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Microwave-Accelerated Click Chemistry: Expeditious Synthesis of Novel Triazole-linked Salicylic β-D-*O*-Glycosides with PTP1B Inhibitory Activity

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The incorporation of microwave irradiation with the prevalent "click chemistry" is currently of considerable synthetic interest. We describe here the introduction of such laboratorial shortcut into carbohydrate-based drug discovery, resulting in the rapid formation of a series of triazole-linked salicylic β-D-*O*-glycosides with biological activities. All "clicked" products were achieved in excellent yields (≈ 90%) within only a quarter. In addition, based on the structural characteristics of the afforded glycomimetics, their inhibitory activities were evaluated toward protein tyrosine phosphatases 1B (PTP1B) and a panel of homologous protein tyrosine phosphatases (PTPs). Docking simulation was also conducted to plausibly propose binding modes of this glycosyl salicylate series with the enzymatic target.

Key Words: Click chemistry, Microwave irradiation, Carbohydrate-based drug discovery, PTP1B inhibitor, Docking simulation

Introduction

Carbohydrates ubiquitously exist in nature and govern various biological and pathological events including cell-cell recognition,[2] signal transduction[3] and tumour metastasis.[4] Considerable efforts have consequently been devoted by biologists toward the revelation of the substantial functions carbohydrates display as pivotal mediators in intricate cellular processes.[5] On the other hand, numerous chemical approaches based on the synthesis of glycomimetics that possess great biological value have also been developed and proven indispensable as powerful allies for deciphering the genetic code that carbohydrates bear.[1,6]

Synthesized glycomimetics owning widely ranged biological applications could serve as, for example, biosensors,[7] vaccines[8] and glycan array substrates.[9] Furthermore, in view of their intrinsic merits such as conformational flexibility, high biocompatibility and low toxicity, the abundantly affordable carbohydrates have been proposed as ideal scaffolds for sugar-based drug discovery.[10,11] Such relatively untapped natural source do have subsequently provided exclusive opportunities for the advancement of small-molecule therapeutics.[12] Hence, the development of potent and easily accessible synthetic methodologies for the efficient preparation of carbohydrate-based bioactive compounds leading to the facilitation of modern drug discovery has become quite intriguing.

The recently defined "click chemistry" of terminal alkynes with organic azides promoted by Cu(I)[13] is a modular, selective and high yielding tool for organic synthesis.[14] With these ideal features, it has been branded by Wong *et al*. as an excellent example for facilitating the fabrication of sugar-based bioactive compounds.[15] Thus, the employment of click chemistry in such field has been continually delineated. For instance, triazolyl glycoconjugates were identified as human Fuc-T,[15] carbonic anhydrase,[16] glycosyltransferase,[17] and PTP1B inhibitors.[18a]

Microwave irradiation was validated as a powerful assistant for enhancing the reactivity and tremendously economizing the reaction time in a broad area of organic synthesis.[19] Its usage in click chemistry for combinatorial synthesis has also been successfully achieved.[20] However, though microwave-improved click chemistry leading to the accomplishment of functionalized glycomimetics are gradually being disclosed,[21] reports on the rapid formation of sugar-based bioactive small molecules *via* such upgraded methodology remain scant.[22]

With a continuing interest on the construction of sugar-based bioactive compounds *via* click chemistry,[18] we describe here the microwave-accelerated synthesis of a series of triazole-linked salicylic glycosides and their biological assessment. Our drug target is PTP1B (protein tyrosine phosphatase 1B), which represents a negative factor of type-2 diabetes, obesity and breast cancer.[23] Because of the structural similarity between salicylate and pTyr (phosphotyrosine) substrate, salicylic derivatives have

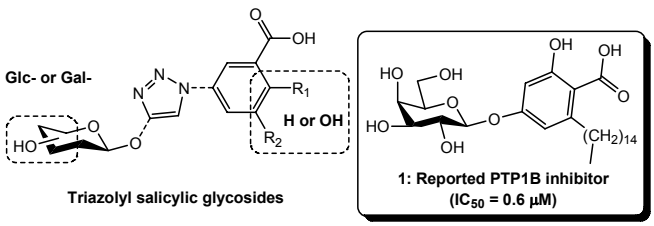


Figure 1. Salicylic *O*-glycoside derivatives as PTP1B inhibitors.

been developed as potent competitive PTP1B inhibitors.[24] Seo *et al*. also revealed in a recent study that a hydrolyzed natural *O*-galactoside (**1**, Fig. 1) displayed PTP1B inhibitory activity with the salicylic precursor being the critical pharmacophore.[25]

Prompted by such compelling evidence, we have designed and synthesized triazole-linked salicylic glycosides based on click chemistry (Fig. 1). Salicylic azides with position-varied or omitted hydroxyl group on benzoate ring were simultaneously prepared for SAR (structure-activity relationship) evaluation. Galactosyl and glucosyl alkynes were employed in this study for investigating the reactant tolerance and configuration impact of sugar moiety toward the bioactivity. The inhibitory activities of the afforded glycosyl compounds were subsequently assayed toward PTP1B and a panel of homologous PTPs. Docking simulation was also conducted to plausibly propose binding modes of this triazole-linked glycosyl salicylate series with the enzymatic target.

Experimental Section

General. All purchased chemicals and reagents were of high commercially available grade. Solvents were purified by standard procedures. ^{1}H and ^{13}C NMR spectrum were recorded on a Bruker AM-400 spectrometer in $CDCl_3$, D_2O or DMSO-d_6 solutions. Microwave-assisted reactions were performed in a Yalian (YL8023B1) system at 40 °C with a ramp time of 6 min and hold time of 8 min. All reactions were monitored by TLC (thin-layer chromatography) with detection by UV or by spraying with 6 N H_2SO_4 and charring at 300 °C. Optical rotations were measured using a Perkin-Elmer 241 polarimeter at room temperature and a 10-cm 1-mL cell. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier XE spectrometer using standard conditions (ESI, 70 eV).

General procedure for the preparation of azides. To a soln. of salicylates (1 equiv.) in acetone (10 mL) and water (10 mL), were added K_2CO_3 (4 equiv.) and 1,2-dibromoethane (3 equiv.), stirring at rt for 6 h. Upon completion, NaN_3 (3 equiv.) was directly added and the mixture was stirred at 60 °C for another 6 h. The mixture was then washed with water, extracted with EtOAc and dried over $MgSO_4$. After filtration and concentration, the crude residue was purified by column chromatography.

Methyl 3-(2-azidoethoxy)benzoate (5): From **2** (830 mg, 5.46 mmol), column chromatography (EtOAc/petroleum ether, 1:1) afforded **5** as a colorless syrup (555.3 mg, 47.5%). R_f = 0.41 (EtOAc/petroleum ether, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.6 Hz, 1H), 7.55 (s, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.12 (dd, J = 2.4 Hz, 8.2 Hz, 1H), 4.16 (t, J = 4.6 Hz, 2H), 3.89 (s, 3H), 3.58 (t, J = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 158.2, 131.5, 129.5, 122.6, 120.0, 114.6, 67.1, 52.1, 50.1.

