Novel Antidiabetic and Hypolipidemic Agents. 3. Benzofuran-Containing Thiazolidinediones‡

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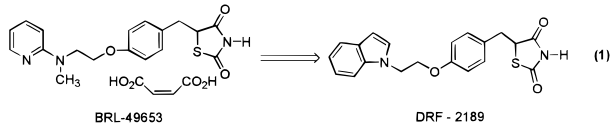
Several thiazolidinedione derivatives having 5-hydroxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran moieties and their 5-benzyloxy derivatives and 5-hydroxy-2,4,6,7-tetramethylbenzofuran moieties were synthesized and evaluated in db/db mice. Insertion of an N-Me group into the linker between thiazolidinedione and substituted benzofuran pharmacophores showed considerable improvement in their euglycemic activity. Further improvement has been observed when a pyrrolidine moiety is introduced in the structure to give 5-[4-[*N*-[3(*R*/*S*)-5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]phenylene]-thiazolidine-2,4-dione (**21a**). At a 100 mg/kg/day dose of the maleate salt, compound **21a** reduced the plasma glucose and triglyceride to the level of lean littermate, i.e. 8 ± 1 mM, and is the most potent and efficacious compound reported in this series.

Introduction

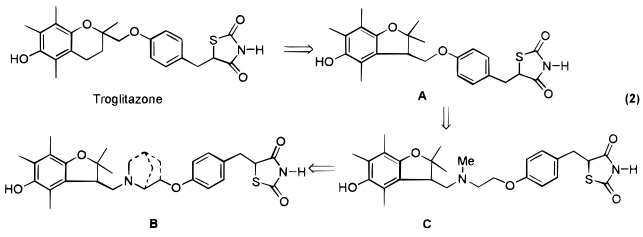
Since the pioneering discovery of ciglitazone,[1] there has been a surge of interest in the development of novel antihyperglycemic agents that can reverse the insulin resistance[2] in non-insulin-dependent diabetes mellitus (type 2) patients. In rodent models of obesity, insulin resistance, and hyperglycemia, thiazolidinediones ameliorate insulin resistance[3] and normalize plasma glucose and insulin without causing hypoglycemia, even at very high doses.[4] However, due to the unsatisfactory efficacy and safety profile of these agents,[5] there has been concern about thiazolidinediones being antidiabetic drugs for the treatment of diabetes. The encouraging reports from clinicians on troglitazone, which is now marketed in Japan and North America[6] (although it still causes liver toxicity in a limited number of patients),[7] have encouraged pharmaceutical companies to continue the development of new thiazolidinedione analogues.[8−11]

We believe that the liver toxicity in the case of troglitazone is idiosyncratic and may not be related to the thiazolidinedione (TZD) pharmacophore. Therefore, we decided to develop a new class of TZDs having a structural motif similar to the chroman ring found in troglitazone.

We have recently reported that DRF 2189, which is conceptually a compound generated by cyclizing the methyl group on nitrogen of BRL-49653 to form a five-membered ring heterocycle along with the adjacent carbon atom of the pyridyl group, shows very good hypolipidemic and euglycemic activities.[2e,12] (eq 1).



In our preliminary studies, we have found that the contraction of the chroman moiety of troglitazone to afford a benzofuran moiety (structure A) leads to a decrease in euglycemic and hypolipidemic activities compared to troglitazone when tested in db/db mice.[13] However, insertion of a $CH_2N(Me)CH_2$ group in structure A leads to improved euglycemic and hypolipidemic activities compared to troglitazone (structure C, eq 2).



In the present study, we are reporting a detailed systematic structure−activity relationship (SAR) of several TZDs having features as shown in structures B and C.

Chemistry

A general strategy to synthesize thiazolidinedione A is shown in Scheme 1. 2,3-Dihydro-2,2,4,6,7-pentamethyl-5-benzyloxybenzofuran-3-carbinol (**1**) was prepared by a reported method[14] and mesylated to furnish

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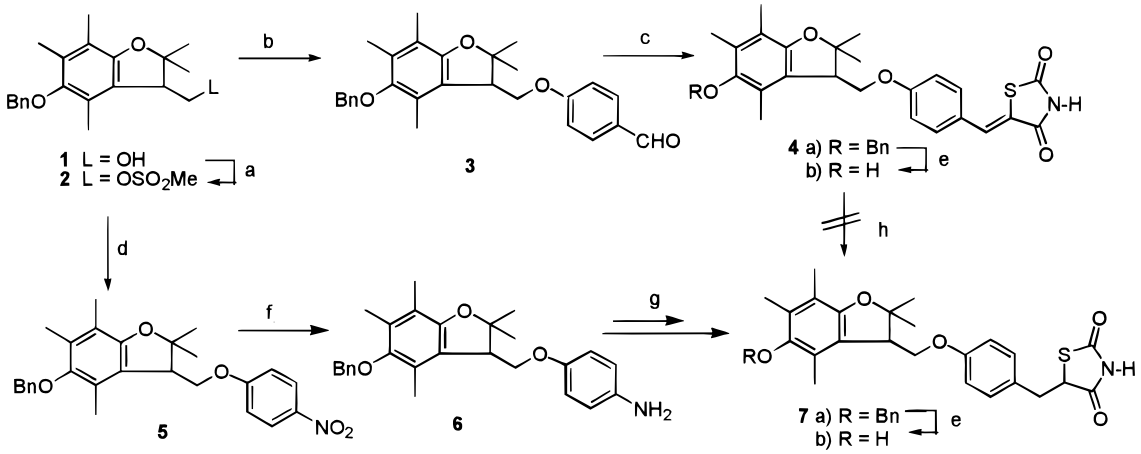
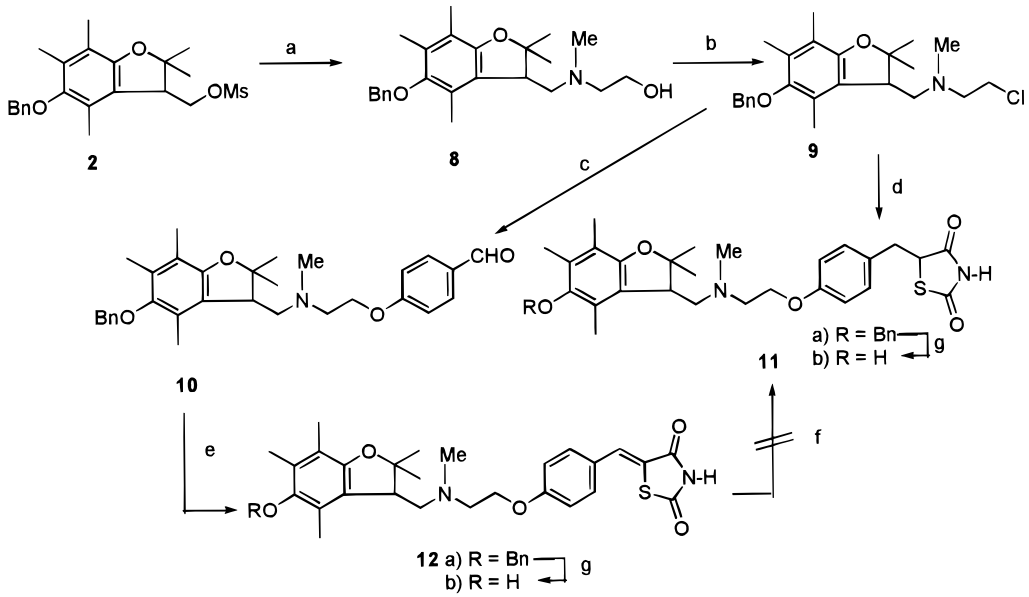
Scheme 1[a]



[a] (a) CH_3SO_2Cl, Et_3N, DCM, 0−25 °C, 5 h, 99%; (b) 4-hydroxybenzaldehyde, K_2CO_3, DMF, 70−80 °C, 12 h, 51%; (c) 2,4-thiazolidinedione (TZD), $C_6H_5CH_3$, piperidinium benzoate, 130 °C, 2 h, 75%; (d) 4-fluoronitrobenzene, NaH, DMF, 25 °C, 3 h, 67%; (e) CH_3COOH concd HCl (3:1), 60 °C, 1−2 h, 54−63%; (f) Pd−C (10%), H_2, 60 psi, EtOAc, 25 °C, 48 h, 75%; (g) (i) HBr, $NaNO_2$, H_2O, CH_3COCH_3, CH_3OH, $CH_2{=}CHCOOC_2H_5$, Cu_2O, 0−40 °C, 0.5 h, 37%, (ii) H_2NCSNH_2, NaOAc, EtOH, 12 h, Δ, 2 N HCl, 80 °C, 12 h, 73%; (h) Mg−CH_3OH, 25 °C, 12 h, or Pd−C (10%), H_2, 60 psi, EtOAc, 25 °C, 60 h.

Scheme 2[a]



[a] (a) $MeNHCH_2CH_2OH$, 170 °C, 20 h, 75%; (b) $SOCl_2$, C_6H_6, ca. 25 °C, 1 h, 97%; (c) 4-hydroxybenzaldehyde, DMF, 50−60 °C, 24 h, 99%; (d) 5-(4-hydroxyphenylmethyl)thiazolidine-2,4-dione, DMF, NaH, 50 °C, 12 h, 41%; (e) 2,4-thiazolidinedione (TZD), $C_6H_5CH_3$, piperidinium benzoate, 130 °C, 2 h, 63%; (f) Mg−CH_3OH, 25 °C, 12 h, or Pd−C (10%), H_2, 60 psi, EtOAc, 25 °C, 60 h; (g) CH_3COOH, concd HCl (3:1), 60 °C, 1−2 h, 57−90%.

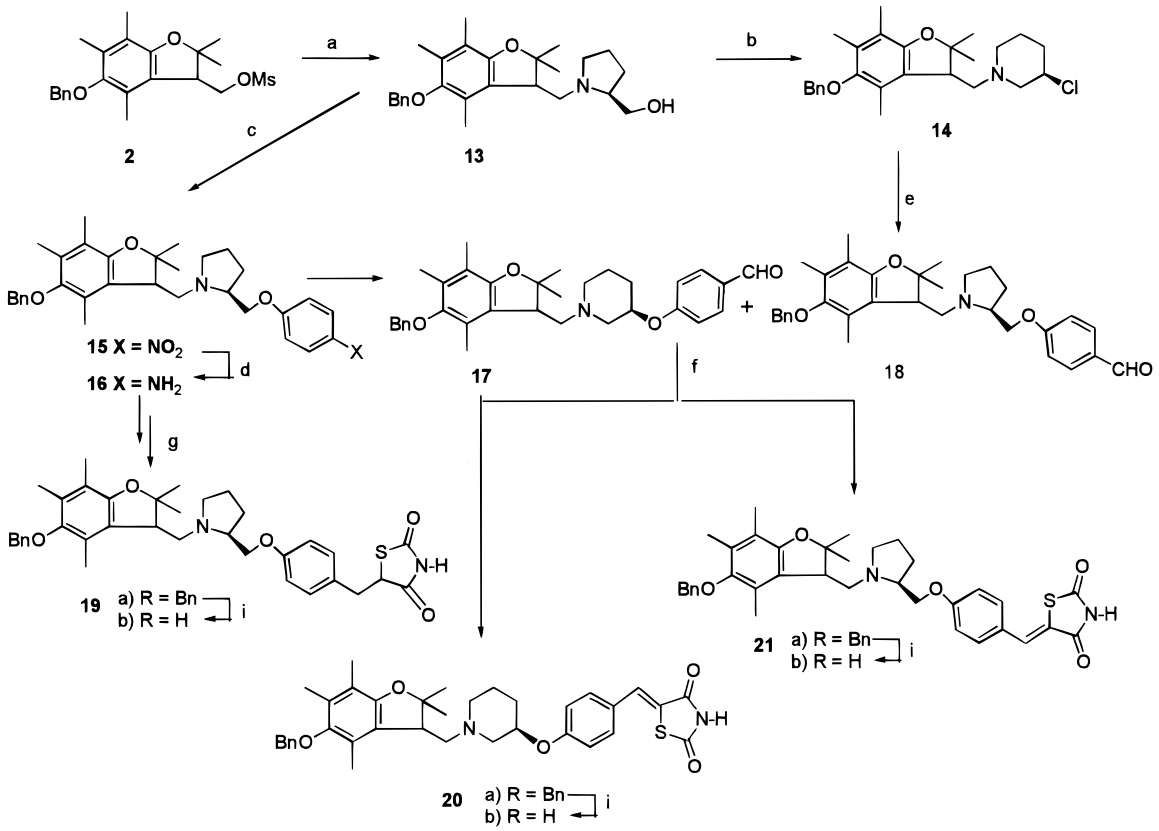
>95% yield of **2**. The mesylate **2** was treated with 4-hydroxybenzaldehyde in the presence of K_2CO_3 in DMF at 70−80 °C for 12 h to furnish the aldehyde **3** (51%) (Scheme 1).

The aldehyde **3** was reacted with 2,4-thiazolidinedione (TZD) in the presence of piperidinium benzoate to furnish good yield (75%) of benzylidenethiazolidinedione analogue **4a**. The benzyl protecting group was removed by refluxing **4a** in a mixture of acetic acid and concentrated HCl to furnish **4b** (63%).

