



Synthesis of substituted 2-(β -D-glucopyranosyl)-benzimidazoles and their evaluation as inhibitors of glycogen phosphorylase



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ABSTRACT

Microwave assisted condensation of O-perbenzoylated C-(β -D-glucopyranosyl)formic acid with 1,2-diaminobenzenes in the presence of triphenylphosphite gave the corresponding O-protected 2-(β -D-glucopyranosyl)-benzimidazoles in moderate yields. O-Perbenzoylated C-(β -D-glucopyranosyl)formamide and -thioformamide were transformed into the corresponding ethyl C-(β -D-glucopyranosyl)formimide and -thioformimide, respectively, by Et₃O-BF₄. Treatment of the formimide with 1,2-diaminobenzenes afforded O-protected 2-(β -D-glucopyranosyl)-benzimidazoles in good to excellent yields. Similar reaction of the thioformimide gave these compounds in lower yields. The O-benzoyl protecting groups were removed by the Zemplén protocol. These test compounds were assayed against rabbit muscle glycogen phosphorylase (GP) *b*, the prototype of liver GP, the rate limiting enzyme of glycogen degradation. The best inhibitors were 2-(β -D-glucopyranosyl)-4-methyl-benzimidazole (K_i = 2.8 μ M) and 2-(β -D-glucopyranosyl)-naphtho[2,3-*d*]imidazole (K_i = 2.1 μ M) exhibiting a \sim 3–4 times stronger binding than the unsubstituted parent compound.

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1. Introduction

Inhibition of glycogen phosphorylase (GP) has been considered as an effective therapeutic approach in combating type 2 diabetes (for the biochemical and pharmacological background of targeting liver GP as a validated concept for lowering blood glucose levels, please survey recent review articles^{1–6}). Furthermore, the pharmaceutical utility of GP inhibitors in the intervention of other diseased states associated with GP activity (e.g., cardiovascular disorders,^{7–9} ischaemic lesions,^{10–13} and tumorous growth^{11,14–16}) has also been under investigation.

A large array of compounds were shown to have an inhibitory effect against this enzyme^{17–19} including glucose derivatives^{20,21} which primarily bind to the catalytic site of the enzyme. In the course of searching for potent glucose based inhibitors, several C- β -D-glucopyranosyl heterocycles (Chart 1), such as tetrazole²² **1A**, 1,3,4-oxadiazoles^{22–24} **1B**, 1,2,4-oxadiazoles^{23,25,26} **1C,D**, benzothiazole²² **1E** and benzimidazole²² **1F** have been synthesized and some of them proved to be efficient against rabbit muscle glycogen phosphorylase *b* (RMGP*b*, the prototype of GP enzymes for enzymatic tests²). In this class, 2-(β -D-glucopyranosyl)-benzimidazole (**1F**) was the first compound to have a K_i value in the low micromolar range.^{22,27} As evidenced by X-ray crystallography, the strong binding in the catalytic centre is the result of direct and water

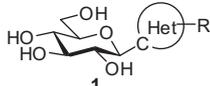
mediated H-bonds between the protein and the heteroaromatic ring, and van der Waals interactions of the large aromatic part in the so-called β -channel of the enzyme.²⁷ The higher affinity of **1F** in comparison with its thio counterpart **1E** can be attributed to the direct H-bond of the imidazole NH with the His377 main chain carbonyl group of the enzyme which is certainly absent for benzothiazole **1E**.²⁷ Analogous NH-(His377)CO interactions were identified in other GP enzyme-inhibitor complexes (e.g., in cases of spiro(thio)hydantoin^{28,29} and *N*-acyl- β -D-glucopyranosylamine type inhibitors³⁰) indicating the prominent importance of this special H-bridge, as well. Additionally, X-ray crystallographic investigation of **1F** in complex with RMGP*b* revealed that besides the active site the compound also occupied the new allosteric site, and a new binding cleft called the benzimidazole site was also discovered.²⁷

To get an insight into the structure–activity relationship of this type of inhibitors the aim of our present work has been to synthesize a series of substituted 2-(β -D-glucopyranosyl)-benzimidazoles and to evaluate their effect on RMGP*b*.

For the formation of 2-C-glycosyl-benzimidazoles several synthetic methods are known from the literature most of which have been described for furanose based derivatives. Furanosyl benzimidazoles were prepared (a) by acid catalysed condensation of C-glycofuranosyl formic acids and *o*-phenylenediamine (OPD),^{31,32} (b) by coupling of C-glycofuranosyl formic acids or their chlorides with 1,2-diaminobenzenes, followed by acid or POCl₃ mediated ring closure of the resulting amide type intermediates,^{33,34} (c) in the reaction of C-glycofuranosyl formaldoximoyl chlorides (actually

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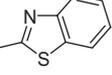
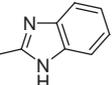
	Het	R	K_i [μM]
A		-	No inhibition ²²
B		CH ₃	145 ²⁷ 212 ²²
		2-naphthyl	10 % at 625 μM ²³
C		2-naphthyl	38 ²⁵
D		2-naphthyl	2.4 ²³
E		-	76 ²⁷ 229 ²²
F		-	8.6 ²⁷ 11 ²²

Chart 1. Inhibitory potency (K_i) of C-glucosyl heterocyclic derivatives against rabbit muscle glycogen phosphorylase b (RMGPb).

the nitrile oxide obtained by base induced dehydrochlorination) with OPD,³⁵ (d) by intramolecular ring closure of suitably protected 2-(pentitol-1'-yl)-benzimidazoles obtained from 2-lithiated benzimidazoles and sugar lactone or acyclic pentose derivatives,^{36–38} and (e) by acid induced cyclodehydration of unprotected 2-(tetritol-1'-yl)-benzimidazoles.³⁹

For the synthesis of 2-C-glycopyranosyl-benzimidazoles three procedures were reported: (a) acid catalysed condensation of unprotected C-glycopyranosylmethanals (generated in situ from the appropriate dimethyl acetals) with OPD, followed by spontaneous oxidation of the intermediate benzimidazolines,⁴⁰ (b) reaction of O-perbenzoylated ethyl C-(β -D-glucopyranosyl)thioformimidate hydrochloride (prepared from the corresponding glycosyl cyanide) with OPD,²² and (c) treatment of O-peracetylated C-glycopyranosyl formaldoximoyl chlorides with OPD.⁴¹ In addition, a 2-benzimidazolyl moiety was also attached to C-1 of D-galactal in the reaction of methyl C-(2-deoxy-D-lyxo-hex-1-enopyranosyl)formimidate and the dihydrochloride salt of OPD.⁴²

In this paper, we disclose further synthetic possibilities to construct benzimidazole at the anomeric centre of the pyranose unit.

2. Results and discussion

2.1. Syntheses

C-(β -D-Glucopyranosyl)formic acid **5**, prepared from cyanide **2** via amide **3**⁴³ by the literature protocol⁴⁴ (Table 1), was reacted with 1,2-diaminobenzenes (**a**, **f**, **h**) in the presence of triphenylphosphite in pyridine under microwave irradiation (conditions were adapted from a published procedure applied for non-sugar based compounds⁴⁵). Although the conversions were complete at 140 °C in 20 min, the desired products could be isolated only in moderate yields (**8a**: 45%, **8f**: 53%, **8h**: 43%). Nevertheless, it has to be noted, that earlier attempts to transform **5** into benzimidazole **8a** by the classical acid catalysed procedure with conventional heating brought about no reaction even at elevated temperatures.²² Therefore, application of the more reactive imino-

esters **6** and **7** was envisaged for the construction of benzimidazoles.

Previously, hydrochloride salt of O-perbenzoylated ethyl C-(β -D-glucopyranosyl)thioformimidate obtained from glucopyranosyl cyanide **2** by an acid catalysed addition of EtSH to the nitrile group was used for this purpose.²² Since these conditions were rather unpleasant and subsequent transformation of the salt gave benzimidazole **8a** in a 34% yield only, we set out to produce and use the free form of this type of precursor. Free thioimide **7** was obtained from thioamide **4** by Et₃O·BF₄. The preparation of **4**⁴⁶ was also modified to avoid the use of H₂S; thus, cyanide **2** was reacted with P₄S₁₀ in refluxing EtOH as described for the synthesis of aliphatic and aromatic thioamides.⁴⁷ Similarly to **7**, imidate **6** was obtained from amide **3** by Et₃O·BF₄.

