-}5''-H\text{-}4'} = 6.3$ Hz, $J_{H\text{-}5''-H\text{-}5'} = 12.3$ Hz, H-5″), 5.22 (dd, 1H, $J_{H\text{-}3'-H\text{-}4'} = 3.0$ Hz, $J_{H\text{-}3'-H\text{-}2'} = 6.6$ Hz, H-3′), 5.28 (m, 1H, H-4′), 5.34 (t, 1H, $J_{H\text{-}2'-H\text{-}1'} = 5.7$ Hz, $J_{H\text{-}2'-H\text{-}3'} = 6.6$ Hz, H-2′), 5.64 (d, 1H, $J_{H\text{-}1'-H\text{-}2'} = 5.7$ Hz, H-1′), 7.50 (d, 2H, $J = 7.9$ Hz, ArH), 7.83 (d, 2H, $J = 7.9$ Hz, ArH). Anal. Calcd for $C_{20}H_{19}ClN_4O_7S_2$ (527.0): C, 45.59; H, 3.63; N, 10.63; S, 12.17. Found: C, 45.61; H, 3.59; N, 10.44; S, 12.08.

*4.1.2.4. 3-(2,3,4-Tri-O-acetyl-α-L-arabinopyranosylthio)-6-(4-nitrophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**4d**)* Yield 497 mg (44%, A), 484 mg (90%, B); orange yellow crystals, mp 196–198 °C ($R_f = 0.50$). IR: 3068, 2927, 1747, 1605, 1531, 1456, 1407, 1373, 1348, 1299, 1225, 1157, 1090, 1063, 1005, 935, 888, 855, 798, 753, 713, 688, 673, 600, 509, 457; $^1$H NMR ($CDCl_3$) δ 2.06, 2.09, 2.11 (3s, 3H each, $CH_3CO$), 3.72 (dd, 1H, $J_{H\text{-}5'-H\text{-}4'} = 3.1$ Hz, $J_{H\text{-}5'-H\text{-}5''} = 12.3$ Hz, H-5′), 4.20 (dd, 1H, $J_{H\text{-}5''-H\text{-}4'} = 6.3$ Hz, $J_{H\text{-}5''-H\text{-}5'} = 12.3$ Hz, H-5″), 5.22 (dd, 1H, $J_{H\text{-}3'-H\text{-}4'} = 3.1$ Hz, $J_{H\text{-}3'-H\text{-}2'} = 6.6$ Hz, H-3′), 5.26 (m, 1H, H-4′), 5.32 (t, 1H, $J_{H\text{-}2'-H\text{-}1'} = 5.7$ Hz, $J_{H\text{-}2'-H\text{-}3'} = 6.6$ Hz, H-2′), 5.65 (d, 1H, $J_{H\text{-}1'-H\text{-}2'} = 5.7$ Hz, H-1′), 8.10 (td, 2H, $J = 2.1$, 9.0 Hz, ArH), 8.36 (td, 2H, $J = 2.1$, 9.0 Hz, ArH); $^{13}$C NMR ($CDCl_3$) δ 18.88, 18.98, 19.06 ($CH_3$), 63.01, 65.08, 67.09, 68.02 (C-2′–C-5′), 90.63 (C-1′), 122.87, 122.92, 127.10, 132.44, 148.18, 158.86, 167.98, 168.04, 168.11 (ArC, triazolothiadiazole C, C=O). Anal. Calcd for $C_{20}H_{19}N_5O_9S_2$ (537.5): C, 44.69; H, 3.56; N, 13.03; S, 11.93. Found: C, 44.47; H, 3.51; N, 12.96; S, 11.87.

