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Synthesis and antiviral activity of novel 3,5-disubstituted1,2,4-triazole glycoside derivatives

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ABSTRACT

New 1,2,4-triazoles linked to different condensed azole and quinolin-8-yloxymethyl moieties were synthesized. Glycosylation of the produced 1,2,4-triazoles followed by deacetylation afforded the free hydroxyl N-glycosides. The antiviral activity against H5N1 avian influenza virus strain A/Egypt/M7217B/2013 was reported and a number of compounds showed moderate activity.

Keywords: Triazoles, benzothiazole, benzoimidazole, glycosides, antiviral activity

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INTRODUCTION

The design and synthesis of new antiviral drugs became one of the most urgent needs because of the rabid evolution of drug resistance. Major interest has been directed to the synthesis of 1,2,4-triazole compounds because of their effective biological and synthetic importance. Compounds with 1,2,4-triazole system showed antimicrobial, sedatives, anti-inflammatory, antianxiety, CNS stimulants [1,2] and antimycotic activity [3,4]. Triazolam [5], Alprazolam [6], Etizolam [7], and Furacylin [8] are drugs with 1,2,4-triazolekey skeleton in their structures. The 1,2,4-triazole motif was also found in a number of natural products [9].

Carbohydrates and their structurally related analogs are of great interest owing to their biological importance. Glycosylation at certain levels performs molecular changes, whichjoin malignant transformations characteristic for cancer cells. Improving the selectivity of compounds for cancerous cell lines can be expected to be one of the important roles of carbohydrate moieties [10]. The careful systematic alteration of the glycon and/or aglycon constituents was employed as auseful developing tool resulting in synthesizing new nucleoside analogs as therapeutic agents with antiviral and anticancer activities in addition to non-radioactive fluorescent labeling for DNA [11–18]. 5-β-D-Glucopyranosyl-substituted-1,2,4-triazoles were designed and synthesized as sub-micromolar inhibitors of glycogen phosphorylases [19-21]. Ribavirin is one of the important drugs to which viral DNA/RNA polymerases and cellular enzymes are main targets [22,23]. It is a broad antiviral compound and has been widely used for (HSV) [22], (HIV-1) [22], influenza virus [24], and hepatitis C virus (HCV) [25], among other viruses. In the same direction of the mentioned facts and in our continuing research aiming for discovering new antiviral and anticancer compounds by the synthesis of heterocycles and their sugar derivatives [26-32], herein a number of tricyclic 1,2,4-triazole compounds having different azolyl moieties were prepared and evaluated against H5N1 avian influenza virus.

MATERIALS AND METHODS

Chemistry

Melting points were determined with a Kofler block apparatus (C. Reichert, Vienna, Austria) and are uncorrected. The IR spectra were recorded on a Perkin-Elmer model 1720 FTIR spectrometer for KBr disc (Perkin-Elmer, Norwalk, CT, USA). NMR spectra were recorded on a Varian Gemini 200 NMR Spectrometer at 500 MHz for ^{1}H NMR (Varian Inc., Palo Alto, CA, USA) and 125 MHz for ^{13}C NMR with TMS as a standard and DMSO-d_6 as solvent (Bruker Bioscience, Billerica, MA, USA). The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F245. Elemental analyses were performed at the Microanalytical Data Centre at Faculty of Science, Cairo University, Egypt. Biological screening against avian influenza (H5N1) virus was conducted at the Virology Laboratory, Department of Water Pollution Research, National Research Centre, Giza, Egypt.

***General procedure for preparation of the triazoles*(3-7)**

A mixture of nitrile **1a-c**(2 mmol), acid hydrazide **2a,b** (1 mmol), and K_2CO_3 (0.5 mmol) in *n*-BuOH (10 mL) was stirred and refluxed at 150^{0}C for 6-8 hours. The progress of the reaction was monitored on TLC. After completion of the reaction, the solvent was removed under reduced pressure and ice-cooled water (30 mL) was added with vigorous stirring for 1 h. The mixture wasleft standing overnight and the precipitated solid was filtered, washed with water and cooled ethanol and dried to afford compounds **3-7**.

1,1'-((1*H*-1,2,4-Triazole-3,5-diyl)bis(methylene))bis(1*H*-benzo[*d*][1,2,3]triazole) (3)

Pale white powder; (yield 77%); m.p195-197^{o}C; IR (KBr) υ cm^{-1}: 3403 (NH), 1618 (C=N); ^{1}H NMR (DMSO-d_6) δ ppm: 4.94(s, 4H, 2CH_2), 7.29-7.31 (m, 2H, Ar-H), 7.40-7.47(m, 2H, Ar-H), 7.61-7.65(m, 2H, Ar-H), 7.94-7.97(m, 2H, Ar-H),10.95(bs, 1H, NH);^{13}C NMR (DMSO-d_6) δ ppm: 49.8,53.5 (2CH_2), 115.3, 119.6, 126.6, 130.8, 132.9, 135.1, 145.8, 147.3, 148.5, 153.5, 157.9 (Ar-C and triazole-C);Ms: *m/z*331 (M^+, 24%);Anal. calcd. for $C_{16}H_{13}N_9$(331.34):C, 58.00; H, 3.95; N, 38.05. Found (%):C, 58.03; H, 3.97; N, 37.97.

8-((3-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-1*H*-1,2,4-triazol-5-yl)methoxy)quinolone (4)

Pale white powder; (yield 69%); m.p 175-176^{o}C; IR (KBr) υ cm^{-1}: 3398 (NH), 1605 (C=N); ^{1}H NMR (DMSO-d_6) δ ppm: 4.92 (s, 2H, CH_2), 5.10 (s, 2H, CH_2), 7.29-7.45 (m, 5H, Ar-H),7.80-7.97 (m, 3H, Ar-H), 8.25-8.28 (m, 1H, Ar-H), 8.76-8.79 (m, 1H, Ar-H), 12.20 (bs, 1H, NH); Ms: *m/z*357 (M^+, 7%); Anal. calcd. for $C_{19}H_{15}N_7O$ (357.38) (%):C, 63.86; H, 4.23; N, 27.44. Found (%):C,63.84; H, 4.21; N, 27.40.