Next, the preparation of benzimidazole **8a** from either **6** or **7** was compared in preliminary experiments. Reaction of **6** or **7** with OPD gave **8a** in 89% and 62% yields, respectively. Therefore, also taking into account the instability of **7** (decomposition was observed on storage at rt after a few days), further reactions to get the desired benzimidazoles were performed with **6**.

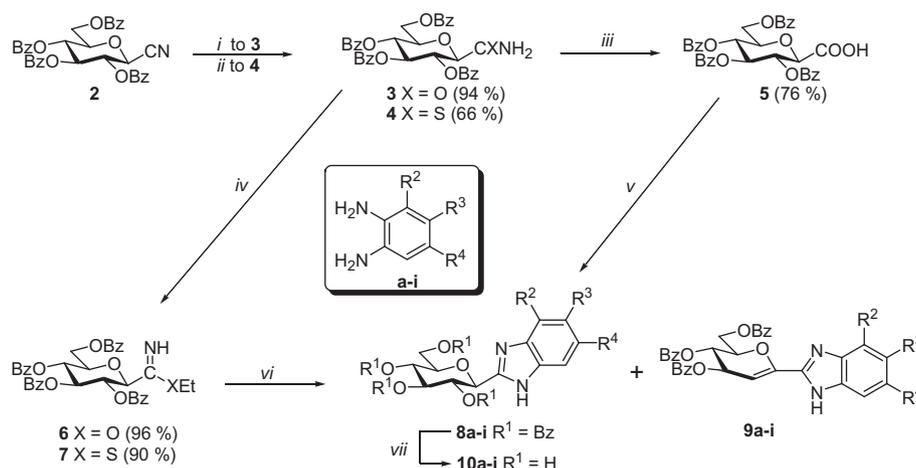
Similarly to **8a**, high yields were also achieved in reactions of **6** with methyl-substituted 1,2-diaminobenzenes **f–h** and 2,3-diaminonaphthalene **i**, respectively (Table 1). A comparison of the yields for **8a,f,h** obtained from acid **5** under conditions v and from imidate **6** under conditions vi, respectively, showed the ring closure of **6** with 1,2-diaminobenzenes to be superior to that of **5**.

On treatment of imidate **6** with 1,2-diaminobenzenes containing electron withdrawing substituents (**b–e**) benzoic acid elimination was also observed, and beside the 2-glucopyranosyl benzimidazoles **8b–e** 4-substituted-2-(3',4',6'-tri-O-benzoyl-2'-deoxy-D-arabino-hex-1-enopyranosyl)-benzimidazoles (1-C-benzimidazolyl glucals, **9b–e**) were also isolated. Furthermore, total consumption of the starting material **6** in reaction with 4-nitro-1,2-diaminobenzene (**e**) required higher temperature, thus cyclization was performed in boiling ethanol to yield benzimidazole **8e** together with **9e**. This tendency for elimination might be attributed to an increased acidity of the C-1-H proton in the 2-glucosyl-benzimidazoles probably due to the presence of the electron withdrawing substituent in the aromatic ring system.

For enzymatic studies removal of the benzoyl protecting groups of **8b–i** was effected by the Zemplén method to give test compounds **10b–i** in good yields.

The structure of the new compounds was determined by ¹H and ¹³C NMR spectroscopy. The presence of a β -D-configured glucopyranosyl moiety in the ⁴C₁ conformation was confirmed by the vicinal proton–proton coupling constants for compounds **6**, **7**, **8b–i** and **10b–i**, respectively. In the ¹H NMR spectra of 1-C-hetaryl glucals **9b–e** the observed small couplings between the vicinal ring protons (3–6 Hz) suggested a conformational change of the pyranose ring (from chair to half chair).⁴⁸ In the ¹³C NMR spectra of **9b–e** characteristic resonances appeared for C-1' (143–145 ppm) and C-2' (99–101 ppm) providing evidence for the unsaturated nature of the pyranoid ring.⁴⁸ Among ¹³C NMR signals of the benzimidazole units only those for C-2 appeared as sharp peaks at 146–158 ppm, the others usually gave broad signals. These observations are in accord with the literature experiences,^{35,41} and may be explained by the rapid proton exchange between N-1 and N-3 of the benzimidazole moiety.^{35,41,49} Additionally, in the ¹³C NMR spectra duplication of certain carbon peaks was also observed (primarily for the benzimidazole carbon signals for example, in **8b**, **9c**, **9e** and **10b**), which may refer to the coexistence of the tautomeric pairs. For the fluoro-benzimidazole **8b** this phenomenon seemed quite clear as 14 resonances were observed in the ¹³C NMR spectrum which could be tentatively assigned on the basis of the characteristic C–F couplings⁵⁰ as illustrated in Figure 1.

Table 1
Synthesis of 2-(β -D-glucopyranosyl)-benzimidazoles



i) HBr-AcOH, rt;⁴³ ii) P₄S₁₀, abs. EtOH, reflux; iii) NO₂, abs. CH₂Cl₂, rt;⁴⁴ iv) Et₃O-BF₄, abs. CH₂Cl₂,

Ar, rt; v) P(OPh)₃ (1.2 equiv.), **a** or **f** or **h** (1.0 equiv), abs. pyridine, μ W, 140 °C, 20 min; vi) **a-i** (2

equiv.), abs. CH₂Cl₂, reflux; vii) ~1 M NaOMe in abs. MeOH, rt.

Reagent	R ²	R ³	R ⁴	Conditions and yields (%)				
				8	9	10		
a	H	H	H	v	45	—	vii	— ^{c,d}
				vi	89 (from 6)	—		
				vi	62 ^a (from 7)	—		
b	H	F	H	vi	46	35	vii	54
c	H	Cl	H	vi	76	24	vii	89
d	H	Br	H	vi	54	29	vii	58
e	H	NO ₂	H	vi ^b	46	20	vii	53
f	H	Me	H	v	53	—	vii	87
				vi	83	—		
g	Me	H	H	vi	79	—	vii	73
h	H	Me	Me	v	43	—	vii	78
				vi	81	—		
i	H			vi	79	—	vii	77

^a Reported yield of **8a** by the earlier method from perbenzoylated β -D-glucopyranosyl cyanide via the thioimide hydrochloride salt: 34%.²²

^b Modified reaction conditions were necessary for complete consumption of the starting material **6**: abs. EtOH, reflux.

^c Debenzoylation of **8a** by the Zemplén protocol was carried out earlier. Reported yield of **10a**: 84%.²²

^d Reported yield of **10a** by a different method: 54%.⁴⁰

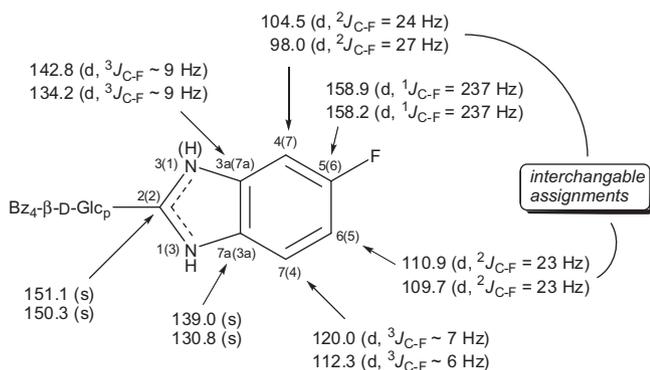


Figure 1. Tentative assignment of ¹³C NMR signals for tautomers of compound **8b**.

2.2. Enzyme kinetic studies

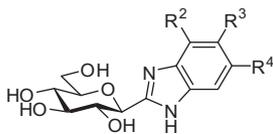
Enzyme kinetic measurements with rabbit muscle glycogen phosphorylase *b* were performed as described previously,^{51,52}

and the obtained inhibitor constants are given in Table 2. The new compounds showed inhibitory effects in the micromolar range and some of them proved equivalent or somewhat better inhibitors than **10a** (= **1F** in Chart 1).

