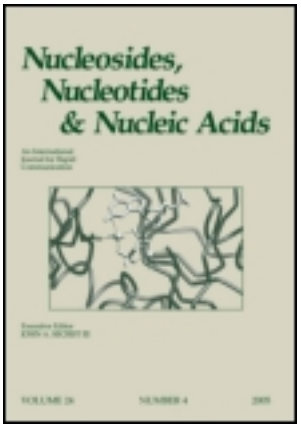


Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn20

Nucleosides 7[9]: Synthesis, Structure, and Biological Activity of New 6-Arylidenamino-2-Thio- and 2-Benzylthiopyrimidine N-Nucleosides

Mosselhi A. N. Mosselhi [a] & Laila M. Break [b]

[a] Department of Chemistry, Faculty of Science, Taif University, Taif, Saudi Arabia

[b] Department of Chemistry, Faculty of Science (Girls), Taif University, Taif, Saudi Arabia

Published online: 08 Sep 2011.

To cite this article: Mosselhi A. N. Mosselhi & Laila M. Break (2011): Nucleosides 7[9]: Synthesis, Structure, and Biological Activity of New 6-Arylidenamino-2-Thio- and 2-Benzylthiopyrimidine N-Nucleosides, Nucleosides, Nucleotides and Nucleic Acids, 30:9, 681-695

To link to this article: http://dx.doi.org/10.1080/15257770.2011.597628

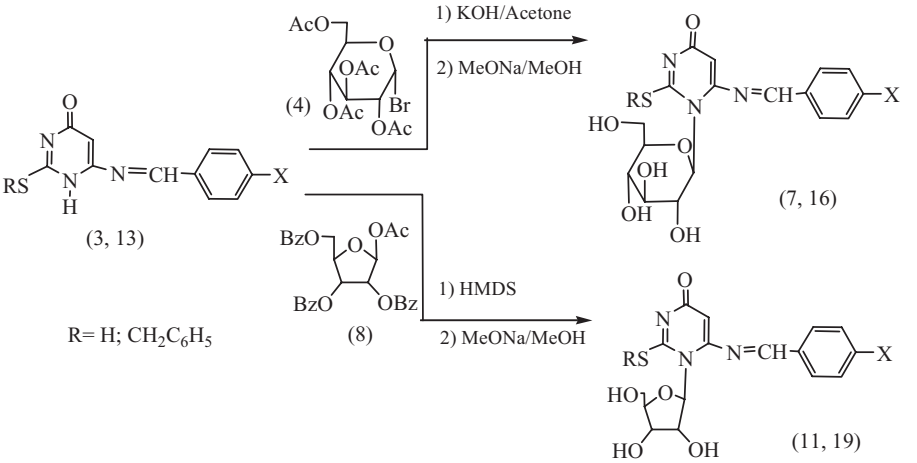
Nucleosides, Nucleotides and Nucleic Acids, 30:681–695, 2011

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770.2011.597628

NUCLEOSIDES 7[9]: SYNTHESIS, STRUCTURE, AND BIOLOGICAL ACTIVITY OF NEW 6-ARYLIDENAMINO-2-THIO- AND 2-BENZYLTHIOPYRIMIDINE *N*-NUCLEOSIDES

Mosselhi A. N. Mosselhi[1] and Laila M. Break[2]
[1]*Department of Chemistry, Faculty of Science, Taif University, Taif, Saudi Arabia*
[2]*Department of Chemistry, Faculty of Science (Girls), Taif University, Taif, Saudi Arabia*

Graphical Abstract:



□ *The condensation of 6-amino-2-thioxo-2,3-dihydro-1H-pyrimidine-4-one [compound* ***(1)****] with aromatic aldehydes* ***(2)*** *afforded azomethine derivatives* ***(3)****. The formed azomethines underwent glycosidation with α-acetobromoglucose* ***(4)*** *to form the corresponding pyrimidine N-glycosides* ***(6)*** *and not S-glycosides* ***(5)****. The interaction of* ***(3)*** *with 1-O-acetyl-2, 3, 5-tri-O-benzoyl-β-D-ribofuranose* ***(8)*** *afforded the corresponding pyrimidine N-riboside* ***(10)*** *and not S-riboside* ***(9)****. Deacetylation and debenzoylation of each of* ***(6)*** *and* ***(10)*** *by using methanolic sodium methoxide afforded the corresponding free N-nucleosides* ***(7)*** *and* ***(11)****, respectively. Next, the reaction of 2-benzylthio-6-benzylidenaminouracil* ***(13)*** *with* ***(4)*** *and* ***(8)*** *did not yield the corresponding protected N-nucleosides* ***(14)*** *and* ***(17)****, whereas it afforded* ***(15)*** *and* ***(18)****, respectively. The latter compounds* ***(15)*** *and* ***(18)*** *were stirred in methanolic sodium methoxide to yield the corresponding*

Received 15 September 2010; accepted 10 June 2011.
The authors thank the Taif University, Taif, Saudi Arabia, for the financial support for this project, grant numbers 1-430-403 and 2-431-403.
Address correspondence to Mosselhi A. N. Mosselhi, Department of Chemistry, Faculty of Science, Taif University, P. O. 888, Taif, Saudi Arabia. E-mail: mosselhi2008@hotmail.com

*free N-nucleosides **(16)** and **(19)**, respectively. The structures of products have been elucidated and reported and also some of the products were screened for their antimicrobial activity.*

Keywords 6-Arylidenaminothiopyrimidines; α-D-glucopyranosyl bromide; β-D-ribofuranose; *N*-pyrimidine glycoside; *N*-pyrimidine nucleoside; antimicrobial activity

INTRODUCTION

Nucleosides are the most frequently used effective class of antiviral agents, with over 20 drugs currently approved for the treatment of viral diseases and a number of candidates in the clinical trials.[1a,1b,2] Consequently, the intense search for new nucleoside derivatives attracted extensive attention. For example, Mackman synthesized a novel nucleoside phosphonate that had anti-HIV activity.[3] Being bioactive molecules, pyrimidines are important components of the biological macromolecules, such as DNA and RNA. Therefore, introducing the pyrimidines into nucleoside derivatives may result in the discovery of a number of novel derivatives with potential antitumor and antiviral activities. The explosion of new approaches for their synthesis and, most importantly, their selective synthesis is an interesting subject of organic and bioorganic chemistry.

