Molecules **2012**, *17*, 9887-9899; doi:10.3390/molecules17089887

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Article

Straightforward Synthesis of Novel 1-(2′-α-*O*-D-Glucopyranosyl ethyl) 2-Arylbenzimidazoles

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Received: 27 June 2012; in revised form: 27 July 2012 / Accepted: 13 August 2012 / Published: 17 August 2012

Abstract: A series of novel 1-(2′-α-*O*-D-glucopyranosyl ethyl) 2-arylbenzimidazoles has been prepared via one-pot glycosylation of ethyl-1-(2'-hydroxyethyl)-2-arylbenzimidazole-5-carboxylate derivatives. Synthesis of the 2-arylbenzimidazole aglycones from 4-fluoro-3-nitrobenzoic acid was accomplished in four high-yielding steps. The reduction and cyclocondensation steps for the aglycone synthesis proceeded efficiently under microwave irradiation to afford the appropriate benzimidazoles in excellent yields within 2–3 min. Glycosylation of the hydroxyethyl aglycones with the perbenzylated 1-hydroxy-glucopyranose, pretreated with the Appel-Lee reagent, followed by catalytic hydrogenolysis delivered the desired 1-(2′-α-*O*-D-glucopyranosyl ethyl) 2-aryl-benzimidazoles in a simple and straightforward manner.

Keywords: 2-arylbenzimidazole; microwave-assisted synthesis; α-glycoside; glycosylation; glycomimetic

1. Introduction

Carbohydrate-protein interactions on cell surfaces mediate important biological processes and disease states, including cancer metastasis, inflammation, pathogenicity and Alzheimer's disease [1–7]. Participating in such interactions are α-glycoside epitopes, found on bacteria, e.g., *Mycoplasma*, and on numerous mammalian oligosaccharides, for instance sialyl Lewis X (sLe^x). The synthesis of oligosaccharide ligands as potential inhibitors, however, remains laboriously demanding [8–10].

Alternatively, these oligosaccharides can be simplified by retaining functional groups essential for key binding interactions and replacing the unwanted parts with heterocyclic scaffolds. This simplification strategy has led to the emergence of pharmaceutically relevant glycomimetics as potent inhibitors against new carbohydrate-based disease targets [8,9,11,12]. In recent years, considerable synthetic efforts were devoted to the preparation of glycosyl-modified heterocycles as sLe^x glycomimetics designed to inhibit selectin involvement in cancer metastasis and inflammation [4,5,9,11]. Additionally, several pyranosyl benzothiazoles and benzimidazoles have been found to inhibit α-glycosidases and glycogen phosphorylases, which are promising targets for treatment of diabetes mellitus [13–16].

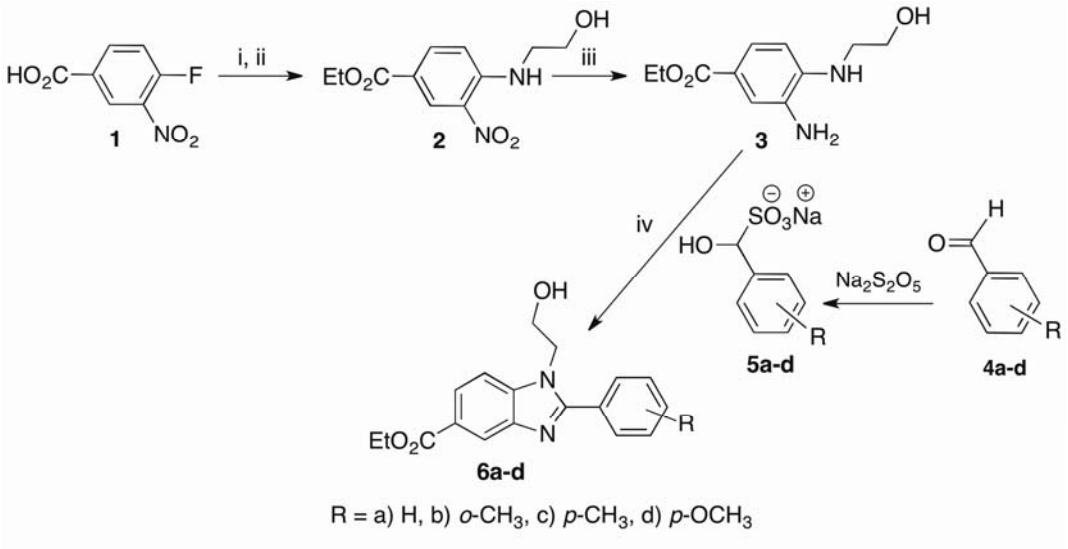
Benzimidazoles are important heterocycles in medicinal chemistry with established clinical examples including the proton pump inhibitor omeprazole [17] and the antihelmintic albendazole [18,19]. Additionally, 1,2-difunctionalised benzimidazoles have shown diverse biological activities as antagonists against prostaglandin D2 [20] and angiotensin II receptors [21]. They have been prepared as guanine biomimetics that selectively suppress angiogenesis *in vitro* and *in vivo* [22]. Due to their biological significance, we became interested in the synthesis of substituted 2-arylbenzimidazoles as potential anti-infective and anti-proliferative agents.

