

Full-length article

Rhodanine derivatives as novel peroxisome proliferator-activated receptor γ agonists¹

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Key words

rhodanine derivatives; peroxisome proliferator-activated receptor; structure-activity relationship; adipogenesis

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Abstract

Aim: To characterize the *in vitro* bioactivities of rhodanine derivatives as novel peroxisome proliferator-activated receptor (PPAR) γ modulators, based on a hit (SH00012671) identified during high-throughput screening (HTS) of a diverse synthetic compound library, and to preliminarily elucidate the structure-activity relationship of this class of PPAR γ agonists. **Methods:** Full-length PPAR γ and retinoid X receptor α (RXR α), biotinylated PPAR response element (PPRE), [³H]BRL49653 (rosiglitazone), and streptavidin-coated FlashPlate or microbeads were used to measure the receptor-binding properties of various compounds based on the scintillation proximity assay (SPA) technology. A recombinant PPRE vector was transiently cotransfected with PPAR γ and RXR α plasmids into the African green monkey kidney (CV-1) cells, and the effects of BRL49653 and test compounds on transcription mediated by PPAR γ were determined by examining luciferase (reporter) responses. 3T3-L1 cells were employed to determine whether the compounds facilitated adipogenesis upon PPAR γ activation. **Results:** Of the 16 000 samples screened with the SPA method, only 1 compound (SH00012671) displayed a similar binding affinity ($K_i=186.7$ nmol/L) to PPAR γ as BRL49653, but it was inactive in the cell-based assays. A series of rhodanine derivatives were synthesized based on the core structure of SH00012671 and 8 of them showed agonist activities in both cotransfection and pre-adipocyte differentiation assays. To reduce intrinsic cytotoxicities, the sulphur on the rhodanine was changed to oxygen. This alteration led to a decrease in receptor-binding affinities while modified analogues generally maintained agonist efficacies in the cell-based assays. Of the analogues studied, compound 31 exhibited about 70% the efficacy exerted by BRL49653 in both cotransfection and pre-adipocyte differentiation assays. **Conclusion:** Through minor chemical modifications on the core structure of the initial HTS hit, SH00012671 was transformed to possess both molecular (PPAR γ binding) and cellular (adipogenesis) activities. The rhodanine derivatives reported here may represent a new scaffold in further understanding the molecular mechanism of agonism at PPAR γ .

Introduction

Peroxisome proliferator-activated receptor (PPAR) γ , one of the subtypes of PPARs, is a ligand-dependent transcription factor of the nuclear hormone receptor superfamily^[1]. PPAR γ is mainly present in the adipose tissue, skeletal muscle, and liver^[2]. Two other family members include PPAR α , which is present in the liver, kidney and heart, and the ubiquitously-

expressed PPAR δ ^[3]. Upon ligand binding, PPARs release relevant corepressors and form heterodimers with retinoid X receptors (RXRs)^[4]. The heterodimers bind to peroxisome proliferator response elements (PPREs) and recruit co-activators to initiate the transcription of target genes^[5,6].

Type 2 diabetes mellitus is a heterogeneous disease resulting from a dynamic interaction between defects in insulin secretion and insulin action^[7]. In animal models and

humans affected by this disorder, treatment with thiazolidinediones decreases elevated plasma glucose, triglyceride, and insulin concentrations^[8,9]. Their actions also lead to the stimulation of adipogenesis and the recovery of insulin sensitivity in the target tissues^[9]. The antidiabetic effects of thiazolidinediones are directly mediated through binding to PPAR γ , thereby resulting in an active conformation of the receptor^[10].

While the clinical benefits of PPAR γ agonists in treating type 2 diabetes have been clearly demonstrated, the current generation of glitazones is associated with undesired side-effects, such as weight gain and edema^[11]. Thus, there has been significant interest in the design of novel PPAR γ -modulating drugs that retain efficacious insulin sensitizing properties while minimizing potential adverse effects, especially for long-term use.

SH00012671 is a core structure discovered in a high-throughput screening campaign directed towards PPAR γ ^[12]. It displayed a relatively higher binding affinity to the receptor, but was almost inactive in cell-based assays. In this paper, we describe the design, synthesis, and biological evaluation of a series of analogues to SH00012671 with the aim of identifying novel PPAR γ agonists.