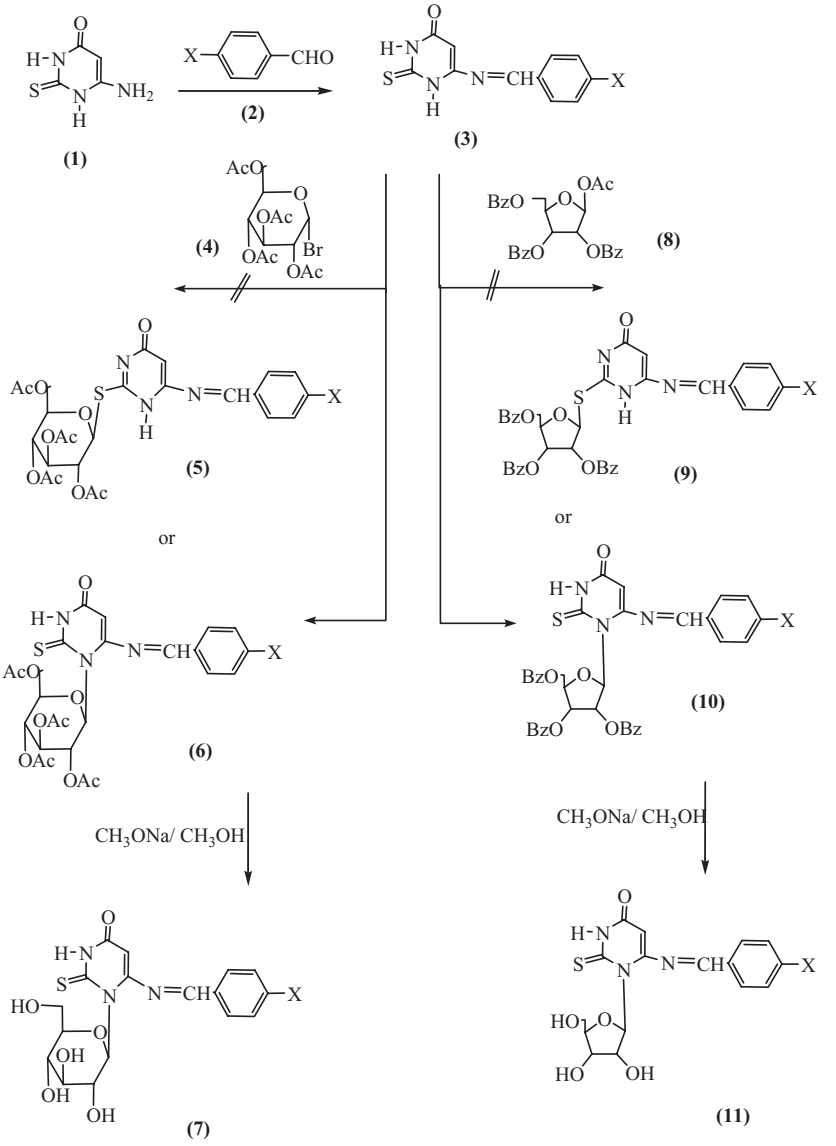
Furthermore, 2-thiopyrimidine nucleosides are known to adopt referentially a rigid C3′-endo sugar ring conformation; therefore, in RNA duplexes, a modified s2U-A base pair is more stabilized than the unmodified one.[4–8]

Owing to the biological importance of pyrimidine nucleosides and as a part of our continuing interest in the synthesis of new nucleosides[9,10–14] as expected new potential antivirals, we have been encouraged to study a synthetic strategy of new derivatives of thiopyrimidine *N*-nucleosides that have not yet been reported in the literature.

RESULTS AND DISCUSSION

Condensation of equimolar quantities of 6-amino-2-thioxo-2,3-dihydro-*1H*-pyrimidine-4-one [compound **(1)**] with aromatic aldehydes **(2)** in dimethylformamide (DMF) in the presence of drops of acetic acid gave the corresponding 6-arylidenamino-2-thioxo-2,3-dihydro-*1H*-pyrimidin-4-ones **(3)** (see Scheme 1). The elucidation of the structures of **(3)** was based on the spectral evidence (see Experimental section). Thus, the infrared (IR) spectra of **(3)** revealed absorption bands for C=S group at $\nu = 1175–1179$ cm^{-1}. The ^1H NMR spectra showed characteristic signals for N=CH proton at $\delta = 7.80–7.95$.

Reaction of the potassium salt of 6-arylidenamino-2-thioxo-2,3-dihydro-*1H*-pyrimidin-4-ones **(3)** with 2,3,4,6-tetracetyl-*O*-acetyl-α-D-glucopyranosyl bromide **(4)** in dry acetone did not give the *S*-glycosides **(5)**; instead, it gave the corresponding new *N*-glycosides **(6)** (see Scheme 1).



SCHEME 1

Thin layer chromatography (TLC) showed the formation of a single unique compound in each case. The structure of the products **(6)** was established and confirmed by elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR; see Experimental section). IR spectra of **(6)** revealed absorption bands for acetoxy carbonyl groups at $\nu = 1740–1750\ cm^{-1}$. The ^{1}H NMR spectrum of **(6a)** taken as a typical example of the prepared series showed the

anomeric proton as a doublet at $\delta = 6.35$ with spin–spin coupling constant of $J_{1',2'} = 5.5$ Hz corresponding to diaxial orientation of the H-1′ and H-2′ protons[13]. The other six protons of the glucopyranosyl ring resonated at $\delta = 3.95$–6.35 region, whereas the four acetoxy groups appeared as four singlets at $\delta = 2.20$–2.25, in addition to the other expected signals for aromatic and olefinic protons. However, ^{13}C NMR spectrum of **(6a)** was characterized by a signal of $\delta = 62.0$–82.5 corresponding to the C's atoms of the β-D-glucopyranose, the four signals appearing at $\delta = 165.0$–167.5 due to the four acetoxy carbonyl carbon atoms, and the characteristic signal at $\delta = 173$ due to the presence of C=S, the six signals at $\delta = 20.5$–21.5 are attributed to the acetate methyl carbon atoms. Another signal at $\delta = 158.5$ corresponds to N=CH (see Experimental section).

Deacetylation of the blocked glycosides **(6)** was achieved in methanolic sodium methoxide to afford the corresponding free *N*-nucleosides **(7)** (see Scheme 1). The ^{1}H NMR of **(7)** showed the expected base moiety protons in addition to the sugar moiety protons (see Experimental section).

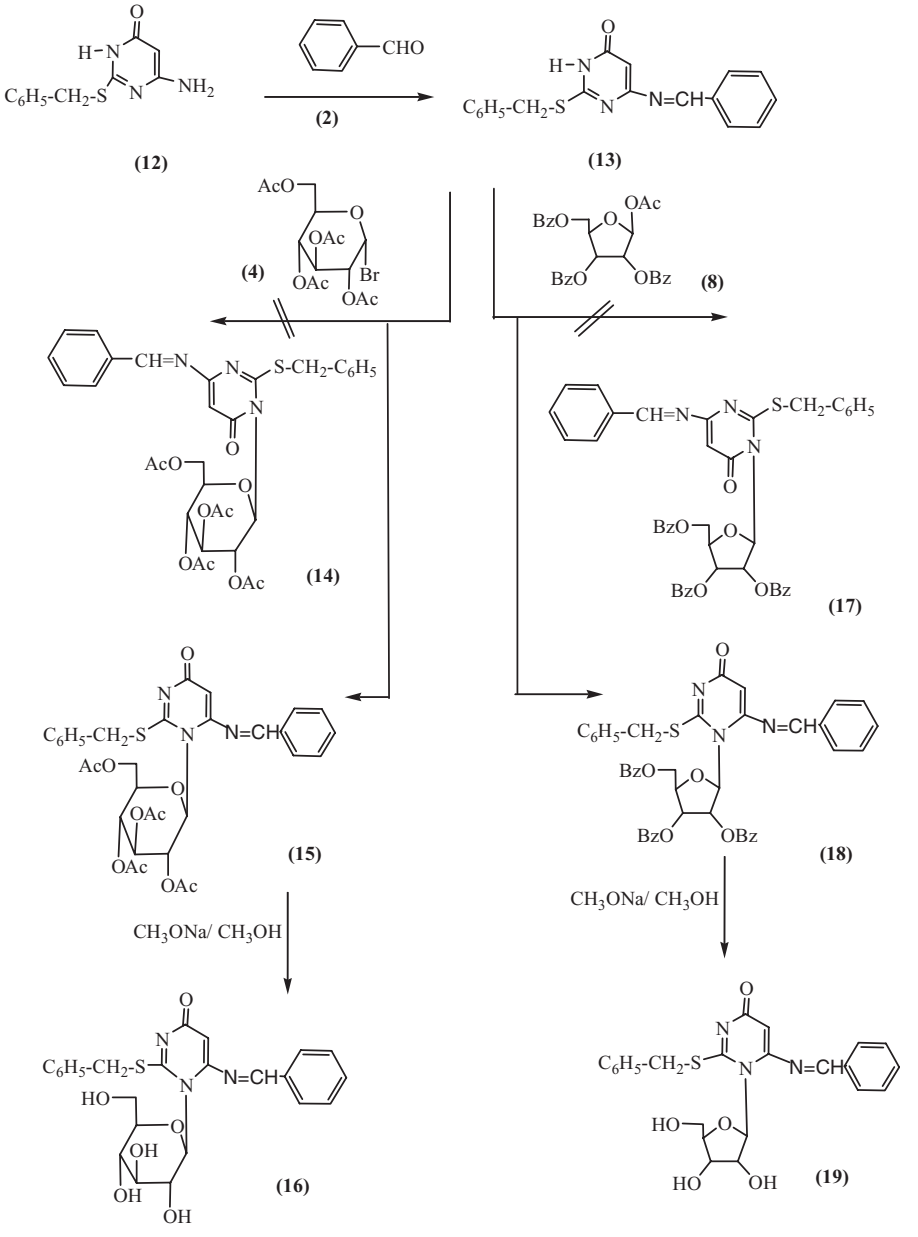
Next, the ribosylation of **(3)** (X=H) with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose **(8)** was carried out by the silylation method according to Vorbruggen[15] by refluxing of **(3)** in hexamethyl disilazane (HMDS) with ammonium sulfate as a catalyst and then stirring of the silylated product with ribose derivative **(8)** in dry acetonitrite and trimethylsilane [(TMS) triflate; $CF_3SO_2OSiMe_3$] at room temperature for 48 hours. This method yielded a product in 65% of the benzoylated nucleosides **(9)** or **(10)** (see Scheme 1).