Among benzimidazoles with a halogen substituent in the 5-position fluoro derivative **10b** exhibited modest activity, while the chloro (**10c**) as well as bromo (**10d**) compounds were as good inhibitors as **10a**. Substitution of the benzimidazole ring in the same position by a nitro group (**10e**) brought about a significant decrease of the inhibition. Among the alkyl substituted derivatives the 5-methyl- (**10f**) and 4-methyl-benzimidazoles (**10g**) displayed similar and slightly better (~3-fold increase) potency than **10a**, respectively. However, introduction of two methyl groups into the 5- and 6-positions of the heterocycle (**10h**) resulted in a remarkable weakening of the inhibition. Finally, the naphtho[2,3-*d*]imidazole **10i** showed ~4 times stronger binding than **10a** and proved to be the most effective inhibitor of this series. To elucidate the nature of the binding modes of the new compounds to GP enzyme X-ray crystallographic studies are in progress and will be reported elsewhere.

Table 2

Kinetic data on the inhibition of rabbit muscle glycogen phosphorylase *b* by the new compounds **10b–i**



10	R ²	R ³	R ⁴	K _i (μM)
a	H	H	H	8.6 ²⁷ 11 ²²
b	H	F	H	55
c	H	Cl	H	9.7
d	H	Br	H	7.5
e	H	NO ₂	H	179
f	H	Me	H	12
g	Me	H	H	2.8
h	H	Me	Me	152
i	H			2.1

3. Conclusion

New synthetic pathways were elaborated for the formation of substituted 2-(β-D-glucopyranosyl)-benzimidazoles by heterocyclizations of 2,6-anhydro-aldehydic acid derivatives as precursors. Condensation of *O*-perbenzoylated *C*-(β-D-glucopyranosyl)formic acid with 1,2-diaminobenzenes in the presence of P(OPh)₃ under microwave irradiation gave the desired benzimidazoles in moderate yields. Ring closure of *O*-perbenzoylated ethyl *C*-(β-D-glucopyranosyl)formimidate, prepared from the corresponding formamide by Et₃O·BF₄, with the 1,2-diaminobenzenes afforded a more efficient procedure. With electron depleted aromatic diamines undesirable β-elimination of benzoic acid from the 1,2-positions of the glucopyranosyl moiety also took place to yield 1-*C*-benzimidazolyl glucals besides the target compounds. Enzyme kinetic studies with the new 2-(β-D-glucopyranosyl)-benzimidazoles showed the compounds to inhibit RMGPb in the low micromolar range. Substitution of the benzimidazole moiety by a methyl group in the 4-position or further annelation of a benzene ring provided more efficient inhibitors than the unsubstituted parent compound.

4. Experimental

4.1. General methods

Melting points were measured on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at rt. NMR spectra were recorded with Bruker 360 (360/90 MHz for ¹H/¹³C) spectrometer. Chemical shifts are referenced to Me₄Si (¹H), or to the residual solvent signals (¹³C). Microwave assisted procedures were performed in a CEM-Discover Focused Microwave Synthesis System (2450 MHz) with a built-in infrared temperature sensor and a CEM-Explorer computer controlled robotic sampler.

TLC was performed on DC-Alurolle Kieselgel 60 F₂₅₄ (Merck), and the plates were visualized under UV light and by gentle heating. For column chromatography Kieselgel 60 (Merck, particle size 0.063–0.200 mm) was used. Dichloromethane was distilled from P₄O₁₀ and stored over 4 Å molecular sieves. 2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl cyanide,⁴³ *C*-(2,3,4,6-tetra-*O*-benzoyl-

β-D-glucopyranosyl)formamide⁴³ and *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formic acid⁴⁴ were synthesized according to published procedures.

4.2. *C*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-thioformamide (**4**)

A solution of phosphorus pentasulfide (2.23 g, 10 mmol) in anhydrous EtOH (20 mL) was stirred at rt for 1.5 h, then 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl cyanide⁴³ (**2**, 3.02 g, 5 mmol) was added and the mixture was heated at reflux temperature for 2 h. After cooling the heterogenous mixture to rt, the precipitate was filtered off and washed with EtOH to yield 2.1 g (66%) of **4** as a pale yellowish solid. Mp: 199–201 °C (Lit.⁴⁶ mp: 198–200 °C). ¹H and ¹³C NMR data correspond to the reported spectra.⁴⁶

4.3. Ethyl *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-formimidate (**6**)

C-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)formamide⁴³ (**3**, 1.0 g, 1.60 mmol) and Et₃O·BF₄ (0.91 g, 4.80 mmol) were dissolved in anhydrous CH₂Cl₂ (15 mL), the mixture was stirred at rt under Ar and monitored by TLC (1:1 EtOAc–hexane). After completion of the reaction (2 days), the mixture was diluted with CH₂Cl₂ (30 mL), extracted with satd aq NaHCO₃ solution (30 mL) and then with water (30 mL). The organic phase was dried over MgSO₄, filtered and the solvent was evaporated. The crude pale yellow amorphous product (1.0 g, 96%) was used without further purification. *R*_f: 0.55 (1:1 EtOAc–hexane); ¹H NMR (CDCl₃) δ (ppm): 8.06–7.25 (21H, m, aromatics, NH), 5.99, 5.72, 5.55 (3 × 1H, 3 pseudo t, *J* = 10.6, 9.2 Hz in each, H-2, H-3, H-4), 4.70 (1H, dd, *J* = 11.9, 2.6 Hz, H-6a), 4.52 (1H, dd, *J* = 11.9, 5.3 Hz, H-6b), 4.25 (1H, ddd, *J* = 9.2, 5.3, 2.6 Hz, H-5), 4.21 (1H, d, *J* = 9.2 Hz, H-1), 4.12–3.91 (2H, m, CH₂), 0.84 (3H, t, 6.6 Hz, CH₃); ¹³C NMR (CDCl₃) δ (ppm): 167.5, 166.1, 165.7, 165.1 (2) (CO, CNH), 133.5–128.2 (aromatics), 75.8, 74.6, 73.6, 70.7, 69.1 (C-1–C-5), 62.8, 62.1 (C-6, CH₂), 13.4 (CH₃).

4.4. Ethyl *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-thioformimidate (**7**)

C-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)thioformamide (**4**, 0.2 g, 0.31 mmol) and Et₃O·BF₄ (0.18 g, 0.94 mmol) were dissolved in anhydrous CH₂Cl₂ (4 mL), the mixture was stirred at rt under Ar and monitored by TLC (1:1 EtOAc–hexane). After completion of the reaction (2 days), the mixture was diluted with CH₂Cl₂ (10 mL), extracted with satd aq NaHCO₃ solution (15 mL), then with water (15 mL). The organic phase was dried over MgSO₄, filtered and the solvent was evaporated. The crude pale yellow amorphous product (0.19 g, 90%) was used without further purification. *R*_f: 0.62 (1:1 EtOAc–hexane); ¹H NMR (CDCl₃) δ (ppm): 8.06–7.24 (21H, m, aromatics, NH), 5.95, 5.74, 5.70 (3 × 1H, 3 pseudo t, *J* = 9.8, 9.1 Hz in each, H-2, H-3, H-4), 4.68 (1H, dd, *J* = 11.9, 2.8 Hz, H-6a), 4.51 (1H, dd, *J* = 11.9, 4.9 Hz, H-6b), 4.39 (1H, d, *J* = 9.1 Hz, H-1), 4.22 (1H, ddd, *J* = 9.1, 4.9, 2.8 Hz, H-5), 2.88–2.71 (2H, m, CH₂), 1.17 (3H, pseudo t, 7.7, 7.0 Hz, CH₃); ¹³C NMR (CDCl₃) δ (ppm): 172.7 (CNH), 166.1, 165.7, 165.1, 164.9 (CO), 133.4–128.2 (aromatics), 80.6, 76.1, 73.9, 70.9, 69.1 (C-1–C-5), 62.8 (C-6), 23.1 (CH₂), 13.1 (CH₃).

