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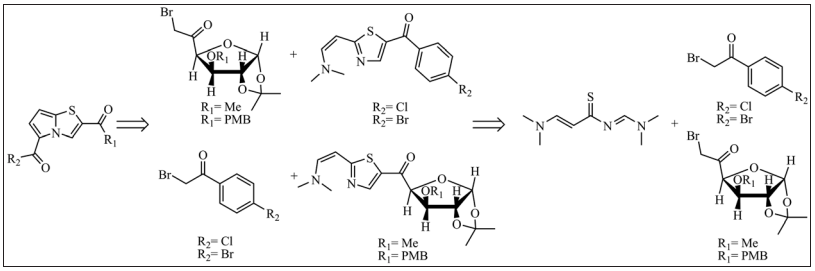

Herein, we describe the synthesis of pyrrolo[2,1-*b*]thiazoles substituted on C-2 or C-5 with a protected carbohydrate moiety. The new fused bicyclic heterocycles were obtained via thiazole intermediates, and the N-alkylation step was assisted by microwave irradiation. The new products were completely characterized by physical and spectroscopic techniques. The cytotoxicity and antiviral activity against Junín virus of the methylated derivates was also evaluated.

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INTRODUCTION

Nitrogen- and sulfur-containing heterocycles are a very attractive class of compounds in the medicinal chemistry field because of their wide spectrum of biological activities. Particularly, heterocyclic fused thiazoles have attracted the attention of many researchers because they have been shown to posses anthelmintic [1], antiviral [2,3], antihypertensive [4], anti-inflammatory [5,6], fungicidal [7], herbicidal [8], and antitumor [9–14] activities. In previous works [3,15,16], we reported the synthesis of imidazo [2,1-*b*]thiazoles 2,5 disubstituted with a *p*-halophenyl and a protected carbohydrate groups. We also reported the antiviral evaluation against Junín virus (JUNV) of some of these derivates [3,15].

JUNV is the etiological agent of argentine hemorrhagic fever, and up to the moment, there is no specific and safe chemotherapy available. Our results showed that the 3-(*p*-halobenzoyl)-5-(1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranos-5-ulo-5-il)imidazo[2,1-*b*]thiazoles possessed greater antiviral activity and selectivity than ribavirin, the only drug in clinical use for arenavirus treatment, which was evaluated in parallel as a reference substance.

These results encourage us to extend the study of imidazo [2,1-*b*]thiazoles to pyrrolo[2,1-*b*]thiazoles in order to evaluate the influence of the isosteric replacement of nitrogen for carbon atoms at position 7 in the antiviral activity of these compounds. Two series of pyrrolo[2,1-*b*]thiazoles substituted with a *p*-halophenyl and 1,2-*O*-isopropylidene-3-*O*-methyl carbohydrate group at C-2 and C-5 position were synthesized, and their antiviral activity against JUNV was evaluated.

Besides, two series of *p*-methoxybenzyl derivatives were also synthesized. This acid-labile protective group could be removed in the future to analyze the impact of an enhancement of the hydrophilicity in the antiviral activity of this heterocyclic family.

Herein, we report our new results.

RESULTS AND DISCUSSION

Figure 1 shows the targets compounds, two series of pyrrolo[2,1-*b*]thiazoles substituted with a carbohydrate derivate and an *p*-halophenyl group. Differences between the series are due to the relative position of the substituent. Series 1 has the carbohydrate moiety as a substituent of position 5, whereas, in series 2, the carbohydrate is at the 2-position.

The reaction of the thiazadiene (**1**) with an α-haloketone led to the obtention of the thiazoles intermediates from which the final heterocycles were synthesized.

Compound **1** was obtained from 3-dimethylaminoacrylonitrile by sulfhydration, followed by a condensation reaction with *N*,*N*-dimethylformamide dimethylacetal [3]. Treatment of compound **1** with 2-chloro-1-(4-chlorophenyl)ethanone or 2-bromo-1-(4-chlorophenyl)ethanone yields compounds **2** or **3** [3].

On the other hand, the reaction of compound **1** with 6-bromo-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hexofuranos-5-ulose (**4**) [17] or 6-bromo-6-deoxy-1,2-*O*-isopropylidene-3-*O*-*p*-methoxybenzyl-α-D-*xylo*-hexofuranos-5-ulose (**5**) [15] leads to the obtention of thiazole derivatives **6** or **7**, respectively (Scheme 1). To simplify reading of the spectroscopic data, compounds were numbered as is indicated in Scheme 1 (Experimental section).

