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A unique and rapid approach toward the efficient development of novel protein tyrosine phosphatase (PTP) inhibitors based on 'clicked' pseudo-glycopeptides

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ABSTRACT

There has been considerable interest in the development of protein tyrosine phosphatase (PTP) inhibitors since many of the PTP members are tightly associated with major human diseases including autoimmune disorders, diabetes and cancer. We report here a unique and rapid approach toward the development of novel PTP inhibitor entities based on triazolyl pseudo-glycopeptides. By employing microwave-accelerated Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC or 'click reaction'), a series of triazole-linked serinyl, threoninyl, phenylalaninyl and tyrosinyl 1-*O*-gluco- or galactosides have been efficiently synthesized in high yields within only ~30 min. Successive biological assay identified these glycopeptidotriazoles as favorable PTP1B and CDC25B inhibitors with selectivity over TCPTP, LAR, SHP-1 and SHP-2. Both the structural diversity of the amino acid (Ser, Thr, Phe and Tyr) introduced and the epimeric identity (Glc or Gal) on monosaccharide scaffold were determined to impact the corresponding inhibitory activity and selectivity. In addition, the benzylated sugar scaffold was demonstrated to act as a crucial role for enhancing the binding affinity of the inhibitors with the targeted PTP. Docking simulation was eventually conducted to propose plausible binding modes of this compound series with PTP1B and CDC25B. Our approach readily realized from naturally abundant raw materials (sugar and amino acid) and via facile, regioselective and expeditious synthetic method (microwave-assisted click reaction) might provide new insights toward the 'click' fabrication of structurally diverse PTP inhibitors.

The protein tyrosine phosphatase (PTP) superfamily comprises over 100 PTP members and is responsible for, together with protein tyrosine kinases, the synergistic modulation of tyrosine phosphorylation events on cellular level.[1] Inappropriately functioned regulation of many PTP members has been reported causative toward the pathogenesis of major human diseases involving autoimmune disorders, diabetes and cancer.[1b,2]

PTP1B represents one of the best therapeutically characterized signaling enzyme that negatively regulates insulin and leptin receptor pathways. Enhanced insulin sensitivity and ameliorated glycemic control and resistance to diet-induced obesity were observed on PTP1B-null mice, suggesting the inhibition of PTP1B may efficiently combat type 2 diabetes and obesity.[3] The cell division cycle 25 homolog B (CDC25B) participates in cell division and induces cell cycle arrest, leading to DNA repair or apoptosis.[4a] Its overexpression in various cancers including breast, lung, gastric, etc. has made CDC25B attractive as a novel therapeutic target toward anticancer treatment.[4b]

Considering such compelling evidence, numerous programs have been launched for the development of PTP inhibitors by both pharmaceutical enterprises and the academia.[5,6] However, only limited drug candidates have entered clinical trials due to the inadequate pharmacological properties of most phosphate analogs for achieving competitive PTP inhibition. In addition, non-specific inhibitors such as quinone derivatives those constitute the majority of CDC25 inhibitor class release reactive oxygen species (ROS), simultaneously bringing unsatisfactory toxicity on normal tissues.[5c] Consequently, the development of new chemical entities that may effectively inhibit disease-related PTPs remains highly desirable.

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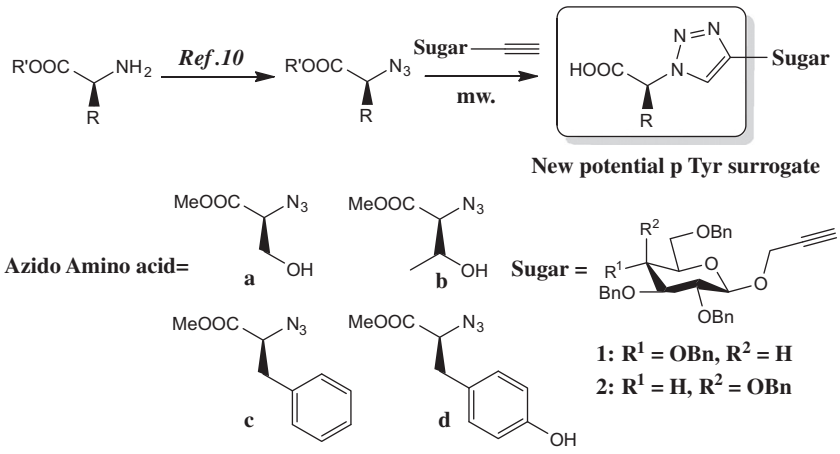


