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Synthesis of triazole-linked β-*C*-glycosyl dimers as inhibitors of PTP1B

Li Lin [a,b], Qiang Shen [c], Guo-Rong Chen [b,*], Juan Xie [a,*]

[a] *PPSM, ENS Cachan, CNRS, UniverSud, 61 av President Wilson, F-94230 Cachan, France*
[b] *Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Shanghai 200237, PR China*
[c] *National Center for Drug Screening, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, PR China*

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ABSTRACT

Protein tyrosine phosphatase 1B (PTP1B) has emerged as a promising target for type 2 diabetes. We have successfully synthesized dimeric acetylated and benzoylated β-*C*-D-glucosyl and β-*C*-D-galactosyl 1,4-dimethoxy benzenes or naphthalenes by click chemistry. These compounds were further transformed into the corresponding β-*C*-D-glycosyl-1,4-quinone derivatives by CAN oxidation. The in vitro inhibition test showed that dimeric benzoylated β-*C*-D-glycosyl 1,4-dimethoxybenzenes or 1,4-benzoquinones were good inhibitors of PTP1B (IC_{50}: 0.62–0.88 μM), with no significant difference between gluco and galacto derivatives.

1. Introduction

Protein tyrosine phosphatase 1B (PTP1B) is an important regulator of tyrosine kinase receptor-mediated responses, and influences negatively insulin sensitivity.[1–3] Indeed, PTP1B knockout mice display increased insulin sensitivity and tyrosine phosphorylation of the insulin receptor.[4,5] These results attracted considerable interest for the development of pharmacological PTP1B inhibitors for the treatment of insulin resistance, in particular non-insulin-dependent diabetes mellitus (type 2 diabetes),[6,7] which is characterized by a deficient insulin cascade and is therefore also termed insulin resistance (IR). Up to date, various therapeutic strategies have been developed for targeting PTP1B in diabetes.[8–18] Inhibitors of PTP1B generally fall into two categories: non-hydrolysable phosphotyrosine mimetics (or affinity-based) and covalent inactivators. The first category has received the most attention; numerous phosphotyrosine mimetics have been reported, including difluoromethylphosphonates, cinnamic acid, oxalylamino benzoic acid, isoxazole carboxylic acid, salicyclic acid, α-ketocarboxylic acid, etc. The second category of inhibitors consists largely of reactive molecules which modify the active site Cys215, like naphthoquinone as Michael acceptor or oxidant, and halomethyl ketones as alkylating agents. Recently, we found that β-*C*-glucopyranosyl-1,4-benzoquinone (compound **I**, Fig. 1) showed a good inhibition against PTP1B (IC_{50} = 4.85 μM).[19] This result prompted us to prepare other *C*-glycosyl quinone derivatives as new sugar-based small molecule inhibitors of PTP1B. Two naturally occurring allosteric binding sites have recently been identified in the PTP1B, which are located ~8 and ~20 Å, respectively, from the catalytic site.[20–22] Potent bidentate inhibitors of PTP1B have been developed based on this structural feature.[8–13,23,24] We then decided to prepare dimeric β-*C*-aryl glycosides as well as their quinones derivatives as potential bidentate inhibitors of PTP1B.

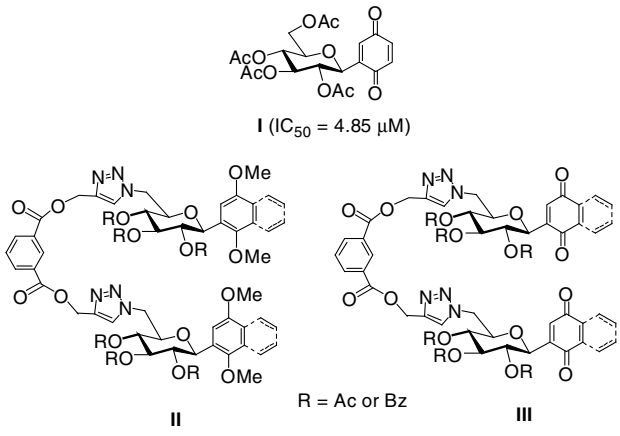

Figure 1. Structure of PTP1B inhibitors.

* Corresponding authors. Tel.: +86 21 64253016; fax: +86 21 64252758 (G.-R. Chen); tel.: +33 1 47 40 55 86; fax: +33 1 47 40 24 54 (J. Xie).
E-mail addresses: mrs_guorongchen@ecust.edu.cn (G.-R. Chen), joanne.xie@ppsm.ens-cachan.fr (J. Xie).

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The recently developed 'click chemistry' or Cu(I)-catalysed Huisgen 1,3-dipolar cycloadditions of terminal alkynes with organic azides were shown to be very effective and versatile and have been receiving attention as a highly efficient and regioselective reaction associated with excellent functional groups compatibility.[25,26] In addition, the 1,2,3-triazole ring is resistant to hydrolysis, oxidation, reduction, or other modes of cleavage. These important features have allowed the synthesis of complex molecules including dendrimers, bioconjugates, functionalized polymers and sugar derivatives.[27–30] Synthesis of PTP1B inhibitors with click chemistry has also been reported.[24,31] However, dimeric *C*-glycosyl compounds have never been designed as inhibitors of PTP1B. Herein, we reported the synthesis of dimeric β-*C*-glucosyl or β-*C*-galactosyl derivatives via click chemistry (compounds **II** and **III**, Fig. 1) and their inhibitory activity towards PTP1B.

2. Results and discussion

Dimeric β-*C*-aryl glycosides **II** (Fig. 1) can be obtained by Huisgen 1,3-dipolar cycloaddition between 6-azido-6-deoxy-β-*C*-glycosides with dipropargyl isophthalate. Firstly, we have prepared 6-azido functionalized β-*C*-aryl glycosides (Scheme 1). The peracetylated gluco and galacto β-*C*-glycosides **1**[32] and **5**[32] were first deacetylated under Zemplén condition and tritylated at 6-position to furnish the compounds **2** and **6**, followed by addition of BzCl to protect the secondary hydroxyl groups as benzoyl ester in one-pot. Detritylation with TFA gave the 6-OH free β-*C*-aryl glycosides **3** and **7** which were converted into the 6-azido-β-*C*-aryl glycosides **4** and **8** through activation as mesylate followed by nucleophilic substitution with NaN_3. For the synthesis of acetyl protected β-*C*-glucosyl and β-*C*-galactosyl-1,4-dimethoxynaphthalene derivatives **12** and **16**, TBS has been used to selectively protect the 6-OH group of β-*C*-glycosyl-1,4-dimethoxynaphthalene **9**[33] and **13**[33] to compounds **10** and **14**. Subsequent desilylation with TBAF led however to a mixture of 6-OH and 6-OAc products resulting from intramolecular transesterification reaction. We then decided to realize the desilylation under acidic condition (AcCl in MeOH). The gluco derivative **11** can be obtained in excellent yield. However, the yield of desilylation is only 38% for the galacto derivative **15**. The yield for **15** became worse when trityl was used as the protecting group. The desired compounds **12** and **16** were obtained after mesylation followed by azide substitution in good yields.

We then studied the Huisgen 1,3-dipolar cycloaddition reaction between 6-azido-β-*C*-aryl glycosides and dipropargyl isophthalate **17** which can be easily prepared by treatment of isophthalic chloride with propargylic alcohol (Scheme 2). Click reactions were realized with $CuSO_4$ and sodium ascorbate in a mixture of dichloromethane and water at room temperature. Reaction of dipropargyl isophthalate **17** with aryl β-*C*-glucosides **4** and **12**, or aryl β-*C*-galactosides **8** and **16** worked very well. The dimeric β-*C*-aryl glycosides **18**, **19**, **22**, and **23** were obtained in more than 86% yield (Scheme 2). These compounds have been fully characterized by NMR and mass spectrometry. Mild oxidation with CAN in a mixture of acetonitrile and water converted these 1,4-dimethoxy aromatic derivatives into the corresponding 1,4-benzoquinone or 1,4-naphthoquinone derivatives **20**, **21**, **24**, and **25**.

