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Synthesis of seven-membered iminosugars fused thiazolidin-4-one and benzthiazinan-4-one and their HIV-RT inhibitory activity

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ABSTRACT

Novel seven-membered iminosugars fused thiazolidin-4-one and benzthiazinan-4-one were conveniently synthesized by the tandem Staudinger/aza-Wittig/cyclization reaction under microwave radiation. Benzoyl group (Bz) migrations were found in the synthesis of **8c** and **9b** using D-galactoside or D-mannoside as starting materials, respectively, which was suggested by HMBC and X-ray. The new bi/tricyclic iminosugars **3**~**4**(**a**–**d**) and **5**(**b**–**d**) were examined for their HIV reverse transcriptase (RT) inhibitory activities. The result showed that all compounds except **5b** could effectively inhibit RT activity. Among them, compounds **3c** and **4c** were the best ones with the IC_{50} values of RT inhibitory activities of 2.11 μM and 2.73 μM, respectively. Structure–activity relationship analysis suggested that the phenyl group in the tricyclic azasugars was beneficial for their anti-HIV RT activity.

1. Introduction

Iminosugars or azasugars, which exhibit effective inhibition against carbohydrate-processing enzymes, have attracted great interest for their potential clinical applications as anti-HIV, antidiabetic, and anti-cancer agents and immunomodulators in past decades.[1–4] The bicyclic azasugars, including the naturally occurring compounds (**A**–**D**)[5–8] and the synthetic ones (**E**–**F**)[9–17] (Fig. 1), have also been paid much attention due to their increased possibility leading to the discovery of new bioactive therapeutic agents. To date, a large number of bicyclic azasugars bearing six-membered nitrogen heterocycle have been synthesized and evaluated.[18–20] Much less efforts have been put into higher ring size analogs.[21,22] Additionally, the tricyclic azasugars were so far scarcely reported for their synthesis and biological activity study.

Recently, by using microwave-assisted one-pot Staudinger/aza-Wittig/condensation reaction, we have conveniently synthesized a series of novel bi/tricyclic azasugars fused thiazolidin-4-one and thiazinan-4-one (**1** and **2**, Fig. 1).[23–26] The biological evaluation indicated that these bi/tricyclic azasugars (**1** and **2**) exhibited strong HIV reverse transcriptase (HIV-RT) inhibitory activities but poor inhibitory against glycosidases.[23,25] The promising activity against HIV-RT inspired us to explore its innovative analogs to develop novel iminosugar-based drugs with higher activity.

Polyhydroxyazepanes, having the more flexibility and higher water solubility compared with five- or six-membered rings, are potentially useful as drug candidates or structural motifs.[27] As a continuation of our researches, herein, we would like to report the synthesis of the novel bi/tricyclic seven-membered azasugars fused thiazolidin-4-one and thiazinan-4-one (**3**–**5**, Fig. 2). Such newly synthetic azasugars were evaluated for their HIV-RT inhibitory activity in order to further investigate the structure–activity relationship (SAR).

2. Results and discussion

2.1. Synthesis of the bi/tricyclic seven-membered azasugars fused thiazolidin-4-one and thiazinan-4-one (3–5)

The requisite azidosugars **6a–c** (Table 1) were prepared from D-glucose, D-galactose, D-mannose according to the literatures.[28,29] The key reaction for the synthesis of the bi/tricyclic azasugars fused thiazolidin-4-one and benzthiazinan-4-one (**7–9**) was the microwave-assisted one-pot Staudinger/aza-Wittig/cyclization reaction using **6a–c** as the starting materials (Scheme 1). Following the reported procedures,[23,24] the microwave-assisted reactions afforded mainly two diastereoisomers of the bi/tricyclic seven-membered azasugars in low yields with low stereoselectivity except the case of entry 5. In entry 5, the reaction of **6c** with mercaptoacetic acid stereospecifically afforded single diastereoisomer **9b** and

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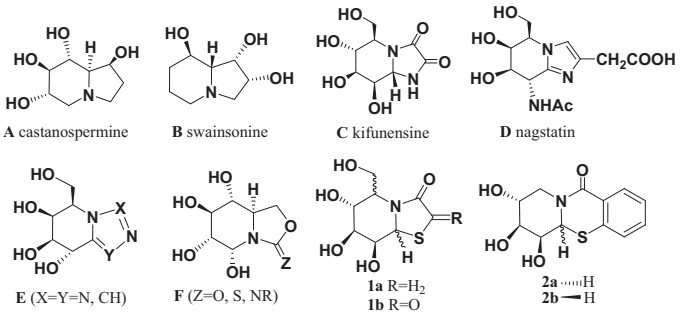


Fig. 1. The structures of some bi/tricyclic azasugars.

its benzoyl group (Bz) migrated analogs **9b-1**, **9b-2**, and **9b-3**, possibly due to the synergistic hindrance effects of the *cis* neighboring Bz groups at 8, 9 positions, which made a dominant *exo*-attack of the sulfur atom to the intermediate imine (I) (Scheme 2). However, the reactions of **6c** with 2-mercaptobenzoic acid (Entry 6) afforded two diastereoisomers **9c** and **9d** with equal amount. The hypothesized formation mechanism of the 4-benzthiazinanone-azasugar hybrids **9c** and **9d** was shown in Scheme 2. It was likely that the phenyl group could stabilize the delocalized anionic charge in the intermediate (II) by conjugated effect, which made the racemization at C-9a. The byproduct that was generated by intramolecular nucleophilic addition from the corresponding intermediate imine was obtained in entry 2 (Scheme 3).[30] The excessive consumption of imine maybe caused the low yields of the reactions. After workup and purification by silica gel column chromatography, each pair of the diastereoisomeric products **7–9** was obtained, respectively.

It should be noted that Bz migrations were observed in the products in entries 4 and 5. The position of the naked hydroxyl group was determined by the analysis of the HMBC spectra of the products (see supporting information). Taken the **9b** as example (Fig. 3), the C and H signals of 6, 7, 8, 9, and 9a were assigned by the key J_{C-H} couplings between C-3/9a-H(δ_H 5.11 ppm), C-9a(δ_C 62.8 ppm)/2-H, 5-H, 8-H(δ_H 6.28 ppm) and 9-H(δ_H 5.70 ppm), C-9(δ_C 76.3 ppm)/2-H, 9a-H and 7-H(δ_H 6.05 ppm), C-8(δ_C 67.8 ppm)/6-H(δ_H 4.58 ppm), C-7(δ_C 72.4 ppm)/9-H, and the absent correlations between C-9/6-H; C-6(δ_C 67.7 ppm)/9-H in the HMBC spectrum, then the unprotected hydroxyl group at C-6 was deduced from the cross peaks of the C — O on Bz and 7-H, 8-H, and 9-H. Using the same protocol, compounds **7a**, **7c**, **8a**, **8b**, **9b-1**, **2**, **3**, and **9c** were checked for their positions of the unprotected hydroxyl groups by HMBC.

Deprotection in NaOMe solution at room temperature, the corresponding bi/tricyclic azasugars fused thiazolidin-4-one **3~4**(**a–b**) and **5b**, and benzthiazinan-4-one **3~5**(**c–d**) were obtained in good yields. The structures of all the newly synthesized bi-/tricyclic iminosugars were determined by their ^{1}H, ^{13}C NMR, and HRMS (ESI) spectra. Both analytical and spectral data of compounds are in agreement with the proposed structures. The typical coupling constants of 9a-H and 9-H (Table 2) indicated that compounds **3a**, **3c**, **4a, 4c, 5b**, and **5d** with big $J_{9,9a}$ values should have *trans*-relationship between 9a-H and 9-H, while their corresponding diastereomers

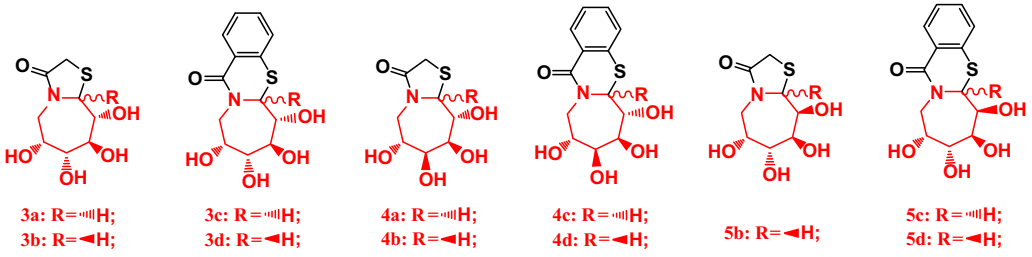
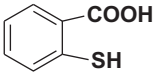
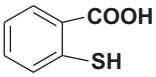
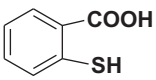


Fig. 2. The synthetic bi/tricyclic seven-membered azasugars fused thiazolidin-4-one and thiazinan-4-one.

