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Synthesis and antimicrobial activity of acyclo *C*-nucleosides: 3-(alditol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-*a*]pyrimidines

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Condensation of 2-hydrazino-4-oxo-6-phenylpyrimidine (**1**) with aldopentoses **2a**–**d** or aldohexoses **2e**–**g** gave the corresponding *aldehydo*-sugar (4-oxo-6-phenylpyrimidin-2-yl)hydrazones **3a**–**g** which were acetylated to the corresponding poly-*O*-acetyl-*aldehydo*-sugar (3-acetyl-4-oxo-6-phenylpyrimidin-2-yl)hydrazones **4a**–**g**. The latter compounds underwent oxidative cyclization with bromine in acetic acid and in the presence of sodium acetate to the corresponding 8-acetyl-3-(poly-*O*-acetyl-alditol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-*a*]pyrimidines **6a**–**g**. Compounds **6a**–**g** were also obtained by consecutive one-pot oxidative cyclization/acetylation in which the parent hydrazones **3a**–**g** were treated with bromine/acetic acid/sodium acetate followed by acetic anhydride. Deacetylation of **6a**–**g** with ammonium hydroxide in methanol gave the title compounds **7a**–**g**. The antibacterial and antifungal activities of compounds **3c**, **3f**, **7c** and **7f** are reported.

1. Introduction

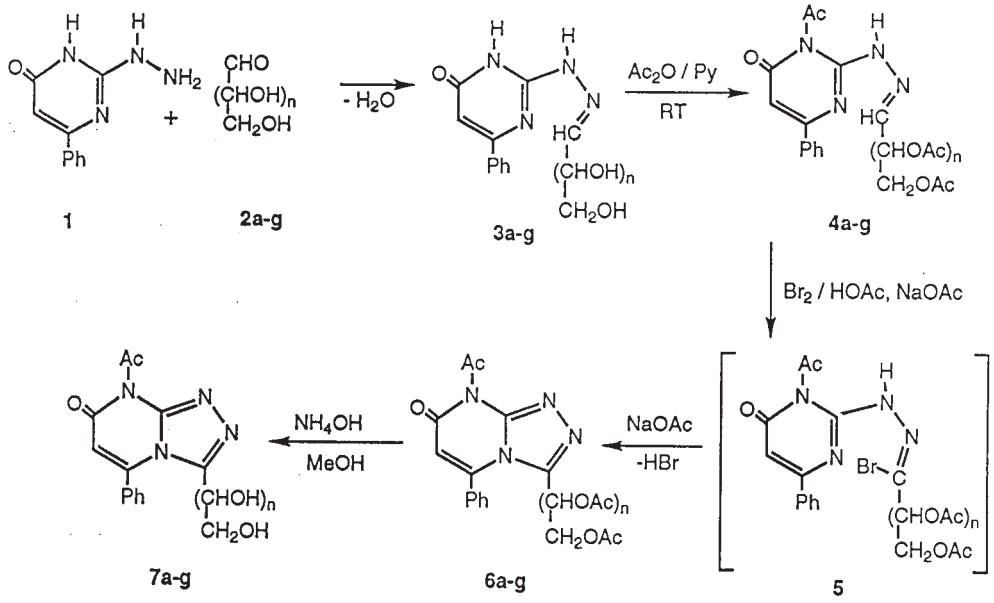
The chemistry of *C*-nucleosides, their acyclo, carbocyclo, homo and reverse analogs, have recently been reviewed [1, 2]. Many of these compounds exhibit various biological activities due to their ability to mimic isosteric *N*-nucleosides [1, 2]. Synthesis of the acyclo analogs has been actively pursued since the isolation of the naturally occurring acyclo *C*-nucleosides: pyridindolol {1-[(1*R*)-2-dihydroxyethyl]-3-hydroxymethyl-9*H*-pyrido[3,4-*b*]indole}, from the fermentation broth of *Streptomyces alboverticillatus* [3, 4], the antibiotic CV-1 [5-hydroxy-4-D-*arabino*-tetritol-1-yl)imidazolidin-2-one], from a strain of *Streptomyces* sp. II [5], and the antibiotic gualamycin {(2*R*,3*S*,4*S*)-2-*O*-(2-amino-2-deoxy-β-D-glucopyranosyl)-α-D-galactopyranosyl]-2,3,4-trihydroxy-4-[(2*S*,3*S*,4*S*,5*S*)-3,4-dihydroxy-5-hydroxymethyl-pyrrolidin-2-yl]butanoic acid}, from *Streptomyces* sp. NK11687 [6–8]. In addition to these naturally occuring acyclo *C*-nucleosides, various synthetic members were found to be active against viruses [9], bacteria [10] and fungi [11].

In this article we report on the synthesis and antimicrobial activity of the title compunds as a part of a program addressing the preparation [11–17] of acyclo *C*-nucleosides.

2. Investigations, results and discussion

Condensation of aldopentose and aldohexose monosaccharides, namely: D-arabinose (**2a**), L-arabinose (**2b**), D-xylose (**2d**), D-galactose (**2e**), D-glucose (**2f**) and D-mannose (**2g**) with equimolar amounts of 2-hydrazino-4-oxo-6-phenylpyrimidine [18] (**1**) gave the corresponding *aldehydo*-sugar (4-oxo-6-phenylpyrimidin-2-yl)hydrazones **3a**–**g** (Scheme 1). IR spectra of these hydrazones showed absorptions at 3383–3220 (OH + NH), 1673–1637 (CON) and 1609–1577 cm^{-1} (C=N). Their UV spectra exhibited a maximum characteristic of hydrazono-azo equilibrium (−NH−N=CH− ⇌ −N=N−CH_2−) at 198.6–198.3 nm.

