Research Paper

Journal of Chemical Research

Journal of Chemical Research
1–4

DOI: 10.1177/1747519819901251
journals.sagepub.com/home/chl
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Synthesis and anticholinesterase activities of novel glycosyl benzoxazole derivatives

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Abstract

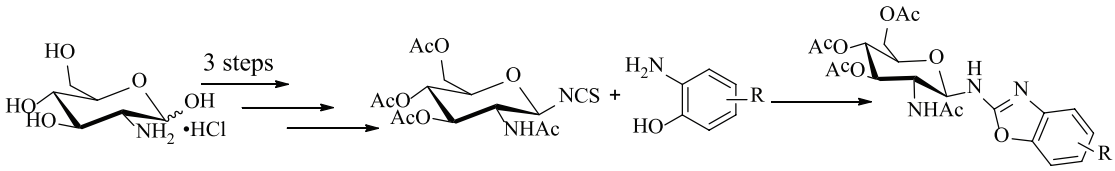
Eight glycosyl benzoxazole derivatives are synthesized by nucleophilic addition reactions of glycosyl isothiocyanate with *o*-aminophenol in tetrahydrofuran. The reaction conditions are optimized, and good yields (86%–94%) were obtained. The structures of all new products are confirmed by infrared, ^{1}H nuclear magnetic resonance, and high-resolution mass spectrometry (electrospray ionization). In addition, the in vitro cholinesterase inhibitory activities of these new compounds are tested by Ellman's method.

Keywords

benzoxazole, cholinesterase inhibitory activity, glucosamine

Date received: 27 August 2019; accepted: 11 December 2019

Synthetic pathway to glycosyl benzoxazole derivatives.



Introduction

As a natural monosaccharide, glucosamine is an indispensable substance in human cartilage and other tissues.[1] It is abundant in marine organisms and has a wide range of sources and broad application prospects.[2] Glucosamine has a wide spectrum of biological activities, and the synthesis of its derivatives has become a recent research hotspot for improving its biological activities.[3] Many studies have shown that glucosamine derivatives have strong biological properties, including antioxidant, anticancer, antibacterial, and anticholinesterase.[4–8]

Benzoxazole is a type of heterocyclic compound containing nitrogen and oxygen atoms. It has anti-inflammatory, anticancer, antibacterial, and plant virus killing activities,[8–12] and is widely used in medicine, pesticides, and biological fields. Examples of main clinical drugs containing the benzoxazole skeleton include suvorexant for insomnia and flunoxaprofen for anti-inflammatory and analgesic activity.[13,14]

In recent years, many studies have used molecular hybrid-based approaches to search for new compounds with potential biological activities.[15–17] Based on such approaches, we have designed and synthesized a series of novel glycosyl benzoxazole derivatives in an attempt to find new potent cholinesterase inhibitors. The inhibitory activities of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) were tested by the Ellman method, and glycosylated heterocyclic compounds with improved AChE and BuChE inhibitory activity were obtained.

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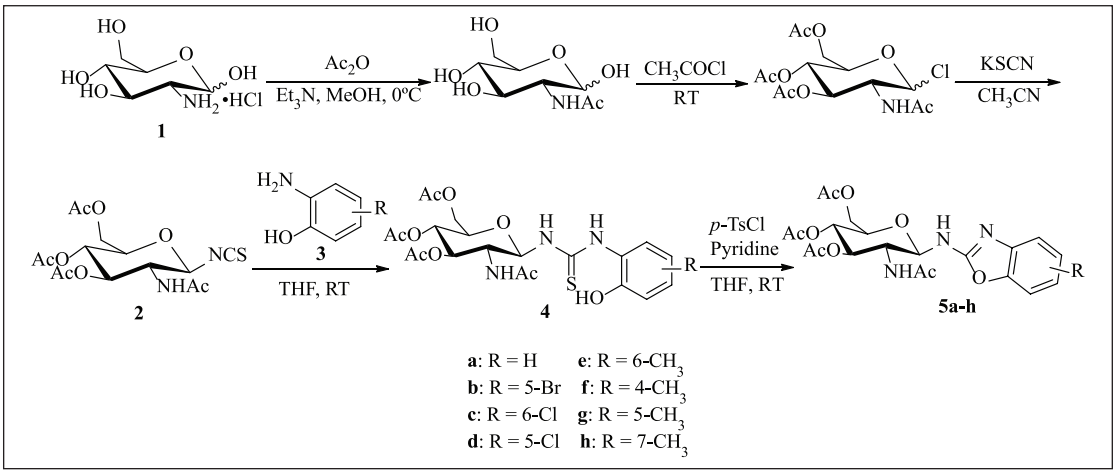

Scheme 1. Synthetic pathway toward the glycosyl benzoxazole derivatives **5**.