Table 1
The synthesis of the bi-/tricyclic azasugars **7~8**(**a–d**) and **9**(**b–d**) by the microwave-assisted one-pot tandem Staudinger/aza-Wittig/cyclization reactions

Azido sugars	Mercaptan acids	Entry	DCC (equiv.)	Products		Total yields (%)[a]	Ratio of 9a*S*:9a*R*[b]
				9a*S*	9a*R*		
6a	$SHCH_2COOH$	1	–[c]	**7a**	**7b**	55.5	1.8:1
		2	1.2[d]	**7c**	**7d**	20.5	2.0:1
6b	$SHCH_2COOH$	3	1.2	**8a**	**8b**	18.4	1.2:1
		4	1.2	**8c**	**8d**	13.7	1.2:1
6c	$SHCH_2COOH$	5	1.2	N. D.[e]	**9b, 9b-1 9b-2, 9b-3**	38[f]	0:1
		6	1.2	**9c**	**9d**	20	1:1.1

[a] Isolated yield.
[b] Determined by ^{1}H NMR.
[c] **6a** (or **6b**, **6c**) and Ph_3P were firstly stirred in 3 mL dry toluene for 10 min at M. W. 80 °C, then mercaptan acid was added for another 15 min stirring at M. W. 80 °C. The ratio of reactants: **6a** (1 mmol) : Ph_3P : mercaptan acid = 1 : 1.5 : 2, and the reaction was performed in 10 mL sealed tube.
[d] DCC (1.2 equiv.) was added accompanied with mercaptan acid, then the mixture was stirred for another 20 min at M. W. 100 °C.
[e] Not detected.
[f] The total yields of **9b**, **9b-1**, **9b-2**, and **9b-3**.

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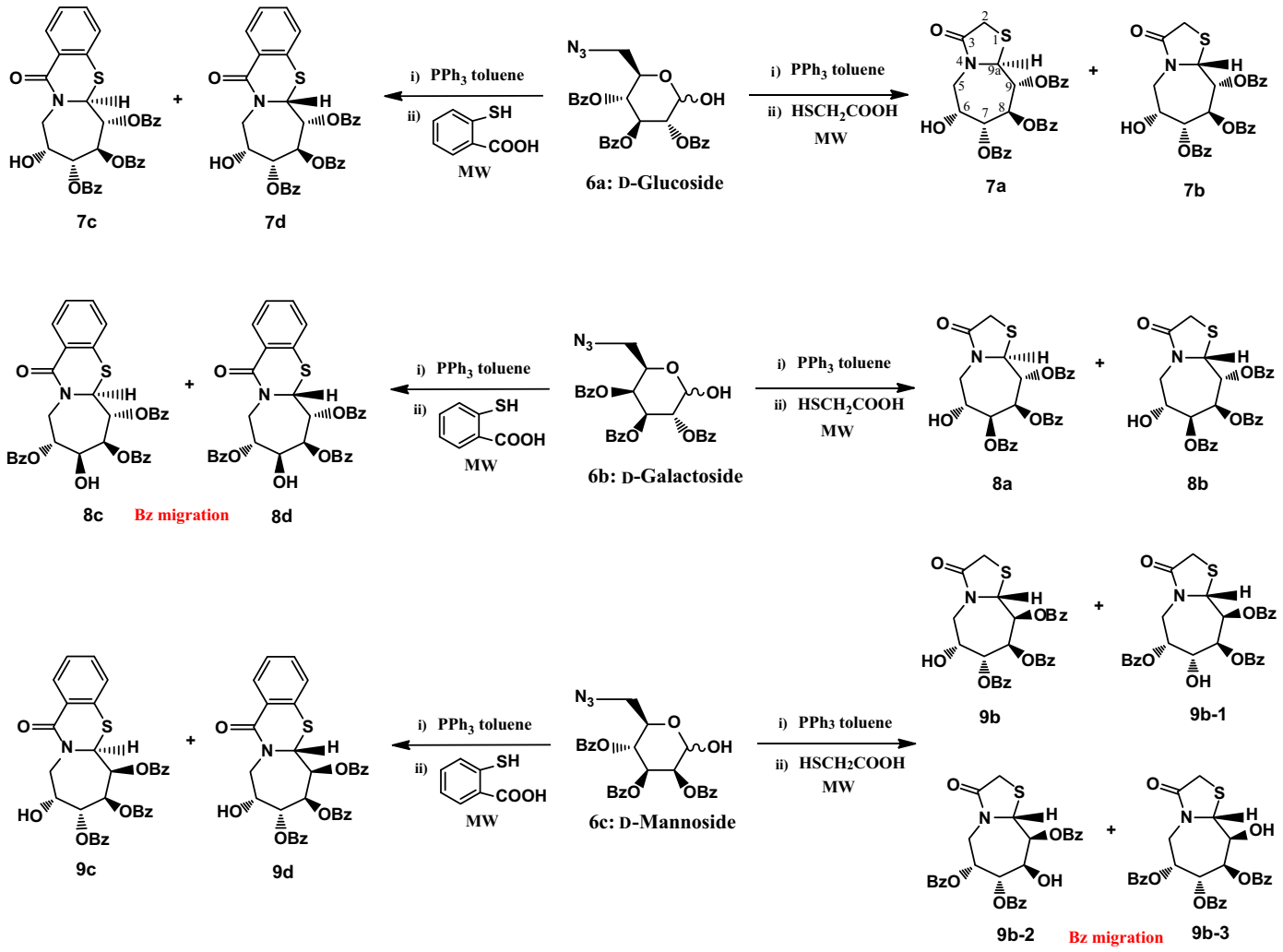
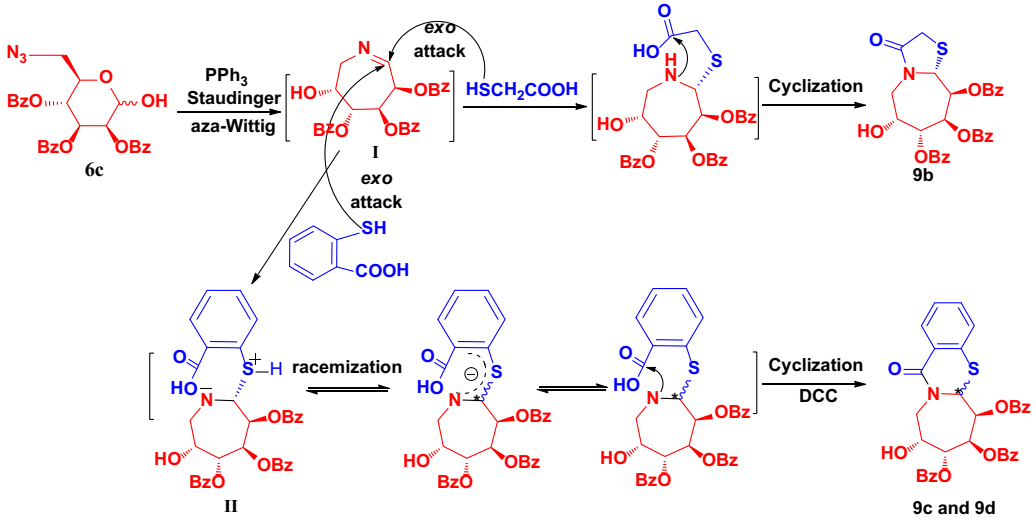


Scheme 1. The synthesis of the bi-/tricyclic azasugars **7~8**(**a–d**) and **9**(**b–d**) by the microwave-assisted reaction using **6a–c**.

are of *cis* forms. Thus, the absolute configuration of compounds **3a**, **3c**, **4a, 4c,** and **5c** could be determined to be of (9a*S*), the others were of (9a*R*). The absolute configuration of compound **4a** was determined to be of (9a*S*) by its X-ray crystallographic data (Fig. 4),[31] being consistent with the above NMR result. The X-ray crystallographic structure of the Bz protected compound **8d** further supported its absolute configurations of (9a*R*) and Bz migration from hydroxyl group on C-7 to C-6(Fig. 4).



