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Synthesis and Biological Evaluation of Heterocyclic Ring-substituted Chalcone Derivatives as Novel Inhibitors of Protein Tyrosine Phosphatase 1B

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Protein tyrosine phosphatase 1B (PTP1B) is a key factor in negative regulation of the insulin pathway, and is a promising target for the treatment of type-II diabetes, obesity and cancer. Herein, compound (**4**) was first observed to have moderate inhibitory activity against PTP1B with an IC_{50} value of 13.72 ± 1.53 μM. To obtain more potent PTP1B inhibitors, we synthesized a series of chalcone derivatives using compound (**4**) as the lead compound. Compound **4l** (IC_{50} = 3.12 ± 0.18 μM) was 4.4-fold more potent than the lead compound **4** (IC_{50} = 13.72 ± 1.53 μM), and more potent than the positive control, ursolic acid (IC_{50} = 3.40 ± 0.21 μM). These results may help to provide suitable drug-like lead compounds for the design of inhibitors of PTP1B as well as other PTPs.

Key Words : Chalcone, Protein tyrosine phosphatase 1B, Inhibitor, SAR

Introduction

Protein tyrosine phosphatase (PTP) superfamily comprises > 100 enzymes.[1] PTPs have essential roles in intracellular signal transduction by regulating the cellular level of tyrosine phosphorylation to control the growth and differentiation of cells, metabolism, cell migration, gene transcription, ion-channel activity, immune responses, apoptosis, and bone development.[2-5] Unregulated operation of PTPs is responsible for several human diseases, including cancer, diabetes, obesity, and osteoporosis.[6-9] Among PTPs, protein tyrosine phosphatase 1B (PTP1B) activates *c*-Src in human breast cancer, and also influences the down-regulation of insulin signaling by dephosphorylating the insulin receptor, including insulin receptor substrate-1 (IRS-1) and insulin receptor substrate-2 (IRS-2).[10-13] Therefore, PTP1B can be a useful target for the treatment of type-II diabetes mellitus (DM), obesity and cancer, and small molecular inhibitors of PTP1B could be promising drug candidates.[14,15]

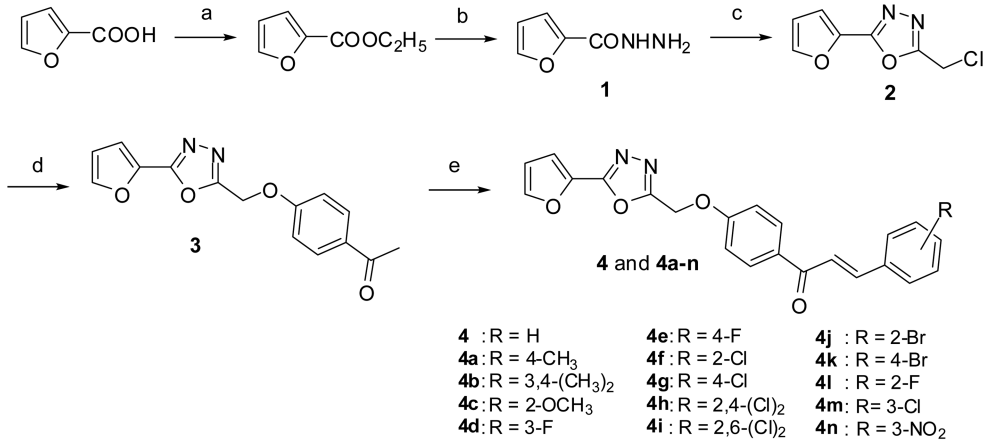
In recent years, along with the elucidation of its protein structure, many synthetic PTP1B inhibitors with submicro-, even nano-molar activity were discovered through high-throughput screening (HTS) and structure-based design.[16,17] However, previously developed PTP1B inhibitors had two major drawbacks. First, they lacked sufficient cell permeability due to the presence of highly negatively charged residues mimicking the phosphate group in IRS.[18] Second, because of their highly conserved catalytic domain, the selectivity between PTP1B and the most homogeneous T-cell protein tyrosine phosphatase (TCPTP) was still low.[19]

