Synthesis and Antimicrobial Activity of New Tetrazole Derivatives from 1((1H-tetrazol-5-yl) methyl)-1H-benzo[d][1,2,3]triazole as synthon

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Abstract: A series of benzotriazoles and tetrazole derivatives was synthesized using 1((1*H*-tetrazol-5-yl) methyl)-1*H*-benzo[*d*][1,2,3]triazole **3** as starting material. Treatment of **3** with ethyl bromoacetate gave **4**, which was treated with hydrazine hydrate to give the hydrazide **5.** The hydrazide **5** was reacted with aromatic aldehydes or D-mannose and D-xylose to give the corresponding hydrazones **6** and **7a,b**, which were reacted with acetic anhydride in pyridine at room temperature and with reflux to afford the corresponding per-O-acetyl derivatives **8a,b** and cyclised products **9a,b**, respectively. The antimicrobial screening showed that many of these newly synthesized compounds had good antimicrobial activities comparable to streptomycin and fusidic acid as positive standards.
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1. Introduction:

The importance of triazole-derivatives lie in the field that these have occupied a unique position in heterocyclic chemistry due to their agricultural, industrial, and biological activities [1-6]. The 1,2,3-triazole system has wide spread uses, and it has been considered as an interesting component in terms of antimicrobial activity [7-9]. Also, the heterocyclic system containing benzotriazole moieties system is of wide interest because of their diverse biological activities [11-13]. They exhibit useful pharmacological properties and clinical applications [8-11]. In addition to these considerable biological applications, benzotriazoles are important intermediates, protecting groups and final products in organic synthesis [13-16]. In view of these observations and as continuation of our previous work in heterocyclic chemistry [17-20], we have synthesized some new heterocyclic compounds containing azole moiety, and tested their selected as anti-microbial agents.

2. Experimental

Chemistry

Melting points were determined using a Büchi apparatus. IR spectra (KBr) were recorded with a Bruker-Vector 22 instrument (Bruker, Bremen, Germany). ^{1}H NMR spectra were recorded with a Varian Gemini spectrometer at 300 MHz and 200 MHz with TMS as internal standard. Chemical shifts were reported in δ scale (ppm) relative to TMS as a standard, and the coupling constants (J values) are given in Hz. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F_{245}. EI-mass spectra were recorded with a HP D5988 A 1000 MHz instrument (Hewlett-Packard, Palo Alto, CA, USA).

2-(1H-Benzo[d][1,2,3]triazol-1-yl)acetonitrile (2)

To a solution of benzotriazole **1** (5.59 g, 0.05 mol) and anhydrous potassium carbonate (7 g, 0.05 mol) in *N*,*N*-dimethylformamide (DMF 20 mL), chloroacetonitrile (3.8 g, 0.05 mol) was added dropwsily. The reaction mixture was stirred overnight at room temperature, poured into water, the crud product was extracted with ethylacetate, dried over anhydrous sodium sulphate, evaporated under reduced pressure. The obtained residue was triturated with diethyl ether, filtered off and crystallized from ethanol to give compound **2** as colourless crystals. Yield 94%, m.p. 86−88°C; MS: m/z = 158 (M^+). Anal. Calcd. for

$C_8H_6N_4$: C, 60.75; H, 3.82; N, 35.42. Found: C, 60.70; H, 3.75; N, 35.36.

1((1H-Tetrazol-5-yl)methyl)-1H-benzo[d][1,2,3]-triazole (3)

A mixture of compound **2** (2.2g, 0.01 mol), sodium azide (0.91g, 0.014 mol) and ammonium chloride (0.75g, 0.014 mol) in DMF (7 mL) was heated under reflux for 1h. The reaction mixture was evaporated under reduced pressure, the obtained residue was solidified with water (20 mL) and the resulting precipitate (first portion) was collected by filtration. The filtrate was acidified with dilute hydrochloric acid to pH ~ 2, after cooling; the obtained solid (second portion) was filtered off, washed with water. The two portions were combined with together and crystallized from methanol to give compound **3** as a white page powder. Yield 92%; m.p. 180−182 °C; IR (KBr) υ: 3220 (NH), 2970 (aliphatic C-H) cm^{-1}; MS: *m/z* = 201 (M^+); Anal. Calcd. for $C_8H_7N_7$: C, 47.76; H, 3.51; N, 48.73. Found: C, 47.70; H, 3.46; N, 48.68.