The saturated analogue **7** could not be prepared by either hydrogenation of **4a** with Pd−C or electron-transfer method of Watt (CH_3OH−Mg).[15] Hence, an alternate route was adopted as shown in Scheme 1. The carbinol **1** was treated with 4-fluoronitrobenzene to give the nitro derivative **5** which was subsequently reduced to amino derivative **6**. The amino compound **6** was converted to saturated thiazolidinedione **7a** by a similar method reported elsewhere.[2b] A similar synthetic strategy (Scheme 2) was adopted for the synthesis of various derivatives of C (eq 2).

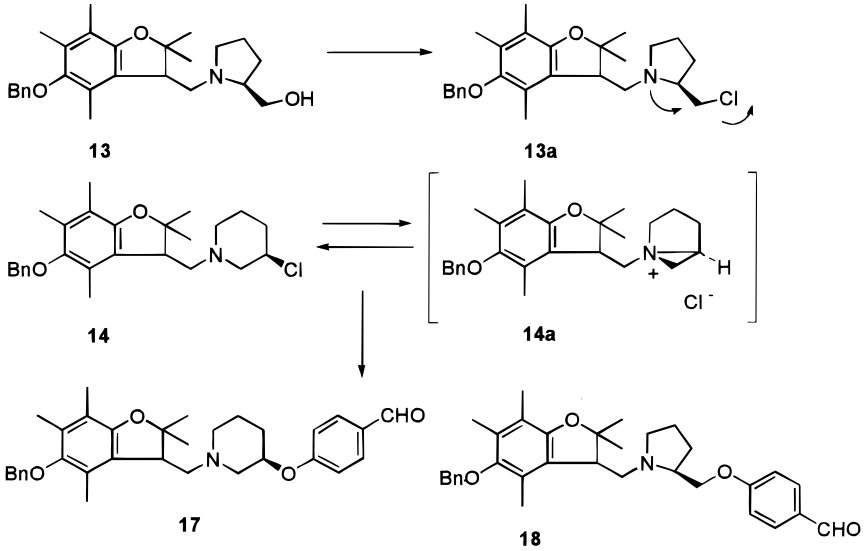
The mesylate **2** was heated with *N*-methylaminoethanol to afford 75% yield of the amino alcohol **8**. The treatment of **8** with thionyl chloride in toluene furnished good yield of chloro compound **9**. The chloro compound **9** when reacted with 4-hydroxybenzaldehyde in the presence of K_2CO_3 in DMF for 24 h furnished quantitative yield of aldehyde **10**. The latter was condensed with 2,4-thiazolidinedione under reported conditions[8d] to furnish a good yield (63%) of unsaturated TZD analogue **12a**. The saturated analogue **11a** was prepared in 41% yield by direct reaction of **9** with 5-(4-hydroxyphenylmethyl)thiazolidine-2,4-dione using NaH (60%) in DMF at ca. 50 °C.

Scheme 3[a]



[a] (a) (*S*)-Prolinol (4 equiv), neat, Δ, 120 °C, 12 h, 73%; (b) $SOCl_2$, C_6H_6, ca. 25 °C, 1 h, 73%; (c) 4-fluoronitrobenzene, NaH, DMF, 25 °C, 3 h, 67%; (d) 4-hydroxybenzaldehyde, K_2CO_3, DMF, 80 °C, 12 h (**17**:**18**, 13%, 65%); (e) Pd−C (10%), H_2, 60 psi, EtOAc, 25 °C, 48 h, 55%; (f) (i) HBr, $NaNO_2$, H_2O, CH_3COCH_3, CH_3OH, $CH_2{=}CHCOOC_2H_5$, Cu_2O, 0−40 °C, 0.5 h, 38%, (ii) H_2NCSNH_2, NaOAc, EtOH, 12 h, Δ, 2 N HCl, 80 °C, 12 h, 83%; (g) 2,4-thiazolidinedione (TZD), $C_6H_5CH_3$, piperidinium benzoate, 130 °C, 2 h, 43−84%; (h) CH_3COOH, concd HCl (3:1), 60 °C, 1−2 h, 43−63%.

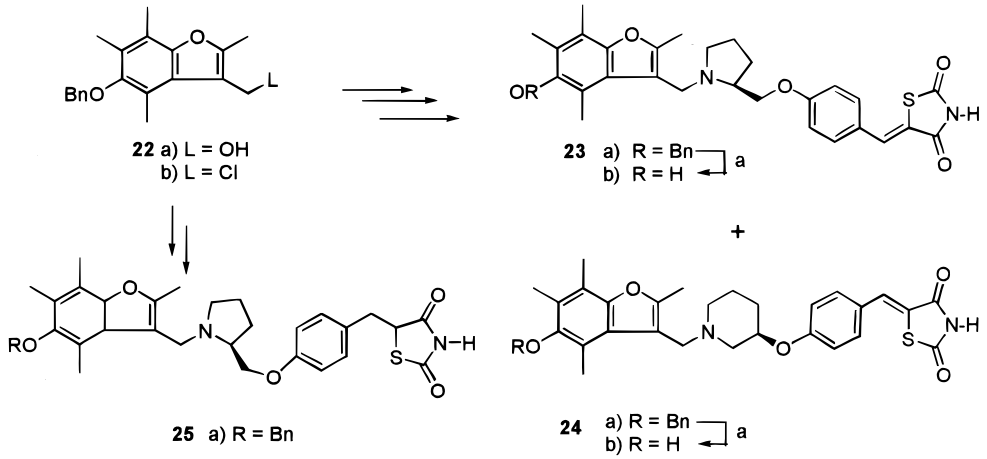
Scheme 4. Mechanism of Transformation of Pyrrolidine Derivative **13** to Piperidine Derivatives **14** and to Aldehydes **17** and **18**



An analogous strategy was adopted to prepare thiazolidinedione derivatives B mentioned in eq 2. The synthetic routes are outlined in Scheme 3.

The mesylate **2** was heated with (*S*)-prolinol (4 equiv) at 120 °C for 12 h to furnish pyrrolidine derivative **13** in 73% yield. The reaction of **13** with thionyl chloride in benzene at ca. 25 °C for 1 h furnished **14** in 91% yield. The formation of 3-chloropiperidine derivative **14** may be visualized by the reaction of $SOCl_2$ with prolinol derivative **13** to furnish 3-chloromethylpyrrolidine derivative **13a** which can undergo intramolecular displacement reaction by the attack of nitrogen to give an aziridine intermediate **14a** (Scheme 4).[16] The chloride ion can attack intramolecularly to furnish a strain-free 3-chloropiperidine derivative **14**. Interestingly, the reaction of **14** with 4-hydroxybenzaldehyde in the presence

Scheme 5. Synthesis of Benzofuran Derivative via Analogous Synthetic Transformations Reported in Scheme 2



of K_2CO_3 (4 equiv) in DMF at 80 °C for 12 h furnished a mixture of five- and six-membered ring products (**17** and **18**) in almost a 1:1 ratio (69%).

Finally, the mixture of aldehydes **17** and **18** was condensed with 2,4-thiazolidinedione to afford a mixture of unsaturated compounds **20a** and **21a**, respectively, which were separated by flash chromatography over silica gel. The unsaturated TZD analogue **21a** was refluxed in AcOH−HCl, to afford debenzylated product **21b**. The saturated TZD analogue **19a** was prepared by an alternate route since our attempts to saturate **21a** by Pd−C (10%)/H_2 or CH_3OH−Mg failed to give the desired results. Thus, the prolinol derivative **13** was treated with 4-fluoronitrobenzene to give 67% yield of the nitro compound **15** which was subsequently reduced to amino derivative **16** (Scheme 3). The amino compound **16** was converted to saturated TZD **19a** using a two-step process reported earlier.[8d] The latter was deprotected to TZD **19b** using CH_3COOH−HCl in good yield. We also prepared hydrochloride and maleate salts of unsaturated TZD **21a** and saturated TZD **19a**.

A similar strategy was followed for the preparation of benzofuran analogues **23a**, **23b**, and **24a** (Scheme 5).

Biological Procedure

Euglycemic and Hypolipidemic Studies. 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. The 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. In db/db mice, the test compounds were administered at different doses orally for 6 days. Troglitazone (200 mg/kg) was used as a standard drug. The control animals were given vehicle (0.5% carboxymethylcellulose; dose 10 mL/kg). The blood sample (25−50 μL) was collected from the retro-orbital sinus through heparinized capillary tubes in tubes containing EDTA at different time intervals. In db/db mice, blood samples were collected 1 h after drug administration. After centrifugation, plasma was separated, and glucose and triglyceride were estimated using commercial kits (Dr. Reddy's Laboratories Diagnostic Division, India). The percent reductions in plasma glucose and triglyceride level were calculated.[17] The results are summarized in Table 1.

Table 1. Euglycemic and Hypolipidemic Activities of Thiazolidinediones in db/db Mice

no.	compd no.	yield[a] (%)	dose[b] (mg/kg/day)	PG[c]	TG[d]
1	troglitazone	54	200	26	50
2	**4a**	75	200	10	NA
3	**4b**	63	200	11	NA
4	**7b**	54	200	12	31
5	**12a**	63	200	23	NA
6	**12b**	90	100	28	76
7	**11b**	57	200	19	ND
8	**21a**	67	100	66	52
9	**21b**	43	100	19	NA
10	**19a**	75	100	48	31
11	**19b**	10	100	37	33
12	**20a**	84	100	NA	52
13	**23a**	56	100	50	NA
14	**24b**	47	100	22	NA
15	**25a**	20	100	NA	NA
16	**24a**	75	100	NA	NA

[a] Yield in the last step of synthesis. [b] Dose through oral gavage. [c] Percent reduction of plasma glucose after 6 days of treatment. SD = ± 5%. This is the mean of standard deviation observed in plasma glucose in various animals as well as in control animals and is calculated according to the formula cited in ref 19. [d] Percent reduction in plasma triglyceride after 6 days of treatment. SD = ± 5%. This is the mean of standard deviation observed in plasma triglyceride in various animals as well as in control animals. NA, not active; ND, not determined.

Pharmacokinetic Studies

Pharmacokinetics of selected compounds and troglitazone were carried out in female Wistar rats (National Institute of Nutrition, Hyderabad, India). The animals (200−225 g) were fasted for 12 h (overnight) before starting the experiment and had free access to water throughout the experimental period. The animals were fed after 3 h of drug administration.

Single-Dose Pharmacokinetics

The animals were dosed with the test compound at 100 mg/kg (po) as 0.5% CMC suspension, and about 0.45 mL of blood sample was collected into heparinized microfuge tubes at different time points from the retro-orbital sinus. The samples were analyzed by reverse-phase HPLC to generate plasma concentration−time profiles. Englitazone[18] was used as the internal standard.

Results and Discussion

All thiazolidinedione analogues including troglitazone were examined for their glucose- and triglyceride-lowering activities at 30−200 mg/kg dose for 6 days in db/db mice. In a separate experiment, a dose−response study was performed for troglitazone in db/db mice for 11 days. Dose-related reduction in the plasma glucose level in experimental animals was observed. It is noteworthy that animals treated even with the highest dose (800 mg/kg) of troglitazone showed reduction in glucose level only to an extent of 15 ± 1 mM, which is higher than the plasma glucose level of lean littermates (8 ± 1 mM). It is interesting to note that 25% of the animals did not respond to troglitazone treatment. Kobayashi has also made a similar observation in patients.[19] Thus, it appears imperative to search for a more efficacious and potent compound than troglitazone. Toward achieving this goal, we first prepared TZDs containing 2,3-dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran in place of the chroman ring in troglitazone. The unsaturated thiazolidinedione analogues **4a** and **4b** and saturated **7b** were prepared by different routes (Scheme 1) and evaluated in db/db mice at 200 mg/kg/day dose (po) for 6 days. For comparison, troglitazone was also dosed at 200 mg/kg/day for 6 days. The results after 6 days of treatment (Table 1, entries 1−3) suggest that benzofuran analogues **4a** and **4b** do not possess plasma glucose (PG)- and triglyceride (TG)-lowering activities. The corresponding saturated analogue **7b** (Table 1, entry 4) also did not show improvement of pharmacological profile. Thus, ring contraction of chroman to benzofuran did not result in a better compound.

Further, we prepared compounds with a $-N(Me)-CH_2-CH_2-$ group between 5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran and *p*-hydroxyphenylmethylthiazolidine-2,4-dione as depicted in structure C in eq 1. Initially, we examined unsaturated thiazolidinediones **12a** and **12b** at 200 mg/kg dose in db/db mice. The 5-benzyloxy TZD **12a** or 5-hydroxy TZD **12b** showed only moderate euglycemic activity. In contrast, the saturated TZD analogue **11b** showed very poor activity (Table 1, entry 7). Further, we decided to explore the thiazolidinediones in which the N-Me group is cyclized to form a part of the linker moiety as shown in structure B (eq 1). Thus, we prepared a number of compounds having pyrrolidine linkers. The unsaturated TZD **21a** showed excellent euglycemic and hypolipidemic activities at 100 mg/kg/day dose (Table 1, entry 8), and the plasma glucose reached the level of lean littermates (8 ± 1 mM). This result encouraged us to examine the related thiazolidinediones. The removal of the benzyl protecting group gave **21b**, which showed inferior PG- and TG-lowering activities compared to **21a** (Table 1, entry 9). A similar trend was observed in their corresponding saturated TZD analogues **19a** and **19b** although less pronounced (Table 1, entries 10 and 11). In contrast to the pyrrolidine derivatives **19a**, **19b**, **21a**, and **21b,** the piperidine derivative **24a** (Table 1, entry 12) did not show any PG-lowering activity.