Table 1. Optimization of the cyclization reagent and catalyst.

Entry	Cyclization reagent/catalyst	Yield (%)
1	TMSCl	NR
2	TBDPSCl	NR
3	EDC·HCl	16
4	*p*-TsCl	25
5	*p*-TsCl/TEA	47
6	*p*-TsCl/pyridine	89
7	*p*-TsCl/K_2CO_3	33
8	*p*-TsCl/$NaHCO_3$	21

Results and discussion

Chemistry

To develop a simple synthetic pathway toward glycosyl benzoxazole compounds, 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl isothiocyanate **2** proved to be an important intermediate. In our studies, an acetyl group was used as the protecting group to realize the selective chemical modification of the hydroxyl on the glucosamine. First, glycosyl isothiocyanate **2** was synthesized according to the literature.[18,19] Using tetrahydrofuran (THF) as the solvent, glycosyl isothiocyanate **2** was reacted with different *o*-aminophenols overnight, and then *p*-toluenesulfonyl chloride (*p*-TsCl) and pyridine were added resulting in desulfuration and cyclization to give glycosyl benzoxazole derivatives **5a–h** (Scheme 1).

In the second stage, glycosyl thiourea **4a** was used as a model compound to optimize the reaction conditions for the synthesis of compound **5a**. The molar ratio, solvent, temperature, time, catalyst, and cyclization reagent were screened, and the results are summarized in Tables 1 and 2.

Biological activity

The AChE and BuChE inhibition activities of the newly synthesized compounds **5** were evaluated in vitro by Ellman's method.[20,21] Their inhibitory potency was determined from the inhibition rate, and the results are summarized in Table 3.

As shown in Table 3, the inhibitory activity of all the prepared compounds on AChE and BuChE was higher than that of precursor compound glucosamine hydrochloride **1**, which indicated that the presence of the benzoxazole unit led to enhanced activity.

Conclusion

Eight glycosyl benzoxazole derivatives were designed and synthesized by a green, efficient, and convenient method. The optimum reaction conditions were determined, that is, compound **4**, *p*-TsCl, and pyridine (molar ratio: 1:1.2:2.1) were dissolved in THF at room temperature for 8 h. All yields of products **5** were above 86%. These structures of the products were determined by NMR, IR, and HRMS. All the compounds exhibited in vitro cholinesterase (AChE and BuChE) inhibitory activity, which in all cases was better than that of glucosamine hydrochloride **1**. Among them, compound **5f** showed the best AChE inhibitory activity, with the inhibition rate of 21%; compound **5d** showed the best BuChE inhibitory activity, with the inhibition rate of 27%. This work provides a basis for the research of aminosaccharide derivatives in the treatment of Alzheimer's disease.

Experimental

Chemistry

All chemicals were purchased from commercial sources and were used without further purification unless otherwise stated. Melting points were determined on a Yanaco melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Tensor 27 spectrometer as KBr discs. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 MHz spectrometer at ambient temperature using dimethyl sulfoxide–d_6 (DMSO-d_6) as the solvent and tetramethylsilane

Table 2. Optimization of the conditions for the synthesis of **5a.**

Entry	**4a**/*p*-TsCl/Pyridine	Time (h)	Solvent	Yield (%)
1	1:1.0:1	8	THF	56
2	1:1.1:1.5	8	THF	63
3	1:1.2:1.8	8	THF	76
4	1:1.2:2.1	8	THF	89
5	1:1.3:2.1	8	THF	89
6	1:1.3:2.4	8	THF	90
7	1:1.2:2.1	1	THF	13
8	1:1.2:2.1	2	THF	24
9	1:1.2:2.1	4	THF	55
10	1:1.2:2.1	6	THF	73
11	1:1.2:2.1	10	THF	89
12	1:1.2:2.1	8	NMP	9
13	1:1.2:2.1	8	CH_3CN	53
14	1:1.2:2.1	8	CH_2Cl_2	37
15	1:1.2:2.1	8	DCE	24
16	1:1.2:2.1	8	DMF	21

Table 3. In vitro cholinesterase inhibition activities of compounds **5a**–**h**.

