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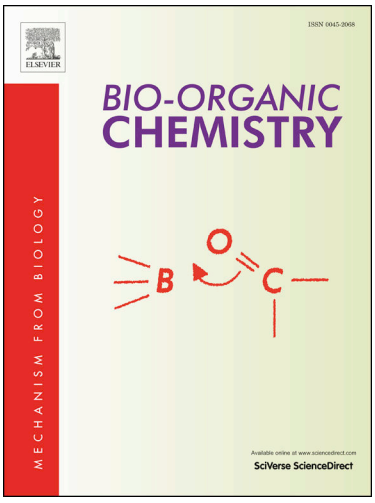

Short communication

5-Aryl-furan derivatives bearing a phenylalanine- or isoleucine-derived rhodanine moiety as potential PTP1B inhibitors

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5-Aryl-furan derivatives bearing a phenylalanine- or isoleucine-derived rhodanine moiety as potential PTP1B inhibitors

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Abstract

Two series of 5-aryl-furan derivatives bearing a phenylalanine- or isoleucine-derived rhodanine moiety were identified as competitive protein tyrosine phosphatase 1B (PTP1B) inhibitors. Among the compounds studied, **5g** was found to have the best PTP1B inhibitory potency (IC_{50} = 2.66 ± 0.16 μM) and the best cell division cycle 25 homolog B (CDC25B) inhibitory potency (IC_{50} = 0.25 ± 0.02 μM). Enzymatic data together with molecular modeling results demonstrated that the introduction of a *sec*-butyl group at the 2-position of the carboxyl group remarkably improved the PTP1B inhibitory activity.

Keywords: PTP1B inhibitor; Furan; Rhodanine; Phenylalanine; Isoleucine

Protein tyrosine phosphatase 1B (PTP1B), an intracellular protein tyrosine phosphatase (PTP), is a key negative regulator in the insulin and leptin-signaling pathway, which acts by dephosphorylating the insulin receptor (IR), insulin receptor substrate-1 (IRS-1) and IRS-2, and JAK2, a kinase downstream of the leptin receptor [1-4]. PTP1B-knockout mice exhibited phenotypes of increased insulin sensitivity, improved glucose tolerance, and resistance to diet-induced obesity. PTP1B-deficient mice had normal growth and longevity [5-6]. Previous studies have shown that the overexpression of PTP1B is sufficient to drive tumorigenesis in mice [7-8]. Therefore, PTP1B is widely recognized as an attractive target for the treatment of type II diabetes mellitus, obesity, and cancer, and the development of small molecule inhibitors of PTP1B has become a promising way to treat these diseases.

Following the elucidation of the basic structural requirements for PTP1B-substrate and -inhibitor interactions, various PTP1B inhibitors with high activity have been identified in the last decade. However, their assessment in clinical trials was restricted, mainly because of two major drawbacks. First, the low cell permeability and bioavailability of these compounds, because of the presence of highly negatively charged residues that mimic the phosphate group in the IRS, has limited their development as effective drugs [9-10]. Second, because of the structural homology

present throughout many PTP families, it is challenging to identify selective inhibitors specific for each PTP [11-12]. Therefore, it is desirable to develop novel compounds with new core scaffolds that not only inhibit PTP1B with sufficient efficacy, but which also possess suitable pharmaceutical properties.

