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Synthesis of Novel *N*-Alkyl/Aryl-*N′*-(4-arylthiazol-2-yl)-*N″*-xylosyl Guanidines

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ABSTRACT: *The reaction of 2,3,4-tri-O-acetyl-β-D-xylopyranosyl isothiocyanate (***1***) and 2-amino-4-arylthiazoles (***2***) gave xylosylthioureas* **3**. *These thiourea derivatives reacted with alkyl/aryl amine in the presence of $HgCl_2$ to give a new series of N-alkyl/aryl-N″-(4-arylthiazol-2-yl)-N″-xylosyl guanidines* **4**. *Some of the synthesized guanidines were screened for their biological activity.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:688–694, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20379

INTRODUCTION

Guanidine-containing sugars and sugar-like molecules have a wide range of biologically important applications such as inhibition of inappropriate mitogenic signaling [1], therapy for bacterial infections [2], treatment of non–insulin-dependent diabetes [3], and inhibition of enzymes including thrombin [4], glycosidases [5], and nitric oxide synthases [6]. A number of compounds containing thiazole moiety have been reported to exhibit remarkable antibacterial [7], bactericidal [8], antiuder [9], and antagonism of MRP1 [10] activities. In addition, their syntheses have generated continued research interest in recent years, resulting in many new efficient synthetic methods and guanidinylation reagents for different classes of guanidine compounds [11–14]. We are interested in the preparation of *N*,*N′*,*N″*-substituted guanidines that contain sugar and thiazole moieties with the objective of obtaining new biologically active compounds using common reagent $HgCl_2$ that can be conveniently obtained everywhere.

RESULTS AND DISCUSSION

The easily accessible xylosyl isothiocyanate **1** [15] reacted with 2-amino-4-arylthiazoles **2** [16] in benzene to give xylosylthioureas **3** (Scheme 1). *N*,*N′*-Substituted xylosyl thioureas reacted smoothly with amine in the presence of $HgCl_2$. The incoming amine may be either alkyl or aryl. Thus, this process provides a very efficient route to *N*,*N′*,*N″*-substituted xylosylguanidines. It compares very favorably with the existing methods for the preparation of glycosylguanidines in that the present methods are both effective and convenient.

Thus, in the course of guanylation, a less polar intermediate was obtained, which then converted to the desired guanidine product. The intermediates were presumed to be carbodiimides. These observations are consistent with the reaction mechanism

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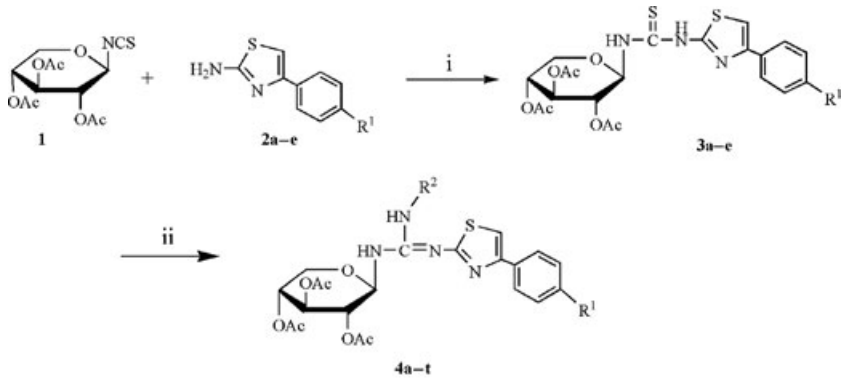

2a, 3a, 4a–d: R^1 = H
2b, 3b, 4e–h: R^1 = Cl
2c, 3c, 4i–l: R^1 = Br
2d, 3d, 4m–p: R^1 = CH_3
2e, 3e, 4q–t: R^1 = OCH_3

4a, 4e, 4i, 4m, 4q: R^2 = $(CH_3)_2CH$
4b, 4f, 4j, 4n, 4r: R^2 = $PhCH_2$
4c, 4g, 4k, 4o, 4s: R^2 = Ph
4d, 4h, 4l, 4p, 4t: R^2 = *p*-CH_3O-Ph

SCHEME 1 Reagents and Conditions: (i) benzene, reflux: (ii) Et_3N, alkyl/aryl amine, $HgCl_2$, DMF.

proposed for guanylation of bisbutyloxycarbonyl thioureas [17]: $HgCl_2$ promotes a formal elimination of H_2S from thiourea starting material to produce carbodiimide intermediates; amines then add to the carbodiimides to yield guanidine products. It appears that $HgCl_2$ causes the first step to proceed efficiently regardless of the nature of the substituents. The guanylation reactions were performed with the selected thiourea substrate in the presence of less than 1 equivalent of the incoming amine.

