Novel Antidiabetic and Hypolipidemic Agents. 5. Hydroxyl versus Benzyloxy Containing Chroman Derivatives†

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Several thiazolidinediones having chroman moieties were synthesized and evaluated for their euglycemic and hypolipidemic activities. Some of the analogues having an aminoalkyl group as a linker between the chroman ring and 4-[5-(2,4-dioxo-1,3-thiazolidinyl)methyl]phenoxy moiety seem to be better than troglitazone. In vitro transactivation assays of PPARγ have been carried out with these glitazones to understand their molecular mechanism. For the first time we have found that some of the unsaturated thiazolidinediones are superior to their saturated counterpart in the in vivo assay. A more potent thiazolidinedione analogue than troglitazone is reported. Pharmacokinetic studies have shown that protection of the OH group in the chroman moiety leads to a decrease in metabolism, thereby resulting in a superior pharmacological profile.

Introduction

Non-insulin-dependent diabetes mellitus (type 2) is a metabolic disorder characterized by hyperglycemia leading to secondary complications such as neuropathy, nephropathy, retinopathy, and other cardiovascular diseases.[1] It is characterized by insulin deficiency and peripheral insulin resistance.[2] The treatment generally prescribed for type 2 diabetes has been a combination of diet, exercise, and oral hypoglycemic agents, commonly sulfonyl urea and biguanides.[3] However, sulfonylurea therapy has many problems associated with primary and secondary failure of efficacy, incidence of hypoglycemia,[4] and obesity.[5] Hence a drug that can control plasma glucose tightly without significant side effects would be an important addition to diabetes therapy. The pioneering discovery of ciglitazone by Sohda et al.[6] opened a new avenue for novel antihyperglycemic agents that reverse insulin resistance[7] in type 2 patients.

In rodent models of obesity, insulin resistance, and hyperglycemia, thiazolidinediones such as ciglitazone ameliorate insulin resistance and normalize plasma glucose and insulin without causing hypoglycemia even at very high doses.[8] However, due to the unsatisfactory efficacy and safety profile of these agents,[9] there has been concern about thiazolidinediones as antidiabetic drugs. The encouraging clinical reports on troglitazone which is now marketed in Japan and North America (although it still causes liver toxicity in a limited number of patients)[10] have encouraged pharmaceutical companies to continue the development of new thiazolidinedione analogues.[11−14] Tocopherol, which is present in vitamin E, is known to be an interceptor of peroxy radicals, superoxy radicals, and singlet oxygen[15] and thereby inhibit lipid peroxidation[16] which is implicated in the alternation of glucose transport in type 2 diabetes.[17] Troglitazone,[7c] which posseses the tocopherol moiety, has been reported to show these beneficial effects.

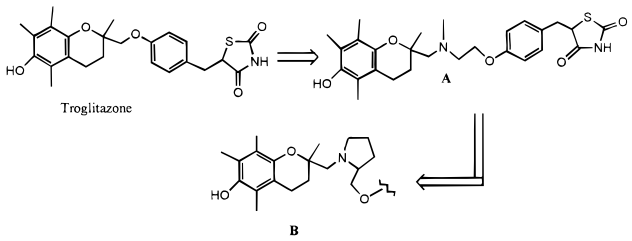

Figure 1. Approach to modify troglitazone.

In our preliminary studies, we have demonstrated that insertion of an N−Me group between the chroman moiety and phenoxyethyl moiety of troglitazone resulted in compound **A** which has improved euglycemic and hypolipidemic activity compared to troglitazone in db/db and ob/ob mice[18] (Figure 1).

We have also observed a notable enhancement of hypolipidemic and euglycemic activities in a separate study when the methyl group on the nitrogen atom is cyclized to a five-membered heterocyclic ring along with the adjacent carbon of the group to which the NCH_3 is attached. This strategic modification of BRL-49653 led to the discovery of DRF-2189 reported earlier from our research group (Figure 2).[19]

We reasoned whether a similar improvement in euglycemic and hypolipidemic activities could be observed when the N−Me group in structure **A** is incorporated in a cyclic ring structure as shown in **B** (Figure 1). This would result in compounds having the toco-

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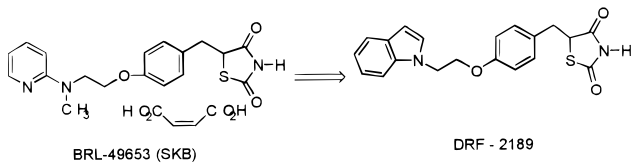


Figure 2. Approach to DRF 2189.

pherol moiety in the structural motif. In the present article, we report a systematic structure−activity relationship (SAR) with respect to plasma glucose and triglyceride lowering activities. Pharmacokinetic studies of selected molecules were carried out.

Chemistry

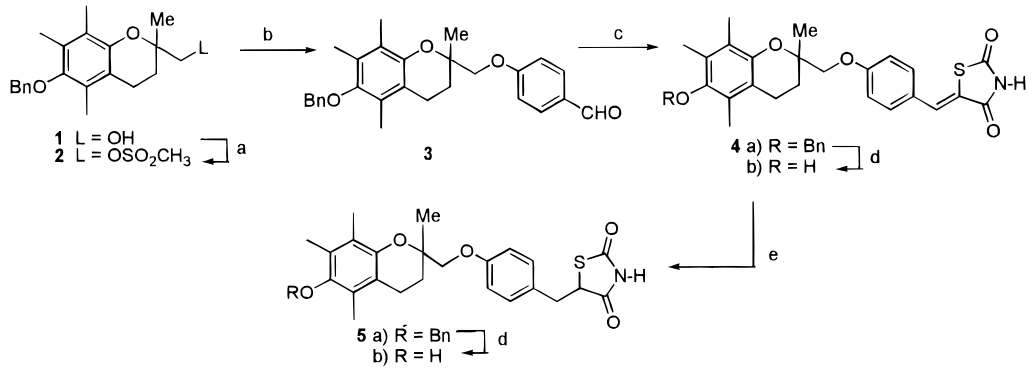
General strategies to synthesize thiazolidinediones are shown in Scheme 1−3. 6-Benzyloxy-2,5,7,8-tetramethylchroman-2-carbinol **1** was prepared by a known method[20] and was converted to mesylate **2** in excellent yield (90%). The mesylate **2** was treated with 4-hydroxybenzaldehyde in the presence of ^{t}BuOK in DMF at ca. 25 °C for 15 h to furnish aldehyde **3** in good yield (60%).

The aldehyde **3** was then reacted with 2,4-thiazolidinedione (TZD) in the presence of piperidinium benzoate to furnish unsaturated thiazolidinedione analogue **4a** (60%). The benzyl protecting group can be removed by heating **4a** at 70 °C in acetic acid and concentrated HCl to furnish **4b** (52%) (Scheme 1).

The unsaturated TZD **4a** can be reduced by using CH_3OH-Mg[21] to furnish the saturated TZD **5a** (54%). The removal of benzyl protecting group was achieved by the method described above to afford troglitazone **5b**. A similar synthetic strategy was adopted for the synthesis of various derivatives of **A** (Figure 1) in which $-N(CH_3)-CH_2CH_2-$ has been incorporated between the chroman ring and the phenoxy moiety (Scheme 2).

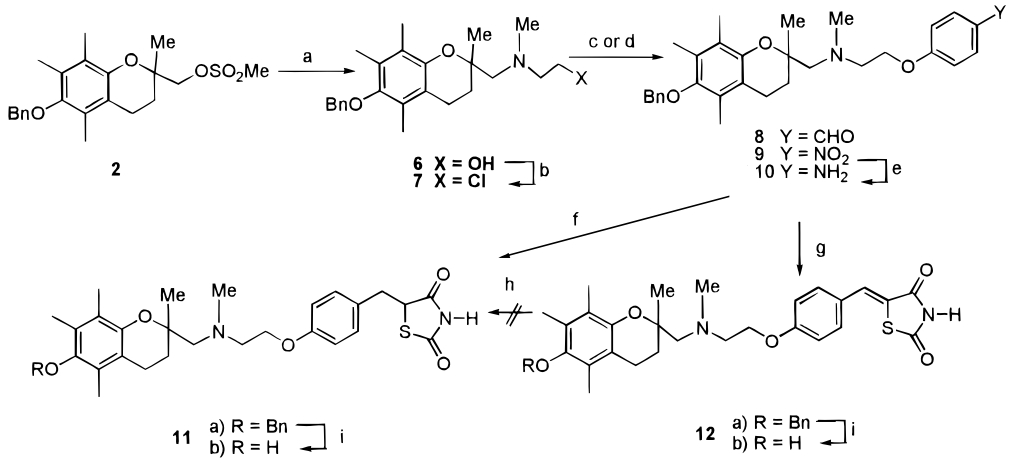
The mesylated derivative **2** was heated with 2-(methylamino)ethanol to afford **6** in 95% yield. The treatment of **6** with thionyl chloride in benzene furnished a good yield of chloro compound **7** (96%). The chloro compound **7** was reacted with 4-hydroxybenzaldehyde in the presence of K_2CO_3 in DMF for 6 h to furnish a 94% yield of aldehyde **8** which was condensed with 2,4-thiazolidinedione under reported conditions[22] to give an excellent yield (99%) of unsaturated TZD analogue **12a** (Scheme 2). The benzyl group was removed by treating **12a** with AcOH and concentrated HCl at 60 °C for 1 h to get **12b** (94%). The saturated analogue **11b** can be prepared by the

Scheme 1[a]



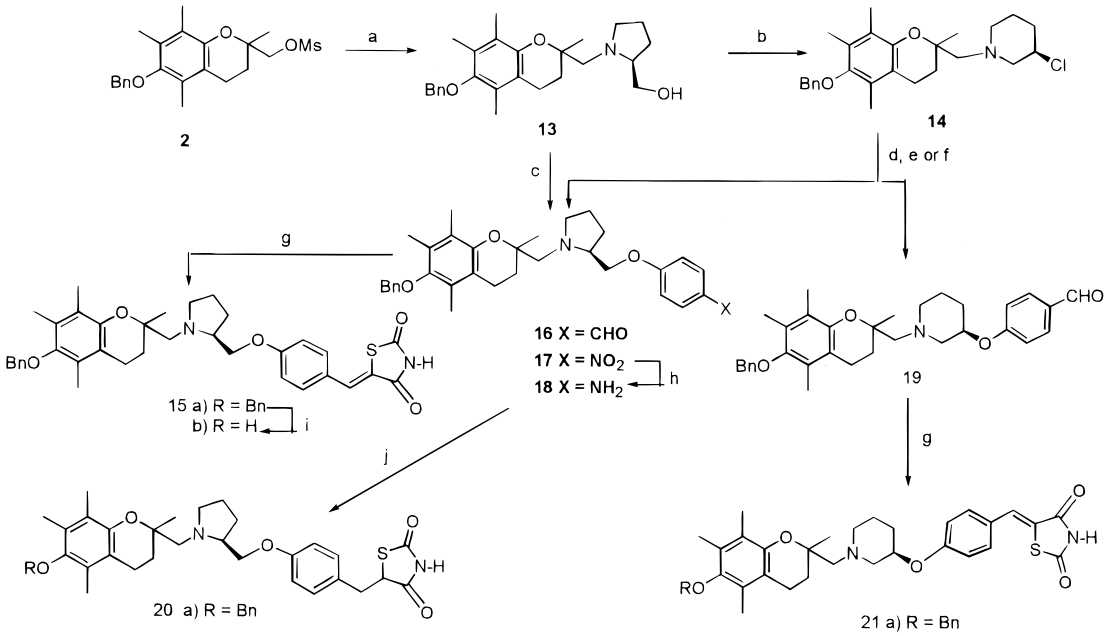
[a] Reagents and conditions: (a) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 2 h, 25 °C, 90%; (b) 4-fluorobenzaldehyde, KO^{t}Bu, DMF, 15 h, 25 °C, 60%; (c) 2,4-thiazolidinedione, piperidine, benzoic acid, toluene, 120 °C, 2−4 h, 60%; (d) $CH_3COOH-HCl$ (3:1) 70−80 °C, 24−48 h, 52−70%; (e) Mg/MeOH, 45 °C, 8 h, 54%.

