Arch Pharm Res Vol 34, No 7, 1085-1096, 2011
DOI 10.1007/s12272-011-0706-y

Archives of Pharmacal Research
www.springer.com/12272

Synthesis and Antimicrobial Activity of New 1-[(tetrazol-5-yl)methyl] indole Derivatives, their 1,2,4-Triazole Thioglycosides and Acyclic Analogs

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(Received July 18, 2010/Revised November 11, 2010/Accepted December 20, 2010)

New 1-[(tetrazol-5-yl)methyl]indole derivatives, their acyclic nucleoside analogs and the corresponding glycoside derivatives were synthesized. Furthermore, the [(1,2,4-triazol-3-yl)methyl]-2*H*-tetrazole derivative as well as the corresponding thioglucoside were prepared. The synthesized compounds were tested for their antimicrobial activity against *Aspergillus Niger*, *Penicillium sp*, *Candida albican*, *Bacillus subtilis, Streptococcus lacti*, *Escherichia coli*, *Pseudomonas sp*., and *streptomyces sp*. Compounds **3**, **5** and **19b** exhibited potent antibacterial activity and compounds **4**, **5** and **10** exhibited high activities against the tested fungi compared with fusidic acid.

Key words: Indole, 1,2,4-Triazole thioglycosides, Tetrazole glycosides, Antibacterial, Antifungal activity

INTRODUCTION

Indole is an important structural motif present in many biologically active natural products (Saxton, 1983; Hashimoto et al., 1984; Shimizu et al., 1984; Kamijo and Yamamoto, 2003). The chemistry of indoles has been increasingly studied because of their interesting biological activities (Nakashima et al., 1984; Chen et al., 1998; Hong et al., 2002; Chang et al., 2005). They have been reported to possess a wide variety of biological properties including anti-inflammatory (Andreani et al., 1994; Misra et al., 1996), antibacterial (Pandeya et al., 1999; Samosorn et al., 2006), antiviral (Bal et al., 2005; Pirrung et al., 2005), anti-TB (Sriram et al., 2005) and antifungal activities (Lundt and Anderson, 1971) as well as analgesic (Dekker et al., 1975), and antitumor effects (Blum et al., 2001; Zhang et al., 2005). A number of indole derivatives are inhibitors of the Nor A efflux pump in the human pathogenic (bacterium Staphylococcus*)* (Markham et al., 1999). Investigation of the structure-activity relationships for many indole compounds revealed that *N*-alkylation (Webber et al., 1996; Velezheva et al., 2004) is effective in causing a marked rise in activity against various bacteria, fungi and viruses. On the other hand, tetrazole derivatives have been found to have applications as carboxylic surrogates, bioisosteres of carboxylic acids (Herr, 2002; Master et al., 2005) and lipophilic spacers in pharmaceuticals. This has led to therapeutic appli- cations resulting in compounds with antihypertensive, antiallergic and antibiotic activities (Bond et al., 2006). Structural fragments or formulas with tetrazole derivatives having pronounced antimicrobial activities include the *N*-substituted tetrazole **I** (Fig. 1) which also has antinociceptive activity (Rajasekaran and Thampi, 2005). It has been reported that the attachment of sugar moieties to the 1,2,4-triazole nucleus through a thioglycosidic linkage enhances its antimicrobial activity. The 1,2,4-triazole thioglycosides with formula **II** (Fig. 1) have been shown to possess potential antimicrobial activity (Khalil, 2006, 2007). The above facts and our interest (El-Sayed et al., 2008a, 2008b, 2009a, 2009b, 2009c) in novel biologically active leads by means of attaching of carbohydrate moieties to newly synthesized heterocycles promoted us to synthesize new substituted tetrazole glycosides, their acyclic analogs and

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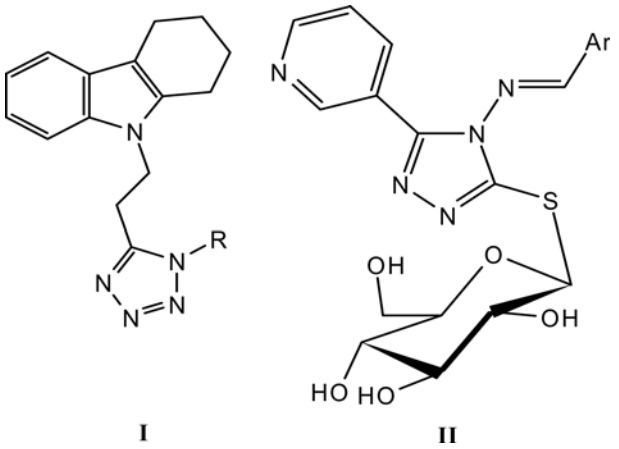


Fig. 1. Antimicrobial substituted tetrazole and trriazole derivatives

1,2,4-triazoles thioglycosides, and to evaluate their antimicrobial activity. Furthermore, it was of interest to determine the influence of attachment of sugar moieties to the synthesized tetrazole and substituted 1,2, 4-triazole derivatives on their antimicrobial activity.

MATERIALS AND METHODS

Melting points were determined using a kofler block apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer model 1720 FTIR spectrometer using KBr discs. NMR spectra were recorded on a Varian Gemini 300 NMR Spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C or on a Bruker Ac-250 FT spectrometer at 250 MHz for ^{1}H and at 62.9 MHz for ^{13}C with TMS as a standard. Progress of the reactions was monitored by TLC (aluminum silica gel plates 60 F 245). Elemental analyses were performed at the Microanalytical Data Centre at Faculty of Science, Cairo University, Egypt.

(3-Acetyl-1*H*-indol-1-yl)acetonitrile (2)

To a solution of 3-acetylindole (3.18 g, 20 mmol) and sodium hydride (0.24 g, 20 mmol) in *N*,*N*-dimethylformamide (30 mL), was added chloroacetonitrile (1.51 g, 20 mmol) dropwise and the reaction mixture was stirred for 12 h at room temperature, then poured into ice water. The obtained precipitate was filtered, dried, and recrystallized from ethanol to give compound **2**. Pale yellow powder (2.89 g, 73%), m.p. 182-183ºC; IR (KBr) ν 2214 (CN), 1705 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 2.48 (s, 3H, *CH*$_3$CO), 5.32 (s, 2H, CH$_2$), 7.28 (m, 1H, Ar-H), 7.38 (m, 1H, Ar-H), 7.42 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.82 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.74 (s, 1H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ 26.75 (*CH*$_3$CO), 44.5 (CH$_2$), 116.85 (CN), 118.25, 122.95, 133.67, 137.12, 139.95, 141.20, 145,66, 149.25 (Ar-8C), 182.16 (C=O). Anal. Calcd. for $C_{12}H_{10}N_2O$ (198.22): C, 72.71; H, 5.08; N, 14.13. Found: C, 72.43; H, 4.89; N, 13.92.