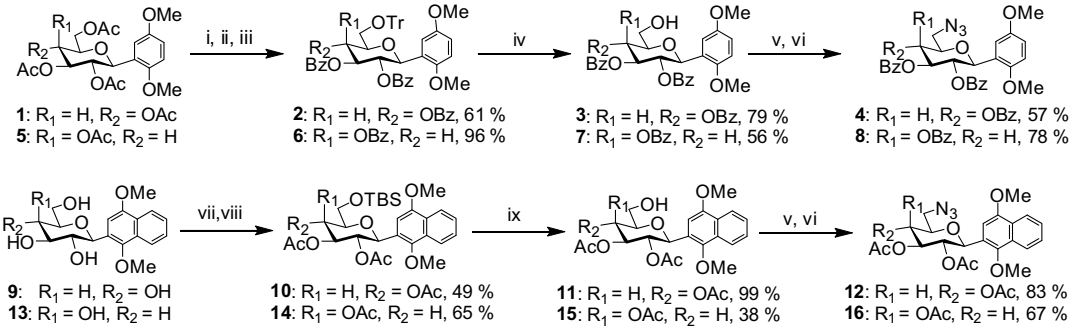
Various dimeric compounds have been evaluated as PTP1B inhibitors and biological results are shown in Table 1. Benzoylated β-*C*-glycosyl 1,4-dimethoxybenzenes or 1,4-benzoquinones (compounds **18**–**21**) showed good inhibition against PTP1B, with approximately the same IC_{50} value in submicromolar range. These dimeric compounds were slightly better inhibitors than the parent monomer **I** (IC_{50} = 4.85 μM). There is no difference between gluco and galacto derivatives (**18** vs **19** and **20** vs **21**). Furthermore, 1,4-dimethoxybenzene derivatives are as potent as 1,4-benzoquinone derivatives (**18** vs **20** and **19** vs **21**). However, compounds bearing 1,4-dimethoxynaphthalene or 1,4-naphthoquinone moiety (compounds **22**–**25**) showed very weak inhibition against PTP1B. Larger substituents at the anomeric position seemed to hamper the interaction with the enzyme. Meanwhile, benzoyl protecting groups seem to contribute to the PTP1B inhibitory activity, probably by binding in a hydrophobic pocket of enzyme.

In summary, dimeric acetylated and benzoylated β-*C*-aryl gluco- and galacto-pyranosides have been successfully prepared by Huisgen 1,3-dipolar cycloaddition reaction between 6-azido-β-*C*-aryl glycosides and dipropargyl isophthalate in good yield. Mild oxidation converted β-*C*-glycosyl-1,4-dimethoxy benzenes or naphthalenes into the corresponding β-*C*-glycosyl 1,4-benzoquinone or 1,4-naphthoquinone derivatives. Benzoylated glucosyl and galactosyl dimers containing a 1,4-dimethoxybenzene or 1,4-benzoquinone moiety showed submicromolar inhibitory activity (IC_{50}: 0.62 to 0.88 μM) against PTP1B, with no significant difference between gluco and galacto derivatives.

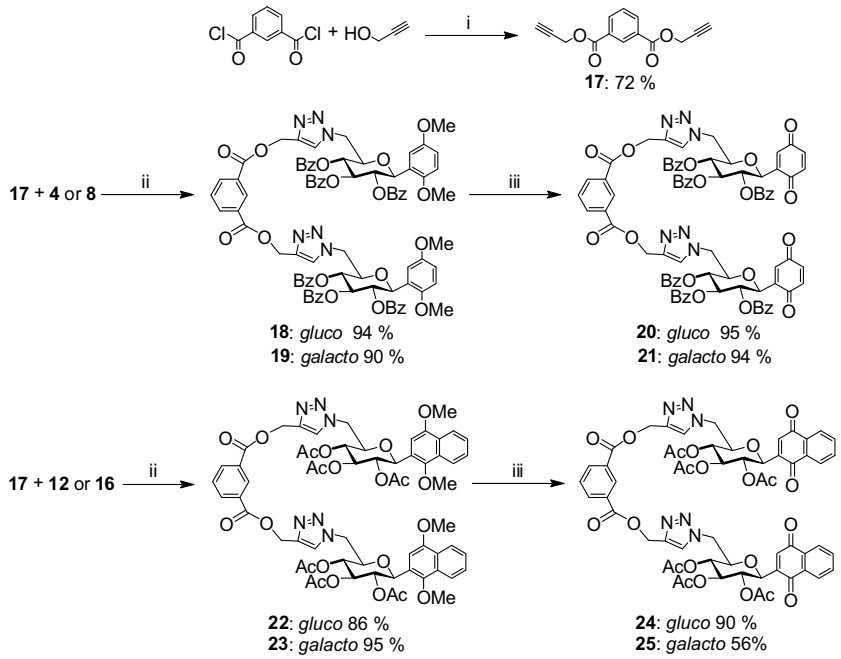
3. Experimental

3.1. Synthesis

Solvents were purified by standard procedures. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-500, AC-300 or AGH-250 spectrometers in $CDCl_3$ solutions. Optical rotations were measured using a Perkin-Elmer 241 polarimeter at room temperature and a 10-cm 1-mL cell. Column chromatography was performed on E. Merck Silica Gel 60 (230−400 mesh). Analytical thin-layer chromatography was performed on E. Merck aluminum percolated plates of Silica Gel 60F-254 with detection by UV and by spraying with 6 N H_2SO_4 and heating about 2 min at 300 °C. High resolution mass spectra (HRMS) were recorded on a MA1212 instrument using standard conditions (ESI, 70 eV).



Scheme 1. Reagents and conditions: (i) MeONa, MeOH; (ii) TrCl, Pyr.; (iii) BzCl; (iv) TFA, wet CH_2Cl_2; (v) MsCl, TEA; (vi) NaN_3, DMF, 90 °C; (vii) TBSCl, Pyr., DMAP; (viii) Ac_2O; (ix) AcCl, MeOH.



Scheme 2. Reagents and conditions: (i) Et_3N, DMAP; (ii) $CuSO_4$, Na ascorbate, CH_2Cl_2/H_2O; (iii) CAN, H_2O/MeCN.

Table 1
In vitro PTP1B enzyme inhibitory activity for compounds **18**–**25**

Compound	Inhibition[a] (%)	IC_{50} (μM)
18	97.8	0.87 ± 0.04
19	98.5	0.88 ± 0.01
20	95.8	0.62 ± 0.06
21	95.5	0.72 ± 0.05
22	12.5	—
23	7.5	—
24	8.5	—
25	0.8	—

[a] Values tested at 20 μg/mL concentration.

3.1.1. General procedure for the tritylation and tribenzoylation

Compounds **2** and **6** were synthesized by this procedure. The known 2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosyl-1,4-dimethoxybenzene (**1** or **5**)[32] was dissolved in MeOH, and 1–2 drops of a 1 M methanolic MeONa soln was added. The reaction mixture was kept at rt until completion of the reaction (TLC 10:1 CH_2Cl_2/MeOH). Resin (H^+ form) was then added to remove sodium ion. Filtration and concentration afford the fully deprotected glycosides which were used directly without purification. The deprotected compound was dissolved in dry pyridine (5 mL) and triphenylmethyl chloride (2.7 equiv) was added. The reaction mixture was stirred at rt until TLC indicated the disappearance of the starting materials, cooled to 0 °C and then BzCl (4 equiv) was added dropwise. The reaction mixture was stirred at rt for 6–10 h, H_2O (10–15 mL) was added to quench the reaction. The organic layer was diluted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$ and concentrated in vacuum, the residue was purified by column chromatography (10:1 to 5:1, petroleum ether/EtOAc).

3.1.1.1. 2-(2′,3′,4′-Tri-*O*-benzoyl-6′-*O*-triphenylmethyl-β-D-glucopyranosyl)-1,4-dimethoxy benzene (2). From compound **1** (402 mg, 0.86 mmol), column chromatography (10:1 to 5:1, petroleum ether/EtOAc) afforded **2** as a white solid (449 mg, 61%). TLC: R_f = 0.55 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = −19.3 (c = 0.6, $CHCl_3$); mp = 79–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13–7.07 (m, 31H, H-Ar), 6.79 (dd, $J_{5,3}$ = 2.9 Hz, $J_{5,6}$ = 8.8 Hz, 1H, H-5, dimethoxybenzene), 6.64 (d, $J_{6,5}$ = 8.8 Hz, 1H, H-6, dimethoxybenzene), 5.92 (m, 2H, H-3′, H-4′), 5.70 (dd, $J_{2',1'}$ = 10.3 Hz, $J_{2',3'}$ = 8.8 Hz, 1H, H-2′), 5.30 (d, $J_{1',2'}$ = 9.6 Hz, 1H, H-1′), 4.06 (m, 1H, H-5′), 3.78, 3.58 (2s, 6H, 2 × O*Me*), 3.41 (d, $J_{6'a,6'b}$ = 10.7 Hz, 1H, H-6′a), 3.18 (dd, $J_{6'b,5'}$ = 4.4 Hz, $J_{6'b,6'a}$ = 10.3 Hz, 1H, H-6′b); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 165.9, 164.7 (C=O), 153.7, 151.5 (C-1, C-4, dimethoxybenzene), 146.8, 133.6, 133.1, 132.9, 130.1, 129.9, 129.7, 129.1, 128.8, 128.5, 128.2, 128.1, 127.9, 127.8, 127.7, 127.2 (C-Ar), 125.4, 115.4, 112.8, 111.5 (C-2, C-3, C-5, C-6, dimethoxybenzene), 79.3, 76.7, 74.6, 73.8, 73.2 (C-1′ to C-5′), 61.0 (C-6′), 55.9, 55.8 (2 × O*Me*). HRESIMS: calcd for $C_{54}H_{46}O_{10}Na$: 877.2989; found: *m/z* 877.2979.