Methyl 3-(2-azidoethoxy)-5-hydroxybenzoate (6): From **3** (1600 mg, 9.51 mmol), column chromatography (EtOAc/petroleum ether, 1:1) afforded 6 as a yellow solid (973.9 mg, 50.1%). R_f = 0.41 (EtOAc/petroleum ether, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 7.2 Hz, 2H), 6.65 (s, 1H), 5.63 (s, 1H), 4.16 (t, J = 4.6 Hz, 2H), 3.90 (s, 3H), 3.59 (t, J = 3.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 159.6, 159.2, 132.1, 110.1, 108.3, 107.2, 67.2, 52.4, 50.0.

Methyl 5-(2-azidoethoxy)-2-hydroxybenzoate (7): From **4** (1500 mg, 8.95 mmol), column chromatography (EtOAc/petroleum ether, 1:1) afforded **7** as a yellow syrup (1002 mg, 52.3%). R_f = 0.41 (EtOAc/petroleum ether, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 3.1 Hz, 1H), 7.12 (dd, J = 3.1 Hz, 9.0 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 4.11 (t, J = 5.0 Hz, 2H), 3.94 (s, 3H), 3.57 (t, J = 5.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 156.4, 150.6, 124.5, 118.6, 113.1, 111.9, 67.8, 52.3, 50.1.

General procedure of microwave-assisted click reaction. To a soln. of sugar alkyne (1.0 mmol) in CH_2Cl_2/H_2O (10 mL/10 mL), were added azide (1.2 mmol), VcNa (2.0 mmol) and $CuSO_4 \cdot 5H_2O$ (1.0 mmol) which was then transferred to the microwave oven. After stirring for a ramp time of 6 min and heating time of 8 min, the mixture was washed with sat $NaHCO_3$, water and extracted with CH_2Cl_2 for three times. The combined organic layers were then dried over $MgSO_4$, concentrated and purified by column chromatography.

Triazole tetra-*O*-acetyl-β-D-*O*-glucosyl methyl benzoate (10): From **8** (50 mg, 0.13 mmol) and **5** (34.4 mg, 0.15 mmol), column chromatography (EtOAc/petroleum ether, 1:1) afforded **10** as a white powder (69.4 mg, 87.9%). R_f = 0.41 (EtOAc/petroleum ether, 2:1); $[\alpha]_D$ = −88.9 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.51-7.50 (m, 1H), 7.36 (t, J = 8.1 Hz, 1H), 7.07 (dd, J = 2.6 Hz, 8.2 Hz, 1H), 5.19 (t, J = 9.4 Hz, 1H), 5.09 (t, J = 9.7 Hz, 1H), 5.01 (dd, J = 8.0 Hz, 9.4 Hz, 1H), 4.94 (d, J = 12.6 Hz, 1H), 4.82 (d, J = 12.6 Hz, 1H), 4.79 (t, J = 4.9 Hz, 2H), 4.67 (d, J = 7.9 Hz, 1H), 4.41 (t, J = 4.9 Hz, 2H), 4.26 (dd, J = 4.7 Hz, 12.3 Hz, 1H), 4.14 (dd, J = 2.2 Hz, 12.3 Hz, 1H), 3.89 (s, 3H), 3.72-3.68 (m, 1H), 2.06 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.1, 169.4, 169.3, 166.5, 157.7, 144.2, 131.6, 129.7, 123.9, 123.0, 119.8, 114.7, 99.7, 72.7, 71.9, 71.2, 68.3, 66.4, 62.7, 61.8, 52.2, 49.7, 20.7, 20.5; HRMS: calcd. for $C_{27}H_{33}N_3O_{13}$+H: 608.2092, found: 608.2092.

Triazole tetra-*O*-acetyl-β-D-*O*-glucosyl methyl 5-hydroxybenzoate (11): From **8** (50 mg, 0.13 mmol) and **6** (35.6 mg, 0.15 mmol), column chromatography (EtOAc/petroleum ether, 1:1) afforded **11** as a white powder (75.8 mg, 93.6%). R_f = 0.26 (EtOAc/petroleum ether, 3:1); $[\alpha]_D$ = −61.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.19 (brs, 1H), 7.06 (brs, 1H), 6.56 (t, J = 1.9 Hz, 1H), 5.20 (t, J = 9.4 Hz, 1H), 5.12 (t, J = 9.4 Hz, 1H), 5.06-5.02 (m, 1H), 4.98 (d, J = 12.6 Hz, 1H), 4.84 (d, J = 12.7 Hz, 1H), 4.78-4.68 (m, 2H), 4.64 (d, J = 7.9 Hz, 1H), 4.41-4.32 (m, 2H), 4.27 (dd, J = 4.6 Hz, 12.3 Hz, 1H), 4.15 (dd, J = 1.6 Hz, 12.3 Hz, 1H), 3.88 (s, 3H), 3.73-3.70 (m, 1H), 2.07 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.3, 169.7, 169.5, 166.6, 158.7, 158.1, 143.9, 132.1, 124.4, 110.5, 107.1, 106.5, 99.5, 72.7, 71.7, 71.2, 68.2, 66.3, 62.3, 61.7, 52.2, 49.7, 20.6, 20.4; HRMS: calcd. For $C_{27}H_{33}N_3O_{14}$+H: 624.2041, found: 624.2040.

Triazole tetra-*O*-acetyl-β-D-*O*-glucosyl methyl 2-hydroxybenzoate (12): From **8** (50 mg, 0.13 mmol) and **6** (35.6 mg, 0.15 mmol), column chromatography (EtOAc/petroleum ether, 1:1) afforded **12** as a white powder (71.3 mg, 88.0%). R_f = 0.53 (EtOAc/petroleum ether, 3:1); $[\alpha]_D$ = −33.6 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.71 (s, 1H), 7.25 (d, J = 3.1 Hz, 1H), 7.05 (dd, J = 3.1 Hz, 9.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 5.19 (t, J = 9.4 Hz, 1H), 5.10 (t, J = 9.7 Hz, 1H), 5.02 (dd, J = 8.0 Hz, 9.4 Hz, 1H), 4.95 (d, J = 12.6 Hz, 1H), 4.83

(d, J = 12.6 Hz, 1H), 4.74 (t, J = 4.9 Hz, 2H), 4.67 (d, J = 8.0 Hz, 1H), 4.32 (t, J = 4.9 Hz, 2H), 4.27 (dd, J = 4.7 Hz, 12.3 Hz, 1H), 4.14 (dd, J = 2.2 Hz, 12.3 Hz, 1H), 3.93 (s, 3H), 3.72-3.68 (m, 1H), 2.07 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.0, 169.9, 169.3, 169.2, 156.5, 150.0, 144.1, 124.3, 123.9, 118.7, 113.1, 111.9, 99.6, 72.6, 71.7, 71.1, 68.2, 67.0, 62.7, 61.7, 52.3, 49.7, 20.6, 20.5; HRMS: calcd. For $C_{27}H_{33}N_3O_{14}$+H: 624.2041, found: 624.2039.