Rhodanine, 2-thioxo-1,3-thiazolidin-4-one, has emerged as an important privileged structure in medicinal chemistry [13]. Molecules based on the rhodanine core have received much attention because of their pharmacological properties, including antibacterial [14-17], anticancer [18-19], antidiabetic [20], anti-inflammatory [21], antiviral [22], and anti-HIV [23] activities. As reported recently, rhodanine-3-acetic acid derivatives (**1**) have been identified as PTP1B inhibitors, in which the rhodanine-3-acetic acid moiety can replicate the interactions of the pTyr residue with the catalytic site of the enzyme (Fig. 1) [24]. In our previous work, two series of 1,3-diaryl pyrazole derivatives containing rhodanine-3-alkanoic acid groups (**2** and **3**) were identified as potent competitive PTP1B inhibitors [25]. Preliminary structure–activity relationships (SARs) revealed that the substituents at positions 5 and N-3 of rhodanine play an important role in modulating PTP1B inhibitory activity. Introducing a benzyl group at the 2-position of the carboxyl group of compound **3** was shown to remarkably improve the PTP1B inhibitory activity and selectivity toward other PTPs. Additionally, the 1,3-diaryl pyrazole group enhanced the PTP1B inhibitory activity by extending into the hydrophobic sub-pocket near the catalytic site and forming hydrophobic interactions with the protein. Thus, these findings encouraged us to make additional structural modifications at positions 5 and N-3 of rhodanine to obtain novel PTP1B inhibitors and further investigate the SARs.

As a part of our ongoing studies into the development of rhodanine PTP1B inhibitors, based on the structure of compound **3**, a series of compounds, (*S,Z*)-2-(4-oxo-5-((5-substituted-phenylfuran-2-yl)methylene)-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (**4**), were designed by replacing the pyrazole ring with a furan ring as a bioisosteric surrogate and simplification from a diaryl moiety to a monoaryl moiety. Subsequently, a (2*S*)-3-methyl-2-((*Z*)-4-oxo-5-((5-substituted-phenylfuran-2-yl)methylene)-2-thioxoth

iazolidin-3-yl)pentanoic acid (**5**) series was also designed by the modification of the phenylalanine moiety to an isoleucine (Fig. 2). All of the compounds showed moderate to strong inhibitory activity against PTP1B. In the present work, we developed two series of 5-aryl-furan derivatives bearing rhodanine moieties as novel and potent inhibitors of PTP1B, and their mechanism of inhibition of PTP1B along with their SARs were investigated.

Compounds **4** and **5** were synthesized as shown in Scheme 1. The synthesis procedure and spectral data have been previously described [26].

All the compounds were evaluated for inhibitory activity against the PTP1B enzyme, using *p*-nitrophenyl phosphate as a substrate and oleanolic acid as a positive control [27]. As shown in Table 1, all of the compounds tested showed moderate to strong PTP1B inhibitory activity against PTP1B with IC_{50} values ranging from 2.66 ± 0.16 to 20.84 ± 1.81 μM. Of these, **5g** was the most potent with an IC_{50} value of 2.66 ± 0.16 μM.

On the basis of the evaluation results, we analyzed preliminary SARs. As shown in Table 1, all compounds **4a–l** and **5a–l** exhibited inhibitory activities against PTP1B (IC_{50} = 3.02 ± 0.14 to 20.84 ± 1.81 μM and 2.66 ± 0.16 to 16.85 ± 3.49 μM, respectively). Compared with compound **4h** bearing a non-substituted phenyl ring, the introduction of substituted phenyl rings**,** containing either electron-donating (**4a–g**) or withdrawing (**4j–l**) groups, did not improve the activity of the compounds. In compounds **4h** (IC_{50} = 3.02 ± 0.14 μM) and **4i** (IC_{50} = 14.48 ± 1.24 μM), the introduction of a naphthalene ring instead of a phenyl ring resulted in a significant decrease in inhibitory activity, as **4i** was five-fold less potent than compound **4h**. No clear pattern was found for the SAR between the PTP1B inhibitory activity and the position and physicochemical properties of the different substituents on the phenyl ring. Similar trends were also observed for compounds in the **5** series. Interestingly, except for **4b** vs. **5b**, **4j** vs. **5j**, and **4l** vs. **5l**, most of the isoleucine-derived rhodanine (**5**) derivatives generally exhibited higher levels of inhibitory activity (1- to 5-fold) compared with the corresponding phenylalanine-derived rhodanine derivatives (**4**). These results indicated that introducing a *sec*-butyl group at the 2-position of the

carboxyl group might enhance inhibitory activity compared with introducing a benzyl group. The *sec*-butyl group may not only form steric interactions with Phe182, Leu195, and Gly220, but may also be conducive for the formation of stronger hydrogen bond interactions between the isoleucine-derived rhodanine fragment and Cys215, Ser216, Ala217, Ile219, and Gly220 of PTP1B, as suggested by the docking study (Figure 3C). These findings demonstrated that it may be necessary to make further structural modifications at the 2-position to optimize the binding potency in the active site of the tyrosine phosphate binding pocket.

