Novel Euglycemic and Hypolipidemic Agents. 4. Pyridyl- and Quinolinyl-Containing Thiazolidinediones‡

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A series of substituted pyridyl- and quinolinyl-containing 2,4-thiazolidinediones having interesting cyclic amine as a linker have been synthesized. Both unsaturated thiazolidinediones **5** and saturated thiazolidinediones **6** and their various salts were evaluated in db/db mice for euglycemic and hypolipidemic effects and compared with BRL compound **11** and BRL-49653, respectively. Some of the potent compounds were converted to various salts in order to obtain improved activities. Among all the salts evaluated, the maleate salt of unsaturated TZD **5a** was found to be a very potent euglycemic and hypolipidemic compound. Some of the more interesting compounds have also been evaluated in ob/ob mice and compared with rosiglitazone (maleate salt of BRL-49653). Oral glucose tolerance tests were performed in both db/db and ob/ob mice. Pharmacokinetic studies of **5a** maleate are also reported. Receptor binding studies of PPARγ by **5a**/**5a** maleate did not show any significant transactivation of PPARα or PPARγ.

Introduction

Impaired insulin action is thought to be the cause of hyperglycemia and type 2 diabetes (non-insulin-dependent diabetes mellitus).[1] The reason for such insulin resistance still evades our present knowledge of understanding. The mechanism of action of drugs which enhance the action of insulin remains by and large elusive. Despite our poor understanding, several thiazolidinedione classes of compounds have been developed for achieving tight blood glucose control in type 2 diabetes patients.[2] Recently, troglitazone has been approved in several countries for the treatment of diabetes; however, several clinicians raised their concerns regarding the safety of troglitazone as well as the thiazolidinedione class of compounds.[3] In the United States and Japan, several cases of liver damage and drug-related deaths due to liver damage[3] have been reported; however, weighing the benefit against the idiosyncratic liver toxicity in troglitazone-treated patients, the U.S. Food and Drug Administration authority has allowed the marketing of troglitazone with a change of labeling instructions together with regular monitoring of liver enzyme levels. More recently, the Public Citizen's Health Research group has requested the U.S. Food and Drug Administration to initiate action to ban troglitazone because of 560 cases of liver toxicity related to troglitazone which have been reported since the drug was first marketed in March 1997.[4] Hence, there is a definite need for a safe and efficacious euglycemic agent for the treatment of type 2 diabetic patients.

There has been speculation that the liver toxicity observed with troglitazone may be associated with the thiazolidinedione class of molecules,[3] which in turn may be due to their binding to peroxisome proliferator activator receptor (PPAR) belonging to the steroid/thyroid/retinoid receptor superfamily of ligand-activated transcription factors. There have been a number of reports that the thiazolidinediones (TZDs) are high-affinity PPARγ agonists, and there is a direct correlation between the in vitro potency at the PPARγ receptor and the in vivo antihyperglycemic potency in C57BL/6J/ob/ob mice for a series of TZDs.[5] Mukherjee et al.[6] have recently proposed an indirect agonism of PPARγ through another nuclear receptor called retinoid X receptor (RXR), which forms a heterodimer with PPARγ. They suggest that this may lead to a new pathway for treating type 2 diabetics. Although there has been no conclusive evidence in support or against these hypotheses, research has been directed toward finding appropriate molecules which ameliorate insulin resistance without binding to PPARγ. Recently, Aicher et al.[7] have reported a new class of insulin sensitizers (not TZDs) which do not act through PPAR mechanism, although they significantly improved glucose metabolism and insulin sensitivity in ob/ob mice. In fact, a similar observation has been reported on a potent antidiabetic thiazolidinedione, MCC-555, which shows excellent euglycemic activity, comparable to BRL-49653.[8] The TZD MCC-555 exhibits binding affinity for PPARγ less than 1/10 that of BRL-49653. Reginato et al.[8] explained these observations based on the effect of MCC-555 binding on PPARγ transcriptional activity which is highly context-specific, such that it can function as full agonist, partial agonist, or antagonist depending on the cell type or DNA binding site. These transcriptional properties are partially explained by unique partial agonism of coactivator recruitment to PPARγ. The context-specific selectivity

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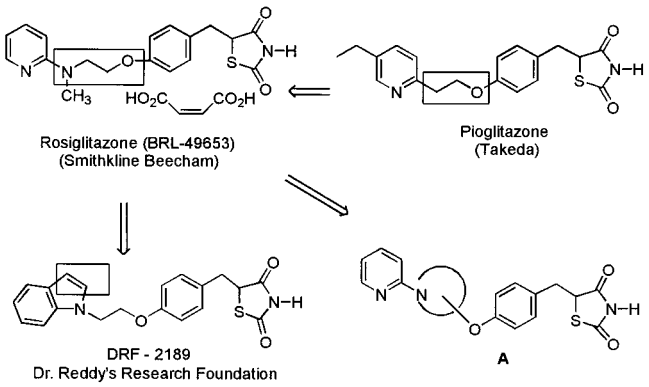


Figure 1. Approach to novel thiazolidinediones derived from BRL-49653.

of MCC-555 may contribute to its enhanced hypoglycemic potency in vivo despite reduced affinity for PPARγ. This raises the possibility that only a subset of the functions of activated PPARγ contributes to insulin sensitivity and that therapeutic strategies for NIDDM that target these functions may lead to compounds with increased potency and decreased toxicity.

We have also found recently that several TZDs which are weak agonists of PPARγ also exhibit good euglycemic activity.[9] With this mechanistic point in view, we planned to search for molecules which may show good euglycemic activities without agonizing PPARγ and therefore may show less toxicity, if transactivation of PPARγ is associated with their toxicity profile. In the recent past, we have been interested in developing novel thiazolidinediones which show a superior safety and efficacy profile.[10,11] Rosiglitazone (maleate salt of BRL-49653) which is an excellent PPARγ agonist has recently been approved by the U.S. FDA and is known to be severalfold superior in efficacy to troglitazone. Rosiglitazone is also superior in efficacy to pioglitazone, which can very well be visualized as its own congener (Figure 1). This perception led us to modify rosiglitazone which resulted in the discovery of DRF-2189[10] (Figure 1). The latter is equipotent to rosiglitazone and is currently undergoing further studies. However, our search for thiazolidinediones having similar efficacy and potency with low PPARγ transactivation activities and an improved safety profile continued. In the present article we describe our attempts to modify the structural motif of BRL-49653 which resulted in an equally efficacious thiazolidinedione (vide infra) without having any significant PPARγ activity.

Earlier, we disclosed the results of our attempts of incorporating the methyl group on the nitrogen of BRL-49653 in a ring with or without the help of a carbon or nitrogen atom.[10] In the present article, we wish to report our strategy of the incorporation of the same N-Me group of BRL-49653 in the side chain of the linker with the help of a carbon atom or other heteroatom as shown in Figure 1 (structure A) and also the structure−activity relationship of this class of thiazolidinediones.

Chemistry

Several pyridyl- and quinolinyl-containing thiazolidinediones were prepared. A general synthetic route is shown in Scheme 1. Substituted 2-chloropyridine or 2-chloroquinoline **1** was treated with different cyclic amines **2** such as (*S*)-prolinol, piperidine, or morpholine-3-carbinol to furnish excellent yield (50−100%) of compound **3** which was reacted with 4-fluorobenzaldehyde to afford aldehyde **4** (36−67%). The latter was treated with 2,4-thiazolidinedione[12] to furnish the unsaturated compound **5** (52−100%) which can be reduced either by hydrogenation or by Mg−CH_3OH[13] to afford the saturated thiazolidinedione **6** (Scheme 1). Alternatively, the saturated TZDs are also prepared via the reaction of 4-fluoronitrobenzene with **3** to afford **7**. Compound **7** was reduced to give aniline derivative **10**. The latter was converted to saturated TZD **6** by a known method.[14] Various salts of unsaturated TZD **5** or saturated TZD **6** were prepared for pharmacological evaluation and to study their pharmacokinetic profiles. The results are collected in Tables 1−3.

Biological Procedures

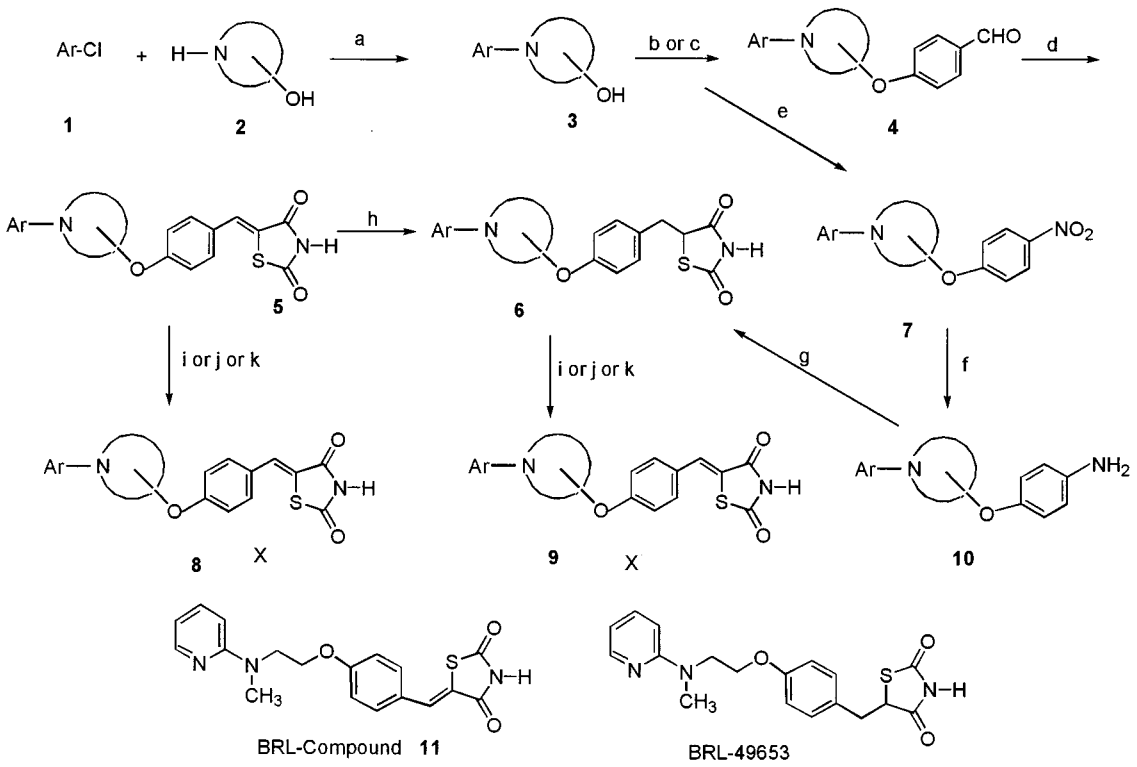
Euglycemic and Hypolipidemic Activity Studies. Male C57BL/KsJ-db/db mice were obtained at 6 weeks age from Jackson Laboratories (Bar Harbor, ME) and maintained at 25 ± 2 °C on a 12-h light/12-h dark cycle. The animals were given standard laboratory chow (National Institute of Nutrition, Hyderabad, India) 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. Rosiglitazone (30 mg/kg) was used as a standard drug. The control animals were given vehicle (0.5% carboxymethylcellulose, CMC; dose 10 mL/kg). On the final day blood samples (25−50 μL) were collected after 1 h of drug adminstration from the retro-orbital sinus through heparinized capillary in EDTA-containing tubes. After centrifugation, plasma was separated and glucose and triglyceride were estimated using commercial kits (Dr. Reddy's Laboratories Diagnostic Division, India). Only selected compounds were tested in ob/ob mice.