In the IR spectra of compounds **4a–4t**, there are characteristic absorption bands of guanidyl at 1620 cm^{-1}, while the absorption bands of NHCSNH in compounds **3a–3e** at 1510 cm^{-1} disappeared in compounds **4a–4t**. Otherwise, the spectra display a broad band at 3410 cm^{-1} (NH) and at about 1750 cm^{-1} (CO in sugar ring) in all products.

^{1}H NMR spectra show two signals of NH in compounds **3a–3e** that appeared at about δ 10.00–11.50, whereas one of NH signals shifted to δ 5.30–5.70 in compounds **4a–4t**. It is possible that the deshielding effect of CS is stronger than that of CN and the anisotropic effect of the aromatic ring, namely, this NH proton, which is at the *syn*-position of the imino group, must shift upfield. Therefore, in compounds **3a–3e**, the sugar ring C_1—H displayed signals at about δ 5.80; it appeared at higher field in compounds **4a–4t** at about δ 5.40. The sugar ring C_1—H reveals a triplet due to its coupling with C_2—H and N—H. The signal for NH proton in compounds **4c, 4d, 4g, 4h, 4k, 4l, 4o, 4p, 4s**, and **4t** appeared at δ 11.00–11.60, whereas in the remaining compounds of **4**, it appeared at δ 9.90–10.50. This result is not surprising as the aryl moiety shifts these signals to a lower field region.

In the ESI-MS, the molecular ion peaks of compounds **4** were obtained as base peaks, which indicate that all products of **4** are stable.

BIOLOGICAL ACTIVITY

The HIV-1 protease inhibitory activity of synthesized compounds **4a, 4b, 4e, 4f**, and **4g** were tested. Reference drug indinavir was provided by Glaxo Co. Substrate was supplied by MP Co. The HIV-1 protease enzyme was synthesized in the laboratory and stored at −85°C. Potential inhibitors were first solubilized in DMSO or distilled water just before the biological activity assay, and the following final drug concentrations were routinely used for evaluation: 250, 50, 10, 2.0, and 0.40 μg/mL. The diluted solution was mixed with buffer containing fluorescence-labeled HIV-1 substrate and then with gene-engineered HIV-1 protease. The mixture was incubated under optimal conditions and the fluorescent intensity was determined by FLUO Star Galaxy fluorometry. The HIV-1 protease inhibitory activity was analyzed and expressed as 50% inhibitory concentration (IC_{50}). The results are summarized in Table 1. The results showed that compounds **4b** and **4e** exhibited moderate HIV-1 protease inhibitory activity. Meanwhile, compounds **4a, 4b, 4e, 4f**, and **4g** were tested against angiotensin-converting enzyme (ACE), and **4g** showed activity against ACE.

EXPERIMENTAL

Melting points were taken on a Yanaco MP-S3 micro melting point apparatus. IRspectra were recorded in

TABLE 1 Anti-HIV-1 Protease Inhibitory Results of Tested Compounds

	Concentration (μg/mL)					
Compound	*250*	*50*	*10*	*2.0*	*0.40*	*IC_{50}*
4a	23.6	3.88	1.45	−1.59	−5.24	–
4b	42.8	2.82	−17.56	−6.88	−15.34	118.29
4e	66.76	2.44	−2.38	−10.94	−5.34	23.50
4f	12.48	−2.27	−1.41	−7.12	−8.29	–
4g	39.75	11.47	−2.30	7.79	4.03	–

KBr pellets on a Brucker Equinox 55 FT-IR apparatus. ^{1}H NMR spectra were recorded on an Inova-400 (using TMS as internal standard, chemical shifts expressed in δ ppm). Mass spectra were obtained on HP 1100-MS mass spectrometry workstation via ESI^+. TLC was performed on silica gel GF_{254} (Qindao of China), with ethyl acetate and light petroleum (fraction boiling in the range of 60°C–90°C) and detection by UV light or iodine. Column chromatography was performed on 200–300 mesh silica gel.

Preparation of Thiourea Derivatives **3a–3e**

An equimolecular mixture of **2** (23 mmol) and xylosyl isothiocyanate (25 mmol) in 30 mL of dry benzene were refluxed in a water bath for more than 10 h. After cooling, the solid product was filtered and washed with ether and water, then finally crystallized from ethanol to give thiourea derivatives **3a**–**3e**.

N-(4-Phenylthiazol-2-yl)-N′-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)thiourea (**3a**). Yield, 62%; mp 194°C–196°C; IR: ν = 3425 (NH), 1748 (C=O), 1566 (aryl), 1510 (N—C=S), 1040 (C—O—C), 908 cm^{-1} (sugar ring C_1—H); ^{1}H NMR ($CDCl_3$): δ = 2.02 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.18 (s, H, CH_3), 3.90–5.37 (m, 5H, sugar ring-H), 5.83 (t, 1H, sugar ring C_1—H, J = 9.4 Hz), 6.78 (s, 1H, thiazole C_4—H), 7.20–7.83 (m, 5H, Ar—H), 10.12 (br, 1H, NH), 11.04 (br, 1H, NH). MS: *m/z*(%) 493 (100) Anal. calcd. for $C_{21}H_{23}N_3O_7S_2$ (493.55): C, 51.11%; H, 4.70%; N, 8.51%. Found: C, 51.26%; H, 4.71%; N, 8.48%.