On the basis of the PTP1B enzyme inhibitory activity, compounds **4g**, **4h, 5g**, and **5h** were selected to investigate their effect against other PTPs [27]. As shown in Table 2, these compounds showed 1- to 2.5-fold greater selectivity for PTP1B than for homogeneous T-cell protein tyrosine phosphatase, approximately 1–2-fold selectivity for PTP1B over src homology phosphatase-1 (SHP-1), and approximately 2.5–7-fold selectivity for PTP1B over SHP-2. None of the compounds inhibited leukocyte antigen-related phosphatase (LAR) activity at 20 μg/mL. Interestingly, the compounds possessed 2- to 16-fold more potent inhibitory activity against CDC25B than against PTP1B. CDC25B, a dual-specificity phosphatase, is an attractive therapeutic antitumor target for potential small molecule intervention because of its central role in controlling malignant cell proliferation by regulating cyclin dependent kinases and because it is highly expressed in many human tumors [28]. Further structural modification of these compounds may lead to the discovery of novel inhibitory agents against the Cdc25 phosphatases.

To further understand the mechanisms of the rhodanine derivatives in the inhibition of PTP1B, compound **5g** was selected to evaluate the inhibitory kinetics [27]. As shown in Fig. 3A, **5g** demonstrated time-independent inhibition of PTP1B, which showed that it was a fast-binding and specific inhibitor of PTP1B. As shown in Fig. 3B, the inhibition modality of **5g** towards PTP1B exhibited the characteristics typical of a competitive inhibitor, including increased K_m values and unchanged V_{max} values following increases in the inhibitor concentration. The Lineweaver–Burk plot showed straight lines that intersected with each other on the 1/v axis (Fig. 3C). These results

indicated that **5g** binds to the catalytic pocket of PTP1B and behaves as a competitive inhibitor. The K_i value was calculated to be 2.34 μM.

To investigate the binding mode of **4g** and **5g** with PTP1B, docking simulation studies were carried out using MOE Dock in MOE v2014.0901 to predict the binding affinity with PTP1B (PDB code: 2vey) [25]. The docking scores of **4g** and **5g** are shown in Table 3 and were −7.23 kcal/mol and −7.33 kcal/mol, respectively, for PTP1B. These computational results indicated that **4g** and **5g** can interact with PTP1B and their binding ability with PTP1B was in the order **5g** > **4g**, which might explain the difference in activity between compounds **4** and **5**.

The binding mode of **4g** with PTP1B is illustrated in Fig. 4A. The oxygen atom of the hydroxyl group and the carbonyl of the carboxyl group, regarded as a hydrogen bond donor and an acceptor, respectively, interact via hydrogen bonds with the side chain of Asp181 and the backbone of Ala217 in the catalytic site of PTP1B, respectively. The sulfur atom of the carbon-sulfur double bond of the thiazole ring, regarded as a hydrogen bond acceptor, forms one hydrogen bond with the backbone of Phe182 in PTP1B. The benzyl group at the 2-position of the carboxyl group provides a good van der Waals interaction with Phe182 in PTP1B. The 5-aryl-furan fragment interacts hydrophobically with the side chains of Phe182, Ile219, and Gly259 in PTP1B.