Materials and methods

Reagents Edetic acid, insulin, and dexamethasone were purchased from Sigma-Aldrich (St Louis, MO, USA). BRL49653 (rosiglitazone) was bought from Cayman Chemical Co (Ann Arbor, MI, USA). [³H]BRL49653 (53 Ci/mmol) was obtained from American Radiolabeled Chemicals (St Louis, MO, USA), FlashPlate and flat-bottom Isoplate were from PerkinElmer (Boston, MA, USA), and the streptavidin-coated microbeads were from Amersham Biosciences UK (Buckinghamshire, England). The plasmids of human nuclear receptors used in this study were from Dr Xu SHEN of Shanghai Institute of Materia Medica, Chinese Academy of Sciences (Shanghai, China) and Dr Sai-juan CHEN of Shanghai Institute of Hematology (Shanghai, China). Full-length PPAR γ and RXR α were produced with a baculovirus expression system using fall armyworm (*Spodoptera frugiperda*) immature ovarian (IPLB-SF-21-AE) cells^[13]. The PPRE reporter vector was purchased from Panomics (Redwood City, CA, USA), the Steady-Glo luciferase assay system was from Promega (Madison, WI, USA), the FuGene 6 transfection reagent was from Roche Diagnostics (Indianapolis, IN, USA), and the triglyceride (TG) detection kit was from Ningbo Asia-Pacific Biotechnology Co (Zhejiang, China).

Chemistry Figure 1 depicts the syntheses of the rho-

danine derivatives designed based on SH00012671. Esterification of aromatic acid 1 by methanol and then hydrazinolysis of the resulting methyl ester provided the substituted benzoyl hydrazine 2. The reaction of 2 with carbon disulphide in ethanol in the presence of potassium hydroxide for 2 h resulted in the formation of potassium β -acyldithiocarbazinate 3, which was used without further purification. According to Tadashi and Masaki^[14] when 3 was added to a solution of chloroacetic acid and saturated sodium carbonate, stirred at room temperature for 30 min, and acidified by aqueous HCl, 3-benzoylamino rhodanine 4 would be separated out and then solidify. However, we found that when acidifying with aqueous HCl, the intermediate (2-benzoyl-thiocarbazyl) mercaptoacetic acid, instead of 3-benzoyl-amino rhodanine 4, was separated out as evidenced by ¹H-NMR (Nuclear magnetic resonance) and ESI (Electrospray ionization). This intermediate was thus refluxed in dioxane for 1 h to give 3-benzoylaminorhodanine 4, which could also be obtained by dissolving 3-amino rhodanine 5 in pyridine with benzoyl chloride. The final compounds 7–19 were obtained through the condensation of 4 with benzaldehyde 6 by refluxing in glacial acetic acid in the presence of sodium acetate.

Next, we changed the substitutions on R₄ or R₅ while R₁ or R₂ was fixed with chloro (Cl), Br (bromo), or H (hydrogen; Figure 1). We used *p*-hydroxy benzaldehyde or *m*-hydroxy benzaldehyde 43 as the raw material. It was alkylated with different halogenated aralkyl 44 of which the chain length was changed from 1 to 3. Compounds 20–37 were obtained through the condensation of 4 with benzaldehyde 45 by refluxing in glacial acetic acid in the presence of sodium acetate. Compounds 38–42 were made by substituting thio on the rhodanine with oxygen, in which the former rhodanine was refluxed with excessive chloroacetic acid in ethanol and water (Figure 1).

Receptor-binding assay Biotinylated PPRE (2 μ L from a stock solution of 10 g/L) was mixed with the assay buffer (10 mL) containing fish sperm DNA (Shanghai Sangon Biotechnology Co, Shanghai, China; 10 μ L from a 10 g/L stock solution) and 4 mg streptavidin-coated microbeads in a conical polypropylene centrifuge tube (Corning, Corning, NY, USA) and incubated overnight at 4 °C. The mixture was centrifuged for 10 min at 1 500 \times g. The supernatant was then removed and washed 3 times with 10 mL of the assay buffer. The reaction solution 10 mL containing 700 μ g human PPAR γ extract protein (70 mg/L), 47 μ g human RXR α extract protein (4.7 mg/L), 10 nmol/L [³H]BRL49653, and various concentrations of BRL49653 or test compounds were distributed to each well of the Isoplate (100 μ L/well) and incubated at 4 °C for 4 h before counting by the MicroBeta counte (PerkinElmer,

