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β-*C*-Glycosiduronic acids and β-*C*-glycosyl compounds: New PTP1B inhibitors

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ABSTRACT

β-*C*-Glycosiduronic acid quinones and β-*C*-glycosyl compounds have been synthesized as sugar-based PTP1B inhibitors. Benzoyl protected quinone derivatives (**14** and **35**) as well as aryl β-*C*-glycosyl compounds (**18**, **22**, **23** and **34**) showed IC_{50} values of 0.77–5.27 μM against PTP1B, with compounds **18** and **23** bearing an acidic function being the most potent.

Protein tyrosine phosphatase 1B (PTP1B) has recently been identified as new drug target for type 2 diabetes.[1] In fact, PTP1B has been shown to be an important regulator of tyrosine kinase receptor-mediated responses, and influences negatively insulin sensitivity.[2] PTP1B knockout mice display increased insulin sensitivity and tyrosine phosphorylation of the insulin receptor.[3] 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).[4] Various strategies have been developed to design and synthesize potent and selective PTP1B inhibitors. The principle approach is based on mimicking the phosphotyrosine (pTyr) moiety. Numerous pTyr mimetics have been reported, including difluoromethylphosphonates,[5] cinnamic acid,[6] oxalylamino benzoic acid,[7] isoxazole carboxylic acid,[8] salicyclic acid,[9] α-ketocarboxylic acid,[10] etc. However, these highly polar and charged compounds have limited cell membrane permeability.

Considerable effort has been devoted to the synthesis and structure modification of *C*-glycosyl compounds owing to their wide natural existence, their biological interest and their high stability towards acid- and enzyme-catalyzed hydrolysis.[11] Furthermore, sugar hydroxyl groups can be easily protected with various protecting groups to modulate their hydrophilicity/hydrophobicity. Consequently, sugar derivatives are promising starting point for drug design. We have recently found that acetylated β-*C*-glucopyranosyl-1,4-benzoquinone (compound **I**, Fig. 1) showed a good inhibition against PTP1B (IC_{50} = 4.85 μM).[12] This result prompted us to prepare other β-*C*-glycosyl compounds as sugar-based PTP1B inhibitors. Since the active site of PTP1B is defined by residues 214–221 (the P-loop) and has a clear preference for acidic residues, we then decided to introduce a carboxylic acid function on the *C*-

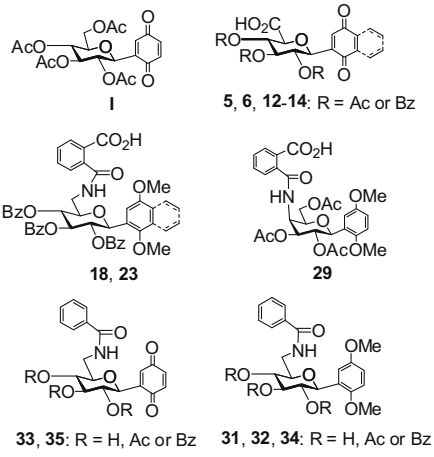

Figure 1. Compounds synthesized or referred in this study.

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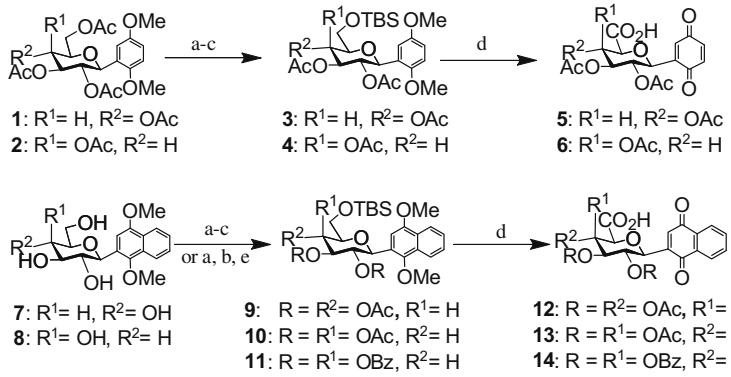
glycosyl compounds (compounds **5**, **6**, **12**–**14**, **18**, **23** and **29**, Fig. 1). Both *gluco*- and *galacto*- derivatives have been synthesized. For structure–activity comparison, we have also prepared 6-benzoylamino derivatives (compounds **31**–**35**).

Synthesis of β-*C*-glycosiduronic acid quinone derivatives is shown in Scheme 1. The *gluco* and *galacto* β-*C*-glycosides **1**[13] and **2**[13] were first deacetylated under Zemplén condition and silylated at 6-position, followed by addition of Ac_2O to furnish compounds **3** and **4** in one-pot. Treatment of these silylated β-*C*-glycosyl 1,4-dimethoxybenzenes with Jones reagent led directly to the target compounds **5**[14] and **6.**[14] Similarly, we have prepared the acetyl or benzoyl protected naphthoquinone derivatives **12**–**14**[14] from the *gluco* and *galacto* β-*C*-glycosides **7**[15] and **8.**[15] Jones reagent has been very efficient to realise the one-pot desilylation and oxidation reactions of compounds **9**–**11**.

