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## SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL EVALUATION OF SOME NOVEL GLYCOSYL 1,3,4-THIADIAZOLE DERIVATIVES AS ACETYLCHOLINESTERASE INHIBITORS

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**Abstract** – The corresponding 4-substituted glycosyl thiosemicarbazide derivatives (**6a-6l**) were obtained by the reaction of glycosyl isothiocyanate **4** with various hydrazides. Further cyclization with the system of *p*-TsCl/TEA led to the formation of *N*-glycosyl-5-substituted 1,3,4-thiadiazole-2-amine (**7a-7l**). Subsequent removal of the acetyl groups were conducted using the system of NaOMe/MeOH. The chemical structures of all new products were confirmed by IR, <sup>1</sup>H NMR and ESI-HRMS. The acetylcholinesterase (AChE) inhibitory activities of those compounds were tested by Ellman's method. Among them, the compound **8h** possessed the best acetylcholinesterase-inhibition activity with IC<sub>50</sub> of 18.38 ± 0.89 μM.

## INTRODUCTION

Over the past few years, glycobiology, and carbohydrate chemistry have been paid enormous attention owing to the remarkable role played in many biological events.<sup>1-3</sup> D-Glucosamine, as a natural amino monosaccharide, widely exists in ocean organisms, and is an indispensable substance of our human beings' gristle, ligament, muscle tendon.<sup>4</sup> Furthermore, D-glucosamine and its derivatives present many excellent bioactivities such as antitumor, antibacterial, anti-inflammatory, liver-protecting and improving

immune function.<sup>5-9</sup> Recently, the C1-glycosyl heterocycles have given rise to considerable interest, mainly due to their role in a multitude of biological and pharmaceutical applications like biological inhibitors and probes,<sup>10-13</sup> antitumor,<sup>14,15</sup> antimicrobial,<sup>16</sup> and anti-inflammatory.<sup>17</sup>

On the other hand, the 1,3,4-thiadiazoles are commonly utilized heterocyclic pharmacophores, which display a broad spectrum of biological activities including antimicrobial,<sup>18,19</sup> anticancer,<sup>20,21</sup> antioxidant,<sup>22,23</sup> antidepressant,<sup>24,25</sup> anticonvulsant,<sup>26,27</sup> antihypertensive,<sup>28</sup> and antifungal activity.<sup>29,30</sup> In particular, the most significant 2-amino-1,3,4-thiadiazole derivatives are used in treatment of glaucoma,<sup>31</sup> epileptic seizures,<sup>32</sup> hemiplegic migraine,<sup>33</sup> cystinuria,<sup>34</sup> tuberculosis,<sup>35</sup> etc. Moreover, some 1,3,4-thiadiazoles also exhibit high potential employed as acetylcholinesterase inhibitors for the treatment of Alzheimer's disease (AD).<sup>36,37</sup>

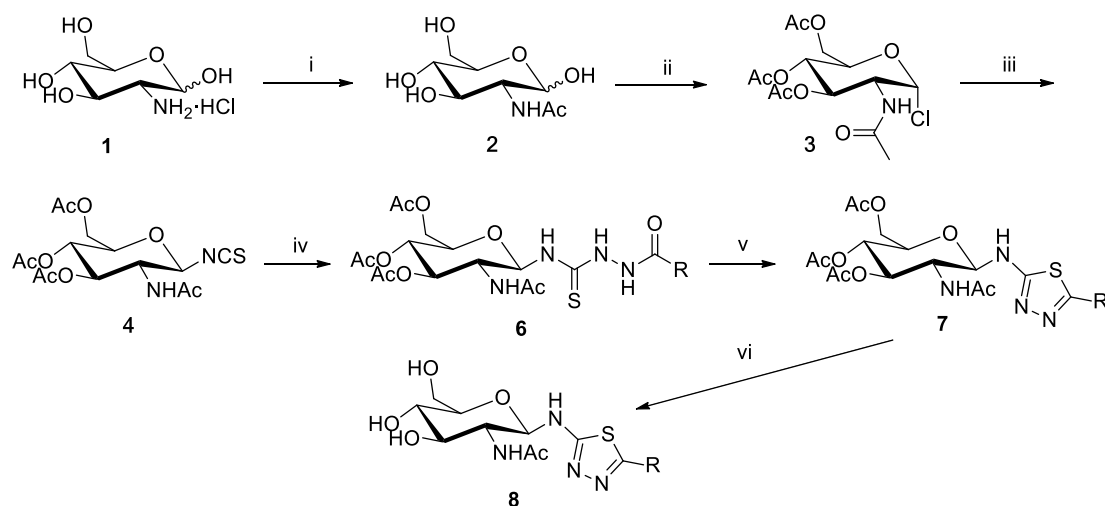
Therefore, it is very interesting for us to report the synthesis of a series of new compounds in which the glycosyl moieties have been used as carriers for the heterocycles possessing thiadiazole ring.

Following our previous studies in searching of novel AChE inhibitors,<sup>38,39</sup> the acetylated GlcNAc of *N*-bit modification didn't show enough inhibitory activity toward AChE. Here, we report a mild and convenient protocol for the synthesis of glycosyl 1,3,4-thiadiazole derivatives via the link of nitrogen glycoside evaluated by Ellman's method in order to screen a novel AChE inhibitor and explore the influence of GlcNAc unit against AChE-inhibition activity.

