Synthesis and Antimicrobial Activity of New 1,2,3-Triazolopyrimidine Derivatives and Their Glycoside and Acyclic Nucleoside Analogs

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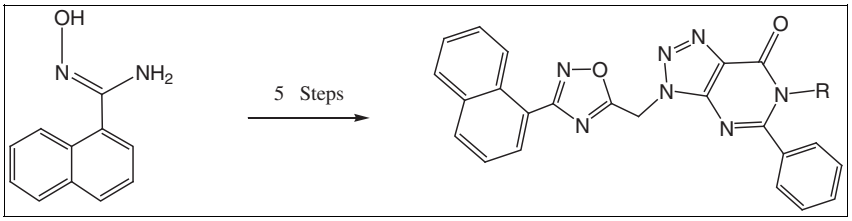

New [1,2,4-oxadiazolyl]methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin derivatives were synthesized starting from *N*′-Hydroxy-1-naphthimidamide. The *N*-substituted acyclic nucleoside analogs as well as the substituted glycosides were also prepared by reaction with the corresponding reagents. The antimicrobial results indicated that most of the tested compounds exhibited moderate to high antimicrobial activity whereas few compounds were found to exhibit little or no activity against the tested microorganisms.

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INTRODUCTION

The 1,2,3-triazole nucleus is found in a large number of compounds with agrochemical and pharmaceutical uses [1] and shows activities such as anti-HIV [2], anti-microbial [3], antibacterial [4], and antitumor [5] properties and has also found many applications in chemical industries [6]. Pyrimidines and fused pyrimidines, being an integral part of DNA and RNA in it, play an essential role in several biological processes. The pyrimidine ring can be found in nucleoside antibiotics, antibacterials, cardio-vascular, as well as agrochemical and veterin products [7–9]. Fused pyrimidines are found in a variety of natural products (e.g., purines), agrochemicals, and veterinary products [10–12]. Pyrimidine derivatives and heterocyclic annulated pyrimidines continue to attract much interest due to the wide variety of interesting biological activities observed for these compounds, such as anticancer [13], antiviral [14], antitumor [15], anti-inflammatory [16], antimicrobial [17(a,b)], antifungal [18], antihistaminic [19], and analgesic [20] activities. The study of triazolopyrimidine heterocyclic systems has known a considerable development due to their varied effects in diverse domains. Last years, research became intensified on the synthesis of these compounds [21–25] and the study of their activities in the pharmacological and agrochemical fields. These compounds are known for their anti-tumor [26], antibiotic [27], antifungal, antibacterial [27–34], anti-inflammatory [35], herbicidal, and CNS depressant activities [36]. Furthermore, nucleoside analogs are structurally, metabolically, and pharmacodynamically related agents that have diverse biological actions and therapeutic effects including antiviral [37,38] and antitumor [39–41] activities. The above facts and our interest [38,42–46] in the attachment of carbohydrate moieties to newly synthesized heterocycles searching for new biologically active leads promoted us to synthesize new substituted triazolopyrimidine glycosides and their acyclic analogous and evaluate their antimicrobial activity.

RESULTS AND DISCUSSION

In this investigation, 1-naphthonitrile (**1**) was reacted with hydroxylamine hydrochloride in presence of 8-hydroxyquinoline to afford *N*′-Hydroxy-1-naphthimidamide (**2**) in 73% yield. When the oxime derivative **2** was reacted with chloroacetyl chloride in acetone, the 1,2,4-oxadiazole derivative **3** was obtained. Conversion of the substituted 1,2,4-oxadiazole derivative **3** to the corresponding azide derivative **4** was performed by reaction with sodium azide in DMF at 70°C. The IR spectrum of compound **2** revealed the presence of absorption bands at 3486 and 3327 cm^{-1} for the hydroxyl and amino groups, respectively. The ^1H NMR spectrum of compound **3** showed signals the CH_2 in addition to the aromatic protons. Its IR spectrum of compound **4** showed characteristic absorption band at 2090 cm^{-1} for the azide group.