Recently, however, we encountered persistent problems with the solubility of such compounds during routine biological screening. To circumvent this solubility problem, we reasoned that by linking a sugar moiety to the 2-arylbenzimidazoles *via* a hydroxyethyl linker, not only could the sugar moiety modulate the solubility of the 2-arylbenzimidazoles, but it might also elicit novel pharmacological effects as an α-*O*-glycoside [12,23–25]. Furthermore, to the best of our knowledge, these α-*O*-glucosyl arylbenzimidazoles has not yet been reported. Thus, in this paper we describe, for the first time, a straightforward synthesis of novel 1-(2′-α-*O*-D-glucopyranosyl ethyl) 2-arylbenzimidazoles via one-pot glycosylation of hydroxyethyl arylbenzimidazole aglycones and 2,3,4,6-tetra-*O*-benzyl 1-hydroxylglucose employing the Appel-Lee reagent [26,27].

2. Results and Discussion

Our synthetic work started with esterification of the inexpensive precursor, 4-fluoro-3-nitrobenzoic acid (**1**). Treatment of the ester with 2-aminoethanol gave the amino intermediate **2**. Attempted reduction of the aromatic nitro group by refluxing with ammonium formate and 10% Pd/C for 3 h afforded the diamine **3** [28] in a modest 60% yield. After optimisation, microwave irradiation of the same reaction mixture at 100 °C for 2 min afforded **3** in a much improved 85% yield (Scheme 1).

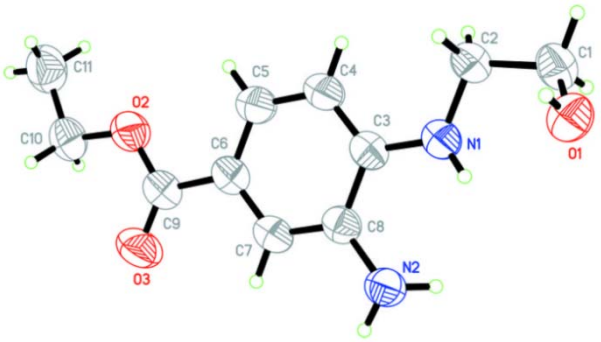
Scheme 1. Synthesis of benzimidazole aglycones **6a**–**d**.



Reagents and Conditions: (i) H_2SO_4/EtOH, reflux, 75%; (ii) 2-aminoethanol, DIPEA, RT, ON, 89%; (iii) $HCOONH_4$, Pd/C, MW, 2 min, 85%; (iv) MW, DMF, 2–3 min, 82–94%.

This diamine was found to be stable at room temperature, unlike other alkylated phenylenediamine derivatives that we had prepared previously; these turned brown and decomposed, even when stored at 5–10 °C. The stability of the amino derivative **3** was possibly due to intramolecular hydrogen bonding between the OH and NH_2 groups, as apparent from single X-ray crystallographic analysis (Figure 1) [28].

Figure 1. ORTEP digram of **3** (CCDC 788495).



Next we turned our attention to the synthesis of 2-arylbenzimidazoles **6a**–**d**. These are typically prepared via condensation reactions of phenylenediamines with the corresponding acids or aldehydes [29,30]. Harsh, dehydrating conditions are often a requisite in cyclocondensation reactions with aromatic acids. More facile condensations can be achieved via arylaldehydes by employing oxidative reagents, such as $Cu(OAc)_2$, air, 1,4-benzoquinone, I_2/KI and sodium metabisulfite [29,31–33]. After taking into consideration previous reports and the availability of commercial benzaldehydes, we initially attempted the cyclocondensation with the diamine **3**, aromatic aldehydes and sodium metabisulfite in one pot as reported by Navarrete-Vázquez *et al.* [33] under conventional heating conditions. The one-pot cyclocondensation failed to afford the benzimidazole products. Upon heating under microwave conditions, the same reaction gave multiple spots on TLC, but we were unable to isolate the desired benzimidazoles. Due to the unsuccessful attempts at the one-pot cyclocondensation

