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# Novel thiazolidinedione derivatives with anti-obesity effects: Dual action as PTP1B inhibitors and PPAR-γ activators

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ABSTRACT

Benzylidene-2,4-thiazolidinedione derivatives with substitutions at both the *ortho* and *para*-positions of the phenyl group were synthesized as PTP1B inhibitors with $IC_{50}$ values in a low micromolar range. Compound **18l**, the lowest, bore an $IC_{50}$ of 1.3 μM. In a peroxisome proliferator-activated receptor-γ (PPAR-γ) promoter reporter gene assay, **18l** was found to activate the transcription of the reporter gene with potencies comparable to those of troglitazone, rosiglitazone, and pioglitazone. In vivo efficacy of **18l** as an anti-obesity and hypoglycemic agent was evaluated in a mouse model system. Compound **18l** significantly suppressed weight gain and significantly improved blood parameters such as TG, total cholesterol and NEFA without overt toxic effects.



2,4-Thiazolidinediones (TZDs) have long been considered anti-hyperglycemic compounds by ameliorating insulin resistance and thereby normalizing elevated blood glucose levels.[1–4] Some members of this group, such as ciglitazone, troglatizone, rosiglitazone and pioglitazone (Fig. 1), are known to have insulin-sensitizing effects and act as PPAR-γ agonists.[5] Some of these compounds have been marketed for the treatment of type 2 diabetes mellitus (T2DM). Ciglitazone was not used as a medication but was developed as an anti-diabetic agent earlier than the marketed TZDs.[6] Troglitazone, the first TZD marketed as an anti-diabetic agent, was withdrawn due to liver toxicity in several patients.[7] Rosiglitazone and pioglitazone, the two drugs currently on the market in the TZD class, are potent ligands of PPAR-γ and show efficient insulin sensitization in type 2 diabetes patients.[8]

Recently, several studies have demonstrated TZD-like scaffolds bind enzymes other than PPAR. Among those, azolidinediones (e.g., **A**), a modified thiazolidinedione (e.g., **B**), and isothiazolidinones (e.g., **C**) have been reported to inhibit protein tyrosine phosphatase 1B (PTP1B).[9–11] PTP1B is a cytosolic protein tyrosine phosphatase expressed in various cells, including liver, muscle and fat.[12] This enzyme is known to be an important negative regulator of insulin and leptin signaling cascades.[13–15] Therefore, PTP1B was proposed as a target for the treatment of diabetes, obesity and other related metabolic diseases.[16] Over the last decade, numerous different PTP1B inhibitors have been reported.[17–19] Among them, only two compounds, ertiprotafib and trodusquemine, have progressed to clinical trials. Ertiprotafib, however, dropped in phase II due either to side effects or a low rate of in vivo efficacy.[20] Trodusquemine is currently in a phase I clinical challenge with promising preclinical results in diet-induced obese (DIO) rats.[21] A first-in-class drug has yet to be launched, nevertheless, extensive research is under way to develop a potential blockbuster drug.

Previously reported compounds containing TZD or related scaffolds can be characterized by a central phenyl ring substituted by a TZD-like group and a major substituent in a *para*-orientation, or less commonly, *meta*- or *ortho*-orientations. In a recent study, we synthesized TZD derivatives with the major substituent at the *ortho*-position of the TZD group and demonstrated their inhibitory activity against PTP1B.[22] In mouse experiments, the most potent

*Abbreviations:* TZD, thiazolidinedione; T2DM, type 2 diabetes mellitus; PTP1B, protein tyrosine phosphatase 1B; DIO, diet-induced obese; MOM, methoxymethyl; *p*NPP, *p*-nitrophenyl phosphate; HFD, high fat diet; LFD, low fat diet; TG, triglycerides; NEFA, non-esterified fatty acids; FFA, free fatty acids; TLC, thin-layer chromatography.

