Synthesis of Novel Guanidinogalactosides

Jin-Feng Yang (楊金鳳) and Ling-Hua Cao* (曹玲華)
College of Chemistry and Chemical Engineering, Xinjiang University, Urumqi, Xinjiang 830046, P. R. China

This paper involves the preparation of thioureas, which couple with per-*O*-acetylated galactosyl isothiocyanate **1** and 2-aminobenzothiazole **2** to give incorporating galactosylthiourea derivatives **3**. Nucleophilic addition of active primary amine to **3** in the presence of $HgCl_2$ afforded the per-*O*-acetylated guanidinogalactoside **4a-4d**, **5a-5d**, **6a-6d**, **7a-7d** in good yield. These adducts were subjected to deacetylation in MeOH/NaOMe and furnished the corresponding unprotected guanidinogalactosides **8a-8d**, **9a-9d**, **10a-10d**, **11a-11d**. The structures of all newly synthesized compounds were established by IR, ^{1}H NMR, MS and elemental analysis.

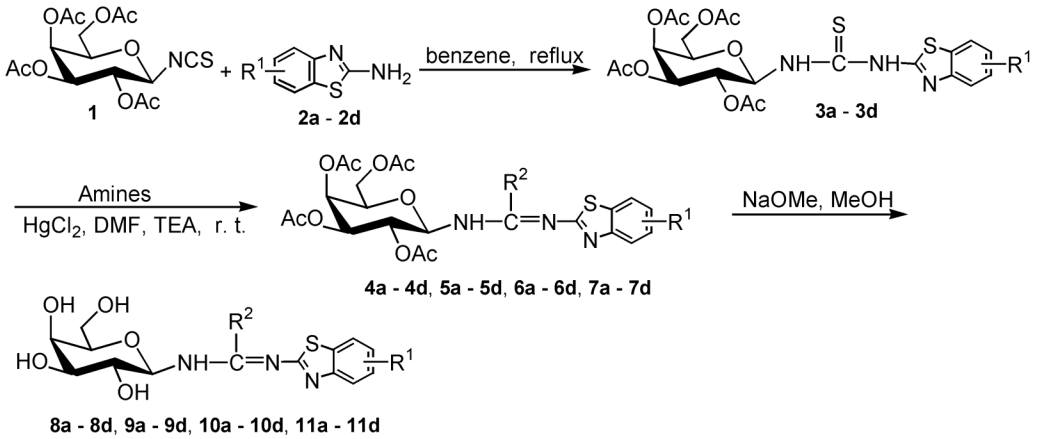
Keywords: Galactosyl isothiocyanate; Benzothiazole; Guanidinogalactoside.

INTRODUCTION

Guanidines are structurally novel molecules reported to exhibit remarkable biological and pharmacological activities, which are affected by the guanidine functionality.[1] The guanidine moiety has been incorporated into many drugs covering a variety of therapeutic areas.[2] A number of benzothiazolyl guanidines have been synthesized and reported to exhibit antibacterial and antitubercular activity.[3] Guanidino-containing sugar and sugar-like molecules also have a wide range of biologically important uses such as inhibition of replication of HIV,[4] antihypertensives,[5] antibacterial activity,[6] and inhibition of nitric oxide syntheses.[7] So, guanidine-containing sugars have attracted the attention of the pharmaceutical industry.[8] D-galactose is a normal reducing sugar in the body.[9] Glycoside analogs of β-galactosylceramide are a novel class of small molecule antiviral agents that inhibit HIV-1 entry.[10] In recent years, galactose has become of considerable importance as a pharmacophoric group, which has been synthesized by many methods.[11,12] However, guanidine-like molecules which contain galactosyl have not been reported.

In recent years, many efficient methods of preparing guanidine have been demonstrated. However, some of these methods showed limited success on account of unde-

Scheme I



4a-4d, **8a-8d**: R^1 = H; **5a-5d**, **9a-9d**: R^1 = 4-CH_3; **6a-6d**, **10a-10d**: R^1 = 6-CH_3; **7a-7d**, **11a-11d**: R^1 = 6-OCH_3;
4-11a: R^2 = *i*-propylamino; **4-11b**: R^2 =*n*-propylamino; **4-11c**: R^2 = *p*-chloroanilino; **4-11d**: R^2 = anisidino

* Corresponding author. E-mail: clhxj@xju.edu.cn

sirable conditions and unstable starting materials, especially in the synthesis of guanidine containing sugars,[13] and these reactions were considered to go via a carbodiimide intermediates. In contrast, we have synthesized a series of new guanidinogalactoside in one step and did not isolate carbodiimide intermediates in the work. The results indicated that the electron-donating groups on the benzene ring were favorable to the addition reaction. The resultant amine can be either alkyl or aryl.

Isothiocyanates are vesertile synthetic intermediates in organic chemistry due to their availability and their tendency to undergo nucleophilic additions.[14,15] Particularly in the carbohydrate field, sugar isothiocyanates play a pivotal role in the preparation of a broad spectrum of carbohydrate derivatives, mostly having a thiourea structure, for biological and pharmaceutical interests.[16,17] In order to broaden the synthesis and activities research of glycosylguanidine, we obtained a series of new guanidinogalactosides. HIV PR inhibitory and anti-inflluenza activity of these compounds have been evaluated, some of which did not display obvious biological activity.