Triazole tetra-*O*-acetyl-β-D-*O*-galactosyl methyl benzoate (13): From compound **9** (50 mg, 0.13 mmol) and **5** (34.4 mg, 0.15 mmol), column chromatography (EtOAc/petroleum ether, 1:1) afforded **13** as a white powder (68.4 mg, 86.7%). R_f = 0.32 (EtOAc/petroleum ether, 2:1); $[\alpha]_D$ = −44.2 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.51 (brs, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.08 (dd, J = 2.1 Hz, 8.0 Hz, 1H), 5.38 (d, J = 3.2 Hz, 1H), 5.23 (dd, J = 8.0 Hz, 10.4 Hz, 1H), 5.00 (dd, J = 3.4 Hz, 10.5 Hz, 1H), 4.98 (d, J = 12.6 Hz, 1H), 4.82 (d, J = 13.4 Hz, 1H), 4.79 (t, J = 5.2 Hz, 2H), 4.64 (d, J = 7.9 Hz, 1H), 4.41 (t, J = 4.8 Hz, 2H), 4.18-4.10 (m, 2H), 3.94 (t, J = 6.7 Hz, 1H), 3.89 (s, 3H), 2.13 (s, 3H), 2.04 (s, 3H), 1.95 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.1, 169.9, 169.4, 166.4, 157.7, 144.1, 131.5, 129.6, 123.9, 122.8, 119.6, 114.6, 100.1, 70.7, 68.6, 67.0, 66.4, 62.6, 61.2, 52.2, 49.6, 20.6, 20.5; HRMS: calcd. for $C_{27}H_{33}N_3O_{13}$+H: 608.2092, found: 608.2090.

Triazole tetra-*O*-acetyl-β-D-*O*-galactosyl methyl 5-hydroxybenzoate (14): From compound **9** (50 mg, 0.13 mmol) and **6** (35.6 mg, 0.15 mmol), column chromatography (EtOAc/petroleum ether, 1:1) afforded **14** as a white powder (76.6 mg, 94.5%). R_f = 0.19 (EtOAc/petroleum ether, 1:1); $[\alpha]_D$ = −14.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (brs, 1H), 7.19 (s, 1H), 7.05 (s, 1H), 6.58 (s, 1H), 5.39 (d, J = 3.3 Hz, 1H), 5.25 (dd, J = 7.9 Hz, 10.4 Hz, 1H), 5.03 (dd, J = 3.4 Hz, 10.4 Hz, 1H), 5.00 (d, J = 12.7 Hz, 1H), 4.83-4.70 (m, 3H), 4.63 (d, J = 7.9 Hz, 1H), 4.40-4.32 (m, 2H), 4.19-4.09 (m, 2H), 3.95 (t, J = 6.5 Hz, 1H), 3.87 (s, 3H), 2.14 (s, 3H), 2.04 (s, 3H), 1.97 (ds, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.3, 170.2, 169.9, 166.6, 158.7, 158.1, 132.1, 110.4, 107.1, 106.6, 100.0, 70.8, 70.7, 68.8, 67.0, 66.4, 62.4, 61.2, 52.2, 49.8, 20.6, 20.5; HRMS: calcd. For $C_{27}H_{33}N_3O_{14}$+H: 624.2041, found: 624.2042.

Triazole tetra-*O*-acetyl-β-D-*O*-galactosyl methyl 2-hydroxybenzoate (15): From compound **9** (50 mg, 0.13 mmol) and **7** (35.6 mg, 0.15 mmol), column chromatography (EtOAc/petroleum ether, 1:1) afforded **15** as a white powder (74.6 mg, 92.1%). R_f = 0.28 (EtOAc/Dichloromethane, 1:2); $[\alpha]_D$ = −79.2 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 7.76 (brs, 1H), 7.06 (dd, J = 3.0 Hz, 9.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 5.39 (d, J = 3.2 Hz, 1H), 5.24 (dd, J = 7.9 Hz, 10.3 Hz, 1H), 5.01 (dd, J = 3.4 Hz, 10.4 Hz, 1H), 4.95-4.80 (m, 2H), 4.74 (t, J = 4.5 Hz, 2H), 4.65 (d, J = 7.9 Hz, 1H), 4.32 (t, J = 4.7 Hz, 2H), 4.19-4.08 (m, 3H), 3.94 (s, 3H), 2.13 (s, 3H), 2.04 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.2, 170.0, 169.9, 169.4, 156.6, 150.1, 124.4, 118.8, 113.1, 111.9, 100.3, 70.8, 68.7, 67.1, 67.0, 62.7, 61.2, 52.4, 49.9, 20.6, 20.5; HRMS: calcd. For $C_{27}H_{33}N_3O_{14}$+H: 624.2041, found: 624.2039.

General procedure of deacetylation. To a soln. of acetylated *O*-glycosides in 10 mL MeOH and 2.5 mL H_2O, was added dropwise ammonia water (excessive), refluxed for 6 h. After which, the mixture was evaporated and the residue was directly purified by column chromatography.

Triazole β-D-*O*-glucosyl methyl benzoate (16): From **10** (24.9 mg, 0.04 mmol), column chromatography (EtOAc/EtOH, 1:1) afforded **16** as a white powder (15.3 mg, 87.6%). R_f = 0.50 (*n*-Butanol/water/acetic acid, 3:5:1); $[\alpha]_D$ = −70.0 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.57-7.56 (m, 1H), 7.45 (brs, 2H), 7.24-7.23 (m, 1H), 5.04 (brs, 1H), 4.94-4.93 (m, 2H), 4.88-4.87 (m, 1H), 4.78 (brs, 2H), 4.66-4.63 (m, 1H), 4.57 (brs, 1H), 4.48 (brs, 2H), 4.27-4.25 (m, 1H), 3.85 (s, 3H), 3.71 (brs, 1H), 3.46 (brs, 1H), 3.17-2.98 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.0, 157.8, 143.8, 130.9, 129.9, 124.7, 121.8, 119.7, 114.6, 102.0, 76.8, 76.6, 73.3, 70.0, 66.3, 61.4, 52.0, 48.9; HRMS: calcd. for $C_{19}H_{25}N_3O_9$+H: 440.1669, found: 440.1667.