Scheme 2[a]



[a] Reagents and conditions: (a) 2-(methylamino)ethanol, 120 °C, 12 h, 95%; (b) $SOCl_2$, C_6H_6, 0 °C, 2 h, 96%; (c) 4-hydroxybenzaldehyde, K_2CO_3, DMF, 80 °C, 6 h, 94%; (d) 4-nitrophenol, K_2CO_3, DMF, 80 °C, 4 h, 90%; (e) Pd/C (10%), H_2 (60 psi), EtOAc, 30 °C, 8 h, 95%; (f) (i) $NaNO_2$, aqueous HBr, MeOH−acetone, ethyl acrylate, Cu_2O, 38 °C, 46%, (ii) thiourea, NaOAc, EtOH, 5 h, Δ, (iii) 2 N HCl, EtOH, 12 h, 55%; (g) 2,4-thiazolidinedione, piperidine, benzoic acid, toluene, 120 °C, 2−4 h, 60%; (h) $CH_3COOH-HCl$ (3:1) 70−80 °C, 24−48 h, 52−70%; (e) Mg/MeOH, 45 °C, 8 h, 54%; (i) $CH_3COOH-HCl$ (3:1), 70−80 °C, 24−48 h, 52−94%.

Scheme 3[a]



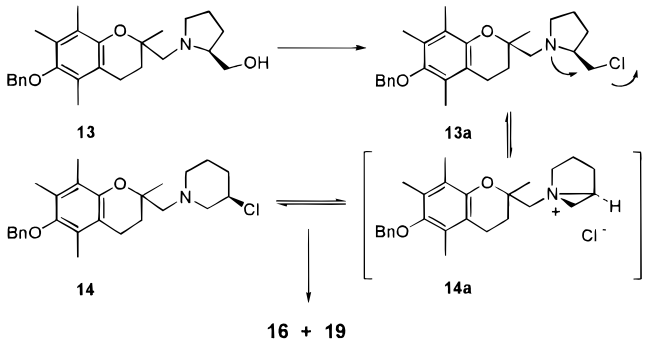
[a] Reagents and conditions: (a) *(S)*-prolinol, 120 °C, 6 h, 75%; (b) $SOCl_2$, C_6H_6, 25 °C, 1 h, 73%; (c) 4-fluoronitrobenzene, NaH, DMF, 25 °C, 2 h, 81%; (d) 4-hydroxybenzaldehyde, K_2CO_3, DMF, 80 °C, 2 h, **16** + **19**, 33% + 35%; (e) 4-hydroxybenzaldehyde, DEAD, Ph_3P THF, (**16** + **19**, 41% + 40%); (f) 4-fluorobenzaldehyde, KO^{t}Bu, DMF, 36 h, 25 °C, 60%; (g) 2,4-thiazolidinedione, piperidine, $C_6H_5CO_2H$, toluene, 120 °C, 2 h, 57−93%; (h) Pd/C (10%), H_2 (60 psi), EtOAc, 6 h, 91%; (i) CH_3COOH−HCl (3:1), 70−80 °C, 98%. (j) (i) $NaNO_2$, aqueous HBr, MeOH−acetone, ethyl acrylate, Cu_2O, 38 °C, 47%, (ii) thiourea, NaOAc, EtOH, Δ, 5 h, (iii) 2 N HCl, EtOH, Δ, 12 h, 85%.

electron transfer method (Mg−MeOH)[21] in good yield (95%) from **12b**.

The TZD derivative **11a** was also prepared by an alternate route. The chloro compound **7** when treated with 4-hydroxynitrobenzene in the presence of K_2CO_3 gave **9** (90%), which upon hydrogenation afforded amino compound **10** (95%). The amine **10** was transformed to saturated TZD **11a** by a known method.[23] The compound **11a** was also converted to **11b** (95%) by a hydrolytic method described earlier. Thereafter, we concentrated our efforts to prepare thiazolidinediones of type **B**. The synthetic strategies adopted to prepare thiazolidinedione derivatives **B** (Figure 1) are outlined in Scheme 3. The mesylate **2** was heated with L-prolinol (4 equiv) at 120 °C for 6 h to furnish pyrrolidine derivative **13** in 75% yield. The reaction of **13** with thionyl chloride in benzene at ca. 25 °C for 1 h furnished **14** in 73% yield (Scheme 3).

Interestingly, the reaction of **14** with *p*-hydroxybenzaldehyde in the presence of K_2CO_3 (4 equiv) in DMF at 80 °C for 2 h furnished a mixture of five-membered and six-membered products **16** and **19** in almost 1:1 ratio (70% yield). The compounds **16** and **19** were also obtained in 1:1 ratio in the reaction of pyrrolidine derivative **13** with 4-hydroxybenzaldehyde under Mitsunobu conditions (DEAD, PPh_3, 81% yield).[25] In contrast, when compound **13** was treated with potassium *tert*-butoxide to generate an alkoxide ion which can react with 4-fluorobenzaldehyde, a high yield (70%) of **16** was obtained and no rearrangement product **19** was isolated. The formation of 3-chloropiperidine derivative **14** and the condensation product **19** can be understood in terms of the pathways shown in Scheme 4. 3-Chloropiperidine may arise by the reaction of $SOCl_2$ with pyrrolidine derivative **13** to form 2-chloromethylpyrrolidine derivative **13a** which undergoes an intramolecular displacement reaction by the attack of nitrogen to give an aziridine intermediate **14a** (Scheme 4).

Scheme 4. Mechanism of Formation of **16** and **19** from Pyrrolidine Derivative **13**

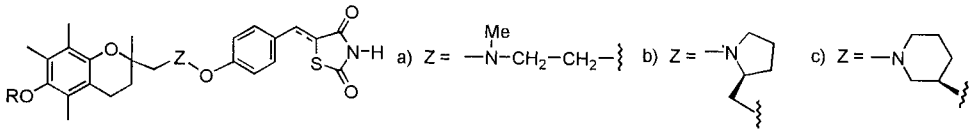


The chloride ion generated in this reaction can further react to furnish a strain-free 3-chloropiperidine derivative **14**. On the other hand, when 3-chloropiperidine derivative **14** is treated with 4-hydroxybenzaldehyde in the presence of a base, both products **16** and **19** may arise via the intermediates **14** and **14a**. Similar rearrangement of pyrrolidine derivatives to piperidine derivatives are known.[24]

Finally, the aldehydes **16** and **19** were condensed with 2,4-thiazolidinedione to afford the unsaturated compounds **15a** (93%) and **21a** (57%), respectively. The unsaturated TZD analogue **15a** was heated at 60 °C in AcOH−HCl to afford debenzylated product **15b** (98%).

The saturated TZD analogue **20a** was prepared by a different route starting from pyrrolidine derivative **13**. The treatment of **13** with 4-fluoronitrobenzene in the presence of NaH gave the nitro derivative **17** in good yield (81%). The catalytic hydrogenation of **17** in the presence of 10% Pd/C afforded the amine derivative **18**

Table 1. Euglycemic and Hypolipidaemic Activities of Thiazolidinediones



S. no.	compd no.	R	DB[a]	Z = a/b/c	dose[b]	6th day PG[c] (mean ± SE)	6th day TG[d] (mean ± SE)
1	**5b** (troglitazone)	H	No		200	24 ± 7	50 ± 1.0
					100	26 ± 9	ND
2	**5a**	Bn	no		100	64 ± 4	34 ± 4
3	**4a**	Bn	yes		100	39 ± 9	38 ± 6
4	**4b**	H	yes		100	62 ± 8	26 ± 8
5	**12a**	Bn	yes	a	200	45 ± 8	NA
6	**12b**	H	yes	a	200	36 ± 7	ND
7	**11b**	H	no	a	200	3 ± 3	ND
8	**15a** + **21a**	Bn	yes	b/c (21:4)	200	52 ± 7	ND
9	**15a** + **21a**	Bn	yes	b/c (3:7)	200	53 ± 6	ND
10	**15a**	Bn	yes	b	100	68 ± 4	ND
11	**20a**	Bn	no	b	100	26 ± 3	ND
12	**21a**	Bn	yes	c	100	5 ± 7	24 ± 7
13	**15b**	H	yes	b	100	37 ± 5	36 ± 4

[a] DB = double bond; dotted lines, optional double bond. [b] Dose in mg/kg/day given through oral gavage. [c] Percent reduction of plasma glucose (mean ± SE; $n = 4$) after 6 days of treatment (calculated according to the formula reported in ref 26). [d] Percent reduction of plasma triglyceride (mean ± SE; $n = 4$) after 6 days of treatment (calculated according to the formula reported in ref 26). NA: Not active; ND: Not done.

in an excellent yield (91%). The compound **18** was converted to **20a** by a known method.[23]

Biological Procedure

Male C57BL/KsJ-db/db mice were obtained at 6 weeks age from Jackson Laboratories (Bar Harbor, ME) and maintained at 25 ± 2 °C on a 12 h light/12 h dark cycle. Animals were given standard laboratory chow (National Institute of Nutrition, Hyderabad, India) and water, ad libitum.

The db/db mice were used for experiments at 8 weeks of age. Four to six animals were used in each treatment group whose initial plasma glucose levels were similar. In db/db mice, the test compounds were administered at different doses orally for 6 days. Troglitazone (200 mg/kg) was used as the standard drug. The control animals were given vehicle (0.5% carboxymethylcellulose; dose 10 mL/kg). Blood samples (25−50 μL) were collected from the retro-orbital sinus through heparinised capillary tubes in tubes containing EDTA at different time intervals. In db/db mice, blood samples were collected after 1 h of drug administration on days 0 and 6 of treatment. After centrifugation, plasma was separated for glucose and triglyceride estimations using commercial kits (Dr. Reddy's Laboratories Diagnostic Division, India). The percentage reduction in plasma glucose level was calculated according to the formula.[26] The results are summarized in Table 1.

Results and Discussion

We have examined several thiazolidinedione analogues, including troglitazone, for their euglycemic activity in db/db mice. A dose of 200 mg/kg was administered to db/db mice for 6 days, and the plasma glucose and triglyceride levels were examined. In the case of troglitazone, a dose−response study was performed in db/db mice. Dose-related reduction in the plasma glucose level was observed. Interestingly, even at a dose as high as 800 mg/kg, 25% of the animals did not respond to troglitazone therapy.[27a] Moreover, the maximum reduction in plasma glucose observed was only 52%, and even at this dose, the plasma glucose in db/db mice (15 ± 1 mM) did not reach the level of lean littermates db+/db− (8 ± 1 mM). Similar observations have been reported by Kobayashi et al. in troglitazone-treated patients.[27b] Therefore, there is a need for new thiazolidinedione analogues with improved efficacy, higher potency, and fewer side effects.

We have initially examined several modified troglitazone analogues by introducing unsaturation between the thiazolidinedione moiety and the phenyl ring or by protecting the phenolic OH of chroman ring to see the structure−activity relationship. The results are summarized in Table 1.