1-[1-(2*H*-Tetrazol-5-ylmethyl)-1*H*-indol-3-yl] ethanone (3)

A mixture of compound **2** (3.96 g, 20 mmol), sodium azide (1.3 g, 20 mmol) and ammonium chloride (1.06 g, 20 mmol) in *N*,*N*-dimethylformamide (30 mL) was heated for 7 h at 120ºC. The solvent was removed under reduced pressure and the residue was dissolved in water (100 mL) and carefully acidified with conc. hydrochloric acid to pH 2. The solution was cooled to 5ºC in an ice bath to precipitate compound **3**. Pale yellow powder (3.42 g, 71%), m.p. 212-213ºC; IR (KBr) ν 3265 (NH), 1708 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 2.48 (s, 3H, *CH*$_3$CO), 5.33 (s, 2H, CH$_2$), 7.31 (m, 1H, Ar-H), 7.42 (m, 1H, Ar-H), 7.46 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.87 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.72 (s, 1H, Ar-H), 12.15 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 26.76 (*CH*$_3$CO), 44.52 (CH$_2$), 119.24, 123.55, 134.61, 138.33, 140.05, 141.80, 145,69, 149.84 (Ar-8C), 156.81 (C=N), 182.18 (C=O). Anal. Calcd. for $C_{12}H_{11}N_5O$ (241.10): C, 59.74; H, 4.60; N, 29.03. Found: C, 59.61; H, 4.49; N, 28.79.

Ethyl{5-[(3-acetyl-1*H*-indol-1-yl)methyl]-2*H*-tetrazol-2-yl}acetate (4)

To a solution of compound **3** (2.41 g, 10 mmol) and anhydrous potassium carbonate (1.38 g, 10 mmol) in *N*,*N*-dimethylformamide (30 mL), ethyl chloroacetate (1.22 g, 10 mmol) was added dropwise. The mixture was stirred at room temperature for 8 h and then poured into ice-cold water. The formed solid was filtered, dried and recrystallized from ethanol to afford compound **4**. Pale yellow powder (2.42 g, 74%), m.p. 139-140ºC; IR (KBr) ν 1745 (C=O), 1705 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 1.44 (t, 3H, *J* = 5.8 Hz, CH$_2$*CH*$_3$), 2.42 (s, 3H, *CH*$_3$CO), 3.92 (q, 2H, *J* = 5.8 Hz, *CH*$_2$CH$_3$), 4.55 (s, 2H, CH$_2$), 5.41 (s, 2H, CH$_2$), 7.33 (m, 1H, Ar-H), 7.40 (m, 1H, Ar-H), 7.47 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.84 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.72 (s, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 20.15, 26.76 (2CH$_3$), 39.20, 42.76, 45.85 (3CH$_2$), 118.89, 123.79, 135.11, 138.54, 140.10, 141.87, 145.62, 149.95 (Ar-8C), 156.81 (C=N), 169.25, 182.21 (2C=O). Anal. Calcd. for $C_{16}H_{17}N_5O_3$ (327.34): C, 58.71; H, 5.23; N, 21.39. Found: C, 58.52; H, 5.11; N, 21.14.

2-{5-[(3-Acetyl-1*H*-indol-1-yl)methyl]-2*H*-tetrazol-2-yl}acetohydrazide (5)

A mixture of compound **4** (3.27 g, 10 mmol) and hydrazine hydrate (2 mL, 99%) was refluxed in dry

ethanol (20 mL) for 4 h. The solvent was reduced under vacuum and left to stand overnight at 5°C. The precipitated solid was filtered, washed several times with cold ethanol, dried and recrystallized from an ethanol-water mixture (1:1) to give compound **5**. Pale yellow powder (2.51 g, 80%), m.p. 225-226°C; IR (KBr) ν 3342 (NH_2), 3315 (NH), 1705 cm^{-1} (C=O), 1668 (C=O); ^{1}H-NMR (DMSO-d_6): δ 2.40 (s, 3H, CH_3CO), 4.57 (s, 2H, CH_2), 5.38 (s, 2H, CH_2), 5.58 (s, 2H, NH_2), 7.30 (m, 1H, Ar-H), 7.38 (m, 1H, Ar-H), 7.47 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.82 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.74 (s, 1H, Ar-H), 9.87 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 26.50 (CH_3), 42.45, 45.59 ($2CH_2$), 118.84, 123.72, 134.88, 138.24, 139.79, 141.15, 145.60, 148.68 (Ar-8C), 156.14 (C=N), 167.12, 182.17 (2C=O). Anal. Calcd. for $C_{14}H_{15}N_7O_2$ (313.31): C, 53.67; H, 4.83; N, 31.29. Found: C, 53.52; H, 5.10; N, 31.14.

1-{2-[5-[(3-Acetyl-1*H*-indol-1-yl)methyl]-2*H*-tetrazol-2-yl]acetyl}-4-(4-chlorophenyl)thiosemicarbazide (6)

To a well-stirred solution of compound **5** (3.31 g, 10 mmol) in absolute ethanol (30 mL), *p*-chlorophenylisothiocyanate (1.86 g, 10 mmol) was added and the reaction mixture was heated under reflux for 2 h. The mixture was poured into ice water and the precipitate was filtered, washed several times with water, dried and recrystallized from dioxan to give compound **6**. Pale yellow powder (3.89 g, 78%), m.p. 219-220°C; IR (KBr) ν 3322 (NH), 1705 (C=O), 1665 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3CO), 4.54 (s, 2H, CH_2), 5.40 (s, 2H, CH_2), 7.20 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.31 (m, 1H, Ar-H), 7.39 (m, 1H, Ar-H), 7.45 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.62 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.80 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.74 (s, 1H, Ar-H), 9.78 (s, 1H, NH), 10.12 (bs, 2H, 2NH); ^{13}C-NMR (DMSO-d_6): δ 26.51 (CH_3), 42.64, 45.59 ($2CH_2$), 118.50-149.97 (Ar-14C), 156.23 (C=N), 167.43 (C=O), 173.86 (C=S), 182.27 (C=O). Anal. Calcd. for $C_{21}H_{19}ClN_8O_2S$ (482.95): C, 52.23; H, 3.97; N, 23.20. Found: C, 52.11; H, 4.05; N, 23.10.

3-Acetyl-1-{2-[[4-(4-chlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-3-yl]methyl]-2*H*-tetrazol-5-yl}methyl-1*H*-indole (7)

Compound **6** (2.50 g, 5 mmol) was heated under reflux in 30 mL of 2*N* sodium hydroxide solution for 4 h. The reaction mixture was cooled and acidified with diluted hydrochloric acid to afford a precipitate which was filtered, washed with ice-cold water, dried and crystallized from ethanol to give compound **7**. Pale yellow powder (1.76 g, 76%), m.p. 207-208°C; IR (KBr) ν 3322 (NH), 1705 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 2.41 (s, 3H, CH_3CO), 4.56 (s, 2H, CH_2), 5.42 (s, 2H, CH_2), 7.22 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.33 (m, 1H, Ar-H), 7.38 (m, 1H, Ar-H), 7.42 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.69 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.87 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.72 (s, 1H, Ar-H), 12.88 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ 25.89 (CH_3), 42.62, 45.25 ($2CH_2$), 119.18-149.62 (Ar-14C), 155.95, 156.24 (2C=N), 170.87 (C=S), 182.21 (C=O). Anal. Calcd. for $C_{21}H_{17}ClN_8OS$ (464.93): C, 54.25; H, 3.69; N, 24.10. Found: C, 54.18; H, 3.80; N, 23.89.

