HETEROCYCLES, Vol. 91, No. 11, 2015, pp. 2113 - 2125. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 27th August, 2015, Accepted, 2nd October, 2015, Published online, 8th October, 2015
DOI: 10.3987/COM-15-13310

# EXPEDIENT SYNTHESIS OF NOVEL GLYCOSYL THIAZOLE DERIVATIVES

**Feng-chang Cheng,[1,2] Long Yin,[1] Wei-wei Liu,[1,2,3,*] Qu-xiang Li,[2] Li-juan Tang,[1,3] Da-hua Shi,[1,3] and Zhi-ling Cao[1,3]**

[1]School of Chemical Engineering, Huaihai Institute of Technology, Lianyungang 222005, P.R. of China. E-mail: liuww323@aliyun.com; [2]School of Chemical Engineering, China University of Mining and Technology, XuZhou 221116, P.R. of China; [3]Jiangsu Marine Resources Development Research Institute, Lianyungang 222005, P.R. of China

**Abstract** – An efficient protocol for the synthesis of novel glycosyl thiazole derivatives starting from the commercially available D-glucosamine hydrochloride was described by reaction of 1-(1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranos-2-yl)thiourea **8** with each of substituted *α*-bromoacetophenone in ethanol. 1-(1,3,4,6-Tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranos-2-yl)thiourea was an important intermediate, and its synthetic methods were discussed by comparing two different synthetic routes. Moreover, 2-isothiocyanate-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose was obtained in a new and convenient way. Finally, a series of novel glycosyl incorporated with thiazole moiety was synthesized in good purities and overall yields.

## INTRODUCTION

The numerous carbohydrates, which play an important role in living systems, are underscored by their high abundance and molecular diversity.[1] Sugars are not only regarded as structural support and energy storage molecules, but also vital potential drug in physiological and pathophysiological processes.[2,3] Among these sugars, glucosamine has been paid great attention amongst synthetic chemists over the years, because of their diverse biological activities demonstrated. Glucosamine, a naturally occurring amino sugar, is a key component in a variety of biologically important glycoconjugates. It is found in several natural products such as tunicamycins and neomycin,[4] which are used as antibiotics, and bacillithiol,[5]

which is used as bacterial antioxidants. Aside from the natural products, it is found in gastrointestinal mucosal membranes and the cartilage tissues. Thus, glucosamine plays a crucial role on cell recognition, adhesion[6,7] and migration,[8] cell-cell interaction[9] and communication.[10] It is well known as an alternative therapy for the treatment of osteoarthritis (OA), which is a joint disease characterized by cartilage degeneration, joint paint and variable degrees of joint inflammation.[11] Furthermore, D-glucosamine has been reported to exert anti-inflammatory acitivity[12,13] and suppress tumer growth,[14,15] and it could be effectively employed as an additive in health or functional food to alleviate oxidative stress.[16] Recently it is found that glucosamine derivatives have been utilized as an efficient inhibitor for the Alzheimer's disease.[17]

One of the successful and effective approaches in the search for new bioactive agents from natural products is to synthesize novel compounds by simple chemical modifications of naturally occurring lead compounds.[18] In order to obtain potential biological lead compounds, the modifications of D-glucosamine have gained great attention. The hydroxyl groups are the active sites for phosphorylation and glycosylation when the C(2)-amino is protected, and the 4-hydroxy group of *N*-acetylglucosamine derivatives nevertheless is a very poor nucleophile in glycosylation reactions.[19] Masuko et al. reported the synthesis of *N*-acetylglucosamine-1-phosphate and tested for their recognition by the GlmU uridyltransferase enzyme.[20] Serpi et al. reported a novel series of *O*-4/*O*-3 *N*-acetyl-D-glucosamine phosphoramidates, which were able to significantly decrease the loss of glycosaminoglycan at noncytotoxic concentrations.[21] Although the modifications of hydroxyl groups are common, reports on the functionalization of amino are rare, especially a heterocycle linked to the aminothiazole, one of the most important scaffolds in heterocyclic chemistry and drug design and discovery, plays vital roles in many biologically active compounds such as tiazofurin[22] (antineoplastic agents) and ritonavir[23] (anti-HIV drug). Thiazole containing compounds have reported to exhibit versatile biological activities such as antimicrobial,[24] anti-inflammatory,[25] antiviral and antiparasitic,[26] antihistaminic properties, antiallergic.[27] The recent reports have been declared that the presence of thiazole ring as a part of drug structure could be determinant for its physicochemical and pharmacokinetic properties. Taking into account the important role of thiazoles in various biological phenomena, we synthesized a series of novel glucosamine derivatives containing thiazole attached to the C(2)-amino group.

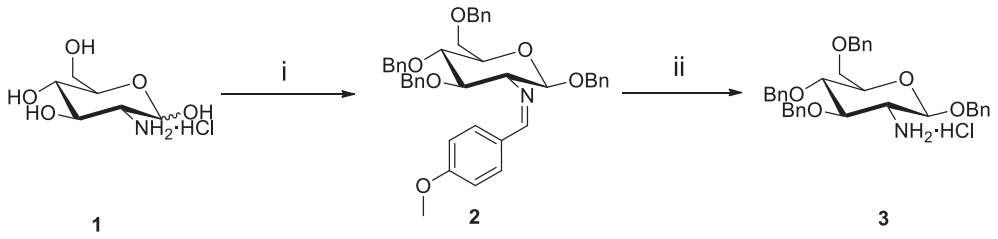
Various methods have been reported for the synthesis of thiazole derivatives such as Hantzsch synthesis, solid supported and solution phase. Recently, various catalysts are employed to synthesize thiazole derivatives like iodine,[28] silyl chloride,[29] PEG,[30] $NaICl_2$[31] and ammonium chloride.[32] But Hantzsch synthesis is most commonly used among these methods, which involves reaction of $\alpha$-halo carbonyl compounds with thiourea or thioamides.[33] Herein, a convenient and mild protocol for the synthesis of glycosyl thiazole derivatives was developed, which involved the reaction of glycosyl thiourea and

substituted $\alpha$-bromoacetophenone via Hantzsch synthesis. It is the first time to introduce thiazole ring to the glucosamine in a convenient way.