Triazole β-D-*O*-glucosyl methyl 5-hydroxybenzoate (17): From **11** (199.2 mg, 0.3 mmol), column chromatography (EtOAc/EtOH, 1:1) afforded **17** as a white powder (141.6 mg, 97.5%). R_f = 0.47 (*n*-Butanol/water/acetic acid, 3:5:1); $[\alpha]_D$ = −105.8 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.20 (s, 1H), 6.99 (s, 1H), 6.90 (s, 1H), 6.60 (s, 1H), 5.05 (d, J = 4.4 Hz, 1H), 4.95-4.94 (m, 2H), 4.84 (d, J = 12.0 Hz, 1H), 4.74 (t, J = 4.0 Hz, 2H), 4.64 (d, J = 12.1 Hz, 1H), 4.58 (t, J = 5.7 Hz, 1H), 4.39 (t, J = 4.3 Hz, 2H), 4.27 (d, J = 7.7 Hz, 1H), 3.81 (s, 3H), 3.72-3.68 (m, 1H), 3.49-3.44 (m, 1H), 3.17-3.13 (m, 2H), 3.08-3.02 (m, 1H), 3.00-2.95 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.2, 164.1, 163.8, 149.1, 136.7, 129.8, 114.3, 111.7, 110.9, 107.3, 81.8, 78.5, 75.2, 71.4, 66.5, 66.2, 56.9; HRMS: calcd. for $C_{19}H_{25}N_3O_{10}$+H: 456.1618, found: 456.1618.

Triazole β-D-*O*-glucosyl methyl 2-hydroxybenzoate (18): From **12** (131.3 mg, 0.2 mmol), column chromatography (EtOAc/EtOH, 1:1) afforded **18** as a white powder (87.9 mg, 91.9%). R_f = 0.43 (*n*-Butanol/water/acetic acid, 3:5:1); $[\alpha]_D$ = −60.0 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.20 (s, 1H), 7.24 (s, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 5.05 (d, J = 4.7 Hz, 1H), 5.00-4.97 (m, 2H), 4.86 (d, J = 12.0 Hz, 1H), 4.72 (brs, 2H), 4.65 (d, J = 12.2 Hz, 1H), 4.60 (t, J = 5.6 Hz, 1H), 4.36 (brs, 2H), 4.26 (d, J = 7.6 Hz, 1H), 3.88 (s, 3H), 3.70 (dd, J = 6.0 Hz, 10.4 Hz, 1H), 3.49-3.43 (m, 1H), 3.17-3.11 (m, 2H), 3.08-3.03 (m, 1H), 3.01-2.95 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.2, 155.4, 149.1, 129.8, 129.1, 123.5, 118.7, 117.4, 107.2, 81.9, 78.6, 78.5, 75.2, 72.1, 66.5, 66.3, 57.3, 54.2; HRMS: calcd. for $C_{19}H_{25}N_3O_{10}$+H: 456.1618, found: 456.1617.

Triazole β-D-*O*-galactosyl methyl benzoate (19): From **13** (167.8 mg, 0.3 mmol), column chromatography (EtOAc/EtOH, 1:1) afforded **19** as a white powder (118.3 mg, 97.6%). R_f = 0.51 (*n*-Butanol/water/acetic acid, 3:5:1); $[\alpha]_D$ = −63.6 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.48 (brs, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.17 (dd, J = 2.4 Hz, 8.2 Hz, 1H), 4.93 (d, J = 12.3 Hz, 1H), 4.79 (t, J = 4.9 Hz, 1H), 4.75 (t, J = 12.3 Hz, 2H), 4.45 (t, J = 4.9 Hz, 2H), 4.27 (d, J = 7.5 Hz, 1H), 3.87 (s, 3H), 3.77 (d, J = 2.9 Hz, 1H), 3.66 (d, J = 5.9 Hz, 2H), 3.47-3.41 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 157.8, 143.9, 130.9, 129.7, 124.5, 121.8, 119.4, 114.5, 102.5, 75.1, 73.3, 70.5, 68.2, 66.2, 61.1,

60.5, 51.7, 48.9; HRMS: calcd. for $C_{19}H_{25}N_3O_9$+H: 440.1669, found: 440.1670.

Triazole β-D-*O*-galactosyl methyl 5-hydroxybenzoate (20): From **14** (224.8 mg, 0.4 mmol), column chromatography (EtOAc/EtOH, 1:1) afforded **20** as a white powder (132.7 mg, 81.0%). R_f = 0.48 (*n*-Butanol/water/acetic acid, 3:5:1); $[\alpha]_D$ = −101.7 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.19 (s, 1H), 6.98 (s, 1H), 6.91 (s, 1H), 6.58 (s, 1H), 4.89 (d, *J* = 4.5 Hz, 1H), 4.85 (d, *J* = 11.8 Hz, 1H), 4.74 (t, *J* = 4.9 Hz, 2H), 4.69 (d, *J* = 4.9 Hz, 1H), 4.63-4.59 (m, 2H), 4.40-4.38 (m, 2H), 4.36 (d, *J* = 5.1 Hz, 1H), 4.20 (d, *J* = 7.5 Hz, 1H), 3.81 (s, 3H), 3.63-3.62 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 158.9, 158.8, 143.8, 131.4, 124.5, 109.2, 106.5, 105.3, 102.5, 75.1, 73.2, 70.5, 68.1, 66.1, 61.2, 60.4, 51.7, 48.8; HRMS: calcd. for $C_{19}H_{25}N_3O_{10}$+Na: 478.1438, found: 478.1438.

Triazole β-D-*O*-galactosyl methyl 2-hydroxybenzoate (21): From **15** (127.9 mg, 0.2 mmol), column chromatography (EtOAc/EtOH, 1:1) afforded **21** as a white powder (132.7 mg, 89.2%). R_f = 0.44 (*n*-Butanol/water/acetic acid, 3:5:1); $[\alpha]_D$ = −74.5 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.18 (s, 1H), 7.24 (s, 1H), 7.15 (brs, 1H), 6.92 (brs, 1H), 4.88 (s, 1H), 4.86 (d, *J* = 11.3 Hz, 1H), 4.72 (brs, 3H), 4.63 (d, *J* = 12.1 Hz, 2H), 4.36 (brs, 3H), 4.24-4.19 (m, *J* = 3.1 Hz, 1H), 3.88 (s, 3H), 3.63 (brs, 1H), 3.53 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.3, 158.1, 143.9, 124.7, 124.6, 118.4, 113.8, 113.5, 102.6, 75.2, 73.4, 70.4, 68.1, 66.9, 61.2, 60.5, 52.2, 48.9; HRMS: calcd. for $C_{19}H_{25}N_3O_{10}$+H: 456.1618, found: 456.1615.

General procedure of saponification. To a soln. of esters in 10 mL THF and 2.5 mL water, was added LiOH (3 equiv.), stirring for 6 h. The resulting mixture was acidified with 1 N HCl, evaporated then purified by column chromatography.