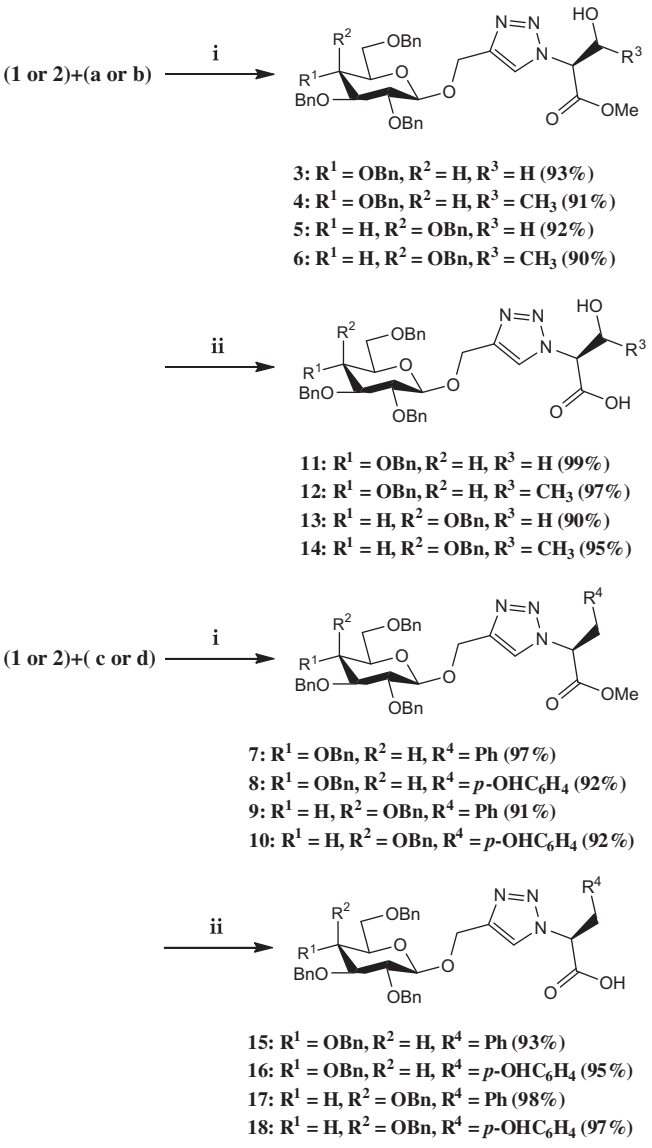
Figure 1. 'Click' strategy and azido amino acids and sugar alkynes used for click reaction in this study.

Glycopeptides universally exist in nature, governing a multitude of pivotal biological and pathological events.[7] Considerable efforts have been devoted to the synthesis of glycopeptide mimetics in the passing decade.[8] Two independent research groups (i.e., Dondoni et al.[9a] and Rutjes and co-workers[9b]) first reported a range of novel glycopeptide derivatives wherein the bioactive amino acid and sugar moieties are rigidly coupled via the click reaction.[10] The expediently formed triazolyl linkage may furnish stable conjugation pattern between amino acid residue and the glycosyl scaffold, which was also envisioned to display biological activity due to its heterocyclic nature.[9b]