Compound	R	Inhibition (%)[a]	
		AChE	BuChE
I	–	2.33 ± 0.02	1.59 ± 0.07
5a	H	12.98 ± 0.03	13.28 ± 0.02
5b	5-Br	14.77 ± 0.09	24.59 ± 0.01
5c	6-Cl	15.19 ± 0.05	17.09 ± 0.02
5d	5-Cl	8.99 ± 0.04	26.91 ± 0.01
5e	6-CH3	7.91 ± 0.04	14.16 ± 0.05
5f	4-CH3	20.87 ± 0.05	14.47 ± 0.11
5g	5-CH3	11.54 ± 0.11	17.31 ± 0.07
5h	7-CH3	9.76 ± 0.07	11.33 ± 0.11

[a]The inhibition activities of the compounds at a concentration of 100 μg mL^{-1}; the results are the mean ± standard deviations (*SD*s).

(TMS) as an internal standard. Chemical shifts are reported in ppm. High-resolution mass spectrometry (HRMS) (electrospray ionization (ESI)) analysis was performed on an Agilent 6230 mass spectrometer. Flash column chromatography was performed on silica gel (200–300 mesh).

General procedure for the synthesis of N-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-N′-o-hydroxyphenylthioureas **4a**–**h**

The *o*-aminophenol compound **3** (1.85 mmol) was dissolved in 2 mL of THF in a 50-mL flask. Compound **2** (1.85 mmol) was dissolved in THF (3 mL) and slowly added dropwise using a constant pressure funnel. After stirring overnight, a white solid precipitated out to give a suspension. The suspension, without purification, can be directly used in the next step.

General procedure for the synthesis of glycosyl benzoxazoles **5a**–**h**

Pyridine (2.1 mmol) was added directly to the suspension of compound **4**. *p*-TsCl (2.22 mmol) was dissolved in THF (10 mL) and added dropwise to the reaction solution, which was then stirred for 30 min at room temperature. After the reaction was complete, the mixture was poured into 100 mL H_2O and extracted with EtOAc (3 × 30 mL). The organic phase was dried and purified by column chromatography (MeOH/CH_2Cl_2 = 1:100) to give the compounds **5**.

2-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)amino-1,3-benzoxazole (5a): White solid; yield 0.74 g (86%); m.p. 58–60 °C; IR (cm^{-1}): 3442, 1749, 1638, 1587, 1242, 1126, 1045, 913; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.87 (d, *J* = 10.0 Hz, 1H, NH), 8.08 (d, *J* = 10.0 Hz, 1H, NH), 7.43 (d, *J* = 10.0 Hz, 1H, ArH), 7.35 (d, *J* = 5.0 Hz, 1H, ArH), 7.20 − 7.16 (m, 1H, ArH), 7.09 − 7.05 (m, 1H, ArH), 5.36 (t, *J* = 10.0 Hz, 1H, H-1^{GlcN}), 5.23 (t, *J* = 10.0 Hz, 1H, H-3^{GlcN}), 4.89 (t, *J* = 10.0 Hz, 1H, H-4^{GlcN}), 4.23 (dd, *J* = 10.0, 5.0 Hz, 1H, H-6a^{GlcN}), 4.06 − 3.93 (m, 3H, H-2^{GlcN}, H-5^{GlcN}, H-6b^{GlcN}), 2.00 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.73 (s, 3H, CH_3); ESI-HRMS (*m/z*): calcd for $C_{21}H_{25}N_3NaO_9$ $[M + Na]^+$: 486.1483; found: 486.1487.

