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Research Article

Synthesis of Novel 3-aryl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene Derivatives and Their Biological Evaluation Against Protein Tyrosine Phosphatase 1B

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A series of novel 3-aryl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene derivatives were designed, synthesized, and evaluated as a new class of inhibitors against protein tyrosine phosphatase 1B. Among them, compound 6f displayed moderate inhibitory activity with IC_{50} of 2.87 ± 0.24 μM *and can be used as a novel lead compound for the design of inhibitors of protein tyrosine phosphatase 1B.*

Key words: 3-aryl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene derivatives, inhibitors, one-pot synthesis, protein tyrosine phosphatase 1B, structure–activity relationships

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Introduction

Protein tyrosine phosphatase 1B (PTP1B) is a prototypic member of the PTP family that appears to be involved in the regulation of several cellular functions (1). Biochemical and genetic experiments have established that PTP1B is a key negative regulator of insulin receptor and leptin receptor-mediated signaling pathway and plays a critical role in insulin and leptin signaling (2). Besides its central role in the insulin cascade, PTP1B is involved in other important pathways related to human breast and ovarian cancers (3,4). Consequently, the inhibition of PTP1B was considered to be a potential therapeutic for the treatment of type 2 diabetes mellitus, obesity, and cancer. A variety of PTP1B inhibitors have been disclosed among academic and industrial laboratories (5–8). However, some challenges, such as high polarity and low enzyme selectivity (9), must still be overcome for the development of novel PTP1B inhibitors (5). Therefore, there is a need to discover novel potential drug scaffolds targeting PTP1B with high selectivity, desirable physicochemical properties and *in vivo* efficacies.

Many synthetic and naturally occurring spiroisoxazolines have been found as pharmacophores with a wide array of bioactivities (10–12). One such series is 3-aryl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene derivatives, which are selective antagonists of the somatostatin subtype receptor 5 (SSTR5) and useful for the treatment of type 2 diabetes (13). However, spiroisoxazoline-containing compounds, to our knowledge, have seldom been used as candidates for PTP1B inhibitors.

Previously, we identified *1H*-2,3-dihydroperimidine derivatives as potent PTP1B inhibitors (14). To explore the structural diversity of PTP1B inhibitors, our initial approach was to adjust the conformation between aryl ring and hydroprimidine ring, using conformational restriction strategy to replace aryl–dihydroprimidine unit with 1-oxa-2,8-diazaspiro[4.5]dec-2-ene unit (Figure 1), and synthesize *tert*-butyl 3-aryl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylates and their derivatives for biological evaluation against PTP1B. General and classical syntheses of 1-oxa-2,8-diazaspiro[4.5]dec-2-ene derivatives are carried out via a two-step reaction by 1,3-dipolar cycloadditions between alkenes and a nitrile oxide (15,16). However, in the reported examples, the oxime and the nitrile oxide precursors are preformed separately before reaction with the alkenes. These methods are cumbersome and time-consuming, and the yields are not satisfactory (15–17). Therefore, we presented a simplified method to synthesize 3-aryl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene derivatives. The approach involved a one-pot, sequential synthesis of an oxime and a nitrile oxide, followed by a 1,3-dipolar cycloaddition between the nitrile oxide and the *tert*-butyl 4-methylene piperidine-1-carboxylate. Also, inspired by some reported PTP1B dimer inhibitors (18–20), some dimer derivatives were synthesized using oxalyl, succinyl, terephthaloyl, or [1,1′-biphenyl]-4,4′-dicarbonyl a as linker. All of the synthesized compounds were evaluated for their inhibitory activities against PTP1B.

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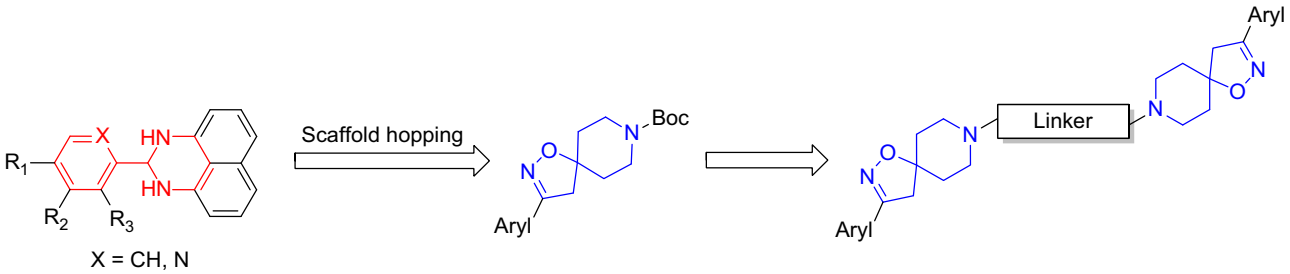


Figure 1: Structures of *1H*-2,3-dihydroperimidine derivatives and 3-aryl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene derivatives.

