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Synthesis and biological activity of novel thiazolidin-4-ones with a carbohydrate moiety

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ABSTRACT

Some novel 2-aryl-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl] thiazolidin-4-ones were synthesized by the three-component condensation of an amino sugar **1**, an aromatic aldehyde **2**, and mercaptoacetic acid **3** in the presence of DCC and DMAP at room temperature. Two diastereoisomers **4** and **5** were afforded as the main products in totally isolated yields of 25.4–70%. The reaction was carried out with almost no observed stereoselectivity except in the case of **2c**, which showed a moderate stereoselectivity. The structures of the new compounds were determined by NMR spectroscopy and mass spectrometry (MS), and the configuration of the newly generated chiral carbon (C-2) in the thiazolidin-4-one ring was tentatively assigned based on the X-ray crystallographic structure of **5d** and the comparison of their corresponding NMR signals. The antitumor (human cervical cancer cells) activity and the inhibition against the glycosidases (α-glucosidase, β-glucosidase, α-amylase) have been evaluated for the new compounds, some of which exhibited antitumor activity.

1. Introduction

Thiazolidinones are of considerable importance as pharmacophoric groups due to their known biological activities that include bactericidal, pesticidal, anticonvulsant, antiinflammatory, antithyroidal activities, among others.[1,2] For instance, some 2,3-diaryl-1,3-thiazolidin-4-ones have been reported to show strong and selective anti-HIV activities.[3–8] Therefore, studies of the synthesis and pharmacology of thiazolidinone derivatives have attracted more interest in recent years.[9] However, such compounds are generally connected with lipophilic groups as the substituents, and to the best of our knowledge, only a few reports on the synthesis and pharmacology of the thiazolidinones containing hydrophilic groups such as amino acids[10] and sugar moieties[11,12] have been published. We turned our interest to the synthesis of such thiazolidinone derivatives for investigating their biological activities and developing structure–activity relationships.

Generally, thiazolidin-4-one derivatives can be synthesized by the three-component condensation of a primary amine, an aldehyde, and mercaptoacetic acid as shown in Figure 1.[2] The reaction is usually performed in refluxing toluene for 2–48 hours, but the yields are generally not satisfactory.[3,8,12] The applications of some new synthetic methods, such as microwave-assisted synthesis,[13,14] and reagents, such as Hünig's base,[10] ionic liquids,[15] and KSF clay,[16] have been recently explored for improving the synthesis of the thiazolidin-4-one derivatives. We also reported a simple and convenient microwave-assisted synthesis of 2-aryl-3-naphthyl-1,3-thiazolidin-4-ones.[17] Herein, we would like to disclose a more convenient method for synthesizing novel thiazolidin-4-one derivatives bearing a sugar moiety at room temperature with a short

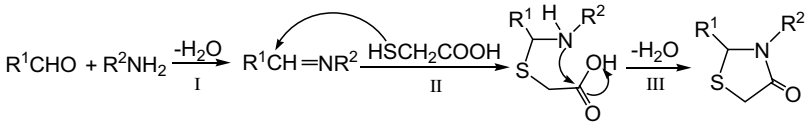

Figure 1. A general thiazolidin-4-one synthesis.

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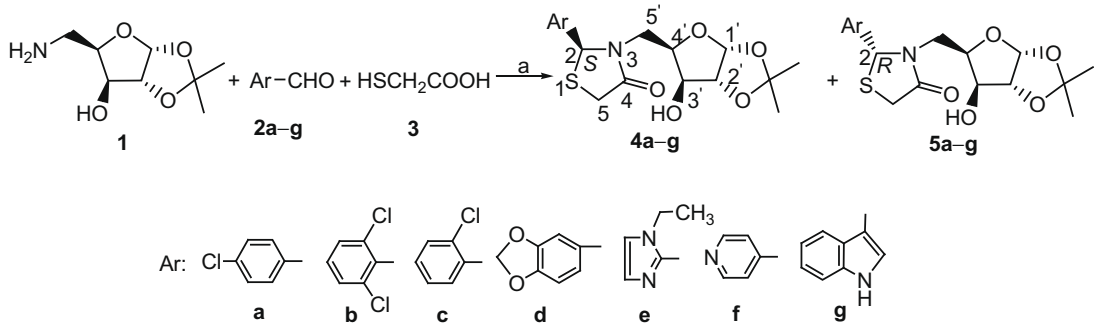

Scheme 1. Reagents and conditions: (a) MeOH, DMAP, DCC, rt, 1 h.

reaction time. The antitumor and glycosidase inhibitory activities of the new compounds were examined.