The ob/ob mice were used for experiments at 10 weeks of age, and blood samples were collected on days 0 and 14 of treatment as described above. Dose−response studies for selected TZDs were carried out in both db/db and ob/ob mice. Animals were treated with different doses for 14−15 days. Plasma glucose and triglyceride were measured on days 0, 3, 6, 9, 12, and 15. The percentage reduction in plasma glucose level was calculated.[15] Oral glucose tolerance test (OGTT) was performed after 14/15 days of treatment in both db/db and ob/ob mice. In the case of db/db animals, mice were fasted overnight and challenged with glucose (3 g/kg, po). Blood samples were collected at 0, 30, 60, and 120 min for measuring plasma glucose level. The improvement in glycemic control was calculated as percentage reduction in the area under the plasma glucose content versus time curve (AUC). The AUC was calculated using trapezoidal rule.

Similarly, OGTT was performed in ob/ob mice after 15 days of treatment; however, the mice were challenged with glucose (3 g/kg, po) after a 5-h fast. Blood samples were collected at different time intervals as described earlier.

Pharmacokinetic Studies. Pharmacokinetic study of **5a** maleate was carried out in male Wistar rats (n =

Scheme 1[a]



[a] (a) Neat, 160 °C, 50−100% yield; (b) 4-fluorobenzaldehyde, NaH, DMF, 40−76% yield; (c) (i) methanesulfonyl chloride, triethylamine, CH_2Cl_2, 83−90% yield, (ii) 4-hydroxybenzaldehyde, K_2CO_3, DMF, 80 °C, 36−45% yield; (d) 2,4-thiazolidinedione, piperidine, C_6H_5COOH, toluene, Δ, 63−100% yield; (e) 4-fluoronitrobenzene, NaH, DMF, 36−67% yield; (f) Fe, HCl, EtOH, 96−100% yield; (g) (i) ethyl acrylate, $NaNO_2$, HBr or HCl, Cu_2O, acetone, MeOH, 44−85% yield, (ii) thiourea, NaOAc, EtOH, 80 °C or thiourea, sulfolane, 120−130 °C; 2 N HCl, EtOH, 80 °C, 62−95%; (h) Mg−MeOH, 48−65% yield; (i) maleic acid, acetone/Et_2O, 70−80% yield; (j) HCl; (g) acetone, 73−86% yield; (k) NaOMe, MeOH, 52−91% yield.

3) obtained from the National Institute of Nutrition (Hyderabad, India). The animals (200−225 g) were fasted 12 h before starting the experiment, and they had free access to water throughout the experimental period. Animals were given feed 3 h after drug administration. Pharmacokinetic parameters: $AUC_{(0-\infty)}$ is the area under the plasma concentration versus time curve extrapolated to infinity, C_{max} is the observed maximum plasma concentration, and t_{max} is the time at which maximum concentration (C_{max}) is reached.

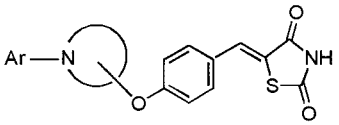
Single-Dose Pharmacokinetics. Animals were dosed with **5a** maleate at 10 mg/kg via oral gavage as 0.5% CMC suspension, and about 0.30 mL of blood sample was collected into heparinized microfuge tubes at different time points from the retro-orbital sinus. The samples were analyzed by reverse-phase HPLC to generate plasma concentration−time profiles (Figure 4).

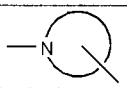
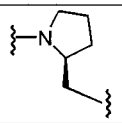
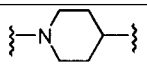
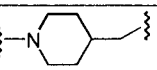
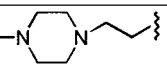
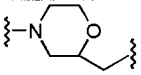
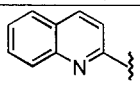
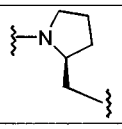
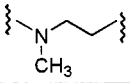
Sample Preparation and Analysis. To 0.1 mL of plasma was added internal standard (another thiazolidinedione), and drug was extracted from the plasma using 2 mL of extracting solvent (ethyl acetate:dichloromethane, 1:1). The organic layer (1.5 mL) was evaporated to dryness and reconstituted in 200 μL of mobile phase; 100 μL of the sample was injected onto HPLC. The calibration, control, and recovery samples were prepared by spiking blank plasma and were processed similarly. The HPLC system consisted of a Waters LC Module-1 with Millennium software and a KROMASIL KR100-5C18-250A (5 μm, 4.6 mm × 250 mm) column (Hichrom, U.K.). Analysis of **5a** maleate was carried out using 0.05 M NaH_2PO_4 buffer (pH 4.0):methanol (25:75) as mobile phase at a flow rate of 1 mL/min, and the eluent was monitored with UV dector at 345 nm. Under these conditions, retention times for **5a** maleate and internal standard were 12.6 and 8.4 min, respectively. Absolute recovery was >95%, the limit of quantification was 0.1 μg/mL, and the response was linear up to 50 μg/mL.

Results and Discussion

We prepared several thiazolidinedione analogues containing pyridine or quinoline moieties and evaluated their pharmacological profiles for plasma glucose- and triglyceride-lowering activities in db/db mice. The animals were treated for 6 days at a dose of 100 mg/kg/day (Table 1). We have used unsaturated BRL compound **11** for comparison. The results are shown in Table 1. The unsaturated TZD **5a**, which was readily prepared by the reaction of 2-chloropyridine with (*S*)-prolinol as shown in Scheme 1, showed very good euglycemic and hypolipidemic activities in db/db mice (Table 1, entry 1). In contrast, unsaturated TZDs resulting from the combination of 2-chloropyridine and other cyclic amines as the linker group such as piperidine or piperazine (Table 1, entries 2−4) showed much poorer pharmacological activities. However, compound **5e** containing morpholine as the cyclic linker showed appreciably good euglycemic and hypolipidemic activities (Table 1, entry 5). It appears that 2-(*S*)-prolinol is the most suitable linker for this class of compounds. Thus, we examined the combination of quinoline with (*S*)-prolinol, which afforded unsaturated TZD **5f**. The

Table 1. Euglycemic and Hypolipidemic Activities of Unsaturated TZDs



Entry	Compound No.	Ar		Dose	PG[a]	TG[b]
1	**5a**			100	57 ± 3.37	77.75 ± 9.37
2	**5b**			100	38 ± 9.51	40.25 ± 13.77
3	**5c**			100	NS	27.33 ± 8.21
4	**5d**			100	35.75 ± 18.18	69.75 ± 16.92
5	**5e**			100	55.25 ± 6.34	52.50 ± 9.74
6	**5f**			100	63.75 ± 5.22	NS
7	BRL Compound **11**			100	55.5 ± 3.39	35.0 ± 2.24

[a] Percentage reduction in plasma glucose after 6 days of treatment in db/db mice via oral gavage. [b] Percentage reduction in plasma triglyceride. BRL compound **11** was prepared according to the reported procedure;[12] NS, not significant.

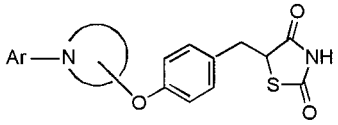
TZD **5f** showed very good euglycemic activity but barely had any effect on the triglyceride level (Table 1, entry 6). From these initial screenings, we concluded that a further examination of saturated TZDs resulting from the combination of pyridine or quinoline with (*S*)-prolinol and morpholine derivatives is essential.

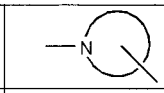
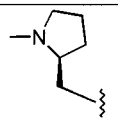
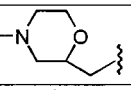
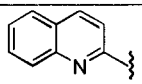
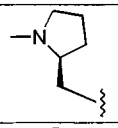
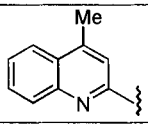
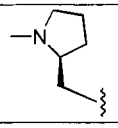
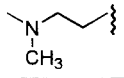
Hence, we prepared saturated TZDs **6a** and **6e** by saturating potent unsaturated TZDs **5a** and **5e**, respectively. Surprisingly, in both the cases, even at a 30 mg/kg/day dose (Table 2) the euglycemic activity remained impressive, although the hypolipidemic activity of **5e** completely disappeared (Table 2, entries 1 and 2). BRL-49653 was used as positive control (Table 2, entry 5). In contrast, the quinolinyl-substituted TZD **6f** prepared from **5f** or through an independent route as shown in Scheme 1 showed excellent euglycemic and hypolipidemic activities at 30 mg/kg dose in db/db mice (Table 2, entry 3), and the plasma glucose reached the level of lean littermates (8 ± 1 mM). We have also examined the effect of an electron-donating CH_3 group at the C_4 position of quinoline (Table 2, entry 4), which resulted in reduction in euglycemic activity; however, an improvement in hypolipidemic activity was observed (**6g** versus **6f**).

From the above studies, it is clear that the unsaturated TZDs **5a**, **5e**, and **5f** and their saturated counterparts **6a**, **6e**, and **6f** constitute a potent class of TZDs, and they need further detailed evaluation. Thus we prepared various salts of **5a** and **5e** which are the most potent unsaturated TZDs and evaluated their biological activities. Interestingly, the maleate, hydrochloride, or sodium salt of **5a** showed improved euglycemic and hypolipidemic activities when compared to their parent compound **5a** (Table 1, entry 1 versus Table 3, entries 1−3; although comparison cannot be done at different doses). The hydrochloride salt of **5e** (Table 3, entry 4) showed moderate activity. Even at 30 mg/kg/day dose, the maleate, hydrochloride, and sodium salts of **5a** showed superior euglycemic activities (Table 3, entries 1−3) compared to the parent compound **5a** (Table 1, entry 1) which was evaluated at 100 mg/kg/day dose. The improvement in euglycemic activities of various salts of **5a** may be attributed to the improvement of the pharmacokinetic profile.