Triazole β-D-*O*-glucosyl benzoate (22): From **16** (190.9 mg, 0.3 mmol), column chromatography (EtOAc/EtOH, 1:1 to 1:2) afforded **22** as a white powder (130.7 mg, 94.7%). R_f = 0.38 (*n*-Butanol/water/acetic acid, 3:5:1); $[\alpha]_D$ = −95.4 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, D_2O) δ 7.90 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.13-7.09 (m, 2H), 6.78 (dd, *J* = 2.0 Hz, 8.0 Hz, 1H), 4.59 (dd, *J* = 4.4 Hz, 9.2 Hz, 4H), 4.26-4.24 (m, 3H), 3.62 (dd, *J* = 1.2 Hz, 12.4 Hz, 1H), 3.46-3.41 (m, 1H), 3.22 (t, *J* = 9.2 Hz, 1H), 3.18-3.11 (m, 2H), 3.04 (dd, *J* = 8.0 Hz, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 157.2, 143.4, 137.6, 129.5, 125.9, 122.2, 117.8, 114.8, 101.2, 75.7, 75.5, 72.9, 69.4, 66.5, 62.4, 61.7, 60.5, 49.8; HRMS: calcd. for $C_{18}H_{23}N_3O_9$+H: 426.1513, found: 426.1511.

Triazole β-D-*O*-glucosyl 5-hydroxybenzoate (23): From **17** (145 mg, 0.3 mmol), column chromatography (EtOAc/EtOH, 1:1 to 1:2) afforded **23** as a white powder (139.9 mg, 99.4%). R_f = 0.36 (*n*-Butanol/water/acetic acid, 3:5:1); $[\alpha]_D$ = −75.4 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (brs, 1H), 8.20 (s, 1H), 7.08-6.96 (m, 2H), 6.44 (s, 1H), 5.05 (brs, 1H), 4.97 (brs, 1H), 4.86 (d, *J* = 12.4 Hz, 1H), 4.75 (brs, 2H), 4.64 (d, *J* = 12.4 Hz, 1H), 4.57 (t, *J* = 5.6 Hz, 2H), 4.35 (brs, 2H), 4.26 (d, *J* = 8.0 Hz, 1H), 3.73-3.68 (m, 1H), 3.46-3.44 (m, 1H), 3.17-3.11 (m, 2H), 3.07 (d, *J* = 8.4 Hz, 1H), 2.98 (brs, 1H); ^{13}C NMR (100 MHz, D_2O) δ 158.6, 156.7, 143.7, 135.4, 125.9, 109.7, 107.3, 106.2, 101.2, 75.8, 75.6, 72.9, 69.5, 66.6, 61.7, 60.6, 60.4, 49.8; HRMS: calcd. for $C_{18}H_{23}N_3O_{10}$+Na: 464.1281, found: 464.1279.

Triazole β-D-*O*-glucosyl 2-hydroxybenzoate (24): From **18** (95.6 mg, 0.2 mmol), column chromatography (EtOAc/EtOH, 1:1 to 1:2) afforded **24** as a white powder (86.2 mg, 93.1%). R_f = 0.29 (*n*-Butanol/water/acetic acid, 3:5:1); $[\alpha]_D$ = -63.1 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, D_2O) δ 8.01 (s, 1H), 7.18 (d, *J* = 2.8 Hz, 1H), 6.87 (dd, *J* = 2.8 Hz, 8.8 Hz, 1H), 6.71 (d, *J* = 9.2 Hz, 1H), 4.82-4.70 (m, 5H), 4.35-4.33 (m, 2H), 3.72 (d, *J* = 11.6 Hz, 1H), 3.57-3.54 (m, 1H), 3.30 (t, *J* = 8.4 Hz, 1H), 3.28-3.20 (m, 2H), 3.13 (t, *J* = 8.0 Hz, 1H); HRMS: calcd. for $C_{18}H_{23}N_3O_9$+H: 442.1462, found: 442.1485.

Triazole β-D-*O*-galactosyl benzoate (25): From **19** (121.1 mg, 0.3 mmol), column chromatography (EtOAc/EtOH, 1:1 to 1:2) afforded **25** as a white powder (114.7 mg, 97.7%). R_f = 0.31 (*n*-Butanol/water/acetic acid, 3:5:1); $[\alpha]_D$ = −72.3 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, D_2O) δ 7.98 (s, 1H), 7.38 (d, *J* = 7.0 Hz, 1H), 7.19-7.16 (m, 2H), 6.94 (d, *J* = 7.4 Hz, 1H), 4.78-4.70 (m, 4H), 4.28 (brs, 2H), 4.19 (d, *J* = 7.2 Hz, 1H), 3.70 (d, *J* = 2.3 Hz, 1H), 3.59-3.51 (m, 2H), 3.42-3.30 (m, 3H); ^{13}C NMR (100 MHz, D_2O) δ 157.5, 143.5, 131.8, 129.9, 126.0, 122.8, 119.9, 115.2, 101.6, 75.1, 72.6, 70.5, 68.5, 66.5, 61.5, 60.8, 60.4, 49.9; HRMS: calcd. for $C_{18}H_{23}N_3O_9$+H: 426.1513, found: 426.1511.

Triazole β-D-*O*-galactosyl 5-hydroxybenzoate (26): From **20** (112.9 mg, 0.3 mmol), column chromatography (EtOAc/EtOH, 1:1 to 1:2) afforded **26** as a white powder (101.3 mg, 91.8%). R_f = 0.32 (*n*-Butanol/water/acetic acid, 3:5:1); $[\alpha]_D$ = −74.2 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, D_2O) δ 8.20 (s, 1H), 7.03 (d, *J* = 7.6 Hz, 2H), 6.60 (s, 1H), 5.01-4.84 (m, 4H), 4.54 (t, *J* = 4.8 Hz, 2H), 4.36 (d, *J* = 7.0 Hz, 1H), 3.89 (d, *J* = 1.2 Hz, 1H), 3.80-3.71 (m, 2H), 3.58-3.53 (m, 3H); ^{13}C NMR (100 MHz, D_2O) δ 168.9, 158.6, 156.6, 125.9, 123.2, 109.4, 107.1, 105.3, 101.5, 75.0, 72.6, 70.5, 68.5, 66.5, 61.4, 60.8, 60.4, 49.8; HRMS: calcd. for $C_{18}H_{23}N_3O_9$+H: 442.1462, found: 442.1474.