The substituted 1-{[3-(naphthalen-1-yl)-1,2,4-oxadiazol-5-yl]methyl}-1H-1,2,3-triazole derivative **5** was obtained by reaction of the azide **4** with cyanoacetamide in presence of sodium ethoxide at reflux temperature. Its IR spectrum showed

absorption bands at 3372 and 1679 cm^{-1} corresponding to the amino and carbonyl groups, respectively, and its ^1H NMR spectrum agreed with the assigned structure. Reaction of the 1,2,3-triazole-4-carboxamide derivative **5** with ethyl benzoate in ethanol at reflux temperature gave the 1,2,3-triazolopyrimidine derivative **6**. Its ^1H NMR spectrum showed the presence of the signals corresponding to CH_2, NH, and the aromatic protons in addition to the disappearance of the NH_2 signals.

When the 1,2,3-triazolopyrimidine derivative **6** was allowed to react with different oxygenated alkyl halides and bromosugars, the corresponding *N*-substituted derivatives was obtained. Thus, reaction of **6** with chloroethylmethyl ether, 2-(2-chloroethoxy)ethanol, 3-chloropropane-1,2-diol or ethyl iodide, the corresponding *N*-substituted acyclic nucleoside analogs and alkyl derivatives **7–10**, respectively, were obtained. The structures of these products were confirmed by their spectral and analytical data (see experimental part) which agreed with the assigned structures. The ^1H NMR spectrum of **9** as a representative example showed signals at δ 4.55 and 4.68 ppm for the two CH_2 and the signals for the hydroxyl groups at δ 4.87 and 4.92 ppm in addition to the aromatic proton signals at δ 7.31–8.26 ppm.

When the 1,2,3-triazolopyrimidine derivative **6** was reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide in DMF in presence of triethylamine, the corresponding glycosides **11** and **12,** respectively, were obtained in 76–78% yields. The IR spectra of these glycosides showed characteristic absorption bands at 1738–1740 cm^{-1} for the acetylcarbonyl groups. The ^1H NMR spectra showed the acetyl methyl proton signals at δ 1.94–2.14 ppm in addition to the signals of the sugar chain protons. The anomeric proton signal appeared as doublet at δ 5.88 and 5.89 ppm with coupling constants 10.4 and 10.2 Hz for **11** and **12**, respectively, indicating the β-configuration of the produced glycosides [45]. The ^{13}C NMR of **11** and **12** showed the acetyl-methyl signals at 19.30–20.23 ($4CH_3CO$) and those corresponding to the acetyl-carbonyl at 169.52–171.69. Deacetylation of the glycoside derivatives **11** and **12** with methanolic ammonia at room temperature afforded the corresponding free hydroxyl glycoside derivatives **13** and **14** in 78–79% yields. The IR spectra showed absorption bands for the hydroxyl groups and the ^1H NMR spectra showed signals corresponding to the sugar hydroxyls in addition to the rest of the sugar chain protons (see experimental part).

Antimicrobial activity. The synthesized compounds were evaluated for their antimicrobial activity against three microorganisms; *Bacillus subtilis* (ATCC 6633) (Gram-positive), *Pseudomonas aeruginosa* (ATCC 27853) (Gram-negative), and *Streptomyces* species (Actinomycetes). The values of minimal inhibitory concentrations (MICs) of the tested compounds are presented in Table 1. The MIC values of the most active compounds were in accordance with the results obtained in the primary screening.

Table 1

Minimum inhibitory concentrations (MIC-μg/mL) of the title compounds negative control DMSO, no activity.

	Gram positive	Gram negative	Actinomycetes
Compound	*Bacillus subtilis*	*Pseudomonas aseuginosa*	*Streptomyces species*
2	250	125	500
3	100	100	250
4	–	250	500
5	100	100	125
6	250	500	250
7	100	250	125
8	125	75	100
9	75	100	75
10	75	100	100
11	250	250	125
12	125	250	100
13	100	100	100
14	75	100	75
Penicillin	31	45	34

[a]Totally inactive (MIC > 500 μg/mL).

The result revealed that compounds showed varying degrees of inhibition against the tested microorganisms. In general, compounds **9**, **10,** and **14** displayed the highest activity against *B. subtilis* followed by compounds **3**, **5**, **7,** and **13**. Compound **8** displayed the highest inhibition activity against *P. aeruginosa* with MIC value of 75 μg/mL while compounds **9** and **14** revealed the highest activity against *Streptomyces* species (Actinomycetes).

