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Design, synthesis, and discovery of stilbene derivatives based on lithospermic acid B as potent protein tyrosine phosphatase 1B inhibitors

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Abstract—Dihydroxy stilbene derivatives were designed based on lithospermic acid B and were prepared from 4-(chloromethyl)benzoic acid. The inhibitory activities of the novel compounds against protein tyrosine phosphatase 1B (PTP1B) were evaluated. 3,4-Dihydroxy stilbene carbonyl compounds (**7**, **11b**, **27b**) inhibited PTP1B with IC_{50} values comparable to molybdate, while the conjugation-extended compound (**15b**) showed inhibition 3-fold better than preclinical RK682. The introduction of electron withdrawing groups or amides into the second phenyl ring, or extension of the conjugation into the stilbene molecule may increase stability of the generated radicals.

Non-insulin-dependent diabetes mellitus (type II) represents 80–90% of the human population with diabetes,[1a] and worldwide estimates approach 215 million cases by 2010.[1b] However, clinically useful type-II antidiabetic drugs based on PTP1B inhibition are not available at the present time. Protein tyrosine phosphatases (PTPs) act in opposition with protein tyrosine kinases to control the tyrosine phosphorylation levels of proteins. Reversible tyrosine phosphorylation plays an important role in signal transduction and regulation of cell processes such as growth, differentiation, and proliferation.[2] As anticipated from the importance of tyrosine phosphorylation, PTPases are implicated in diverse human diseases including diabetes, obesity, autoimmune diseases, and neurodegeneration. Type II diabetes is believed to be associated with a defect in insulin receptor signaling which begins with the receptor autophosphorylation and the receptor tyrosine kinase activation.[3a] Insulin signaling is negatively regulated by dephosphorylation of the receptor by PTPases and, therefore, the defect in insulin sensitivity is possibly reversed by the inhibition of the relevant PTPases.[3b] The most likely candidates include PTP1B, LAR, PTPa, and SHP-2. Among those, protein tyrosine phosphatase 1B (PTP1B) has been most intensively studied as a target for the development of inhibitors aiming at the treatment of type II diabetes and obesity.[3c]

Recent studies have provided compelling evidence that one of the main functions of intracellular PTP1B is to suppress insulin action.[4a] Reducing PTP1B abundance in mice not only enhances insulin sensitivity and improves glucose metabolism, but also protects against obesity induced by high-fat feeding.[4b] Protein tyrosine phosphatase 1B functions in the negative regulation of insulin signaling, and thus establishes PTP1B as an attractive therapeutic target for diabetes.

Inhibition of PTP1B in insulin sensitive tissues using novel antisense oligonucleotides has shown enhanced insulin signaling and glucose tolerance in preclinical

Keywords: Lithospermic acid B (LAB); Protein tyrosine phosphatase (PTP1B); Stilbene derivatives.
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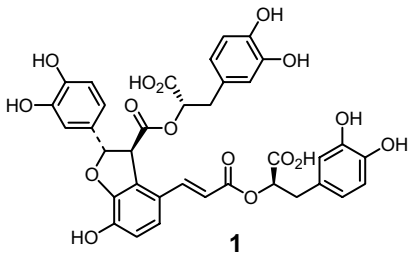
models.[4c] However, there are very few PTPase inhibitors that have been advanced into clinical trials.

Small molecule PTP1B inhibitors may find an important clinical role as novel insulin sensitizers in the treatment of type II diabetes.[4d,e] Lithospermic acid B (LAB)[5] **1** is a polyphenol compound extracted from *Salvia miltorrhiza Bunge*. Although LAB itself shows no in vitro inhibition of PTP1B, it was shown to reduce the glomerular proteinuria in in vivo experiments, and to show a strong in vitro aldose reductase inhibition and has been studied as an antidiabetic drug candidate.[6] In structural aspects, it is tetramer of caffeic acid with seven phenolic hydroxyl groups, which cause the antioxidant effect of this compound.



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In this article, we wish to report the design, synthesis, and discovery of dihydroxy stilbene derivatives based on natural lithospermic acid B as potent PTP1B inhibitors.