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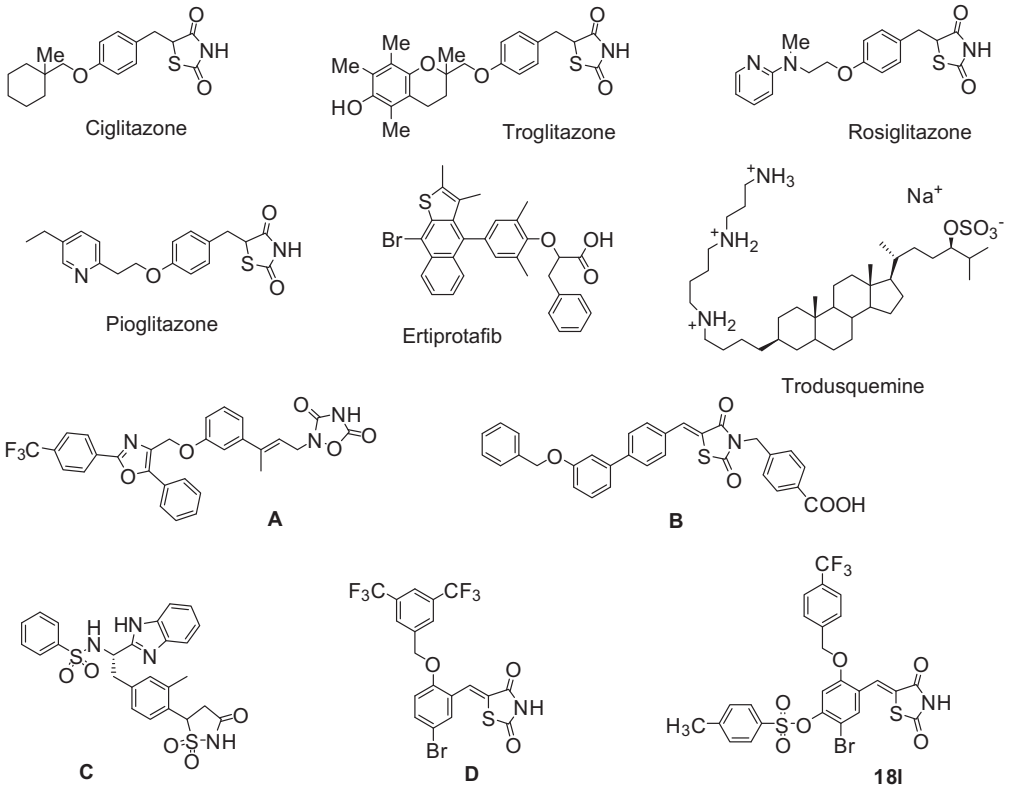



**Figure 1.** Thiazolidinedione derivatives and related compounds reported as PPAR-γ activators or PTP1B inhibitors.

inhibitor, **D**, suppressed weight gain and improved lipid-related blood parameters. Significant improvement of glucose tolerance was also observed. Compound **D** also promoted the effect of PPAR-γ as a transcription activator in a cell-based reporter gene assay.

In this study, we extended the previous study to TZD derivatives containing an additional substituent in a *para*-orientation on the central phenyl ring anticipating extra effects by the *para*-substituent. Actually most of the precedent TZD series of PPAR-γ agonists contain a major substituent in a *para*-orientation. The doubly substituted TZD derivatives were synthesized and tested for in vitro efficacy against PTP1B. With the promising in vitro inhibitory potency of these new classes of TZDs, the most potent PTP1B inhibitor, **18l**, was tested for in vivo anti-hyperglycemic and anti-obesity effects.