Ethyl 2-(5-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-1H-tetrazol-1-yl)acetate (4)

To a stirred solution of compound **3** (5.3g, 0.02 mol) in DMF (15 mL) containing anhydrous potassium carbonate (3.7g, 0.02 mol), ethyl bromoacetate (4.4g, 0.02 mol) was added dropwisly at room temperature. The reaction mixture was allowed to react under the above same conditions for 24 h, poured into ice water. The resulting oil material was extracted by chloroform, dried over anhydrous calcium chloride, and evaporated under reduced pressure to give an oily compound **4** in pure form. Yield 98%; IR (KBr) υ: 2970 (aliphatic C-H), 1744 (C=O) cm^{-1}; Anal. Calcd. for $C_{12}H_{13}N_7O_2$: C, 50.17; H, 4.56; N, 34.13. Found: C, 50.12; H, 4.50; N, 34.08.

2-(5-((1H-Benzo[d][1,2,3]triazol-1-yl)methyl)-1H-tetrazol-1-yl)acetohydrazide (5)

A mixture of the ester **4** (7.4 g, 0.02 mol) and hydrazine hydrate (0.7 mL, 0.16 mol) in absolute ethanol (15 mL) was refluxed for 2 h. The reaction mixture was diluted with cold water (5 mL), the obtained precipitate was filtered off, washed with water, dried, and crystallized from ethanol to afford the corresponding hydrazide **5** as white crystals. Yield 55%**;** m.p. 120−122 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.37 (s, 2H, CH_2), 5.72 (s, 2H, CH_2), 6.40 (bs, 2H, NH_2), 7.46-8.1 (m, 4H, Ar-H), 9.27 (bs, 1H, NH); IR (KBr) υ: 3450-3405 (NH_2), 3324 (NH), 1692 (C=O) cm^{-1}; Anal. Calcd. for $C_{10}H_{11}N_9O$: C, 43.95; H, 4.06; N, 46.13. Found: C, 43.90; H, 4.00; N, 46.08.

General procedure for the synthesis of hydrazones 6a-d

To a solution of hydrazide **5** (0.27g, 0.001 mol) in thanol (10 mL), aldehydes, namely, *p*-fluoro-benzaldehyde, *p*-bromobenzaldehyde, 3,4,5-tri-methoxybenzaldehyde or pyridine-3-carboxaldehyde (0.0015 mol) and glacial acetic acid (0.5 mL) were added. The reaction mixture was refluxed for 1-3 h, concentrated under reduced pressure, after cooling, the obtained solid was filtered off and crystallized from the proper solvent to afford the corresponding hydrazone derivatives **6a-d**, respectively.

2-(5-((1H-Benzo[d][1,2,3]triazol-1-yl)methyl)-1H-tetrazol-1-yl)-N'-(4-fluorobenzylidene)aceto-hydrazide (6a): As white powder, yield 37%; m.p. 150−152 °C; MS: *m/z* = 378 (M^+-1) ; Anal. Calcd. for $C_{17}H_{14}FN_9O$: C, 53.82; H, 3.72; F, 5.01; N, 33.23. Found: C, 53.76; H, 3.68; F, 4.96; N, 33.18.

2-(5-((1H-Benzo[d][1,2,3]triazol-1-yl)methyl)-1H-tetrazol-1-yl)-N'-(4-bromobenzylidene)-acetohydrazide (6b): As white powder, yield 49%; m.p. 178-180 °C; MS: *m/z* = 437 (M^+-2); Anal. Calcd. for $C_{17}H_{14}BrN_9O$: C, 46.38; H, 3.21; Br, 18.15; N, 28.63. Found: C, 46.30; H, 3.17; Br, 18.10; N, 28.60.