2. Results and discussion

2.1. The synthesis of thiazolidin-4-ones bearing a sugar moiety

The requisite 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**1**) was prepared according to the literature procedure.[18] The one-pot, three-component synthesis was performed (Scheme 1) as follows: First, the condensation of amino sugar **1** and the aromatic aldehyde **2** was carried out in dry methanol at room temperature with stirring for 15–30 min until the starting materials disappeared on TLC. Then to the reaction mixture 2 equivalents of mercaptoacetic acid **3** were added, followed by DMAP (0.2 equivalents) and DCC (2 equivalents) with stirring for 20 min. Finally, the mixture was stirred for another 20 min to complete the reaction. It should be mentioned that the reaction yield has not been observed to improve by prolonging the reaction time. After workup and purification by silica gel column chromatography, the diastereoisomeric products **4** (the less polar component) and **5** (the more polar component) were obtained, respectively,

Table 1
The synthesis of thiazolidin-4-ones **4** and **5**

Entry	Ar	Yield[a] (%)			
		Total	**4**	**5**	**4**:**5**
1	**a**	70.0	39.4	30.6	1.29
2	**b**	41.4	18.4	23.0	0.8
3	**c**	62.9	49.6	13.3	3.73
4	**d**	59.5	30.3	29.2	1.03
5	**e**	59.1	28.7	30.4	0.94
6	**f**	64.5	31.0	33.5	1.08
7	**g**	25.4	14.6	10.8	1.35

[a] Isolated yield.

Table 2
The effect of temperature on the synthesis of thiazolidin-4-ones **4d** and **5d**

Entry	Temperature (°C)	Total yield (%)
1	rt	59.2
2	40	54.2
3	50	46.6
4	Reflux	48.6

in overall yields of 25.4–70% and the results are listed in (Table 1). It was found that the reaction proceeded with almost no stereoselectivity, and only in the case of 2-chlorobenzaldehyde (**2c**), a moderate stereoselectivity (**4c**:**5c** = 3.73) was observed (Table 1, entry 3).

The reaction was remarkably influenced by the reaction temperature as shown in Table 2. Taking the piperonal derivatives **4d** and **5d** as examples, when the reaction temperature was increased from room temperature to 50 °C, the total yield decreased from 59.2% to 46.6%. But in a refluxing methanol solution, the reaction yield increased slightly to 48.6%. Moreover, when the reaction was performed at 100 °C in a sealed tube, a small amount of the products were obtained, probably because of the decomposition of the newly generated products.

2.2. The structure of the compounds 4 and 5

The structures of the products **4** and **5** were determined by the analyses of their spectral data including ^{1}H NMR, ^{13}C NMR, and MS. The structure of **5d** was determined by X-ray crystallography (Fig. 2). From the perspective view of **5d**, the configuration of C-2 is confirmed as *R*. Accordingly, its diastereomer **4d** should be of the *S* configuration. Furthermore, each diastereoisomers of **4** and **5** exhibited similar NMR signals in H-2 and C-2 as shown in Table 3, that is, H-2 of the less polar **4** was in more downfield than that of the more polar **5**. In contrast, C-2 of **4** appeared more upfield in comparison to that of **5**. According to the X-ray structure of **5d**

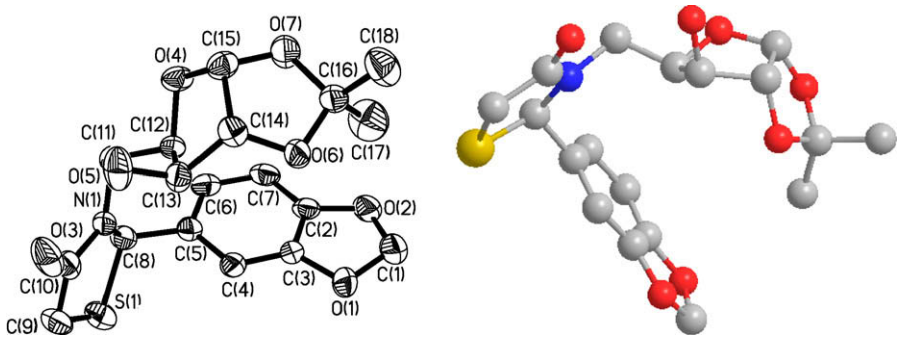

Figure 2. Perspective view of compound **13d**.

Table 3
chemicals shifts of H-2 ($\delta_{H\text{-}2}$) and C-2 ($\delta_{C\text{-}2}$)

Ar	$\delta_{H\text{-}2}$ (ppm)		$\delta_{C\text{-}2}$ (ppm)	
	4(*S*)	**5**(*R*)	**4**(*S*)	**5**(*R*)
a	5.67	5.60	64.13	66.71
b	5.88	5.77	59.73	61.41
c	6.12	6.01	61.33	66.70
d	5.61	5.56	64.90	67.44
e	5.91	5.90	60.77	60.78
f	5.68	5.61	63.22	65.57
g	6.09	5.99	59.09	61.54

Table 4
The cytotoxicity of the compounds **4** and **5** against human cervical cancer cells

Compounds	Inhibition % (in vitro at 100 μM)
4a	17.6
4b	–[a]
4c	31.8
4d	28.0
4e	–
4f	–
4g	20.5
5a	–
5b	20.2
5c	11.4
5d	15.7
5e	–
5f	–
5g	9.9

[a] No inhibition.

and the consistencies of their spectral data (Table 3) and their polarities, the configurations of C-2 in **4** and **5** could be tentatively assigned as *S* and *R*, respectively.