2-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)amino-5-bromo-1,3-benzoxazole (5b): Light yellow solid; yield 0.88 g (88%); m.p. 71–73 °C; IR (cm^{-1}): 3421, 1747, 1638, 1588, 1240, 1126, 1046, 911; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.12 (d, *J* = 9.5 Hz, 1H, NH), 8.08 (d, *J* = 8.5 Hz, 1H, NH), 7.54 (d, *J* = 2.0 Hz, 1H, ArH), 7.42 (d, *J* = 8.5 Hz, 1H, ArH), 7.23 (dd, *J* = 8.5, 2.0 Hz, 1H, ArH), 5.34 (t, *J* = 9.5 Hz, 1H, H-1^{GlcN}), 5.22 (t, *J* = 9.5 Hz, 1H, H-3^{GlcN}), 4.88 (t, *J* = 10.0 Hz, 1H, H-4^{GlcN}), 4.22 (dd, *J* = 12.5, 4.5 Hz, 1H, H-6a^{GlcN}), 4.06 − 3.93 (m, 3H, H-2^{GlcN}, H-5^{GlcN}, H-6b^{GlcN}), 2.00 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.73 (s, 3H, CH_3); ESI-HRMS (*m/z*): calcd for $C_{21}H_{24}BrN_3NaO_9$ $[M + Na]^+$: 564.0588; found: 564.0591.

2-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)amino-6-chloro-1,3-benzoxazole (5c): Light orange solid; yield 0.82 g (89%); m.p. 65–66 °C; IR (cm^{-1}): 3421, 1747, 1638, 1586, 1236, 1126, 1047, 918; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.07 (d, *J* = 9.5 Hz, 1H, NH), 8.08 (d, *J* = 9.0 Hz, 1H, NH), 7.63 (d, *J* = 2.0 Hz, 1H, ArH), 7.34 (d, *J* = 8.5 Hz, 1H, ArH), 7.23 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 5.33 (t, *J* = 9.5 Hz, 1H, H-1^{GlcN}), 5.22 (t, *J* = 10.0 Hz, 1H, H-3^{GlcN}), 4.88 (t, *J* = 10.0 Hz, 1H, H-4^{GlcN}), 4.22 (dd, *J* = 12.5, 4.5 Hz, 1H, H-6a^{GlcN}), 4.03 − 3.93 (m, 3H, H-2^{GlcN}, H-5^{GlcN}, H-6b^{GlcN}), 2.00 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.73 (s, 3H, CH_3); ESI-HRMS (*m/z*): calcd for $C_{21}H_{24}ClN_3NaO_9$ $[M + Na]^+$: 520.1093; found: 520.1090.

2-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)amino-5-chloro-1,3-benzoxazole (5d): Light yellow solid; yield 0.83 g (90%); m.p. 69–72 °C; IR (cm^{-1}): 3441, 1746, 1638, 1591, 1243, 1123, 1047, 921; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.12 (d, *J* = 9.0 Hz, 1H, NH), 8.08 (d, *J* = 9.0 Hz, 1H, NH), 7.46 (d, *J* = 8.5 Hz, 1H,

ArH), 7.42 (d, J=2.0 Hz, 1H, ArH), 7.10 (dd, J=8.5, 2.5 Hz, 1H, ArH), 5.34 (t, J=9.5 Hz, 1H, H-1^{GlcN}), 5.22 (t, J=10.0 Hz, 1H, H-3^{GlcN}), 4.88 (t, J=10.0 Hz, 1H, H-4^{GlcN}), 4.22 (dd, J=12.0, 4.0 Hz, 1H, H-6a^{GlcN}), 4.03−3.93 (m, 3H, H-2^{GlcN}, H-5^{GlcN}, H-6b^{GlcN}), 2.00 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.73 (s, 3H, CH_3); ESI-HRMS (*m/z*): calcd for $C_{21}H_{24}ClN_3NaO_9$ $[M+Na]^+$: 520.1093; found: 520.1091.

2-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)amino-6-methyl-1, 3-benzoxazole (5e): Light yellow solid; yield 0.81 g (92%); m.p. 62–64 °C; IR (cm^{-1}): 3415, 1748, 1638, 1585, 1244, 1113, 1044, 918; ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.75 (d, J=9.5 Hz, 1H, NH), 8.07 (d, J=9.0 Hz, 1H, NH), 7.25 (s, 1H, ArH), 7.21 (d, J=8.0 Hz, 1H, ArH), 6.99 (d, J=8.0 Hz, 1H, ArH), 5.33 (t, J=9.5 Hz, 1H, H-1^{GlcN}), 5.22 (t, J=10.0 Hz, 1H, H-3^{GlcN}), 4.88 (t, J=9.5 Hz, 1H, H-4^{GlcN}), 4.22 (dd, J=12.5, 8.0 Hz, 1H, H-6a^{GlcN}), 4.02−3.91 (m, 3H, H-2^{GlcN}, H-5^{GlcN}, H-6b^{GlcN}), 2.36 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.73 (s, 3H, CH_3); ESI-HRMS (*m/z*): calcd for $C_{22}H_{27}N_3NaO_9$ $[M+Na]^+$: 500.1640; found: 500.1637.