3-Acetyl-1-{2-[[4-(4-chlorophenyl)-5-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylthio)-4*H*-1,2,4-triazol-3-yl]methyl]-2*H*-tetrazol-5-yl}methyl-1*H*-indole (9)

To a solution of compound **7** (2.33 g, 5 mmol) in aqueous potassium hydroxide [0.28 g, 5 mmol in distilled water (3 mL)] was added a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2.06 g, 5 mmol) in acetone (30 mL). The reaction mixture was stirred at room temperature until the reaction was complete as assessed by TLC (chloroform/methanol 99.5:0.5). The solvent was evaporated under reduced pressure at 40°C and the residue was washed with distilled water to remove potassium bromide formed. The product was dried and crystallized from ethanol to give compound **8**. Pale yellow powder (3.18 g, 80%), m.p. 149-150°C; IR (KBr) ν 1745 (C=O), 1705 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 1.95, 2.05, 2.11, 2.14, 2.41 (5s, 15H, 5 CH_3CO), 4.05 (m, 1H, H-5), 4.14 (dd, 1H, $J_{6,6}$ = 11.4 Hz, $J_{5,6}$ = 2.8 Hz, H-6), 4.17 (m, 1H, H-6), 4.85 (s, 2H, CH_2), 4.95 (t, 1H, $J_{3,4}$ = 9.3 Hz, H-4), 5.25 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 5.37 (t, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 5.39 (s, 2H, CH_2), 5.76 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 7.25 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.37 (m, 1H, Ar-H), 7.41 (m, 1H, Ar-H), 7.50 (m, 3H, Ar-H), 7.88 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.73 (s, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 19.30, 19.55, 20.19, 20.23, 25.41 (5CH_3CO), 49.30, 52.27 ($2CH_2$), 62.71 (C-6), 64.23 (C-4), 68.72 (C-3), 71.24 (C-2), 71.92 (C-5), 87.12 (C-1), 119.10-150.05 (Ar-14C), 156.40, 157.05, 159.41 (3C=N), 169.64, 170.30, 171.27, 171.49, 182.18 (5C=O). Anal. Calcd. for $C_{35}H_{35}ClN_8O_{10}S$ (795.22): C, 52.86; H, 4.44; N, 14.09. Found: C, 52.67; H, 4.25; N, 13.88.

3-Acetyl-1-{2-[[4-(4-chlorophenyl)-5-(β-D-glucopyranosylthio)-4*H*-1,2,4-triazol-3-yl]methyl]-2*H*-tetrazol-5-yl}methyl-1*H*-indole (10)

Dry gaseous ammonia was passed through a solution of a protected glucoside **9** (3.98 g, 5 mmol) in dry methanol (20 mL) at 0°C for 1 h and then stirring was continued at room temperature for 5 h. The solvent was evaporated under reduced pressure at 40°C to give a solid residue, which was recrystallized from ethanol to give compound **10**. Pale yellow powder (2.45 g,

78%), m.p. 189-190°C; IR (KBr) ν 3467-3440 (OH), 1710 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 2.42 (s, 3H, CH_3CO), 3.39 (m, 2H, H-6,6), 3.49 (m, 1H, H-5), 3.73 (m, 2H, H-3, H-4), 4.20 (t, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 4.27 (t, 1H, *J* = 6.4 Hz, OH), 4.35 (m, 1H, OH), 4.87 (s, 2H, CH_2), 4.95 (m, 1H, OH), 5.12 (t, 1H, *J* = 6.2 Hz, OH), 5.41 (s, 2H, CH_2), 5.80 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 7.25 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.37 (m, 1H, Ar-H), 7.41 (m, 1H, Ar-H), 7.48 (m, 3H, Ar-H), 7.84 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.74 (s, 1H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ 25.41 (CH_3), 49.25, 52.21 (2CH_2), 62.83 (C-6), 65.12 (C-4), 69.10 (C-3), 70.82 (C-2), 72.61 (C-5), 89.66 (C-1), 119.18-149.89 (Ar-14C), 156.42, 157.12, 159.42 (3C=N), 182.42 (C=O). Anal. Calcd. for $C_{27}H_{27}ClN_8O_6S$ (627.07): C, 51.71; H, 4.34; N, 17.87. Found: C, 51.40; H, 4.25; N, 17.67.

General procedure of Synthesis of compounds 11, 13, 15 and 16

To a well-stirred solution of compound **3** (1.21 g, 5 mmol) and anhydrous potassium carbonate (0.69 g, 5 mmol) in *N*,*N*-dimethylformamide (15 mL) was added 2-(2-chloroethoxy)ethanol, 3-chloropropane-1,2-diol, 2-chloro-1,1-dimethoxyethane or chloroethylmethyl ether (5 mmol) and stirring was continued at 70°C for 6-9 h (TLC). The solvent was evaporated under reduced pressure and the residue was recrystallized from ethanol to give compounds **11**, **13**, **15** and **16**.

General procedure of Synthesis of 12 and 14

To a solution of compound **11** or **13** (5 mmol) in pyridine (10 mL) was added acetic anhydride (5 mmol or 10 mmol, respectively). The solution was stirred at room temperature for 6-8 h (TLC). The reaction mixtures were poured into ice water with stirring and the solids that precipitated were collected by filtration, washed with water, dried and recrystallized from dioxane/ethanol to give compounds **12** or **14**, respectively.

1-{1-[[2-[-(2-Hydroxyethoxy)ethyl]-2*H*-tetrazol-5-yl]methyl]-1*H*-indol-3-yl}ethanone (11)

Pale yellow powder (1.23 g, 75%), m.p. 203-204°C; IR (KBr) ν 3426 (OH), 1705 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 2.42 (s, 3H, CH_3CO), 3.87 (t, 2H, *J* = 5.8 Hz, CH_2), 4.12 (m, 2H, CH_2), 4.24 (t, 2H, *J* = 5.8 Hz, CH_2), 4.88 (m, 1H, OH), 5.10 (t, 2H, *J* = 5.6 Hz, CH_2), 5.35 (s, 2H, CH_2), 7.28 (m, 1H, Ar-H), 7.37 (m, 1H, Ar-H), 7.48 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.84 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.71 (s, 1H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ 26.76 (CH_3CO), 48.32, 49.70, 60.74, 64.12, 69.52 (5CH_2), 119.30, 123.51, 134.62, 137.37, 140.12, 142.10, 145,71, 150.11 (Ar-8C), 156.84 (C=N), 182.44 (C=O). Anal. Calcd. for $C_{16}H_{19}N_5O_3$ (329.35): C, 58.35; H, 5.81; N, 21.26. Found: C, 58.30; H, 5.84; N, 21.31.