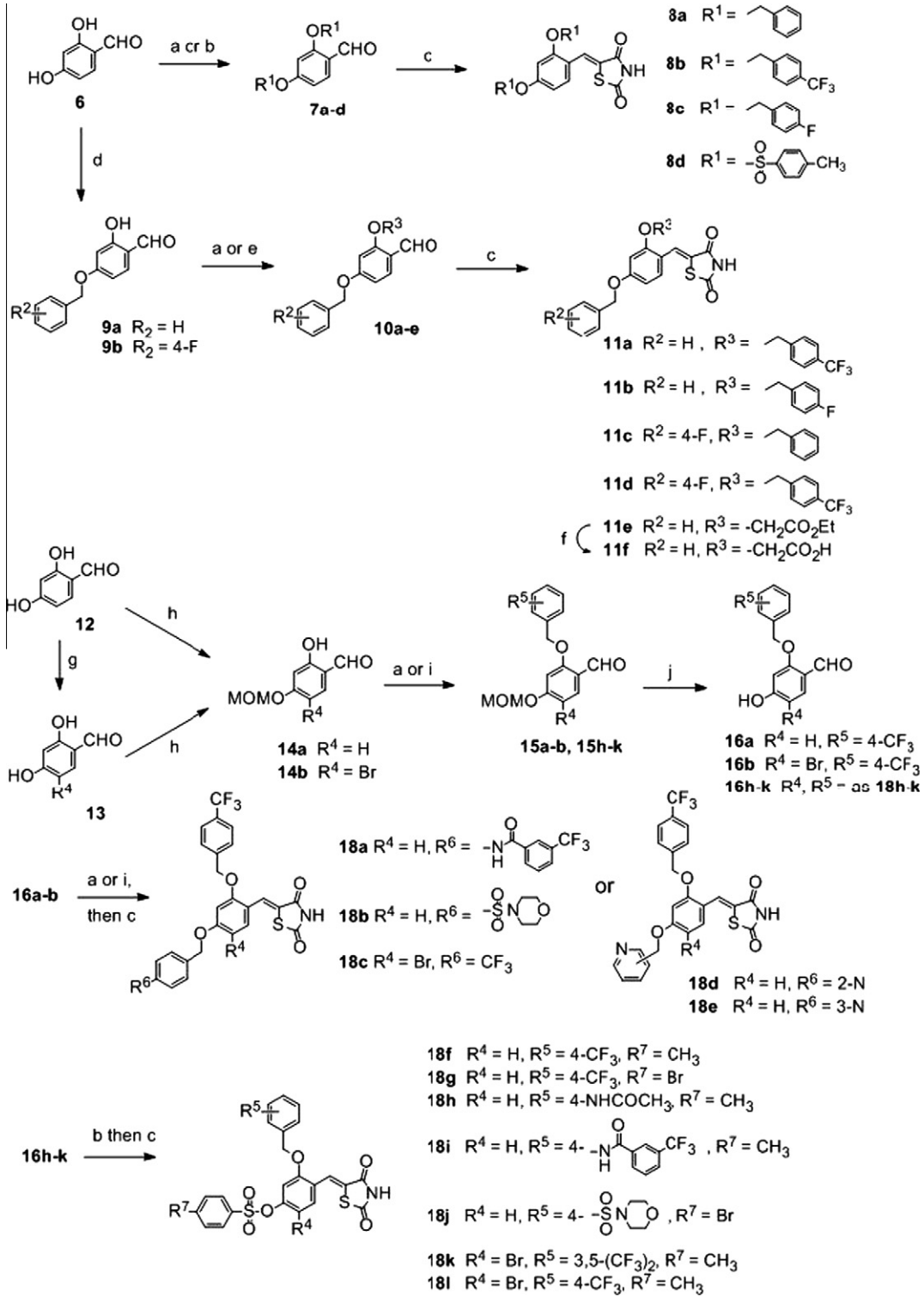
Benzylidene-2,4-thiazolidinedione derivatives with substitutions on the phenyl ring at *ortho* and *para*-positions of the TZD group were synthesized as depicted in Scheme 1. In every case, the TZD group was introduced in the last step of the synthesis by condensation of the benzaldehyde derivatives and TZD in the presence of piperidine as a base.[23] Compounds **8a–8d** were prepared in simple two steps starting from commercially available 2,4-dihydroxybenzaldehyde **6**. To prepare **10a–10e** as precursors for the synthesis of **11a–11f**, *ortho*- and *para*-substituents were introduced independently through selective benzylation[24] at the 4-hydroxyl group of **6**, followed by alkylation at the 2-hydroxyl group with appropriate benzyl bromides or ethyl bromoacetate.

For other TZD derivatives, the 4-hydroxyl group of **6** was selectively protected by the methoxymethyl (MOM) group before the introduction of appropriately substituted benzyl groups at the 2-OH of the benzaldehyde.[25] The MOM protecting group was then removed and the resulting free 4-OH group of the benzaldehyde functionalized with structurally diverse chemicals.