Similar observations were made with saturated TZDs **6a**, **6e**, **6f**, and **6g**. In all cases maleate, hydrochloride, and sodium salts were prepared (only the maleate and sodium salts were made for **6e**), and all of them were studied in db/db mice at 30 mg/kg dose (Table 3); rosiglitazone (maleate salt of BRL-49653) was used as the standard drug for comparison purposes. All the salts of TZD **6a** (Table 3, enties 5−7) showed excellent euglycemic activities at 30 mg/kg dose, and the plasma glucose level in these animals reached the level of lean littermates (i.e. 8 ± 1 mM). Although all the salts of **6a** (Table 3, entries 5−7) showed equal effects on glucose level, it is not clear why they show different levels of triglyceride lowering. It is believed that different salts play a role in bioavailability of the drug and should not be affected by the mechanism of action of the drug. With the present understanding, it is difficult to speculate the reason for varying effects on triglyceride levels due

Table 2. Euglycemic and Hypolipidemic Activities of Unsaturated TZDs



Entry	Compound No.	Ar		Dose	PG[a]	TG[b]
1	**6a**			30	52.25 ± 6.43	65.5 ± 15.95
2	**6e**			30	57.5 ± 15.97	NS
3	**6f**			30	72.25 ± 3.45	49.0 ± 9.06
4	**6g**			30	40.5 ± 9.63	66.25 ± 4.55
5	BRL – 49653			30	35.0 ± 2.75	40.21 ± 8.67

[a] Percentage reduction in plasma glucose after 6 days of treatment in db/db mice via oral gavage. [b] Percentage reduction in plasma triglyceride. BRL-49653 was prepared according to the reported procedure;[12] NS, not significant.

Table 3. Euglycemic and Hypolipidemic Activities of Various Salts of TZDs **5** and **6**

entry no.	compd no.	dose	PG[a]	TG[b]
1	**5a** maleate	30	63.6 ± 4.61	66.4 ± 9.76
2	**5a** HCl	30	70.8 ± 4.36	31.67 ± 14.4
3	**5a** Na	30	56.5 ± 7.19	56.0 ± 8.76
4	**5e** HCl	30	35.5 ± 9.5	NS
5	**6a** maleate	30	62.5 ± 4.33	44.75 ± 14.84
6	**6a** HCl	30	50.5 ± 6.9	50.5 ± 7.29
7	**6a** Na	30	65.5 ± 5.45	NS
8	**6e** Na	30	63.5 ± 7.41	56.75 ± 12.93
9	**6f** maleate	30	NS	NS
10	**6f** HCl	30	15.75 ± 16.87	NS
11	**6f** Na	30	61.5 ± 13.33	24.75 ± 7.47
12	**6g** maleate	30	NS	53.0 ± 5.15
13	**6g** HCl	30	25.25 ± 7.5	42.0 ± 6.88
14	**6g** Na	30	30.25 ± 4.63	58.5 ± 6.12
15	rosiglitazone	30	64.6 ± 5.35	41.0 ± 17.7

[a] Percentage reduction in plasma glucose after 6 days of treatment in db/db mice via oral gavage. [b] Percentage reduction in plasma triglyceride. Rosiglitazone was prepared according to the reported procedure;[12] NS, not significant.

to various salts (Table 3, entries 5−7; triglyceride 50%−NS). In the case of the sodium salt of saturated TZD **6e**, there was no improvement in euglycemic activity but significant changes were observed in the hypolipidemic activity at 30 mg/kg dose (compared to parent compound **6e** Table 3, entry 8 versus Table 2, entry 2). In contrast, the salts of **6f** were inferior in their euglycemic and hypolipidemic activities when compared to saturated TZD **6f** (Table 3, entries 9−11 versus Table 2, entry 2). Similar observations were made with various salts of TZD **6g** which showed poorer euglycemic and hypolipidemic activities than their parent compound **6g** (Table 3, entries 12−14 versus Table 2, entry 4). Although there seems to be a meaningful structure−activity relationship between unsaturated TZDs **5a**−**5f** and saturated TZDs **6a**, **6e**, **6f**, and **6g**, it is not possible to draw any meaningful SAR in the case of their various salts (Table 3, entries 1−14). When we compare the different salts of TZDs reported in Table 3 with BRL-49653 (Table 3, entry 15), it is clear that maleate and hydrochloride salts of TZD **5a** (Table 3, entries 1 and 2) or their saturated counterparts, i.e., **6a** (Table 3, entries 5 and 6) and sodium salt of TZD **6e** (Table 3, entry 8), are comparable to rosiglitazone (Table 3, entry 15) in their pharmacological activities.

Finally, we selected the maleate and hydrochloride salts of **5a**, maleate salt of saturated TZD **6a**, and sodium salt of **6e** for dose−response studies in db/db mice and compared them with BRL-49653. The animals were treated with different doses for 14−15 days, and plasma glucose and triglyceride levels were measured in each case. The results are summarized in Table 4.

Rosiglitazone showed superior euglycemic activity at 3 mg/kg dose (plasma glucose, 42 ± 2%; triglyceride, 47 ± 15%) than **5a** maleate, **6a** maleate, and **6e** sodium salt; however, at higher doses, i.e., 10 and 30 mg/kg, all four compounds were equipotent or sometimes superior to rosiglitazone (BRL-49653). In addition, **5a** maleate especially showed better triglyceride-lowering activities at 10 and 30 mg/kg dose than rosiglitazone. It is pertinent to mention that an efficient control of triglyceride levels in type 2 diabetic patients has shown beneficial effects in diabetes-related complications especially atherosclerosis and cardiovascular diseases. Thus, a consensus has emerged in the recent past that the drugs which control both PG and TG tightly would be more suitable candidates for further development for the treatment of type 2 diabetes.

Table 4. Dose−Response Studies of Selected TZDs in db/db Mice

compd no.	dose (mg/kg/day)	PG[a]	TG[b]
5a maleate	3	12.75 ± 4.55	75.00 ± 5.31
	10	49.60 ± 6.95	78.40 ± 3.64
	30	63.60 ± 4.61	71.25 ± 10.58
5a HCl	3	53.80 ± 2.33	
	10	61.00 ± 2.30	43.80 ± 6.17
	30	70.80 ± 4.36	31.67 ± 14.44
6a maleate	3	8.50 ± 6.96	41.50 ± 16.14
	10	40.33 ± 3.53	NS
	20	41.25 ± 9.04	34.50 ± 11.59
6e Na	3	34.67 ± 9.39	39.25 ± 12.32
	10	66.00 ± 3.94	39.00 ± 5.85
rosiglitazone	3	41.60 ± 2.29	47.00 ± 15.04
	10	47.25 ± 5.74	35.25 ± 20.40
	30	65.00 ± 5.36	41.00 ± 17.70

[a] Percentage reduction in plasma glucose after 14 days of treatment in db/db mice. [b] Percentage reduction in triglyceride after 14 days of treatment in db/db mice via oral gavage; NS, not significant.

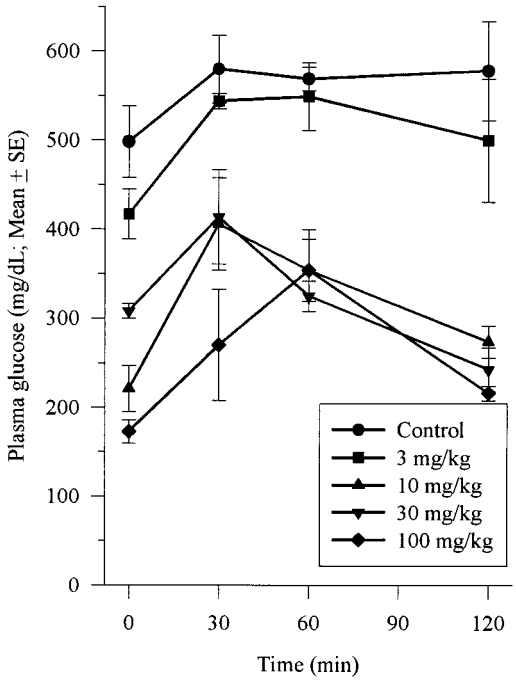


Figure 2. Oral glucose tolerance test of **5a** maleate in db/db mice.

From the above dose−response studies in db/db mice, it is clear that **5a** maleate and **5a** hydrochloride are suitable candidates for further studies. The ED_{50} values for **5a** maleate and **5a** hydrochloride are in the range of 11−7 mg/kg. An oral glucose tolerance test performed after 14 days of treatment of **5a** maleate in db/db mice showed remarkable improvement in glucose tolerance as shown in Figure 2.

We further performed dose−response studies of **5a** maleate, **5a** hydrochloride, and **6e** sodium in another animal model (C57BL/6J/ob/ob) to examine the species variation. In ob/ob mice also **5a** maleate showed excellent plasma glucose- and triglyceride-lowering activities, when treated for 14 days (Table 5).

We also carried out oral glucose tolerance test especially with **5a** maleate in ob/ob mice after 15 days of treatment. The results are shown in Figure 3. It is clear that **5a** maleate showed impressive improvement in glucose tolerance even at 10 mg/kg dose.

Table 5. Dose−Response Studies of Selected TZDs in ob/ob Mice

compd no.	dose (mg/kg/day)	PG[a]	TG[b]
5a maleate	1	52.40 ± 6.36	65.75 ± 10.48
	3	40.25 ± 13.48	59.00 ± 14.10
	10	69.25 ± 4.01	41.50 ± 6.44
	30	73.00 ± 1.73	68.50 ± 2.40
5a HCl	1	18.80 ± 7.14	46.60 ± 4.03
	3	50.20 ± 3.80	39.33 ± 11.02
	10	42.40 ± 7.26	35.00 ± 13.43
	30	37.20 ± 5.34	53.00 ± 7.51
6e Na	1	30.00 ± 8.15	NS
	3	35.60 ± 7.84	NS
	10	39.80 ± 6.61	NS

[a] Percentage reduction in plasma glucose after 14 days of treatment in ob/ob mice. [b] Percentage reduction in triglyceride after 14 days of treatment in ob/ob mice via oral gavage; NS, not significant.

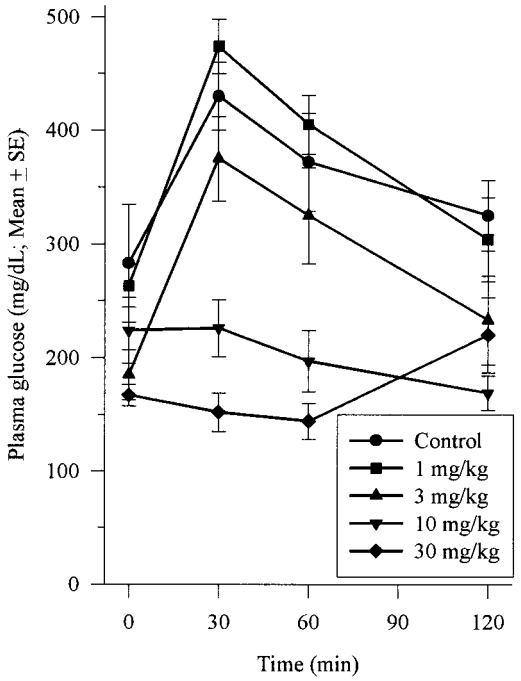


Figure 3. Oral glucose tolerance test of **5a** maleate in ob/ob mice.