## RESULTS AND DISCUSSION

In the last few years, the thiourea is of interest as synthetic intermediate. The preparation of thiourea was achieved by the reaction of primary amine with thiocyanate directly. Our first attempt aimed at synthesizing the glycosyl thiourea by the reaction of thiocyanate with 2-amino-2-deoxy-$\beta$-D-glucopyranose. To our disappointment, the desired product was not obtained employing this method. We had to design a devious way in which the hydroxyl groups were protected at the beginning.

To accomplish the reaction on amino, the four hydroxyl groups should be under protection during the process. The benzyl group was selected to protect the hydroxy groups from a large number of the protection methods for the hydroxy group due to its versatile and stabilized for protecting hydroxyl groups in carbohydrate chemistry. The experiment steps are as follows: Firstly, the amino was protected by using *p*-methoxybenzaldehyde to get Shiff base, then followed by the benzylation of the four hydroxyl groups with NaH and BnBr in DMF ranging from 0 °C to room temperature for 12 h, and at last the 2-amino-1,3,4,6-tetra-*O*-benzyl-2-deoxy-$\beta$-D-glucopyranose hydrochloride **3** was prepared after the hydrolysis of **2** by hydrochloric acid (Scheme 1).

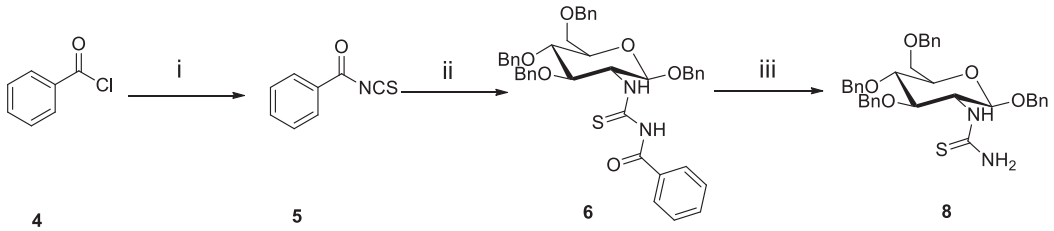



1 2 3

**Scheme 1.** Synthesis of 2-amino-1,3,4,6-tetra-*O*-benzyl-2-deoxy-$\beta$-D-glucopyranose hydrochloride. Reagents and conditions: (i) 1, NaOH, *p*-methoxybenzaldehyde, $H_2O$, rt, yield: 81%. 2, NaH, BnBr, DMF, 0 °C - rt, yield: 75%. (ii) 5 mol/L HCl, acetone, 35 °C, yield: 60%.

To develop a simple way to the synthesis of compounds containing D-glucosamine and thiazole, glycosyl thiourea was an important intermediate in this reaction. Through long time probing, we have formed diversified studying methods about the synthesis of glycosyl thiourea. At the onset of the experiments, we envisaged that glycosyl thiourea could be obtained by amide bond cleavage of glycosyl acylthiourea under alkaline conditions. In this way, glycosyl acylthiourea must be synthesized at first. At the beginning of experiment, benzoyl chloride reacted with KSCN to afford benzoyl isothiocyanate using a few drops of PEG-400 as catalyst in the mixture of dichloromethane and acetone. Then

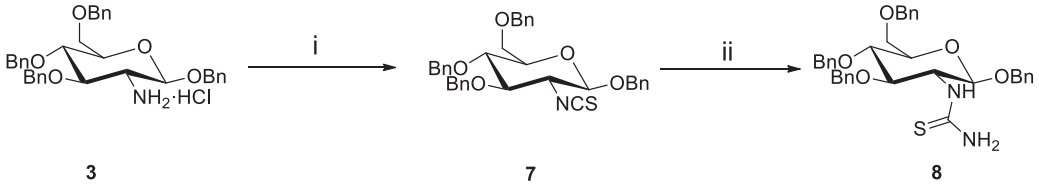
1-benzoyl-3-(1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranos-2-yl)thiourea **6** was synthesized from benzoyl isothiocyanate and 2-amino-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose hydrochloride **3**. To our delight, **6** was converted to **8** successfully by treatment with potassium carbonate in methanol under refluxing (Scheme 2). And **8** is a novel intermediate prepared for the first time.




**Scheme 2.** Synthesis of 1-(1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranos-2-yl)thiourea. Reagents and conditions: (i) KSCN, PEG-400, DCM, acetone, rt, yield: 95%. (ii) **3**, $Et_3N$, DCM, rt, yield: 92%. (iii) $K_2CO_3$, MeOH, refluxing, yield: 93%.

However, 1-(1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranos-2-yl)thiourea was synthesized by multi-step in low yield, the most important was that this method needed long time and difficult separation. Therefore, it is still highly expected to synthesis of **8** from readily available starting materials by convenient procedures in higher yield.