2.3. Biological activities

Glycosidase inhibition and antitumor activities were preliminarily evaluated with all the compounds **4** and **5**. The cytotoxicity of the compounds against Hela cell lines (human cervical cancer cells) was examined by the modified Mosmann's protocol,[19] and the results are shown in Table 4. Some compounds, such as **4c**, **4d**, **4g,** and **5b**, showed weak cytotoxicity at 100 μM. The glycosidase inhibitory activities were measured on hydrolytic reactions of α-amylase, α-glucosidase, and β-glucosidase by comparison with acarbose, respectively, but none of the compounds had any inhibitory activity.

In conclusion, we have synthesized a series of novel thiazolidin-4-one derivatives bearing sugar moieties by the one-pot, three-component condensation of an amino sugar, an aromatic aldehyde, and mercaptoacetic acid at room temperature, providing a convenient method for constructing such thiazolidin-4-one derivatives under very mild conditions. The configurations of the diastereomers were determined by NMR spectroscopy and X-ray crystallographic structural analyses. The preliminary biological evaluation of compounds **4** and **5** showed weak antitumor activities, but no inhibition of glycosidases. Further syntheses and biological studies of new thiazolidin-4-ones containing sugar moieties are underway in this laboratory.

3. Experimental

3.1. General methods

Melting points were measured on an SGW® X-4 micro melting point apparatus and are uncorrected. Optical rotations were determined on an SGW®-1 automatic polarimeter. ^{1}H NMR, ^{13}C NMR spectra were measured on a RT-NMR Bruker AVANCE 400 NMR spectrometer using tetramethylsilane (Me_4Si) as the internal standard. High-resolution mass spectra (HRMS) were carried out on a FTICR-MS (Ionspec 7.0T) mass spectrometer in the electrospray-ionization (ESI) mode. X-ray crystallographic measurements were made on a Bruker SMART CCD diffractometer. The optical densities for examining the activities of glycosidase inhibition and antitumor were measured on a TU-1901 UV–vis spectrophotometer and a Bio-Rad Model 3550 microplate spectrophotometer, respectively. Thin-layer chromatography (TLC) was performed on precoated plates (Qingdao GF_{254}) with detection by UV light or with phosphomolybdic acid in EtOH–H_2O followed by heating. Column chromatography was performed using SiO_2 (Qingdao 300–400 mesh).

3.2. General procedure for the synthesis of thiazolidin-4-ones

The partially protected amino sugar **1** (0.189 g, 1 mmol) was dissolved in 3 mL anhyd MeOH. The aromatic aldehyde **2** (1 mmol) was then added to the solution, and the mixture was stirred in room temperature for 15–30 min. Mercaptoacetic acid **3** (0.14 ml, 2 mmol) was then added. After continued stirring for 20 min at rt, DMAP (0.2 mmol, 24.4 mg) and DCC (2 mmol, 412 mg) were added. After a further 20 min of stirring, DCU was removed by filtration, and the mixture was neutralized with solid KCO_3. The solvent was evaporated under reduced pressure to get a crude product that was purified using flash column chromatography (4:1:1 CH_2Cl_2–Et_2O–cyclohexane) to get two diastereomers, **4** and **5**.

3.2.1. (2*S*)-2-(4-Chlorophenyl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (4a)

White solid; mp 154–156 °C; $[\alpha]_D$ −95.8; (*c* 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.32 (3H, s, CH_3); 1.52 (3H, s, CH_3); 5.87 (1H, d, J = 3.5 Hz, H-1′); 4.59 (1H, d, J = 3.6 Hz, H-2′); 4.31 (1H, d, J = 2.8 Hz, H-3′); 4.13–4.15 (1H, m, H-4′); 2.91 (1H, dd, J_1 = 14.4 Hz, J_2 = 4.0 Hz, H-5′); 3.83–3.90 (2H, m, H-5′, H-5); 3.73 (1H, d, J = 16.0 Hz, H-5); 5.67 (1H, s, H-2); 7.21–7.40 (4H, m, Ar–H); 4.15 (1H, s, OH). δ_C (100 MHz, $CDCl_3$): 26.31, 27.18, 32.83, 40.72, 64.13 (C-2), 74.40, 77.84, 85.23, 105.13, 112.03, 128.63, 130.01, 135.89, 137.67, 173.41. HRESIMS: calcd for $C_{17}H_{20}ClNO_5S$-Na ($[M+Na]^+$), 408.0643, found: 408.0649.