N-[4-(p-Chlorophenyl)thiazol-2-yl]-N′-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)thiourea (**3b**). Yield, 66%; mp 210°C–203°C; IR: ν = 3400 (NH), 1742 (C=O), 1579 (aryl), 1506 (N—C=S), 1036 (C—O—C), 909 cm^{-1} (sugar ring C_1—H); ^{1}H NMR ($CDCl_3$): δ = 1.97 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 3.88–5.33 (m, 5H, sugar ring-H), 5.79 (t, 1H, sugar ring C_1—H, J = 9.6 Hz), 6.69 (s, 1H, thiazole C_4—H), 7.16–7.87 (m, 4H, Ar—H), 10.21 (br, 1H, NH), 11.24 (br, 1H, NH). MS: *m/z* (%) 527 (100), 529 (33). Anal. calcd. for $C_{21}H_{22}ClN_3O_7S_2$ (527.99): C, 47.77%; H, 4.20%; N, 7.96%. Found: C, 47.61%; H, 4.21%; N, 7.97%.

N-[4-(p-Bromophenyl)thiazol-2-yl]-N′-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)thiourea (**3c**). Yield, 76%; mp 208°C–210°C; IR: ν = 3403 (NH), 1746 (C=O), 1579 (aryl), 1501 (N—C=S), 1045 (C—O—C), 909 cm^{-1} (sugar ring C_1—H); ^{1}H NMR ($CDCl_3$): δ = 1.95 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 3.86–5.30 (m, 5H, sugar ring-H), 5.76 (t, 1H, sugar ring C_1—H, J = 9.6 Hz), 6.65 (s, 1H, thiazole C_4—H), 7.23–7.82 (m, 4H, Ar—H), 10.23 (br, 1H, NH), 11.26 (br, 1H, NH). MS: *m/z* (%) 571 (100), 573 (97). Anal. calcd. for $C_{21}H_{22}BrN_3O_7S_2$ (571.45): C, 44.06%; H, 3.87%; N, 7.34%. Found: C, 44.18%; H, 3.85%; N, 7.36%.

N-[4-(p-Methylphenyl)thiazol-2-yl]-N′-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)thiourea (**3d**). Yield, 73%; mp 200°C–202°C; IR: ν = 3400 (NH), 1752 (C=O), 1579 (aryl), 1510 (N—C=S), 1041 (C—O—C), 907 cm^{-1} (sugar ring C_1—H); ^{1}H NMR ($CDCl_3$): δ = 1.97 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.74–5.40 (m, 5H, sugar ring-H), 5.77 (t, 1H, sugar ring C_1—H, J = 9.2 Hz), 6.78 (s, 1H, thiazole C_4—H), 7.01–7.75 (m, 4H, Ar—H), 10.26 (br, 1H, NH), 11.28 (br, 1H, NH). MS: *m/z* (%) 507 (100). Anal. calcd. for $C_{22}H_{25}N_3O_7S_2$ (507.58): C, 52.06%; H, 4.96%; N, 8.28%. Found: C, 51.90%; H, 4.93%; N, 8.30%.

N-[4-(p-Methoxylphenyl)thiazol-2-yl]-N′-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)thiourea (**3e**). Yield, 67%; mp 190°C–192°C; IR: ν = 3387 (NH), 1755 (C=O), 1564 (aryl), 1509 (N—C=S), 1034 (C—O—C), 910 cm^{-1} (sugar ring C_1—H); ^{1}H NMR ($CDCl_3$): δ = 2.01 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 3.80 (s, 3H, CH_3O), 3.88–5.40 (m, 5H, sugar ring-H), 5.86 (t, 1H, sugar ring C_1—H, J = 9.6 Hz), 6.89 (s, 1H, thiazole C_4—H), 7.05–7.80 (m, 4H, Ar—H), 10.32 (br, 1H, NH), 11.34 (br, 1H, NH).

MS: *m/z* (%) 523 (100). Anal. calcd. for $C_{22}H_{25}N_3O_8S_2$ (523.58): C, 50.47%; H, 4.81%; N, 8.03%. Found: C, 50.62%; H, 4.79%; N, 8.00%.