Scheme 1

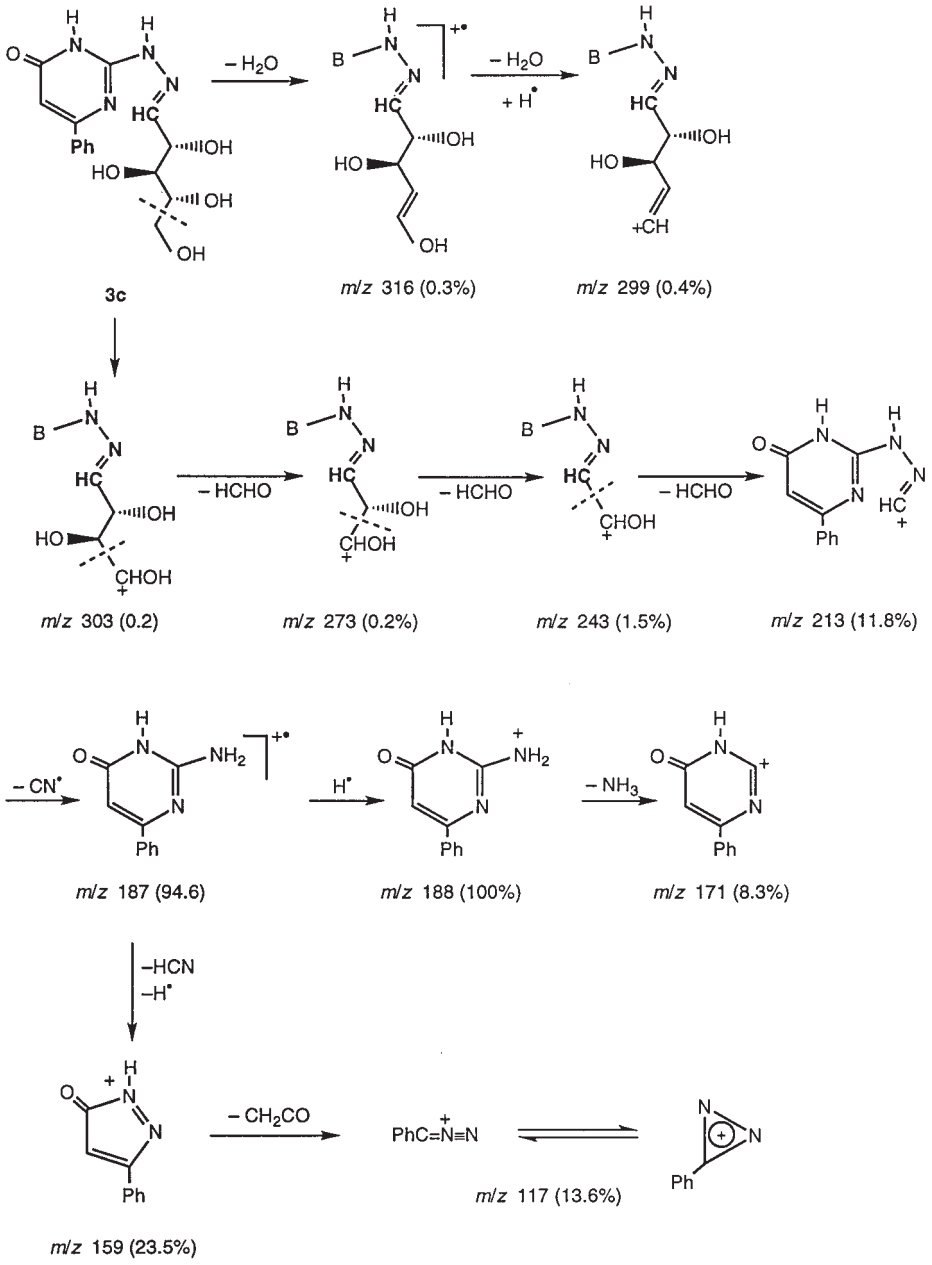


The ^{1}H NMR spectra showed, in addition to the expected signals of the phenyl and pyrimidinyl ring protons, an exchangeable hydrazono proton (=N−NH−) and an azomethine proton (−CH=N−) signals at δ 11.30–10.60 and 7.63–7.30, respectively. In most cases, the alditolyl chain protons together with the pyrimidinone ring proton were associated with the solvent absorption [$(CD_3)_2SO$] forming a broad signal at δ 3.55–3.20. The MS of **3c**, as an example, showed the M + 1 peak at m/z 335 and its detailed fragmentation is shown in Scheme 2.

Subjecting the prepared *aldehydo*-pentose hydrazones **3a–d** to acetylation with acetic anhydride and pyridine gave the corresponding crystalline acetates **4a–d** which showed IR absorptions characteristic of OAc, CON and C=N. These acetates were analyzed correctly for the molecular formula $C_{25}H_{28}N_4O_{10}$ indicating the introduction of five acetyl groups in the parent hydrazone molecules; four of which as *O*-acetyl groups blocking the tetritolyl chain hydroxyls and the fifth might has replaced either the hydrazono proton (=N−NH−) or the pyrimidinone ring N3−H. The MS of **4d** showed the molecular ion peak at m/z 544 in addition to the fragments depicted in Scheme 3. Formation of a fragment ion **11** at m/z 213 indicated that the fifth acetyl group has actually replaced the pyrimidinone ring proton (N3−H), and the acetylation products were assigned the 2,3,4,5-tetra-*O*-acetyl-*aldehydo*-pentose (3-acetyl-4-oxo-6-phenylpyrimidin-2-yl)hydrazones structures **4a–d**. The ^{13}C NMR spectrum of **4a** showed the expected signals of its carbon skeleton (see Experimental). Similarly, acetylation of the *aldehydo*-hexose hydrazones **3e–g** gave the corresponding 2,3,4,5,6-penta-*O*-acetyl-*aldehydo*-hexose (3-acetyl-4-oxo-6-phenyl-pyrimidin-2-yl)hydrazones **4e–g**.

Oxidative cyclization of the hydrazone acetates **4a–g** with bromine in acetic acid and in the presence of anh. sodium acetate afforded crystalline products that lacked the IR NH absorption as well as the ^{1}H NMR azomethine proton (CH=N) signal of the starting hydrazone acetates. The oxi-