Methods and Materials

General procedure for the synthesis of compounds 4a–4n (exemplified by 4a)

A mixture of aldehyde **1a** (159 mg, 1.5 mmol), hydroxylamine hydrochloride (125 mg, 1.8 mmol), and K_2CO_3 (304 mg, 2.2 mmol) in ethyl acetate (2 mL) was refluxed. After the consumption of aldehyde as indicated by TLC analysis (3 h), the reaction mixture was cooled to 0 °C, followed by the addition of **3** (purchased from Titanchem, Shanghai, China) (197 mg, 1.0 mmol) in ethyl acetate (1 mL), and NCS (334 mg, 2.5 mmol) was added portionwise under vigorous stirring. It was then stirred at room temperature for an additional 40 min. The organic layer was separated, and the residual aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were then processed in the usual way and chromatographed to yield the desired compound **4a** (268 mg, 85%).

General procedure for the synthesis of compounds 6a–6k (exemplified by 6f)

A solution of **4a** (316 mg, 1.0 mmol) in HCl/THF (3M, 2 mL) was stirred for 5 h at room temperature. The precipitate was filtered and dried to give **5a** (155 mg, 61%) as a white solid. The mixture of **5a** (111 mg, 0.44 mol) and triethylamine (92 μL, 0.66 mmol) in anhydrous dichloromethane (2 mL) was stirred at 0 °C for 20 min, followed by biphenyl-4,4′-dicarbonyl dichloride (60 mg, 0.22 mmol). The mixture was warmed up to room temperature and stirred for 6 h. When the reaction was completed, the mixture was purified by column chromatography (DCM: MeOH = 80:1) to give **6f** (83 mg, 59%) as a white solid.

Protein tyrosine phosphatase 1B and related PTPs' biological assay

A colorimetric assay to measure inhibition against PTP1B and TCPTP was performed in 96-well plates. Briefly, the tested compounds were solubilized in DMSO and serially diluted into concentrations for the inhibitory test. The assays were carried out in a final volume of 100 μL containing 50 mmol/L MOPS, pH 6.5, 2 mmol/L *p*NPP, 21 nmol/L GST-PTP1B or GST-TCPTP, and 2% DMSO, and the catalysis of *p*NPP was continuously monitored on a SpectraMax 340 microplate reader at 405 nm for 3 min at 30 °C. The IC_{50} value was calculated from the nonlinear curve fitting of the percent inhibition [inhibition (%)] versus the inhibitor concentration using the following equation: %inhibition = $100/\{1 + (IC_{50}/[I]k\}$, where k is the Hill coefficient.

To study the inhibition on the other PTPase family members, SHP1, SHP2, and LAR were prepared and assays were performed according to the procedures described previously (14,18). Briefly, the enzymatic activities of the SHP1, SHP2, and LAR were determined at 30 °C by monitoring the dephosphorylation of the substrate 3-o-methylfluorescein phosphate (OMFP), and the product was then detected at a 485 nm excitation wavelength and 530 nm emission wavelength by the EnVision multilabel plate reader (Perkin-Elmer Life Sciences, Boston, MA, USA). The assays were carried out in a final volume of 50 μL containing 50 mmol/L MOPS, pH 6.8, 10 μmol/L OMFP, 20 nmol/L recombinant enzyme, 2 mmol/L dithiothreitol, 1 mmol/L EDTA, and 2% DMSO. The initial rate of dephosphorylation was presented by the early linear region of the enzymatic reaction kinetic curve, and the inhibitory activity of the compound was continuously monitored.