2-{3-[5-[(3-Acetyl-1*H*-indol-1-yl)methyl]-2*H*-tetrazol-2-yl]propoxy}ethyl acetate (12)

Pale yellow powder (1.46 g, 79%), m.p. 157-158°C; IR (KBr) ν 1742 (C=O), 1710 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 2.08, 2.44 (2s, 6H, 2CH_3CO), 3.87 (t, 2H, *J* = 5.8 Hz, CH_2), 4.12 (t, 2H, *J* = 5.6 Hz, CH_2), 4.24 (t, 2H, *J* = 5.6 Hz, CH_2), 5.10 (t, 2H, *J* = 5.8 Hz, CH_2), 5.37 (s, 2H, CH_2), 7.28 (m, 2H, Ar-H), 7.36 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.50 (d, 1H, *J* = 8.0 Hz, Ar-H), 8.74 (s, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 20.14, 26.76 (2CH_3), 48.50, 49.77, 60.90, 64.44, 69.58 (5CH_2), 119.15, 123.57, 134.60, 137.42, 140.23, 142.15, 145.731, 149.91 (Ar-8C), 156.92 (C=N), 169.89, 182.44 (2C=O). Anal. Calcd. for $C_{18}H_{21}N_5O_4$ (371.39): C, 58.21; H, 5.70; N, 18.86. Found: C, 58.25; H, 5.76; N, 18.91.

1-{1-[[2-(2,3-Dihydroxypropyl)-2*H*-tetrazol-5-yl]methyl]-1*H*-indol-3-yl}ethanone (13)

Pale yellow powder (1.17 g, 74%), m.p. 214-215°C; IR (KBr) ν 3428 (OH), 1708 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 2.47 (s, 3H, CH_3CO), 4.62 (d, 2H, *J* = 6.4 Hz, CH_2), 4.92 (m, 2H, CH_2), 5.05 (m, 1H, *CH*OH), 5.12 (d, 1H, *J* = 5.4 Hz, OH), 5.20 (m, 1H, OH), 5.35 (s, 2H, CH_2), 7.28 (m, 1H, Ar-H), 7.37 (m, 1H, Ar-H), 7.51 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.84 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.73 (s, 1H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ 26.76 (CH_3CO), 50.40, 53.34, 64.18 (3CH_2), 78.18 (*C*HOH), 118.98, 124.23, 134.65, 137.29, 140.15, 142.12, 145.73, 150.12 (Ar-8C), 156.79 (C=N), 182.42 (C=O). Anal. Calcd. for $C_{15}H_{17}N_5O_3$ (315.33): C, 57.13; H, 5.43; N, 22.21. Found: C, 56.90; H, 5.18; N, 21.92.

3-{5-[(3-Acetyl-1*H*-indol-1-yl)methyl]-2*H*-tetrazol-2-yl}propane-1,2-diyl diacetate (14)

Pale yellow powder (1.60 g, 80%), m.p. 151-152°C; IR (KBr) ν 1742 (C=O), 1708 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 2.05, 2.11, 2.47 (3s, 9H, 3CH_3CO), 4.64 (d, 2H, *J* = 6.2 Hz, CH_2), 4.93 (d, 2H, *J* = 6.4 Hz, CH_2), 5.12 (m, 1H, *CH*OAc), 5.40 (s, 2H, CH_2), 7.30 (m, 1H, Ar-H), 7.39 (m, 1H, Ar-H), 7.52 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.87 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.74 (s, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 20.12, 20.55, 26.74 (3CH_3), 50.55, 53.42, 64.78 (3CH_2), 78.20 (*C*HOAc), 119.28, 124.51, 134.71, 138.32, 140.24, 143.08, 146.10, 150.11 (Ar-8C), 156.88 (C=N), 169.91, 170.92, 182.40 (3C=O). Anal. Calcd. for $C_{19}H_{21}N_5O_5$ (399.40): C, 57.14; H, 5.30; N, 17.53. Found: C, 56.92; H, 5.17; N, 17.12.

1-{1-[[2-(2,2-Dimethoxyethyl)-2*H*-tetrazol-5-yl]methyl]-1*H*-indol-3-yl}ethanone (15)

Pale yellow powder (1.27 g, 77%), m.p. 157-158°C; IR (KBr) ν 1708 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3CO), 3.72 (s, 6H, 2OCH_3), 4.94 (d, 2H, *J* = 6.2

Hz, CH_2), 5.12 (d, 1H, *J* = 6.2 Hz, *CH*OCH_3), 5.42 (s, 2H, CH_2), 7.32 (m, 1H, Ar-H), 7.38 (m, 1H, Ar-H), 7.52 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.88 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.78 (s, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 26.74 (CH_3), 35.12 ($2CH_3$), 51.52, 53.40 ($2CH_2$), 78.21 (*C*HOCH_3), 119.28, 124.51, 134.71, 138.32, 140.24, 143.08, 146.10, 150.11 (Ar-8C), 156.89 (C=N), 182.40 (C=O). Anal. Calcd. for $C_{16}H_{19}N_5O_3$ (329.35): C, 58.35; H, 5.81; N, 21.26. Found: C, 58.18; H, 5.69; N, 21.18.

1-{1-[[2-(2-Methoxyethyl)-2*H*-tetrazol-5-yl]methyl]-1*H*-indol-3-yl}ethanone (16)

Pale yellow powder (1.18 g, 79%), m.p. 152-153°C; IR (KBr) ν 1705 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 2.43 (s, 3H, *CH*$_3$CO), 3.72 (s, 3H, OCH_3), 4.11 (t, 2H, *J* = 5.8 Hz, CH_2), 4.88 (t, 1H, *J* = 5.8 Hz, CH_2), 5.35 (s, 2H, CH_2), 7.29 (m, 1H, Ar-H), 7.38 (m, 1H, Ar-H), 7.52 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.49 (d, 1H, *J* = 8.4 Hz, Ar-H), 8.72 (s, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 26.76 (*CH*$_3$CO), 35.25 (CH_3), 49.39, 52.35, 64.22 ($3CH_2$), 119.28, 124.25, 135.18, 137.44, 140.28, 142.33, 145.81, 149.76 (Ar-8C), 156.72 (C=N), 182.43 (C=O). Anal. Calcd. for $C_{15}H_{17}N_5O_2$ (299.33): C, 60.19; H, 5.72; N, 23.40. Found: C, 59.91; H, 5.58; N, 23.18.

3-Acetyl-1-{2-[(*O*-acetyl-β-D-glycopyranosyl)-2*H*-tetrazol-5-yl]methyl}-1*H*-indole (18a,b)

To a solution of compound **3** (1.21 g, 5 mmol) in *N*,*N*-dimethylformamide (7 mL) was added Et_3N (0.85 mL, 6 mmol) and 2,3,4,6-tetr-*O*-acetyl-α-D-gluco or 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (6 mmol) and the reaction mixture was stirred at room temperature until complete as assessed by TLC (chloroform/methanol 99.7:0.3). The reaction mixture was concentrated under reduced pressure, diluted with CH_2Cl_2 (40 mL) and washed with water (3×, 30 mL). The organic layer was dried (Na_2SO_4), filtered, evaporated under reduced pressure and the residue was triturated with petroleum ether (bp 40-60°C: 45 mL) and the solid product was filtered, dried and recrystallized from ethanol.