We also examined benzofuran-derived unsaturated as well as saturated thiazolidinediones. Thus, pyrrolidine derivatives **23a** and **23b** were evaluated for their plasma glucose- and triglyceride-lowering activities in db/db mice for 6 days. Although TZD **23a** showed good PG-lowering activity at 100 mg/kg dose, it had no effect on triglyceride level (Table 1, entry 13). In contrast, **23b** showed very poor euglycemic activity (data not shown). Surprisingly, saturated TZD **25a** did not show any activity at all (Table 1, entry 15). Similarly, piperidine derivative **24a** was devoid of euglycemic and hypolipidemic activity (Table 1, entry 16).

Table 2. Percentage Reduction in Plasma Glucose and Triglyceride for Selected TZDs and Their Salts

parameter	**19a**	**19b**	**19a** maleate	**21a**	**21a** maleate	**21a** HCl	Trog
PG[a]	37	28	24	40	45	25	NA
TG[a]	22	29	64	38	42	57	NA

[a] All the db/db animals were dosed for 6 days at 30 mg/kg/po dose with the test compounds and troglitazone. The values reported are the percent reduction in plasma glucose and triglyceride calculated according to formula cited in ref 19. SD = ± 5% for both plasma glucose and triglyceride.

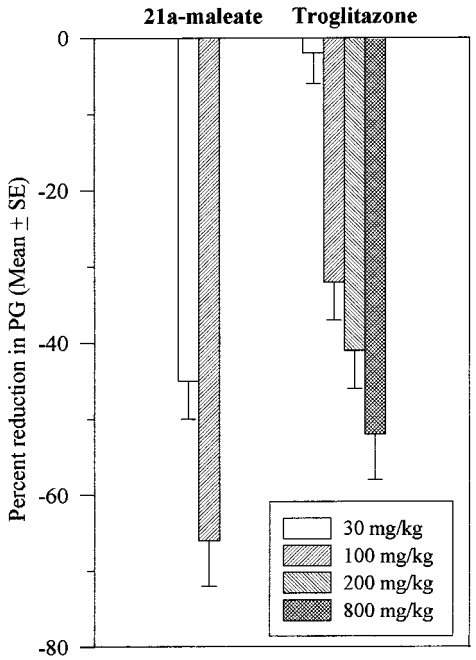


Figure 1. Dose-related reduction in plasma glucose in db/db mice using **21a** maleate and troglitazone.

From these in vivo studies, we selected **19a**, **19b**, and **21a**, for further evaluation. These test compounds were given to db/db mice at 30 mg/kg/day dose for 6 days, and plasma glucose and triglyceride levels were measured (Table 2). From the results we see that TZDs **19a** and **21a** showed good euglycemic activity, whereas troglitazone did not show any activity at 30 mg/kg/day dose. Finally, we prepared the maleate salt of **19a** and **21a** and also the hydrochloride salt of **21a** in order to examine if the formation of salt alters its pharmacological profile due to improvement in pharmacokinetic parameters. From the results in Table 2, it is clear that **21a** and **21a** maleate are the best TZDs of this series among the compounds studied.

We also carried out a dose−response study of troglitazone at 30, 100, 200, and 800 mg/kg/day dose and **21a** maleate at 30 and 100 mg/kg/day dose for 11 days. The result of dose-related percent reduction in plasma glucose is depicted in Figure 1. From Figure 1 it is quite clear that at 100 mg/kg/day dose, **21a** maleate showed

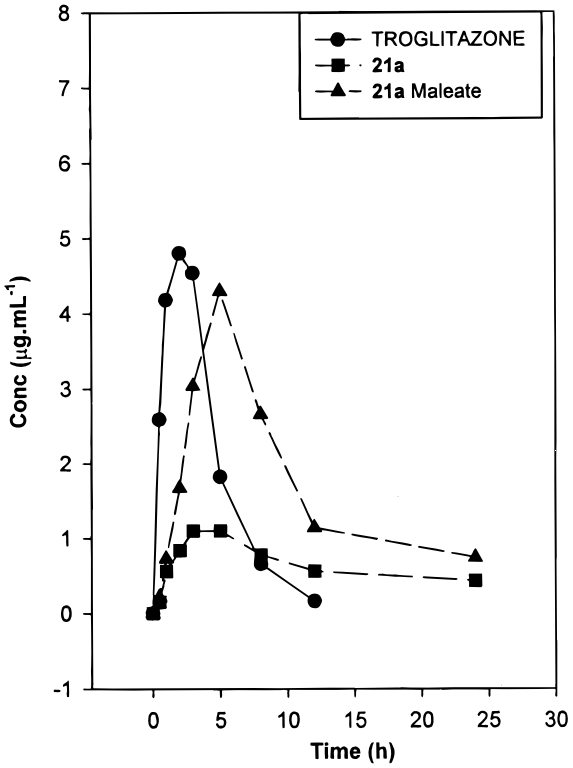


Figure 2. Comparative plasma concentration versus time profiles of troglitazone (▲), **21a** (●), and **21a** maleate (■) in female Wistar rats at 100 mg/kg/po dose.

Table 3. Activation of PPARα and PPARγ Receptors by Thiazolidinediones[a]

compd no.	fold activation	
	PPARα (50 μM)	PPARγ (1 μM)
19a	0.33	0.17
19b	0.46	1.21
21a	0.43	1.03
21b	0.28	0.84
troglitazone	1.12	3.16

[a] GAL4-PPAR chimeric expression constructs and the reporter plasmids were a gift from Novo Nordisk (Denmark). GAL4 fusions were made by fusing human PPARα-LBD (amino acids 167−468) or human PPARγ1-LBD (amino acids 174−475) receptor to the C-terminal end of the yeast GAL4 DBD (amino acids 1−147) of the pM1 vector. For luciferase assays, response element (five copies of a GAL4 DNA binding element) was cloned upstream of pGL2−SV40−Luc reporter (Promega).

ca. 70% reduction in plasma glucose and it reached the level of lean littermate db+/db− (8 ± 1 mM). In contrast, even at 800 mg/kg/day dose of troglitazone, only 52% reduction in plasma glucose was observed and still the plasma glucose (15 ± 1 mM) was much above the normal level. As reported earlier, 25% of the animals did not respond to troglitazone treatment even at 800 mg/kg/dose. In contrast, all the db/db animals showed reduction in plasma glucose when treated with 100 mg/kg/day of **21a** maleate.

On the basis of the in vivo activity in db/db mice, we selected **19a, 19b, 21a**, and **21b** to evaluate their PPARα and PPARγ transactivations to get some insight into the mechanism of action of these TZDs.[20] The results in Table 3 indicate that none of these compounds showed transactivation of either PPARα or PPARγ. They exhibited much lower transactivation of PPARγ than troglitazone, although they showed comparable or

Table 4. Pharmacokinetic Parameters of Thiazolidinedione Analogues in Female Wistar Rats at 100 mg/kg po

pharmacokinetic parameters	**21a**[a]		**21a** maleate[a]		troglitazone[a]	
	mean	SD	mean	SD	mean	SD
$AUC_{(0-t)}$ (μg·h·mL^{-1})	15.50	8.17	53.79	12.63	25.94	5.97
$AUC_{(0-\infty)}$(μg·h·mL^{-1})	23.60	12.10	65.04	16.01	27.40	5.75
C_{max} (μg·mL^{-1})	1.25	0.50	4.30	1.23	5.47	0.64
T_{max} (h)	3.50	2.12	5.00	0.00	2.25	0.96
K_{el} (h^{-1})	0.05	0.00	0.07	0.01	0.20	0.10
$T_{1/2}$ (h)	13.09	0.24	10.08	1.72	4.01	1.38

[a] Results are mean ± SD of four animals in each group. $AUC_{(0-\infty)}$, K_{el}, half-life, C_{max}, and T_{max} were calculated using noncompartmental model analysis. $AUC_{(0-\infty)}$ is the area under the plasma concentration versus 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.

better euglycemic activity than troglitazone in db/db mice. This suggests that this class of compounds may be exhibiting their pharmacological activities through some other mechanism, not solely mediated through PPARγ.[20] Similar observations have been recently reported by Aicher et al.[21] in another class of insulin sensitizers (not TZDs) which do not show PPARγ transactivation, although they significantly improve glucose metabolism and insulin sensitivity in ob/ob mice. It is also interesting to note that the OBn-protected analogues of TZDs **19a** and **21a** showed better euglycemic and hypolipidemic activities at the same dose than their debenzylated counterparts (**19b** and **21b**, respectively) (Table 1, entry 8 vs 9 and entry 10 vs 11).

Troglitazone, which possesses a free phenolic OH, is known to undergo extensive metabolism by formation of glucuronide sulfate as well as oxidation at the phenolic OH position of the tocopherol moiety.[22] By simple protection of the phenolic OH by OBn, one would expect them to show longer half-lives as compared to troglitazone.[23] Presumably this may be one of the reasons why TZD analogues **19a** and **21a** showed better activities in db/db mice. On the basis of this conjecture, we selected TZD **21a** for pharmacokinetic studies in Wistar rats. Interestingly, we found that the systemic exposure of **21a** is far inferior to troglitazone despite its superior plasma glucose- and triglyceride-lowering activities (Table 4).

The pharmacokinetics data suggest that **21a** is absorbed slowly and reached a maximum in ca. 3−5 h, and the C_{max} is only 1.2−1.5 μg·mL^{-1}. In contrast, troglitazone reached C_{max} (ca. 5−6 μg·mL^{-1}) in 2−3 h. On the basis of this finding, we carried out the pharmacokinetic studies of the maleate salt of **21a** in Wistar rats. Maleate salt of **21a** showed slow absorption of the drug (ca. 5 h) and reached C_{max} (ca. 4.5 μg·mL^{-1}) in a time frame similar to that seen with troglitazone. In addition, the compound is eliminated slowly, and $t_{1/2}$ of the maleate salt of **21a** is more than double that of troglitazone. Thus, pharmacokinetic behavior of the maleate salt appears to be desirable.

In conclusion, the TZDs containing the dihydrobenzofuran moiety in structural motif have shown good euglycemic and hypolipidemic activity. However, if the phenolic OH at the 5 position of dihydrobenzofuran is protected as a benzyl ether, it resulted in improved pharmacokinetics and better euglycemic activity than

the corresponding 5-hydroxy analogue. However, based on the present knowledge, it is difficult to assign the exact reason for such a change in pharmacological behavior. Second it may act as a prodrug and release 5-hydroxydihydrobenzofuran-containing TZD in vivo to exhibit better pharmacodynamic activity, although we have no evidence in favor of or against this assumption. Third, these TZDs which do not exhibit PPARγ transactivation may be acting by a different mechanism.

Experimental Section

Materials and 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 obtained with a Varian Gemini 200-MHz spectrometer and are reported as parts per million (ppm) downfield to TMS. The infrared spectra were recorded on a Perkin-Elmer FT-IR 1600 spectrometer. The mass spectra were obtained with an HP 5989A mass spectrometer. 2,5,6-Trimethylbenzoquinone[24] and 5-bezyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-carbinol[12c] were prepared by the reported procedures. Proline, *N*-methylaminoethanol, 2,4-thiazolidinedione, 4-hydroxybenzaldehyde, and 4-fluorobenzaldehyde were purchased and used directly. Troglitazone was prepared by the reported method of Horikoshi et al.[19]

Pharmacokinetics Experiment. Sample preparation of 0.2 mL of plasma was employed for the analysis. For troglitazone, englitazone (10 μg) was used as an internal standard and extraction solvent (2 mL) was ethyl acetate:dichloromethane (6:4). Extraction solvent for **21a** and its maleate salt was a mixture of methanol:ethyl acetate (1:1). For **21a** and its maleate salt, external standard method was employed for the analysis. The organic layer was evaporated to dryness and was reconstituted in 200 μL of respective mobile phase; 100 μL of the sample was injected on the HPLC system. The calibration, control, and recovery samples were prepared by spiking blank plasma and were processed similarly.