2-(5-((1H-Benzo[d][1,2,3]triazol-1-yl)methyl)-1H-tetrazol-1-yl)-N'-(3,4,5-trimethoxybenzylidene)-acetohydrazide (6c): As pale brown bellets, yield 70%; m.p. 170−172 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.73 (s, 6H, 2 x *m*-OCH_3), 3.86 (s, 3H, *p*-OCH_3), 5.62 (s, 2H, CH_2), 6.01(s, 2H, CH_2), 7.13 (m, 2H. Ar-H), 7.95 (s, 1H, CH=N), 8.10 (s, 2H, Ar-H), 12.01 (s, 1H, NH); Anal. Calcd. for $C_{20}H_{21}N_9O_4$: C, 53.21; H, 4.69; N, 27.92. Found: C, 53.16; H, 4.62; N, 27.88.

2-(5-((1H-Benzo[d][1,2,3]triazol-1-yl)methyl)-1H-tetrazol-1-yl)-N'-(pyridin-3-yl-methylene) aceto-hydrazide (6d): Crystallized from ethanol as white crystals. Yield 51%; m.p. 240−242 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.65 (s, 2H, CH_2), 6.13 (s, 2H, CH_2), 7.45 (m, 2H. Ar-H), 7.68 (m, 2H. Ar-H), 7.75 (m, 2H, Ar-H), 7.82 (d, 1H. *J* = 7.6 Hz, Ar-H), 7.95 (s, 1H, CH=N), 8.65 (s, 1H. *J* = 7.6 Hz, Ar-H), 10.26 (s, 1H, NH); Anal. Calcd. for $C_{16}H_{14}N_{10}O$: C, 53.03; H, 3.89; N, 38.66. Found: C, 52.95; H, 3.82; N, 38.60.

General procedure for the synthesis of sugar hydrazinyl derivatives 7a,b

Hydrazide derivative **5** (1.36 g, 0.005 mol) in ethanol (30 mL) was added to a well stirred solution of the respective monosaccharides (0.007 mol) in water (1 mL) and glacial acetic acid (1 mL). The reaction mixture was heated under reflux for 6 hrs, the resulting solution was concentrated under reduced pressure and

left to cool. The formed solid was separated by filtration, washed with water, cold ethanol and recrystallized from ethanol to afford the corresponding sugar hydrazones **7a,b**, respectively.

2-(5-((1H-Benzo[d][1,2,3]triazol-1-yl)methyl)-1H-tetrazol-1-yl)-N'-(2,3,4,5,6-pentahydroxy-hexylidene)acetohydrazide (7a): Pale yellow gum, yield 60%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.26-3.69 (m, 3H, H-6,6′, H-5), 4.31 (m, 2H, H-4, H-3), 4.47 (s, 2H, CH_2), 4.59 (s, 2H, CH_2), 4.88 (m, 2H, H-2, OH), 4.95 (m,1H, OH), 5.08 (t, 1H, J = 6.4 Hz, OH), 5.21 (m, 1H, OH), 5.33 (m, 1H, OH), 7.45 (m, 2H, Ar-H), 7.69 (d, 1H, J = 7.8 Hz, H-1), 7.80 (m, 2H, Ar-H), 11.54 (s, 1H, NH); IR (KBr) υ: 3400-3370 (broad beak OH), 3300 (NH), 1685 (C=O) cm^{-1}; Anal. Calcd. for $C_{16}H_{21}N_9O_6$: C, 44.14; H, 4.86; N, 28.95. Found: C, 44.10; H, 4.80; N, 28.90.

2-(5-((1H-Benzo[d][1,2,3]triazol-1-yl)methyl)-1H-tetrazol-1-yl)-N'-(2,3,4,5-tetra-hydroxy-pentylidene)acetohydrazide (7b): As a brown powder, yield 55%; m.p. 125−127 ^{o}C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.33-3.59 (m, 2H, H-5,5′), 4.15 (m, 2H, H-3,4), 4.38 (m, 1H, H-2), 4.50 (s, 2H, CH_2), 4.90 (s, 2H, CH_2), 4.97 (m, 1H, OH), 5.15-18 (m, 2H, 2 x OH), 5.38 (m, 1H, OH), 7.50 (m, 2H, Ar-H), 7.79 (d, 1H, J = 7.6 Hz, H-1), 8.12 (s, 2H, Ar-H), 11.40 (s, 1H, NH); IR (KBr) υ: 3400-3375 (broad beak OH), 3382 (NH) cm^{-1}; Anal. Calcd. for $C_{15}H_{19}N_9O_5$: C, 44.44; H, 4.72; N, 31.10. Found: C, 44.40; H, 4.68; N, 31.05.