The synthesized TZD derivatives were evaluated for their inhibitory activity against PTP1B using *p*-nitrophenyl phosphate (*p*NPP) as the substrate. The assay results are summarized in Table 1. The initial set of compounds, **8a–8c** and **11a–11d**, were substituted at both the *ortho*- and *para*-positions of the central phenyl group with either identical benzyloxy groups in **8a–8c** or different benzyloxy groups **11a–11d**. These compounds exhibited $IC_{50}$ values from 4 to 10 μM. Even though the $IC_{50}$ values were in a narrow range, a $CF_3PhCH_2O$– substituent at the *ortho*-position resulted in the lowest $IC_{50}$ value within the group. Therefore, the *ortho*-substituent was fixed at $CF_3PhCH_2O$- for the next set of compounds (**18a–18g, 18l**).

Among the compounds with benzyloxy-based substituents at the *para*-position (**18a–18b, 18d–18e**), none of the compounds showed $IC_{50}$ values lower than parent compounds **11a** or **11d**. Among the compounds with benzenesulfoxy substituents at the *para*-position (**18f–18g**), **18f** exhibited improved inhibitory potency ($IC_{50}$ = 2.3 μM) against PTP1B. With the *para*-substituent fixed at the toluenesulfoxy group, the $CF_3$-group of the *ortho*- substituent was further varied in **18h, 18i** and **18j**. All the changes of the *ortho*-substituents reduced inhibitory potency, implying that the $CF_3PhCH_2O$ might be the choice for the *ortho*-position.

To examine the possibility of further substitution on the central benzene ring, Br was introduced at C-5 of the central benzene ring of **8b**. The resulting compound (**18c**) was 6.4-fold more potent compared to the parent compound **8b**. When Br was introduced at the equivalent position of **18f**, the corresponding compound (**18l**) showed an improved inhibitory potency with $IC_{50}$ value of 1.3 μM, 1.8-fold lower than **18f**. As the most potent compound in this study, **18l** was proven to be 3.9-fold more potent than compound **D**, previously reported by us as the most potent PTP1B inhibitor among the *ortho*-monosubstituted TZD compounds. It is interesting to note that there is inconsistency in the improvements of potency due to the brominations from **8b** to **18c** and from **18f** to **18l** (Table 1). The latter two compounds differ from the former ones in having the sulfonic ester moiety between the central and one of the terminal phenyl groups. This sulfonic ester group seems




**Scheme 1.** Reagents and conditions: (a) $RPhCH_2Cl$ or $RPhCH_2Br$, $K_2CO_3$, DMF or acetone, reflux, 1–3 h; (b) $RPhSO_2Cl$, DIPEA, DMF, 0 °C to rt, 3 h; (c) 2,4-TZD, EtOH, piperidine, reflux, overnight; (d) $R_2PhCH_2Cl$, KI, $NaHCO_3$, $CH_3CN$, rt to 90 °C, 24 h; (e) $BrCH_2COOEt$, $K_2CO_3$, DMF, 90 °C, 3 h; (f) NaOH, MeOH, $H_2O$, 70 °C, 1 h; (g) $Br_2$, $CH_2Cl_2$, 0 °C to rt, 3 h; (h) MOMCl, $K_2CO_3$, acetone, 0 °C to rt, 6 h; (i) $RPhCH_2Br$, $K_2CO_3$, DMF, rt, 1–3 h; (j) THF/HCl, 50 °C, 2 h.

to play a predominant role in the inhibition. It is also worth to note that **18k** showed 2.5-fold increased potency compared with the compound **D** by the presence of an additional toluenesulfoxy group at the *para*-position.