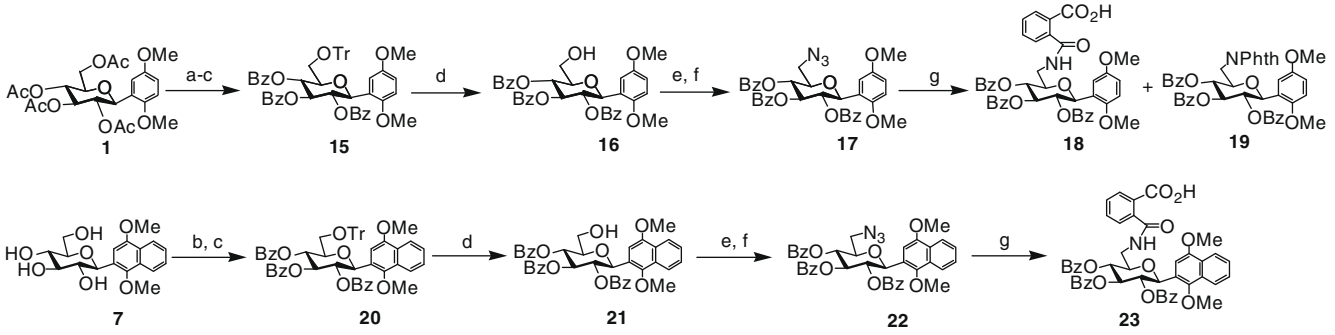
To prepare 2-carbamoylbenzoic acid derivatives **18** and **23** (Scheme 2), β-*C*-aryl glucosides **1** and **7** were first tritylated at 6-position, followed by protection of secondary hydroxyl function as benzoyl ester. To avoid intramolecular transesterification reaction, detritylation has been realized under acidic condition with TFA to afford **16** and **21** in good yield. The 6-hydroxy group was then transformed into azide via mesylate. PMe_3 mediated Staudinger protocol[16] was then employed to convert azido sugars to carbamoylbenzoic acid derivatives.

Reaction of **17** with phthalic anhydride in CH_2Cl_2 led to a mixture of the desired compound **18** (47%) and *N*-phthalimide derivative **19** (22%). However, treatment of **22** with phthalic anhydride in THF afforded **23** in 90% yield.

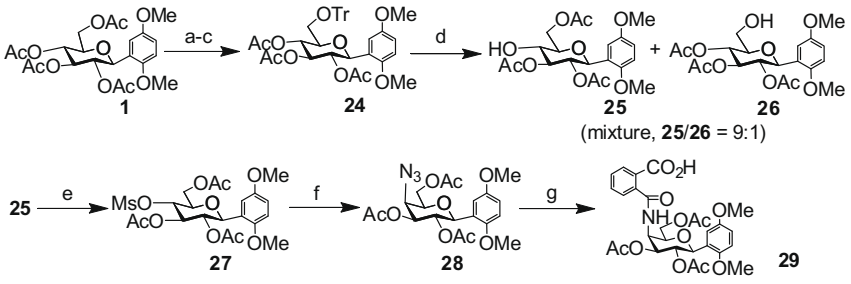
When acetyl group was used as protecting group in **24** (Scheme 3), detritylation with TFA led to an inseparable mixture of **25** and



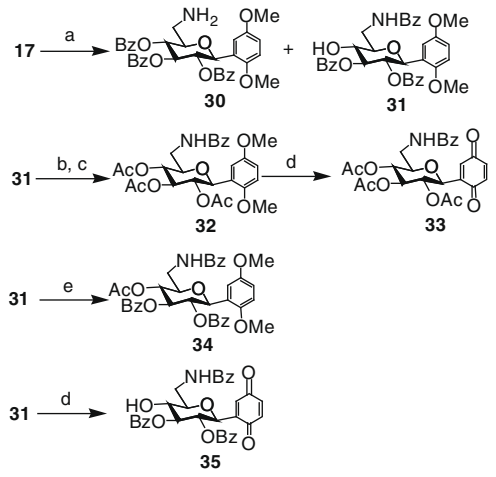
Scheme 1. Reagents and conditions: (a) MeONa, MeOH; (b) TBDMSCl, DMAP, pyr.; (c) Ac_2O, 64% for **3**, 72% for **4,** 49% for **9** and 65% for **10**; (d) Jones reagent, 22% for **5**, 19% for **6**, 78% for **12**, 72% for **13** and 42% for **14**; (e) BzCl, pyr, 58% for **11**.