## RESULTS AND DISCUSSION

### Chemistry

The starting material, *N*-acetyl-tri-*O*-acetyl- $\beta$ -D-glucopyranosyl isothiocyanate **4**, was prepared from the corresponding D-glucosamine hydrochloride **1** via acylation, chlorination and S<sub>N</sub>2 reaction.<sup>40,41</sup> Treatment of the isothiocyanate **4** with various hydrazides **5** in ethanol at 78 °C for 2 h afforded the glycosyl acylthiosemicarbazides **6a-6l** with almost quantitative yield. A series of glycosyl 1,3,4-thiadiazoles (**7a-7l**) were synthesized by cyclizing system of *p*-TsCl/TEA in *N*-methylpyrrolidone (NMP) under mild conditions from the compounds **6a-6l** and gave satisfactory isolated yields (65%–89%). The acetyl derivatives **7** were efficiently deprotected to the hydroxyl derivatives **8** in the presence of NaOMe/MeOH. The general synthetic pathway to prepare glycosyl 1,3,4-thiadiazole derivatives was performed in Scheme 1. The chemical structures of all the new compounds were confirmed by IR, <sup>1</sup>H NMR and high resolution mass spectroscopy (HRMS), which were in agreement with the proposed structures.



**6a, 7a, 8a** : R = Me

**6e, 7e, 8e** : R = 4-FC<sub>6</sub>H<sub>4</sub>

**6i, 7i, 8i** : R = 4-MeCO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>

**6b, 7b, 8b** : R = C<sub>6</sub>H<sub>5</sub>

**6f, 7f, 8f** : R = 2-ClC<sub>6</sub>H<sub>4</sub>

**6j, 7j, 8j** : R = 4-(*N,N*-di-Me)-C<sub>6</sub>H<sub>4</sub>

**6c, 7c, 8c** : R = 4-MeC<sub>6</sub>H<sub>4</sub>

**6g, 7g, 8g** : R = 4-IC<sub>6</sub>H<sub>4</sub>

**6k, 7k, 8k** : R = 3-C<sub>6</sub>H<sub>4</sub>N

**6d, 7d, 8d** : R = 3-MeOC<sub>6</sub>H<sub>4</sub>

**6h, 7h, 8h** : R = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>

**6l, 7l, 8l** : R = 2-C<sub>5</sub>H<sub>3</sub>S

**Scheme 1:** Synthetic pathways of glycosyl 1,3,4-thiadiazoles. Reagents and conditions: (i) Ac<sub>2</sub>O, TEA, MeOH, 0 °C; (ii) AcCl, rt; (iii) KSCN, (*n*-C<sub>4</sub>H<sub>9</sub>)<sub>4</sub>NHSO<sub>4</sub>, MeCN, 4 Å molecular sieves; (iv) RCONHNH<sub>2</sub> (**5**) EtOH, reflux; (v) *p*-TsCl, TEA, NMP, rt; (vi) NaOMe, MeOH, rt.

In the IR spectra, characteristic absorption bands (the compounds **7**) for fragments: C=O and C-O-C are visible in the ranges of: 1660-1750 cm<sup>-1</sup> and 1035-1042 cm<sup>-1</sup>, respectively. There are moderate bands in the region about 3307-3429 cm<sup>-1</sup> corresponding to  $\nu$  (N-H) and band of  $\nu$  (C-H) appears in the region 2924-2936 cm<sup>-1</sup>. In the products **8**, the wide and strong hydroxyl absorption bands in the region 3614-3630 cm<sup>-1</sup> appeared. Meanwhile, the strong absorption peaks (C=O) about 1743-1750 cm<sup>-1</sup> disappeared. In the <sup>1</sup>H NMR spectra, all the compounds **7** showed a characteristic triplet within 5.20–5.35 ppm region having a coupling constant (*J*) in the range of 8.6-9.8 Hz, which indicated sugar ring was  $\beta$ -configuration, due to the presence of H<sub>1</sub> proton of the sugar ring coupled by the C<sub>2</sub>-H and N-H while the signals of other glycosyl aliphatic protons were shown in the range 3.86-5.20 ppm. In compounds **8**, the presence of only a single peak (CH<sub>3</sub>) in the chemical shift of about 2.0 indicated that hydroxy protection groups have been removed. However, the chemical shift of H proton on the sugar ring varied little.

In the mass spectra (ESI), the compounds **7** and **8** all show molecular ion peaks and give (M+H)<sup>+</sup>, (M+Na)<sup>+</sup> and (M+K)<sup>+</sup> peak stating this kind of compounds easily combine with metal ions. The detailed results of IR, <sup>1</sup>H NMR, and ESI-MS are presented in the experimental part.

### Biological activity

The AChE-Inhibition activities of the newly synthesized compounds were evaluated *in vitro* by Ellman's method,<sup>42</sup> in which the AChE extracts from *Electric eel* were used. Their inhibitory potency was described as the inhibition rate and the half of maximal inhibitory concentration, IC<sub>50</sub>. Tacrine was measured as a standard for the comparative purpose. The results were summarized in Table 1.