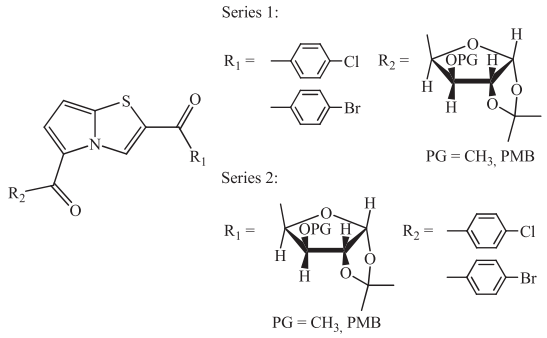
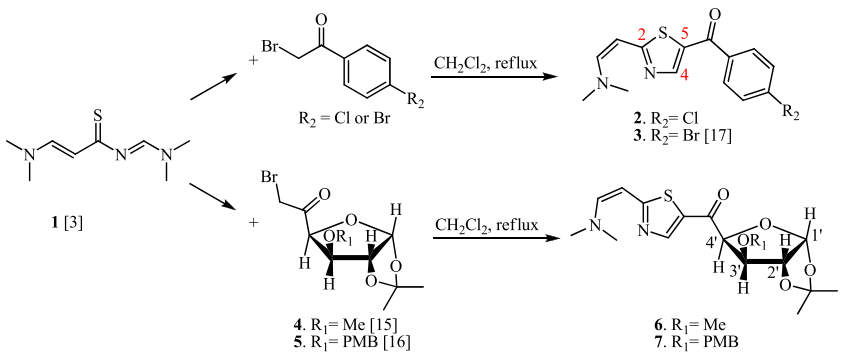


Figure 1. Substituted pyrrolo[2,1-*b*]thiazoles.

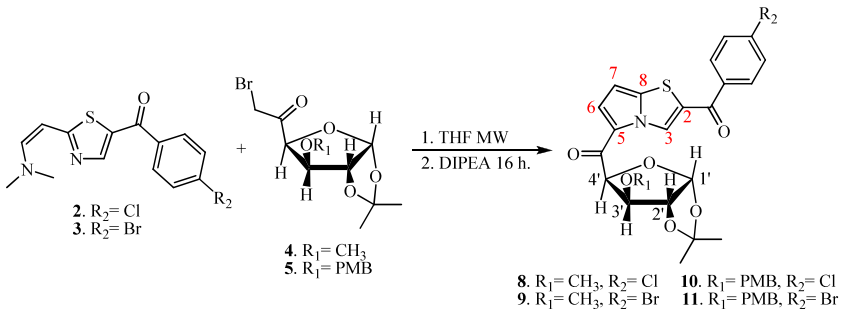
Substituted pyrrolo[2,1-*b*]thiazoles (**8–15**) were obtained from the corresponding thiazoles, with moderate yield (Schemes 2 and 3). It is important to note that the N-alkylation step of the thiazole ring was carried out using microwave irradiation to reduce reactions times [3].

The evaluation of the antiviral inhibitory potential of compounds **8**, **9**, **12**, and **13** against JUNV was preceded by cytotoxicity studies to find out the maximum noncytotoxic concentration for Vero cells after 48 h of treatment. The antiviral activity of the methylated derivates was evaluated by determining the inhibition of JUNV replication in the presence of 10 μ*M* of each compound, determined as a noncytotoxic concentration for all of them (Table 1).

Scheme 1



Scheme 2



Scheme 3

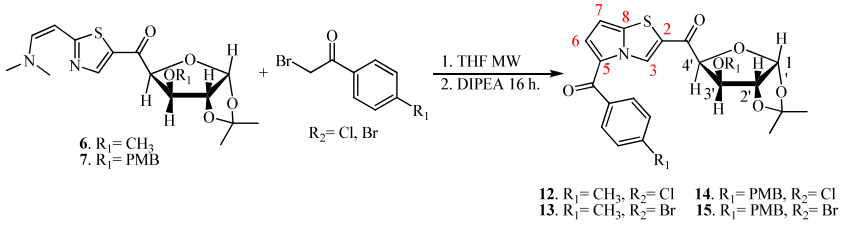


Table 1

Cytotoxicity and antiviral activity of pirrolo[2,1-*b*]thiazoles.

Compound	Cytotoxicity MNCC (μM)[a]	Antiviral activity % inhibition[b]
8	12.5	97.8
9	12.5	98.1
12	>50	75.0
13	>50	Inactive

[a]Maximum noncytotoxic concentration (MNCC): maximum compound concentration at which there were no morphological differences when compared with control cells after 48 h incubation.
[b]Antiviral activity was determined as % inhibition in virus yield after 48 h of infection in cells infected with JUNV in the presence of 10 μM of each compound in comparison with cells infected without compound treatment.

As can be seen in Table 1, most of the compounds were active inhibitors of JUNV infection, because only compound **4** was unable to inhibit the replication of JUNV in Vero cells at the tested concentration, but unfortunately, the most active heterocycles were cytotoxic at lower concentrations than the less active ones.

We are working now in the deprotection of the *p*-metoxybenzyl derivates (**10**, **11**, **14**, and **15**) to further analyze the impact of the enhancement of the hydrophilicity in the antiviral activity of this heterocyclic family.