Scheme 2

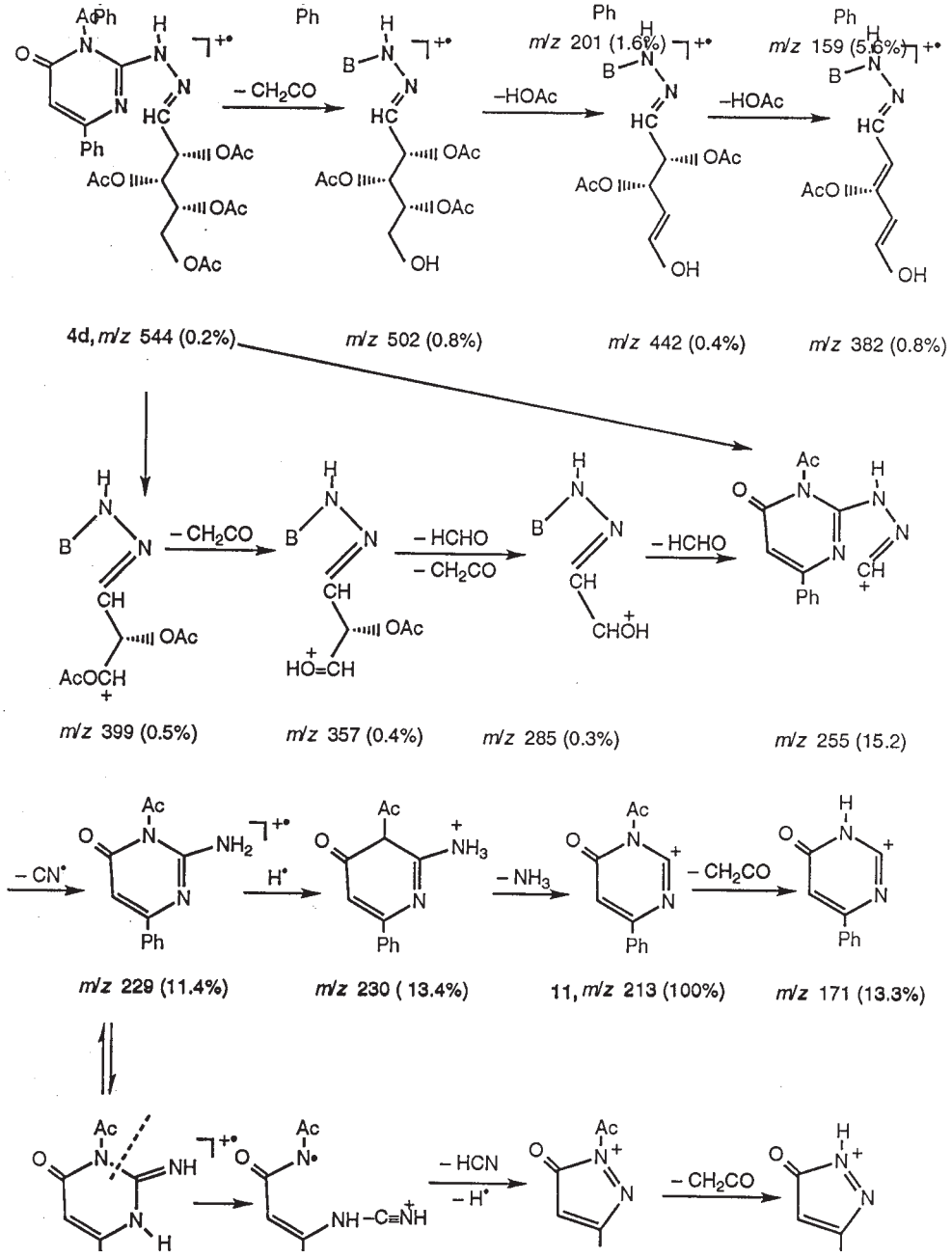


dative cyclization products analyzed for two hydrogens less than the starting hydrazone acetates and were accordingly assigned, the 8-acetyl-3-(poly-*O*-acetyl-alditol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-*a*]pyrimidines **6a**–**g**. Formation of **6a**–**g** presumably took place through hydrogen bromide elimination from the hydrazonyl bromide intermediates **5** [19]. The MS of **6c** (Scheme 4) did not reveal the molecular ion peak, yet showed fragments **12**–**14** at m/z 253, 267 and 283, respectively, characteristic of the assigned structure. Fragment **14**, in particular, corresponding to the protonated formyl heterocyclic moiety is known to be diagnostic of C-nucleoside structures [20]. The ^{13}C NMR spectrum of **6a** gave characteristic signals in accordance with its structure (see Experimental).

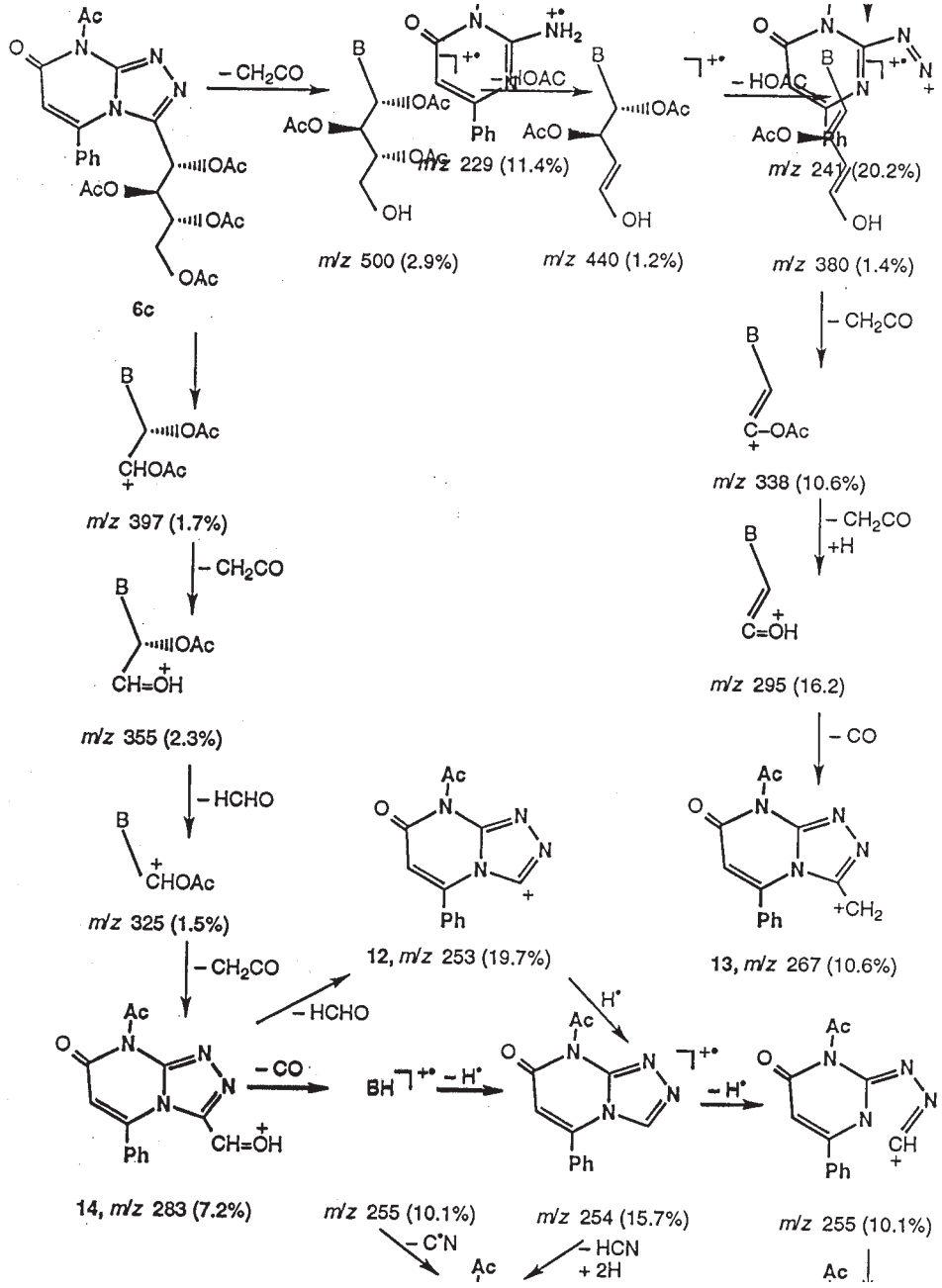
De-*O*-acetylation of **6a**–**g** with ammonium hydroxide in methanol gave the corresponding 8-acetyl-3-(alditol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-*a*]pyrimidines **7a**–**g**. IR spectra of the latter compounds showed OH, CON and C=N absorptions and their ^{1}H NMR revealed signals of phenyl and *N*-acetyl; the alditolyl chain proton signals appeared, in most cases, as a broad signal between δ 4.25 to 2.45 due to the association with the solvent $[CD_3)_2SO]$. The MS of **7c** showed the molecular ion peak at m/z 374.

