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

Liang-Peng Sun, Zhe Jiang, Li-Xin Gao, Li Sheng, Ying-Chun Quan, Jia Li, * and Hu-Ri Piao *

Key Laboratory of Natural Resources of Changbai Mountain & Functional Molecules, Ministry of Education, Yanbian University College of Pharmacy, Yanji 133000, China. E-mail: piaohuri@yahoo.com.cn

Received October 4, 2012, Accepted January 7, 2013

Key Words: Protein tyrosine phosphatase 1B, Inhibitors, Furan-chalcone, SAR

Protein tyrosine phosphatase 1B (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 thiophuran, 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 IC50 value of 6.94 ± 0.69 µM (Fig. 1). To obtain more potent 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 inhibitory activities of all the synthesized compounds against PTP1B were measured using p-nitrophenyl phosphate (pNPP) as a substrate, and the results are summarized in Table 1. The known PTP1B inhibitor, ursoic 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 IC50 values ranging from 2.49 ± 0.23 to 35.31 ± 4.50 µM. The IC50 values of compounds 2b and 2m (2.90 ± 0.12, 2.49 ± 0.23 µM, respectively) were better or similar to that of ursoic 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-f 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 significant influence on the PTP1B inhibitory activity. Except 2a and 2i, compounds with electron-withdrawing groups (i.e., 2b-f) seemed to show better

Figure 1. The screening of the lead compound. *Not active at 20 µg/mL concentration.

*These authors contributed equally to this work.
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 2b dramatically improved PTP1B inhibitory activity with IC50 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.4

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 Km values and unchanged Vmax 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 Ks value calculated from Figure 2(d) was 0.54 µM.

In conclusion, a series of furan-chalcone derivatives were identified as reversible and competitive PTP1B inhibitors with IC50 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.

Acknowledgments. This work was supported by the National Natural Science Foundation of China (Grants 20962021 and 81125023) and the National Program on Key Basic Research Project of China (973 Program, 2012CB524906). And the publication of this paper was supported by the Korean Chemical Society.

References