8-((3-((1*H*-Benzo[d]imidazol-2-yl)methyl)-1*H*-1,2,4-triazol-5-yl)methoxy)-quinolone (5)

Pale white powder; (yield 70%); m.p 165-166^{o}C; IR (KBr) υ cm^{-1}: 3421 (NH), 1608 (C=N); ^{1}H NMR (DMSO-d_6) δ ppm: 3.40(s, 2H, CH_2), 4.30(s, 2H, CH_2), 7.11-7.14 (m, 2H, Ar-H), 7.37-7.56 (m, 5H, Ar-H), 7.77-7.83 (m, 2H, Ar-H), 8.02-8.05(m, 1H, Ar-H), 12.30 (bs, 1H, NH), 13.88 (bs, 1H, NH);^{13}C NMR (DMSO-d_6) δ ppm: 53.2, 66.3 (2CH_2), 111.5, 115.2, 118.5, 120.3, 122.4, 126.3, 127.1, 129.9, 132.0, 133.1, 135.7, 145.8, 146.9, 148.5, 153.2, 157.1 (Ar-C and triazole-C).Ms: *m/z* 356 (M^+, 6%), Anal. calcd. for $C_{20}H_{16}N_6O$ (356.39) (%):C, 67.40; H, 4.53; N, 23.58. Found (%):C,67.43; H, 4.51; N, 23.57.

1-((3-((1*H*-Benzo[d]imidazol-2-yl)methyl)-1*H*-1,2,4-triazol-5-yl)methyl)-1*H*-benzo[*d*][1,2,3]triazole (6)

Pale white powder; (yield 75%); m.p 254-255^{o}C; IR (KBr) υ cm^{-1}: 3894 (NH), 1610 (C=N); ^{1}H NMR (DMSO-d_6) δ ppm: 4.29(s, 2H, CH_2), 4.31(s, 2H, CH_2), 7.11-7.15 (m, 2H, Ar-H), 7.39-7.51 (m, 3H, Ar-H), 7.79-8.05 (m, 3H, Ar-H), 12.38 (bs, 1H, NH), 12.75 (bs, 1H, NH); Ms: *m/z* 330 (M^+, 24%),Anal. calcd. for $C_{17}H_{14}N_8$ (330.36) (%):C, 61.81; H, 4.27; N, 33.92. Found (%):C,61.78; H, 4.26; N, 33.96.

2-((5-((1*H*-Benzo[d][1,2,3]triazol-1-yl)methyl)-1*H*-1,2,4-triazol-3-yl)methyl)benzo[*d*]thiazole (7)

Pale white powder; (yield 77%); m.p 139-140^{o}C; IR (KBr) υ cm^{-1}: 3452 (NH), 1612 (C=N); ^{1}H NMR (DMSO-d_6) δ ppm4.11 (s, 2H, CH_2), 4.19(s, 2H, CH_2),7.15-7.25(m, 3H, Ar-H), 7.52-7.55(m, 1H, Ar-H), 7.75-7.78 (m, 2H, Ar-H), 7.98-8.01 (m, 2H, Ar-H),11.99 (bs, 1H, NH);Ms: *m/z* 347 (M^+, 11%), Anal. calcd. for $C_{17}H_{13}N_7S$ (347.40) (%):C, 58.78; H, 3.77; N, 28.22. Found (%):C,58.81; H, 3.76; N, 28.20.

General procedure for the preparation of the acetylated glycosides 8-13.

Sodium hydride (12mmol) was added portion wise during 15 min. to a solution of compound**3, 4**or**7**(5 mmol) in dry DMF (15 ml) at 0^{o}C and the mixture was stirred at room temperature for another 45min. A solution of 2,3,4,6-tetra-

O-acetyl-α-D-gluco- or xylopyronosyl bromide (5 mmol) in dry DMF (10 ml) was added slowly within 30 min and the resulting mixture was stirred at room temperature for 6-8 h (completion was monitored by TLC). Ice water mixture (30 mL) was added with stirring and the precipitatewas filtered then triturated with pet. ether (40-60%, 25 mL), dried and crystallized from ethanol.

1,1'-((1-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl)-1*H*-1,2,4-triazole-3,5-diyl)bis(methylene))bis(1*H*-benzo [*d*][1,2,3]triazole) (8)
Pale yellow powder; (yield 78%); m.p130-131^oC; IR (KBr) υ cm^{-1}: 1749 (C=O), 1620 (C=N); ^1H NMR (DMSO-d_6) δ ppm:1.91, 1.99, 2.03, 2.07 (4s, 12H, 4 CH_3),3.58 (m, 1H, H-5′),4.02-4.07 (dd, 1H, *J* = 3.8, 10.2 Hz, H-6′′), 4.17-4.19 (dd, 1H, *J*= 11.3, 3.8 Hz, H-6′), 4.60-4.62 (m, 1H, H-4′), 4.90-4.96 (m, 3H, CH_2 and H-3′), 5.17-5.20 (dd, 1H, *J* = 6.6 Hz, H-2′), 5.25 (s, 2H, CH_2), 5.98 (d, 1H, *J* = 8.5 Hz, H-1′), 7.12-7.15 (m, 2H, Ar-H), 7.46-7.49 (m, 3H, Ar-H), 7.80-7.82 (m, 1H, Ar-H), 7.95-7.99 (m, 1H, Ar-H), 8.01-8.04 (m, 1H, Ar-H);^{13}C NMR (DMSO-d_6) δ ppm: 20.9, 21.4, 21.7, 21.9 (4CH_3), 51.1,53.8 (2CH_2), 61.9 (C-6), 67.3 (C-4), 69.9 (C-2), 72.8 (C-3), 75.9 (C-5), 93.9 (C-1), 115.2, 119.1, 126.6, 131.9, 133.2, 135.4, 145.8, 147.4, 148.2,154.8, 159.3 (Ar-C and triazole-C), 169.0, 169.4, 169.7, 170.2 (4C=O).Anal. calcd. for $C_{30}H_{31}N_9O_9$(661.22) (%):C, 54.46; H, 4.72; N, 19.05. Found (%): C, 54.48; H, 4.74; N, 19.01.