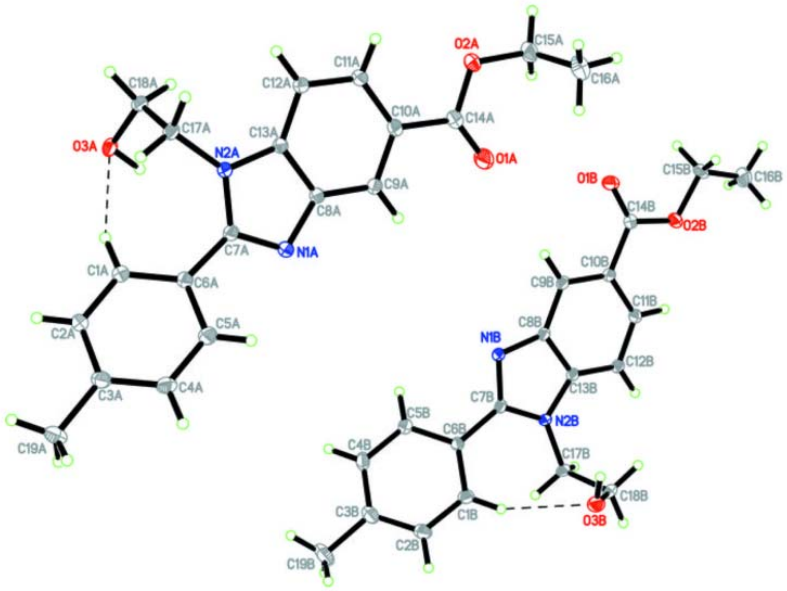
reaction, we then decided to react the diamine **3** with the metabisulfite adducts of arylaldehydes **5a**–**d** [33,34]. The conventional reaction conditions (refluxing in DMF) initially suffered from long reaction times and afforded only moderate yields of the desired benzimidazoles **6a**–**d**. When the same reactions were performed under optimised microwave conditions [33,35], the benzimidazole aglycones **6a**–**d** were obtained in excellent 82–94% yields within 2–3 min (Table 1) using minimal solvent (0.5–1 mL). Our results show that using microwaves as a heating source not only improves yields of the desired benzimidazoles, but it also brings about tremendous reductions in reaction times and the amount of solvent required.

Table 1. Influence of microwave irradiation and conventional heating on the synthesis of benzimidazole derivatives **6a**–**d**.

Entry	Products	R	Conventional heating		Microwave heating	
			Time (h)	Yield (%)	Time (min)	Yield (%)
1	**6a**	H	3.5	62	3	88
2	**6b**	o-CH_3	3	65	2.5	82
3	**6c**	*p*-CH_3	2.5	67	2	94
4	**6d**	*p*-OCH_3	3	60	2	89

The ^{1}H-NMR spectrum of benzimidazole **6c** showed the loss of the broad singlet NH_2 peak at δ 4.60–4.85, which corroborates with the formation of the imine (C=N) that resonated at δ 156.1 in the ^{13}C-NMR spectrum. High resolution mass spectrometry data revealed a peak at *m/z* = 325.1549 (M+H requires 325.1547), which corresponds to **6c**. Single crystal X-ray analysis [36] confirmed the structure of **2c** (Figure 2). Arylbenzimidazoles derivatives **6a**, **6b** and **6d** showed similar spectroscopic patterns.

Figure 2. ORTEP digram of **6c** (CCDC 786546).

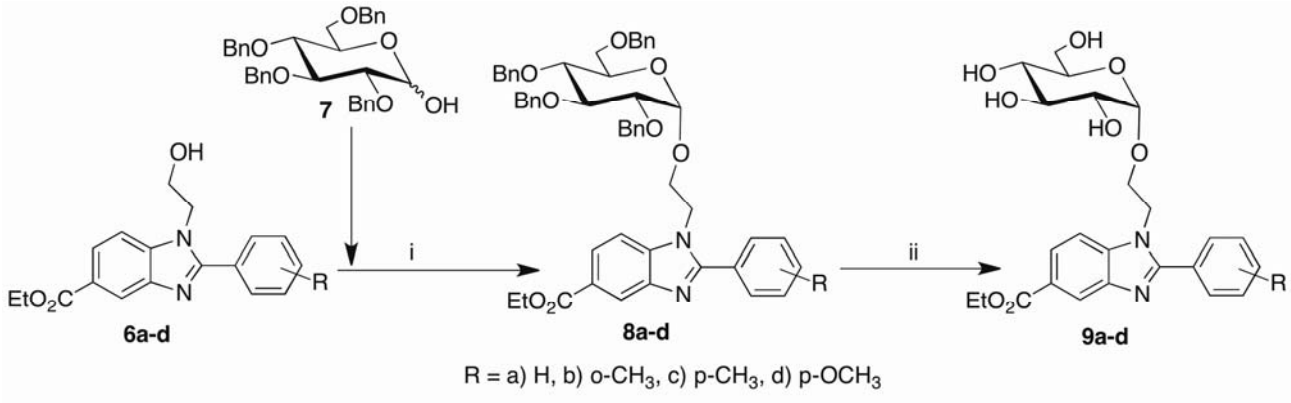


With the alcohols **6a**–**d** in hand, we next required a suitable glycosylation method to furnish the α-*O*-glycosyl benzimidazoles in a facile manner. Derivatives of α-*O*-glycosides can be accessed in a

number of ways [37,38], one of the most efficient being the established *in situ* anomerisation procedure which employs a 1-bromo sugar as the glycosyl donor. The tedious and costly preparation of glycosyl bromides coupled with the corrosive nature of HBr gas prompted the search for alternative methods to generate the desired bromides *in situ*. Several one-pot reactions were reported to furnish glucosyl [39], galactosyl [40] and fucosyl [41] intermediates in moderate to good yields. Recently, Shingu *et al*. described a practical one pot α-glycosylation method based on the Appel-Lee reaction utilizing PPh_3 and CBr_4 [23,42].