The antimicrobial activity results and structure activity relationship indicated that substitution at *N*-1 in the pyrimidine ring in the 1,2,3-triazolyl moiety resulted in an increase in the antimicrobial activity with respect to the three microorganisms. It is also clear that the acyclic nucleoside analog **8** with free hydroxyl group showed the highest activity against *B. subtilis* and *Streptomyces* species. Moreover, substitution at *N*-1 with long oxygenated alkyl chain with terminal free hydroxyl group resulted in a marked increase in activity against *P. aeruginosa*.

The carboxamide derivative **5** with free two amino groups showed relatively higher activity than the corresponding azid derivative Additionally, the antimicrobial activity observed for the *N*-substituted 1,2,3-triazolpyrimidine glycosides **13** and **14** indicated the importance of the free hydroxyl glycopyranosyl 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 unsubstituted precursor. Moreover, the antibacterial activity observed for the xylopyranosyl derivative was relatively higher than that of the corresponding glucopyranosyl **13**.

In conclusion, new [1,2,4-oxadiazolyl]methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin derivatives, their *N*-substituted acyclic nucleoside analogs as well as the substituted glycosides were prepared and studied for their antimicrobial activity.

Substitution at the free *N*-1 in the pyrimidine ring in the 1,2,3-triazolyl moiety afforded compounds with increased inhibition activities with respect to the three microorganisms.

EXPERIMENTAL

Melting points were determined with a Kofler block apparatus and are uncorrected. The IR spectra were recorded on a Perkin–Elmer model 1720 FTIR spectrometer for KBr disc. NMR spectra were recorded on a varian Gemini 200 NMR Spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C or on a brucker Ac-250 FT spectrometer at 250 MHz for ^{1}H and at 62.9 MHz for ^{13}C with TMS as a standard. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F 245. Elemental analyses were performed at the Microanalytical data centre at Faculty of science, Cairo University, Egypt.

***N′*-Hydroxy-1-naphthimidamide (2).** To a solution of 1-naphthonitrile (**1**) (10 mmol, 1.53 g) and 8-hydroxyquinoline (0.3 g) in ethanol (20 mL) were added hydroxylamine hydrochloride (10 mmol, 0.69 g) and the reaction mixture was heated under reflux for 4 h (Scheme 1). The solvent was reduced under vacuum and the precipitated solid was filtered off and recrystallized from ethanol. White solid (1.36 g, 73%), m.p. 212–213°C; IR (KBr) ν: 3486 (OH), 3327 (NH_2), 1610 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) δ 6.18 (s, 2H, NH_2), 7.29 (m, 2H, Ar-H), 7.48 (m, 2H, Ar-H), 7.68 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.92 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.24 (d, 1H, *J* = 7.8 Hz, Ar-H), 9.81 (s, 1H, OH). Anal. Calcd. for $C_{11}H_{10}N_2O$ (186.21): C, 70.95; H, 5.41; N, 15.04. Found: C, 70.63; H, 5.28; N, 14.92.

5-(Chloromethyl)-3-(naphthalen-1-yl)-1,2,4-oxadiazole (3). To a solution of compound **2** (10 mmol, 1.86 g) in acetone (30 mL) was added potassium carbonate (10 mmol) and chloroacetyl chloride (10 mmol, 1.13 g). The solution was heated under reflux for 4 h. The solvent was removed under reduced pressure and the resulting residue was purified on a column chromatography to give compound **3** as a pale yellow powder (1.84 g, 75%), m.p. 186–187°C; IR (KBr) ν: 1610 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) δ 4.58 (s, 2H, CH_2), 7.31 (m, 2H, Ar-H), 7.49 (m, 2H, Ar-H), 7.70 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.92 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.25 (d, 1H, *J* = 7.8 Hz, Ar-H). Anal. Calcd. for $C_{13}H_9ClN_2O$ (244.68): C, 63.81; H, 3.71; N, 11.45. Found: C, 63.65; H, 3.58; N, 11.29.