Table 1. In vitro inhibitory activities of glycosyl 1,3,4-thiadiazoles against AChE

Compound	R	Inhibition	
		Inhibition (%) <sup>a</sup>	IC <sub>50</sub> (μM)
7a	Me	< 10	–
7b	C <sub>6</sub> H <sub>5</sub>	20.34	–
7c	4-MeC <sub>6</sub> H <sub>4</sub>	24.89	–
7d	3-MeOC <sub>6</sub> H <sub>4</sub>	19.76	–
7e	4-FC <sub>6</sub> H <sub>4</sub>	< 10	–
7f	2-ClC <sub>6</sub> H <sub>4</sub>	43.67	–
7g	4-IC <sub>6</sub> H <sub>4</sub>	25.60	–
7h	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	64.52	21.91±1.64
7i	4-MeCO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	< 10	–
7j	4-( <i>N,N</i> -di-Me)-C <sub>6</sub> H <sub>4</sub>	53.21	35.14±2.18
7k	3-C <sub>6</sub> H <sub>4</sub> N	27.53	–
7l	2-C <sub>5</sub> H <sub>3</sub> S	58.76	28.86±4.24
8c	4-MeC <sub>6</sub> H <sub>4</sub>	32.64	
8d	3-MeOC <sub>6</sub> H <sub>4</sub>	23.42	
8h	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	73.11	18.38±0.89
8j	4-( <i>N,N</i> -di-Me)-C <sub>6</sub> H <sub>4</sub>	59.23	30.53±1.32
m <sup>b</sup>		18.12	
n <sup>c</sup>		14.96	
Tacrine			0.26±0.004

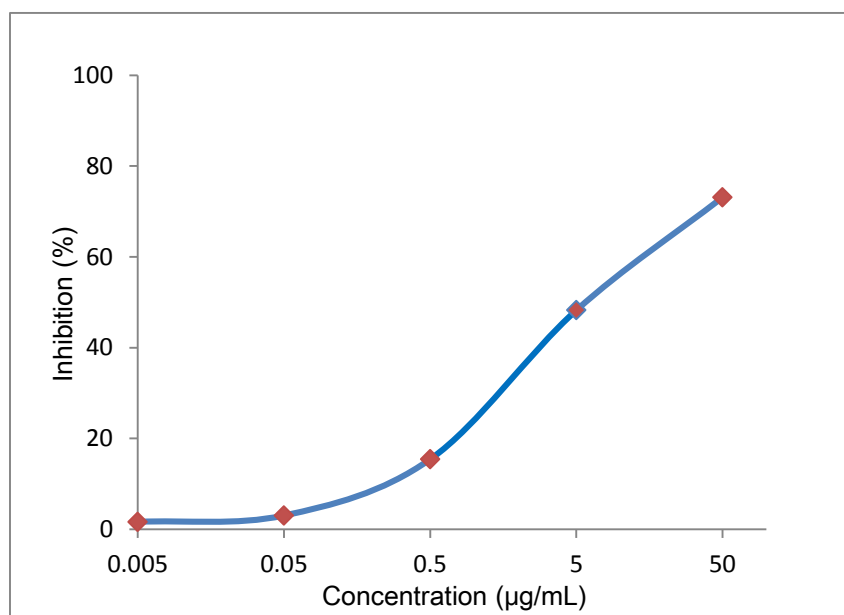
<sup>a</sup> The inhibition activities of the compounds at the concentration of 50 μg/mL.

<sup>b</sup> m stands for 5-(4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>)-1,3,4-thiadiazole-2-amine.

<sup>c</sup> n stands for 5-[4-(*N,N*-di-Me)-C<sub>6</sub>H<sub>4</sub>]-1,3,4-thiadiazole-2-amine.

As shown in the Table 1, it was found that 13 of the 16 tested compounds showed the AChE-inhibition activities. Among them, the compounds **7h**, **7l** with 4-nitrophenyl and 2-thienyl substituent exhibited a moderate inhibition on AChE with IC<sub>50</sub> = 21.91 μM and 28.86 μM, respectively. Deprotected compound **8h** showed the best AChE-inhibition activity with the IC<sub>50</sub> value of 18.38 μM. Compared with the positive control tacrine (IC<sub>50</sub> = 0.26 μM) of the first drug used for the treatment of AD,<sup>43</sup> it presented

promising inhibition activity against AChE, potentially useful in the treatment of AD. In addition, the compounds **m** and **n** showed weak inhibitory against AChE compared with compound **7** and **8**, indicating that the presence of GlcNAc unit improved activities of 1,3,4-thiadiazole compounds. And compound **8c**, **d**, **h**, **j** all revealed higher potency as compared with **7c**, **d**, **h**, **j**, suggesting that the removal of hydroxyl protection groups also improved activities in a certain extent. This may be due to the removal of acetyl groups leading to better water solubility of the compound **8**. Compound **8h** inhibited AChE with a dose-dependent relationship (Figure. 1).