Chalcones (considered to be the precursors of flavonoids and isoflavonoids) are abundant in edible plants. They comprise open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α,β-unsaturated carbonyl system. Studies have revealed that compounds with a chalcone-based structure have anti-viral,[20] anti-fungal,[21] anti-malarial[22] and anti-bacterial activities.[23] Appropriately substituted chalcones have recently been shown to selectively inhibit enzymes such as PTP1B.[24] In addition, many compounds containing 1,3,4-oxadiazoline and furan rings are often used in drug design.[25-28]

In this work, we aimed to discover a new type of PTP1B inhibitor. We tried to design and synthesize hybrid molecules having the features of those moieties of chalcone, 1,3,4-oxadiazoline and furan rings. We found (*E*)-1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one (**4**) to be a moderate PTP1B inhibitor. To obtain more potent PTP1B inhibitors, we synthesized a series of chalcone derivatives using (*E*)-1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one (**4**) as the lead compound.

Experimental

Chemistry. Melting points were determined in open capillary tubes and were uncorrected. Reaction courses were monitored by thin-layer chromatography (TLC) on silica gel-pre-coated F254 Merck (Whitehouse Station, NJ, USA) plates. Developed plates were examined with ultraviolet (UV) lamps (254 nm). Infrared (IR) spectra were recorded (in KBr) on a FTIR1730 system. ^{1}H NMR spectra were measured on a Bruker AV-300 spectrometer (Bruker, Billerica, MA, USA) using tetramethylsilane as the internal standard. Mass spectra were measured on an HP1100LC system (Agilent Technologies, Santa Clara, CA, USA). Elemental analyses for C, H, N, and S were within ± 0.4% of the



Scheme 1. Reagents and conditions: (a) H_2SO_4, CH_3CH_2OH; (b) $NH_2NH_2{\cdot}H_2O$, CH_3CH_2OH; (c) $ClCH_2COOH$, $POCl_3$; (d) *p*-hydroxyacetophenone, K_2CO_3, CH_3COCH_3; (e) NaOH, CH_3CH_2OH.

theoretical values and were carried out on a 204Q CHN Rapid Analyzer (Perkin-Elmer, Waltham, MA, USA). The major chemicals were purchased from Sigma-Aldrich and Fluka (both based in (St Louis, MO, USA).

The synthesis of new heterocyclic ring-substituted chalcone derivatives is summarized in Scheme 1. 1-(4-((5-(Furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)ethanone (**3**) was synthesized according to a previously described method using commercially available 2-furoic acid as a starting material.[29,30] Compounds **4** and **4a-n** were prepared by the Claisen-Schmidt condensation of 1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)ethanone (**3**) and substituted benzaldehyde by a previously described method.[31] The structures of the desired compounds were determined by IR and ^{1}H NMR as well as mass spectral and elemental analyses.

General Procedure for the Preparation of Compounds 4 and 4a-n. To a solution of 1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)ethanone (**3**) (0.01 mol) and substituted benzaldehyde (0.012 mol) in EtOH (10 mL) was added 2 M NaOH (8 mL). The reaction mixture was stirred for 40 min and kept in a refrigerator overnight. The resulting products were collected by filtration and purified by recrystallization (95% EtOH). The yield, melting point and spectral data of each compound are given below.

(*E*)-1-(4-((5-(Furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)-phenyl)-3-phenylprop-2-en-1-one, 4: Yield 53%; mp 136-137 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^{1}H NMR ($CDCl_3$) δ 5.36 (s, 2H, CH_2), 6.62 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.51 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.80 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.14-8.09 (m, 11H, 9Ar-H and 2FuranH). MS *m/z* 373 (M+1). Anal. Calcd for $C_{22}H_{16}N_2O_4$: C, 70.96; H, 4.33; N, 7.52. Found: C, 70.87; H, 4.38; N, 7.46.

(*E*)-1-(4-((5-(Furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)-phenyl)-3-p-tolylprop-2-en-1-one, 4a: Yield 52%; mp 159-160 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H, CH_3), 5.40 (s, 2H, CH_2), 6.62 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.45 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.76 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.12-8.07 (m, 10H, 8Ar-H and 2FuranH). MS *m/z* 387 (M+1). Anal. Calcd for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25. Found: C, 71.23; H, 4.89; N, 7.34.

