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Synthesis and Biological Evaluation of Furan-chalcone Derivatives as Protein Tyrosine Phosphatase Inhibitors

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Protein tyrosine phosphatase1B (PTP1B) has become an attractive therapeutic target for the treatment of type 2 diabetes mellitus and obesity due to its negative regulator in the insulin and leptin receptor pathways.[1,2] In recent years, following the elucidation of the protein structure of PTP1B, many synthetic PTP1B inhibitors with submicromolar or nanomolar activities have been discovered through high-throughput screening and structure-based design. However, the low selectivity and poor pharmacokinetic properties of these synthetic inhibitors mean that novel PTP1B inhibitors with improved pharmacological properties are still sought after.[3,4]

Recently, several chalcones derived from natural products and their derivatives have been identified as PTP1B inhibitors.[5-7] These reports suggested that chalcones might be promising PTP1B inhibitors. To develop a new type of PTP1B inhibitors based on the chalcone structure, we decided to further extend our research using the new chaclone core, which possesses a heterocycle.

In the present study, we performed the *in vitro* screening of some heterocyclic chalcone derivatives bearing thiofuran, furan, pyridine and quinoline moieties from our in-house collection, and identified (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (**1b**) to be a moderate PTP1B inhibitor, with an IC_{50} value of 6.94 ± 0.69 μM (Fig. 1). To obtain more potent

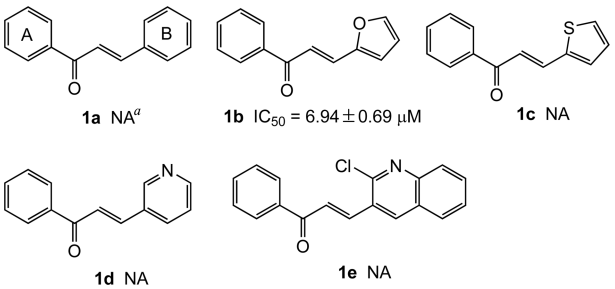

Figure 1. The screening of the lead compoumd. [a]Not active at 20 μg/mL concentration.

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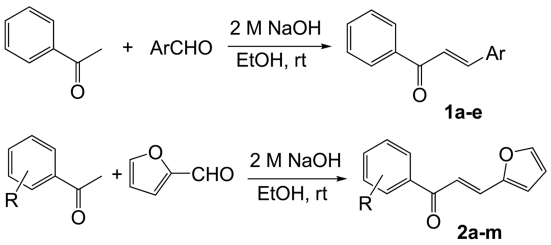

R: **2a**: 4-F; **2b**: 3-Cl; **2c**: 4-Cl; **2d**: 2,4-Cl_2; **2e**: 4-Br; **2f**: 4-NO_2; **2g**: 3-OCH_3; **2h**: 4-OCH_3; **2i**: 4-CH_3; **2j**: 2,4-$(CH_3)_2$; **2k**: 2-OH; **2l**: 3-OH; **2m**: 2,4-OH

Scheme 1. Synthesis of target compounds **1a-e** and **2a-m**.

PTP1B inhibitors and further investigate the structure- activity relationships, we tried to design and synthesize a series of furan-chalcone derivatives with variation of substituents using **1b** as the lead compound.

The synthetic pathways **1a-e** and **2a-m** are illustrated in Scheme 1. The synthesis procedure and spectral data of the compounds **1a-e**, **2a-m** were previously described by our laboratory.[8]

The inhibitory activities of all the synthesized compounds against PTP1B were measured using *p*-nitrophenyl phosphate (*p*NPP) as a substrate, and the results are summarized in Table 1. The known PTP1B inhibitor, ursolic acid (3.40 ± 0.17 μM), was used as the positive control.[6]

As shown in Table 1, 11 compounds out of the 14 test compounds dose-dependently inhibited PTP1B with IC_{50} values ranging from 2.49 ± 0.23 to 35.31 ± 4.50 μM. The IC_{50} values of compounds **2b** and **2m** (2.90 ± 0.12, 2.49 ± 0.23 μM, respectively) were better or similar to that of ursolic acid.