Scheme 2. Hypothesized formation mechanism of the 4-benzthiazinanone-azasugar hybrids **9b–9d**.

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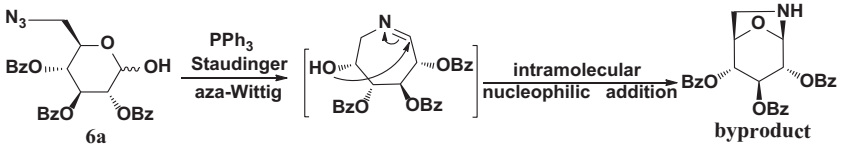

Scheme 3. The formation of the main byproduct.

2.2. HIV-RT inhibition assay

HIV-1 reverse transcriptase (RT) inhibitory activity was preliminarily evaluated with the bi/tricyclic azasugars **3~4**(**a–d**) and **5**(**b–d**) (Fig. 2) by determining their percentage inhibition of HIV-RT activity in HIV-1-RT kit by comparison with AZT.[32] The results are shown in Table 3. It could be seen that all the newly synthesized bi/tricyclic azasugars **3–5** except **5b** showed significant HIV-RT inhibitory activity, better than that of positive control AZT. Especially, compounds **3c** and **4c** showed a more significant HIV-RT inhibitory activity with the IC_{50} value of 2.11 μM and 2.73 μM, respectively,

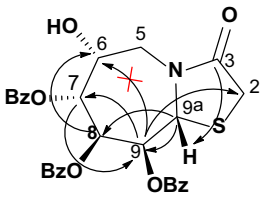

Fig. 3. Key HMBC (C→H) correlations of **9b**.

Table 2
The coupling constants (Hz) of 9a-H and 9-H in **3~4**(**a-d**) and **5**(**b-d**)

Cis (9a*R*)	$J_{9a,9}$/Hz	*Trans* (9a*S*)	$J_{9a,9}$/Hz
3b	1.8	**3a**	9.6
3d	1.8	**3c**	9.6
4b	1.8	**4a**	8.4
4d	1.8	**4c**	9.0
		5b (9a*R*)	7.8
5c (9a*S*)	1.8	**5d** (9a*R*)	9.6

which indicated that both of them might be better accommodated into the HIV-1 RT binding site. The inhibitory activities of the tricyclic azasugars fused benzthiazinan-4-one **3~5**(**c–d**) (bearing phenyl group) are much higher than those of bicyclic azasugars fused thiazolidin-4-one **3~4**(**a–b**) and **5b**, respectively, which indicated that the phenyl group would be favorable to the HIV-RT inhibitory activities of the compounds. Moreover, the inhibitory activities of the bi/tricyclic azasugars **3~4**(**a–d**) derived from glucoside and galactoside were more active than those of **5**(**b–d**) derived from mannoside, suggesting that the configuration of hydroxyl groups would have certain effect on their anti-HIV-RT activities.

In conclusion, novel bi-/tricyclic seven-membered azasugars fused thiazolidin-4-one and benzthiazinan-4-one **3~4**(**a–d**) and **5**(**b–d**) were conveniently synthesized by the microwave-assisted one-pot Staudinger/aza-Wittig/cyclization reaction. Bz migrations were found in the cases using D-galactoside or D-mannoside as starting materials, which was proved by HMBC and X-ray. All the newly synthesized bi/tricyclic azasugars showed significant HIV-RT inhibitory activity except **5b**. Among them, compounds **3c** and **4c** were the best ones with the IC_{50} values of RT inhibitory activities of 2.11 μM and 2.73 μM, respectively. The structure activity relationship (SAR) analysis indicated that the phenyl group in the tricyclic azasugars would be favorable to their anti-HIV-RT inhibitory activity.

3. Experiments

3.1. General methods

All microwave-assisted reactions were carried out on a CEM Discover S-Class Synthesizer (CEM Co. Ltd., USA). Melting points were measured on an SGW® X-4 micro melting point apparatus and were uncorrected. Optical rotations were determined on an SGW®-1 automatic polarimeter. ^{1}H- and ^{13}C- NMR spectra were measured on

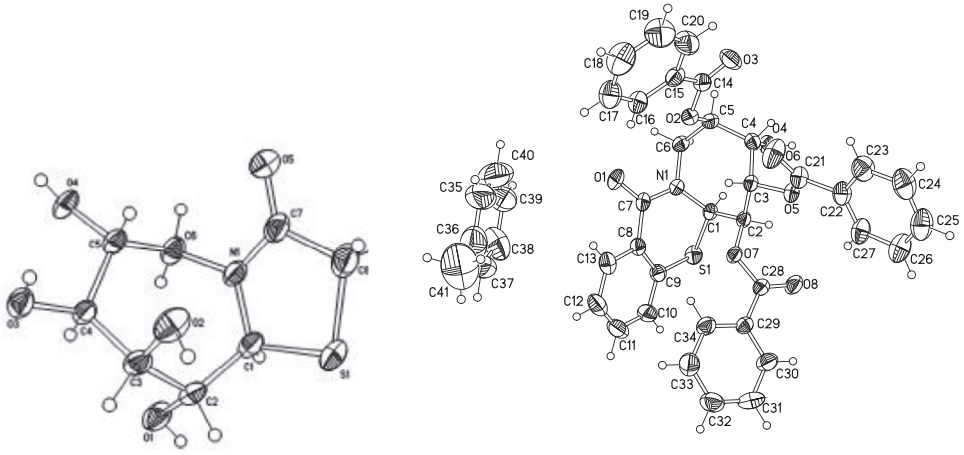

Fig. 4. X-ray crystographical structure of **4a** and **8d**.

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Table 3
In vitro HIV-1-RT kit assay for the bi/tricyclic azasugars

Compounds	IC_{50} (μM) (HIV-RT kit assay)	Compounds	IC_{50} (μM) (HIV-RT kit assay)
3a	4.49 ± 0.42	**3b**	11.01 ± 1.15
3c	2.11 ± 0.35	**3d**	3.44 ± 0.38
4a	7.71 ± 0.62	**4b**	6.84 ± 0.57
4c	2.73 ± 0.63	**4d**	5.51 ± 0.49
5b	28.09 ± 4.86	**5c**	17.17 ± 3.31
5d	13.44 ± 3.82	AZT	20.14 ± 1.32

an RT-NMR Bruker AVANCE 400 and a Bruker AVANCE 600 (400 MHz and 600 MHz), NMR spectrometer using tetramethylsilane (Me_4Si) as an internal standard. Mass Spectra (MS) and High Resolution Mass Spectra (HRMS) were carried out on an 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 HIV-RT inhibition were measured on a BioRad Model 3550 microplate spectrophotometer. Thin-layer chromatography (TLC) was performed on precoated plates (Qingdao GF_{254}) with detection of phosphomolybdic acid in EtOH/H_2O followed by heating. Column chromatography was performed using SiO_2 (Qingdao 300–400 mesh).

3.2. Experimental procedures

3.2.1. Synthesis of compounds 7a and 7b

A mixture of azidosugar **6a** (1.0 mmol) and PPh_3 (393 mg, 1.5 mmol) was dissolved in 3 mL anhydrous toluene and was stirred in sealed tube at 80 °C under microwave irradiation in a CEM Discover S-Class Synthesizer for 10 min. After cooling, mercaptoacetic acid (140 μL, 2.0 mmol) was added and the mixture was stirred at 80 °C in sealed tube by irradiating microwave for another 15 min reaction. After the reaction was finished, solid K_2CO_3 was added to the solution to neutralize mercaptoacetic acid and then was removed by filtration. Subsequently, the solution was extracted with CH_2Cl_2 (10 mL×3), then the organic layer was combined and dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to get a crude product that was purified using flash column chromatography (ethyl acetate–cyclohexane V/V = 1:3~2:1) to get two diastereoisomers **7a** and **7b**.