(*E*)-3-(3,4-Dimethylphenyl)-1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)prop-2-en-1-one, 4b: Yield 48%; mp 152-153 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 6H, CH_3), 5.40 (s, 2H, CH_2), 6.62 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.45 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.67 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.12-8.07 (m, 9H, 7Ar-H and 2FuranH). MS *m/z* 401 (M+1). Anal. Calcd for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00. Found: C, 71.94; H, 5.11; N, 7.05.

(*E*)-1-(4-((5-(Furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)-phenyl)-3-(2-methoxyphenyl)prop-2-en-1-one, 4c: Yield 36%; mp 157-158 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H, OCH_3), 5.40 (s, 2H, CH_2), 6.62 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.59 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.67 (d, *J* = 15.6 Hz, 1H, CH=CH), 6.93-8.13 (m, 10H, 8Ar-H and 2FuranH). MS *m/z* 403 (M+1). Anal. Calcd for $C_{23}H_{18}N_2O_5$: C, 68.65; H, 4.51; N, 6.96. Found: C, 68.35; H, 4.23; N, 6.68.

(*E*)-3-(3-Fluorophenyl)-1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)prop-2-en-1-one, 4d: Yield 52%; mp 157-158 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^{1}H NMR ($CDCl_3$) δ 5.36 (s, 2H, CH_2), 6.61 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.49 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.73 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.13-8.08 (m, 10H, 8Ar-H and 2FuranH). MS *m/z* 391 (M+1). Anal. Calcd for $C_{22}H_{15}FN_2O_4$: C, 67.69; H, 3.87; N, 7.18. Found: C, 67.76; H, 3.67; N, 7.03.

(*E*)-3-(4-Fluorophenyl)-1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)prop-2-en-1-one, 4e: Yield 42%; mp 158-159 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^{1}H NMR ($CDCl_3$) δ 5.36 (s, 2H, CH_2), 6.61 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.48 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.78 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.08-8.07 (m, 10H, 8Ar-H and 2FuranH). MS *m/z* 391 (M+1). Anal. Calcd for $C_{22}H_{15}FN_2O_4$: C, 67.69; H, 3.87; N, 7.18. Found: C, 67.76; H, 3.57; N, 7.11.

(*E*)-3-(2-Chlorophenyl)-1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)prop-2-en-1-one, 4f: Yield 47%; mp 152-153 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^{1}H NMR

($CDCl_3$) δ 5.33 (s, 2H, CH_2), 6.61 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.45 (d, *J* = 15.6 Hz, 1H, CH=CH), 8.15 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.13-8.20 (m, 10H, 8Ar-H and 2FuranH). MS *m/z* 407 (M+1). Anal. Calcd for $C_{22}H_{15}ClN_2O_4$: C, 64.95; H, 3.72; N, 6.89. Found: C, 64.75; H, 3.78; N, 6.66.

(*E*)-3-(4-Chlorophenyl)-1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)prop-2-en-1-one, 4g: Yield 37%; mp 153-154 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^1H NMR ($CDCl_3$) δ 5.36 (s, 2H, CH_2), 6.61 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.46 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.72 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.03-8.07 (m, 10H, 8Ar-H and 2FuranH). MS *m/z* 407 (M+1). Anal. Calcd for $C_{22}H_{15}ClN_2O_4$: C, 64.95; H, 3.72; N, 6.89. Found: C, 64.75; H, 3.78; N, 6.53.

(*E*)-3-(2,4-Dichlorophenyl)-1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)prop-2-en-1-one, 4h: Yield 43%; mp 157-158 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^1H NMR ($CDCl_3$) δ 5.35 (s, 2H, CH_2), 6.61 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.44 (d, *J* = 15.6 Hz, 1H, CH=CH), 8.07 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.13-8.12 (m, 9H, 7Ar-H and 2FuranH). MS *m/z* 441 (M+1). Anal. Calcd for $C_{22}H_{14}Cl_2N_2O_4$: C, 59.88; H, 3.20; N, 6.35. Found: C, 59.65; H, 3.17; N, 6.26.