HPLC Assay. The HPLC system consisted of a Waters LC Module-1 with Shimadzu fluorescence detector (RF-10AXL) with system controller (SCL10A), Millennium software, and a HiChrom C_{18} (ODS) column (5 μm, 4.6 mm × 250 mm). The analysis of troglitazone was carried out using 0.05 M NaH_2PO_4 buffer:acetonitrile:methanol:tetrahydrofuran (33:55:12:2) as mobile phase at a flow rate of 1 mL/min, and the excitation and emission wavelengths were 292 and 325 nm, respectively. Under these conditions the retention times for troglitazone and englitazone[20] were 10.0 and 12.0 min, respectively. For analysis of both **21a** and its maleate salt, mobile phase used was 0.05 M NaH_2PO_4 buffer:methanol (10:90) at a flow rate of 1.0 mL/min and UV detection at 345 nm was employed. Retention time for both **21a** and its maleate salt was 12.0 min. The assay method was validated to ensure specificity, linearity, recovery, accuracy, and precision. The limit of quantification for troglitazone was 0.05 μg/mL, whereas for **21a** and its maleate salt it was 0.10 μg/mL. The response was linear up to 50 μg/mL, and absolute recoveries were >95%.

Preparation of 5-Benzyloxy-2,4,6,7-tetramethyl-1-benzofuran-3-carbinol (1c). (a) Preparation of Ethyl 5-Hydroxy-2,4,6,7-tetramethyl-1-benzofuran-3-carboxylate. A suspension of $ZnCl_2$ (13.0 g, 95.38 mmol) in ethanol (10 mL) was heated to 80 °C until $ZnCl_2$ dissolved and cooled to ca. 25 °C. A solution of ethyl acetoacetate (24.0 g, 184.41 mmol) in ether (20 mL) was added. After stirring for 10 min, trimethylbenzoquinone[26] (10.0 g, 66.6 mmol) in ethanol (10 mL) was added dropwise over a period of 30 min, and the stirring was continued at 80 °C for an additional 40 h. The reaction mixture was cooled to room temperature, quenched with 5% aqueous HCl solution, and extracted with EtOAc (3 × 75 mL). The organic layer was washed with water (100 mL) and brine (100 mL) and dried (Na_2SO_4). The solvent was evaporated, and the crude product was purified by column chromatography using EtOAc−petroleum ether (1.5:8.5) as eluent to give the title compound (6.0 g, 34%) as a solid: mp 78−80 °C; IR υ_{max} (KBr) 3447, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.4 (t, J = 7.0 Hz, 3 H), 2.3 (s, 3 H), 2.4 (s, 3 H), 2.5 (s, 3 H), 2.6 (s, 3 H), 4.4 (q, J = 7.0 Hz, 2 H), 4.7 (s, 1 H, D_2O exchangeable); MS *m*/*z* (relative intensity) 263 (M^+, 10%), 262 (100%).

(b) Ethyl 5-Benzyloxy-2,4,6,7-tetramethyl-1-benzofuran-3-carboxylate. A mixture of ester derivative obtained from step a (4.5 g, 17.1 mmol), benzyl bromide (4.4 g, 25.7 mmol), and potassium carbonate (9.5 g) in DMF (40 mL) was stirred at ca. 25 °C for 18 h. Water (50 mL) was added, and the reaction mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water (75 mL) and brine (75 mL) and dried (Na_2SO_4). The solvent was evaporated to give the title compound (5.6 g, 92%): IR υ_{max} (KBr) 2926, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.4 (t, J = 7.0 Hz, 3 H), 2.3 (s, 3 H), 2.4 (s, 3 H), 2.6 (s, 3 H), 2.7 (s, 3 H), 4.4 (q, J = 7.0 Hz, 2 H), 4.8 (s, 2 H), 7.0−7.5 (m, 5 H); MS *m*/*z* (relative intensity) 352 (M^+, 10%), 91 (100%).

(c) Reduction of Ester to Alcohol. To a suspension of $LiAlH_4$ (0.906 g, 23.8 mmol) in THF (20 mL) was added dropwise a solution of the ester obtained in step b above (5.6 g, 15.9 mmol) in THF (30 mL) at 0 °C. Stirring was continued at 10 °C for 1 h. The reaction was quenched with saturated Na_2SO_4 solution (10 mL), the resulting mixture was filtered, and the residue was washed with hot EtOAc (50 mL). The combined filtrate was dried over (Na_2SO_4) and evaporated to dryness to give 5-benzyloxy-2,4,6,7-tetramethyl-1-benzofuran-3-carbinol (**1c**) (4.0 g, 81%): IR υ_{max} (KBr) 3468, 2927, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 3 H), 2.3 (s, 3 H), 2.5 (s, 3 H), 2.6 (s, 3 H), 4.8 (s, 2 H), 7.0−7.5 (m, 5 H); MS *m*/*z* (relative intensity) 310 (M^+, 10%), 91 (100%).

Preparation of 5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl Methanesulfonate (2). To a solution of 5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-carbinol (**1**)[12c] (11.4 g, 35.0 mmol) in dichloromethane (100 mL) was added triethylamine (11.6 g, 115.0 mmol) under nitrogen atmosphere at ca. 25 °C. Methanesulfonyl chloride (8.81 g, 77.0 mmol) was added to the above reaction mixture at 0 °C, and stirring was continued for a further 3 h at 25 °C. Water (50 mL) was added to the reaction mixture, and the mixture was extracted with dichloromethane (2 × 75 mL). The combined organic extracts were washed with water (50 mL), dried (Na_2SO_4), and filtered, and the solvent was evaporated under reduced pressure. The residue was triturated with petroleum ether to afford **2** (14.0 g, 99%) as a cream-colored solid: mp 88−90 °C; IR υ_{max} (KBr) 2930, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.60 (s, 3 H), 2.08 (s, 3 H), 2.18 (s, 3 H), 2.25 (s, 3 H), 2.89 (s, 3 H), 3.29 (t, J = 5.7 Hz, 1 H), 4.29 (d, J = 5.2 Hz, 2 H), 4.70 (s, 2 H), 7.40 (m, 5 H); MS *m*/*z* (relative intensity) 404 (M^+, 10%), 313 (100%).

4-(5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethoxy)benzaldehyde (3a). A mixture of 5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl methanesulfonate (**2**) (4.2 g, 10.39 mmol), 4-hydroxybenzaldehyde (1.9 g, 15.57 mmol), and potassium carbonate (5.7 g, 41.30 mmol) in dimethylformamide (75 mL) was stirred for 12 h at 70−80 °C, and the reaction mixture was cooled to room temperature (ca. 25 °C). Water (50 mL) was added, and the mixture was extracted with ethyl acetate (2 × 75 mL). The combined organic extract was washed with water (50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was chromatographed over silica gel using a mixture of ethyl acetate and petroleum ether (1:9) to afford **3** (2.26 g, 51%) as a white solid: mp 78−80 °C; IR υ_{max} (KBr) 1694, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.52 (s, 3H), 2.09 (s, 3 H), 2.09 (s, 3H), 2.20 (s, 3H), 2.25 (s, 3H), 3.40 (m, 1H), 4.06 (m, 2H), 4.70 (s, 2 H), 6.92 (d, J = 8.6 Hz, 2 H), 7.39 (m, 5 H), 7.80 (d, J = 8.6 Hz, 2 H), 9.85 (s, 1 H); MS *m*/*z* (relative intensity) 430 (M^+, +1, 10%), 339 (100%), 217 (58%), 91 (55%).

5-[4-(5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethoxy)phenylmethylene]thiazolidine-2,4-dione (4a). A solution of 4-(5-benzyloxy-2,3-dihydro-

2,2,4,6,7-pentamethylbenzofuran-5-ylmethoxy)benzaldehyde (**3**) (2.4 g, 5.59 mmol) and 2,4-thiazolidinedione (0.65 g, 5.59 mmol) with a catalytic quantity of piperidinium benzoate was refluxed in toluene with removal of water in a Dean−Stark apparatus for 2 h. The reaction mixture was cooled to 25 °C, and the solid separated was collected by filtration which was crystallized from ethanol to give the title compound (2.2 g, 75%): mp 210−211 °C; IR υ_{max} (KBr) δ 3111, 2974, 1747, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3 H), 1.62 (s, 3 H), 2.21 (s, 3 H), 2.28 (s, 3 H), 2.31 (s, 3 H), 3.41 (m, 1 H), 4.10 (m, 2 H), 4.78 (s, 3 H), 7.01 (d, J = 7.58 Hz, 2 H), 7.45 (m, 5 H), 7.82 (s, 1 H); MS *m/z* (relative intensity) 529 (M^+, 9%), 438 (100%), 217 (58%), 205 (52%), 91 (67%). Anal. Calcd for $C_{31}H_{31}NO_5S$: C, 70.29; H, 5.89; N, 2.64. Found C, 70.19; H, 6.00; N, 2.65.

5-[4-(2,3-Dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran-3-ylmethoxy)phenylmethylene]thiazolidine-2,4-dione (4b). To a solution of **4a** (2.0 g, 3.78 mmol) in acetic acid (8 mL) was added concentrated hydrochloric acid (2 mL). The resulting mixture was heated at 90 °C for 1.5 h. The solvent was removed under reduced pressure, neutralized with NH_4OH (25 mL), and extracted with ethyl acetate (2 × 75 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure. The crude product was chromatographed over silica gel using a mixture of methanol and chloroform (1:9) to give the title compound **4b** (1.0 g, 63%) as a pale yellow solid: mp 198−200 °C; IR υ_{max} (KBr) 3288, 1751, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.55 (s, 3 H), 2.10 (s, 3 H), 2.15 (s, 3 H), 2.21 (s, 3 H), 3.35 (m, 1 H), 4.05 (m, 2 H), 6.96 (d, J = 7.8 Hz, 2 H), 7.43 (d, J = 7.85 Hz, 2 H), 7.79 (s, 1 H), 8.28 (bs, D_2O exchangeable, 1 H); MS *m/z* (relative intensity) 439 (M^+, 35%), 219 (80%), 205 (100%), 105 (60%). Anal. Calcd for $C_{24}H_{25}NO_5S$: C, 65.58; H, 5.73; N, 3.18. Found: C, 65.55; H, 5.71; N, 3.20.

Preparation of 5-[4-(5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethoxy)phenylmethyl]-thiazolidine-2,4-dione (7a). (a) Preparation of 4-(5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethoxy)nitrobenzene (5). To a suspension of sodium hydride (95%) (0.44 g, 18.0 mmol) in dry dimethylformamide (5 mL) was added a solution of 5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-carbinol (**1**) (5.0 g, 15.33 mmol) in dry dimethylformamide (15 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 25 °C for 1 h. To the above reaction mixture was added 4-fluoronitrobenzene (2.16 g, 15.3 mmol) dropwise, and stirring was continued at 25 °C for a further 3 h. Water (50 mL) was added, and the mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water (50 mL), dried (Na_2SO_4), and filtered, and the solvent was evaporated under reduced pressure. The crude product was crystallized from ethanol to give **5** (4.6 g, 67%) as a pale yellow solid: mp 149−150 °C; IR υ_{max} (KBr) 1595, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3 H), 1.62 (s, 3 H), 2.12 (s, 3 H), 2.28 (s, 3 H), 2.31 (s, 3 H), 3.45 (m, 1 H), 4.12 (m, 2 H), 4.75 (s, 2 H), 6.94 (d, J = 7.69 Hz, 2 H); MS *m/z* (relative intensity) 357 (M^+ − 91, 56%), 219 (53%), 205 (100%), 91 (20%).

(b) Preparation of 4-(5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethoxy)aniline (6). To a solution of **5** (7.0 g, 15.65 mmol) in ethyl acetate (80 mL) was added 10% palladium on carbon (0.7 g). The reaction mixture was stirred under 60 psi of hydrogen pressure at ambient temperature for 48 h. The reaction mixture was filtered through a bed of Celite, and the bed was washed with ethyl acetate (2 × 25 mL). The combined filtrates were concentrated under reduced pressure. The crude product was chromatographed over silica gel using a mixture of ethyl acetate and petroleum ether (2:8) to give the title compound **6** (4.85 g, 75%) as a thick oil: IR υ_{max} (KBr) 3421, 3341, 1829 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3 H), 1.60 (s, 3 H), 2.12 (s, 3 H), 2.22 (s, 3 H), 2.28 (s, 3 H), 3.35 (t, J = 5.8 Hz, 1 H), 3.42 (bs, D_2O exchangeable, 2 H), 3.92 (d, J = 6.45 Hz, 2 H), 4.72 (s, 2 H), 6.66 (m, 4 H), 7.45 (m, 5 H); MS *m/z* (relative intensity) 417 (M^+, 12%), 326 (66%), 217 (39%), 122 (47%), 91 (100%).