**Figure 1.** Dose-dependent inhibition of compound **8h** against AChE. Values are means  $\pm$  SD,  $n = 3$ .

## EXPERIMENTAL

### Chemistry

All chemicals and solvents were purchased from commercial sources and used without further purification unless otherwise stated. Melting points were measured on a Yanaco melting point apparatus and were uncorrected. IR spectra were recorded on a Bruker Tensor 27 spectrometer with KBr pellets.  $^1\text{H}$  NMR spectra were recorded on a Bruker Avance 400 MHz instrument using DMSO- $d_6$  or  $\text{D}_2\text{O}$  as solvents and tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in ppm and coupling constants ( $J$ ) are reported in Hz. HRMS (ESI) analysis was performed on a Agilent 6230 Q-TOF mass spectrometer. The purity of the compounds was checked by TLC on plates precoated with silica gel GF254. Flash column chromatography was performed on silica 200-300 mesh. The compounds **2**, **3** and **4**

were prepared in this laboratory according to the procedure reported in literature.<sup>40,41</sup>

### General procedure for the preparation of glycosyl acylthiosemicarbazide (6a–6l)

Glycosyl isothiocyanate **4** (0.388 g, 1 mmol) was added in one portion to a stirred solution of hydrazide **5** (1 mmol) in EtOH (10 mL). The reaction mixture was reflux for 1-2 h, and then the solvent was removed via a rotary evaporator. The residue was recrystallized from aqueous EtOH to obtain the desired product. (The characterization of the representative compound **6a** was only presented in this paper.)

#### *N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl)-*N'*-methyl-acylthiosemicarbazide (**6a**)

Yield 84%, white solid, mp 148-149 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3320 (NH), 2972 (C-H), 1749 (CH<sub>3</sub>C=O), 1667 (NHC=O), 1044 (C-O-C). <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$ : 9.79 (br, 1H, NH), 9.72 (br, 1H, NH), 8.21 (d, *J* = 8.9 Hz, 1H, NH), 7.84 (d, *J* = 7.3 Hz, 1H, NH), 5.32 (m, 1H, H<sub>1</sub>), 5.15 (d, *J* = 9.4 Hz, 1H, H<sub>3</sub>), 4.82 (t, *J* = 9.8 Hz, 1H, H<sub>4</sub>), 4.19-3.81 (m, 4H, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>, H<sub>6</sub>'), 1.99-1.77 (5s, 15H, 5CH<sub>3</sub>). ESI-HRMS (*m/z*): Calcd for C<sub>17</sub>H<sub>26</sub>N<sub>4</sub>O<sub>9</sub>SNa (M+Na)<sup>+</sup>: 485.1313; Found: 485.1326.

### General procedure for the preparation of glycosyl 1,3,4-thiadiazole (7a–7l)

Tosyl chloride (0.21 g, 1.1 mmol) was added to a stirred solution of acylthiosemicarbazide **6** (1 mmol) and triethylamine (0.29 mL, 2.1 mmol) in NMP (5 mL). The solution was stirred at room temperature for 4-6 h (TLC), and extracted with EtOAc (2×10 mL) and distilled water (2×10 mL). After the aqueous layer removed, the aqueous layer was re-extracted thrice with EtOAc (3×10 mL). The organic phases were combined and dried over anhydrous MgSO<sub>4</sub>. The solid was filtered out and the solution was evaporate to afford the crude product, which was purified by column chromatography on silica gel (MeOH/DCM) to give the pure product.

*N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl)-5-methyl-1,3,4-thiadiazole-2-amine (**7a**): Yield 81%, White solid, mp 209-210 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3328 (NH), 2928 (C-H), 1749 (CH<sub>3</sub>C=O), 1662 (NHC=O), 1040 (C-O-C). <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$ : 8.33 (d, *J* = 9.3 Hz, 1H, NH), 8.06 (d, *J* = 9.0 Hz, 1H, NH), 5.20 (t, *J* = 8.6 Hz, 1H, H<sub>1</sub>), 5.15 (t, *J* = 8.9 Hz, 1H, H<sub>3</sub>), 4.85 (t, *J* = 9.8 Hz, 1H, H<sub>4</sub>), 4.20 (dd, *J* = 12.4, 4.4 Hz, 1H, H<sub>6</sub>), 3.97-3.86 (m, 3H, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>'), 1.98-1.74 (4s, 12H, COCH<sub>3</sub>), 1.24 (s, 3H, CH<sub>3</sub>). ESI-HRMS (*m/z*): Calcd for C<sub>17</sub>H<sub>24</sub>N<sub>4</sub>O<sub>8</sub>SNa (M+Na)<sup>+</sup>: 467.1207; Found: 467.1202.