The structure of the latter product was established and confirmed on the bases of its elemental analyses and spectral data (see Experimental section), which were consistent with the structure of nucleoside **(10)** and not **(9)**. Thus, the analytical data for **(10)** revealed in its ^{1}H NMR spectrum a doublet at $\delta = 6.0$ assigned to the anomeric proton of the ribose moiety with a spin–spin coupling constant equal to 10 Hz that corresponds to a diaxial orientation for the 1′- and 2′-H protons, i.e., the β-configuration.[9,10–14] ^{13}C NMR spectrum of **(10)** revealed C=S chemical shifts of δ 175.

Reaction of **(10)** with methanolic sodium methoxide at room temperature yielded the corresponding free *N*-nucleoside **(11)** (see Scheme 1). The ^{1}H NMR of **(11)** showed the expected base moiety protons in addition to the sugar moiety protons.

A distinction between the *O*-, *N*-, and *S*-nucleosides was possible by comparison of the ^{1}H NMR and ^{13}C NMR spectra with those of literature data of similar compounds.[16] ^{13}C=S chemical shifts of δ 172.0 were reported for cycloalkyl[4,5]-thieno[2,3-d]pyrimidin-4-one-2-thione, whereas 2-alkylthio-cycloalkyl[4,5]thieno[2,3-d]pyrimidin-4-one show chemical shifts of C-2 (=C−S−) around δ 159 ppm. For example, ^{13}C NMR spectrum of our nucleosides **(6a)** showed the characteristic signal at $\delta = 173$ due to the presence of C=S. This finding indicates the formation of *N*-nucleosides.[16]

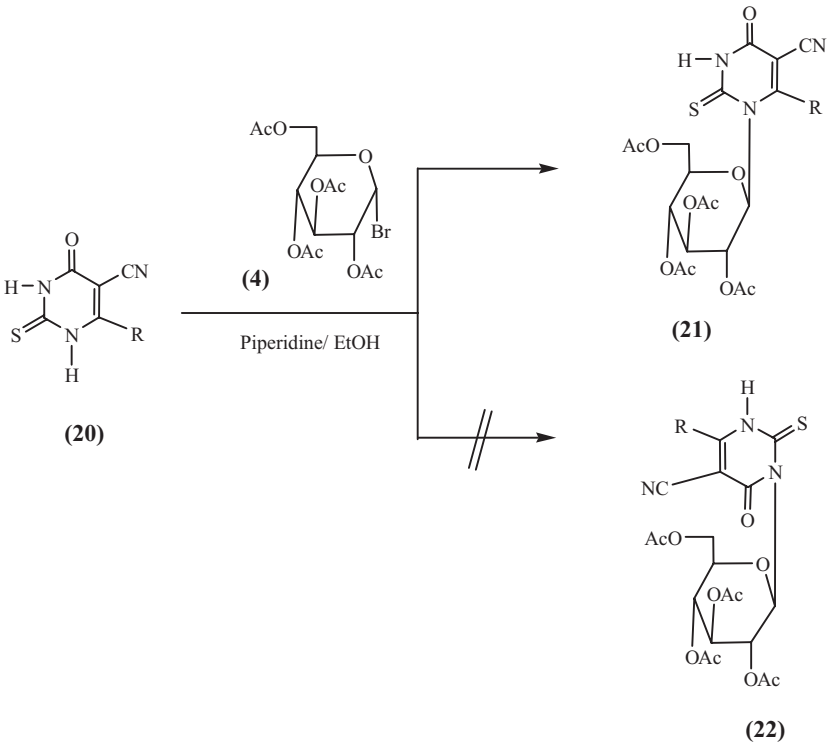
The results of further investigation into the formation of *N*-nucleosides showed that the reaction of 6-benzylideneamino-2-benzylthioxo-2,3-dihydro-1H-pyrimidine-4-one **(13)**, which is unreported in the literature and was obtained by heating 6-amino-2-benzylthioxo-2,3-dihydro-*1H*-pyrimidine-4-one **(12)** with benzaldehyde **(2)** in DMF and drops of acetic acid (see Scheme 2),



SCHEME 2

with saugers **(4)** and **(8)**, was achieved in a similar manner to yield the corresponding protected *N*-nucleosides **(15)** and **(18)**, respectively, and not the products **(14)** and **(17)** (see Scheme 2). Compounds **(15)** and **(18)** were deprotected in methanolic sodium methoxide to give the corresponding free *N*-nucleosides **(16)** and **(19)**, respectively (see Scheme 2). The structures of products **(15)**, **(16)**, **(18)**, and **(19)** are confirmed by spectral [methylsilane (MS), IR, and ^{1}H NMR] data (see Experimental section).

The formation of *N*-nucleoside **(15)** and not **(14)** is consistent with the results reported by L. Strekowski.[17] He reported that the reaction of 6-aryl-5-cyano-2-thiouracil **(20)** with α-acetobromoglucose **(4)** in ethanolic piperidine afforded the corresponding *N*-glycoside **(21)** and did not give the *N*-glycoside **(22)** (see Scheme 3).