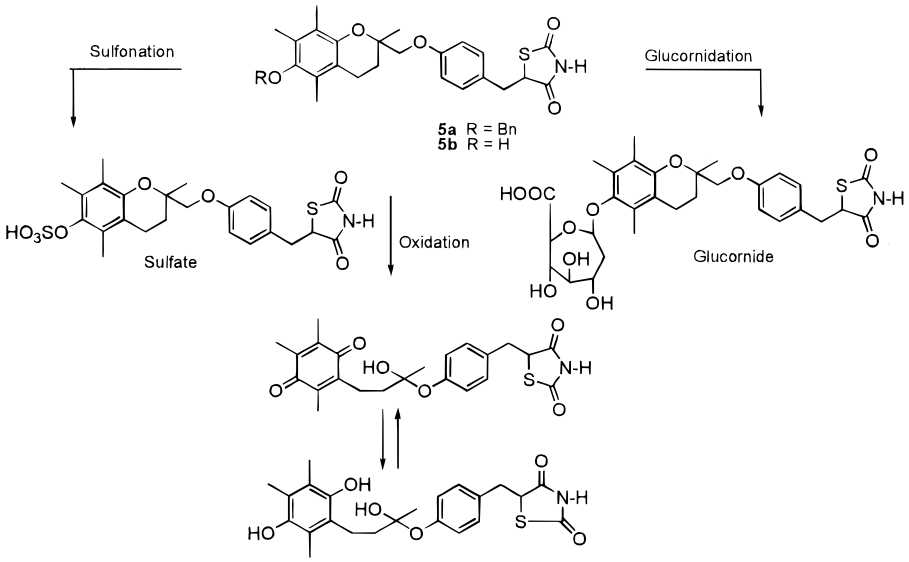
The rationale for the selection of troglitazone as the drug candidate is probably due to the presence of tocopherol moiety that has antioxidant property; however, the reason for its liver toxicity is still elusive. We assumed that the liver toxicity may be due to enterohepatic circulation of the metabolites which troglitazone is known to undergo.[28] Thus, we prepared unsaturated TZD **4a** in which the OH group in the chroman ring is protected as OBn. This compound showed marginal improvement in plasma glucose lowering activity over troglitazone. The removal of the OBn protecting group resulted in **4b** (Table 1, entry 3) which showed considerable improvement in euglycemic activity when compared to troglitazone (Table 1, entries 1 vs 3). The TZD **4b**, like troglitazone, is also expected to show antioxidant properties. We have also prepared the *O*-benzyl derivative of troglitazone, i.e., **5a** which showed euglycemic activity similar to that of **4b**. Interestingly, the plasma glucose level in individual db/db mice treated with TZD **4b** was nearly equal to that of the lean littermates (db+/db−; 8 ± 1 mM). This is remarkable in the sense that the animals treated with even 800 mg/kg troglitazone did not show a lowering of plasma glucose and triglyceride to the level of lean littermates.

Table 2. Pharmacokinetic Paramters of Thiazolidinedione Analogues in Female Wistar Rats at 100 mg/kg, p.o. Dose[a]

pharmacokinetic parameters	**4a** mean ± SD	**4b** mean ± SD	**5a** mean ± SD	**5b** mean ± SD
$AUC_{(0-t)}$ (μg h mL^{-1})	14.40 ± 5.30	2.44 ± 0.66	15.96 ± 2.01	25.94 ± 5.97
$AUC_{(0-\infty)}$ (μg h mL^{-1})	18.50 ± 6.24	3.12 ± 1.05	32.05 ± 7.88	27.40 ± 5.75
C_{max} (μg mL^{-1})	1.09 ± 0.45	0.68 ± 0.18	1.83 ± 0.27	5.47 ± 0.64
T_{max} (h)	4.33 ± 1.15	1.75 ± 0.96	3.25 ± 1.26	2.25 ± 0.96
K_{el} (h^{-1})	0.07 ± 0.01	0.25 ± 0.03	0.07 ± 0.02	0.20 ± 0.10
$t_{1/2}$ (h)	10.36 ± 0.92	2.82 ± 0.32	10.30 ± 2.66	4.01 ± 1.38

[a] Results are mean ± SD of four female Wistar rats in each group; $AUC_{(0-\infty)}$, K_{el}, $t_{1/2}$ half-life, C_{max}, and t_{max} were calculated using noncompartmental model analysis. $AUC_{(0-\infty)}$ is the area under the plasma concentration vs time curve extrapolated to infinity, K_{el} is the elimination rate constant, C_{max} is the observed maximum plasma concentration, and t_{max} is the time at which maximum concentration (C_{max}) is reached.

Scheme 5. Metabolism of Troglitazone in Wistar Rats



The reasons for improved activities can only be speculated with the present knowledge of understanding: i.e., (a) by protecting the free OH of the tocopherol moiety of troglitazone, the drug is less metabolized and may have longer half-life (vide infra); (b) the compound **5a** may act as a prodrug and the troglitazone (**5b**) gets released in vivo by the cleavage of benzyl protecting group of **5a**. However, we do not have evidence to show that compound **5a** may act as a prodrug for troglitazone.

Thus, we carried out pharmacokinetic studies of **4a**, **4b**, **5a**, and **5b** in Wistar rats at 100 mg/kg/p.o. dose to shed light on our present understanding. The results are summarized in Table 2.

From the results it is clear that TZD **4b**, which showed good pharmacodynamic behavior, was relatively poor in its pharmacokinetic aspects when compared with troglitazone (**5b**). For example, compound **4b** showed very poor AUC and C_{max} and was also excreted relatively rapidly. This suggests that **4b** appears to be more potent than **5b** since, even at low systemic exposure and **4b**'s shorter half-life, it exhibits a better pharmacodynamic profile than **5b**. On the other hand, TZD **5a** showed low C_{max}, although AUC was comparable to that of troglitazone. This may be attributed to the slow elimination of **5a** by having a higher $t_{1/2}$ for **5a** when compared to troglitazone (**5b**) (Figure 3).

Further, we indirectly examined the difference in metabolism of O-benzylated compound **5a** and OH compound **5b**. It is known that troglitazone (**5b**) undergoes rapid and extensive metabolism mainly via sulfonation, glucuronidation, and oxidation as shown in Scheme 5.[28] These metabolites are known to undergo entero-hepatic circulation. It is known that gender difference in pharmacokinetics of troglitazone (**5b**) in Wistar rats is solely due to the difference in metabolism in male and female species.[28] Troglitazone is metabo-

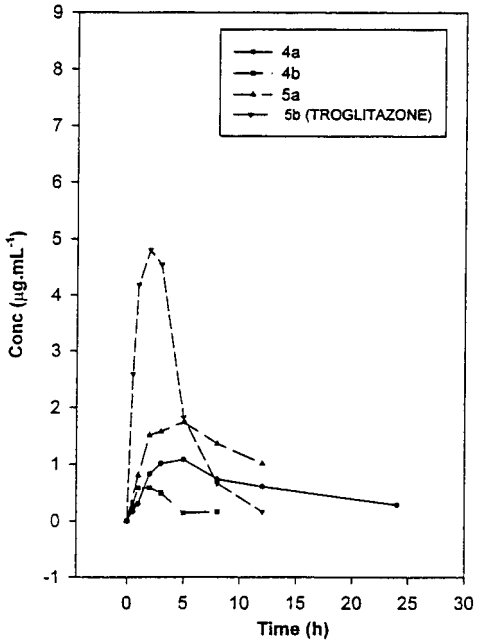


Figure 3. Plasma concentration of **4a**, **4b**, **5a**, and **5b** versus time profile.

Table 3. Pharmacokinetic Parameters of Thiazolidinedione Analogues in Wistar Rats at 100 mg/kg, p.o. Dose

pharmacokinetic parameters	**5a**[a] male mean ± SD	**5a**[a] female mean ± SD	**5b** (Troglitazone)[a] male mean ± SD	**5b** (Troglitazone)[a] female mean ± SD
$AUC_{(0-t)}$ (μg h mL^{-1})	14.26 ± 5.67	15.83 ± 2.44	5.09 ± 1.10	25.94 ± 5.97
$AUC_{(0-\infty)}$ (μg h mL^{-1})	21.02 ± 7.34	29.76 ± 7.85	5.68 ± 1.60	27.40 ± 5.75
C_{max} (μg mL^{-1})	2.17 ± 1.00	1.83 ± 0.33	0.77 ± 0.25	5.47 ± 0.64
T_{max} (h)	4.33 ± 1.15	3.33 ± 1.53	2.00 ± 1.15	2.25 ± 0.96
K_{el} (h^{-1})	0.12 ± 0.02	0.08 ± 0.02	0.19 ± 0.05	0.20 ± 0.10
$t_{1/2}$	5.78 ± 1.19	9.27 ± 2.07	3.90 ± 1.14	4.01 ± 1.38

[a] In each group four male and four female animals were used. The results are mean ± SD.

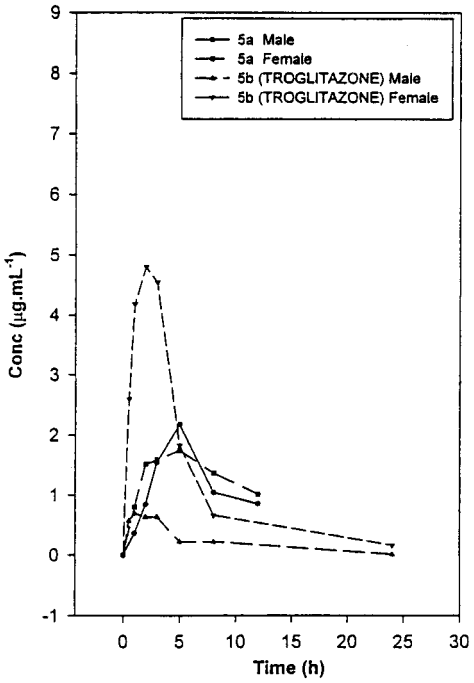


Figure 4. Pharmacokinetic behavior of **5a** and **5b** in male and female wistar rats.

lized to a larger extent in male rats than in female rats. This is reflected in the systemic exposure of troglitazone as evidenced in our pharmacokinetics results in male and female rats (Table 3). In contrast, the pharmacokinetics of *O*-benzyl compound **5a** in Wistar rats did not show any dramatic gender difference (Figure 4).

In troglitazone the phenolic OH of the chroman ring is known to be involved in metabolism. The protection of this phenolic OH group with the OBn group might have prevented the formation of the respective metabolites. Hence, there was no difference in systemic exposure (AUC) and C_{max} of compound **5a** in female and male Wistar rats.

From these studies, we are tempted to suggest that liver toxicity related to troglitazone might have an origin in the entero-hepatic circulation of the metabolites and the prolonged exposure of drug in the liver. In contrast, TZD **5a** did not show such metabolism. It may also be possible that the TZDs having *O*-benzyl protection at the chroman ring might act as prodrugs and slowly metabolize on chronic administration to release free phenolic analogue in vivo which may still have the benefit of antioxidant properties present in a troglitazone-type molecule. However, on the basis of the present study, we do not have evidence to say that the *O*-benzyl group gets cleaved in vivo to generate free OH compound. We therefore continued our search for superior euglycemic and hypolipidemic compounds having a chroman moiety.

We introduced the $-N(CH_3)-CH_2-CH_2-$ group between the chroman ring and the phenoxy moiety of troglitazone to examine its effect. As reported earlier,[19b] introduction of the N−Me group resulted in **12a** (Table 1, entry 5) which showed good euglycemic activity in db/db mice at 200 mg/kg dose. The removal of the benzyl protecting group from **12a** gave **12b** (Table 1, entry 6) which showed no improvement in biological profile. Therefore, we prepared the saturated analogue of **12b** viz **11b**; however, we were surprised to find that **11b** did not show any activity (Table 1, entry 7).

Earlier, we had attempted to incorporate the methyl group of N−Me moiety of BRL-49653 (rosiglitazone) in the cyclic ring structure, which resulted in a novel and potent thiazolidine analogue DRF-2189 (Figure 2).[19] We envisaged that a similar incorporation of the methyl moiety of the N−Me group of **12a** into a cyclic structure may lead to further improvement in euglycemic and hypolipidemic activity. Hence, we synthesized compounds having structural features shown in **C** (Figure 1).

Several pyrrolidinyl and piperidinyl analogues were prepared and tested in db/db mice. The results are summarized in Table 1. Initially, we examined a mixture of TZDs **15a** and **21a** in the ratio 21:4 and 3:7 obtained during fractionation by column chromatography (Table 1, entries 8 and 9, respectively) at 200 mg/kg dose in db/db mice. In both the cases, the plasma glucose was reduced by 52−53% after 6 days of treatment. It seemed that both pyrrolidine and piperidine analogues of TZD may be equipotent. Later, we examined the pure pyrrolidine analogue **15a** at 100 mg/kg and 30 mg/kg dose for 6 days in db/db mice. The plasma glucose lowering activity of **15a** was found to be excellent (Table 1, entries 10 and 11). Contrary to our expectation, the thiazolidinedione **21a** did not show any effect on plasma glucose and triglyceride dose in db/db mice (Table 1, entry 12). Thus, we continued our research for better euglycemic compounds in pyrrolidine series of TZDs. The saturated analogue of TZD **15a**, viz. **20a** (Table 1, entry 11), showed inferior euglycemic activity compared to **15a**. This observation further corroborates with our earlier observation in which the saturated TZD showed inferior euglycemic activity compared to its unsaturated counterpart (vide supra). The removal of the benzyl protecting group from **15a** gave **15b** (Table 1, entry 13) which has antioxidant property but diminished euglycemic activity. From the above structure−activity relationship, it is clear that the unsaturated thiazolidinediones (**15a**) are better than their saturated counterpart (**20a**) and that the *O*-benzyl

Table 4. Percentage Reduction in Plasma Glucose and Triglyceride for Selected TZDs and Their Salts

parameter	**15a**	**20a**	**15a**-maleate	**20a**-maleate	**20a**-HCl	**15a**-Na	**20a**-Na	trog.
PG[a]	41 ± 3	23 ± 17	48 ± 9	24 ± 9	12 ± 10	8 ± 14	36 ± 3	NA
TG[a]	26 ± 8	ND	47 ± 6	35 ± 8	NA	58 ± 7	66 ± 8	NA

[a] All animals were treated with test compounds at a dose of 30 mg/kg for 6 days. The percent reduction of plasma glucose and triglyceride (mean ± SE; $n = 4$) is calculated according to the formula given in ref 26. ND = not done; NA = not active.