*4.1.2.5. 2-(2,3,4-Tri-O-acetyl-α-L-arabinopyranosyl)-6-phenyl-2H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-3-thione (**5a**).* Yield 290 mg (28%, A), pale yellow crystals, mp 142–144 °C ($R_f = 0.85$). IR: 3066, 3043, 2924, 2853, 1748, 1557, 1522, 1469, 1371, 1244, 1062, 1002, 948, 764, 687, 602, 497; $^1$H NMR ($CDCl_3$) δ 1.96, 2.04, 2.22 (3s, 3H each, $CH_3CO$), 3.99 (d, 1H, $J_{H\text{-}5'-H\text{-}5''} = 13.5$ Hz, H-5′), 4.20 (dd, 1H, $J_{H\text{-}5''-H\text{-}4'} = 1.9$ Hz, $J_{H\text{-}5''-H\text{-}5'} = 13.5$ Hz, H-5″), 5.29 (dd, 1H, $J_{H\text{-}3'-H\text{-}4'} = 3.4$ Hz, $J_{H\text{-}3'-H\text{-}2'} = 10.2$ Hz, H-3′), 5.43 (d, 1H, $J_{H\text{-}4'-H\text{-}5''} = 1.9$ Hz, H-4′), 5.88 (t, 1H, $J_{H\text{-}2'-H\text{-}1'} = 9.0$ Hz, $J_{H\text{-}2'-H\text{-}3'} = 10.2$ Hz, H-2′), 6.19 (d, 1H, $J_{H\text{-}1'-H\text{-}2'} = 9.0$ Hz, H-1′), 7.48–7.63 (m, 3H, ArH), 7.93 (td, 2H, $J = 1.2$, 7.2 Hz, ArH). Anal. Calcd for $C_{20}H_{20}N_4O_7S_2$ (492.5): C, 48.77; H, 4.09; N, 11.38; S, 13.02. Found: C, 48.80; H, 4.15; N, 11.45; S, 12.98.

*4.1.2.6. 2-(2,3,4-Tri-O-acetyl-α-L-arabinopyranosyl)-6-(4-aminophenyl)-2H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-3-thione (**5b**).* Yield 277 mg (26%, A), yellow crystals, mp 154–156 °C ($R_f = 0.75$). IR: 3377, 3228, 3016, 2934, 2854, 2360, 1748, 1632, 1582, 1497, 1472, 1456, 1429, 1418, 1377, 1339, 1313, 1266, 1224, 1177, 1121, 1062, 1002, 933, 841, 823, 777, 717, 686, 670, 649, 625, 600, 495, 424, 406; $^1$H NMR ($CDCl_3$) δ 1.96, 2.04, 2.21 (3s, 3H each, $CH_3CO$),

3.98 (d, 1H, $J_{H\text{-}5'-H\text{-}5''} = 13.5$ Hz, H-5′), 4.20 (dd, 1H, $J_{H\text{-}5''-H\text{-}4'} = 1.8$ Hz, $J_{H\text{-}5''-H\text{-}5'} = 13.5$ Hz, H-5″), 4.72 (br s, 2H, $D_2O$ exchangeable $NH_2$), 5.28 (dd, 1H, $J_{H\text{-}3'-H\text{-}4'} = 3.3$ Hz, $J_{H\text{-}3'-H\text{-}2'} = 10.2$ Hz, H-3′), 5.43 (dd, 1H, $J_{H\text{-}4'-H\text{-}3'} = 3.3$ Hz, $J_{H\text{-}4'-H\text{-}5''} = 1.8$ Hz, H-4′), 5.90 (t, 1H, $J_{H\text{-}2'-H\text{-}1'} = 9.0$ Hz, $J_{H\text{-}2'-H\text{-}3'} = 10.2$ Hz, H-2′), 6.18 (d, 1H, $J_{H\text{-}1'-H\text{-}2'} = 9.0$ Hz, H-1′), 6.74 (d, 2H, $J = 8.1$ Hz, ArH), 7.71 (d, 2H, $J = 8.1$ Hz, ArH). Anal. Calcd for $C_{20}H_{21}N_5O_7S_2$ (507.5): C, 47.33; H, 4.17; N, 13.80; S, 12.63. Found: C, 47.57; H, 4.07; N, 13.69; S, 12.55.