1,1'-((1-(2,3,4-Tri-*O*-acetyl-*β*-D-xylopyranosyl)-1*H*-1,2,4-triazole-3,5-diyl)bis(methylene))bis(1*H*-benzo[*d*] [1,2,3] triazole) (9)
Pale yellowpowder; (yield 76%); m.p 138-139^oC; IR (KBr) υ cm^{-1}: 1738 (C=O), 1612 (C=N); ^1H NMR (DMSO-d_6) δ ppm:1.93, 1.99, 2.07 (3s, 9H, 3 CH_3), 4.01 (dd, 1H, *J* = 3.8, 10.2 Hz, H-5′′), 4.04 (dd, 1H, *J* = 11.3, 3.8 Hz, H-5′), 4.30 (s, 4H, 2CH_2), 4.62 (m, 1H, H-4′), 4.87-4.92 (m, 1H, H-3′), 5.22-5.25 (t, 1H, *J* = 6.6 Hz, H-2′), 5.97 (d, 1H, *J* = 8.5 Hz, H-1′), 7.13-7.16 (m, 1H, Ar-H), 7.36-7.65 (m, 3H, Ar-H),7.69-7.82 (m, 2H, Ar-H), 7.98-8.06 (m, 2H, Ar-H); Anal. calcd. For$C_{27}H_{27}N_9O_7$ (589.56) (%): C, 55.01; H, 4.62; N, 21.38. Found (%): 55.05; H, 4.60; N, 21.40.

8-((3-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-1-(2,3,4,5-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-1*H*-1,2,4-triazol-5-yl)methoxy)quinolone (10)
Brownishpowder; (yield 70%); m.p 129-131^oC; IR (KBr) υ cm^{-1}: 1745 (C=O), 1610 (C=N); ^1H NMR (DMSO-d_6) δ ppm:1.90, 1.97, 1.99, 2.06(4s, 12H, 4 CH_3),3.61 (m, 1H, H-5′),4.03-4.07 (dd, 1H, *J* = 3.8, 10.2 Hz, H-6′′), 4.16-4.19 (dd, 1H, *J*= 11.3, 3.8 Hz, H-6′),4.58-4.61(m, 1H, H-4′), 4.92-5.12 (m, 3H, $CH_2$and H-3′), 5.22-5.34(m, 3H, $CH_2$and H-2′), 5.98 (d, 1H, *J* = 8.5 Hz, H-1′), 7.10-7.21 (m, 3H, Ar-H), 7.45-7.55 (m, 3H, Ar-H), 7.84-7.95 (m, 4H, Ar-H);Anal. calcd. For $C_{33}H_{33}N_7O_{10}$ (687.66) (%): C, 57.64; H, 4.84; N, 14.26. Found (%):C, 57.61; H, 4.82; N, 14.31

8-((3-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-1-(2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosyl)-1*H*-1,2,4-triazol-5-yl) methoxy)quinolone (11)
Brownishpowder; (yield 68%); m.p 134-136^oC; IR (KBr) υ cm^{-1}: 1742 (C=O), 1605 (C=N); ^1H NMR (DMSO-d_6) δ ppm:1.94, 1.96, 2.06 (3s, 9H, 3 CH_3),3.98-4.04 (dd, 1H, *J* = 3.8, 10.2 Hz, H-5′′),4.14-4.19 (dd, 1H, *J* = 11.3, 3.8 Hz, H-5′), 4.89 (s, 2H, CH_2),4.96 (m, 1H, H-4′),5.15 (s, 2H, CH_2), 5.28-5.31 (m, 1H, H-3′),5.40-5.44 (t, 1H, *J* = 6.6 Hz, H-2′),5.97 (d, 1H, *J* = 8.5 Hz, H-1′),7.31-7.40 (m, 2H, Ar-H), 7.42-7.52 (m, 3H, Ar-H), 7.8-7.96 (m, 3H, Ar-H), 8.18 (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 20.8, 21.3, 21.7 (3CH_3), 53.6 (CH_2), 65.9 (C-5), 67.1 (CH_2), 68.3 (C-4), 69.1 (C-2), 69.9 (C-3), 95.7 (C-1), 111.7, 115.4, 118.6, 120.1, 122.4, 126.5, 126.9,129.8, 131.9, 133.2, 135.4, 145.8, 147.4, 148.2,153.6, 157.5(Ar-C and triazole-C), 169.5, 169.8, 170.3 (3C=O).Anal. calcd. for $C_{30}H_{29}N_7O_8$ (615.59) (%): C, 58.53; H, 4.75; N, 15.93. Found (%):C, 58.52; H, 4.77; N, 15.92.

2-((5-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-1-(2,3,4,5-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-1*H*-1,2,4-triazol-3-yl)methyl)benzo[*d*]thiazole (12)
Pale yellow powder; (yield 75%); m.p 118-119^oC; IR (KBr) υ cm^{-1}: 1740 (C=O), 1608 (C=N); ^1H NMR (DMSO-d_6) δ ppm:1.95, 1.97, 2.01, 2.05 (4s, 12H, 4 CH_3),3.64 (m, 1H, H-5′),3.88-3.96 (dd, 1H, *J* = 3.8, 10.2 Hz, H-6′′), 4.08-4.18 (dd, 1H, *J* = 11.3, 3.8 Hz, H-6′), 4.75-4.79 (m, 1H, H-4′), 4.92-5.14(m, 3H, H-3′ and CH_2), 5.19 (s, 2H, CH_2),5.46-5.49 (t, 1H, *J* = 6.6 Hz, H-2′), 5.97 (d, 1H, *J* = 8.5 Hz, H-1′), 7.34-7.49 (m, 5H, Ar-H), 7.79-7.90 (m, 3H, Ar-H); Anal. calcd. for $C_{31}H_{31}N_7O_9S$ (677.68) (%): C, 54.94; H, 4.61; N, 14.47. Found (%): C, 54.96; H, 4.59; N, 14.49.

2-((5-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-1-(2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosyl)-1*H*-1,2,4-triazol-3-yl) methyl)benzo[*d*]thiazole (13)
Pale yellow powder; (yield 71%); m.p 127-128°C; IR (KBr) υ cm^{-1}: 1742 (C=O), 1610 (C=N); ^{1}H NMR (DMSO-d$_6$) δ ppm:1.96, 1.99, 2.04 (3s, 9H, 3 CH_3),3.90-3.97 (dd, 1H, *J* = 3.8, 10.2 Hz, H-5″), 4.14-4.18 (dd, 1H, *J* = 11.3, 3.8 Hz, H-5′), 4.61-4.66 (m, 1H, H-4′), 4.90-5.03(m, 3H, $CH_2$and H-3′), 5.21(s, 2H, CH_2),5.33-5.38 (t, 1H, *J* = 6.6 Hz, H-2′), 5.96 (d, 1H, *J* = 8.5 Hz, H-1′), 7.42-7.53 (m, 3H, Ar-H), 7.65-7.74 (m, 2H, Ar-H), 7.83-7.93 (m, 3H, Ar-H); Anal. calcd. for $C_{28}H_{27}N_7O_7S$ (605.62) (%): C, 55.53; H, 4.49; N, 16.19. Found (%): C, 55.50; H, 4.47; N, 16.22.