*N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl)-5-phenyl-1,3,4-thiadiazole-2-amine (**7b**): Yield 84%, White solid, mp 225-226 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3358 (NH), 2928 (C-H), 1744

(CH<sub>3</sub>C=O), 1670 (NHC=O), 1035 (C-O-C). <sup>1</sup>H NMR (400 MHz, DMSO) δ: 8.77 (d, *J* = 9.1 Hz, 1H, NH), 8.12 (d, *J* = 9.0 Hz, 1H, NH), 7.79 (dd, *J* = 7.2, 2.3 Hz, 2H, Ar-H), 7.48 (m, 3H, Ar-H), 5.31 (t, *J* = 9.5 Hz, 1H, H<sub>1</sub>), 5.19 (t, *J* = 9.9 Hz, 1H, H<sub>3</sub>), 4.88 (t, *J* = 9.8 Hz, 1H, H<sub>4</sub>), 4.22 (dd, *J* = 12.4, 4.1 Hz, 1H, H<sub>6</sub>), 3.99-3.91 (m, 3H, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>), 1.99-1.76 (4s, 12H, COCH<sub>3</sub>). ESI-HRMS (*m/z*): Calcd for C<sub>22</sub>H<sub>26</sub>N<sub>4</sub>O<sub>8</sub>S-Na (M+Na)<sup>+</sup>: 529.1364; Found: 529.1365.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(4-methylphenyl)-1,3,4-thiadiazole-2-amine (7c):** Yield 89%, White solid, mp 207-208 °C. IR (KBr) ν (cm<sup>-1</sup>): 3307 (NH), 2924 (C-H), 1747 (CH<sub>3</sub>C=O), 1660 (NHC=O), 1037 (C-O-C). <sup>1</sup>H NMR (400 MHz, DMSO) δ: 8.70 (d, *J* = 9.2 Hz, 1H, NH), 8.11 (d, *J* = 9.0 Hz, 1H, NH), 7.67 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.29 (d, *J* = 8.1 Hz, 2H, Ar-H), 5.29 (t, *J* = 9.4 Hz, 1H, H<sub>1</sub>), 5.18 (t, *J* = 9.8 Hz, 1H, H<sub>3</sub>), 4.88 (t, *J* = 9.7 Hz, 1H, H<sub>4</sub>), 4.22 (dd, *J* = 12.4, 4.3 Hz, 1H, H<sub>6</sub>), 3.99-3.90 (m, 3H, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>), 2.35 (s, 3H, CH<sub>3</sub>), 1.98-1.76 (4s, 12H, COCH<sub>3</sub>). ESI-HRMS (*m/z*): Calcd for C<sub>23</sub>H<sub>29</sub>N<sub>4</sub>O<sub>8</sub>S (M+H)<sup>+</sup>: 521.1701; Found: 521.1703.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(3-methoxyphenyl)-1,3,4-thiadiazole-2-amine (7d):** Yield 86%, White solid, mp 208-209 °C. IR (KBr) ν (cm<sup>-1</sup>): 3269 (NH), 2936 (C-H), 1747 (CH<sub>3</sub>C=O), 1668 (NHC=O), 1042 (C-O-C). <sup>1</sup>H NMR (400 MHz, DMSO) δ: 8.77 (d, *J* = 9.1 Hz, 1H, NH), 8.10 (d, *J* = 9.0 Hz, 1H, NH), 7.41 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.33 (t, *J* = 4.4 Hz, 2H, Ar-H), 7.06 (m, 1H, Ar-H), 5.29 (t, *J* = 9.4 Hz, 1H, H<sub>1</sub>), 5.19 (t, *J* = 9.8 Hz, 1H, H<sub>3</sub>), 4.88 (t, *J* = 9.7 Hz, 1H, H<sub>4</sub>), 4.22 (dd, *J* = 12.4, 4.4 Hz, 1H, H<sub>6</sub>), 3.99-3.91 (m, 3H, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>), 3.82 (s, 3H, CH<sub>3</sub>), 1.99-1.76 (4s, 12H, COCH<sub>3</sub>). ESI-HRMS (*m/z*): Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>4</sub>O<sub>9</sub>S (M+H)<sup>+</sup>: 537.1650; Found: 537.1662.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(4-fluorophenyl)-1,3,4-thiadiazole-2-amine (7e):** Yield 89%, White solid, mp 206-207 °C. IR (KBr) ν (cm<sup>-1</sup>): 3348 (NH), 2957 (C-H), 1743 (CH<sub>3</sub>C=O), 1662 (NHC=O), 1041 (C-O-C). <sup>1</sup>H NMR (400 MHz, DMSO) δ: 8.74 (d, *J* = 9.1 Hz, 1H, NH), 8.09 (d, *J* = 9.0 Hz, 1H, NH), 7.84 (m, 2H, Ar-H), 7.33 (t, *J* = 8.8 Hz, 2H, Ar-H), 5.30 (t, *J* = 9.4 Hz, 1H, H<sub>1</sub>), 5.19 (t, *J* = 9.8 Hz, 1H, H<sub>3</sub>), 4.88 (t, *J* = 9.7 Hz, 1H, H<sub>4</sub>), 4.22 (dd, *J* = 12.4, 4.4 Hz, 1H, H<sub>6</sub>), 4.00-3.92 (m, 3H, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>), 1.99-1.76 (4s, 12H, COCH<sub>3</sub>). ESI-HRMS (*m/z*): Calcd for C<sub>22</sub>H<sub>25</sub>FN<sub>4</sub>O<sub>8</sub>S-Na (M+Na)<sup>+</sup>: 547.1269; Found: 547.1269.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-5-(2-chlorophenyl)-1,3,4-thiadiazole-2-amine (7f):** Yield 78%, White solid, mp 198-199 °C. IR (KBr) ν (cm<sup>-1</sup>): 3332 (NH), 2930 (C-H), 1748 (CH<sub>3</sub>C=O), 1663 (NHC=O), 1039 (C-O-C). <sup>1</sup>H NMR (400 MHz, DMSO) δ: 8.78 (d, *J* = 9.2 Hz, 1H, NH), 8.10 (d, *J* = 9.0 Hz, 1H, NH), 7.99 (m, 1H, Ar-H), 7.64 (m, 1H, Ar-H), 7.51 (m, 2H, Ar-H), 5.33 (t, *J*