Characterization of the inhibitor on enzyme kinetics

In the fast-binding inhibition experiment, PTP1B was preincubated with compounds (2% DMSO) on the ice for different times, and then, a 10-μL mixture of enzyme and compounds was added to the 90-μL assay system. To characterize the inhibitor of PTP1B, the assay was carried out in a 100-μL system containing 50 mmol/L MOPS, pH 6.5, 14 nmol/L PTP1B, *p*NPP in twofold dilution from 80 mmol/L, and different concentrations of the inhibitor. In the presence of the competitive inhibitor, the Michaelis–Menten equation is described as $1/v = (K_m/[V_{max}[S]])(1 + [I]/K_i)+1/V_{max}$, where K_m is the Michaelis constant, v is the initial rate, V_{max} is the maximum rate, and [S] is the substrate concentration. The K_i value was obtained by the linear replot of apparent K_m/V_{max} (slope) from the primary

reciprocal plot versus the inhibitor concentration [I] according to the equation $K_m/V_{max} = 1 + [I]/K_i$.

Results and Discussion

Chemistry

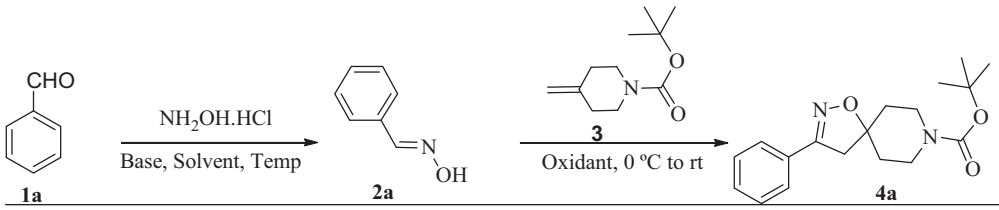
We screened the experimental parameters extensively to optimize the one-pot reaction protocol. Initially, benzaldehyde (**1a**) was chosen as a model substrate (Table 1). We found that increasing the amount of benzaldehyde resulted in high yields (entries 1–3). Various bases were investigated. Compared to K_2CO_3, Cs_2CO_3 was less effective, whereas organic bases such as Et_3N and DIPEA were completely ineffective (entries 5-6). The substitution of NCS with bleach or TBHP was proved to be less effective (entries 7-8). When using EtOAc as the solvent, the yield was slightly improved compared to CH_2Cl_2 (entry 9). After an increase in temperature, the yield was improved remarkably (entry 10). Some of the commonly used solvents, such as CH_3CN, DMF, THF, and EtOH, were used at 90 °C as oil bath temperature, and the results demonstrated that EtOAc was the most efficient solvent among them. The reaction time was also investigated, and the results showed that 3 h was the best choice for the model reaction. To our delight, the yield of compound **4a** was higher using the optimized condition, with the yield of 85% versus 57% as reported (15).

Based on the optimized reaction conditions, a series of *tert*-butyl 3-aryl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylates were synthesized. The results (Table 2) showed that this methodology can be applied to benzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4-bromobenzaldehyde, 3-bromobenzaldehyde, 3-fluorobenzaldehyde, or picolinaldehyde in moderate yields. However, the desired products (**4d**, **4g**, **4h**, **4j**, **4l**, **4m**, **4n**) were obtained in low yields using 4-(methylthio)benzaldehyde, 2-bromobenzaldehyde, 4-fluorobenzaldehyde, 2-fluorobenzaldehyde, 6-bromonicotinaldehyde, furan-2-carbaldehyde, or thiophene-2-carbaldehyde. After the removal of the Boc group from compounds **4a**–**4c** and **4h**–**4j**, the produced compounds **5a**–**5c** and **5h**–**5j** were coupled with oxalyl dichloride, succinyl dichloride, terephthaloyl dichloride, and [1,1′-biphenyl]-4,4′-dicarbonyl dichloride, respectively, to yield compounds **6a**–**6k** (Scheme 1).