Triazole β-D-*O*-galactosyl 2-hydroxybenzoate (27): From **21** (93.3 mg, 0.2 mmol), column chromatography (EtOAc/EtOH, 1:1 to 1:2) afforded **27** as a white powder (88.5 mg, 97.8%). R_f = 0.29 (*n*-Butanol/water/acetic acid, 3:5:1); $[\alpha]_D$ = −14.8 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 7.24 (d, *J* = 3.0 Hz, 1H), 6.93 (dd, *J* = 3.0 Hz, 8.8 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 4.88-4.75 (m, 4H), 4.40 (t, *J* = 4.8 Hz, 2H), 4.25 (d, *J* = 7.0 Hz, 1H), 3.77 (d, *J* = 2.3 Hz, 1H), 3.68-3.59 (m, 2H), 3.46-3.39 (m, 3H); HRMS: calcd. for $C_{18}H_{23}N_3O_9$+H: 442.1462, found: 442.1467.

Inhibitory assay. Recombinant human PTP1B catalytic domain was expressed and purified according to procedures described previously.[27a] Enzymatic activity of PTP1B was 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. To study the inhibition selectivity on other PTP family members, human TCPTP, SHP1, SHP2 and LARD1 were prepared and assays were performed according to procedures described previously.[27b]

Result and Discussion

Formation of the triazolyl glycosides. As illustrated in Scheme 1, the azido methyl benzoate (**5**, **6** and **7**) were prepared from commercially available methyl 3-hydroxybenzoate (**2**), methyl 3,5-dihydroxybenzoate (**3**) and methyl 2,5-dihydroxybenzoate (**4**) in one-pot. Etherification of **2-4** were realized in the presence of K_2CO_3 and 1,2-dibromoethane, followed by straightforward azide substitution with NaN_3, furnishing the desired products **5**, **6** and **7** in 47.5, 50.1 and 52.3% yield, respectively. The known sugar alkynes **8** and **9** were synthesized according to literature procedures from readily available acetyl-β-*O*-glucoside (**8'**) and acetyl-β-*O*-galactoside (**9'**).[26]

With the click ingredients ready, we successively handled the microwave-assisted 1,3-dipolar cycloaddition promoted by Cu(I) (Scheme 1). This was performed in a Yalian (YL8023B1) system at 40 °C with a ramp time of 6 min and hold time of 8 min. By using a condition involving 2 equiv. sodium ascorbate and 1 equiv. $CuSO_4$ as catalyst in 1:1 CH_2Cl_2/H_2O (v/v) solvent mixture, the click reaction between the azides and sugar alkynes proceeded smoothly. Both glucosyl (**8**) and galactosyl (**9**) alkynes were tolerable glyco-donors in such ambiance, affording the click products **10-15** in considerable yields of 86.7 - 94.5%. Interestingly, **6** (with *meta*-OH substitution on benzoate ring) represented the most efficient azido reactant which gave the corresponding triazole **11** and **14** in excellent yields of 93.6 and 94.5%, respectively.

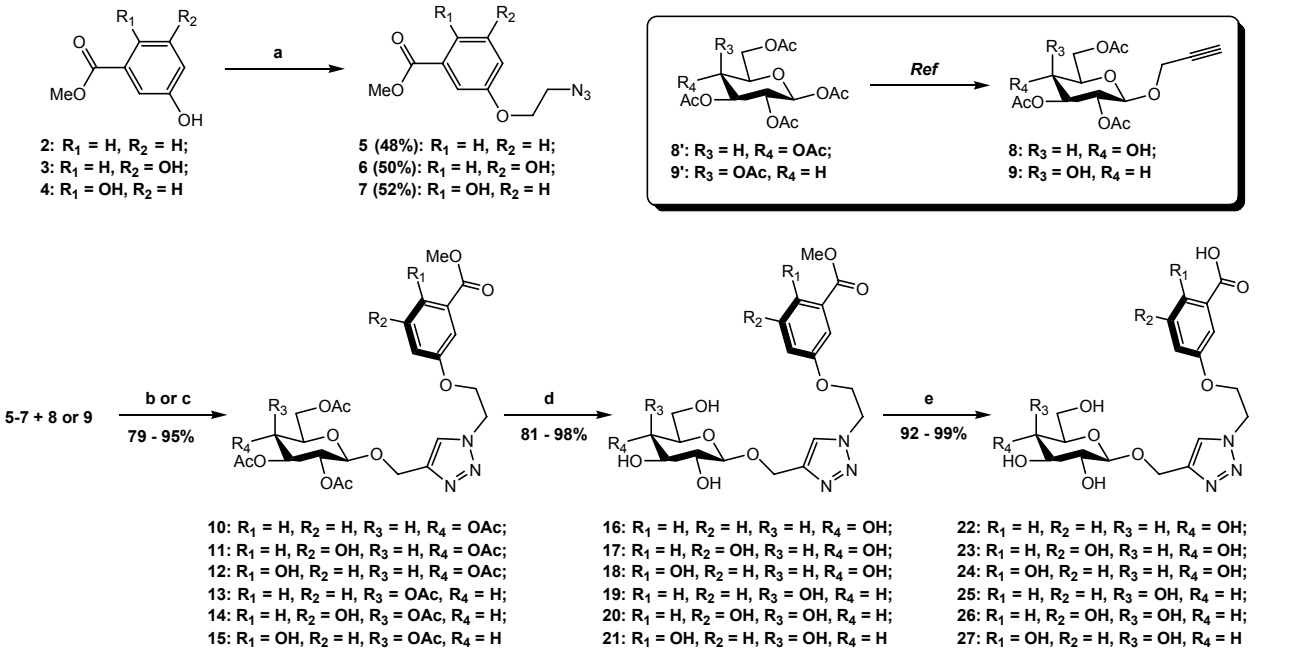
In order to study the predominance of the performed click reaction *via* microwave irradiation, we also initiated the same reactions under conventional condition (rt, stirring). The parallel results were listed in Table 1. Clearly, comparing to the microwave-accelerated synthesis, the final yields of the afforded products **10-15** did not change significantly whereas much prolonged reaction time was required (6 h). This experimental outcome unambiguously demonstrated the introduction of microwave irradiation into this study worthwhile, yielding the desired key products in a much faster manner.

Next, as illustrated in Scheme 1, after deacetylation with ammonia water in MeOH, the OH-free triazole esters **16-21** were afforded in 81.0 - 97.5% yield. Successive saponification with LiOH led to the achievement of final acids **22-27** (yield: 91.8%-quantitive).