SCHEME 3

The ^{1}H NMR spectrum of **(15)** showed the anomeric proton of the glucose moiety as a doublet at $\delta = 5.83$ with a coupling constant $J = 5.50$ Hz indicating β-configuration of the anomeric center.[13] The other protons of the glucopyranose ring resonated at $\delta = 3.90$–5.55, whereas the four acetoxy groups appeared as four singlets at $\delta = 2.25$–2.30. The ^{13}C NMR revealed the absence of a thione carbon atom at about $\delta = 173$. The signals at $\delta = 164.0$–166.0 are due to the four acetoxy carbonyl carbon atoms and the

signals at $\delta = 20.6$–20.7 are assigned to the acetate methyl carbon atoms. The five signals at $\delta = 62.5$–81.5 were assigned to C-6′, C-4′, C-2′, C-3′, and C-5′, respectively. The IR spectrum of compound **(15)** showed a signal at 1675 cm^{-1} for the C=O group and stretching vibration frequencies of the acetate carbonyl groups at 1745 cm^{-1}.

However, the ^1H NMR spectrum of **(18)** revealed an anomeric proton signal around $\delta = 6.6$ with a coupling constant value of 9.4 Hz consistent with the reported data for other *N*-nucleosides.[9,10–14]

The ^1H NMR of **(16)** and **(19)** showed the expected base moiety protons in addition to the sugar moiety protons (see Experimental section).

ANTIMICROBIAL ACTIVITY

Eight products, **(6a)**, **(7a)**, **(10)**, **(11)**, **(15)**, **(16)**, **(18)**, and **(19)**, were evaluated for their antibacterial and antifungal activities against two bacterial species, namely, *Escherichia coli* (EC) and *Staphylococcus aureus* (SA), as well as two fungal species, namely, *Aspergillus fumigatus* (AF) and *Candida albicans* (CA).

The antibacterial and antifungal activities were carried out in the Microbiology Division of Microanalytical Center of Cairo University; using the diffusion plate method,[18–20] a bottomless cylinder containing a measured quantity (1 mL, mg/mL) of the sample is placed on an inhibition zone (9 cm diameter) containing a solid bacterial medium (nutrient agar broth) or fungal medium (Dox's medium) that has been heavily seeded with the spore suspension of the test organism. After incubation (24 hours for bacteria and 5 days for fungi), the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism.

Most of the compounds were tested in vitro against gram-negative bacteria (EC anaerobic), gram-positive bacteria (SA), and antifungal activity against CA and AF. The antibiotics ampicillin and tetracycline were used as references to evaluate the potency of the tested compounds under the same condition. The test results are depicted in Table 1 on the following basis: The solvent used was dimethylsulfoxide and the concentration of the sample was 100 $\mu g/mL$.

EXPERIMENTAL

All chemicals were supplied by Sigma-Aldrich and Merck (Germany). IR spectra were recorded for KBr discs on Testscan Shimadzu FTIR 8000 Series and Bruker IFS 113V spectrophotometers (Germany); ^1H NMR and ^{13}C-spectra were recorded on a Varian Gemini 200 MHz NMR spectrometer (Germany) by using TMS as an internal standard in $CDCl_3$ and DMSO-d6 as a solvent. TLC was performed on silica gel sheets F 1550 LS 254 of Schleicher

TABLE 1 Antibacterial and antifungal activities of the synthesized compounds' inhibition zone diameter (IZD[a]; mm/mg compound tested)

Compound no.	Gram (−) EC	Gram (+) SA	Fungi AF	Fungi CA
Control: DMSO	0.0	0.0	0.0	0.0
Tetracycline antibacterial agent	28	26	—	—
	+++	+++		
Amphotericin B antifungal agent	—	—	16	15
			++	++
(6a)	10	10	0.0	0.0
	+	+	−	−
(7b)	13	13	0.0	12
	++	++	−	++
(10)	15	14	0.0	0.0
	++	++	−	−
(11)	12	12	0.0	13
	++	++	−	++
(15)	13	11	0.0	0.0
	++	++	−	−
(16)	11	12	0.0	14
	++	++	−	++
(18)	13	12	0.0	13
	++	++	−	++
(19)	14	12	0.0	14
	++	++	−	++

Note: The test results revealed that all compounds exhibited moderate activity against the two bacterial species and all compounds, except **(6a)** showed moderate activity against one fungal species, CA (DMSO = dimethyl sulfoxide).

[a]IZD = 2–10 mm beyond control = + (low activity); IZD = 11–24 mm beyond control = ++ (moderate activity); IZD = 25–35 mm beyond control = +++ (high activity).

& Schull and column chromatography on Merck silica gel 60 (particle size 0.063–0.20 mm). Melting points were measured on a Gallenkamp melting point apparatus (UK) and are uncorrected. Elemental analyses were carried out at the Microanalytical Centre (Cairo University, Egypt).

The starting materials, 6-amino-2-thioxo-2, 3-dihydro-*1H*-pyrimidine-4-one **(1)**,[21] and 6-amino-2-benzylthioxo-2,3-dihydro-*1H*-pyrimidine-4-on **(12)**,[22] were prepared as in the literature reported methods.

6-Arylidenamino-2-thioxo-2, 3-dihydro-*1H*-pyrimidin-4-ones (3) and 6-Benzylidenamino-2-benzylthio-2, 3-dihydro-*1H*-pyrimidin-4-ones (13)

General method: To a solution of 6-amino-2-thioxo-2, 3-dihydro-*1H*-pyrimidine-4-one **(1)**[21] or 6-amino-2-benzylthioxo-2,3-dihydro-*1H*-pyrimidine-4-one **(12)**[22] (1.43 g, 0.01 mol) in DMF (30 mL), an equivalent amount of aromatic aldehyde **(2)** (0.01 mol) and few drops of acetic acid were added. The reaction mixture was heated under reflux for 4 hours and then left to cool. The solid product formed after pouring into ice/

water was filtered and crystallized from the ethanol/dioxane mixture to give 6-arylidenamino-2-thioxo-2,3-dihdro-*1H*-pyrimidin-4-ones **(3)** and 6-benzylidenamino-2-benzylthio-2,3-dihydro-*1H*-pyrimidin-4-ones **(13)**, respectively. Compounds **(3a)** and **(3c)** are reported in the literature.[23]

Compound **(3b)**: Yield (75%); yellow crystals; mp 279°C–280°C; IR (KBr cm^{-1}): 3386 (NH), 1658 (C=O), 1179 (C=S); ^1H NMR (DMSO-d_6): δ 2.60 (s, 3H, CH_3), 5.35 (s, 1H, H-5), 6.89 (d, 2H, Ar–H, $J = 8.0$ Hz), 6.95(d, 2H, Ar–H, $J = 8.0$ Hz), 7.95 (s, 1H, N=CH), 11.30 (s, 1H, NH), 11.90 (s, 1H, NH); Anal. Calcd. for $C_{12}H_{11}N_3OS$ (245.2): C, 58.76; H, 4.52; N, 17.13; S, 13.07. Found: C, 58.50%; H, 4.20%; N, 17.00%; S, 13.25%.

Compound **(3d)**: Yield (63%); yellow crystals; mp 352°C–354°C; IR (KBr cm^{-1}): 3385 (NH), 1658 (C=O), 1175 (C=S); ^1H NMR (DMSO-d_6): δ 5.34 (s, 1H, H-5), 6.99 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.10 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.90 (s, 1H, N=CH), 11.42 (s, 1H, NH), 11.98 (s, 1H, NH); Anal. Calcd. for $C_{11}H_8N_3ClOS$ (265.72): C, 49.72; H, 3.03; N, 15.81; S, 12.07. Found: C, 55.10; H, 4.00; N, 16.22; S, 12.30%.