Scheme 2. Reagents and conditions: (a) MeONa, MeOH; (b) TrCl, pyr.; (c) BzCl, 61% (d) TFA, CH_2Cl_2, H_2O, **16**: 79%, **21**: 83%; (e) MsCl, TEA; (f) NaN_3, DMF, 57%; (g) phthalic anhydride, Me_3P, CH_2Cl_2 for **18** and **19** (**18**: 47%, **19**: 22%), THF for **23** (90%).



Scheme 3. Reagents and conditions: (a) MeONa, MeOH; (b) TrCl, pyr.; (c) Ac_2O, 89% (d) TFA, CH_2Cl_2, H_2O, 78%; (e) MsCl, TEA, 55%; (f) NaN_3, DMF, 71%; (g) phthalic anhydride, Me_3P, CH_2Cl_2, 74%.



Scheme 4. Reagents and conditions: (a) Ph_3P, THF, H_2O, **31**: 47%; (b) MeONa, MeOH; (c) Ac_2O, 81% (d) CAN, CH_3CN, H_2O, **33**: 99%, **35**: 77%; (e) Ac_2O, pyr., 85%.

26, with the predominant formation of the transesterification product **25**. Subsequent mesylation allowed us to isolate the mesylate **27** which was then transformed into 4-azido β-*C*-galactoside **28** with a SN_2 mechanism.[17] Treatment with phthalic anhydride and PMe_3 in CH_2Cl_2 afforded the 2-carbamoylbenzoic acid derivative **29**.

Synthesis of 6-benzoylamino derivatives is described in Scheme 4. Staudinger reduction of azido function of **17** led to a mixture of amine **30** contaminated with $Ph_3P{=}O$ and the transamidation product **31** with a free hydroxyl group at 4-position. Structure of **31** was confirmed by RMN analysis of the 4-*O*-acetylated product **34.**[18] Treatment of **31** with MeONa followed by acetylation afforded the compound **32** which was oxidized to the 1,4-benzoquinone derivative **33** with CAN as oxidant. Direct CAN oxidation of **31** led to the quinone **35** without affecting the 4-hydoxy group.

The effect of synthesized compounds on PTP1B was firstly studied at 20 μg/mL concentration.[19,20] Except compounds **29**, **32** and **33**, all tested compounds showed good PTP1B inhibitory activity (70.3–99.7%). Substitution of 6-OAc by 6-NHBz in compound **I** depress the potency (**I** vs. **33**). The acetylated β-*C*-glycosiduronic acid quinone derivatives **5**, **6**, **12** and **13** inhibited PTP1B with IC_{50} values from 16 to 28 μM. No significant difference can be observed between *gluco* and *galacto* derivatives (**5** vs. **6**, **12** vs. **13**). However, these compounds are less effective than the parent compound **I**.

Table 1
In vitro PTP1B inhibition results.

Compound	Inhibition[a] (%)	Inhibition IC_{50}[b] (μM)
I		4.85
5	84.7	20.43 (±5.23)
6	70.3	27.61 (±4.08)
12	83.1	15.95 (±0.49)
13	88.2	16.55 (±0.84)
14	99.5	1.12 (±0.03)
18	99.7	2.44 (±0.20)
22	96.5	2.36 (±0.22)
23	92.1	0.77 (±0.09)
29	49.5	nd
31	94.9	4.13 (±0.19)
32	12.1	nd
33	26.6	nd
34	83.4	4.52 (±0.07)
35	94.1	5.27 (±0.61)

[a] Values tested at 20 μg/mL concentration.
[b] Values are means of three experiments, standard deviation is given in parentheses (nd, not determinated).

Surprisingly, the benzoyl protected derivative **14** showed more potent inhibition, with an IC_{50} value of about 1 μM. Apparently, all benzoyl protected compounds (**18**, **22**, **23**, **34** and **35**) displayed better inhibition than compound **I**, with the 2-carbamoylbenzoic acid derivative **23** as the best inhibitor (IC_{50} = 0.77 μM). Presence of 2-carbamoylbenzoic acid function on sugar ring improves slightly the inhibition constant (**18** vs. **34**, **23** vs. **22**) (See Table 1).

In summary, a series of β-*C*-glycosiduronic acid quinones and β-*C*-glycosyl compounds have been prepared. Benzoyl protected sugars exhibited good inhibitory activities against PTP1B with IC_{50} in micromolar ranges. These results demonstrated the potential of *C*-glycosyl compounds as a new class of small molecular inhibitors of PTP1B.