Since LAB has high molecular weight and polarity, it does not satisfy the Lipinski's rule for potential drug candidates with good bioavailability.[7a] High molecular weight makes LAB unsuitable for further derivatization, so we sought a novel simplified lead compound with low molecular weight that retained high antioxidant effect. We found that stilbene derivatives (**7**) inhibited PTP1B with an IC_{50} = 25.6 μM in preliminary studies. Recently, novel stilbene analogs were reported as potent human cytochrome P450 inhibitors.[8] The stilbene derivative is a neutral molecule without charge, having a structure well-suited to derivatization. We proposed the lead compound structure **15** to be a derivative of the caffeic acid dimer, the central part of LAB **1** with two phenolic hydroxyl groups on the phenyl ring as a stable radical generator. This molecule is a sort of trans-stilbene, in which two benzene rings are connected via one double bond, derived from the core structure of the LAB. It satisfies the Lipinski's rule.[7a] Two phenolic hydroxyl groups and the conjugation throughout the whole system may contribute to the expected high radical scavenging effect by increasing stability of the generated radicals.

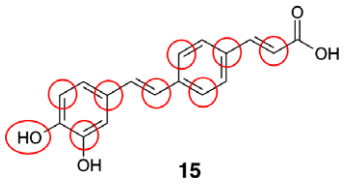

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Figure 1 shows the delocalization of spin density of the phenolic O-centered radical, which was calculated using Titan program with DFT/6-31G method. The spin density is delocalized throughout the whole structure of this compound due to the planarity and the aromaticity of the structure. Two hydroxyl groups attached to the central phenyl ring have been removed to reduce the hydrophilicity of the compound. Moreover, the terminal carboxylic acid group can be substituted to make derivatives with improved physical and chemical properties. It is suitable for assessment by medicinal chemistry, as it satisfied the lead likeness rule proposed by Teague et al.[7b] We can expect high radical scavenging effects and long half-life for this compound because the spin density generated at the para position hydroxyl group through interaction with other radicals can be delocalized throughout the conjugated structure. In addition, the radical at the para hydroxyl group can be stabilized to form a hydrogen bond with the meta-position hydroxyl group. Therefore, we expect this compound and its derivatives to be useful as potent antioxidants with high radical scavenging effects that can eventually be developed as anti-diabetic drug candidates.

For initial assessment of the structure–activity relationship, the chemical structures of stilbene derivatives were designed by substitution at various positions of the stilbene skeleton as listed in the following Figure 2 and synthesized as shown in Schemes 1–4. Wittig reaction[9] of the protected aromatic aldehyde **5** and the appropriate aromatic ylide obtained from the phosphonium salt **3** as prepared by literature procedure[10,11] afforded the protected stilbene derivative **6**[12] in 85% yield in the *E*/*Z* isomer ratio of 1/1 (Scheme 1). The mixture of *E* and *Z* product isomers was separated by flash chromatography. Regiochemistry of *E*-form of **6** was identified by higher coupling constant J = 16.3 Hz, doublet at δ 6.97, 7.15 compared with lower J = 12.2 Hz, doublet at δ 6.51, 6.61 for *Z*-form, respectively. Removal of the tert-butyl dimethylsilyl (TBDMS) groups from *E*-stilbene **6**[11] using tetrabutylammonium fluoride provided compound **7** (*E*-form: R_f = 0.10 (hexane/ethyl acetate, 2/1, v/v). δ 7.97 (d, 1H, J = 16.25Hz), 7.58 (d, 1H, J = 16.25Hz). Further reduction of 4′-ester of the intermediate *E*-form **6** with DIBAL-H to **8** and **10** and subsequent deprotection of TBDMS groups of **8**, **10** with TBAF afforded trans compounds **9**, **11a**, respectively (Scheme 1).[11] Cis form, **26b** (Fig. 2), of compound **9** was similarly prepared from *Z*-form of stilbene **6**.