RESULTS AND DISCUSSION

We used per-*O*-acetylated galactosyl isothiocyanate

Table 1. Physical data, the elemental analysis and MS data of new compounds

Compd.	Formula	Yield%	m.p./°C	Elemental analysis (calcd) %			MS *m/z* (%)
				C	H	N	
3a	$C_{22}H_{25}N_3O_9S_2$	80	211-212	49.03 (48.97)	4.65 (4.67)	7.76 (7.79)	540 ([M+H]$^+$, 100)
3b	$C_{23}H_{27}N_3O_9S_2$	82	219-220	49.95 (49.90)	4.90 (4.92)	7.57 (7.59)	554 ([M+H]$^+$, 100)
3c	$C_{23}H_{27}N_3O_9S_2$	85	198-199	49.84 (49.90)	4.91 (4.92)	7.56 (7.59)	554 ([M+H]$^+$, 100)
3d	$C_{23}H_{27}N_3O_{10}S_2$	84	188-189	48.45 (48.50)	4.76 (4.78)	7.41 (7.38)	570 ([M+H]$^+$, 100)
4a	$C_{25}H_{32}N_4O_9S$	85	154-155	53.11 (53.17)	5.70 (5.72)	9.96 (9.93)	563 ([M–H]$^-$, 100)
4b	$C_{25}H_{32}N_4O_9S$	82	149-150	53.22 (53.17)	5.69 (5.72)	9.91 (9.93)	563 ([M–H]$^-$, 100)
4c	$C_{28}H_{29}N_4O_9SCl$	75	191-193	53.08 (53.15)	4.64 (4.62)	8.83 (8.86)	632 ([M–H]$^-$, 100)
4d	$C_{29}H_{32}N_4O_{10}S$	78	118-120	55.46 (55.40)	5.15 (5.13)	8.90 (8.92)	627 ([M–H]$^-$, 100)
5a	$C_{26}H_{34}N_4O_9S$	82	174-175	53.91 (53.96)	5.92 (5.93)	9.71 (9.69)	577 ([M–H]$^-$, 100)
5b	$C_{26}H_{34}N_4O_9S$	76	148-150	54.01 (53.96)	5.91 (5.93)	9.66 (9.69)	577 ([M–H]$^-$, 100)
5c	$C_{29}H_{31}N_4O_9SCl$	72	178-179	53.79 (53.86)	4.82 (4.84)	8.68 (8.67)	646 ([M–H]$^-$, 100)
5d	$C_{30}H_{34}N_4O_{10}S$	80	198-199	56.00 (56.06)	5.36 (5.34)	8.75 (8.72)	641 ([M–H]$^-$, 100)
6a	$C_{26}H_{34}N_4O_9S$	81	158-159	53.99 (53.96)	5.91 (5.93)	9.71 (9.69)	577 ([M–H]$^-$, 100)
6b	$C_{26}H_{34}N_4O_9S$	85	163-165	53.91 (53.96)	5.94 (5.93)	9.67 (9.69)	577 ([M–H]$^-$, 100)
6c	$C_{29}H_{31}N_4O_9SCl$	70	183-185	53.91 (53.86)	4.82 (4.84)	8.64 (8.67)	646 ([M–H]$^-$, 100)
6d	$C_{30}H_{34}N_4O_{10}S$	71	182-183	56.01 (56.06)	5.33 (5.34)	8.75 (8.72)	641 ([M–H]$^-$, 100)
7a	$C_{26}H_{34}N_4O_{10}S$	79	98-99	52.57 (52.51)	5.78 (5.77)	9.41 (9.43)	593 ([M–H]$^-$, 100)
7b	$C_{26}H_{34}N_4O_{10}S$	78	144-146	52.48 (52.51)	5.75 (5.77)	9.45 (9.43)	593 ([M–H]$^-$, 100)
7c	$C_{29}H_{31}N_4O_{10}SCl$	72	198-199	52.49 (52.56)	4.73 (4.72)	8.49 (8.46)	662 ([M–H]$^-$, 100)
7d	$C_{30}H_{34}N_4O_{11}S$	73	184-186	54.75 (54.70)	5.19 (5.21)	8.52 (8.51)	657 ([M–H]$^-$, 100)
8a	$C_{17}H_{24}N_4O_5S$	89	123-125	51.57 (51.50)	6.09 (6.11)	14.10 (14.14)	395 ([M–H]$^-$, 100)
8b	$C_{17}H_{24}N_4O_5S$	80	129-130	51.45 (51.50)	6.12 (6.11)	14.17 (14.14)	395 ([M–H]$^-$, 100)
8c	$C_{20}H_{21}N_4O_5SCl$	81	145-146	51.65 (51.71)	4.55 (4.56)	12.09 (12.07)	464 ([M–H]$^-$, 100)
8d	$C_{21}H_{24}N_4O_6S$	79	188-190	54.73 (54.77)	5.23 (5.26)	12.15 (12.17)	459 ([M–H]$^-$, 100)
9a	$C_{18}H_{26}N_4O_5S$	81	123-124	52.71 (52.66)	6.37 (6.39)	13.64 (13.66)	409 ([M–H]$^-$, 100)
9b	$C_{18}H_{26}N_4O_5S$	85	120-122	52.62 (52.66)	6.40 (6.39)	13.68 (13.66)	409 ([M–H]$^-$, 100)
9c	$C_{21}H_{23}N_4O_5SCl$	80	142-144	52.76 (52.71)	4.83 (4.85)	11.75 (11.72)	478 ([M–H]$^-$, 100)
9d	$C_{22}H_{26}N_4O_6S$	81	208-210	55.76 (55.68)	5.50 (5.53)	11.78 (11.81)	473 ([M–H]$^-$, 100)
10a	$C_{18}H_{26}N_4O_5S$	79	116-118	52.62 (52.66)	6.41 (6.39)	13.62 (13.66)	409 ([M–H]$^-$, 100)
10b	$C_{18}H_{26}N_4O_5S$	81	123-125	52.73 (52.66)	6.37 (6.39)	13.63 (13.66)	409 ([M–H]$^-$, 100)
10c	$C_{21}H_{23}N_4O_5SCl$	79	154-156	52.76 (52.71)	4.83 (4.85)	11.74 (11.72)	478 ([M–H]$^-$, 100)
10d	$C_{22}H_{26}N_4O_6S$	76	140-142	55.74 (55.68)	5.50 (5.53)	11.83 (11.81)	473 ([M–H]$^-$, 100)
11a	$C_{18}H_{26}N_4O_6S$	80	137-138	50.62 (50.69)	6.14 (6.15)	13.17 (13.14)	425 ([M–H]$^-$, 100)
11b	$C_{18}H_{26}N_4O_6S$	82	112-114	50.73 (50.69)	6.17 (6.15)	13.12 (13.14)	425 ([M–H]$^-$, 100)
11c	$C_{21}H_{23}N_4O_6SCl$	78	150-152	50.94 (51.00)	4.68 (4.69)	11.39 (11.34)	494 ([M–H]$^-$, 100)
11d	$C_{22}H_{26}N_4O_7S$	80	206-207	53.81 (53.86)	5.35 (5.35)	11.47 (11.43)	489 ([M–H]$^-$, 100)