(6*R*,7*R*,8*S*,9*R*,9a*S*)-6-hydroxy-3-oxooctahydrothiazolo[3,2-*a*]azepine-7,8,9-triyl tribenzoate (7a): white solid, yield 35.5 %, mp. 219–221 °C, $[\alpha]\ ^{30}_D$ –119.1 (c 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.90 (brs, 4H, Bz-H), 7.76 (d, *J* = 7.6 Hz, 2H, Bz-H), 7.21–7.50 (m, 9H, Bz-H), 6.23 (t, *J* = 8.8 Hz, 1H, CH), 5.58 (t, *J* = 9.2 Hz, 1H, CH), 5.45 (d, *J* = 9.6 Hz, 1H, CH), 5.59 (d, *J* = 10.0 Hz, 1H, CH), 4.61 (brs, 1H, CH), 3. 93 (d, *J* = 14.4 Hz, 1H, CH), 3.74 (d, *J* = 15.6 Hz, 1H, CH_2), 3.54 (d, *J* = 14.8 Hz, 1H, CH_2), 3.36–3.40 (m, 2H, CH_2, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.6, 165.7, 165.5, 165.3, 133.6, 133.4, 133.3, 129.8, 129.8, 129.6, 129.0, 128.8, 128.5, 128.4, 128.3, 75.0, 74.7, 711, 68.8, 60.6, 47.3, 30.5; HR-ESI-MS: calcd for $C_{29}H_{26}NO_8S$ ($[M+H]^+$), 548.1379, found: 548.1365.

(6*R*,7*R*,8*S*,9*R*,9a*R*)-6-hydroxy-3-oxooctahydrothiazolo[3,2-*a*]azepine-7,8,9-triyl tribenzoate (7b): white solid, yield 20.1 %, mp. 96–98 °C, $[\alpha]\ ^{30}_D$ +25.6 (c 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.85–7.95 (m, 7H, Bz-H), 7.21–7.50 (m, 8H, Bz-H), 5.86 (q, *J* = 7.0 Hz, 1H, CH), 5.60–5.65 (m, 2H, 2CH), 5.35 (s, 1H, CH), 4.60 (brs, 1H, CH), 4.41 (q, *J* = 14.2 Hz, 1H, CH), 3.59 (d, *J* = 15.6 Hz, 1H, CH_2), 3.39–3.45 (m, 2H, CH_2), 3.33 (1H, d, *J* = 5.4 Hz, OH);^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.8, 166.2, 164.6, 164.5, 133.7, 133.6, 133.6, 129.9, 129.8, 128.7, 128.5, 128.4, 76.6, 76.1, 70.2, 68.0, 60.1, 46.0, 32.4; HR-ESI-MS: calcd for $C_{29}H_{25}NO_8SNa$ ($[M+Na]^+$), 570.1198, found: 570.1206.

3.2.2. Synthesis of compounds 8(a-b), 9b, and 7–9(c-d)

A mixture of azidosugar **6** (1.0 mmol) and PPh_3 (393 mg, 1.5 mmol) was dissolved in 3 mL anhydrous toluene and was stirred in sealed tube at 80 °C under microwave irradiation in a CEM Discover S-Class Synthesizer for 10 min. After cooling, 2-mercaptobenzoic acid (2.0 mmol) and DCC (1.2 mmol) were added and the mixture was stirred at 100 °C in sealed tube by irradiating microwave for another 20 min reaction. After the reaction was finished, solid K_2CO_3 was added to the solution to neutralize 2-mercaptobenzoic acid and then was removed with DCU by filtration. Subsequently, the solution was extracted with CH_2Cl_2 (10 mL×3), then the organic layer was combined and dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to get a crude product that was purified using flash column chromatography (ethyl acetate–cyclohexane V/V = 1:3~2:1) to get two diastereoisomers **7c** and **7d**.

Using the same procedure, the iminosugars fused thiazolidin-4-one **8(a-b)** and **9b**, and benzthiazinan-4-one **8–9**(**c-d**) were obtained.

(5a*S*,6*R*,7*S*,8*R*,9*R*)-9-hydroxy-12-oxo-6,7,8,9,10,12-hexahydro-5a*H*-benzo[5,6][1,3]thiazino[3,2-*a*]azepine-6,7,8-triyl tribenzoate (7c): white solid, yield 13.7 %, mp. 129–130 °C, $[\alpha]\ ^{22}_D$ +221.8 (c 1.0, EtOAc), ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.16 (d, *J* = 7.2 Hz, 1H, CH), 8.05 (d, *J* = 7.2 Hz, 1H, CH), 7.89 (d, *J* = 7.2 Hz, 2H, CH), 7.71–7.74 (m, 1H, CH), 7.57–7.62 (m, 6H, CH), 7.45–7.48 (m, 3H, CH), 7.35–7.38 (m, 1H, CH), 7.13–7.22 (m, 4H, CH), 5.90–5.96 (m, 2H, CH), 5.52 (d, *J* = 9.6 Hz, 1H, CH), 5.21 (d, *J* = 9.6 Hz, 1H, CH), 5.04–5.07 (m, 1H, CH), 4.83–4.85 (m, 1H, CH), 3.54–3.58 (m, 1H, CH); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 165.3, 164.2, 163.8, 163.1, 133.8, 133.3, 133.2, 132.9, 130.4, 130.0, 129.7, 128.8, 128.7, 128.4, 128.2, 127.4, 126.7, 74.5, 74.3, 69.8, 65.3, 62.7, 50.9; HR-ESI-MS: calcd for $C_{34}H_{27}NO_8SNa$ ($[M+Na]^+$), 632.1355, found: 632.1361.

(5a*R*,6*R*,7*S*,8*R*,9*R*)-9-hydroxy-12-oxo-6,7,8,9,10,12-hexahydro-5a*H*-benzo[5,6][1,3]thiazino[3,2-*a*]azepine-6,7,8-triyl tribenzoate (7d): white solid, yield 6.8 %, mp. 206–207 °C, $[\alpha]\ ^{28}_D$ +167.4 (c 1.0, $CHCl_3$), ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.25 (d, *J* = 6.0 Hz, 1H, CH), 8.04 (d, *J* = 6.0 Hz, 1H, CH), 7.84 (dd, *J* = 17.4 Hz, 7.8 Hz, 4H, CH), 7.41 (q, *J* = 15.0 Hz, 3H, CH), 7.23–7.33 (m, 4H, CH), 7.16 (d, *J* = 12.0 Hz, 2H, CH), 7.07–7.10 (m, 1H, CH), 6.96–7.01 (m, 3H, CH), 6.88 (d, *J* = 6.0 Hz, 1H, CH), 6.14 (dd, *J* = 9.0 Hz, 6.0 Hz, 1H, CH), 5.97 (dd, *J* = 5.4 Hz, 3.6 Hz, 1H, CH), 5.72 (dd, *J* = 9.0 Hz, 1.8 Hz, 1H, CH), 5.20 (d, *J* = 5.4 Hz, 1H, CH), 5.10 (dd, *J* = 15.0 Hz, 3.0 Hz, 1H, CH_2), 4.56 (brs, 1H, CH), 3.53 (dd, *J* = 15.0 Hz, 3.0 Hz, 1H, CH); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 167.1, 165.8, 164.9, 164.8, 134.6, 133.3, 132.9, 132.4, 130.6, 129.9, 129.7, 129.6, 128.9, 128.4, 128.3, 128.2, 128.0, 127.8, 126.9, 126.4, 125.6, 77.9, 72.9, 70.7, 60.3, 53.1, 52.1; HR-ESI-MS: calcd for $C_{34}H_{27}NO_8SNa$ ($[M+Na]^+$), 632.1355, found: 632.1376.