General procedure for the synthesis of per-O-acetyl-sugar hydrazinyl derivatives 8a,b

Acetic anhydride (0.5 g, 0.005 mol) was added to a solution of sugar hydrazones **7a,b** (0.001 mol) in pyridine (3 mL) with stirring at room temperature for 15h. The resulting solution was poured onto crushed-ice and the product that separated out was filtered off, washed with water, and then dried. The obtained products were crystallized from ethanol to afford the corresponding protected compounds **8a,b**, respectively.

6-(2-(2-(5-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-1H-tetrazol-1-yl)acetyl)hydrazono)-hexane-1,2,3,4,5-pentylpentaacetate (8a): Pale yellow gum, yield 39%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.94, 1.99, 2.03. 2.05, 2.15 (5s, 15H, 5xCH_3CO), 3.94 (dd, 1H, J = 2.8 Hz, J = 11.4 Hz, H-6), 4.10 (m, 1H, H-6′), 4.26 (m, 1H, H-5), 4.42 (m, 1H, H-4), 5.05 (s, 2H. CH_2), 5.13 (s, 2H, CH_2), 5.26 (t, 1H, J = 6.4 Hz, H-3), 5.48 (dd, 1H, J = 6.4 Hz, J = 7.8 Hz, H-2), 7.26 (m, 2H Ar-H), 7.74 (d, 1H, J = 7.8 Hz, H-1), 8.02 (m, 2H, Ar-H), 9.61 (s, 1H, NH); Anal. Calcd. for $C_{26}H_{31}N_9O_{11}$: C, 48.37; H, 4.84; N, 19.53. Found: C, 48.32; H, 4.80; N, 19.48.

5-(2-(2-(5-((1H-benzo[d][1,2,3]triazol-1-yl)methyl-1H-terazol-1-yl)acetyl)hydrazono)-pentane-1,2,3,4-tetrayl tetraacetate (8b): As black powder, yield 45%; m.p. 145−147 ^{o}C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.97, 2.02, 2.08, 2.12 (4s, 12H, 4xCH_3CO), 4.03 (m, 1H, H-5), 4.18 (dd, 1H, J = 3.4 Hz, J = 10.6 Hz, H-5′), 4.41 (m, 1H, H-4), 4.62 (s, 2H, CH_2), 4.85 (t, 1H, J = 6.2 Hz, H-3), 5.02 (s, 2H. CH_2), 5.21 (dd, 1H, J = 6.2 Hz, J = 7.8 Hz, H-2), 7.40 (m, 2H Ar-H), 7.72 (d, 1H, J = 7.8 Hz, H-1), 8.18 (m, 2H, Ar-H),9.21 (s, 1H, NH); Anal.Calcd. for $C_{23}H_{27}N_9O_9$: C, 48.17; H, 4.75; N, 21.98. Found: C, 48.12; H, 4.70; N, 21.92.

General procedure for the synthesis of 1,3,4-oxadiazolines 9a,b

A solution of sugar hydrazones **7a,b** (0.001 mol) in acetic anhydride (0.5,0.005 mol) was heated at 100^{o}C for 20 h. The resulting solution was poured onto crushed-ice and the product that separated out was filtered off, washed with water, and then dried. The products were crystallized from ethanol to give **9a,b**, respectively.