General procedure for preparation of the deacetylated glycosides 14-19.
Compound **8-13**(5 mmol) was dissolved with stirring at 0°C in dry methanol saturated with ammonia gas (25 mL) and stirring was continued at room temperature for 6 h at which TLC showed completion of the deacetylation [TLC, methanol: chloroform (4 : 96)].The solvent was evaporated under reduced pressure and the remained residue was treated with pet. ether : diethyl ether (1 :1) mixture to afford a solid which was collected by filtration and crystallized from ethanol.

1,1'-((1-(*β*-D-glucopyranosyl)-1*H*-1,2,4-triazole-3,5-diyl)bis(methylene))bis(1*H*-benzo[*d*][1,2,3]triazole) (14)
Brownish powder; (yield 74%); m.p 205-207°C; IR (KBr) υ cm^{-1}: 3485-3465 (OH), 1608 (C=N); ^{1}H NMR (DMSO-d$_6$) δ ppm: 3.26-3.32 (m, 2H, H-6,6′), 3.34-3.37 (m, 1H, H-5), 3.52-3.63 (m, 2H, H-3,4), 4.20 (m, 1H, H-2), 4.25-4.53 (m, 5H, OH and 2CH_2), 4.53 (m, 1H, OH), 4.95 (m, 1H, OH),5.64 (m, 1H, OH), 5.80 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 7.43-7.47 (m, 2H, Ar-H), 7.50-7.68 (m, 3H, Ar-H), 7.91-8.05 (m, 3H, Ar-H).Anal.calcd. for $C_{22}H_{23}N_9O_5$ (493.48) (%): C, 53.55; H, 4.70; N, 25.55. Found (%): C, 53.58; H, 4.72; N, 25.60.

1,1'-((1-(*β*-D-xylopyranosyl)-1*H*-1,2,4-triazole-3,5-diyl)bis(methylene))bis(1*H*-benzo[*d*][1,2,3]triazole) (15)
Brownishpowder; (yield 71%); m.p 211-212°C; IR (KBr) υ cm^{-1}: 3480-3450 (OH), 1612 (C=N); ^{1}H NMR (DMSO-d$_6$) δ ppm: 3.32-3.39 (m, 2H, H-5,5′), 3.92-4.18 (m, 2H, H-3,4), 4.26 (m, 1H, H-2), 4.45 (m, 1H, OH), 4.62-4.85 (m, 5H, OH and 2CH_2), 5.42 (m, 1H, OH), 5.84 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 7.39-7.46 (m, 2H, Ar-H), 7.52-7.67 (m, 3H, Ar-H), 7.90-8.11 (m, 3H, Ar-H). Anal. calcd. for $C_{21}H_{21}N_9O_4$ (463.45) (%): C, 54.42; H, 4.57; N, 27.20. Found (%): C, 54.41; H, 4.55; N, 27.22.

8-((3-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-1-(*β*-D-glucopyranosyl)-1*H*-1,2,4-triazol-5-yl)methoxy) quinolone (16)
Brownishpowder; (yield 77%); m.p 210-212°C; IR (KBr) υ cm^{-1}: 3490-3460 (OH), 1602 (C=N); ^{1}H NMR (DMSO-d$_6$) δ ppm: 3.27-3.36 (m, 2H, H-6,6′), 3.51-3.54 (m, 1H, H-5), 3.65-3.79 (m, 2H, H-3,4), 4.30 (m, 1H, H-2), 4.53 (m, 1H, OH), 4.87-5.16 (m, 5H, 2CH_2 andOH), 5.41 (m, 1H, OH), 5.60 (m, 1H, OH),5.99 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 7.41-7.52 (m, 3H, Ar-H), 7.59-7.69 (m, 3H, Ar-H), 7.91-8.04 (m, 2H, Ar-H), 8.27-8.30 (m, 2H, Ar-H). Anal.calcd. for$C_{25}H_{25}N_7O_6$ (519.51) (%): C, 57.80; H, 4.85; N, 18.87. Found (%): C, 57.83; H, 4.84; N, 18.71.

8-((3-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-1-(*β*-D-xylopyranosyl)-1*H*-1,2,4-triazol-5-yl)methoxy)quinolone (17)
Brownish powder; (yield 70%); m.p 220-221°C; IR (KBr) υ cm^{-1}: 3475-3450 (OH), 1605 (C=N); ^{1}H NMR (DMSO-d$_6$) δ ppm: 3.36-3.48 (m, 2H, H-5,5′), 3.63-3.80 (m, 2H, H-3,4), 4.26 (m, 1H, H-2), 4.40-4.48 (m, 1H, OH), 4.95-5.17 (m, 5H, OH and 2CH_2),5.60 (m, 1H, OH), 5.98 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 7.31-7.44 (m, 3H, Ar-H), 7.50-7.56 (m, 2H, Ar-H), 7.74-7.80 (m, 2H, Ar-H), 7.86-7.90(m, 2H, Ar-H), 8.05 (d, 1H, J = 7.8 Hz, Ar-H).Anal.calcd. for $C_{24}H_{23}N_7O_5$ (489.48) (%): C, 58.89; H, 4.74; N, 20.03. Found (%):C, 58.91; H, 4.76; N, 20.07.

2-((5-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-1-(*β*-D-glucopyranosyl)-1*H*-1,2,4-triazol-3-yl)methyl)benzo[*d*] thiazole (18)
Pale yellow powder; (yield 75%); m.p 185-187°C; IR (KBr) υ cm^{-1}: 3485-3460 (OH), 1615 (C=N); ^{1}H NMR (DMSO-d$_6$) δ ppm: 3.36-3.44 (m, 2H, H-6,6′), 3.54-3.63 (m, 1H, H-5), 3.79-3.91 (m, 2H, H-3,4), 4.28 (m, 1H, H-2), 4.58-4.62 (m, 1H, OH), 4.76-5.17 (m, 5H, OH and 2CH_2), 5.34 (m, 1H, OH), 5.59 (m, 1H, OH), 5.98 (d, 1H, $J_{1,2}$= 9.8 Hz, H-1), 7.38-7.48 (m, 2H, Ar-H), 7.62-7.75 (m, 3H, Ar-H), 7.88-8.02 (m, 3H, Ar-H). Anal.calcd. for $C_{23}H_{23}N_7O_5S$ (509.54) (%): C, 54.22; H, 4.55; N, 19.24. Found (%): C, 54.18; H, 4.51; N, 19.27.