3.2.2. (2*R*)-2-(4-Chlorophenyl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (5a)

White solid; mp 147–149 °C; $[\alpha]_D$ −17.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.19 (3H, s, CH_3); 1.24 (3H, s, CH_3); 5.77 (1H, d, J = 3.6 Hz, H-1′); 4.47 (1H, d, J = 3.6 Hz, H-2′); 4.68 (1H, d, J = 2.2 Hz, H-3′); 3.77–3.93 (4H, m, OH, H-5′, H-5); 3.16–3.23 (2H, m, H-4′, H-5′); 5.60 (1H, s, H-2); 7.26–7.39 (4H, m, Ar–H). δ_C (100 MHz, $CDCl_3$): 26.68, 26.94, 33.47, 43.20, 66.71 (C-2), 74.02, 77.72, 84.93, 105.00, 112.12, 128.63, 130.01, 135.89, 137.67, 173.84. HRESIMS: calcd for $C_{17}H_{20}ClNO_5SNa$ ($[M+Na]^+$), 408.0643, found: 408.0651.

3.2.3. (2*S*)-2-(2,6-Dichlorophenyl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (4b)

White solid; mp 59–61 °C; $[\alpha]_D$ −49.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.32 (3H, s, CH_3); 1.51 (3H, s, CH_3); 6.73 (1H, d, J = 2.4 Hz, H-1′); 4.49 (1H, d, J = 2.6 Hz, H-2′); 4.60 (1H, d, J = 3.4 Hz, H-3′); 4.21 (1H, m, H-4′); 2.78 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.00 Hz, H-5′); 3.86–3.92 (2 H, m, H-5′, H-5); 3.79 (1H, d, J = 15.6 Hz, H-5); 5.88 (1H, d, J = 3.4 Hz, H-2); 7.24–7.39 (3H, m, Ar–H); 4.08 (1H, s, OH). δ_C (100 MHz, $CDCl_3$): 26.55, 27.32; 34.36, 40.50, 59.73 (C-2), 74.14, 77.73, 85.10, 105.27, 112.26; 128.63,

130.01, 135.89, 136.48, 173.95. HRESIMS: calcd for $C_{17}H_{19}Cl_2NO_5S$-Na ([M+Na]$^+$), 442.0254, found: 442.0258.

3.2.4. (2*R*)-2-(2,6-Dichlorophenyl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (5b)

White solid; mp 127–129 °C; $[\alpha]_D$ −30.8 (*c* 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.15 (3H, s, CH_3); 1.24 (3H, s, CH_3); 6.75 (1H, d, *J* = 2.6 Hz, H-1′); 4.82 (1H, d, *J* = 2.6 Hz, H-2′); 4.51 (1H, d, *J* = 3.4 Hz, H-3′); 3.37–3.40 (m, 1H, H-4′); 3.24 (1H, dd, J_1 = 14.4 Hz, J_2 = 4.0 Hz, H-5′); 3.80–3.97 (3H, m, H-5′, H-5); 5.78 (1H, d, *J* = 3.4 Hz, H-2); 7.23–7.40 (3H, m, Ar–H); 4.08 (1H, s, OH). δ_C (100 MHz, $CDCl_3$): 26.65, 27.15, 34.89, 43.57, 61.41 (C-2), 74.65, 77.75, 85.17, 104.83, 111.91, 129.69, 131.15, 131.29, 132.66, 136.31, 136.44, 174.34. HRESIMS: calcd for $C_{17}H_{19}Cl_2NO_5S$-Na ([M+Na]$^+$), 442.0254, found: 442.0252.

3.2.5. (2*S*)-2-(2-Chlorophenyl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (4c)

White solid; mp 185–187 °C; $[\alpha]_D$ −129.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, CCl_3); 1.32 (3H, s, CH_3); 1.53 (3H, s, CH_3); 5.88 (1H, d, *J* = 3.5 Hz, H-1′); 4.61 (1H, d, *J* = 3.4 Hz, H-2′); 4.49 (1H, d, *J* = 2.2 Hz, H-3′); 4.20–4.21 (1H, m, H-4′); 2.98 (1H, dd, J_1 = 14.3 Hz, J_2 = 3.60 Hz, H-5′); 3.93–4.0 (1H, q, *J* = 14.3 Hz, H-5′); 3.67 (1H, d, *J* = 15.9 Hz, H-5); 3.78 (1H, d, *J* = 15.9, H-5); 6.12 (1H, s, H-2); 7.13–7.45 (4H, m, Ar–H); 4.09 (1H, s, OH). δ_C (100 MHz, $CDCl_3$): 26.41, 27.24, 32.29, 41.08, 61.33 (C-2), 74.23, 77.93, 85.21, 105.17, 112.14, 129.69, 131.15, 131.29, 136.31, 136.44, 174.35. HRESIMS: calcd for $C_{17}H_{20}ClNO_5S$ ([M]$^+$), 385.0751, found: 385.0747.