3-Acetyl-1-{2-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2*H*-tetrazol-5-yl]methyl}-1*H*-indole (18a)

Pale yellow powder (2.23 g, 78%), m.p. 157-158°C; IR (KBr) ν 1750 (C=O), 1708 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 1.90, 1.94, 1.99, 2.04, 2.48 (5s, 15H, 5*CH*$_3$CO), 4.08 (m, 1H, H-5), 4.14 (dd, 1H, $J_{6,6}$ = 11.4 Hz, $J_{5,6}$ = 2.8 Hz, H-6), 4.19 (dd, 1H, $J_{6,6}$ = 11.4 Hz, $J_{5,6}$ = 3.2 Hz, H-6), 5.10 (t, 1H, $J_{3,4}$ = 9.4 Hz, H-4), 5.22 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 9.4 Hz, H-3), 5.27 (t, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 5.38 (s, 2H, CH_2), 5.87 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 7.29 (m, 1H, Ar-H), 7.41 (m, 1H, Ar-H), 7.49 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.90 (d, 1H, *J* = 8.4 Hz, Ar-H), 8.75 (s, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 19.27, 19.23, 20.44, 20.65, 26.76 (5*CH*$_3$CO), 49.50 (CH_2), 118.78, 123.51, 134.62, 138.38, 141.12, 141.88, 146.10, 149.92 (Ar-8C), 157.05 (C=N), 169.41, 170.55, 171.28, 171.70, 182.42 (5C=O). Anal. Calcd. for $C_{26}H_{29}N_5O_{10}$ (571.54): C, 54.64; H, 5.11; N, 12.25. Found: C, 64.49; H, 4.89; N, 12.15.

3-Acetyl-1-{2-[(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-2*H*-tetrazol-5-yl]methyl}-1*H*-indole (18b)

Pale yellow powder (1.92 g, 77%), m.p. 159-160°C; IR (KBr) ν 1748 (C=O), 1708 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 1.91, 1.95, 2.10, 2.45 (4s, 12H, 4*CH*$_3$CO), 4.08 (m, 1H, H-4), 4.14 (dd, 1H, $J_{5,5}$ = 11.2 Hz, $J_{4,5}$ = 2.8 Hz, H-5), 4.19 (dd, 1H, $J_{5,5}$ = 11.2 Hz, $J_{4,5}$ = 3.2 Hz, H-5), 5.10 (t, 1H, $J_{2,3}$ = 9.4 Hz, H-3), 5.27 (t, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 5.36 (s, 2H, CH_2), 5.86 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 7.31 (m, 1H, Ar-H), 7.42 (m, 1H, Ar-H), 7.51 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.90 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.75 (s, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 19.27, 19.23, 20.65, 26.76 ($4CH_3$), 459.56 (CH_2), 61.94 (C-5), 68.12 (C-3), 71.18 (C-2), 71.98 (C-4), 92.87 (C-1), 119.18, 123.48, 134.67, 137.89, 142.08, 142.61, 146.25, 149.95 (Ar-8C), 157.18 (C=N), 169.41, 170.55, 171.18, 182.40 (4C=O). Anal. Calcd. for $C_{23}H_{25}N_5O_8$ (499.47): C, 55.31; H, 5.05; N, 14.02. Found: C, 55.19; H, 4.90; N, 13.89.

3-Acetyl-1-{2-[(β-D-glycopyranosyl)-2*H*-tetrazol-5-yl]methyl}-1*H*-indole (19a,b)

Gaseous ammonia was passed through a solution of protected glycosides **18a,b** (5 mmol) in dry methanol (20 mL) at 0°C for 1 h and then the mixture was stirred at room temperature for 8 h. The solvent was evaporated under reduced pressure at 40°C to give a solid residue, which was recrystallized from ethanol to give compound **19a**,**b**.

3-Acetyl-1-{2-[(β-D-glucopyranosyl)-2*H*-tetrazol-5-yl]methyl}-1*H*-indole (19a)

Pale yellow powder (1.56 g, 82%), m.p. 197-198°C; IR (KBr) ν 3441-3460 (OH), 1708 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.44 (m, 2H, H-6,6), 3.49 (m, 1H, H-5), 4.12 (m, 2H, H-3,4), 4.35 (t, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 4.75 (t, 1H, *J* = 6.2 Hz, OH), 4.85 (d, 1H, *J* = 6.4 Hz, OH), 5.21 (m, 1H, OH), 5.28 (m, 1H, OH), 5.38 (s, 2H, CH_2), 5.82 (d, 1H, *J* = 10.2 Hz, H-1), 17.28 (m, 2H, Ar-H), 7.43 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.51 (d, 1H, *J* = 8.4 Hz, Ar-H), 8.74 (s, 1H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ 26.11 (CH_3), 49.92 (CH_2), 62.69 (C-6), 64.42 (C-4), 68.67 (C-3), 71.29 (C-2), 72.28 (C-5), 90.14 (C-1), 119.89, 124.49, 135.12, 13858, 142.32, 141.93, 146.14, 150.24 (Ar-8C), 157.12 (C=N), 182.44 (C=O). Anal. Calcd. for

$C_{18}H_{21}N_5O_6$ (403.39): C, 53.59; H, 5.25; N, 17.36. Found: C, 53.41; H, 5.18; N, 17.27.

3-Acetyl-1-{2-[(β-D-xylopyranosyl)-2*H*-tetrazol-5-yl]methyl}-1*H*-indol (19b)

Pale yellow powder (1.49 g, 80%), m.p. 195-196°C; IR (KBr) ν 3450-3472 (OH), 1705 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.45 (m, 2H, H-5,5), 4.18 (m, 2H, H-3,4), 4.54 (t, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 4.79 (d, 1H, J = 6.4 Hz, OH), 5.21 (m, 1H, OH), 5.29 (m, 1H, OH), 5.40 (s, 2H, CH_2), 5.68 (d, 1H, J = 9.9 Hz, H-1), 7.30 (m, 1H, Ar-H), 7.41 (m, 1H, Ar-H), 7.52 (d, 1H, J = 8.0 Hz, Ar-H), 7.90 (d, 1H, J = 8.2 Hz, Ar-H), 8.73 (s, 1H, Ar-1H); ^{13}C-NMR ($CDCl_3$): δ 26.11 (CH_3CO), 46.12 (CH_2), 62.69 (C-5), 68.69 (C-3), 71.30 (C-2), 72.33 (C-4), 91.46 (C-1), 119.82, 123.49, 135.14, 138.49, 141.32, 144.93, 146.21, 150.14 (Ar-8C), 156.78 (C=N), 182.45 (C=O). Anal. Calcd. for $C_{17}H_{19}N_5O_5$ (373.36): C, 54.69; H, 5.13; N, 18.76. Found: C, 54.42; H, 4.94; N, 18.57.

Antimicrobial activity

The antibacterial activities of the synthesized compounds were tested against *Bacillus subtilis, Streptococcus lactis* (Gram-positive bacteria), *Escherichia coli*, *Pseudomonas sp.* (Gram-negative bacteria) in nutrient agar medium. The antifungal activities of the compounds were tested against *Candida albicans, Aspergillus Niger and Pencillium sp.* in Sabouraud dextrose agar medium.