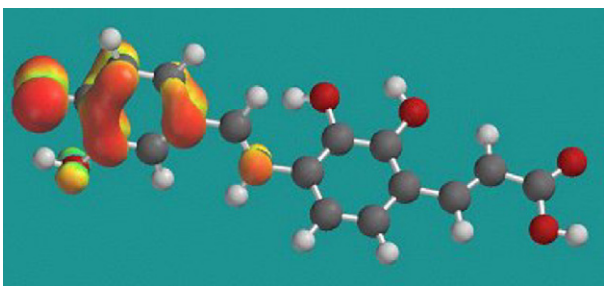


Figure 1. Radical-scavenging part/hydrophobic binding part generated using Titan version 1.0.

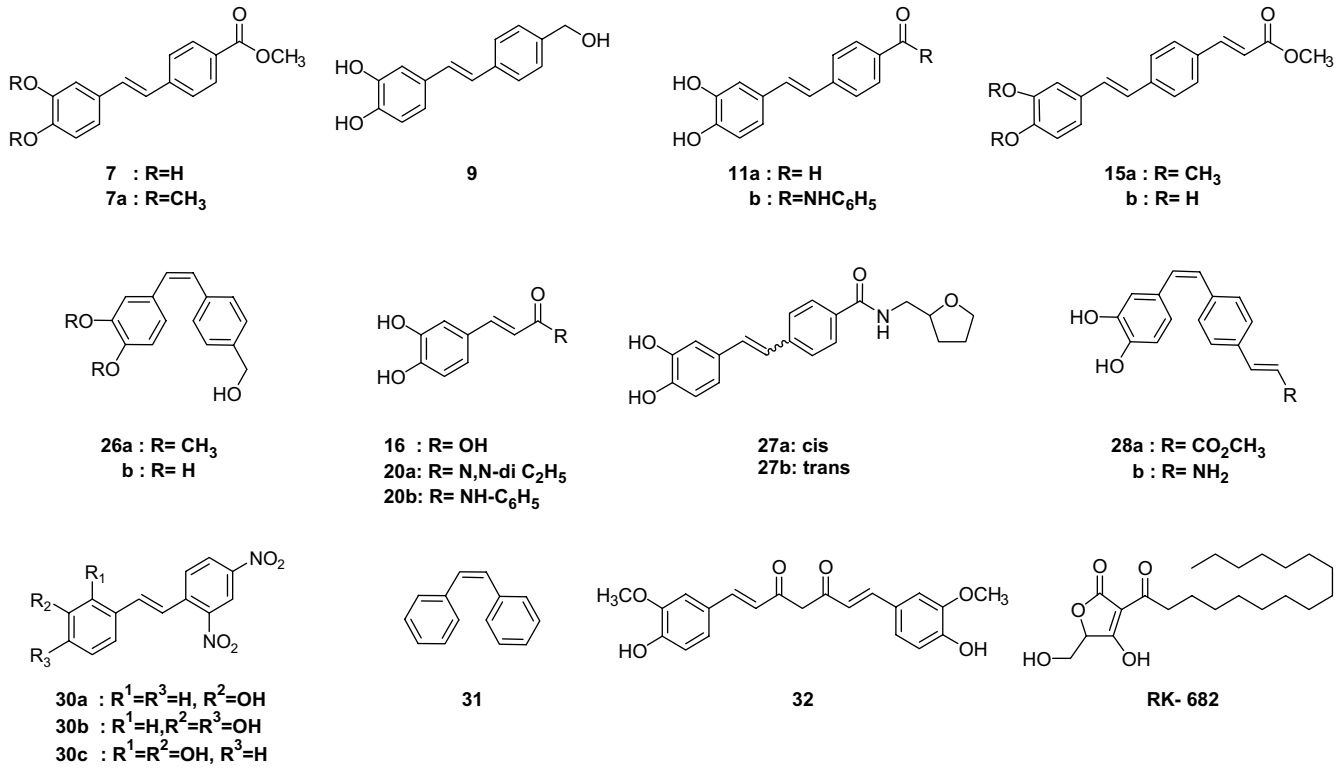