Finally, we carried out pharmacokinetic studies of **5a** maleate in order to assess its oral bioavailability and half-life ($t_{1/2}$) in animals (Figure 4). From the results it is clear that **5a** maleate showed high AUC (26.55 ± 9.27 μg h mL^{-1}), is absorbed very rapidly (t_{max} 1 h), and reached C_{max} (8.42 ± 1.9 μg mL^{-1}). The compound is also excreted (K_{el} 0.37 ± 0.08 h^{-1}) fast and has $t_{1/2}$ of ca. 2 h (1.94 ± 0.41 h).

Although **5a** maleate showed a short half-life, still it exerts its euglycemic and hypolipidemic activities quite effectively. Further, to understand the mode of action of **5a** and **5a** maleate, we carried out a receptor transactivation assay. Thus, we carried out transactivation studies (PPARγ at 0.1, 1, and 10 μM concentration and PPARα at 50 μM concentration) for **5a** and **5a** maleate. We were rather gratified to find that neither **5a** nor **5a** maleate showed significant PPARα or PPARγ activation.[5] (PPARγ activation for **5a** maleate at 0.1, 1.0, and 10 μM showed 0.9-, 1.1-, and 1.0-fold transactivation.) We also examined the PPARγ transactivation of corresponding saturated TZD **6a** at similar concentrations (i.e. 0.1, 1.0, and 10 μM). Interestingly, the

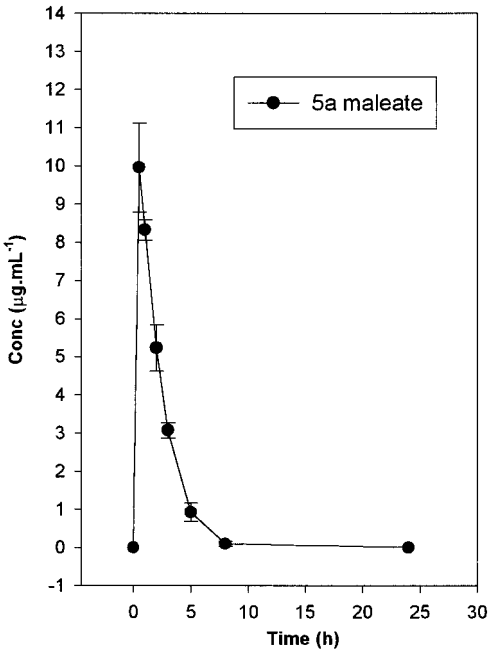


Figure 4. Drug plasma concentration (**5a** maleate) versus time curve in Wistar rats.

saturated compound **6a** showed 3.5-, 7.4-, and 7.2-fold transactivation of PPARγ, although **6a** is not so impressive in controlling plasma glucose in db/db mice.

It is interesting to note that **5a** maleate is the first unsaturated thiazolidinedione showing such impressive euglycemic- and triglyceride-lowering activities. It remains to be seen how this compound exhibits its pharmacological activities, and further studies in this class of compounds may reveal new mechanisms of action of this class of TZDs.

Experimental Section

General. Thin-layer chromatography was performed on silica gel plates (60 F254, Merck). Flash chromatography was performed on silica gel (SRL 230−400 mesh). Melting points were recorded on 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) from downfield to TMS. The infrared spectra were recorded on a Perkin-Elmer FT-IR 1600 spectrometer. The mass spectra were obtained with a HP 5989A mass spectrometer. Optical rotations were measured on a Jasco-DIP-370 digital polarimeter. (*S*)-(+)-Prolinol, 2-(hydroxymethyl)morpholine, and 4-(hydroxymethyl)piperidine were prepared by the reported procedure.[16] 4-Piperidinol, 4-(hydroxymethyl)piperidine, piperazine, 2-chloropyridine, 2-chloroquinoline, 4-hydroxybenzaldehyde, 4-fluoronitrobenzene, and 2,4-thiazolidinedione were purchased and used directly. Compound **11**, BRL-49653, and rosiglitazone were prepared by the reported procedure.[12] All moisture-sensitive reactions were conducted under an argon atmosphere in oven-dried glassware.

(*S*)-2-(Hydroxymethyl)-1-(pyridin-2-yl)pyrrolidine (3a). A mixture of 2-chloropyridine (33.7 g, 297 mmol) and L-prolinol (20 g, 198 mmol) was heated under nitrogen atmosphere at 160 °C with stirring for 4 h. The mixture was cooled to room temperature and poured into water (100 mL), and the solution was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The crude product was chromatographed over silica gel using 2% methanol in chloroform to afford 19.4 g (55%) of the title compound as a syrupy liquid: IR ν_{max} (neat) 3372, 1600, 1491, 1442, 1377 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.7 (m, 1H), 2.05 (m, 3 H), 3.2−3.9 (m, 4 H), 4.25 (m, 1 H), 6.43 (d, J = 8.4 Hz, 1 H), 6.58 (t, J = 6.0 Hz,1 H), 7.5 (m, 1 H), 8.02 (d, J = 4.2 Hz, 1 H); Mass *m*/*z* (relative intensity) 179 (M^+ + 1, 29), 147 (100).

(*S*)-4-[[1-(Pyridin-2-yl)pyrrolidin-2-yl]methoxy]benzaldehyde (4a). To a stirred suspension of sodium hydride (3 g, 60% w/w dispersion) in DMF (20 mL) was added (*S*)-2-(hydroxymethyl)-1-(pyridin-2-yl)pyrrolidine (9 g, 50.5 mmol) in dry DMF (20 mL), and the mixture was stirred for 30 min. A solution of 4-fluorobenzaldehyde (10.8 mL, 101 mmol) in dry DMF (20 mL) was added and stirred for 12 h at room temperature. The reaction mixture was quenched with water (200 mL) and 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 of ethyl acetate and petroleum ether (4:96) as eluent to get 9.6 g (67%) of title compound as a viscous liquid: IR ν_{max} (neat) 1690, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.1 (m, 4 H), 3.3 (m, 1 H), 3.5 (m, 1 H), 3.96 (t, J = 8.7 Hz, 1 H), 4.4 (dd, J = 9.6 and 3.4 Hz, 1 H), 4.55 (m, 1 H), 6.41 (d, J = 8.8 Hz, 1 H), 6.59 (m, 1 H), 7.13 (d, J = 8.8 Hz, 2 H), 7.46 (m, 1 H), 7.82 (d, J = 8.8 Hz, 2 H), 8.18 (d, J = 3.8 Hz, 1 H), 9.87 (s, 1H); Mass *m*/*z* (relative intensity) 283 (M^+ + 1, 7.5), 147 (100).

5-[4-[[1-(Pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethylene]thiazolidine-2,4-dione (5a). A mixture of *(S)*-4-[[1-(pyridin-2-yl)pyrrolidin-2-yl]methoxy]benzaldehyde (7.93 g, 28.12 mmol), thiazolidine-2,4-dione (3.94 g, 33.74 mmol), benzoic acid (0.446 g, 3.65 mmol), and piperidine (0.359 g, 4.2 mmol) in toluene (80 mL) was refluxed for 4 h with continuous removal of water using a Dean−Stark water separator. The reaction mixture was cooled to room temperature and filtered. The filtrate was washed with water (100 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was triturated with methanol and filtered to afford 9.9 g (90%) of the title compound: mp 164 °C; $[\alpha]_D^{27}$ = −73.6 (*c* 1.0, DMSO); IR ν_{max} (KBr) 1735.5, 1699.7, 1598 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.15 (m, 4 H), 3.30 (m, 1 H), 3.55 (m, 1 H), 3.79 (t, J = 9.2 Hz, 1 H), 4.35 (dd, J = 9.0 and 3.2 Hz, 1 H), 4.6 (m, 1 H), 6.47 (d, J = 8.4 Hz, 1 H), 6.65 (t, J = 6.8 Hz, 1 H), 7.01 (d, J = 8.8 Hz, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 7.48 (s, 1 H), 7.56 (t, J = 6.0 Hz, 1 H), 8.16 (d, J = 3.8 Hz, 1 H); Mass *m*/*z* (relative intensity) 382 (M^+ + 1, 25), 249 (15), 147 (100). Anal. Calcd for $C_{20}H_{19}N_3O_3S$ (381.45): C, 62.97; H, 5.02; N, 11.01. Found: C, 62.81; H, 4.97; N, 11.05.

5-[4-[[1-(Pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethylene]thiazolidine-2,4-dione (5a) Maleate. A solution of 5-[4-[[1-(pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethylene]thiazolidine-2,4-dione (50 g, 13.1 mmol) and maleic acid (16.7 g, 14.39 mmol) in dry acetone (2 L) was stirred at room temperature for 20 h. The resulting solid was filtered, washed with cold acetone (2 × 200 mL), and dried under reduced pressure to obtain 52 g (80%) of the title compound: mp 132 °C; $[\alpha]_D^{27}$ = −77.3 (*c* 1.0, DMSO); IR ν_{max} (KBr) 1733, 1685, 1624 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.13 (bs, 4 H), 3.34 (m, 1 H), 3.56 (m, 1H), 4.05 (m, 1H), 4.28 (dd, J = 9.6 and 3.8 Hz, 1H), 4.53 (bs, 1 H), 6.25 (s, 2 H), 6.76 (m, 2 H), 7.19 (d, J = 8.8 Hz, 2 H), 7.59 (d, J = 8.8 Hz, 2H), 7.72 (m, 1 H), 7.79 (s, 1 H), 8.13 (d, J = 4.2 Hz, 1 H), 12.6 (bs, exchangeable with D_2O, 1 H); Mass *m*/*z* (relative intensity) 382 (free base M^+ + 1, 70), 147 (100). Anal. Calcd for $C_{24}H_{23}N_3O_7S$ (497.52): C, 57.94; H, 4.65; N, 8.44. Found: C, 57.69; H, 4.81; N, 8.5.

5-[4-[[1-(Pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethylene]thiazolidine-2,4-dione (5a) Hydrochloride. To a solution of 5-[4-[[1-(pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]phenylmethylene]thiazolidine-2,4-dione (40 g, 10.49 mmol) in dry acetone (2 L) at 0 °C was bubbled HCl gas for 30 min, and the resulting solid was filtered, washed with cold acetone (2 × 200 mL), and dried under reduced pressure to get 33 g (78%) of the title compound as a white solid: mp 241−243 °C; $[\alpha]_D^{27}$ = −131.9 (*c* 1.0, DMSO); IR ν_{max} (KBr) 1739, 1702, 1598 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.1 (m, 4

H), 3.5 (m, H), 3.8 (m, 1 H), 4.19 (d, $J = 5.4$ Hz, 2 H), 4.8 (m, 1 H), 6.95 (t, $J = 6.4$ Hz, 1 H), 7.06 (d, $J = 8.4$ Hz, 2 H), 7.29 (d, $J = 9.0$ Hz, 1 H), 7.54 (d, $J = 8.8$ Hz, 2 H), 7.74 (s, 1 H), 8.0 (m, 2 H), 12.6 (bs, exchangeable with D_2O, 1 H), 14.0 (bs, exchangeable with D_2O, 1 H); Mass *m/z* (relative intensity) 382 (free base $M^+ + 1$, 4.4), 287 (4.0), 147 (100). Anal. Calcd for $C_{20}H_{20}ClN_3O_3S$ (417.91): C, 57.48; H, 4.82; N, 10.05. Found: C, 57.55; H, 4.92; N, 9.97.