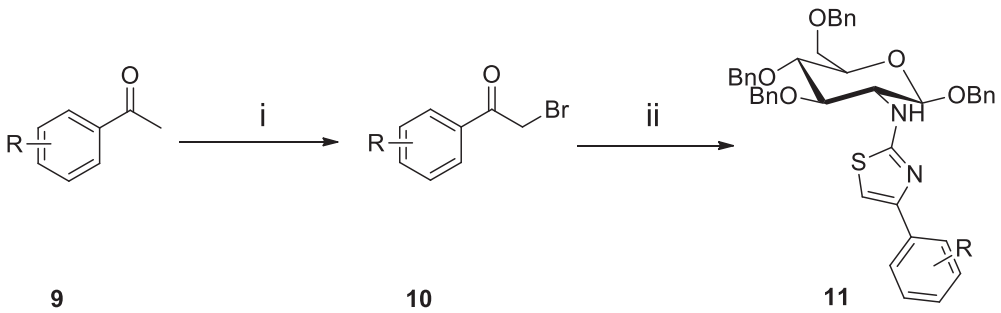
In a further experiment, the amino group of 2-amino-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose hydrochloride was expected to converted into thiourea directly by simple steps. And in this way we tried to find a facile way to synthesis of **8** in high yield. According to this idea, we tried to turn the amino of **3** into isothiocyanates to improve reactivity. Isothiocyanates, a reactive functional group in chemical synthesis, which can be converted to thiourea easily, has higher reactivity compared with amino group. Numerous synthetic methods have been reported to convert readily available amines into the isothiocyanate analogue,[34-36] but the employed reagents are often harsh, such as thiophosgene, which has high toxicity and incompatability with many functional groups, and there are very few reports available in which glycosyl isothiocyanate can be generated using a convenient and mild method. Herein, a facile protocol for the preparation of isothiocyanates from amine of D-glucosamine is reported. To a solution of **3** in acetonitrile was added triethylamine at 0 °C, followed by addition of carbon disulfide dropwise into the reaction mixture via bysyringe pump. The mixture was stirred for 2 h. Then tosyl chloride (TsCl) was added to the reaction mixture. For another 0.5 h, glycosyl isothiocyanate was provided in 90% yield from **4**. It is the first time that the conversion between the amine of D-glucosamine and isothiocyanates has been studied by using this method. Treatment of **7** in methylene chloride at room temperature with ammonia, provided **6** in 95% yield from **7**. The method have some advantages such as gentle reaction conditions, high yield and simple operation.




3 7 8

**Scheme 3.** Synthesis of 1-(1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranos-2-yl)thiourea. Reagents and conditions: (i) 1, $Et_3N$, $CS_2$, 0 °C, 1.5 h. 2, TsCl, 0.5 h, yield: 90%. (ii) ammonia, DCM, 2 h, 40 °C, yield: 95%.

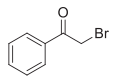
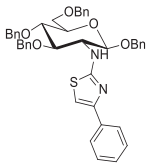
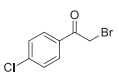
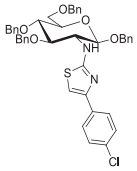
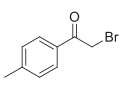
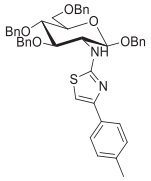
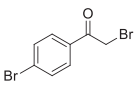
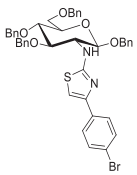
**9** was brominated by $CuBr_2$ under refluxing ethyl acetate and chloroform, and it was quite evident that the dark solvent changed into light green one with white CuBr after the reaction completed. The filtrate was extracted by water until the organic layer was transparent and without other dispose, **8** was put into the filtrate to afford **11** under refluxing for 15 min, which was a quite simple and convenient method to give **11** (Scheme 3). $^1$H NMR of **11** exhibited the signal for the anomeric proton at δ 3.88 with coupling constant of 9.4 Hz assigned as the *β*-anomer.

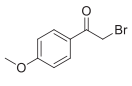
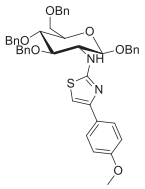
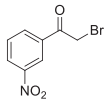
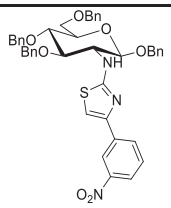
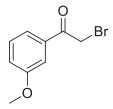
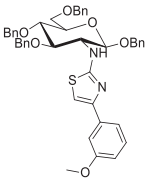
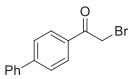
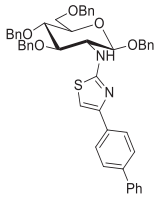
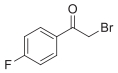
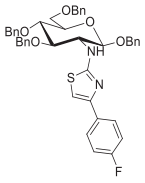



9 10 11

**Scheme 4**. Synthesis of the desired product **11**. Reagents and conditions: (i) $CuBr_2$, EtOAc, $CHCl_3$, reflux, yield: 95%. (ii) **8**, EtOH, reflux, yield: 92%.

**Table 1**. Synthesis of the desired product **11**

| Entry | Comp. **10** | Comp. **11** | Yield (%) | Entry | Comp. **10** | Comp. **11** | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 |  **10a** |  **11a** | 92 | 6 |  **10f** |  **11f** | 87 |
| 2 |  **10b** |  **11b** | 93 | 7 |  **10g** |  **11g** | 90 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 3 |  **10c** |  **11c** | 88 | 8 |  **10h** |  **11h** | 89 |
| 4 |  **10d** |  **11d** | 90 | 9 |  **10j** |  **11i** | 90 |
| 5 |  **10e** |  **11e** | 89 | | | | |

In conclusion, a series of novel glycosyl thiazole have been synthesized starting from D-glucosamine. Synthesis methods of glycosyl thiourea have been discussed by comparing two different synthesis routes. Although glycosyl thiourea was obtained by the hydrolysis of 1-benzoyl-3-(1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose-2-yl)thiourea by employing $K_2CO_3$, this route was time consuming and involved several complicated procedures. A new and effective approach for preparing glycosyl thiourea was introduced, which has characteristics of quickness, simpleness and high efficiency. In this route, glycosyl isothiocyanate, as an important intermediates, was synthesized using method of mild conditions, convenient operation and low toxicity. The target compounds have been prepared directly in good yields with glycosyl thiourea in hand.

## EXPERIMENTAL

All chemicals were purchased from commercial sources and used without further purification unless otherwise stated. All reactions were monitored by TLC. TLC plates were detected with 254 nm UV light. Melting points were determined on a Yanaco melting point apparatus and were uncorrected. IR spectra were recorded on a Bruker Tensor 27 spectrometer with KBr pellets. $^1$H NMR were recorded with Bruker Avance at 300 Hz using TMS as an internal standard and DMSO-$d_6$ as a solvent. HRMS(ESI) analysis was performed on a Agilent 6500 mass spectrometer. Flash column chromatography was performed on silica 200-300 mes.