3.2.6. (2*R*)-2-(2-Chlorophenyl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (5c)

White solid; mp 52–54 °C; $[\alpha]_D$ +16.2 (*c* 2.07, $CHCl_3$); δ_H (400 MHz, $CDCl_3$); 1.17 (3H, s, CH_3); 1.23 (3H, s, CH_3); 5.78 (1H, d, *J* = 3.4 Hz, H-1′); 4.49 (1H, d, *J* = 3.4 Hz, H-2′); 4.66 (1H, s, H-3′); 4.11–4.14 (1H, m, H-4′); 3.68–3.83 (2H, m, H-5′, H-5); 3.89 (1H, d, *J* = 16.0 Hz, H-5); 3.34 (1H, d, *J* = 12.3 Hz, H-5'); 6.01 (1H, s, H-2); 7.26–7.42 (4H, m, Ar-H); 3.99 (1H, s, OH). δ_C (100 MHz, $CDCl_3$): 26.64, 27.08, 34.34, 43.44, 66.70 (C-2), 74.40, 77.65, 85.13, 104.93, 111.98, 128.00, 131.07, 133.82, 174.36. HRESIMS: calcd for $C_{17}H_{20}ClNO_5SNa$ ([M+Na] $^+$), 408.0649, found: 408.0654.

3.2.7. (2*S*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (4d)

White solid; mp 70–72 °C; $[\alpha]_D$ +98.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$); 1.32 (3H, s, CH_3); 1.52 (3H, s, CH_3); 5.86 (1H, d, *J* = 3.5 Hz, H-1′); 4.60 (1H, d, *J* = 3.4 Hz, H-2′); 4.50 (1H, d, *J* = 2.5 Hz, H-3′); 4.11–4.13 (1H, m, H-4′); 2.98 (1 H, dd, J_1 = 14.2 Hz, J_2 = 3.60 Hz, H-5′); 3.83–3.87 (1 H, m, H-5′); 3.72 (1H, d, *J* = 16.0 Hz, H-5); 3.81 (1H, d, *J* = 14.2 Hz, H-5); 5.61 (1H, s, H-2); 6.74–6.80 (3H, m, Ar–H); 4.03 (1H, s, OH); 6.00 (2H, s, O–CH_2–O). δ_C (100 MHz, $CDCl_3$): 26.33, 27.21, 32.93, 40.40, 64.90 (C-2), 74.27, 77.72, 85.20, 102.03, 105.14, 107.02, 108.82, 112.00; 121.66, 132.52, 149.21, 173.39. HRESIMS: calcd for $C_{18}H_{22}NO_7S$ ([M+H]$^+$), 396.1110, found: 396.1106.

3.2.8. (2*R*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (5d)

White solid; mp 138–140 °C; $[\alpha]_D$ −8.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$); 1.24 (3H, s, CH_3); 1.25 (3H, s, CH_3); 5.78 (1H, d, *J* = 3.5 Hz, H-1′); 4.50 (1H, d, *J* = 3.4 Hz, H-2′); 4.81 (1H, s, H-3′); 3.37 (1H, m, H-4′); 3.18 (1H, dd, J_1 = 14.0 Hz, J_2 = 4.0 Hz, H-5′); 3.82–3.89 (2H, m, H-5′, H-5); 3.77 (1H, t, *J* = 16.2 Hz, H-5); 5.56 (1H, s, H-2); 6.78–6.94 (3H, m, Ar–H); 3.91 (1H, s, OH); 5.95–5.99 (2H, d, *J* = 15.7 Hz, O–CH_2–O). δ_C (100 MHz, $CDCl_3$): 26.72, 26.94; 33.53, 42.97, 67.44 (C-2), 74.02, 77.90, 85.03, 102.05, 105.03, 108.26, 108.75, 111.96; 122.77, 132.42, 148.92, 149.50, 173.79. HRESIMS: calcd for $C_{18}H_{21}NO_7S$ ([M+H]$^+$), 396.1110, found: 396.1114.

3.2.9. (2*S*)-2-(1-Ethyl-1*H*-imidazol-2-yl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (4e)

White solid; mp 69–71 °C; $[\alpha]_D$ +63.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$); 1.27 (3H, s, CH_3); 1.36 (3H, s, CH_3); 5.82 (1H, d, *J* = 3.6 Hz, H-1′); 4.53 (1H, d, *J* = 3.5 Hz, H-2′); 4.14 (1H, s, H-3′); 3.49–3.52 (1H, m, H-5′); 3.61–3.73 (3H, m, H-4′, H-5′, H-5); 3.88–3.92 (1H, dd, J_1 = 15.8 Hz, J_2 = 1.4 Hz, H-5); 5.91 (1H, d, *J* = 1.4 Hz, H-2); 6.95 (1H, s, Ar–H); 7.02 (1H, s, Ar–H); 3.97–4.07 (2H, m, N–CH_2); 1.47 (3H, t, *J* = 7.2 Hz, N–CH_2–CH_3). δ_C (100 MHz, $CDCl_3$): 16.46, 26.62, 27.15, 32.84, 41.59, 42.77, 60.77 (C-2), 74.48, 77.73, 85.41, 104.86, 112.00, 121.41, 129.16, 143.18, 173.14; HRESIMS: calcd for $C_{16}H_{24}N_3O_5S$ ([M+H]$^+$), 370.1430, found: 370.1428.