Table 5. Pharmacokinetic Parameters of Thiazolidinedione Analogues in Female Wistar Rats at 100 mg/kg, p.o. Dose[a]

pharmacokinetic parameters	**12a** mean ± SD	**12b** mean ± SD	**15a** mean ± SD	maleate of **15a** mean ± SD
$AUC_{(0-t)}$ (μg h mL^{-1})	27.47 ± 10.35	44.20 ± 3.14	21.32 ± 6.24	44.65 ± 2.07
$AUC_{(0-\infty)}$ (μg h mL^{-1})	34.49 ± 13.67	44.94 ± 3.06	34.47 ± 11.49	51.72 ± 1.60
C_{max} (μg mL^{-1})	4.12 ± 1.60	9.92 ± 1.11	2.54 ± 0.66	4.40 ± 0.42
T_{max} (h)	3.25 ± 2.06	1.38 ± 1.11	4.00 ± 1.15	4.50 ± 1.00
K_{el} (h^{-1})	0.15 ± 0.05	0.38 ± 1.11	0.10 ± 0.02	0.10 ± 0.02
$T_{1/2}$ (h)	4.87 ± 1.82	1.86 ± 0.22	7.32 ± 1.27	7.12 ± 1.11

[a] The results are mean ± SD of four animals in each group.

protected unsaturated TZDs (**15a**) are better than free OH compounds (**15b**) as far as euglycemic activity is concerned. We carried out evaluation of **15a** and **20a** and their various salts at 30 mg/kg/day dose in db/db mice for selection of a suitable compound for further studies. Results are shown in Table 4.

From the results it is clear that the maleate salt of **15a** shows very good activity (Table 4). The other acid salts of **15a** and **20a** did not show a good pharmacological profile; however, the sodium salt of both **15a** and **20a** exhibited good triglyceride lowering activities but poor euglycemic activities. The difference in the pharmacological profiles of different salts is difficult to rationalize here.

We carried out pharmacokinetic studies of **12a**, **12b**, and **15a**. Both TZDs **12a** and **15a** showed similar pharmacokinetic behavior, but **15a** was distinctly superior to **12a** in terms of the half-life ($t_{1/2}$) of the drug. However, **15a** needs further improvement as far as systemic exposure is concerned (Table 5).

Thus we examined the pharmacokinetic profile of the maleate salt of **15a** and compared it with that of **12a**, **12b**, and **15a**. The plasma concentration of the drug (μg mL^{-1}) versus time profile is shown in Figure 5.

Although TZD **12b** showed good AUC and C_{max}, the rapid elimination and short half-life is not favorable. On the other hand, the maleate salt of **15a** has good AUC and C_{max} and has slow elimination and longer half-life. In addition, **15a**-maleate showed good euglycemic and hypolipidemic activities (PG ↓50%, TG ↓50%) which would perhaps have a better effect in the management of type 2 diabetes.

PPARα and PPARγ Transactivation Studies. To get some mechanistic insight, we decided to carry out nuclear receptor transactivation assays of TZDs **4a**, **4b**, **5a**, **5b**, **and 15a**-maleate. Thus, all these TZDs were tested for PPARα and PPARγ transactivation. The results are summarized in Table 6.

Surprisingly, the results of PPAR transactivation assays do not exactly correlate with their glucose and triglyceride lowering activities in animal studies. It has been proposed earlier that the compounds which show higher fold activation of PPARγ generally have superior glucose lowering activities in animal experiments.[29,30] A similar relationship has been reported with triglyceride lowering activities versus PPARα transactivation assay.[31] However, the absence of linear correlation between in vitro PPAR transactivation assays and the in vivo pharmacological profile in db/db mice may be attributed to several reasons, for example, the test compounds are administered orally and hence metabo-

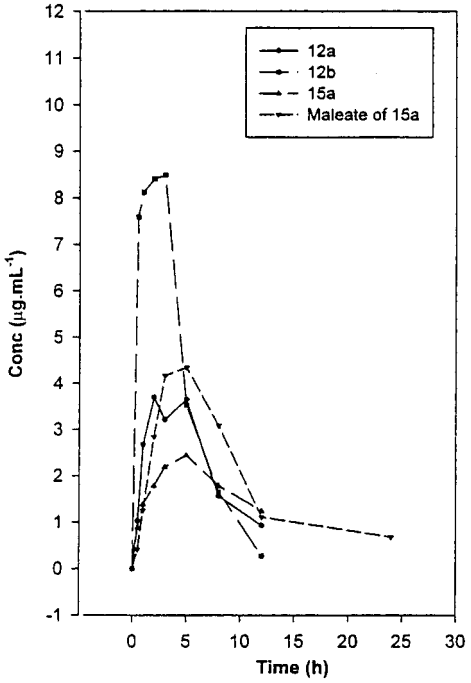


Figure 5. Pharmacokinetic profile of **12a**, **12b**, **15a**, and **15a**-maleate.

Table 6. Activation of PPARα and PPARγ Nuclear Receptors by Thiazolidinediones[a]

compd no.	fold activation PPARα (50 μM)	fold activation PPARγ (1 μM)
4a	0.67	0.57
4b	0.58	2.28
5a	1.79	1.65
5b (troglitazone)	1.12	3.16
15a-maleate	1.12	0.67

[a] Results are the mean of three experiments and within ±0.5% of deviation. GAL4-PPAR chimeric expression constructs and the reporter plasmids were obtained as a gift by Novo Nordisk (Denmark). GAL4 fusions were made by fusing human PPARα-LBD (amino acids 167−468) or human PPARγ1LBD (amino acids 174−475) receptor to the C-terminal end of the yeast GAL4 DBD (amino acids 1−147) of pM1 vector.[33] For luciferase assays, the response element (five copies of a GAL4 DNA binding element) was cloned upstream of pGL2∼SV40∼Luc reporter (Promega).

lism, absorption, etc. of the test compounds may play important roles.

To minimize the factors related to absorption and metabolism which influence the activity of the test compound, a chronic subcutaneous administration of the test compounds in the db/db mice may be visualized. However, these experiments could not be performed due to difficulties in administering the drug for several days subcutaneously in db/db mice. In the present study, although troglitazone (**5b**) showed highest fold PPARγ transactivation (PPARγ 3.16), it shows a PG lowering activity inferior to that of **4b** or **5a** (cf. Table 2). One may only conclude with the limited understanding of the mechanism of action of these drugs that these TZDs might be exhibiting their euglycemic and hypolipidemic activities through other mechanisms, in addition to binding to PPARα and PPARγ. Recently, Aicher et al.[12g] have reported a new class of insulin sensitizer (not TZDs) which do not act through PPAR mechanism, although they significantly improve glucose metabolism and insulin sensitivity in ob/ob mice.

Transactivation assays of PPARα and PPARγ with TZD **15a**-maleate also did not show high transactivation (PPARα 1.12-fold; PPARγ 0.67-fold), although **15a**-maleate was found to be the most preferred TZD analogue of this series both in terms of euglycemic and hypolipidemic activities. It has been reported that the unsaturated TZDs show lesser fold transactivation of PPARα and PPARγ than the saturated analogues,[11c,d] which corroborates with our in vitro transactivation studies. However, these unsaturated TZDs, **4b**, **12a**, **15a**, and **15a**-maleate, showed a better in vivo pharmacological profile than their saturated counterpart.

In conclusion, the new thiazolidinedione analogues with modified chroman moieties of troglitazone have superior euglycemic and hypolipidemic profiles.

Experimental Section

Chemical Methods. Thin-layer chromatography was performed on precoated silica gel plates (F254, Merck). Flash chromatography was performed on silica gel (SRL 230−400 mesh). Melting points were recorded on a Veego melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer and are reported as parts per million (ppm) from downfield to TMS. The infrared spectra were recorded on a Perkin-Elmer FT-IR 1600 spectrometer. The mass spectra were recorded on a HP 5989A mass spectrometer. 2,5,6-Trimethylbenzoquinone, was purchased from Aldrich chemicals, and 2,3-dihydro-2,2,4,6,7-pentamethyl-5-benzyloxybenzofuran-3-carbinol[20] was prepared by reported procedure. L-Proline, 2-(methylamino)ethanol, 2,4-thiazolidinedione, 4-hydroxybenzaldehyde, and 4-fluorobenzaldehyde were purchased from commercial sources and were used directly. Troglitazone was prepared by the reported method of Horikoshi et al.[29a] Englitazone was obtained from Pfizer Inc. USA as gift.

PPARα and PPARγ Activation Study. Plasmids. For luciferase assays, the response element was cloned upstream of the pGL2∼SV40∼Luc reporter (Promega) that contains the Simian virus early promoter. The response element with the underlined consensus sequence is as follows: $UAS_G \times 5$ (5′...CGACGGAGTACTGTCCTCCGAGCT...3′, five copies). GAL4 fusions were made by fusing human PPARαLBD (amino acids 167−468) or human PPARγ1LBD (amino acids 174−475) receptor to the C-terminal end of the yeast GAL4 DBD (amino acids 1−147) of pM1 vector.[32]

Transient Transfection Assay. HEK-293 cells were transfected with the relevant plasmids using superfect according to the manufacturer's instruction.[33] Cells were maintained with DMEM supplemented with 10% delipidated serum (DFCS) after transfection. After 43 h of transfection, cells were seeded in 96 well plates and treated with 50 μM and 1 μM solutions of test compound for PPARα and PPARγ transactivation assays, respectively. DMSO (1:1000) was used as a blank. Luciferase activity was determined as fold activation relative to untreated cells. All results are the mean of three to four experiments and are summarized in Table 6.

Pharmacokinetic Studies. All studies were carried out in female Wistar rats obtained from the National Institute of Nutrition (Hyderabad, India). The animals (200−225 g) were fasted 12 h before starting the experiment and had free access to water throughout the experimental period. The animals were fed 3 h after drug administration. For compound **5a** and **5b**, single dose pharmacokinetics were performed in male and female Wistar rats.

(a) Single Dose Pharmacokinetics. The animals were dosed with the drug at 100 mg/kg/p.o. as a 0.5% CMC suspension, and 0.4 mL of blood sample was collected into heparinized microfuge tubes at different time points from the retro-orbital sinus. The samples were analyzed by HPLC to generate plasma drug concentration versus time profiles. Comparative plasma concentration versus time profiles for troglitazone (**5b**) and the derivatives **4a**, **4b**, and **5a** are shown in Figure 3. The pharmacokinetics of TZD **5a** and **5b** were also carried out in male and female rats to study the gender differences, and the results are represented in Figure 4. Further, comparative pharmacokinetic profiles were generated for TZDs **12a**, **12b**, **15a**, and the maleate salt of **15a** which are shown in Figure 5.

Pharmacokinetic parameters such as $AUC_{(0-\infty)}$, K_{el}, $t_{1/2}$, C_{max}, and t_{max} were calculated using noncompartmental model analysis. $AUC_{(0-\infty)}$ is the area under the plasma concentration vs time curve extrapolated to infinity, K_{el} is the elimination rate constant, C_{max} is the observed maximum plasma concentration, and t_{max} is the time at which C_{max} is achieved. The pharmacokinetic parameters for various compounds are summarized in Tables 2, 3, and 5.