2-((5-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl)-1-(*β*-D-xylopyranosyl)-1*H*-1,2,4-triazol-3-yl)methyl)benzo[*d*] thiazole (19)

Pale yellow powder; (yield 73%); m.p 192-193°C; IR (KBr) υ cm^{-1}: 3470-3450 (OH), 1608 (C=N); ^{1}H NMR (DMSO-d_6) δ ppm: 3.38-3.47 (m, 2H, H-5,5′), 3.86-3.99 (m, 2H, H-3,4), 4.31 (m, 1H, H-2), 4.39 (m, 1H, OH), 4.79-5.19 (m, 5H, OH and $2CH_2$),4.61 (m, 1H, OH), 5.97 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 7.37-7.46 (m, 2H, Ar-H), 7.62-7.77 (m, 3H, Ar-H), 7.85-7.98 (m, 3H, Ar-H).Anal.calcd. for $C_{22}H_{21}N_7O_4S$ (479.51) (%): C, 55.11; H, 4.41; N, 20.45. Found (%):C, 55.13; H, 4.43; N, 20.42.

General procedure for the preparation of the acetylated glycosides 20 and 21.

To a solution of the disubstituted triazole derivative**5**or**6**(5 mmol) in dry DMF (20 ml) was added sodium hydride (20 mmol) at 0°C portion wise during 15 min. and the mixture was stirred at0°Cfor additional15 min. then stirring was continued at room temperature for 1 h. A solution of 2,3,4-tri-*O*-acetyl-α-D-xylopyronosyl bromide (10 mmol) in dry DMF (15 ml) was added slowly within 30 min and the resulting mixture was stirred at room temperature for 7-8 h (completion was monitored by TLC). Ice water mixture (30 mL) was added with stirring and the precipitate was filtered then triturated with pet. ether (40-60%, 30 mL), dried and crystallized from ethanol.

8-((1-(2,3,4-Tri-*O*-acetyl-*β*-D-xylopyranosyl)-3-((1-(2,3,4-Tri-*O*-acetyl-*β*-D-xylopyranosyl)-1*H*-benzo[d] imidazol-2-yl)methyl)-1*H*-1,2,4-triazol-5-yl)methoxy)quinolone (20)

Pale white powder; (yield 78%); m.p 123-125°C; IR (KBr) υ cm^{-1}: 1738 (C=O), 1610 (C=N); ^{1}H NMR (DMSO-d_6) δ ppm: 1.90-2.07 (6s, 18H, 6 CH_3), 4.04-4.09 3.98-4.04(m, 2H, H-5′a,5′b), 4.13-4.18 (dd, 1H, *J* = 11.3, 8.4 Hz,H-5′′a), 4.19-4.21 (m, 1H, *J* = 11.3, 3.8 Hz, H-5′′b),4.29-4.33(m, 2H,H-4′aand H-4′b), 4.89-4.97 (m, 3H, and H-3′aandCH$_2$), 4.99-5.08 (dd, 1H, *J* = 8.4, 9.8 Hz, H-3′b), 5.34-5.46 (m, 4H, H-2′a, H-2′band CH_2), 5.97 (d, 1H, *J* = 10.2 Hz, H-1′), 5.98 (d, 1H, *J* = 9.5 Hz, H-1′), 7.11-7.14(m, 2H, Ar-H), 7.39-7.45 (m, 4H, Ar-H), 7.80-7.92 (m, 2H, Ar-H), 8.02-8.05 (m, 2H, Ar-H).).Anal.calcd. for $C_{42}H_{44}N_6O_{15}$ (872.83) (%): C, 57.80; H, 5.08; N, 9.63. Found (%): C, 57.74; H, 5.11; N, 9.61.

1-((1-(2,3,4-Tri-*O*-acetyl-*β*-D-xylopyranosyl)-3-((1-(2,3,4-Tri-*O*-acetyl-*β*-D-xylopyranosyl)-1*H*-benzo[d] imidazol -2-yl)methyl)-1*H*-1,2,4-triazol-5-yl)methyl)-1*H*-benzo[*d*][1,2,3]triazole (21)

Pale yellow powder; (yield 73%); m.p 155-156°C; IR (KBr) υ cm^{-1}: 1745 (C=O), 1612 (C=N); ^{1}H NMR (DMSO-d_6) δ ppm: 1.90-2.07 (6s, 18H, 6 CH_3), 3.98-4.02 (m, 2H, H-5′a,5′b), 4.13-4.15 (dd, 1H, *J* = 11.3, 8.4 Hz, H-5′′a), 4.16-4.19(dd, 1H, *J* = 11.3, 3.8 Hz, H-5′′b),4.93-5.16 (m, 6H, H-4′a, H-4′band $2CH_2$), 5.37-5.39 (dd, 1H, *J* = 8.4, 9.8 Hz, H-3′a),5.41-5.44(m, 3H, H-3′b, H-2′a and H-2′b), 5.94 (d, 1H, *J* = 10.2 Hz, H-1′), 5.97 (d, 1H, *J* = 9.5 Hz, H-1′),7.12-7.26 (m, 3H, Ar-H), 7.35-7.49 (m, 4H, Ar-H), 8.06-8.08 (d, 1H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 20.6, 21.2, 21.5 (6CH_3CO), 39.6,53.5 ($2CH_2$), 64.9 (C-5a), 64.9 (C-5b), 66.3 (C-4a), 66.6 (C-4b), 69.6 (C-2a), 69.9 (C-2b), 70.6 (C-3a), 70.9 (C-3b), 93.9 (C-1a), 95.6 (C-1a), 111.9, 115.4, 119.3, 126.8, 131.8, 133.4, 135.7, 145.8, 147.9, 148.2, 149.8,154.8, 159.3 (Ar-C and triazole-C), 168.9, 169.5, 169.7, 170.3 (6C=O).Anal. calcd. for $C_{39}H_{42}N_8O_{14}$ (846.80) (%): C, 55.32; H, 5.00; N, 13.23. Found (%):C, 55.29; H, 5.01; N, 13.25.