1-(5-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-1H-tetrazol-1-yl)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)pentane-1,2,3,4,5-pentaylpentaacetate (9a): Black powder, yield 43.5 %; m.p. 154−156 ^{o}C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.97, 2.03, 2.06, 2.08, 2.11, 2.21 (6s, 18H, 6xCH_3CO), 3.87 (m, 1H, H-5), 4.16 (dd, 1H, J = 3.4 Hz, J = 10.6 Hz, H-5′), 4.29 (m, 1H, H-4), 4.88 (s, 2H, CH_2), 5.05 (m, 1H, H-3), 5.15 (s, 2H, CH_2), 5.29 (t, 1H, J = 6.8 Hz, H-2), 5.41 (dd, 1H, J = 6.8 Hz, J = 8.2 Hz, H-1), 5.62 (d, 1H, oxadiazoline H-5), 7.45 (s, 2H, Ar-H), 7.90 (s, 2H, Ar-H); IR (KBr) υ: 1745 (ester C=O), 1660 (amide C=O), 1618 (C=N) cm^{-1}; Anal. Calcd. for $C_{28}H_{33}N_9O_{12}$: C, 48.91; H, 4.84; N, 18.33; Found: C, 48.85; H, 4.79; N, 18.26.

1-(5-((5-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-1H-tetrazol-1-yl)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)butane-1,2,3,4-tetrayl tetraacetate (9b): Brown powder, yield 57%; m.p. > 300 ^{o}C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.91, 2.03, 2.06, 2.07, 2.21 (5s, 15H, 5xCH_3CO), 3.85 (m, 1H, H-4), 4.06 (dd, 1H, J = 3.4 Hz, J = 10.6 Hz, H-4′), 4.22 (m, 1H, H-3), 4.89 (s, 2H, CH_2), 5.25 (s, 2H, CH_2), 5.31 (t, 1H, J = 6.8 Hz, H-2), 5.65 (dd, 1H, J = 6.8 Hz, J = 8.2 Hz, H-1), 5.73 (d, 1H, oxadiazoline H-5), 7.49 (s, 2H, Ar-H), 7.91 (s, 2H, Ar-H); IR (KBr) υ: 1738 (ester C=O), 1672 (amide C=O), 1623 (C=N) cm^{-1};Anal. Calcd. for $C_{25}H_{29}N_9O_{10}$: C, 48.78; H, 4.75; N, 20.48;. Found: C, 48.73; H, 4.70; N, 20.42.

Antimicrobial screening

Media

The following media were used:

1- PDA medium: this medium was used for fungi cultivation .It consists of 4gm dextrose /L Potatoes extract.

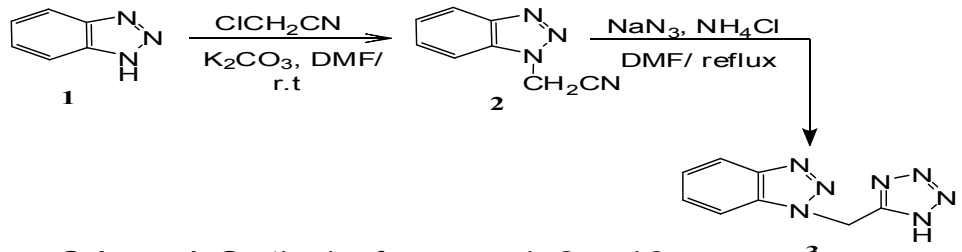
2- Czapek Dox medium: It consists of 10g glucose, 2gm KNO_3, 1g K_2HPO_4, 0.5 KCl, 0.5 $MgSO_4$, and 0.05 ferrous sulphate/L distilled water. This medium is specialized for bacteria cultivation.

3- Medium 3: It consists of 10 glucose, 5g peptone, 3 yeast extract, and 3 Malt extract. It used for yeast cultivation.