Protein tyrosine phosphatase 1B inhibitory activities and structure–activity relationships

The inhibitory activities of all synthesized compounds against PTP1B were measured using *p*-nitrophenyl phos-

Table 1: Optimization studies of the one-pot reaction condition for compound **4a**[a]

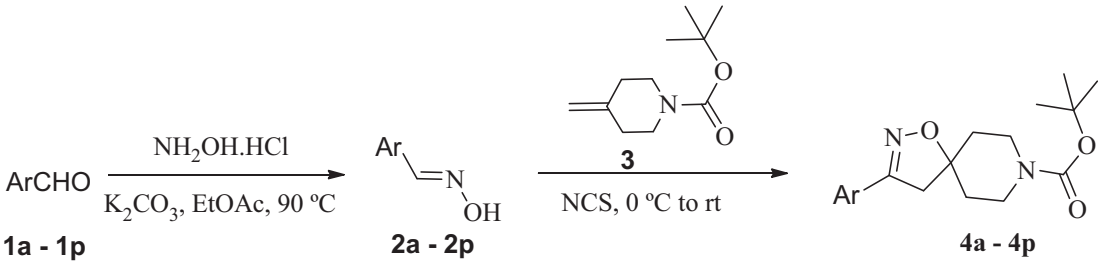


1a 2a 4a

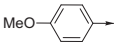
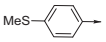
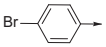
Entry	**1a** (mmol)	Base	Solvent	Temp (°)	Time (h)	Oxidant	Yield[b] (%)
1	1	K_2CO_3	CH_2Cl_2	Reflux	3	NCS	40
2	1.2	K_2CO_3	CH_2Cl_2	Reflux	3	NCS	42
3	1.5	K_2CO_3	CH_2Cl_2	Reflux	3	NCS	62
4	1.5	Cs_2CO_3	CH_2Cl_2	Reflux	3	NCS	47
5	1.5	Et_3N	CH_2Cl_2	Reflux	3	NCS	Trace
6	1.5	DIPEA	CH_2Cl_2	Reflux	3	NCS	Trace
7	1.5	K_2CO_3	CH_2Cl_2	Reflux	3	Bleach	40
8	1.5	K_2CO_3	CH_2Cl_2	Reflux	3	TBHP	Trace
9	1.5	K_2CO_3	EtOAc	40	3	NCS	65
10	1.5	K_2CO_3	EtOAc	Reflux	3	NCS	85
11	1.5	K_2CO_3	CH_3CN	Reflux	3	NCS	57
12	1.5	K_2CO_3	DMF	90	3	NCS	37
13	1.5	K_2CO_3	THF	Reflux	3	NCS	Trace
14	1.5	K_2CO_3	EtOH	Reflux	3	NCS	Trace
15	1.5	K_2CO_3	EtOAc	Reflux	1	NCS	32
16	1.5	K_2CO_3	EtOAc	Reflux	2	NCS	52
17	1.5	K_2CO_3	EtOAc	Reflux	4	NCS	83

[a]Reaction conditions: hydroxylamine hydrochloride (1.8 mmol, 1.8 eq), 3 (1 mmol, 1eq), solvent (3 mL), base (2.2 mmol, 2.2 eq), oxidant (2.5 mmol, 2.5 eq).
[b]Isolated yield after chromatographic purification.

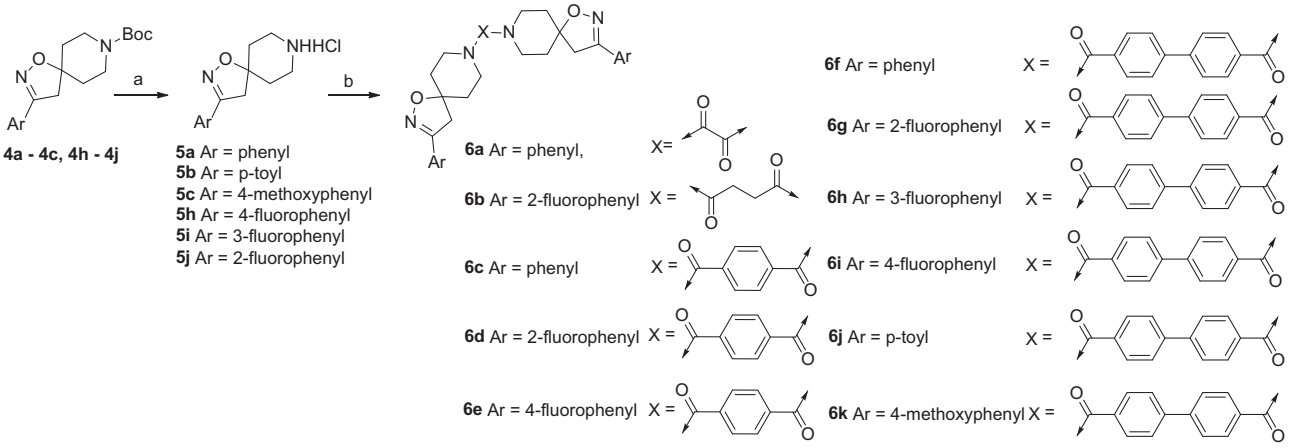
Table 2: Synthesis of tert-butyl 3-aryl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylates under optimal conditions