Agar diffusion medium

All compounds were screened *in vitro* for their antimicrobial activity using an agar diffusion method (Cruickshank et al., 1975). A suspension of the organisms were added to sterile nutrient agar media at 45°C, the mixture was transferred to sterile Petri dishes and allowed to solidify. Holes of 10 mm in diameter were made using a cork borer. An amount of 0.1 mL of the synthesized compounds was added inside the holes. A hole filled with DMSO was also used as control. The plates were pre-incubated for 1 h at room temperature as a period of diffusion to minimize the effects to variation in time between the applications of the different solutions. The plates were then incubated at 37°C for 24 h and observed for antibacterial activity. The diameters of the zone of inhibition were measured and compared with those of the standards; ciprofloxacin (Dahiya, 2008; Su et al., 2010) (50 μg/mL) and fusidic acid (Poyner and Dass, 1996; Al-Omar and Amr, 2010) (50 μg/mL) were used as

Table I. Inhibition zone in mm as a criterion for antibacterial and antifungal activities of the newly synthesized compounds

Compound	Microorganism zone of inhibition diameter (mm)						
	Gram-positive bacteria		Gram-negative bacteria		Fungi		
	Bacillus subtilis	*Streptococcus lactis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*	*Aspergillus niger*	*Penicillium* sp.
2	6	3	7	6	6	1	2
3	21	20	13	15	6	2	6
4	6	3	6	6	13	15	14
5	26	16	22	23	17	16	18
6	18	15	10	11	11	11	10
7	3	4	8	6	6	8	3
9	22	19	14	14	5	16	15
10	24	21	16	15	17	16	16
11	6	2	4	4	12	3	6
12	15	12	13	12	16	13	14
13	6	6	6	9	9	4	6
14	12	9	6	12	8	11	8
15	10	8	15	8	5	5	6
16	12	9	9	8	7	7	5
18a	17	13	11	14	5	6	8
18b	16	15	13	11	5	4	6
19a	18	14	16	14	11	8	6
19b	24	14	17	16	9	6	5
Ciprofloxacin	23	21	13	14	–	–	–
Fucidic acid	–	–	–	–	15	14	15

Table II. MIC* in mg/mL of the newly synthesized compounds against Gram-positive and Gram-negative bacteria

Compound	Gram-positive bacteria		Gram-negative bacteria	
	Bacillus subtilis	*Streptococcus lactis*	*Escherichia coli*	*Pseudomonas aeruginosa*
3	0.14	0.17	0.42	0.20
5	0.12	0.21	0.10	0.17
9	0.34	0.34	0.18	0.34
10	0.24	0.14	0.22	0.24
12	0.68	0.34	0.34	0.27
19a	0.34	0.34	0.12	0.19
19b	0.12	0.24	0.12	0.18
Ciprofloxacin	0.12	0.15	0.10	0.19

*MIC values were calculated as the concentration at which there was >99% inhibition of the microorganism on the plate.

standards for antibacterial and antifungal activities, respectively. The observed zone of inhibitions are presented in Table I.

Minimum inhibitory concentration

Minimum inhibitory concentration (MIC) of the test compounds were determined by an agar streak dilution method. Stock solution (68 mg/mL) of the synthesized compounds were made using DMSO as the solvent. From this stock solution, the following concentrations (0.17; 0.34; 0.68; 0.85 and 1.7 mg/mL) of the tested compounds solutions were mixed with the known quantities of molten sterile agar media aseptically. About 20 mL of the media containing the tested compound was dispensed into each sterile Petri dish. Then the media were allowed to solidify. Microorganisms were then streaked on the agar plates aseptically. The plates were then incubated at 37°C for 24 h or 48 h for bacterial and fungal plates, respectively. Then the plates were observed for the growth of microorganisms. The lowest concentration of the synthesized compounds inhibiting the growth of the given bacteria/fungus was considered as the MIC of the test compounds. The MIC values of each compound against various bacteria and fungus are tabulated in Tables II and III. MIC values of compounds against bacteria (Table II) were calculated as the concentration which resulted in > 99% inhibition of the microorganism on the plate.

RESULTS AND DISCUSSION

In this investigation (3-acetyl-1*H*-indol-1-yl)acetonitrile (**2**) was synthesized by reaction of 3-acetylindole (**1**) with chloroacetonitrile in DMF with the presence of sodium hydride. When compound **2** was reacted with sodium azide in DMF in the presence of ammonium chloride at 100°C, the tetrazole derivative **3** was obtained in 71% yield. The IR spectrum of **3** showed absorption bands at 3265 cm^{-1} for the NH and 1708 cm^{-1} for the C=O which appeared in the ^{13}C-NMR spectrum at δ 182.18 ppm. The ^{1}H-NMR spectrum revealed the presence of the acetyl-methyl signal at δ 2.48 ppm and the CH_2 as singlet at δ 5.33 ppm which have been confirmed in the ^{13}C-NMR spectrum at δ 26.76 and 44.52, respectively.

Table III. MIC in mg/mL of the newly synthesized compounds against fungi

Compound	*Candida albicans*	*Aspergillus niger*	*Penicillium* sp.
4	0.21	0.11	0.14
5	0.11	0.14	0.10
9	>100	0.15	0.14
10	0.11	0.16	0.10
12	0.15	0.18	0.16
Fucidic acid	0.10	0.11	0.08

Reaction of the tetrazole derivative **3** with ethyl chloroacetate in DMF at room temperature afforded the corresponding *N*-substituted ethyl ester derivative **4** in 69% yield. When the ester **3** was allowed to react with hydrazine hydrate in ethanol, the corresponding acid hydrazide derivative **5** was obtained in 80% yield. The ^{1}H-NMR spectrum of the ester **4** showed the signals of the ethyl group which are not present in the ^{1}H-NMR spectrum of the hydrazide **5**. Instead, a signal corresponding to the NH_2 group observable. In addition, the ^{13}C-NMR spectra of **4** and **5** are in accordance with the assigned structure.

Reaction of the acid hydrazide **5** with *p*-chlorophenylisothiocyante at reflux temperature afforded the corresponding thiosemicarbazide derivative **6**. The IR spectrum showed characteristic absorption bands at 1705 and 1664 for the C=O groups and its ^{13}C-NMR spectrum showed the signals of the aromatic carbons at δ 118.50-149.67 ppm in addition to the C=S signal at δ 173.86 ppm. It is well known that thiosemicar-

bazide derivatives are useful intermediates for the synthesis of a variety of five-membered heterocyclic compounds. Thus, when compound **6** was heated in 2 *N* sodium hydroxide solution at reflux temperature, the 1,2,4-triazole derivative **7** was obtained in 78% yield. The structure of the resulting 1,2,4-triazole derivative **7** was confirmed by IR, ^{1}H- and ^{13}C-NMR spectra as well as elemental analysis. When the 1,2,4-tiazole derivative **7** was reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**8**), the corresponding substituted *S*-glucoside derivative **9** was afforded in 80% yield. The ^{1}H-NMR spectrum showed the anomeric proton of the sugar moiety at δ 5.76 ppm as a doublet, with a coupling constant equal to 10.2 Hz, indicating the β-orientation of the thioglycosidic bond. The absence of a signal corresponding to the C=S in the ^{13}C-NMR spectrum confirmed the attachment of the sugar moiety at the sulfur atom, rather than the nitrogen atom, which has also been supported by the chemical shift of the anomeric proton. Deacetylation afforded the *S*-glucoside derivative **10** whose spectral and analytical data were in agreement with the assigned structure (see experimental part).