Table 2. IR spectral data for new compounds

Compd.	IR (KBr) ν/cm^{-1}
3a	3376 (m, NH), 1757 (s, C=O), 1512 (m, N-C=S), 1216 (s, C–O–C), 911 (m, C_1–H)
3b	3347 (m, NH), 1747 (s, C=O), 1515 (m, N-C=S), 1217 (s, C–O–C), 913 (m, C_1–H)
3c	3334 (m, NH), 1750 (s, C=O), 1518 (m, N-C=S), 1218 (s, C–O–C), 914 (m, C_1–H)
3d	3356 (m, NH), 1749 (s, C=O), 1517 (m, N-C=S), 1221 (s, C–O–C), 913 (m, C_1–H)
4a	3434 (s, NH), 3371 (s, NH), 1747 (s, C=O), 1616 (s, guanidino), 1216 (s, C–O–C), 908 (m, sugar ring C_1–H)
4b	3421 (m, NH), 1757 (s, C=O), 1618 (s, guanidino), 1220 (s, C–O–C), 910 (m, sugar ring C_1–H)
4c	3446 (m, NH), 1748 (s, C=O), 1614 (s, guanidino), 1216 (s, C–O–C), 913 (m, sugar ring C_1–H)
4d	3447 (m, NH), 1754 (s, C=O), 1616 (s, guanidino), 1222 (s, C–O–C), 915 (m, sugar ring C_1–H)
5a	3427 (m, NH), 3390 (s, NH), 1748 (s, C=O), 1617 (s, guanidino), 1223 (s, C–O–C), 910 (m, sugar ring C_1–H)
5b	3440 (m, NH), 1749 (s, C=O), 1617 (s, guanidino), 1217 (s, C–O–C), 916 (m, sugar ring C_1–H)
5c	3438 (m, NH), 1748 (s, C=O), 1620 (s, guanidino), 1224 (s, C–O–C), 917 (m, sugar ring C_1–H)
5d	3445 (m, NH), 1753 (s, C=O), 1616 (s, guanidino), 1232 (s, C–O–C), 913 (m, sugar ring C_1–H)
6a	3430 (m, NH), 3363 (s, NH), 1758 (s, C=O), 1612 (s, guanidino), 1221 (s, C–O–C), 910 (m, sugar ring C_1–H)
6b	3456 (m, NH), 1750 (s, C=O), 1616 (s, guanidino), 1221 (s, C–O–C), 914 (m, sugar ring C_1–H)
6c	3446 (m, NH), 1748 (s, C=O), 1620 (s, guanidino), 1229 (s, C–O–C), 913 (m, sugar ring C_1–H)
6d	3451 (m, NH), 1751 (s, C=O), 1612 (s, guanidino), 1219 (s, C–O–C), 913 (m, sugar ring C_1–H)
7a	3444 (m, NH), 3380 (m, NH), 1751 (s, C=O), 1615 (s, guanidino), 1216 (s, C–O–C), 910 (m, sugar ring C_1–H)
7b	3472 (m, NH), 1756 (s, C=O), 1615 (s, guanidino), 1216 (s, C–O–C), 906 (m, sugar ring C_1–H)
7c	3453 (m, NH), 1748 (s, C=O), 1621 (s, guanidino), 1216 (s, C–O–C), 913 (m, sugar ring C_1–H)
7d	3429 (m, NH), 1746 (s, C=O), 1606 (s, guanidino), 1216 (s, C–O–C), 910 (m, sugar ring C_1-H)
8a	3523 (s, NH), 3346 (s, OH), 1613 (s, guanidino), 1215 (s, C–O–C), 913 (m, sugar ring C_1–H)
8b	3527 (s, NH), 3347 (m, OH), 1608 (s, guanidino), 1218 (s, C–O–C), 918 (m, sugar ring C_1–H)
8c	3532 (s, NH), 3328 (m, OH), 1616 (s, guanidino), 1209 (s, C–O–C), 913 (m, sugar ring C_1–H)
8d	3527 (s, NH), 3331 (m, OH), 1612 (s, guanidino), 1218 (s, C–O–C), 913 (m, sugar ring C_1–H)
9a	3538 (s, NH), 3349 (m, OH), 1609 (s, guanidino), 1210 (s, C-O-C), 914 (m, sugar ring C_1–H)
9b	3567 (s, NH), 3358 (m, OH), 1607 (s, guanidino), 1211 (s, C–O–C), 910 (m, sugar ring C_1–H)
9c	3543 (s, NH), 3328 (m, OH), 1608 (s, guanidino), 1218 (s, C–O–C), 915 (m, sugar ring C_1–H)
9d	3537 (s, NH), 3336 (m, OH), 1612 (s, guanidino), 1210 (s, C–O–C), 913 (m, sugar ring C_1–H)
10a	3549 (s, NH), 3356 (m, OH), 1611 (s, guanidino), 1209 (s, C–O–C), 911 (m, sugar ring C_1–H)
10b	3563 (s, NH), 3355 (m, OH), 1613 (s, guanidino), 1216 (s, C–O–C), 913 (m, sugar ring C_1–H)
10c	3546 (s, NH), 3361 (m, OH), 1606 (s, guanidino l), 1220 (s, C–O–C), 913 (m, sugar ring C_1–H)
10d	3569 (s, NH), 3546 (m, OH), 1608 (s, guanidino), 1218 (s, C–O–C), 913 (m, sugar ring C_1–H)
11a	3563 (s, NH), 3353 (m, OH), 1606 (s, guanidino), 1210 (s, C–O–C), 910 (m, sugar ring C_1–H)
11b	3476 (s, NH), 3343 (m, OH), 1611 (s, guanidino), 1208 (s, C–O–C), 908 (m, sugar ring C_1–H)
11c	3555 (s, NH), 3364 (m, OH), 1618 (s, guanidino l), 1216 (s, C–O–C), 913 (m, sugar ring C_1–H)
11d	3567 (s, NH), 3362 (m, OH), 1614 (s, guanidino), 1213 (s, C–O–C), 917 (m, sugar ring C_1–H)