### Preparation of 2-amino-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose hydrochloride (3)

To a solution of **1** (30 g, 139.1 mmol) in water (150 mL) at room temperature with stirring NaOH (5.6 g,

0.14 mmol) was added, and 15 min later, *p*-methoxybenzaldehyde (17.1 mL, 0.14 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for additional 24 h, after which the resulting white solid was filtrated and washed by 500 mL water to afford 2-(4-methoxy-benzylidene)-2-deoxy-*β*-D-glucopyranose (33.3 g, 81%). To a mixture of 2-(4-methoxy-benzylidene)-2-deoxy-*β*-D-glucopyranose (6.6 g, 22.2 mmol) and BnBr (14 mL, 117.9 mmol) in DMF (50 mL) at 0 °C, NaH (60%, 5 g, 125 mmol) was added portion wise. The reaction mixture was allowed to room temperature and stirred for 12 h. After the completion of reaction, the solution was diluted by a large amount of water and extracted with $CH_2Cl_2$ (3×50 mL). The solvent was eliminated under reduced pressure to give a kind of yellow viscous liquid. The solution of the yellow liquid in acetone (100 mL) was treated with hydrochloric acid (7 mL, 5 N) to afford a white solid under refluxing for 1 h. The mixture was filtrated and wash with acetone to give **3** (7.5 g, 59%, overall yield 50%).

**Synthesis of 1-benzoyl-3-(1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose-2-yl)thiourea (6)**

To a solution of benzoyl chloride (0.23 mL, 2 mmol) in $CH_2Cl_2$ (15 mL) and acetone (15 mL), KSCN (0.2 g, 2 mmol) was added at room temperature utilizing a few drops of PEG-400 as catalyst and the reaction mixture was stirred for additional 2 h. The mixture was filtrated and the filtrate was evaporated under reduced pressure to give benzoyl isothiocyanate (**5**). To a solution of **3** (1.2 g, 2 mmol) in $CH_2Cl_2$, triethylamine was added dropwise until the solution was clarified, and **6** was prepared by treating the solution with benzoyl isothiocyanate at room temperature. The solvent was eliminated under reduced pressure to afford a crude product which was purified by column chromatography using EtOAc and petroleum ether as the eluent.

Data for **6**: yield = 92%, 1.3 g, white powder; mp 82-84 °C; IR (KBr) *v* ($cm^{-1}$): 3322 (N-H), 3029 (C-H, Ph), 2921 (C<u>H</u>$_2$-Ph), 1685 (C=O), 1542 (C=S), 1455 (C=C, Ph), 1073 (C-O-C), 744 (C=C<u>H</u>, Ph), 697 (C=C<u>H</u>, Ph); $^1$H NMR (300 MHz, DMSO): δ 11.36 (s, 1H, NH), 10.99 (d, 1H, *J* = 9.3 Hz, NH), 8.00-7.87 (m, 2H, Ph), 7.63 (t, 1H, *J* = 7.4 Hz, Ph), 7.51 (t, 2H, *J* = 7.6 Hz, Ph), 7.33 (t, 5H, *J* = 5.0 Hz, Ph), 7.31-7.22 (m, 9H, Ph), 7.22-7.15 (m, 6H, Ph), 4.84 (d, 2H, *J* = 6.1 Hz, PhC$H_2$-), 4.78 (d, 1H, *J* = 7.6 Hz, PhC$H_2$-), 4.70 (d, 2H, *J* = 10.7 Hz, PhC$H_2$-), 4.63 (d, 1H, *J* = 3.0 Hz, PhC$H_2$-), 4.60-4.51 (m, 4H, PhC$H_2$-, -C$H_2$-), 4.01 (t, 1H, *J* = 9.1 Hz, $H^{Glu}$), 3.71 (t, 2H, *J* = 9.4 Hz, $H^{Glu}$), 3.60-3.53 (m, 2H, $H^{Glu}$). ESI-HRMS: Calcd for $C_{42}H_{42}N_2O_6S$ $[M+Na]^+$ 725.2656. Found 725.2643.

**Synthesis of 2-isothiocyanate-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose (7)**

Triethylamine (3 mmol) was added to a solution of **3** (1 mmol, 1 equiv.) in MeCN (15 mL) in the condition of ice bath. Carbon disulfide (1 mmol) was added by dropwise into the reaction mixture via by syringe pump. The mixture was stirred for 2 h. Then tosyl chloride (TsCl) (1 mmol) was added to the mixture. The mixture was stirred for another 0.5 h. The crude product was recrystallized from EtOH to

give product **7**.

Data for **7**: yield = 90%, white amorphous powder; mp 55-56 °C; IR (KBr) *v* ($cm^{-1}$): 3433, 3030 (C-H, Ph), 2873 ($\underline{CH_2}$-Ph), 2078 (-N=C=S), 1454 (C=C, Ph), 1359 (C=C, Ph), 1313 (C=C, Ph), 1068 (C-O-C). $^1$H NMR (300 MHz, DMSO), δ: 7.45-7.25 (m, 18H, Ph), 7.24-7.17 (dd, 2H, *J* = 7.3, 1.9 Hz, Ph), 4.88-4.75 (m, 4H, Ph-$CH_2$), 4.73-4.62 (m, 2H, Ph-$CH_2$), 4.54 (dt, 3H, *J*=12.4, 10.5 Hz, Ph-$CH_2$, $H^{Glu}$), 3.95-3.87 (m, 2H, $H^{Glu}$), 3.67 (ddd, 3H, *J*=12.3, 11.7, 6.9 Hz, $H^{Glu}$), 3.54 (dd, 1H, *J*=11.7, 6.9 Hz, $H^{Glu}$). ESI-HRMS: Calcd for $C_{35}H_{35}NO_5S$ $[M+Na]^+$ 604.2128. Found 604.2130.