CONCLUSIONS

In conclusion, the versatile synthetic strategy chosen allowed us to successfully obtain two series of pyrrolo[2,1-*b*]thiazoles differing in the relative position of the substituent, and microwave radiation was used to assist the N-alkylation step. With respect to antiviral activity, compounds **8** and **9** showed the highest percentage of inhibition in virus yield; however, these derivatives were cytotoxic at low concentrations.

EXPERIMENTAL

General methods. Syntheses were carried out using reagents as purchased, without further purification. Solvents were reagent grade and, in most cases, dried and distilled before use according to standard procedures. Analytical TLC was conducted on Silica Gel 60G (Merck, Darmstadt, Germany) on precoated plates, and visualization was made by UV light and ethanol/sulfuric acid (10:1) or cerium molybdate followed by heating. Column-chromatographic separations were performed on Silica Gel (240–400 mesh, Merck). Microwave reactions were carried out using an Anton-Paar Monowave 300 microwave reactor (Graz, Austria). Elemental analysis was performed on an Exeter Analytical CE-440 elemental analyzer (Coventry, UK). Optical rotations were recorded at 20°C on a Perkin Elmer 343 polarimeter (Waltham, MA), and melting points were uncorrected. The nmr spectra were recorded on either a Bruker AC-200 or a Bruker AMX-500 spectrometer (Rheinstetten, Germany). Assignments of the ^{1}H and ^{13}C nmr spectra were confirmed with the aid of two-dimensional techniques (COSY, HSQC, and HMBC). Chemical shifts (δ) are reported in parts per million downfield from TMS or solvent residual peak as internal standard.

5-(p-Chlorobenzoyl)-2-(2-dimethylaminovinyl)thiazole (2). A solution of thiazadiene **1** (86.6 mg, 0.47 mmol) and 2-bromo-1-(4-chlorophenyl)ethanone (131.1 mg, 0.56 mmol) in dichloromethane (10 mL) was heated at 50°C with constant stirring, under argon atmosphere for 4 h, and the reaction was monitored by ccd. Then, the solution is kept at room temperature, and TEA was added (1.5:1 TEA/α-bromoketone molar relation). The reaction mixture was maintained for 4 h at room temperature with stirring. Then, the solvent was evaporated, and the residue was purified by chromatography. Compound **2** was obtained as amorphous solid (118.4 mg, 88%): mp 155–158°C; ^{1}H nmr (deuteriochloroform, 200 MHz): δ 2.97 (s, 6H, CH_3), 5.43 (d, 1H, J = 12.9 Hz, =CH(N$(CH_3)_2$), 7.58 (d, 1H, J = 12.9 Hz, =CH-thiazole); 7.44 (d, 2H, J = 8.5 Hz, aromatic protons), 7.75 (d, 2H, J = 8.5 Hz, aromatic protons), 7.87 (s, 1H, H-4); ^{13}C nmr (deuteriochloroform, 50 MHz): δ 41.2 (CH_3), 90.7 (=CH-thiazole), 128.7, 130.1, 131.0, 138.1 (aromatic carbons), 137.0 (C-5), 148.0 (C-4), 150.9 (=CH(N$(CH_3)_2$), 177.5 (C-2), 185.3 (C=O). *Anal*. Calcd. for $C_{14}H_{13}ClN_2OS$: C, 57.43; H, 4.48. Found: C, 57.68; H, 4.40.

General procedure to synthesize compounds 6 and 7. Compounds **6** and **7** were obtained by reaction of one of the 3-*O*-protected sugar derivate **4** or **5** with the thiazadiene **1** in a molar relation of 1:1.25, respectively, in anhydrous dichloromethane (10 mL) at reflux during 4 h under argon atmosphere. After heating, TEA (molar relation 1.5:1 amine/sugar) was added, and the mixture was stirred at room temperature overnight. The crude products were purified by column chromatography on silica gel using mixtures of cyclohexane/acetone (90:10 to 75:25) as eluents.