(c) Preparation of Ethyl 2-Bromo-3-[4-(5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethoxy)phenyl]propanoate. A solution of sodium nitrite (0.83 g, 12 mmol) in water (2.5 mL) was slowly added to a cold mixture of 4-(5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethoxy)aniline (**6**) (4.6 g, 11.03 mmol), aqueous hydrobromic acid (5.3 mL), methanol (5 mL), and acetone (35 mL) below 5 °C. The solution was stirred at ca. 5 °C for 30 min, ethyl acrylate (6.62 g, 66.2 mmol) was added, and the temperature was raised to 38 °C. Powdered Cu_2O (72 mg) was added in small portions to the vigorously stirred reaction mixture. After N_2 gas evolution had ceased, the reaction mixture was concentrated in vacuo. The residue was diluted with water (50 mL), made alkaline with NH_4OH solution, and extracted with ethyl acetate (2 × 75 mL). The organic extracts were washed with water (50 mL), brine (50 mL) and dried (Na_2SO_4), and filtered, and the solvent was evaporated under reduced pressure. The crude product was chromatographed over silica gel using a mixture of ethyl acetate and petroleum ether (1:9) to give the title compound (2.38 g, 37%) as an oil: IR υ_{max} (KBr) 1739, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7.0 Hz, 3 H), 1.40 (s, 3 H), 1.56 (s, 3 H), 2.10 (s, 3 H), 2.20 (s, 3 H), 2.24 (s, 3 H), 3.21 (m, 1 H), 3.38 (m, 2 H), 3.98 (m, 2 H), 4.18 (q, J = 6.45 Hz, 2 H), 4.32 (t, J = 7.7 Hz, 1 H), 4.75 (s, 2 H), 6.80 (d, J = 8.38 Hz, 2 H), 7.14 (d, J = 8.38 Hz, 2 H), 7.42 (m, 5 H); MS *m/z* (relative intensity) 491 (9%), 411 (31%), 326 (45%), 217 (54%), 91 (100%).

(d) Preparation of 7a. A mixture of ethyl 2-bromo-3-[4-(5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuranylmethoxy)phenyl]propanoate (2.38 g, 4.0 mmol), thiourea (0.31 g, 4.09 mmol), and sodium acetate (0.33 g, 4.09 mmol) in ethanol (25 mL) was stirred under reflux for 12 h. The solvent was evaporated under reduced pressure, and water (50 mL) was added to the residue and extracted with ethyl acetate (2 × 50 mL). The organic extract was washed with water (50 mL), dried (Na_2SO_4), filtered, and concentrated to get 2-imino-5-[4-(5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethoxy)phenylmethyl]-4-thiazolidinone.

The above crude compound was suspended in ethanol (25 mL), and 2 N hydrochloric acid (10 mL) was added. The reaction mixture was stirred under reflux for 12 h and concentrated in vacuuo. The residue was diluted with water (25 mL), neutralized with aqueous $NaHCO_3$, and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water (25 mL) and brine (25 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the crude product was chromatographed over silica gel using a mixture of ethyl acetate and petroleum ether (1:9) to afford thiazolidinedione **7a** (1.58 g, 73%) as a white solid: mp 98−100 °C; IR υ_{max} (neat) 3205, 2926, 1754, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3 H), 1.54 (s, 3 H), 2.10 (s, 3 H), 2.14 (s, 3 H), 2.21 (s, 3 H), 2.92 (m, 1 H), 3.45 (m, 2 H), 3.98 (m, 2 H), 4.48 (m, 1 H), 6.84 (d, J = 8.75 Hz, 2 H), 7.12 (d, J = 8.75 Hz, 2 H), 7.42 (m, 5 H); MS *m/z* (relative intensity) 531 (M^+, +1, 3%), 440 (38%), 217 (37%), 91 (100%). Anal. Calcd for $C_{31}H_{33}NO_5S$: C, 69.97; H, 6.20; N, 2.63. Found: C, 69.98; H, 6.15; N, 2.60.

5-[4-(2,3-Dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran-3-ylmethoxy)phenylmethyl]thiazolidine-2,4-dione (7b). The thiazolidinedione **7a** (1.58 g, 2.97 mmol) and concentrated hydrochloric acid (1.6 mL) in acetic acid (3.2 mL) were heated at ca. 90 °C for 1−2 h to furnish **7b** (0.7 g, 54%): mp 77−79 °C; IR υ_{max} (KBr) 3447, 3200, 1753, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.54 (s, 3 H), 2.08 (s, 3 H), 2.15 (s, 3 H), 2.20 (s, 3 H), 3.10 (m, 1 H), 3.39 (m, 2 H), 3.95 (m, 2 H), 4.28 (s, D_2O exchangeable, 1 H), 4.5 (m, 1 H), 6.82 (d, J = 8.1 Hz, 2 H), 7.11 (d, J = 8.1 Hz, 2 H), 8.28 (s, D_2O exchangeable, 1 H); MS *m/z* (relative intensity) 441 (M^+, 41%), 383 (17%), 205 (100%), 107 (33%), 91 (27%). Anal. Calcd for $C_{24}H_{27}NO_5S$: C, 65.28; H, 6.16; N, 3.17. Found: C, 65.19; H, 6.05; N, 3.15.

Preparation of 4-[2-[*N*-(5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl)-*N*-methylamino]ethoxy]benzaldehyde (10). To a suspension

of sodium hydride (0.285 g, 11.87 mmol) in dry dimethylformamide (4 mL) was added 4-hydroxybenzaldehyde (1.21 g, 9.91 mmol) in dry dimethylformamide (10 mL) at ca. 0 °C under nitrogen atmosphere. After 30 min, this mixture was added dropwise to a solution of 2-[*N*-(5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl)-*N*-methylamino]ethyl chloride in dry dimethylformamide (10 mL). The reaction mixture was stirred at 50−60 °C for 24 h. The reaction mixture was cooled to room temperature, and water (50 mL) was added. The reaction mixture was extracted with ethyl acetate (2 × 40 mL). The combined organic extracts were washed with 5% aqueous sodium hydroxide (25 mL), water (40 mL), and brine (25 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure to give the title compound **10** (4.84 g, 99%) as a thick liquid: IR υ_{max} (KBr) 1692, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.61 (s, 3 H), 2.10 (s, 3 H), 2.22 (s, 3 H), 2.27 (s, 3 H), 2.40 (s, 3 H), 2.69 (m, 2 H), 2.92 (m, 1 H), 3.09 (m, 2 H), 4.10 (t, J = 5.2 Hz, 2 H), 4.71 (s, 2 H), 6.98 (d, J = 8.69 Hz, 2 H), 7.41 (m, 5 H), 7.81 (d, J = 8.69 Hz, 2 H), 9.89 (s, 1 H); MS *m*/*z* (relative intensity) 487 (M^+, 3%), 396 (4%), 192 (100%), 91 (26%).

Preparation of 5-[4-[2-[*N*-(5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl)-*N*-methylamino]ethoxy]phenylmethylene]thiazolidine-2,4-dione (12a). Using a method described for the preparation for **4a**, **12a** was prepared from **10** (4.7 g, 9.6 mmol) and 2,4-thiazolidinedione (1.13 g, 9.6 mmol) (3.54 g, 63%) as a pale yellow solid: mp 58−60 °C; IR υ_{max} (KBr) 3340, 1742, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.62 (s, 3 H), 2.12 (s, 3 H), 2.21 (s, 3 H), 2.26 (s, 3 H), 2.41 (s, 3 H), 2.76 (m, 2 H), 2.94 (m, 1 H), 3.10 (m, 2 H), 4.11 (t, J = 5.5 Hz, 2 H), 4.72 (s, 2 H), 6.95 (d, J = 8.2 Hz, 2 H), 7.42 (m, 7 H), 7.83 (s, 1 H); MS *m*/*z* (relative intensity) 495 (M^+, −91, 31%), 291 (86%), 205 (11%), 91 (100%). Anal. Calcd for $C_{34}H_{38}N_2O_5S$: C, 69.59; H, 6.51; N, 4.77. Found: C, 70.0; H, 6.90; N, 5.0.

Preparation of 5-[4-[2-[*N*-(2,3-Dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl)-*N*-methylamino]ethoxy]phenylmethylene]thiazolidine-2,4-dione (12b). Following the procedure described for the preparation of **4b**, **12b** (0.69 g, 90%) was prepared from **12a** (0.9 g, 1.53 mmol): mp 92−94 °C; IR υ_{max} (KBr) 3480, 3398, 1740, 1704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.56 (s, 3 H), 2.08 (s, 3 H), 2.11 (s, 3 H), 2.17 (s, 3 H), 2.38 (s, 3 H), 2.68 (m, 2 H), 3.02 (m, 3 H), 4.05 (d, J = 5.72 Hz, 2 H), 6.59 (d, J = 8.72 Hz, 2 H), 7.42 (d, J = 8.72 Hz, 2 H), 7.80 (s, 1 H); MS *m*/*z* (relative intensity) 497 (M^+, +1, 4%), 291 (100%), 205 (11%). Anal. Calcd for $C_{27}H_{32}N_2O_5S$: C, 65.30; H, 6.49; N, 5.64. Found: C, 65.25; H, 6.50; N, 5.62.

Preparation of 2-[*N*-(5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl)-*N*-methylamino] ethanol (8). A mixture of 5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl methanesulfonate (**2**) (21.7 g, 53.71 mmol) and 2-(methylamino)ethanol (40.34 g, 537.86 mmol) was heated under nitrogen atmosphere at 170 °C with stirring for 20 h. The mixture was cooled to 25 °C, poured into water (100 mL), and extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and filtered, and the solvent was evaporated under reduced pressure to give **8** (15.38 g, 75%) as a colorless solid: mp 90−93 °C; IR υ_{max} (KBr) 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.58 (s, 3 H), 2.08 (s, 3 H), 2.19 (s, 3 H), 2.22 (s, 3 H), 2.34 (s, 3 H), 2.39 (m, 2 H), 2.71 (m, 2 H), 3.08 (m, 1 H), 3.62 (m, 2 H), 4.73 (s, 2 H), 7.43 (m, 5 H); MS *m*/*z* (relative intensity) 384 (M^+, +1, 72%), 309 (100%), 292 (24%), 217 (39%), 189 (69%), 175 (44%).

Preparation of 2-[*N*-(5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl)-*N*-methylamino] ethyl Chloride (9). To a solution of **8** (12.7 g, 33.15 mmol) in dry benzene (50 mL) was added thionyl chloride (12.0 mL), and the mixture stirred at room temperature (ca. 25 °C) for 1 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with aqueous sodium bicarbonate solution (2 × 30 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure to give the title compound **9** (12.95 g, 97%) as a cream-colored solid: mp 80−84 °C; IR υ_{max} (KBr) 2970, 1592, 1457 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.59 (s, 3 H), 2.08 (s, 3 H), 2.19 (s, 3 H), 2.21 (s, 3 H), 2.34 (s, 3 H), 2.70 (m, 2 H), 2.81 (m, 2 H), 3.08 (m, 1 H), 3.53 (t, J = 5.5 Hz, 2 H), 4.71 (s, 2 H), 7.43 (m, 5 H); MS *m*/*z* (relative intensity) 401 (M^+, 3%), 106 (100%), 91 (33%).

Preparation of 5-[4-[2-[*N*-(5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl)-*N*-methylamino]ethoxy]phenylmethyl]thiazolidine-2,4-dione (11a). The title compound **11a** (1.82 g, 41%) was prepared as a thick liquid from 2-[*N*-(5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl)-*N*-methylamino]-ethyl chloride (**9**) (3.0 g, 7.47 mmol) and 5-(4-hydroxyphenylmethyl)thiazolidine-2,4-dione (1.67 g, 7.47 mmol) in DMF in the presence of NaH (95%) while stirring at 50 °C for 12 h: IR υ_{max} (KBr) 2910, 1754, 1692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.58 (s, 3 H), 2.08 (s, 3 H), 2.18 (s, 3 H), 2.23 (s, 3 H), 2.38 (s, 3 H), 2.72 (m, 2 H), 2.91 (m, 1 H), 3.10 (m, 3 H), 3.45 (m, 1 H), 4.00 (t, J = 5.59 Hz, 2 H), 4.49 (dd, J = 9.32 and 3.89 Hz, 1 H), 4.70 (s, 2 H), 6.82 (d, J = 8.59 Hz, 2 H), 7.12 (d, J = 8.59 Hz, 2 H), 7.41 (m, 5 H); MS *m*/*z* (relative intensity) 497 (M^+, −91, 26%), 293 (100%), 91 (21%).

5-[4-[2-[*N*-(2,3-Dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl)-*N*-methylamino]ethoxy]phenylmethyl]thiazolidine-2,4-dione (11b). The title compound (0.87 g, 57%) was prepared as a pale yellow solid from **11a** (1.8 g, 3.06 mmol) as described in the preparation of **4b**: mp 68−70 °C; IR υ_{max} (KBr) 3320, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3 H), 1.57 (s, 3 H), 2.08 (s, 3 H), 2.12 (s, 3 H), 2.17 (s, 3H), 2.37 (s, 3 H), 2.71 (m, 2 H), 2.92 (m, 1 H), 3.10 (m, 3 H), 3.42 (m, 1 H), 4.01 (t, J = 5.81 Hz, 2 H), 4.02 (dd, J = 9.23 and 3.97 Hz, 1 H), 4.16 (s, D_2O exchangeable, 1 H), 6.81 (d, J = 8.63 Hz, 2 H), 7.13 (d, J = 8.63 Hz, 2 H); MS *m*/*z* (relative intensity) 499 (M^+, +1, 5%), 293 (100%), 235 (96%), 107 (30%). Anal. Calcd for $C_{27}H_{34}N_2O_5S$: C, 65.03; H, 6.87; N, 5.61. Found: C, 65.0; H, 6.99; N, 5.70.