5-(Azidomethyl)-3-(naphthalen-1-yl)-1,2,4-oxadiazole (4). A solution of compound **3** (10 mmol, 2.44 g) and sodium azide (10 mmol, 0.65) in DMF (15 mL) was stirred at 70°C for 6 h. The solvent was removed under reduced pressure and the resulting residue was triturated with excess diethyl ether to afford **4** as a white solid. (1.78 g, 71%), m.p. 90–91°C; IR (KBr) ν: 2090 (N_3), 1612 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) δ 4.25 (s, 2H, CH_2), 7.29 (m, 2H, Ar-H), 7.44 (m, 2H, Ar-H), 7.69 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.92 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.24 (d, 1H, *J* = 7.8 Hz, Ar-H). Anal. Calcd. for $C_{13}H_9N_5O$ (251.24): C, 62.15; H, 3.61; N, 27.87. Found: C, 61.95; H, 3.57; N, 27.69.

5-Amino-1-{[3-(naphthalen-1-yl)-1,2,4-oxadiazol-5-yl]methyl}-1*H*-1,2,3-triazole-4-carboxamide (5). Cyanacetamide (11 mmol, 0.934 g) was added to a stirred solution of sodium ethoxide (0.253 g, 0.011 g atom of Na) in absolute ethanol (10 mL), and stirring was continued for 30 min. A solution of compound **4** (10.0 mmol, 2.51 g) in absolute ethanol (10 mL) was slowly added to the suspension, and then the mixture was heated under reflux for 2 h. The reaction mixture was concentrated *in vacuo* and treated with H_2O, and the insoluble material was collected by filtration and purified by recrystallization from ethanol to afford compound **5** as yellow crystals (2.35 g, 70%), m.p. 186–187°C; IR (KBr) ν: 3372 (NH_2), 1679 (C=O), 1614 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) δ 5.10 (s, 2H, CH_2), 6.05 (bs, 2H, NH_2), 7.31 (m, 2H, Ar-H), 7.45 (m, 2H, Ar-H), 7.70 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.91 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.12 (bs, 2H, NH_2), 8.27 (d, 1H, *J* = 7.8 Hz, Ar-H). Anal. Calcd. for $C_{16}H_{13}N_7O_2$ (335.32): C, 57.31; H, 3.91; N, 29.24. Found: C, 57.11; H, 3.77; N, 29.14.

3-{[3-(Naphthalen-1-yl)-1,2,4-oxadiazol-5-yl]methyl}-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (6). To a solution of the carboxamide derivative **5** (10 mmol, 3.35 g) in ethanol (30 mL) was added ethyl benzoate (12 mmol, 1.8 g) and the reaction mixture was heated under reflux for 6 h. The solvent was reduced under *vacuo* and the precipitated solid was filtered off and recrystallized from ethanol to give **6** as a white solid. (2.9 g, 69%), m.p. 169–170°C; IR (KBr) ν: 3218 (NH), 1671 (C=O), 1612 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) δ 5.05 (s, 2H, CH_2), 7.31 (m, 2H, Ar-H), 7.45 (m, 3H, Ar-H), 7.64 (m, 2H, Ar-H), 7.82 (m, 2H, Ar-H), 7.94 (m, 2H, Ar-H), 8.27 (d, 1H, *J* = 7.8 Hz, Ar-H), 10.02 (s, 1H, NH). Anal. Calcd. for $C_{23}H_{15}N_7O_2$ (421.41): C, 65.55; H, 3.59; N, 23.27. Found: C, 65.37; H, 3.32; N, 23.18.