5-(1,2-O-Isopropylidene-3-O-methyl-α-D-xylofuranos-5-ulo-5-yl)-2-(2- dimethylaminovinyl)thiazole (6). After purification, compound **6** was obtained as a waxy solid (301.9 mg, 68%): $[\alpha]_D$ − 49.3 (c 0.1, chloroform); ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.34 (s, 3H, C$(CH_3)_2$), 1.49 (s, 3H, C$(CH_3)_2$), 2.93 (s, 6H, N$(CH_3)_2$), 3.28 (s, 3H, OCH_3), 4.14 (d, 1H, $J_{3',4'}$ = 3.5 Hz, H-3′), 4.59 (d, 1H, $J_{2',1'}$ = 3.6 Hz, H-2′), 5.01 (d, 1H, $J_{4',3'}$ = 3.5 Hz, H-4′), 5.38 (d, 1H, J = 12.9 Hz,=CH(N$(CH_3)_2$), 6.11 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1′), 7.53 (d, 1H, J = 12.9 Hz, =CH-thiazole), 8.40 (s, 1H, H-4); ^{13}C nmr (deuteriochloroform, 50 MHz): δ 26.3 (C($CH_3)_2$), 26.9 (C($CH_3)_2$), 40.7 (N$(CH_3)_2$), 58.5 (OCH_3), 81.4 (C-2′), 85.0 (C-4′), 86.2 (C-3′), 90.7 (=CH-thiazole), 105.7 (C-1′), 112.4 (C($CH_3)_2$), 130.7 (C-5), 147.7 (C-4), 150.8 (=CH(N$(CH_3)_2$), 177.2 (C-2), 187.1 (C = O). *Anal*. Calcd. for $C_{16}H_{22}N_2O_5S$: C, 54.22; H, 6.26. Found: C, 54.08; H, 6.40.

5-(1,2-O-Isopropylidene-3-O-p-methoxybenzyl-α-D-xylofuranos-5-ulo-5-yl)-2-(2-dimethylaminovinyl)thiazole (7). After purification, compound **7** was obtained as a waxy solid (361 mg, 64%): $[\alpha]_D$ − 61.3 (c 0.2, chloroform); ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.34 (s, 3H, C$(CH_3)_2$), 1.50 (s, 3H, C$(CH_3)_2$), 2.96 (s, 6H, N$(CH_3)_2$), 3.75 (s, 3H, OCH_3), 4.35 (d, 1H, $J_{3',4'}$ = 3.5 Hz, H-3′), 4.42 (d, 1H, J = 5.8 Hz, methylene proton), 4.58 (m, 2H, H-2′ and methylene proton), 5.06 (d, 1H, $J_{4',3'}$ = 3.5 Hz, H-4′), 5.41 (d, 1H, J = 12.9 Hz, =CH(N$(CH_3)_2$), 6.15 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1′), 6.76 (d, 2H, J = 8.6 Hz, aromatic protons), 7.03 (d, 2H, J = 8.6 Hz, aromatic protons), 7.55 (d, 1H, J = 13.0 Hz, =CH-thiazole), 8.37 (s, 1H, H-4); ^{13}C nmr (deuteriochloroform, 50 MHz): δ 26.4 (C($CH_3)_2$), 26.9 (C($CH_3)_2$), 40.8 (N$(CH_3)_2$), 55.2 (OCH_3), 72.3 (methylene carbon), 82.3 (C-4′), 83.3 (C-3′), 85.1 (C-2′), 90.8 (=CH-thiazole), 105.8 (C-1′), 112.4 (C($CH_3)_2$), 113.7, 129.3, 129.6,159.3 (aromatic carbons), 130.1 (C-5), 147.6 (C-4), 150.7 (=CH(N$(CH_3)_2$), 177.1

(C-2), 187.1 (C═O). *Anal*. Calcd. for $C_{23}H_{28}N_2O_6S$: C, 59.98; H 6.13. Found: C, 60.01; H, 6.25.

General procedure to synthesize compounds 8–11. Compounds **8–11** were obtained by reaction of the 3-*O*-protected sugar derivate **4** [17] or **5** [15] with the corresponding 5-(*p*-chlorobenzoyl)-2-(2-dimethylaminovinyl)thiazole (**2**) or 5-(*p*-bromobenzoyl)-2-(2-dimethylaminovinyl)thiazole [18] (**3**) in a molar relation of (1:1.5) in anhydrous THF (7 mL) under microwave radiation (300 W, 125°C, 150 min). After irradiation, the solution was diluted with 15 mL of anhydrous THF, then diisopropylethylamine was added (molar relation 1.5:1 amine/sugar), and the mixture was stirred at room temperature overnight. The crude products were purified by column chromatography on silica gel using mixtures of cyclohexane/acetone (90:10 to 80:20) as eluents.