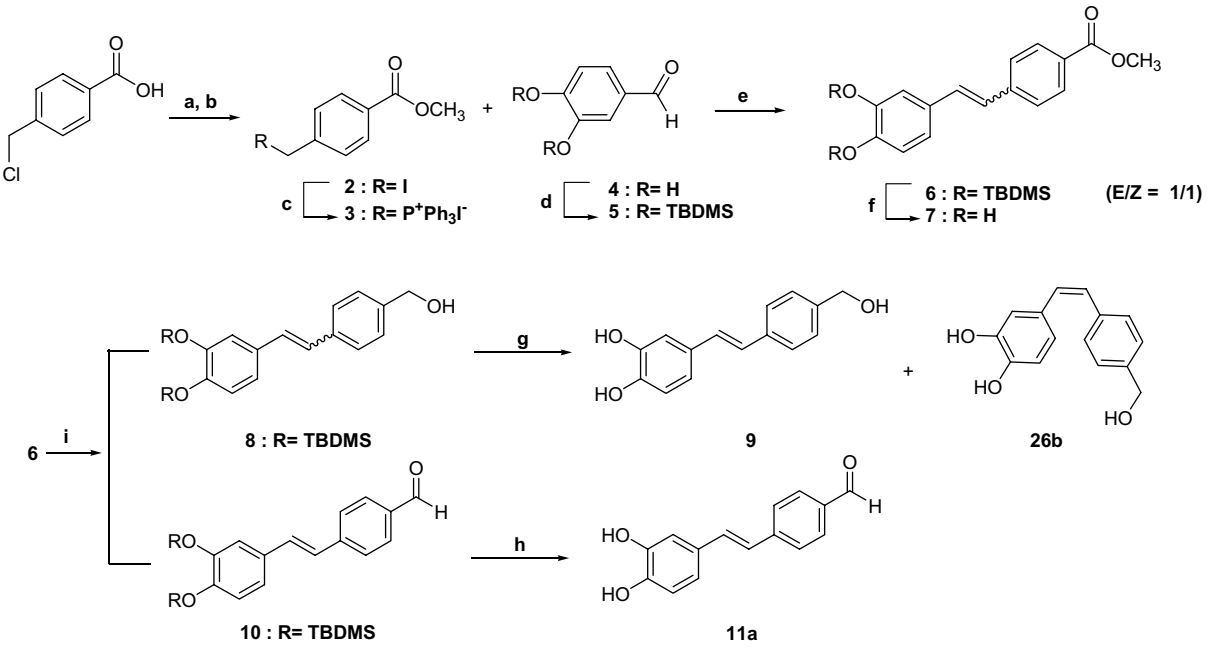
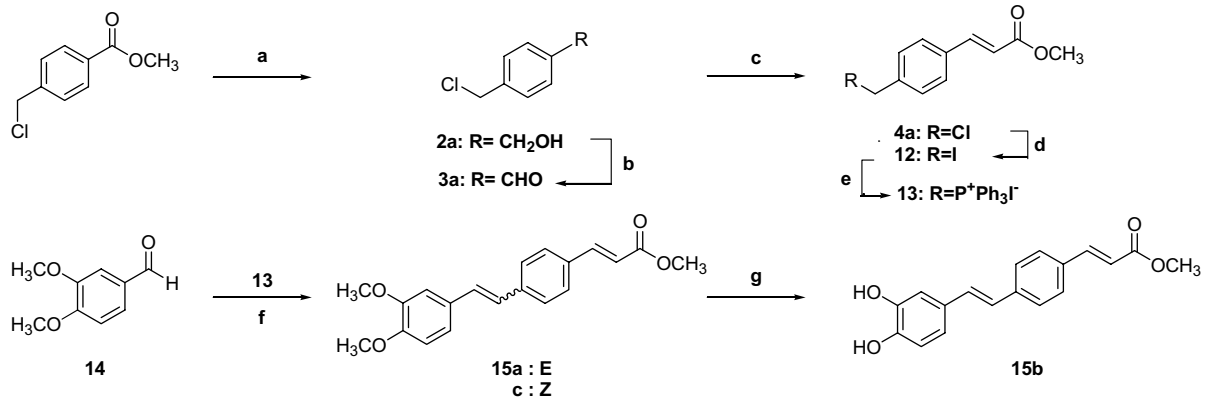


Figure 2. Structures of stilbene derivatives designed, synthesized, and screened against PTP1B.