The binding mode of **5g** with PTP1B is illustrated in Fig. 4C. The oxygen atom of the carbonyl of the carboxyl group, regarded as a hydrogen bond acceptor, forms hydrogen bonds with the side chain of Cys215 and the backbone of Ser216 as well as Ala217 in PTP1B. The oxygen atom of the hydroxyl of the carboxyl group, regarded as a hydrogen bond acceptor, forms one hydrogen bond with the side chain of Ser216 in PTP1B. The sulfur atom of the carbon-sulfur double bond of the thiazole ring, regarded as a hydrogen bond acceptor, interacts via hydrogen bonds with the backbone of Ala217, Ile219, and Gly220 in PTP1B. Some van der Waals interactions and hydrophobic interactions were also observed, including interactions between the *sec*-butyl group at the 2-position of the carboxyl group and Phe182, Leu195, and Gly220 and the 5-aryl-furan fragment and Phe182, Ile219, and Gly259 in PTP1B.

In conclusion, two series of 5-aryl-furan derivatives bearing a phenylalanine-derived rhodanine or isoleucine-derived rhodanine group were identified as novel competitive PTP1B inhibitors. Compound **5g** showed the best PTP1B inhibitory potency (IC_{50} = 2.66 ± 0.16 μM) and the best CDC25B inhibitory potency (IC_{50} = 0.25 ± 0.02 μM). Enzymatic data together with molecular modeling results demonstrated that the introduction of a *sec*-butyl group at the 2-position of the carboxyl group remarkably improved the PTP1B inhibitory activity. The results obtained in this work demonstrate that isoleucine-derived rhodanine scaffolds might represent a good starting point for developing more active inhibitors of PTP1B as well as CDC25B.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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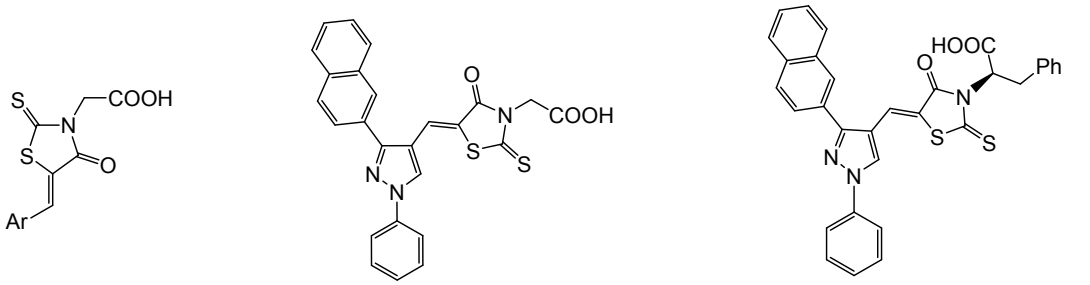


1 **2** IC_{50} **(PTP1B) = 4.78 ± 0.27 μM** **3** IC_{50} **(PTP1B) = 1.81 ± 0.22 μM**

Fig. 1. Structures of known rhodanine PTP1B inhibitors and target compounds.