Preparation of Guanidine Derivatives **4a–4t**

The starting thiourea, amine (1.1 mmol), and triethylamine (2.2 mmol) were dissolved in dimethylformamide (5 mL/mmol substrate) at room temperature. The mixture was cooled in an ice bath. Then $HgCl_2$ (1.1 mmol) was added and the mixture was stirred for 20 min, before it was warmed to room temperature. When the reaction was completed (TLC, in the solvent system of EtOAc/petroleum ether 2:1, v/v), the reaction mixture was diluted with ethyl acetate and filtered through celite, washing the celite cake with additional ethyl acetate. The filtrate was washed with water, then with brine, and finally the organic phase was dried with $MgSO_4$. The crude product thus obtained was purified by flash chromatography on a silica column (in the solvent system of EtOAc/petroleum ether 1:1, v/v) to give compounds **4a**–**4t**.

*N-Isopropyl-N′-(4-phenylthiazol-2-yl)-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)guanidine (***4a***).* Yield, 80%; mp 135°C–137°C; IR: ν = 3349 (NH), 1738 (C=O), 1626 (guanidine), 1575 (aryl), 1038 (C—O—C), 907 cm^{-1} (C_1—H); ^1H NMR ($CDCl_3$): δ = 1.35 (d, 6H, isopropyl-2CH_3, J = 6.1 Hz), 1.99 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 3.90–5.29 (m, 6H, sugar ring-H, isopropyl-CH), 5.37 (t, 1H, sugar ring C_1—H, J= 9.6 Hz), 5.50 (br, 1H, NH), 6.89 (s, 1H, thiazole C_4—H), 7.06–7.87 (m, 5H, Ar—H), 10.11 (br, 1H, NH). MS: *m/z* (%) 519 (100). Anal. calcd. for $C_{24}H_{30}N_4O_7S$ (518.58): C, 55.59%; H, 5.83%; N, 10.80%. Found: C, 55.42%; H, 5.85%; N, 10.77%.

*N-Benzyl-N′-(4-phenylthiazol-2-yl)-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl) guanidine (***4b***).* Yield, 85%; mp 140°C–142°C; IR: ν = 3410 (NH), 1740 (C=O), 1621 (guanidine), 1585 (aryl), 1036 (C—O—C), 907 cm^{-1} (sugar ring C_1—H); ^1H NMR ($CDCl_3$): δ = 2.02 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 3.71–5.25 (m, 7H, sugar ring-H, benzyl-CH_2), 5.36 (t, 1H, sugar ring C_1—H, J = 9.2 Hz), 5.48 (br, 1H, NH), 6.85 (s, 1H, thiazole C_4—H), 7.12–7.81 (m, 10H, Ar—H), 10.58 (br, 1H, NH). MS: *m/z* (%) 567 (100). Anal. calcd. for $C_{28}H_{30}N_4O_7S$ (566.63): C, 59.35%; H, 5.34%; N, 9.89%. Found: C, 59.50%; H, 5.30%; N, 9.86%.

*N-Phenyl-N′-(4-phenylthiazol-2-yl)-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl) guanidine (***4c***).* Yield, 70%; mp 182°C–184°C; IR: ν = 3362 (NH), 1746 (C=O), 1626 (guanidine), 1590 (aryl), 1039 (C—O—C), 910 cm^{-1} (sugar ring C_1—H); ^1H NMR ($CDCl_3$): δ = 2.10 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.82–5.32 (m, 5H, sugar ring-H), 5.43 (t, 1H, sugar ring C_1—H, J = 9.2 Hz), 5.57 (br, 1H, NH), 6.64 (s, 1H, thiazole C_4—H), 6.98–7.66 (m, 10H, Ar—H), 11.20 (br, 1H, NH). MS: *m/z* (%) 553 (100). Anal. calcd. for $C_{27}H_{28}N_4O_7S$ (552.60): C, 58.69%; H, 5.11%; N, 10.14%. Found: C, 58.86%; H, 5.12%; N, 10.11%.

*N-(p-Methoxylphenyl)-N′-(4-phenylthiazol-2-yl)-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl) guanidine (***4d***).* Yield, 70%; mp 190°C–192°C; IR: ν = 3380 (NH), 1738 (C=O), 1619 (guanidine), 1558 (aryl), 1040 (C—O—C), 906 cm^{-1} (sugar ring C_1—H); ^1H NMR ($CDCl_3$): δ = 2.01 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 3.81 (s, 3H, CH_3O), 3.90–5.24 (m, 5H, sugar ring-H), 5.36 (t, 1H, sugar ring C_1—H, J = 9.6 Hz), 5.50 (br, 1H, NH), 6.88 (s, 1H, thiazole C_4—H), 7.10–7.82 (m, 9H, Ar—H), 11.49 (br, 1H, NH). MS: *m/z* (%) 583 (100). Anal. calcd. for $C_{28}H_{30}N_4O_8S$ (582.63): C, 57.72%; H, 5.19%; N, 9.62%. Found; C, 57.54%; H, 5.21%; N, 9.65%.

