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# Design, synthesis, and evaluation of bromo-retrochalcone derivatives as protein tyrosine phosphatase 1B inhibitors

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ABSTRACT

A series of bromo-retrochalcones was designed, synthesized and evaluated as PTP1B inhibitors based on licochalcone A and E. Compounds **6**, **12**, **13**, **14**, **25**, **36**, **37**, **39**, and **41** showed potent inhibitory effects against PTP1B, and compound **37**, the most potent among the series, had an $IC_{50}$ value of 1.9 μM, about two-fold better than that of the positive control, ursolic acid.

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The critical down-regulatory step in the insulin signaling pathway is associated with protein tyrosine phosphatase. Protein tyrosine phosphatase 1B (PTP1B) plays a major role in modulating insulin and leptin signaling pathways. PTP1B knockout mice show enhanced insulin sensitivity, lower plasma glucose and insulin levels, and are protected against weight gain when fed a high-fat diet compared to control mice as a result of prolonged phosphorylation of the insulin receptor substrate proteins.[1] The PTP1B-null mice also have normal development and longevity. In addition, antisense-based oligonucleotides targeting PTP1B have shown efficacy in type 2 diabetes and have entered phase 2 clinical trials.[2] Accordingly, inhibition of PTP1B has been proposed as one of the best validated biological targets for drug discovery in the treatment of type 2 diabetes and obesity.[3] Although several types of PTP1B inhibitors have been reported, the low selectivity and poor pharmacokinetic properties of these synthetic inhibitors has led to a continued search for new types of PTP1B inhibitors with improved pharmacological properties.[4]

We have been searching for a lead compound from natural products as a potential preclinical candidate for the treatment of type 2 diabetes mellitus over the last few years. Recently, we reported that the licochalcones A and E, with a 3,3-dimethylallyl and a 2,3-dimethylallyl group at position 5 in the B ring, respectively, showed good PTP1B inhibitory activities (Fig. 1).[5] And one of the licochalcone A derivatives, methyllicochalcone A, which is methylated at the 4′-hydroxy position of licochalcone A, exhibited approximately two-fold better activity than licochalcone A.[5]

Thus, it has been postulated that the retrochalcones with diversely substituted aryl groups could display enhanced PTP1B inhibitory activity. Interestingly, replacement of the substituted allyl group in licochalcone E with bromine provided a compound with much better activity than allyl retrochalcones as a PTP1B inhibitor. For example, compound **1** had an $IC_{50}$ of 13.7 μM compared to licochalcone A and E with $IC_{50}$s of 19.1 μM and 20.7 μM, respectively. Herein, we report the design, synthesis, and evaluation of bromo-retrochalcones as a new class of PTP1B inhibitor.

General method for the synthesis of the retrochalcone is depicted in Schemes 1 and 2. Bromination of 2,4-dihydroxybenzaldehyde followed by selective THP protection of the 4-hydroxyl group provided 5-bromo-2-hydroxy-4-(tetrahydropyran-2-yloxy)-benzaldehyde.