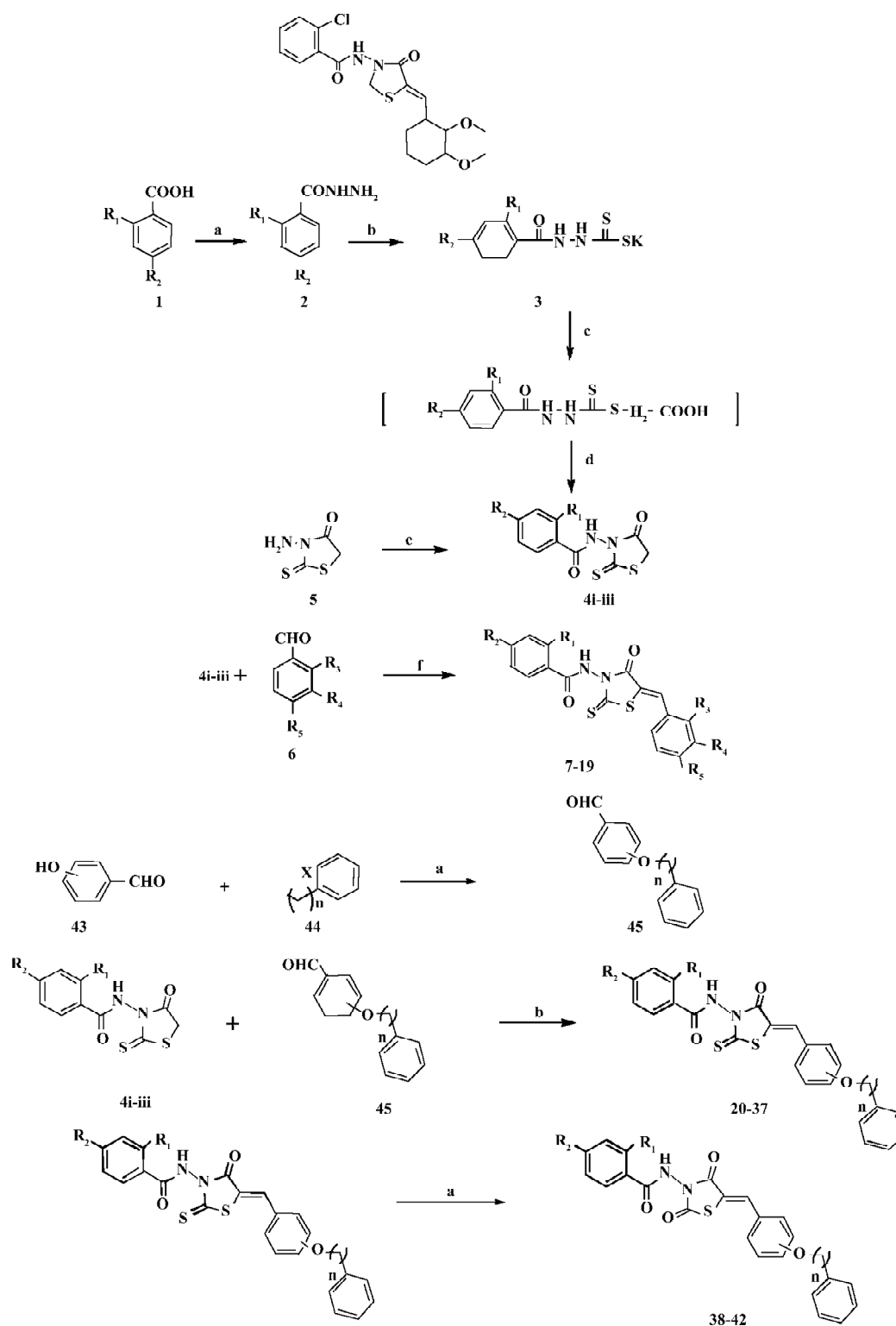


Figure 1. Top, structure of the initial hit SH00012671. Reagents and conditions. a, methanol containing a few drops of concentrated sulfuric acid, reflux for 18 h, and then the addition of 99% hydrazine hydrate followed by further reflux for 10 h; b, potassium hydroxide in ethanol before the addition of carbon disulphide; c, chloroacetic acid/saturated sodium carbonate; d, 1,4-dioxane reflux for 1 h; e, benzoyl chloride in pyridine; f, sodium acetate/acetic acid (HAc) reflux for 1 d; g, potassium carbonate and benzyl triethyl ammonium chloride (TEBA) in ethyl acetate or alcohol, reflux for 1 d; h, sodium acetate/HAc, reflux for 1 d; i, chloroacetic acid/ethanol/water.