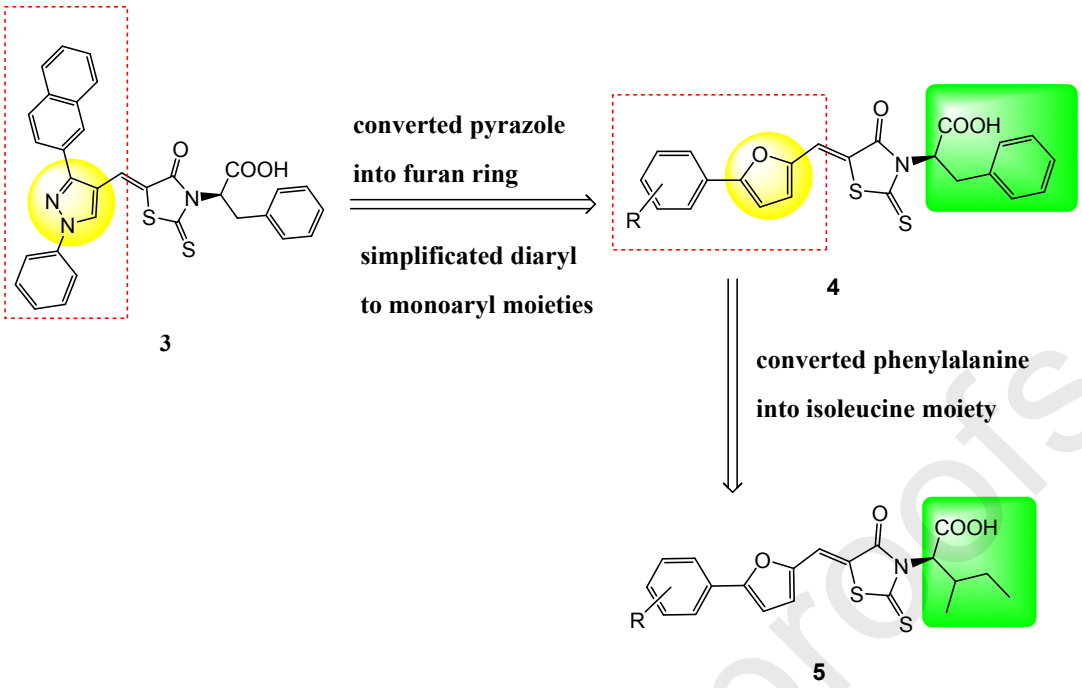


Fig. 2. The designed strategy for the title compounds.

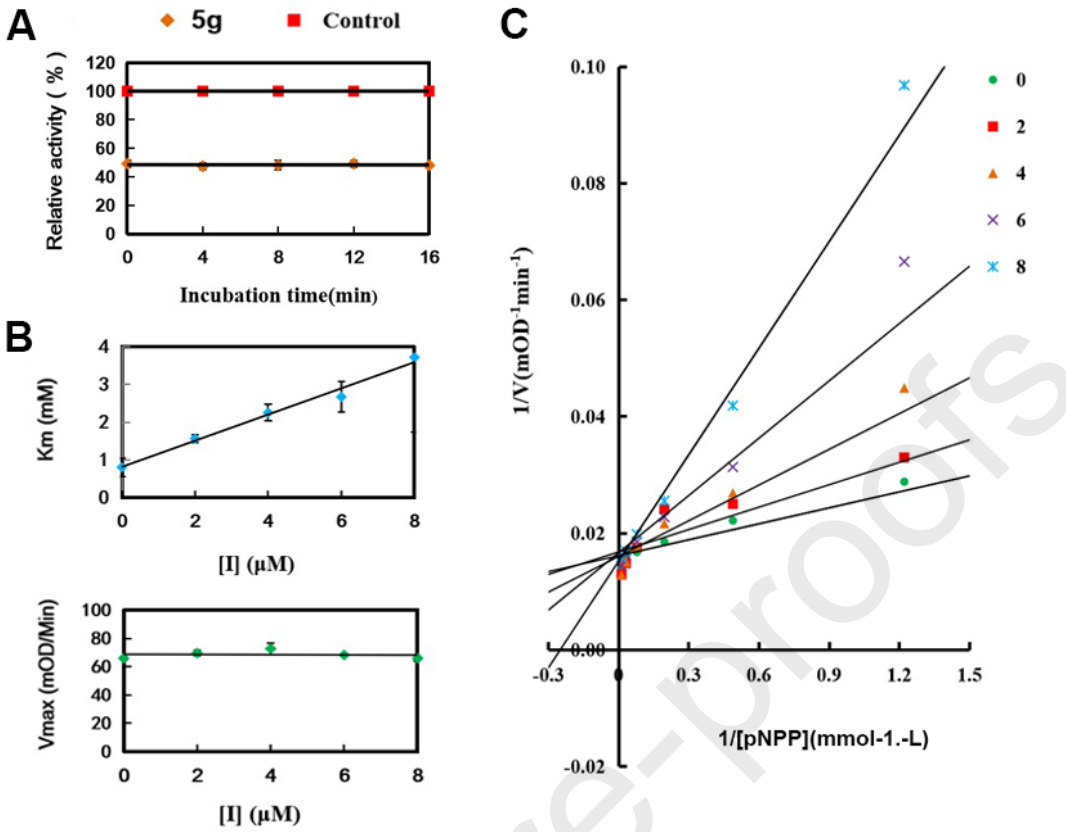


Fig. 3. Characterization of **5g** to PTP1B.