as the starting material, which reacted with 2-aminobenzothiazole derivatives in dry benzene to give galactosylthioureas **3a-3d**. Treatment of **3a-3d** with various active amines, and using $HgCl_2$ as a regent for desulfurization, a series of new guanidinoglycoside compounds **4a-4d**, **5a-5d**, **6a-6d**, **7a-7d** have been obtained. These compounds were further deacetylated in MeOH/NaOMe to generate the corresponding deacetylated guanidinogalactosides **8a-8d**, **9a-9d**, **10a-10d**, **11a-11d**.

In the IR spectra, all new compounds **4-7** showed peaks in the region of 3500-3200 cm^{-1} (N–H stretching), 1750 cm^{-1} (C=O stretching) and 1240-1210 cm^{-1} (C–O–C). In contrast with compounds **3a-3d**, which showed bands of thioureido at about 1500 cm^{-1}, the compounds **4-11** were characterized by a strong band at about 1610 cm^{-1}, assigned to guanidine. And then there were no bands of thioureido at about 1500 cm^{-1}. The band at 913 cm^{-1} indicated that all new compounds were in common $^4C_1$ (β-nomer).

In the ^{1}H NMR spectra of compounds **4a-4d**, **5a-5d**, **6a-6d** and **7a-7d**, the proton signal of the acetyl group in the glycosyl ring appeared at about δ 2.00-2.65 and showed the four independent absorption peaks in the event of the chemical environmental difference. The resonance peaks of the δ 3.80-5.40 were assigned to sugar ring protons. It is the signal of sugar ring C_1–H that appeared at δ 5.50 which shifted to the low-field displacement and presented triplet