(*E*)-3-(2,6-Dichlorophenyl)-1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)prop-2-en-1-one, 4i: Yield 45%; mp 159-160 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^1H NMR ($CDCl_3$) δ 5.40 (s, 2H, CH_2), 6.61 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.63 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.82 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.13-8.07 (m, 9H, 7Ar-H and 2FuranH). MS *m/z* 441 (M+1). Anal. Calcd for $C_{22}H_{14}Cl_2N_2O_4$: C, 59.88; H, 3.20; N, 6.35. Found: C, 59.45; H, 3.07; N, 6.12.

(*E*)-3-(2-Bromophenyl)-1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)prop-2-en-1-one, 4j: Yield 46%; mp 156-157 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^1H NMR ($CDCl_3$) δ 5.41 (s, 2H, CH_2), 6.61 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.66 (d, *J* = 15.6 Hz, 1H, CH=CH), 8.09 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.13-8.15 (m, 10H, 8Ar-H and 2FuranH). MS *m/z* 451 (M+1). Anal. Calcd for $C_{22}H_{15}BrN_2O_4$: C, 58.55; H, 3.35; N, 6.21. Found: C, 58.45; H, 3.35; N, 6.15.

(*E*)-3-(4-Bromophenyl)-1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)prop-2-en-1-one, 4k: Yield 52%; mp 158-159 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^1H NMR ($CDCl_3$) δ 5.40 (s, 2H, CH_2), 6.61 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.48 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.71 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.06-8.07 (m, 10H, 8Ar-H and 2FuranH). MS *m/z* 451 (M+1). Anal. Calcd for $C_{22}H_{15}BrN_2O_4$: C, 58.55; H, 3.35; N, 6.21. Found: C, 58.35; H, 3.29; N, 6.13.

(*E*)-3-(2-Fluorophenyl)-1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)prop-2-en-1-one, 4l: Yield 57%; mp 156-154 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^1H NMR ($CDCl_3$) δ 5.33 (s, 2H, CH_2), 6.61 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.45 (d, *J* = 15.6 Hz, 1H, CH=CH), 8.15 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.13-8.20 (m, 10H, 8Ar-H and 2FuranH). MS *m/z* 391 (M+1). Anal. Calcd for $C_{22}H_{15}FN_2O_4$: C, 67.69; H, 3.87; N, 7.18. Found: C, 67.66; H, 3.57; N, 7.11.

(*E*)-3-(3-Chlorophenyl)-1-(4-((5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)prop-2-en-1-one, 4m: Yield 42%; mp 156-157 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^1H NMR ($CDCl_3$) δ 5.36 (s, 2H, CH_2), 6.61 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.49 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.73 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.13-8.08 (m, 10H, 8Ar-H and 2FuranH). MS *m/z* 407 (M+1). Anal. Calcd for $C_{22}H_{15}ClN_2O_4$: C, 64.95; H, 3.72; N, 6.89. Found: C, 64.72; H, 3.72; N, 6.51.

(*E*)-1-(4-((5-(Furan-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)-phenyl)-3-(3-nitrophenyl)prop-2-en-1-one, 4n: Yield 37%; mp 226-227 °C. IR (KBr) cm^{-1}: 1600 (C=O). ^1H NMR ($CDCl_3$) δ 5.38 (s, 2H, CH_2), 6.63 (t, *J* = 2.56 Hz, 1H, Furan-H), 7.60 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.81 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.16-8.52 (m, 10H, 8Ar-H and 2FuranH). MS *m/z* 418 (M+1). Anal. Calcd for $C_{22}H_{15}N_3O_6$: C, 63.31; H, 3.62; N, 10.07. Found: C, 63.11; H, 3.55; N, 10.25.

Pharmacology. The recombinant human PTP1B catalytic domain was expressed and purified according to the previously described procedures.[32] The enzymatic activity of PTP1B was determined at 30 °C by monitoring the hydrolysis of *p*-nitrophenyl phosphate (*p*NPP). Dephosphorylation of *p*NPP generates a product *p*NP, which can be monitored at 405 nm. In a typical 100-μL assay, mixtures 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 (SpectraMax, Silicon Valley, CA, USA) at 405 nm for 2 min at 30 °C. The initial rate of hydrolysis was determined using the early linear region of the enzymatic reaction kinetic curve. For calculation of the half-maximal inhibitory concentration (IC_{50}), inhibition assays were undertaken 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. The IC_{50} value was calculated from the non-linear curve fitting of percentage inhibition (inhibition (%)) *versus* inhibitor concentration [I] using the following equation:

$$\text{Inhibition (\%)} = 100/\{1 + (IC_{50}/[I])k\}$$

where *k* is the Hill coefficient.