***N*-[(3*R*/*S*)-5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidine-2-methanol (13).** A mixture of (3*R*/*S*)-5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl methanesulfonate (**2**) (15.0 g, 37.12 mmol) and L-prolinol (14.99 g, 148.4 mmol) was heated under nitrogen atmosphere at 120 °C with stirring for 12 h. The reaction mixture was cooled to room temperature and poured into water, and the mixture was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and filtered, and the solvent was evaporated under reduced pressure. The residue was triturated with petroleum ether to afford **13** (11.0 g, 73%) as a cream-colored solid: mp 99−101 °C; $[\alpha]_D^{26} = -32.8$ (c = 1.00% in $CHCl_3$); IR υ_{max} (KBr) 3245, 1457 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30, 1.34 (2s, 3 H), 1.58, 1.62 (2s, 3 H), 1.78 (m, 4 H), 2.12 (s, 3 H), 2.20, 2.22 (2s, 3 H), 2.28, 2.30 (2s, 3 H), 2.33 (m, 2 H), 2.68 (d, J = 6.0 Hz, 1 H), 3.09 (m, 1 H), 3.30 (m, 2 H), 3.36 (m, 1 H), 3.68 (m, 1 H), 4.76 (s, 2 H), 7.46 (s, 5 H); MS *m*/*z* (relative intensity) 410 (M^+, +1, 6%), 205 (3%), 114 (100%), 91 (27%).

***N*-[(3*R*/*S*)-5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(3*R*)-chloropiperidine (14).** To a solution of *N*-[(3*R*/*S*)-5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidine-2-methanol (**13**) (11.0 g, 26.89 mmol) in benzene (50 mL) was added thionyl chloride (9.8 mL). The resulting mixture was stirred at room temperature for 1 h, diluted with ethyl acetate (50 mL), washed with water (40 mL), brine (40 mL) and dried (Na_2SO_4), and filtered, and the solvent was evaporated in vacuo to give the title compound (10.5 g, 91%) as a thick liquid: IR υ_{max} (KBr) 2945, 1592, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.62 (bs, 5 H), 1.80 (m, 2 H), 2.11 (s, 3 H), 2.23 (s, 6 H), 2.30 (m, 2 H), 2.53 (m, 2 H), 2.86 (m, 1 H), 3.06 (m, 1 H), 3.22 (m, 1 H), 4.0 (m, 1 H), 4.71 (s, 2 H), 7.43 (m, 5 H); MS *m*/*z* (relative intensity) 428 (M^+, +1, 3%), 132 (100%), 91 (47%).

Reaction of 14 with 4-Hydroxybenzaldehyde. A mixture of *N*-[(3*R*/*S*)-5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentam-

ethylbenzofuran-3-ylmethyl]-(3*R*)-chloropiperidine (**14**) (6.4 g, 14.97 mmol), 4-hydroxybenzaldehyde (1.83 g, 14.97 mmol), and potassium carbonate (8.26 g, 59.85 mmol) in dry dimethylformamide (60 mL) was stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature, water (100 mL) was added, and the mixture was extracted with ethyl acetate (2 × 75 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and filtered, and the solvent was evaporated under reduced pressure. The crude product was chromatographed over silica gel using a mixture of ethyl acetate and petroleum ether (1:9) to give 4-[*N*-[(3*R*/*S*)-5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(3*R*)-piperidinyloxy]benzaldehyde (**18**) (2.66 g, 35%) as a thick oil: IR υ_{max} (neat) 1692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (double s, 3 H), 1.55 (double s, 3 H), 1.83 (m, 2 H), 2.17 (double s, 3 H), 2.20 (double s, 3 H), 2.30 (double s, 3 H), 2.60 (m, 2 H), 2.90 (complex, 5 H), 3.60 (d, J = 5.91 Hz, 2 H), 4.45 (m, 1 H), 4.65 (s, 2 H), 6.90 (double d, J = 8.63 Hz, 2 H), 7.45 (m, 5 H), 7.80 (double d, J = 8.67 Hz, 2 H), 9.9 (double s, 1 H); MS *m*/*z* (relative intensity) 514 (M^+, 2%), 218 (100%), 91 (46%).

Further elution of the column gave 4-[*N*-[(3*R*/*S*)-5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]benzaldehyde (**17**; 2.58 g, 34%): IR υ_{max} (neat) 1692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.64 (s, 3 H), 1.80 (m, 4 H), 2.12 (s, 3 H), 2.21 (s, 3 H), 2.30 (s, 3 H), 2.45 (m, 2 H), 2.72 (m, 1 H), 3.15 (m, 2 H), 3.35 (m, 1 H), 3.89 (m, 1 H), 4.08 (m, 1 H), 4.75 (s, 2 H), 6.96 (d, J = 10.4 Hz, 2 H), 7.44 (m, 5 H), 7.85 (d, J = 10.4 Hz, 2 H), 9.94 (s, 1 H); MS *m*/*z* (relative intensity) 514 (M^+, +1, 2%), 218 (100%), 91 (26%).

5-[4-[*N*-[(3*R*/*S*)-5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]phenylmethylene]thiazolidine-2,4-dione (21a). Compound **21a** was prepared as a pale yellow solid from compound **18** (1.0 g, 1.94 mmol) and 2,4-thiazolidinedione (0.23 g, 1.96 mmol) by a procedure described in the preparation for **4a** (0.8 g, 67% yield): mp 68−70 °C; $[\alpha]_D^{24} = -205.5$ (c = 1.00 in $CHCl_3$); IR υ_{max} (KBr) 3453, 1741, 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.58 (s, 3 H), 1.82 (m, 4 H), 2.08 (s, 3 H), 2.18 (s, 3 H), 2.25 (s, 3 H), 2.42 (m, 2 H), 2.76 (m, 1 H), 3.14 (m, 2 H), 3.35 (m, 1 H), 3.84 (m, 1 H), 4.02 (m, 1 H), 4.71 (s, 2 H), 6.95 (d, J = 8.7 Hz, 2 H), 7.45 (m, 7 H), 7.80 (s, 1 H); MS *m*/*z* (relative intensity) 317 (16%), 217 (6%), 177 (100%), 91 (16%). Anal. Calcd for $C_{36}H_{40}N_2O_5S$: C, 70.56; H, 6.57; N, 4.57. Found: C, 70.10; H, 6.50; N, 5.00.

5-[4-[*N*-[(3*R*/*S*)-5-Hydroxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]phenylmethylene]thiazolidine-2,4-dione (21b). The compound **21b** (0.13 g, 43%) was prepared as a yellow solid from **21a** (0.4 g, 0.65 mmol) by a similar procedure to that described for **4b** from **4a**: mp 75−77 °C; $[\alpha]_D^{29} = -175.5$ (c = 1.00 in $CHCl_3$); IR υ_{max} (KBr) 3446, 1738, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3 H), 1.58 (s, 3 H), 1.85 (m, 4 H), 2.09 (s, 3 H), 2.13 (s, 3 H), 2.22 (s, 3 H), 2.38 (m, 2 H), 2.76 (m, 1 H), 3.11 (m, 2 H), 3.36 (m, 1 H), 3.85 (dd, J = 9.1 and 6.4 Hz, 1 H), 4.06 (dd, J = 9.1 and 4.9 Hz), 4.16 (bs, 1 H), 6.95 (d, J = 8.7 Hz, 2 H), 7.43 (d, J = 8.7 Hz, 2 H), 7.8 (s, 1 H); MS *m*/*z* (relative intensity) 407 (9%), 317 (100%), 218 (9%), 205 (12%), 107 (19%). Anal. Calcd for $C_{29}H_{34}N_2O_5S$: C, 66.64; H, 6.55; N, 5.35. Found C, 66.60; H 6.52; N, 5.3.

5-[4-[*N*-[(3*R*/*S*)-5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(3*R*)-piperidinyloxy]-phenylmethylene]thiazolidine-2,4-dione (20a). The title compound **20a** (1.5 g, 84%) was prepared from compound **17** (1.5 g, 2.92 mmol) and 2,4-thiazolidinedione (0.34 g, 2.92 mol) in the presence of piperidinium benzoate as described in the preparation for **4a**: mp 150−152 °C; $[\alpha]_D^{24} = +87.0$ (c = 1.00 in $CHCl_3$); IR υ_{max} (KBr) 3173, 1741, 1699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13, 1.37 (2s, 3 H),1.43−1.69 (m, 5 H), 1.88 (m, 2 H), 2.09 (s, 3 H), 2.11 (s, 3 H), 2.19 (s, 3 H), 2.36 (m, 2 H), 2.63 (m, 2 H), 2.91 (m, 1 H), 3.09 (m, 2 H), 4.42 (m, 1 H), 4.71 (s, 2 H), 6.95 (m, 2 H), 7.45 (m, 7 H), 7.81 (s, 1 H); MS *m*/*z* (relative intensity) 317 (28%), 217 (18%), 91 (100%). Anal. Calcd for $C_{36}H_{40}N_2O_5S$: C, 70.56; H, 6.57; N, 4.57. Found: C, 70.50; H, 6.80; N, 4.66.

5-[4-[*N*-[(3*R*/*S*)-5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]phenylmethyl]thiazolidine-2,4-dione (19a). (a) Preparation of 4-[*N*-[(3*R*)-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]nitrobenzene (15). The title compound (7.25 g, 67%) was prepared as an oil from **13** (8.4 g, 20.53 mmol) and 4-fluoronitrobenzene (3.47 g, 24.64 mmol) by a similar procedure reported for the preparation of **5**: IR υ_{max} (KBr) 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3 H), 1.35 (s, 3 H), 1.56 (s, 3 H), 1.59 (s, 3 H), 1.85 (m, 8 H), 2.06 (s, 3 H), 2.09 (s, 3 H), 2.12 (s, 3 H), 2.20 (s, 3 H), 2.27 (s, 6 H), 2.45 (m, 3 H), 2.82 (m, 3 H), 3.00 (m, 1 H), 3.18 (m, 4 H), 3.38 (m, 1 H), 3.58 (m, 2 H), 3.86 (m, 1 H), 4.08 (m, 1 H), 4.65 (d, J = 7.8 Hz, 2 H), 4.72 (s, 2 H), 6.74 (d, J = 9.0 Hz, 2 H), 6.93 (d, J = 9.00 Hz, 2 H), 7.48 (m, 10 H), 8.13 (d, J = 9.0 Hz, 2 H), 8.19 (d, J = 9.0 Hz, 2 H); MS *m*/*z* (relative intensity) 530 (M^+, 1%), 439 (1%), 409 (1%), 309 (2%), 235 (88%), 205 (100%), 91 (28%).

(b) Preparation of 4-[*N*-[(3*R*/*S*)-5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]aniline (16). The title compound **16** (5.1 g, 55%) was prepared as a brown oil from **15** (9.8 g, 18.49 mmol) and 10% Pd−C (1.0 g) by a similar procedure described in the preparation of **6**: IR υ_{max} (KBr) 3480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31, 1.33 (2s, 3 H), 1.56 1.61 (2s, 3 H), 1.84 (m, 4 H), 2.10 (s, 3 H), 2.22 (s, 3 H), 2.28 (s, 3 H), 2.45 (m, 2 H), 2.79 (m, 1 H), 3.12 (m, 2 H), 3.35 (m, 1 H), 3.75 (m, 1 H), 3.98 (m, 1 H), 4.75 (m, 2 H), 6.68 (m, 4 H), 7.46 (m, 5 H); MS *m*/*z* (relative intensity) 409 (M^+, −91, 1%), 378 (1%), 245 (7%), 205 (100%), 91 (14%).

(c) Preparation of Ethyl 2-Bromo-3-[4-[*N*-[(3*R*/*S*)-5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]phenyl]propanoate. The title compound (2.5 g, 38%) was prepared as an oil from **16** (5.0 g, 10.0 mmol) by a similar procedure described in step c of the preparation of **7a**: IR υ_{max} (KBr) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (m, 6 H), 1.58, 1.60 (2s, 3 H), 1.76 (m, 4 H), 2.08 (s, 3 H), 2.22 (s, 3 H), 2.28 (s, 3 H), 2.42 (m, 2 H), 2.78 (m, 1 H), 2.99 (m, 1 H), 3.15 (m, 2 H), 3.32 (m, 1 H), 3.56 (m, 1 H), 3.72 (m, 1 H), 3.96 (m, 1 H), 4.15 (q, J = 6.0 Hz, 2 H), 4.33 (m, 1 H), 4.71 (m, 2 H), 6.68 (d, J = 8.0 Hz, 1 H), 6.75 (d, J = 8.0 Hz, 1 H), 7.10 (m, 2 H), 7.45 (m, 5 H); MS *m*/*z* (relative intensity) 586 (M^+, −Br, 1%), 540 (1%), 448 (1%), 368 (7%), 290 (100%).