Acknowledgments

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14. Compounds **5**, **6**, **12**–**14** were prepared according to the following procedure. To a soln of 6-*O*-silylated β-*C*-aryl glycosides (0.1 mmol) in 2 mL of acetone, was added dropwise 170 μL of Jones reagent (2.2 g CrO_3 in 3.5 M H_2SO_4) at 0 °C. After 20 h reaction, another 100 μL of Jones reagent was added and the mixture was stirred for 20 h. This operation was repeated two times until that TLC indicated the complete consumption of the starting material. The mixture was diluted with water and then extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over $MgSO_4$ and purified by preparative layer chromatography (CH_2Cl_2: MeOH = 20:1). Compound **5**: $[\alpha]_D = -3.4$ (*c* 0.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.25–6.71 (m, 3H), 5.74–5.10 (m, 4H), 3.86 (m, 1H), 2.00 (s, 9H). HRMS: calcd for $C_{18}H_{18}O_{11}$: 433.0747; found: *m/z* 433.0753. Compound **6**: $[\alpha]_D = -20.0$ (*c* 0.26, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.04 (s, 1H), 6.73 (m, 2H), 5.79 (s, 1H), 5.16 (m, 2H), 4.58 (d, 1H,

J = 7.7 Hz), 4.26 (s, 1H), 2.10, 1.99, 1.90 (3s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.7, 186.2, 170.8, 170.7, 170.6, 169.7, 144.3, 137.2, 137.0, 135.0, 76.4, 72.5, 72.0, 70.0, 69.1, 21.2. HRMS: calcd for $C_{18}H_{18}O_{11}$: 433.0747; found: m/z 433.0748. Compound **12**: $[\alpha]_D$ = −11.3 (c 0.44, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07, 7.76 (2s, 4H), 7.19 (s, 1H), 5.46–4.94 (m, 4H), 4.02–3.64 (m, 1H), 2.17, 2.03, 1.87 (3s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.6, 183.4, 170.2, 170.0, 169.8, 169.5, 145.4, 136.4, 134.3, 134.2, 131.9, 126.7, 126.5, 125.8, 73.2, 72.3, 72.2, 69.4, 63.3, 20.9, 20.7, 20.5. HRMS: calcd for $C_{22}H_{20}O_{11}$: 483.0903; found: m/z 483.0886. Compound **13**: $[\alpha]_D$ = +4.9 (c 0.82, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03, 7.69 (2 m, 4H), 7.23 (s, 1H), 5.82–4.32 (m, 4H), 3.95 (m, 1H), 2.06, 1.94, 1.82 (3s, 9H). HRMS: calcd for $C_{22}H_{20}O_{11}$: 483.0903; found: m/z 483.0897. Compound **14**: $[\alpha]_D$ = +8.8 (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93–7.17 (m, 20H), 6.23, 5.76, 4.99 (3 s, 4H), 4.28 (s, 1H). HRMS: calcd for $C_{37}H_{26}O_{11}Na$: 669.1373; found: m/z 669.1380.

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17. Inversion of configuration at C-4 can be confirmed by the small coupling constant between H-3 and H-4: $J_{4,3}$ = 3.7 Hz. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (d, 1H, J = 2.2 Hz, H–Ar), 6.80 (m, 2H, H–Ar), 5.51 (t, 1H, $J_{2,3} = J_{2,1}$ = 9.9 Hz, H-2), 5.27 (dd, 1H, $J_{3,2}$ = 9.9 Hz, $J_{3,4}$ = 3.7 Hz, H-3), 4.85 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 4.31–4.20 (m, 2H, H-6a, H-6b), 4.14 (d, 1H, $J_{4,3}$ = 3.7 Hz, H-4), 3.94 (m, 1H, H-5), 3.78, 3.77 (2s, 6H, 2× OMe), 2.12, 2.08, 1.80 (3s, 9H, 3× COCH_3).
18. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92–7.26 (m, 15H, Ph), 7.04 (d, 1H, J = 3.3 Hz, H–Ar), 6.75 (dd, 1H, J = 2.9 Hz, J = 8.8 Hz, H–Ar), 6.66 (m, 2H, H–Ar, N*H*CO), 5.82 (t, 1H, $J_{3,4} = J_{3,2}$ = 9.6 Hz, H-3), 5.68 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{2,1}$ = 9.9 Hz, H-2), 5.35 (t, 1H, $J_{4,5} = J_{4,3}$ = 9.6 Hz, H-4), 5.18 (d, 1H, $J_{1,2}$ = 9.9 Hz, H-1), 4.08–3.97 (m, 2H, H-6a, H-5), 3.73, 3.60 (2s, 6H, 2× OCH_3), 3.47 (m, 1H, H-6b), 2.04 (s, 3H, COCH_3).
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20. 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 (%)) vs inhibitor concentration [I] by using the following equation inhibition (%) = 100/{1 + (IC_{50}/[I])k}, where k is the Hill coefficient.