3.1.1.2. 2-(2′,3′,4′-Tri-*O*-benzoyl-6′-*O*-triphenylmethyl-β-D-galactopyranosyl)-1,4-di-methoxybenzene (6). From compound **5** (440 mg, 0.94 mmol), column chromatography (5:1 to 3:1, petroleum ether/EtOAc) afforded **6** as a white solid (764 mg, 96%). TLC: R_f = 0.57 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = +28.5 (c = 3.5, $CHCl_3$); mp = 72–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03–7.11 (m, 31H, H-Ar), 6.78 (dd, $J_{5,3}$ = 2.9 Hz, $J_{5,6}$ = 8.8 Hz, 1H, H-5, dimethoxybenzene), 6.68 (d, $J_{6,5}$ = 8.8 Hz, 1H, H-6, dimethoxybenzene), 6.28 (d, $J_{4',3'}$ = 2.9 Hz, 1H, H-4′), 5.97 (t, $J_{2',3'} = J_{2',1'}$ = 9.9 Hz, 1H, H-2′), 5.85 (dd, $J_{3',4'}$ = 3.3 Hz, $J_{3',2'}$ = 10.3 Hz, 1H, H-3′), 5.26 (d, $J_{1',2'}$ = 9.9 Hz, 1H, H-1′), 4.31 (dd, $J_{6'b,5'}$ = 5.9 Hz, $J_{6'a,5}$ = 8.1 Hz, 1H, H-5′), 3.82, 3.68 (2s, 6H, 2 × O*Me*), 3.54 (dd, $J_{6'b,5'}$ = 5.5 Hz, $J_{6'b,6'a}$ = 8.8 Hz, 1H, H-6′b), 3.35 (t, $J_{6'a,6'b} = J_{6'a,5'}$ = 8.4 Hz, 1H, H-6′a); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 165.2, 164.7 (C=O), 153.6, 151.2 (C-1, C-4, dimethoxybenzene), 143.3, 128.5, 127.7, 133.0, 132.9, 132.7, 129.8, 129.8, 129.5, 129.8, 129.4, 129.3, 128.4, 128.1, 128.1, 126.8 (C-Ar), 126.2, 114.4, 114.0, 111.5 (C-2, C-3, C-5, C-6, dimethoxybenzene), 86.8, 76.4, 73.5, 71.1, 68.9 (C-1′ to C-5′), 61.0 (C-6′), 55.8, 55.5 (2 × O*Me*). HRESIMS: calcd for $C_{54}H_{46}O_{10}Na$: 877.2989; found: *m/z* 877.2997.

3.1.2. General procedure for the detritylation

Compounds **3** and **7** were synthesized by this procedure. 6-*O*-triphenylmethyl β-*C*-aryl glycosides were dissolved in CH_2Cl_2

(5 mL) containing TFA (0.3 mL) and water (0.05 mL). The reaction mixture was kept for 3–5 h at rt, then diluted with CH_2Cl_2, washed with water, saturated aq $NaHCO_3$ and water. The organic phase was separated, dried and concentrated in vacuum. The residue was purified by column chromatography.

3.1.2.1. 2-(2′,3′,4′-Tri-*O*-benzoyl-β-D-glucopyranosyl)-1,4-dimethoxybenzene (3). From compound **2** (425 mg, 0.50 mmol), column chromatography (5:1 to 2:1, petroleum ether/EtOAc) afforded **3** as a white solid (240 mg, 79%). TLC: R_f = 0.31 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = −52.3 (c = 0.67, $CHCl_3$); mp = 75–78 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99–7.21 (m, 15H, 3 × OCOPh*H*), 7.13 (d, $J_{3,\ 5}$ = 2.9 Hz, 1H, H-3, dimethoxybenzene), 6.76 (dd, $J_{5,3}$ = 2.9 Hz, $J_{5,6}$ = 8.8 Hz, 1H, H-5, dimethoxybenzene), 6.65 (d, $J_{6,5}$ = 8 Hz, 1H, H-6, dimethoxybenzene), 6.07 (t, $J_{3',2'} = J_{4',3'}$ = 9.5 Hz, 1H, H-3′), 5.73 (t, $J_{2',1'} = J_{2',3'}$ = 9.6 Hz, 1H, H-2′), 5.61 (t, $J_{3',4'} = J_{4',5'}$ = 9.5 Hz, 1 H, H-4′), 5.30 (d, $J_{1',2'}$ = 9.5 Hz, 1H, H-1′), 3.96 (m, 1H, H-5′), 3.85 (m, 2H, H-6′a, H-6′b), 3.79, 3.65 (2s, 6H, 2 × O*Me*), 2.52 (br s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 166.1, 164.9 (C═O), 153.9, 151.5 (C-1, C-4, dimethoxybenzene), 133.7, 133.2, 133.1, 130.1, 129.9, 129.8, 130.0, 129.4, 129.3, 128.6, 128.4, 128.3 (C-Ar), 125.6, 115.5, 113.4, 111.8 (C-2, C-3, C-5, C-6, dimethoxybenzene), 79.2, 74.8, 73.9, 73.2, 70.2 (C-1′ to C-5′), 62.1 (C-6′), 56.1, 55.9 (2 × O*Me*). HRESIMS: calcd for $C_{35}H_{32}O_{10}Na$: 635.1893; found: *m/z* 635.1885.

3.1.2.2. 2-(2′,3′,4′-Tri-*O*-benzoyl-β-D-galactopyranosyl)-1,4-dimethoxybenzene (7). From compound **6** (757 mg, 0.89 mmol), column chromatography (5:1 to 2:1, petroleum ether/EtOAc) afforded **7** as a white solid (302 mg, 56%). TLC: R_f = 0.20 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = +76.5 (c = 0.75, $CHCl_3$); mp = 126–129 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18–7.23 (m, 15H, 3 × OCOPh*H*), 7.17 (d, $J_{3,5}$ = 3.3 Hz, H-3, 1H, dimethoxybenzene), 6.77 (dd, $J_{5,3}$ = 2.9 Hz, $J_{5,6}$ = 8.8 Hz, 1H, H-5, dimethoxybenzene), 6.67 (d, $J_{6,5}$ = 8.8 Hz, 1H, H-6, dimethoxybenzene), 6.10 (t, $J_{2',3'} = J_{2',1'}$ = 9.9 Hz, 1H, H-2′), 5.93 (d, $J_{4',3'}$ = 3.3 Hz, 1H, H-4′), 5.74 (dd, $J_{3',4'}$ = 3.3 Hz, $J_{3',2'}$ = 10.0 Hz, 1H, H-3′), 5.26 (d, $J_{1',2'}$ = 9.9 Hz, 1H, H-1′), 4.19 (m, 1H, H-5′), 3.84–3.63 (m, 2H, H-6′a, H-6′b), 3.78, 3.67 (2s, 6H, 2 × O*Me*), 2.59 (br s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 165.5, 164.9 (C═O), 153.6, 151.3 (C-1, C-4, dimethoxybenzene), 133.6, 133.1, 132.8, 129.9, 129.7, 129.5, 129.3, 129.0, 129.0, 128.6, 128.2, 128.0 (C-Ar), 126.0, 114.6, 114.0, 111.6 (C-2, C-3, C-5, C-6, dimethoxybenzene), 78.0, 73.4, 70.9, 69.8 (C-1′ to C-5′), 61.0 (C-6′), 55.8, 55.6 (2 × O*Me*). HRESIMS: calcd for $C_{35}H_{32}O_{10}Na$: 635.1893; found: *m/z* 635.1901.