Table 3. ^{1}H NMR spectral data of new compounds

Compd.	^{1}H NMR ($CDCl_3$, 400 MH_Z), δ
3a	1.98, 2.02, 2.06, 2.18 (4s, 12H, 4 × $COCH_3$), 3.91-5.34 (m, 6H, sugar ring 2,3,4,5,6–H), 5.45 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.03-7.46 (m, 4H, ArH), 10.11-10.33 (br, 1H, NH), 11.44-11.77 (s, 1H, NH)
3b	1.52 (s, 3H, CH_3), 1.98, 2.04, 2.16, 2.50 (4s, 12H, 4 × $COCH_3$), 3.95-5.25 (m, 6H, sugar ring 2,3,4,5,6–H), 5.45 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.03-7.48 (m, 3H, ArH), 10.11-10.33 (br, 1H, NH), 11.39-11.72 (br, 1H, NH)
3c	1.43 (s, 3H, CH_3), 2.00, 2.08, 2.18, 2.42 (4s, 12H, 4 × $COCH_3$), 4.10-5.24 (m, 6H, sugar ring 2,3,4,5,6–H), 5.44 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.14-7.60 (m, 3H, ArH), 10.11-10.33 (br, 1H, NH), 11.46-11.71 (br, 1H, NH)
3d	2.00, 2.04, 2.20, 2.42 (4s, 12H, 4 × $COCH_3$), 3.78 (s, 3H, OCH_3), 3.95-5.18 (m, 6H, sugar ring 2,3,4,5,6–H), 5.42 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.13-7.62 (m, 3H, ArH), 10.11-10.33 (br, 1H, NH), 11.36-11.70 (br, 1H, NH)
4a	1.23-1.34 (d, *J* = 7.2 Hz, 6H, 2 × CH_3), 1.98, 2.02, 2.05, 2.18 (4s, 12H, 4 × $COCH_3$), 3.66 (s, 1H, NH), 3.95-5.32 (m, 7H, sugar ring 2,3,4,5,6–H, CH), 5.49 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.03-7.46 (m, 4H, ArH), 10.09 (s, 1H, NH)
4b	1.01 (t, *J* = 6.0 Hz, 3H, CH_3), 1.64 (m, 2H, CH_2), 1.98, 2.00, 2.04, 2.18 (4s, 12H, 4 × $COCH_3$), 3.14 (m, 2H, CH_2), 3.89-5.22 (m, 6H, sugar ring 2,3,4,5,6–H), 5.39 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 5.62 (s, 1H, NH), 7.03-7.48 (m, 4H, ArH), 10.29 (s, 1H, NH)
4c	1.98, 2.02, 2.07, 2.19 (4s, 12H, 4 × $COCH_3$), 4.08-5.40 (m, 6H, sugar ring 2,3,4,5,6–H), 5.58 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.09-7.58 (m, 7H, ArH), 10.11 (d, 1H, NH), 12.12 (d, 1H, NH)
4d	1.98, 2.02, 2.06, 2.19 (4s, 12H, 4 × $COCH_3$), 3.80 (s, 3H, OCH_3), 3.95-5.26 (m, 6H, sugar ring 2,3,4,5,6–H), 5.46 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.06-7.46 (m, 7H, ArH), 10.12 (d, *J* = 9.2 Hz, 1H, NH), 12.05 (s, 1H, NH)
5a	1.23-1.36 (d, *J* = 7.2 Hz, 6H, 2 × CH_3), 1.52 (s, 3H, CH_3), 2.02, 2.04, 2.18, 2.54 (4s, 12H, 4 × $COCH_3$), 3.62 (s, 1H, NH), 4.05-5.25 (m, 7H, sugar ring 2,3,4,5,6–H, CH), 5.48 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.03-7.48 (m, 3H, ArH), 10.52 (s, 1H, NH)
5b	1.01 (t, *J* = 6.0 Hz, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.64 (m, 2H, CH_2), 2.00, 2.05, 2.17, 2.51 (4s, 12H, 4 × $COCH_3$), 3.14 (m, 2H, CH_2), 3.95-5.21 (m, 7H, sugar ring 2,3,4,5,6–H, NH), 5.48 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.05-7.48 (m, 3H, ArH), 10.49 (s, 1H, NH)
5c	1.54 (s, 3H, CH_3), 2.00, 2.04, 2.24, 2.52 (4s, 12H, 4 × $COCH_3$), 4.12-5.40 (m, 6H, sugar ring 2,3,4,5,6–H), 5.63 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.09-7.58 (m, 7H, ArH), 10.21 (d, 1H, NH), 12.33 (s, 1H, NH)
5d	1.53 (s, 3H, CH_3), 2.00, 2.06, 2.18, 2.50 (4s, 12H, 4 × $COCH_3$), 3.78 (s, 3H, OCH_3), 3.89-5.26 (m, 6H, sugar ring 2,3,4,5,6–H), 5.41 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.06-7.57 (m, 7H, ArH), 10.02 (d, *J* = 9.2 Hz, 1H, NH), 12.03 (s, 1H, NH)
6a	1.25-1.34 (d, *J* = 7.0 Hz, 6H, 2 × CH_3), 1.42 (s, 3H, CH_3), 2.00, 2.18, 2.20, 2.39 (4s, 12H, 4×$COCH_3$), 3.70 (s, 1H, NH), 4.10-5.25 (m, 7H, sugar ring 2,3,4,5,6–H, CH), 5.48 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.15-59 (m, 3H, ArH), 10.52 (s, 1H, NH)
6b	1.04 (t, *J* = 6.0 Hz, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.60 (m, 2H, CH_2), 2.00, 2.08, 2.19, 2.40 (4s, 12H, 4 × $COCH_3$), 3.14 (m, 3H, CH_2), 4.10-5.22 (m, 7H, sugar ring 2,3,4,5,6–H, NH), 5.45 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.14-7.64 (m, 3H, ArH), 10.49 (s, 1H, NH)
6c	1.42 (s, 3H, CH_3), 2.00, 2.08, 2.17, 2.41 (4s, 12H, 4 × $COCH_3$), 4.06-5.22 (m, 6H, sugar ring 2,3,4,5,6–H), 5.43 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.09-7.58 (m, 7H, ArH), 10.11 (d, 1H, NH), 12.26 (s, 1H, NH)
6d	1.41 (s, 3H, CH_3), 1.98, 2.08, 2.18, 2.44 (4s, 12H, 4 × $COCH_3$), 3.78 (s, 3H, OCH_3), 3.89-5.24 (m, 6H, sugar ring 2,3,4,5,6–H), 5.41 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.06-7.57 (m, 7H, ArH), 10.12 (d, *J* = 9.2 Hz, 1H, NH), 12.06 (s, 1H, NH)
7a	1.26-1.38 (d, *J* = 7.2 Hz, 6H, 2 × CH_3), 2.00, 2.04, 2.18, 2.44 (4s, 12H, 4 × $COCH_3$), 3.69 (s, 1H, NH), 3.80 (s, 3H, OCH_3), 3.98-5.13 (m, 7H, sugar ring 2,3,4,5,6–H, CH), 5.28 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.22-7.68 (m, 3H, ArH), 10.76 (s, 1H, NH)
7b	1.03 (t, *J* = 6.0 Hz, 3H, CH_3), 1.58 (m, 3H, CH_2), 2.00, 2.04, 2.20, 2.42 (4s, 12H, 4 × $COCH_3$), 3.12 (m, 2H, CH_2), 3.73 (s, 3H, OCH_3), 3.95-5.08 (m, 6H, sugar ring 2,3,4,5,6–H), 5.22 (t, *J* = 9.6 Hz, 1H, sugar ring C_1-H), 5.37 (s, 1H, NH), 7.13-7.69 (m, 3H, ArH), 10.67 (s, 1H, NH)
7c	2.00, 2.10, 2.18, 2.42 (4s, 12H, 4 × $COCH_3$), 3.78 (s, 3H, OCH_3), 3.95-5.20 (m, 6H, sugar ring-H 2,3,4,5,6–H), 5.42 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.11-7.52 (m, 7H, ArH), 10.09 (d, *J* = 9.2 Hz, 1H, NH), 12.24 (s, 1H, NH)
7d	2.00, 2.06, 2.17, 2.45 (4s, 12H, 4 × $COCH_3$), 3.79 (s, 6H, 2 × OCH_3), 3.95-5.20 (m, 6H, sugar ring 2,3,4,5,6–H), 5.42 (t, *J* = 9.6 Hz, 1H, sugar ring C_1–H), 7.06-7.56 (m, 7H, ArH), 10.12 (d, *J* = 9.2 Hz, 1H, NH), 12.16 (s, 1H, NH);
8a	1.23-1.34 (d, *J* = 7.2 Hz, 6H, 2 × CH_3), 3.23-3.67 (m, 7H, sugar ring 2,3,4,5,6–H, NH), 4.34 (t, *J* = 9.4 Hz, 1H, sugar ring C_1–H), 4.23-5.64 (m, 5H, sugar ring–OH, CH), 7.04-7.48 (m, 4H, ArH), 9.72 (d, *J* = 9.2 Hz, 1H, NH)
8b	1.01 (t, *J* = 6.0 Hz, 3H, CH_3), 1.64 (m, 2H, CH_2), 3.14 (m, 2H, CH_2), 3.23-3.64 (m, 6H, sugar ring 2,3,4,5,6–H), 4.34 (t, *J* = 9.4 Hz, 1H, sugar ring C_1–H), 4.23-5.65 (m, 5H, sugar ring–OH, NH), 7.03-7.48 (m, 4H, ArH), 9.69 (d, *J* = 9.2 Hz, 1H, NH)