General procedure for preparation of the deacetylated glycosides 22 and 23

Compound **20**or **21**(5 mmol) was dissolved with stirring at 0°C in dry saturated methanolic ammonia solution (35 mL) and stirring was continued at room temperature for 7-8 h. After completion of the reaction [TLC, methanol: chloroform (5 : 95)] the solvent was evaporated under reduced pressure. The residue was triturated with pet. ether : diethyl ether (1 :1) mixture and the obtained solid was collected by filtration and crystallized from ethanol.

8-((1-(*β*-D-xylopyranosyl)-3-((1-(*β*-D-xylopyranosyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-1*H*-1,2,4-triazol-5-yl) methoxy)quinolone (22)

Brownishpowder; (yield 80%); m.p 188-190°C; IR (KBr) υ cm^{-1}: 3460-3445 (OH), 1605 (C=N); ^{1}H NMR (DMSO-d_6) δ ppm: 3.32-3.59(m, 4H, H-5′a,5′b,5′′a,5′′b), 3.64 (m, 3H, H-4′a,H-4′b,H-3′a,),3.97-4.01 (m, 1H, H-3′b),4.29-4.32 (m, 4H, H-2′a, H-2′b, 2OH), 4.56-4.85 (m, 5H, OH and $2CH_2$), 5.50-5.64 (m, 3H,3OH), 5.97-5.99 (m, 2H, *J* = H-1′a and 1′b), 7.11-7.14 (m, 2H, Ar-H), 7.39-7.51 (m, 4H, Ar-H), 7.79-7.88 (m, 3H, Ar-H), 8.02-8.04 (d, *J* = 8.2, 1H, Ar-H). Anal. calcd. for $C_{30}H_{32}N_6O_9$ (620.62) (%): C, 58.06; H, 5.20; N, 13.54. Found (%):C, 57.95; H, 5.10; N, 13.31.

1-((1-(*β*-D-xylopyranosyl)-3-((1-(*β*-D-xylopyranosyl)-1*H*-benzo[d]imidazol-2-yl)methyl)-1*H*-1,2,4-triazol-5-yl)methyl)-1*H*-benzo[*d*][1,2,3]triazole (23)

Pale yellow powder; (yield 79%); m.p 230-231°C; IR (KBr) υ cm^{-1}: 3480-3460 (OH), 1612 (C=N); ^{1}H NMR (DMSO-d_6) δ ppm: 3.33-3.62 (m, 4H, H-5′a,5′b,5′′a,5′′b), 3.66-3.73(m, 3H, H-4′a,H-4′b and H-3′a), 3.85-3.92 (m, 1H,H-3′b), 4.30-4.41 (m, 4H, H-2′a, H-2′b and 2OH), 4.59-4.87 (m, 5H, OH and $2CH_2$), 5.52 (m, 3H,3OH), 5.96-5.98 (m, 2H, *J* = H-1′a and 1′b), 7.16-7.25(m, 2H, Ar-H), 7.60-7.74(m, 3H, Ar-H), 7.81-7.90(m, 3H, Ar-H). Anal. calcd. for $C_{27}H_{30}N_8O_8$ (594.58) (%): C, 54.54; H, 5.09; N, 18.85. Found (%):C, 54.57; H, 5.12; N, 18.79.

ANTIVIRAL ACTIVITY

MTT cytotoxicity assay (TC50)

Samples were 10-fold serially diluted with Dulbecco's Modified Eagle's Medium (DMEM). Stock solutions of the test compounds were prepared in 10 % DMSO in dH_2O. The cytotoxic activity of the extracts were tested in Madin Darby Canine kidney (MDCK) cells by using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method [33] with minor modification. Briefly, the cells were seeded in 96 well-plates (100 µl/well at a density of $3×10^5$ cells/ml) and incubated for 24 hrs at 37°C in 5%CO_2. After 24 hrs, cells were treated with various concentrations of the tested compounds in triplicates. After further 24 hrs, the supernatant was discarded and cell monolayers were washed with sterile phosphate buffer saline (PBS) 3 times and MTT solution (20 µl of 5 mg/ml stock solution) was added to each well and incubated at 37 °C for 4 hrs followed by medium aspiration. In each well, the formed formazan crystals were dissolved with 200 µl of acidified isopropanol (0.04 M HCl in absolute isopropanol = 0.073 ml HCL in 50 ml isopropanol). Absorbance of formazan solutions were measured at λmax. 540 nm with 620 nm as a reference wavelength using a multi-well plate reader. The percentage of cytotoxicity compared to the untreated cells was determined with the following equation.

$$\% \text{ Cytotoxicity} = \frac{(\text{Absorbance of cell without treatment} - \text{Absorbance of cell with treatment}) \times 100}{\text{Absorbance of cell without treatment}}$$

The plot of % cytotoxicity versus sample concentration was used to calculate the concentration which exhibited 50% cytotoxicity (LD50).

Plaque reduction assay

Assay was carried out according to a reported method [34] with some modifications, in a six well plate where MDCK cells (10^5 cells / ml) were cultivated for 24 hrs at 37°C. A/CHICKEN/7217B/1/2013 (H5N1) virus was diluted to give around (40-70)PFU/ well and mixed with the safe concentration of the tested compounds, and incubated for 30 minutes at 37°C before being added to the cells. Growth medium was removed from the cell culture plates and virus-Cpd or virus-extract and Virus-Amantadine mixtures were inoculated (100 µl / well), After 1 hour contact time for virus adsorption, the inoculums were removed and the cells were washed one time with PBS (phosphate buffer saline), afterwards 3 ml of DMEM supplemented with 2% agarose containing the compounds corresponding to each concentration were added onto the cell monolayer. Plates were left to solidify and incubated at 37°C till formation of viral plaques (3 to 4 days). Formalin (10%) was added for two hours then plates were stained with 0.1 %crystalviolet in distilled water. Control wells were included where untreated virus was incubated with MDCK cells and finally plaques were counted and percentage reduction in plaques formation in comparison to control wells was recorded as following:

% inhibition = viral count (untreated) - viral count (treated)/viral count (untreated) x 100