= 9.4 Hz, 1H, H<sub>1</sub>), 5.19 (t, *J* = 9.8 Hz, 1H, H<sub>3</sub>), 4.89 (t, *J* = 9.7 Hz, 1H, H<sub>4</sub>), 4.22 (dd, *J* = 12.4, 4.4 Hz, 1H, H<sub>6</sub>), 4.00-3.93 (m, 3H, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>), 1.99-1.76 (4s, 12H, COCH<sub>3</sub>). ESI-HRMS (*m/z*): Calcd for C<sub>22</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>8</sub>SNa (M+Na)<sup>+</sup>: 563.0974; Found: 563.0970.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl)-5-(4-iodophenyl)-1,3,4-thiadiazole-2-amine (7g):** Yield 82%, White solid, mp 232-233 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3348 (NH), 2927 (C-H), 1743 (CH<sub>3</sub>C=O), 1661 (NHC=O), 1041 (C-O-C). <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$ : 8.81 (d, *J* = 9.0 Hz, 1H, NH), 8.11 (d, *J* = 9.0 Hz, 1H, NH), 7.86 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.59 (d, *J* = 8.6 Hz, 2H, Ar-H), 5.31 (t, *J* = 9.4 Hz, 1H, H<sub>1</sub>), 5.19 (t, *J* = 9.7 Hz, 1H, H<sub>3</sub>), 4.89 (t, *J* = 9.9 Hz, 1H, H<sub>4</sub>), 4.22 (dd, *J* = 12.4, 4.4 Hz, 1H, H<sub>6</sub>), 4.01-3.92 (m, 3H, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>), 1.99-1.76 (4s, 12H, COCH<sub>3</sub>). ESI-HRMS (*m/z*): Calcd for C<sub>22</sub>H<sub>25</sub>IN<sub>4</sub>O<sub>8</sub>SNa (M+Na)<sup>+</sup>: 655.0330; Found: 655.0316.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl)-5-(4-nitrophenyl)-1,3,4-thiadiazole-2-amine (7h):** Yield 83%, Yellow solid, mp 117-118 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3422 (NH), 2927 (C-H), 1749 (CH<sub>3</sub>C=O), 1662 (NHC=O), 1041 (C-O-C). <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$ : 9.01 (d, *J* = 9.0 Hz, 1H, NH), 8.33 (m, 2H, Ar-H), 8.08 (m, 3H, NH, Ar-H), 5.35 (t, *J* = 9.3 Hz, 1H, H<sub>1</sub>), 5.20 (t, *J* = 9.8 Hz, 1H, H<sub>3</sub>), 4.90 (t, *J* = 9.7 Hz, 1H, H<sub>4</sub>), 4.22 (dd, *J* = 12.4, 4.4 Hz, 1H, H<sub>6</sub>), 4.02-3.96 (m, 3H, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>), 1.99-1.76 (4s, 12H, COCH<sub>3</sub>). ESI-HRMS (*m/z*): Calcd for C<sub>22</sub>H<sub>25</sub>N<sub>5</sub>O<sub>10</sub>SNa (M+Na)<sup>+</sup>: 574.1214; Found: 574.1208.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl)-5-(4-acetoxyphenyl)-1,3,4-thiadiazole-2-amine (7i):** Yield 76%, White solid, mp 116-117 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3382 (NH), 2936 (C-H), 1750 (CH<sub>3</sub>C=O), 1666 (NHC=O), 1040 (C-O-C). <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$ : 8.75 (d, *J* = 9.1 Hz, 1H, NH), 8.09 (d, *J* = 9.1 Hz, 1H, NH), 7.84 (m, 2H, Ar-H), 7.26 (m, 2H, Ar-H), 5.31 (t, *J* = 9.4 Hz, 1H, H<sub>1</sub>), 5.19 (t, *J* = 9.8 Hz, 1H, H<sub>3</sub>), 4.89 (t, *J* = 9.7 Hz, 1H, H<sub>4</sub>), 4.22 (dd, *J* = 12.4, 4.4 Hz, 1H, H<sub>6</sub>), 3.99-3.91 (m, 3H, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>), 2.31 (s, 3H, CH<sub>3</sub>), 1.99-1.76 (4s, 12H, COCH<sub>3</sub>). ESI-HRMS (*m/z*): Calcd for C<sub>24</sub>H<sub>28</sub>N<sub>4</sub>O<sub>10</sub>SNa (M+Na)<sup>+</sup>: 587.1418; Found: 587.1410.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl)-5-(4-*N,N*-dimethylphenyl)-1,3,4-thiadiazole-2-amine (7j):** Yield 88%, White solid, mp 197-198 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3429 (NH), 2927 (C-H), 1748 (CH<sub>3</sub>C=O), 1662 (NHC=O), 1042 (C-O-C). <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$ : 8.50 (d, *J* = 9.2 Hz, 1H, NH), 8.09 (d, *J* = 8.9 Hz, 1H, NH), 7.58 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.76 (d, *J* = 9.0 Hz, 2H, Ar-H), 5.26 (t, *J* = 9.4 Hz, 1H, H<sub>1</sub>), 5.16 (m, 1H, H<sub>3</sub>), 4.87 (dd, *J* = 11.5, 8.5 Hz, 1H, H<sub>4</sub>), 4.21 (m, 1H, H<sub>6</sub>), 4.00-3.93 (m, 3H, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>), 2.98 (s, 6H, CH<sub>3</sub>), 1.99-1.75 (4s, 12H, COCH<sub>3</sub>). ESI-HRMS (*m/z*):