(b) Analysis of Plasma: (1) Sample Preparation. Sample preparation was carried out as reported earlier.[19b]

(2) HPLC Assay. The HPLC system consisted of a Waters LC Module-1, Shimadzu fluorescence detector (RF-10AxL), autoinjector (SIL10A), Millennium software, and a HiChrom C_{18} (ODS) column (5 μm, 4.6 mm × 250 mm). Details of analytical conditions are summarized in Table 7.

The assay methods were validated to ensure specificity, linearity, recovery, accuracy, and precision. The limit of quantitation for all the compounds including troglitazone was 50 ng/mL. The response was linear up to 50 μg/mL. The absolute recoveries were >95%.

(2*R*/*S*)-[6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]methane Sulfonate (2). Methanesulfonyl chloride (21.5 g, 0.19 mol) was added dropwise to a stirred solution of (2*R*/*S*)-[6-benzyloxy-2,5,7,8-tetramethylchroman-2-yl]-carbinol (**1**) (51 g, 0.16 mol) and triethylamine (23.8 g, 0.24 mol) in dichloromethane (400 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then washed with water (200 mL), dried (Na_2SO_4), and concentrated. The crude product was triturated with methanol (200 mL) to obtain 56.9 g (90%) of **2**: mp 102−104 °C; IR ν_{max} (KBr) 1458, 1354 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.3 (s, 3 H), 1.8 (m, 1 H), 2.0 (m, 1 H), 2.05−2.22 (3s, 9 H), 2.6 (t, J = 6.7 Hz, 2 H), 3.0 (s, 3 H), 4.2 (dd, J_1 = 26.9 Hz, J_2 = 104 Hz, 2 H), 4.65 (s, 2 H), 7.4 (m, 5 H); Mass *m*/*e* (relative intensity) 404 (M^+, 8.3), 313 (100).

4-[6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy]benzaldehyde (3). To a stirred solution of (6-benzyloxy-2,5,7,8-tetramethylchroman-2-yl)carbinol (**1**) (10 g, 30.67 mmol) in dry DMF (80 mL) at 25 °C was added ^{t}BuOK (6.87 g, 61.35 mmol), and the mixture was stirred for 1 h to which 4-fluorobenzaldehyde (6.58 mL, 61.35 mmol) in dry DMF (20 mL) was added and stirred for 15 h at room temperature (ca. 25 °C). The reaction mixture was quenched with water (200 mL) and

Table 7. Analytical and HPLC Conditions for Thiazolidinediones[a]

compd no.	extraction solvent[a] (v/v)	mobile phase[b] (v/v)	detector (nm)	retention times of TZDs and std (min)
4a	M:E (1:1)	M:SPB (9:1)	UV (345)	26/8.0
4b	D:E (1:2)	M:SPB (8:2)	UV (345)	17/23.4
5a	D:M (1:2)	M:SPB (9:1)	UV (230)	11.7/7.3
5b	E:D (3:2)	A:M:THF:SPB (55:12:2:33)	fluorescence (ex: 292, em: 325)	10/12
12a	M:E (1:1)	M:SPB (8:2)	UV (345)	11.4/5.3
12b	E:D (1:1)	M:SPB (7.5:2.5)	UV (345)	5/8.5
15a	M:E (1:1)	M:SPB[c] (8.5:1.5)	UV (345)	9, 10/16
15a-maleate	M:E (1:1)	M:SPB[c] (8.5:1.5)	UV (345)	9, 10/16

[a] A: acetonitrile, D: dichloromethane, E: ethyl acetate, M: methanol, S: internal standard (various other TZDs were used as the internal standard as found suitable), SPB: sodium dihydrogen orthophosphate buffer (pH 5.0), THF: tetrahydrofuran. [b] Mobile phase flow rate was 1 mL/min. [c] Mobile phase flow rate was 0.8 mL/min.

extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was chromatographed over silica gel using a mixture (0.5:9.5−0.75:9.25) of ethyl acetate and petroleum ether as eluent to get 7.9 g (60%) of **3** as a viscous liquid: IR ν_{max} (neat) 1692, 1601 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 3 H), 1.95 (m, 1 H), 2.1 (s, 3 H), 2.2 (m, 1 H), 2.2 (s, 3 H), 2.25 (s, 3 H), 2.65 (m, 2 H), 4.05 (q, J = 9.5 Hz, 2 H), 4.7 (s, 2 H), 7.05 (d, J = 9.0 Hz, 2 H), 7.35−7.55 (m, 5 H), 7.85 (d, J = 8.71 Hz, 2 H), 9.98 (s, 1 H); Mass *m/e* (relative intensity) 430 (M^+, 4.8), 339 (56), 91 (100).

5-[4-[6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy]phenylmethylene]thiazolidine-2,4-dione (4a). A mixture of 4-[6-benzyloxy-2,5,7,8-tetramethyl chroman-2-ylmethoxy]benzaldehyde (**3**) (4.8 g, 11.16 mmol), thiazolidine-2,4-dione (1.56 g, 13.3 mmol), benzoic acid (0.16 g, 1.67 mmol), and piperidine (0.176 g, 1.45 mmol) in toluene (50 mL) was refluxed for 4 h with continuous removal of water using a Dean−Stark water separator. The reaction mixture was cooled to ca. 25 °C, and the resultant crystalline compound was filtered, washed with water (2 × 100 mL), dried, and recrystallized from MeOH to afford 4.0 g (60%) of **4a**: mp 146−148 °C; IR ν_{max} (KBr) 1745, 1689 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.5 (s, 3 H), 1.97 (m, 1 H), 2.1 (s, 3 H), 2.2 (s, 3 H), 2.2 (m, 1 H), 2.25 (s, 3 H), 2.7 (m, 2 H), 4.0−4.1 (q, J = 9.0 Hz, 2 H), 4.75 (s, 2 H), 7.08 (d, J = 9.0 Hz, 2 H), 7.35−7.6 (m, 7 H), 7.85 (s, 1 H); Mass *m/z* (relative intensity) 529 (M^+, 1.6), 439 (17.5), 91 (100). Anal. Calcd for $C_{31}H_{31}NO_5S$ (529.6): C, 70.24; H, 5.85; N, 2.64. Found: C, 70.20; H, 5.86; N, 2.7.

5-[4-[6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy]phenylmethyl]thiazolidine-2,4-dione (5a). A suspension of 5-[4-[6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy]phenylmethylene]thiazolidine-2,4-dione (**4a**) (2.0 g, 3.7 mmol) and magnesium turnings (1.6 g, 66.1 mmol) in dry MeOH (30 mL) was stirred at 45 °C for 8 h. The reaction mixture was acidified with 6 N HCl to pH 5.0 and extracted with dichloromethane (2 × 50 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated. The crude product was chromatographed over silica gel using a mixture of MeOH:$CHCl_3$ (0.2:9.8) as eluent to yield **5a** (1.1 g, 54%): mp 107−109 °C; IR ν_{max} (KBr) 1762, 1679 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.43 (s, 3 H), 1.87 (m, 1 H), 2.2 (m, 1 H), 2.09 (s, 3 H), 2.17 (s, 3 H), 2.22 (s, 3 H), 2.6 (t, J = 6.24 Hz, 2 H), 3.04 (dd, J_1 = 14.1, J_2 = 9.5 Hz, 1 H), 3.41 (dd, J_1 = 14.1 Hz, J_2 = 3.65 Hz, 1 H), 3.86 (q, J = 9.23 Hz, 2 H), 4.47 (dd, J_1 = 9.3, J_2 = 3.92 Hz, 1 H), 4.69 (s, 2 H), 6.86 (d, J = 8.5 Hz, 2 H), 7.12 (d, J = 8.5 Hz, 2 H), 7.4 (m, 5 H); Mass *m/e* (relative intensity) 460 (4.3), 441 (48), 91 (100). Anal. Calcd for $C_{31}H_{33}NO_5S$ (531.68): C, 69.97; H, 6.2; N, 2.6. Found: C, 69.92; H, 6.25; N, 2.5.

5-[4-[6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy]phenylmethylene]thiazolidine-2,4-dione (4b). A mixture of 5-[4-[6-benzyloxy-2,5,7,8-tetramethyl chroman-2-ylmethoxy]phenylmethylene]thiazolidine-2,4-dione (**4a**) (2.3 g, 4.3 mmol), glacial acetic acid (13.8 mL), and concentrated HCl (4.6 mL) was stirred at 70 °C for 48 h. The reaction mixture was cooled to 15 °C and neutralized to pH 7.0 with 10% Na_2CO_3 solution. The resulting pale yellow colored solid was filtered and washed with excess water. The compound was dried and recrystallized from MeOH to yield 1.0 g (52%) of **4b**: mp 206−208 °C; IR ν_{max} (KBr) 3479, 1735, 1689 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 3 H), 1.9 (m, 1 H), 2.1 (m, 1 H), 2.08 (s, 3 H), 2.11 (s, 3 H), 2.16 (s, 3 H), 2.62 (m, 2 H), 3.98 (q, J = 7.48 Hz, 2 H), 6.99 (d, J = 8.71 Hz, 2 H), 7.41 (d, J = 8.71 Hz, 2 H), 7.8 (s, 1 H); Mass *m/e* (relative intensity) 439 (M^+, 100). Anal. Calcd for $C_{24}H_{25}NO_5S$ (439.5): C, 65.53; H, 5.69; N, 3.18. Found: C, 65.52; H, 5.71; N, 3.2.

5-[4-[6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy]phenylmethyl]thiazolidine-2,4-dione (Troglitazone, 5b). The title compound **5b** (0.58 g, 70%) was prepared from 5-[4-[6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy]-phenylmethyl]thiazolidine-2,4-dione (**5a**) (1 g, 1.9 mmol) by a procedure similar to that described for the preparation of **4b**: mp 180−181 °C (lit.[23] mp 183−186 °C).

2-[*N*-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethanol (6). A mixture of (6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)methane sulfonate (**2**) (20.0 g, 0.05 mol) and 2-(methylamino)ethanol (80 mL) was heated under a nitrogen atmosphere at 120 °C with stirring for 12 h. The mixture was cooled to room temperature and poured into water (100 mL). The solution was extracted with ethyl acetate repeatedly (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give 18.0 g (95%) of **6**: IR ν_{max} (neat) 3500 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.2 (s, 3 H), 1.7 (m, 1 H), 2.0 (m, 1 H), 2.15 (s, 3 H), 2.2 (s, 3 H), 2.25 (s, 3 H), 2.45 (s, 3 H), 2.55−2.85 (m, 6 H), 3.6 (t, J = 5.1 Hz, 2 H), 4.7 (s, 2 H), 7.3−7.55 (m, 5 H); Mass *m/z* (relative intensity) 383 (M^+, 12.3), 88 (100).

2-[*N*-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethyl Chloride (7). Thionyl chloride (2.5 mL) was added dropwise to a stirred, ice cooled solution of 2-[*N*-[6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-*N*-methyl]aminoethanol (**6**) (4.0 g, 10.4 mmol) in dry benzene (10 mL). The resulting mixture was stirred at 0 °C for 2 h and then diluted with ethyl acetate (40 mL), washed with saturated aqueous sodium bicarbonate solution (2 × 25 mL), H_2O (50 mL), and brine (50 mL), and dried (Na_2SO_4). The ethyl acetate layer was evaporated, and the residue was chromatographed over silica gel with 20% EtOAc in petroleum ether as an eluent to give 4.0 g (96%) of **7**: IR ν_{max} (neat) 2935 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (s, 3 H), 1.6−1.8 (m, 1 H), 1.9−2.07 (m, 1 H), 2.10 (s, 3 H), 2.17 (s, 3 H), 2.22 (s, 3 H), 2.49 (s, 3 H), 2.55−2.75 (m, 4 H), 2.94 (t, J = 7.0 Hz, 2 H), 3.6 (t, J = 1.0 Hz, 2 H), 4.69 (s, 2 H), 7.3−7.6 (m, 5 H); Mass *m/e* (relative intensity) 416 (M^+, 12.7), 106 (100).