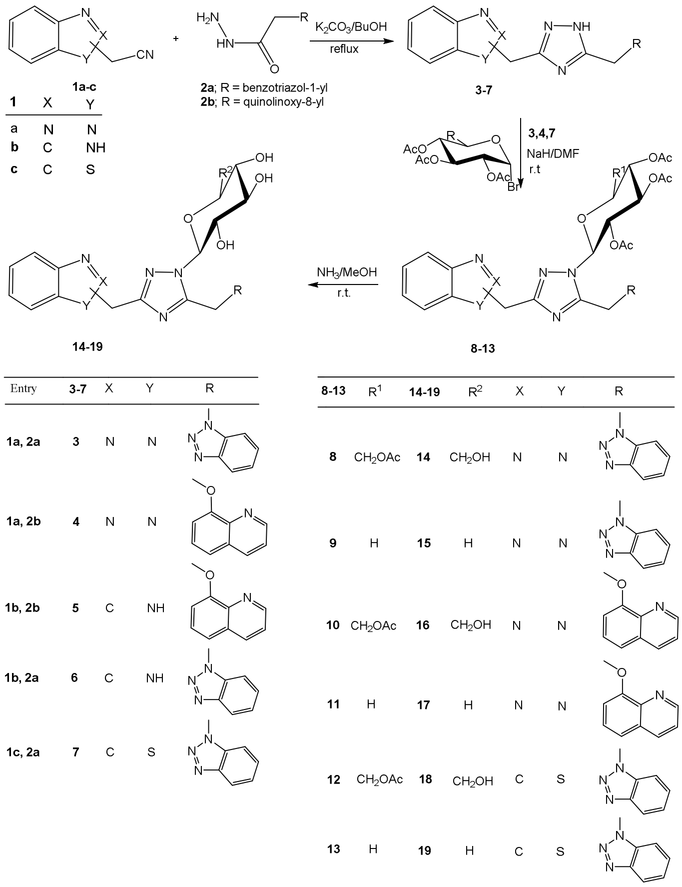
RESULTS AND DISCUSSION

Chemistry

A reaction involving two bond formation was employed for the preparation of 3,5-disubstituted 1,2,4-triazole as nucleobase analog. The hydrazides **2a,b** were allowed to react with the heteroaryl substituted acetonitrile derivatives **1a-c** using catalytic amount of K_2CO_3 and *n*-butanol as a solvent to afford the disubstituted 1,2,4-triazoles **3-7** bearing benzothiazole, benzotriazole, quinoloxymethyl and benziimidazole ring systems in moderate yields. The structures of compounds **3-7** were confirmed by their spectral data. Their IR spectra revealed the disappearance of the characteristic hydrazide carbonyl and cyano absorption bands. The ^{1}H NMR spectra showed signals corresponding to the two methylene protons in addition to the aryl and NH proton of the 1,2,4-triazole ring.

Glycosylation of the 1,2,4-triazole, substituted with benzotriazol-1-ylmethyl, quinolinoxy-8-ylmethyl,benzothiazolyl-2-ylmethyl **3**,**4** and **7** respectively, by reaction with acetylated gluco- and xylopyranosyl bromide in basic medium produced the corresponding heteroaryl-1,2,4-*N*-glycosides **8-13** in good yields. The Infra-Red spectra showed the carbonyl of the acetyl groups in addition to the disappearance of the NH band. Their ^{1}H NMR spectra showed the acetyl methyl signals in addition to signals of the sugar protons and the aromatic protons signals. The coupling constant value *J*of the anomeric protons 9.8-10.2 Hz indicated that attachment of the sugar moiety is in the *beta* conformation leading to the formation of the 1,2,4-triazole-*β*-glycoside confirming the assigned structure which is also in agreement with their ^{13}C NMR spectra.

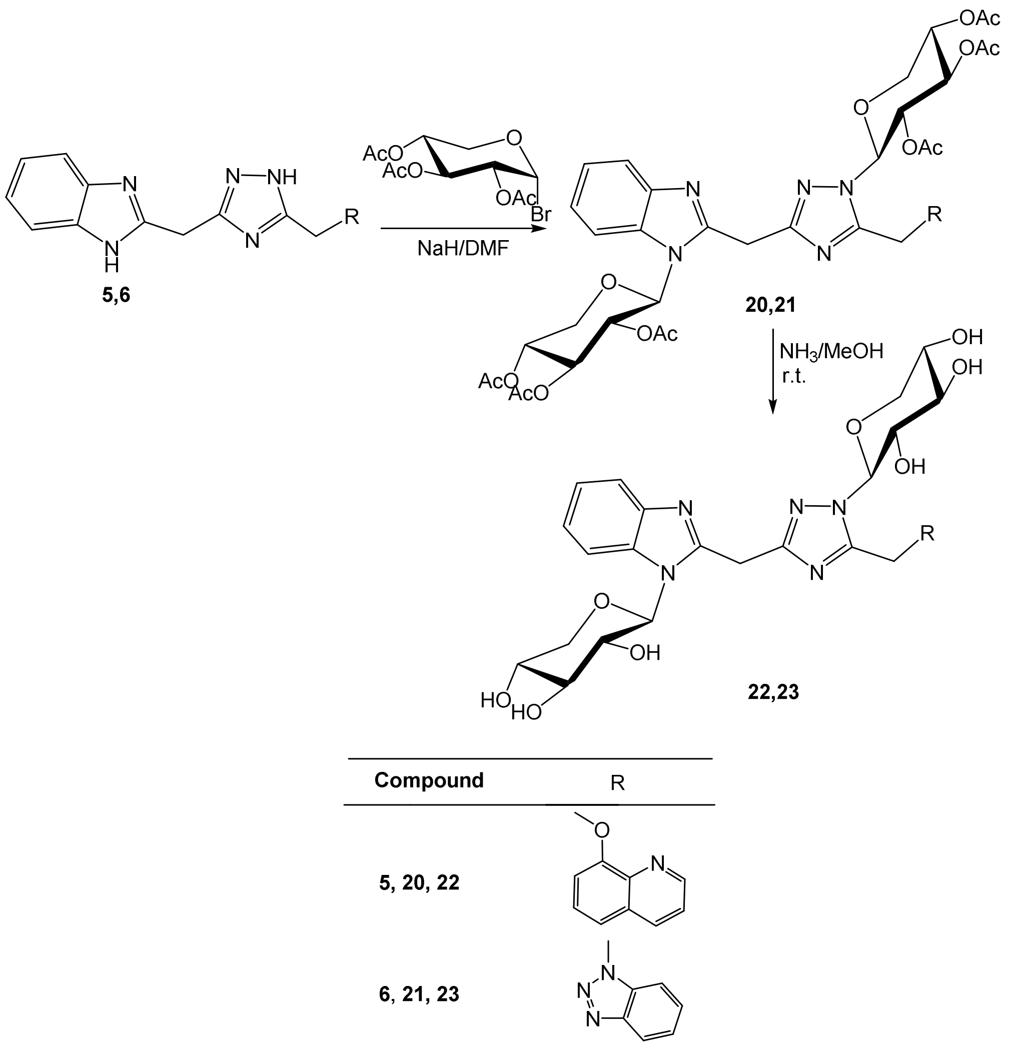
Compounds **8-13** were deacetylated using saturated methanolic ammonia solution to give the deprotected glycosides **14-19** with free hydroxyls in the resulting glycosides (Scheme 1). The ^{1}H NMR and IR spectra of the latter glycoside derivatives are in agreement with the assigned structure revealing the appearance of the hydroxyl groups and disappearance of the acetyl-methyl protons.