Compound **(13)**: Yield (78%); yellow crystals; mp 233°C–235°C; IR (KBr cm^{-1}): 3375 (NH), 1665 (C=O), ^1H NMR (DMSO-d_6): δ 4.45 (s, 2H, CH_2), 5.50 (s, 1H, H-5), 7.20–7.50 (m, 10H, Ar–H), 7.90 (s, 1H, N=CH), 11.50 (s, 1H, NH); Anal. Calcd. for $C_{18}H_{15}N_3OS$ (321.40): C, 67.27; H, 4.70; N, 13.07; S, 9.98. Found: C, 67.10; H, 4.50; N, 13.08; S, 10.00%.

Synthesis of 6-Arylidenamino-1-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosy)-2-thioxo-2,3-dihydro-*1H*-pyrimidin-4-ones (6) and 6-Benzylidenamino-1-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosy)-2-benzylthio-2,3-dihydro-*1H*-pyrimidin-4-ones (15)

General method: To a solution of **(3)** or **(13)** (5 mmol) in aqueous potassium hydroxide [(0.28 g, 5 mmol) in distilled H_2O (4 mL)] was added a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **(4)** (2.06 g, 5 mmol) in acetone (20 mL). The reaction mixture was stirred at room temperature overnight (12 hours) and judged to be complete by TLC ($CHCl_3$/MeOH 9:1). The solvent was evaporated under reduced pressure at 40°C, and the crude product was filtered off and washed with distilled H_2O (3 × 4 mL) to remove potassium bromide formed. The product was dried and crystallized from the proper solvent to afford the desired product **(6)** or **(15)**.

Compound **(6a)**: Yield (65%), m.p. 220°C–221°C (Ethanol); IR (KBr) ν cm^{-1}: 1750, 1665, 1540, 1185; ^1H NMR (DMSO-d_6): δ 2.20–2.25 (4s, 12H, 4$COCH_3$), 3.95 (m, 1H, H-5′), 4.15–4.30 (d, 2H, H-6′, $J = 5.1$ Hz), 4.95 (t, 1H, H-4′, $J = 4.9$ Hz), 5.20 (t, 1H, H-3′, $J = 5.0$ Hz), 5.35 (s, 1H, H-5), 5.50 (t, 1H, H-2′, $J = 5.0$ Hz), 6.35 (d, 1H, H-1′, $J_{1',2'} = 5.5$ Hz), 6.95–7.15 (m, 5H, Ar–H), 7.90 (s, 1H, N = CH), 11.42 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ

20.5–21.5 (4 $COCH_3$), (62.7, 75.5, 77.3, 80.8, 82.5) (glucose C's), 95.0 (C5), 129.0, 130.0, 132.0, 134.0 (Ar–C's), 158.5 (N=CH), 159.8 (C6), 164.2 (C4), 165.0–167.5 (4 CO), 173.0 (C=S); Anal. Calcd. for $C_{25}H_{27}N_3O_{10}S$ (561.56): C, 53.47; H, 4.85; N, 7.48; S, 5.71%.; Found: C, 53.22; H, 4.90; N, 7.40; S, 5.50%.

Compound **(6b)**: Yield (72%), m.p. 225–227°C (Ethanol); IR (KBr) ν cm^{-1}: 1743, 1670, 1515, 1175; ^{1}H NMR (DMSO-d_6): δ 2.10–2.16 (4s, 12H, 4$COCH_3$), 2.50 (s, 3H, CH_3), 3.95 (m, 1H, H-5′), 4.10–4.20 (d, 2H, H-6′, J = 5.1 Hz), 4.95 (t, 1H, H-4′, J = 4.85 Hz), 5.15 (t, 1H, H-3′, J = 5.0 Hz), 5.40 (s, 1H, H-5), 5.55 (t, 1H, H-2′, J = 5.0 Hz), 6.50 (d, 1H, H-1′, $J_{1',2'}$ = 5.4 Hz), 6.90 (d, 2H, Ar–H, J = 8.0 Hz), 7.00 (d, 2H, Ar–H, J = 8.0 Hz), 7.90 (s, 1H, N=CH), 11.80 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 20.5–21.5 (4 $COCH_3$), 25.5 (CH_3), (62.5, 75.0, 77.3, 80.0, 81.5) (glucose C's), 93.5 (C5), 129.8, 130.9, 135.2, 140.0 (Ar–C's), 159.5 (N=CH), 160.4 (C6), 163.8 (C4), 165.6–167.0 (4 CO), 173.2 (C=S); Anal. Calcd. for $C_{26}H_{29}N_3O_{10}S$ (575.59): C, 54.25; H, 5.08; N, 7.30; S, 5.57%.; Found: C, 54.20; H, 4.95; N, 7.15; S, 5.60%.

Compound **(6c)**: Yield (68%), m.p. 205°C–206°C (Ethanol); IR (KBr) ν cm^{-1}: 1740, 1669, 1520, 1182; ^{1}H NMR (DMSO-d_6): δ 2.12–2.20 (4s, 12H, 4$COCH_3$), δ 3.75 (s, 3H, OCH_3), 3.95 (m, 1H, H-5′), 4.15–4.25 (d, 2H, H-6′, J = 5.1 Hz), 5.00 (t, 1H, H-4′ J = 4.9 Hz), 5.10 (t, 1H, H-3′, J = 5.0 Hz), 5.35 (s, 1H, H-5), 5.45 (t, 1H, H-2′, J = 5.0 Hz), 6.35 (d, 1H, H-1′, $J_{1',2'}$ = 5.4 Hz), 6.95 (d, 2H, Ar–H, J = 8.0 Hz), 7.20 (d, 2H, Ar–H, J = 8.0 Hz), 7.89 (s, 1H, N=CH), 11.65(s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 20.5–21.5 (4 $COCH_3$), 55.1 (OCH_3), (63.0, 74.5, 78.0, 80.5, 82.5) (glucose C's), 92.8 (C5), 130.8, 132.9, 134.0, 157.8 (Ar–C's), 160.1 (N=CH), 161.5 (C6), 163.9 (C4), 164.8–167.5 (4 CO), 173.8 (C=S); Anal. Calcd. for $C_{26}H_{29}N_3O_{11}S$ (591.60): C, 52.79; H, 4.94; N, 7.10; S, 5.42%.; Found: C, 53.00; H, 4.85; N, 7.15; S, 5.50%.

Compound **(6d)**: Yield (55%), m.p. 212°C–214°C (Ethanol); IR (KBr) ν cm^{-1}: 1745, 1666, 1518, 1190; ^{1}H NMR (DMSO-d_6): δ 2.10–2.16 (4s, 12H, 4$COCH_3$), 3.90 (m, 1H, H-5′), 4.10–4.22 (d, 2H, H-6′, J = 5.1 Hz), 4.98 (t, 1H, H-4′, J = 5.0 Hz), 5.15 (t, 1H, H-3′, J = 5.0 Hz), 5.40 (s, 1H, H-5), 5.50 (t, 1H, H-2′, J = 5.0 Hz), 6.40 (d, 1H, H-1′, $J_{1',2'}$ = 5.5 Hz), 6.95 (d, 2H, Ar–H, J = 8.0 Hz), 7.25 (d, 2H, Ar–H, J = 8.0 Hz), 7.85 (s, 1H, N=CH), 11.50 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 20.5–21.5 (4 $COCH_3$), (62.5, 75.0, 77.5, 80.0, 81.5) (glucose C's), 88.5 (C5), 130.8, 132.9, 134.0, 137.8 (Ar–C's), 159.1 (N=CH), 161.0 (C6), 163.0 (C4), 163.9–166.5 (4 CO), 172.9 (C=S); Anal. Calcd. for $C_{25}H_{26}ClN_3O_{11}S$ (596.01): C, 50.38; H, 4.40; N, 7.05; S, 5.38%.; Found: C, 50.20; H, 4.45; N, 7.10; S, 5.30%.

