Tetrahedron 64 (2008) 9911–9920

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Stereoselective synthesis and biological activity of novel spiro-oxazinanone-*C*-glycosides

Xiaoliu Li [a,b,*], Rui Wang [a], Yanpo Wang [a], Hua Chen [a], Zhiwei Li [a], Cuilan Ba [a], Jinchao Zhang [a,b]

[a] *Laboratory of Chemical Biology, College of Chemistry and Environmental Science, Hebei University, Baoding, Hebei 071002, China*
[b] *Key Laboratory of Medicinal Chemistry and Molecular Diagnosis, Ministry of Education, Hebei University, Baoding, Hebei 071002, China*

ARTICLE INFO

Article history:
Received 18 April 2008
Received in revised form 29 July 2008
Accepted 5 August 2008
Available online 8 August 2008

Keywords:
Spironucleoside
Microwave irradiation
1,3-Dipolar cycloaddition
Nitrones
exo-Glycal

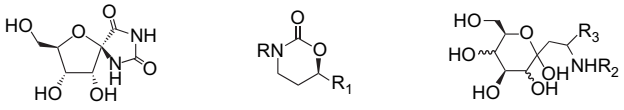
ABSTRACT

The stereoselective synthesis of novel spiro-oxazinanone nucleosides **9** and **10** has been achieved by microwave assisted 1,3-dipolar cycloaddition of *exo*-glucal (**1**) and nitrones (**2**), and followed by reduction, stereospecific recyclization, and catalytic deprotection. The structures of the spironucleosides were determined according to the ^{1}H NMR, ^{13}C NMR, 2D NMR, MS, and X-ray analyses, and the biological activities of the title compounds against glycosidases (α-amylase, α-glucosidase, and β-glucosidase) and cytotoxicity were also evaluated.

1. Introduction

Anomeric spironucleoside is a class of spiranic sugar derivatives of which the anomeric carbon belongs simultaneously to the sugar ring and to a heterocyclic base.[1] The synthesis of the spironucleoside derivatives has attracted considerable attention in recent years[1–4] due to their potential biological activities.[5] However, most of such compounds focused on the analogues of natural spironucleoside (+)-hydantocidin (**A**) in which the heterocycle was a five-membered ring.[3] The spironucleoside with six-membered or seven-membered heterocycle has not been investigated extensively,[4] although the six-membered 1,3-oxazinan-2-one ring (**B**) exists in many drug molecules as the core substructure and its derivatives are of very important biological activities.[6]

The six-membered ring of 1,3-oxazinan-2-one (**B**) can be conventionally constructed by the cyclization of 1,3-amino alcohols. Recently, we have developed a convenient method to access the amino-*C*-glycosides (**C**), a typical 1,3-amino alcohol with a sugar moiety, by the 1,3-dipolar cycloaddition of *exo*-glycal with nitrones, and then reductive cleavage of the O–N bond.[7] We envisaged that such amino-*C*-glycosides would be a very good precursor for constructing oxazinanone derivatives containing sugar moiety, which would provide a convenient access to a new type of spironucleosides with six-membered oxazinanone. From this point of view, we would like to report herein a stereoselective synthesis of novel aryl substituted spiro-oxazinanone glucosides **9** and **10** as the continuation of our work[3o,7,8] on the synthesis of functional *C*-glycosides applying the 1,3-dipolar cycloaddition of *exo*-glucal (**1**) with nitrones (**2**) (see Scheme 1 and Table 1).



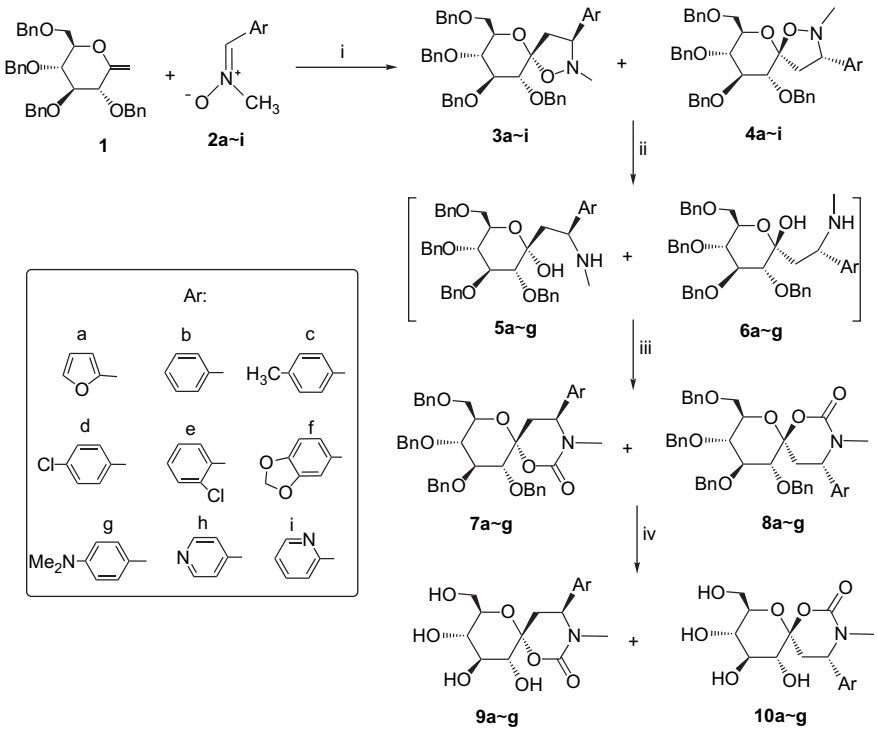
A: (+)-Hydantocidin **B**: 1,3-Oxazinan-2-one **C**: Amino-C-glycosides

2. Results and discussion

The synthetic pathway is shown in Scheme 1. Following the microwave assisted procedure we recently developed,[8] the cycloaddition of **1** and **2a–i** was carried out very efficiently in diglyme solution under microwave irradiation at 200 °C for 2 min in a sealed pressure vial and stereoselectively afforded the corresponding adducts of spiro-isoxazolidine glycosides as the α- and β-anomeric mixture of **3a–i** and **4a–i** in 30–80% yield. The reductive cleavage of O–N bond was completed by the treating the mixture with Zn/AcOH/H_2O to generate the intermediate of amino-*C*-glycoside derivatives **5** and **6**, which were reacted with triphosgene[9] to form the cyclized key intermediate of spiro-oxazinanone

* Corresponding author. Tel./fax: +86 312 5971116.
E-mail address: lixl@hbu.cn (X. Li).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.08.002

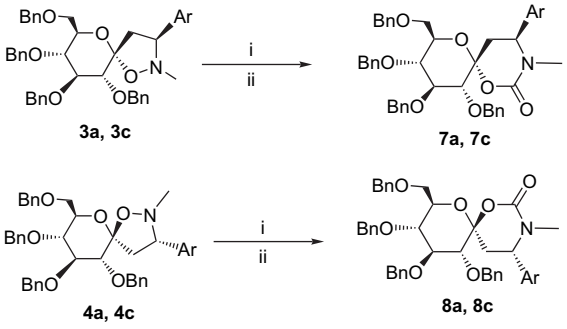


Scheme 1. *Conditions and reagents*: (i) diglyme, MW, 200 °C, 2 min, 30–81%; (ii) Zn, 85% AcOH, rt; (iii) triphosgene, Et_3N, 0 °C to rt, DCM; (iv) MeOH, $Pd(OH)_2/C$, H_2.

Table 1
The yields (%) of the synthetic reaction of spiro-oxazinanone glycosides from **1** and **2**

Run	Ar	**3** and **4**[a]	**7**	**8**	**9**	**10**
1	**a**	81.1 (1.5:1)[b]	35.8	23.9	**a1**: 33.3 **a2**: 66.7	**a1**: 40.0 **a2**: 60.0
2	**b**	72.7 (1.2:1)	34.5	28.2	Quantitative	
3	**c**	74.9 (1:1)[b]	26.6	26.4	99.3	97.2
4	**d**	75.2 (1.2:1)	28.2	23.1	100	95.5
5	**e**	68.8 (1.5:1)	28.9	19.2	98.1	96.6
6	**f**	43.8 (2.3:1)	35.2	15.6	98.8	99.2
7	**g**	41.3 (2.1:1)	34.3	15.4	97.5	98.3
8	**h**	35.6 (1.3:1)				
9	**i**	37.3 (1.6:1)				

[a] Calculated according to the proportions of the corresponding proton signals in the ^1H NMR.
[b] Isolated yields.



Scheme 2. *Conditions and reagents*: (i) Zn, 85% AcOH, rt; (ii) triphosgene, Et_3N, 0 °C to rt, DCM.

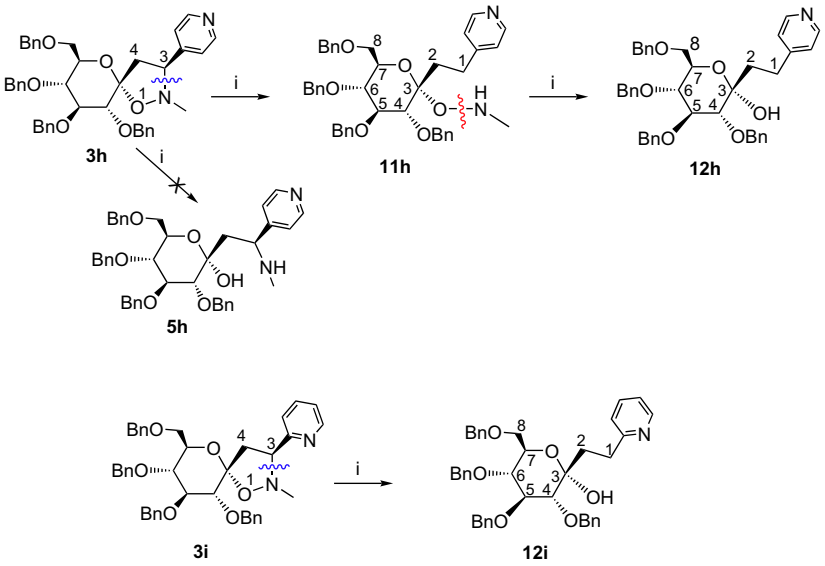
derivatives **7** and **8**, followed by deprotection with catalytic hydrogenation to afford the spiro-oxazinanone glycosides **9** and **10**, respectively.

It should be mentioned that the anomeric mixture of the cycloaddition products **3** and **4** was very difficult to separate because of their similar polarity, and only **3a**, **4a** and **3c**, **4c** were isolated by repeated silica gel column chromatographic separation. With the separated **3a**, **3c**, **4a**, and **4c** the reductive opening of the isoxazolidine ring and recyclization of the generated intermediates (**5a**, **5c**, **6a**, and **6c**) with triphosgene were then examined, respectively (Scheme 2).