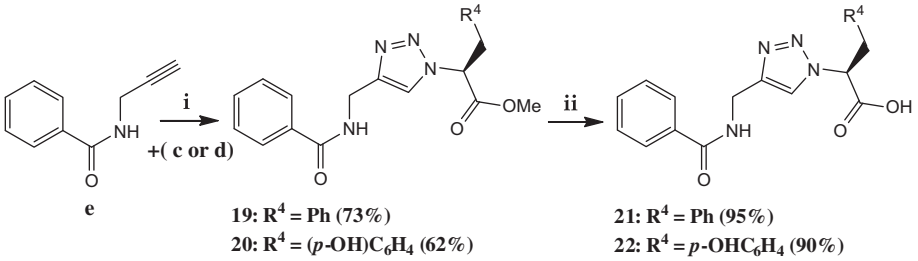
More recently, Goddard-Borger and Stick[11a] revealed a new diazotransfer reagent based on sulfonyl imidazolate, enabling the convenient conversion of the primary amine of amino acids into an azide. These amino acid derivatives bearing an azido precursor could be further used as a starting material for the CuAAC, resulting in the formation of triazolyl acids that may potentially serve as a new pTyr surrogate similar to the previously reported heterocyclic carboxylates by *Abbott*'s[12a] and *Novo Nordisk*'s[12b] groups.

We then sought to prepare, as shown in Figure 1, a series of glycosyl triazolyl acids via click reaction as new PTP inhibitors. L-Ser-OMe, L-Thr-OMe, L-Phe-OMe and L-Tyr-OMe employed for our preliminary investigation were first converted to the corresponding azides **a**–**d** via the method established by Goddard-Borger and Stick (Fig. 1).[11a] As noted, the pTyr itself is insufficient for potently binding to its specific PTP and appropriately appended residues such as benzene groups with pTyr may largely enhance the entire binding affinity.[5] We have identified in a very recent study that the benzylated sugars could display micromole-ranged PTP1B inhibitory activity for the first time.[11b] Therefore, the benzyl 1-*O*-propynyl glyco- and galactoside[13] were used to couple with the azido amino acids for concomitantly targeting the periphery hydrophobic enzymatic surface of PTPs, enhancing the binding affinity of the designed products (Fig. 1). Furthermore, in order to evaluate the predominance of the benzyl sugar scaffold toward PTP inhibition, triazolyl amino acid-benzamide conjugates were prepared for structure–activity relationship (SAR) study.

The click reaction was initiated with the assistance of microwave irradiation that has already proven practical toward the synthesis of glycopeptide mimetics.[14] As shown in Scheme 1, the starting amino acid azide (**a**–**d**) and sugar alkyne (**1** or **2**) were first dissolved in DMF/H_2O (1:2, V/V), followed by the addition of 2 equiv Na ascorbate and 1 equiv $CuSO_4{\cdot}5H_2O$. The mixture was then transferred to a Yalian (YL8023B1) microwave oven with vigorous stirring at a ramp time of 6 min and heating time of 10 min.[17] To our delight, all click reactions promoted by the micro-



Scheme 1. Reagents and conditions: (i) VcNa, $CuSO_4{\cdot}5H_2O$ in DMF/H_2O (1:2, V/V), mw; (ii) $LiOH{\cdot}H_2O$ in MeOH, mw.



Scheme 2. Reagents and conditions: (i) VcNa, $CuSO_4 \cdot 5H_2O$ in DMF/H_2O (1:2, V/V), mw; (ii) $LiOH \cdot H_2O$ in MeOH, mw.

wave irradiation proceeded smoothly, rapidly affording the glycopeptide triazoles **3**–**10** in excellent yields of >90% within this 16 min pattern. The following microwave-assisted saponification with $LiOH \cdot H_2O$ gave the desired triazolyl acids **11**–**18** in excellent to quantitative yields (90–99%).

In a similar way, as shown in Scheme 2, the triazolyl phenylalanine and tyrosine-benzamide conjugates **19** and **20** for SAR study were afforded via the microwave-assisted click reaction between the known *N*-(prop-2-yn-1-yl)benzamide **e** and azides **c** and **d**, respectively in moderate yields. The saponification with $LiOH \cdot H_2O$ under microwave irradiation of ester **19** and **20** successively gave the desired acids **21** and **22** in good yields (for the full characterization of all new compounds (**3**–**22**), see Supplementary data associated with this Letter).

