Click Synthesis of Triazolyl Phenylalaninyl and Tyrosinyl Derivatives as New Protein Tyrosine Phosphatase Inhibitors

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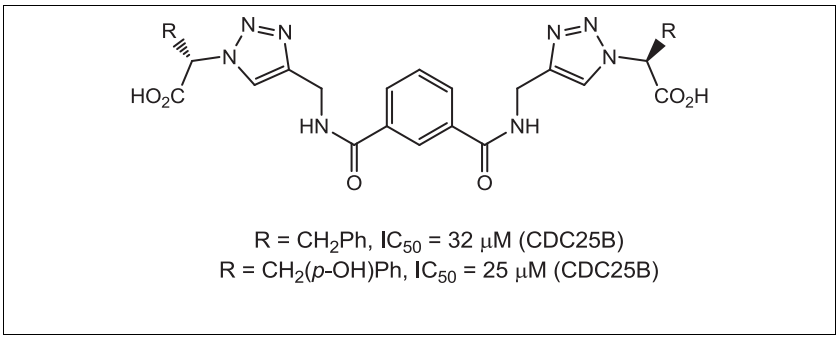

The efficient construction of triazolyl peptidomimetics via the powerful click chemistry for the discovery of small molecule-based chemotherapeutic agents represents a promising strategy in drug development today. Herein, the synthesis of novel mono-triazolyl or bis-triazolyl amino acid derivatives was rapidly achieved via microwave-assisted Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC). Subsequent *in vitro* enzymatic assay on several homologous protein tyrosine phosphatases (PTPs) identified the triazolyl dimers as new specific inhibitors of Cell Cycle Division 25B (CDC25B) phosphatase and Protein Tyrosine Phosphatase 1B (PTP1B).

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INTRODUCTION

With an everlasting objective of effectively producing molecules having therapeutic values, Sharpless and coworkers addressed the notion of "click chemistry" more than one decade ago, supporting the utilization of regioselective carbon-heteroatom ligation reactions toward the synthesis of useful compound libraries [1]. The Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) [2,3] represents unquestionably the best example for click chemistry, which has indeed boosted the advancement of modern drug discovery over the past decade. Numerous starting materials containing alkynyl or azido functional groups have been employed as participants for the versatile CuAAC reaction [4–8]. However, without doubt, the primary metabolites of Mother Nature, namely, the peptides, sugars, and nucleotides are among the most ideal ones for developing functional compounds because of their structural diversity, relatively easy modifiability and particularly, high biocompatibility [9–15].

Considerable efforts have been devoted to the preparation of multifunctional triazolyl peptidomimetics wherein the structurally rigid triazole ring was used to replace the amide bond that is liable toward enzymatic cleavage [9]. However, studies in which these interesting compounds were developed as protein ligands have rarely been reported [15].

Protein tyrosine phosphatases (PTPs) are a class of functional enzymes regulating the dephosphorylation processes involved in numerous crucial biological and pathological events. The dysfunction and overexpression of many PTPs have been demonstrated causative toward a number of human major diseases. Therefore, the efficient discovery of their inhibitors featuring good bioavailability became fairly desirable [16,17].

Herein, we described the efficient preparation of some new mono-amino or bis-amino acid derivatives via microwave-assisted click chemistry. Subsequent *in vitro* enzymatic assay identified some of the triazolyl dimers as new CDC25B and PTP1B inhibitors with micromole-ranged activity and good specificity over other PTPs tested.