4.5. General procedure I for the synthesis of substituted 2-(2',3',4',6'-tetra-*O*-benzoyl-β-D-glucopyranosyl)-benzimidazoles from *O*-perbenzoylated *C*-(β-D-glucopyranosyl)formic acid (**5**)

C-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)formic acid⁴⁴ (**5**, 0.1 g, 0.16 mmol), a 1,2-diaminobenzene (**a** or **f** or **h**, 0.16 mmol,

1 equiv) and triphenyl phosphite (50 μ l, 0.19 mmol, 1.2 equiv) were dissolved in anhydrous pyridine (2 mL). The closed vial was irradiated by microwaves for 20 min at 140 °C (maximum pressure: 20 bar, power 220 W). The completion of the reaction was monitored by TLC (1:1 EtOAc–hexane). The reaction mixture was concentrated under reduced pressure, traces of pyridine were removed by repeated co-evaporations with toluene. The crude product was purified by column chromatography (2:3 EtOAc–hexane).

4.6. General procedure II for the synthesis of substituted 2-(2',3',4',6'-tetra-O-benzoyl- β -D-glucopyranosyl)-benzimidazoles from O-perbenzoylated ethyl (C- β -D-glycopyranosyl) formimidate (**6**)

Ethyl C-(2,3,4,6-tetra-O-benzoyl- β -D-glycopyranosyl)formimidate (**6**, 0.1 g, 0.15 mmol) and a 1,2-diaminobenzene (**a-i**, 0.30 mmol, 2 equiv) were dissolved in anhydrous CH_2Cl_2 (3 mL). The mixture was refluxed and monitored by TLC (2:3 EtOAc–hexane). After completion of the reaction the solvent was evaporated, and the residue was purified by column chromatography.

4.7. General procedure III for the Zemplén-deacylation

A benzoylated compound was dissolved in dry MeOH (5 mL/100 mg, a few drops of CHCl_3 were added in case of incomplete dissolution) and a catalytic amount of a NaOMe solution (~1 M in MeOH) was added. The mixture was kept at rt and monitored by TLC (7:3 CHCl_3 –MeOH). When the starting material was consumed the mixture was neutralised with a cation exchange resin Amberlyst 15 (H^+ form), then the resin was filtered off and the solvent removed. The residue was purified by column chromatography.

4.8. 2-(2',3',4',6'-Tetra-O-benzoyl- β -D-glucopyranosyl)-benzimidazole (**8a**)

A: From acid **5** (0.1 g, 0.16 mmol) and *o*-phenylenediamine (**a**, 0.02 g, 0.16 mmol) according to General procedure I. Yield: 0.05 g (45%).

B: From imidate **6** (0.10 g, 0.15 mmol) and *o*-phenylenediamine (**a**, 0.04 g, 0.30 mmol) according to General Procedure II. Reaction time: 3 h. Purified by column chromatography (2:3 EtOAc–hexane) to yield 0.09 g (89%) of white solid. Mp: 122–124 °C (Lit.²² mp: 120–123 °C). ^1H and ^{13}C NMR data correspond to the reported spectra.²²

4.9. 5(6)-Fluoro-2-(2',3',4',6'-tetra-O-benzoyl- β -D-glucopyranosyl)-benzimidazole (**8b**) and 5(6)-fluoro-2-(3',4',6'-tri-O-benzoyl-2'-deoxy-D-arabino-hex-1-enopyranosyl)-benzimidazole (**9b**)

From imidate **6** (0.10 g, 0.15 mmol) and 1,2-diamino-4-fluorobenzene (**b**, 0.04 g, 0.30 mmol) according to General Procedure II. Reaction time: 5 h. Purified by column chromatography (1:2, then 2:3 EtOAc–hexane) to give **9b** as the first than **8b** as the second fraction.

Compound **8b**: Yield: 0.051 g (46%) pale yellow solid; R_f : 0.31 (2:3 EtOAc–hexane); mp: 124–126 °C; $[\alpha]_D = -39$ (c 0.5, DMSO); ^1H NMR (CDCl_3) δ (ppm): 11.58 (1H, br s, benzimidazole NH), 7.96–6.76 (23H, m, aromatics), 6.30–6.21, 6.02 (3 \times 1H, 3 pseudo t, $J = 9.2$, 9.2 Hz in each, H-2', H-3', H-4'), 5.36 (1H, d, $J = 9.2$ Hz, H-1'), 4.69 (1H, dd, $J = 12.3$, <1 Hz, H-6'a), 4.57 (1H, dd, $J = 12.3$, 5.3 Hz, H-6'b), 4.52 (1H, ddd, $J = 9.2$, 5.3, <1 Hz, H-5'); ^{13}C NMR ($\text{DMSO}-d_6$) δ (ppm): 165.4, 165.1, 164.8, 164.3 (CO), 158.9 (d, $^1J_{\text{C-F}} = 237$ Hz, benzimidazole), 158.2 (d, $^1J_{\text{C-F}} = 237$ Hz, benzimidazole), 151.1, 150.3 (benzimidazole), 142.8 (d, $^3J_{\text{C-F}} = 9$ Hz, benzimidazole), 139.0 (br s, benzimidazole), 134.2 (d, $^3J_{\text{C-F}} = 9$ Hz, benzimidazole), 133.7–133.3 (aromatics), 130.9 (br s, benzimidazole),

129.3–128.5 (aromatics), 120.0 (d, $^3J_{\text{C-F}} = 7$ Hz, benzimidazole), 112.3 (d, $^3J_{\text{C-F}} = 6$ Hz, benzimidazole), 110.9 (d, $^2J_{\text{C-F}} = 23$ Hz, benzimidazole), 109.7 ($^2J_{\text{C-F}} = 23$ Hz, benzimidazole), 104.5 (d, $^2J_{\text{C-F}} = 24$ Hz, benzimidazole), 98.0 (d, $^2J_{\text{C-F}} = 27$ Hz, benzimidazole), 79.1, 74.8, 74.2, 73.4, 71.5, 69.0 (C-1'–C-5'), 62.8 (C-6'). Anal. Calcd for $\text{C}_{41}\text{H}_{31}\text{FN}_2\text{O}_9$ (714.69): C, 68.90; H, 4.37; N, 3.92. Found: C, 68.84; H, 4.29; N, 4.03.

Compound **9b**: Yield: 0.032 g (35%), pale yellow syrup; R_f : 0.58 (2:3 EtOAc–hexane); $[\alpha]_D = -7$ (c 0.5, CHCl_3); ^1H NMR (CDCl_3) δ (ppm): 10.41 (1H, br s, benzimidazole NH), 8.02–6.94 (18H, m, aromatics), 6.43 (1H, br s, H-2'), 5.95–5.92 (2H, m, H-3', H-4'), 4.88 (1H, ddd, $J = 4.0$, <1 Hz, H-5'), 4.79 (2H, s, H-6'a, H-6'b); ^{13}C NMR (CDCl_3) δ (ppm): 166.2, 165.6, 165.0 (CO), 159.8 (d, $^1J_{\text{C-F}} = 239$ Hz, benzimidazole C-5), 146.8 (benzimidazole C-2), 145.0 (C-1'), 143.1, 139.8 (2 br s, benzimidazole C-3a, C-7a), 133.5–128.4 (aromatics), 120.2 (br s, benzimidazole C-4 or C-7), 111.9 (d, $^2J_{\text{C-F}} = 25$ Hz, benzimidazole C-6), 104.4 (br s, benzimidazole C-4 or C-7), 99.4 (C-2'), 75.2, 67.9, 67.3 (C-3'–C-5'), 61.7 (C-6'). Analysis: $\text{C}_{34}\text{H}_{25}\text{FN}_2\text{O}_7$ (592.57), ESI-MS (positive mode) m/z : 615.157 $[\text{M}+\text{Na}]^+$, 1207.327 $[2\text{M}+\text{Na}]^+$.

4.10. 5(6)-Chloro-2-(2',3',4',6'-tetra-O-benzoyl- β -D-glucopyranosyl)-benzimidazole (**8c**) and 5(6)-chloro-2-(3',4',6'-tri-O-benzoyl-2'-deoxy-D-arabino-hex-1-enopyranosyl)-benzimidazole (**9c**)

From imidate **6** (0.10 g, 0.15 mmol) and 1,2-diamino-4-chlorobenzene (**c**, 0.04 g, 0.30 mmol) according to General Procedure II. Reaction time: 5 h. Purified by column chromatography (2:3 EtOAc–hexane) to give **9c** as the first and **8c** as the second fraction.