*N-Isopropyl-N′-[4-(p-chlorophenyl)thiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)guanidine (***4e***).* Yield, 82%; mp 140°C–142°C; IR: ν = 3353 (NH), 1739 (C=O), 1620 (guanidine), 1590 (aryl), 1032 (C—O—C), 912 cm^{-1} (sugar ring C_1—H); ^1H NMR ($CDCl_3$): δ = 1.30 (d, 6H, isopropyl-2CH_3,J = 5.9 Hz), 1.99 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 3.93–5.31 (m, 6H, sugar ring-H, isopropyl-CH), 5.35 (t, 1H, sugar ring C_1—H, J = 9.7Hz), 5.52 (br, 1H, NH), 6.83 (s, 1H, thiazole C_4—H), 6.92–7.89 (m, 4H, Ar—H), 10.25 (br, 1H, NH). MS: *m/z* (%) 553 (100), 555 (35). Anal. calcd. for $C_{24}H_{29}ClN_4O_7S$ (552.03): C, 52.12%; H, 5.29%; N, 10.13%. Found: C, 51.96%; H, 5.30%; N, 10.10%.

*N-Benzyl-N′-[4-(p-chlorophenyl)thiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl) guanidine (***4f***).* Yield, 83%; mp 153°C–155°C; IR: ν = 3407 (NH), 1746 (C=O), 1627 (guanidine), 1583 (aryl), 1037 (C—O—C), 908 cm^{-1} (sugar ring C_1—H); ^1H NMR ($CDCl_3$): δ = 2.03 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.70–5.26 (m, 7H, sugar ring-H, benzyl-CH_2), 5.35 (t, 1H, sugar ring C_1—H, J = 9.2 Hz), 5.46 (br, 1H, NH), 6.84 (s, 1H, thiazole C_4—H), 7.05–7.80 (m, 9H, Ar—H), 10.60 (br, 1H, NH). MS: *m/z* (%) 601 (100), 603 (33). Anal. calcd. for $C_{28}H_{29}ClN_4O_7S$ (600.14): C, 55.95%; H, 4.86%; N, 9.32%. Found; C, 56.13%; H, 4.84%; N, 9.35%.

*N-Phenyl-N′-[4-(p-chlorophenyl)thiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)guanidine (**4g**).* Yield, 68%; mp 178°C–180°C; IR: ν = 3368 (NH), 1739 (C=O), 1621 (guanidine), 1598 (aryl), 1032 (C—O—C), 913 cm^{-1} (sugar ring C_1—H); ^1H NMR ($CDCl_3$): δ = 2.10 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.81–5.20 (m, 5H, sugar ring-H), 5.39 (t, 1H, sugar ring C_1—H, J = 9.2 Hz), 5.58 (br, 1H, NH), 6.85 (s, 1H, thiazole C_4—H), 6.96–7.52 (m, 9H, Ar—H), 11.27 (br, 1H, NH). MS: *m/z* (%) 587 (100), 589 (32). Anal. calcd. for $C_{27}H_{27}ClN_4O_7S$ (586.12): C, 55.24%; H, 4.64%; N, 9.54%. Found: C, 55.06%; H, 4.62%; N, 9.57%.

*N-(p-Methoxylphenyl)-N′-[4-(p-chlorophenyl)thiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)guanidine (**4h**).* Yield, 65%; mp 169°C–171°C; IR: ν = 3382 (NH), 1746 (C=O), 1618 (guanidine), 1587 (aryl), 1038 (C—O—C), 912 cm^{-1} (sugar ring C_1—H); ^1H NMR ($CDCl_3$): δ = 2.12 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.69 (s, 3H, CH_3O), 3.86–5.21 (m, 5H, sugar ring-H), 5.42 (t, 1H, sugar ring C_1—H, J = 9.6 Hz), 5.56 (br, 1H, NH), 6.76 (s, 1H, thiazole C_4—H), 6.98–7.82 (m, 8H, Ar—H), 11.38 (br, 1H, NH). MS: *m/z* (%) 617 (100), 619 (33). Anal. calcd. for $C_{28}H_{29}ClN_4O_8S$ (616.13): C, 54.50%; H, 4.74%; N, 9.08%. Found: C, 54.60%; H, 4.72%; N, 9.06%.

*N-Isopropyl-N′-[4-(p-bromophenyl)thiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)guanidine (**4i**).* Yield, 82%; mp 141°C–143°C; IR: ν = 3355 (NH), 1737 (C=O), 1621 (guanidine), 1594 (aryl), 1031 (C—O—C), 910 cm^{-1} (sugar ring C_1—H); ^1H NMR ($CDCl_3$): δ = 1.33 (d, 6H, isopropyl-2CH_3, J = 6.0 Hz), 2.10 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.92–5.33 (m, 6H, sugar ring-H, isopropyl-CH), 5.36 (t, 1H, sugar ring C_1—H, J = 9.6 Hz), 5.56 (br, 1H, NH), 6.88 (s, 1H, thiazole C_4—H), 7.02–7.89 (m, 4H, Ar—H), 10.23 (br, 1H, NH). MS: *m/z* (%) 597 (100), 599 (97). Anal. calcd. for $C_{24}H_{29}BrN_4O_7S$ (596.09): C, 48.25%; H, 4.89%; N, 9.38%. Found; C, 48.12%; H, 4.90%; N, 9.40%.