RESULTS AND DISCUSSION

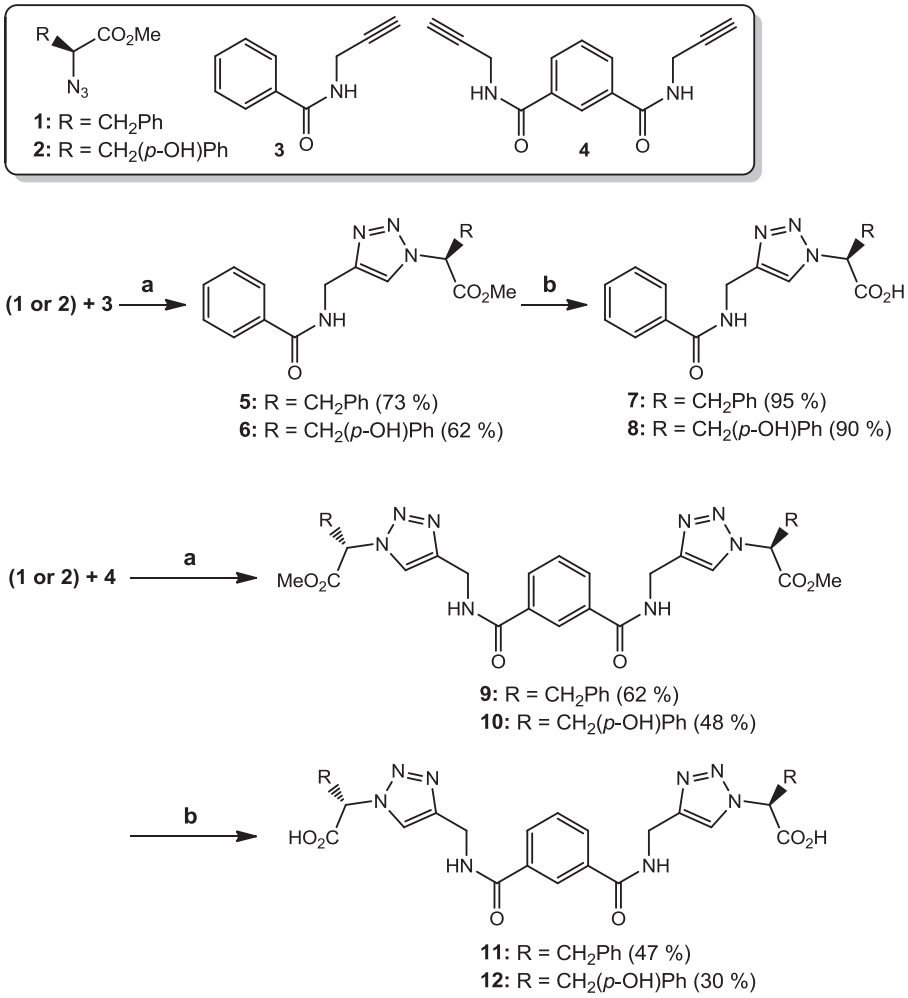
Synthesis. Microwave irradiation is a validated synthetic accessory for potently reducing the time consumption of

chemical reactions, which has also proven efficacious in enhancing the efficiency of Cu(I)-catalyzed *Huisgen* [3 + 2] 1,3-dipolar cycloadditions [18]. We therefore chose to realize the "click" synthesis of the desired triazoles under microwave irradiation shown in Scheme 1. Our previously prepared azido phenylalanine **1** and tyrosine **2** [19,20] via a method established by Goddard-Borger and Stick [21] and the mono- and di-2-*N*-propynyl benzene **3** and **4** [22] were used to construct new mono-triazoles or bis-triazoles. All microwave-assisted reactions were performed in a Yalian system (YL8023B1) (Shanghai Yalian Microwave S&T Co., Ltd., Shanghai, PR China).

Mono-*N*-propynyl benzene **3** and the azido carboxylic ester **1** or **2** were first equivalently added to a solvent mixture of CH_2Cl_2/DMF/water, followed by 1 equiv. Na ascorbate and 0.4 equiv. $CuSO_4{\cdot}5H_2O$. This mixture was then transferred to the microwave oven (with a ramp time of 8 min until 60°C). To our delight, after stirring for only 5 min, the mono-triazolyl phenylalanine **5** and tyrosine **6** were given in moderate yields of 73% and 62%, respectively. However, our successive attempt with respect to the dual click reaction of bis-*N*-propynyl **4** with azides **1** and **2** under the same condition failed to give the title bis-triazoles. It has been noted that the click reactions performed on a dipropargyl molecular template require accessorial catalyst loading to overcome the steric hindrance [20]. Hence, we further conducted the dual click reactions with increased Na ascorbate (3 equiv.) and $CuSO_4{\cdot}5H_2O$ (2.5 equiv.) under microwave heating, leading successfully to the formation of bis-triazolyl phenylalanine **9** and tyrosine **10** in modest yields of 62% and 48%, respectively, within 5 min.