5-[4-[[1-(Pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethylene]thiazolidine-2,4-dione (5a) Sodium Salt. To a solution of 5-[4-[[1-(pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]-methoxy]phenylmethylene]thiazolidine-2,4-dione (1 g, 2.6 mmol) in dry MeOH (10 mL) at room temperature was added NaOMe in MeOH [prepared in situ by dissolving Na (66 mg, 2.8 mmol) in MeOH (5 mL)]. The reaction mixture was stirred for 1 h and then diluted with Et_2O (10 mL). The resulting solid was filtered and dried over P_2O_5 under reduced pressure to get the title compound as a white solid 550 mg (52%): mp 254−250 °C; $[\alpha]_D^{27} = -85.2$ (*c* 1.0, DMSO); IR ν_{max} (KBr) 1683, 1599.8, 1558.3 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2.0 (m, 4 H), 3.2 (m, 1 H), 3.5 (m, 1 H), 3.88 (t, $J = 8.8$ Hz, 1 H), 4.21 (dd, $J = 9.2$ and 3.0 Hz, 1 H), 4.4 (bs, 1 H), 6.55 (m, 2 H), 7.06 (d, $J = 8.8$ Hz, 2 H), 7.24 (s, 1 H), 7.25 (m, 3 H), 8.11 (d, $J = 4.0$ Hz, 1 H); Mass *m/z* (relative intensity) 320 (2.7), 161 (100).

***(S)*-4-[[1-(Pyridin-2-yl)pyrrolidin-2-yl]methoxy]nitrobenzene (7a).** A solution of *(S)*-2-(hydroxymethyl)-1-(pyridin-2-yl)pyrrolidine (5 g, 28 mol) in DMF (15 mL) was added dropwise to a suspension of sodium hydride (60% w/w dispersion in paraffin oil, 1.68 g, 42.1 mmol) in DMF (10 mL). The mixture was stirred at room temperature (ca.. 25 °C) for 30 min, after which 4-fluoronitrobenzene (5.94 g, 42.1 mmol) in DMF (10 mL) was added dropwise and stirred at the same temperature for 1 h. Water (50 mL) was added to the reaction mixture, extracted with ethyl acetate (2 × 100 mL), and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give the crude product (7.0 g) which was chromatographed on silica gel using 5% ethyl acetate in petroleum ether as an eluent to afford the title compound (5.0 g, 60%) as a yellow-colored semisolid: IR ν_{max} (KBr) 1593, 1499, 1442 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.09 (m, 4 H), 3.26 (t, $J = 6.64$ Hz, 1 H), 3.48 (t, $J = 6.14$ Hz, 1 H), 3.93 (t, $J = 9.09$ Hz, 1 H), 4.41 (dd, $J = 3.32$ and 3.23 Hz, 1 H), 4.55 (m, 1 H), 6.4 (d, $J = 8.39$ Hz, 1 H), 6.57 (q, $J = 4.98$ Hz, 1 H), 7.1 (d, $J = 9.27$ Hz, 2 H), 7.43 (t, $J = 6.87$ Hz, 1 H), 8.17 (d, $J = 9.04$ Hz, 3 H); Mass *m/z* (relative intensity) 299 (M^+, 2.5), 161 (50), 147 (100).

***(S)*-4-[[1-(Pyridin-2-yl)pyrrolidin-2-yl]methoxy]aniline (10a).** To a stirred suspension of (*S*)-4-[[1-(pyridin-2-yl)-pyrrolidin-2-yl]methoxy]nitrobenzene (4 g, 13.37 mmol) and Fe (7.47 g, 133.7 mmol) in EtOH (20 mL) was added concentrated HCl (20 mL), and the mixture stirred for 1 h. The reaction mixture was filtered, neutralized with saturated sodium carbonate solution to pH 7.0, and extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with brine (20 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford 3.5 g (97%) of the title compound as a brown-colored semisolid: IR ν_{max} (KBr) 3400, 1597, 1511 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.03 (m, 4 H), 3.24 (m, 1 H), 3.50 (m, 1 H), 3.71 (t, $J = 8.8$ Hz, 1 H), 4.13 (dd, $J = 3.36$ and 3.4 Hz, 1 H), 4.42 (m, 1 H), 6.4 (d, $J = 8.39$ Hz, 1 H), 6.51 (m, 3 H), 6.77 (d, $J = 8.81$ Hz, 2 H), 7.38 (m, 1 H), 8.15 (d, $J = 3.51$ Hz, 1H); Mass *m/z* (relative intensity) 269 (M, 4.3), 161 (100).

Ethyl 2-Bromo-3-[*(S)*-4-[[1-(pyridin-2-yl)pyrrolidin-2-yl]methoxy]phenyl]propanoate. A solution of $NaNO_2$ (0.942 g, 13.66 mmol) in H_2O (1.73 mL) was added dropwise to a stirred and ice-cold mixture of *(S)*-4-[[1-(pyridin-2-yl)pyrrolidin-2-yl]methoxy]aniline (3.5 g, 13.01 mmol), aqueous HBr (48%, 2.82 mL), MeOH (3.5 mL), and acetone (7 mL). After the mixture stirred for 30 min, ethyl acrylate (14.09 mL, 130 mmol) was added. The temperature was raised to 38 °C, and powdered Cu_2O (0.111 g, 0.78 mmol) was added in small portions to the vigorously stirred mixture. After the N_2 gas evolution ceased, the reaction mixture was concentrated under reduced pressure. The residue was diluted with water, made alkaline with concentrated NH_4OH, and extracted with EtOAc (2 × 100 mL). The combined EtOAc extract was washed with brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was chromatographed on silica gel using 6% ethyl acetate in petroleum ether to afford 2.5 g (44.4%) of the title compound as a syrupy liquid: IR ν_{max} (KBr) 1738, 1598, 1512, 1478, 1441 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.05 (m, 4 H), 3.11 (m, 3 H), 3.78 (m, 1 H), 4.11 (m, 4 H), 4.36 (m,1 H), 6.4 (d, $J = 8.4$ Hz, 1 H), 6.53 (m, 1 H), 6.89 (d, $J = 8.48$ Hz, 2 H), 7.09 (d, $J = 8.39$ Hz, 2 H), 7.40 (m, 1 H), 8.16 (d, $J = 3.5$ Hz, 1 H); Mass *m/z* (relative intensity) 434 ($M^+ + 1$, 0.8), 147 (100).

5-[4-[[1-(Pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethyl]thiazolidine-2,4-dione (6a). Method A: A suspension of 5-[4-[[1-(pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethylene]thiazolidine-2,4-dione (10 g, 26.2 mmol) and magnesium turnings (10.06 g, 0.4 mol) in dry MeOH (250 mL) was stirred at room temperature for 4 h. The reaction mixture was acidified with 6 N HCl to pH 6.5 and extracted with dichloromethane (2 × 150 mL). The combined organic layer was washed with water (100 mL) and brine (50 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed over silica gel using 0.5% MeOH in chloroform as eluent to afford 6.5 g (65%) of the title compound as a white-colored fluffy solid.

Method B: A mixture of ethyl 2-bromo-3-[*(S)*-4-[[1-(pyridin-2-yl)pyrrolidin-2-yl]methoxy]phenyl]propanoate (2 g, 4.61 mmol), thiourea (0.703 g, 9.23 mmol), NaOAc (0.757 g, 9.23 mmol), and EtOH (15 mL) was stirred under reflux for 5 h. The reaction mixture was cooled, extracted with EtOAc (2 × 40 mL), dried (Na_2SO_4), and concentrated to afford 2-imino-5-[4-[[1-(pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]phenylmethyl]-4-thiazolidinone which was used in the next step without further purification.

A mixture of the above crude product, 2 N HCl (20 mL), and EtOH (20 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 × 30 mL). The combined EtOAc extract was washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed on silica gel with 0.5% MeOH in $CHCl_3$ as an eluent to afford 1.1 g (62%) of the title compound as a white fluffy solid: mp 79−80 °C; $[\alpha]_D^{27} = -107.9$ (*c* 1.0 $CHCl_3$); IR ν_{max} (KBr) 1697, 1599 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.1 (m, 4 H), 3.05 (m, 1 H), 3.2−3.6 (m, 3 H), 3.82 (t, $J = 8.8$ Hz, 1 H), 4.15 (m, 1 H), 4.45 (m, 2 H), 6.44 (d, $J = 8.6$ Hz, 1 H), 6.56 (t, $J = 6.0$ Hz, 1 H), 6.9 (d, $J = 8.4$ Hz, 2 H), 7.15 (d, $J = 8.4$ Hz, 2 H), 7.46 (m, 1 H), 8.14 (d, $J = 2.4$ Hz, 1 H); Mass *m/z* (relative intensity) 384 ($M^+ + 1$, 3.3), 326 (4.4), (100). Anal. Calcd for $C_{20}H_{21}N_3O_3S$ (383.47): C, 62.64; H, 5.51; N, 10.95. Found: C, 62.75; H, 5.49, N, 11.03.

5-[4-[[1-(Pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethyl]thiazolidine-2,4-dione (6a) Maleate. A solution of 5-[4-[[1-(pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenyl methyl]thiazolidine-2,4-dione (4 g, 10.4 mmol) and maleic acid (1.32 g, 11.38 mmol) in dry Et_2O (30 mL) was stirred at room temperature for 20 h. The resulting solid was filtered and washed with cold Et_2O (2 × 10 mL) and dried under reduced pressure to get 4.1 g (79%) of the title compound: mp 58−60 °C; $[\alpha]_D^{27} = -80.5$ (*c* 1.27, DMSO); IR ν_{max} (KBr) 1698.7, 1643, 1583 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.25 (m, 4 H), 3.05−3.4 (m, 2 H), 3.6 (m, 1 H), 3.8 (m, 1 H), 4.1 (m, 2 H), 4.5 (m, 1 H), 4.7 (m, 1 H), 6.3 (s, 2 H), 6.7−7.0 (m, 4 H), 7.12 (d, $J = 8.4$ Hz, 2 H), 7.69 (t, $J = 7.4$ Hz, 1 H), 8.23 (d, $J = 4.4$ Hz, 1 H); Mass *m/z* (relative intensity) 383 (free base M^+, 5.2), 147 (100). Anal. Calcd for $C_{24}H_{25}N_3O_7S$ (499.54): C, 57.70; H, 5.04; N, 8.41. Found: C, 57.59; H, 4.98; N, 8.52.