1a - 1p **2a - 2p** **4a - 4p**

Comp	Ar	Yield[a] (%)	Comp	Ar	Yield[a] (%)
4a[b]		85	**4h**		34
4b		53	**4i**		51
4c		69	**4j**		32
4d		22	**4k**		59
4e		51	**4l**		10
4f		41	**4m**		19
4g		18	**4n**		31

[a]Isolated yield after chromatographic purification.
[b]Compound **4a** was reported in reference (15).



Scheme 1: Reagents and conditions: (a) HCl/THF, 48–86%; (b) dicarboxylic acid dichloride, Et_3N, DCM, 43-96%.

phate (*p*NPP) as the substrate (14,18), and the results are detailed in Table 3. As for compounds **4a**–**4e**, compound **4a, w**hich has unsubstituted phenyl group, exhibited slightly better inhibitory activity than compounds **4b**–**4d,** which have electron-donating substitutes at the para position of the phenyl ring, while compound **4e,** which has electron-withdrawing group (Br), showed slightly better inhibitory activity than compound **4a**.

To further investigate the SAR of substitutes on the phenyl ring, compounds **4f**–**4j** were synthesized. Among compounds **4e**–**4g**, compound **4g** with Br at the ortho position

Table 3: Protein tyrosine phosphatase 1B inhibitory activities of compounds **4a**–**4n** and **6a**–**6k**

Comp	Inhibition(%) at 20 μg/mL	IC_{50} (μM)[a]	Comp	Inhibition(%) at 20 μg/mL	IC_{50} (μM)[a]
4a	31.83	NT[b]	**4n**	37.59	NT
4b	18.58	NT	**6a**	18.33	NT
4c	24.62	NT	**6b**	3.63	NT
4d	9.52	NT	**6c**	11.87	NT
4e	34.29	NT	**6d**	4.38	NT
4f	38.54	NT	**6e**	2.65	NT
4g	44.04	NT	**6f**	96.16	2.87 ± 0.24
4h	25.21	NT	**6g**	95.99	4.96 ± 0.61
4i	44.84	NT	**6h**	72.85	5.33 ± 0.81
4j	47.69	NT	**6i**	31.35	NT
4k	11.07	NT	**6j**	24.86	NT
4l	40.67	NT	**6k**	31.71	NT
4m	19.77	NT	**PC**[c]	–	1.95 ± 0.29

[a]The *p*NPP assay. IC_{50} values were determined by regression analyses and expressed as means ± SD of three replications.
[b]NT means not tested.
[c]PC: using oleanolic acid as positive control for protein tyrosine phosphatase 1B.

showed better inhibitory activity than compound **4e** with Br at the para position and compound **4f** with Br at the meta position. Similar results were observed among compounds **4h**–**4j**. These results indicated that the o-, m-, and p-substitutions on the phenyl ring had some effect on the inhibitory activity. Replacement of the phenyl group (**4a**) with pyridin-2-yl group (**4k**) and the furan-2-yl group (**4m**) led to decreased potency compared to compound **4a**, while replacement of the phenyl group with thiophen-2-yl group (compound **4n)** exhibited similar activity compared to compound **4a**. On the other hand, compound **4l** with the 6-bromopyridin-3-yl group slightly improved the inhibitory activity compared to compound **4e** with 4-bromophenyl group. These results indicated that replacement of the phenyl ring on the spiroisoxazoline derivatives with heterocyclic ring may impact the enzyme inhibition. Also, dimer derivatives **6a**–**6k** were synthesized using oxalyl, succinyl, terephthaloyl, or [1,1′-biphenyl]-4,4′-dicarbonyl as a linker. Compound **6a** with oxalyl group, compound **6b** with succinyl group, or compounds **6c**–**6e** with terephthaloyl group decreased the potency compared to their corresponding compounds **4a**, **4j,** or **4h,** respectively. When using [1,1′-biphenyl]-4,4′-dicarbonyl as a linker, however, the activities of compounds **6f**–**6k** were improved significantly compared to their corresponding compounds. Notably, compounds **6f**–**6g** showed inhibitory activities against PTP1B in the low micromolar range, especially compound **6f** with IC_{50} of 2.87 ± 0.24 μM.