Biological assays on PTPs. The set of freshly prepared salicylic glycosides (**10-27**) were assayed toward PTP1B and a panel of homologous PTPs including TCPTP, SHP-1, SHP-2

Table 1. Cu-catalyzed click reaction

Azide	Sugar	Microwave		Conventional	
		Time (min)	Product (yield, %)	Time (min)	Product (yield, %)
5		14	10 (87.9)	360	10 (87.3)
6	**8**	14	**11 (93.6)**	360	11 (78.7)
7		14	12 (88.0)	360	12 (93.8)
5		14	13 (86.7)	360	13 (74.6)
6	**9**	14	**14 (94.5)**	360	14 (92.5)
7		14	15 (92.1)	360	15 (94.1)



Scheme 1. Reagents and Conditions: (a) K_2CO_3, 1,2-dibromoethane in Acetone/H_2O (6:1, v/v) then NaN_3, reflux; (b) VcNa/$CuSO_4$ in CH_2Cl_2/H_2O under microwave irradiation (40 °C, 14 min); (c) VcNa/$CuSO_4$ in CH_2Cl_2/H_2O at rt (6 h); (d) ammonia water in MeOH, reflux; (e) LiOH in THF/H_2O

Table 2. Inhibitory activities of synthesized glycosides

Compd	Inhibition rate-% (IC_{50}-μM)				
	PTP1B	TCPTP	SHP-1	SHP-2	LAR
10	NA[b]	NA	NA	NA	NA
11	NA	NA	NA	NA	NA
12	**84.53 ± 6.32 (36.6)**	29.96 ± 4.11 (> 160)	NA	NA	NA
13	54.59 ± 3.72 (> 160)	NA	NA	NA	NA
14	NA	NA	NA	NA	NA
15	**73.95 ± 10.82 (66.2)**	NA	NA	NA	NA
16	71.99 ± 2.48 (> 160)	24.11 ± 4.12 (> 160)	NA	NA	NA
17	NA	26.13 ± 6.67 (> 160)	NA	NA	NA
18	**89.88 ± 5.90 (97.2)**	50.89 ± 11.93 (> 160)	NA	NA	NA
19	35.27 ± 15.23 (> 160)	NA	NA	NA	NA
20	31.15 ± 4.01 (> 160)	NA	NA	NA	NA
21	NA	NA	NA	NA	NA
22	**98.26 ± 0.79 (50.5)**	52.74 ± 7.48 (> 160)	NA	NA	NA
23	56.12 ± 4.42 (> 160)	33.94 ± 5.01 (> 160)	NA	NA	NA
24	30.39 ± 5.73 (> 160)	NA	NA	NA	NA
25	35.34 ± 5.33 (> 160)	NA	NA	NA	NA
26	NA	NA	21.86 ± 4.36 (> 160)	NA	NA
27	55.70 ± 3.29 (> 160)	NA	NA	NA	NA

[a]Values are mean of 3 experiments at a compound concentration of 100 μg/mL; [b]No activity (Inhibition rate at 100 μg/mL is lower than 20% and IC_{50} is higher than 160 μM).

and LAR according to previously described procedure.[27]

As listed in Table 2, among the acetyl glycoside class (**10**-**15**), glucoside **12** and galactoside **15** displayed higher inhibitions (84.5 and 74.0%, respectively) toward PTP1B, indicating that OH-substitution on *ortho*-position of benzoate ring was spatially preferential for the inhibitory potency. In addition, the glucosyl compound **12** possessed an almost 2-fold enhanced IC_{50} value (36.6 μM) than that of the galactosyl compound **15** (66.2 μM). However, when the acetyl group was removed, the corresponding PTP1B inhibition of galactosides **19** and **21** significantly decreased. In contrary, the deacetylated glucosides **16** and **18** exhibited increased PTP1B inhibition (*vs*. **10** and **12**, respectively) whereas the inhibitory potency of **18** (IC_{50} = 97.2 μM) lowered moderately. Notably, the acids **23**-**27** which were expected as PTP1B inhibitors displayed weak inhibitions with **22** as an exception (98.4% inhibition).

As reported, the achievement of selective PTP1B inhibitors is an intractable issue.[23,28a] Obviously, all assayed compounds (Table 2) that possessed more than 50% inhibition on PTP1B (**12**, **13**, **15**, **16**, **18**, **22**, **23** and **27**) showed reasonably better inhibitions over TCPTP with no inhibitions on SHP-1, SHP-2 and LAR at 100 μg/mL. For example, the best hit **12** owning an IC_{50} value of 36.6 μM was at least 4-fold more selective over other homologous PTPs tested (IC_{50} > 160 μM). More interestingly, compounds **12** (36.6 μM) and **15** (66.2 μM) which differ only in C-4 configuration on monosaccharide moiety exhibited almost 2-fold varied IC_{50} value. Such difference was also observed by comparing **22** which is the only acid sample having displayed measurable IC_{50} value (50.5 μM at 98.4% inhibition) and its C-4 epimer **25** (35.3% inhibition) with the equatorial bond being privileged. This clearly demonstrated that the carbohydrate moiety contributed to the inhibitory activity and more importantly, was able to perform as desirable chiral scaffolds for probing the configurational preference of PTP1B.

Binding mode investigation. We then sought to provide a plausible explanation toward the inhibitory deficiency of the afforded acid-free salicylic glycosides (**22**-**27**, Table 2) comparing to the reported natural product **1**[25] *via* docking study. We started with a crystal structure in complex with a reference ligand (PDB code: 3EB1). Water was removed from the original structure, and the rest protein was prepared using the Protein preparation wizard (Schrödinger, LLC, New York, NY, 2005). Then the compounds were docked to the active site of the protein using the Induced Fit Docking workflow (Schrödinger, LLC, New York, NY, 2005). The center atom was set to be a virtual center of referenced key residues: Phe182, Cys215 and Gly259.

Apparently, as shown in Fig. 2A, multiple hydrogen bonds were made between the salicylic precursor of the reported inhibitor **1** and the active site of PTP1B (Cys215, Arg221, Gln266, Gln262 and Ile210) which strongly indicated a typical competitive inhibition pattern. Additional hydrogen bonds were also generated between the sugar moiety and Asp48 of the YRD motif. Interestingly, the long alkyl chain attached on salicylic core concomitantly provided hydrophobic interactions with Phe182, thus preventing the closure of WPD loop, which may regard as the key factor toward the submicromole-ranged IC_{50} value (0.6 μM on PTP1B) of inhibitor **1**. In contrast, the inhibitor (**22**, Fig. 2B) synthesized in this study adopted a relatively different binding manner with PTP1B. Although the benzoic acid moiety similarly occupied the active site by making hydrogen bonds with Cys215, Arg221, Ala217, Gly218 and Ile219, however, the monosaccharide moiety tended to bind with the residue Asp265 of the second phosphotyrosine site while one additional hydrogen bond was made by the triazole ring with Gln266 in the same pocket. Evidently, being short of the essential long