5-[4-[[1-(Pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethyl]thiazolidine-2,4-dione (6a) Sodium Salt. The title compound (0.3 g, 56%) was prepared as a white solid from 5-[4-[[1-(pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]phenylmethyl]thiazolidine-2,4-dione (0.5 g, 1.3 mmol) and NaOMe (74 mg, 1.37 mmol) in MeOH by a similar procedure to that

described for **8a** sodium salt: mp 260−262 °C; $[\alpha]_D^{27} = -63.0$ (*c* 0.5, DMSO); IR ν_{max} (KBr) 1661, 1598, 1583 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.05 (m, 4 H), 2.45−2.7 (m, 2 H), 3.25 (m, 1 H), 3.5 (m, 1 H), 3.8 (t, $J = 8.8$ Hz, 1 H), 4.1 (m, 2 H), 4.4 (bs, 1 H), 6.55 (m, 2 H), 6.89 (d, $J = 8.4$ Hz, 2 H), 7.1 (d, $J = 8.4$ Hz, 2 H), 7.5 (m, 1 H), 8.12 (d, $J = 3.8$ Hz, 1 H); Mass *m/z* (relative intensity) 308 (6), 161 (100).

5-[4-[[1-(Pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethyl]thiazolidine-2,4-dione (6a) Hydrochloride. The title compound (2 g, 73%) was prepared as a white solid from 5-[4-[[1-(pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethyl]thiazolidine-2,4-dione (2.6 g, 6.79 mmol) by an analogous procedure to that described for **8a** hydrochloride: mp 220 °C; IR ν_{max} (KBr) 1696, 1640, 1550 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.17 (m, 4 H), 3.14 (t, $J = 9.37$ Hz, 2 H), 3.30 (m, 1 H), 3.69 (m, 1 H), 3.98 (t, $J = 10.05$ Hz, 2 H), 4.3 (bs, 1 H), 4.43 (t, $J = 3.64$ Hz, 1 H), 6.75 (d, $J = 7.66$ Hz, 3 H), 6.92 (t, $J = 3.16$ Hz, 1 H), 7.09 (d, $J = 7.24$ Hz, 2 H), 7.78 (d, $J = 4.29$ Hz, 1 H), 8.2 (s, 1 H), 8.5 (bs, exchangeable with D_2O, 1 H); Mass *m/z* (relative intensity) 382 (free base $M^+ - 1$, 4), 147 (100). Anal. Calcd for $C_{20}H_{22}ClN_3O_3S$ (419.93): C, 57.2; H, 5.28; N, 8.44. Found C, 57.31; H, 5.17; N, 8.50.

1-(Pyridin-2-yl)-4-piperidinol (3b). The title compound (3.5 g, 50%) was prepared as a semisolid from 2-chloropyridine (6.7 g, 59 mmol) and 4-piperidinol (4 g, 39.6 mmol) by an analogous procedure to that described for **3a**: IR ν_{max} (neat) 3345, 1596, 1485, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.3 (m, 2 H), 1.8 (m, 3 H), 2.84 (t, $J = 11.7$ Hz, 2 H), 3.54 (d, $J = 6.2$ Hz, 2 H), 4.32 (approximately d, $J = 13.0$ Hz, 2 H), 6.59 (t, $J = 5.9$ Hz, 1 H), 6.67 (d, $J = 8.8$ Hz, 1 H), 7.46 (m, 1 H), 8.18 (d, $J = 3.6$ Hz, 1 H); Mass *m/z* (relative intensity) 179 (M^+, 100), 161 ($M^+ - OH$, 63.2), 133 (96.5).

1-(Pyridin-2-yl)piperidin-4-yl Methanesulfonate. Methanesulfonyl chloride (1.69 mL, 21.9 mmol) was added dropwise to a stirred solution of 1-(pyridin-2-yl)-4-piperidinol (2.35 g, 18.3 mmol) and triethylamine (8.14 mL, 58.4 mmol) in dichloromethane (20 mL) at 0 °C. The resulting mixture was stirred at room temperature for 2 h, then washed with water (50 mL), dried (Na_2SO_4), and concentrated to afford 4.2 g (90%) of the title compound as a semisolid: IR ν_{max} (neat) 1593, 1563, 1481, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.35 (m, 2 H), 1.8−2.15 (m, 3 H), 2.85 (t, $J = 12.2$ Hz, 2 H), 3.02 (s, 3 H), 4.1(d, $J = 6.2$ Hz, 2 H), 4.35 (approximately d, $J = 12.8$ Hz, 2 H), 6.6 (m, 2 H), 7.48 (t, $J = 7.8$ Hz, 1 H), 8.18 (d, $J = 3.8$ Hz, 1 H); Mass *m/z* (relative intensity) 256 (M^+, 14.5), 161 (100).

4-[1-(Pyridin-2-yl)piperidin-4-yloxy]benzaldehyde (4b). To a stirred solution of 1-(pyridin-2-yl)piperidin-4-yl methanesulfonate (4.5 g, 17.56 mmol) and 4-hydroxybenzaldehyde (2.5 g, 21.13 mmol) in dry DMF was added K_2CO_3 (9.7 g, 70.28 mmol), and the mixture was stirred for 10 h at 80 °C. The reaction mixture was cooled to room temperature (ca. 25 °C); water was added (100 mL) and the mixture extracted with ethyl acetate (2 × 40 mL). The combined organic extracts were washed with 5% aqueous Na_2CO_3 solution and brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford 1.8 g (36.3%) of the title compound as a pale-yellow solid: mp 114−116 °C; IR ν_{max} (KBr) 1689.7, 1597, 1570, 1478 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.9 (m, 2 H), 2.1 (m, 2 H), 3.5 (m, 2 H), 3.9 (m, 2 H), 4.7 (m, 1 H), 6.7 (m, 2 H), 7.03 (d, $J = 8.6$ Hz, 2 H), 7.49 (m, 1 H), 7.85 (d, $J = 8.8$ Hz, 2 H), 8.2 (d, $J = 3.4$ Hz, 1 H), 9.89 (s, 1 H); Mass *m/z* (relative intensity) 283 ($M^+ + 1$, 62.9), 282 (M^+, 36), 161 (100).

5-[4-[1-(Pyridin-2-yl)piperidin-4-yloxy]phenylmethylene]thiazolidine-2,4-dione (5b). The title compound (1.5 g, 74%) was prepared as a yellow solid from 4-[1-(pyridin-2-yl)-4-piperidinyloxy]benzaldehyde (1.5 g, 5.3 mmol) and thiazolidinedione (0.622 g, 5.31 mmol) by an analogous procedure to that described for **5a**: mp 218−220 °C; IR ν_{max} (KBr) 1739.9, 1697.9, 1595.5 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ 1.9 (m, 2 H), 2.1 (m, 2 H), 3.5 (m, 2 H), 3.9 (m, 2 H), 4.65 (m, 1 H), 6.62 (t, $J = 5.9$ Hz, 1 H), 6.72 (d, $J = 8.6$ Hz, 1 H), 7.02 (d, $J = 8.4$ Hz, 2 H), 7.5 (m, 3 H), 7.74 (s,1 H), 8.18 (d, $J = 4.0$ Hz, 1 H); Mass *m/z* (relative intensity) 382 ($M^+ + 1$, 4.3), 192 (5.2), 161 (14.6), 86 (100). Anal. Calcd for $C_{20}H_{19}N_3O_3S$ (381.45): C, 62.97; H, 5.02; N, 11.01. Found: C, 62.83; H, 4.95; N, 10.96.

4-(Hydroxymethyl)-1-(pyridin-2-yl)piperidine (3c). The title compound (2.7 g, 80%) was prepared as a syrupy liquid from 2-chloropyridine (7.8 g, 69 mmol) and 4-(hydroxymethyl)-piperidine (2 g, 17 mmol) by a procedure similar to that described for **3a**: IR ν_{max} (KBr) 3355, 2922, 2853, 1597, 1561, 1486 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.3 (m, 2 H), 1.8 (m, 3 H), 2.84 (t, $J = 11.7$ Hz, 2 H), 3.54 (d, $J = 6.2$ Hz, 2 H), 4.32 (approx d, $J = 13.0$ Hz, 2 H), 6.59 (t, $J = 5.9$ Hz, 1 H), 6.67 (d, $J = 8.8$ Hz,1 H), 7.46 (m, 1 H), 8.18 (d, $J = 3.6$ Hz, 1 H); Mass *m/z* (relative intensity) 192 (M^+, 100), 151 (40), 133 (50), 107 (76).

[1-(Pyridin-2-yl)piperidin-4-yl]methyl Methanesulfonate. The title compound (2.1 g, 83%) was prepared as a semisolid from 4-(hydroxymethyl)-1-(pyridin-2-yl)piperidine (1.8 g, 9.4 mmol) and methanesulfonyl chloride (0.8 mL, 10.3 mmol) by a procedure similar to that described for the preparation of 1-(pyridin-2-yl)piperidin-4-yl methanesulfonate: IR ν_{max} (KBr) 2975, 2937, 1599, 1483, 1441, cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.35 (m, 2 H), 1.8−2.15 (m, 3 H), 2.85 (t, $J = 12.2$ Hz, 2 H), 3.02 (s, 3 H), 4.1 (d, $J = 6.2$ Hz, 2 H), 4.35 (approx, d, $J = 12.8$ Hz, 2 H), 6.6 (m, 2 H), 2.48 (t, $J = 7.8$ Hz, 1 H), 8.18 (d, $J = 3.8$ Hz, 1 H); Mass *m/z* (relative intensity) 270 (M^+, 66), 191 (100), 175 (84), 161 (28), 146 (25), 133 (48), 121 (28), 107 (82), 94 (27).

4-[[1-(Pyridin-2-yl)piperidin-4-yl]methoxy]benzaldehyde (4c). The title compound (1.0 g, 45%) was prepared as a semisolid from [1-(pyridin-2-yl)piperidin-4-yl]methyl methanesulfonate (2.0 g, 7.4 mmol) and 4-hydroxybenzaldehyde (1.1 g, 9.0 mmol) by a similar procedure to that described for **4b**: IR ν_{max} (KBr) 1690, 1597, 1562, 1508, 1475, 1431 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.45 (m, 2 H), 1.8−2.25 (m, 3 H), 2.89 (m, 2 H), 3.92 (d, $J = 6.2$ Hz, 2 H), 4.36 (approximately d, $J = 12.8$ Hz, 2 H), 6.62 (m, 2 H), 6.99 (d, $J = 8.6$ Hz, 2 H), 7.47 (m, 1 H), 7.83 (d, $J = 8.6$ Hz, 2 H), 8.19 (d, $J = 3.6$ Hz, 1 H), 9.88 (s, 1 H); Mass *m/z* (relative intensity) 296 (M^+, 65.6), 271 (16), 191 (31), 175 (78.1), 161 (32), 149 (32), 133 (62), 121 (50), 107 (100).