Motivated by these findings, we attempted the glycosylation of the alcohols **6a**–**d** by pre-treating commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**7**) with the Appel-Lee reagents for 3 h. This resulted in the *in situ* formation of glycosyl bromide, which underwent glycosylation with the alcohols **6a**–**d** after a further 24 h. This one-pot glycosylation step yielded the perbenzylated α-*O*-glucosyl benzimidazoles **8a**–**d** in 70–73% yields. Finally, catalytic hydrogenolysis step afforded the target hydroxyl sugars **9a**–**d** (Scheme 2).

Scheme 2. Synthesis of α-*O*-glucosyl benzimidazoles **9a**–**d**.



Reactions and Conditions: (i) CBr_4, PPh_3, CH_2Cl_2, 3 h, followed by DIPEA, 24 h, 70–73%; (ii) H_2, Pd/C, 48 h, 62–66%.

Via the optimised conditions, the glycosylated products were obtained as a mixture of α:β anomers (95:5), which is comparable to the ratios reported by Shingu [42]. The ^{1}H-NMR of the isolated anomer **8c** showed the α-proton appearing at δ 4.60 as a doublet (J = 3.3 Hz). This small J value strongly indicated the successful formation of the desired α-*O*-glycosidic linkage between the glucopyranoside moiety and 2'-hydroxyethyl 2-arylbenzimidazole scaffold. Further confirmation came from the ^{1}H-NMR spectrum and HRMS of the deprotected sugar **9c**. Absence of benzylic protons in **9c** revealed the characteristic α-proton (δ 4.61–4.68), and the HRMS showed the molecular peak at 487.2077 (M+H requires 487.2075) corresponding to the hydroxyl sugar **9c**. The structures of the remaining α-*O*-glucosylated arylbenzimidazole derivatives were established spectroscopically and corroborated with **8c** and **9c**.

3. Experimental

3.1. General

All ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker 300 and 400 MHz instruments in $CDCl_3$ and DMSO-d_6. High resolution mass spectrometry (HRMS) measurements of the benzimidazole derivatives were acquired on an Agilent 6520 Quadrupole Time of Flight Mass Spectrometer (Agilent Technologies, Santa Clara, CA, USA) operating in the MS mode. Microwave-assisted syntheses were performed in CEM Discover™ microwave synthesizer. Melting points were measured on a Stuart SMP10 instrument and are uncorrected. Preparative thin layer chromatography (PLC) was performed using Merck 60 GF_{254} silica gel coated (1 mm) on glass plates (20 × 20 cm). TLC experiments were performed on alumina-backed silica gel 40 F254 plates (Merck, Darmstadt, Germany). Visualisation of TLC plates was performed under UV light and aided by $KMnO_4$, iodine staining and 2% H_2SO_4 in EtOH (charcoal staining for sugar). All commercially available starting materials and solvents are from Sigma Aldrich, Acros and Merck; they were used without further purification.

Synthesis of ethyl 3-amino-4-(2-hydroxyethylamino)benzoate (**3**). A solution of 4-fluoro-3-nitrobenzoic (**1**, 10 g, 0.054 mol) was refluxed in EtOH (100 mL) and conc. H_2SO_4 (4 mL) for 8 h. After completion of reaction, evidenced by TLC analysis, the excess solvent was removed under reduced pressure. The aqueous layer was extracted with EtOAc (50 × 2 mL). Upon washing with 10% $NaHCO_3$ (100 mL), the combined organic layer was dried over Na_2SO_4 and concentrated. Crystallisation of the crude product with hot hexane yielded the desired ethyl ester as colourless crystals (8.6 g). A portion of the benzoate (2.0 g, 9.2 mmol) in dichloromethane (25 mL) was added to a solution of ethanolamine (0.687 g, 14.0 mmol) and DIPEA (1.45 g, ~2 mL, 11.2 mmol) in dichloromethane (25 mL). The reaction mixture was stirred overnight at room temperature, then washed with water (20 mL × 2) and 10% Na_2CO_3 (20 mL × 2). The dichloromethane layer was collected, dried over Na_2SO_4 and removed under reduced pressure to afford the amino compound **2** (2.07 g, 89%). The amine **2** was used in the next step without purification, thus to a solution of the amine **2** (500 mg, 1.96 mmol) in EtOH (4 mL) was added $HCOONH_4$ (430 mg, 6.82 mmol) and 10% Pd/C (250 mg, 2.34 mmol). The reaction mixture was irradiated using a CEM Discover™ microwave synthesizer for 2 min at 100 °C. After completion, the mixture was filtered through a bed of Celite and the filtrate evaporated under reduced pressure to afford the title product **3** as white crystals (0.45 g, 85%). Mp 116–118 °C; ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 1.26 (t, J = 6.3 Hz, CH_3, 3H), 3.16–3.21 (m, CH_2, 2H), 3.61–3.69 (m, CH_2, 2H), 4.18 (q, J = 7.2 Hz, OCH_2, 2H), 4.73 (br s, NH_2, 2H), 5.17–5.21 (m, NH, 1H), 6.46 (d, J = 8.1 Hz, 1H), 7.18–7.24 (m, 2H) ppm. ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 15.3, 46.3, 60.1, 60.3, 108.7, 117.7, 134.9, 141.5, 167.2 ppm. ESI-MS *m/z* 225.2 (M+1). CCDC 788495 contains the supplementary crystallographic data for structure **3**.