3.2.10. (2*R*)-2-(1-Ethyl-1*H*-imidazol-2-yl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (5e)

White solid; mp 76–78 °C; $[\alpha]_D$ −164.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$); 1.30 (3H, s, CH_3); 1.50 (3H, s, CH_3); 5.76 (1H, d, *J* = 3.5 Hz, H-1′); 4.54 (1H, d, *J* = 3.5 Hz, H-2′); 4.11 (1H, d, *J* = 2.1 Hz, H-3′); 4.15–4.22 (1H, m, H-4′); 3.18 (1H, dd, J_1 = 14.6 Hz, J_2 = 4.60 Hz, H-5′); 3.90–3.98 (3H, m, H-5′, N–CH_2); 3.62 (1H, d, *J* = 15.6 Hz, H-5); 3.84 (1H, d, *J* = 15.6 Hz, H-5); 5.91 (1H, d, *J* = 1.4 Hz, H-2); 6.95 (1H, s, Ar-H); 7.01 (1H, s, Ar–H); 1.46 (3H, t, *J* = 7.2 Hz, N–CH_2–CH_3). δ_C (100 MHz, $CDCl_3$): 16.41, 26.39, 27.20, 32.32, 41.30, 42.46, 60.78 (C-2), 74.83, 78.57, 85.54, 105.17, 111.98, 121.08, 128.93, 143.63, 173.37. HRESIMS: calcd for $C_{16}H_{24}N_3O_5S$ ([M+H]$^+$), 370.1430, found: 370.1434.

3.2.11. (2*S*)-2-(Pyridin-4-yl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (4f)

White solid; mp 71–73 °C; $[\alpha]_D$ −106.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$); 1.32 (3H, s, CH_3); 1.53 (3H, s, CH_3); 5.88 (1H, d, *J* = 3.5 Hz, H-1′); 4.59 (1H, d, *J* = 3.5 Hz, H-2′); 4.09–4.58 (2H, m, H-3′, H-4′); 2.90 (1H, dd, J_1 = 14.6 Hz, J_2 = 4.4 Hz, H-5′); 3.73 (1H, d, *J* = 15.9 Hz, H-5); 3.86 (1H, dd, J_1 = 15.9 Hz, J_2 = 1.7 Hz, H-5); 3.96 (1H, q, *J* = 14.6 Hz, H-5′); 5.68 (1H, d, *J* = 1.5 Hz, H-2); 7.17–8.66 (4H, m, Py–H); 3.99 (1H, s, OH). δ_C (100 MHz, $CDCl_3$): 26.31, 27.16; 32.58, 41.34, 63.22 (C-2), 74.60, 78.22, 85.28, 105.16, 112.10, 121.43, 148.52, 151.31, 173.44. HRESIMS: calcd for $C_{16}H_{20}N_2O_5SNa$ ([M+Na]$^+$), 375.0985, found: 375.0979.

3.2.12. (2*R*)-2-(Pyridin-4-yl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (5f)

White solid; mp 129–131 °C; $[\alpha]_D$ +14.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$); 1.20 (3H, s, CH_3); 1.23 (3H, s, CH_3); 5.78 (1H, d, *J* = 3.52 Hz, H-1′); 4.57 (2H, d, *J* = 3.5 Hz, H-2′); 4.49 (1H, d, *J* = 3.5 Hz, H-3′); 3.45–3.49 (1H, m, H-4′); 3.36 (1H, dd, J_1 = 14.2 Hz, J_2 = 3.8 Hz, H-5′); 3.71–3.75 (1H, m, H-5′); 3.78 (1H, d, *J* = 16.0 Hz, H-5); 3.89–3.93 (1H, dd, J_1 = 16.0 Hz, J_2 = 1.8 Hz, H-5); 5.61 (1 H, d, *J* = 1.4 Hz, H-2); 7.31(2 H, d, *J* = 4.8 Hz, Py–H), 8.66 (2H, d, *J* = 4.4 Hz, Py–H); 3.96 (1H, d, *J* = 1.4 Hz, OH). δ_C (100 MHz, $CDCl_3$): 26.58, 27.09, 33.16, 43.22, 65.57 (C-2), 74.32, 77.74, 85.04, 104.93, 112.15; 122.49, 148.59, 151.19, 174.07. HRESIMS: calcd for $C_{16}H_{20}N_2O_5SNa$ ([M+Na]$^+$), 375.0985, found: 375.0990.