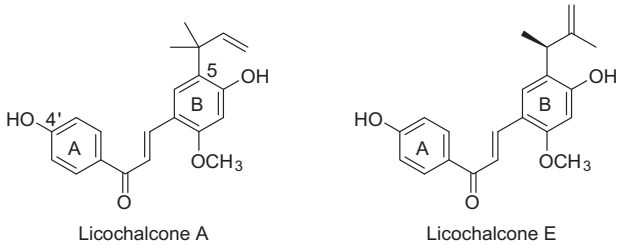


**Figure 1.** Structures of licochalcone A and E.

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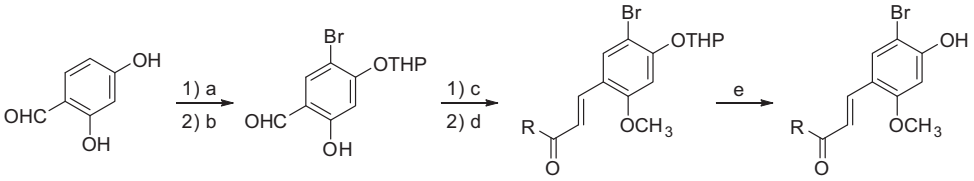
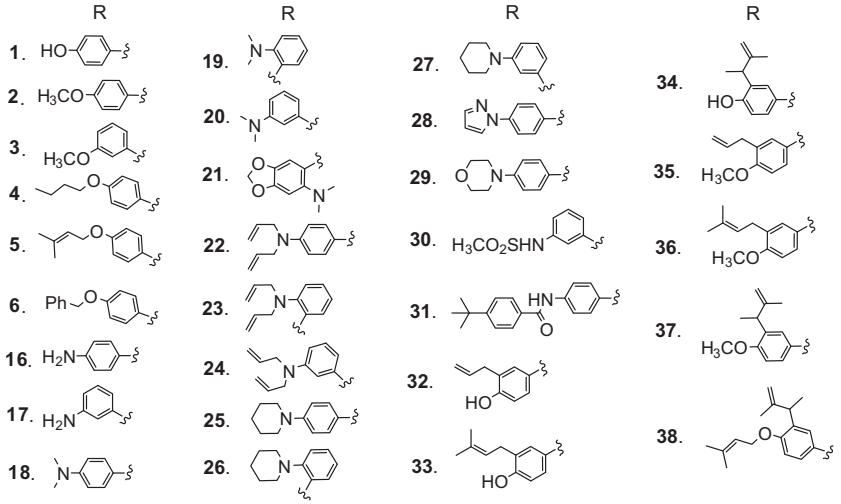
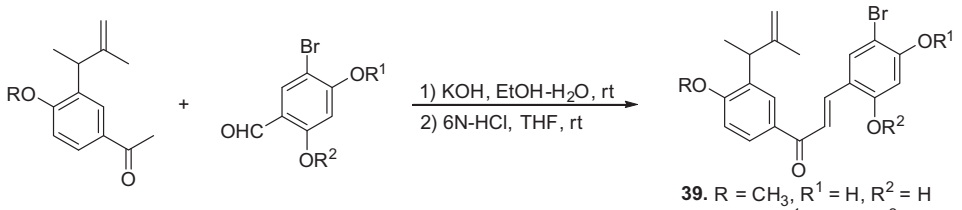



(a) $Br_2$, AcOH, rt, 83% (b) 3,4-Dihydro-2*H*-pyran, PPTS, $CH_2Cl_2$, rt, 89% (c) $CH_3I$, $K_2CO_3$, acetone, rt, 88%
(d) Substituted acetophenone, KOH, EtOH-$H_2O$, rt (e) 6N-HCl, THF, rt




**Scheme 1.** General synthesis of bromo-retrochalcones.



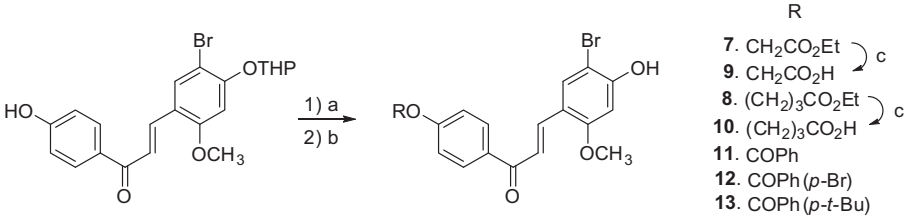

**39.** R = $CH_3$, $R^1$ = H, $R^2$ = H
**40.** R = H, $R^1$ = THP, $R^2$ = $CH_3$
**41.** R = $CH_3$, $R^1$ = THP, $R^2$ = H

**Scheme 2.** Bromo-retrochalcones with modified B ring.

The 2-hydroxyl group was then methylated with MeI/$K_2CO_3$ to furnish the aldehyde.[6] All bromo-retrochalcones were synthesized by aldol condensation of 5-bromo-2-methoxy-4-(tetrahydropyran-2-yloxy)-benzaldehyde with prepared acetophenones in ethanolic KOH solution followed by removal of the THP protecting group, if necessary.[7]

In the case of compounds with an ester, acid or sulfonate functional group such as **7**–**15**, the aldol condensation product of 4-hydroxyacetophenone and 5-bromo-2-methoxy-4-(tetrahydropyran-2-yloxy)-benzaldehyde was alkylated, acylated or sulfonated with the appropriate alkyl halide, acyl halide or sulfonyl chloride and then deprotected under acidic conditions (Scheme 3).

The inhibitory activities of the synthesized retrochalcones against PTP1B were measured using *p*-nitrophenyl phosphate (*p*NPP) as a substrate, and the results are summarized in Table 1.[8] The known PTP1B inhibitor, ursolic acid ($IC_{50}$ = 3.1 μM), was used as the positive control. All synthetic compounds, except com-




(a) RX, $K_2CO_3$, acetone, rt for **7** and **8**; RX, pyridine, rt for **11**-**15**
(b) 6N-HCl,THF, rt (c) 1M NaOH, EtOH, 40 °C