Calcd for C<sub>24</sub>H<sub>31</sub>N<sub>5</sub>O<sub>8</sub>SNa (M+Na)<sup>+</sup>: 572.1786; Found: 572.1776.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl)-5-(3-pyridyl)-1,3,4-thiadiazole-2-amine (7k):** Yield 71%, Yellow solid, mp 113-114 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3426 (NH), 2930 (C-H), 1749 (CH<sub>3</sub>C=O), 1663 (NHC=O), 1040 (C-O-C). <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$ : 8.98 (d, *J* = 2.1 Hz, 1H, Pyridine), 8.89 (d, *J* = 9.0 Hz, 1H, NH), 8.65 (dd, *J* = 4.8, 1.5 Hz, 1H, Pyridine), 8.18 (m, 1H, Pyridine), 8.13 (d, *J* = 9.0 Hz, 1H, NH), 7.53 (dd, *J* = 7.9, 4.8 Hz, 1H, Pyridine), 5.33 (t, *J* = 9.3 Hz, 1H, H<sub>1</sub>), 5.19 (t, *J* = 9.9 Hz, 1H, H<sub>3</sub>), 4.89 (t, *J* = 9.8 Hz, 1H, H<sub>4</sub>), 4.23 (dd, *J* = 12.4, 4.3 Hz, 1H, H<sub>6</sub>), 4.00-3.93 (m, 3H, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>), 1.99-1.76 (4s, 12H, COCH<sub>3</sub>). ESI-HRMS (*m/z*): Calcd for C<sub>21</sub>H<sub>25</sub>N<sub>5</sub>O<sub>8</sub>SNa (M+Na)<sup>+</sup>: 530.1316; Found: 530.1320.

***N*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl)-5-(2-thienyl)-1,3,4-thiadiazole-2-amine (7l):** Yield 65%, White solid, mp 201-202 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3418 (NH), 2926 (C-H), 1745 (CH<sub>3</sub>C=O), 1668 (NHC=O), 1037 (C-O-C). <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$ : 8.76 (d, *J* = 9.1 Hz, 1H, NH), 8.10 (d, *J* = 9.0 Hz, 1H, NH), 7.68 (dd, *J* = 5.1, 1.1 Hz, 1H, Thiophene), 7.50 (dd, *J* = 3.7, 1.1 Hz, 1H, Thiophene), 7.15 (dd, *J* = 5.1, 3.7 Hz, 1H, Thiophene), 5.27 (t, *J* = 9.4 Hz, 1H, H<sub>1</sub>), 5.18 (t, *J* = 9.8 Hz, 1H, H<sub>3</sub>), 4.88 (t, *J* = 9.8 Hz, 1H, H<sub>4</sub>), 4.22 (dd, *J* = 12.4, 4.5 Hz, 1H, H<sub>6</sub>), 4.00-3.91 (m, 3H, H<sub>2</sub>, H<sub>5</sub>, H<sub>6</sub>), 1.99-1.76 (4s, 12H, COCH<sub>3</sub>). ESI-HRMS (*m/z*): Calcd for C<sub>20</sub>H<sub>24</sub>N<sub>4</sub>O<sub>8</sub>S<sub>2</sub>Na (M+Na)<sup>+</sup>: 535.0928; Found: 535.0930.

#### General procedure for deprotection of *O*-acetyl-substituted compounds **7** to hydroxy derivatives **8**

A solution of compound **7** (0.5 mmol) in MeOH (5 mL) was treated with sodium methoxide (1 M in MeOH, 0.2 mL). The mixture was stirred at ambient temperature for 2 h and then neutralized with Amberlite IR 120 H+ resin and filtered. The filtrate was concentrated to afford the deprotected product **8**. Selected products **8c**, **d**, **h**, **j** are characterized below.