It has been found that in the two-step process of opening isoxazolidine ring and forming the oxazinanone ring, α-anomers **3a** and **3c** were converted to their corresponding spiro-oxazinanones **7a** and **7c** possessing the α-anomeric configuration exclusively, and β-anomers **4a** and **4c** afforded the sole β-anomeric spiro-oxazinanones **8a** and **8c**, respectively. It would be concluded that in the process the configurations of the anomeric carbons were in retention. Namely, the conversion from spiro-isoxazolidine glycosides (**3** and **4**) to spiro-oxazinanone glycosides (**7** and **8**) proceeded stereospecifically and no anomerization occurred for the intermediates of hemiketals (**5** and **6**). Consequently, the ratio of the spiro-oxazinanone glycosides **7** and **8** was equal to that of the α- and β-anomers in the mixture of cycloadducts **3** and **4** according to the ^1H NMR spectra.

Following the above procedures, the spiro-oxazinanone glycosides **7a**–**g** and **8a**–**g** were synthesized from the mixtures of **3a**–**g** and **4a**–**g**. However, in the case of **3h** where exists a 4-pyridinyl group, the reductive opening of its isoxazolidine ring did not give the corresponding 1,3-amino alcoholic ketose (**5h**), but the C–N bond cleaved derivatives **11h** and **12h** were insteadly obtained as shown in Scheme 3. Under this reductive condition the isoxazolidine ring of **3h** could be firstly opened at the C–N bond to generate the hydroxylamine derivative **11h**, followed by the cleavage of the O–N bond to afford the ketose-like product **12h**.

Similarly, the spiro-isoxazolidine glycoside **3i** with a 2-pyridinyl group gave product **12i** under the same condition (Scheme 3). Besides, various other reductive conditions and methods,[10] such as with $LiAlH_4$ and DIBAL-H, were examined in order to cleave O–N bond of 1,3-amino alcoholic intermediate (**5h**), but all the approaches were unsuccessful. The existence of pyridinyl group might

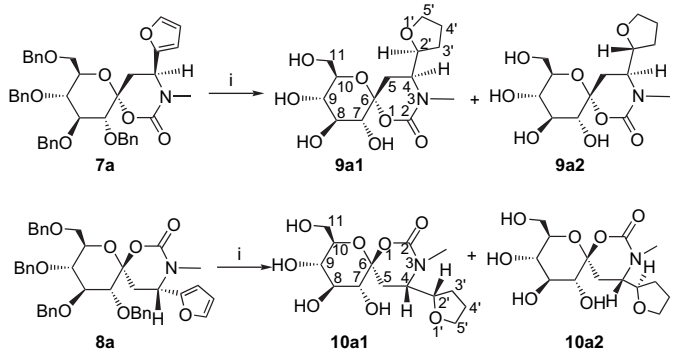


Scheme 3. *Conditions and reagents*: (i) Zn, 85% AcOH, rt.

make the C-3 of the isoxazolidine ring (an α-C to pyridine ring) more electron-deficient. Consequently, the C–N bond could be more sensitive to reductive condition than the O–N bond, and the C–N bond could be firstly cleaved under the reductive conditions.

Subsequently, the debenzylation of the spiro-oxazinanone derivatives **7a**–**g** and **8a**–**g** were carried out by catalytic hydrogenation with $Pd(OH)_2/C$ in MeOH solution at room temperature to give the corresponding debenzylated spiro-oxazinanone glycosides **9a**–**g** and **10a**–**g** in almost quantitative yields (step (iv) in Scheme 1 and Table 1). However, in the cases of **7a** and **8a**, the furan group was also hydrogenated to form a saturated tetrahydrofuran ring to afford the four diastereomers of **9a1**, **9a2** and **10a1**, **10a2**, respectively, as shown in Scheme 4.

The structures of all the intermediates **3a**–**h**, **4a**–**h**, **7a**–**g**, **8a**–**g**, **11**, and **12**, and final products **9a**–**g** and **10a**–**g** were determined by the analyses of their spectral data of ^{1}H NMR, ^{13}C NMR, 2D-COSY and NOESY, MS, and the X-ray crystallographic structure of **9a1** (Fig. 1). It has been reported[11] that in the ^{13}C NMR spectra of *C*-glycosides and spiro-glycosides the signals of the anomeric carbon in the α-isomers appeared in upfield compared with the β-isomers, which has been successfully used in the assignment of the anomeric configurations of spiro-isoxazolidine *C*-glycosides.[7,8] Accordingly, the anomeric configurations of **3a**–**h**, **4a**–**h**, **7a**–**g**, **8a**–**g**, **9a**–**g**, and **10a**–**g** were determined by the comparison of the anomeric signals of the ^{13}C NMR spectra between each two anomeric isomers (see Table 2) with the combination of the X-ray crystallographic structure of **9a1**.



Scheme 4. *Conditions and reagents*: (i) MeOH, $Pd(OH)_2/C$, H_2, 2 h, ~100%.

The X-ray crystallographic structure[12] of **9a1**, as shown in Figure 1, revealed that the anomeric (spiro) C_6 possessed α-configuration, and both C_4 in oxazinanone ring and $C_{2'}$ in tetrahydrofuran cycle were in *S*-form. Accordingly, its diastereomer **9a2** had *S*-form in the C_4 and *R*-form at the $C_{2'}$. In addition, the D-glucopyranosyl ring had a chair form with all OH and CH_2OH groups in equatorial position; the spiro-oxazinanone ring was in a twist-boat form perpendicular to the glucopyranose ring, plane and the tetrahydrofuran cycle kept an envelope conformation vertically above the oxazinanone ring. This conformation was consistent with its NOESY correlation analysis as shown in Figure 2(a).

The NOESY correlations of the diastereomers of **9a1** and **10a1** are shown in Figure 2(a) and (b), respectively. The NOESY correlations between H_{5a}-H_4 and H_{5a}-H_7 in **9a1** (Fig. 2(a)) supported the *S*-form of C_4, which was identical to that in the X-ray crystallographic structure (Fig. 1). Similarly, the *S*-configuration at C_4 in the β-anomer (**10a1**) could also be assigned based on the NOESY correlations between H_{5a}-H_4 and H_{5a}-H_7 (Fig. 2(b)). For the other **9** and **10**, the similar NOESY correlations between H_{5a}-H_4 and H_{5a}-H_7 were observed, indicating that **9** and **10** had *S*-configuration at C_4. Accordingly, the key intermediates **7** and **8**, and the cycloadducts of **3** and **4** would be tentatively deduced to possess the *S*-configuration at the corresponding carbons considering that the configurations were in retention during the conversion from the spiro-isoxazolidine (**3** and **4**) to the spiro-oxazinanone (**7** and **8**) as shown in Scheme 1.

According to the X-ray crystallographic structure of **9a1** (Fig. 1), its diastereomer (**9a2**) had an *R*-form at the corresponding $C_{2'}$ (Fig. 3). In addition, the ^{1}H NMR signals of $H_{2'}$ in the four isomers **9a1**, **9a2** and **10a1**, **10a2** (Table 3) provided further useful information for determining the configuration of the $C_{2'}$. It can be seen from Table 3 that the ^{1}H NMR signals of $H_{2'}$ in **9a1** and **9a2** were very similar to those in **10a1** and **10a2**, which implied that **9a1** and **10a1**, **9a2** and **10a2** would have the same configurations at the $C_{2'}$, respectively. With combination of the above analyses on the *S*-configuration of C_4, the configuration of $C_{2'}$ would be tentatively assigned to be *S*-form in **10a1** and *R*-form in **10a2** as shown in Figure 3.

The glycosidase inhibition and antitumor activities of compounds **9** and **10** were preliminarily evaluated. The glycosidase inhibitory activities were measured on hydrolytic reactions of

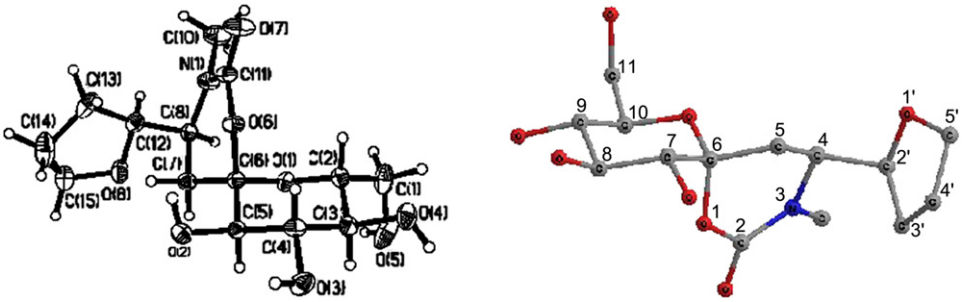


Figure 1. ORTEP X-ray crystallographic structure of **9a1** represented with ball and stick model (hydrogen atoms were omitted for clarity).

Table 2
Chemical shifts (ppm) of the anomeric carbon of **7a–g**, **8a–g**, **9a–g**, and **10a–g**

	3	4	7	8	9	10
a	105.74	107.42	100.44	101.81	**a1**: 102.08 **a2**: 101.54	**a1**: 102.52 **a2**: 102.24
b	104.99	106.29	100.59	101.85	101.52	102.36
c	104.94	106.18	100.56	100.78	101.48	102.32
d	104.92	106.61	100.59	101.78	101.52	102.28
e	104.89	106.86	100.83	102.03	101.52	102.16
f	101.44	106.18	100.58	101.80	101.75	102.07
g	101.18	105.98	100.60	101.83	101.20	101.25
h	105.25	107.60				
i	105.65	107.69				

α-amylase, α-glucosidase, and β-glucosidase using acarbose as a control, respectively. As shown in Table 4, although the compounds showed low inhibitory activities on the glycosidases compared to the positive control, they exhibited a certain selective inhibition to β-glucosidase. The cytotoxicity of the compounds **9** and **10** against Hela cell lines (human cervical cancer cells) was also examined by the modified Mosmann protocol.[13] It has been found that only a few of them exhibited a slight cytotoxicity to Hela cell lines, for instance, the inhibition of **9a1**, **9a2**, **9g**, and **10f** at the concentration of 10 μmol/L were 12.75, 12.35, 11.09, and 15.38%, respectively; the other compounds showed no activity against this cell.

In summary, the stereoselective synthesis of a series of novel aryl spiro-oxazinanone glucosides has been achieved by the steps of the stereoselectively microwave assisted 1,3-dipolar cycloaddition of *exo*-glucal with aryl nitrones, the reductive cleavage of the O–N bound with Zn/AcOH/H_2O, and recyclization with triphosgene to afford the key intermediates of benzyl protected aryl spiro-oxazinanone glucosides **7** and **8**, which provided a convenient new method for constructing spironucleoside. The catalytic hydrogenation of **7** and **8** with $Pd(OH)_2$/C furnished the corresponding title compounds **9a–g** and **10a–g** quantitatively. Some of **9** and **10** showed a certain selective inhibition against β-glucosidase and a slightly antitumor activity. The further synthesis and biological study of new spironucleosides are under way in this lab.

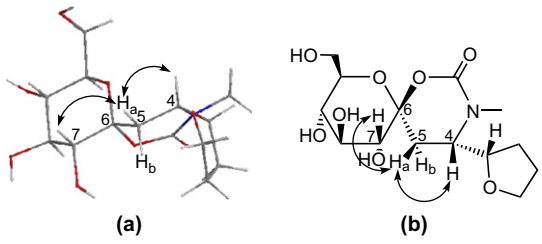


Figure 2. NOESY of (a) **9a1** and (b) **10a1**.