4-[2-[*N*-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]benzaldehyde (8). To a mixture of 2-[*N*-(6-benzyloxy-2,5,7,8-tetramethyl chroman-2-ylmethyl)-*N*-methylamino]ethyl chloride (**7a**) (9.4 g, 0.023 mol) and 4-hydroxybenzaldehyde (34.0 g, 0.28 mol) in DMF (50 mL) was added K_2CO_3 (4.8 g, 0.035 mmol), and the mixture was stirred at 80 °C for 6 h. To the reaction mixture was added water (100 mL), and the mixture was extracted with ethyl acetate (2 × 100 mL). The extracts were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under reduced pressure to give 10.5 g (94%) of **8**: IR ν_{max} (neat) 1692, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (s, 3 H),

1.65 (m, 1H), 2.0 (m, 1 H), 2.1 (s, 3 H), 2.18 (s, 3 H), 2.2 (s, 3 H), 2.5 (s, 3 H), 2.55−2.85 (m, 4 H), 3.05 (m, 2 H), 4.19 (t, J = 5.8 Hz, 2 H), 4.7 (s, 2 H), 6.98 (d, J = 8.6 Hz, 2 H), 7.4 (m, 5 dH), 7.8 (d, J = 8.8 Hz, 2 H), 9.85 (s, 1 H); Mass *m/e* 487 (M^+, 11.1), 396 (100).

5-[4-[2-[*N*-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]phenylmethylene]-thiazolidine-2,4-dione (12a). A solution of 4-[2-[*N*-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]benzaldehyde (**8**) (12.8 g, 0.026 mol) and 2,4-thiazolidinedione (3.2 g, 0.027 mol) in toluene (100 mL) containing piperidine (0.3 g, 3.5 mmol) and benzoic acid (0.4 g, 3.2 mmol) was heated at reflux for 2 h using a Dean−Stark apparatus. The reaction mixture was cooled and filtered, and the filtrate was washed with H_2O (100 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was chromatographed on silica gel using 2−10% (gradient elution) of methanol in benzene to afford 15.3 g (99%) of **12a**: mp 74−76 °C; IR ν_{max} (KBr) 1739, 1699, 1596 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (s, 3 H), 1.70 (m, 1 H), 2.0 (m, 1 H), 2.07 (s, 3 H), 2.18 (s, 3 H), 2.2 (s, 3 H), 2.52 (s, 3 H), 2.65 (t, J = 10.9 Hz, 2 H), 2.7 (s, 2 H), 3.05 (t, J = 5.8 Hz, 2 H), 4.15 (t, J = 5.8 Hz, 2 H), 4.7 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.4 (m, 7 H), 7.75 (s, 1 H); Mass *m/e* (relative intensity) 587 (M^+, 3.8), 291 (81.3), 91 (100). Anal. Calcd for $C_{34}H_{38}N_2O_5S$ (586.73): C, 69.54; H, 6.48; N, 4.77. Found: C, 69.53; H, 6.49; N, 4.78.

5-[4-[2-[*N*-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]phenylmethylene]-thiazolidine-2,4-dione (12b). To a solution of 12.5 g (0.021 mol) of 5-[4-[2-[*N*-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]phenylmethylene]thiazolidine-2,4-dione (**12a**) in 120 mL of acetic acid was added 40 mL of concentrated hydrochloric acid. The resulting mixture was heated at 60 °C for 1 h. The solvent was removed under reduced pressure, and the residue was diluted with acetone. The resulting white solid was filtered and washed with an excess of acetone. The solid was suspended in methanol, and the pH was adjusted to 7 by the addition of triethylamine. The solvent was removed under reduced pressure, and the resulting residue was dissolved in EtOAc (100 mL) which was washed with H_2O (100 mL) followed by brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed by distillation under reduced pressure. The crude product was purified by column chromatography on silica gel using 2−10% (gradient elution) of methanol in chloroform to afford 9.8 g (94%) of **12b**: mp 98−100 °C; IR ν_{max} (KBr) 3411, 1736, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.2 (s, 3 H), 1.65 (m, 1 H), 2.0 (m, 1 H), 2.05 (s, 3 H), 2.1 (s, 3 H), 2.15 (s, 3 H), 2.51 (s, 3 H), 2.65 (m, 2 H), 2.7 (s, 2 H), 3.0 (t, J = 5.6 Hz, 2 H), 4.15 (t, J = 5.8 Hz, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.4 (d, J = 8.8 Hz, 2 H), 7.8 (s, 1 H); Mass *m/e* 496 (M^+, 22.2), 205 (100). Anal. Calcd for $C_{27}H_{32}N_2O_5S$ (496.61): C, 65.24; H, 6.44; N, 5.64. Found: C, 65.20; H, 6.45; N, 5.68.

4-[2-[*N*-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]nitrobenzene (9). A stirred mixture of 2-[*N*-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethyl chloride (**7**) (4.0 g, 0.01 mol), 4-nitrophenol (1.4 g, 0.01 mol), and K_2CO_3 (3.5 g, 0.025 mol) in anhydrous DMF (20 mL) was heated at 80 °C for 4 h. The reaction mixture was cooled, water (50 mL) was added, and the mixture was extracted with EtOAc (50 mL). The extract was washed with 5% aqueous Na_2CO_3 (25 mL) followed by brine (25 mL) and dried (Na_2SO_4). The solvent was removed by distillation under reduced pressure to give 4.5 g (90%) of **9** as an oil: IR ν_{max} (neat) 2934, 1593 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (s, 3 H), 1.6−1.8 (m, 1 H), 1.95−2.05 (m, 1 H), 2.06 (s, 3 H), 2.17 (s, 3 H), 2.20 (s, 3 H), 2.52 (s, 3 H), 2.55−2.75 (m, 4 H), 3.04 (m, 2 H), 4.15 (m, 2 H), 4.68 (s, 2 H), 6.92 (d, J = 9.2 Hz, 2 H), 7.35−7.60 (m, 5 H), 8.17 (d, J = 9 Hz, 2 H); Mass *m/e* (relative intensity) 505 ($M^+ + 1$, 14.3), 413 (100).

4-[2-[*N*-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]aniline (10). 4-[2-[*N*-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]nitrobenzene (**9**) (1.0 g, 2 mmol) was dissolved in EtOAc (6 mL) and was reduced with hydrogen (60 psi) in the presence of 10% palladium on charcoal (100 mg) at ambient temperature until hydrogen uptake (nearly 8 h) ceased. The solution was filtered through a bed of Celite (1.0 g), and the filter pad was washed with EtOAc (3 × 10 mL). The combined filtrate was evaporated to dryness under reduced pressure. The crude product was chromatographed on silica gel using 2−10% (gradient elution) of methanol in $CHCl_3$ to afford 0.9 g (95%) of **10** as an oil: IR ν_{max} (neat) 1699 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.28 (s, 3 H), 1.65−1.90 (m, 1 H), 1.95−2.10 (m, 1 H), 2.11 (s, 3 H), 2.18 (s, 3 H), 2.23 (s, 3 H), 2.53 (s, 3 H), 2.6−2.8 (m, 4 H), 3.0 (m, 2 H), 4.05 (t, J = 6.2 Hz, 2 H), 4.71 (s, 2 H), 6.63 (d, J = 8.8 Hz, 2 H), 6.75 (d, J = 8.8 Hz, 2 H), 7.35−7.65 (m, 5 H); Mass *m/e* (relative intensity) 474 (M^+, 8.9), 179 (100).

Ethyl-2-bromo-3-[4-[2-[*N*-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]-phenyl]propanoate. A solution of $NaNO_2$ (1.48 g, 21 mmol) in H_2O (2.9 mL) was added dropwise to a stirred and ice cooled mixture of 4-[2-[*N*-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]aniline (**10**) (10.0 g, 21.0 mmol), aqueous HBr (48%, 14.5 mL), MeOH (19.4 mL), and acetone (48 mL) below 5 °C. The solution was stirred at 5 °C for 30 min, ethyl acrylate (13.7 mL) was added, and the temperature was raised to 38 °C. Powder Cu_2O (182 mg, 1.3 mmol) was added in small portions to the vigorously stirred mixture. After the N_2 gas evolution had ceased, the reaction mixture was concentrated in vacuo. The residue was diluted with H_2O (100 mL), made alkaline with concentrated NH_4OH (25 mL), and extracted with EtOAc (2 × 100 mL). The EtOAc extract was washed with brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to give 6.2 g (46%) of the title compound: IR ν_{max} (neat) 1738, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10−1.40 (m, 6 H), 1.6−1.8 (m, 1 H), 1.90−2.05 (m, 1 H), 2.08 (s, 3 H), 2.16 (s, 3 H), 2.20 (s, 3 H), 2.51 (s, 3 H), 2.55−2.75 (m, 4 H), 3.0 (m, 2 H), 3.10−3.25 (m, 1 H), 3.3−3.5 (m, 1 H), 4.0−4.25 (m, 4 H), 4.28−4.4 (m, 1 H), 4.70 (s, 2 H), 6.8 (d, J = 8.6 Hz, 2 H), 7.1 (d, J = 8.6 Hz, 2 H), 7.3−7.6 (m, 5 H); Mass *m/e* (relative intensity) 638 (M^+, 6.4), 344 (100).

5-[4-[2-[*N*-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-ethylamino]ethoxy]phenylmethyl]-thiazolidine-2,4-dione (11a). A mixture of ethyl 2-bromo-3-[4-[2-[*N*-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]phenyl]propanoate (0.75 g, 1.2 mmol), thiourea (0.18 g, 2.4 mmol), NaOAc (0.2 g, 2.4 mmol), and EtOH (5 mL) was stirred under reflux for 5 h. The reaction mixture was cooled and extracted with EtOAc (2 × 15 mL). The organic extracts were dried (Na_2SO_4) and concentrated to get 2-imino-5-[4-[2-[*N*-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]phenyl methyl]-4-thiazolidinone which was used in the next step without further purification.

A mixture of the above crude product, 2 N HCl (7 mL), and EtOH (7 mL) was stirred under reflux for 12 h. The reaction mixture was concentrated in vacuo. The residue was diluted with H_2O (20 mL), neutralized with saturated aqueous $NaHCO_3$, and extracted with EtOAc (2 × 25 mL). The EtOAc extract was washed with brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was chromatographed over silica gel with 40% EtOAc in petroleum ether as eluent to afford 0.38 g (55%) of **11a**: IR ν_{max} (neat) 1751, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.26 (s, 3 H), 1.6−1.8 (m, 1 H), 1.9−2.05 (m, 1 H), 2.09 (s, 3 H), 2.17 (s, 3 H), 2.22 (s, 3 H), 2.52 (s, 3 H), 2.6−2.8 (m, 4 h), 2.9−3.2 (m, 3 H), 3.35−3.5 (m, 1 H), 4.1 (m, 2 H), 4.4−4.55 (m, 1 H), 4.69 (s, 2 H), 6.82 (d, J = 8.2 Hz, 2 H), 7.12 (d, J = 8.2 Hz, 2 H), 7.3−7.6 (m, 5 H); Mass *m/e* (relative intensity) 588 (M^+, 3.4), 380 (6.9), 293 (27.6), 91 (100).

5-[4-[2-[*N*-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]phenylmethyl]-thiazolidine-2,4-dione (11b). To a stirred suspension of 5-[4-[2-[*N*-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]phenylmethylene]thiazolidine-2,4-dione (**12b**) (4.25 g, 8.6 mmol) in methanol (50 mL) at room

temperature was added magnesium turnings (3.7 g, 150 mmol), and the reaction mixture was stirred overnight at the same temperature. The reaction mixture was added to ice water (920 mL), the pH was adjusted to 6.5−7 using 10% aqueous hydrochloric acid, and the solution was extracted with chloroform (3 × 75 mL). The combined organic extract was washed with H_2O and dried ($CaCl_2$), and the solvent was removed under reduced pressure. The residual mass was chromatographed over silica gel using 3% methanol in chloroform to give 4.0 g (95%) of **11b**: mp 74−75 °C; IR ν_{max} (KBr) 3437, 1752, 1691 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (s, 3 H), 1.7 (m, 1 H), 2.0 (m, 1 H), 2.09 (s, 3 H), 2.11 (s, 3 H), 2.15 (s, 3 H), 2.5 (s, 3 H), 2.65 (bs, 4 H), 2.97 (m, 2 H), 3.1 (dd, J_1 = 14.1 Hz and J_2 = 9.4 Hz, 1 H), 3.42 (dd, J_1 = 14.0 Hz, J_2 = 3.8 Hz, 1 H), 4.05 (m, 2H), 4.5 (dd, J_1 = 8.9 Hz, J_2 = 4.0 Hz, 1 H), 6.8 (d, J = 9.35 Hz, 2 H), 7.15 (d, J = 9.55 Hz, 2 H); Mass *m/e* (relative intensity) 498 (M^+, 6.0), 235 (100). Anal. Calcd for $C_{27}H_{34}N_2O_5S$ (498.62): C, 64.98; H, 6.82; N, 5.61. Found: C, 64.99; H, 6.8; N, 5.65.