3.2. General Procedure for the Microwave-Assisted Synthesis of Benzimidazoles **6a–d**

The metabisulfite adduct **5** (2.0 eq.) was added to a solution of 3-amino-4-(2-hydroxyethylamino) benzoate (**3**, 1.0 eq.) in DMF (0.5–1 mL). The reaction mixture was heated under microwave conditions at 130 °C for 2 min. After completion, the mixture was diluted with EtOAc (10 mL) and

washed with H_2O (10 mL). The organic layer was collected, dried over Na_2SO_4 and evaporated *in vacuo* to yield a crude residue, which was recrystallised from EtOAc to afford the desired benzimidazole as colourless crystals.

Ethyl 2-phenyl-1-(2-hydroxyethyl)-1H-benzimidazole-5-carboxylate (**6a**). Colourless crystals (0.97 g, 88%). Mp 123–125 °C; IR (KBr) 3400, 1637, 1265, 740 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.46 (t, CH_3, 3H), 4.15–4.29 (m, $2CH_2$, 4H), 4.41 (q, CH_2, 2H), 6.05–6.18 (s, 1H), 7.20–7.84 (m, 8H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.8, 47.5, 60.7, 61.2, 110.0, 121.4, 124.3, 125.1, 128.8, 129.0, 130.2, 130.4, 138.3, 141.6, 156.1, 167.1 ppm. HRMS (ESI/Q-TOF): *m/z* calcd for $C_{18}H_{18}N_2O_3$ (M+H), 311.1390; found 311.1391.

Ethyl 1-(2-hydroxyethyl)-2-o-tolyl-1H-benzimidazole-5-carboxylate (**6b**). White crystals (0.35 g, 82%). Mp 119–121 °C; IR (KBr) 3398, 1641, 1273, 752 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.41 (t, CH_3, 3H), 2.12 (s, CH_3, 3H), 3.69 (t, J = 5.7 Hz, CH_2, 2H), 4.04 (t, J = 5.7 Hz, CH_2, 2H), 4.39 (q, CH_2, 2H), 7.17–7.42 (m, 5H), 7.92–7.95 (dd, J = 8.5, 1.6 Hz, 1H), 8.38 (d, J = 1.2 Hz, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.4, 19.6, 46.6, 60.3, 61.0, 110.2, 121.7, 124.2, 124.7, 125.7, 129.2, 130.1, 130.2, 130.5, 137.9, 138.0, 142.0, 155.3, 167.2 ppm. HRMS (ESI/Q-TOF): *m/z* calcd for $C_{19}H_{20}N_2O_3$ (M+H), 325.1547; found 325.1548.

Ethyl 1-(2-hydroxyethyl)-2-p-tolyl-1H-benzimidazole-5-carboxylate (**6c**). Colourless crystals (1.0 g, 94%). Mp 138–140 °C; IR (KBr) 3377, 1639, 1275, 749 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.47 (t, J = 7.2 Hz, CH_3, 3H), 2.38 (s, CH_3, 3H), 4.18–4.30 (m, $2CH_2$, 4H), 4.41 (q, J = 7.2 Hz, OCH_2, 2H), 6.25–6.40 (s, 1H), 7.00 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 8.7 Hz, 1H), 7.78 (s, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.8, 21.8, 47.5, 60.7, 61.2, 109.9, 121.2, 124.1, 125.0, 126.1, 129.4, 130.3, 138.3, 140.2, 141.5, 156.1, 167.0 ppm. HRMS (ESI/Q-TOF): *m/z* calcd for $C_{19}H_{20}N_2O_3$ (M+H), 325.1547; found 325.1549. CCDC 786546 contains the supplementary crystallographic data for structure **6c**.

Ethyl 1-(2-hydroxyethyl)-2-(4-methoxyphenyl)-1H-benzimidazole-5-carboxylate (**6d**). Colourless crystals (0.94 g, 89%). Mp 120–122 °C; IR (KBr) 3402, 1642, 1265, 740 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.47 (t, CH_3, 3H), 3.83 (s, OCH_3, 3H), 4.22–4.30 (m, $2CH_2$, 4H), 4.41 (q, CH_2, 2H), 6.71 (d, J = 9.0 Hz, 2H), 7.19 (d, J = 8.4 Hz, 1H), 7.67–7.73 (m, 4H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.9, 47.5, 55.6, 60.7, 61.2, 109.7, 114.1, 121.0, 121.2, 124.0, 125.0, 132.0, 138.1, 141.4, 156.0, 161.1, 167.0 ppm. HRMS (ESI/Q-TOF): *m/z* calcd for $C_{19}H_{20}N_2O_4$ (M+H), 341.1496; found 341.1499.