8c	3.34-3.64 (m, 6H, sugar ring 2,3,4,5,6–H,), 4.34 (t, J = 9.6 Hz, 1H, sugar ring C_1–H), 4.58-5.22 (m, 4H, sugar ring–OH), 7.09-7.56 (m, 7H, ArH), 10.11 (d, J = 9.2 Hz, 1H, NH), 12.12 (s, 1H, NH)
8d	3.34-3.64 (m, 6H, sugar ring 2,3,4,5,6–H,), 3.81 (s, 3H, OCH_3), 4.32 (t, J = 9.6 Hz, 1H, sugar ring C_1–H), 4.58-5.22 (m, 4H, sugar ring–OH), 7.06-7.48 (m, 7H, ArH), 10.08 (d, J = 8.8 Hz, 1H, NH), 12.05 (s, 1H, NH)
9a	1.24-1.36 (d, J = 7.2 Hz, 6H, 2 × CH_3), 2.52 (s, 3H, CH_3), 3.34-3.64 (m, 7H, sugar ring 2,3,4,5,6–H, NH), 4.34 (t, J = 9.6 Hz, 1H, sugar ring C_1–H), 4.58-5.22 (m, 5H, sugar ring–OH, CH), 7.03-7.48 (m, 3H, ArH), 10.43 (d, J = 8.8 Hz, 1H, NH)
9b	1.01 (t, J = 6.0 Hz, 3H, CH_3), 2.51 (s, 3H, CH_3), 1.64 (m, 2H, CH_2), 3.14 (m, 2H, CH_2), 3.34-3.64 (m, 6H, sugar ring 2,3,4,5,6–H), 4.34 (t, J = 9.6 Hz, 1H, sugar ring C1–H), 4.40-5.22 (m, 5H, sugar ring–OH, NH), 7.05-7.48 (m, 3H, ArH), 10.12 (d, J = 8.8 Hz, 1H, NH)
9c	2.51 (s, 3H, CH_3), 3.34-3.68 (m, 6H, sugar ring 2,3,4,5,6–H), 4.34 (t, J = 9.6 Hz, 1H, sugar ring C_1–H), 4.58-5.22 (m, 4H, sugar ring–OH), 7.09-7.58 (m, 7H, ArH), 9.66 (d, J = 8.8 Hz, 1H, NH), 12.21 (s, 1H, NH)
9d	2.51 (s, 3H, CH_3), 3.30-3.80 (m, 9H, sugar ring 2,3,4,5,6–H, OCH_3), 4.32 (t, J = 9.6 Hz, 1H, sugar ring C_1–H), 4.58-5.21 (m, 4H, sugar ring–OH), 7.06-7.56 (m, 7H, ArH), 9.64 (d, J = 9.2 Hz, 1H, NH), 12.03 (s, 1H, NH)
10a	1.25-1.34 (d, J = 7.0 Hz, 6H, 2 × CH_3), 1.48 (s, 3H, CH_3), 3.34-3.72 (m, 7H, sugar ring 2,3,4,5,6–H, NH), 4.34 (t, J = 9.6 Hz, 1H, sugar ring C_1–H), 4.58-5.25 (m, 5H, sugar ring–OH, CH), 7.15-7.59 (m, 3H, ArH), 9.68 (d, J = 8.8 Hz, 1H, NH)
10b	1.04 (t, J = 7.0 Hz, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.60 (m, 2H, CH_2), 3.14 (m, 3H, CH_2), 3.32-3.69 (m, 6H, sugar ring 2,3,4,5,6–H), 4.34 (t, J = 9.6 Hz, 1H, sugar ring C_1–H), 4.58-5.64 (m, 5H, sugar ring–OH, NH), 7.12-7.61 (m, 3H, ArH), 9.59 (d, J = 8.8 Hz, 1H, NH)
10c	1.42 (s, 3H, CH_3), 3.32-3.64 (m, 6H, sugar ring 2,3,4,5,6–H), 4.34 (t, J = 9.6 Hz, 1H, sugar ring C_1–H), 4.58-5.23 (m, 4H, sugar ring–OH), 7.06-7.54 (m, 7H, ArH), 9.64 (d, J = 8.8 Hz, 1H, NH), 12.02 (s, 1H, NH)
10d	1.41 (s, 3H, CH_3), 3.32-3.86 (m, 9H, sugar ring 2,3,4,5,6–H, OCH_3), 4.34 (t, J = 9.6 Hz, 1H, sugar ring C_1–H), 4.58-5.23 (m, 4H, sugar ring–OH), 7.06-7.57 (m, 7H, ArH), 9.58 (d, J = 9.2 Hz, 1H, NH), 12.06 (s, 1H, NH)
11a	1.26-1.34 (d, J = 7.2 Hz, 6H, 2 × CH_3), 3.32-3.71 (m, 7H, sugar ring 2,3,4,5,6–H, NH), 3.78 (s, 3H, OCH_3), 4.34 (t, J = 9.6 Hz, 1H, sugar ring C_1–H), 4.58-5.23 (m, 4H, sugar ring–OH), 7.17-7.64 (m, 3H, ArH), 9.67 (d, J = 9.2 Hz, 1H, NH)
11b	1.03 (t, J = 7.0 Hz, 3H, CH_3), 1.58 (m, 3H, CH_2), 3.12 (m, 2H, CH_2), 3.32-3.64 (m, 6H, sugar ring 2,3,4,5,6–H), 3.80 (s, 3H, OCH_3), 4.32 (t, J = 9.6 Hz, 1H, sugar ring C_1–H), 4.58-5.37 (m, 5H, sugar ring–OH, NH), 7.18-7.65 (m, 3H, ArH), 9.72 (d, J = 8.8 Hz, 1H, NH)
11c	3.32-3.65 (m, 6H, sugar ring 2,3,4,5,6-H), 3.81 (s, 3H, OCH_3), 4.35 (t, J = 9.6 Hz, 1H, sugar ring C_1–H), 4.58-5.23 (m, 4H, sugar ring–OH), 7.11-7.54 (m, 7H, ArH), 9.66 (d, J = 8.8 Hz, 1H, NH), 12.04 (s, 1H, NH)
11d	3.34-3.64 (m, 6H, sugar ring 2,3,4,5,6–H), 3.79 (s, 6H, 2 × OCH_3), 4.34 (t, J = 9.6 Hz, 1H, sugar ring C_1–H), 4.55-5.25 (m, 4H, sugar ring–OH), 7.06-7.56 (m, 7H, ArH), 9.62 (d, J = 8.8 Hz, 1H, NH), 12.02 (s, 1H, NH)