3. Result and discussion

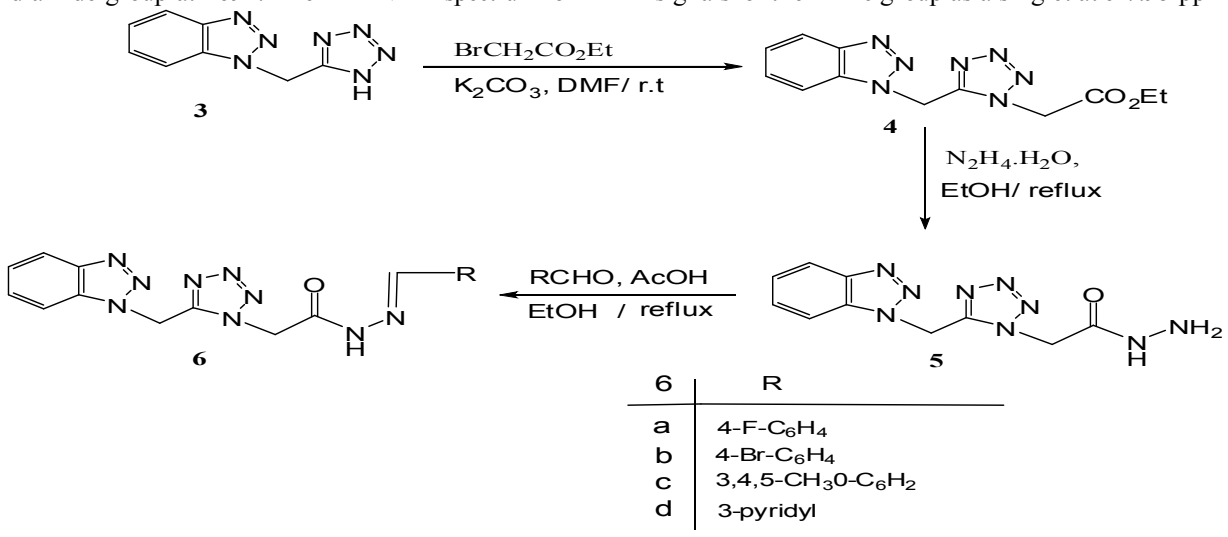
Chemistry

2-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)acetonitrile **2** was synthesizd by the reaction of benzotriazole **1** with chloroacetonitrile in the presence of anhydrous potassium carbonate in DMF at room temperature in 94% yield. Mass spectra of **2** showed that the molecular weight at 158. Compound **2** was refluxed with sodium azide in dimethylformamide in the presence of ammonium chloride to afford 1((1*H*-tetrazol-5-yl)methyl)-1*H*-benzo[*d*][1,2,3]triazole **3** (Scheme 1). The IR spectra of **3** showed the absorption band at 3220 cm^{-1} characteristic to the NH group.



Scheme 1. Synthesis of compounds **2** and **3**

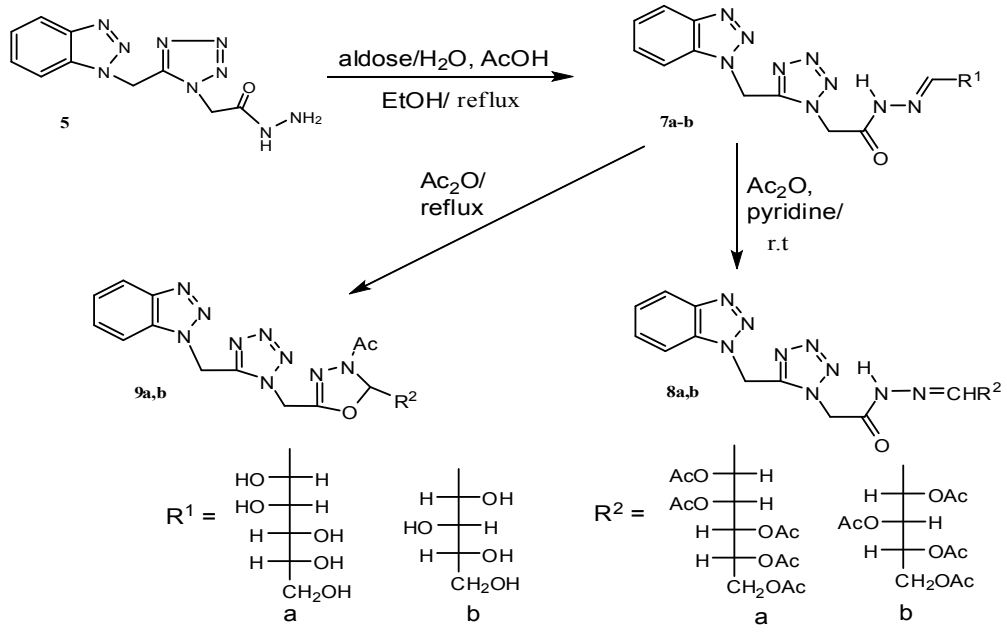
Esterfication of **3** with ethyl bromoacetate in the presence of anhydrous potassium carbonate in DMF at room temperature afforded ethyl 2-(5-((1*H*-benzo[*d*][1,2,3]-triazol-1-yl)methyl)-1*H*-tetrazol-1-yl)acetate **4**. The IR spectrum of **4** showed a characteristic absorption band of the carbonyl group at 1744 cm^{-1} and disappearance of NH group in compound **3.** The acid hydrazide **5** was synthesized by refluxing of the ester **4** with hydrazine hydrate in ethanol. The IR spectrum of **5** showed the presence of characteristic absorption bands of the NH group at 3324 cm^{-1}, NH_2 group in the region of 3450-3405 cm^{-1}, and amide group at 1692. The ^{1}H-NMR spectrum of the **5** showed a signal corresponding to the NH_2 group as a singlet at δ 6.40 ppm, and signal as singlet at δ 9.27 ppm of NH group. When the hydrazide **5** reacted with aldehydes, namely, *p*-fluorobenzaldehyde, *p*-bromobenzaldehyde, 3,4,5-trimethoxybenzaldehyde or pyridine-3-carboxaldehyde in the presence of few drops of glacial acetic acid in ethanol afforded the corresponding acetohydrazide derivatives **6a-d** respectively (Scheme 2). Mass spectra show the presence of molecular ion peaks of **6a** and **6b** at m/z 378 (M^+-1) and 437 (M^+-2), respectively. The ^{1}H-NMR spectrum of the **6c** and **6d** showed the signals of the imine group as a singlet at δ 7.95 ppm.