3.3. General Procedure for the Synthesis of 1-(2'-α-O-D-glucopyranosyl ethyl) 2-arylbenzimidazoles **8a–d**

A solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**7**, 1.0 eq.), PPh_3 (3.0 eq.) and CBr_4 (3.0 eq.) in CH_2Cl_2 (3 mL) was stirred for 3 h under N_2 atmosphere at room temperature. Upon completion of reaction as evidenced by TLC analysis, a solution of DIPEA (2.5 eq.) followed by substituted benzimidazole **6** (3.0 eq.) were added to the reaction mixture, which was stirred at room temperature under N_2 atmosphere for a further 24 h. The crude reaction mixture was purified by column chromatography using EtOAc-hexanes (3:7) to afford the product as a semi-solid.

Ethyl 1-[2'-α-O-D-(2,3,4,6-tetra-O-benzylglucopyranosyl)ethyl]-2-phenyl-1H-benzimidazole-5-carboxylate (**8a**). Isolated as low melting solid (0.27 g, 70%). IR (film) 3409, 1611, 1265, 740 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.44 (t, CH_3, 3H), 3.23–3.30 (m, H-2), 3.32–3.36 (m, H-4), 3.46–3.51 (m, CH_2, 2H), 3.54–3.60 (m, H-6_a), 3.68–3.73 (m, H-6_b), 3.76–3.82 (m, H-5), 3.98–4.06 (m, H-3), 4.37–4.41 (m, CH_2, 2H), 4.42–4.45 (m, CH_2, 2H), 4.59 (d, *J* = 3.3 Hz, H-1), 4.46–4.94 (m, $PhCH_2$, 8H), 7.11–8.59 (m, Ar-H, 28H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.3, 44.6, 60.8, 65.9, 68.2, 70.5, 73.3, 73.4, 74.7, 75.7, 76.6, 79.8, 81.7, 97.6, 110.2, 122.2, 124.4, 124.8, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 128.8, 129.1, 129.2, 129.8, 130.1, 138.2, 138.2, 142.6, 155.8, 167.0 ppm. HRMS (ESI/Q-TOF): *m/z* calcd for $C_{52}H_{52}N_2O_8$ (M+H), 833.3797; found 833.3799.

Ethyl 1-[2'-α-O-D-(2,3,4,6-tetra-O-benzylglucopyranosyl)ethyl]-2-o-tolyl-1H-benzimidazole-5-carboxylate (**8b**). Isolated as low melting solid (0.20 g, 73%). IR (film) 3408, 1621, 1266 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.41 (t, CH_3, 3H), 2.23 (s, CH_3, 3H), 3.23–3.30 (m, H-2), 3.35–3.39 (m, H-4), 3.45–3.49 (m, CH_2, 2H), 3.51–3.61 (m, H-6_a), 3.76–3.80 (m, H-6_b), 3.81–3.87 (m, H-5), 4.18–4.25 (m, H-3), 4.27–4.37 (m, CH_2, 2H), 4.38–4.44 (m, CH_2, 2H), 4.53 (d, *J* = 3.3 Hz, H-1), 4.46–4.97 (m, $PhCH_2$, 8H), 7.10–8.58 (m, 27H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.8, 20.1, 44.3, 61.2, 66.5, 68.7, 71.0, 73.7, 73.8, 75.2, 76.1, 80.2, 82.1, 98.1, 110.7, 122.7, 124.7, 125.3, 126.3, 128.0, 128.1, 128.2, 128.3, 128.4, 128.7, 128.8, 129.9, 130.6, 130.9, 138.1, 138.3, 138.5, 138.6, 139.1, 143.1, 155.6, 167.4 ppm. HRMS (ESI/Q-TOF): *m/z* calcd for $C_{53}H_{54}N_2O_8$ (M+H), 847.3953; found 847.3953.

Ethyl 1-[2'-α-O-D-(2,3,4,6-tetra-O-benzylglucopyranosyl)ethyl]-2-p-tolyl-1H-benzimidazole-5-carboxylate (**8c**). Isolated as low melting solid (0.17 g, 72%). IR (film) 3392, 1645, 1261, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.41 (t, *J* = 7.1 Hz, CH_3, 3H), 2.42 (s, CH_3, 3H), 3.24–3.31 (m, H-2, 1H), 3.32–3.38 (m, H-4, 1H), 3.47–3.50 (m, CH_2, 2H), 3.51–3.55 (m, H-6_a, 1H), 3.65–3.73 (m, H-6_b, 1H), 3.75–3.82 (m, H-5, 1H), 3.98–4.05 (m, H-3, 1H), 4.37–4.39 (m, CH_2, 2H), 4.40–4.44 (m, CH_2, 2H), 4.60 (d, *J* = 3.3 Hz, H-1, 1H), 4.45–4.94 (m, $PhCH_2$, 8H), 7.10–7.35 (m, Ar-H, 22H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 8.04–8.08 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.57 (d, *J* = 1.5 Hz, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.8, 21.9, 45.0, 61.3, 66.4, 68.6, 70.9, 73.6, 73.7, 73.8, 75.2, 76.1, 80.2, 82.1, 98.0, 110.6, 122.6, 124.7, 125.5, 127.2, 128.0, 128.1, 128.2, 128.3, 128.4, 128.7, 128.8, 129.9, 130.0, 138.1, 138.3, 138.6, 139.1, 139.3, 140.7, 143.0, 156.4, 167.5 ppm. HRMS (ESI/Q-TOF): *m/z* calcd for $C_{53}H_{54}N_2O_8$ (M+H), 847.3953; found 847.3953.