Compound **8c**: Yield: 0.085 g (76%), pale yellow solid; R_f : 0.29 (2:3 EtOAc–hexane); mp: 123–125 °C; $[\alpha]_D = -61$ (c 0.5, CHCl_3); ^1H NMR (CDCl_3) δ (ppm): 11.33 (1H, br s, benzimidazole NH), 7.94–6.95 (23H, m, aromatics), 6.21, 6.14, 6.00 (3 \times 1H, 3 pseudo t, $J = 9.4$, 9.4 Hz in each, H-2', H-3', H-4'), 5.31 (1H, d, $J = 9.4$ Hz, H-1'), 4.72 (1H, dd, $J = 12.3$, <1 Hz, H-6'a), 4.60 (1H, dd, $J = 12.3$, 4.4 Hz, H-6'b), 4.50 (1H, ddd, $J = 9.4$, 4.4, <1 Hz, H-5'); ^{13}C NMR (CDCl_3) δ (ppm): 166.5, 166.0, 165.1 (2) (CO), 149.8 (benzimidazole C-2), 142.0, 137.8 (2 br s, benzimidazole C-3a, C-7a), 133.3–127.8 (aromatics), 126.9, 123.3, 119.3 (br s), 112.4 (br s) (benzimidazole C-4–C-7), 77.0, 75.5, 74.1, 71.7, 69.5 (C-1'–C-5'), 63.4 (C-6'). Anal. Calcd for $\text{C}_{41}\text{H}_{31}\text{ClN}_2\text{O}_9$ (731.15): C, 67.35; H, 4.27; N, 3.84. Found: C, 67.47; H, 4.13; N, 3.90.

Compound **9c**: Yield: 0.022 g (24%), pale yellow syrup; R_f : 0.59 (2:3 EtOAc–hexane); $[\alpha]_D = -5$ (c 0.5, CHCl_3); ^1H NMR (CDCl_3) δ (ppm): 11.40 (1H, br s, benzimidazole NH), 8.00–7.07 (18H, m, aromatics), 6.45 (1H, d, $J = 4.0$ Hz, H-2'), 5.98 (1H, pseudo t, $J = 6.6$, 5.9 Hz, H-3' or H-4'), 5.94 (1H, pseudo t, $J = 5.9$, 4.0 Hz, H-3' or H-4'), 4.81 (1H, ddd, $J = 6.6$, 4.6, 4.0 Hz, H-5'), 4.71–4.70 (2H, m, H-6'a, H-6'b); ^{13}C NMR (CDCl_3) δ (ppm): 166.1, 165.6, 164.9 (CO), 146.8 (br s, benzimidazole C-2), 145.0 (C-1'), 144.1, 141.8 (2 br s, benzimidazole C-3a, C-7a), 133.6–133.2 (aromatics), 132.0 (br s, benzimidazole C-5), 129.8–128.3 (aromatics), 123.9, 120.3, 119.1, 112.2, 111.3 (br s for each, benzimidazole C-4, C-6, C-7), 99.8 (C-2'), 75.2, 68.1, 67.3 (C-3'–C-5'), 61.7 (C-6'). Analysis: $\text{C}_{34}\text{H}_{25}\text{ClN}_2\text{O}_7$ (609.02), ESI-MS (positive mode) m/z : 631.123 $[\text{M}+\text{Na}]^+$, 1239.257 $[2\text{M}+\text{Na}]^+$.

4.11. 5(6)-Bromo-2-(2',3',4',6'-tetra-O-benzoyl- β -D-glucopyranosyl)-benzimidazole (**8d**) and 5(6)-bromo-2-(3',4',6'-tri-O-benzoyl-2'-deoxy-D-arabino-hex-1-enopyranosyl)-benzimidazole (**9d**)

From imidate **6** (0.10 g, 0.15 mmol) and 1,2-diamino-4-bromobenzene (**d**, 0.06 g, 0.30 mmol) according to General Procedure II. Reaction time: 3 h. Purified by column chromatography (2:3 EtOAc–hexane) to give **9d** as the first and **8d** as the second fraction.

Compound **8d**: Yield: 0.064 g (54%) pale yellow solid; R_f : 0.31 (2:3 EtOAc–hexane); mp: 126–128 °C; $[\alpha]_D = -62$ (c 0.5, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 8.02–6.76 (23H, m, aromatics), 6.42, 6.29, 6.14 (3 \times 1H, 3 pseudo t, $J = 9.6$, 9.6 Hz in each, H-2', H-3', H-4'), 5.39 (1H, d, $J = 9.6$ Hz, H-1'), 4.72 (1H, dd, $J = 12.3$, 2.2 Hz, H-6'a), 4.63 (1H, dd, $J = 12.3$, 4.9 Hz, H-6'b), 4.56 (1H, ddd, $J = 9.6$, 4.9, 2.2 Hz, H-5'); ¹³C NMR (CDCl₃) δ (ppm): 166.4, 166.0, 165.0 (2) (CO), 149.6 (benzimidazole C-2), 140.9, 138.1 (2 br s, benzimidazole C-3a, C-7a), 133.3–127.7 (aromatics), 125.9, 119.0 (br s), 117.3 (br s), 115.9 (benzimidazole C-4, C-5, C-6, C-7), 77.0, 75.5, 74.1, 71.7, 69.4 (C-1'–C-5'), 63.4 (C-6'). Analysis: C₄₁H₃₁BrN₂O₉ (775.60), ESI-MS (positive mode) m/z : 799.112 [M+Na]⁺, 1573.242 [2M+Na]⁺.

Compound **9d**: Yield: 0.029 g (29%) pale yellow syrup; R_f : 0.61 (2:3 EtOAc–hexane); $[\alpha]_D = -4$ (c 0.25, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 10.06 (1H, br s, imidazole NH), 8.04–7.33 (18H, m, aromatics), 6.46 (1H, br s, H-2'), 5.97–5.93 (2H, m, H-3', H-4'), 4.91 (1H, ddd, $J = 4.0$, <1 Hz, H-5'), 4.81 (2H, s, H-6'a, H-6'b). Analysis: C₃₄H₂₅BrN₂O₇ (653.48), ESI-MS (positive mode) m/z : 677.074 [M+Na]⁺, 1329.197 [2M+Na]⁺.

4.12. 5(6)-Nitro-2-(2',3',4',6'-tetra-O-benzoyl- β -D-glucopyranosyl)-benzimidazole (**8e**) and 5(6)-nitro-2-(3',4',6'-tri-O-benzoyl-2'-deoxy-D-arabino-hex-1-enopyranosyl)-benzimidazole (**9e**)

From imidate **6** (0.10 g, 0.15 mmol) and 1,2-diamino-4-nitrobenzene (**e**, 0.05 g, 0.30 mmol) according to General procedure **II** in anhydrous ethanol. Reaction time: 1 day. Purified by column chromatography (1:2 EtOAc–hexane) to give **9e** as the first and **8e** as the second fraction.

Compound **8e**: Yield: 0.052 g (46%) yellow solid; R_f : 0.25 (2:3 EtOAc–hexane); mp: 134–136 °C; $[\alpha]_D = -65$ (c 0.5, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 12.87 (1H, br s, benzimidazole NH), 8.45–6.96 (23H, m, aromatics), 6.20, 6.12, 6.01 (3 \times 1H, 3 pseudo t, $J = 9.4$, 9.4 Hz in each, H-2', H-3', H-4'), 5.33 (1H, d, $J = 9.4$ Hz, H-1'), 4.77 (1H, dd, $J = 11.8$, <1 Hz, H-6'a), 4.63 (1H, dd, $J = 11.8$, <1 Hz, H-6'b), 4.51 (1H, ddd, $J = 9.4$, <1 Hz, H-5'); ¹³C NMR (CDCl₃) δ (ppm): 166.3, 165.8, 165.1, 164.8 (CO), 152.7 (benzimidazole C-2), 143.3 (benzimidazole C-5), 141.6, 138.0 (2 br s, benzimidazole C-3a, C-7a), 133.5–127.6 (aromatics), 118.9, 116.1, 111.6 (br s for each, benzimidazole C-4, C-6, C-7), 77.1, 75.4, 74.0, 71.7, 69.0 (C-1'–C-5'), 63.2 (C-6'). Anal. Calcd for C₄₁H₃₁N₃O₁₁ (741.70): C, 66.39; H, 4.21; N, 5.67. Found: C, 66.26; H, 4.13; N, 5.79.