5-[4-[[1-(Pyridin-2-yl)piperidin-4-yl]methoxy]phenylmethylene]thiazolidine-2,4-dione (5c). The title compound (0.46 g, 63%) was prepared as a pale-yellow solid from 4-[[1-(pyridin-2-yl)piperidin-4-yl]methoxy]benzaldehyde (0.55 g, 1.85 mmol) and 2,4-thiazolidinedione (0.268, 2.2 mmol) by a procedure similar to that described for **5a**: IR ν_{max} (KBr) 3438, 2944, 1734, 1688, 1583, 1509, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.45 (m, 2 H), 1.9−2.2 (m, 3 H), 2.9 (t, $J = 11.7$ Hz, 2 H), 3.9 (d, $J = 6.2$ Hz, 2 H), 4.38 (approximately d, $J = 13.0$ Hz, 2 H), 6.61 (t, $J = 5.8$ Hz, 1 H), 6.71 (d, $J = 8.6$ Hz, 1 H), 6.99 (d, $J = 8.8$ Hz, 2 H), 7.5 (m, 3 H), 7.75 (s, 1 H), 8.18 (d, $J = 3.8$ Hz, 1 H); Mass *m/z* (relative intensity) 395 (M^+, 35), 175 (85), 165 (22), 146 (41), 121 (59), 107 (100). Anal. Calcd for $C_{21}H_{21}N_3O_3S$ (395.48): C, 63.78; H, 5.35; N, 10.62. Found: C, 63.82; H, 5.28; N, 10.69.

1-(Pyridin-2-yl)piperazine. A mixture of 2-chloropyridine (15 g, 13.2 mol) and piperazine (114 g, 1.32 mol) was heated under nitrogen atmosphere at 120 °C with stirring for 8 h. The mixture was cooled to room temperature, poured into water (250 mL), and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and evaporated under reduced pressure; the crude product was chromatographed over silica gel using 0.5% MeOH in chloroform to afford 15 g (70%) of the title compound as a white solid: mp 85−87 °C; IR ν_{max} (neat) 3293, 1594, 1562, 1482 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.9 (t, $J = 5$ Hz, 4 H), 3.5 (t, $J = 5.2$ Hz, 4 H), 6.6 (m, 2 H), 7.4 (t, $J = 7.0$ Hz, 1 H), 8.2 (d, $J = 4.2$ Hz, 1 H); Mass *m/z* (relative intensity) 163 (M^+, 35), 133 (20), 121 (80), 95 (100).

2-[4-(Pyridin-2-yl)piperazin-1-yl]ethanol (3d). To a mixture of 1-(pyridin-2-yl)piperazine (2 g, 12.2 mmol) and K_2CO_3 (5.0 g, 36 mmol) in anhydrous DMSO (25 mL) was added 2-bromoethanol (2.3 g, 18 mmol), and the reaction mixture was heated at 80 °C for 8 h. The mixture was cooled, water (50

mL) was added, and the mixture was extracted with EtOAc (60 mL). The organic extract was washed with brine (25 mL) and dried over sodium sulfate. The solvent was removed by distillation under reduced pressure to give 0.8 g (31%) of the title compound as a thick liquid: IR ν_{max} (KBr) 1806, 1594, 1482, cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.6 (t, J = 5 Hz, 6 H), 3.5 (t, J = 5.2 Hz, 6 H), 6.6 (m, 2 H), 7.4 (t, J = 6.8 Hz, 1 H), 8.2 (d, J = 3.8 Hz, 1 H); Mass *m/z* (relative intensity) 208 (M^+, 62), 189 (29), 176 (91), 147 (83), 121 (91), 107 (100).

4-[2-[4-(Pyridin-2-yl)piperazin-1-yl]ethoxy]benzaldehyde (4d). A solution of [4-(pyridin-2-yl)piperazin-1-yl]ethanol (2 g, 9.6 mmol) in DMF (10 mL) was added dropwise to a suspension of sodium hydride (50% dispersion in paraffin oil, 0.278 g, 11.0 mmol) in DMF (10 mL). The mixture was stirred at room temperature (ca. 25 °C) for 0.5 h after which 4-fluorobenzaldehyde (1.3 g, 16 mmol) was added dropwise and stirring was continued for 2 h. Water (30 mL) was added to the reaction mixture, extracted with ethyl acetate (2 × 50 mL), and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give 3 g of crude product which was chromatographed on silica gel using 10−20% (gradient elution) of EtOAc in petroleum ether to afford 1.2 g (40%) of **4d** as a thick liquid: IR ν_{max} (KBr) 1691, 1598, 1570, 1437, 1245, 1163, 1022, 833, 774, 597 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.78 (t, J = 4.6 Hz, 4 H), 2.96 (t, J = 5.6 Hz, 2 H), 3.64 (t, J = 5 Hz, 4 H), 4.29 (t, J = 5.4 Hz, 2 H), 6.66 (m, 2 H), 7.03 (d, J = 8.6 Hz, 2 H), 7.5 (m, 1 H), 7.85 (d, J = 8.6 Hz, 2 H), 8.2 (d, J = 3.8 Hz, 1 H), 9.9 (s, 1 H); Mass *m/z* (relative intensity) 312 (M^+, 33), 190 (50), 107 (100).

5-[4-[2-[4-(Pyridin-2-yl)piperazin-1-yl]ethoxy]phenylmethylene]thiazolidine-2,4-dione (5d). The title compound (0.85 g, 64%) was prepared as a pale-yellow solid from 4-[2-[4-(pyridin-2-yl)piperazin-1-yl]ethoxy]benzaldehyde (1.0 g, 3.2 mmol) and 2,4-thiazolidinedione (0.45 g, 3.8 mmol) by a procedure similar to that described for **6a**: mp 158−160 °C; IR ν_{max} (KBr) 3397, 1722, 1691, 1594, 1508, 1434, 1293, 1244, 1159, 1019, 958, 769, 686, 557 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ 2.88 (m, 4 H), 2.98 (m, 2 H), 3.65 (m, 4 H), 4.25 (m, 2 H), 6.67 (m, 2 H), 6.92 (d, J = 8.4 Hz, 2 H), 7.33 (d, J = 8.6 Hz, 2 H), 7.48 (m, 2 H), 8.2 (d, J = 3.6 Hz, 1 H); Mass *m/z* (relative intensity) 411 (M^+, 8), 190 (25), 118 (100), 107 (75). Anal. Calcd for $C_{21}H_{22}N_4O_3S$ (410.49): C, 61.44; H, 5.40; N, 13.6. Found: C, 61.37; H, 5.45; N, 13.56.

2-(Hydroxymethyl)-4-(pyridin-2-yl)morpholine (3e). The title compound (33.5 g, 72%) was prepared as a colorless thick liquid from 2-chloropyridine (54.32 g, 0.48 mol) and 2-(hydroxymethyl)morpholine (28 g, 0.24 mol) by a similar procedure to that described for the preparation of **3a**: IR ν_{max} (neat) 3405, 1594, 1481, 1437, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.70−2.90 (m, 1 H), 2.9 (d, J = 11.95 and 3.33 Hz, 1 H), 3.56−3.90 (m, 4 H), 3.90−4.20 (m, 3 H), 6.58−6.79 (m, 2 H), 7.51 (t, J = 6.89 Hz, 1 H), 8.20 (d, J = 3.73 Hz, 1 H); Mass *m/z* (relative intensity) 194 (38), 164 (4), 163 (100), 133 (39).

4-[[4-(Pyridin-2-yl)morpholin-2-yl]methoxy]benzaldehyde (4e). The title compound (39 g, 75.7%) was prepared as a colorless thick liquid from 2-(hydroxymethyl)-4-(pyridin-2-yl)morpholine (33.5 g, 0.172 mol) and 4-fluorobenzaldehyde (27.8 g, 0.19 mol) by a procedure similar to that described for the preparation of **4a**: IR ν_{max} (neat) 2858, 1689, 1600, 1480, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.89 (d, J = 12.36 and 1.89 Hz, 1 H), 3.05 (td, J = 12.36 and 3.46 Hz, 1 H), 3.70−4.40 (m, 7 H), 6.60−6.80 (m, 2 H), 7.06 (d, J = 8.72 Hz, 2 H), 7.54 (t, J = 7.20 Hz, 1 H), 7.85 (d, J = 8.72 Hz, 2 H), 2 H), 8.25 (d, J = 3.83 Hz, 1 H), 9.90 (s, 1 H); Mass *m/z* (relative intensity) 298 (M^+, 23) 177 (23), 163 (100).

5-[4-[[4-(Pyridin-2-yl)morpholin-2-yl]methoxy]phenylmethylene]thiazolidine-2,4-dione (5e). The title compound (20.6 g, 97%) was prepared as a yellow solid from 4-[[4-(pyridin-2-yl)morpholin-2-yl]methoxy]benzaldehyde (16 g, 53.69 mmol) and 2,4-thiazolidinedione (6.9 g, 59.06 mmol) by a procedure similar to that described for the preparation of **5a**: mp 158 °C; IR ν_{max} (KBr) 2866, 1693, 1595, 1508, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.82−3.18 (m, 2 H), 3.70−4.40 (m, 7 H), 6.61−6.80 (m, 2 H), 7.02 (d, J = 8.72 Hz, 2 H), 7.41 (d, J = 8.72 Hz, 2 H), 7.55 (t, J = 6.73 Hz, 1 H), 7.68 (s, 1 H), 8.23 (d, J = 3.10 Hz, 1 H); Mass *m/z* (relative intensity) 397 (M^+, 28.4), 177 (64.6), 163 (100). Anal. Calcd for $C_{20}H_{19}N_3O_4S$ (397.45): C, 60.43; H, 4.81; N, 10.57. Found: C, 60.35; H, 4.75; N, 10.63.

5-[4-[[4-(Pyridin-2-yl)morpholin-2-yl]methoxy]phenylmethylene]thiazolidine-2,4-dione (5e) Hydrochloride. The title compound (0.17 g, 78%) was prepared as a pale-yellow solid from 5-[4-[[(pyridin-2-yl)morpholin-2-l]methoxy]phenylmethyl]thiazolidine-2,4-dione (0.2 g, 0.03 mmol) by a procedure similar to that described for the preparation of **6a** hydrochloride: mp 238 °C; IR ν_{max} (KBr) 2959, 1736, 1694, 1601, 1511, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.91−3.20 (m, 2 H), 3.61−4.22 (m, 7 H), 6.92−7.01 (m, 2 H), 7.14 (d, J = 8.68 Hz, 2 H), 7.38 (d, J = 8.68 Hz, 2 H), 7.58 (t, J = 6.83 Hz, 1 H), 7.71 (s, 1 H), 7.86 (d, J = 3.20 Hz, 1 H); Mass *m/z* (relative intinsity) 397 (free base M^+, 42), 177 (67), 163 (100). Anal. Calcd for $C_{20}H_{22}ClN_3O_4S$: C, 55.10; H, 5.08; N, 9.63. Found: C, 55.02; H, 5.14; N, 9.58.