The obtained triazolyl esters were subsequently subjected to microwave-assisted saponification in the presence of LiOH (1.5 equiv./ester) for 5 min (with a ramp time of 3 min until 20°C), giving the final mono-triazolyl or bis-triazolyl carboxylic acids. The mono-acids **7** and **8** were

Scheme 1. Reagents and conditions: (a) Na ascorbate, $CuSO_4{\cdot}5H_2O$, CH_2Cl_2/DMF/water, microwave irradiation (60 °C); LiOH, MeOH/H_2O, microwave irradiation (20 °C).



afforded in excellent yields of 95% and 90%, respectively, whereas the bis-acids **11** and **12** were obtained in much lesser yields of 47% and 30%, respectively. The lower yields of the latter could possibly be ascribed to the patial cleavage of the amide bonds under strong basic condition.

Biological assay. Some triazolyl bis-amino acids were recently prepared and identified as novel AMPA receptor ligand, which implied the value of triazolyl amino acids in medicinal chemistry [15]. The bioactivities of the prepared triazolyl amino acid derivatives **5–12** were subsequently assessed on a panel of homologous PTPs including CDC25B, PTP1B, TCPTP, SHP-1, SHP-2, and LAR via our previously developed methods at a compound concentration of 100 μg/mL [23,24].

As listed in Table 1, the mono-esters **5** and **6** and the mono-phenylalaninyl acid **7** were inactive on all PTPs tested. However, the mono-tyrosinyl acid **8** displayed measurable IC_{50} value on CDC25B and showed no inhibitory effect on other homologous PTPs, indicating that its additional hydroxyl group on tyrosine residue has contribution to the activity. Similarly, whereas the bis-phenylalaninyl ester **9** was not an inhibitor of PTPs, its tyrosinyl counterpart **10** could weakly suppress the catalytic activity of CDC25B. The bis-acids **11** and **12** showed considerably much enhanced inhibitory potency on both CDC25B and PTP1B with the bis-tyrosinyl derivative **12** being slightly more potent. These data are in accordance with former reports elaborating that the active sites of the PTPs are prone to accommodate polar moieties such as aryl carboxylic acids [16,17]. Moreover, the most active compounds in this series (**11**, **12**) simultaneously possessed remarkable selectivity over other homologous PTPs including TCPTP, SHP, and LAR. This may qualify as an essential merit for the further development of specific PTP1B and CDC25B inhibitors.

CONCLUSION

To summarize, we realized in this study the efficient and prompt microwave-assisted click ligation synthesis of novel series of monotriazolyl- and bis-triazolyl phenylalaninyl and tyrosinyl derivatives. Subsequently, performed biological assay revealed some of these triazolyl peptidomimetics as new CDC25B and PTP1B inhibitors with good selectivity over other homologous PTPs tested. This paper would therefore furnish new insights into the development of bioactive small-molecule PTPs inhibitors on the basis of the structurally diverse and potentially biocompatible triazolyl amino acids.

EXPERIMENTAL

General. All purchased chemicals and reagents are of commercially high available grade. Solvents were purified by standard procedures. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer in $CDCl_3$ or DMSO-d_6 solutions. Microwave-assisted reactions were performed in a Yalian (YL8023B1) system at 60°C with a ramp time of 8 min. All reactions were monitored by thin-layer chromatography (TLC) with detection by UV or by spraying with 6 N H_2SO_4 in EtOH and charring at 300°C. Optical rotations were measured using a Perkin–Elmer 241 polarimeter at room temperature and a 10-mm/1-mL cell at rt. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier XE spectrometer using standard conditions (ESI, 70 eV).

General procedure for the microwave-assisted click reaction. To a solution of the alkyne (1 equiv.) and the azide (1.0 or 2.0 equiv.) dissolved in CH_2Cl_2/DMF/water (1:0.5:1, V/V/V), Na ascrobate (1–3 equiv.) and $CuSO_4{\cdot}5H_2O$ (0.4–2.5 equiv.) were added. This mixture was then transferred into the microwave oven with vigorous stirring for 5 min (ramp time: 8 min). The solvent was then removed in vacuum, and the residue was washed with brine and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and then concentrated to give a crude product, which was purified by column chromatography.