Compound **9e**: Yield: 0.019 g (20%) yellow syrup; R_f : 0.39 (2:3 EtOAc–hexane); $[\alpha]_D = +1$ (c 0.5, CHCl₃); ¹H NMR (DMSO-*d*₆) δ (ppm): 13.51 (1H, br s, benzimidazole NH), 8.13–7.48 (18H, m, aromatics), 6.40 (1H, br s, H-2'), 6.02 (1H, pseudo t, $J = 5.3$, 4.0 Hz, H-3' or H-4'), 5.93 (1H, pseudo t, $J = 6.6$, 5.9 Hz, H-3' or H-4'), 5.23 (1H, ddd, $J = 5.9$, 5.3, 3.3 Hz, H-5'), 4.89 (1H, dd, $J = 12.6$, 5.3 Hz, H-6'a), 4.78 (1H, dd, $J = 12.6$, 3.3 Hz, H-6'b); ¹³C NMR (DMSO-*d*₆) δ (ppm): 165.3, 165.0, 164.5 (CO), 150.5 (br s), 149.7 (br s), 147.5 (br s), 145.0, 143.0, 142.3 (br s), 138.7 (br s) (benzimidazole, C-1'), 133.8–128.7 (aromatics), 119.2, 118.5, 117.8, 115.2, 112.3, 108.4 (br s for each, benzimidazole), 100.5 (C-2'), 74.6, 67.9, 67.0 (C-3'–C-5'), 61.5 (C-6'). Analysis: C₃₄H₂₅N₃O₉ (619.58), ESI-MS (positive mode) m/z : 642.148 [M+Na]⁺, 1261.309 [2M+Na]⁺.

4.13. 5(6)-Methyl-2-(2',3',4',6'-tetra-O-benzoyl- β -D-glucopyranosyl)-benzimidazole (**8f**)

A: From acid **5** (0.1 g, 0.16 mmol) and 3,4-diaminotoluene (**f**, 0.02 g, 0.16 mmol) according to General procedure **I**. Yield: 0.06 g (53%).

B: From imidate **6** (0.10 g, 0.15 mmol) and 3,4-diaminotoluene (**f**, 0.04 g, 0.30 mmol) according to General Procedure **II**. Reaction time: 2 h. Purified by column chromatography (2:3 EtOAc–hexane) to yield 0.09 g (83%) of pale yellow syrup. R_f : 0.41 (1:1 EtOAc–hexane); $[\alpha]_D = -65$ (c 0.5, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 10.73 (1H, br s, benzimidazole NH), 7.92–6.90 (23H, m, aromatics), 6.19, 6.11, 5.96 (3 \times 1H, 3 pseudo t, $J = 9.2$, 9.2 Hz in each, H-2', H-3', H-4'), 5.32 (1H, d, $J = 9.2$ Hz, H-1'), 4.68 (1H, dd, $J = 12.2$, 2.6 Hz, H-6'a), 4.54 (1H, dd, $J = 12.2$, 5.3 Hz, H-6'b), 4.44 (1H, ddd, $J = 9.2$, 5.3, 2.6 Hz, H-5'), 2.32 (3H, s, CH₃); ¹³C NMR (CDCl₃) δ (ppm): 166.4, 165.9, 165.2 (2) (CO), 148.1 (benzimidazole C-2), 142.4, 138.8 (2 br s, benzimidazole C-3a, C-7a), 133.4–128.0 (aromatics, benzimidazole C-5), 124.4, 118.9, 111.1 (br s for each, benzimidazole C-4, C-6, C-7), 76.8, (C-1'), 75.3, 74.1, 71.5, 69.5 (C-1'–C-5'), 63.4 (C-6'), 21.5 (CH₃). Anal. Calcd for C₄₂H₃₄N₂O₉ (710.73): C, 70.98; H, 4.82; N, 3.94. Found: C, 70.83; H, 4.96; N, 4.09.

4.14. 4(7)-Methyl-2-(2',3',4',6'-tetra-O-benzoyl- β -D-glucopyranosyl)-benzimidazole (**8g**)

From imidate **6** (0.10 g, 0.15 mmol) and 2,3-diaminotoluene (**g**, 0.04 g, 0.30 mmol) according to General Procedure **II**. Reaction time: 5 h. Purified by column chromatography (1:2 EtOAc–hexane) to yield 0.087 g (79%) of yellow solid. Mp: 117–119 °C; $[\alpha]_D = -43$ (c 0.5, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 10.88 (1H, br s, benzimidazole NH), 7.96–6.88 (23H, m, aromatics), 6.18, 6.06, 5.92 (3 \times 1H, 3 pseudo t, $J = 9.2$, 9.2 Hz in each, H-2', H-3', H-4'), 5.38 (1H, d, $J = 9.2$ Hz, H-1'), 4.69 (1H, dd, $J = 11.7$, <1 Hz, H-6'a), 4.51 (1H, dd, $J = 11.7$, 5.3 Hz, H-6'b), 4.44 (1H, ddd, $J = 9.2$, 5.3, <1 Hz, H-5'), 2.33 (3H, s, CH₃); ¹³C NMR (CDCl₃) δ (ppm): 166.3, 165.8, 165.3, 165.2 (CO), 147.7 (benzimidazole C-2), 142.1 (br s, benzimidazole C-3a, C-7a), 133.4–128.0 (aromatics), 123.1, 122.4, 116.8, 108.8 (br s for each, benzimidazole C-4–C-7), 76.8, 75.2, 73.9, 71.4, 69.5 (C-1'–C-5'), 63.3 (C-6'), 16.5 (CH₃). Anal. Calcd for C₄₂H₃₄N₂O₉ (710.73): C, 70.98; H, 4.82; N, 3.94. Found: C, 70.87; H, 4.90; N, 3.85.

4.15. 5,6-Dimethyl-2-(2',3',4',6'-tetra-O-benzoyl- β -D-glucopyranosyl)-benzimidazole (**8h**)

A: From acid **5** (0.1 g, 0.16 mmol) and 1,2-diamino-4,5-dimethylbenzene (**h**, 0.02 g, 0.16 mmol) according to General procedure **I**. Yield: 0.05 g (43%).

B: From imidate **6** (0.10 g, 0.15 mmol) and 1,2-diamino-4,5-dimethylbenzene (**h**, 0.04 g, 0.30 mmol) according to General procedure **II**. Reaction time: 3 h. Purified by column chromatography (2:3 EtOAc–hexane) to yield 0.09 g (81%) of pale yellow solid. Mp: 207–209 °C; $[\alpha]_D = -64$ (c 0.5, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 11.00 (1H, br s, benzimidazole NH), 7.98–6.92 (22H, m, aromatics), 6.27, 6.21, 6.05 (3 \times 1H, 3 pseudo t, $J = 9.2$, 9.2 Hz in each, H-2', H-3', H-4'), 5.34 (1H, d, $J = 9.2$ Hz, H-1'), 4.67 (1H, dd, $J = 11.9$, 2.6 Hz, H-6'a), 4.54 (1H, dd, $J = 11.9$, 5.3 Hz, H-6'b), 4.48 (1H, ddd, $J = 9.2$, 5.3, 2.6 Hz, H-5'), 2.17 (6H, s, CH₃); ¹³C NMR (CDCl₃) δ (ppm): 166.3, 165.9, 165.1, 165.0 (CO), 147.5 (benzimidazole C-2), 141.1 (br s, benzimidazole C-3a, C-7a), 133.2–127.9 (aromatics, benzimidazole C-5, C-6), 119.5, 111.6 (2 br s, benzimidazole C-4, C-7), 76.8, 75.6, 74.3, 71.7, 69.5 (C-1'–C-5'), 63.3 (C-6'), 20.2 (2 \times CH₃). Anal. Calcd for C₄₃H₃₆N₂O₉ (724.75): C, 71.26; H, 5.01; N, 3.87. Found: C, 71.15; H, 4.92; N, 3.99.