Oxidative cyclization of hydrazones derived from unsymmetrically disubstituted pyrimidin-2-ylhydrazines such as the parent unacetylated hydrazones **3a**–**g** may involve N1 or N3 of the pyrimidinone ring to give either 7-oxo-1,2,4-triazolo[4,3-*a*]pyrimidines (**9**) [15, 21, 22] or 5-oxo-1,2,4-triazolo[4,3-*a*]pyrimidines (**10**) [23, 24] respectively (Scheme 5). Performing consecutive one-pot oxidative cyclization/acetylation on hydrazones **3a**–**g** by treatment with bromine/acetic acid/anhydrous sodium acetate fol-

Scheme 3



Scheme 4



lowed by treatment with acetic anhydride afforded products which were found identical with the corresponding **6a**–**g** prepared by oxidative cyclization of the acetates **4a**–**g** (Scheme 1). Evidently, oxidative cyclization of **3a**–**g** took place through the hydrazonyl bromide intermediates **8** and involved the more nucleophilic N1 rather than the less nucleophilic N3 of the pyrimidinone ring.

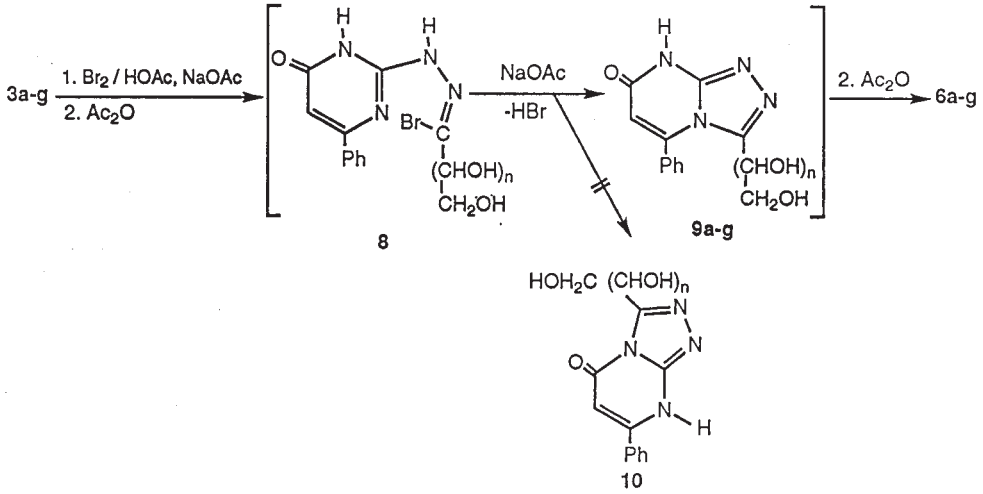
Compounds **3c**, **3f**, **7c** and **7f** were evaluated for antibacterial activity *in vitro* against the Gram negative bacterium *Escherichia coli* and the two Gram positive bacteria *Bacillus subtilis* and *Staphylococcus aureus* as well as for antifungal activity against *Candida albicans* and *Aspergillus*

Table: Antimicrobial activity

Compl.	Conc. (mg(ml)	Inhibition zones (mm)[a]				
		E. coli	*B. subtilis*	*S. aureus*	*C. albicans*	*A. niger*
3c	0.24	8	–	–	8	9
3f	0.24	9	–	–	–	8
7c	0.24	13	8	–	–	10
7f	0.24	7	8	–	9	10
Ampicillin	0.24	21	21	17	–	–
Streptomycin	0.24	30	35	22	–	–

[a] Inhibition zones of less than 10 mm in diameter were considered to indicate weak activity

Scheme 5



niger using the agar diffusion method [25]. These compounds showed weak antibacterial activity against *E. coli* and *B. subtilis* and were devoid of activity against *S. aureus*. They also showed weak antifungal activity against *C. albicans* and *A. niger* (Table).

3. Experimental

Melting points were determined using a MEL-TEMP II apparatus in open glass capillaries and are uncorrected. The IR spectra were recorded using potassium bromide discs on a Pye-Unicam SP-1025 spectrophotometer. UV spectra were performed on a Unicam SP-1750 spectrophotometer. ^{1}H NMR spectra were carried out on a Varian EM390 spectrometer and ^{13}C NMR spectra were carried out on a Varian Gemini 200 spectrometer at 50 MHz. MS were performed on a Du Pont 21–419 mass spectrometer interfaced with a Du Pont 492–094 data-acquisition station. The homogeneity of products and progress of reactions were checked by TLC on plates precoated with silica gel G (Merck; layer thickness 0.25 mm), used without pretreatment. TLC plates were visualized by exposure to iodine for a few minutes. Elemental microanalyses were preformed at the Microanalysis Unit, Cairo University, Cairo, Egypt. The prepared compounds gave satisfactory elemental analyses.

3.1. Aldehydo-sugars (4-oxo-6-phenylpyrimidin-2-yl)hydrazones (**3a–g**)

A solution of **1** (5 mmol) in C_2H_5OH (30 ml) was added to the respective sugar **2a–g** (5 mmol) in H_2O (2 ml) and the solution was heated on a boiling water bath for 15 min, then kept for 24 h at room temperature. The crystalline product which separated, was filtered, washed several times with ethanol and crystallized from H_2O/C_2H_5OH.

3.1.1. aldehydo-D-Arabinose (4-oxo-6-phenylpyrimidin-2-yl)hydrazone (**3a**)

Yield: 90%; m.p.: 172 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.74; IR (KBr): 3282 (OH + NH), 1640 (OCN), 1605 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 241.2 (4.23), 198.6 (4.34); ^{1}H NMR [$(CD_3)_2SO$]: δ 11.15 (broad s, 1 H, exchangeable, N−NH−), 7.85 (m, 2 H, phenyl 2 H), 7.30 (m, 4 H, −CH=N−+ phenyl 3 H), 6.15 (s, 1 H, pyrimidinyl H), 5.65 (m, 1 H, exchangeable, OH), 4.90 (m, 2 H, exchangeable, 2 OH), 4.45 (s, 4 H, alditolyl 4 H).
$C_{15}H_{18}N_4O_5$ (334)

3.1.2. aldehydo-L-Arabinose (4-oxo-6-phenylpyrimidin-2-yl)hydrazone (**3b**)

Yield: 87%; m.p.: 248 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.87; IR (KBr): 3272 (OH + NH), 1638 (OCN), and 1603 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 240 (4.29), 198.3 (4.39); ^{1}H NMR [$(CD_3)_2SO$]: δ 11.00 (broad s, 1 H, exchangeable, =N−NH−), 7.80 (m, 2 H, phenyl 2 H), 7.30 (m, 4 H, −CH=N−+ phenyl 3 H), 6.15 (s, 1 H, pyrimidinyl H), 5.10 (broad s, 1 H, exchangeable, OH), 4.40 (m, 2 H, alditolyl 2 H).
$C_{15}H_{18}N_4O_5$ (334)

3.1.3. aldehydo-D-Ribose (4-oxo-6–phenylpyrimidin-2-yl)hydrazone (**3c**)

Yield: 85%; m.p.: 205 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.76; IR (KBr): 3291 (OH + NH), 1637 (OCN), and 1605 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 308.1 (3.96), 241.2 (4.40), 198.3 (4.46); ^{1}H NMR [$(CD_3)_2SO$]: δ 11.25 (broad s, 1 H, exchangeable, =N−NH−), 7.88 (m, 2 H, phenyl 2 H), 7.50 (d, 1 H, −CH=N−), 7.35 (m, 3 H, phenyl 3 H), 6.15 (s, 1 H, pyrimidinyl H), 5.20, 4.75, 4.63 (3 d, 1 H each, exchangeable, 3 OH), 4.30 (m, 2 H, exchangeable OH + alditolyl H), 3.50 (m, 3 H, alditolyl 3 H); m/z 335 (M + 1).
$C_{15}H_{18}N_4O_5 \cdot 1\frac{1}{2}\,H_2O$ (361)