Ethyl 1-[2'-α-O-D-(2,3,4,6-tetra-O-benzylglucopyranosyl)ethyl]-2-p-methoxyphenyl-1H-benzimidazole-5-carboxylate (**8d**). Isolated as low melting solid (0.28 g, 71%). IR (film) 3421, 1630, 1265, 740 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.40 (t, CH_3, 3H), 3.24–3.30 (m, H-2), 3.32–3.36 (m, H-4), 3.46–3.48 (m, CH_2, 2H), 3.49–3.54 (m, H-6_a), 3.70–3.78 (m, H-6_b), 3.81 (s, OCH_3, 3H), 3.82–3.84 (m, H-5), 3.98–4.04 (m, H-3), 4.35–4.39 (m, CH_2, 2H), 4.40–4.43 (m, CH_2, 2H), 4.60 (d, *J* = 3.6 Hz, H-1), 4.46–4.92 (m, $PhCH_2$, 8H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.10–7.33 (m, 20H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 9 Hz, 2H), 8.01–8.05 (dd, *J* = 1.5, 8.4 Hz, 1H), 8.54 (d, *J* = 1.5 Hz, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.8, 45.0, 55.7, 61.2, 66.3, 68.6, 70.9, 73.7, 73.8, 75.2, 76.1, 80.3, 82.2, 98.0, 110.4, 114.7, 122.4, 124.6, 125.5, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.7, 128.8, 131.7, 138.1,

138.6, 139.1, 139.4, 143.0, 156.2, 161.5, 167.5 ppm. HRMS (ESI/Q-TOF): *m/z* calcd for $C_{19}H_{20}N_2O_3$ (M+H), 863.3902; found 863.3901.

3.4. General Procedure for the Catalytic Hydrogenolysis

A solution of perbenzylated glucopyranosyl arylbenzimidazole **8** (200 mg, 0.23 mmol) in MeOH (10 mL) was hydrogenated in the presence of 10% Pd/C (100 mg, 0.93 mmol) at room temperature for 48 h. The reaction mixture was filtered through a bed of Celite and washed with MeOH (10 mL × 3). The solvent was removed *in vacuo* to afford a crude residue which was purified by column chromatography in $CHCl_3$–MeOH (9:1) to give the desired product as a light yellow semisolid.

Ethyl 1-[2'-α-O-D-glucopyranosyl ethyl]-2-phenyl-1H-benzimidazole-5-carboxylate (**9a**). Isolated as light yellow semisolid (0.14 g, 62%). IR (film) 3411, 1635, 1275, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.34 (t, CH_3, 3H), 2.64 (d, *J* = 9.3 Hz, H-4), 3.15 (d, *J* = 8.1 Hz, H-2), 3.24–3.30 (m, CH_2, 2H), 3.34–3.38 (m, H-3), 3.39–3.42 (m, H-5), 3.69–3.77 (m, H-6_a), 3.93–4.03 (m, H-6_b), 4.29 (q, CH_2, 2H), 4.33–4.49 (m, CH_2, 2H), 4.57–4.64 (m, H-1), 7.37–7.51 (m, 4H), 7.75–7.76 (m, 2H), 7.92–7.94 (m, 1H), 8.43 (s, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.7, 44.8, 60.9, 61.5, 65.6, 69.3, 71.8, 72.2, 74.1, 99.0, 110.7, 122.3, 124.8, 125.4, 129.3, 129.7, 130.1, 130.7, 139.0, 142.5, 156.4, 167.6 ppm. HRMS (ESI/Q-TOF): *m/z* calcd for $C_{24}H_{28}N_2O_8$ (M+H), 473.1919; found 473.1919.

Ethyl 1-[2'-α-O-D-glucopyranosyl ethyl]-2-o-tolyl-1H-benzimidazole-5-carboxylate (**9b**). Isolated as pale yellow semisolid (0.11 g, 66%). IR (film) 3404, 1635, 1265, 744 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, CH_3, 3H), 2.16 (s, CH_3, 3H), 2.71 (d, *J* = 9.3 Hz, H-4), 3.22–3.26 (m, H-2), 3.27–3.30 (m, CH_2, 2H), 3.41–3.43 (m, H-3), 3.44–3.51 (m, H-5), 3.58–3.62 (m, H-6_a), 3.80–3.91 (m, H-6_b), 4.18–4.28 (m, CH_2, 2H) 4.34 (q, CH_2, 2H), 4.60 (d, *J* = 2.7 Hz, H-1), 7.31–7.39 (m, 3H), 7.50–7.57 (m, 2H), 7.98–8.02 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.47 (d, *J* = 1.2 Hz, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.7, 20.0, 44.3, 61.2, 61.4, 66.2, 69.6, 71.9, 72.2, 74.1, 99.1, 110.9, 122.4, 124.8, 125.3, 126.5, 129.4, 130.8, 131.0, 138.1, 138.5, 142.5, 155.8, 167.8 ppm. HRMS (ESI/Q-TOF): *m/z* calcd for $C_{25}H_{30}N_2O_8$ (M+H), 487.2075; found 487.2079.