Next, we assessed the inhibitory activity of the obtained products **11**–**18** and **20**–**22** on a panel of homologous PTPs including PTP1B, CDC25B, T-Cell Protein Tyrosine Phosphatase (TCPTP), Leukocyte Antigen-Related Tyrosine Phosphatase (LAR), SH2-Containing Protein Tyrosine Phosphatase1 (SHP1) and SHP2 by our previously established methods.[15] As listed in Table 1, the majority of the glycosyl triazolyl acids constructed showed moderate-to-good IC_{50} values on PTP1B and CDC25B in micromole range and several-fold selectivity over TCPTP, SHP-1, SHP-2 and LAR whereas no inhibitory potency was displayed while by the amino acid-benzamide triazoles.

For the glucosyl amino acid series (**11**, **12**, **15** and **16**), both serinyl and threoninyl triazoles **11** (28.1 μM) and **12** (31.2 μM) possess almost equal IC_{50} values on PTP1B while slightly better inhibitory activity was shown by the threonine **12** on CDC25B (IC_{50} = 25.4 μM) comparing to the serine **11** (IC_{50} = 43.3 μM on CDC25B). Moreover, they are not potent inhibitors of TCPTP, SHP-1, SHP-2 and LAR with IC_{50} values >50 μM. In contrast, the phenylalaninyl and tyrosinyl triazoles **15** and **16** that bear additional aryl residues exhibited remarkably enhanced inhibitory activity comparing to compound **11** and **12**. The IC_{50} value (5.1 μM) of the phenylalanine **15** on PTP1B is twofold smaller than that on CDC25B (9.9 μM) while a reverse inhibitory pattern was observed by comparing the IC_{50} values of the tyrosine **16** on same PTPs (IC_{50} = 8.3 μM on PTP1B and 3.9 μM on CDC25B). In addition, the PTP1B-privileged inhibitor **15** showed relatively worse selectivity over CDC25B (1.9-fold), TCPTP (1.5-fold), SHP-1 (3.5-fold), SHP-2 (3.1-fold) compared with the CDC25B-privilegded inhibitor **16** (2.1-fold over PTP1B, 4.5-fold over TCPTP, 6.6-fold over SHP-1 and 5.3-fold over SHP-2) whereas both compounds showed weak inhibitory activity on LAR (>50 μM).

On the other hand, the galactosyl amino acid series (**13**, **14**, **17** and **18**) adopted similar but slightly varied inhibition fashion compared with their C4 epimers. Almost equal IC_{50} values were shown by both compound **13** (39.7 μM) and **14** (38.2 μM) on CDC25B whereas the serine **13** (IC_{50} = 16.8 μM) acted as a better PTP1B inhibitor than the threonine **14** (IC_{50} = 42.3 μM) considering its lesser IC_{50} value. Similar to their glucosyl epimer **11** and **12**, they exhibited weak inhibitory potency on TCPTP, SHP-1, SHP-2 and LAR (IC_{50} >50 μM). However, phenylalaninyl triazole **17** and tyrosinyl triazole **18** exhibited identical IC_{50} values on both PTP1B and CDC25B, which is different from the inhibitory mode of their epimeric **15** and **16**. Meanwhile, they showed low-to-moderate selectivity (1.8 to 4.7-fold) over TCPTP, SHP-1 and SHP-2 and weak inhibitory activity on LAR (IC_{50} >50 μM).

An obvious difference was observed by comparing the inhibitory profile of glucosyl tyrosine **16** and the galactosyl tyrosine **18**. Glucoside **16** (IC_{50} = 3.9 μM) that bears an equatorial bond at C4 position of monosaccharide scaffold possesses more then threefold enhanced inhibitory potency on CDC25B comparing to its epimer **18** (IC_{50} = 11.9 μM) with a C4 axial bond. Moreover, compound **16** is also more specific than compound **18** when comparing their IC_{50} values on other homologous PTPs, suggesting that the epimeric identity on the sugar scaffold may impact the inhibitory profile of the corresponding triazolyl glycopeptide derivatives in certain cases.