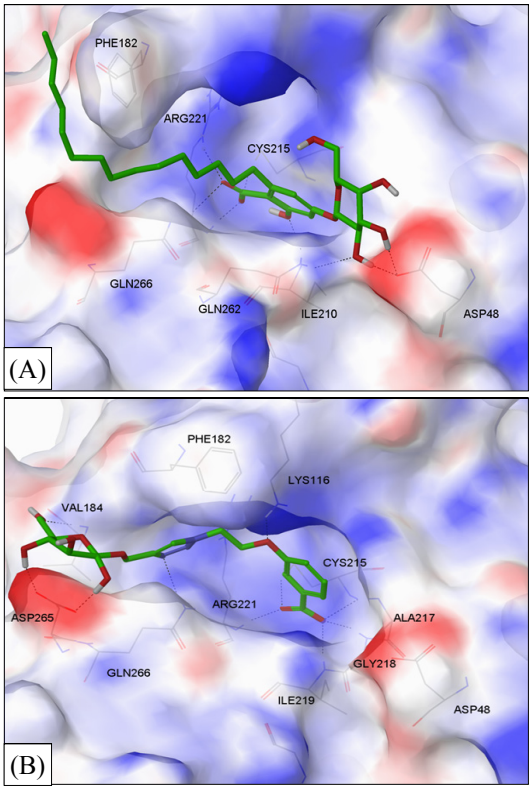


Figure 2. Binding mode of ligands (**1** in **A** and **22** in **B**) with PTP1B by docking simulation. Carbon atoms are in gray for PTP1B and green for ligands, nitrogen atoms are in blue and oxygen atoms are in red.

alkyl chain, the inhibitor **22** failed to make hydrophobic interactions with the phenylalanine residue Phe182, leading to the conventional WPD close conformation of PTP1B.

Consequently, we postulate the limitation of inhibitory activity of the synthesized compounds in this study is possibly resulted by the scarcity of hydrophobic functionalities conjugated with the salicylic glycosides which impedes the generation of nonpolar interactions with the WPD loop of PTP1B.

Conclusions

In conclusion, we have expeditiously prepared a series of triazole-linked salicylic β-D-*O*-glycosides *via* the highly efficacious microwave-accelerated click chemistry. Both glucosyl and galactosyl alkynes were tolerable glyco-donors toward such concise methodology, rapidly furnishing the desired products in high yields. The afforded products displayed promising selectivity over TCPTP, SHP-1, SHP-2 and LAR, howbeit with limited inhibitory activities on PTP1B. In addition, we have discovered that the versatile carbohydrate moiety could serve as promising chiral scaffold toward the probing of spatial preference of PTP1B. Docking study plausibly proposed binding modes of both the reported natural product **1** and synthesized compound **22** with the enzymatic target, which suggests the limited inhibitory potency of the salicylic glycosides prepared in the present study ascribable to the lack of hydrophobic functionalities on salicylate moiety to interact with Phe182 of the WPD loop. Our future efforts would thus be devoted to the preparation of sugar-based PTP1B inhibitors that simultaneously contain hydrophobic functionalities.

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Reference and Notes

1. Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357.
2. Hakomori, S. *Glycoconjugate J.* **2004**, *21*, 125.
3. Sacchettini, J. C.; Baum, L. G.; Brewer, C. F. *Biochemistry* **2001**, *40*, 3009.
4. Monsigny, M.; Mayer, R.; Roche, A. C. *Carbohydr. Lett.* **2000**, *4*, 35.
5. Feizi, T. *Glycoconjugate J.* **2001**, *17*, 553.
6. Seeberger, P. H.; Werz, D. B. *Nature* **2007**, *446*, 1046.
7. Jelinek, R.; Kolusheva, S. *Chem. Rev.* **2004**, *104*, 5987.
8. Slovin, S. F.; Keding, S. J.; Ragupathi, G. *Immunol. Cell Biol.* **2005**, *83*, 418.
9. Liang, P. H.; Wu, C. Y.; Greenberg, W. A.; Wong, C. H. *Curr. Opin. Chem. Biol.* **2008**, *12*, 86.
10. Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491.
11. Meutermans, W.; Le, G. T.; Becker, B. *ChemMedChem* **2006**, *1*, 1164.
12. Ernst, B.; Magnani, J. L. *Nat. Rev. Drug Discov.* **2009**, *8*, 661.
13. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.
14. Mamidyala, S. K.; Finn, M. G. *Chem. Soc. Rev.* **2010**, *39*, 1252.
15. Lee, L. V.; Mitchell, M. L.; Huang, S. J.; Fokin, V. V.; Sharpless, K. B.; Wong C. H. *J. Am. Chem. Soc.* **2003**, *125*, 9588.
16. Wilkinson, B. L.; Bornaghi, L. F.; Houston, T. A.; Innocenti, A.; Vullo, D.; Supuran C. T.; Poulsen S.-A. *J. Med. Chem.* **2007**, *50*, 1651.
17. Kajimoto, T.; Node, M. *Synthesis* **2009**, *19*, 3179.
18. (a) Lin, L.; Shen, Q.; Chen, G. R.; Xie, J. *Bioorg. Med. Chem.* **2008**, *16*, 9757. (b) Deng, Q.; Zheng, R.-R.; Ding, N.-N.; He, X.-P.; Chen, G.-R. *Bull. Korean Chem. Soc.* **2010**, *31*, 1055.
19 Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325.
20. (a) Kappe, C. O.; Van der Eycken, E. *Chem. Soc. Rev.* **2010**, *39*, 1280. (b) Xue, J.-L.; Yang, J.-W.; Deng, Q.; He, X.-P.; Chen, G.-R. *Bull. Korean Chem. Soc.* **2010**, *31*, 1825.
21. Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207.
22. For a very recent example, see: Dedola, S.; Hughes, D. L.; Nepogodiev, S. A.; Rejzek, M.; Field, R. A. *Carbohydr. Res.* **2010**, *345*, 1123.
23. Zhang, S.; Zhang, Z. Y. *Drug Discovery Today* **2007**, *12*, 373.
24. (a) Shrestha, S.; Bhattarai, B. R.; Lee, K.-H.; Cho, H. *Bioorg. Med. Chem.* **2007**, *15*, 6535. (b) Shrestha, S.; Lee, K.-H.; Cho, H. *Bull. Korean Chem. Soc.* **2004**, *25*, 1303.
25. Seo, C.; Sohn, J. H.; Oh, H.; Kim, B. Y.; Ahn, J. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6095.
26. Mereyala, H. B.; Gurrala, S. R. *Carbohydr. Res.* **1998**, *307*, 351.
27. (a) Zhang, W.; Hong, D.; Zhou, Y.-Y.; Zhang, Y.-N.; Shen, Q.; Li, J.-Y.; Hu, L.-H.; Li, J. *Biochim. Biophys. Acta* **2006**, *1760*, 1505. (b) Shi, L.; Yu, H. P.; Zhou, Y. Y.; Du, J. Q.; Shen, Q.; Li, J. Y.; Li, J. *Acta Pharmacol. Sin.* **2008**, *29*, 278.
28. Vintonyak, V. V.; Antonchick, A. P.; Rauh, D.; Waldmann, H. *Curr. Opin. Chem. Biol.* **2009**, *13*, 272-283.