2-(p-Chlorobenzoyl)-5-(1,2-O-isopropylidene-3-O-methyl-α-D-xylofuranos-5-ulo-5-yl)pyrrolo[2,1-b]thiazole (8). After purification, compound **8** was obtained as a waxy solid (48.6 mg, 41%): $[\alpha]_D$ − 32.9 (c 1, chloroform); ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.39 (s, 3H, $C(CH_3)_2$), 1.55 (s, 3H, $C(CH_3)_2$), 3.31 (s, 3H, OCH_3), 4.19 (d, 1H, $J_{3',4'}$ = 3.5 Hz, H-3′), 4.66 (d, 1H, $J_{2',1'}$ = 3.6 Hz, H-2′), 5.14 (d, 1H, $J_{4',3'}$ = 3.6 Hz, H-4′), 6.16 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1′), 6.44 (d, 1H, $J_{7,6}$ = 4.4 Hz, H-7), 7.71 (d, 2H, J = 8.5 Hz, aromatic protons), 7.78 (d, 2H, J = 8.3 Hz, aromatic protons), 7.83 (d, 1H, $J_{6,7}$ = 4.4 Hz, H-6), 9.26 (s, 1H, H-3); ^{13}C nmr (deuteriochloroform, 50 MHz): δ 26.3 ($C(\underline{C}H_3)_2$), 27.0 ($C(\underline{C}H_3)_2$), 58.4 (OCH_3), 81.0 (C-2′), 84.1 (C-4′), 86.4 (C-3′), 101.7 (C-7), 105.6 (C-1′), 112.3 ($\underline{C}(CH_3)_2$), 124.6 (C-5), 129.3, 130.2, 135.3, 139.5 (aromatic carbons), 128.1 (C-3), 131.1 (C-6), 133.5 (C-2), 141.8 (C-8), 182.2 (C═O), 186.3 (C═O). *Anal*. Calcd. for $C_{22}H_{20}ClNO_6S$: C, 57.20; H, 4.36. Found: C, 57.23; H, 4.41.

2-(p-Bromobenzoyl)-5-(1,2-O-isopropylidene-3-O-methyl-α-D-xylofuranos-5-ulo-5-yl)pyrrolo[2,1-b]thiazole (9). After purification, compound **9** was obtained as waxy solid (37.4 mg, 31%): $[\alpha]_D$ − 43.3 (c 0.9, chloroform); ^{1}H nmr (deuteriochloroform, 500 MHz): δ 1.39 (s, 3H, $C(CH_3)_2$), 1.56 (s, 3H, $C(CH_3)_2$), 3.32 (s, 3H, OCH_3), 4.20 (d, 1H, $J_{3',2'}$ = 3.6 Hz, H-3′), 4.66 (d, 1H, $J_{2',1'}$ = 3.7 Hz, H-2′), 5.14 (d, 1H, $J_{4',3'}$ = 3.6 Hz, H-4′), 6.16 (d, 1H, $J_{1',2'}$ = 3.7 Hz, H-1′), 6.44 (d, 1H, $J_{7,6}$ = 4.4 Hz, H-7), 7.53 (d, 2H, J = 8.6 Hz, aromatic protons), 7.83 (d, 1H, $J_{6,7}$ = 4.1 Hz, H-6); 7.83 (d, 2H, J = 8.6 Hz, aromatic protons), 9.25 (s, 1H, H-3); ^{13}C nmr (deuteriochloroform, 125 MHz): δ 26.3 ($C(\underline{C}H_3)_2$), 27.0 ($C(\underline{C}H_3)_2$), 58.4 (OCH_3), 81.0 (C-2′), 84.1 (C-4′), 86.4 (C-3′), 101.7 (C-7), 105.6 (C-1′), 112.3 ($\underline{C}(CH_3)_2$), 124.6 (C-5), 128.0, 130.3, 131.3, 135.8 (aromatic carbons), 128.3 (C-3), 131.2 (C-6), 133.4 (C-2), 141.8 (C-8), 182.2 (C═O), 186.3 (C═O). *Anal*. Calcd. for $C_{22}H_{20}BrNO_6S$: C, 52.18; H, 3.98. Found: C, 52.06; H, 4.03.

2-(p-Chlorobenzoyl)-5-(1,2-O-isopropylidene-3-O-p-methoxy benzyl-α-D-xylofuranos-5-ulo-5-yl)pyrrolo[2,1-b]thiazole (10). After purification, compound **10** was obtained as a waxy solid (48.6 mg, 41%): $[\alpha]_D$ − 45.0 (c 0.7, chloroform); ^{1}H nmr (deuteriochloroform, 500 MHz): δ 1.38 (s, 3H, $C(CH_3)_2$), 1.55 (s, 3H, $C(CH_3)_2$), 3.74 (s, 3H, OCH_3), 4.30 (d, 1H, J = 11.9 Hz, methylene proton), 4.37 (d, 1H, $J_{3',4'}$ = 3.7 Hz, H-3′), 4.51 (d, 1H, J = 11.9 Hz, methylene proton), 4.63 (d, 1H, $J_{2',1'}$ = 3.7 Hz, H-2′), 5.19 (d, 1H, $J_{4',3'}$ = 3.6 Hz, H-4′), 6.19 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1′), 6.39 (d, 1H, $J_{7,6}$ = 4.4 Hz, H-7), 6.63 (d, 2H, J = 8.6 Hz, aromatic protons), 6.89 (d, 2H, J = 8.5 Hz, aromatic protons), 7.55 (d, 2H, J = 8.5 Hz, aromatic protons), 7.63 (d, 1H, $J_{6,7}$ = 4.4 Hz, H-6), 7.85 (d, 2H, J = 8.5 Hz, aromatic protons), 9.20 (s, 1H, H-3); ^{13}C nmr (deuteriochloroform, 125 MHz): δ 26.4 ($C(\underline{C}H_3)_2$), 27.0 ($C(\underline{C}H_3)_2$), 55.2 (OCH_3), 72.2 (methylene carbon), 82.2 (C-4′), 83.6 (C-3′), 83.9 (C-2′), 101.6 (C-7), 105.8 (C-1′), 112.4 ($\underline{C}(CH_3)_2$), 113.5, 128.9, 129.1, 129.3, 130.2, 135.3, 139.6 (aromatic carbons), 124.4 (C-5), 127.4 (C-3), 130.9 (C-6), 133.4 (C-2), 141.3 (C-8), 182.2 (C═O), 186.3 (C═O). *Anal*. Calcd. for $C_{29}H_{26}ClNO_7S$: C, 61.32; H 4.61. Found: C, 61.72; H, 4.37.