Interestingly, as shown in the last two entries in Table 1, while the benzylated sugar scaffold was replaced by a benzaminde moiety to couple with the relatively more bioactive phenylalaninyl and tyrosinyl azide via the triazole, the corresponding inhibitory activity of compounds **20** and **22** totally faded on all PTPs tested. This unambiguously demonstrated the benzyl sugar scaffold advantageous for largely enhancing the binding affinity of the triazole-linked glycopeptide mimetics with the targeted PTP.

In an attempt to investigate the possible binding modes of the identified pseudo-glycopeptide-based inhibitors with the corresponding PTP, we conducted docking simulation of compound **15** with PTP1B and compound **16** with CDC25B, respectively. As shown in Figure 2A, compound **15** possibly adopted a hydrogen bonding-dominated binding behavior, occupying the PTP1B catalytic site (His214-Arg221). The carboxylic precursor of phenylalaninyl residue has made several hydrogen bonds with amino acid residues including Gly218, Ile219, Gly220 and Arg221, respectively. One hydrogen bond was also generated by the triazole ring

Table 1
Inhibitory activities on PTPs for triazolyl acids **11**–**18**

Code	Structure[b]	IC_{50}[a] (μM)					
		PTP1B	CDC25B	TCPTP	SHP-1	SHP-2	LAR
11	Glc-Ser	28.1	43.3	>50	>50	>50	>50
12	Glc-Thr	31.2	25.4	>50	>50	>50	>50
13	Gal-Ser	16.8	39.7	>50	>50	>50	>50
14	Gal-Thr	42.3	38.2	>50	>50	>50	>50
15	Glc-Phe	5.1	9.9	7.7	17.7	15.7	>50
16	Glc-Tyr	8.3	3.9	17.6	25.7	20.6	>50
17	Gal-Phe	7.0	7.0	12.6	18.5	17.4	>50
18	Gal-Tyr	11.2	11.9	29.9	53.1	33.3	>50
20	—	>50	>50	>50	>50	>50	>50
22	—	>50	>50	>50	>50	>50	>50

[a] Values are means of three experiments.
[b] *Abbreviations*: Glc, glucose; Gal, galactose; Ser, serine; Thr, threonine; Phe, phenylalanine; Tyr, tyrosine.

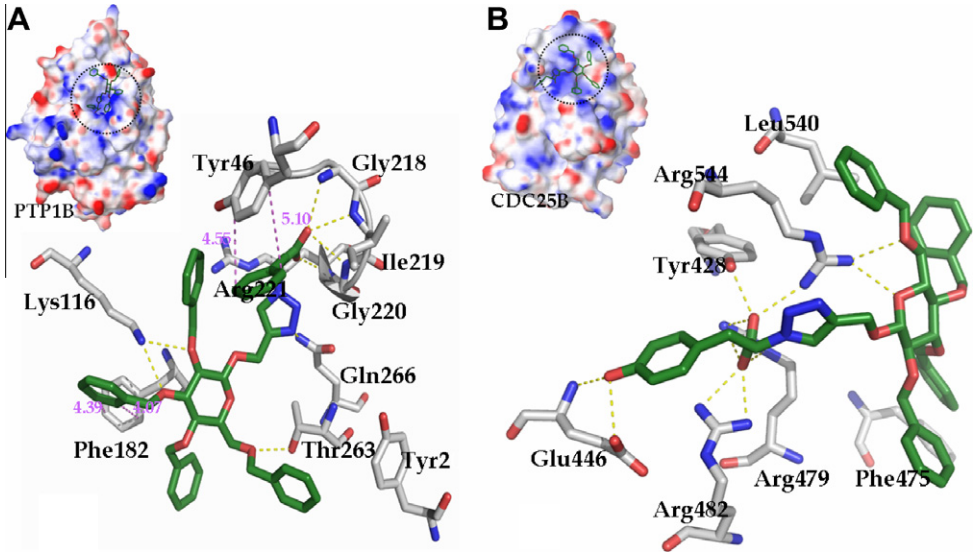


Figure 2. (A) PTP1B in complex with compound **15**. (B) CDC25B in complex with compound **16**. The surface of the protein was shown as colored in property of electrostatic potential. The compounds were shown as green stick and residues in PTP were shown as light grey line. Nitrogen atoms are in blue and oxygen atoms in red. Hydrogen bonds were shown as yellow dash lines and all nonpolar interactions were indicated by pink dash lines.

with Gln266 while three oxygen atoms on 2-, 3- and 6-position of sugar moiety have made additional hydrogen bonds with Lys116 and Thr263, respectively.