Results and Discussion

The inhibitory activities of all the synthesized compounds against PTP1B were measured using *p*NPP as the substrate; the results are summarized in Table 1. A known PTP1B inhibitor, ursolic acid (IC_{50} = 3.40 ± 0.21 μM), was used as the positive control.[32]

As shown in Table 1, the lead compound (**4**) was first observed to have moderate inhibitory activity with an IC_{50} value of 13.72 ± 1.53 μM. Similarly, compounds **4c** and **4n** showed no activity at the threshold value (20 μg/mL) against PTP1B, whereas others displayed favorable inhibition with a moderate-to-good IC_{50}. The inhibitory activity of compounds **4a**, **4b**, **4d** and **4h** was slightly lower than that of the lead compound **4.** Compounds **4e**, **4f**, **4g**, **4i**, **4j**, **4k**, **4l** and **4m** possessed better inhibitory potency among all of the assayed compounds compared with lead compound **4**. Of these, **4l** displayed excellent inhibition (99.17%) at a 20 μg/mL concentration and a reasonable IC_{50} value (3.12 ± 0.18 μM) slightly lower than ursolic acid (IC_{50} = 3.40 ± 0.21 μM).

Analyzing the activities of synthesized compounds **4** and

Table 1. Inhibitory activity of **4** and **4a-n** on PTP1B

Compounds	PTP1B	
	Inhibition rate[a] (%)	IC_{50}[b] (μM)
4	96.51	13.72 ± 1.53
4a	94.71	14.24 ± 1.37
4b	83.46	19.32 ± 0.67
4c	9.77	NA[c]
4d	62.77	41.02 ± 9.96
4e	93.55	10.97 ± 1.51
4f	80.35	10.78 ± 2.55
4g	87.36	6.01 ± 0.93
4h	75.47	18.43 ± 1.74
4i	98.23	5.88 ± 1.06
4j	73.22	13.62 ± 3.08
4k	90.59	12.17 ± 1.99
4l	99.17	3.12 ± 0.18
4m	91.28	6.42 ± 0.74
4n	2.35	NA
UA[d]	99.06	3.40 ± 0.21

[a]Values tested at 20 μg/mL concentration. [b]The *p*NPP assay. IC_{50} values were determined by regression analyses and expressed as means ± SD of three replications. [c]Not active at 20 μg/mL concentration. [d]Positive control.

4a-n, the following structure–activity relationships (SAR) were obtained. Comparing with compound **4**, compounds **4g**, **4i**, **4l**, and **4m** had better inhibitory potency. It seemed that the substituent on chalcone B ring might be important in the inhibitory activity of PTP1B. However, compounds **4c** and **4n** that bore substituent on the B ring did not show any inhibitory effect at a concentration of 20 μg/mL. These results indicated that the character of substituent on the B ring had a signicant inuence on the PTP1B inhibitory activity. The compounds with electron-withdrawing groups on the B ring (**4e-g**, **4i-m**) showed better activity than compounds **4a-c** containing the electron-donating groups. These results indicated that electron-withdrawing groups contributed more to the inhibitory activity of PTP1B than the electron-donating groups. Furthermore, the position of the substituent on the B ring significantly influenced PTP1B inhibitory activities, with an order of activity of *o*-F > *p*-F > *m*-F for fluorinated compounds, and *p*-Br > *o*-Br for brominated compounds. For the chlorinated compounds, the order of activity was 2,6-Cl_2 > *p*-Cl > *m*-Cl > *o*-Cl > 2,4-Cl_2. Derivative **4l** (IC_{50} = 3.12 ± 0.18 μM) was 4.4-fold more potent than the lead compound **4** (IC_{50} = 13.72 ± 1.53 μM).

In conclusion, we synthesized a series of novel chalcone derivatives containing 1,3,4-oxadiazoline and furan ring moieties, and determined their PTP1B inhibitory activities. Most of the compounds had potential PTP1B inhibitory activities. Among them, compound **4l** was found to have the most potent inhibitory capacity. This is an initial report and optimization of these compounds is in progress.

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