**Synthesis of 1-(1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose-2-yl)thiourea (8)**

Route (1) Potassium carbonate (0.28 g, 2 mmol) was added to a solution of **5** (0.7 g, 1 mmol) in MeOH (25 mL). The reaction mixture was stirred under refluxing and monitored by TLC. After the reaction was over, MeOH was removed under reduced pressure. The product obtained was dissolved in $CH_2Cl_2$ and washed with water. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The desired compound was purified by column chromatography using EtOAc and petroleum ether as the eluent.

Route (2) **7** (0.58 g, 1 mmol) was dissolved in $CH_2Cl_2$ (20 mL), then ammonia was passed though the $CH_2Cl_2$ solution in room temperature for 2 h. After the reaction, $CH_2Cl_2$ was removed to give the product **8**.

Data for **8**: (1) yield = 90%, (2) yield = 95%, white solid; mp 149-150 °C; IR (KBr) *v* ($cm^{-1}$): 3431 (N-H), 3219 (N-H), 3036 (C-H, Ph), 2868 ($\underline{CH_2}$-Ph), 1627 (C=S), 1537 (N-H), 1497 (C=C, Ph), 1081 (C-O-C), 749 (C=$\underline{CH}$, Ph), 698 (C=$\underline{CH}$, Ph); $^1$H NMR (300 MHz, DMSO): δ 7.94 (d, 1H, *J* = 9.0 Hz, NH), 7.32 (m, 20H, Ph), 7.20 (d, 2H, *J* = 5.7 Hz, $NH_2$), 4.81 (d, 1H, *J* = 12.1 Hz, $PhCH_2$-), 4.71 (d, 2H, *J* = 10.8 Hz, $PhCH_2$-), 4.62 (dd, 2H, *J* = 11.2, 5.4 Hz, $PhCH_2$-), 4.51 (dd, 4H, *J* = 11.6, 7.8 Hz, $PhCH_2$-), 3.69-3.48 (dd, 4H, *J* = 17.1, 9.7 Hz, -$CH_2$-, $H^{Glu}$), 3.59-3.48 (m, 2H, $H^{Glu}$). ESI-HRMS: Calcd for $C_{35}H_{38}N_2O_5S$ $[M+Na]^+$ 621.2394. Found 621.2383.

**General procedure for the synthesis of 2-(4-arylthiazol-2-yl)-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose (11a-11i)**

Cupric bromide (0.5 g, 2.2 mmol) was added to a solution of **9** (1 mmol) in EtOAc (15 mL) and $CHCl_3$ (15 mL). The reaction mixture was stirred and monitored by TLC. After completion of reaction, the mixture was filtrated and the solvent was washed by water until it was colorless. The solvent was eliminated under reduced pressure to give **10**. Without any purification, **10** was used in the next process. **8** was added to the solution of **10** in EtOH (25 mL). The mixture was completed in 15 min under refluxing followed by the elimination of EtOH. The crude product was added into $Et_2O$ and broken by ultrasonic wave. Filtrating the mixture to afford pure desired compound **11**.

**2-(4-Phenylthiazol-2-yl)-1,3,4,6-tetra-*O*-benzyl-2-deoxy -*β*-D-glucopyranose (11a)**

Following the general procedure, the reaction of **8** (0.3 g, 0.5 mmol) and **10a** (0.1 g, 0.5 mmol) afforded **11a** (0.32 g, 92%); claybank solid; mp 46-47 °C; IR (KBr) *v* ($cm^{-1}$): 3420 (N-H), 3030 (C-H, Ph), 2922 ($\underline{CH_2}$-Ph), 2868 ($\underline{CH_2}$-Ph), 1627 (C=N), 1550 ($\underline{C=C}$-S), 1496 (N-H), 1453 (C=C, Ph), 1069 (C-O-C), 736 (C=$\underline{CH}$, Ph), 697 (C=$\underline{CH}$, Ph) $cm^{-1}$; $^1$H NMR (300 MHz, DMSO): δ 7.99 (d, 1H, *J* = 7.8 Hz, NH), 7.83 (d, 2H, *J* = 7.3 Hz, Ph), 7.47-7.11 (m, 23H, Ph), 7.08 (s, 1H, C=CH), 4.83 (d, 1H, *J* = 12.6 Hz, $PhCH_2$-), 4.77-4.69 (m, 3H, $PhCH_2$-), 4.57 (dd, 4H, *J* = 16.7, 12.0 Hz, $PhCH_2$-), 3.88 (d, 1H, *J* = 9.1 Hz, H-1), 3.72-3.60 (m, 6H, H-2, H-3, H-4, H-5, H-6a, H-6b); ESI-HRMS: Calcd for $C_{43}H_{42}N_2O_5S$ $[M+H]^+$ 699.2887. Found 699.2900.

**2-(4-(4-Methylphenyl)thiazol-2-yl)-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose (11b)**

Following the general procedure, the reaction of **8** (0.3 g, 0.5 mmol) and **10b** (0.16 g, 0.5 mmol) afforded **11b** (0.33 g, 93%); yellow solid; mp 63-64 °C; IR (KBr) *v* ($cm^{-1}$): 3420 (N-H), 3029 (C-H, Ph), 2920 ($CH_2$-Ph), 2865 ($CH_2$-Ph), 1628 (C=N), 1550 (C=C-S), 1496 (N-H), 1453 (C=C, Ph), 1059 (C-O-C), 736 (C=CH, Ph), 697 (C=CH, Ph) $cm^{-1}$; $^1$H NMR (300 MHz, DMSO): δ 7.93 (d, 1H, *J* = 8.7 Hz, NH), 7.72 (d, 2H, *J* = 8.1 Hz, Ph), 7.38-7.27 (m, 9H, Ph), 7.24-7.15 (m, 11H, Ph), 6.99 (s, 1H, C=CH), 4.83 (d, 1H, *J* = 12.5 Hz, $PhCH_2$-), 4.77-4.65 (m, 4H, $PhCH_2$-, $H^{Glu}$), 4.57 (dd, 4H, *J* = 16.7, 12.1 Hz, $PhCH_2$-), 3.83 (d,1H, *J* = 8.9 Hz, $H^{Glu}$), 3.73 (dd, 2H, *J* = 11.6, 7.0 Hz, $H^{Glu}$), 3.68-3.54 (m, 3H, $H^{Glu}$); ESI-HRMS: Calcd for $C_{44}H_{44}N_2O_5S$ $[M+H]^+$ 713.3044. Found 713.3042.