6	R
a	4-F-C_6H_4
b	4-Br-C_6H_4
c	3,4,5-CH_3O-C_6H_2
d	3-pyridyl

Scheme 2. Synthesis of compounds **4** ,**5** and **6a–d**

When the hydrazide derivative **5** was reacted with D-mannose and D-xylose in an aqueous ethanolic solution containing a catalytic amount of acetic acid afforded the corresponding sugar (E)-2-(5-((1*H*-benzo-[*d*][1,2,3]triazol-1-yl)methyl)-1*H*-tetra-zol-1-yl)-N'-(-2,3,4,5,6-penta-hydroxyhexylidene)-acetohydrazide **7a** and (Z)-2-(5-((1*H*-benzo-[*d*]-[1,2,3]triazol-1-yl)methyl)-1*H*-tetra-zol-1-yl)-N'-((2R)-2,3,4,5-tetrahydroxypentylidene)aceto-hydrazide **7b,** respectively. The IR spectra of **7a,b** showed the presence of characteristic absorption bands corresponding to the hydroxy groups in the region of 3400-3370 cm^{-1}. The ^1H NMR spectra of **7a,b** showed the signals of the sugar chain protons at δ 3.26-3.69 and 3.33-3.59 ppm. The reaction of the sugar hydrazones **7a,b** with acetic anhydride in pyridine at room temperature gave the corresponding per-*O*-acetyl derivatives **8a,b,** respectively. The reaction of sugar arylhydrazones with boiling acetic anhydride is well known to give either the corresponding per-*O,N*-acetyl derivatives or the respective per-*O,N*-acetyl-1,3,4-oxadiazolin derivatives. However, reaction of the sugar hydrazones **7a,b** with acetic anhydride at 100°C gave the sugar-substituted 1,3,4-oxadiazoline derivatives **9a,b**. The IR spectra of **9a,b** showed characteristic absorption bands at 1672-1660 cm^{-1} and 1745-1738 cm^{-1} corresponding to the carbonyl amide and the carbonyl ester groups, respectively, indicating the presence of an *N*-acetyl group in addition to the *O*-acetyl groups (Scheme 3).