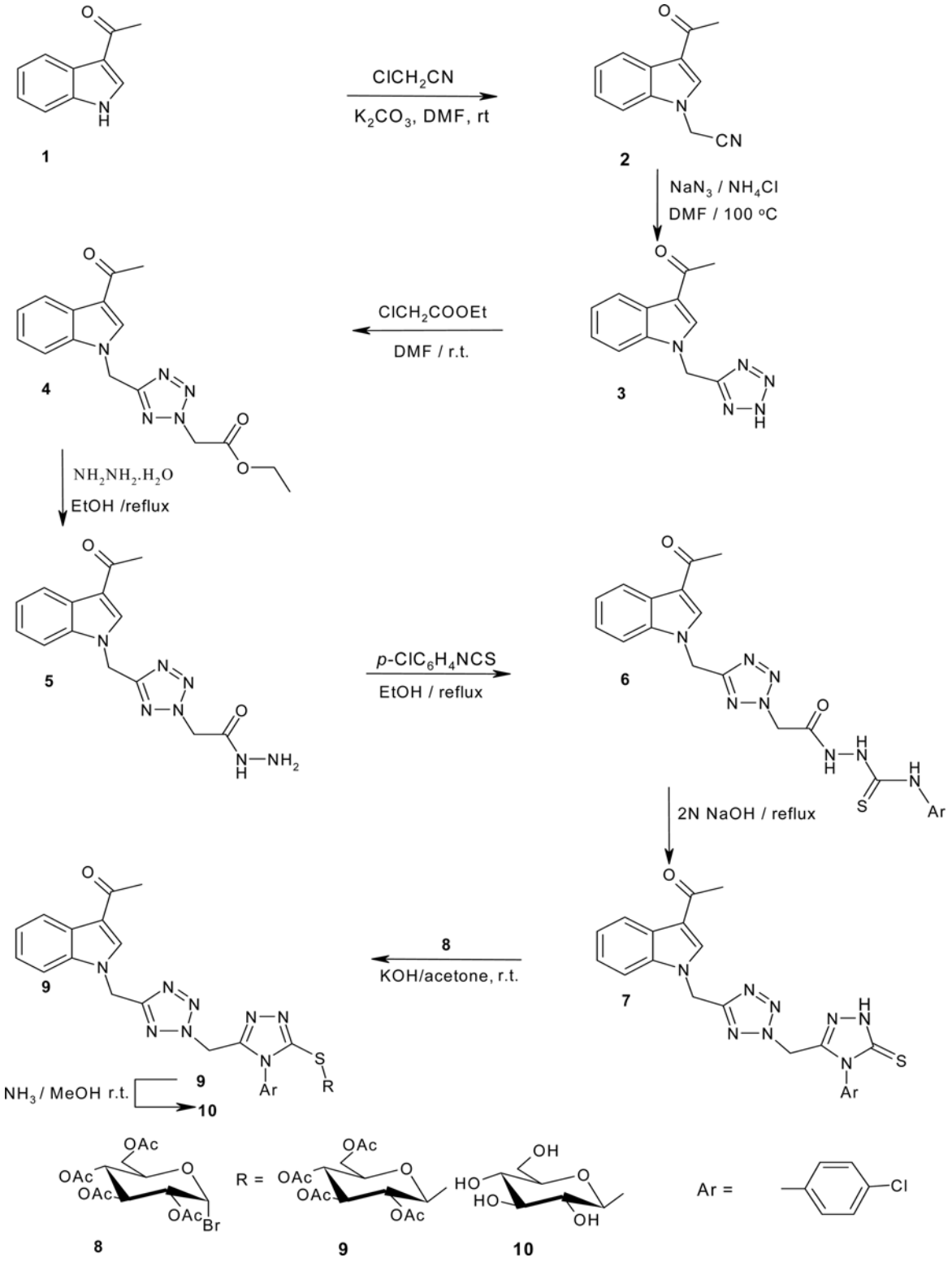
Reaction of the tetrazole derivatives **3** with 2-(2-chloroethoxyehanol), 3-chloropropane-1,2-diol, 2-chloro-1,1-dimethoxyethane or 1-chloro-2-methoxyethane in DMF at 70ºC afforded the *N*-substituted acyclic nucleoside analogues **11**, **13**, **15** and **16**, respectively. Acetyalation of compounds **11** and **13** using acetic anhydride afforded the corresponding *O*-acetyl derivatives **12** and **14**, respectively. The ^{1}H-NMR spectra of the acetylated derivatives **12** and **14** revealed the presence of the *O*-acetyl methyl groups which appeared in the ^{13}C-NMR spectrum at δ 20.14 and 20.55 ppm in addition to the *O*-acetyl carbonyl carbons at δ 169.89-182.44 ppm for compounds **12** and **14**, respectively. Reaction of **2** with acetobromo sugars **17a**, **b** gave the acetylated *N*-glycoside derivatives **18a**, **b**, respectively. The ^{1}H-NMR spectra showed the anomeric proton of the sugar moiety in the range of δ 5.86-5.89 ppm as a doublet, with coupling constants equal to 10.2 and 9.6 Hz indicating the β-orientation of the glycosidic bond. Deprotection of **18a**, **b** gave the deacetylated *N*-glycoside derivatives **19a**, **b** (Scheme 2) whose spectral and analytical data were in agreement with the assigned structure (see experimental part).

Antimicrobial activity

The synthesized compounds were tested for their *in vitro* antimicrobial activity against a panel of standard strains of the Gram-positive bacteria (*Bacillus subtilis* and *Streptococcus lactis*), the Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and the yeast-like pathogenic fungus (*Candida albicans, Aspergillus niger and Penicillium sp.*). The results of the preliminary antibacterial and the antifungal activates are shown in Table I. The results revealed that compounds showed varying degrees of inhibition against the tested microorganisms. In general, the best antibacterial activity was displayed by compounds **3**, **5**, **9**, **10** and **19b**. Compounds **19a** and **19b** showed strong activity against the Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*, while compounds **5** displayed strong activity against *Escherichia coli*. These results proved that the attachment of substituted tetrazolyls or [(triazol-3-yl)methyl]-2*H*-tetrazol-5-yl to the indole derivative **2** resulted in increased inhibitory activity. This is clear as the activity increased in the resulting compounds compared to the relatively low activity of **2**. Compounds **3**, **5** and **10** showed good activity against *Streptococcus lactis* followed by compounds **9**, **12**, **19a** and **19b** which were moderately active. Compounds **5** and **19b** showed good activity against *Pseudomonas sp.* followed by compounds **3**, **9**, **10**, **12** and **19a**. The antifungal activities depicted in Table I revealed that compounds **5** and **10** exhibited interestingly high antifungal activities followed by compounds **4**, **9**, and **12**, which also showed strong to moderate activity.