2-(p-Bromobenzoyl)-5-(1,2-O-isopropylidene-3-O-p-methoxy benzyl-α-D-xylofuranos-5-ulo-5-yl)pyrrolo[2,1-b]thiazole (11). After purification, compound **11** was obtained as a waxy solid (37.4 mg, 31%): $[\alpha]_D$ − 28.1 (c 0.5, chloroform); ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.36 (s, 3H, $C(CH_3)_2$), 1.54 (s, 3H, $C(CH_3)_2$), 3.73 (s, 3H, OCH_3), 4.28 (d, 1H, J = 11.9 Hz, methylene proton), 4.35 (d, 1H, $J_{3',4'}$ = 3.4 Hz, H-3′), 4.50 (d, 1H, J = 11.9 Hz, methylene proton), 4.62 (d, 1H, $J_{2',1'}$ = 3.4 Hz, H-2′), 5.17 (d, 1H, $J_{4',3'}$ = 3.1 Hz, H-4′), 6.17 (d, 1H, $J_{1',2'}$ = 3.3 Hz, H-1′), 6.36 (d, 1H, $J_{7,6}$ = 4.3 Hz, H-7), 6.61 (d, 2H, J = 8.3 Hz, aromatic protons), 6.87 (d, 2H, J = 8.6 Hz, aromatic protons), 7.62 (d, 1H, $J_{6,7}$ = 4.3 Hz, H-6), 7.69 (d, 2H, J = 8.6 Hz, aromatic protons), 7.76 (d, 2H, J = 8.7 Hz, aromatic protons), 9.18 (s, 1H, H-3); ^{13}C nmr (deuteriochloroform, 50 MHz): δ 26.4 ($C(\underline{C}H_3)_2$), 27.0 ($C(\underline{C}H_3)_2$), 55.2 (OCH_3), 72.2 (methylene carbon), 82.2 (C-4′), 83.6 (C-3′), 83.8 (C-2′), 101.6 (C-7), 105.8 (C-1′), 112.4 ($\underline{C}(CH_3)_2$), 113.5, 128.1, 128.9, 129.1, 130.3, 132.2, 135.7, 159.2 (aromatic carbons), 124.4 (C-5), 127.4 (C-3), 130.9 (C-6), 133.4 (C-2), 141.3 (C-8), 182.2 (C═O), 186.4 (C═O). *Anal*. Calcd. for $C_{29}H_{26}BrNO_7S$: C, 56.87; H, 4.28. Found: C, 56.28; H, 4.15.

General procedure to synthesize compounds 12–15. Compounds **12–15** were obtained by reaction of the 2-(dimethylaminovinyl)thiazole carbohydrate derivative **6** or **7** with the corresponding 2-bromo-1-(4-chlorophenyl)ethanone or 2-bromo-1-(4-bromophenyl)ethanone a molar relation of (1:1.5) in anhydrous THF (7 mL) under microwave radiation (300 W, 105°C, 90 min). Then, the solution was diluted with 15 mL of anhydrous THF, diisopropylethylamine was added (molar relation 1.5:1 amine/sugar), and the mixture was stirred at room temperature overnight. The crude products were purified by column chromatography on silica gel using mixtures of cyclohexane/acetone (90:10 to 80:20) as eluents.