(A) Time-independent inhibition of PTP1B by **5g**. (B) At various fixed concentrations of **5g** the initial velocity was determined with various concentrations of *p*NPP. (C) Typical competitive inhibition of **5g** shown by Lineweaver-Burk plot.

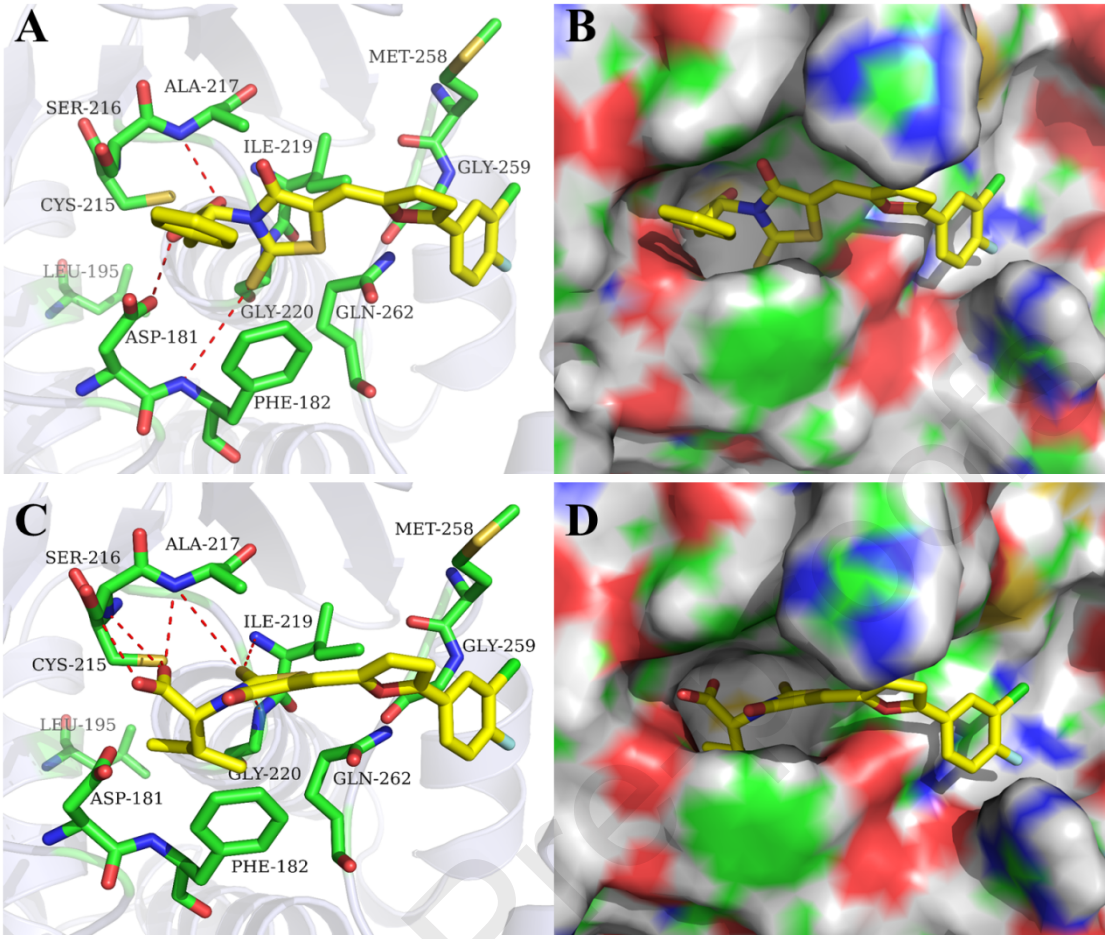
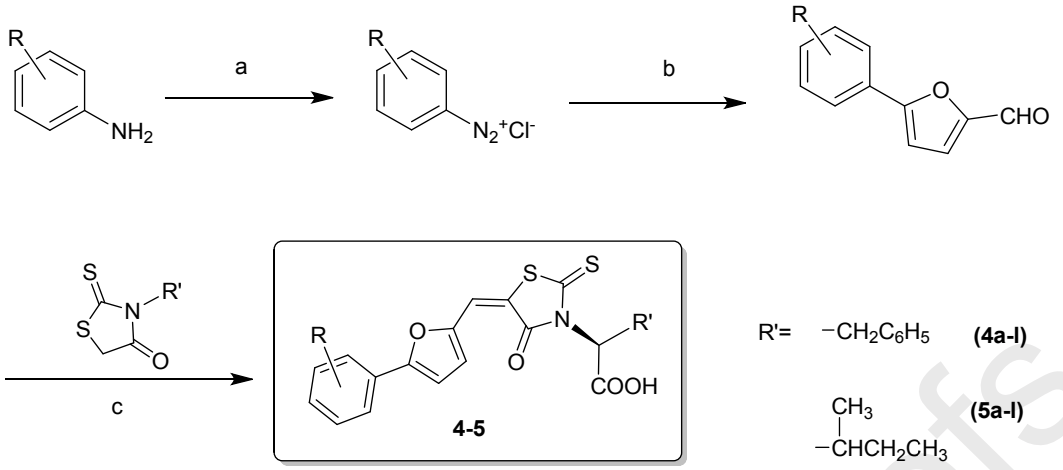