5-[4-[2-[*N*-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]phenylmethyl]-thiazolidine-2,4-dione (11b). The title compound **11b** (0.4 g, 95%) was also prepared from 5-[4-[2-[*N*-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-*N*-methylamino]ethoxy]phenylmethyl]thiazolidine-2,4-dione (**11a**) (0.5 g, 0.85 mmol) by a procedure similar to that described for the preparation of **10b**. The analytical data is identical with that described previously for **11b**.

***N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methanol (13).** A mixture of (2*R*/*S*)-[6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-methanesulfonate (**2**) (100 g, 0.25 mol) and (*S*)-prolinol (100 g, 0.99 mol) was heated under nitrogen atmosphere at 120 °C with stirring for 6 h. The mixture was cooled to ca. 25 °C and poured into water (250 mL), and the solution was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were washed with brine (250 mL), dried (Na_2SO_4), and evaporated to dryness under reduced pressure to give 101 g (100%) of the crude product which was chromatographed over silica gel using 0.5% methanol in chloroform to afford 75.7 g (75%) of **13** as a syrupy liquid: $[\alpha]_D^{27} = -9.5$ (*c* 1.0, $CHCl_3$); IR ν_{max} (neat) 3459 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.19, 1.25 (2s, 3 H), 1.55−2.05 (m, 6 H), 2.11 (s, 3 H), 2.18 (s, 3 H), 2.22 (s, 3 H), 2.35−3.0 (m, 6 H), 3.25−3.75 (m, 3 H), 4.7 (s, 2 H), 7.2−7.6 (m, 5H); Mass *m/z* (relative intensity) 409 (M^+, 3.8), 114 (100).

N-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(3*R*)-3-chloropiperidine (14). Thionyl chloride (6 mL, 0.082 mol) was added dropwise to a stirred, ice cooled solution of *N*-[2(*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methanol (**13**) (17 g, 0.042 mol) in dry benzene (200 mL). The resulting mixture was stirred at room temperature for 1 h, diluted with ethyl acetate (50 mL), washed with saturated aqueous sodium bicarbonate solution (100 mL), water (100 mL), and brine (100 mL), and dried (Na_2SO_4). The solution was filtered, and the filtrate was evaporated. The residue was chromatographed on a silica gel column using 12% EtOAc in petroleum ether as eluent to give 13.0 g (73%) of **14** as a viscous liquid: IR ν_{max} (neat) 2941, 1456, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.24 (s, 3 H), 1.4−2.5 (m, 8 H), 2.1 (s, 3 H), 2.18 (s, 3 H), 2.23 (s, 3 H), 2.53 (s, 2 H), 2.63 (t, J = 6.8 Hz, 2 H), 2.8 (m, 1 H), 3.3 (m, 1 H), 4.0 (m, 1 H), 4.7 (s, 2 H), 7.3−7.6 (m, 5 H); Mass *m/z* (relative intensity) 427 (M^+, 8.9), 336 (100).

Reaction of *N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(3*R*)-3-chloropiperidine (14) with 4-Hydroxybenzaldehyde. To a mixture of *N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(3*R*)-3-chloropiperidine (**14**) (5.0 g, 0.012 mol) and 4-hydroxybenzaldehyde (1.7 g, 0.14 mol) in dry DMF (30 mL) was added K_2CO_3 (6.4 g, 0.046 mol), and the mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled to room temperature. Water (20 mL) was added, and the reaction mixture was extracted with EtOAc (2 × 50 mL). The EtOAc extract was washed with 5% aqueous Na_2CO_3 solution, followed by brine (100 mL), and dried over anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure to give 4.2 g (70%) of the crude product as a mixture (1:1) of pyrrolidine (**16**) and piperidine **19** derivatives. The crude product was separated by column chromatography on silical gel using 2−10% (gradient elution) EtOAc in petroleum ether to afford 4-[*N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy benzaldehyde (**16**) (2.0 g, 33%) as a syrupy liquid and 4-[*N*-[(2*R*/S)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(3*R*)-piperidinyloxy]benzaldehyde (**19**) (2.1 g, 35%) as a semisolid.

Compound 16: IR ν_{max} (neat) 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.2 (s, 3 H), 1.5−2.05 (m, 6 H), 2.09−2.3 (6s, 9 H), 2.35−3.2 (m, 6 H), 3.4 (m, 1 H), 3.8 (m, 1 H), 4.05 (m, 1 H), 4.7 (s, 2 H), 7.0 (m, 2 H), 7.3−7.6 (m, 5 H), 7.75 (m, 2 H), 9.9 (s, 1 H); Mass *m/z* (relative intensity) 514 ($M^+ + 1$, 2.6), 218 (100).

Compound 19: IR ν_{max} (neat) 1692 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.2 (s, 3 H), 1.3−2.7 (m, 12 H), 1.9 (s, 3 H), 2.09 (s, 3 H), 2.12 (s, 3 H), 2.8 (m, 1 H), 3.25 (m, 1 H), 4.4 (m, 1 H), 4.62 (s, 2 H), 6.9 (m, 2 H), 7.2−7.6 (m, 5 H), 7.78 (m, 2 H), 9.8 (s, 1 H). Mass (*m/z*) (relative intensity) 514 ($M^+ + 1$, 7.5), 218 (100).

Reaction of *N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methanol (13) with 4-Hydroxybenzaldehyde. To a mixture of *N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2S)-pyrrolidine-2-methanol (**13**) (16.0 g, 39.0 mmol), 4-hydroxybenzaldehyde (5.2 g, 42.6 mmol), and triphenyl phosphine (11.8 g, 45.0 mmol) in THF (200 mL) was added diisopropyl azodicarboxylate (15 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc (100 mL), washed with water (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a 1:1 mixture of **16** and **19** which was separated by column chromatography using 2−10% (gradient elution) ethyl acetate in petroleum ether to give **16** (8.2 g, 41%) as a syrupy liquid and **19** (8 g, 40%) as a semisolid.

4-[*N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]benzaldehyde (16). To a solution of *N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methanol (**13**) (0.5 g, 1.22 mmol) in DMF (10 mL) was added ^{t}BuOK (0.27 g, 2.44 mmol), and the mixture was stirred at room temperature for 30 min. To this was added 4-fluorobenzaldehyde (0.3 g, 2.44 mmol), and the mixture was stirred for 36 h at the same temperature. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (2 × 15 mL). The combined organic layer was washed with water (2 × 25 mL), dried, and concentrated. The crude product was chromatographed on silica gel using 4% EtOAc in petroleum ether as eluent to get 0.38 g (60%) of **16** as a syrupy liquid.

5-[4-[*N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenylmethylene]thiazolidine-2,4-dione (15a). A solution of 4-[*N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]benzaldehyde (**16**) (1.2 g, 2.34 mmol) and 2,4-thiazolidinedione (0.27 g, 2.31 mmol) in toluene (30 mL) containing piperidine (30 mg, 0.35 mmol) and benzoic acid (37 mg, 0.3 mmol) was heated at reflux for 2 h using a Dean−Stark apparatus. The reaction mixture was cooled, diluted with EtOAc (25 mL), and filtered, and the filtrate was washed with H_2O (50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude product obtained above was chromatographed on silica gel using 0−5% (gradient elution) of methanol in chloroform to afford 1.3 g (93%) of **15a** as a pale yellow fluffy solid: mp 86 °C; $[\alpha]_D^{24} = -17.3$ (*c* 1.0, $CHCl_3$); IR (KBr) 1739, 1698, 1595 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.21, 1.26 (2s, 3 H), 1.5−2.05 (m, 6 H), 2.08−2.22 (6s, 9 H), 2.35−3.15 (m, 6 H), 3.4 (m, 1 H), 3.8 (m, 1 H), 4.0 (m, 1 H), 4.7 (s, 2 H), 6.95 (m, 2 H), 7.3−7.6 (m, 7 H), 7.8 (s, 1 H); Mass *m/z* (relative intensity) 613 ($M^+ + 1$, 2.9), 302 (100). Anal. Calcd for $C_{36}H_{40}N_2O_5S$ (612.79): C, 70.5; H, 6.53; N, 4.57. Found: C, 70.45; H, 6.56; N, 4.62.

5-[4-[*N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(3*R*)-piperidinyloxy]phenylmethylene]-thiazolidine-2,4-dione (21a). The title compound **21a** (1 g, 57%) was prepared as a pale yellow solid from 4-[*N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(3*R*)-piperidinyloxy]benzaldehyde (**19**) (1.5 g, 2.92 mmol) and thiazolidine-2,4-dione (0.34 g, 2.92 mmol) by a procedure similar to that described for **15a**: mp 142 °C; IR ν_{max} (KBr) 1739, 1697, 1594 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22 (s, 3 H), 1.3−1.90 (m, 6 H), 2.0 (s, 3 H), 2.19 (s, 6 H), 1.95−2.8 (m, 6 H), 2.9 (m, 1 H), 3.25 (m, 1 H), 4.4 (m, 1 H), 4.69 (s, 2 H), 6.95 (m, 2 H), 7.3−7.6 (m, 7 H), 7.78 (s, 1 H); Mass *m*/*z* (relative intensity) 613 ($M^+ + 1$, 5), 392 (100). Anal. Calcd for $C_{36}H_{40}N_2O_5S$ (612.79): C, 70.5; H, 6.53; N, 4.57. Found: C, 70.42; H, 6.55; N, 4.61.

5-[4-[*N*-[(2*R*/*S*)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenylmethylene]thiazolidine-2,4-dione (15b). To a solution of 0.5 g (0.82 mmol) of 5-[4-[*N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenylmethylene]-thiazolidine-2,4-dione (**15a**) in 6 mL of acetic acid was added concentrated HCl (2 mL). The resulting mixture was heated at 60 °C for 2 h. The solvent was removed under reduced pressure, and the residue was diluted with $CHCl_3$ (10 mL) and washed with aqueous sodium bicarbonate solution (5 mL) followed by brine (5 mL). The organic layer was dried over anhydrous calcium chloride, and the solvent was removed by distillation under reduced pressure. The crude product was purified by column chromatography on silica gel using 0−1% (gradient elution) methanol in chloroform to afford 0.42 g (98%) of **15b** as a pale yellow solid: mp 82−84 °C; $[\alpha]_D^{27} = -29.44$ (*c* 0.9, $CHCl_3$); IR ν_{max} (KBr) 1736, 1696, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.21, 1.25 (2s, 3 H), 1.5−2.05 (m, 6 H), 2.13 (m, 9 H), 2.3−3.2 (m, 6 H), 3.4 (m, 1 H), 3.9 (m, 1 H), 4.05 (m, 1 H), 6.95 (d, $J = 7.4$ Hz, 2 H), 7.45 (m, 2 H), 7.82, 7.83 (2s, 1 H); Mass *m*/*z* (relative intensity) 523 ($M^+ + 1$, 6.1), 317 (100). Anal. Calcd for $C_{29}H_{34}N_2O_5S$ (522.66): C, 66.58; H, 6.51; N, 5.36. Found: C, 66.54; H, 6.53; N, 5.39.