3.1.4. aldehydo-D-Xylose (4-oxo-6-phenylpyrimidin-2-yl)hydrazone (**3d**)

Yield: 80%; m.p.: 202 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.73; IR (KBr): 3316 (OH + NH), 1653 (OCN), and 1601 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 241.2 (4.25), 198.6 (4.33): ^{1}H NMR [$(CD_3)_2SO$]: δ 11.00 (broad s, 1 H, exchangeable, =N−NH−), 8.66 (s, 1 H, exchangeable, 4-oxopyrimidinyl-NH), 7.83 (m, 2 H, phenyl 2 H), 7.45 (d, 1 H, CH=N−), 7.35 (m, 3 H, phenyl 3 H), 6.15, 6.05 (2 s, 1 H each, pyrimidinyl H and alditolyl H), 5.75 (d, 1 H, exchangeable, OH), 5.25 (m, 1 H, exchangeable, OH), 4.85 (m, 2 H, exchangeable, 2 OH), 4.35 (m, 2 H, alditolyl 2 H).
$C_{15}H_{18}N_4O_5$ (334)

3.1.5. aldehydo-D-Galactose (4-oxo-6-phenylpyrimidin-2-yl)hydrazone (**3e**)

Yield: 90%; m.p.: 194 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.68; IR (KBr): 3333, 3220 (OH + NH), 1653 (OCN), 1601 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 240.6 (4.16), 198.9 (4.19): ^{1}H NMR [$(CD_3)_2SO$]: δ 10.60 (s, 1 H, exchangeable, =N−NH−), 8.75 (s, 1 H, exchangeable, 4-oxopyrimidinyl-NH), 7.80 (m, 2 H, phenyl 2 H), 7.30 (m, 4 H, −CH=N−+ phenyl 3 H), 6.10, 5.95 (2s, 1 H each, pyrimidinyl H and alditolyl H), 5.60 (d, 1 H, exchangeable, OH), 5.25–5.05 4.70–4.50 (2m, 1 H each, exchangeable, OH), 4.50–4.25 (m, 1 H, alditolyl H), 4.25–3.95 (m, 2 H, exchangeable, 2 OH).
$C_{16}H_{20}N_4O_6$ (364)

3.1.6. aldehydo-D-Glucose (4-oxo-6-phenylpyrimidin-2-yl)hydrazone (**3f**)

Yield: 85%; m.p.: 162 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.61; IR (KBr): 3383 (OH + NH), 1641 (OCN), 1609 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 306.0 (3.94), 240.0 (4.40), 198.6 (4.44); ^{1}H NMR [$(CD_3)_2SO$]: δ 11.15 (s, 1 H, exchangeable, =N−NH−), 8.90 (s, 1 H, exchangeable, 4-oxopyrimiidinyl-NH), 7.80 (m, 2 H, phenyl 2 H), 7.45 (d, 1 H, −CH=N−), 7.33 (m, 3 H, phenyl 3 H), 6.15, 6.00 (2s, 1 H each, pyrimidinyl H and alditolyl H), 5.75 (d, 1 H, exchangeable, OH), 5.33, 4.90 (2m, 1 H each, exchangeable, 2 OH), 4.50 (s, 2 H, exchangeable, 2 OH), 4.30 (m, 2 H, alditolyl 2 H).
$C_{16}H_{20}N_4O_6$ (364)

3.1.7. aldehydo-D-Mannose (4-oxo-6-phenylpyrimidin-2-yl)hydrazone (**3g**)

Yield: 80%; m.p.: 205 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.67; IR (KBr): 3373, 3239 (OH + NH), 1673 (OCN), 1577 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 307.8 (3.86), 241.8 (4.32), 198.3 (4.37); ^{1}H NMR [$(CD_3)_2SO$]: δ 11.30 (broad s, 1 H, exchangeable, =N−NH−), 7.85 (m, 2 H, phenyl 2 H), 7.63 (d, 1 H, −CH=N−), 7.35 (m, 3 H, phenyl 3 H), 6.15 (s, 1 H, pyrimidinyl H), 5.15 (d, 1 H, exchangeable, OH), 4.30 (m, 3 H, alditolyl 3 H), 3.53 (m, 4 H, exchangeable, 4 OH).
$C_{16}H_{20}N_4O_6$ (364)

3.2. Poly-O-acetyl-aldehydo-sugar (3-acetyl-4-oxo-6-phenylpyrimidin-2–yl)hydrazones (4a–g)

A solution of the appropriate hydrazone **3a–g** (3 mmol) in pyridine (3 ml) was treated with Ac_2O (15 ml) and the mixture was kept at ambient temperature for 24 h with stirring. The reaction mixture was poured onto ice and water and extracted with $CHCl_3$ (3×20 ml) and the $CHCl_3$ extract was washed with 10% $NaHSO_4$ solution (2×20 ml), H_2O, and dried (Na_2SO_4). The solvent was evaporated and the residue was crystallized from CH_3OH.

3.2.1. 2,3,4,5-Tetra-O-acetyl-aldehydo-D-arabinose (3-acetyl-4-oxo-6-phenylpyrimidin-2-yl)hydrazone (4a)

Yield: 68%; m.p.: 182 °C; TLC in 9:1 chloroform/methanol, R_f: 0.72; IR (KBr): 3437 (NH), 1750 (OAc), 1677 (OCN), 1597 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.80 (m, 2 H, phenyl 2 H), 7.35 (m, 3 H, phenyl 3 H), 7.20 (s, 1 H, −CH=N−), 6.45 (s, 1 H, pyrimidinyl H), 5.65 (d, 1 H, alditolyl H-1), 5.50 (dd, 1 H, alditolyl H-2), 5.66 (m, 1 H, alditolyl H-3), 4.16 (m, 2 H, alditolyl H-4 + H-4′), 2.55 (s, 3 H, NAc), 2.15, 2.05, 2.00, 1.85 (4s, 3 H each, 4 OAc); ^{13}C NMR ($CDCl_3$): δ 171.23, 170.21, 169.57 (4 OO**C**CH$_3$), 162.62 (NCOCH$_3$), 160.01 (C4 + C6), 149.53 (C2 + HC=N−NH), 135.62–127.17 (Ph carbons), 104.22 (C5), 70.68, 68.45, 67.61, 67.26 (alditolyl C2′, C3′, C4′, C5′, respectively), 23.67 (NCO**C**H$_3$), 20.65, 20.57, 20.48, 19.83 (4 OOC**C**H$_3$).
$C_{25}H_{28}N_4O_{10}$ (544)

3.2.2. 2,3,4,5-Tetra-O-acetyl-aldehydo-L-arabinose (3-acetyl-4-oxo-6-phenylpyrimidin-2-yl)hydrazone (4b)