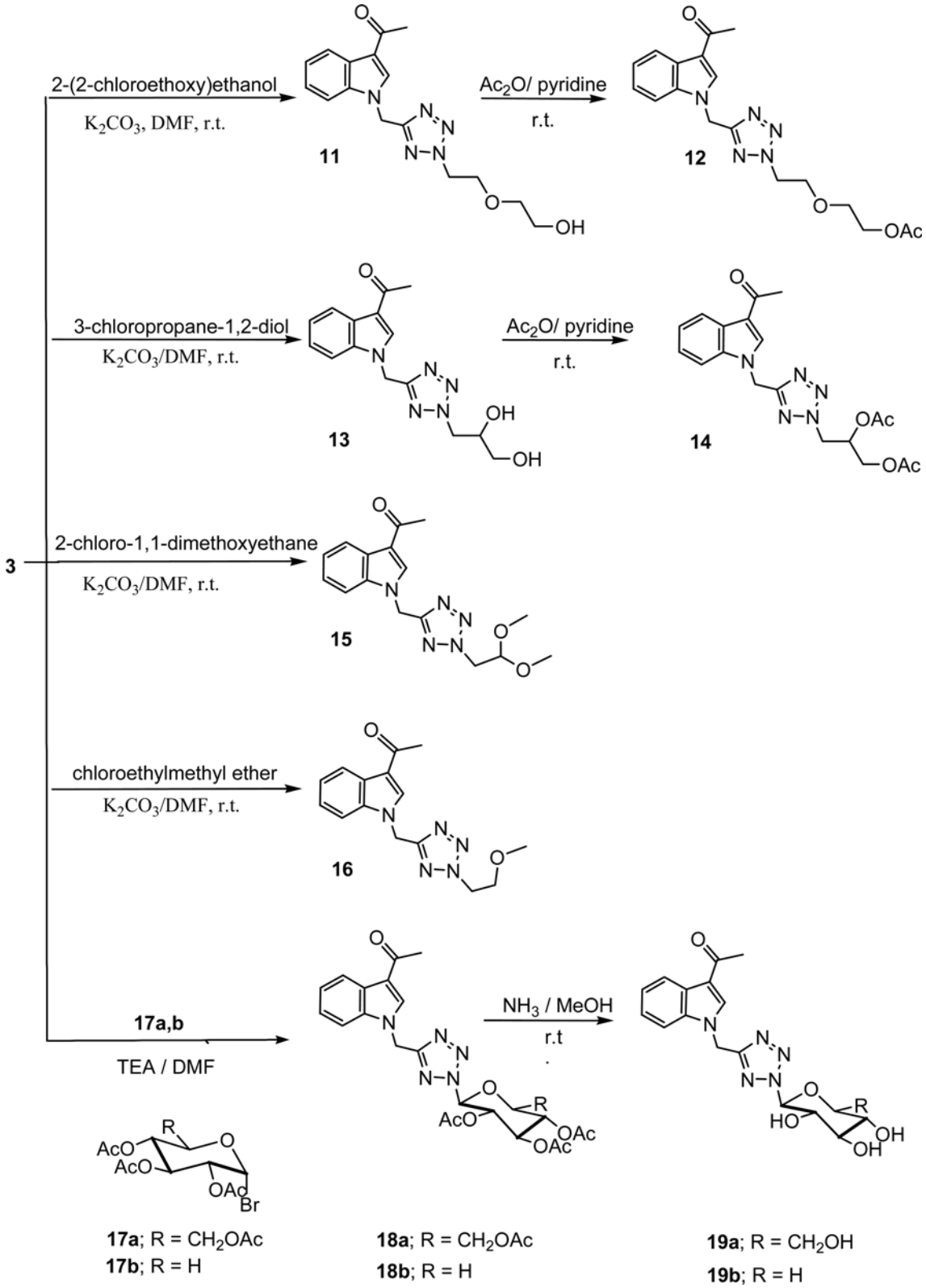
The MIC of the most active compounds, the antibacterial antibiotic ciprofloxacin and the antifungal drug fusidic acid, which are shown in Tables II and III, were in accordance with the results obtained in the primary screening.

The antimicrobial activities and structure-activity relationships indicated that the attachment of glycosyl moieties to the substituted 1,2,4-triazole ring through a thioglycosidic linkage resulted in marked increases in inhibition activity. Furthermore, tetrazoles with a free NH and the *N*-substituted hydrazide **5** displayed the highest activities. This tetrazole hydrazide showed high activity against Gram-positive bacteria (*Bacillus subtilis*), the Gram-negative bacteria (*Escherichia coli and Pseudomonas aeruginosa*), and the yeast-like pathogenic fungi (*Candida albicans, Aspergillus niger and Penicillium sp.*). Additionally, the antibacterial activity observed for the *N*-substituted tetrazole glycosides **19a**, **b** indicated the importance of the free hydroxyl glycopyranosylthio moiety as the activity was reduced when this group was replaced with the corresponding *O*-acetylated glycosyles in the protected derivatives as well as the acyclic analogs. The antibacterial activity observed for the xylopyranosyl derivative was also relatively higher than that of the corresponding glucopyranosyl **19a**.



Scheme 1. Synthesis of [(1,2,4-triazol-3-yl)methyl]-2H-tetrazole glycoside derivatives

The antibacterial activities also indicated that the attachment of glycopyranosyl sugar moieties to the synthesized 1,2,4-triazole derivatives resulted in a marked increase in activity as the activity was obviously increased in compounds **9** and **10** when compared to compound **7**. On the other hand, the attach-



Scheme 2. Synthesis of N-substituted tetrazole derivatives

ment of the xylopyranosyl sugar moiety to the synthesized tetrazole derivative resulted in an increase in antibacterial activities against *Bacillus subtilis* and *Escherichia coli*.

The antifungal activity test revealed that the *N*-substituted hydrazide of the tetrazolyl moiety **5** and the free hydroxyl glucoside of the substituted 1,2,4-triazole **10** are most potent. Furthermore, the results indicated that the activities of the glycosides of the substituted 1,2,4-triazole were higher than that of those attached to the tetrazolyl moieties. It was also obvious that the free hydroxyl glycosides were highly active then their corresponding *O*-acetylated analogs. In addition, the *N*-substituted tetrazole ethyl ester which displayed weak activity against Gram-positive bacteria and Gram-negative bacteria showed high activity against the yeast-like pathogenic fungi (*Candida albicans*, *Aspergillus niger* and *Penicillium sp.*). The antifungal activities indicated that the attachment of sugar moieties to the synthesized 1,2,4-triazole derivatives led to markedly increased activities as the activity was increased for glycoside **10** compared to the triazole **7**. On the other hand, the attachment of sugar moieties to the tetrazole **3** resulted in a moderate increase in antifungal activities against *Candida albicans* and *Aspergillus niger*.

New 1-[(tetrazol-5-yl)methyl]indoles, the corresponding glycoside derivatives, their acyclic analogous and the [(1,2,4-triazol-3-yl)methyl]-2*H*-tetrazole derivative as well as the corresponding thioglucosides were synthesized and evaluated for their antimicrobial activities. Some of the synthesized compounds were highly active with respect to their antibacterial and antifungal activities. The attachment of free hydroxyl glycosyl moieties to tetrazole and 1,2,4-triazole ring systems increased their antibacterial activity, whereas only 1,2,4-triazole thioglucosides revealed high antifungal activity.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. El-Sayed E. Mostafa, Department of Microbial Chemistry, National Research Center, Cairo, Egypt for performing the antimicrobial activity assays of the synthesized compounds.

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