The inhibitory activity of compound **18l** was evaluated against a broad range of PTPs including TC-PTP, membrane proximal catalytic domain LAR (LAR-D1), the catalytic domain of SHP-1 (SHP-1cat) and two microbial PTPs, YOP and YPTP1 (Table 2). Compound **18l** displayed $\geqslant$10-fold selectivity over LAR-D1, TC-PTP and YPTP1, and a few-fold selectivity over SHPTP-1cat and YOP. The exceptionally large selectivity against LAR-D1 is probably due to the differences in key determinants in substrate recognition between PTP1B and LAR-D1. In spite of the similarities in the phosphotyrosine binding pocket, significant variations were observed

**Table 1**
Inhibitory effect of TZD derivatives against PTP1B

| Compound | $IC_{50}$[a] (μM) |
|---|---|
| **8a** | 10 ± 0.7 |
| **8b** | 9.0 ± 1.0 |
| **8c** | 8.0 ± 1.0 |
| **8d** | 16 ± 1 |
| **11a** | 4.0 ± 0.4 |
| **11b** | 9.0 ± 0.6 |
| **11c** | 9.0 ± 1.0 |
| **11d** | 4.0 ± 0.5 |
| **11f** | 136 ± 27 |
| **18a** | 6.0 ± 1.6 |
| **18b** | 19 ± 1 |
| **18d** | 12 ± 1 |
| **18e** | 12 ± 1 |
| **18f** | 2.3 ± 0.2 |
| **18g** | 6.0 ± 0.5 |
| **18h** | 33 ± 2 |
| **18i** | 11 ± 3 |
| **18j** | 14 ± 1 |
| **18c** | 1.4 ± 0.2 |
| **18k** | 2.0 ± 0.1 |
| **18l** | 1.3 ± 0.2 |
| D | 5.0 ± 0.1[b] |
| Ertiprotafib | 1.4 ± 0.1[c] |

[a] Values are the means ± standard deviations of two or more experiments.
[b] Data reproduced from our previous publication.[22]
[c] Data reproduced from our previous publication.[28]

in the amino acid residues in the proximity of the active sites of these enzymes.[26,27]

Kinetic study showed a mixed type of inhibition pattern by compound **18l** in contrast to competitive inhibition by compound **D** (data not shown). Compound **18l** might possibly favor binding to the second phosphotyrosine binding site present near the active site of PTP1B. However, it awaits further study to explain these apparently contradictory results and to elucidate the binding site of **18l** on PTP1B.

In order to gain insight into the biological function of **18l** and **D**, we examined the effect of **18l** and **D** on trans-activating activity of PPAR-γ. In this assay, activated PPAR binds peroxisome proliferator hormone response element (PPRE) located in the promoter of a luciferase gene, thus activates the transcription of the reporter gene. The activating effect of **18l** and **D** was compared with well-defined PPAR-γ agonists, troglitazone, rosiglitazone and pioglitazone. HepG2 cells were transfected with a PPRE-driven luciferase reporter construct or the basic luciferase reporter as a negative control, which lacks PPRE site. Six hours post transfection, troglitazone, rosiglitazone, pioglitazone, **18l** and **D** were added to the culture medium and cells were lysed 24 h later to measure the luciferase activity and β-galactosidase activity as a transfection control.

As shown in Figure 2, the compounds **18l** and **D** were found to activate the transcription of the PPRE-driven luciferase with potencies comparable to those of glitazone series of compounds (troglitazone, rosiglitazone, and pioglitazone) indicating that **18l** and **D** acted as PPAR agonists. The maximal activation doses of **18l** and **D** were 1.5 and 4.0 μM, respectively and $EC_{50}$s were 0.34 and 0.87 μM, respectively (data not shown). Since **18l** and **D** are derivatives of TZD, we expect that they regulate PPAR-γ activity rather than PPAR-α or PPAR-ß/δ.

The anti-obesity and anti-hyperglycemic effects of **18l**, which showed the highest potency against PTP1B in in vitro assays was tested in high fat diet (HFD)-induced diabetic mice (C57BL/6J Jms Slc male).[28] Twenty-four mice (5 wk old after acclimatization for 1 wk) were divided into two groups: 16 mice fed HFD ad libitum for further 8 wk to develop the HFD-induced diabetes/obesity; the remaining 8 provided with low fat diet (LFD) to serve as a lean control group. After 8 wk, the HFD-fed mice were divided into two groups; one group continued on the HFD as an obesity/diabetic control group whereas the other group was provided with HFD + **18l** for a further 4 wk. Compound **18l** was administered as a mixture with the food (1.0 g of **18l**/kg of diet). The daily uptake of **18l** was approximated as 2.6 mg/day/mouse, equivalent to 78 mg/day/kg of mouse weight. For the lean control group, LFD was fed throughout the test period.