Scheme 1. Synthesis of substituted triazole glycosides

Reaction of the 1,2,4-triazoles, substituted with benzoimidazol-2-ylmethyl- moiety and incorporating two -NH centers,**5** and **6** with tri-*O*-acetyl-D-xylopyranosyl bromide resulted in the formation of the acetylated glycoside derivatives **20** and **21**, respectively in good yields. Their corresponding spectral data revealed the attachment of two xylopyranosyl moieties at the two NH positions in the compound. The mode of attachment as *β*-type was also obvious from the coupling *J* value of H-1 in the sugar moiety.

Deacetylation of the latter benzoimidazolyl-1,2,4-triazolxylopyranoside derivatives **20** and **21** by means ofammonia solution in methanol resulted in the formation of the free hydroxyl glycoside derivatives **22** and **23**, respectively(Scheme 2). Their IR data showed the presence of the hydroxyl bands and the NMR spectra agreed with the assigned structure (see experimental part).



Scheme 2. Synthesis of benzoimidazolyl triazole glycosides

Antiviral activity
A number of the synthesized compounds were studied for their antiviral activity against H5N1 influenza virus strain A/Egypt/M7217B/2013 using MTT cytotoxicity assay (TC50) and Plaque reduction assay investigating the inhibition % and cytotoxicity% values. The results of inhibition activities and cytotoxicity results were formulated(Table 1, Table 2 and Fig. 1).

The results revealed that the tested compounds displayed a range from no inhibition to weak and moderate inhibition. Compound **8** showed no cytotoxicity at all concentrations in this investigation with TC50 more than 200 µg/µl (Table 1). On the other hand, compounds **8**, **6**, **9** and **3** showed no inhibition activity.

The results of antiviral activity indicated that compounds **21**, **7** and **4** were the most active with 34%, 30.5% and 29% inhibition. Compound **7** showed higher inhibition activity at 25 µg/µl than its inhibition at 50 µg/µl concentration. Compounds **5** and **10** were found to be weak in inhibition activity at 25 and 50 µg/µl, respectively(Table 2).It was also found that compound**21**showed no or little cytotoxicity values at most of the concentrations with TC50 value 1250 µg/µl. In addition, compounds**4** and **9** showed 0% cytotoxicity at 50 and 100 µg/µl concentrations(Table 1).

Table 1. Cytotoxicity and TC50 of tested compounds

Compound	Cytotoxicity%				TC50 µg/µl
	50 µg/µl	100 µg/µl	150 µg/µl	200 µg/µl	
3	0	8	14	37	276
4	0	0	27	75	173
5	0	8	18	47	>200
6	14	88	89	89	81
7	40	47	54	58	125
9	0	0	9	73	189
10	0	26	38	44	205
21	0	0	5	5	1250

Table 2. Antiviral activity measured using Plaque reduction assay

Sample	Conc.µg/µl	Initial viral count	Viral count (PFU/ml)	Inhibition%
4	25	72×10^5	61×10^5	15
	50		51×10^5	29
5	25	60×10^5	53×10^5	12
	50		60×10^5	0
7	25	72×10^5	50×10^5	30.5
	50		63×10^5	12.5
10	25	65×10^5	65×10^5	0
	50		58×10^5	10
21	25	65×10^5	45×10^5	31
	50		43×10^5	34
Amantadine	1		0	100

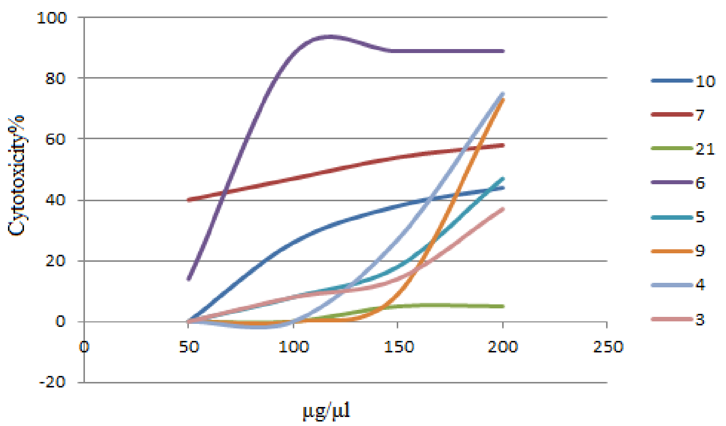


Fig 1: The relation of cytotoxicity% and concentration of tested compounds by *µg/µl*

In correlation of the obtained results with the structures of tested compounds, the results indicated that the 1,2,4-triazole compound linked to benzoimidazole and benzo-1,2,3-triazole ring systems and incorporating two glycosyl moieties was the most active in such investigation against H5N1. This indication reveals the importance of the xylosyl units as the activity was raised by the attachment of such glycosyl constituents to the free triazole compound linked to both ring systems.

On the other hand, in this investigation, it was also found that the unsymmetrical 1,2,4-triazole compound with both benzotriazole and benzothiazole in addition to the 1,2,4-triazole having both quinolin-8-yloxy 1,2,3-benzotriazole structures were higher in activity than symmetrical compounds or other triazoles with free NH groups. Although the tricyclic symmetrical triazole **3** and the compound with quinolin-8-yloxy structure **5** showed no or little inhibition activity, the low cytotoxicity values of both compound could be the basis of possible proposed structural modification in such compounds for attempting to achieve efficient inhibition in future research

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