3. Experimental

3.1. General methods

Melting points were measured on a SGW® X-4 micro melting point apparatus and were uncorrected. Optical rotations were determined on a SGW®-1 automatic polarimeter. ^{1}H NMR and ^{13}C NMR spectra were measured on a RT-NMR Bruker AVANCE 400 (400 MHz) NMR spectrometer using tetramethylsilane (Me_4Si) as an internal standard. Mass spectra (MS) and high resolution mass spectra (HRMS) were carried out on a FTICR-MS (Ionspec 7.0T) mass spectrometer with electrospray ionization (ESI). 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 BioRad Model 3550 microplate spectrophotometer, respectively. The microwave assisted reaction was carried out on a CEM DISCOVER S-Class Chemical Synthesis System in a 10 mL (or 35 mL) seamless pressure vial. 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 microwave assisted 1,3-dipolar cycloaddition of *exo*-glucal (1) with nitrones (2a–i)

A solution of *exo*-glucal (2.0 mmol), nitrone (2.6 mmol) in diglyme (2 mL) was irradiated with microwave at 200 °C for 2 min. The reaction mixture was cooled to room temperature and then submitted to silica gel column chromatography (petroleum ether/ethyl acetate v/v=6:1) to purify products **3a–i** and **4a–i**. The results are listed in Table 1.

3.3. General procedure for the synthesis of spiro-oxazinanones 7 and 8

A mixture of compounds **3** and **4** (0.90 mmol) and zinc (1.784 g) in acetic acid 85% (16 mL) was vigorously stirred for 10 h. Upon completion, the reaction mixture was neutralized with saturated aq Na_2CO_3 carefully with cooling, and then extracted with EtOAc three times. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to give intermediates **5** and **6** as a syrup. The mixture **5** and **6** was dissolved in 15 mL of dry dichloromethane (DCM), and Et_3N (0.72 mL) was added. The solution was stirred at 0 °C for 20 min and a solution of triphosgene (0.597 g, 0.9 mmol) in DCM (15 mL) was added dropwise during 1 h at the same temperature. The reaction mixture was stirred at room temperature for 12 h, then the reaction was quenched by adding small amount of H_2O. The mixture was extracted with DCM two times. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under

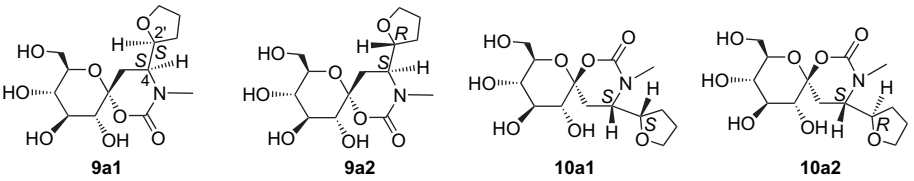


Figure 3. The configurations of C_4 and $C_{2'}$ in **9a** and **10a**.

Table 3
The ^{1}H NMR signals of $H_{2'}$ and the configurations of C_4–$C_{2'}$ in **9a** and **10a**

	9a1	9a2	10a1	10a2
$\delta_{H2'}$	4.15 (q)	4.44 (t)	4.19 (q)	4.37 (t)
Configurations of C_4–$C_{2'}$	*S*–*S*	*S*–*R*	*S*–*S*	*S*–*R*

Table 4
Inhibitory activities of some of compounds **9** and **10** against glycosidases

Compounds	Inhibition % (in vitro)[a]		
	α-Amylase	α-Glucosidase	β-Glucosidase
9a1	5.41	3.51	7.56
9a2	3.32	1.98	—[b]
9b	—[b]	—[b]	2.78
10b	3.57	1.30	10.35
9c[c]	5.75	2.87	19.44
10c	—[b]	—[b]	—[b]
9d	2.24	—[b]	13.73
10d	4.82	2.39	16.41
9e	2.58	0.91	9.21
10e	2.65	3.93	3.93
Control (acarbose)	88.8	—[b]	—[b]

[a] The concentration of the inhibitor is 1.0 mg/mL.
[b] No inhibition.
[c] The concentration is 2.5 mg/mL.

reduced pressure. The residue was applied to silica gel column chromatography (petroleum ether/ethyl acetate v/v=5:1) to afford the products **7** and **8**. From the mixture, spiro-oxazinanone glucosides **7** and **8** were isolated by repeated column chromatographic separation (cyclohexane/ethyl acetate v/v=8:1). The results are shown in Table 1.

3.3.1. Compound ***7a***

White solid, mp: 193–194 °C; $[\alpha]_D^{25}$ +41.53 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.74 (dd, 1H, *J*=13.8, 4.6 Hz, 5-H), 2.57 (t, 1H, *J*=13.0 Hz, 5-H), 2.73 (s, 3H, NCH_3), 3.40 (d, 1H, *J*=9.6 Hz, 7-H), 3.66 (d, 1H, *J*=10.8 Hz, 11-H), 3.77 (d, 1H, *J*=3.2 Hz, 11-H), 3.80 (t, 1H, *J*=9.6 Hz, 9-H), 4.04–4.06 (m, 1H, 10-H), 4.32 (t, 1H, *J*=10.2 Hz, 8-H), 4.50 (d, 1H, *J*=12.0 Hz, CH_2Ph), 4.58–4.69 (m, 4H, 4-H, CH_2Ph), 4.89 (d, 1H, *J*=9.6 Hz, CH_2Ph), 4.91 (s, 2H, CH_2Ph), 5.00 (d, 1H, *J*=12.0 Hz, CH_2Ph), 6.26 (d, 1H, *J*=3.2 Hz, furyl), 6.36 (q, 1H, *J*=3.2 Hz, furyl), 7.20–7.42 (m, 21H, ArH); ^{13}C NMR ($CDCl_3$) δ: 33.44 (NCH_3), 33.80 (5-C), 50.71 (4-C), 68.69 (11-C), 72.97 (CH_2Ph), 73.65 (10-C), 75.04 (CH_2Ph), 75.79 (CH_2Ph), 76.23 (CH_2Ph), 78.15 (9-C), 81.60 (7-C), 82.69 (8-C), 100.44 (6-C), 109.51 (furyl), 109.70 (furyl), 127.69 (Ar–C), 127.92 (Ar–C), 128.09 (Ar–C), 128.17 (Ar–C), 128.23 (Ar–C), 128.39 (Ar–C), 128.54 (Ar–C), 128.73 (Ar–C), 128.79 (Ar–C), 138.16 (Ar–C), 138.36 (Ar–C), 138.80 (Ar–C), 143.30 (furyl), 151.55 (furyl), 152.15 (C=O); ESI-MS: 712 $[M+Na]^+$.

3.3.2. Compound ***8a***

Colorless syrup; $[\alpha]_D^{30}$ +10.13 (*c* 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.37 (dd, 1H, *J*=14.8, 4.4 Hz, 5-H), 2.67–2.70 (m, 1H, 5-H), 2.74 (s, 3H, NCH_3), 3.63–3.65 (m, 4H, 7-H, 11-H, 9-H), 3.78–3.79 (m, 2H, 10-H, 8-H), 4.54–4.60 (m, 4H, 4-H, CH_2Ph), 4.75 (d, 1H, *J*=10.8 Hz, CH_2Ph), 4.77 (d, 1H, *J*=10.8 Hz, CH_2Ph), 4.84 (d, 1H, *J*=10.8 Hz, CH_2Ph), 4.88 (d, 1H, *J*=10.8 Hz, CH_2Ph), 5.01 (d, 1H, *J*=11.2 Hz, CH_2Ph), 6.25 (d, 1H, *J*=3.2 Hz, furyl), 6.34 (q, 1H, *J*=4.0 Hz, furyl), 7.20–7.36 (m, 21H, ArH); ^{13}C NMR ($CDCl_3$) δ: 28.78 (NCH_3), 33.78 (5-C), 50.12 (4-C), 69.59 (11-C), 73.74 (10-C), 74.96 (CH_2Ph), 75.49 (CH_2Ph), 75.59 (CH_2Ph), 76.19 (CH_2Ph), 78.21 (9-C), 83.36 (7-C), 83.67 (8-C), 101.81 (6-C), 109.71 (furyl), 110.77 (furyl), 127.85 (Ar–C), 128.03 (Ar–C), 128.15 (Ar–C), 128.19 (Ar–C), 128.24 (Ar–C), 128.31 (Ar–C), 128.51 (Ar–C), 128.82 (Ar–C), 128.86 (Ar–C), 129.22 (Ar–C), 138.18 (Ar–C), 138.35 (Ar–C), 138.59 (Ar–C), 143.47 (furyl), 151.24 (furyl), 152.26 (C=O); ESI-MS: 712 $[M+Na]^+$.

3.3.3. Compound ***7b***

White solid, mp:151–153 °C; $[\alpha]_D^{30}$ +64.04 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.83 (dd, 1H, *J*=14.0, 5.2 Hz, 5-H), 2.28 (t, 1H, *J*=13.0 Hz, 5-H), 2.69 (s, 3H, NCH_3), 3.39 (d, 1H, *J*=9.6 Hz, 11-H), 3.71 (d, 1H, *J*=10.4 Hz, 11-H), 3.77–3.82 (m, 2H, 9-H, 7-H), 4.09 (d, 1H, *J*=9.6 Hz, 10-H), 4.33 (t, 1H, *J*=9.4 Hz, 8-H), 4.51 (t, 1H, *J*=2.4 Hz, 4-H), 4.54 (d, 1H, *J*=2.4 Hz, CH_2Ph), 4.59–4.64 (m, 3H, CH_2Ph), 4.89–4.91 (m, 3H, CH_2Ph), 4.97 (d, 1H, *J*=12.0 Hz, CH_2Ph), 7.21–7.36 (m, 25H, ArH); ^{13}C NMR ($CDCl_3$) δ: 34.73 (NCH_3), 37.64 (5-C), 58.07 (4-C), 68.80 (11-C), 73.02 (CH_2Ph), 73.63 (10-C), 75.04 (CH_2Ph), 75.84 (CH_2Ph), 76.22 (CH_2Ph), 78.23 (9-C), 81.94 (7-C), 82.71 (8-C), 100.59 (6-C), 127.30 (Ar–C), 127.70 (Ar–C), 127.91 (Ar–C), 128.06 (Ar–C), 128.16 (Ar–C), 128.36 (Ar–C), 128.72 (Ar–C), 128.79 (Ar–C), 129.43 (Ar–C), 138.15 (Ar–C), 138.40 (Ar–C), 138.82 (Ar–C), 140.17 (Ar–C), 152.99 (C=O); ESI-MS: 722 $[M+Na]^+$.