(6*R*,7*S*,8*S*,9*R*,9a*S*)-6-hydroxy-3-oxooctahydrothiazolo[3,2-*a*]azepine-7,8,9-triyl tribenzoate (8a): oily, yield 10.2%, $[\alpha]\ ^{25}_D$ –80 (c 0.2, CH_2Cl_2), ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.09 (dd, *J* = 7.8 Hz, 1.2 Hz, 2H, Ph-H), 8.00 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H, Ph-H), 7.95 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H, Ph-H), 7.39–7.62 (m, 9H, Ph-H), 6.03 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H, CH-8), 5.92 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H, CH-7), 5.84 (dd, *J* = 7.8 Hz, 4.2 Hz, 1H, CH-9), 5.11 (dd, *J* = 4.2 Hz, 1.8 Hz, 1H, CH-9a), 4.69–4.70 (m, 1H, CH-6), 4.43 (dd, *J* = 14.4 Hz, 4.8 Hz, 1H, CH-5), 3.49 (d, *J* = 15.6 Hz, 1H, CH-2), 3.44 (d, *J* = 15.6 Hz, 1H, CH-2), 3.31 (dd, *J* = 14.4 Hz, 9.0 Hz, 1H, CH-5); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 171.6, 165.9, 165.3, 165.2, 133.8, 133.7, 133.6, 130.0, 129.8, 129.7, 129.2, 128.7, 128.7, 128.6, 74.6, 73.7, 71.4, 66.8, 63.4, 46.5, 31.7; HR-ESI-MS: calcd for $C_{29}H_{25}NO_8SNa$ ($[M+Na]^+$), 570.1198, found: 570.1186.

(6*R*,7*S*,8*S*,9*R*,9a*R*)-6-hydroxy-3-oxooctahydrothiazolo[3,2-*a*]azepine-7,8,9-triyl tribenzoate (8b): oily, yield 8.2%, $[\alpha]\ ^{25}_D$ +120 (c 0.2, CH_2Cl_2), ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.06–8.08 (m, 4H, Ph-H), 7.94 (dd, *J* = 7.8 Hz, 1.2 Hz, 2H, Ph-H), 7.38–7.62 (m, 9H, Ph-H), 6.02–6.06 (m, 2H, CH-8, CH-9), 5.77 (d, *J* = 6.0 Hz, 1H, CH-7), 5.30

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(dd, *J* = 3.6 Hz, 1.2 Hz, 1H, CH-9a), 4.46 (dd, *J* = 15.0 Hz, 2.4 Hz, 1H, CH-5), 4.35 (brs, 1H, CH-6), 3.69–3.72 (m, 2H, CH-5, CH-2), 3.54 (d, *J* = 15.6 Hz, 1H, CH-2), 3.29 (d, *J* = 4.8 Hz, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 173.8, 165.6, 164.8, 164.6, 133.7, 133.6, 133.5, 130.0, 129.9, 129.7, 129.3, 128.9, 128.7, 128.6, 128.5, 75.3, 71.0, 70.6, 70.2, 62.5, 47.5, 32.6; HR-ESI-MS: calcd for $C_{29}H_{25}NO_8SNa$ ($[M + Na]^+$), 570.1198, found: 570.1203.

(5a*S*,6*R*,7*S*,8*S*,9*R*)-8-hydroxy-12-oxo-6,7,8,9,10,12-hexahydro-5a*H*-benzo[5,6][1,3]thiazino[3,2-*a*]azepine-6,7,9-triyl tribenzoate (8c): oily, yield 7.5%, [α] $^{25}_D$ +75 (c 0.2, CH_2Cl_2), ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.11 (d, *J* = 7.2 Hz, 2H, Bz-H), 8.01 (d, *J* = 7.2 Hz, 2H, Bz-H), 7.97 (d, *J* = 7.2 Hz, 2H, Bz-H), 7.89 (d, *J* = 7.2 Hz, 1H, Bz-H), 7.11–7.63 (m, 12H, Bz-H), 5.91 (brs, 1H, CH), 5.78 (d, *J* = 9.0 Hz, 1H, CH), 5.60 (brs, 1H, CH), 5.18 (d, *J* = 14.4 Hz, 6.6 Hz, 1H, CH-5), 4.90–4.96 (m, 2H, 2CH), 3.24 (dd, *J* = 14.4 Hz, 9.0 Hz, 1H, CH-5), 3.09 (brs, 1H, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 165.9, 164.6, 164.5, 162.8, 133.6, 133.5, 133.0, 132.7, 130.5, 130.1, 130.0, 130.0, 129.2, 129.0, 128.7, 128.6, 128.4, 128.4, 128.2, 127.6, 126.6, 75.3, 73.9, 73.8, 66.5, 62.9, 52.1; HR-ESI-MS: calcd for $C_{34}H_{27}NO_8SNa$ ($[M + Na]^+$), 632.1355, found: 632.1381.

(5a*R*,6*R*,7*S*,8*S*,9*R*)-8-hydroxy-12-oxo-6,7,8,9,10,12-hexahydro-5a*H*-benzo[5,6][1,3]thiazino[3,2-*a*]azepine-6,7,9-triyl tribenzoate (8d): white solid, yield 6.2%, mp. 109–110 °C, [α] $^{25}_D$ –25 (c 0.2, CH_2Cl_2), ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.27 (d, *J* = 7.8 Hz, 2H, Bz-H), 8.21 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H, Bz-H), 7.88 (dd, *J* = 7.2 Hz, 1.2 Hz, 2H, Bz-H), 7.12–7.64 (m, 14H, Bz-H), 6.14 (dd, *J* = 7.8 Hz, 4.2 Hz, 1H, CH), 5.71 (d, *J* = 7.8 Hz, 1H, CH), 5.51 (d, *J* = 4.2 Hz, 1H, CH), 5.40–5.42 (m, 1H, CH), 5.19 (d, *J* = 15.0 Hz, 1H, CH-5), 4.61 (t, *J* = 5.4 Hz, 1H, CH), 4.25 (s, 1H, OH), 3.61 (dd, *J* = 15.0 Hz, 2.4 Hz, 1H, CH-5); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 166.2, 166.0, 165.3, 162.9, 135.1, 133.3, 133.3, 133.0, 132.0, 130.4, 130.3, 129.8, 129.8, 129.6, 129.3, 129.1, 128.6, 128.4, 128.3, 128.2, 127.9, 126.3, 125.6, 125.3, 76.7, 76.5, 72.7, 72.2, 59.9, 49.2; HR-ESI-MS: calcd for $C_{34}H_{27}NO_8SNa$ ($[M + Na]^+$), 632.1355, found: 632.1356.

(6R,7R,8S,9S,9aR)-6-hydroxy-3-oxooctahydrothiazolo[3,2-*a*]azepine-7,8,9-triyl tribenzoate (9b): oily, yield 9.5%, [α] $^{25}_D$ –67 (c 0.2, CH_2Cl_2), ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.13 (d, *J* = 7.2 Hz, 2H, Bz-H), 7.96 (d, *J* = 7.2 Hz, 2H, Bz-H), 7.85 (d, *J* = 7.2 Hz, 2H, Bz-H), 7.27–7.69 (m, 9H, Bz-H), 6.28 (dd, *J* = 9.6 Hz, 1.2 Hz, 1H, CH-8), 6.05 (dd, *J* = 9.6 Hz, 3.0 Hz, 1H, CH-7), 5.70 (t, *J* = 1.8 Hz, 1H, CH-9), 5.11 (d, *J* = 1.8 Hz, 1H, CH-9a), 4.54–4.59 (m, 2H, CH-6, CH-5), 3.79 (dd, *J* = 15.6 Hz, 1.8 Hz, 1H, CH-2), 3.71 (dd, *J* = 15.6 Hz, 0.6 Hz, 1H, CH-2), 3.41 (d, *J* = 14.4 Hz, 1H, CH-5); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 172.8, 165.9, 165.1, 165.0, 134.0, 133.4, 133.3, 129.9, 129.8, 129.7, 129.0, 128.9, 128.9, 128.4, 128.3, 76.3, 72.4, 67.8, 67.7, 62.8, 44.5, 32.4; HR-ESI-MS: calcd for $C_{29}H_{25}NO_8SNa$ ($[M + Na]^+$), 570.1198, found: 570.1195.