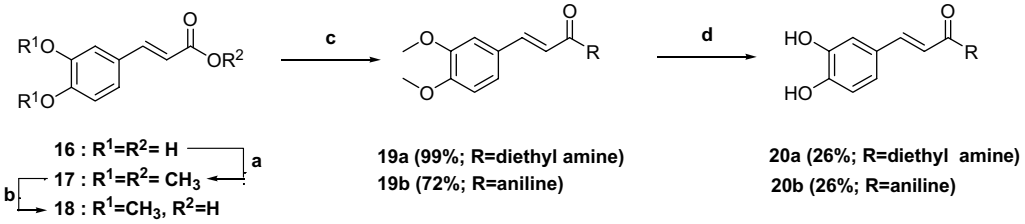


Scheme 1. Reagents and conditions: (a) Me_2SO_4, K_2CO_3, acetone, 87%; (b) NaI, dry Acetone, reflux, 89%; (c) PPh_3, dry ether reflux, 99%; (d) TBDMSCl, imidazole, DMF, 25 °C, 89%; (e) NaH/THF, 0 °C, 86%; (f–h) TBAF, THF, 0–25 °C, 1 h, 77–90%; (i) DIBAL-H, CH_2Cl_2, −78 °C, 87%.

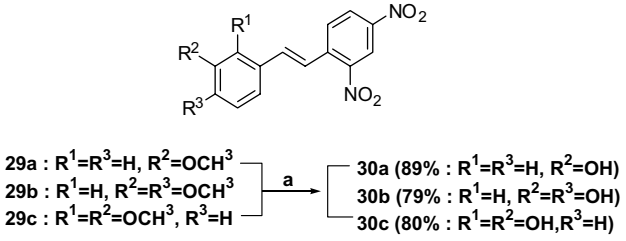
Methyl-(2*E*)-3-[4-(iodomethyl)phenyl]-2-propenoate **12** was prepared from methyl-4-(chloromethyl)benzoate via **3a** and **4a** in the literature procedure.[9] Reaction of **12** with triphenylphosphite afforded the phosphonium salt **13** in 91% yield. Wittig reactions[9] of the ylide generated from **13** with commercially available aromatic aldehyde **14** in the presence of *n*-butyllithium in THF yielded an olefin compound **15**[8,13] in 62% yield in the *E*/*Z* ratio of 1/1 (Scheme 2). After separation of *E*- and *Z*-form of **15** by column chromatography, demethylation of 3,4-dimethoxy groups of the trans form of compound **15a** by boron tribromide in CH_2Cl_2 cleanly afforded trans



Scheme 2. Reagents and conditions: (a) DIBAL-H, −78°C, CH_2Cl_2, N_2, 91%; (b) PCC, 0 °C, CH_2Cl_2, N_2, 90%; (c) $(CH_3O)_2P(O)CH_2CO_2CH_3$, $NaOCH_3$, MeOH, 91%; (d) NaI, N_2, acetone, reflux, 90%; (e) TPP, $NaOCH_3$, MeOH, 91%; (f) *n*-BuLi, THF, 0 °C, 12 h, 62%; (g) BBr_3, CH_2Cl_2, 0 °C, 28%.



Scheme 3. Reagents and conditions: (a) CH_2N_2, Et_2O, 0 °C, 40%; (b) 1 N-LiOH, THF/H_2O (1/1), rt, 90%; (c) HOBt, EDC, amine, CH_2Cl_2, rt; (d) BBr_3, CH_2Cl_2, 0 °C.



Scheme 4. Reagents and conditions: (a) BBr_3, CH_2Cl_2, 0 °C, 2 h.

stilbene derivative **15b**[8,13] [28% yield, a yellow solid: $R_f = 0.47$ (hexane/ethyl acetate, 1/1, v/v); ^1H NMR (500 MHz, CD_3OD) δ 7.72 (d, 1H, $J = 16.00$ Hz, trans, vinyl H), δ 7.60–7.55 (m, 4H, aromatic H), δ 7.20 (d, $J = 16.00$, 1H, trans, vinyl H), δ 7.07 (s, 1H, aromatic H), δ 6.98 (d, 1H, $J = 16.50$, vinyl H), δ 6.94 (d, 1H, $J = 9.00$, aromatic H), δ 6.80 (d, 1H, $J = 8.50$, aromatic H), δ 6.70 (d, 1H, $J = 8.50$, aromatic H), δ 6.55 (d, 1H, $J = 16.50$ trans vinyl H), δ 3.82 (s, 3H, $-OCH_3$). IR υ_{max} 3413, 3020, 1634, 1439, 1251 cm^{-1}. HRMS (MALDI-TOF): *m/z* 297.0743 ($[M+H]^+$, obsd), 296.1049 (calcd for $C_{18}H_{16}O_4$).