*4.1.2.7. 2-(2,3,4-Tri-O-acetyl-α-L-arabinopyranosyl)-6-(4-chlorophenyl)-2H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-3-thione (**5c**).* Yield 77 mg (7%, A), pale yellow crystals, mp 210–212 °C ($R_f = 0.81$). IR: 3024, 2968, 2360, 1748, 1580, 1553, 1522, 1470, 1391, 1340, 1311, 1263, 1223, 1120, 1089, 1061, 1000, 950, 875, 835, 794, 726, 651, 624, 599, 496, 459, 444, 433, 428, 417; $^1$H NMR ($CDCl_3$) $\delta$ 1.95, 2.03, 2.21 (3s, 3H each, $CH_3CO$), 3.98 (dd, 1H, $J_{H\text{-}5'-H\text{-}4'} = 0.9$ Hz, $J_{H\text{-}5'-H\text{-}5''} = 13.3$ Hz, H-5′), 4.19 (dd, 1H, $J_{H\text{-}5''-H\text{-}4'} = 1.8$ Hz, $J_{H\text{-}5''-H\text{-}5'} = 13.3$ Hz, H-5″), 5.29 (dd, 1H, $J_{H\text{-}3'-H\text{-}4'} = 3.3$ Hz, $J_{H\text{-}3'-H\text{-}2'} = 10.2$ Hz, H-3′), 5.43 (dd, 1H, $J_{H\text{-}4'-H\text{-}3'} = 3.3$ Hz, $J_{H\text{-}4'-H\text{-}5''} = 1.8$ Hz, H-4′), 5.85 (t, 1H, $J_{H\text{-}2'-H\text{-}1'} = 9.3$ Hz, $J_{H\text{-}2'-H\text{-}3'} = 10.2$ Hz, H-2′), 6.17 (d, 1H, $J_{H\text{-}1'-H\text{-}2'} = 9.3$ Hz, H-1′), 7.51 (td, 2H, $J = 2.1$, 8.7 Hz, ArH), 7.86 (td, 2H, $J = 2.1$, 8.7 Hz, ArH). Anal. Calcd for $C_{20}H_{19}ClN_4O_7S_2$ (527.0): C, 45.59; H, 3.63; N, 10.63; S, 12.17. Found: C, 45.63; H, 3.71; N, 10.42; S, 12.09.

*4.1.2.8. 2-(2,3,4-Tri-O-acetyl-α-L-arabinopyranosyl)-6-(4-nitrophenyl)-2H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-3-thione (**5d**).* Yield 124 mg (11%, A); pale yellow crystals, mp 170–172 °C ($R_f = 0.88$). IR: 3071, 2928, 2849, 1748, 1605, 1532, 1487, 1394, 1372, 1347, 1245, 1118, 1087, 1063, 1001, 936, 854, 795, 752, 716, 687, 598, 501, 453; $^1$H NMR ($CDCl_3$) $\delta$ 1.95, 2.03, 2.21 (3s, 3H each, $CH_3CO$), 3.99 (d, 1H, $J_{H\text{-}5'-H\text{-}5''} = 13.4$ Hz, H-5′), 4.20 (dd, 1H, $J_{H\text{-}5''-H\text{-}4'} = 1.5$ Hz, $J_{H\text{-}5''-H\text{-}5'} = 13.4$ Hz, H-5″), 5.29 (dd, 1H, $J_{H\text{-}3'-H\text{-}4'} = 3.0$ Hz, $J_{H\text{-}3'-H\text{-}2'} = 10.2$ Hz, H-3′), 5.43 (dd, 1H, $J_{H\text{-}4'-H\text{-}5''} = 1.5$ Hz, $J_{H\text{-}4'-H\text{-}3'} = 3.0$ Hz, H-4′), 5.84 (t, 1H, $J_{H\text{-}2'-H\text{-}1'} = 9.0$ Hz, $J_{H\text{-}2'-H\text{-}3'} = 10.2$ Hz, H-2′), 6.17 (d, 1H, $J_{H\text{-}1'-H\text{-}2'} = 9.0$ Hz, H-1′), 8.12 (td, 2H, $J = 2.1$, 8.7 Hz, ArH), 8.39 (td, 2H, $J = 2.1$, 8.1 Hz, ArH); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.54, 20.71, 20.91 ($CH_3$), 67.25, 67.59, 67.81, 71.12 (C-2′–C-5′), 83.63 (C-1′), 124.65, 128.67, 133.66, 149.68, 150.35, 161.90, 162.53, 169.34, 169.84, 170.23 (ArC, triazolothiadiazole C, C=O). Anal. Calcd for $C_{20}H_{19}N_5O_9S_2$ (537.5): C, 44.69; H, 3.56; N, 13.03; S, 11.93. Found: C, 44.61; H, 3.38; N, 13.14; S, 11.99.

*4.1.3. Deacetylation of compounds **4a** and **5a**. General procedure*

Dry gaseous ammonia was passed through a solution of each of compounds **4a** and **5a** (1 mmol) in dry methanol (10 mL) for about 1 h with cooling and stirring then the reaction mixture was stirred at room temperature over night. The resulting mixture was then concentrated at reduced pressure to afford a solid residue which was washed several times via boiling in chloroform (100 mL) and decantation. The residue was dried at room temperature, column chromatographed (chloroform → 90% methanol/chloroform), and recrystallised from methanol to give compounds **7** and **8**. $R_f$ values of the latter compounds were determined on TLC aluminum sheets using chloroform/methanol (95:5, v/v) as a developing system. Compound **2a** (35 mg, 15%) was eluted from the same column used to separate compound **7** using methanol as an eluent. Identification of compound **2a** was assigned by its mp, mixed mp, analytical and spectral data compared to reported data [68].