3.3.4. Compound ***8b***

Pale yellow syrup; $[\alpha]_D^{30}$ +68.56 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.35–2.46 (m, 2H, 5-H), 2.73 (s, 3H, NCH_3), 3.65–3.71 (m, 4H, 7-H, 11-H, 9-H), 3.80–3.85 (m, 2H, 10-H, 8-H), 4.46 (dd, 1H, *J*=6.0, 10.8 Hz, 4-H), 4.58–4.89 (m, 7H, CH_2Ph), 4.99 (d, 1H, *J*=11.2 Hz, CH_2Ph), 7.07–7.39 (m, 25H, ArH); ^{13}C NMR ($CDCl_3$) δ: 32.99 (NCH_3), 34.70 (5-C), 57.53 (4-C), 69.63 (11-C), 73.76 (CH_2Ph), 75.03 (10-C), 75.51 (CH_2Ph), 75.56 (CH_2Ph), 76.13 (CH_2Ph), 78.28 (9-C), 83.36 (7-C), 83.77 (8-C), 101.85 (6-C), 127.27 (Ar–C), 127.86 (Ar–C), 128.02 (Ar–C), 128.13 (Ar–C), 128.25 (Ar–C), 128.36 (Ar–C), 128.80 (Ar–C), 128.88 (Ar–C), 129.53 (Ar–C), 138.17 (Ar–C), 138.46 (Ar–C), 138.59 (Ar–C), 138.63 (Ar–C), 139.80 (Ar–C), 153.15 (C=O); ESI-MS: 700 $[M+H]^+$.

3.3.5. Compound ***7c***

Colorless syrup; $[\alpha]_D^{30}$ +69.18 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.87 (dd, 1H, *J*=14.0, 5.2 Hz, 5-H), 2.31 (t, 1H, *J*=13.0 Hz, 5-H), 2.39 (s, 3H, $ArCH_3$), 2.69 (s, 3H, NCH_3), 3.39 (d, 1H, *J*=9.6 Hz, 7-H), 3.70 (d, 1H, *J*=10.4 Hz, 11-H), 3.79–3.83 (m, 2H, 9-H, 11-H), 4.09 (d, 1H, *J*=9.6 Hz, 10-H), 4.33 (t, 1H, *J*=9.4 Hz, 8-H), 4.49–4.52 (m, 1H, 4-H), 4.54 (d, 1H, *J*=12.4 Hz, CH_2Ph), 4.61 (d, 1H, *J*=10.8 Hz, CH_2Ph), 4.64 (d, 1H, *J*=12.0 Hz, CH_2Ph), 4.90 (d, 1H, *J*=10.8 Hz, CH_2Ph), 4.91 (s, 2H, CH_2Ph), 4.97 (d, 1H, *J*=11.6 Hz, CH_2Ph), 7.09–7.37 (m, 24H, ArH); ^{13}C NMR ($CDCl_3$) δ: 21.51 ($ArCH_3$), 34.63 (NCH_3), 37.56 (5-C), 57.68 (4-C), 68.71 (11-C), 72.94 (CH_2Ph), 73.61 (10-C), 75.00 (CH_2Ph), 75.80 (CH_2Ph), 76.19 (CH_2Ph), 78.15 (9-C), 81.98 (7-C), 82.66 (8-C), 100.56 (6-C),

126.90 (Ar–C), 127.26 (Ar–C), 127.66 (Ar–C), 127.88 (Ar–C), 128.04 (Ar–C), 128.11 (Ar–C), 128.15 (Ar–C), 128.22 (Ar–C), 128.35 (Ar–C), 128.70 (Ar–C), 128.71 (Ar–C), 128.77 (Ar–C), 129.67 (Ar–C), 130.07 (Ar–C), 137.02 (Ar–C), 138.14 (Ar–C), 138.35 (Ar–C), 138.49 (Ar–C), 138.79 (Ar–C), 152.99 (C=O); ESI-MS: 713 $[M]^+$.

3.3.6. Compound **8c**

White solid, mp: 98–100 °C; $[\alpha]_D^{23}$ +71.56 (*c* 3.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 1.85 (dd, 1H, *J*=14.0, 5.2 Hz, 5-H), 2.30 (t, 1H, *J*=13.0 Hz, 5-H), 2.37 (s, 3H, $ArCH_3$), 2.68 (s, 3H, NCH_3), 3.37 (d, 1H, *J*=9.6 Hz, 11-H), 3.68 (d, 1H, *J*=9.6 Hz, 11-H), 3.76–3.80 (m, 2H, 9-H, 7-H), 4.09 (d, 1H, *J*=9.6 Hz, 10-H), 4.32 (t, 1H, *J*=9.6 Hz, 8-H), 4.48–4.53 (m, 2H, 4-H, CH_2Ph), 4.58–4.63 (m, 3H, CH_2Ph), 4.88–4.89 (m, 3H, CH_2Ph), 4.95 (d, 1H, *J*=12.0 Hz, CH_2Ph), 7.02–7.35 (m, 24H, ArH); ^{13}C NMR ($CDCl_3$) δ: 21.69 ($ArCH_3$), 34.82 (NCH_3), 37.84 (5-C), 57.93 (4-C), 69.00 (11-C), 73.20 (CH_2Ph), 73.83 (10-C), 75.22 (CH_2Ph), 76.04 (CH_2Ph), 76.39 (CH_2Ph), 78.44 (9-C), 82.27 (7-C), 82.89 (8-C), 100.78 (6-C), 127.48 (Ar–C), 127.89 (Ar–C), 128.09 (Ar–C), 128.32 (Ar–C), 128.36 (Ar–C), 128.44 (Ar–C), 128.54 (Ar–C), 128.92 (Ar–C), 128.98 (Ar–C), 130.28 (Ar–C), 137.27 (Ar–C), 138.39 (Ar–C), 138.61 (Ar–C), 138.71 (Ar–C), 139.03 (Ar–C), 153.21 (C=O); ESI-MS: 714 $[M+H]^+$.

3.3.7. Compound **7d**

Colorless syrup; $[\alpha]_D^{30}$ +64.61 (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 1.80 (dd, 1H, *J*=14.0, 5.2 Hz, 5-H), 2.21 (t, 1H, *J*=12.0 Hz, 5-H), 2.70 (s, 3H, NCH_3), 3.41 (d, 1H, *J*=9.6 Hz, 11-H), 3.71 (d, 1H, *J*=10.4 Hz, 11-H), 3.80–3.84 (m, 2H, 9-H, 7-H), 4.11 (d, 1H, *J*=9.6 Hz, 10-H), 4.35 (t, 1H, *J*=9.4 Hz, 8-H), 4.50–4.55 (m, 2H, 4-H, CH_2Ph), 4.60–4.65 (m, 3H, CH_2Ph), 4.91–4.93 (m, 3H, CH_2Ph), 4.99 (d, 1H, *J*=12.0 Hz, CH_2Ph), 7.13–7.38 (m, 24H, ArH); ^{13}C NMR ($CDCl_3$) δ: 34.77 (NCH_3), 37.59 (5-C), 57.56 (4-C), 68.82 (11-C), 73.11 (CH_2Ph), 73.68 (10-C), 75.11 (CH_2Ph), 75.90 (CH_2Ph), 76.27 (CH_2Ph), 78.24 (9-C), 81.85 (7-C), 82.73 (8-C), 100.59 (6-C), 127.76 (Ar–C), 127.98 (Ar–C), 128.14 (Ar–C), 128.22 (Ar–C), 128.29 (Ar–C), 128.39 (Ar–C), 128.49 (Ar–C), 128.67 (Ar–C), 128.77 (Ar–C), 129.72 (Ar–C), 134.52 (Ar–C), 138.14 (Ar–C), 138.38 (Ar–C), 138.80 (Ar–C), 152.91 (C=O); ESI-MS: 734 $[M+H]^+$.

3.3.8. Compound **8d**

Colorless syrup; $[\alpha]_D^{22}$ +63.02 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 2.29–2.43 (m, 2H, 5-H), 2.70 (s, 3H, NCH_3), 3.63–3.69 (m, 4H, 7-H, 11-H, 9-H), 3.79–3.84 (m, 2H, 10-H, 8-H), 4.44 (dd, 1H, *J*=5.2, 12.0 Hz, 4-H), 4.57–4.63 (m, 3H, CH_2Ph), 4.75–4.92 (m, 4H, CH_2Ph), 4.97 (d, 1H, *J*=11.2 Hz, CH_2Ph), 7.12–7.38 (m, 24H, ArH); ^{13}C NMR ($CDCl_3$) δ: 32.98 (NCH_3), 34.69 (5-C), 56.98 (4-C), 69.64 (11-C), 73.75 (CH_2Ph), 75.10 (10-C), 75.52 (CH_2Ph), 75.57 (CH_2Ph), 76.13 (CH_2Ph), 78.25 (9-C), 83.34 (7-C), 83.73 (8-C), 101.78 (6-C), 127.86 (Ar–C), 128.06 (Ar–C), 128.18 (Ar–C), 128.24 (Ar–C), 128.34 (Ar–C), 128.39 (Ar–C), 128.63 (Ar–C), 128.82 (Ar–C), 129.76 (Ar–C), 134.67 (Ar–C), 138.11 (Ar–C), 138.37 (Ar–C), 138.54 (Ar–C), 153.00 (C=O); ESI-MS: 756 $[M+Na]^+$.

3.3.9. Compound **7e**

White solid, mp: 53–55 °C; $[\alpha]_D^{21}$ +81.51 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 2.12 (m, 1H, 5-H), 2.73 (m, 1H, 5-H), 2.76 (s, 3H, NCH_3), 3.49 (d, 1H, *J*=9.6 Hz, 11-H), 3.73–3.90 (m, 4H, 7-H, 9-H, 10-H, 11-H), 4.22 (m, 1H, 8-H), 4.60–5.10 (m, 9H, 4-H, CH_2Ph), 7.12–7.45 (m, 24H, ArH); ^{13}C NMR ($CDCl_3$) δ: 32.37 (NCH_3), 36.51 (5-C), 56.53 (4-C), 68.68 (11-C), 73.41 (CH_2Ph), 73.66 (10-C), 75.16 (CH_2Ph), 75.86 (CH_2Ph), 75.93 (CH_2Ph), 78.31 (9-C), 81.93 (7-C), 82.79 (8-C), 100.83 (6-C), 126.90 (Ar–C), 127.86 (Ar–C), 128.03 (Ar–C), 128.12 (Ar–C), 128.24 (Ar–C), 128.33 (Ar–C), 128.41 (Ar–C), 128.51 (Ar–C), 128.78 (Ar–C), 128.86 (Ar–C), 129.09 (Ar–C), 129.30 (Ar–C), 130.25 (Ar–C), 132.77 (Ar–C), 137.63 (Ar–C), 138.19 (Ar–C), 138.25 (Ar–C), 138.60 (Ar–C), 138.87 (Ar–C), 152.91 (C=O); ESI-MS: 733 $[M]^+$.

3.3.10. Compound **8e**

Colorless syrup; $[\alpha]_D^{30}$ +23.61 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 2.21 (m, 1H, 5-H), 2.56 (m, 1H, 5-H), 2.75 (s, 3H, NCH_3), 3.67–3.85 (m, 6H, 7-H, 8-H, 9-H, 10-H, 11-H), 4.58–4.65 (m, 3H, 4-H, CH_2Ph), 4.76–4.99 (m, 6H, CH_2Ph), 7.16–7.40 (m, 24H, ArH); ^{13}C NMR ($CDCl_3$) δ: 30.89 (NCH_3), 35.02 (5-C), 53.85 (4-C), 69.43 (11-C), 73.72 (CH_2Ph), 75.11 (10-C), 75.60 (CH_2Ph), 75.71 (CH_2Ph), 76.23 (CH_2Ph), 78.25 (9-C), 83.39 (7-C), 83.85 (8-C), 102.03 (6-C), 126.85 (Ar–C), 127.91 (Ar–C), 127.96 (Ar–C), 128.15 (Ar–C), 128.22 (Ar–C), 128.40 (Ar–C), 128.52 (Ar–C), 128.79 (Ar–C), 128.82 (Ar–C), 128.92 (Ar–C), 129.42 (Ar–C), 129.72 (Ar–C), 130.33 (Ar–C), 133.10 (Ar–C), 137.15 (Ar–C), 138.13 (Ar–C), 138.42 (Ar–C), 138.64 (Ar–C), 153.56 (C=O); ESI-MS: 756 $[M+Na]^+$.