*N-Benzyl-N′-[4-(p-bromopheny)lthiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl) guanidine (**4j**).* Yield, 80%; mp 156°C–158°C; IR: ν = 3410 (NH), 1748 (C=O), 1622 (guanidine), 1588 (aryl), 1032 (C—O—C), 912 cm^{-1} (sugar ring C_1—H); ^1H NMR ($CDCl_3$): δ = 2.11 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.73–5.32 (m, 7H, sugar ring-H, beneyl-CH_2), 5.43 (t, 1H, sugar ring C_1—H, J = 9.2 Hz), 5.56 (br, 1H, NH), 6.75 (s, 1H, thiazole C_4—H), 6.98–7.80 (m, 9H, Ar—H), 10.60 (br, 1H, NH). MS: *m/z* (%) 645 (100), 647 (96). Anal. calcd. for $C_{28}H_{29}BrN_4O_7S$ (644.09): C, 52.10%; H, 4.53%; N, 8.68%. Found: C, 52.25%; H, 4.52%; N, 8.65%.

*N-Phenyl-N′-[4-(p-bromophenyl)thiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)guanidine (**4k**).* Yield, 71%; mp 179°C–181°C; IR: ν = 3365 (NH), 1740 (C=O), 1627 (guanidine), 1592 (aryl), 1038 (C—O—C), 908 cm^{-1} (sugar ring C_1—H); ^1H NMR ($CDCl_3$): δ = 2.02 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 3.82–5.23 (m, 5H, sugar ring-H), 5.41 (t, 1H, sugar ring C_1—H, J = 9.2 Hz), 5.58 (br, 1H, NH), 6.64 (s, 1H, thiazole C_4—H), 6.96–7.64 (m, 9H, Ar—H), 11.29 (br, 1H, NH). MS: *m/z* (%) 631 (100), 633 (97). Anal. calcd. for $C_{27}H_{27}BrN_4O_7S$ (630.07): C, 51.35%; H, 4.31%; N, 8.87%. Found: C, 51.52%; H, 4.30%; N, 8.85%.

*N-(p-Methoxylphenyl)-N′-[4-(p-bromophenyl)thiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)-guanidine (**4l**).* Yield, 68%; mp 166°C–168°C; IR: ν = 3362 (NH), 1743 (C=O), 1619 (guanidine), 1592 (aryl), 1030 (C—O—C), 920 cm^{-1} (sugar ring C_1—H); ^1H NMR ($CDCl_3$): δ = 2.12 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.58 (s, 3H, CH_3O), 3.87–5.23 (m, 5H, sugar ring-H), 5.39 (t, 1H, sugar ring C_1—H, J = 9.6 Hz), 5.56 (br, 1H, NH), 6.68 (s, 1H, thiazole C_4—H), 6.98–7.81 (m, 9H, Ar—H), 11.34 (br, 1H, NH). MS: *m/z* (%) 661 (100), 663 (98). Anal. calcd. for $C_{28}H_{29}BrN_4O_8S$ (660.09): C, 50.84%; H, 4.42%; N, 8.47%. Found: C, 50.99%; H, 4.40%; N, 8.49%.

*N-Isopropyl-N′-[4-(p-methylphenyl)thiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)guanidine (**4m**).* Yield, 80%; mp 133°C–135°C; IR: ν = 3345 (NH), 1750 (C=O), 1622 (guanidine), 1590 (aryl), 1040 (C—O—C), 907 cm^{-1} (sugar ring C_1—H); ^1H NMR ($CDCl_3$): δ = 1.34 (d, 6H, isopropyl-2CH_3, J = 5.9 Hz), 1.98 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 3.90–5.30 (m, 6H, sugar ring-H, isopropyl-CH), 5.17 (t, 1H, sugar ring C_1—H, J= 9.4Hz), 5.49 (br, 1H, NH), 6.78 (s, 1H, thiazole C_4—H), 7.18–7.63 (m, 4H, Ar—H), 10.25 (br, 1H, NH). MS: *m/z* (%) 533 (100). Anal. calcd. for $C_{25}H_{32}N_4O_7S$ (532.61): C, 56.38%; H, 6.06%; N, 10.52%. Found: C, 56.21%; H, 6.08%; N, 10.55%.