Yield: 67%; m.p.: 176 °C; TLC in 9:1 chloroform/methanol, R_f: 0.67; IR (KBr): 3496 (NH), 1750 (OAc), 1676 (OCN), and 1597 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.75 (m, 2 H, phenyl 2 H), 7.33 (m, 3 H, phenyl 3 H), 7.10 (s, 1 H, −CH=N−), 6.40 (s, 1 H, pyrimidinyl H), 5.70 (d, 1 H, alditolyl H-1), 5.35 (dd, 1 H, alditolyl H-2), 5.15–4.85 (m, 1 H, alditolyl H-3), 4.15 (m, 2 H, alditolyl H-4 + H-4′), 2.55 (s, 3 H, NAc), 2.15, 2.05, 2.00, 1.85 (4s, 3 H each, 4 OAc).
$C_{25}H_{28}N_4O_{10}$ (544)

3.2.3. 2,3,4,5-Tetra-O-acetyl-aldehydo-D-ribose (3-acetyl-4-oxo-6-phenylpyrimidin-2-yl)hydrazone (4c)

Yield: 62%; m.p.: 85 °C; TLC in 9:1 chloroform/methanol, R_f: 0.62; IR (KBr): 3428 (NH), 1746 (OAc), 1668 (OCN), 1600 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.75 (m, 2 H, phenyl 2 H), 7.30 (m, 4 H, −CH=N−+ phenyl 3 H), 6.45 (s, 1 H, pyrimidinyl H), 5.75–5.15 (m, 3 H, alditolyl H-1 + H-2 + H-3), 4.40–4.00 (m, 2 H, alditolyl H-4 + H-4′), 2.60 (s, 3 H, NAc), 2.20, 2.15, 2.05, 1.90 (4s, 3 H each, 4 OAc).
$C_{25}H_{28}N_4O_{10}$ (544)

3.2.4. 2,3,4,5-Tetra-O-acetyl-aldehydo-D-xylose (3-acetyl-4-oxo-6-phenylpyrimidin-2-yl)hydrazone (4d)

Yield: 65%; m.p.: 225 °C; TLC in 9:1 chloroform/methanol, R_f: 0.70; IR (KBr): 3466 (NH), 1750 (OAc), 1666 (OCN), 1599 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.75 (m, 2 H, phenyl 2 H), 7.35 (m, 4 H, −CH=N−+ phenyl 3 H), 6.70 (s, 1 H, pyrimidinyl H), 5.95 (d, 1 H, alditolyl H-1), 5.28–4.75 (m, 2 H, alditolyl H-2 + H-3), 4.25–3.85, 3.55–3.15 (2m, 1 H each, alditolyl H-4, H-4′), 2.45 (s, 3 H, NAc), 2.05 (s, 3 H, OAc), 2.00 (s, 9 H, 3 OAc); m/z 544 (M^+).
$C_{25}H_{28}N_4O_{10}$ (544)

3.2.5. 2,3,4,5-Penta-O-acetyl-aldehydo-D-galactose (3-acetyl-4-oxo-6-phenylpyrimidin-2-yl)hydrazone (4e)

Yield: 70%; m.p.: 183 °C; TLC in 9:1 chloroform/methanol, R_f: 0.65; IR (KBr): 3429 (NH), 1749 (OAc), 1670 (OCN), 1597 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.65 (m, 2 H, phenyl 2 H), 7.23 (m, 4 H, −CH=N−+ phenyl 3 H), 6.40 (s, 1 H, pyrimidinyl H), 5.60 (d, 1 H, alditolyl H-1), 5.45–5.15, 5.15–4.80 (2m, 1 H each, alditolyl H-2, H-3), 4.60–4.25 (m, 1 H, alditolyl H-4), 4.15–3.65 (m, 2 H, alditolyl H-5 + H-5′), 2.50 (s, 3 H, NAc), 2.10, 2.00 (2s, 3 H each, 2 OAc), 1.95 (s, 6 H, 2 OAc), 1.90 (s, 3 H, OAc).
$C_{28}H_{32}N_4O_{12}$ (616)

3.2.6. 2,3,4,5-Penta-O-acetyl-aldehydo-D-glucose (3-acetyl-4-oxo-6-phenylpyrimidin-2-yl)hydrazone (4f)

Yield: 62%; m.p.: 110 °C; TLC in 9:1 chloroform/methanol, R_f: 0.58; IR (KBr): 3463 (NH), 1754 (OAc), 1669 (OCN), 1600 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.75 (m, 2 H, phenyl 2 H), 7.30 (m, 4 H, −CH=N−+ phenyl 3 H), 6.65 (s, 1 H, pyrimidinyl H), 6.00 (d, 1 H, alditolyl H-1), 5.35–4.65 (m, 2 H, alditolyl H-2 + H-3), 4.20–3.95 (m, 1 H, alditolyl H-4), 3.95 to 3.45 (m, 2 H, alditolyl H-5 + H-5′), 2.45 (s, 3 H, NAc), 2.15 (s, 3 H, OAc), 2.00 (s, 6 H, 2 OAc), 1.90, 1.85 (2s, 3 H each, 2 OAc).
$C_{28}H_{32}N_4O_{12}$ (616)

3.2.7. 2,3,4,5-Penta-O-acetyl-aldehydo-D-mannose (3-acetyl-4-oxo-6-phenylpyrimidin-2-yl)hydrazone (4g)

Yield: 60%; m.p.: 118 °C; TLC in 9:1 chloroform/methanol, R_f: 0.75; IR (KBr): 3467 (NH), 1748 (OAc), 1679 (OCN), 1601 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.70 (m, 2 H, phenyl 2 H), 7.33 (m, 4 H, −CH=N−+ phenyl 3 H), 6.45 (s, 1 H, pyrimidinyl H), 5.80–5.95 (m, 4 H, alditolyl H-1 + H-2 + H-3 + H-4), 4.30–3.85 (m, 2 H, alditolyl H-5 + H-5′), 2.10 (s, 3 H, NAc), 2.00 (s, 15 H, 5 OAc).
$C_{28}H_{32}N_4O_{12}$ (616)

3.3. 8-Acetyl-3-(per-O-acetyl-alditol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo-[4,3-a]pyrimidines (6a–g)

Method A: A solution of bromine (3 mmol) in glacial acetic acid (5 ml) was gradually added to a stirred mixture of **3a–g** (3 mmol) and anh. sodium acetate (9 mmol) in glacial acetic acid (15 ml). The reaction mixture was stirred for a further 2 h at room temperature and then treated with Ac_2O (15 ml) for 24 h. Evaporation of the reaction mixture gave a residue which was extracted with chloroform (2×25 ml); the CH_3Cl-soluble fraction was evaporated and crystallized from CH_3OH.
Method B: A solution of bromine (1 mmol) in glacial acetic acid (5 ml) was gradually added to a stirred mixture of **4a–g** (1 mmol) and anh. sodium acetate (3 mmol) in glacial acetic acid (15 ml). The reaction mixture was stirred for 2 h and evaporated. The CH_3Cl-soluble portion of the obtained residue was evaporated and crystallized from CH_3OH.