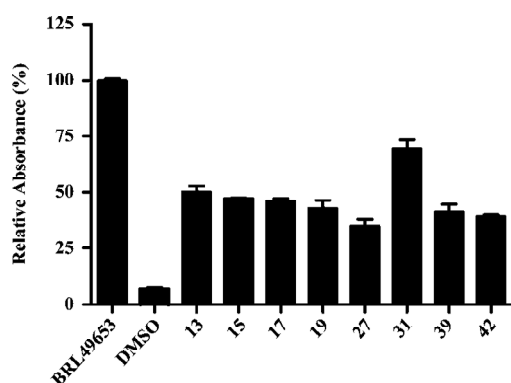


Figure 2. Effects of the rhodanine analogues on pre-adipocyte 3T3-L1 differentiation. The cells were induced to differentiate following stimulation with BRL49653 (0.5 $\mu\text{mol/L}$; control) or the rhodanine analogues (5 $\mu\text{mol/L}$). Triglyceride quantification was performed 7 days afterwards. Data presented are the means \pm SEM.

USA).

Cotransfection assay The CV-1 cells (1×10^6 per well) were inoculated into 6 cm culture plates and incubated in 5% CO_2 /air at 37 $^\circ\text{C}$ for 6 h. Dulbecco's modified Eagle's medium (DMEM; Gibco, Grand Island, NY, USA) containing 10% fetal bovine serum (FBS) and 10 mL/L penicillin-streptomycin (5 000 IU/mL and 5 000 mg/mL, respectively; Gibco, USA) was used as the culture medium. The cells were transiently transfected with PPRE, PPAR γ , and RXR α expression vectors using FuGene 6. Sixteen hours after transfection, the cells were inoculated into 96-well plates, and following 2 h incubation in 5% CO_2 /air at 37 $^\circ\text{C}$, the test compounds were added and the cells were further incubated for 48 h. Luciferase assay substrate (Promega, USA) was introduced to each well and the intensity of emitted luminescence was determined using EnVision (PerkinElmer, USA). PPAR γ transcriptional activity was expressed as the relative luminescence intensity to that of the control. For antagonist effects, the test compounds were added to the cells 30 min before the addition of BRL49653 (1 $\mu\text{mol/L}$) and incubated for 24 h. Luciferase activity was determined as above.

Adipogenesis assay 3T3-L1 cells (20 000 cells/well) were planted onto 24-well culture plates and maintained for 2 d after reaching confluence. The culture medium (DMEM, Gibco, USA) was then changed with the differentiation medium (DMEM containing 10% FBS, 1 $\mu\text{mol/L}$ dexamethasone, and 1 $\mu\text{g/mL}$ insulin). The cells were treated with BRL49653 (0.5 $\mu\text{mol/L}$) or the test compounds (5 $\mu\text{mol/L}$) for 2 d. Following the change of the medium containing the compounds, the cells were cultured for an additional 3 d. The differentiation medium was replaced by the adipocyte growth medium (DMEM supplemented with 10% FBS and 1 $\mu\text{g/mL}$ insulin)

and incubated for a further 2 d. The cells were washed with phosphate-buffered saline and lysed by 0.1% Nonidet P-40 (Sigma-Aldrich, USA). The supernatant of the preparation was examined by the TG detection kit at a wavelength of 500 nm on VERSA^{max} (Molecular Devices, Sunnyvale, CA, USA).

Data analysis Data were analyzed using GraphPad Prism software (GraphPad, San Diego, CA, USA). Non-linear regression analyses were performed to generate dose-response curves. K_i values were calculated from the half maximal inhibitory concentration (IC_{50}) using the equation of Cheng and Prusoff^[15]:

$$K_i = \frac{\text{IC}_{50}}{1 + \frac{[\text{radioligand}]}{K_d}}$$

Results

A group of 16 analogues to SH00012671 were synthesized initially (Figure 1) with various substitutions at R₁-R₅, of which only compounds 13, 15, and 17 showed submicromolar binding affinities to PPAR γ , but not as potent as the initial hit (Table 1). However, they displayed some agonist activities with less than 50% efficacies when compared to rosiglitazone in the cotransfection assay (see Table 4 below). We next synthesized another group of 18 rhodanine derivatives by making small modifications on the R₁ or R₂ (substitution of H with Cl or Br in *meta*- or *para*-site) and with different chain lengths. In this case (Table 2), significant improvement in PPAR γ binding was observed among one-half of these compounds (21, 23, 25, 27, 29, 31, 33, 35, and 37), to the extent that some of them displayed K_i values similar to that of rosiglitazone (21, 27, 31, and 37). In the cotransfection assay, compounds 21, 25, 31, and 37 exhibited similar half maximal effective concentration (EC_{50}) values compared to rosiglitazone with lower efficacies (23%–69%; see Table 4 below). When tested in the antagonist mode, compounds 27, 31, 29, and 37, with good binding affinities and modest transactivation efficacies, were unable to suppress luciferase activity induced by rosiglitazone (1 $\mu\text{mol/L}$).

To reduce intrinsic cytotoxicities associated with this class of molecules, the atom thio on the rhodanine was changed to oxygen (Figure 1). This alteration led to a decrease in receptor-binding affinities (Table 3) while the modified analogues maintained efficacies in the cotransfection assay, with the exception of compound 42 (42 vs 37; Table 4).

Representative compounds from each of the above 3 groups were evaluated in the pre-adipocyte differentiation assay. All of the 8 compounds tested were able to induce adipogenesis in 3T3-L1 cells with compound 31 being the

Table 1. PPAR γ binding affinities of the rhodanine derivatives.

Compound	R ₁	R ₂	R ₃	R ₄	R ₅	hPPAR γ binding K_i (nmol/L)
4i	Cl	H				NA
4ii	H	OH				NA
4iii	H	H				NA
7	Cl	H	OCH ₃	H	OCH ₃	NA
8	H	OH	OCH ₃	H	OCH ₃	NA
9	Cl	H	H	OCH ₃	2-furancarboxy	NA
10	H	OH	H	OCH ₃	2-furancarboxy	NA
11	Cl	H	H	OCH ₂ CH ₃	OCH ₂ CONH ₂	NA
12	H	H	H	OCH ₂ CH ₃	OCH ₂ CONH ₂	NA
13	H	H	H	benzyloxy	OCH ₃	767.2
14	H	OH	H	benzyloxy	OCH ₃	NA
15	Cl	H	H	benzeneethoxy	OCH ₃	321.2
16	H	H	H	benzeneethoxy	OCH ₃	NA
17	Cl	H	H	OCH ₃	benzeneethoxy	689.3
18	H	H	H	OCH ₃	benzeneethoxy	NA
19	H	OH	H	OCH ₃	benzeneethoxy	3789.5
SH00012671						186.7
Rosiglitazone						47.4

The compounds were evaluated for their binding abilities to PPAR γ in competition with [³H]BRL49653. Each value represents the mean of the triplicate determinations obtained in the K_i studies. NA, not active.

Table 2. PPAR γ binding affinities of the rhodanine derivatives.

Compound	R ₁	R ₂	<i>m</i> or <i>p</i>	<i>n</i>	hPPAR γ binding K_i (nmol/L)
20	H	H	<i>p</i>	1	572.1
21	H	H	<i>m</i>	1	58.4
22	H	H	<i>p</i>	2	28800
23	H	H	<i>m</i>	2	118.5
24	H	H	<i>p</i>	3	9071
25	H	H	<i>m</i>	3	85.3
26	Cl	H	<i>p</i>	1	826.2
27	Cl	H	<i>m</i>	1	30
28	Cl	H	<i>p</i>	2	598.7
29	Cl	H	<i>m</i>	2	76
30	Cl	H	<i>p</i>	3	421.7
31	Cl	H	<i>m</i>	3	39
32	H	Br	<i>p</i>	1	NA
33	H	Br	<i>m</i>	1	78.3
34	H	Br	<i>p</i>	2	1432
35	H	Br	<i>m</i>	2	76
36	H	Br	<i>p</i>	3	3261
37	H	Br	<i>m</i>	3	34
Rosiglitazone					47.4

The compounds were evaluated for their binding abilities to PPAR γ in competition with [³H]BRL49653. Each value represents the mean of the triplicate determinations obtained in the K_i studies. NA, not active.