3.1.3. General procedure for 6-azidation

Compounds **4**, **8**, **12**, and **16** were synthesized by this procedure. To a soln of sugar alcohol in dry CH_2Cl_2 (3–5 mL), MsCl (1.5 equiv) and Et_3N (1.8 equiv) were added at 0 °C. The ice-bath was removed and stirring was continued for 18 h. After which, MeOH (around 100 μL) was added, the soln was concentrated. The residue was dissolved in EtOAc (20–30 mL), washed with H_2O, aq $NaHCO_3$ (5%) and brine successively. The organic layer was dried over $MgSO_4$, filtered and concentrated to an oil, which was used directly without purification. The mesylate was dissolved in dried DMF (2–3 mL) and NaN_3 (5 equiv) was added. The reaction mixture was heated to 90 °C for around 20 h. After TLC indicated the formation of a single product, the mixture was concentrated in vacuum. The residue was diluted in EtOAc (30 mL), washed successively with water and brine, dried with $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography.

3.1.3.1. 2-(6′-Azido-2′,3′,4′-tri-*O*-benzoyl-6′-deoxy-β-D-glucopyranosyl)-1,4-dimethoxy benzene (4). From compound **3** (872 mg, 1.42 mmol), column chromatography (6:1 to 5:1, petroleum ether/EtOAc) afforded **4** as a white solid (513 mg, 57%). TLC: R_f = 0.58 (cyclohexane/EtOAc, 3:2); $[\alpha]_D$ = +24.2 (c = 0.98, $CHCl_3$); mp = 131–133 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01–7.29 (m, 15H, 3 × OCOPh*H*), 7.19 (d, $J_{3,5}$ = 2.9 Hz, 1H, H-3, dimethoxybenzene), 6.80 (dd, $J_{5,3}$ = 2.9 Hz, $J_{5,6}$ = 8.8 Hz, 1H, H-5, dimethoxybenzene), 6.67 (d, $J_{6,5}$ = 8.8 Hz, 1H, H-6, dimethoxybenzene), 6.07 (t, $J_{3',4'} = J_{2',3'}$ = 9.6 Hz, 1H, H-3′), 5.73 (t, $J_{2',1'} = J_{2',3'}$ = 9.5 Hz, 1H, H-2′), 5.68 (t, $J_{3',4'} = J_{4',5'}$ = 9.6 Hz, 1H, H-4′), 5.37 (d, $J_{1',2'}$ = 9.9 Hz, 1H, H-1′), 4.17 (m, 1H, H-5′), 3.82, 3.65 (2s, 6H, 2 × O*Me*), 3.61 (dd, $J_{6'a,5'}$ = 2.6 Hz, $J_{6'a,6'b}$ = 12.9 Hz, 1H, H-6′a), 3.43 (dd, $J_{6'b,5'}$ = 5.5 Hz, $J_{6'a,6'b}$ = 13.2 Hz, 1H, H-6′b); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 165.2, 164.6 (C═O), 153.8, 151.0 (C-1, C-4, dimethoxybenzene), 133.4, 133.0, 132.8, 129.8, 129.6, 129.5, 129.2, 129.0, 128.8, 128.4, 128.1, 128.0 (C-Ar), 125.1, 115.8, 112.3, 111.5 (C-2, C-3, C-5, C-6, dimethoxybenzene), 77.7, 74.5, 73.8, 73.2, 70.3 (C-1′ to C-5′), 55.7, 55.7 (2 × O*Me*), 51.1 (C-6′). HRESIMS: calcd for $C_{35}H_{31}N_3O_9Na$: 660.1958; found: *m/z* 660.1957.

3.1.3.2. 2-(6′-Azido-2′,3′,4′-tri-*O*-benzoyl-6′-deoxy-β-D-galactopyranosyl)-1,4-dimethoxy benzene (8). From compound **7** (286 mg, 0.47 mmol), column chromatography (5:1 to 3:1, petroleum ether/EtOAc) afforded **8** as a white solid (231 mg, 78%). TLC: R_f = 0.50 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = +22.2 (c = 4.0, $CHCl_3$); mp = 62–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15–7.24 (m, 15H, 3 × OCOPh*H*), 7.22 (d, $J_{3,5}$ = 2.9 Hz, 1H, H-3, dimethoxybenzene), 6.77 (dd, $J_{5,3}$ = 2.9 Hz, $J_{5,6}$ = 8.8 Hz, 1H, H-5, dimethoxybenzene), 6.67 (d, $J_{6,5}$ = 8.8 Hz, 1H, H-6, dimethoxybenzene), 6.03 (t, $J_{2',3'} = J_{2',1'}$ = 9.9 Hz, 1H, H-2′), 5.97 (d, $J_{4',3'}$ = 3.3 Hz, 1H, H-4′), 5.72 (dd, $J_{3',4'}$ = 3.3 Hz, $J_{3',2'}$ = 10.3 Hz, 1H, H-3′), 5.28 (d, $J_{1',2'}$ = 10.3 Hz, 1H, H-1′), 4.23 (m, 1H, H-5′), 3.80, 3.66 (2s, 6H, 2 × O*Me*), 3.61 (dd, $J_{6'a,5'}$ = 7.1 Hz, $J_{6'a,6'b}$ = 12.8 Hz, 1H, H-6′a), 3.43 (dd, $J_{6'b,5'}$ = 4.8 Hz, $J_{6'a,6'b}$ = 12.9 Hz, 1H, H-6′b); ^{13}C NMR (75 MHz, $CDCl_3$): 165.6, 165.6, 164.8 (C═O), 153.6, 151.3 (C-1, C-4, dimethoxybenzene), 133.5, 133.1, 132.8, 129.8, 129.7, 129.5, 129.3, 129.2, 128.9, 128.6, 128.1, 128.0 (C-Ar), 125.8, 114.7, 113.7, 111.5 (C-2, C-3, C-5, C-6, dimethoxybenzene), 76.6, 73.3, 70.6, 69.5 (C-1′ to C-5′), 55.8, 55.6 (2 × O*Me*), 51.0 (C-6′). HRESIMS: calcd for $C_{35}H_{31}N_3O_9Na$: 660.1958; found: *m/z* 660.1969.

3.1.4. General procedure for the 6-*O*-silylation and 2,3,4-*O*-acetylation

Compounds **10** and **14** were synthesized by this procedure. To a soln of aryl glycosides **9**[33] or **13**[33] in dry pyridine (2–3 mL), TBDMSCl (1.5 equiv) and DMAP (0.2 equiv) were added at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was warmed to rt and stirred continuously for 20 h, Ac_2O (5 equiv) was added at rt and the reaction mixture kept stirring until TLC indicated completion of the reaction. The resulting mixture was diluted with water and then extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuum to give a crude residue, and then purified by column chromatography.

3.1.4.1. 2-(2′,3′,4′-Tri-*O*-acetyl-6′-*O*-tert-butyldimethylsilyl-β-D-glucopyranosyl)-1,4-di methoxynaphthalene (10). From compound **9** (369 mg, 1.05 mmol), column chromatography (10:1 to 5:1, petroleum ether/EtOAc) afforded **10** as a white solid (307 mg, 49%). TLC: R_f = 0.47 (petroleum ether/EtOAc, 3:1); $[\alpha]_D$ = −3.05 (c = 0.3, $CHCl_3$); mp = 46–48 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.22, 8.03 (2d, J = 7.5 Hz, 2H, H-5, H-8, Ar*H*), 7.51 (m, 2H, H-6, H-7, Ar*H*), 6.77 (s, 1H, H-3, Ar*H*), 5.42 (m, 2H, H-2′, H-3′), 5.32 (m, 1H, H-4′), 5.07 (d, $J_{1',2'}$ = 10.0 Hz, 1H, H-1′), 3.97, 3.92 (2s, 6H, 2 × O*Me*), 3.80–3.73 (m, 3H, H-5′, H-6′a, H-6′b), 2.06, 2.02, 1.71 (3s, 9H, 3 × OCOCH_3), 0.83 (s, 9H, *t*Bu), −0.06, −0.01 (2*s*, 6H, 2 × *Me*); HRESIMS: calcd for $C_{30}H_{42}O_{10}SiNa$: 613.2445; found: *m/z* 613.2432.