3.3.11. Compound **7f**

Colorless syrup; $[\alpha]_D^{20}$ +58.74 (*c* 3.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 1.78 (dd, 1H, *J*=14.0, *J*=5.2 Hz, 5-H), 2.21 (t, 1H, *J*=13.2 Hz, 5-H), 2.67 (s, 3H, NCH_3), 3.36 (d, 1H, *J*=9.6 Hz, 11-H), 3.66 (d, 1H, *J*=11.2 Hz, 11-H), 3.75–3.80 (m, 2H, 9-H, 7-H), 4.06 (d, 1H, *J*=9.6 Hz, 10-H), 4.30 (d, 1H, *J*=9.6 Hz, 8-H), 4.41 (dd, 1H, *J*=12.0, 5.2 Hz, 4-H), 4.48 (d, 1H, *J*=12.0 Hz, CH_2Ph), 4.56–4.61 (m, 3H, CH_2Ph), 4.86–4.88 (m, 3H, CH_2Ph), 4.95 (d, 1H, *J*=12.0 Hz, CH_2Ph), 5.95 (s, 2H, CH_2), 6.59–6.64 (m, 2H, ArH), 6.75 (d, 1H, *J*=8.4 Hz, ArH), 7.18–7.33 (m, 20H, ArH); ^{13}C NMR ($CDCl_3$) δ: 34.53 (NCH_3), 37.58 (5-C), 57.80 (4-C), 68.81 (11-C), 73.04 (CH_2Ph), 73.66 (10-C), 75.08 (CH_2Ph), 75.91 (CH_2Ph), 76.25 (CH_2Ph), 78.26 (9-C), 82.04 (7-C), 82.74 (8-C), 100.58 (6-C), 101.77 (CH_2), 107.31 (Ar–C), 108.87 (Ar–C), 121.04 (Ar–C), 127.75 (Ar–C), 127.96 (Ar–C), 128.12 (Ar–C), 128.21 (Ar–C), 128.41 (Ar–C), 128.76 (Ar–C), 128.83 (Ar–C), 133.92 (Ar–C), 138.23 (Ar–C), 138.42 (Ar–C), 138.85 (Ar–C), 148.06 (Ar–C), 148.83 (Ar–C), 152.92 (C=O); ESI-MS: 744 $[M+H]^+$.

3.3.12. Compound **8f**

Colorless syrup; $[\alpha]_D^{20}$ −26.25 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 2.28–2.38 (m, 2H, 5-H), 2.70 (s, 3H, NCH_3), 3.63–3.66 (m, 4H, 7-H, 11-H, 9-H), 3.75–3.80 (m, 2H, 10-H, 8-H), 4.34 (dd, 1H, *J*=6.0, 10.8 Hz, 4-H), 4.53–4.61 (m, 3H, CH_2Ph), 4.75–4.86 (m, 4H, CH_2Ph), 4.96 (d, 1H, *J*=11.2 Hz, CH_2Ph), 5.96 (m, 2H, CH_2), 6.62–6.65 (m, 2H, ArH), 6.74 (d, 1H, *J*=8.0 Hz, ArH), 7.24–7.35 (m, 20H, ArH); ^{13}C NMR ($CDCl_3$) δ: 32.88 (NCH_3), 34.48 (5-C), 57.22 (4-C), 69.62 (11-C), 73.74 (CH_2Ph), 75.01 (10-C), 75.55 (CH_2Ph), 76.15 (CH_2Ph), 78.27 (9-C), 83.37 (7-C), 83.80 (8-C), 101.80 (6-C, CH_2), 107.22 (Ar–C), 108.90 (Ar–C), 120.99 (Ar–C), 127.87 (Ar–C), 128.04 (Ar–C), 128.17 (Ar–C), 128.27 (Ar–C), 128.39 (Ar–C), 128.83 (Ar–C), 128.90 (Ar–C), 133.54 (Ar–C), 138.17 (Ar–C), 138.46 (Ar–C), 138.60 (Ar–C), 138.63 (Ar–C), 148.15 (Ar–C), 148.89 (Ar–C), 153.05 (C=O); ESI-MS: 766 $[M+Na]^+$.

3.3.13. Compound **7g**

Pale yellow syrup; $[\alpha]_D^{22}$ +71.05 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 1.87 (dd, 1H, *J*=14.0, 5.2 Hz, 5-H), 2.34 (t, 1H, *J*=12.0 Hz, 5-H), 2.67 (s, 3H, NCH_3), 2.95 (s, 6H, NCH_3), 3.37 (d, 1H, *J*=9.6 Hz, 11-H), 3.67 (d, 1H, *J*=10.8 Hz, 11-H), 3.76–3.81 (m, 2H, 9-H, 7-H), 3.10 (m, 1H, 10-H), 4.31 (t, 1H, *J*=9.6 Hz, 8-H), 4.46–4.62 (m, 5H, 4-H, CH_2Ph), 4.86–4.89 (m, 3H, CH_2Ph), 4.94 (d, 1H, *J*=12.0 Hz, CH_2Ph), 6.68 (d, 2H, *J*=8.4 Hz, ArH), 7.05 (d, 2H, *J*=8.4 Hz, ArH), 7.18–7.33 (m, 20H, ArH); ^{13}C NMR ($CDCl_3$) δ: 34.46 (NCH_3), 37.56 (5-C), 40.91 (NCH_3), 57.35 (4-C), 68.82 (11-C), 72.97 (CH_2Ph), 73.65 (10-C), 75.04 (CH_2Ph), 75.88 (CH_2Ph), 76.21 (CH_2Ph), 78.29 (9-C), 82.23 (7-C), 82.74 (8-C), 100.60 (6-C), 113.03 (Ar–C), 127.15 (Ar–C), 127.72 (Ar–C), 127.92 (Ar–C), 128.07 (Ar–C), 128.14 (Ar–C), 128.20 (Ar–C), 128.38 (Ar–C), 128.78 (Ar–C), 128.82 (Ar–C), 138.30 (Ar–C), 138.47 (Ar–C), 138.91 (Ar–C), 150.89 (Ar–C), 153.11 (C=O); ESI-MS: 765 $[M+Na]^+$.

3.3.14. Compound ***8g***

Pale yellow syrup; $[\alpha]_D^{22}$ −40.59 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 2.33–2.38 (m, 2H, 5-H), 2.68 (s, 3H, NCH_3), 2.95 (s, 6H, NCH_3), 3.61–3.68 (m, 4H, 7-H, 11-H, 9-H), 3.75–3.81 (m, 2H, 10-H, 8-H), 4.33 (dd, 1H, *J*=6.0, 10.8 Hz, 4-H), 4.53–4.85 (m, 7H, CH_2Ph), 4.99 (d, 1H, *J*=11.2 Hz, CH_2Ph), 6.67 (d, 2H, *J*=8.4 Hz, ArH), 7.03 (d, 2H, *J*=8.4 Hz, ArH), 7.19–7.36 (m, 20H, ArH); ^{13}C NMR ($CDCl_3$) δ: 32.74 (NCH_3), 34.40 (5-C), 40.88 (NCH_3), 56.76 (4-C), 69.63 (11-C), 73.74 (CH_2Ph), 74.91 (10-C), 75.42 (CH_2Ph), 75.55 (CH_2Ph), 76.13 (CH_2Ph), 78.31 (9-C), 83.35 (7-C), 83.82 (8-C), 101.83 (6-C), 113.04 (Ar–C), 126.77 (Ar–C), 127.86 (Ar–C), 127.98 (Ar–C), 128.04 (Ar–C), 128.12 (Ar–C), 128.23 (Ar–C), 128.30 (Ar–C), 128.38 (Ar–C), 128.79 (Ar–C), 128.88 (Ar–C), 138.23 (Ar–C), 138.60 (Ar–C), 138.69 (Ar–C), 150.96 (Ar–C), 153.20 (C=O); ESI-MS: 765 $[M+Na]^+$.

3.4. General procedure for the catalytic hydrogenation of 7 and 8

To a solution of **7** or **8** (150 mg) in MeOH (10 mL) was added $Pd(OH)_2/C$ catalyst (100 mg) and the mixture was vigorously stirred under H_2 atmosphere for 2 h. The catalyst was removed by filtration, the filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography using ethyl acetate/MeOH (5:1) as the eluent to give the corresponding spiro-oxazinanone glucosides **9** or **10** (almost quantitatively), respectively. In the cases of **7a** and **8a**, the furyl-hydrogenated products **9a1**, **9a2** and **10a1**, **10a2** were quantitatively obtained. The results are listed in Table 1.

3.4.1. Compound ***9a1***

White solid, mp: 222–224 °C; $[\alpha]_D^{22}$ +62.34 (*c* 0.3, H_2O); ^1H NMR (D_2O) δ: 1.52–1.56 (m, 1H, 3′-H), 1.81–1.85 (m, 2H, 4′-H), 1.89–2.01 (m, 2H, 5-H, 3′-H), 2.07–2.13 (m, 1H, 5-H), 2.92 (s, 3H, NCH_3), 3.31 (d, 1H, *J*=9.6 Hz, 11-H), 3.38 (t, 1H, *J*=9.6 Hz, 11-H), 3.52–3.55 (m, 1H, 10-H), 3.60–3.80 (m, 6H, 7-H, 8-H, 9-H, 5′-H, 4-H), 4.15 (q, 1H, *J*=14.4, 7.2 Hz, 2′-H); ^{13}C NMR (D_2O) δ: 25.57 (4′-C), 26.78 (3′-C), 29.20 (NCH_3), 35.01 (5-C), 55.37 (4-C), 60.57 (5′-C), 69.29 (11-C), 69.47 (10-C), 73.18 (9-C), 73.82 (7-C), 74.68 (8-C), 80.18 (2′-C), 102.08 (6-C), 155.32 (C=O); HRMS (ESI): calcd for $C_{14}H_{23}NO_8$ (M^+): 333.1424, found: 333.1422.

3.4.2. Compound ***9a2***

White solid, mp: 174–176 °C; $[\alpha]_D^{22}$ +28.67 (*c* 0.3, H_2O); ^1H NMR (D_2O) δ: 1.62–1.69 (m, 1H, 3′-H), 1.91–1.98 (m, 2H, 3′-H, 4′-H), 2.03–2.10 (m, 2H, 5-H, 4′-H), 2.30 (t, 1H, *J*=12.0 Hz, 5-H), 3.02 (s, 3H, NCH_3), 3.43 (d, 1H, *J*=9.6 Hz, 11-H), 3.49 (t, 1H, *J*=9.6 Hz, 11-H), 3.62–3.65 (m, 1H, 10-H), 3.71–3.92 (m, 6H, 7-H, 8-H, 9-H, 5′-H, 4-H), 4.44 (t, 1H, *J*=7.2 Hz, 2′-H); ^{13}C NMR (D_2O) δ: 25.87 (4′-C), 26.94 (3′-C), 27.10 (NCH_3), 33.72 (5-C), 55.40 (4-C), 60.66 (5′-C), 69.60 (11-C), 69.68 (10-C), 73.23 (9-C), 73.86 (7-C), 74.68 (8-C), 77.26 (2′-C), 101.54 (6-C), 155.50 (C=O); HRMS (ESI): calcd for $C_{14}H_{23}NO_8Na$: 356.1321, found: 356.1327.