(d) Preparation of 5-[4-[*N*-[(3*R*/*S*)-2,3-Dihydro-5-benzyloxy-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]phenylmethyl]-2-imino-4-thiazolidinone. The title compound (2.0 g, 87%) was prepared as a colorless fluffy solid from the product obtained in step c (2.5 g, 76 mmol) by a similar procedure described for the preparation of **7a**. The crude product was chromatographed over silica gel using ethanol and dichloromethane (5:95) as eluent: mp 132−136 °C; IR υ_{max} (KBr) 3425, 1641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 and 1.33 (2s, 3 H), 1.56 and 1.59 (2s, 3 H), 1.76 (m, 4 H), 2.07 (s, 3 H), 2.18 (s, 3 H), 2.25 (s, 3 H), 2.40 (m, 2 H), 2.76 (m, 1 H), 2.92 (m, 2 H), 3.01 (brs, 1 H), 3.35 (m, 1 H)3. 503 (m, 2 H), 3.75 (m, 1 H), 3.95 (m, 1 H), 4.44 (m,1 H), 4.65 (m, 2H), 6.76 (m, 2 H), 7.08 (m, 2H), 7.43 (m, 5H); MS *m*/*z* (relative intensity) 318 (M^+, −295, 10%), 217 (16%), 91 (100%).

(e) 5-[4-[*N*-[(3*R*/*S*)-5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]phenylmethyl]thiazolidine-2,4-dione (19a). Hydrolysis of the product obtained in step d (4.0, 6.52 mmol) was carried out by a similar procedure described for the preparation of **7a**. The crude product was chromatographed over silica gel using ethanol and dichloromethane (1:99) as eluent to give **19a** (3.0 g, 75%): mp 107−109 °C; $[\alpha]_D^{29} = -79.5$ (c = 1.00 in $CHCl_3$); IR υ_{max} (KBr) 3452, 1753, 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30, 1.34 (2s, 3 H), 1.57, 1.60 (s, 3 H), 1.79 (m, 4 H), 2.09 (s, 3 H), 2.19 (s, 3 H), 2.26 (s, 3 H), 2.45 (m, 2 H), 2.78 (m, 1 H), 3.03 (m, 1 H), 3.14 (m, 2 H), 3.38 (m, 1 H), 3.55 (m, 1 H), 3.74 (m, 1 H), 3.98 (m, 1 H), 4.46 (m, 1 H), 4.70

(m, 2 H), 6.78 (m, 2 H), 7.10 (m, 2 H), 7.42 (m, 5 H); MS *m/z* (relative intensity) 392 (M^+, $-C_{10}H_8NO_3S$), (37%), 309 (100%), 217 (30%). Anal. Calcd for $C_{36}H_{42}N_2O_5S$: C, 70.35; H, 6.84; N, 4.56. Found: C, 70.46; H, 6.74; N, 4.36.

Further elution of the column using ethanol and dichoromethane (2:98) as eluent furnished 5-[4-[*N*-[(3*R*/*S*)-2,3-dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]phenylmethyl]thiazolidine-2,4-dione (**19b**) (0.65 g, 19%) as a colorless solid: mp 72−75 °C; $[\alpha]_D^{29} = -84.2$ ($c = 1.00$ in $CHCl_3$); IR υ_{max} (KBr) 3452, 1753, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26, 1.30 (2s, 3 H), 1.53, 1.58 (2s, 3 H), 1.78 (m, 4 H), 2.08 (s, 3 H), 2.11 (s, 3 H), 2.17, 2.20 (2s, 3 H), 2.36 (m, 2 H), 2.72 (m, 1 H), 2.98 (m, 1 H), 3.13 (m 2 H), 3.45 (m, 2 H), 3.75 (m, 1 H), 3.98 (m, 1 H), 4.19 (s, 1 H), 4.50 (dd, $J = 9.4$ and 3.8 Hz, 1 H), 6.76 (m, 2 H), 7.12 (m, 2 H); MS *m/z* (relative intensity) 319 (M^+, −205, 100%), 218 (3%), 205 (3%). Anal. Calcd for $C_{29}H_{36}N_2O_5S$: C, 66.41; H, 6.87; N, 5.34. Found: C, 66.44; H, 6.90; N, 5.35.

5-[4-[*N*-[(3*R*/*S*)-5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]phenylmethylene]thiazolidine-2,4-dione, Hydrochloride. To a stirred solution of **21a** (0.1 g, 0.16 mmol) in 2-propanol (3 mL) was added 2-propanol−HCl (5 mL, 15% v/w), and stirring was continued for 2 h at 25 °C. The solution was cooled in a refrigerator overnight, and the solid that precipitated was filtered, washed with ether (5 mL), and dried under reduced pressure vacuum to give the title compound (90 mg, 85%): mp 217−221 °C; IR υ_{max} (KBr) 3424, 1741, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3 H), 1.60 (s, 3 H), 1.80 (m, 4 H), 2.08 (s, 3 H), 2.19 (s, 3 H), 2.26 (s, 3 H), 2.50 (m, 2 H), 2.90 (m, 1 H), 3.25 (m, 2 H), 3.40 (m, 1 H), 4.12 (m, 1 H), 4. 30 (m, 1 H), 4.71 (s, 2 H), 7.08 (d, $J = 8.6$ Hz, 2 H), 7.49 (m, 7 H), 7.76 (s, 1 H); MS *m/z* (relative intensity) 479 (M^+, −170, 1%), 317 (9%), 217 (10%), 91 (100%). Anal. Calcd for $C_{36}H_{41}ClN_2O_5S$: C, 66.59; H, 6.36; N, 4.31. Found: C, 66.60; H, 6.40; N, 4.26.

5-[4-[*N*-[(3*R*/*S*)-5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]phenylmethylene]thiazolidine-2,4-dione, Maleate. To a stirred solution of **21a** (0.1 g, 0.10 mmol) in dry ether (5 mL) at room temperature (0 °C) was added maleic acid (0.08 g, 0.179 mmol) in absolute ethanol (2 mL). The reaction mixture was stirred at 25 °C for 2 h. The separated solids were filtered, washed with dry ether (2 × 10 mL), and dried under reduced pressure over P_2O_5 for 6 h to get a pale yellow solid (0.11 g, 92%): mp 158−161 °C; $[\alpha]_D^{25} = -107.26$ ($c = 1.00$ in $CHCl_3$); IR υ_{max} (KBr) 3445, 1738, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.63 (s, 3 H), 1.95 (m, 4 H), 2.10 (s, 3 H), 2.22 (s, 3 H), 2.27 (s, 3 H), 2.63 (m, 2 H), 3.16 (m, 1 H), 3.30 (m, 2 H), 3.52 (m, 1 H), 3.85 (m, 1 H), 4.03 (m, 1 H), 4.72 (s, 2 H), 6.28 (s, 2 H), 7.03 (d, $J = 8.4$ Hz, 2 H), 7.48 (m, 7 H), 7.79 (s, 1 H); MS *m/z* (relative intensity) 317 (M^+, −411, 11%), 217 (13%), 91 (100%). Anal. Calcd for $C_{40}H_{44}N_2O_9S$: C, 65.93; H, 6.04; N, 3.84. Found: C, 65.99; H, 6.00; N, 3.86.

5-[4-[*N*-[(3*R*/*S*)-5-Benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]phenylmethyl]thiazolidine-2,4-dione, Maleate. The title compound (0.44 g, 79%) was prepared as a pale yellow solid from **19a** (0.47 g, 0.77 mmol) by a similar procedure described above: mp 179−182 °C; $[\alpha]_D^{25} = 2.400$ ($c = 1.0$ in $CHCl_3$); IR υ_{max} (KBr) 3425, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36, 1.40 (2s, 3 H), 1.62, 1.67 (2s, 3 H), 2.06−2.45 (complex-m, 15 H), 2.81 (m, 1 H), 3.14−3.64 (complex-m, 5 H), 4.16−4.21 (m, complex, 2 H), 4.50 (m, 1 H), 4.64−4.72 (complex-m, 2 H), 6.27 (s, 2 H), 6.82 (m, 2 H), 7.17 (m, 2 H), 7.43 (m, 5 H); MS *m/z* (relative intensity) 391 (M^+, −339, 1%), 319 (80%), 91 (100%). Anal. Calcd for $C_{40}H_{46}N_2O_9S$: C, 65.75; H, 6.3; N, 3.83. Found: C, 65.87; H, 6.05; N, 3.86.

***N*-(5-Benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(2*S*)-pyrrolidine-2-methanol.** To a solution of carbinol **22a** (20.0 g, 64.5 mmol) in CH_2Cl_2 (150 mL) was added thionyl chloride (38.38 g, 322 mmol) dropwise at ca. −20 °C. The reaction mixture was allowed to warm to 0 °C, and stirring was continued at this temperature for 5 h. Excess of thionyl chloride was removed under reduced pressure, and the crude product **22b** was triturated with petroleum ether, filtered, and dried to give the title compound (20.0 g, 95%). This product was used in the next step without further purification.

The crude compound **22b** obtained from the above step (9.0 g, 27.39 mmol), L-prolinol (4.15 g, 41.08 mmol), and potassium carbonate (16 g) in dimethylformamide (75 mL) were stirred at room temperature continuously for 10 h. The reaction was quenched with water (100 mL), and the mixture was extracted with EtOAc (3 × 50 mL). The combined EtOAc layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated to give the title compound (7.5 g, 69%): mp 98−100 °C; IR υ_{max} (KBr) 3352, 1451, 1232 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (m, 4 H), 2.36 (s, 3 H), 2.41 (s, 3 H), 2.48 (s, 3 H), 2.50 (m, 1 H), 2.64 (s, 3 H), 2.76 (m, 1 H), 3.04 (m, 1 H), 3.34 (dd, $J = 10.8$ and 2.5 Hz, 1 H), 3.51 (dd, $J = 10.2$ and 3.5 Hz, 1 H), 3.60 (d, $J = 13.2$ Hz, 1 H), 3.95 (d, $J = 13.2$ Hz, 1 H), 4.78 (s, 2 H), 7.48 (m, 5 H); MS *m/z* (relative intensity) 393 (M^+, 10%), 293 (100%); $[\alpha]_D^{20} = -15.5$ ($c = 1.0$, $CHCl_3$).

***N*-(5-Benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(3*R*)-chloropiperidine.** To a solution of pyrrolidine derivative from the previous step (9.0 g, 22.9 mmol) in dichloromethane (100 mL) was added thionyl chloride (3.62 g, 114.5 mmol) dropwise at 0 °C. Stirring was continued at room temperature for 5 h. Excess $SOCl_2$ was removed under reduced pressure, and the reaction mixture was diluted with EtOAc (100 mL) to give a precipitate which was basified by adding ammonia solution (10 mL) and extracted with EtOAc (3 × 50 mL). The combined EtOAc layers were washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated to give the title compound as a white solid (9.0 g, 95%): mp 90−92 °C; IR υ_{max} (KBr) 3379, 1642, 1232, 1081 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (m, 3 H), 2.19 (m, 3 H), 2.36 (s, 3 H), 2.45 (s, 6 H), 2.62 (s, 3 H), 2.78 (m, 1 H), 3.13 (m, 1 H), 3.51 (d, $J = 6.2$ Hz, 2 H), 3.92 (m, 1 H), 4.72 (s, 2 H), 7.47 (m, 5 H); MS *m/z* (relative intensity) 412 (M^+, 25%), 293 (100%); $[\alpha]_D^{20} = -49.7$ ($c = 1.0$, $CHCl_3$).

Reaction of *N*-(5-Benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(3*R*)-chloropiperidine with 4-Hydroxybenzaldehyde. A mixture of *N*-(5-benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(3*R*)-chloropiperidine (3.0 g, 7.29 mmol), 4-hydroxybenzaldehyde (0.89 g, 7.29 mmol), and potassium carbonate (4.03 g) in dimethylformamide (30 mL) was stirred at ca. 25 °C for 12 h. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined EtOAc layers were washed with water (100 mL) and brine (75 mL) and dried (Na_2SO_4). The filtrate was concentrated, and the crude product was purified by column chromatography using EtOAc−dichloromethane (0.2:9.8) as eluent to give 4-[*N*-(5-benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(2*S*)-pyrrolidin-2-ylmethoxy]benzaldehyde (1.0 g, 27%) as an oil: IR υ_{max} (neat) 1680, 1604, 1263, 1082 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (m, 4 H), 2.08 (m, 1 H), 2.30 (s, 3 H), 2.37 (s, 3 H), 2.42 (s, 3 H), 2.59 (s, 3 H), 3.03 (m, 2 H), 3.59 (d, $J = 12.9$ Hz, 1 H), 3.79 (dd, $J = 9.6$ and 6.8 Hz, 1 H), 3.93 (dd, $J = 9.6$ and 5.2 Hz, 1 H), 3.79 (dd, $J = 9.6$ and 6.8 Hz, 1 H), 3.93 (dd, $J = 9.6$ and 5.2 Hz, 1 H), 4.05 (d, $J = 12.9$ Hz, 1 H), 4.70 (s, 2 H), 6.80 (d, $J = 8.6$ Hz, 2 H), 7.48 (m, 5 H), 7.77 (d, $J = 8.6$ Hz, 2 H), 9.86 (s, 1 H); MS *m/z* (relative intensity) 497 (M^+, 3%), 293 (100%); $[\alpha]_D^{22} = +51.0$ ($c = 1.0$, CH_2Cl_2).