4.16. 2-(2',3',4',6'-Tetra-O-benzoyl- β -D-glucopyranosyl)-naphtho[2,3-*d*]imidazole (**8i**)

From imidate **6** (0.10 g, 0.15 mmol) and 2,3-diamino-naphthalene (**i**, 0.05 g, 0.30 mmol) according to General procedure **II**. Reaction time: 4 h. Purified by column chromatography (4:5

EtOAc–hexane) to yield 0.091 g (79%) of pale brown solid. Mp: 184–186 °C; $[\alpha]_D = -113$ (c 0.25, CHCl₃); ¹H NMR (CDCl₃) δ (ppm): 10.64 (1H, br s, naphthoimidazole NH), 7.81–6.92 (26H, m, aromatics), 6.14, 6.05, 5.90 (3 \times 1H, 3 pseudo t, $J = 9.6$, 9.6 Hz in each, H-2', H-3', H-4'), 5.29 (1H, d, $J = 9.6$ Hz, H-1'), 4.64 (1H, dd, $J = 12.3$, <1 Hz, H-6'a), 4.49 (1H, dd, $J = 12.3$, 5.3 Hz, H-6'b), 4.39 (1H, ddd, $J = 9.6$, 5.3, <1 Hz, H-5'); ¹³C NMR (CDCl₃) δ (ppm): 166.2, 165.9, 165.1 (2) (CO), 152.9 (naphthoimidazole C-2), 142.7 (br s, naphthoimidazole C-3a, C-9a), 133.2–127.8, 123.6 (aromatics), 116.2, 107.8 (2 br s, naphthoimidazole C-4, C-9), 76.9, 75.6, 74.2, 71.7, 69.5 (C-1'–C-5'), 63.4 (C-6'). Analysis: C₄₅H₃₄N₂O₉ (746.76), ESI-MS (positive mode) m/z : 769.219 [M+Na]⁺, 1516.457 [2M+Na]⁺.

4.17. 5(6)-Fluoro-2-(β -D-glucopyranosyl)-benzimidazole (10b)

From **8b** (0.22 g, 0.30 mmol) according to General Procedure III. Reaction time: 3.5 h. Purified by column chromatography (4:1 CHCl₃–MeOH) to yield 0.048 g (54%) of pale yellow syrup. R_f : 0.19 (10:3 CHCl₃–MeOH); $[\alpha]_D = +9$ (c 0.2, DMSO); ¹H NMR (CD₃OD) δ (ppm): 7.48 (1H, s, benzimidazole H-4), 7.21 (1H, d, $J = 8.7$ Hz, benzimidazole H-7), 6.97 (1H, t, $J = 8.7$ Hz, benzimidazole H-6), 4.46 (1H, d, $J = 9.4$ Hz, H-1'), 3.88 (1H, dd, $J = 11.8$, <1 Hz, H-6'a), 3.73 (1H, dd, $J = 11.8$, <1 Hz, H-6'b), 3.61 (1H, pseudo t, $J = 9.8$, 9.8 Hz, H-2' or H-3' or H-4'), 3.52–3.47 (3H, m, H-2' and/or H-3' and/or H-4', H-5'); ¹³C NMR (DMSO-*d*₆) δ (ppm): 158.3 (d, ¹ $J_{C-F} = 236$ Hz, benzimidazole C-5), 153.9, 143.2, 138.9, 133.7, 130.6, 119.7, 112.0, 109.7, 104.0, 98.0 (br s for each, benzimidazole), 81.4, 77.8, 75.9, 72.7, 70.0 (C-1'–C-5'), 61.3 (C-6'). Anal. Calcd for C₁₃H₁₅FN₂O₅ (298.27): C, 52.35; H, 5.07; N, 9.39. Found: C, 52.26; H, 5.21; N, 9.33.

4.18. 5(6)-Chloro-2-(β -D-glucopyranosyl)-benzimidazole (10c)

From **8c** (0.24 g, 0.33 mmol) according to general procedure III. Reaction time: 5 h. Purified by column chromatography (4:1 CHCl₃–MeOH) to yield 0.092 g (89%) of colourless syrup. R_f : 0.23 (4:1 CHCl₃–MeOH); $[\alpha]_D = +23$ (c 0.5, DMSO); ¹H NMR (CD₃OD) δ (ppm): 7.50 (1H, d, $J = 1.4$ Hz, benzimidazole H-4), 7.45 (1H, d, $J = 8.9$ Hz, benzimidazole H-7), 7.15 (1H, dd, $J = 8.9$, 1.4 Hz, benzimidazole H-6), 4.47 (1H, d, $J = 8.9$ Hz, H-1'), 3.88 (1H, dd, $J = 11.6$, <1 Hz, H-6'a), 3.73 (1H, dd, $J = 11.6$, 4.8 Hz, H-6'b), 3.61 (1H, pseudo t, $J = 8.9$, 8.9 Hz, H-2' or H-3' or H-4'), 3.55–3.45 (3H, m, H-2' and/or H-3' and/or H-4', H-5'); ¹³C NMR (CD₃OD) δ (ppm): 155.2 (benzimidazole C-2), 140.3, 138.1 (2 br s, benzimidazole C-3a, C-7a), 129.2 (benzimidazole C-5), 124.1, 117.1 (br s), 115.9 (br s) (benzimidazole C-4, C-6, C-7), 82.2, 79.2, 77.3, 74.8, 71.2 (C-1'–C-5'), 62.8 (C-6'). Anal. Calcd for C₁₃H₁₅ClN₂O₅ (314.72): C, 49.61; H, 4.80; N, 8.90. Found: C, 49.72; H, 4.87; N, 8.75.

4.19. 5(6)-Bromo-2-(β -D-glucopyranosyl)-benzimidazole (10d)

From **8d** (0.27 g, 0.35 mmol) according to General procedure III. Reaction time: 6 h. Purified by column chromatography (8:1 CHCl₃–MeOH) to yield 0.073 g (58%) of colourless syrup. R_f : 0.23 (10:3 CHCl₃–MeOH); $[\alpha]_D = +21$ (c 0.43, DMSO); ¹H NMR (CD₃OD) δ (ppm): 7.65 (1H, s, benzimidazole H-4), 7.41, 7.29 (2 \times 1H, 2d, $J = 8.4$ Hz, benzimidazole H-6, H-7), 4.47 (1H, d, $J = 9.4$ Hz, H-1'), 3.88 (1H, dd, $J = 11.8$, <1 Hz, H-6'a), 3.74 (1H, dd, $J = 11.8$, <1 Hz, H-6'b), 3.61 (1H, pseudo t, $J = 9.4$, 8.4 Hz, H-2' or H-3' or H-4'), 3.53–3.46 (3H, m, H-2' and/or H-3' and/or H-4', H-5'); ¹³C NMR (DMSO-*d*₆) δ (ppm): 153.8 (benzimidazole C-2), 141.5, 134.8 (2 br s, C-3a, C-7a), 124.5, 121.0, 113.9, 113.8 (br s for each, benzimidazole C-4–C-7), 81.5, 77.8, 75.9, 72.8, 70.0 (C-1'–C-5'), 61.3 (C-6').

Anal. Calcd for C₁₃H₁₅BrN₂O₅ (359.17): C, 43.47; H, 4.21; N, 7.80. Found: C, 43.43; H, 4.34; N, 7.93.