(6*R*,7*R*,8*S*,9*S*,9a*R*)-7-hydroxy-3-oxooctahydrothiazolo[3,2-*a*]azepine-6,8,9-triyl tribenzoate (9b-1): oily, yield 7.5%, [α] $^{25}_D$ –35 (c 0.2, CH_2Cl_2), ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.05–8.11 (m, 6H, Bz-H), 7.46–7.69 (m, 12H, Bz-H), 6.07 (dd, *J* = 9.0 Hz, 1.2 Hz, 1H, CH-8), 5.77 (dd, *J* = 3.0 Hz, 1.8 Hz, 1H, CH-9), 5.68–5.70 (m, 1H, CH-6), 5.10 (t, *J* = 1.8 Hz, 1H, CH-7), 4.73 (dd, *J* = 14.4 Hz, 5.4 Hz, 1H, CH-5), 4.67 (brs, 1H, CH-9a), 3.63 (d, *J* = 17.4 Hz, 1H, CH-2), 3.58 (d, *J* = 14.4 Hz, 1H, CH-2), 3.39 (dd, *J* = 15.0 Hz, 1.8 Hz, 1H, CH-5); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 171.3, 166.1, 165.7, 164.9, 134.0, 133.6, 133.4, 129.9, 129.9, 129.8, 129.8, 129.5, 129.2, 129.0, 128.9, 128.8, 128.6, 128.5, 75.4, 70.5, 70.5, 70.1, 62.2, 42.0, 32.0; HR-ESI-MS: calcd for $C_{29}H_{25}NO_8SNa$ ($[M + Na]^+$), 570.1198, found: 570.1187.

(6*R*,7*R*,8*S*,9*S*,9a*R*)-8-hydroxy-3-oxooctahydrothiazolo[3,2-*a*]azepine-6,7,9-triyl tribenzoate (9b-2): oily, yield 8.5%, [α] $^{25}_D$ –110 (c 0.2, CH_2Cl_2), ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.10 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H, Bz-H), 7.95–7.97 (m, 4H, Bz-H), 7.39–7.66 (m, 9H, Bz-H), 5.91–5.93 (m, 1H, CH-6), 5.87 (dd, *J* = 8.4 Hz, 3.0 Hz, 1H, CH-7), 5.54 (dd, *J* = 4.2 Hz, 1.8 Hz, 1H, CH-9), 5.16 (d, *J* = 4.2 Hz, 1H, CH-9a), 4.72–4.74 (m, 1H, CH-8), 4.58 (dd, *J* = 14.4 Hz, 6.6 Hz, 1H, CH-5), 3.65 (d, *J* = 16.2 Hz, 1H, CH-2), 3.57 (d, *J* = 15.6 Hz, 1H, CH-2), 3.47 (dd, *J* = 14.4 Hz, 2.4 Hz, 1H, CH-5); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 171.5, 165.9, 165.5, 133.9, 133.6, 133.3, 129.9, 129.9, 129.8, 129.5, 129.0, 128.9, 128.8, 128.6, 128.5, 77.1, 72.8, 68.0, 67.5, 61.2, 42.5, 31.8; HR-ESI-MS: calcd for $C_{29}H_{25}NO_8SNa$ ($[M + Na]^+$), 570.1198, found: 570.1212.

(6*R*,7*R*,8*S*,9*S*,9a*R*)-9-hydroxy-3-oxooctahydrothiazolo[3,2-*a*]azepine-6,7,8-triyl tribenzoate (9b-3): white solid, yield 12.5%, mp. 120–122 °C, [α] $^{25}_D$ –55 (c 0.2, CH_2Cl_2), ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.00 (d, *J* = 7.2 Hz, 2H, Bz-H), 7.91 (d, *J* = 7.2 Hz, 2H, Bz-H), 7.78 (d, *J* = 7.8 Hz, 2H, Bz-H), 7.58-7.21 (m, 9H, Bz-H), 6.19 (dd, *J* = 9.6 Hz, 3.6 Hz, 1H, CH-7), 6.06 (d, *J* = 9.6 Hz, 1H, CH-8), 5.74 (brs, 1H, CH-6), 5.04 (brs, 1H, CH-9a), 4.58 (dd, *J* = 15 Hz, 5.4 Hz, 1H, CH-5), 4.30 (brs, 1H, CH-9), 3.61 (t, *J* = 16.2 Hz, 2H, CH-2), 3.46 (d, *J* = 14.4 Hz, 1H, CH-5); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 171.4, 165.6, 165.5, 165.4, 133.4, 133.3, 133.2, 129.7, 129.7, 129.0, 129.0, 128.5, 128.4, 128.3, 74.8, 70.4, 69.9, 68.3, 63.9, 41.8, 32.3; HR-ESI-MS: calcd for $C_{29}H_{25}NO_8SNa$ ($[M + Na]^+$), 570.1198, found: 570.1201.

(5a*S*,6*S*,7*S*,8*R*,9*R*)-9-hydroxy-12-oxo-6,7,8,9,10,12-hexahydro-5a*H*-benzo[5,6][1,3]thiazino[3,2-*a*]azepine-6,7,8-triyl tribenzoate (9c): oily, yield 9.5%, [α] $^{25}_D$ –10 (c 0.2, CH_2Cl_2), ^{1}H NMR (150 MHz, $CDCl_3$) δ (ppm) 8.05 (d, *J* = 7.8 Hz, 1H, Bz-H), 7.93 (d, *J* = 7.2 Hz, 2H, Bz-H), 7.74 (d, *J* = 7.2 Hz, 2H, Bz-H), 7.68 (d, *J* = 7.2 Hz, 2H, Bz-H), 6.99–7.55 (m, 12H, Bz-H), 6.18 (t, *J* = 2.4 Hz, 1H, CH-7), 6.12 (dd, *J* = 10.2 Hz, 3.0 Hz, 1H, CH-8), 5.85 (dd, *J* = 9.6 Hz, 2.4 Hz, 1H, CH-9), 5.46 (d, *J* = 1.8 Hz, 1H, CH-9a), 4.80–4.83 (m, 1H, CH-6), 4.78 (dd, *J* = 14.4 Hz, 4.8 Hz, 1H, CH-5) 4.01 (dd, *J* = 14.4 Hz, 5.4 Hz, 1H, CH-5), ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 165.4, 164.9, 164.6, 134.7, 133.4, 133.3, 133.2, 131.9, 130.6, 129.9, 129.8, 129.7, 129.1, 128.8, 128.6, 128.4, 128.2, 127.9, 126.5, 125.6, 74.4, 72.5, 69.6, 67.9, 60.4, 47.8; HR-ESI-MS: calcd for $C_{34}H_{27}NO_8SNa$ ($[M + Na]^+$), 632.1355, found: 632.1359.

(5a*R*,6*S*,7*S*,8*R*,9*R*)-9-hydroxy-12-oxo-6,7,8,9,10,12-hexahydro-5a*H*-benzo[5,6][1,3]thiazino[3,2-*a*]azepine-6,7,8-triyl tribenzoate (9d): white solid, yield 10.5%, mp. 225–227 °C, [α] $^{25}_D$ +115 (c 0.2, CH_2Cl_2), ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.25 (d, *J* = 7.8 Hz, Bz-H), 7.94–7.98 (m, 6H, Bz-H), 7.23–7.62 (m, 12H, Bz-H), 6.24 (dd, *J* = 8.4 Hz, 3.0 Hz, 1H, CH), 5.99 (dd, *J* = 8.4 Hz, 4.8 Hz, 1H, CH), 5.94 (dd, *J* = 9.6 Hz, 3.0 Hz, 1H, CH), 5.07 (d, *J* = 9.6 Hz, 1H, CH), 5.00 (d, *J* = 13.8 Hz, 1H, CH-5), 4.54–4.55 (m, 1H, CH), 4.28–4.29 (d, *J* = 9.6 Hz, 1H, CH) 3.77 (dd, *J* = 15.6 Hz, 4.8 Hz, 1H, CH-5); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 165.6, 165.2, 164.7, 164.6, 133.7, 133.5, 133.4, 131.2, 130.0, 129.9, 129.6, 128.7, 128.5, 128.3, 127.7, 126.5, 70.2, 70.1, 70.0, 69.7, 62.0, 53.4; HR-ESI-MS: calcd for $C_{34}H_{27}NO_8SNa$ ($[M + Na]^+$), 632.1355, found: 632.1365.

3.2.3. Synthesis of compounds 3~4(a-d) and 5(b-d)

Compounds **7~8(a–d)** or **9(b–d)** (1 mmol) were dissolved in 10 mL anhydrous methanol. The solution was stirred under nitrogen atmosphere at room temperature for 5 min, and then sodium methoxide (54 mg, 1 mmol) was added to the solution; the solution was stirred for another 30 min. After the reaction was finished, Cationic resin H^+ (Dowex-50) was added to the solution to neutralize sodium methoxide and then was removed by filtration. The solvent was evaporated under reduced pressure to get a crude product that was purified using flash column chromatography (ethyl acetate–methanol V/V = 5:1~3:1) to get compounds **3~4(a–d)** and **5(b–d)**, respectively.