(S)-methyl 2-(4-(benzamidomethyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropanoate (5). From compound **1** (103 mg, 0.5 mmol) and **3** (93 mg, 0.6 mmol), Na ascorbate (99 mg, 0.5 mmol), $CuSO_4{\cdot}5H_2O$ (61 mg, 0.25 mmol), column chromatography (petroleum ether/EtOAc, 3:1) afforded **5** as a white solid (134 mg, 73%); $R_f = 0.58$ (petroleum ether/EtOAc = 3:2); $[\alpha]_D = -100$ ($c = 0.1$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.79$ (d, 2H, $J = 7.2$ Hz), 7.70 (s, 1H), 7.50 (t, 1H, $J = 7.2$ Hz), 7.42 (t, 2H,

Table 1

Inhibitory activities of compounds **5–12** on PTPs.

	IC_{50} (μM)[a]					
Compound	CDC25B	PTP1B	TCPTP	SHP-1	SHP-2	LAR
5	> 140	> 140	> 140	> 140	> 140	> 140
6	> 140	> 140	> 140	> 140	> 140	> 140
7	> 140	> 140	> 140	> 140	> 140	> 140
8	79.5 ± 21.7	> 140	> 140	> 140	> 140	> 140
9	> 140	> 140	> 140	> 140	> 140	> 140
10	113.9 ± 26.7	> 140	> 140	> 140	> 140	> 140
11	31.9 ± 5.4	54.9 ± 1.7	> 140	> 140	> 140	> 140
12	24.7 ± 1.3	42.4 ± 2.3	> 140	> 140	> 140	> 140

[a] Values in the table are means of three experiments.

J = 7.6 Hz), 7.19–7.17 (m, 3H), 7.03–7.01 (m, 3H), 5.54 (dd, 1H, J = 6.0, 8.8 Hz), 4.73–4.62 (m, 2H), 3.75 (s, 3H), 3.53 (dd, 1H, J = 6.4, 14.4 Hz), 3.44 (dd, 1H, J = 9.2, 14.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 167.5, 145.0, 134.7, 134.0, 131.6, 128.9, 128.7, 128.5, 127.5, 127.2, 123.0, 64.1, 53.1, 38.6, 35.3; HRMS: calcd for $C_{20}H_{20}N_4O_3$ + Na: 387.1433. Found: 387.1426.

(S)-2-(4-(benzamidomethyl)-1H-1,2,3-triazol-1-yl)-3-(4-hydroxyphenyl)propanoate methyl ester (6). From compound **2** (75 mg, 0.3 mmol) and **3** (66 mg, 0.4 mmol), Na ascorbate (67 mg, 0.3 mmol), $CuSO_4 \cdot 5H_2O$ (42 mg, 0.1 mmol), column chromatography (petroleum ether/EtOAc, 2:3) afforded **6** as a white solid (80 mg, 62%); TLC: R_f = 0.2 (petroleum ether/EtOAc, 2:3); $[\alpha]_D = -33$ (c = 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, 2H, J = 7.6 Hz), 7.68 (s, 1H), 7.51 (t, 1H, J = 7.2 Hz), 7.43 (t, 1H, J = 7.6 Hz), 6.97 (brs, 1H), 6.83 (d, 2H, J = 8.4 Hz), 6.64 (d, 2H, J = 8.4 Hz), 5.51 (dd, 1H, J = 5.6, 8.8 Hz), 4.73–4.62 (m, 2H), 3.78 (s, 3H), 3.45 (dd, 1H, J = 5.6, 14.0 Hz), 3.35 (dd, 1H, J = 9.2, 14.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 168.1, 156.1, 144.6, 133.6, 131.8, 130.0, 128.5, 127.2, 127.19, 125.6, 123.2, 115.8, 64.5, 53.1, 37.8, 35.1; HRESIMS: calcd for $C_{20}H_{20}N_4O_4$ + Na: 403.1382. Found: 403.1375.