3.2.13. (2*S*)-2-(1*H*-Indole-3-yl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (4g)

White solid; mp 99–101 °C; $[\alpha]_D$ −65.3 (*c* 1.0, $CHCl_3$); δ_H(400 MHz, $CDCl_3$); 1.32 (3H, s, CH_3); 1.53 (3H, s, CH_3); 5.84 (1H, d, *J* = 3.5 Hz, H-1′); 4.60 (1H, d, *J* = 3.49 Hz, H-2′); 4.70 (1H, d, *J* = 2.6 Hz, H-3′); 4.15 (1H, m, H-4′); 3.09 (1H, dd, J_1 = 14.2 Hz, J_2 = 3.6 Hz, H-5′); 3.78–3.81 (1H, m, H-5′); 3.85 (1H, d, *J* = 17.7 Hz,

H-5); 3.89–3.94 (1H, d, J = 17.8 Hz, H-5); 6.10 (1H, s, H-2); 7.14–7.51 (5H, m, Ar–H); 8.28 (1H, s, NH); 3.94 (1H, s, OH). δ_C (100 MHz, $CDCl_3$): 26.32, 27.22, 33.48, 40.01, 59.09 (C-2), 74.22, 77.73, 85.19, 102.05, 105.12, 111.93, 112.29, 112.85, 119.49, 121.22, 123.77, 124.78, 124.98, 137.53, 149.50, 173.33. HRESIMS: calcd for $C_{19}H_{23}N_2O_5S$ ($[M+H]^+$), 391.1321, found: 391.1328.

3.2.14. (2*R*)-2-(1*H*-Indole-3-yl)-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-one (5g)

White solid; mp 227–229 °C; $[\alpha]_D$ +24.7 (c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$); 0.69 (3H, s, CH_3); 1.21 (3H, s, CH_3); 5.71 (1H, d, J = 3.5 Hz, H-1′); 4.42 (1H, d, J = 3.5 Hz, H-2′); 5.08 (1H, d, J = 2.0 Hz, H-3′); 3.19–3.24 (2H, m, H-4′, H-5′); 3.82–3.97 (4H, m, H-5′, H-5, OH); 5.99 (1H, s, H-2); 7.17–7.68 (5H, m, Ar–H); 8.46 (1H, s, NH). δ_C (100 MHz, $CDCl_3$): 26.62, 33.87, 42.78, 61.54 (C-2), 74.10, 77.93, 85.06, 104.85, 111.89; 112.40, 120.11, 121.19, 123.75, 125.18, 125.59, 137.58, 173.87. HRESIMS: calcd for $C_{19}H_{23}N_2O_5S$ ($[M+H]^+$), 391.1321, found: 391.1326.

3.3. Single-crystal X-ray crystallographic analysis of 5d[20]

A single crystal of compound **5d** was obtained by recrystallization from the solution of CH_2Cl_2 and mounted on a Bruker SMART CCD diffractometer for analysis. The intensity data were collected with graphite-monochromated MoKα radiation (λ = 0.71073 Å) using the $\theta/2\omega$ scan technique from a single-crystal of 0.20 mm × 0.18 mm × 0.16 mm, and a semi-empirical absorption correction was applied for all complexes. The crystal system was monoclinic, and the space group was $P2(1)$. The structures were solved by direct methods and refined by full-matrix least-squares on F^2. The absolute structure parameter was 0.92(9). All non-hydrogen atoms were refined anisotropically. The crystallographic structure is shown in Figure 2.

3.4. Biological activity assays

3.4.1. Inhibition of glycosidases

The inhibitory activity of the synthesized compounds against α-amylase, α-glucosidase and β-glucosidase: The enzymes α-glucosidase (yeast) and β-glucosidase (almonds) were obtained from Fluka; α-amylase (*Bacillaceae*, 4000 U/mg) from Sanland-chen International Inc, Xiamen, China. Two substrates, *p*-nitrophenyl α-glucopyranoside (PNPG) and (−)-D-salicin, were purchased from Sigma Chemical Co. All other commercial reagents were used as received. Each enzyme assay was measured as follows.

The α-amylase assay was performed using 1% starch as substrate in phosphate buffer, pH 6.0, at 50 °C. The enzyme solution (0.1 mL, 5 mg of solid enzyme in 50 mL of pH 6.0 phosphate buffer), 0.1 mL of inhibitor (1 mg/mL) and 1 mL of buffer were incubated for 10 min, and then 1 mL of substrate was added. After 10 min, 2 mL of 3,5-dinitrosalicylic acid was added, and then the reaction was heated in boiling water for 5 min. The solution was finally diluted to 20 mL after cooling down. Absorbance readings were taken on a TU-1901 UV–vis spectrophotometer at 540 nm using distilled deionized water as a blank control and acarbose as a positive control.

The β-glucosidase assay was performed using (−)-D-salicin (2 mg/mL) as substrate in phosphate buffer, pH 4.8, at 35 °C. The enzyme solution (0.1 mL, 10 mg of solid enzyme in 10 mL of pH 4.8 acetate buffer), 0.1 mL of inhibitor (1 mg/mL), and 0.9 mL of buffer were incubated for 10 min, and then 0.8 mL of substrate was added. After 10 min, 2 mL of 3,5-dinitrosalicylic acid was added, and then the reaction mixture was heated in boiling water for 5 min. The solution was finally diluted to 20 mL after cooling down. Absorbance readings were taken on a TU-1901 UV–vis spectrophotometer at 540 nm using distilled deionized water as a blank control.