3.3.1. 8-Acetyl-3-(1,2,3,4-tetra-O-acetyl-D-arabino-tetritol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-a]pyrimidine (6a)

Yield: Method A: 60%; method B: 62%; m.p.: 208 °C; TLC in 9:1 chloroform/methanol, R_f: 0.54; IR (KBr): 1748 (OAc), 1683 (OCN), and 1601 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.43 (m, 5 H, phenyl 5 H), 6.85 (s, 1 H, pyrimidinyl H), 5.75 (d, 1 H, alditolyl H-1), 5.60–5.30 (m, 1 H, alditolyl H-2), 4.40–4.05 (m, 3 H, alditolyl H-3 + H-4 + H-4′), 2.25 (s, 3 H, NAc), 2.20 (s, 3 H, OAc), 2.10 (s, 6 H, 2 OAc), 1.95 (s, 3 H, OAc); ^{13}C NMR [$(CD_3)_2SO$]: δ 170.37, 169.63, 169.59, 168.88 (4 OO**C**CH$_3$), 160.40 (N**C**OCH$_3$), 153.85 (C7), 150.20 (C8a), 149.73 (C5), 147.29 (C3), 138.87–127.43 (Ph carbons), 94.98 (C6), 70.84, 68.15, 66.99, 63.14 (alditolyl C1′, C2′, C3′, C4′, respectively), 24.07 (NCO**C**H$_3$), 20.11, 20.06, 20.02, 19.81 (4 OOC**C**H$_3$).
$C_{25}H_{26}N_4O_{10}$ (542)

3.3.2. 8-Acetyl-3-(1,2,3,4-tetra-O-acetyl-L-arabino-tetritol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-a]pyrimidine (6b)

Yield: Method A: 63%; method B: 60%; m.p.: 149 °C; TLC in 9:1 chloroform/methanol, R_f: 0.52; IR (KBr): 1747 (OAc), 1683 (OCN), and 1600 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 326.4 (3.58), 248.4 (3.94); ^1H NMR ($CDCl_3$): δ 7.36 (m, 5 H, phenyl 5 H), 6.75 (s. 1 H, pyrimidinyl H), 5.70 (d, 1 H, alditolyl H-1), 5.55–5.15 (m, 2 H, alditolyl H-2 + H-3), 4.40–3.90 (m, 2 H, alditolyl H-4 + H-4′), 2.10 (s, 3 H, NAc), 2.05 (s, 3 H, OAc), 2.00 (s, 6 H, 2 OAc), 1.85 (s, 3 H, OAc).
$C_{25}H_{26}N_4O_{10}$ (542)

3.3.3. 8-Acetyl-3-(1,2,3,4-tetra-O-acetyl-D-ribo-tetritol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-a]pyrimidine (6c)

Yield: Method A: 58%; method B: 51%; m.p.: 190 °C; TLC in 9:1 chloroform/methanol, R_f: 0.64; IR (KBr): 1756, 1740 (OAc), 1672 (OCN), 1602 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 325.8 (4.07) and 251.1 (4.43); ^1H NMR ($CDCl_3$): δ 7.60–7.25 (m, 5 H, phenyl 5 H), 7.10 (s. 1 H, pyrimidinyl H), 6.75 (d, 1 H, alditolyl H-1), 5.65 (t, 1 H, alditolyl H-2), 5.40 to 5.10 (m, 1 H, alditolyl H-3), 4.33–3.90 (m, 2 H, alditolyl H-4 + H-4′), 2.05 (s, 3 H, NAc), 1.95 (s, 12 H, 4 OAc).
$C_{25}H_{26}N_4O_{10}$ (542)

3.3.4. 8-Acetyl-3-(1,2,3,4-tetra-O-acetyl-D-xylo-tetritol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-a]pyrimidine (6d)

Yield: Method A: 54%; method B: 50%; m.p.: 183 °C; TLC in 9:1 chloroform/methanol, R_f: 0.67; IR (KBr): 1746 (OAc), 1666 (OCN), 1586 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 325.8 (4.01) and 250.2 (4.36); ^1H NMR ($CDCl_3$): δ 7.368 (m, 5 H, phenyl 5 H), 7.05 (s. 1 H, pyrimidinyl H), 6.60 (d, 1 H, alditolyl H-1), 5.65 (dd, 1 H, alditolyl H-2), 5.30 (m, 1 H, alditolyl H-3), 4.40–3.90 (m, 2 H, alditolyl H-4 + H-4′), 2.10 (s, 3 H, NAc), 2.05 (s, 9 H, 3 OAc), 1.85 (s, 3 H, OAc).
$C_{25}H_{26}N_4O_{10}$ (542)

3.3.5. 8-Acetyl-3-(1,2,3,4-penta-O-acetyl-D-galacto-pentitol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-a]pyrimidine (6e)

Yield: Method A: 65%; method B: 62%; m.p.: 160 °C; TLC in 9:1 chloroform/methanol, R_f: 0.65; IR (KBr): 1739 (OAc), 1669 (OCN), 1580 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 319.5 (3.85), 248.7 (4.31); ^1H NMR ($CDCl_3$): δ 7.50 (m, 5 H, phenyl 5 H), 6.95 (s. 1 H, pyrimidinyl H), 5.85 (d, 1 H, alditolyl H-1), 5.70–5.00 (m, 2 H, alditolyl H-2 + H-3), 4.45–3.95

(m, 3 H, alditolyl H-4 + H-5 + H-5′), 2.20 (s, 3 H, NAc), 2.05 (s, 12 H, 4 OAc), 1.95 (s, 3 H, OAc).
$C_{28}H_{30}N_4O_{12}$ (614)

3.3.6. 8-Acetyl-3-(1,2,3,4-penta-O-acetyl-D-gluco-pentitol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-a]pyrimidine (**6f**)

Yield: Method A: 60%; method B: 55%; m.p.: 194 °C; TLC in 9 : 1 chloroform/methanol, R_f: 0.69; IR (KBr): 1741 (OAc), 1666 (OCN), 1579 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 323.8 (3.93), 246.6 (4.38); ^{1}H NMR ($CDCl_3$): δ 7.35 (m, 5 H, phenyl 5 H), 7.20 (s. 1 H, pyrimidinyl H), 6.75 (d, 1 H, alditolyl H-1), 5.85 (t, 1 H, alditolyl H-2), 5.50 (dd, 1 H, alditolyl H-3), 5.15 (m, 1H, alditolyl H-4), 4.25 (m, 2H, alditolyl H-5 + H-5′), 2.20 (s, 9 H, NAc + 2 OAc), 2.18, 2.15, 2.05 (3s, 3 H each, 3 OAc).
$C_{28}H_{30}N_4O_{12}$ (614)

3.3.7. 8-Acetyl-3-(1,2,3,4-penta-O-acetyl-D-manno-pentitol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-a]pyrimidine (**6g**)

Yield: Method A: 62%; method B: 50%; m.p.: 133 °C; TLC in 9 : 1 chloroform/methanol, R_f: 0.62; IR (KBr): 1744 (OAc), 1689 (OCN), 1604 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 319.2 (3.87), 251.4 (4.33); ^{1}H NMR ($CDCl_3$): δ 7.55 (m, 5 H, phenyl 5 H), 7.15 (s. 1 H, pyrimidinyl H), 6.35 (d, 1 H, alditolyl H-1), 5.75 (dd, 1 H, alditolyl H-2), 5.10, 4.60 (2m, 1 H each, alditolyl H-3 + H-4), 4.10 (m, 2 H, alditolyl H-5 + H-5′), 2.15 (s, 3 H, NAc), 2.10 (s, 3 H OAc), 2.05 (s, 9 H, 3 OAc), 1.85 (s, 3 H, OAc).
$C_{28}H_{30}N_4O_{12}$ (614)

3.4. 8-Acetyl-3-(alditol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-a]-pyrimidines (**7a–g**)

A solution of the appropriate acetate **8a–g** (2 mmol) in CH_3OH (25 ml) was treated with a 20% aqueous ammonia solution (10 ml) and kept at ambient temperature for 24 h. Evaporation of the solvents under reduced pressure gave a residue which crystallized from a H_2O/C_2H_5OH mixture.