*N-Benzyl-N′-[4-(p-methylpheny)lthiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)guanidine (**4n**).* Yield, 74%; mp 125°C–127°C; IR: ν = 3350 (NH), 1758 (C=O), 1620 (guanidine), 1580 (aryl), 1032 (C—O—C), 909 cm^{-1} (sugar ring C_1—H); ^1H NMR ($CDCl_3$): δ = 2.01 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.70–5.30 (m, 7H, sugar ring-H, beneyl-CH_2), 5.35 (t, 1H, sugar

ring C_1—H, J = 9.4 Hz), 5.45 (br, 1H, NH), 6.69 (s, 1H, thiazole C_4—H), 6.99–7.84 (m, 9H, Ar—H), 10.55 (br, 1H, NH). MS: *m/z* (%) 581 (100). Anal. calcd. for $C_{29}H_{32}N_4O_7S$ (580.66): C, 59.99%; H, 5.55%; N, 9.65%. Found: C, 59.86%; H, 5.57%; N, 9.63%.

N-Phenyl-N′-[4-(p-methylphenyl)thiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)guanidine (**4o**). Yield, 70%; mp 110°C–112°C; IR: ν = 3410 (NH), 1755 (C=O), 1622 (guanidine), 1587 (aryl), 1030 (C—O—C), 911 cm^{-1} (sugar ring C_1—H); ^{1}H NMR ($CDCl_3$): δ = 2.02 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.88–5.06 (m, 5H, sugar ring-H), 5.24 (t, 1H, sugar ring C_1—H, J = 9.2 Hz), 5.43 (br, 1H, NH), 6.75 (s, 1H, thiazole C_4—H), 7.01–7.64 (m, 9H, Ar—H), 11.21 (br, 1H, NH). MS: *m/z* (%) 567 (100). Anal. calcd. for $C_{28}H_{30}N_4O_7S$ (566.63): C, 59.35%; H, 5.34%; N, 9.89%. Found; C, 59.47%; H, 5.36%; N, 9.87%.

N-(p-Methoxylphenyl)-N′-[4-(p-methylphenyl)thiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)-guanidine (**4p**). Yield, 60%; mp 110°C–111°C; IR: ν = 3380 (NH), 1753 (C=O), 1621 (guanidine), 1585 (aryl), 1029 (C—O—C), 920 cm^{-1} (sugar ring C_1—H); ^{1}H NMR ($CDCl_3$): δ = 2.02 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.80 (s, 3H, CH_3O), 3.86–5.26 (m, 5H, sugar ring-H), 5.36 (t, 1H, sugar ring C_1—H, J = 9.2 Hz), 5.48 (br, 1H, NH), 6.77 (s, 1H, thiazole C_4—H), 6.98–7.88 (m, 9H, Ar—H), 11.47 (br, 1H, NH). MS: *m/z* (%) 597 (100). Anal. calcd. for $C_{29}H_{32}N_4O_8S$ (596.66): C, 58.38%; H, 5.41%; N, 9.39%. Found; C, 58.21%; H, 5.39%; N, 9.42%.

N-Isopropyl-N′-[4-(p-methoxylphenyl)thiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylpyranosyl)guanidine (**4q**). Yield, 83%; mp 159°C–160°C; IR: ν = 3365 (NH), 1756 (C=O), 1618 (guanidine), 1578 (aryl), 1038 (C—O—C), 913 cm^{-1} (sugar ring C_1—H); ^{1}H NMR ($CDCl_3$): δ = 1.36 (d, 6H, isopropyl-2CH_3, J = 6.0 Hz), 2.02 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.85 (s, 3H, CH_3O), 3.90–5.23 (m, 6H, sugar ring-H, isopropyl-CH), 5.41 (t, 1H, sugar ring C_1—H, J = 9.6 Hz), 5.51 (br, 1H, NH), 6.68 (s, 1H, thiazole C_4—H), 7.03–7.79 (m, 4H, Ar—H), 10.35 (br, 1H, NH). MS: *m/z* (%) 549 (100). Anal. calcd. for $C_{25}H_{32}N_4O_8S$ (548.61): C, 54.37%; H, 5.88%; N, 10.21%. Found: C, 54.55%; H, 5.86%; N, 10.19%.

N-Benzyl-N′-[4-(p-methoxylpheny)lthiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)guanidine (**4r**). Yield, 80%; mp 135°C–137°C; IR: ν = 3412 (NH), 1746 (C=O), 1621 (guanidine), 1578 (aryl), 1039 (C—O—C), 910 cm^{-1} (sugar ring C_1—H); ^{1}H NMR ($CDCl_3$): δ = 1.99 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 3.72 (s, 3H, CH_3O), 3.91–5.33 (m, 7H, sugar ring-H, beneyl-CH_2), 5.37 (t, 1H, sugar ring C_1—H, J = 9.4 Hz), 5.52 (br, 1H, NH), 6.80 (s, 1H, thiazole C_4—H), 7.10–7.78 (m, 9H, Ar—H), 10.52 (br, 1H, NH). MS: *m/z* (%) 597 (100). Anal. calcd. for $C_{29}H_{32}N_4O_8S$ (596.66): C, 58.38%; H, 5.41%; N, 9.39%. Found: C, 58.20%; H, 5.42%; N, 9.41%.