3.4.3. Compound ***10a1***

White solid, mp: 186–188 °C; $[\alpha]_D^{20}$ −15.82 (*c* 0.4, CH_3OH); ^1H NMR (D_2O) δ: 1.55–1.61 (m, 1H, 3′-H), 1.79–1.89 (m, 2H, 3′-H, 4′-H), 1.91–1.98 (m, 2H, 5-H, 4′-H), 2.22 (dd, 1H, *J*=15.2, 5.2 Hz, 5-H), 2.89 (s, 3H, NCH_3), 3.34–3.46 (m, 4H, 7-H, 10-H, 11-H), 3.57–3.64 (m, 2H, 5′-H, 4-H), 3.70–3.78 (m, 3H, 8-H, 9-H, 5′-H), 4.19 (q, 1H, *J*=14.4, 7.2 Hz, 2′-H); ^{13}C NMR (D_2O) δ: 22.16 (4′-C), 25.68 (3′-C), 26.50 (NCH_3), 34.41 (5-C), 54.17 (4-C), 61.04 (5′-C), 69.40 (11-C), 69.77 (10-C), 73.69 (9-C), 74.67 (7-C), 75.64 (8-C), 79.54 (2′-C), 102.52 (6-C), 155.15 (C=O); HRMS (ESI): calcd for $C_{14}H_{24}NO_8$ ($[M+H]^+$): 334.1502, found: 334.1509.

3.4.4. Compound ***10a2***

White solid, mp: 129–131 °C; $[\alpha]_D^{21}$ +58.68 (*c* 0.3, H_2O); ^1H NMR (D_2O) δ: 1.56–1.61 (m, 1H, 3′-H), 1.83–1.88 (m, 2H, 4′-H), 1.95–2.01 (m, 2H, 5-H, 3′-H), 2.26 (dd, 1H, *J*=15.2, 5.2 Hz, 5-H), 2.89 (s, 3H, NCH_3), 3.37–3.48 (m, 4H, 7-H, 10-H, 11-H), 3.55–3.61 (m, 2H, 5′-H, 4-H), 3.70–3.81 (m, 3H, 8-H, 9-H, 5′-H), 4.37 (t, 1H, *J*=7.2 Hz, 2′-H); ^{13}C NMR (D_2O) δ: 20.55 (4′-C), 25.88 (3′-C), 26.95 (NCH_3), 33.43 (5-C), 54.51 (4-C), 61.03 (5′-C), 69.66 (11-C), 69.76 (10-C), 73.69 (9-C), 74.72 (7-C), 75.64 (8-C), 77.00 (2′-C), 102.24 (6-C), 155.30 (C=O); HRMS (ESI): calcd for $C_{14}H_{23}NO_8$ (M^+): 333.1424, found: 333.1428.

3.4.5. Compound ***9b***

White solid, mp: 226–228 °C; $[\alpha]_D^{20}$ +39.41 (*c* 0.5, H_2O); ^1H NMR (D_2O) δ: 2.20–2.24 (m, 1H, 5-H), 2.38–2.45 (m, 1H, 5-H), 2.64 (s, 3H, NCH_3), 3.37–3.52 (m, 2H, 11-H), 3.71–3.82 (m, 4H, 10-H, 9-H, 8-H 7-H), 4.74–4.78 (m, 1H, 4-H), 7.37–7.43 (m, 5H, ArH); ^{13}C NMR (D_2O) δ: 34.51 (NCH_3), 36.76 (5-C), 57.74 (4-C), 60.76 (11-C), 69.63 (10-C), 73.24 (9-C), 73.73 (7-C), 74.79 (8-C), 101.52 (6-C), 127.75 (Ar–C), 129.11 (Ar–C), 129.71 (Ar–C), 139.57 (Ar–C), 155.58 (C=O); HRMS (ESI): calcd for $C_{16}H_{21}NO_7Na$ ($[M+Na]^+$): 362.1216, found: 362.1222.

3.4.6. Compound ***10b***

White solid, mp: 184–186 °C; $[\alpha]_D^{21}$ −43.62 (*c* 0.5, H_2O); ^1H NMR (D_2O) δ: 2.24 (d, 1H, *J*=14.4 Hz, 5-H), 2.50 (dd, 1H, *J*=10.4, 5.2 Hz, 5-H), 2.56 (s, 3H, NCH_3), 3.41–3.55 (m, 4H, 11-H, 10-H, 7-H), 3.67 (dd, 1H, *J*=10.4, 5.2 Hz, 9-H), 3.85 (d, 1H, *J*=12.4 Hz, 8-H), 4.48 (dd, 1H, *J*=8.4, 4.8 Hz 4-H), 7.28–7.39 (m, 5H, ArH); ^{13}C NMR (D_2O) δ: 30.55 (NCH_3), 34.45 (5-C), 57.00 (4-C), 61.24 (11-C), 69.88 (10-C), 73.75 (9-C), 74.73 (7-C), 75.81 (8-C), 102.36 (6-C), 127.84 (Ar–C), 129.20 (Ar–C), 129.69 (Ar–C), 139.12 (Ar–C), 155.36 (C=O); HRMS (ESI): calcd for $C_{16}H_{22}NO_7$ ($[M+H]^+$): 340.1396, found: 340.1408.

3.4.7. Compound ***9c***

White solid, mp: 227–229 °C; $[\alpha]_D^{21}$ +108.68 (*c* 0.5, H_2O); ^1H NMR (D_2O) δ: 2.15–2.19 (m, 1H, 5-H), 2.30 (s, 3H, CH_3), 2.36–2.43 (m, 1H, 5-H), 2.63 (s, 3H, NCH_3), 3.38–3.43 (m, 1H, 11-H), 3.45–3.53 (m, 1H, 11-H), 3.71–3.84 (m, 4H, 10-H, 9-H, 8-H, 7-H), 4.74–4.76 (m, 1H, 4-H), 7.24–7.25 (m, 4H, ArH); ^{13}C NMR (D_2O) δ: 20.64 (CH_3), 34.40 (NCH_3), 36.75 (5-C), 57.41 (4-C), 60.77 (11-C), 69.65 (10-C), 73.24 (9-C), 73.74 (7-C), 74.77 (8-C), 101.48 (6-C), 127.75 (Ar–C), 130.21 (Ar–C), 136.49 (Ar–C), 139.42 (Ar–C), 155.54 (C=O); HRMS (ESI): calcd for $C_{17}H_{23}NO_7Na$ ($[M+Na]^+$): 376.1372, found: 376.1377.

3.4.8. Compound ***10c***

White solid, mp: 142–144 °C; $[\alpha]_D^{22}$ −16.81 (*c* 0.5, H_2O); ^1H NMR (D_2O) δ: 2.29 (m, 4H, 5-H, CH_3), 2.50 (m, 1H, 5-H), 2.60 (s, 3H, NCH_3), 3.49–3.60 (m, 4H, 11-H, 10-H, 9-H), 3.73–3.74 (m, 1H, 7-H), 3.89–3.91 (m, 1H, 8-H), 4.50–4.51 (m, 1H, 4-H), 7.24 (m, 4H, ArH); ^{13}C NMR (D_2O) δ: 20.63 (CH_3), 30.50 (NCH_3), 34.33 (5-C), 56.65 (4-C), 61.21 (11-C), 69.86 (10-C), 73.73 (9-C), 74.70 (7-C), 75.77 (8-C), 102.32 (6-C), 127.82 (Ar–C), 130.18 (Ar–C), 136.03 (Ar–C), 139.53 (Ar–C), 155.32 (C=O); HRMS (ESI): calcd for $C_{17}H_{23}NO_7Na$ ($[M+Na]^+$): 376.1372, found: 376.1381.

3.4.9. Compound ***9d***

Pale yellow solid, mp: 239–241 °C; $[\alpha]_D^{22}$ +18.41 (*c* 0.5, H_2O); ^1H NMR (D_2O) δ: 2.20–2.24 (m, 1H, 5-H), 2.39–2.46 (m, 1H, 5-H), 2.65 (s, 3H, NCH_3), 3.41 (d, 1H, *J*=9.6 Hz, 11-H), 3.50 (t, 1H, *J*=8.0 Hz, 11-H), 3.71–3.88 (m, 4H, 10-H, 9-H, 8-H 7-H), 4.72–4.81 (m, 1H, 4-H), 7.37–7.45 (m, 4H, ArH); ^{13}C NMR (D_2O) δ: 34.51 (NCH_3), 36.76 (5-C), 57.73 (4-C), 60.76 (11-C), 69.63 (10-C), 73.23 (9-C), 73.71 (7-C), 74.78 (8-C), 101.52 (6-C), 127.75 (Ar–C), 129.10 (Ar–C), 129.70 (Ar–C), 139.55 (Ar–C), 155.57 (C=O); HRMS (ESI): calcd for $C_{16}H_{20}ClNO_7Na$ ($[M+Na]^+$): 396.0826, found: 396.0829.

3.4.10. Compound ***10d***

White solid, mp: 199–201 °C; $[\alpha]_D^{25}$ +60.58 (*c* 0.8, H_2O); ^1H NMR (D_2O) δ: 2.24–2.30 (m, 1H, 5-H), 2.49–2.52 (m, 1H, 5-H), 2.66 (s, 3H, NCH_3), 3.24–3.29 (m, 1H, 11-H), 3.45–3.57 (m, 3H, 10-H, 11-H, 7-H), 3.69–3.78 (m, 1H, 9-H), 3.87–3.90 (m, 1H, 8-H), 4.49–4.53 (m, 1H, 4-H), 7.19–7.39 (m, 4H, ArH); ^{13}C NMR (D_2O) δ: 30.58 (NCH_3), 34.33 (5-C), 57.00 (4-C), 61.27 (11-C), 69.91 (10-C), 73.80 (9-C), 74.71 (7-C), 75.84 (8-C), 102.28 (6-C), 127.70 (Ar–C), 129.12 (Ar–C), 129.62 (Ar–C), 139.08 (Ar–C), 155.29 (C═O); HRMS (ESI): calcd for $C_{16}H_{20}ClNO_7Na$ ($[M+Na]^+$): 396.0826, found: 396.0835.