The α-glucosidase assay was performed using PNPG (1 mg/mL) as substrates in phosphate buffer, pH 6.8, at 37 °C. The enzyme solution (0.1 mL, 10 mg of solid enzyme in 10 mL of pH 6.8 phosphate buffer), 0.1 mL of inhibitor (1 mg/mL), 1.9 mL of buffer, and 0.05 mL glutathione (reduced, 1 mg/mL) were incubated for 10 min, and then 0.15 mL of substrate was added. The reaction was quenched with 10 mL of sodium carbonate (0.1 mol/L) after 10 min, and the solution was finally diluted to 20 mL after cooling down. Absorbance readings were taken on a TU-1901 UV–vis spectrophotometer at 400 nm using distilled deionized water as a blank control.

3.4.2. Antitumor activity

The cytotoxicity of the compounds against Hela cell lines (human cervical cancer cells) was examined by the modified Mosmann's protocol as follows: Briefly, cells (10^4 cells per well) were plated in 96-well culture plates and cultured overnight at 37 °C in a 5% CO_2 humidified incubator. Compounds were added to the wells at final concentrations of 1, 10, and 100 μmol/L. Control wells were prepared by addition of DMEM. Wells containing DMEM without cells were used as blanks. The plates were incubated at 37 °C in a 5% CO_2 incubator for 48 h. Upon completion of the incubation, stock MTT dye solution (10 μL, 5 mg/mL) was added to each well. After 4 h of incubation, the supernatant was removed and DMSO (100 μL) was added to dissolve the MTT. The optical density of each well was measured on a microplate spectrophotometer at a wavelength of 570 nm. The inhibition rate was calculated according to the formula: $(OD_{control} - OD_{treated})/OD_{control} \times 100\%$. The results are listed in Table 4.

Supplementary data

Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 694699. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

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References

1. Brown, C. F. *Chem. Rev.* **1961**, *61*, 463–520.
2. Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. *Chem. Rev.* **1981**, *81*, 175–203.
3. Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Bioorg. Med. Chem.* **2007**, *15*, 3134–3142.
4. Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Bioorg. Med. Chem.* **2007**, *15*, 1725–1731.
5. Rawal, R. K.; Prabhakar, Y. S.; Rawal, R. K.; De Clercq, E. *Bioorg. Med. Chem.* **2005**, *13*, 6771–6776.
6. Rao, A.; Balzarini, J.; Carbone, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zappalà, M. *Antiviral Res.* **2004**, *63*, 79–84.
7. Barreca, M. L.; Chimirri, A.; De Clercq, E.; De Luca, L.; Monforte, A. M.; Monforte, P.; Rao, A.; Zappala, M. *Il Farmaco* **2003**, *58*, 259–263.
8. Barreca, M. L.; Balzarini, J.; Chimirri, A.; De Clercq, E.; De Luca, L.; Höltje, H. D.; Höltje, M.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Rao, A.; Zappalà, M. *J. Med. Chem.* **2002**, *45*, 5410–5413.
9. Verma, A.; Saraf, S. K. *Eur. J. Med. Chem.* **2008**, *43*, 897–905.
10. Gududuru, V.; Nguyen, V.; Dalton, J. T.; Miller, D. D. *Synlett* **2004**, 2357–2358.

11. Al-Thebeiti, M. S. *J. Carbohydr. Chem.* **1999**, *6*, 667–674.
12. Rauter, A. P.; Padilha, M.; Figueiredo, J. A.; Ismael, M. I.; Justino, J.; Ferreira, H.; Ferreira, M. J.; Rajendran, C.; Wilkins, R.; Vaz, P. D.; Calhorda, M. J. *J. Carbohydr. Chem.* **2005**, *24*, 275–296.
13. Rao, A.; Chimirri, A.; Ferro, S.; Monforte, A. M.; Monforte, P.; Zappalà, M. *Arkivoc* **2004**, *V*, 147–155.
14. Sriram, D.; Yogeeswari, P.; Kumar, TG A. *J. Pharm. Pharm. Sci.* **2005**, *8 3*, 426–429.
15. Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron* **2003**, *59*, 6121–6130.
16. Dandia, A.; Singh, R.; Khaturia, S.; Me-rienne, C.; Morgantc, G.; Loupyd, A. *Bioorg. Med. Chem.* **2006**, *14*, 2409–2417.
17. Chen, H.; Bai, J.; Zhao, L.; Yuan, X. G.; Li, X. L.; Cao, K. Q. *Chin. J. Org. Chem.* **2008**, *28*, 1092–1096.
18. Li, X. L.; Zhang, P. Z.; Tian, J.; Duan, K. F.; Chen, H. *Chin. J. Org. Chem.* **2007**, *27*, 1013–1017.
19. Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55–63.