#### ***N*-(2-Acetamido-2-deoxy- $\beta$ -D-glucopyranosyl)-5-(4-methylphenyl)-1,3,4-thiadiazole-2-amine (8c):**

Yield 90%, White solid, mp 156-157 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3414 (OH), 2928 (C-H), 1626 (NHC=O), 1074 (C-O-C). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta$ : 7.66 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.29 (d, *J* = 8.0 Hz, 2H, Ar-H), 4.81 (t, *J* = 8.7 Hz, 1H, H<sub>1</sub>), 3.66-3.15 (m, 6H, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>, H<sub>6</sub>), 2.34 (s, 3H, CH<sub>3</sub>), 1.81 (s, 3H, CH<sub>3</sub>). ESI-HRMS (*m/z*): Calcd for C<sub>17</sub>H<sub>22</sub>N<sub>4</sub>O<sub>5</sub>SNa (M+Na)<sup>+</sup>: 417.1203; Found: 417.1202.

#### ***N*-(2-Acetamido-2-deoxy- $\beta$ -D-glucopyranosyl)-5-(3-methoxyphenyl)-1,3,4-thiadiazole-2-amine (8d):**

Yield 88%, White solid, mp 101-102 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3416 (NH), 2934 (C-H), 1629 (NHC=O), 1044 (C-O-C). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta$ : 7.39 (m, 1H, Ar-H), 7.32 (m, 2H, Ar-H), 7.03 (m, 1H, Ar-H),

4.85 (t,  $J = 9.0$  Hz, 1H, H<sub>1</sub>), 3.76-3.21 (m, 6H, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>, H<sub>6</sub>), 3.80 (s, 3H, CH<sub>3</sub>), 1.82 (s, 3H, CH<sub>3</sub>).

ESI-HRMS ( $m/z$ ): Calcd for C<sub>17</sub>H<sub>22</sub>N<sub>4</sub>O<sub>6</sub>SNa (M+Na)<sup>+</sup>: 433.1152 ; Found: 433.1150.

***N*-(2-Acetamido-2-deoxy- $\beta$ -D-glucopyranosyl)-5-(4-nitrophenyl)-1,3,4-thiadiazole-2-amine (8h):**

Yield 81%, Yellow solid, mp 175-176 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3430 (OH), 2926 (C-H), 1634 (NHC=O), 1048 (C-O-C). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta$ : 8.30 (m, 2H, Ar-H), 8.10 (m, 2H, Ar-H), 4.92 (t,  $J = 8.9$  Hz, 1H, H<sub>1</sub>), 3.81-3.26 (m, 6H, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>, H<sub>6</sub>), 1.84 (s, 3H, CH<sub>3</sub>). ESI-HRMS ( $m/z$ ): Calcd for C<sub>16</sub>H<sub>19</sub>N<sub>5</sub>O<sub>7</sub>SNa (M+Na)<sup>+</sup>: 448.0897 ; Found: 448.0895.

***N*-(2-Acetamido-2-deoxy- $\beta$ -D-glucopyranosyl)-5-(4-*N,N*-dimethylphenyl)-1,3,4-thiadiazole-2-amine**

**(8j):** Yield 84%, White solid, mp 184-185 °C. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3412 (OH), 2925 (C-H), 1627 (NHC=O), 1074 (C-O-C). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta$ : 7.63 (d,  $J = 7.3$  Hz, 2H, Ar-H), 6.83 (d,  $J = 7.2$  Hz, 2H, Ar-H), 4.91 (d,  $J = 9.4$  Hz, 1H, H<sub>1</sub>), 3.73-3.24 (m, 6H, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>, H<sub>6</sub>), 3.02 (s, 6H, CH<sub>3</sub>), 1.90 (s, 3H, CH<sub>3</sub>). ESI-HRMS ( $m/z$ ): Calcd for C<sub>18</sub>H<sub>25</sub>N<sub>5</sub>O<sub>5</sub>SNa (M+Na)<sup>+</sup>: 446.1469; Found: 446.1468.

**Biological tests**

Acetylcholinesterase (AChE, from *Electric eel*), acetylthiocholine iodide (ATCI), 5,5-dithiobis-(2-nitrobenzoic acid) (DTNB) and tacrine were purchased from Sigma-Aldrich (America). AChE activities were measured by Ellman's colorimetric method with a slight modification,<sup>42</sup> using tacrine as the reference compounds. In assays, 10  $\mu$ L of rat cortex homogenate was incubated with 10  $\mu$ L of tested compounds and 140  $\mu$ L of 0.1 M PBS (pH 8.0) for 10 min in 96-well microplates before addition of 20  $\mu$ L of 3.33 mM DTNB solution and 20  $\mu$ L of 5.30 mM ATCI solution. After the addition of DTNB and ATCI, the 96-well microplates were read at 412 nm with a microplate reader (SPECTRAFLUOR, TECAN, Sunrise, Austria) for 15 min. One triplicate sample without inhibitors was always present to yield 100% of AChE activity. One triplicate sample with 20  $\mu$ M tacrine was always present to yield 100% AChE inhibition (to obviate the ChE-independent substrate hydrolysis). The reaction rates were compared and the percent inhibition due to the presence of tested compounds was calculated. Each concentration was assayed in triplicate. The 50% inhibitory concentration (IC<sub>50</sub>) was calculated from a dose-response curve obtained by plotting the percentage of inhibition versus the log concentration with the use of Origin 8.0 software. The results were described as the mean  $\pm$  standard deviation (SD).

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