**2-(4-(4-Methoxylphenyl)thiazol-2-yl)-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose (11c)**

Following the general procedure, the reaction of **8** (0.3 g, 0.5 mmol) and **10c** (0.12 g, 0.5 mmol) afforded **11c** (0.32 g, 88%); white solid; mp 139-141 °C; IR (KBr) *v* ($cm^{-1}$): 3431 (N-H), 3028 (C-H, Ph), 2870 ($CH_2$-Ph), 1612 (C=N), 1511 (C=C-S), 1496 (N-H), 1453 (C=C, Ph), 1064 (C-O-C), 748 (C=CH, Ph), 697 (C=CH, Ph); $^1$H NMR (300 MHz, DMSO): δ 7.92 (d, 1H, *J* = 8.9 Hz, NH), 7.74 (d, 2H, *J* = 8.7 Hz, Ph), 7.35-7.15 (m, 20H, Ph), 6.91 (d, 2H, *J* = 8.8 Hz, Ph), 6.88 (s, 1H, C=CH), 4.81 (d, 1H, *J* = 12.5 Hz, $PhCH_2$-), 4.74-4.64 (m, 4H, $PhCH_2$-, $H^{Glu}$), 4.53 (t, 4H, *J* = 7.9 Hz, $PhCH_2$-), 3.84 (d, 1H, *J* = 7.6 Hz,$H^{Glu}$), 3.74 (s, 3H, $CH_3$), 3.69 (dd, 2H, *J* = 11.1, 7.5 Hz, $H^{Glu}$), 3.59-3.52 (m, 3H, $H^{Glu}$); ESI-HRMS: Calcd for $C_{44}H_{44}N_2O_6S$ $[M+H]^+$ 729.2993. Found 729.2992.

**2-(4-(3-Methoxylphenyl)thiazol-2-yl)-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose (11d)**

Following the general procedure, the reaction of **8** (0.3 g, mmol) and **10d** (0.12 g, 0.5 mmol) afforded **11d** (0.35 g, 90%); white solid; mp 147-149 °C; IR (KBr) *v* ($cm^{-1}$): 3446 (N-H), 3028 (C-H, Ph), 2932 ($CH_2$-Ph), 2873 ($CH_2$-Ph), 1615 (C=N), 1527 (C=C-S), 1495 (N-H), 1453 (C=C, Ph), 1054 (C-O-C), 748 (C=CH, Ph), 700 (C=CH, Ph); $^1$H NMR (300 MHz, DMSO): δ 7.41-7.15 (m, 24H, Ph), 7.13 (s, 1H,

C=CH), 6.88 (d, 1H, *J* = 7.7 Hz, NH), 4.84 (d, 1H, *J* = 12.5 Hz, $PhCH_2$-), 4.73 (d, 4H, *J* = 10.2 Hz, $PhCH_2$-), 4.62-4.52 (m, 4H, $PhCH_2$-, $H^{Glu}$), 3.85 (d, 1H, *J* = 8.9 Hz, $H^{Glu}$), 3.77 (s, 3H, $OCH_3$), 3.72 (dd, 2H, *J* = 10.9, 9.2 Hz, $H^{Glu}$), 3.64-3.56 (m, 3H, $H^{Glu}$); ESI-HRMS: Calcd for $C_{44}H_{44}N_2O_6S$ $[M+H]^+$ 729.2993. Found 729.3016.

**2-(4-(4-Fluorophenyl)thiazol-2-yl)-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose (11e)**

Following the general procedure, the reaction of **8** (0.3 g, mmol) and **10e** (0.11 g, 0.5 mmol) afforded **11e** (0.32 g, 89%); yellow solid; mp 116-118 °C; IR (KBr) *v* ($cm^{-1}$): 3420 (N-H), 3029 (C-H, Ph), 2922 ($CH_2$-Ph), 2853 ($CH_2$-Ph), 1640 (C=N), 1553 (C=C-S), 1496 (N-H), 1453 (C=C, Ph), 1061 (C-O-C), 734 (C=CH, Ph), 696 (C=CH, Ph); $^1$H NMR (300 MHz, DMSO): δ 8.00 (d, 1H, *J* = 9.6 Hz, NH), 7.90-7.76 (m, 2H, Ph), 7.37-7.16 (m, 24H, Ph), 7.06 (s, 1H, C=CH), 4.82 (d, 1H, *J* = 12.5 Hz, $PhCH_2$-), 4.72 (m, 4H, *J* = 11.1 Hz, $PhCH_2$-, $H^{Glu}$), 4.63 (d, 1H, *J* = 8.4 Hz, $PhCH_2$-), 4.58-4.52 (m, 3H, $PhCH_2$-) , 3.86 (d, 1H, *J* = 7.2 Hz, $H^{Glu}$), 3.73 (dd, 3H, *J* = 11.5, 7.0 Hz, $H^{Glu}$), 3.57 (d, 2H, *J* = 6.4 Hz, $H^{Glu}$); ESI-HRMS: Calcd for $C_{43}H_{41}FN_2O_5S$ $[M+H]^+$ 717.2793. Found 717.2794.