3.1.4.2. 2-(2′,3′,4′-Tri-*O*-acetyl-6′-*O*-tert-butyldimethylsilyl-β-D-galactopyranosyl)-1,4-dimethoxynaphthalene (14). From compound **13**[33] (101.8 mg, 0.29 mmol), column chromatography (10:1 to 5:1, petroleum ether/EtOAc) afforded **14** as a white solid (112 mg, 65%). TLC: R_f = 0.60 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = −11.7 (*c* = 1.4, $CHCl_3$); mp = 53–56 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22, 8.05 (2d, *J* = 7.5 Hz, 2H, H-5, H-8, Ar*H*), 7.52 (m, 2H, H-6, H-7, Ar*H*), 6.82 (s, 1H, H-3, Ar*H*), 5.70 (m, 2H, H-2′, H-4′), 5.31 (dd, $J_{3',4'}$ = 3.3 Hz, $J_{3',2'}$ = 9.9 Hz, 1H, H-3′), 5.08 (d, $J_{1',2'}$ = 9.9 Hz, 1H, H-1′), 4.01, 3.93 (2s, 6H, 2 × O*Me*), 3.98 (m, 1H, H-5′), 3.76–3.59 (m, 2H, H-6′a, H-6′b), 2.23, 2.00, 1.72 (3s, 9H, 3 × OCOC*H*$_3$), 0.84 (s, 9H, *t*Bu), −0.01, −0.01 (2s, 6H, 2 × *Me*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 170.2, 169.4 (C=O), 152.3, 148.9 (C-1, C-4, Ar*C*), 128.3, 127.2, 126.8, 126.2, 124.1, 122.6, 122.4 (C-2, C-5 to C-10, Ar*C*), 102.1 (C-3, Ar*C*), 78.0, 74.9, 73.1, 68.8, 68.1 (C-1′ to C-5′), 63.5 (OCH_3), 60.9 (C-6′), 55.8 (O*Me*), 25.8 (*t*Bu), 21.0, 20.8, 20.7 (3 × OCOCH_3), 18.3 (C_q, *t*Bu), −5.4, −5.6 (2 × *Me*). HRESIMS: calcd for $C_{30}H_{42}O_{10}SiNa$: 613.2445; found: *m/z* 613.2437.

3.1.5. General procedure for the deprotection of silyl group

Compounds **11** and **15** were synthesized by this procedure. To a stirred soln of silylated glycosides (**10** or **14**) in dry MeOH (2–3 mL) was added AcCl (0.15 equiv) at ice-bath temperature. The reaction mixture was stirred at rt for 5 h. After completion of the reaction (monitored by TLC), CH_2Cl_2 (15–20 mL) was added, the reaction mixture was neutralized with 5% $NaHCO_3$ (2–3 mL) and washed with H_2O (5 mL). Finally, the organic layer was dried over $MgSO_4$ and concentrated in vacuum to give a crude residue, which was used directly in next step or purified by column chromatography.

3.1.5.1. 2-(2′,3′,4′-Tri-*O*-acetyl-β-D-glucopyranosyl)-1,4-dimethoxynaphthalene (11). From compound **10** (452 mg, 0.77 mmol), the crude product **11** was obtained as a colorless oil (360 mg, 99%). TLC: R_f = 0.19 (cyclohexane/EtOAc, 3:2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.23, 8.04 (2d, *J* = 7.5 Hz, 2H, H-5, H-8, Ar*H*), 7.52 (m, 2H, H-6, H-7, Ar*H*), 6.75 (s, 1H, H-3, Ar*H*), 5.52–5.47 (m, 2H, H-3′, H-4′), 5.24 (t, $J_{2',1'} = J_{2',3'}$ = 9.5 Hz, 1H, H-2′), 5.14 (d, $J_{1',2'}$ = 9.5 Hz, 1H, H-1′), 4.00, 3.93 (2s, 6H, 2 × OCH_3), 3.81–3.65 (m, 3H, H-5′, H-6′a, H-6′b), 2.10, 2.03, 1.72 (3s, 9H, 3 × OCOC*H*$_3$). HRESIMS: calcd for $C_{24}H_{28}O_{10}Na$: 499.1580; found: *m/z* 499.1573.

3.1.5.2. 2-(2′,3′,4′-Tri-*O*-acetyl-β-D-galactopyranosyl)-1,4-dimethoxynaphthalene (15). From compound **14** (352 mg, 0.60 mmol), column chromatography (5:1 to 2:1, petroleum ether/EtOAc) afforded **15** as a pale brown solid (107 mg, 38%). TLC: R_f = 0.29 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = +6.0 (*c* = 0.84, $CHCl_3$); mp = 67–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23, 8.04 (2d, *J* = 7.7 Hz, 2H, H-5, H-8, Ar*H*), 7.53 (m, 2H, H-6, H-7, Ar*H*), 6.80 (s, 1H, H-3, Ar*H*), 5.75 (t, $J_{2',1'} = J_{2',3'}$ = 9.9 Hz, 1H, H-2′), 5.56 (d, $J_{4',3'}$ = 3.3 Hz, 1H, H-4′), 5.32 (dd, $J_{3',4'}$ = 3.7 Hz, $J_{3',2'}$ = 9.9 Hz, 1H, H-3′), 5.10 (d, $J_{1',2'}$ = 9.9 Hz, 1H, H-1′), 4.04 (m, 1H, H-5′), 4.02, 3.93 (2s, 6H, 2 × O*Me*), 3.74 (dd, $J_{6'a,5'}$ = 7.0 Hz, $J_{6'a,6'b}$ = 11.8 Hz, 1H, H-6′a), 3.93 (dd, $J_{6'b,5'}$ = 5.9 Hz, $J_{6'b,6'a}$ = 11.8 Hz, 1H, H-6′b), 2.27, 2.02, 1.73 (3s, 9H, 3 × OCOC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 170.3, 169.4 (C=O), 152.4, 149.0 (C-1, C-4, Ar*C*), 128.3, 127.2, 127.0, 126.3, 123.9, 122.7, 122.4 (C-2, C-5 to C-10, Ar*C*), 102.0 (C-3, Ar*C*), 78.2, 75.0, 72.8, 69.0, 68.7 (C-1′ to C-5′), 63.5 (O*Me*), 61.2 (C-6′), 55.9 (O*Me*), 21.0, 20.8, 20.7 (3 × OCOCH_3). HRESIMS: calcd for $C_{24}H_{28}O_{10}Na$: 499.1580; found: *m/z* 499.1562.

3.1.6. 2-(2′,3′,4′-Tri-*O*-acetyl-6′-azido-6′-deoxy-β-D-glucopyranosyl)-1,4-dimethoxy naphthalene (12)

Compound **11** (307 mg, 0.64 mmol) was treated with MsCl/Et_3N and NaN_3 according to the general procedure. Column chromatography (3:1, petroleum ether/EtOAc) afforded **12** as a white solid (251 mg, 83%). TLC: R_f = 0.69 (cyclohexane/EtOAc, 1:1); $[\alpha]_D$ = +5.2 (*c* = 1.6, $CHCl_3$); mp = 143–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22, 8.03 (2d, *J* = 7.7 Hz, 2H, H-5, H-8, Ar*H*), 7.51 (m, 2 H, H-6, H-7, Ar*H*), 6.78 (s, 1H, H-3, Ar*H*), 5.45 (m, 2H, H-2′, H-4′), 5.34 (t, $J_{3',4'} = J_{3',2'}$ = 9.6 Hz, 1H, H-3′), 5.14 (d, $J_{1',2'}$ = 9.2 Hz, 1H, H-1′), 3.97, 3.93 (2s, 6H, 2 × O*Me*), 3.95 (m, 1H, H-5′), 3.52 (dd, $J_{6'a,5'}$ = 2.2 Hz, $J_{6'a,6'b}$ = 13.6 Hz, 1H, H-6′a), 3.21 (dd, $J_{6'b,5'}$ = 4.8 Hz, $J_{6'a,6'b}$ = 13.6 Hz, 1H, H-6′b), 2.06, 2.02, 1.71 (3s, 9H, 3 × OCOC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 169.4, 168.8 (C=O), 152.3, 148.3 (C-1, C-4, Ar*C*), 127.9, 127.0, 126.7, 126.0, 123.4, 122.5, 122.1 (C-2, C-5 to C-10, Ar*C*), 101.1 (C-3, Ar*C*), 76.6, 74.5, 73.9, 71.2, 69.5 (C-1′ to C-5′), 63.1, 55.6 (2 × O*Me*), 50.7 (C-6′), 20.5, 20.3 (3 × OCOCH_3). HRESIMS: calcd for $C_{24}H_{27}N_3O_9Na$: 524.1645; found: *m/z* 524.1651.