Table 3. PPAR γ binding affinities of the thiazodinediones.

Compound	R ₁	R ₂	<i>m</i> or <i>p</i>	<i>n</i>	hPPAR γ binding K_i (nmol/L)
38	Cl	H	<i>p</i>	3	885.1
39	Cl	H	<i>m</i>	3	123.6
40	Cl	H	<i>m</i>	2	106.7
41	Cl	H	<i>m</i>	1	137.5
42	H	Br	<i>m</i>	3	155.2
Rosiglitazone					47.4

The compounds were evaluated for their binding abilities to PPAR γ in competition with [³H]BRL49653. Each value represents the mean of the triplicate determinations obtained in the K_i studies.

best inducer relative to BRL49653, consistent with its performance in both the PPAR γ -binding and cotransfection assays (Figure 2; Tables 2, 4).

Discussion

In a previous study^[12], we reported the discovery of 12 hit compounds with selective PPAR γ binding properties, of which 2 belong to the thiazodinedione class, including SH00012671 with a relatively lower IC₅₀ value (0.2 μ mol/L).

Table 4. Activity of compounds in cell-based co-transfection assay.

Compound	hPPAR γ agonist		Compound	hPPAR γ agonist	
	EC ₅₀ (μ mol/L)	Eff. (%)		EC ₅₀ (μ mol/L)	Eff. (%)
13	27.0 \pm 1.5	36.5 \pm 3.1	33	>100	25.3 \pm 1.5
15	24.5 \pm 4.5	53.4 \pm 10	37	0.9 \pm 0.1	22.9 \pm 7.2
17	11.7 \pm 3.8	43.9 \pm 4.5	38	26.5 \pm 7.3	14.4 \pm 2.8
19	1.7 \pm 0.1	17.3 \pm 3.1	39	0.8 \pm 0.1	49.0 \pm 4.8
21	1.1 \pm 0.1	23.0 \pm 2.5	40	2.9 \pm 1.7	36.1 \pm 0.7
23	>100	15.8 \pm 1.1	41	2.4 \pm 1.4	18.1 \pm 6.4
25	0.8 \pm 0.5	30.3 \pm 1.1	42	4.2 \pm 1.1	49.0 \pm 1.5
27	2.4 \pm 0.4	28.5 \pm 6.8	SH00012671	2.1 \pm 0.8	11.0 \pm 4.0
29	2.2 \pm 0.4	38.6 \pm 6.6	Rosiglitazone	0.7 \pm 0.1	100
31	1.1 \pm 0.6	68.8 \pm 2.3			

The agonist activities of the compounds were assessed in the CV-1 cells co-transfected with PPAR γ , RXR α and PPRE-driven luciferase genes. Values shown represent means \pm SEM obtained from at least two independent experiments. Eff., efficacy using rosiglitazone as control (100%).

When tested for its effects on cells, it acted either as a poor activator in the cotransfection assay (Table 4) or was inactive in stimulating pre-adipocyte (3T3-L1) differentiation. We thus started some limited chemistry efforts by modifying the rhodanine core structure to better understand the molecular basis of this discrepancy. Three compounds synthesized initially (4i, 4ii, and 4iii) did not bind to PPAR γ at all (Table 1), suggesting that benzylidene is required for receptor-binding properties. Therefore, the 5-substituted benzylidene group was introduced, and simple substitutions at R₃, R₄ and R₅ with methoxy, ethoxy, 2-furancarboxy, or aminocarbonylmethoxy did not change the binding situation (Table 1). However, when R₄ or R₅ was substituted with benzyloxy or benzeneethoxy, 4 derivatives (13, 15, 17, and 19) possessed both receptor-binding and PPAR γ agonist properties (Tables 1, 4). Hydroxy in R₂ (14) abolished the receptor-binding ability of 13, while chloride in R₁ may be responsible for PPAR γ agonist activity (15 vs 16 and 17 vs 18; Tables 1, 4). Cytotoxicity was noted in the cells treated with 19 (data not shown) and this might have led to the lower agonist efficacy observed (Table 4).