(2S,2'S)-2,2'-(4,4'-((isophthaloylbis(azanediyl))bis(methylene))bis(1H-1,2,3-triazole-4,1-diyl))bis(3-phenylpropanoate) methyl diester (9). From compound **1** (85 mg, 0.4 mmol) and **4** (50 mg, 0.2 mmol), Na ascorbate (82 mg, 0.4 mmol), $CuSO_4 \cdot 5H_2O$ (103 mg, 0.4 mmol), column chromatography (EtOAc/EtOH, 20:1) afforded **9** as a white solid (83 mg, 62%); R_f = 0.2 (petroleum ether/EtOAc, 1:6); $[\alpha]_D = -90$ (c = 0.1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1H), 7.91–7.89 (m, 4H), 7.76 (brs, 2H), 7.37–7.33 (m, 1H), 7.14–7.13 (m, 6H), 7.02–7.00 (m, 4H), 5.57 (t, 2H, J = 7.6 Hz), 4.57 (brs, 4H), 3.69 (brs, 6H), 3.52 (dd, 2H, J = 6.4, 14.4 Hz), 3.43 (dd, 2H, J = 9.2, 13.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 166.7, 144.8, 134.7, 134.1, 130.6, 128.9, 128.8, 127.5, 125.2, 123.0, 64.2, 53.1, 38.6, 35.3; HRESIMS: calcd for $C_{34}H_{34}N_8O_6$ + Na: 673.2499. Found: 673.2510.

(2S,2'S)-2,2'-(4,4'-((isophthaloylbis(azanediyl))bis(methylene))bis(1H-1,2,3-triazole-4,1-diyl))bis(3-(4-hydroxyphenyl)propanoate) methyl diester (10). From compound **2** (124 mg, 0.6 mmol) and **4** (70 mg, 0.3 mmol), Na ascorbate (195 mg, 1.0 mmol), $CuSO_4 \cdot 5H_2O$ (175 mg, 0.7 mmol), column chromatography (EtOAc/EtOH, 15:1) afforded **10** as a white solid (91 mg, 48%); TLC: R_f = 0.5 (dichloromethane/MeOH, 9:1); $[\alpha]_D = -80$ (c = 0.1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (dd, 2H, J = 1.6, 8.0 Hz), 7.80 (s, 1H), 7.67 (s, 2H), 7.54 (t, 1H, J = 7.6 Hz), 7.30–7.26 (m, 2H), 6.68 (d, 4H, J = 8.0 Hz), 6.50 (d, 4H, J = 8.4 Hz), 5.51 (dd, 2H, J = 4.8, 11.6 Hz), 4.76 (dd, 2H, J = 7.6, 15.2 Hz), 4.48 (dd, 2H, J = 4.8, 14.4 Hz), 3.88 (s, 6H), 3.51 (dd, 2H, J = 4.4, 14.0 Hz), 3.27 (dd, 2H, J = 11.6, 14.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 165.7, 156.1, 144.8, 134.3, 129.9 (1), 129.9 (2), 128.4, 126.5, 125.7, 123.2, 115.1, 63.3, 52.7, 36.0, 34.8; HRESIMS: calcd for $C_{34}H_{34}N_8O_8$ + Na: 705.2397. Found: 705.2396.

General procedure for the microwave-assisted saponification. To a solution of the ester dissolved in MeOH/H_2O (1:1, V/V/V), LiOH (1.5 equiv./ester), which was then transferred into the microwave oven with vigorous stirring for 5 min (ramp time: 3 min) was added. H^+ resin was then added to the resulting mixture for removing lithium salts. After filtration, the filtrate was concentrated in vacuum, and the residue was successively purified by column chromatography.

(S)-2-(4-(benzamidomethyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropanoic acid (7). From compound **5** (130 mg, 0.4 mmol), column chromatography (EtOAc/EtOH = 3:1) afforded **7** as a white solid (119 mg, 95%); R_f = 0.40 (CH_2Cl_2/MeOH = 8:1); $[\alpha]_D = -8$ (c = 0.1, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.03 (t, 1H, J = 6.0 Hz), 7.93 (s, 1H), 7.89 (d, 2H, J = 7.2 Hz), 7.53 (t, 1H, J = 7.2 Hz), 7.47 (t, 2H, J = 7.6 Hz), 7.14–7.04 (m, 5H), 5.25 (dd, 1H, J = 3.6, 10.0 Hz), 4.47–4.41 (m, 2H), 3.51 (dd, 1H, J = 4.0, 14.4 Hz), 3.29 (dd, 1H, J = 10.8, 14.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.4, 166.1, 144.2, 137.8, 134.1, 131.2, 128.7, 128.2, 128.0, 127.2, 126.2, 122.5, 66.3, 38.2, 34.8; HRESIMS: calcd for $C_{19}H_{18}N_4O_3$ + Na: 373.1277. Found: 373.1274.