Fig. 4. The binding model of **4g** and **5g** with PTP1B. (A) The interaction model of **4g** with PTP1B. (B) The binding model of **4g** on molecular surface of PTP1B. (C) The interaction model of **5g** with PTP1B. (D) The binding model of **5g** on molecular surface of PTP1B. The ligands are colored in yellow, and the surrounding residues in the binding pockets are colored in green. The backbone of the receptor is depicted as lightblue ribbon.

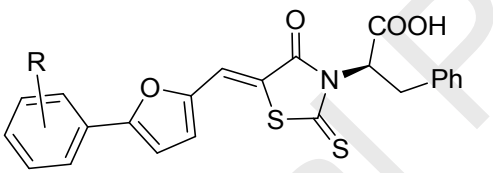


R= a: 2-F; b: 2-Cl; c: 3-Cl; d: 4-Cl; e: 2,5-$(Cl)_2$; f: 4-Br; g: 3-Cl, 4-F; h: H; i: phenyl (3,4-fused); j: 2-CH_3; k: 4-CH_3; l: 4-OCF_3

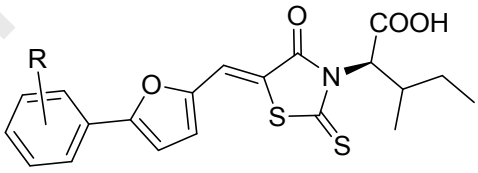
Scheme 1 Regants and conditions: (a) $NaNO_2$, HCl, 0 °C, 1 h; (b) furfural, $CuCl_2$, acetone, 20 °C, 12 h; (c) Piperidine, AcOH, EtOH, 40-50 °C, 4 h.

Table 1

Inhibitory activity of compounds **4a-l and 5a-l** against PTP1B



4a-l



5a-l

Compound	R	IC_{50} (μM) [a]	Compound	R	IC_{50} (μM)
4a	2-F	16.62 ± 1.86	**5a**	2-F	3.41 ± 0.52
4b	2-Cl	4.04 ± 0.19	**5b**	2-Cl	7.17 ± 1.17
4c	3-Cl	4.77 ± 0.24	**5c**	3-Cl	4.47 ± 1.65
4d	4-Cl	20.84 ± 1.81	**5d**	4-Cl	7.80 ± 0.62
4e	2,5-Cl_2	17.94 ± 3.74	**5e**	2,5-Cl_2	6.10 ± 0.42
4f	4-Br	14.18 ± 1.04	**5f**	4-Br	7.98 ± 1.08
4g	3-Cl, 4-F	4.78 ± 0.59	**5g**	3-Cl, 4-F	2.66 ± 0.16
4h	H	3.02 ± 0.14	**5h**	H	3.23 ± 0.41
4i	Phenyl (3,4-fused)	14.48 ± 1.24	**5i**	Phenyl (3,4-fused)	6.73 ± 0.50
4j	2-CH_3	3.98 ± 0.48	**5j**	2-CH_3	16.85 ± 3.49