5-(p-Chlorobenzoyl)-2-(1,2-O-isopropylidene-3-O-methyl-α-D-xylofuranos-5-ulo-5-yl)pyrrolo[2,1-b]thiazole (12). After purification, compound 1**2** was obtained as a waxy solid (40.3 mg, 38%): $[\alpha]_D$ − 66.9 (c 0.7, chloroform); ^{1}H nmr (deuteriochloroform, 500 MHz): δ 1.39 (s, 3H, $C(CH_3)_2$), 1.55 (s, 3H, $C(CH_3)_2$), 3.35 (s, 3H, OCH_3), 4.24 (d, 1H, $J_{3',4'}$ = 3.6 Hz, H-3′), 4.68 (d, 1H, $J_{2',1'}$ = 3.6 Hz, H-2′), 5.13 (d, 1H, $J_{4',3'}$ = 3.6 Hz, H-4′), 6.29 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1′), 6.41 (d, 1H, $J_{7,6}$ = 4.3 Hz, H-7), 7.25 (d, 1H, $J_{6,7}$ = 4.3 Hz, H-6), 7.49 (d, 2H, J = 7.8 Hz, aromatic protons), 7.80 (d, 2H, J = 7.8 Hz, aromatic protons), 9.76 (s, 1H, H-3); ^{13}C nmr (deuteriochloroform, 125 MHz): δ 26.3 ($C(\underline{C}H_3)_2$), 27.0 ($C(\underline{C}H_3)_2$), 58.5 (OCH_3), 81.1 (C-2′), 85.5 (C-4′), 86.5 (C-3′), 101.2 (C-7), 106.0 (C-1′), 112.7 ($\underline{C}(CH_3)_2$), 124.7 (C-5), 128.7, 130.2, 137.3, 137.8 (aromatic carbons), 128.8 (C-3), 131.9 (C-6), 132.5 (C-2), 141.9 (C-8), 181.4 (C═O), 189.6 (C═O). *Anal*. Calcd. for $C_{22}H_{20}ClNO_6S$: C, 57.20; H, 4.36. Found: C, 57.10; H, 4.53.

5-(p-Bromobenzoyl)-2-(1,2-O-isopropylidene-3-O-methyl-α-D-xylofuranos-5-ulo-5-yl)pyrrolo[2,1-b]thiazole (13). After purification, compound **13** was obtained as waxy solid (34 mg, 27%): $[\alpha]_D$ − 54.5 (c 0.9, chloroform); ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.38 (s, 3H, $C(CH_3)_2$), 1.54 (s, 3H, $C(CH_3)_2$), 3.33 (s, 3H, OCH_3), 4.22 (d, 1H, $J_{3',4'}$ = 3.6 Hz, H-3′), 4.67 (d, 1H, $J_{2',1'}$ = 3.6 Hz, H-2′), 5.11 (d, 1H,

$J_{4',3'}$ = 3.6 Hz, H-4′), 6.27 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1′), 6.40 (d, 1H, $J_{7,6}$ = 4.3 Hz, H-7), 7.24 (d, 1H, $J_{6,7}$ = 4.3 Hz, H-6), 7.63 (d, 2H, J = 8.7 Hz, aromatic protons), 7.71 (d, 2H, J = 8.8 Hz, aromatic protons), 9.74 (s, 1H, H-3); ^{13}C nmr (deuteriochloroform, 50 MHz): δ 26.3 (C($\underline{C}H_3)_2$), 26.9 (C($\underline{C}H_3)_2$), 58.5 (OCH_3), 81.0 (C-2′), 85.5 (C-4′), 86.5 (C-3′), 101.3 (C-7), 106.0 (C-1′), 112.7 ($\underline{C}(CH_3)_2$), 124.6 (C-5), 128.6, 130.3, 131.7, 137.8 (aromatic carbons), 128.8 (C-3), 131.9 (C-6), 132.2 (C-2), 141.9 (C-8), 181.5 (C═O), 189.6 (C═O). *Anal*. Calcd. for $C_{22}H_{20}BrNO_6S$: C, 52.18; H, 3.98. Found: C, 52.26; H, 3.87.

5-(p-Chlorobenzoyl)-2-(1,2-O-isopropylidene-3-O-p-metoxy benzyl-α-D-xylofuranos-5-ulo-5-yl)pyrrolo[2,1-b]thiazole (14). After purification, compound **14** was obtained as waxy solid (67.6 mg, 34%): $[\alpha]_D$ − 46.9 (c 1.2, chloroform); ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.37 (s, 3H, C($CH_3)_2$), 1.53 (s, 3H, C($CH_3)_2$), 3.61 (s, 3H, OCH_3), , 4.32 (d, 1H, J = 11.8 Hz, methylene proton), 4.42 (d, 1H, $J_{3',4'}$ = 3.6 Hz, H-3′), 4.53 (d, 1H, J = 11.8 Hz, methylene proton), 4.66 (d, 1H, $J_{2',1'}$ = 3.5 Hz, H-2′), 5.16 (d, 1H, $J_{4',3'}$ = 3.5 Hz, H-4′), 6.27 (d, 1H, $J_{1',2'}$ = 3.4 Hz, H-1′), 6.40 (d, 1H, $J_{7,6}$ = 4.3 Hz, H-7), 6.63 (d, 2H, J = 8.5 Hz, aromatic protons), 7.00 (d, 2H, J = 8.6 Hz, aromatic protons), 7.23 (d, 1H, $J_{6,7}$ = 4.3 Hz, H-6), 7.48 (d, 2H, J = 8.4 Hz, aromatic protons), 7.79 (d, 2H, J = 8.4 Hz, aromatic protons), 9.48 (s, 1H, H-3); ^{13}C nmr (deuteriochloroform, 50 MHz): δ 26.3 (C($\underline{C}H_3)_2$), 27.0 (C($\underline{C}H_3)_2$), 55.1 (OCH_3), 72.0 (methylene carbon), 82.0 (C-3′), 82.9 (C-2′), 85.2 (C-4′), 101.2 (C-7), 106.0 (C-1′), 112.7 ($\underline{C}(CH_3)_2$), 124.7 (C-5), 113.5, 128.4, 128.7, 129.6, 130.1, 137.3, 137.8, 159.3 (aromatic carbons), 128.5 (C-3), 131.1 (C-6), 132.4 (C-2), 141.7 (C-8), 181.3 (C═O), 188.8 (C═O). *Anal*. Calcd. for $C_{29}H_{26}ClNO_7S$: C, 61.32; H 4.61. Found: C, 60.56; H, 4.48.