Selectivity against other PTPs

In addition to the potency improvements, we investigated the selectivity of the representative compound **6f** against other PTPs (TCPTP, SHP-1, SHP-2, LAR). Homogeneous T-cell protein tyrosine phosphatase (TCPTP) inhibitory activities were investigated simultaneously by the same method (14,18). Compound **6f** showed 42.2% inhibition at the concentration of 20 μg/mL (31.35 μM), and the result indicated that compound **6f** had greater selectivity for PTP1B than for TCPTP. Besides TCPTP, we tested the inhibitory activity of **6f** on other three homogenous enzymes SHP-1, SHP-2, and LAR, all of the inhibitory ratios were lower than 10% at the dose of 20 μg/mL, and we concluded that compound **6f** had no visible activities against LAR, SHP-1, and SHP-2.

Characterization of the inhibitor 6f on enzyme kinetics

A kinetic study was performed to identify the inhibitory mechanism of compound **6f** (Figure 2), using the reported

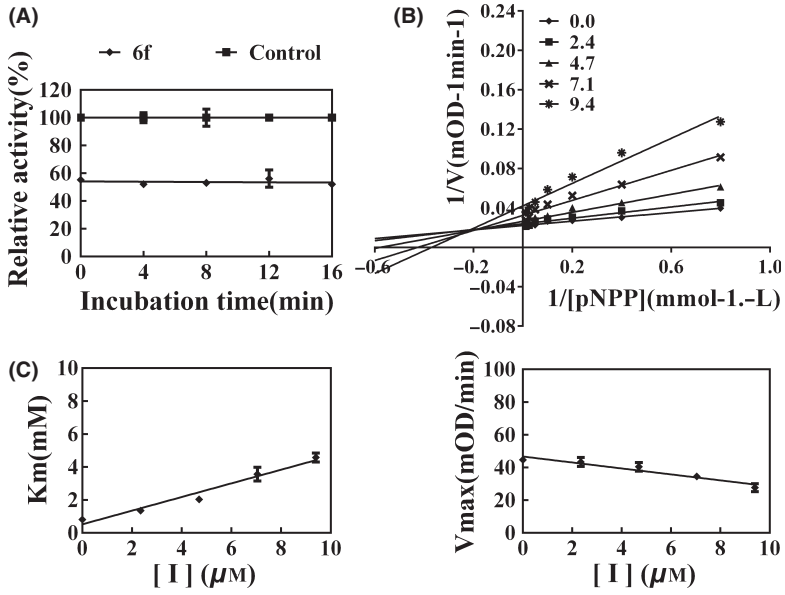


Figure 2: Characterization of **6f** to protein tyrosine phosphatase 1B.

enzyme kinetics assays (14,18). As shown in Figure 2A, compound **6f** demonstrated a fast-binding inhibition of PTP1B. The plots in Figure 2C indicated that compound **6f** was a mixed-type inhibitor due to the increasing k_m value and concomitantly decreasing V_{max} value upon the gradually increased compound concentration. Meanwhile, the result of the Lineweaver–Burk plot further confirmed **6f** as a mixed-type inhibitor of PTP1B for intersecting at second quadrant of a nest of lines with increased inhibitor concentration (Figure 2B) (7).

Conclusion

In summary, we described a convenient method for the synthesis of *tert*-butyl 3-aryl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylates by applying one-pot reaction through two sequential steps and a series of novel dimer derivatives were designed and synthesized. Biological evaluation demonstrated that most of the synthesized compounds showed inhibitory activity against PTP1B, and compound **6f** displayed the best inhibitory activity with IC_{50} of 2.87 ± 0.24 μM and good selectivity for PTP1B over TCPTP. These preliminary results provided a possible opportunity for the development of novel PTP1B inhibitors. Further optimization and evaluation of this series of compounds will be reported in due course.

Acknowledgment

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Conflict of Interest

The authors have declared no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Synthetic details and spectral data of target compounds in this manuscript are provided.