Ethyl 1-[2'-α-O-D-glucopyranosyl ethyl]-2-p-tolyl-1H-benzimidazole-5-carboxylate (**9c**). Isolated as pale yellow semisolid (0.10 g, 65%). IR (film) 3411, 1608, 1420, 1265, 740 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.36 (t, *J* = 7.2 Hz, CH_3, 3H), 2.32 (s, CH_3, 3H), 2.62 (d, *J* = 9.2 Hz, H-4), 3.17 (d, *J* = 11.2 Hz, H-2), 3.26–3.35 (m, CH_2, 2H), 3.36–3.40 (m, H-3), 3.41–3.47 (m, H-5), 3.71–3.73 (m, H-6_a), 3.95–4.03 (m, H-6_b), 4.31 (q, *J* = 7.2 Hz, CH_2, 2H), 4.37–4.43 (m, CH_2, 1H), 4.47–4.57 (m, CH_2, 1H), 4.61–4.68 (m, H-1), 7.25–7.28 (m, 2H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 1H), 8.42 (s, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.7, 21.8, 44.8, 60.9, 61.5, 65.6, 69.4, 71.8, 72.2, 74.2, 99.0, 110.7, 122.2, 124.8, 125.4, 126.7, 130.0, 139.1, 141.0, 142.4, 156.6, 167.7 ppm. HRMS (ESI/Q-TOF): *m/z* calcd for $C_{25}H_{30}N_2O_8$ (M+H), 487.2075; found 487.2077.

Ethyl 1-[2'-α-O-D-glucopyranosyl ethyl]-2-p-methoxyphenyl-1H-benzimidazole-5-carboxylate (**9d**). Isolated as light yellow semisolid (0.06 g, 64%). IR (film) 3402, 1616, 1265, 747 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.35 (t, CH_3, 3H), 2.61 (d, *J* = 9.0 Hz, H-4), 3.13 (d, *J* = 10.5 Hz, H-2),

3.21–3.30 (m, CH_2, 2H), 3.33–3.37 (m, H-3), 3.38–3.46 (m, H-5), 3.72 (s, OCH_3, 3H), 3.73–3.79 (m, H-6_a), 3.94–4.08 (m, H-6_b), 4.30 (q, CH_2, 2H), 4.38–4.57 (m, CH_2, 2H), 4.59–4.64 (m, H-1), 6.95 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8.4 Hz, 1H), 8.39 (s, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.7, 44.8, 55.7, 60.8, 61.4, 65.5, 69.3, 71.8, 72.2, 74.1, 99.0, 110.5, 114.8, 121.8, 122.0, 124.6, 125.3, 131.6, 139.0, 142.4, 156.4, 161.4, 167.7 ppm. HRMS (ESI/Q-TOF): *m/z* calcd for $C_{25}H_{30}N_2O_9$ (M+H), 503.2024; found 503.2025.

4. Conclusions

We have described a simple and straightforward synthesis of a series of novel α-*O*-glucopyranosyl arylbenzimidazoles using the Appel-Lee reagents. The synthesis of the glycosyl acceptors, 2-arylbenzimidazoles **6a**–**d**, was accomplished in four, high-yielding steps from the inexpensive precursor 4-fluoro-3-nitrobenzoic acid. Optimised microwave conditions for the reduction and cyclocondensation steps afforded the 2-arylbenzimidazole aglycones in high yields (82%–94%) and short reaction times (2–3 min) using reduced amount of solvent. This facile approach would allow rapid preparation of similar glycosylated benzimidazoles, which will be further investigated under both conventional and microwave conditions. Bioactivity studies of these glycosyl benzimidazoles will be reported in due course.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/17/8/9887/s1.

Acknowledgments

This work was funded by Universiti Sains Malaysia, RU Grant 1001/PFARMASI/815026, Ministry of Science, Technology and Innovation (MOSTI) under the R&D initiative Grant No: 09-05-lfn-meb-004, and Ministry of Higher Education (MoHE), 203/PFARMASI/671159. We are grateful to Mohd Nazri Ismail and Michael Harvey at Universiti Sains Malaysia (USM) Doping Control Centre for helpful technical discussions and assistance in providing the HRMS analysis. N.A. thanks USM for the award of postdoctoral research fellowship.

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Sample Availability: Samples of the compounds **8a**–**d** and **9a**–**d** are available from the authors.