Glucose metabolism in the mice was examined after 4 wk of a drug-feeding period. Fasting glucose levels were checked after fasting 6 h, starting from the beginning of the light cycle. The fasting glucose level of the **18l**-fed group was not significantly lower than the DIO control group (data not shown). Glucose tolerance was checked right after the measurement of the fasting glucose level. Upon loading extra glucose (1.0 g/kg of body weight) by intraperitoneal injection, the **18l**-fed groups exhibited tendency to normalize blood glucose concentration faster than the HFD control group, although it was not statistically significant ($p = 0.37$ at 60 min, $p = 0.22$ at 90 min, data not shown).

The LFD-fed lean control mice gained less body weight compared to the HFD-fed mice and the two groups were clearly different in external appearance (data not shown). Significant difference in body weight gain between the HFD control group and **18l**-treated group was observed during the 4 wk test period (Fig. 3). In addition, there was no significant difference in body weight gain between the LFD control group and **18l**-treated group during the test period (Fig. 3).

There was no significant difference in cumulative food intake between the HFD control and **18l-**treated mice groups during the

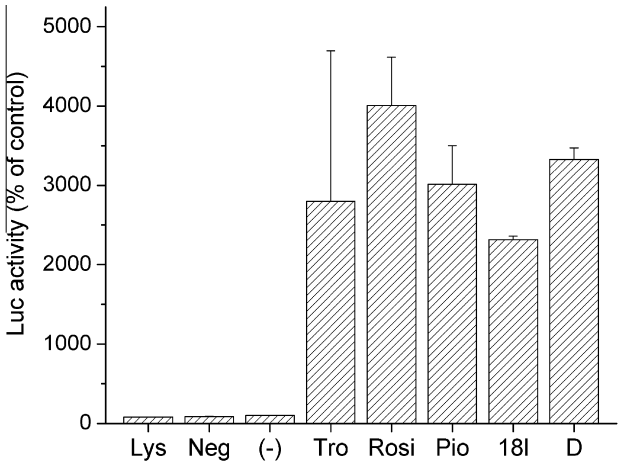



**Figure 2.** Effect of compound **181** on PPAR-γ transcriptional activities. HepG2 cells were transfected with a PPAR-reporter gene (PPRE-driven luciferase reporter construct) and CMV-βGal constructs and then incubated for 24 h with or without 1 μM of test compounds including troglitazone (Tro), rosiglitazone (Rosi), pioglitazone (Pio), **18l**, and **D**. After stimulation, cells were harvested and luciferase activity was measured using luminometer. The luciferase activity was determined by normalizing transfection efficiency using β-galactosidase activity. Data are representative of two independent experiments. Error bar indicates SEM.

**Table 2**
Inhibition of PTP1B and other PTPs by the compound **18l**[a]

| Compound | $IC_{50}$[b] (μM) | | | | | |
|---|---|---|---|---|---|---|
| | PTP1B | TC-PTP | SHP-1cat | LAR-D1 | YOP | YPTP1 |
| **18l** | 1.3 ± 0.2 | 19 ± 2 | 3.0 ± 0.1 | >100 | 3.9 ± 0.1 | 12 ± 0 |

[a] Enzymes were prepared or obtained as described in supplementary materials.
[b] Values are the means ± standard deviations of two or more experiments.