**Scheme 3.** Synthesis of bromo-retrochalcones with an ester, acid or sulfonate functional group.

**Table 1**
PTP1B inhibitory activity of compounds **1**–**41**

| Compound | μM[a] | Compound | μM[a] | Compound | μM[a] |
|---|---|---|---|---|---|
| **1** | 13.7 ± 0.7 | **15** | 18.4 ± 0.7 | **29** | 8.0 ± 0.5 |
| **2** | 9.9 ± 1.4 | **16** | 6.2 ± 0.9 | **30** | 11.3 ± 0.1 |
| **3** | 11.1 ± 0.4 | **17** | 6.8 ± 0.3 | **31** | 3.4 ± 0.2 |
| **4** | 4.2 ± 0.3 | **18** | >30 | **32** | 7.1 ± 0.2 |
| **5** | 3.5 ± 0.6 | **19** | 13.9 ± 0.8 | **33** | 4.4 ± 0.5 |
| **6** | 2.9 ± 0.1 | **20** | 26.4 ± 2.0 | **34** | 6.9 ± 0.1 |
| **7** | 15.2 ± 2.5 | **21** | 6.3 ± 0.3 | **35** | 5.3 ± 0.1 |
| **8** | 10.8 ± 0.4 | **22** | 3.4 ± 1.1 | **36** | 2.9 ± 0.3 |
| **9** | >30 | **23** | 3.5 ± 0.1 | **37** | 1.9 ± 0.1 |
| **10** | 30.0 ± 2.8 | **24** | 4.5 ± 0.6 | **38** | 7.0 ± 1.2 |
| **11** | 4.9 ± 0.2 | **25** | 2.6 ± 0.3 | **39** | 2.6 ± 0.1 |
| **12** | 2.3 ± 0.1 | **26** | 6.8 ± 1.0 | **40** | 10.3 ± 1.4 |
| **13** | 2.4 ± 0.2 | **27** | 4.9 ± 0.1 | **41** | 2.9 ± 1.2 |
| **14** | 2.7 ± 0.1 | **28** | 6.0 ± 0.1 | Ursolic acid | 3.1 ± 0.3 |

[a] Results are expressed as $IC_{50}$ values (μM) and as mean ± SD of three replicates.

pounds **9** and **18**, dose-dependently inhibited PTP1B with $IC_{50}$ values ranging from 1.9 to 26.4 μM, and most of them showed better activity than licochalcone A.[5] Introduction of bromine at the C-5 position, instead of allyl groups, gave compound **1**, which had moderate PTP1B inhibitory activity. But compounds without any substituent at the C-5 position of retrochalcone displayed no PTP1B inhibitory activities.[5] This result indicates that substitution at the C-5 position of retrochalcone is important for the activity and that bromine is a better substituent than 3,3-dimethylallyl or 2,3-dimethylallyl at this position. This finding led us to conduct a quantitative structure–activity relationship study of bromo-retrochalcones such as compound **1**. Methylation of compound **1** at the 4′-hydroxy position gave compound **2**, which had better activity than compound **1**, and this observation was in accord with our previous result.[5] In contrast, bromo-retrochalcones bearing a *meta*-methoxy group, such as compound **3**, showed lower potency than compound **2**. Incorporation of various alkyl groups at the 4′-hydroxy position yielded compounds that were much more potent. For example, introduction of butyl or prenyl group at the 4′-hydroxy position gave compounds **4** ($IC_{50}$ = 4.2 μM) and **5** ($IC_{50}$ = 3.5 μM), respectively, which displayed two- and three-fold increases in activity compared to compound **2** ($IC_{50}$ = 9.9 μM). However, benzylation at the 4′-hydroxy position gave the most active compound **6** ($IC_{50}$ = 2.9 μM). This indicates that a hydrophobic group at this position is preferred for the activity. Alkylation at the 4′-hydroxy position with ethyl bromo-acetate or ethyl bromo-butanoate furnished compound **7** ($IC_{50}$ = 15.2 μM) and **8** ($IC_{50}$ = 10.8 μM), respectively. But hydrolysis of the ester in **7** and **8** provided acidic compounds **9** and **10** with no activity. This result further proved that hydrophobicity is critical for the activity. Benzoylation of the 4′-hydroxy group greatly increased the potency compared to compound **1** as shown in compound **11** ($IC_{50}$ = 4.9 μM). Introduction of *para*-bromo or *para*-*t*-butyl group to the benzoyl moiety provided strongly active compound **12** ($IC_{50}$ = 2.3 μM) and **13** ($IC_{50}$ = 2.4 μM), respectively. *p*-Toluenesulfonylation of the 4′-hydroxy group also greatly increased the potency as shown in compound **14** ($IC_{50}$ = 2.7 μM), but methanesulfonylation provided compound **15** ($IC_{50}$ = 18.4 μM), which had lower activity than compound **1**.