Further elution gave 4-[*N*-(5-Benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(3*R*)-piperidinyloxy]benzaldehyde as a white solid (0.9 g, 24%): mp 142−144 °C; $[\alpha]_D^{23} = -57.5$ ($c = 0.2$, CH_2Cl_2); IR υ_{max} (neat) 1691, 1600, 1254, 1083 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (m, 4 H), 2.18 (m, 2 H), 2.29 (s, 3 H), 2.32 (s, 6 H), 2.62 (s, 3 H), 2.73 (m, 1 H), 3.05 (m, 1 H), 3.45 (d, $J = 5.4$ Hz, 2 H), 4.40 (m, 1 H), 4.77 (s, 2 H), 6.91 (d, $J = 8.6$ Hz, 2 H), 7.49 (m, 5 H), 7.75 (d, $J = 8.7$ Hz, 2 H), 9.84 (s, 1 H); MS *m/z* (relative intensity) 497 (M^+, 8%), 201 (100%).

Preparation of 5-[4-[*N*-(5-Benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(2*S*)-pyrrolidin-2-ylmethoxy]-phenylmethylene]thiazolidine-2,4-dione (23a). A mixture of 4-[*N*-(5-benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-

(3*R*)-piperidinyloxy]benzaldehyde (0.6 g, 1.2 mmol), thiazolidine-2,4-dione (0.141 g, 1.2 mmol), benzoic acid (0.018 g, 0.14 mmol), and piperidine (0.015 g, 0.17 mmol) in 25 mL of toluene was refluxed for 3 h with continuous removal of water using a Dean−Stark water separator. The reaction mixture was cooled to room temperature, and the resultant crystalline compound was filtered, which was purified by column chromatography using EtOAc−petroleum ether (3:7) as eluent to give the title compound **23a (**0.4 g, 56%): mp 168−170 °C; $[\alpha]_D^{24} = +107.72$ (c = 1.0, $CHCl_3$); IR υ_{max} (KBr) 1740, 1684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (m, 4 H), 2.05 (m, 1 H), 2.31 (s, 3 H), 2.38 (s, 3 H), 2.42 (s, 3 H), 2.60 (s, 3 H), 3.00 (m, 2 H), 3.63 (d, J = 12.9 Hz, 1 H), 3.78 (m, 1 H), 3.83 (m,1 H), 4.04 (d, J = 12.9 Hz, 1 H), 4.71 (s, 2 H), 6.78 (d, J = 8.6 Hz, 2 H), 7.44 (m, 7 h), 7.78 (s, 1 H); MS m/z (relative intensity) 596 (M^+, 5%), 376 (100%). Anal. Calcd for $C_{35}H_{36}N_2O_5S$: C, 70.44; H, 6.08; N, 4.69. Found: C, 70.40; H, 6.00; N, 4.70.

Preparation of 5-[4-[*N*-(5-Benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(3*R*)-piperidinyloxy]phenylmethylene]thiazolidine-2,4-dione (24a). A mixture of 4-[*N*-(5-benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(3*R*)-piperidinyloxy]benzaldehyde (1.0 g, 2 mmol), thiazolidine-2,4-dione (0.235 g, 2.0 mmol), benzoic acid (0.03 g, 0.24 mmol), and piperidine (0.025 g, 0.29 mmol) in 50 mL of toluene was refluxed for 3 h with continuous removal of water using a Dean−Stark water separator. The reaction mixture was cooled to room temperature, and the resultant crystalline compound was filtered, washed with 5% EtOAc−petroleum ether, and dried to afford title compound **24a** (0.9 g, 75%) as a solid: mp 100−103 °C; $[\alpha]_D^{20} = -52.4$ (c = 1.0, $CHCl_3$); IR υ_{max} (KBr) 3174, 1738, 1694, 1507, 1253 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (m, 3 H), 1.78 (m, 1H), 2.16 (s, 2 H), 2.33 (s, 3 H), 2.40 (s, 6 H), 2.73 (s, 3 H), 2.78 (m, 1 H), 3.15 (m, 1 H), 3.48 (d, J = 4.9 Hz, 2 H), 4.34 (m, 1 H), 4.77 (s, 2 H), 6.91 (d, J = 8.7 Hz, 2 H), 7.42 (m, 7 H), 7.74 (s, 1 H); MS m/z (relative intensity) 505 (M^+, $-C_7H_7$), 201 (100%). Anal. Calcd for $C_{35}H_{36}N_2O_5S$: C, 70.44; H, 6.08; N, 4.69. Found: C, 70.40; H, 6.00; N, 4.71.

Preparation of 5-[4-[*N*-(5-Hydroxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-2(*S*)-pyrrolidin-2-ylmethoxy]-phenylmethylene]thiazolidine-2,4-dione (23b). A mixture of **23a** (0.7 g, 1.17 mmol) and hydrochloric acid (1 mL) in glacial AcOH (4 mL) was refluxed for 3 h. Acetic acid was removed under reduced pressure, and the resultant solid was suspended in EtOAc (25 mL). The pH was adjusted to pH 8.0 by adding aqueous ammonia solution (5 mL) and extracted with EtOAc (7 mL). The crude product was purified by column chromatography using EtOAc−petroleum ether (4:6) as eluent to give **23b** (0.27 g, 47%): mp 157−159 °C; $[\alpha]_D^{26} = +75.1$ (c = 0.7, EtOAc); IR υ_{max} (KBr) 3465, 1740, 1696, 1595, 1509, 1335 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78 (m, 4 H), 2.04 (m, 1 H), 2.24 (s, 3 H), 2.38 (s, 3 H), 2.40 (s, 3 H), 2.51 (s, 3 H), 3.04 (m, 2 H), 3.62 (d, J = 12.9 Hz, 1H), 3.79 (m, 1 H), 3.83 (m, 1 H), 4.04 (d, J = 12.9 Hz, 1 H), 6.76 (d, J = 8.9 Hz, 2 H), 7.38 (d, J = 8.7 Hz, 2 H); 7.78 (s, 1 H). MS m/z (relative intensity) 286 (M^+, $-C_{10}H_6NO_3S$), 272 (12%), 189 (100%). Anal. Calcd for $C_{28}H_{30}N_2O_5S$: C, 66.37; H, 5.96; N, 5.53. Found: C, 66.30; H, 5.88; N, 5.5.

Preparation of 5-[4-[*N*-(5-Benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(2*S*)-pyrrolidin-2-ylmethoxy]-phenylmethyl]thiazolidinedione (25a). (a) 4-[*N*-(5-Benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(2*S*)-pyrrolidin-2-ylmethoxy]nitrobenzene. To a suspension of NaH (2.93 g, 122 mmol) in dimethylformamide (50 mL) was added a solution of *N*-(5-benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(2*S*)-pyrrolidine-2-methanol (24.0 g, 61 mmol) in dimethylformamide (50 mL) dropwise, and the mixture stirred at room temperature for 3 h. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 100 mL). The combined EtOAc layers were washed with water (200 mL) and brine (200 mL) and dried (Na_2SO_4). The solvent was evaporated to furnish a crude product which was purified by column chromatography using EtOAc−petroleum ether (1:9) as eluent to give a yellow solid: mp 136−139 °C; IR υ_{max} (KBr) 1593, 1506, 1443, 1263, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78 (m, 4 H), 2.06 (m, 1 H), 2.32 (s, 3 H), 2.38 (s, 3 H), 2.40 (s, 3 H), 2.59 (s, 3 H), 3.03 (m, 2 H), 3.63 (d, J = 12.8 Hz, 1H), 3.85 (m, 2 H), 4.0 (d, J = 12.8 Hz, 1 H), 4.72 (s, 2 H), 6.72 (d, J = 9 Hz, 2 H); MS m/z (relative intensity) 514 (M^+, 15%), 293 (100%).

(b) 4-[*N*-(5-Benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(2*S*)-pyrrolidin-2-ylmethoxy]aniline. To a solution of the nitro compound from the previous step (5.0 g, 9.72 mmol) in ethyl acetate (50 mL) was added 10% Pd−C (0.5 g), and the mixture was hydrogenated at 30 psi for 12 h. The mixture was filtered through a bed of Celite, and the catalyst was washed with 100 mL of ethyl acetate. The filtrate was evaporated to dryness under reduced pressure to give the title compound (3.3 g, 70%): IR υ_{max} (KBr) 3385, 1510, 1238, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61 (m, 4 H), 2.10 (m, 1 H), 2.29 (s, 3 H), 2.34 (s, 3 H), 2.40 (s, 3 H), 2.65 (s, 3 H), 2.96 (m, 2 H), 3.41 (bs, exchangeable with D_2O, 2 H), 3.48 (d, J = 13 Hz, 1 H), 3.65 (m, 1 H), 3.85 (m, 1 H), 4.12 (d, J = 13 Hz, 1 H), 4.75 (s, 2 H), 6.62 (s, 4 H), 7.48 (m, 5 H); MS m/z (relative intensity) 484 (M^+, 10%), 293 (100%).

(c) Ethyl 2-Bromo-3-[4-[*N*-(5-benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(2*S*)-pyrrolidin-2-ylmethoxy]phenyl]propanoate. To a mixture of aniline from the previous step (3.3 g, 6.8 mmol), aqueous hydrobromic acid (47%, 1.5 mL), and acetone (33 mL) was added an aqueous sodium nitrite solution (0.517 g) dropwise at 0 °C, and the mixture stirred at 0 °C for an additional 30 min. The reaction mixture was allowed to warm to room temperature, and ethyl acrylate (4.09 g, 40.9 mmol) was added followed by cuprous oxide (0.058 g) in portions. The stirring was continued at ca. 25 °C for a further 1 h and at 40 °C for another 1 h. The solvent was evaporated under vacuum, and the residue was basified by adding ammonia solution (8 mL) and extracted with EtOAc (3 × 50 mL). The combined EtOAc extracts were washed with water (75 mL) and brine (75 mL), dried (Na_2SO_4), and filtered. The solution was filtered, and the filtrate was concentrated. The crude product residue was purified by column chromatography using EtOAc−petroleum ether (0.5:9.5) as an eluent to give the title compound (0.7 g, 15%) as a light brown liquid: IR υ_{max} (KBr) 1738, 1606, 1453, 1243, 1082, 1021 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7 Hz, 3 H), 1.79 (m, 4 H), 2.05 (m, 1 H), 2.31 (s, 3 H), 2.39 (s, 3 H), 2.42 (s, 3 H), 2.65 (s, 3 H), 2.98 (m, 2 H), 3.21 (m, 1 H), 3.40 (m, 1 H), 3.58 (d, J = 12 Hz, 1 H), 3.74 (m, 1 H), 3.91 (m, 1 H), 4.21 (m, 4 H), 4.76 (s, 2 H), 6.73 (d, J = 7.7 Hz, 2 H), 7.10 (d, J = 7.7 Hz, 2 H), 7.48 (m, 5 H); MS m/z (relative intensity) 362 (M^+, $-C_{12}H_{14}BrO_3$), 293 (100%).

(d) Preparation of 5-[4-[*N*-(5-Benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)-(2*S*)-pyrrolidin-2-ylmethoxy]phenylmethyl]thiazolidine-2,4-dione (25a). A mixture of alkoxypropionate from the above step c (2.7 g, 4.1 mmol) and sodium acetate (0.375 g) in ethanol (10 mL) was stirred under reflux for 12 h. The solvent was evaporated under reduced pressure, water (50 mL) was added, and the mixture was extracted with ethyl acetate (3 × 50 mL). The organic extract was washed with water (75 mL), dried (Na_2SO_4), filtered, and concentrated to get 5-[4-[*N*-(5-benzyloxy-2,4,6,7-tetramethylbenzofuran-3-ylmethyl)pyrrolidin-(2*S*)-ylmethoxy]benzyl]-2-imino-4-thiazolidinone. The above crude compound was suspended in ethanol (10 mL), and 2 N hydrochloric acid (10 mL) was added. The reaction mixture was stirred under reflux for 12 h and concentrated in vacuo. The residue was diluted with water (50 mL), neutralized with aqueous ammonia solution (7 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (75 mL) and brine (75 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the crude product was chromatographed on silica gel using EtOAc−petroleum ether (3:7) as eluent, to afford the title compound (0.48 g, 20%): mp 55−57 °C; $[\alpha]_D^{25} = +25.2$ (c = 0.5, $CHCl_3$); IR υ_{max} (KBr) 3191, 1754, 1700, 1512, 1237, 1082 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (m, 4 H), 2.05 (m, 1 H), 2.30 (s, 3 H), 2.37 (s, 3 H), 2.41 (s, 3 H), 2.60 (s, 3 H), 2.98 (m, 2 H), 3.10 (m, 1 H0, 3.41 (m, 1 H), 3.55 (m, 1 H), 3.72 (m, 1 H), 3.90 (m, 1 H), 4.12 (m, 1 H), 4.45 (m, 1 H), 4.74 (s, 2 H),

6.70 (m, 2 H), 7.04 (d, J = 7.0 Hz, 2 H), 7.42 (m, 5 H); MS m/z (relative intensity) 598 (M^+, 10%), 293 (100%). Anal. Calcd for $C_{35}H_{37}N_2O_5S$: C, 70.32; H, 6.24; N, 4.68. Found: C, 70.30; H, 6.20; N, 4.70.

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