3.1.7. 2-(2′,3′,4′-Tri-*O*-acetyl-6′-azido-6′-deoxy-β-D-galactopyranosyl)-1,4-dimethoxy naphthalene (16)

Compound **15** (91 mg, 0.19 mmol) was treated with MsCl/Et_3N and NaN_3 according to the general procedure. Column chromatography (4:1, petroleum ether/EtOAc) afforded **16** as a pale yellow oil (64 mg, 67%). TLC: R_f = 0.42 (cyclohexane/EtOAc, 2:1); $[\alpha]_D$ = −0.7 (*c* = 0.29, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23, 8.05 (2d, *J* = 7.4 Hz, 2H, H-5, H-8, Ar*H*), 7.55 (m, 2H, H-6, H-7, Ar*H*), 6.82 (s, 1H, H-3, Ar*H*), 5.71 (t, $J_{2',3'} = J_{2',1'}$ = 9.9 Hz, 1H, H-2′), 5.56 (d, $J_{4',3'}$ = 2.9 Hz, 1H, H-4′), 5.28 (dd, $J_{3',4'}$ = 3.3 Hz, $J_{3',2'}$ = 10.3 Hz, 1H, H-3′), 5.10 (d, $J_{1',2'}$ = 10.3 Hz, 1H, H-1′), 4.07 (m, 1H, H-5′), 4.02, 3.95 (2s, 6H, 2 × O*Me*), 3.50 (d, $J_{6'a,5'}$ = 7.0 Hz, $J_{6'a,6'b}$ = 12.9 Hz, 1H, H-6′a), 3.32 (dd, $J_{6'b,5'}$ = 5.2 Hz, $J_{6'a,6'b}$ = 12.9 Hz, 1H, H-6′b), 2.28, 2.01, 1.72 (3s, 9H, 3 × OCOC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 170.3, 169.3 (C=O), 152.4, 148.9 (C-1, C-4, Ar*C*), 128.2, 127.2, 126.9, 126.3, 123.7, 122.7, 122.4 (C-2, C-5 to C-10, Ar*C*), 101.9 (C-3, Ar*C*), 76.4, 72.7, 68.9, 68.3 (C-1′ to C-5′), 63.4, 55.8 (2 × O*Me*), 50.9 (C-6′), 21.0, 20.8, 20.6 (3 × OCOC*H*$_3$). HRESIMS: calcd for $C_{24}H_{27}N_3O_9Na$: 524.1645; found: *m/z* 524.1640.

3.1.8. Dipropargyl isophthalate (17)

To a suspension of isophthaloyl chloride (693 mg, 3.41 mmol) and DMAP (83 mg, 0.68 mmol) in dry CH_2Cl_2 (15 mL), propargyl alcohol (403 μL, 6.83 mmol), and Et_3N (3.2 mL, 22.5 mmol) were added at 0 °C. The mixture was stirred at 0 °C for 3 h and then warmed to rt for another 48 h, filtered, and the precipitate was rinsed with CH_2Cl_2. The combined filtrate was washed with 1 M HCl and brine, dried over $MgSO_4$ and concentrated in vacuum to give a pale yellow powder. The crude product was purified by column chromatography (2:1, petroleum ether/EtOAc) to afford **17** as a white powder (598 mg, 72%). TLC: R_f = 0.64 (cyclohexane/EtOAc, 2:1); mp = 82–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74 (s, 1H, H-2, Ar*H*), 8.28 (dd, 2H, *J* = 1.9 and 7.7 Hz, H-4, H-6, Ar*H*), 7.57 (t, 1H, *J* = 7.7 Hz, H-5, Ar*H*), 4.96 (d, 4H, *J* = 1.8 Hz, 2 × CH_2), 2.54 (t, 2H, *J* = 1.8 Hz, 2 × C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8 (C=O), 134.4, 131.1, 128.8 (Ar), 130.0 (C_q, Ar), 77.4 (C_q), 75.3 (*C*H), 52.8 (CH_2).

3.1.9. General procedure for the Huisgen cycloaddition

Compounds **18, 19, 22**, and **23** were synthesized by this procedure. 6-Azido *C*-aryl glycoside (2 equiv) was dissolved in CH_2Cl_2 (1.5 mL), dipropargyl ester **17** (1 equiv), H_2O (1.5 mL), copper sulfate (0.2 equiv) and sodium ascorbate (0.4 equiv) were added successively. The resulting mixture was stirred at rt until TLC indicated the disappearance of the starting materials. The mixture was diluted with CH_2Cl_2 (15 mL), washed with water, dried over $MgSO_4$, filtered and concentrated to give the desired compound. If the residue was chromatographically not uniform, it was purified by column chromatography.

3.1.9.1. Dimeric aryl-β-*C*-D-glucopyranoside 18. From compound **4** (108 mg, 0.17 mmol), Huisgen cycloaddition afforded **18** as a pink solid without purification (121 mg, 94%). TLC: R_f = 0.19 (cyclohexane/EtOAc, 1:1); $[\alpha]_D$ = –18.2 (c = 0.68, $CHCl_3$); mp = 133–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (s, 1H, H-2″, Phth), 8.17 (d, J = 7.7 Hz, 2H, H-4″, H-6″ Phth), 8.02–7.25 (m, 33H, Ar-H, 2 × C*H* triazole), 7.12 (d, $J_{3,5}$ = 2.6 Hz, 2H, 2 × H-3, dimethoxybenzene), 6.76 (dd, $J_{5,3}$ = 2.9 Hz, $J_{5,6}$ = 8.8 Hz, 2H, 2 × H-5, dimethoxybenzene), 6.63 (d, $J_{6,5}$ = 8.8 Hz, 2H, 2 × H-6, dimethoxybenzene), 6.08 (t, $J_{3',2'} = J_{3',4'}$ = 9.3 Hz, 2H, 2 × H-3′), 5.81 (t, $J_{2',1'} = J_{2',3'}$ = 9.5 Hz, 2H, 2 × H-2′), 5.59 (t, $J_{4',5'} = J_{4',3'}$ = 9.5 Hz, 2H, 2 × H-4′), 5.44 (s, 4H, 2 × CH_2), 5.26 (d, $J_{1',2'}$ = 9.9 Hz, 2H, 2 × H-1′), 4.85 (d, $J_{6'a,6'b}$ = 14.3 Hz, 2H, 2 × H-6′a), 4.59 (dd, $J_{6'b,5'}$ = 8.1 Hz, $J_{6'b,6'a}$ = 14.4 Hz, 2H, 2 × H-6′b), 4.43 (m, 2H, 2 × H-5′), 3.78, 3.59 (2s, 12H, 4 × O*Me*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 165.5, 165.2, 164.6 (C=O), 153.6, 151.2 (C-1, 2 × C-4, dimethoxybenzene), 134.0, 133.6, 133.1, 133.0, 130.9, 130.1, 129.9, 129.6, 129.5, 129.0, 128.8, 128.5, 128.4, 128.2, 128.0, 125.5 (C-Ar, C-triazole), 124.6, 115.8, 112.3, 111.5 (C-2, C-3, C-5, C-6, dimethoxybenzene), 77.0 (C-5′), 74.3 (C-3′), 74.0 (C-1′), 72.3 (C-2′), 70.8 (C-4′), 58.2 (*C*H$_2$), 55.7, 55.6 (O*Me*), 51.6 (C-6′); HRESIMS: calcd for $C_{84}H_{72}N_6O_{22}Na$: 1539.4597; found: m/z 1539.4618.

3.1.9.2. Dimeric aryl-β-*C*-D-galactopyranoside 19. From compound **8** (51 mg, 0.08 mmol), column chromatography (1:1, petroleum ether/EtOAc) afforded **19** as a pale yellow solid (54 mg, 90%). TLC: R_f = 0.17 (cyclohexane/EtOAc, 1:1); $[\alpha]_D$ = +130.7 (c = 0.41, $CHCl_3$); mp = 110–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (s, 1H, H-2‴ Phth), 8.23–7.19 (m, 35H, Ar-H, 2 × C*H* triazole), 7.12 (d, $J_{3,5}$ = 2.9 Hz, 2H, 2 × H-3, dimethoxybenzene), 6.75 (dd, $J_{5,3}$ = 2.9 Hz, $J_{5,6}$ = 8.8 Hz, 2H, 2 × H-5, dimethoxybenzene), 6.63 (d, $J_{6,5}$ = 8.8 Hz, 2H, 2 × H-6, dimethoxybenzene), 6.10 (t, $J_{2',3'} = J_{2',1'}$ = 9.9 Hz, 2H, 2 × H-2′), 6.02 (d, $J_{4',3'}$ = 3.3 Hz, 2H, 2 × H-4′), 5.72 (dd, $J_{3',4'}$ = 3.3 Hz, $J_{3',2'}$ = 10.3 Hz, 2H, 2 × H-3′), 5.40 (s, 4H, 2 × CH_2), 5.20 (d, $J_{1',2'}$ = 9.9 Hz, 2H, 2 × H-1′), 4.76 (d, $J_{6'a,6'b}$ = 11.4 Hz, 2H, 2 × H-6′a), 4.55 (m, 4H, 2 × H-5′, 2 × H-6′b), 3.78, 3.59 (2s, 12H, 4 × O*Me*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 165.4, 165.3, 164.8 (C=O), 153.6, 151.4 (C-1, C-4, dimethoxybenzene), 142.4 (C_q, triazole), 134.0, 133.8, 133.1, 133.0, 130.9, 130.1, 129.9, 129.6, 129.5, 129.1, 128.9, 128.8, 128.7, 128.2, 128.1, 128.5 (C-Ar), 125.3, 114.6, 113.8, 111.6 (CH triazole, C-2, C-3, C-5, C-6, dimethoxybenzene), 76.2, 74.4, 73.1, 70.0, 69.6 (C-1′ to C-5′), 58.2 (*C*H$_2$), 55.7, 55.6 (O*Me*), 51.0 (C-6′); HRESIMS: calcd for $C_{84}H_{72}N_6O_{22}Na$: 1539.4597; found: m/z 1539.4562.