In the receptor-binding assay, we found that the removal of methoxy in 5-substituted benzylidene would markedly improve binding activity (Table 2). Among the 18 compounds in this group, *meta*-substitution behaved better than *para*-substitution (21 vs 20, 23 vs 22, 25 vs 24, 27 vs 26, 29 vs 28, 31 vs 30, 33 vs 32, 35 vs 34, and 37 vs 36; Table 2). The chain length also affected the receptor-binding activity. Compounds with *n*=1 or 3 in the chain length bound to PPAR γ more potently than compounds with *n*=2 in the chain length (21, 25 vs 23 and 27, and 31 vs 29; Table 2). When R₁ or R₂ was substituted with halogen, the receptor-binding activity was

also improved (27 vs 21; 29, 35 vs 23; 31, and 37 vs 25; Table 2). In the PPAR γ cotransfection assay, both the chain length and halogen substitution affected the agonist properties. The activities of compounds with *n*=3 in the chain length were better than compounds with *n*=1 or 2 in the chain length (25, 31, 37, and 39; Table 4). The halogen (eg Cl) group also increased the cotransfection activity (27, 29, and 31; Table 4).

To reduce intrinsic cytotoxicities, the atom thio on the rhodanine was changed to oxygen. This alteration led to a decrease in receptor-binding affinities while modified analogues generally maintained efficacies in cell-based assays, except compound 42 (42 vs 37; Table 4). The underlining mechanism of this phenomenon deserves further investigation.

According to Amit and colleagues^[16], a 3-D quantitative structure-activity relationship model of PPAR γ agonist thiazolidine-2,4-dione has 3 biophoric centers, A, B, and C, corresponding to carbonyl oxygen of thiazolidine-2,4-dione, sulphur atom of thiazolidine-2,4-dione, and the oxygen atom attached to the phenyl ring, respectively. These are electron-rich sites capable of donating electrons and may be involved in electrostatic, ionic, and π - π interactions. Site C is essential to the agonistic action of PPAR γ , whereas the carbonyl group of thiazolidinediones (site A) may be responsible for the formation of hydrogen bonds with 2 histidine residues, His 323 and 449, of PPAR γ . This information could certainly help us understand why the benzyloxy, phenylethoxy, and phenylpropoxy groups are important to the PPAR γ agonists described in the present study.

It is conceivable that the modest transactivation efficacies observed with these compounds (68.8% maximum compared to rosiglitazone) were due to partial agonist effects.

The fact that they did not behave as antagonists in the same assay system suggests that their potencies at PPAR γ should be further improved. Likewise, we noted some inconsistencies relative to transactivation versus adipogenesis assays in terms of agonist effects. Although some agonists have relatively potent agonistic activities in the cotransfection assay (eg 39), they acted poorly on pre-adipocyte differentiation. This is in agreement with previous studies on a group of PPAR γ agonists, including KR-62980, GW0072, FMOCL-leucine, PAT5A and nTZDpa^[17]. Biochemical and structural studies with PPAR γ revealed that different ligands may occupy the PPAR γ ligand-binding pocket in different manners, thereby inducing different allosteric changes in its conformation. Such alterations would result in different kinds of interactions between receptor and cofactor proteins, such as steroid receptor co-activator 1 (SRC1), nuclear receptor co-activator TIF2, cAMP response element (CRE) binding protein (CBP), TRAP220/DRIP205, nuclear receptor co-repressor (NcoR), and the silencing mediator of the retinoid and thyroid hormone receptors (SMRT)^[18]. Therefore, the effect of PPAR γ modulators on the downstream adipogenesis and glucose uptake will depend on the context of interaction between the ligand and the receptor.

In summary, 5-benzylidene was required for the receptor-binding properties. Simple substitutions on benzylidene with methoxy, ethoxy, 2-furancarboxy, or amino-carbonyl-methoxy did not change the binding affinity. However, when benzylidene was substituted with aralkyl, both receptor-binding and PPAR γ agonist activities were demonstrable. *Meta*-substitution was better than that of *para*. The chain length also affected the PPAR γ -binding and agonist activities. The best chain length studied was 3. Finally, the substitution of halogen in R₁ or R₂ improved binding activity. Of the analogues studied, compound 31 exhibited about 70% the efficacy exerted by BRL49653 in both the cotransfection and pre-adipocyte differentiation assays, in addition to its weak agonist action on hPPAR α (data not shown). High receptor binding potency ($K_i=47.4$ nmol/L) and less than optimal agonist efficacy ($EC_{50}=700$ nmol/L) relative to rosiglitazone create an opportunity to use rhodanine derivatives as a new scaffold in further understanding the molecular mechanism of agonism at PPARs.

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