**2-(4-(4-Chlorophenyl)thiazol-2-yl)-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose (11f)**

Following the general procedure, the reaction of **8** (0.3 g, mmol) and **10f** (0.12 g, 0.5 mmol) afforded **11f** (0.32 g, 87%); yellow solid; mp 136-138 °C; IR (KBr) *v* ($cm^{-1}$): 3368 (N-H), 3029 (C-H, Ph), 2911 ($CH_2$-Ph), 2857 ($CH_2$-Ph), 1558 (C=N), 1495 (C=C-S), 1476 (N-H), 1453 (C=C, Ph), 1073 (C-O-C), 729 (C=CH, Ph), 696 (C=CH, Ph); $^1$H NMR (300 MHz, DMSO): δ 8.01 (d, 1H, *J* = 8.8 Hz, NH), 7.84 (d, 2H, *J* = 8.5 Hz, Ph), 7.46-7.15 (m, 22H, Ph), 7.14 (s, 1H, C=CH), 4.82 (d, 1H, *J* = 12.6 Hz, $PhCH_2$-), 4.78-4.64 (m, 4H, $PhCH_2$-, $H^{Glu}$), 4.63-4.50 (m, 4H, $PhCH_2$-), 3.83 (d, 1H, *J* = 8.1 Hz, $H^{Glu}$), 3.73 (dd, 3H, *J* = 11.7, 6.8 Hz, $H^{Glu}$), 3.57 (d, 2H, *J* = 6.1 Hz, $H^{Glu}$); ESI-HRMS: Calcd for $C_{43}H_{41}ClN_2O_5S$ $[M+H]^+$ 733.2497. Found 733.2513.

**2-(4-(4-Bromophenyl)thiazol-2-yl)-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose (11g)**

Following the general procedure, the reaction of **8** (0.3 g, mmol) and **10g** (0.14 g, 0.5 mmol) afforded **11g** (0.35 g, 90%); white solid; mp 147-148 °C; IR (KBr) *v* ($cm^{-1}$): 3421 (N-H), 3061 (C-H, Ph), 2938 ($CH_2$-Ph), 2873 ($CH_2$-Ph), 1615 (C=N), 1526 (C=C-S), 1493 (N-H), 1452 (C=C, Ph), 1072 (C-O-C), 744 (C=CH, Ph), 699 (C=CH, Ph); $^1$H NMR (300 MHz, DMSO): δ 8.24 (s, 1H, C=CH), 7.76 (d, 2H, *J* = 8.1 Hz, NH), 7.58 (d, 2H, *J* = 8.5 Hz, Ph), 7.40-7.26 (m, 10H, Ph), 7.22-7.16 (m, 11H, Ph), 4.83 (d, 1H, *J* = 12.5 Hz, $PhCH_2$-), 4.79-4.65 (m, 4H, $PhCH_2$-, $H^{Glu}$), 4.62-4.52 (m, 4H, $PhCH_2$-), 3.84 (d, 1H, *J* = 7.3 Hz, $H^{Glu}$), 3.78-3.68 (m, 3H, $H^{Glu}$), 3.63-3.55 (m, 2H, $H^{Glu}$); ESI-HRMS: Calcd for $C_{43}H_{41}ClN_2O_5S$ $[M+H]^+$ 777.1992. Found 777.1972.

**2-(4-(3-Nitrophenyl)thiazol-2-yl)-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose (11h)**

Following the general procedure, the reaction of **8** (0.3 g, mmol) and **10h** (0.13 g, 0.5 mmol) afforded **11h** (0.33 g, 89%); white solid; mp 130-132 °C; IR (KBr) *v* ($cm^{-1}$): 3420 (N-H), 3028 (C-H, Ph), 2868 ($CH_2$-Ph), 1615 (C=N), 1531 (C=C-S), 1495 (N-H), 1453 (C=C, Ph), 1065 (C-O-C), 744 (C=CH, Ph), 698 (C=CH, Ph); $^1$H NMR (300 MHz, DMSO): δ 8.64-8.58 (m, 1H, Ph), 8.26 (d, 2H, *J* = 7.9 Hz, Ph), 8.13 (dd, 1H, *J* = 8.2, 1.5 Hz, NH), 7.69 (t, 1H, *J* = 8.0 Hz, Ph), 7.42 (s, 1H, C=CH), 7.38-7.14 (m, 20H, Ph), 4.89-4.80 (m, 1H, $PhCH_2$-), 4.79-4.66 (m, 4H, $PhCH_2$-, $H^{Glu}$), 4.63-4.53 (m, 4H, $PhCH_2$-), 3.82 (d, 1H, *J* = 7.5 Hz, $H^{Glu}$), 3.74 (dd, 3H, *J* = 11.3, 6.9 Hz, $H^{Glu}$), 3.63-3.58 (m, 2H, $H^{Glu}$); ESI-HRMS: Calcd for $C_{43}H_{41}N_3O_7S$ $[M+Na]^+$ 744.2557. Found 744.2553.

**2-((1,1'-Biphenyl-4-yl)thiazol-2-yl)-1,3,4,6-tetra-*O*-benzyl-2-deoxy-*β*-D-glucopyranose (11i)**

Following the general procedure, the reaction of **8** (0.3 g, mmol) and **10i** (0.14 g, 0.5 mmol) afforded **11i** (0.35 g, 90%); yellow solid; mp 130-132 °C; IR (KBr) *v* ($cm^{-1}$): 3420 (N-H), 3028 (C-H, Ph), 2921 ($CH_2$-Ph), 2861 ($CH_2$-Ph), 1640 (C=N), 1550 (C=C-S), 1496 (N-H), 1453 (C=C, Ph), 1057 (C-O-C), 734 (C=CH, Ph), 695 (C=CH, Ph); $^1$H NMR (300 MHz, DMSO): δ 8.02 (d, 1H, *J* = 9.2 Hz, NH), 7.93 (d, 1H, *J* = 8.4 Hz, Ph), 7.81 (d, 1H, *J* = 6.7 Hz, Ph), 7.73-7.67 (m, 3H, Ph), 7.56-7.44 (m, 3H, Ph), 7.38-7.35 (m, 4H, Ph), 7.34-7.28 (m, 5H, Ph), 7.25-7.17 (m, 12H, Ph), 7.15 (s, 1H, C=CH), 4.84 (d, 1H, *J* = 12.5 Hz, $PhCH_2$-), 4.78-4.65 (m, 4H, $PhCH_2$-, $H^{Glu}$), 4.62-4.51 (m, 4H, $PhCH_2$-), 3.86 (d, 1H, *J* = 9.6 Hz, $H^{Glu}$), 3.76-3.67 (m, 2H, $H^{Glu}$), 3.57 (t, 3H, *J* = 8.8 Hz, $H^{Glu}$); ESI-HRMS: Calcd for $C_{49}H_{46}N_2O_5S$ $[M+H]^+$ 775.3200. Found 775.3188.