3.4.1. 8-Acetyl-3-(D-arabino-tetritol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo-[4,3-a]pyrimidine (**7a**)

Yield: 58%; m.p.: 235 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.60; IR (KBr): 3348, 3272 (OH), 1679 (OCN), 1561 (C=N) cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$]: δ 7.63 (m, 6 H, phenyl 5 H + pyrimidinyl H), 5.65 (d, 1 H, alditolyl H), 5.20–4.35 (broad m, 3 H, exchangeable, 3 OH), 3.90 (m, 2 H, alditolyl 2 H), 3.70 (s, 3 H, NAc).
$C_{17}H_{18}N_4O_6$ (374)

3.4.2. 8-Acetyl-3-(L-arabino-tetritol-1-yl)-7-oxo-5–phenyl-1,2,4,-triazolo-[4,3-a]pyrimidine (**7b**)

Yield: 55%; m.p.: 238 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.66; IR (KBr): 3382 (OH), 1679 (OCN), 1561 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 323.4 (3.56), 246.6 (3.96); ^{1}H NMR [$(CD_3)_2SO$]: δ 7.35 (m, 6 H, phenyl 5 H + pyrimidinyl H), 5.50 (d, 1 H, alditolyl H), 3.90–3.20 (m, 5 H, NAc + alditolyl 2 H).
$C_{17}H_{18}N_4O_6$ (374)

3.4.3. 8-Acetyl–7-oxo-5–phenyl-3-(D-ribo-tetritol-1-yl)-1,2,4,-triazolo-[4,3-a]pyrimidine (**7c**)

Yield: 50%; m.p.: 234 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.67; IR (KBr): 3397 (OH), 1674 (OCN), 1571 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 322.2 (3.78), and 248.1 (4.15); ^{1}H NMR [$(CD_3)_2SO$]: δ 7.50 (m, 6 H, phenyl 5 H + pyrimidinyl H), 5.45 (d, 1 H, alditolyl H), 5.20–4.35 (broad m, 2 H, exchangeable, 2 OH), 4.00 (d, 1 H, alditolyl H), 3.50 (s, 3 H, NAc); m/z 374 (M^+).
$C_{17}H_{18}N_4O_6$ (374)

3.4.4. 8-Acetyl–7-oxo-5–phenyl-3-(D-xylo-tetritol-1-yl)-1,2,4,-triazolo-[4,3-a]pyrimidine (**7d**)

Yield: 53%; m.p.: 225 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.49; IR (KBr): 3378 (OH), 1673 (OCN), 1574 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 320.7 (3.80), 248.1 (4.17); ^{1}H NMR [$(CD_3)_2SO$]: δ 7.43 (m, 6 H, phenyl 5 H + pyrimidinyl H), 5.35 (d, 2 H, alditolyl 2 H), 5.05–4.15 (broad m, 4 H, exchangeable, 4 OH), 4.05–3.80 (m, 2 H, alditolyl 2 H), 3.45 (s, 3 H, NAc).
$C_{17}H_{18}N_4O_6 \cdot H_2O$ (392)

3.4.5. 8-Acetyl-3-(D-galacto-pentitol-1-yl)-7-oxo-5-phenyl-1,2,4,-triazolo-[4,3-a]pyrimidine (**7e**)

Yield: 55%; m.p.: 275 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.88; IR (KBr): 3367 (OH), 1681 (OCN), 1560 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 325.5 (3.03), 247.2 (3.46); ^{1}H NMR [$(CD_3)_2SO$]: δ 7.40 (m, 6 H, phenyl 5 H + pyrimidinyl H), 5.60–5.10 (m, 2 H, alditolyl H + exchangeable, OH), 4.60–4.20 (m, 2 H, exchangeable, 2 OH), 3.25 (s, 3 H, NAc).
$C_{18}H_{20}N_4O_7$ (404)

3.4.6. 8-Acetyl-3-(D-gluco-pentitol-1-yl)-7-oxo-5–phenyl-1,2,4,-triazolo-[4,3-a]pyrimidine (**7f**)

Yield: 52%; m.p.: 103 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.83; IR (KBr): 3354 (OH), 1678 (OCN), 1560 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 324.0 (2.93), 246.9 (3.34); ^{1}H NMR [$(CD_3)_2SO$]: δ 7.58 (m, 6 H, phenyl 5 H + pyrimidinyl H), 5.55 (d, 1 H, alditolyl H), 4.80–4.35 (m, 2 H, exchangeable, 2 OH), 3.95, 3.70 (2m, 2 H each, alditolyl 4 H), 3.40 (s, 3 H, NAc).
$C_{18}H_{20}N_4O_7$ (404)

3.4.7. 8-Acetyl-3-(D-manno-pentitol-1-yl)-7-oxo-5–phenyl-1,2,4,-triazolo-[4,3-a]pyrimidine (**7g**)

Yield: 54%; m.p.: 267 °C; TLC in 1 : 1 chloroform/methanol, R_f: 0.85; IR (KBr): 3346 (OH), 1681 (OCN), 1567 (C=N) cm^{-1}; UV: $\lambda_{max}^{H_2O}$ nm (log ε): 324.6 (3.53), 248.7 (3.94); ^{1}H NMR [$(CD_3)_2SO$]: δ 7.50 (m, 6 H, phenyl 5 H + pyrimidinyl H), 5.35 (d, 2 H, alditolyl H + exchangeable, OH), 4.23 (m, 2 H, alditolyl 2 H), 3.90–3.40 (m, 5 H, NAc + alditolyl 2 H).
$C_{18}H_{20}N_4O_7$ (404)

3.5. Antimicrobial screening

Sterile nutrient agar plates (100 ml) were separately inoculated with a 24 h broth culture (1 ml) of *E. coli*, *B. subtilis*, *S. aureus*, *C. albicans* and *A. niger*. Solutions (60 µl) of the tested compounds (0.24 mg) in DMF (1 ml) were placed in wells (6 mm diam.) cut in the agar media and the plates were incubated at 37 °C (bacteria) or 25 °C (yeast). The diameter of the resulting inhibition zones were measured after 28 h for bacteria and 96 h for yeast (Table).

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