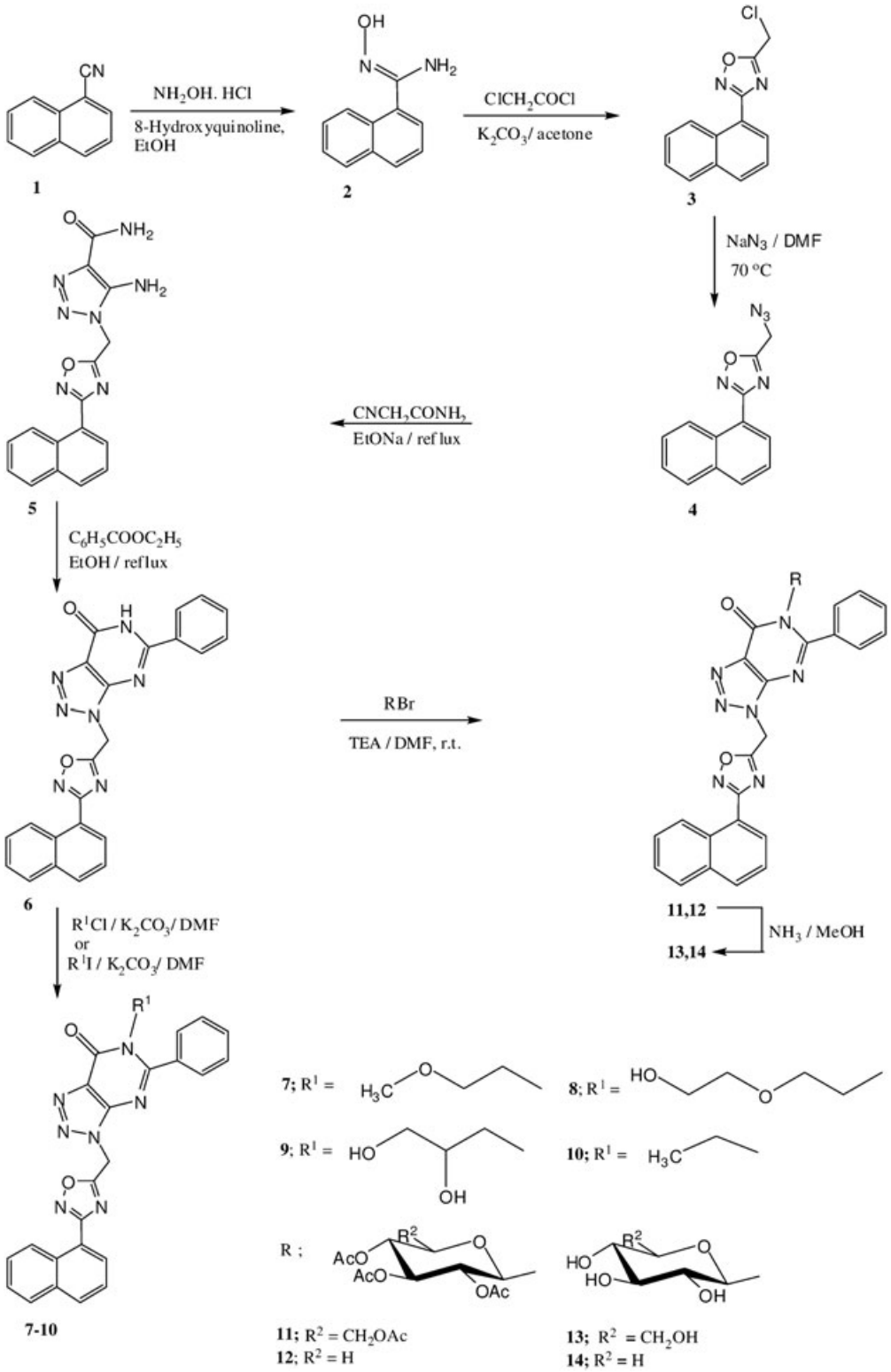
General procedure for the synthesis of compounds 7–10. To a well stirred solution of compound **6** (5 mmol, 2.11 g) and anhydrous potassium carbonate (5 mmol, 0.69 g) in *N*,*N*-dimethylformamide (15 mL) was added chloroethylmethyl ether, 2-(2-chloroethoxy) ethanol, 3-chloropropane-1,2-diol or ethyl iodide (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 **7–10**, respectively.