## ACKNOWLEDGEMENTS

This work was supported by the Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions, Natural Science Foundation of Jiangsu Province (BK20151281), Open-end Funds of Jiangsu Key Laboratory of Marine Biotechnology, Huaihai Institute of Technology (HS2014007, 2013HS004), The Science and Technology Project of Lianyungang (CG1415).

## REFERENCES

1. M. M. L. Zulueta, S. Y. Lin, Y. T. Lin, C. J. Huang, C. C. Wang, C. C. Ku, Z. H. Shi, C. L. Chyan, and S. C. Hung, *J. Am. Chem. Soc*., 2012, **134**, 8988.
2. C. R. Bertozzi and L. L. Kiessling, *Science*, 2001, **291**, 2357.
3. B. Ernst and J. L. Magnani, *Nat. Rev. Drug Discov.*, 2009, **8**, 661.
4. K. Kimura and T. D. H. Bugg, *Nat. Prod. Rep.*, 2003, **20**, 252.
5. J. D. Helmann, *Antioxid. Redox Sign.*, 2011, **15**, 123.
6. R. A. Dwek, *Chem. Rev.*, 1996, **96**, 683.

7. A. Varki, *Glycobiology*, 1993, **3**, 97.
8. Y. E. Tsvetkov, M. Burg-Roderfeld, G. Loers, Ana Ardá, E. V. Sukhova, E. A. Khatuntseva, A. A. Grachev, A. O. Chizhov, H. C. Siebert, M. Schachner, J. Jiménez-Barbero, and N. E. Nifantiev, *J. Am. Chem. Soc*., 2012, **134**, 426.
9. I. Capila and R. J. Linhardt, *Angew. Chem. Int. Ed.*, 2002, **41**, 391.
10. M. Petitou, L. P. Herault, A. Bernat, P. A. Driguez, P. Duchaussoy, J. C. Lormeau, and J. M. Herbert, *Nature*, 1999, **398**, 417.
11. S. Seed, K. Dunica, and A. Lynch, *Geriatrics*, 2009, **64**, 20.
12. J. Hua, K. Sakamoto, and I. Nagaoka, *J. Leukocyte Biol.*, 2002, **71**, 632.
13. J. Hua, S. Suguro, S. Hirano, K. Sakamoto, and I. Nagaoka, *Inflamm. Res.*, 2005, **54**, 127.
14. J. H. Quastel and A. Cantero, *Nature*, 1953, **171**, 252.
15. J. G. Bekesi, Z. Molnar, and R. Winzler, *J. Cancer Res*., 1969, **29**, 353.
16. X. Ronge, L. Song, and G. Z. Yong, *Bioorg. Med. Chem.*, 2006, **14**, 1706.
17. W. W. Liu, Q. X. Li, D. H. Shi, Z. L. Cao, F. C. Cheng, C. Z. Tao, L. Yin, and X. Wang, *Heterocycles*, 2015, **91**, 275.
18. L. Zeng and J. Zhang, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3718.
19. H. Paulsen, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 155.
20. S. Masuko, B. Smritilekha, D. E. Green, M. W. Wei, L. Jian, P. L. DeAngelis, and R. J. Linhardt, *J. Org. Chem.*, 2012, **77**, 1449.
21. M. Serpi, R. Bibbo, S. Rat, C. Hughes, B. Caterson, M. J. Alcaraz, A. T. Gibert, C. R. A. Verson, and C. M. Guigan, *J. Med. Chem.*, 2012, **55**, 4629.
22. J. Das, P. Chen, and D. Norris, *J. Med. Chem.*, 2006, **49**, 6819.
23. A. D. Da Silva, M. V. De Almeida, and M. V. N. De Souza, *Curr. Med. Chem.*, 2003, **10**, 21.
24. P. J. Palmer, R. B. Trigg, and J. V. Warrington, *J. Med. Chem.*, 1971, **14**, 248.
25. F. Haviv, J. D. Ratajczyk, R. W. DeNet, F. A. Kerdesky, R. L. Walters, S. P. Schmidt, J. H. Holms, P. R. Young, and G. W. Carter, *J. Med. Chem.*, 1988, **31**, 1719.
26. P. Haacke, L. P. Bauscher, and J. P. McNeal, *J. Am. Chem. Soc.*, 1971, **93**, 7045.
27. M. Ohkubo, A. Kuno, I. Nakanishi, and H. Takasugi, *Chem. Pharm. Bull.*, 1995, **43**, 1497.
28. M. Kidwai, D. Bhatnagar, P. Mothsra, A. K. Singh, and S. Dey, *J. Sulfur Chem.*, 2009, **30**, 29.
29. H. Karade, M. Sathe, and M. P. Kaushik, *Catal. Commun.*, 2007, **8**, 741.
30. P. Y. Lin, R. S. Hou, H. M. Wang, L. J. Kang, and L. C. Cheng, *J. Chin. Chem. Soc.*, 2009, **56**, 455.
31. S. M. Ghodse and V. N. Telvekar, *Tetrahedron Lett.*, 2015, **56**, 472.
32. V. P. Pagore, S. U. Tekale, B. D. Rupnar, and R. P. Pawar, *Der Chemica Sinica*, 2015, **6**, 49.
33. A. Hantzsch and J. H. Weber, *Ber. Dtsch. Chem. Ges.*, 1887, **20**, 3118.

34. E. Dyer and T. B. Johnson, *J. Am. Chem. Soc.*, 1932, **54**, 777.
35. R. Wong and S. J. Dolman, *J. Org. Chem.*, 2007, **72**, 3969.
36. A. C. Chaskar, B. P. Bandgar, R. K. Modhave, A. B. Patil, and S. Yewale, *Synth. Commun.*, 2009, **39**, 992.