(6*R*,7*R*,8*S*,9*R*,9a*S*)-6,7,8,9-tetrahydroxyhexahydrothiazolo[3,2-*a*]azepin-3(2*H*)-one (3a): white solid, yield 70.5%, mp. 193–195 °C, [α] $^{20}_D$ –107.6 (c 1.0, CH_3OH), ^{1}H NMR (600 MHz, CD_3OD) δ_H (ppm): 4.84 (dd, *J* = 9.6 Hz, 1.8 Hz, 1H, CH-9a), 4.11–4.12 (m, 1H, CH); 3.70 (dd, J = 11.4 Hz, 3.6 Hz, 1H, CH), 3.69 (d, J = 8.4 Hz, 1H, CH), 3.53 (dd, *J* = 16.2 Hz, 1.8 Hz, 1H, CH_2), 3.49 (dd, *J* = 9.0 Hz, 1.8 Hz, 1H, CH_2), 3.31–3.36 (m, 3H, CH_2, CH); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm): 173.6,

76.9, 74.1, 74.0, 68.8, 64.1, 46.7, 29.8; HR-ESI-MS: calcd for $C_8H_{13}NO_5SNa$ ([M + Na]$^+$), 258.0412, found: 258.0422.

(6*R*,7*R*,8*S*,9*R*,9a*R*)-6,7,8,9-tetrahydroxyhexahydrothiazolo[3,2-*a*]azepin-3(2*H*)-one (3b): white solid, yield 83.0%, mp. 70–73 °C, [α] $^{30}_D$ +38.6 (c 1.0, CH_3OH), ^{1}H NMR (600 MHz, CD_3OD) δ_H (ppm): 5.04 (d, *J* = 1.8 Hz, 1H, CH-9a), 4.20 (dd, *J* = 8.4 Hz, 2.4 Hz,1H, CH), 4.14–4.18 (m, 1H, CH), 3.92 (d, *J* = 1.8 Hz, 2H, 2CH), 3.86 (brs, 1H, CH), 3.82 (dd, *J* = 15.0 Hz 1.2 Hz, 1H, CH_2), 3.40 (d, *J* = 15.6 Hz, 1H, CH_2), 3.15 (dd, *J* = 13.2 Hz 1.2 Hz, 1H, CH_2); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm): 170.0, 80.2, 78.9, 73.7, 69.1, 60.5, 45.5, 31.8; HR-ESI-MS: calcd for $C_8H_{13}NO_5SNa$ ([M + Na]$^+$), 258.0412, found: 258.0408.

(5a*S*,6*R*,7*S*,8*R*,9*R*)-6,7,8,9-tetrahydroxy-7,8,9,10-tetrahydro-5aH-benzo[5,6][1,3]thiazino[3,2-*a*]azepin-12(6*H*)-one (3c): white solid, yield 50.0%, mp. 213–215 °C, [α] $^{30}_D$ –97.5 (c 1.0, MeOH), ^{1}H NMR (600 MHz, CD_3OD) δ (ppm) 8.00 (d, *J* = 8.0 Hz, 1H, CH), 7.43 (td, *J* = 7.8 Hz, 1.2 Hz, 1H, CH), 7.34 (d, *J* = 7.8 Hz, 1H, CH), 7.29–7.31 (m, 1H, CH), 4.85 (d, *J* = 9.6 Hz, 1H, CH-9a), 4.48 (dd, *J* = 13.2 Hz, 6.0 Hz, 1H, CH), 4.36–4.38 (m, 1H, CH), 4.09–4.13 (m, 1H, CH), 3.66 (d, *J* = 9.6 Hz, 1H, CH_2), 3.23–3.27 (m, 1H, CH_2); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 163.5, 134.3, 131.9, 129.6, 128.4, 127.7, 125.6, 76.4, 74.7, 74.3, 66.0, 64.4, 48.8; HR-ESI-MS: calcd for $C_{13}H_{15}NO_5SNa$ ([M + Na]$^+$), 320.0568, found: 320.0580.

(5a*R*,6*R*,7*S*,8*R*,9*R*)-6,7,8,9-tetrahydroxy-7,8,9,10-tetrahydro-5aH-benzo[5,6][1,3]thiazino[3,2-*a*]azepin-12(6*H*)-one (3d): white solid, yield 51.1%, mp. 153–155 °C, [α] $^{28}_D$ –260.0 (c 5.0, MeOH), ^{1}H NMR (600 MHz, CD_3OD) δ (ppm) 7.96 (dd, *J* = 7.8 Hz, 0.6 Hz, 1H, CH), 7.36 (td, *J* = 7.8 Hz, 1.2 Hz, 1H, CH), 7.27 (d, *J* = 7.8 Hz, 1H, CH), 7.21–7.23 (m, 1H, CH), 5.05 (d, *J* = 1.8 Hz, 1H, CH-9a), 4.52 (q, *J* = 7.2 Hz, 1H, CH), 4.12–4.14 (m, 2H, CH), 3.97–3.99 (m, 1H, CH_2), 3.94–3.95 (m, 1H, CH_2), 3.62 (dd, *J* = 14.4 Hz, 3.6 Hz, 1H, CH); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 165.5, 136.4, 131.5, 129.4, 128.8, 126.2, 125.1, 80.0, 76.2, 71.2, 69.5, 60.0, 46.3; HR-ESI-MS: calcd for $C_{13}H_{15}NO_5SNa$ ([M + Na]$^+$), 320.0568, found: 320.0571.

(6*R*,7*S*,8*S*,9*R*,9a*S*)-6,7,8,9-tetrahydroxyhexahydrothiazolo[3,2-*a*]azepin-3(2*H*)-one (4a): white solid, yield 62.5%, mp. 98–99 °C, [α] $^{25}_D$ –45 (c 0.2, MeOH), ^{1}H NMR (600 MHz, CD_3OD) δ (ppm) 4.68 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H, CH-9a), 3.92–4.05 (m, 5H, CH-5, CH-6, CH-7, CH-8, CH-9), 3.64 (dd, *J* = 15.6 Hz, 2.4 Hz, 1H, CH-2), 3.43 (d, *J* = 15.6 Hz, 1H, CH-2), 3.06 (dd, *J* = 15.0 Hz, 9.6 Hz, 1H, CH-5); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 172.8, 75.1, 74.5, 73.2, 68.0, 66.3, 46.1, 30.6; HR-ESI-MS: calcd for $C_8H_{13}NO_5SNa$ ([M + Na]$^+$), 258.0412, found: 258.0419.

(6*R*,7*S*,8*S*,9*R*,9a*R*)-6,7,8,9-tetrahydroxyhexahydrothiazolo[3,2-*a*]azepin-3(2*H*)-one (4b): white solid, yield 65.5%, mp. 93–94 °C, [α] $^{25}_D$ +55 (c 0.2, MeOH), ^{1}H NMR (600 MHz, CD_3OD) δ (ppm) 5.08 (t, *J* = 1.8 Hz, 1H, CH-9a), 4.02 (dd, *J* = 6.0 Hz, 1.8 Hz, 1H, CH-7), 3.97–4.00 (m, 1H, CH), 3.89 (dd, *J* = 6.0 Hz, 1.8 Hz, 1H, CH), 3.70–3.78 (m, 3H, CH, CH-5, CH-2), 3.47 (dd, *J* = 13.8 Hz, 4.2 Hz, 1H, CH-5), 3.40 (d, *J* = 15.0 Hz, 1H, CH-2); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 173.9, 74.2, 73.2, 72.9, 68.4, 61.9, 32.0; HR-ESI-MS: calcd for $C_8H_{13}NO_5SNa$ ([M + Na]$^+$), 258.0412, found: 258.0430.