3.1.9.3. Dimeric aryl-β-*C*-D-glucopyranoside 22. From compound **12** (60 mg, 0.12 mmol), column chromatography (1:1 petroleum ether/EtOAc to EtOAc) afforded **22** as a pale yellow solid (63 mg, 86%). TLC: R_f = 0.08 (cyclohexane/EtOAc, 1:1); $[\alpha]_D$ = –10.7 (c = 0.36, $CHCl_3$); mp = 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44 (s, 1H, H-2″ Phth), 8.19, 7.91 (2 m, 4H, 2 × H-5, 2 × H-8, dimethoxynaphthalene), 7.95 (dd, J = 1.9 Hz and 7.7 Hz, 2H, H-4″, H-6″ Phth), 7.66 (s, 2H, 2 × C*H*, triazole), 7.48 (m, 4H, 2 × H-6, 2 × H-7, dimethoxynaphthalene), 7.20 (t, J = 7.7 Hz, 1H, H-4″ Phth), 6.68 (s, 2H, 2 × H-3, dimethoxynaphthalene), 5.46 (m, 4H, 2 × H-2′, 2 × H-3′), 5.32 (s, 4H, 2 × CH_2), 5.06 (m, 4H, 2 × H-1′, 2 × H-4′), 4.65 (dd, $J_{6'a,5'}$ = 2.6 Hz, $J_{6'a,\ 6'b}$ = 14.7 Hz, 2H, 2 × H-6′a), 4.42 (dd, $J_{6'b,5'}$ = 7.7 Hz, $J_{6'b,6'a}$ = 14.7 Hz, 2H, 2 × H-6′b), 4.17 (m, 2H, 2 × H-5′), 3.96, 3.64 (2s, 12H, 4 × O*Me*), 2.12, 2.00, 1.68 (3s, 18H, 6 × OCOC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 169.7, 168.9, 165.1 (C=O), 152.2, 148.8 (C-1, C-4, dimethoxynaphthalene), 142.5 (C_q, triazole), 133.8, 130.6, 129.9, 128.4 (C-1″ to C-6″, Phth), 127.9, 127.0, 126.8, 126.2 (C-6, C-7, C-9, C-10, dimethoxynaphthalene), 125.4 (*C*H, triazole), 122.7, 122.4, 122.1 (C-2, C-5, C-8, dimethoxynaphthalene), 101.0 (C-3, dimethoxynaphthalene), 76.6, 74.2, 74.0, 70.6, 70.0 (C-1′ to C-5′), 63.1 (O*C*H$_3$), 58.1 (*C*H$_2$), 55.6 (O*Me*), 51.0 (C-6′), 20.6, 20.5, 20.2 (OCO*C*H$_3$); HRESIMS: calcd for $C_{62}H_{64}N_6O_{22}Na$: 1267.3971; found: m/z 1267.3981.

3.1.9.4. Dimeric aryl-β-*C*-D-galactopyranoside 23. From compound **16** (49 mg, 0.098 mmol), Huisgen cycloaddition afforded **23** as a pale yellow solid without purification (58 mg, 95%). TLC: R_f = 0.11 (cyclohexane/EtOAc, 1:1); $[\alpha]_D$ = +8.2 (c = 3.2, $CHCl_3$); mp = 88–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.48 (s, 1H, H-2″, Phth), 8.20, 7.90 (2m, 4H, 2 × H-5, 2 × H-8, dimethoxynaphthalene), 8.00 (d, J = 7.4 Hz, 2H, H-4″, H-6″, Phth), 7.49 (m, 6 H, 2 × C*H* triazole, 2 × H-6, 2 × H-7 dimethoxynaphthalene), 7.25 (t, J = 7.7 Hz, 1H, H-4″, Phth), 6.78 (s, 2H, 2 × H-3, dimethoxynaphthalene), 5.74 (t, $J_{2',3'} = J_{2',1'}$ = 9.9 Hz, 2H, H-2′), 5.61 (d, $J_{4',3'}$ = 2.9 Hz, 2H, H-4′), 5.35 (s, 4H, 2 × CH_2), 5.29 (dd, $J_{3',4'}$ = 2.9 Hz, $J_{3',2'}$ = 9.9 Hz, 2H, 2 × H-3′), 5.04 (d, $J_{1',2'}$ = 10.3 Hz, 2H, 2 × H-1′), 4.64–4.45 (m, 6H, 2 × H-5′, 2 × H-6′a, 2 × H-6′b), 4.01, 3.61 (2s, 12H, 4 × O*Me*), 2.28, 2.00, 1.70 (3s, 18H, 6 × COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 170.1, 169.3, 165.2 (C=O), 152.2, 149.1 (C-1, C-4, dimethoxynaphthalene), 142.9 (C_q, triazole), 134.0, 130.8, 130.1, 127.9 (C-1″ to C-6″, Phth), 128.1, 127.1, 126.9, 126.3, 123.2, 122.6, 122.3 (C-2, C-5 to C-10, dimethoxynaphthalene), 125.3 (CH triazole), 101.8 (C-3, dimethoxynaphthalene), 76.1, 74.9, 72.5, 68.9, 67.9 (C-1′ to C-5′), 63.3 (O*C*H$_3$), 58.9 (*C*H$_2$), 55.8 (O*Me*), 49.1 (C-6′), 20.9, 20.7, 20.6 (OCO*C*H$_3$); HRESIMS: calcd for $C_{62}H_{64}N_6O_{22}Na$: 1267.3971; found: m/z 1267.3971.

3.1.10. General procedure for oxidation of 1,4-dimethoxy benzene or naphthalene derivatives

Compounds **18, 19, 22**, and **23** were oxidized by this procedure. A soln of CAN (3 equiv) in water (1–2 mL/mmol) was added to a soln of the 1,4-dimethoxy benzene or naphthalene derivative in MeCN (1–2 mL/mmol). After stirring at rt in the dark for 1 h, the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 soln was washed with brine and dried over $MgSO_4$, then concentrated under diminished pressure. The crude product was purified by column chromatography.

3.1.10.1. Dimeric β-*C*-D-glucopyranosyl 1,4-benzoquinone 20. Oxidation of compound **18** (107 mg, 0.071 mmol) and purification by column chromatography (1:1 petroleum ether/EtOAc to 10:1 CH_2Cl_2/MeOH) afforded **20** as a yellow solid (98 mg, 95%). TLC: R_f = 0.43 (cyclohexane/EtOAc = 2:3); $[\alpha]_D$ = –61.5 (c = 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (s, 1H, Ar-H), 8.22, 8.20 (2s, 2H, C*H* triazole), 8.00–7.23 (m, 33H, Ar-H), 7.01 (d, 2H, $J_{3,5}$ = 2.2 Hz, 2 × H-3 benzoquinone), 6.71 (dd, 2H, $J_{5,3}$ = 2.6 Hz, $J_{5,6}$ = 10.3 Hz, 2 × H-5 benzoquinone), 6.64 (d, 2H, $J_{6,5}$ = 10.3 Hz, 2 × H-6 benzoquinone), 6.08 (t, 2H, $J_{3',4'}$ = 9.6 Hz, $J_{3',2'}$ = 9.2 Hz, 2 × H-3′), 5.58 (m, 4H, 2 × H-2′, 2 × H-4′), 5.48 (s, 4H, 2 × CH_2), 4.93 (d, 2H, $J_{1',\ 2'}$ = 9.5 Hz, 2 × H-1′), 4.83 (d, 2H, $J_{6'a,6'b}$ = 12.9 Hz, 2 × H-6′a), 4.61 (dd, 2H, $J_{6'b,5'}$ = 8.5 Hz, $J_{6'b,6'a}$ = 14.7 Hz, 2 × H-6′b), 4.42 (m, 2H, 2 × H-5′); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.6, 184.9, 165.5, 165.5, 165.3, 165.2 (C=O), 143.3 (C-2, benzoquinone), 142.8 (Cq, triazole), 136.3, 136.3 (C-5, C-6, benzoquinone), 134.0, 133.8, 133.5, 133.5, 133.2, 131.0, 130.1, 129.9, 129.7, 129.5, 128.6, 128.5, 128.4, 128.2, 128.1 (Ar), 125.5 (*C*H triazole), 77.2, 73.4, 72.9, 72.7, 70.3 (C-1′ to C-5′), 58.3 (*C*H$_2$), 51.2 (C-6′). HRESIMS: calcd for $C_{80}H_{60}N_6O_{22}$: 1479.3658; found: m/z 1479.3660.