Replacement of the hydroxyl group at the C-4′ position with an amine led to compound **16** ($IC_{50}$ = 6.2 μM), which exhibited a two-fold gain in the PTP1B inhibitory activity compared to compound **1**. Compound with *meta*-oriented amine such as **17** also displayed the same activity as compound **16**. Dimethylation of the amine in compound **16** gave compound **18**, which surprisingly had no activity. A compound with *ortho*-dimethylamine on ring A such as **19** showed better activity than a compound with *meta*-dimethylamine on ring A such as **20.** Compound **21**, which had a methylenedioxy group in addition to the *ortho*-dimethylamine on ring A, displayed comparable inhibitory activity to **16**. Unlike dimethylamino compounds **18**–**20**, all compounds with a diallylamino group on ring A, **22**–**24**, exhibited excellent inhibitory activities ($IC_{50}$ = 3.4–4.5 μM). In the case of compounds **25**–**27** with piperidine substitution on ring A, the *para*-substituted compound **25** exhibited the most significant activity among the amine derivatives of the bromo-retrochalcones with an $IC_{50}$ of 2.6 μM. Compound **28** with pyrazole and **29** with morpholine at the C-4′ position had $IC_{50}$ values of 6.0 μM and 8.0 μM, respectively. Compound **30** with a methanesulfonamide group at the C-3′ position provided moderate inhibitory activity ($IC_{50}$ = 11.3 μM). Substituted benzoylation of the amine at the C-4′ position as in compound **31** with *p*-isopropylbenzoylated amine greatly increased the inhibitory activity ($IC_{50}$ = 3.4 μM), following a trend similar to that from compound **1** to compound **13**.

Introduction of additional various allyl substituents at the C-3′ position of compound **1** led to compounds **32**–**34** with two- to three-fold increases in activity compared to compound **1**. Among them, prenyl-substituted compound **33** had the best activity with $IC_{50}$ of 4.4 μM. Meanwhile methylation of the C-4′ hydroxyl group of compounds **32**–**34** led to compounds **35**–**37** with the best results. The most active compound **37** with 2,3-dimethylallyl substitution at the C-3′ position had an $IC_{50}$ of 1.9 μM, about two-fold better than that of the positive control, ursolic acid. But introduction of 2,3-dimethylallyl group at the C-3′ position of compound **5** provided compound **38**, which had reduced activity ($IC_{50}$ = 7.0 μM). Compound **39** with a hydroxyl group at the C-2 position exhibited the same potency as compound **36** and the positive control, ursolic acid. Introduction of a tetrahydropyran group at the 4-hydroxy position in compound **34** produced compound **40**, which had decreased activity ($IC_{50}$ = 10.3 μM), but introduction of a tetrahydropyran group at the 4-hydroxy group in compound **39** gave compound **41**, which had potent inhibitory activity ($IC_{50}$ = 2.9 μM).

On the basis of these results, it appeared that the PTP1B inhibitory activities of the bromo-retrochalcones may provide valuable information regarding structure–activity relationships for the development of novel PTP1B inhibitors.

In conclusion, we designed, synthesized, and developed a novel series of retrochalcones with bromine at position 5 in the B ring as potential PTP1B inhibitors. Of the bromo-retrochalcone derivatives, compounds **6**, **12**, **13**, **14**, **25**, **36**, **37**, **39**, and **41** showed potent inhibitory activities with $IC_{50}$ values ranging from 1.9 to 2.9 μM. In particular, compound **37** with 1,2-dimethylallyl group at the C-3′ position and methoxy group at the C-4′ position, the most potent among the series, had an $IC_{50}$ of 1.9 μM, about two-fold better than that of the positive control, ursolic acid. The bromo-retrochalcones with a substituted amine on ring A also showed promising PTP1B inhibitory properties. These results provide a starting point for further optimization of substituted retrochalcones with bromine at position C-5 as a PTP1B inhibitor. Further SAR studies of substituted bromo-retrochalcones in PTP1B inhibition are currently ongoing and the results will be published in due course.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.04.057.

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8. *PTP1B assay*: Recombinant human PTP1B was purchased from BIOMOL International LP. For the inhibition assay, a sample (3 μL in DMSO) was added to a reaction mixture containing enzyme (2 μL), reaction buffer [10 μL, 50 mM citrate (pH 6.0), 0.1 M NaCl, 1 mM EDTA and 1 mM dithiothreitol], water (35 μL) and 50 μL of 4 mM *p*-nitrophenyl phosphate (*p*NPP). The reaction mixture (100 μL) was incubated at 37 °C for 30 min and then quenched by addition of 10 μL of 10 N NaOH. The hydrolysis of *p*NPP was determined by measuring the absorbance at 405 nm.