Nonpolar interactions were simultaneously observed. A relatively distant pi-pi stacking generated between the distal benzene group on the phenylalaninyl residue of compound **15** with Tyr46 may generally account for the enhanced affinity of the phenylalanine and tyrosine-containing inhibitors (**15**–**18**) comparing to the rest (**11**–**14**) that lack this essential benzene (or phenol) group. More interestingly, the other edge-to-face pi-pi stacking made by the distal benzene group on C3 position of the sugar scaffold with Phe182 directly led to the prevention of WPD loop closure which is similar to the reported binding mode of aryl diketoacid derivatives with PTP1B by Zhang and co-workers[16a] Moreover, the sugar C6 benzyl group partially extended to the second phosphotyrosine site of PTP1B, making hydrophobic interactions with Tyr20.

Next, the plausible binding mode of compound **14** with CDC25B was proposed and illustrated in Figure 2B. The triazolyl acid precursor tended to fit in the large 'swimming pool'[16b] cavity adjacent to the catalytic pocket (Cys473, Glu474, Glu478 and Met531), generating densely functionalized hydrogen-bonding array with Tyr428, Glu446, Arg479 and Arg482, respectively. Notably, the two hydrogen bonds made between the hydroxy group on tyrosinyl residue of compound **16** (IC_{50} = 3.9 μM) with Glu446 might be causative toward its 2.5-fold enhanced activity comparing with the phenylalanine **14** (IC_{50} = 9.9 μM). The oxygen atoms on pyranoglucosyl scaffold and on C6 position also contributed to the binding affinity by simultaneously making two hydrogen bonds with the guanidyl residue of Arg544. In addition, apparent hydrophobic interactions were observed between benzyl moieties on glucosyl C-2 and C-6 position with Phe475 and Leu 540, respectively.

In summary, we have fulfilled in this study the rapid and efficient synthesis of triazole-linked glucosyl or galactosyl serine, threonine, phenylalanine and tyrosine derivatives via microwave-accelerated click reaction. The prepared triazolyl acids were identified as novel PTP1B and CDC25B inhibitors with several fold selectivity over other homologous PTPs. Amino acids with aryl residues (Phe and Tyr) were preferential toward PTP inhibition while the C-4 epimeric identity on sugar scaffold also proved unignorable for both inhibitory activity and selectivity. In addition, the benzylated sugar scaffold was demonstrated crucial for largely enhancing the binding affinity of the inhibitors with the targeted PTP. Docking simulation eventually illustrated the plausible binding modes of the most potent inhibitors in this series with PTP1B and CDC25B. Our unique approach presented here by using inexpensive and abundant natural scaffolds (sugar and amino acid) and via facile and expeditious synthetic method (microwave-assisted click reaction) might furnish new insights toward the efficient development of pseudo-glycopeptide-based PTP inhibitor libraries.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.12.126.

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17. *General procedure for the microwave-assisted click reaction*: To a solution of sugar alkyne **1** or **2** (1.0 mmol)[13] and azide **a**–**d** (1.2 mmol) in DMF/H_2O (10 mL/5 mL), were added VcNa (2.0 mmol) and $CuSO_4{\cdot}5H_2O$ (1.0 mmol) which was then transferred to the microwave oven. The mixture was stirred for a ramp time of 6 min and heating time of 10 min at 60 °C. With completion of the reaction (monitored by TLC), the solvents were evaporated under reduced pressure. The resulting residue was dissolved in dichloromethane, washed with water and brine and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated then the crude product was purified by column chromatography.