Compound **(15)**: Yield (69%), m.p. 125°C–126°C (Ethanol); IR (KBr) ν cm^{-1}: 1745, 1675, 1520 1180; ^{1}H NMR (DMSO-d_6): δ 2.25–2.30 (4s, 12H,

4COCH$_3$), 3.90 (m, 1H, H-5′), 4.15–4.25 (d, 2H, H-6′, J = 5.1 Hz), 4.45 (s, 2H, CH$_2$), 4.95 (t, 1H, H-4′, J = 4.8 Hz), 5.20 (t, 1H, H-3′, J = 5.0 Hz), 5.35 (s, 1H, H-5), 5.55 (t, 1H, H-2′, J = 5.0 Hz), 5.83 (d, 1H, H-1′, $J_{1',2'}$ = 5.50 Hz), 7.25–7.80 (m, 10H, Ar–H), 7.95 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6): δ 20.6–20.7 (4 CO CH$_3$), 35.0 (CH$_2$), (62.5, 75.0, 77.3, 80.0, 81.5) (glucose C's), 89.5 (C5), 130.8, 132.9, 134.0, 137.8 (Ar–C's), 159.0 (N=CH), 161.5 (C6), 163.5 (C4), 164.0–166.0 (4 CO); Anal. Calcd. for $C_{32}H_{33}N_3O_{10}S$ (651.68): C, 58.98; H, 5.10; N, 6.45; S, 4.92%.; Found: C, 59.00; H, 5.25; N, 6.25; S, 4.90%.

Synthesis of 6-Arylidenamino-1-(2′,3′,4′,6′-tetra-hydroxy-β-D-glucopyranosyl)-2-thioxo-2,3-dihydro-*1H*-pyrimidin-4-ones (7) and 6-Benzylidenmino-1-(2′,3′,4′,6′-tetra-hydroxy-β-D-gluco-pyranosyl)-2-benzylthio-2,3-dihydro-*1H*-pyrimidin-4-ones (16)

General method: A mixture each of the protected nucleoside **(6)** or **(15)** (2 mmol), absolute methanol (40 mL), and sodium methoxide (120 mg, 2.2 mol) was stirred at room temperature for 24 hours. Evaporation of the solvent under vacuum gave a colorless solid, which was dissolved in hot water and neutralized with acetic acid. The precipitate was filtered off and afforded upon crystallization from water, the free nucleosides **(7)** or **(16)**, respectively, as colorless crystals or powder

Compound **(7a)**: White powder, Yield (55%), m.p. 250°C–251°C; IR (KBr) ν cm^{-1}: 3450 (OH); ^{1}H NMR (DMSO-d_6): δ 1.50 (t, 2H, OH-2′ + OH-3′, J = 5.0 Hz), 1.85 (m, 2H, OH-4′+ OH-5′), 3.70 (s, 1H, H-2′), 4.10 (s, 2H, H-3′+ H-4′), 4.35 (d, 3H, H-5′+ H-6′, J = 5.2 Hz), 5.40 (s, 1H, H-5), 6.51 (t, 1H, H-1′, $J_{1',2'}$ = 5.0), 7.90 (s, 1H, N=CH), 11.50 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ (71.0, 73.5, 77.5, 82.0, 84.5) (glucose C's), 93.0 (C5), 128.9, 129.0, 131.0, 133.8 (Ar–C's), 160.5 (N=CH), 162.0 (C6), 166.2 (C4), 175.0 (C=S); Anal. Calcd. for $C_{17}H_{19}N_3O_6S$ (393.41): C, 51.90; H, 4.87; N, 10.68; S, 8.15%.; Found: C, 51.95; H, 4.75; N, 10.50; S, 8.10%.

Compound **(7b)**: Colorless crystals, Yield (67%), m.p. 235°C–237°C; IR (KBr) ν cm^{-1}: 3445 (OH); ^{1}H NMR (DMSO-d_6): δ 1.80 (t, 2H, OH-2′ + OH-3′, J = 5.0 Hz), 1.96 (m, 2H, OH-4′+ OH-5′), 2.60 (s, 3H, CH$_3$), 3.79 (s, 1H, H-2′), 4.23 (s, 2H, H -3′+ H-4′), 4.45 (d, 3H, H-5′+ H-6′, J = 5.2 Hz), 5.50 (s, 1H, H-5), 6.55 (t, 1H, H-1′, $J_{1',2'}$ = 5.0), 7.00 (d, 2H, Ar–H, J = 8.0 Hz), 7.20 (d, 2H, Ar–H, J = 8.0 Hz), 7.95 (s, 1H, N=CH), 11.43 (s, 1H, NH); Anal. Calcd. for $C_{18}H_{21}N_3O_6S$ (407.44): C, 53.06; H, 5.20; N, 10.31; S, 7.87%.; Found: C, 53.00; H, 5.05; N, 10.40; S, 7.80%.

Compound **(7c)**: Colorless crystals, Yield (67%), m.p. 241°C–242°C; IR (KBr) ν cm^{-1}: 3450 (OH); ^{1}H NMR (DMSO-d_6): δ 1.78 (t, 2H, OH-2′ + OH-3′, J = 5.0 Hz), 1.95 (m, 2H, OH-4′+ OH-5′), 3.40 (s, 3H, OCH$_3$), 3.80 (s, 1H, H-2′), 4.25 (s, 2H, H-3′+ H-4′), 4.43 (d, 3H, H-5′+ H-6′, J = 5.2 Hz), 5.60

(s, 1H, H-5), 6.51 (t, 1H, H-1′, $J_{1',2'} = 5.0$), 7.10 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.25 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.90 (s, 1H, N=CH), 11.50 (s, 1H, NH); Anal. Calcd. for $C_{18}H_{21}N_3O_7S$ (423.44): C, 51.06; H, 5.00; N, 9.92; S, 7.57%.; Found: C, 51.25; H, 5.10; N, 9.75; S, 7.55%.

Compound **(7d)**: White powder, Yield (44%), m.p. 263°C–264°C; IR (KBr) ν cm^{-1}: 3448 (OH); ^1H NMR (DMSO-d_6): δ 1.65 (t, 2H, OH-2′ + OH-3′, $J = 5.0$ Hz), 1.80 (m, 2H, OH-4′+ OH-5′), 3.75 (s, 1H, H-2′), 4.15 (s, 2H, H-3′+ H-4′), 4.25 (d, 3H, H-5′+ H-6′, $J = 5.2$ Hz), 5.50 (s, 1H, H-5), 6.50 (t, 1H, H-1′, $J_{1',2'} = 5.0$), 7.90 (s, 1H, N=CH), 11.45 (s, 1H, NH); Anal. Calcd. for $C_{17}H_{18}ClN_3O_6S$ (427.86): C, 47.72; H, 4.24; N, 9.82; S, 7.49%.; Found: C, 47.55; H, 4.45; N, 10.00; S, 7.55%.