Similarly, demethylation of **15c** (*Z*-form) provided **28a**[14] (Fig. 2) in 54% yield. Reduction and following oxidation of the ester group of compound (trans form) **6** and its cis-form, with subsequent amide coupling and deprotection afforded, **11b** (60%) as a green solid. ^1H NMR (250 MHz, CD_3OD); δ 7.93–7.89 (d, 2H, $J = 8.39$Hz, aromatic H), δ 7.71–7.60 (m, 4H, aromatic H), δ 7.41-7.33 (m, 3H, aromatic H), δ 7.20–7.17(m, 2H, aromatic H, vinyl CH), δ 7.07–6.91 (m, 2H, aromatic H, vinyl CH), δ 6.78–6.75 (d, 1H, $J = 8.2$Hz, aromatic H). IR υ_{max} 3442, 1646, 1600, 1525, 1441 cm^{-1}. HRMS (MALDI-TOF): *m/z* 354.1351 ($[M+Na]^+$, obsd), 331.1208 (calcd for $C_{21}H_{17}NO_3$) and **27a** (Fig. 2) in 20% yields.

For preparation of dihydroxycinnamic acid derivatives, protection of 3,4-dihydroxycinnamic acid, **16**, and selective hydrolysis of **17** and subsequent amide formation of **18** provided compounds **19a** in 99% yield and **19b** in 72% yield as the known procedure,[10] respectively (Scheme 3). Final demethylation[15] of **19a, 19b** by the boron tribromide in CH_2Cl_2 cleanly afforded stilbene derivatives **20a** and **20b** (26% yields, *E*-form: δ 6.55 (d, 1H, $J = 15.6$ Hz, trans vinyl CH), and δ 7.52 (d, 1H, $J = 15.6$ Hz, trans, vinyl CH)).

Similarly, demethylation of nitro stilbenes **29a–c** by the boron tribromide[15] in CH_2Cl_2 cleanly afforded stilbene derivatives **30a–c** in 79–89% yields (Scheme 4). **30c**: $R_f = 0.13$ (hexane/ethyl acetate, 2/1, v/v), *E*-form δ 7.65 (d, 1H, $J = 16.2$ Hz, trans, vinyl CH), δ 7.76 (d, 1H, $J = 16.2$ Hz, trans vinyl CH). IR υ_{max} 3437, 1633, 1529, 1346. HRMS (MALDI-TOF): *m/z* 303.0775 ($[M+H]^+$, obsd), 302.0539 (calcd for $C_{14}H_{10}N_2O_6$).

To examine the structure-activity relationships of dihydroxy stilbene compounds on PTP1B, a variety of

Table 1. Inhibition against PTP1B of stilbene derivatives[a]

Compound	IC_{50} (μM)
7	25.6
7a	—[c]
9	260
11a	101
11b	27.2
15a	—[c]
15b	14.9
16	—[c]
20a	—[c]
20b	—[c]
26a	—[c]
26b	137.5
27a	—[c]
27b	35.4
28a	—[c]
30a	—[c]
30b	190
30c	168
31 (*cis*-stilbene)[17]	—[c]
32 (curcumin)[18]	—[c]
Molybdate[b]	21
RK-682[b,19]	45
DMSO	—[c]

[a] IC_{50} values are means and SD of three experiments.
[b] Positive control($Na_2MoO_4{\cdot}2H_2O$).
[c] Inactive.