6-(2-Methoxyethyl)-3-{[3-(naphthalen-1-yl)-1,2,4-oxadiazol-5-yl]methyl}5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (7). Pale yellow solid; (1.79 g, 75%), m.p. 158–159°C; IR (KBr) ν: 1670 (C=O), 1610 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) δ 3.92 (s, 3H, CH_3), 4.62 (t, 2H, *J* = 5.4 Hz, CH_2), 4.79 (t, 2H, *J* = 5.4 Hz, CH_2), 5.21 (s, 2H, CH_2), 728 (m, 2H, Ar-H), 7.45 (m, 3H, Ar-H), 7.65 (m, 2H, Ar-H), 7.82 (m, 2H, Ar-H), 7.92 (m, 2H, Ar-H), 8.25 (d, 1H, *J* = 7.8 Hz, Ar-H). Anal. Calcd. for $C_{26}H_{21}N_7O_3$ (479.49): C, 65.13; H, 4.41; N, 20.45. Found: C, 64.91; H, 4.31; N, 20.29.

6-[2-(2-Hydroxyethoxy)ethyl]-3-{[3-(naphthalen-1-yl)-1,2,4-oxadiazol-5-yl]methyl}-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (8). White solid; (1.89 g, 74%), m.p. 171–172°C; IR (KBr) ν: 3481 (OH), 1667 (C=O), 1612 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) δ 4.65 (t, 2H, *J* = 5.6 Hz, CH_2), 4.74 (t, 2H, *J* = 5.6 Hz, CH_2), 4.86 (t, 2H, *J* = 5.2 Hz, CH_2), 4.91 (t, 1H, *J* = 5.6 Hz, OH), 4.97 (t, 2H, *J* = 5.2 Hz, CH_2), 5.12 (s, 2H, CH_2), 7.29 (m, 2H, Ar-H), 7.47 (m, 3H, Ar-H), 7.66 (m, 2H, Ar-H), 7.82 (m, 2H, Ar-H), 7.94 (m, 2H, Ar-H), 8.24 (d, 1H, *J* = 7.8 Hz, Ar-H). Anal. Calcd. for $C_{27}H_{23}N_7O_4$ (509.52): C, 63.65; H, 4.55; N, 19.24. Found: C, 63.49; H, 4.41; N, 19.18.

6-(2,3-Dihydroxypropyl)-3-{[3-(naphthalen-1-yl)-1,2,4-oxadiazol-5-yl]methyl}-5-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one (9). Pale yellow solid; (1.88 g, 73%), m.p. 205–206°C; IR (KBr) ν: 3473 (OH), 1668 (C=O), 1615 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) δ 4.55 (d, 2H, *J* = 5.6 Hz, CH_2), 4.68 (m, 2H, CH_2), 4.75 (t, 2H, *J* = 5.2 Hz, C*H*OH), 4.87 (t, 1H, *J* = 6.2 Hz, OH), 4.92 (t, 1H, *J* = 5.8 Hz, OH), 5.12 (s, 2H, CH_2), 7.31 (m, 2H, Ar-H), 7.50 (m, 3H, Ar-H), 7.9 (m, 2H, Ar-H), 7.84 (m, 2H, Ar-H), 7.96 (m, 2H, Ar-H), 8.26 (d, 1H, *J* = 7.8 Hz, Ar-H). Anal. Calcd. for $C_{26}H_{21}N_7O_4$ (495.49): C, 63.02; H, 4.27; N, 19.79. Found: C, 62.89; H, 4.11; N, 19.62.

Scheme 1



6-Ethyl-3-{[3-(naphthalen-1-yl)-1,2,4-oxadiazol-5-yl]methyl}-5-phenyl-3H-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (10). White solid; (1.78 g, 79%), m.p. 159–160°C; IR (KBr) ν: 1669 (C=O), 1612 cm^{-1} (C=N); ^1H NMR (DMSO-d_6) δ 1.48 (t, 3H, J = 4.8 Hz, CH_3), 4.32 (q, 2H, J = 4.8 Hz, CH_2), 5.10 (s, 2H, CH_2), 7.30 (m, 2H, Ar-H), 7.49 (m, 3H, Ar-H), 7.90 (m, 2H, Ar-H), 7.85

(m, 2H, Ar-H), 7.98 (m, 2H, Ar-H), 8.27 (d, 1H, J = 7.8 Hz, Ar-H). Anal. Calcd. for $C_{25}H_{19}N_7O_2$ (449.46): C, 66.81; H, 4.26; N, 21.81. Found: C, 66.65; H, 4.14; N, 21.68.