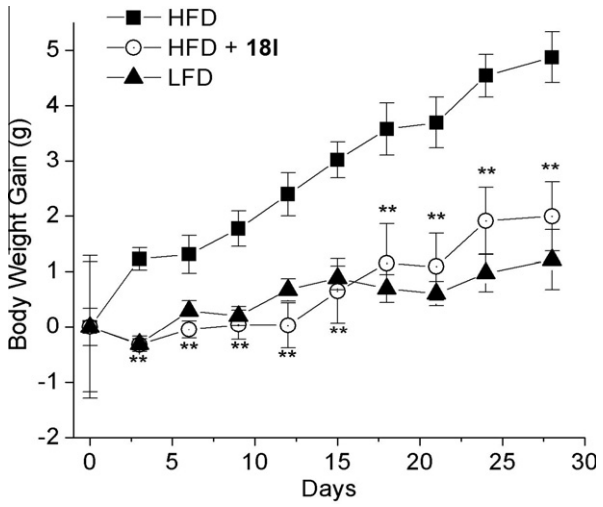



**Figure 3.** Body weight gain during 4 wk of **18l** treatment: Five-wk-old mice were fed HFD for 8 wk, and then divided into two groups (8 mice/group). The 2 groups were fed HFD (■) or HFD + **18l** (○) for four weeks. Compound **18l** (0.1% w/w) in HFD were mixed well and provided with food. The lean control group (▲) was fed LFD throughout the entire 12 wk period. Each point represents the mean value ± SEM; $n$ = 8/group. Significance of the difference between HFD group and **18l**-fed group was calculated by One-way ANOVA, where ** represents $p$ <0.05.

4 wk treatment period (data not shown). Feed efficiency and body weight gain per calories consumed were calculated for the HFD control, **18l**-treated and LFD control groups. The test compound-treated group showed significant differences in feed efficiency compared to the HFD control group (Table 3) revealing that control of HFD-induced body weight gain in the **18l**-treated group was due to lower feed efficiency.

The Epididymal and Retroperitoneal fat pad deposits were significantly lower in **18l**-treated mice compared to HFD control (Table 3). No overt toxicity was observed in body organs such as liver, kidney and lungs, with no significant difference in the weight of these organs in the lean control, HFD control and **18l**-treated mice groups ($p$ >0.05, data not shown). This is an important improvement in this series of compounds considering that compound **D** caused dark-brownish spots in livers of mice suggesting toxic effects.

A significantly lower level of total cholesterol, triglyceride (TG) and non-esterified free fatty acids (NEFA) were found in the serum of **18l**-treated mice compared to HFD control when tested after overnight deprivation of the food at the end of the drug-feeding period (Table 4).

The effects of **18l** in mice can be compared with those of compound **D**. Compound **18l** was administered as a mixture with the food and the daily uptake was 2.6 mg/day/mouse or 78 mg/day/kg of mouse weight. According to our previous report, daily uptake of **D** was 4.8 mg/day/mouse or 143 mg/day/kg of mouse weight.[22]

**Table 4**
Effect of **18l** in serum concentration of total cholesterol, TG, and NEFA levels, after 4 wk treatment[a]

| Mice group | Total cholesterol (mg/dL) | Triglyceride (mg/dL) | NEFA (mM) |
|---|---|---|---|
| HFD[b] | 152 ± 6 | 124 ± 16 | 0.71 ± 0.22 |
| HFD + **18l** | 124 ± 8** | 76 ± 8** | 0.20 ± 0.03** |
| HFD + **D**[b] | 125 ± 7** | 78 ± 10** | 0.22 ± 0.02** |
| LFD[b] | 107 ± 5 | 65 ± 5 | 0.18 ± 0.01 |

[a] Data presented are the mean values ± SEM; $n$ = 8/group. Significance of the difference between HFD group and **18l**-fed group was calculated by One-way ANOVA, where ** represents $p$ <0.05.
[b] Data for **D**-fed group and control groups reproduced from our previous publication.[22]

Daily uptake of **18l** was approximately half of **D** in weight and 65% in number of moles. Under these conditions, compounds **18l** and **D** revealed almost equivalent effects on mouse body weight and lipid-related blood parameters, indicating that **18l** was superior to **D** in body weight control. On the other hand, there was no evidence that **18l** improved glucose tolerance more effectively than **D**. Upon loading extra glucose, the **18l**-fed groups exhibited tendency to normalize blood glucose concentration faster than the HFD control group ($p$ = 0.37 at 60 min, $p$ = 0.22 at 90 min). Compound **D** significantly improved glucose tolerance in mice.