trans-stilbene compounds with two hydroxy groups on phenyl rings of the parent stilbene skeleton were synthesized and the inhibitory activity on PTP1B was determined.[16] All *E*- and *Z*-form were separated by using column silica gel and bioassay was performed as a single regioisomer form. Using the colorimetric assay based on the rate of formation of *p*-nitrophenolate ion indicator, PTP1B activity was assessed in the presence and absence of the indicated compounds. IC_{50} values were calculated based on the method of Burke et al.[16] All measurements are means and SD of n observations, with a typical variability of 10% among observations. As a positive control, the effects of the known inhibitors, molybdate and RK-682, were also evaluated, and the IC_{50} values were found to fall within literature values. As shown in Table 1, 3,4-dimethoxy trans-stilbenes (**7a**, **15a**, and **26a**) with protection of 3,4-dihydroxy groups had no inhibitory effects. This observation supports the idea, predicted by molecular modeling (Fig. 1), that protection with methyl group of the 3,4-dihydroxy groups on phenyl rings inhibits the formation of the stable radical necessary for inhibition of PTP1B. 3,4-Dihydroxy stilbenes (**7** and **15b**) with a methoxy carbonyl on the second phenyl ring showed the best and nearly complete inhibition of PTP1B and had more potency than either 3,4-dihydroxy trans-stilbene (**11a**) with 4′-aldehyde group or 3,4-dihydroxy trans-stilbene (**9**) with 4′-alcohol group. Extension of the conjugated system of **7** to **15b** further increased potency of PTP1B inhibition. The nitro stilbene compounds (**30a**) with only one hydroxy group at C-3 position on the phenyl ring of the parent stilbene skeleton had no inhibitory effects. However, the inhibitory potency was markedly enhanced by introducing another hydroxy group at C-2 or C-4 positions to phenyl ring (**30b** and **30c**), of the parent stilbene skeleton, thus indicating the importance of a hydroxy function at the C-2 or C-4 positions. Furthermore, addition of two phenolic hydroxy groups of cis-stilbene (**31**) to 3,4-dihydroxystilbene (**26b**) markedly increased the inhibitory activity. The inhibition by **30b** and **30c** was of nearly the same magnitude, with perhaps the presence of the hydroxy group at position C-4 having an effect on potency. However, 3,4-dihydroxycinnamic acid **16** and its amide derivatives, **20a** and **20b**, show no inhibition, suggesting necessity of the second phenyl ring connected through the double bond for PTP1B inhibition.

On the basis of these results, it appeared that the 3,4-dihydroxy motif at the parent phenyl ring and 2′,4′-electron withdrawing groups such as ester (**7**, **15b**), aldehyde (**11a**), nitro groups (**30b** and **30c**) and amides (**11b**, **27b**)[20] of trans stilbene analogs enhance inhibitory activity of PTP1B. It is noteworthy that trans derivatives (**15b** and **27b**) are more relatively potent than cis derivatives (**28a** and **27a**) probably due to binding suitability with PTP1B. Especially, the amine derivatives (**28b**) for future testing are expected to have higher antioxidant effect than the ester derivatives because the lone pair of electrons located at the nitrogen atom of the amide group can be conjugated with π-bond system better than that of the oxygen atom of the ester group.[20]

Evaluation of antioxidant activity of stilbene derivatives **7a**, **9**, **15a**, **15b**, **30b** with xanthine oxidase assay revealed that there is no direct correlation of radical scavenging effect with PTP1B inhibition.

In conclusion, we designed, synthesized, and developed novel stilbene derivatives as potential protein tyrosine phosphatase 1B inhibitors. Among them, **7**, **11b**, **15b**, and **27b** showed strong inhibitory activities with IC_{50} values ranging from 14.95 to 35.4 μM against the PTP1B enzyme. Particularly, compound **7** shows inhibitory activity comparable to that of molybdate, while **15b** shows a 3-fold lower IC_{50} than the clinically studied RK682. Compound **15b** deserves further evaluation as a possible type-2 antidiabetic drug candidate based on the mechanism of PTP1B inhibition. This result suggests that introduction of electron withdrawing groups (**7**), amide groups (**11b**, **27b**), or extension of the conjugation (**15b**) into the stilbene molecule may stabilize the generated radicals.

Acknowledgments

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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.2007.06.016.

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