3.1.10.2. Dimeric β-*C*-D-galactopyranosyl 1,4-benzoquinone 21. Oxidation of compound **19** (42 mg, 0.028 mmol) afforded **21** as a yellow solid (38 mg, 94%). TLC: R_f = 0.53 (cyclohexane/EtOAc = 1:2); $[\alpha]_D$ = +27.9 (c = 1.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (s, 1H, Ar-H), 8.15–7.20 (m, 35H, Ar-H, 2 × C*H* triazole), 7.06 (d, 2H, $J_{3,5}$ = 2.6 Hz, 2 × H-3, benzoquinone), 6.70 (dd, 2H, $J_{5,3}$ = 2.6 Hz, $J_{5,6}$ = 10.3 Hz, 2 × H-5, benzoquinone), 6.62 (d,

2H, $J_{6,5}$ = 10.3 Hz, 2 × H-6, benzoquinone), 6.04 (t, 2H, $J_{4',3'}$ = 2.2 Hz, 2 × H-4′), 5.79 (m, 4H, 2 × H-2′, 2 × H-3′), 5.42 (s, 4H, 2 × CH_2), 4.92 (d, 2H, $J_{1',2'}$ = 8.5 Hz, 2 × H-1′), 4.73 (d, 2H, $J_{6'a,6'b}$ = 11.4 Hz, 2 × H-6′a), 4.62–4.51 (m, 4H, 2 × H-6′b, 2 × H-5′); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.1, 185.1, 165.7, 165.6, 165.4, 165.4 (C=O), 144.0 (C-2, benzoquinone), 142.8 (C_q, triazole), 136.5, 136.4 (C-5, C-6, benzoquinone), 134.2, 134.1, 133.8, 133.7, 133.4, 131.0, 130.2, 130.1, 129.8, 129.8, 129.0, 128.7, 128.6, 128.5, 128.4 (Ar) 125.3 (*C*H, triazole), 76.5, 73.2, 72.4, 70.6, 69.2 (C-1′ to C-5′), 58.4 (*C*H_2), 50.9 (C-6′). HRESIMS: calcd for $C_{80}H_{60}N_6O_{22}$: 1479.3658; found: *m/z* 1479.3673.

3.1.10.3. Dimeric β-*C*-D-glucopyranosyl 1,4-naphthoquinone 24. Oxidation of compound **22** (51 mg, 0.041 mmol) afforded **24** as a yellow solid (43 mg, 90%). TLC: R_f = 0.18 (cyclohexane:EtOAc = 1:2); R_f = 0.91 (EtOAc); $[\alpha]_D$ = +21.3 (*c* = 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40 (s, 1H, Ar-H), 8.01–7.88 (m, 6H, Ar-H), 7.79 (s, 2H, 2 × C*H*, triazole,), 7.72 (m, 4H, 2 × H-6, 2 × H-7, naphthoquinone), 7.22 (t, 1H, *J* = 7.7 Hz, H-4‴ isophthaloyl), 7.04 (s, 2H, 2 × H-3, naphthoquinone), 5.41 (dd, 2H, $J_{3',2'}$ = 9.6 Hz, $J_{3',4'}$ = 9.2 Hz, 2 × H-3), 5.39 (s, 4H, 2 × CH_2), 5.06 (t, 2H, $J_{2',3'} = J_{2',1'}$ = 9.6 Hz, 2 × H-2′), 5.02 (dd, 2H, $J_{4',3'}$ = 9.2 Hz, $J_{4',5'}$ = 9.9 Hz, 2 × H-4′), 4.84 (d, 2H, $J_{1',2'}$ = 9.5 Hz, 2 × H-1′), 4.69 (dd, 2H, $J_{6'a,5'}$ = 2.6 Hz, $J_{6'a,6'b}$ = 14.7 Hz, 2 × H-6′a), 4.44 (dd, 2H, $J_{6'b,5'}$ = 8.5 Hz, $J_{6'a,6'b}$ = 14.7 Hz, 2 × H-6′b), 4.13 (m, 2H, 2 × H-5′), 2.10, 1.98, 1.84 (3s, 18H, 6 × COCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.1, 183.0, 169.8, 169.6, 169.5, 165.1 (C=O), 145.3 (C-2, naphthaquinone), 142.9 (C_q, triazole), 135.7, 134.1, 134.0 (C-3, C-5, C-8, naphthaquinone), 133.8, 131.5, 131.5, 130.6, 129.9, 128.4, 126.4, 126.2 (Ar), 125.4 (*C*H triazole), 76.6, 73.2, 72.5, 72.2, 69.7 (C-1′ to C-5′), 58.2 (*C*H_2), 51.0 (C-6′), 20.6, 20.4, 20.3 (COCH_3). HRESIMS: calcd for $C_{58}H_{52}N_6O_{22}$: 1207.3032; found: *m/z* 1207.3007.

3.1.10.4. Dimeric β-*C*-D-galactopyranosyl 1,4-naphthoquinone 25. Oxidation of compound **23** (43 mg, 0.035 mmol) afforded **25** as a yellow solid (23 mg, 56%). TLC: R_f = 0.58 (petroleum ether/EtOAc = 1:2), R_f = 0.91 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1H, Ar-H), 8.12–7.96 (m, 6H, Ar-H), 7.73 (m, 5H, 2 × C*H* triazole, Ar-H), 7.30 (t, 1H, *J* = 8.0 Hz, Ar-H), 7.18 (s, 2H, 2 × H-3, naphthoquinone), 5.59 (d, 2H, $J_{4',3'}$ = 2.4 Hz, 2 × H-4′), 5.40 (s, 4H, 2 × CH_2), 5.31–5.21 (m, 4H, 2 × H-2′, 2 × H-3′), 4.86 (d, 2H, $J_{1',2'}$ = 9.2 Hz, 2 × H-1′), 4.65 (dd, 2H, $J_{6'a,5'}$ = 3.2 Hz, $J_{6'a,6'b}$ = 14.0 Hz, 2 × H-6′a), 4.49 (dd, 2H, $J_{6'b,5'}$ = 8.4 Hz, $J_{6'a,\ 6'b}$ = 14.0 Hz, 2 × H-6′b), 4.40 (m, 2 H, 2 × H-5′), 2.25, 1.99, 1.87 (3s, 18H, 6 × COCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.6, 183.2, 170.0, 169.8, 169.6, 165.2 (C=O), 142.8 (C_q triazole), 135.8, 134.4, 134.3, 134.0, 131.6, 130.3, 129.8, 128.1, 126.9, 126.3 (Ar), 125.2 (CH triazole), 76.2, 73.9, 72.5, 69.9, 67.8 (C-1′ to C-5′), 59.0 (*C*H_2), 49.2 (C-6′), 20.9, 20.7, 20.4 (COCH_3). HRESIMS: calcd for $C_{58}H_{52}N_6O_{22}$: 1207.3032; found: *m/z* 1207.3032.

3.2. PTP1B inhibitory assay

Recombinant human PTP1B catalytic domain was expressed and purified according to procedures described previously.[34] The enzymatic activities of PTP1B catalytic domain were determined at 30 °C by monitoring the hydrolysis of *p*NPP. Dephosphorylation of *p*NPP generates product *p*NP, which can be monitored at 405 nm. In a typical 100 μL assay mixture containing 50 mM MOPS, pH 6.5, 2 mM *p*NPP and recombinant enzymes, PTP1B activities were continuously monitored on a SpectraMax 340 microplate reader at 405 nm for 2 min at 30 °C and the initial rate of the hydrolysis was determined using the early linear region of the enzymatic reaction kinetic curve. For calculating IC_{50}, inhibition assays were performed with 30 nM recombinant enzyme, 2 mM *p*NPP in 50 mM MOPS at pH 6.5, and the inhibitors diluted around the estimated IC_{50} values. IC_{50} was calculated from the nonlinear curve fitting of percent inhibition (inhibition (%)) versus inhibitor concentration [*I*] by using the following equation inhibition (%) = $100/\{1 + (IC_{50}/[I])k\}$, where *k* is the Hill coefficient.

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