5-[4-[*N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenylmethyl]-thiazolidine-2,4-dione (20a). (a) 4-[*N*-(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]nitrobenzene (17). A solution of *N*-[(2*R*/*S*)-6-benzylxoy-2,5,7,8-tetramethyl chroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methanol (**13**) (16.0 g, 0.039 mol) in DMF (100 mL) was added dropwise to a suspension of sodium hydride (50% dispersion in paraffin oil, 2.81 g, 0.059 mol) in DMF (50 mL). The mixture was stirred at room temperature for 0.5 h, after which 4-fluoronitrobenzene (6.6 g, 0.047 mol) was added dropwise and stirred at the same temperature for 2 h. Water (50 mL) was added to the reaction mixture and extracted with ethyl acetate (2 × 100 mL), the mixture was dried (Na_2SO_4), and the solvent was removed under reduced pressure to give 20 g of the crude compound which was chromatographed on silica gel using 10−20% (gradient elution) of EtOAc in petroleum ether to afford 16.8 g (81%) of **17** as a syrupy liquid: IR ν_{max} (neat) 1593, 1513 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25 (m, 3 H), 1.55−3.2 (complex 21 H), 3.4 (m, 1 H), 3.85 (m, 1 H), 4.1 (m, 1 H), 4.7 (s, 2 H), 6.9 (m, 2 H), 7.3−7.6 (m, 5 H), 8.2 (m, 2 H); Mass *m*/*z* (relative intensity) 530 (M^+, 1.7), 205 (100).

(b) 4-[*N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]aniline (18). 4-[*N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethyl chroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]nitrobenzene (**17**) (5.8 g, 11 mmol) was dissolved in EtOAc (30 mL) and was reduced with hydrogen (60 psi) in the presence of 10% palladium on charcoal (0.6 g) at ambient temperature until hydrogen uptake (nearly 6 h) ceased. The solution was filtered through a bed of Celite (1 g), and the filter pad was washed with EtOAc (3 × 50 mL). The combined filtrate was evaporated to dryness under reduced pressure. The crude product was chromatographed on silica gel using 2−10% (gradient elution) of methanol in chloroform to afford 5 g (91%) of **18** as a syrupy liquid: IR ν_{max} (neat) 3361 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.2, 1.3 (2s, 3 H), 1.5−3.2 (complex, 12 h), 2.1 (s, 3 H), 2.15 (s, 3 H), 2.2 (s, 3 H), 3.4 (m, 1 H), 3.75 (m, 1 H), 3.9 (m, 1 H), 4.7 (s, 2 H), 6.7 (m, 4 H), 7.4 (m, 5 H); Mass *m*/*z* (relative intensity) 500 (M^+, 3.2), 205 (100).

(c) Ethyl-2-bromo-3-[4-[*N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenyl]propanoate. A solution of $NaNO_2$ (0.72 g, 1.4 mmol) in H_2O (1.3 mL) was added dropwise to a stirred and ice cooled mixture of 4-[*N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]-aniline (**18**) (4.8 g, 9.6 mmol), aqueous HBr (48%, 6.5 mL), MeOH (8.8 mL), and acetone (21 mL) for 30 min, and then ethyl acrylate (6 mL) was added. The temperature was raised to 38 °C, and powdered Cu_2O (77 mg, 0.54 mmol) was added in small portions to the vigorously stirred mixture. After the N_2 gas evolution had ceased, the reaction mixture was concentrated in vacuo. The residue was diluted with H_2O, made alkaline with concentrated NH_4OH, and extracted with EtOAc (2 × 50 mL). The EtOAc extract was washed with brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was chromatographed on silica gel using 10−20% (gradient elution) of ethyl acetate in petroleum ether to afford 3.0 g (47%) of the title compound as a syrupy liquid: IR ν_{max} (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.2 (m, 6 H), 1.55−3.5 (complex, 15 H), 2.1 (s, 3 H), 2.15 (s, 3 H), 2.2 (s, 3 H), 3.75 (m, 1 H), 3.9 (m, 1 H), 4.2 (m, 2 H), 4.35 (m, 1 H), 4.7 (s, 2 H), 6.7 (m, 2 H), 7.1 (m, 2 H), 7.3−7.6 (m, 5 H); Mass *m*/*z* (relative intensity) 574 ($M^+ -$ Bn, 2.1), 290 (100).

(d) 5-[4-[*N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]-phenylmethyl]thiazolidine-2,4-dione (20a). A mixture of ethyl 2-bromo-3-[4-[*N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenyl]propanoate (7 g, 10.5 mmol), thiourea (1.6 g, 21.0 mmol), NaOAc (1.73 g, 21.0 mmol), and EtOH (42 mL) was stirred under reflux for 5 h. The reaction mixture was cooled and extracted with EtOAc (2 × 40 mL), dried (Na_2SO_4), and concentrated to get 2-imino-5-[4-[*N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenylmethyl]-4-thiazolidinone which was used in the next step without further purification.

A mixture of the above crude product, 2 N HCl (60 mL), and EtOH (60 mL) was stirred under reflux for 12 h. The reaction mixture was concentrated in vacuo. The residue was diluted with H_2O (50 mL), neutralized with saturated aqueous $NaHCO_3$, and extracted with EtOAc (2 × 50 mL). The EtOAc extract was washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel with 40% EtOAc in petroleum ether as eluent to afford **20a** (5.5 g, 85%) as a fluffy solid: mp 62−64 °C; $[\alpha]_D^{27} = -26.4$ (*c* 1.0, $CHCl_3$); IR ν_{max} (KBr) 1754, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25 (m, 3 H), 1.5−2.05 (m, 6 H), 2.1−2.2 (m, 9 H), 2.3−3.25 (m, 7 H), 3.4 (m, 2 H), 3.75 (m, 1 H), 3.95 (m, 1 H), 4.5 (m, 1 H), 4.7 (s, 2 H), 6.8 (m, 2 H), 7.15 (m, 2 H), 7.3−7.6 (m, 5 H); Mass *m*/*z* (relative intensity) 614 (M^+, 2.5), 392 (100). Anal. Calcd for $C_{36}H_{42}N_2O_5S$ (614.81): C, 70.26; H, 6.83; N, 4.55. Found: C, 70.25; H, 6.83; N, 4.56.

5-[4-[*N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)]-(2*S*)-pyrrolidine-2-methoxy]phenylmethylene]thiazolidine-2,4-dione (15a), Maleate. To a solution of 5-[4-[*N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl)]-(2*S*)-pyrrolidine-2-methoxy]phenylmethylene]thiazolidine-2,4-dione (**15a**) (250 mg, 0.41 mmol) in dry Et_2O (5 mL) at room temperature was added maleic acid (47 mg, 0.41 mmol) in Et_2O (5 mL). The reaction mixture was stirred for an additional 30 min, and the Et_2O layer was decanted. The resulting solid was washed twice with Et_2O (2 × 5 mL) and dried under reduced pressure over P_2O_5 for 6 h to get the title compound (220 mg, 74%) as a pale yellow solid: mp 210 °C; $[\alpha]_D^{27} = +27.0$ (*c* 1.0, $CHCl_3$); IR ν_{max} (KBr) 1738, 1700, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25, 1.3 (2s, 3 H), 1.95, 2.0, 2.1 (3s, 9 H), 1.5−4.5 (complex, 15 H), 4.65 (2s, 2 H), 6.1

(s, 2 H), 7.06−7.7 (m, 9 H), 7.8 (s, 1 H); Mass *m*/*z* (relative intensity) 613 (2.8), 157 (100). Anal. Calcd for $C_{40}H_{44}N_2O_5S$ (728.85): C, 65.86; H, 6.04; N, 3.84. Found: C, 65.85; H, 6.04; N, 3.82.

5-[4-[*N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenylmethylene]thiazolidine-2,4-dione (15a), Sodium Salt. To a solution of 5-[4-[*N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenylmethylene]-thiazolidine-2,4-dione (**15a**) (250 mg, 0.41 mmol) in dry Et_2O (15 mL) at room temperature was added NaOMe in MeOH [prepared in situ by dissolving Na (13 mg, 0.57 mmol) in MeOH (1 mL)]. The reaction mixture was stirred at room temperature for 30 min, and the supernatant solvent was decanted. The resulting solid was washed twice with Et_2O (2 × 5 mL) and dried over P_2O_5 under reduced pressure for 6 h to get the title compound (235 mg, 65%) as a pale yellow solid: mp 245 °C; $[\alpha]_D^{27} = -9.3$ (*c* 0.82, $CHCl_3$); IR ν_{max} (KBr) 1676, 1601, 1557, 1509 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.15, 1.2 (2s, 3 H), 2.05, 2.1, 2.15 (3s, 9 H), 1.5−3.6 (complex, 13 H), 3.8 (m, 1 H), 4.0 (m, 1 H), 4.6 (s, 2 H), 7.0 (m, 2 H), 7.5 (m, 8 H); Mass *m*/*z* (relative intensity) 614 (1.6), 301 (100).

5-[4-[*N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenylmethyl]-thiazolidine-2,4-dione (20a), Maleate. The title compound (0.28 g, 94%) was prepared as a pale yellow solid from 5-[4-[*N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenylmethyl]thiazolidine-2,4-dione (**20a**) (0.25 g, 0.41 mmol) and maleic acid (47 mg, 0.41 mmol) by a procedure analogous to that described above for **15a**-maleate: mp 180 °C; $[\alpha]_D^{27} = +19.4$ (*c* 0.66, $CHCl_3$); IR ν_{max} (KBr) 3429, 1752, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.2, 1.25 (2s, 3 H), 2.0, 2.05, 2.1 (3s, 9 H), 1.5−4.5 (complex, 17 H), 4.6 (s, 2 H), 4.9 (m, 1 H), 6.1 (s, 2 H), 6.9 (m, 2 H), 7.2 (m, 2 H), 7.5 (m, 5 H), 12.1 (bs, 1 H, exchangeable with D_2O); Mass *m*/*z* (relative intensity) 615 (8.8), 392 (100). Anal. Calcd for $C_{40}H_{46}N_2O_9S$ (730.8): C, 65.68; H, 6.29; N, 3.83. Found: C, 65.69; H, 6.27; N, 3.85.

5-[4-[*N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenylmethyl]-thiazolidine-2,4-dione (20a), Hydrochloride. To a solution of 5-[4-[*N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy] phenylmethyl]thiazolidine-2,4-dione (**20a**) (0.2 g, 0.33 mmol) in Et_2O (10 mL) at 0 °C was bubbled HCl gas for 30 min. The resulting solution was stirred for an additional 30 min, the supernatant liquid was decanted, and the resulting solid was washed with Et_2O (2 × 5 mL) and dried under reduced pressure over P_2O_5 for 6 h to get the title compound (0.18 g, 86%) as a pale yellow solid: mp 230 °C; $[\alpha]_D^{27} = -9.5$ (*c* 1.0, $CHCl_3$); IR ν_{max} (KBr) 3425, 1751, 1697 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.3, 1.4 (2s, 3 H), 2.0, 2.05, 2.2 (3s, 9 H), 1.5−4.5 (complex, 17 H), 4.6 (s, 2 H), 4.9 (m, 1 H), 6.9 (m, 2 H), 7.2 (m, 2H), 7.5 (m, 5 H), 9.8 (bs, 1 H, exchangeable with D_2O), 12.1 (bs, 1 H, exchangeable with D_2O); Mass *m*/*z* (relative intensity) 615 (19), 224 (100). Anal. Calcd for $C_{36}H_{43}ClN_2O_5S$ (650.5): C, 66.41; H, 6.61; N, 4.30. Found: C, 66.39; H, 6.62; N, 4.30.

5-[4-[*N*-[(2*R*/*S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenylmethyl]-thiazolidine-2,4-dione (20a), Sodium Salt. The title compound (0.27 g, 75%) was prepared as a white solid from 5-[4-[*N*-[(2*R*/*S*)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy]phenylmethyl]thiazolidine-2,4-dione (**20a**) (0.35 g, 0.57 mmol) and Na (19 mg, 0.83 m mol) in MeOH (1 mL) by a procedure analogous to that described above for **15a**-sodium salt: mp 191 °C; $[\alpha]_D^{27} = -23.1$ (*c* 1.0, $CHCl_3$); IR ν_{max} (KBr) 1665, 1563 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.05, 1.25 (2s, 3 H), 2.0 (s, 3 H), 2.1 (s, 6 H), 1.4−4.0 (complex, 17 H), 4.1 (m, 1 H), 4.6 (s, 2 H), 6.8 (m, 2 H), 7.1 (m, 2 H), 7.5 (m, 5 H); Mass *m*/*z* (relative intensity) 558 (3.1), 301 (100).

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