peaks due to the deshielding of O, N. The data J = 8-10 Hz further indicated the β-anomer. In the ^{1}H NMR spectra of compounds **8a-8d**, **9a-9d**, **10a-10d** and **11a-11d**, N–H connected with sugar ring C_1–H appearing at about δ 9.76 and split into two peaks due to the impact of coupling. The proton signal of the glycosyl ring showed multiple peaks at about δ 3.23-3.64. It is worth noting that O–H showed a chemical shift in the range of δ 4.58-5.30 and that it is easy to identify because of its short and lively peak shape of the features. It was confirmed that such absorption by D_2O exchanging was disappearing.

The MS (ESI) spectra displayed that all the compounds had quasi-molecular peaks, most of which were the base peaks. This type of compound is stable.

EXPERIMENT

General method

Melting points were taken on a Yanaco MP-S3 microscopic melting point apparatus. The IR spectra were recorded in KBr pellets on a Bruker Equinox-55 FT-IR apparatus. The ^{1}H NMR spectra were recorded on an INOVA-400 (using TMS as internal standard, DMSO-d_6 or $CDCl_3$ as solvent). Mass spectra were recorded on an HP 1100 LC-MS (ESI). Elemental analyses were performed on a Thermo Flash EA-1112 analyzer. All reagents were commercial products of analytical grade and can be used directly without purification except where especially noted.

1. Compound 1 was prepared according to the reported method[18]

Yield 55%, m.p. 92-93 °C (lit[18]: m.p. 92-94 °C).

2. Compounds 2a-2d were prepared according to the reported method[19]

2a: Yield 85%, m.p. 130-132 °C (lit[19]: 131-132 °C);
2b: Yield 65%, m.p. 126-128 °C (lit[19]: 128-130 °C);
2c: Yield 65%, m.p. 134-136 °C (lit[19]: 135-136 °C);
2d: Yield 72%, m.p. 161-162 °C (lit[19]: 160-162 °C).