Comparing with compound **1b**, compounds **2b** and **2m** had potent PTP1B inhibitory effects. It seemed that the substituent on chalcone A ring might be important in the inhibitory activity of PTP1B. However, compounds **2a** and **2c-l** that bore substituent(s) on the A ring show less activity than **1b**. These results indicated that the character of substituent on the A ring had a signicant inuence on the PTP1B inhibitory activity. Except **2a** and **2i**, compounds with electron-withdrawing groups (*i.e.*, **2b-f**) seemed to show better

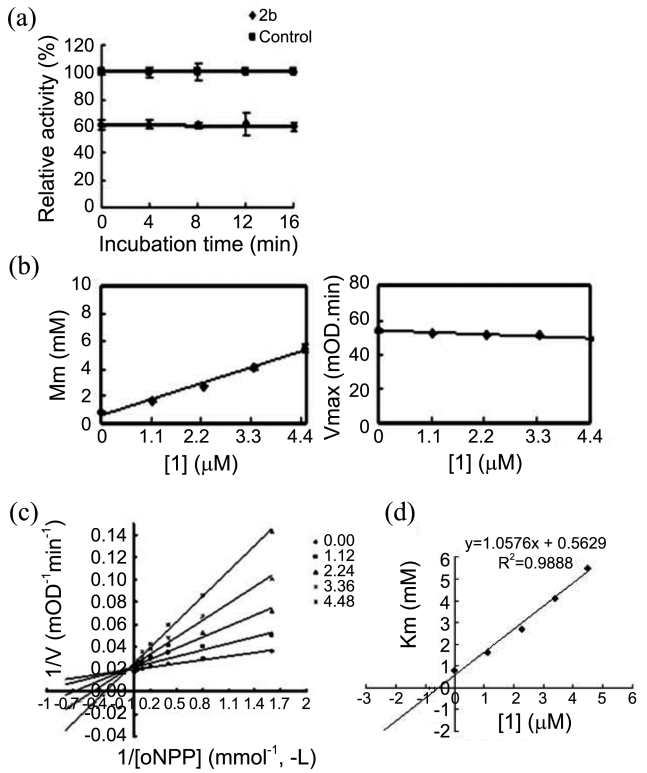

Figure 2. Characterization of **2b** to PTP1B. (a) Time-independent i initial velocity was determined in the presence of various concer Lineweaver-Burk plot. (d) K_i determination.

activity than the compounds containing electron-donating groups (*i.e.*, **2g-j**) on the whole level. These results indicated that electron-withdrawing groups facilitated PTP1B inhibition. Three hydroxy-substituted derivatives (*i.e.*, **2k-m**) were also designed and prepared, containing 2-OH, 3-OH and 2,4-OH. The pharmacology test revealed that monohydroxy-chalcones (*i.e.*, **2k-l**) showed no activity at 20 μg/mL and weaker PTP1B inhibitory activity, respectively. But interestingly, introduction of two hydroxyl groups to compound **1b** at the 2- and 4-position of the A ring (**2m**) dramatically improved PTP1B inhibitory activity with IC_{50} values of 2.49 ± 0.23 μM. The above results suggest that increasing the number of hydroxyl groups on the A ring in chalcones leads to stronger binding and improves potential inhibitory effects against PTP1B. This is consistent with results reported previously.[6]

A kinetic study was performed in order to shed light on the inhibitory mechanism of compound **2b**.[6] As also elucidated in Figure 2, **2b** demonstrated a time-independent inhibition of PTP1B, which showed **2b** was a fast-binding inhibitor of PTP1B (Fig. 2(a)). As shown in Figure 2(b), we further determined the inhibition modality of **2b** which inhibited PTP1B with the characteristics typical of a competitive inhibitor, as indicated by increased K_m values and unchanged V_{max} values when the inhibitor concentration was increased. Meanwhile, the result of the Lineweaver-Burk plot confirmed **2b** as a competitive inhibitor of PTP1B for intersecting at the y-axis of a nest of lines with increased inhibitor concentration (Fig. 2(c)). The results indicate that **2b** binds the catalytic pocket of PTP1B and behaves as a competitor to the substrate. The K_i value calculated from Figure 2(d) was 0.54 μM.

Table 1. Inhibitory activity of **1a-e** and **2a-m** on PTP1B

Compounds	IC_{50}[a] (μM)	Compounds	IC_{50} (μM)
1b	6.94 ± 0.69	**2g**	11.03 ± 0.71
2a	NA[b]	**2h**	35.31 ± 4.50
2b	2.90 ± 0.12	**2i**	NA
2c	10.65 ± 0.56	**2j**	20.28 ± 1.51
2d	21.40 ± 3.47	**2k**	NA
2e	8.45 ± 1.23	**2l**	26.41 ± 0.80
2f	18.99 ± 1.53	**2m**	2.49 ± 0.23
UA[c]	3.40 ± 0.21		

[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.

In conclusion, a series of furan-chalcone derivatives were identified as reversible and competitive PTP1B inhibitors with IC_{50} values in the micromolar range. These results should provide a promising starting point for PTP1B and other PTPs inhibitor design. This is an initial report and optimization of these compounds is in progress.

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