5-(p-Bromobenzoyl)-2-(1,2-O-isopropylidene-3-O-p-metoxy benzyl-α-D-xylofuranos-5-ulo-5-yl)pyrrolo[2,1-b]thiazole (15). After purification, compound **15** was obtained as waxy solid (47.6 mg, 37%): $[\alpha]_D$ − 35.6 (c 1.1, chloroform); ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.37 (s, 3H, C($CH_3)_2$), 1.53 (s, 3H, C($CH_3)_2$), 3.64 (s, 3H, OCH_3), , 4.31 (d, 1H, J = 11.8 Hz, methylene proton), 4.42 (d, 1H, $J_{3',4'}$ = 3.7 Hz, H-3′), 4.53 (d, 1H, J = 11.8 Hz, methylene proton), 4.66 (d, 1H, $J_{2',1'}$ = 3.6 Hz, H-2′), 5.17 (d, 1H, $J_{4',3'}$ = 3.7 Hz, H-4′), 6.27 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1′), 6.41 (d, 1H, $J_{7,6}$ = 4.3 Hz, H-7), 6.62 (d, 2H, J = 8.7 Hz, aromatic protons), 7.00 (d, 2H, J = 8.7 Hz, aromatic protons), 7.23 (d, 1H, $J_{6,7}$ = 4.4 Hz, H-6), 7.63 (d, 2H, J = 8.7 Hz, aromatic protons), 7.72 (d, 2H, J = 8.7 Hz, aromatic protons), 9.46 (s, 1H, H-3); ^{13}C nmr (deuteriochloroform, 50 MHz): δ 26.3 (C($\underline{C}H_3)_2$), 27.0 (C($\underline{C}H_3)_2$), 55.1 (OCH_3), 71.9 (methylene carbon), 82.0 (C-3′), 83.0 (C-2′), 85.1 (C-4′), 101.2 (C-7), 106.0 (C-1′), 112.7 ($\underline{C}(CH_3)_2$), 113.5, 126.3, 128.4, 129.5, 130.3, 131.6, 137.7, 159.3 (aromatic carbons), 124.5 (C-5), 128.6 (C-3), 131.0 (C-6), 132.4 (C-2), 141.7 (C-8), 181.4 (C═O), 188.8 (C═O). *Anal*. Calcd. for $C_{29}H_{26}BrNO_7S$: C, 56.87; H, 4.28. Found: C, 56.37; H, 4.27.

Biological methods. ***Cells and virus.*** Vero (African green monkey kidney) cells were grown in Eagle's minimum essential medium (MEM) supplemented with 5% inactivated calf serum and 50 μg/mL gentamycin. For maintenance medium, the serum concentration was reduced to 1.5%. The IV4454 strain of JUNV was used. Virus stocks were prepared and titrated by plaque formation in Vero cells.

Cytotoxicity assay. The cytotoxic activity of the compounds was determined by incubating confluent cultures of Vero cells grown in 96-well plates with serial dilutions of the compounds, three wells for each concentration, during 48 h at 37°C. Cells were observed daily for the appearance of morphological alterations, and the maximum noncytotoxic concentration was determined as the highest concentration at which there were no morphological differences when compared with control cells.

Antiviral assay. The antiviral activity was determined by a virus yield inhibition assay. Vero cells grown in 24-well plates were infected at a multiplicity of infection of 0.1 plaque-forming unit per cell of JUNV. After 1 h adsorption at 37°C, cells were washed and reefed with maintenance medium containing or not 10 μM of each compound (two wells per concentration). After 48 h of incubation at 37°C, supernatant cultures were harvested, and extracellular virus yields were determined by a plaque assay. The antiviral activity was expressed as the percentage of inhibition in virus yield in compound-treated cultures in comparison with untreated ones.

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