N-Phenyl-N′-[4-(p-methoxylphenyl)thiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)guanidine (**4s**). Yield, 55%; mp 104°C–106°C; IR: ν = 3389 (N—H), 1754 (C=O), 1617 (guanidine), 1579 (aryl), 1041 (C—O—C), 910 cm^{-1} (sugar ring C_1—H);^{1}H NMR ($CDCl_3$): δ = 1.98 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 3.80 (s, 3H, CH_3O), 3.88–5.16 (m, 5H, sugar ring-H), 5.35 (t, 1H, sugar ring C_1—H, J = 9.4 Hz), 5.51 (br, 1H, NH), 6.79 (s, 1H, thiazole C_4—H), 6.95–7.72 (m, 9H, Ar—H), 11.25 (br, 1H, NH). MS: *m/z* (%) 583 (100). Anal. calcd. for $C_{28}H_{30}N_4O_8S$ (582.63): C, 57.72%; H, 5.19%; N, 9.62%. Found: C, 57.89%; H, 5.20%; N, 9.59%.

N-Methoxylphenyl-N′-[4-(p-methoxylphenyl)thiazol-2-yl]-N″-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)-guanidine (**4t**). Yield, 70%; mp 185°C–186°C; IR: ν = 3340 (NH), 1751 (C=O), 1620 (guanidine), 1581 (aryl), 1037 (C—O—C), 908 cm^{-1} (sugar ring C_1—H); ^{1}H NMR ($CDCl_3$): δ = 1.97 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.77 (s, 3H, CH_3O), 3.80 (s, 3H, CH_3O), 3.78–5.20 (m, 5H, sugar ring-H), 5.41 (t, 1H, sugar ring C_1—H, J = 9.6 Hz), 5.51 (br, 1H, NH), 6.84 (s, 1H, thiazole C_4—H), 7.02–7.76 (m, 8H, Ar—H), 11.24 (br, 1H, NH). MS: *m/z* (%) 613 (100). Anal. calcd. for $C_{29}H_{32}N_4O_9S$ (612.65): C, 56.85%; H, 5.26%; N, 9.14%. Found: C, 56.43%; H, 5.28%; N, 9.11%.

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REFERENCES

[1] Cotner, E. S.; Smith, P. J. J Org Chem 1998, 63, 1737.
[2] Streicher, W.; Loibner, H.; Hidebrandt, J.; Turnowsky, F. Drugs Exp Clin Res 1983, 39, 251.
[3] Reitz, A. B.; Tuman, R. W.; Marchione, C. S.; Jordan, A. D., Jr.; Bowden, C. R.; Maryanoff, B. E. J Med Chem 1989, 32, 2110.

[4] Wessel, H. P.; Banner, D.; Gubernator, K.; Hilpert, K.; Muller, K.; Tschopp, T. Angew Chem Int Ed Engl 1997, 36, 751.
[5] Chan, A. W.-Y.; Ganem, B. Tetrahedron Lett 1995, 36, 811.
[6] Gravier-Pelletier, C.; Bourissou; Merrer, Y. L.; Depezay, J.-C. Synlett 1996, 275.
[7] Ram, L.; Bimal, P. S.; Bishwa, N. S. Il Farmaco 2000, 55, 331.
[8] Wagner, B.; Schumann, D.; Linne, U.; Koert, U.; Marahiel, M. A. J Am Chem Soc 2006, 128, 10513.
[9] Gupta, S.; Singh, M.; Madan, A. K. J Chem Inf Comput Sci 1999, 39, 727.
[10] Xia, Z. P.; Smith, C. D. J Org Chem 2001, 66, 3459.
[11] Manimala, J. C.; Anslyn, E. V. Eur J Org Chem 2002, 3909.
[12] Wu, Y.-Q.; Hamilton, S. K.; Wilkinson, D. E.; Hamilton, G. S. J Org Chem 2002, 67, 7553.
[13] Manimala, J. C.; Anslyn, E. V. Tetrahedron Lett 2002, 43, 565.
[14] Kilburn, J. P.; Lau, J.; Jones, R. C. F. Tetrahedron 2002, 58, 1739.
[15] Cao, L.-H.; Zhou, C.-J.; Sun, J.-B.; Liu, Y.-T. Chin. J Org Chem 2003, 23(4), 356 (in Chinese).
[16] King, L. C.; Hlavacek, R. J. J Am Chem Soc 1950, 72, 3722.
[17] Kim, K. S.; Qian, L. Tetrahedron Lett 1993, 34, 7677.