Scheme 3. Synthesis of compounds **7a,b** , **8a,b** and **9a,b**

Antimicrobial activity

The antimicrobial activities of the synthesized compounds **2-9** were determined by agar diffusion method as recommended by national Committee for clinical laboratory standards (NCCLS) [21-23]. The compounds were evaluated for antimicrobial activity against bacteria viz. *Streptomyces sp.*, *Bacillus subtilis, Streptococcus lactis, Escherichia coli,* and *Pseudomonas sp* and antifungal activity against various fungi viz. (*Aspergillus* niger, *Penicillium sp*) and yeast (*Candida albican* and *Rhodotorula ingeniosa*). The concentrations of the tested compounds (10 µg/ml) were used according to modified Kirby-Bauer's disk diffusion method. The sterile discs were impregnated with 10 µg/disc of the tested compound. Each tested compound was performed in triplicate. The solvent DMSO was used as a negative control and streptomycin/ fusidic acid were used as stander calculated average diameters (for triplicates) of the zone of inhibition (in mm) for tested samples with that produced by the stander drugs. Four of the synthesized compounds (**2, 6a**, **6b** and **9a**) exhibited potent antibacterial and antifungal bioactivity compared with stander drug used. The other tested compound were found to exhibit a moderate of low antibacterial activity (Table 1). On the other hand when different concentrations of the compound that exhibited a moderate antibacterial activity (**7b**) were used, this compound exhibit very good antibacterial activity at higher concentration (3x and 4x) (Table 2) while the different concentrations compounds (**3** and **6a**) they exhibited a very good antifungal activity (2x and 3x) (Table 3).

Table 1: Antimicrobial activity of the newly synthesized compounds

Compound No.	Fungi				Str. sp	Bacteria			
	R. I	Cand. alb.	Pen. sp	A. n		Gram -ve		Gram +ve	
						Ps	E.c	S.l	B.s
2	19	20	19	19	11	13	12	10	9
3	14	13	16	15	11	11	12	12	13
4	4	5	4	3	7	8	7	9	8
5	7	5	8	9	6	12	13	13	12
6a	16	16	17	17	22	23	24	23	21
6b	22	21	21	20	12	24	22	23	23
6c	10	12	11	11	13	11	10	12	11
6d	8	8	6	7	11	12	13	13	12
7a	11	12	13	11	14	13	11	12	12
7b	12	10	11	11	21	20	19	20	18
8a	12	12	10	11	9	8	7	9	11
8b	13	12	12	13	11	13	12	10	9
9a	10	13	10	11	21	20	21	23	23
9b	12	12	12	11	13		14	14	13
Streptomycin	-	-	-	-	21	22	21	22	21
Fusidic acid	17	17	18	18	-	-	-	-	-

A.n: *Aspergillus Niger* Pen.sp: *Penicillium sp* C.a: *Candida albican*
Str.sp: Streptomyces sp. R.i: *Rhodotorula ingeniosa* B.s: *Bacillus subtilis*
S.l: *Streptococcus lactis* E. c: *Escherichia coli* P .sp: *Pseudomonas sp*

Table 2: Effect of different concentrations of the compounds showed moderate activity on bacterial growth

Compound NO.	Conc.	Strep. sp	Bacteria			
			Gram -ve		Gram +ve	
			B.s	S.l	E.c	Ps
7b	1x	21	20	19	20	18
	2x	23	23	22	23	22
	3x	25	24	24	24	26
	4x	25	25	27	25	26

Table 3: Effect of different concentrations of the compounds showed moderate activity on fungal growth

Compound NO	Conc.	Fungi			
		A.n	Pen.sp	Cand.alb.	R.I
3	1x	14	13	16	15
	2x	15	15	18	17
	3x	18	17	20	20
	4x	20	19	20	21
6a	1x	16	16	17	17
	2x	17	18	19	19
	3x	19	20	20	21
	4x	20	22	20	21

Where X=10 µg

Conclusion

The synthesized compounds were tested for their antimicrobial activity against three microorganisms and the minimal inhibitory concentrations (MICs) of the tested compounds were determined by the dilution method. The antimicrobial screening showed that many of these newly synthesized compounds have good antimicrobial activities (**2, 6a, 6b** and **9a**) comparable to streptomycin and fusidic acid as positive standards. On the other hand when different concentrations of the compound that exhibited a moderate antibacterial activity (**7b**) were used, this compound exhibit very good antibacterial activity at higher concentration (3x and 4x) (Table 2) while the different concentrations of compounds (**3** and **6a**) they

exhibited a very good antifungal activity (2x and 3x) (Table 3).

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