Compound **(16)**: White powder, Yield (42%), m.p. 240°C–242°C; IR (KBr) ν cm^{-1}: 3452 (OH); ^1H NMR (DMSO-d_6): δ 1.50 (t, 2H, OH-2′ + OH-3′, $J = 5.0$ Hz), 1.85 (m, 2H, OH-4′+ OH-5′), 3.70 (s, 1H, H-2′), 4.10 (s, 2H, H-3′+ H-4′), 4.35 (d, 3H, H-5′+ H-6′, $J = 5.2$ Hz), 5.40 (s, 1H, H-5), 6.45 (t, 1H, H-1′, $J_{1',2'} = 5.0$), 7.20–7.70 (m, 10H, Ar–H), 7.90 (s, 1H, N=CH); Anal. Calcd. for $C_{24}H_{25}N_3O_6S$ (483.54): C, 59.61; H, 5.21; N, 8.69; S, 6.63%.; Found: C, 59.65; H, 5.15; N, 8.60; S, 6.50%.

Synthesis of 6-Benzylidenamino-1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-2-thioxo-2,3-dihydro-*1H*-pyrimidin-4-one (10) and 6-Benzylidenamino-2-benzylthioxo-1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-2,3-dihydro-*1H*-pyrimidin-4-one (18)

General method: A mixture of **(3)** or **(13)** (10 mmol) and dry hexamethyldisilazane (50 mL) was heated under reflux for 10 hours with a catalytic amount of ammonium sulfate (50 mg). After the clear solution was cooled, it was evaporated to dryness under anhydrous condition to give the silylated derivative, which directly was dissolved in 30 mL of dry 1, 2-dichloroethane. To this was added a solution of 1-O-acetyl-2, 3, 5-tri-O-benzoyl-β-D-ribofuranose **(8)** (4.8 g, 9.8 mmol) in dry 1, 2-dichloroethane (20 mL) was then added. The mixture was cooled in an ice bath and a solution of trimethylsilyl trifluoromethanesulfonate (2 mL, 10 mmol) in dry 1, 2-dichloroethane (10 mL) was added dropwise. It was stirred at room temperature for 24 hours, then diluted with chloroform (300 mL), washed with a saturated solution of aqueous sodium bicarbonate (100 mL), water (3 × 50 mL), and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue was chromatographed on silica gel with chloroform as the eluent to afford white solid that was crystallized from ethanol to yield colorless crystals of the corresponding nucleoside derivative **(10)** or **(18)**.

Compound **(10)**: Yield (70%), m.p. 160°C–161°C (Ethanol); IR (KBr) ν cm^{-1}: 1730, 1595, 1175; ^1H NMR ($CDCl_3$): δ 4.60–4.92 (m, 3H, 2 H-5′, H-4′),

5.30 (s, 1H, H-5), 6.00 (d, 1H, H-1′, $J_{1',2'} = 10$ Hz), 6.25–6.30 (pt, 1H, H-3′), 6.40–6.45 (pt, 1H, H-2′), 7.15–7.80 (m, 20H, Ar–H), 7.95 (s, 1H, N=CH), 11.32 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): 59, 71, 78, 84, 93, 121, 125–140, 151, 159, 168 (CO), 175 (C=S); Anal. Calcd. for $C_{37}H_{29}N_3O_8S$ (675.71): C, 65.77; H, 4.33; N, 6.22; S, 4.75%.; Found: C, 65.59; H, 4.30; N, 6.10; S, 4.63%.

Compound **(18)**: Yield (45%), m.p. 125°C–126°C (Ethanol); IR (KBr) ν cm^{-1}: 1734, 1600, 1180; ^{1}H NMR ($CDCl_3$): δ 4.45 (s, 2H, CH_2), 4.66–4.95 (m, 3H, 2 H-5′, H-4′), 5.35 (s, 1H, H-5), 6.20–6.30 (pt, 1H, H-3′), 6.40–6.45 (pt, 1H, H-2′), 6.60 (d, 1H, H-1′, $J_{1',2'} = 9.4$ Hz), 7.15–7.75 (m, 20H, Ar–H), 7.95 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$): 25, 60, 70, 78, 82, 92, 121, 125–140, 151, 159, 166–168 (CO); Anal. Calcd. for $C_{44}H_{35}N_3O_8S$ (766.83): C, 69.01; H, 4.61; N, 5.49; S, 4.19%.; Found: C, 69.00; H, 4.50; N, 5.33; S, 4.13%.

Synthesis of 6-Benzylidinamino-1-(β-D-ribofuranosyl)-2-thioxo-2, 3-dihydro-*1H*-pyrimidin-4-one (11) and 6-Benzylidinamino-2-benzylthio-1-(β-D-ribofuranosyl)-2, 3-dihydro-*1H*-pyrimidin-4-one (19)

General method: A mixture of the protected nucleoside **(10)** or **(18)** (1 mmol), absolute methanol (20 mL), and sodium methoxide (60 mg, 1.1 mol) was stirred at room temperature for 24 hours. Evaporation of the solvent under vacuum gave a colorless solid, which was dissolved in hot water and neutralized with acetic acid. The precipitate was filtered off and afforded upon crystallization from water to give the nucleosides **(11)** or **(19)** as colorless crystals.

Compound **(11)**: Yield (40%), m.p. 255°C–256°C; IR (KBr) ν cm^{-1}: 3355 (OH); ^{1}H NMR (DMSO-d_6): δ 3.5–3.6 (m, 2H, 5′,5′-H); 3.9–4.0 (m, 1H,4′-H); 4.15–4.2 (m, 1H, 3′-H); 4.35–4.45 (m, 1H, 2′-H); 4.7–4.8 (t, 1H, 5′-OH); 5.1–5.2 (d, 1H, 3′-OH); 5.30 (s, 1H, H-5); 5.4–5.5 (d, 1H, 2′-OH); 6.1–6.2 (d, 1H, $J_{1',2'} = 5.0$ Hz, 1′-H); 7.10–7.75 (m, 5H, Ar–H), 7.90 (s, 1H, N=CH), 11.50 (s, 1H, NH); Anal. Calcd. for $C_{16}H_{17}N_3O_5S$ (363.39): C, 52.88; H, 4.72 N, 11.56; S, 8.82%.; Found: C, 52.70; H, 4.54; N, 11.50; S, 8.75%.

Compound **(19)**: Yield (53%), m.p. 242°C–243°C; IR (KBr) ν cm^{-1}: 3352 (OH), ^{1}H NMR (DMSO-d_6): δ 3.5–3.6 (m, 2H, 5′,5′-H); 3.8–3.9 (m, 1H,4′-H); 4.10–4.15 (m, 1H, 3′-H); 4.25–4.35 (m, 1H, 2′-H); 4.45 (s, 2H, CH_2); 4.65–4.75 (t, 1H, 5′-OH); 5.0–5.15 (d, 1H, 3′-OH); 5.25 (s, 1H, H-5); 5.35 (s, 1H, H-5); 5.40–5.50 (d, 1H, 2′-OH); 6.0 (d, 1H, $J_{1',2'} = 5.0$ Hz, 1′-H); 7.15–7.80 (m, 10H, Ar–H), 7.95 (s, 1H, N = CH), 11.45 (s, 1H, NH); Anal. Calcd. for $C_{23}H_{23}N_3O_5S$ (453.51): C, 60.91; H, 5.11; N, 9.27; S, 7.07%.; Found: C, 60.90; H, 5.00; N, 9.20; S, 6.88%.