4.20. 2-(β -D-Glucopyranosyl)-5(6)-nitro-benzimidazole (10e)

From **8e** (0.30 g, 0.40 mmol) according to General procedure III. Reaction time: 1 day. Purified by column chromatography (85:15 CHCl₃–MeOH) to yield 0.07 g (53%) of yellow syrup. R_f : 0.27 (4:1 CHCl₃–MeOH); ¹H NMR (DMSO-*d*₆) δ (ppm): 13.03 (1H, br s, benzimidazole NH), 8.44 (1H, d, $J = 1.3$ Hz, benzimidazole H-4), 8.11 (1H, dd, $J = 9.2$, 1.3 Hz, benzimidazole H-6), 7.70 (1H, d, $J = 9.2$ Hz, benzimidazole H-7), 5.14 (3H, br s, 3 \times OH), 4.60 (1H, br s, OH), 4.42 (1H, d, $J = 9.2$ Hz, H-1'), 3.74 (1H, dd, $J = 11.9$, <1 Hz, H-6'a), 3.63 (1H, pseudo t, $J = 9.2$, 9.2 Hz, H-2' or H-3' or H-4'), 3.49 (1H, dd, $J = 11.9$, 5.3 Hz, H-6'b), 3.39–3.34 (2H, m, H-2' or H-3' or H-4', H-5'), 3.24 (1H, pseudo t, $J = 9.2$, 9.2 Hz, H-2' or H-3' or H-4'); ¹³C NMR (DMSO-*d*₆) δ (ppm): 157.3 (benzimidazole C-2), 142.5 (benzimidazole C-5), 141.4, 138.8 (2 br s, benzimidazole C-3a, C-7a), 117.7, 114.3 (br s), 112.6 (br s) (benzimidazole C-4, C-6, C-7), 81.6, 77.7, 76.0, 72.8, 70.0 (C-1'–C-5'), 61.2 (C-6'). Anal. Calcd for C₁₃H₁₅N₃O₇ (325.27): C, 48.00; H, 4.65; N, 12.92. Found: C, 47.87; H, 4.56; N, 12.96.

4.21. 2-(β -D-Glucopyranosyl)-5(6)-methyl-benzimidazole (10f)

From **8e** (0.27 g, 0.38 mmol) according to General procedure III. Reaction time: 3 h. Purified by column chromatography (85:15 CHCl₃–MeOH) to yield 0.10 g (87%) of colourless syrup. R_f : 0.42 (7:3 CHCl₃–MeOH); $[\alpha]_D = +18$ (c 0.5, MeOH); ¹H NMR (CD₃OD) δ (ppm): 7.41 (1H, d, $J = 7.9$ Hz, benzimidazole H-6 or H-7), 7.32 (1H, s, benzimidazole H-4), 7.03 (1H, d, $J = 7.9$ Hz, benzimidazole H-6 or H-7), 4.49 (1H, d, $J = 9.2$ Hz, H-1'), 3.91 (1H, dd, $J = 11.9$, <1 Hz, H-6'a), 3.76 (1H, dd, $J = 11.9$, 4.0 Hz, H-6'b), 3.66 (1H, pseudo t, $J = 9.2$, 9.2 Hz, H-2' or H-3' or H-4'), 3.61–3.49 (3H, m, H-2' and/or H-3' and/or H-4', H-5'), 2.42 (3H, s, CH₃); ¹³C NMR (CD₃OD) δ (ppm): 153.4 (benzimidazole C-2), 139.0, 137.6 (benzimidazole C-3a, C-7a), 133.6 (benzimidazole C-5), 125.2, 115.9, 115.4 (benzimidazole C-4, C-6, C-7), 82.1, 79.3, 77.3, 74.8, 71.2 (C-1'–C-5'), 62.7 (C-6'), 21.7 (CH₃). Anal. Calcd for C₁₄H₁₈N₂O₅ (294.30): C, 57.13; H, 6.16; N, 9.52. Found: C, 57.29; H, 6.07; N, 9.39.

4.22. 2-(β -D-Glucopyranosyl)-4(7)-methyl-benzimidazole (10g)

From **8g** (0.25 g, 0.35 mmol) according to General Procedure III. Reaction time: 4 h. Purified by column chromatography (4:1 CHCl₃–MeOH) to give 0.075 g (73%) of colourless syrup. R_f : 0.20 (4:1 CHCl₃–MeOH); $[\alpha]_D = +13$ (c 0.5, DMSO); ¹H NMR (DMSO-*d*₆) δ (ppm): 12.46 (1H, br s, benzimidazole NH), 7.32, 7.04, 6.95 (3 \times 1H, benzimidazole), 5.14 (3H, br s, 3 \times OH), 4.64 (1H, br s, OH), 4.36 (1H, d, $J = 10.2$ Hz, H-1'), 3.73–3.24 (6H, m, H-2', H-3', H-4', H-5', H-6'a, H-6'b), 2.50 (3H, s, CH₃); ¹³C NMR (DMSO-*d*₆) δ (ppm): 151.9 (benzimidazole C-2), 141.8, 133.5, 128.4, 121.6, 115.6, 109.0 (br s for each, benzimidazole C-3a, C-7a, C-4–C-7), 81.3, 77.9, 75.9, 72.7, 70.0 (C-1'–C-5'), 61.2 (C-6'). Anal. Calcd for C₁₄H₁₈N₂O₅ (294.30): C, 57.13; H, 6.16; N, 9.52. Found: C, 57.18; H, 6.05; N, 9.64.

4.23. 5,6-Dimethyl-2-(β -D-glucopyranosyl)-benzimidazole (10h)

From **8h** (0.27 g, 0.37 mmol) according to General procedure III. Reaction time: 3 h. Purified by column chromatography (85:15 CHCl₃–MeOH) to yield 0.09 g (78%) of colourless syrup. R_f : 0.42 (7:3 CHCl₃–MeOH); $[\alpha]_D = +24$ (c 0.5, MeOH); ¹H NMR (CD₃OD) δ (ppm): 7.28 (2H, s, benzimidazole H-4, H-7), 4.47 (1H, d, $J = 9.2$ Hz, H-1'), 3.91 (1H, dd, $J = 11.9$, <1 Hz, H-6'a), 3.76 (1H, dd, $J = 11.9$, 5.3 Hz, H-6'b), 3.67 (1H, pseudo t, $J = 9.2$, 9.2 Hz, H-2' or

H-3' or H-4'), 3.59–3.49 (3H, m, H-2' and/or H-3' and/or H-4', H-5'), 2.31 (6H, s, CH₃); ¹³C NMR (CD₃OD) δ (ppm): 152.7 (benzimidazole C-2), 137.6 (benzimidazole C-3a, C-7a), 132.7 (benzimidazole C-5, C-6), 115.9 (benzimidazole C-4, C-7), 82.1, 79.3, 77.3, 74.7, 71.2 (C-1'–C-5'), 62.7 (C-6'), 20.5 (CH₃). Anal. Calcd for C₁₅H₂₀N₂O₅ (308.34): C, 58.43; H, 6.54; N, 9.09. Found: C, 58.56; H, 6.59; N, 8.95.

4.24. 2-(β-D-Glucopyranosyl)-naphtho[2,3-d]imidazole (10i)

From **8i** (0.25 g, 0.33 mmol) according to General Procedure **III**. Reaction time: 4 h. Purified by column chromatography (4:1 CHCl₃–MeOH) to yield 0.085 g (77%) of colourless syrup. R_f: 0.17 (4:1 CHCl₃–MeOH); [α]_D = +10 (c 0.6, DMSO); ¹H NMR (DMSO-*d*₆) δ (ppm): 12.47 (1H, br s, naphthoimidazole NH), 8.06–7.99 (4H, m, aromatics), 7.38–7.36 (2H, m, aromatics), 5.20 (2), 5.11 (3H, br s, 3 × OH), 4.59 (1H, br s, OH), 4.46 (1H, d, J = 9.9 Hz, H-1'), 3.77 (1H, dd, J = 11.2, <1 Hz, H-6'a) 3.71 (1H, pseudo t, J = 9.2, 9.2 Hz, H-2' or H-3' or H-4'), 3.51 (1H, dd, J = 11.2, 6.6 Hz, H-6'b) 3.46–3.36 (2H, m, H-2' or H-3' or H-4', H-5'), 3.26 (1H, pseudo t, J = 9.2, 9.2 Hz, H-2' or H-3' or H-4'); ¹³C NMR (DMSO-*d*₆) δ (ppm): 157.0 (naphthoimidazole C-2), 138.7 (br s), 129.6, 127.7, 123.3, 110.7 (br s) (naphthoimidazole), 81.6, 77.8, 76.1, 72.8, 70.1 (C-1'–C-5'), 61.3 (C-6'). Anal. Calcd for C₁₇H₁₈N₂O₅ (330.34): C, 61.81; H, 5.49; N, 8.48. Found: C, 61.74; H, 5.60; N, 8.55.

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