Because **18l** could act in vivo as a PTP1B inhibitor or a PPAR-γ activator or both, the observations in this study were compared with those after the PTP1B-disruption in mice and after the treatment with the glitazone series of drugs. Recently, two independent laboratories generated PTP1B gene-disrupted mice.[29,30] On feeding HFD, PTP1B$^{-/-}$ male mice gained less weight compared to wild-type male littermates in both laboratories. PTP1B$^{-/-}$ male mice, but not PTP1B$^{+/-}$ mice, exhibited improved glucose tolerance. However, no difference in the serum concentrations of free fatty acids (FFA) was observed between PTP1B$^{-/-}$ and wild-type mice. Treatment with rosiglitazone or poiglitazone improved insulin sensitivity and glucose tolerance in type 2 diabetic patients. Both of these drugs reduced plasma FFA but only pioglitazone is known to lower TG. Aside from these beneficial effects, the glitazone series of drugs are known to cause weight gain. In this study, the DIO mice treated with **18l** were resistant to weight gain, which was in agreement with the PTP1B depletion in mice, but not with the glitazone treatment. The **18l**-feeding showed a tendency to improve glucose tolerance, but not with statistical significance. Reduced serum FFA levels in **18l**-treated mice were consistent with the glitazone treatment, but not with the PTP1B$^{-/-}$ depletion. Lower TG levels in the serum of **18l**-treated mice were partially consistent with the results of glitazone treatment, with the data from PTP1B depletion being unavailable. The overall observations on the **18l**-treated mice are partially consistent with the effects of PTP1B depletion or PPAR-γ activation; the reduced weight gain with PTP1B depletion and the lower FFA levels with PPAR-γ activation. Poor anti-hyperglycemic effect of **18l** is consistent only with the observations in PTP1B$^{+/-}$ mice.

**Table 3**
Effect of **18l** on body weight and related parameters[a]

| Mice group | Body weight gain (g) | Feed efficiency (wt gain/kcal × 100) | Epididymal fat (g) | Retroperitoneal fat (g) |
|---|---|---|---|---|
| HFD[b] | 4.88 ± 0.46 | 1.38 ± 0.11 | 1.87 ± 0.08 | 0.69 ± 0.06 |
| HFD + **18l** | 2.00 ± 0.62** | 0.57 ± 0.17** | 1.29 ± 0.20** | 0.43 ± 0.08** |
| HFD + **D**[b] | 2.16 ± 0.29** | 0.68 ± 0.09** | 1.27 ± 0.17** | 0.42 ± 0.07** |
| LFD[b] | 1.22 ± 0.54 | 0.59 ± 0.09 | 0.49 ± 0.04 | 0.11 ± 0.02 |

[a] The obese and lean control groups were fed HFD or LFD, containing 45% and 10% of the calories from fat, respectively, for 12 wk. The test group (HFD + **18l**) was fed a HFD for 8 wk, and then a HFD mixed with **18l** for 4 wk. All values are the mean values ± SEM; $n$ = 8/group. Significance of the difference between the HFD group and **18l**-fed group was calculated by One-way ANOVA, where ** represents $p$ <0.05.
[b] Data for **D**-fed group and control groups reproduced from our previous publication.[22]

In conclusion, Benzylidene-2,4-thiazolidinedione derivatives with dual substitutions on the phenyl ring in *ortho* and *para*-positions of the TZD group inhibited PTP1B in a low micromolar $IC_{50}$ range; the most potent compound (**18l**) showed an $IC_{50}$ value of 1.3 μM. In a cell-based assay, compounds **18l** and **D** were also found to activate the transcription of PPAR-γ at 1.0 μM concentrations with potencies comparable to those of troglitazone, rosiglitazone, and pioglitazone. Compound **18l** was tested in a DIO mouse model system at a dose level approximately half of **D** for its efficacy as an anti-obesity and/or anti-diabetic agent. At this dose level, **18l** did not significantly improve either fasting glucose level or glucose tolerance in the DIO/diabetic mice. However, obesity-related effects of **18l** in DIO mice were almost equivalent to twofold higher dose of **D**. Feeding **18l** significantly suppressed diet-induced weight gain and significantly improved blood parameters such as TG, total cholesterol, and NEFA. It is also worth to note that compound **18l** is apparently devoid of toxic effects observed with compound **D**.

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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.2010.08.130.

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