3. General procedure for the preparation of galactosyl thiourea derivatives (3a-3d)

An equimolecular mixture of galactosyl isothiocyanates **1** and the 2-amino-4/6-benzothizole **2a-2d** in 15 mL dry benzene was refluxed (TLC, 1:1 EtOAc-petroleum ether) for 12 h, then concentrated *in vacuo*. The residue was crystallized from ethanol to give compounds as colorless crystals in good yield.

4. General procedure for the preparation of *N*-Alkyl-*N*′-(4/6-substituted benzothiazol-2-yl)-*N*″-(2,3,4,6-tetra-*O*-acetyl-β-D-guanidinogalactosides (4a-4d, 5a-5d, 6a-6d, 7a-7d)

A mixture of **3** (1 mmol), amine (1 mmol), $HgCl_2$ (1 mmol) and triethylamine (4 mmol) in dry dimethylformamide was stirred at 0 °C for 40 min. When the color of the reaction mixture changed to black, the reaction was allowed to warm to room temperature. After the reaction was completed (TLC, 1:1 EtOAc-petroleum ether), the reaction mixture was diluted with EtOAc and filtered through celite. The filtrate was washed with brine, and the aqueous phase was extracted by EtOAc. The combined organic phase was dried with $MgSO_4$ and concentrated under reduced pressure to afford crude product, which was recrystallized from ethanol as colorless crystals or amorphous solids.

5. General procedure for the preparation of *N*-Alkyl-*N*′-(4/6-substituted benzothiazol-2-yl)-*N*″-β-D-guanidinogalactosides (8a-8d, 9a-9d, 10a-10d, 11a-11d)

A solution of the corresponding guanidines (**4a-4d**, **5a-5d**, **6a-6d**, **7a-7d**) (1 mmol) in MeOH (15 mL) incorporating NaOMe (3 mmol) was stirred at room temperature for 2.5-3 h. After the reaction was completed (TLC, 1:1 MeOH-$CHCl_3$), the solution was filtered and washed to give the crude product, which was recrystallized from 95% alcohol to give the deacetylated guanidinogalactosides (**8a-8d**, **9a-9d**, **10a-10d**, **11a-11d**).

ACKNOWLEDGEMENT

This work was supported by the financial support of the National Natural Science Foundation of China (No. 20462006) and Xinjiang Key Laboratory of Plant Resources & Natural Products Chemistry. We are grateful to the National Center of China for Drug Screening for the anti-ACE and HIV PR inhibitory test.

Received September 26, 2008.

REFERENCES

1. Han, J.-J.; Xu, Y.-F.; Su, Y.-P.; She, X.-P.; Pan, X.-F. *Catal. Commun.* **2008**, *9*, 2077.
2. Kearney, P. C.; Fernandez, M.; Flygare, J. A. *Tetrahedron Lett.* **1998**, *39*, 2663.
3. Lakhan, R.; Sharma, B. N. *Farmaco* **2000**, *55*, 331.
4. Hui, Y.; Ptak, R.; Paulman, R.; Pallansch, M.; TomChanga, C. W. *Tetrahedron Lett.* **2002**, *43*, 9255.
5. Chalina, E. G.; Chakarova, L. *Eur. J. Med. Chem.* **1998**, *33*, 975.
6. Delaware, D. L.; Sharma, M. S.; Iyengar, B. S.; Remers, W. A. *J. Antibiot.* **1986**, 3*9*, 251.
7. Gravir-Pelletier, C.; Bourissou, D.; Le-Merrer, Y.; Depezay, J. *Synlett* **1996**, 275.
8. Tian, T.; Cao, L.-H. *J. Chin. Chem. Soc.* **2007**, *54*(5), 1369.
9. Lei, M.; Hua, X.-D.; Xiao, M.; Ding, J.; Han, Q.-Y.; Hu, G. *Biochem. Biophys. Res. Commun.* **2008**, *369*, 1082.
10. Garg, H. G.; Prancella, N.; Tony, K. A.; Augustine, L. A.; Barchi, Jr., J. J.; Fantini, J.; Puri, A.; Mootoo, D. R.; Blumenthal, R. *Antiviral. Res.* **2008**, *63*, 2354.
11. Wang, Y.-H.; Yan, Q.-Y.; Wu, J.-P.; Zhang, L.-H.; Ye, X.-S. *Tetrahedron* **2005**, *61*, 4313.
12. Coutrot, F.; Grison, C.; Philippe, C. *C. R. Chimie* **2004**, *7*, 3.
13. Liu, Y.-H.; Cao, L.-H. *Carbohydr. Res.* **2008**, *343*, 615.
14. Mukerjee, A. K.; Ashfre, R. *Chem. Rev.* **1991**, *91*, 1.
15. Jimenez-Blanco, J. L.; Sylla, B.; Ortiz-Mellet, C.; Garcia-Fernandez, J. M. *J. Org. Chem.* **2007**, *72*, 4547.
16. Garca-Fernndez, J. M.; Ortiz-Mellet, C. *Carbohydr. Chem. Biochem.* **2000**, *55*, 35.
17. Gasch, C.; Pradera, M. A.; Salameh, B. A. B.; Molina, J. L.; Fuentes, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1267.
18. Lindhorst, T. K.; Kieburg, C. *Synthesis* **1995**, 1228.
19. Tian, T.; Lian, Z.-B.; Shi, H.-F.; Cao, L.-H. *Chin. J. Org. Chem.* **2004**, *25*, 1071.