(5a*S*,6*R*,7*S*,8*S*,9*R*)-6,7,8,9-tetrahydroxy-7,8,9,10-tetrahydro-5a*H*-benzo[5,6][1,3]thiazino[3,2-*a*]azepin-12(6*H*)-one (4c): white solid, yield 75.5%, mp. 237–238 °C, [α] $^{25}_D$ +20 (c 0.2, MeOH), ^{1}H NMR (600 MHz, CD_3OD) δ (ppm) 8.00 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H, Ph-H), 7.42–7.45 (m, 1H, Ph-H), 7.34 (d, *J* = 7.8 Hz, 1H, Ph-H), 7.28–7.31 (m, 1H, Ph-H), 4.64 (dd, *J* = 13.8 Hz, 6.0 Hz, 1H, CH), 4.42 (d, *J* = 9.0 Hz, 1H, CH-9a), 4.25–4.29 (m, 1H, CH), 3.97 (d, *J* = 3.6 Hz, 1H, CH), 3.76–3.79 (m, 2H, 2CH), 2.91 (dd, *J* = 13.8 Hz, 10.2 Hz, 1H, CH-5); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 163.6, 134.2, 131.8, 129.7, 128.7, 127.6, 125.6, 77.7, 73.9, 73.7, 66.5, 65.9, 52.0; HR-ESI-MS: calcd for $C_{13}H_{15}NO_5SNa$ ([M + Na]$^+$), 320.0568, found: 320.0574.

(5a*R*,6*R*,7*S*,8*S*,9*R*)-6,7,8,9-tetrahydroxy-7,8,9,10-tetrahydro-5a*H*-benzo[5,6][1,3]thiazino[3,2-*a*]azepin-12(6*H*)-one (4d): white solid, yield 80.5%, mp. 211–213 °C, [α] $^{25}_D$ –40 (c 0.2, MeOH), ^{1}H NMR (600 MHz, CD_3OD) δ (ppm) 8.03 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H, Ph-H), 7.37–7.39 (m, 1H, Ph-H), 7.29 (d, *J* = 7.8 Hz, 1H, Ph-H), 7.20–7.23 (m, 1H, Ph-H), 5.11 (d, *J* = 1.8 Hz, 1H, CH-9a), 4.29 (dd, *J* = 14.4 Hz, 2.4 Hz, 1H, CH-5), 3.98–4.03 (m, 2H, 2CH), 3.81–3.88 (m, 3H, 3CH); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 165.9, 137.0, 131.6, 129.2, 127.8, 125.9, 124.7, 76.9, 75.1, 73.8, 72.7, 61.8, 51.9; HR-ESI-MS: calcd for $C_{13}H_{15}NO_5SNa$ ([M + Na]$^+$), 320.0568, found: 320.0553.

(6*R*,7*R*,8*S*,9*S*,9a*R*)-6,7,8,9-tetrahydroxyhexahydrothiazolo[3,2-*a*]azepin-3(2*H*)-one (5b): white solid, yield 70.5%, mp. 152–153 °C, [α] $^{25}_D$ –60 (c 0.2, MeOH), ^{1}H NMR (600 MHz, CD_3OD) δ (ppm) 4.96 (dd, *J* = 7.8 Hz, 1.2 Hz,1H, CH-9a), 4.15–4.16 (m, 1H, CH), 4.02 (s, 2H, CH), 3.97 (dd, *J* = 13.8 Hz, 7.2 Hz, 1H, CH), 3.86 (d, *J* = 5.4 Hz, 1H, CH), 3.55 (brs, 2H, CH), 3.28 (dd, *J* = 13.8 Hz, 3.0 Hz, 1H, CH); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 173.1, 73.8, 70.4, 67.1, 63.6, 44.1, 31.0; HR-ESI-MS: calcd for $C_8H_{13}NO_5SNa$ ([M + Na]$^+$), 258.0412, found: 258.0407.

(5a*S*,6*S*,7*S*,8*R*,9*R*)-6,7,8,9-tetrahydroxy-7,8,9,10-tetrahydro-5a*H*-benzo[5,6][1,3]thiazino[3,2-*a*]azepin-12(6*H*)-one (5c): white solid, yield 65.5%, mp. > 250 °C, [α] $^{25}_D$ +25 (c 0.2, MeOH), ^{1}H NMR (600 MHz, CD_3OD) δ (ppm) 7.89 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H, Ph-H), 7.33–7.36 (m, 1H, Ph-H), 7.28 (d, *J* = 7.8 Hz, 1H, Ph-H), 7.18–7.21 (m, 1H, Ph-H), 5.07 (d, *J* = 1.8 Hz, 1H, CH-9a), 4.10 (t, *J* = 1.8 Hz, 1H, CH), 4.03–4.04 (m, 1H, CH), 3.95 (dd, *J* = 13.8 Hz, 7.2 Hz, 1H, CH-5), 3.88 (dd, *J* = 14.4 Hz, 3.0 Hz, 1H, CH-5), 3.68 (dd, *J* = 8.0 Hz, 1.8 Hz, 1H, CH), 3.62 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H, CH); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 166.0, 137.6, 131.4, 129.8, 128.7, 126.2, 125.0, 75.5, 72.1, 71.8, 68.3, 63.5, 60.9; HR-ESI-MS: calcd for $C_{13}H_{15}NO_5SNa$ ([M + Na]$^+$), 320.0568, found: 320.0549.

(5a*R*,6*S*,7*S*,8*R*,9*R*)-6,7,8,9-tetrahydroxy-7,8,9,10-tetrahydro-5a*H*-benzo[5,6][1,3]thiazino[3,2-*a*]azepin-12(6*H*)-one (5d): white solid, yield 72.0%, mp. 208–209 °C, [α] $^{25}_D$ +65 (c 0.2, MeOH), ^{1}H NMR (600 MHz, CD_3OD) δ (ppm) 8.01 (d, *J* = 7.8 Hz, 1H, Ph-H), 7.45 (t, *J* = 7.2 Hz, 1H, Ph-H), 7.38 (d, *J* = 7.8 Hz, 1H, Ph-H), 7.30 (t, *J* = 7.8 Hz, 1H, Ph-H), 4.84 (d, *J* = 9.6 Hz, 1H, CH-9a), 4.31 (d, *J* = 10.8 Hz, 1H, CH), 4.18 (dd, *J* = 9.6 Hz, 1.8 Hz, 1H, CH), 4.15 (dd, *J* = 6.6 Hz, 2.4 Hz, 1H, CH), 4.08–4.10 (m, 1H, CH), 4.05 (dd, *J* = 7.2 Hz, 3.0 Hz, 1H, CH), 3.67 (dd, *J* = 14.4 Hz, 3.6 Hz, 1H, CH-5); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 165.5, 131.9, 129.9, 128.4, 127.3, 125.6, 71.6, 69.7, 68.7, 63.3, 48.3; HR-ESI-MS: calcd for $C_{13}H_{15}NO_5SNa$ ([M + Na]$^+$), 320.0568, found: 320.0574.

3.3. *In vitro HIV-RT kit assay*

The HIV-RT inhibition assay was performed by using an RT assay kit (Roche), and the procedure for assaying RT inhibition was performed as described in the kit protocol. Briefly, the reaction mixture consists of template/primer complex, 2′-deoxy-nucleotide-5′-triphosphates (dNTPs) and reverse transcriptase (RT) enzyme in the lysis buffer with or without inhibitors. After 1 h incubation at 37 °C the reaction mixture was transferred to streptavidine-coated microtiter plate (MTP). The biotin labeled dNTPs that are incorporated in the template due to activity of RT were bound to streptavidine. The unbound dNTPs were washed using wash buffer and antidigoxigenin-peroxidase (DIG-POD) was added in MTP. The DIG-labeled dNTPs incorporated in the template was bound to anti-DIG-POD antibody. The unbound anti-DIG-POD was washed and the peroxide substrate (ABST) was added to the MTP. A colored reaction product was produced during the cleavage of the substrate catalyses by a peroxide enzyme. The absorbance of the sample was determined at OD 405 nM using microtiter plate ELISA reader. The resulting color intensity is directly proportional to the actual RT activity. The percentage inhibitory activity of RT inhibitors was calculated by comparing to a sample that does not contain an inhibitor. The percentage inhibition was calculated by formula as given below: % Inhibition = 100 – [($OD_{405\,nm}$ with inhibitor/$OD_{405\,nm}$ without inhibitor) × 100].

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.carres.2016.02.011.

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31. CCDC-1425336 (for **4a**) and -1425337 (for **8d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <www.ccdc.cam.ac.uk/data_request/cif>.
32. Reverse Transcriptase Assay, Colorimetric kit, Roche Diagnostics GmbH, Roche Applied Science, Sandhofer Strasse 116, D-68305 Mannheim, Germany.