3.4.11. Compound ***9e***

White solid, mp: 242–244 °C; $[\alpha]_D^{22}$ +45.41 (*c* 0.6, H_2O); ^1H NMR (D_2O) δ: 2.12–2.19 (m, 1H, 5-H), 2.37 (t, 1H, *J*=12.8 Hz, 5-H), 2.60 (s, 3H, NCH_3), 3.23–3.54 (m, 3H, 11-H, 10-H), 3.59–3.82 (m, 3H, 7-H, 9-H, 8-H), 4.74–4.77 (m, 1H, 4-H), 7.24–7.40 (m, 4H, ArH); ^{13}C NMR (D_2O) δ: 34.52 (NCH_3), 36.77 (5-C), 57.74 (4-C), 60.77 (11-C), 69.64 (10-C), 73.24 (9-C), 73.72 (7-C), 74.79 (8-C), 101.52 (6-C), 127.18 (Ar–C), 127.76 (Ar–C), 128.94 (Ar–C), 129.71 (Ar–C), 139.58 (Ar–C), 155.58 (C═O); HRMS (ESI): calcd for $C_{16}H_{20}ClNO_7Na$ ($[M+Na]^+$): 396.0826, found: 396.0831.

3.4.12. Compound ***10e***

White solid, mp: 211–213 °C; $[\alpha]_D^{23}$ −20.32 (*c* 0.4, H_2O); ^1H NMR (CD_3OD) δ: 2.32–2.39 (m, 1H, 5-H), 2.44–2.52 (m, 1H, 5-H), 2.67 (s, 3H, NCH_3), 3.37–3.42 (m, 1H, 11-H), 3.46–3.53 (m, 2H, 10-H, 11-H), 3.57–3.61 (m, 1H, 7-H), 3.68–3.73 (m, 1H, 9-H), 3.96–3.99 (m, 1H, 8-H), 4.58 (dd, 1H, *J*=4.8, 12.0 Hz, 4-H), 7.34–7.48 (m, 4H, ArH); ^{13}C NMR (CD_3OD) δ: 31.11 (NCH_3), 33.72 (5-C), 51.81 (4-C), 61.96 (11-C), 70.59 (10-C), 74.57 (9-C), 75.17 (7-C), 76.54 (8-C), 102.16 (6-C), 127.32 (Ar–C), 128.63 (Ar–C), 129.29 (Ar–C), 139.76 (Ar–C), 154.73 (C═O); HRMS (ESI): calcd for $C_{16}H_{21}ClNO_7$ ($[M+H]^+$): 374.1007, found: 374.1012.

3.4.13. Compound ***9f***

White solid, mp: 238–240 °C; $[\alpha]_D^{23}$ +36.85 (*c* 0.5, H_2O); ^1H NMR (CD_3OD) δ: 2.10 (dd, 1H, *J*=14.0, 5.2 Hz, 5-H), 2.49 (t, 1H, *J*=12.4 Hz, 5-H), 2.71 (s, 3H, NCH_3), 3.28–3.42 (m, 2H, 11-H), 3.71–3.88 (m, 4H, 10-H, 9-H, 8-H, 7-H), 4.72–4.76 (m, 1H, 4-H), 5.98 (s, 2H, CH_2), 6.83–6.86 (m, 3H, ArH); ^{13}C NMR (CD_3OD) δ: 33.48 (NCH_3), 37.26 (5-C), 57.49 (4-C), 60.56 (11-C), 70.34 (10-C), 73.63 (9-C), 74.40 (7-C), 75.40 (8-C), 101.24 (6-C), 101.75 (CH_2), 106.99 (Ar–C), 108.50 (Ar–C), 121.09 (Ar–C), 133.80 (Ar–C), 148.21 (Ar–C), 148.41 (Ar–C), 154.47 (C═O); HRMS (ESI): calcd for $C_{17}H_{21}NO_9Na$ ($[M+Na]^+$): 406.1114, found: 406.1119.

3.4.14. Compound ***10f***

White solid, mp: 178–180 °C; $[\alpha]_D^{22}$ −18.56 (*c* 0.5, H_2O); ^1H NMR (CD_3OD) δ: 2.37–2.48 (m, 2H, 5-H), 2.72 (s, 3H, NCH_3), 3.33–3.54 (m, 4H, 11-H, 10-H, 9-H), 3.69–3.73 (m, 1H, 7-H), 4.10–4.15 (m, 1H, 8-H), 4.51–4.54 (m, 1H, 4-H), 5.99 (s, 2H, CH_2), 6.86 (d, 3H, ArH); ^{13}C NMR (CD_3OD) δ: 30.98 (NCH_3), 33.37 (5-C), 56.90 (4-C), 62.02 (11-C), 70.59 (10-C), 74.64 (9-C), 75.19 (7-C), 76.62 (8-C), 101.75 (CH_2), 102.07 (6-C), 107.06 (Ar–C), 108.49 (Ar–C), 121.10 (Ar–C), 133.54 (Ar–C), 148.25 (Ar–C), 148.90 (Ar–C), 154.61 (C═O); HRMS (ESI): calcd for $C_{17}H_{21}NO_9Na$ ($[M+Na]^+$): 406.1114, found: 406.1121.

3.4.15. Compound ***9g***

White solid, mp: 216–218 °C; $[\alpha]_D^{21}$ −20.52 (*c* 0.3, H_2O); ^1H NMR (CD_3OD) δ: 2.06 (dd, 1H, *J*=8.8, 5.2 Hz, 5-H), 2.53 (t, 1H, *J*=12.4 Hz, 5-H), 2.68 (s, 3H, NCH_3), 2.95 (s, 6H, NCH_3), 3.37–3.45 (m, 2H, 11-H), 3.73–3.89 (m, 4H, 10-H, 9-H, 8-H, 7-H), 4.70 (dd, 1H, *J*=12.0, 4.8 Hz, 4-H), 6.81 (d, 2H, *J*=8.8 Hz, ArH), 7.17 (d, 2H, *J*=8.8 Hz, ArH); ^{13}C NMR (CD_3OD) δ: 33.39 (NCH_3), 37.20 (5-C), 40.00 (NCH_3), 57.10 (4-C), 61.44 (11-C), 70.36 (10-C), 73.67 (9-C), 74.45 (7-C), 75.32 (8-C), 101.20 (6-C), 113.37 (Ar–C), 127.39 (Ar–C), 128.12 (Ar–C), 151.18 (Ar–C), 154.47 (C═O); HRMS (ESI): calcd for $C_{18}H_{27}N_2O_7$ ($[M+H]^+$): 383.1818, found: 383.1824.

3.4.16. Compound ***10g***

White solid, mp: 177–179 °C; $[\alpha]_D^{21}$ +50.68 (*c* 0.7, H_2O); ^1H NMR (CD_3OD) δ: 2.04 (dd, 1H, *J*=8.8, 5.2 Hz, 5-H), 2.51 (t, 1H, *J*=12.4 Hz, 5-H), 2.66 (s, 3H, NCH_3), 2.94 (s, 6H, NCH_3), 3.26 (d, 1H, *J*=9.6 Hz, 11-H), 3.40 (t, 1H, *J*=9.6 Hz, 11-H), 3.69–3.87 (m, 4H, 10-H, 9-H, 8-H, 7-H), 4.68 (dd, 1H, *J*=12.0, 4.8 Hz, 4-H), 6.79 (d, 2H, *J*=8.8 Hz, ArH), 7.15 (d, 2H, *J*=8.8 Hz, ArH); ^{13}C NMR (CD_3OD) δ: 33.34 (NCH_3), 37.18 (5-C), 39.88 (NCH_3), 57.09 (4-C), 61.40 (11-C), 70.34 (10-C), 73.64 (9-C), 74.48 (7-C), 75.34 (8-C), 101.25 (6-C), 113.22 (Ar–C), 127.21 (Ar–C), 128.06 (Ar–C), 151.30 (Ar–C), 154.58 (C═O); HRMS (ESI): calcd for $C_{18}H_{27}N_2O_7$ ($[M+H]^+$): 383.1818, found: 383.1822.

3.4.17. Compound ***11h***

Pale yellow syrup; $[\alpha]_D^{25}$ +2.53 (*c* 3.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 2.01–2.08 (m, 1H, 2-H), 2.29–2.37 (m, 1H, 2-H), 2.43–2.51 (m, 1H, 1-H), 2.69–2.74 (m, 1H, 1-H), 2.79 (s, 3H, NCH_3), 3.61 (d, 1H, *J*=9.6 Hz, 8-H), 3.72–3.89 (m, 4H, 8-H, 6-H, 4-H, 7-H), 4.18 (t, 1H, *J*=9.4 Hz, 5-H), 4.59–4.68 (m, 3H, CH_2Ph), 4.76 (d, 1H, *J*=12.0 Hz, CH_2Ph), 4.89–5.05 (m, 4H, CH_2Ph), 6.96 (d, 2H, *J*=5.6 Hz, ArH), 7.24–7.39 (m, 20H, ArH), 8.45 (d, 2H, *J*=5.6 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ: 29.79 (1-C), 33.15 (2-C), 40.54 (NCH_3), 69.21 (8-C), 72.90 (CH_2Ph), 73.85 (7-C), 75.61 (CH_2Ph), 75.81 (CH_2Ph), 75.97 (CH_2Ph), 79.16 (6-C), 80.30 (4-C), 83.95 (5-C), 104.57 (3-C), 124.30 (Ar–C), 128.03 (Ar–C), 128.11 (Ar–C), 128.27 (Ar–C), 128.44 (Ar–C), 128.75 (Ar–C), 128.81 (Ar–C), 128.92 (Ar–C), 128.96 (Ar–C), 138.51 (Ar–C), 138.84 (Ar–C), 139.02 (Ar–C), 149.93 (Py–C), 151.65 (Py–C); HRMS (ESI): calcd for $C_{42}H_{46}N_2O_6$ (M^+): 674.3356, found: 674.3361.

3.4.18. Compound ***12h***

rColorless syrup; $[\alpha]_D^{23}$ +5.64 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 1.86–1.94 (m, 2H, 2-H), 2.56–2.67 (m, 1H, 1-H), 2.69–2.80 (m, 1H, 1-H), 3.44 (d, 1H, *J*=9.2 Hz, 8-H), 3.68–3.77 (m, 3H, 8-H, 6-H, 4-H), 4.00–4.03 (m, 2H, 7-H, 5-H), 4.53–4.69 (m, 4H, CH_2Ph), 4.84–4.97 (m, 4H, CH_2Ph), 7.00 (d, 2H, *J*=5.6 Hz, ArH), 7.20–7.36 (m, 20H, ArH), 8.44 (d, 2H, *J*=5.6 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ: 28.45 (1-C), 39.34 (2-C), 69.17 (8-C), 72.08 (CH_2Ph), 73.77 (7-C), 75.33 (CH_2Ph), 75.86 (CH_2Ph), 76.05 (CH_2Ph), 78.73 (6-C), 82.10 (4-C), 84.33 (5-C), 98.18 (3-C), 124.29 (Ar–C), 128.07 (Ar–C), 128.15 (Ar–C), 128.26 (Ar–C), 128.50 (Ar–C), 128.77 (Ar–C), 128.83 (Ar–C), 128.88 (Ar–C), 128.93 (Ar–C), 138.13 (Ar–C), 138.62 (Ar–C), 138.71 (Ar–C), 138.91 (Ar–C), 149.92 (Py–C), 151.71 (Py–C); HRMS (ESI): calcd for $C_{41}H_{43}NO_6Na$ ($[M+Na]^+$): 668.2988, found: 668.2996.