*4.1.3.1. 3-(α-L-Arabinopyranosylthio)-6-phenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**7**).* Yield 187 mg (51%); pale yellow crystals, mp 178–180 °C ($R_f = 0.05$). $^1$H NMR (DMSO-$d_6$) $\delta$ 4.10–3.10 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-5″), 4.21 (d, 1H, $J = 6.0$ Hz, $D_2O$ exchangeable OH), 4.57 (d, 1H, $J = 6.0$ Hz, $D_2O$ exchangeable OH), 4.91 (br s, 1H, $D_2O$ exchangeable OH), 5.46 (d, 1H, $J_{H\text{-}1'-H\text{-}2'} = 8.7$ Hz, H-1′), 7.55 (m, 3H, ArH), 7.89 (d, 1H, $J = 7.8$ Hz, ArH), 7.95 (d, 1H, $J = 7.8$ Hz, ArH). Anal. Calcd for $C_{14}H_{14}N_4O_4S_2$ (366.4): C, 45.89; H, 3.85; N, 15.29; S, 17.50. Found: C, 45.79; H, 3.69; N, 15.24; S, 17.41.

*4.1.3.2. 2-α-L-Arabinopyranosyl-6-phenyl-2H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-3-thione (**8**).* Yield 308 mg (84%), pale yellow crystals, mp 170–172 °C ($R_f = 0.11$). IR: 3380 (br), 3053, 2924, 1648, 1595, 1557, 1445, 1420, 1365, 1277, 1149, 1081, 1000, 854, 769, 694, 633; $^1$H NMR (DMSO-$d_6$) $\delta$ 4.40–3.12 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-5″), 4.72 (br s, 1H, $D_2O$ exchangeable OH), 5.00 (br s, 1H, $D_2O$ exchangeable OH), 5.16 (br s, 1H, $D_2O$ exchangeable OH), 5.49 (d, 1H, $J_{H\text{-}1'-H\text{-}2'} = 9.0$ Hz, H-1′), 7.56 (m, 3H, ArH), 7.91 (d, 1H, $J = 7.5$ Hz, ArH), 7.97 (d, 1H, $J = 7.5$ Hz, ArH). Anal. Calcd for $C_{14}H_{14}N_4O_4S_2$ (366.4): C, 45.89; H, 3.85; N, 15.29; S, 17.50. Found: C, 45.93; H, 3.79; N, 15.42; S, 17.38.

*4.2. Pharamacology*

For the antimicrobial screening using the diffusion agar technique [73], compounds **4c** and **5c** were dissolved in dimethyl sulfoxide (DMSO) (5 mg/mL). Further dilutions of the compounds and standard drugs were prepared at the required quantities of 5, 2.5, 1 mg/mL concentrations. All the compounds were tested for their in vitro growth inhibitory activity against different bacteria, yeasts and fungi. Origin of microbial strains are *S. aureus* ATCC 25923 and *B. subtilis* ATCC 6633 as Gram-positive, *E. coli* ATCC 23556 and *P. aeruginosa* ATCC 10145 as Gram-negative bacteria, *C. albicans* ATCC 14053 as yeast, and, *A. fumigatus* ATCC 96918, *P. italicum* ATCC 48114 and *S. racemosum* ATCC 18192) as fungi. Chloramphenicol and Terbinafin were used as control drugs. The antimicrobial activities were expressed as the diameter of the inhibition zones (Table 1).

For the determination of the minimum inhibitory concentrations (MICs), compounds **4c** and **5c** were dissolved in dimethyl sulfoxide (DMSO) (1.6 mg/mL). Further dilutions of the tested compounds and standard drugs in the test medium were prepared at the required quantities of 800, 400, 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 μg/mL concentrations with Mueller–Hinton broth and Sabouraud dextrose broth. The minimum inhibitory concentrations (MICs) were determined using the twofold serial dilution technique [74]. A control test was also performed containing inoculated broth supplemented with only dimethyl sulfoxide (DMSO) at the same dilutions used in our experiments. Gentamycin and Griseofulvin were used as control drugs. The data on the antifungal and antibacterial activities of the compounds and the control drugs as MIC, μg/mL, values are given in Table 2.

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