2-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)amino-4-methyl-1, 3-benzoxazole (5f): Light yellow solid; yield 0.80 g (91%); m.p. 68–71 °C; IR (cm^{-1}): 3419, 1748, 1639, 1591, 1243, 1125, 1045, 915; ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.78 (d, J=10.0 Hz, 1H, NH), 8.07 (d, J=9.0 Hz, 1H, NH), 7.24 (d, J=8.0 Hz, 1H, ArH), 7.00 (d, J=7.5 Hz, 1H, ArH), 6.96 (t, J=7.5 Hz, 1H, ArH), 5.36 (t, J=10.0 Hz, 1H, H-1^{GlcN}), 5.24 (t, J=10.0 Hz, 1H, H-3^{GlcN}), 4.88 (t, J=10.0 Hz, 1H, H-4^{GlcN}), 4.22 (dd, J=12.5, 4.5 Hz, 1H, H-6a^{GlcN}), 4.02−3.95 (m, 3H, H-2^{GlcN}, H-5^{GlcN}, H-6b^{GlcN}), 2.39 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.73 (s, 3H, CH_3); ESI-HRMS (*m/z*): calcd for $C_{22}H_{27}N_3NaO_9$ $[M+Na]^+$: 500.1640; found: 500.1636.

2-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)amino-5-methyl-1, 3-benzoxazole (5g): Light yellow solid; yield 0.80 g (91%); m.p. 68–70 °C; IR (cm^{-1}): 3416, 1748, 1639, 1591, 1243, 1127, 1045, 916; ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.79 (d, J=9.5 Hz, 1H, NH), 8.08 (d, J=9.0 Hz, 1H, NH), 7.29 (d, J=8.0 Hz, 1H, ArH), 7.15 (s, 1H, ArH), 6.87 (d, J=8.0 Hz, 1H, ArH), 5.34 (t, J=10.0 Hz, 1H, H-1^{GlcN}), 5.22 (t, J=10.0 Hz, 1H, H-3^{GlcN}), 4.88 (t, J=10.0 Hz, 1H, H-4^{GlcN}), 4.22 (dd, J=12.5, 4.0 Hz, 1H, H-6a^{GlcN}), 4.02−3.92 (m, 3H, H-2^{GlcN}, H-5^{GlcN}, H-6b^{GlcN}), 2.35 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.73 (s, 3H, CH_3); ESI-HRMS (*m/z*): calcd for $C_{22}H_{27}N_3NaO_9$ $[M+Na]^+$: 500.1640; found: 500.1637.

2-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)amino-7-methyl-1, 3-benzoxazole (5h): Light pink solid; yield 0.83 g (94%); m.p. 63–65 °C; IR (cm^{-1}): 3426, 1748, 1639, 1588, 1242, 1127, 1046, 913; ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.85 (d, J=9.5 Hz, 1H, NH), 8.07 (d, J=9.0 Hz, 1H, NH), 7.16 (d, J=8.0 Hz, 1H, ArH), 7.07 (t, J=7.5 Hz, 1H, ArH), 6.89 (d, J=7.5 Hz, 1H, ArH), 5.35 (t, J=10.0 Hz, 1H, H-1^{GlcN}), 5.23 (t, J=10.0 Hz, 1H, H-3^{GlcN}), 4.88 (t, J=10.0 Hz, 1H, H-4^{GlcN}), 4.22 (dd, J=12.5, 4.5 Hz, 1H, H-6a^{GlcN}), 4.02−3.92 (m, 3H, H-2^{GlcN}, H-5^{GlcN}, H-6b^{GlcN}), 2.38 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.73 (s, 3H, CH_3); ESI-HRMS (*m/z*): calcd for $C_{22}H_{27}N_3NaO_9$ $[M+Na]^+$: 500.1640; found: 500.1636.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Postgraduate Research and Practice Innovation Program of Jiangsu Province (KYCX19-2277, KYCX19-2281), the Open-End Funds of Jiangsu Key Laboratory of Marine Biotechnology (HS2014007), Project 521 funded by Lianyungang (LYG52105-2018023), a project funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD), and the Public Science and Technology Research Funds Projects of Ocean (201505023).

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