4k	4-CH_3	13.11 ± 1.64	**5k**	4-CH_3	7.69 ± 2.08
4l	4-OCF_3	5.30 ± 0.83	**5l**	4-OCF_3	8.79 ± 1.49
OA [b]		3.26 ± 0.61			

[a] The pNPP assay. IC_{50} values were determined by regression analyses and expressed as means ± SD of three replications.

[b] Positive control: Oleanolic acid.

Table 2

Inhibitory activity of selected compounds against related PTPs

Compound	IC_{50} (μM) [a]					
	PTP1B	**TCPTP**	**CDC25B**	**LAR**	**SHP-1**	**SHP-2**
4g	4.78 ± 0.59	7.07 ± 0.03	0.29 ± 0.07	NA [b]	5.48 ± 0.28	31.26 ± 4.50
4h	3.02 ± 0.14	3.08 ± 0.21	0.20 ± 0.02	NA	4.73 ± 1.27	8.32 ± 1.98
5g	2.66 ± 0.16	5.66 ± 0.11	0.25 ± 0.02	NA	5.74 ± 0.28	14.09 ± 0.17
5h	3.23 ± 0.41	8.14 ± 1.44	0.69 ± 0.04	NA	2.73± 2.32	18.85 ± 3.45
Na_3VO_4 [c]			0.21 ± 0.01	11.63 ± 1.97	1.33 ± 0.04	3.46 ± 0.11
Oleanolic acid [c]	3.27 ± 0.61	11.05 ± 0.57				

[a] The *p*NPP assay. IC_{50} values were determined by regression analyses and expressed as means ± SD of three replications.

[b] Not active at 20 μg/mL concentration.

[c] Positive control.

Table 3
The docking score of molecules binding with PTP1B

Ligands	Receptor	Docking score (kcal/mol)
4g	PTP1B	-7.23
5g	PTP1B	-7.33

5-Aryl-furan derivatives bearing a phenylalanine-derived or isoleucine-derived rhodanine moiety as potential PTP1B inhibitors

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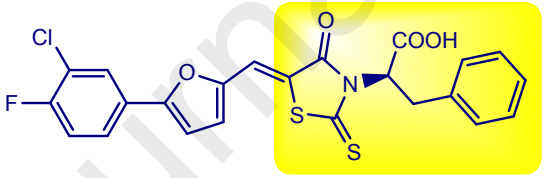
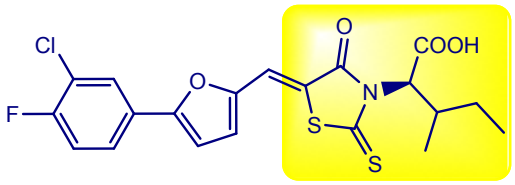
Two series of 5-aryl-furan derivatives bearing a phenylalanine-derived or isoleucine-derived rhodanine moiety were identified as competitive protein tyrosine phosphatase 1B (PTP1B) inhibitors.



4g IC_{50} (PTP1B) = 4.78 ± 0.59 μM

IC_{50} (CDC25B) = 0.29 ± 0.07 μM



5g IC_{50} (PTP1B) = 2.66 ± 0.16 μM

IC_{50} (CDC25B) = 0.25 ± 0.02 μM

Highlights

- Phenylalanine-derived or isoleucine-derived rhodanine groups were identified as pTyr mimetics.

- The most potent compound **5g** showed an IC_{50} value of 2.66 ± 0.16 μM against PTP1B.
- The most potent compound **5g** showed an IC_{50} value of 0.25 ± 0.02 μM against CDC25B.
- Molecular docking studies supported the experimental observations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.