(S)-2-(4-(benzamidomethyl)-1H-1,2,3-triazol-1-yl)-3-(4-hydroxyphenyl)propanoic acid (8). From compound **6** (65 mg, 0.2 mmol), column chromatography (EtOAc/EtOH = 2:1) afforded **8** as a white solid (56 mg, 90%); R_f = 0.5 (CH_2Cl_2/MeOH = 5:1); $[\alpha]_D = -29$ (c = 0.1, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.05 (t, 1H, J = 6.0 Hz), 7.97 (s, 1H), 7.90 (d, 2H, J = 7.2 Hz), 7.53 (t, 1H, J = 7.2 Hz), 7.47 (t, 2H, J = 7.6 Hz), 6.85 (d, 2H, J = 8.4 Hz), 6.55 (d, 2H, J = 8.4 Hz), 5.30 (dd, 1H, J = 4.0, 10.8 Hz), 4.54–4.45 (m, 2H), 3.40 (dd, 1H, J = 4.0, 14.4 Hz), 3.22 (dd, 1H, J = 10.8, 14.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.2, 166.3, 155.9, 144.4, 134.2, 131.3, 129.7, 128.3, 127.3, 122.6, 115.0, 66.0, 37.1, 34.9; HRESIMS: calcd for $C_{19}H_{18}N_4O_4$ + Na: 389.1226. Found: 389.1220.

(2S,2'S)-2,2'-(4,4'-((isophthaloylbis(azanediyl))bis(methylene))bis(1H-1,2,3-triazole-4,1-diyl))bis(3-phenylpropanoic acid) (11). From compound **9** (90 mg, 0.1 mmol), column chromatography (EtOAc/EtOH = 2:1) afforded **11** as a white solid (40 mg, 47%); R_f = 0.5 (CH_2Cl_2/MeOH = 1:1); $[\alpha]_D = -35$ (c = 0.3, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.20 (brs, 2H), 8.45–8.41 (m, 1H), 8.02 (brs, 4H), 7.57 (t, 1H, J = 8.0 Hz), 7.17–7.10 (m, 10H), 5.60 (dd, 2H, J = 4.4, 9.6 Hz), 4.49 (d, 2H, J = 5.2 Hz), 3.52 (dd, 2H, J = 5.2, 14.4 Hz), 3.47–3.40 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.0, 165.7, 144.6, 136.6, 134.2, 130.0, 128.8, 128.4, 128.2, 126.6, 126.5, 123.1, 63.9, 37.0, 34.8; HRESIMS: calcd for $C_{32}H_{30}N_8O_6$ + Na: 645.2186. Found: 645.2180.

(2S,2'S)-2,2'-(4,4'-((isophthaloylbis(azanediyl))bis(methylene))bis(1H-1,2,3-triazole-4,1-diyl))bis(3-(4-hydroxyphenyl)propanoic acid) (12). From compound **10** (90 mg, 0.1 mmol), column chromatography (EtOAc/EtOH = 4:1) afforded **12** as a white solid (27 mg, 30%); R_f = 0.5 (CH_2Cl_2/MeOH = 1:1); $[\alpha]_D = -27$ (c = 0.3, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.27 (brs, 2H), 8.49 (brs, 1H), 8.04–8.00 (m, 4H), 7.56 (t, 1H, J = 7.2 Hz), 6.85 (d, 4H, J = 7.2 Hz), 6.57 (d, 4H, J = 7.6 Hz), 5.31 (brs, 2H), 4.48 (d, 4H, J = 3.6 Hz), 3.38–3.35 (m, 2H), 3.24–3.15 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.7, 165.8, 156.0, 144.3, 134.1, 130.1, 129.6, 128.5, 126.9, 126.4, 122.7, 115.0, 65.6, 36.8. 34.8; HRESIMS: calcd for $C_{32}H_{30}N_8O_8$ + Na: 677.2084. Found: 677.2100.

PTP inhibitory assay. Recombinant human PTP1B catalytic domain was expressed and purified according to procedures described previously [23]. 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 (%)) versus 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 CDC25B, TCPTP, SHP-1, SHP-2, and LARD1 were prepared and assays were performed according to procedures described previously [24].

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