ANTIMICROBIAL ASSAY

Cultures of two bacterial species, namely, EC and SA, as well as two fungal species, namely, AF and CA, were used to investigate the antimicrobial activity of the compounds' eight products, **(6a)**, **(7a)**, **(10)**, **(11)**, **(15)**, **(16)**, **(18)**, and **(19)**. The antimicrobial activity was assayed biologically by using the diffusion plate technique. The latter technique was carried out by pouring a spore suspension of the fungal species (1 cm^3 of sterile water contains approximately 108 conidia) or spreading bacterial suspension over a solidified malt agar medium. The layer is allowed to set for 30 minutes. A solution of the test compounds (1.0 g = cm^3) in DMF was placed onto sterile 5 mm filter paper discs and allowed to dry; then the discs were placed on the center of the malt agar plate and incubated at optimum incubation temperature 28°C ± 2°C. The fungicide Terbinfin and the bactericide chloramphenicol were used as standards under the same conditions. Measurements were considered after 72 hours for fungi and 24 hours for bacteria. The results are summarized in Table 1.

REFERENCES

1. (a) Qin, H.; Liu, C.; Zhang, J.; Guo, Y.; Zhang, S.; Zhang, Z.; Wang, X.; Zhang, L.; Liu, J. Synthesis and biological evaluation of novel 2-aryl alkylthio-4-amino-6-benzylpyrimidines as potent HIV-1 non-nucleoside reverse transcriptase inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, 20, 3003. (b) Qian, X.; Liu, B.; Wu, Q.; Lv, D.; Lin, X.-F. Facile synthesis of novel mutual derivatives of nucleosides and pyrimidines by regioselectively chemo-enzymatic protocol. *Bioorg. Med. Chem.* **2008**, 16, 5181.
2. Bergmana, A.M.; Kuipera, C.M.; Voorn, D.A.; Comijna, E.M.; Myhrenb, F.; Sandvoldb, M.L.; Hendriksc, H.R.; Petersa, G. Antiproliferative activity and mechanism of action of fatty acid derivatives of arabinofuranosylcytosine in leukemia and solid tumor cell lines. *J. Biochem. Pharmacol.* **2004**, 67, 503.
3. Boojamra, C.G.; Mackman, R.L.; Markevitch, D.Y.; Prasad, V.; Adrian, S.; Ray, A.S.; Douglas, J.; Grant, D.; Kim, C.U.; Cihlar, T. Synthesis and anti-HIV activity of GS-9148 (20-Fd4AP), a novel nucleoside phosphonate HIV reverse transcriptase inhibitor. *Bioorg. Med. Chem. Lett.* **2008**, 18, 1120.
4. Sochacka, E.; Frątczak, I. Efficient desulfurization of 2-thiopyrimidine nucleosides to the corresponding 4-pyrimidinone analogues using trans-2-(phenylsulfonyl)-3-phenyloxaziridine. *Tetrahedron Lett.* **2004**, 45, 6729.
5. Sierzputowska-Gracz, H.; Sochacka, E.; Malkiewicz, A.; Kuo, K.; Gehrke, C.W.; Agris, P.F. Chemistry and structure of modified uridines in the anticodon, wobble position of transfer RNA are determined by thiolation. *J. Amer. Chem. Soc.* **1987**, 109, 7171.
6. Kumar, R.K.; Davis, D.R. Synthesis and studies on the effect of 2-thiouridine and 4-thiouridine on sugar conformation and RNA duplex stability. *Nucleic Acids Res.* **1997**, 25, 1272.
7. Testa, S.M.; Turner, D.H.; Kierzek, R. Thermodynamics of RNA-RNA duplexes with 2- or 4-thiouridines: implications for antisense design and targeting a group I intron. *Biochemistry* **1999**, 38, 16655.
8. Shohda, K.; Okamoto, I.; Wada, S.; Seio, K.; Sekine, M. Synthesis and properties of 2′-O-Methyl-2-thiouridine and oligoribonucleotides containing 2′-O-Methyl-2-thiouridine. *Bioorg. Med. Chem. Lett.* **2000**, 10, 1795.
9. Metwally, N.H.; Abdalla, M.A.; Mosselhi, M.A.N.; El-Desoky, E.A. Nucleosides 6: synthesis and antimicrobial activity of some new N-glycosides of 2-thioxo-4-thiazolidinone derivatives. *Carbohydr. Res.* **2010**, 345, 1135.
10. Mosselhi, M.A.N. Nucleoside 1: ribosylation of 8-substituted theophylline derivatives. *Nucleosides Nucleotides Nucleic Acids* **1993**, 12(5), 431.

11. Mosselhi, M.A.N. Nucleosides 2: synthesis and properties of 3,4-diaryl-4,5-Dihydro-1-(β-Dribofuranosyl)-1,2,4-triazole-5-thiones. *Nucleosides Nucleotides Nucleic Acids* **1999**, 18(9), 2043.
12. Mosselhi, M.A.N.; Seliger, H. Nucleosides 3: synthesis of novel 1,3,4-oxadiazole nucleosides. *J. Chem. Res. (S)* **2001**, 359.
13. Break, L.M.; Shmiss, N.A.M.M.; Mosselhi, A.N.M. Nucleosides 4: synthesis of some new *S*-nucleoside derivatives of 2-thioxo and 2,4-dithioxo-5,6,7,8-tetrahydrobenzo-thieno[2,3-d]pyrimidin-4-(3H)ones. *Phosphorus Sulfur Silicon Relat. Elem.* **2010**, 185, 1615.
14. Mosselhi, M.A.N.; Neidlein, R. Nucleosides 5: synthesis of novel 1,2,4-triazolo[3,4-c]-1,2,4-triazole nucleosides. *Nucleosides Nucleotides Nucleic Acids* **2009**, 28, 1095.
15. Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. Nucleoside syntheses, XXII[1]: Nucleoside synthesis with trimethylsilyl triflate and perchlorate as catalysts. *Chem. Ber.* **1981**, 114, 1234.
16. Shawali, A.S.; Ali, N.A.H.; Osman, D.A. Synthesis and biological activity of new functionalized cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-ones. *J. Chem. Res.* **2006**, 5, 327.
17. Abdou, I.M.; Strekowski, L. A facile synthesis of 6-aryl-5-cyano-1-(β-D-pyranosyl or β-D-furanosyl)-2-thiocytosines. *Tetrahedron* **2000**, 56, 8631.
18. Bauer, A.W.; Kirby, W.M.; Sherris, C.; Turck, M. Antibiotic susceptibility testing by a standardized single disk method. *Am. J. Clin. Phath.* **1966**, 45, 493.
19. Pfaller, M.A.; Burmeister, L.; Bartlett, M.A.; Rinaldi, M.G. Multicenter evaluation of four methods of yeast inoulum preparation. *J. Clin. Microbiol.* **1988**, 26, 1437.
20. Matar, M.J.; Ostrosky-Zeichner, L.; Paetznick, V.L.; Rodriguez, J.R.; Chen, E.; Rex, J.H. Correlation between E-test, disk diffusion and microdilution methods for antifungal susceptibility testing of fluconazole and voriconazole. *Antimicrob. Agents Chemother.* **2003**, 47, 1647.
21. Taylor, E.C.; Cheng, C.C. Purine chemistry. VII. An improved synthesis of hypoxanthine. *J. Org. Chem.* **1960**, 25, 148.
22. Gibson, C.L.; La Rosa, S.; Ohta, K.; Boyle, P.H.; Leurquin, F.; Lemacon, A.; Suckling, C.J. The synthesis of 7-deazaguanines as potential inhibitors of guanosine triphosphate cyclohydrolase I. *Tetrahedron* **2004**, 60, 943.
23. Mohamed, N.R.; El-Saidi, M.M.T.; Ali, Y.M.; Elnagdi, M.H. Utility of 6-amino-2-thiouracil as a precursor for the synthesis of bioactive pyrimidine derivatives. *Bioorg. Med. Chem.* **2007**, 15, 6227.