3.4.19. Compound ***12i***

Pale yellow syrup; $[\alpha]_D^{23}$ +10.20 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 1.30–1.33 (m, 1H, 2-H), 1.46–1.49 (m, 1H, 2-H), 2.06–2.16 (m, 1H, 1-H), 2.43–2.47 (m, 1H, 1-H), 3.34 (d, 1H, *J*=9.6 Hz, 8-H), 3.71–3.81 (m, 3H, 8-H, 6-H, 4-H), 4.13–4.15 (m, 5-H), 4.34–4.36 (m, 7-H), 4.56–4.65 (m, 4H, CH_2Ph), 4.77 (d, 1H, *J*=12.0 Hz, CH_2Ph), 4.85–5.05 (m, 3H, CH_2Ph), 7.06–7.39 (m, 22H, ArH), 7.58–7.67 (m, 1H, ArH), 8.56–8.59 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ: 30.09 (1-C), 34.66 (2-C), 69.30 (8-C), 71.33 (CH_2Ph), 73.93 (7-C), 75.34 (CH_2Ph), 76.13 (CH_2Ph), 76.32 (CH_2Ph), 79.08 (6-C), 80.19 (4-C), 83.63 (5-C), 98.75 (3-C), 122.42 (Ar–C), 122.60 (Ar–C), 127.90 (Ar–C), 127.97 (Ar–C), 128.13 (Ar–C), 128.23 (Ar–C), 128.37 (Ar–C), 128.55 (Ar–C), 128.80 (Ar–C), 128.98 (Ar–C), 136.74 (Ar–C), 138.60 (Ar–C), 149.57 (Py–C), 161.72 (Py–C); HRMS (ESI): calcd for $C_{41}H_{44}NO_6$ ($[M+H]^+$): 646.3169, found: 646.3181.

3.5. X-ray crystallographic measurement of single crystal of 9a1

The single crystal of the debenzylated compound **9a1** was obtained by recrystallization from the solution of H_2O/EtOH and applied on a Bruker SMART CCD diffractometer for analysis.

The intensity data were collected on a Bruker SMART CCD diffractometer with graphite-monochromated Mo Kα radiation (λ=0.71073 Å) using the $\theta/2\omega$ scan technique from a single-crystal of 0.30 mm×0.20 mm×0.20 mm, and a semi-empirical absorption correction was applied for all complexes. The structures were solved by direct methods and refined by full-matrix least-squares on F^2. The absolute structure parameter was −0.5 (13). All non-hydrogen atoms were refined anisotropically. The crystallographic structure is shown in Figure 1.

3.6. Biological activity assay

3.6.1. Glycosidases inhibition

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 and the results are listed in Table 4.

α-Amylase assay was performed using 1% starch as substrate in pH=6.0 phosphate buffers at 50 °C. 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 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.

β-Glucosidase assay was performed using D-(−) salicin (2 mg/mL) as substrate in pH=4.8 phosphate buffers at 35 °C. 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 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.

α-Glucosidase assay was performed using PNPG (1 mg/mL) as substrate in pH=6.8 phosphate buffers at 37 °C. 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 sodium carbonate (0.1 mol/L) after 10 min and the solution was 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.

3.6.2. 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 incubation, the supernatant was removed and DMSO (100 μL) was added to solubilize 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: $(OD_{control}-OD_{treated})/OD_{control}\times 100\%$.

Acknowledgements

The financial supports from the National Natural Science Foundations of China (NSFC) (20472015 and 20672027), the Natural Science Foundations of Hebei (2005000106 and B2008000588), and the Research Foundation from the Ministry of Education of China (206013) are gratefully acknowledged.

References and notes

1. (a) Fernández-Bolaños, J.; López, A. B.; Mota, J. F. *Carbohydr. Res.* **1990**, *199*, 239–242; (b) Gasch, C.; Pradera, M. A.; Salameh, B. A. B.; Molina, J. L.; Fuentes, J. *Tetrahedron: Asymmetry* **2000**, *11*, 435–453.
2. For the recent reviews on the synthesis and biological activity of spironucleosides, see: (a) Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395–4421; (b) El Ashry, E. S. H.; El Nemr, A. *Synthesis of Naturally Occurring Nitrogen Heterocycles from Carbohydrates*; Blackwell: Oxford, 2005; (c) Fernández-Bolaños, J. G.; López, Ó. Heterocycles from Carbohydrate Isothiocyanates. In *Topics in Heterocyclic Chemistry*; Gupta, R. R., Ed.; El Ashry, E. S. H., Ed. Heterocycles from Carbohydrate Precursors; Springer: Berlin, 2007; Vol. 7, pp 67–100.
3. For the recent examples of the synthesis and biological activity of spironucleosides, see: (a) Chatgilialoglu, C.; Ferreri, C.; Gimisis, T.; Roberti, M.; Balzarini, J.; Clercq, E. D. *Nucleosides, Nucleotides Nucleic Acids* **2004**, *23*, 1565–1581; (b) Fuentes, J.; Salameh, B. A. B.; Pradera, M. A.; Fernández de Cordoba, F. J.; Gasch, C. *Tetrahedron* **2006**, *62*, 97–111; (c) Gasch, C.; Salameh, B. A. B.; Pradera, M. A.; Fuentes, J. *Tetrahedron Lett.* **2001**, *42*, 8615–8617; (d) Singha, K.; Roy, A.; Dutta, P. K.; Tripathi, S.; Sahabuddin, S.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **2004**, *69*, 6507–6510; (e) Freire, R.; Martín, A.; Pérez-Martín, I.; Suárez, E. *Tetrahedron Lett.* **2002**, *43*, 5113–5116; (f) Pham, T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2005**, *70*, 6369–6377; (g) Renard, A.; Lhomme, J.; Kotera, M. *J. Org. Chem.* **2002**, *67*, 1302–1307; (h) Enderlin, G.; Taillefumier, C.; Didierjean, C.; Chapleur, Y. *Tetrahedron: Asymmetry* **2005**, *16*, 2459–2474; (i) Roy, A.; Achari, B.; Mandal, S. B. *Tetrahedron Lett.* **2006**, *47*, 3875–3879; (j) Shiozaki, M. *Carbohydr. Res.* **2002**, *337*, 2077–2088; (k) Somsák, L.; Kovács, L.; Tóth, M.; Osz, E.; Szilágyi, L.; Gyoergydeák, Z.; Dinya, Z.; Docsa, T.; Tóth, B.; Gergely, P. *J. Med. Chem.* **2001**, *44*, 2843–2848; (l) Fischer, R.; Hyrosova, E.; Druckova, A.; Fisera, L.; Hametner, C.; Cyranski, M. K. *Synlett* **2003**, 2364–2368; (m) Benltifa, M.; Vidal, S.; Gueyard, D.; Goekjian, P. G.; Msaddek, M.; Praly, J. P. *Tetrahedron Lett.* **2006**, *47*, 6143–6147; (n) Elek, R.; Kiss, L.; Praly, J. P.; Somasák, L. *Carbohydr. Res.* **2005**, *340*, 1397–1402; (o) Zhang, P. Z.; Li, X. L.; Chen, H.; Li, Y. N.; Wang, R. *Tetrahedron Lett.* **2007**, *48*, 7813–7816; (p) Colinas, P. A.; Jäger, V.; Lieberknecht, A.; Bravo, R. D. *Tetrahedron Lett.* **2003**, *44*, 1071–1074.
4. To the best of our knowledge, a few of examples on the synthesis of spironucleosides with six-membered heterocycles was published, see: (a) Taillefumier, C.; Thielges, S.; Chapleur, Y. *Tetrahedron* **2004**, *60*, 2213–2224; (b) See Ref. 3g; (c) Gasch, C.; Pradera, M. A.; Salameh, B. A. B.; Molina, J. L.; Fuentes, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1267–1277; (d) Paquette, L. A.; Brand, S.; Behrens, C. *J. Org. Chem.* **1999**, *64*, 2010–2025; (e) Bartolozzi, A.; Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C.; Bacialli, A. P. *J. Org. Chem.* **1999**, *64*, 6490–6494; (f) Krülle, T. M.; Watson, K. A.; Gregoriou, M.; Johnson, L. N.; Crook, S.; Watkin, D. J.; Griffiths, R. C.; Nash, R. J.; Tsitsanou, K. E.; Zographos, S. E.; Oikonomakos, N. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 8291–8294; (g) Sano, H.; Mio, S.; Kitagawa, J.; Sugai, S. *Tetrahedron: Asymmetry* **1994**, *5*, 2233–2240.
5. (a) Nakajima, M.; Itoi, K.; Takamatsu, Y.; Kinoshita, T.; Okazaki, T.; Kawakubo, K.; Shindou, M.; Honma, T.; Toujigamori, M.; Haneishi, T. *J. Antibiot.* **1991**, *44*, 293–300; (b) Siehl, D. L.; Subramanian, M. V.; Walters, E. W.; Lee, S. F.; Anderson, R. J.; Toschi, A. G. *Plant Physiol.* **1996**, *110*, 753–758; (c) Früh, T.; Chemla, P.; Ehrler, J.; Farooq, S. *Pestic. Sci.* **1996**, *46*, 37–47; (d) Somsák, L.; Nagy, V.; Hadady, Z.; Felföldi, N.; Docsa, T.; Gergely, P. *Front. Med. Chem.* **2005**, *2*, 253–272.
6. (a) Cassady, J. M.; Chan, K. K.; Floss, H. G.; Leistner, E. *Chem. Pharm. Bull.* **2004**, *52*, 1–26; (b) Yamana, K.; Suzuki, N.; Takahama, A.; Ine, S. Jpn. Kokai Tokkyo Koho JP 179572, 2002; (c) Jin, F.; Confalone, P. N. PCT Int. Appl. WO 0000481, 2000; (d) Wang, G.; Ella-Menye, J. R.; Sharma, V. *Bioorg. Med. Chem. Lett.* **2005**, *16*, 2177–2181.
7. (a) Li, X. L.; Takahashi, H.; Ohtake, H.; Ikegami, H. S. *Tetrahedron Lett.* **2004**, *45*, 4123–4126; (b) Li, Z. W.; Li, X. L.; Duan, K. F.; Chen, H. *Front. Chem. China* **2006**, *1*,

281–286; (c) Li, X.; Takahashi, H.; Ohtake, H.; Ikegami, S. *Heterocycles* **2003**, *59*, 547–571.
8. Li, X. L.; Wang, Y. P.; Chen, H.; Li, Z. W.; Xing, C. Y. *Chin. J. Org. Chem.* (in Chinese), *28*, in press.
9. Krishnaswamy, D.; Govande, V. V.; Gumaste, V. K.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron* **2002**, *58*, 2215–2225.
10. (a) Walts, A. E.; Roush, W. R. *Tetrahedron* **1985**, *41*, 3463–3478; (b) Chiacchio, U.; Corsaro, A.; Pistara, V.; Rescifina, A.; Romeo, G.; Romeo, R. *Tetrahedron* **1996**, *52*, 7875–7884.
11. (a) Li, X. L.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2001**, *57*, 4283–4295; (b) Li, X.; Takahashi, H.; Ohtake, H.; Shiro, M.; Ikegami, S. *Tetrahedron* **2001**, *57*, 8053–8066.
12. CCDC 694485 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
13. Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55–63.