General procedure for the synthesis of compounds 11 and 12. To a solution of compound **6** (5 mmol, 2.11 g) in DMF (15 mL) was added triethylamine (0.75 mL) and 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (5 mmol). The reaction mixture was stirred at room temperature until reaction was judged complete by TLC using chloroform/methanol (99.5:0.5). The solvent was reduced under reduced pressure and the residue was washed with distilled water to remove the formed potassium bromide. The product was dried, and recrystallized from ethanol to give compounds **11** or **12,** respectively.

6-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3-{[3-(naphthalen-1-yl)-1,2,4-oxadiazol-5-yl]methyl}-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (11). Pale yellow solid; (2.93 g, 78%), m.p. 150–151°C; IR (KBr) ν: 1738 (C=O), 1614 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) δ 1.94, 2.04, 2.11, 2.15, (4s, 12H, 4 CH_3CO), 4.07 (m, 1H, H-5), 4.15 (dd, 1H, $J_{6,6'}$ = 11.4 Hz, $J_{5,6}$ = 2.8 Hz, H-6), 4.18 (m, 1H, H-6′), 4.94 (t, 1H, $J_{3,4}$ = 9.3 Hz, H-4), 5.06 (s, 2H, CH_2), 5.27 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 5.38 (t, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 5.88 (d, 1H, $J_{1,2}$ = 10.4 Hz, H-1), 7.32 (m, 2H, Ar-H), 7.46 (m, 3H, Ar-H), 7.65 (m, 2H, Ar-H), 7.84 (m, 2H, Ar-H), 7.95 (m, 2H, Ar-H), 8.25 (d, 1H, J = 7.8 Hz, Ar-H); ^{13}C NMR ($CDCl_3$) δ 19.30, 19.55, 20.19, 20.23 (4CH_3CO), 51.28 (CH_2), 62.70 (C-6), 64.24 (C-4), 68.72 (C-3), 71.27 (C-2), 71.94 (C-5), 87.14 (C-1), 119.18–151.14 (Ar-16C, pyrimidine C-5,6), 156.42, 157.15, 159.42 (3C=N), 168.05, 169.52, 169.64, 170.30, 171.49 (5C=O). Anal. Calcd. for $C_{37}H_{33}N_7O_{11}$ (751.70): C, 59.12; H, 4.42; N, 13.04. Found: C, 59.02; H, 4.30; N, 12.89.

6-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)-3-{[3-(naphthalen-1-yl)-1,2,4-oxadiazol-5-yl]methyl}-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (12). Pale yellow solid; (2.58 g, 76%), m.p. 153–154°C; IR (KBr) ν: 1740 (C=O), 1614 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) δ 1.94, 2.05, 2.12 (4s, 9H, 3 CH_3CO), 4.15 (dd, 1H, $J_{5,5'}$ = 11.4 Hz, $J_{4,5}$ = 2.8 Hz, H-5), 4.18 (m, 1H, H-5′), 4.94 (m, 1H, H-4), 5.10 (s, 2H, CH_2), 5.27 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 5.38 (t, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 5.89 (d, 1H, $J_{1,2}$ = 10.2 Hz, H-1), 7.31 (m, 2H, Ar-H), 7.48 (m, 3H, Ar-H), 7.69 (m, 2H, Ar-H), 7.85 (m, 2H, Ar-H), 7.95 (m, 2H, Ar-H), 8.25 (d, 1H, J = 7.8 Hz, Ar-H); ^{13}C NMR ($CDCl_3$) δ 19.28, 19.57, 20.21 (3CH_3CO), 51.36 (CH_2), 62.70 (C-5), 64.27 (C-4), 68.74 (C-3), 71.27 (C-2), 88.15 (C-1), 119.12-151.39 (Ar-16C, pyrimidine C-5,6), 156.41, 157.15, 159.45 (3C=N), 168.42, 169.65, 171.42, 171.59 (4C=O). Anal. Calcd. for $C_{34}H_{29}N_7O_9$ (679.64): C, 60.09; H, 4.30; N, 14.43. Found: C, 59.82; H, 4.26; N, 14.30.

General procedure for the synthesis of compounds 13 and 14. Dry gaseous ammonia was passed through a solution of a protected glycosides **11** or **12** (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 afford **13** or **14**.

6-(β-D-Glucopyranosyl)-3-{[3-(naphthalen-1-yl)-1,2,4-oxadiazol-5-yl]methyl}-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (13). Pale yellow solid; (2.31 g, 79%), m.p. 198–199°C; IR (KBr) ν: 3460–3428 (OH), 1668 (C=O), 1612 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) δ 3.38 (m, 2H, H-6,6′), 3.57 (m, 1H, H-5), 3.77 (m, 2H, H-3,4), 4.22 (t, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 4.29 (t, 1H, J = 6.4 Hz, OH), 4.42 (m, 1H, OH), 4.98 (m, 1H, OH), 5.06 (s, 2H, CH_2), 5.16 (t, 1H, J = 6.2 Hz, OH), 5.82 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 7.31 (m, 2H, Ar-H), 7.47 (m, 3H, Ar-H), 7.66 (m, 2H, Ar-H), 7.85 (m, 2H, Ar-H), 7.96 (m, 2H, Ar-H), 8.24 (d, 1H, J = 7.8 Hz, Ar-H); Anal. Calcd. for $C_{29}H_{25}N_7O_7$ (583.55): C, 59.69; H, 4.32; N, 16.80. Found: C, 59.58; H, 4.29; N, 16.69.

6-(β-D-Xylopyranosyl)-3-{[3-(naphthalen-1-yl)-1,2,4-oxadiazol-5-yl]methyl}-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (14). Pale yellow solid; (2.16 g, 78%), m.p. 212–213°C; IR (KBr) ν: 3470–3442 (OH), 1665 (C=O), 1615 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) δ 3.41 (m, 2H, H-5,5′), 3.78 (m, 2H, H-3,4), 4.24 (t, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 4.37 (t, 1H, J = 6.4 Hz, OH), 4.48 (m, 1H, OH), 5.02 (m, 1H, OH), 5.08 (s, 2H, CH_2), 5.82 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 7.33 (m, 2H, Ar-H), 7.48 (m, 3H, Ar-H), 7.65 (m, 2H, Ar-H), 7.84 (m, 2H, Ar-H), 7.98 (m, 2H, Ar-H), 8.25 (d, 1H, J = 7.8 Hz, Ar-H); Anal. Calcd. for $C_{28}H_{23}N_7O_6$ (553.53): C, 60.76; H, 4.19; N, 17.71. Found: C, 60.55; H, 4.11; N, 17.59.

Antimicrobial activity. The synthesized compounds were tested for their antimicrobial activity against three microorganisms, and the MICs of the tested compounds were determined by the dilution method.

Sample preparation. Each of the test compounds and standards were dissolved in 12.5% DMSO at concentrations of 500 μg/mL. Further dilutions of the compounds and standards were made in test medium.

Culture of microorganisms. Bacterial strains were supplied from the Botany Department, Faculty of Science, Menoufia University, Egypt, namely *B. subtilis* (ATCC 6633) (Gram-positive), *P. aeruginosa* (ATCC 27853) (Gram-negative), and *Streptomyces* species (Actinomycetes). The bacterial strains were maintained on MHA (Mueller—Hinton agar) medium (Oxoid, Chemical Co.) for 24 h at 37°C. The medium was molten on a water bath, inoculated with 0.5 mL of the culture of the specific microorganism, and poured into sterile Petri dishes to form a layer of about 3–4 mm. The layer was allowed to cool and harden. With the aid of cork-borer, cups of about 10 mm diameter were produced [47].

Agar diffusion technique. Antibacterial activities were tested against *B. subtilis* (Gram-positive), *P. aeruginosa* (Gram-negative), and *Streptomyces* species (Actinomycetes) using MH medium (17.5 g casein hydrolysate, 1.5 g soluble starch, 1000 mL beef extract). A stock solution of each synthesized compound (500 μg/mL) in DMSO was prepared and incorporated in sterilized liquid MH medium. Different concentrations of the test compounds in DMF were placed separately in cups in the agar medium. All plates were incubated at 37°C overnight. The inhibition zones were measured after 24 h. The MIC was defined as the intercept of the grave of logarithm concentrations versus diameter of the inhibition zones [48].

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