5-[4-[[4-(Pyridin-2-yl)morpholin-2-yl]methoxy]phenylmethyl]thiazolidine-2,4-dione (6e). The title compound (13.2 g, 88%) was prepared as a white solid from 5-[4-[[4-(pyridin-2-yl)morpholin-2-yl]methoxy]phenylmethylene]thiazolidine-2,4-dione (15 g, 37.7 mmol) and Mg (14.5 g, 0.6 mol) by a procedure similar to that described for the preparation of **6a**: mp 63−65 °C; IR ν_{max} (KBr) 2858, 1696, 1603, 1511, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.82−3.18 (m, 2 H), 3.11 (dd, J = 14.12 and 9.78 Hz, 1 H), 3.46 (dd, J = 14.12 and 3.73 Hz, 1 H), 3.81 (td, J = 11.53 and 2.49 Hz, 1 H), 3.90−4.35 (m, 6 H), 4.48 (dd, J = 9.78 and 3.73 Hz, 1 H), 6.65−6.75 (m, 2 H), 6.91 (d, J = 8.63 Hz, 2 H), 7.16 (d, J = 8.63 Hz, 2 H), 7.53 (t, J = 6.87 Hz, 1 H), 8.22 (d, J = 3.41 Hz, 1 H); Mass *m/z* (relative intensity) 400 (M^+ + 1, 100), 342 (23.2), 257 (79.3). Anal. Calcd for $C_{20}H_{21}N_3O_4S$ (399.47): C, 60.13; H, 5.29; N, 10.51. Found: C, 60.06; H, 5.33; N, 10.57.

5-[4-[[4-(Pyridin-2-yl)morpholin-2-yl]methoxy]phenylmethyl]thiazolidine-2,4-dione (6e) Sodium Salt. The title compound (2.9 g, 91%) was prepared as a white solid from 5-[4-[[4-(pyridin-2-yl)morpholin-2-yl]methoxy]phenylmethyl]thiazolidine-2,4-dione and NaOMe (1.26 g, 23.3 mmol) by a procedure similar to that described for the preparation of **6a** sodium salt: mp 272 °C; IR ν_{max} (KBr) 3437, 1594, 1563, 1546, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.51−2.92 (m, 2 H), 3.20−3.40 (m, 1 H), 3.53−3.72 (m, 1 H), 3.74−4.20 (m, 7 H), 4.20−4.40 (m, 1 H), 6.69 (t, J = 5.81 Hz, 1 H), 6.86 (d, J = 8.62 Hz, 2 H), 7.11 (d, J = 5.81 Hz, 1 H), 7.21 (d, J = 8.62 Hz, 2 H), 7.57 (t, J = 8.3 Hz, 1 H), 8.14 (d, J = 4.35 Hz, 1 H); Mass *m/z* (relative intensity) 397 (free base, M^+, 42), 177 (67), 163 (100).

5-[4-[[4-(Pyridin-2-yl)morpholin-2-yl]methoxy]phenylmethyl]thiazolidine-2,4-dione (6e) Maleate. The title compound (0.14 g, 72%) was prepared as a white solid from 5-[4-[[4-(pyridin-2-yl)morpholin-2-yl]methoxy]phenylmethyl]-thiazolidine-2,4-dione (150 mg, 0.38 mmol) and maleic acid (44 mg, 0.38 mmol) by a similar procedure to that described for the preparation of **6a** maleate: mp 165 °C; IR ν_{max} (KBr) 3055, 1750, 1696, 1626, 1583 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.12 (d, J = 4.89 Hz, 1 H), 7.62 (t, J = 7.81 Hz, 1 H), 7.16 (d, J = 8.0 Hz, 2 H), 6.92 (d, J = 8.3 Hz, 2 H), 6.72 (t, J = 6.06 Hz, 2 H), 6.24 (s, 2 H), 4.87 (dd, J = 4.07 and 9.23 Hz, 1 H), 4.32−3.79 (m, 7 H), 3.71−3.58 (m, 1 H), 3.28 (dd, J = 4.07 and 14.1 Hz, 1 H), 3.16−2.64 (m, 3 H); Mass *m/z* (relative intensity) 400 (free base M^+ + 1, 100), 342 (20.0), 257 (75.5). Anal. Calcd for $C_{24}H_{25}N_3O_8S$ (515.54): C, 55.91; H, 4.88; N, 8.15. Found: C, 55.98; H, 4.91; N, 8.02.

(*S*)-2-(Hydroxymethyl)-1-(quinolin-2-yl)pyrrolidine (3f). The title compound (14 g, 100%) was prepared as a thick liquid from 2-chloroquinoline (10 g, 60 mmol) and L-prolinol (37.2 g, 370 mmol) by a similar procedure to that described for the preparation of **3a**: IR ν_{max} (neat) 2870, 1618, 1556, 1509, 1355, 1160, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.7 (m, 1 H), 2.1 (m, 4 H), 3.4−3.9 (m, 4 H), 4.5 (m, 1 H), 6.76 (d, J = 9 Hz, 1 H), 7.24 (m, 1 H), 7.62 (m, 3 H), 7.89 (d, J = 9 Hz, 1 H); Mass *m/z* (relative intensity) 228 (M^+, 10), 209 (5), 197 (100), 182 (7.5), 170 (7.5).

(*S*)-4-[[1-(Quinolin-2-yl)pyrrolidin-2-yl]methoxy]benzaldehyde (4f). The title compound (90 mg, 41%) was prepared as a thick liquid from (*S*)-2-(hydroxymethyl)-1-(quinolin-2-yl)pyrrolidine (0.15 g, 0.65 mmol) and 4-fluorobenzaldehyde (0.16 g, 1.3 mmol) by a similar procedure to that described for the preparation of **4a**: IR (neat) 1681, 1602, 1509 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.2 (m, 4 H), 3.45 (m, 1 H), 3.7 (m, 1 H), 4.01 (t, $J = 9.3$ Hz, 1 H), 4.65 (dd, $J = 10$ and 3 Hz, 1 H), 4.8 (m, 1 H), 6.80 (d, $J = 9$ Hz, 1 H), 6.9−8.0 (m, 9 H), 9.9 (s, 1 H); Mass *m/z* (relative intensity) 332 (M^+, 95), 215 (19), 198 (23.8), 197 (100), 181 (7).

5-[4-[[1-(Quinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethylene]thiazolidine-2,4-dione (5f). The title compound (2 g, 100%) was prepared as a pale-yellow solid from (*S*)-4-[[1-(quinolin-2-yl)pyrrolidin-2-yl]methoxy]benzaldehyde (1.5 g, 4.5 mmol) and 2,4-thiazolidinedione (0.53 g, 4.5 mmol) by a similar procedure to that described for the preparation of **5a**: mp 260−262 °C; $[\alpha]_D^{27} = +49.2$ (*c* 1.0, DMSO); IR (KBr) 1693, 1603, 1510, 1304, 1227, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.15 (m, 4 H), 3.45 (m, 1 H), 3.7 (m, 1 H), 4.0 (t, $J = 9.2$ Hz, 1 H), 4.55 (dd, $J = 10$ and 2.9 Hz, 1 H), 4.75 (s, 1 H), 6.80 (d, $J = 8.8$ Hz, 1 H), 7.15−8.0 (m, 10 H); Mass *m/z* (relative intensity) 336 (18.8), 212 (33.9), 211 (100), 181 (20.7). Anal. Calcd for $C_{24}H_{21}N_3O_3S$ (431.51): C, 66.80; H, 4.90; N, 9.74. Found: C, 66.71; H, 4.98; N, 9.66.

(*S*)-4-[[1-(Quinolin-2-yl)pyrrolidin-2-yl]methoxy]nitrobenzene (7f). The title compound (9 g, 36%) was prepared as a yellow solid from (*S*)-2-(hydroxymethyl)-1-(quinolin-2-yl)-pyrrolidine (16.5 g, 70 mmol) and 4-fluoronitrobenzene (12.3 g, 90 mmol) by a similar procedure to that described for the preparation of **7a**: mp 118−120 °C; IR ν_{max} (KBr) 1605, 1507 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.15 (m, 4 H), 3.45 (m, 1 H), 3.7 (m, 1 H), 4.0 (t, $J = 9.4$ Hz, 1 H), 4.65 (dd, $J = 10.0$ and 3.2 Hz, 1 H), 4.8 (s, 1 H), 6.75 (d, $J = 9.2$ Hz, 1 H), 7.1−8.00 (m, 7 H), 8.27 (d, $J = 9.2$ Hz, 2 H); Mass *m/z* (relative intensity) 349 (M^+ 2.2), 320 (2.2), 211 (100), 182 (9), 169 (11.4).

(*S*)-4-[[1-(Quinolin-2-yl)pyrrolidin-2-yl]methoxy]aniline (10f). The title compound (5.5 g, 100%) was prepared as a brown-colored solid from *(S)*-4-[[1-(quinolin-2-yl)pyrrolidin-2-yl]methoxy]nitrobenzene (6 g, 170 mmol), iron (9.7 g, 170 mmol), and concentrated HCl (40 mL) by a similar procedure to that described for the preparation of **10a**: mp 138−140 °C; IR ν_{max} (KBr) 1606, 1474, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.15 (m, 4 H), 3.4 (m, 1 H), 3.6−4.0 (m, 2 H), 4.4 (dd, $J = 10.0$ and 3.4 Hz, 1 H), 4.87 (s, 1 H), 6.70 (d, $J = 8.8$, Hz, 1 H), 6.8 (d, $J = 9.2$ Hz, 1 H), 7.0 (d, $J = 8.8$ Hz, 2 H), 7.2 (m, 1 H), 7.58 (m, 2 H), 7.76 (d, $J = 8.2$ Hz, 1 H), 7.89 (d, $J = 9.0$ Hz, 1 H); Mass *m/z* (relative intensity) 320 ($M^+ + 1$ 16.6), 211 (100), 197 (70.3), 169 (7.4).

Ethyl 2-Bromo-3-[4-[[1-(quinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]phenyl]propanoate. The title compound (1 g, 76%) was prepared as a thick liquid from (*S*)-4-[[1-(quinolin-2-yl)pyrrolidin-2-yl]methoxy]aniline (0.9 g, 2.8 mmol) and ethyl acrylate (1.7 g, 16 mmol) by a similar procedure to that described for the preparation of ethyl 2-bromo-3-[4-[[1-(pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]phenyl]propanoate: IR ν_{max} (neat) 1738, 1608, 1509, 1478 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, $J = 7.4$ Hz, 3 H), 2.2 (m, 4 H), 3.2 (dd, $J = 14.0$ and 6.8 Hz, 1 H), 3.5 (m, 2 H), 3.7 (m, 1 H), 3.89 (t, $J = 9.4$ Hz, 1 H), 4.2 (m, 2 H), 4.35 (m, 1 H), 4.45 (m, 1 H), 4.75 (s, 1 H), 6.8 (d, $J = 9.0$ Hz, 1 H), 7.2 (m, 5 H), 7.6 (m, 2 H), 7.77 (d, $J = 8.2$ Hz, 1 H), 7.91 (d, $J = 9$ Hz, 1 H); Mass *m/z* (relative intensity) 483 (M^+, 1), 405 (7.9), 359 (1.6), 197 (100).

5-[4-[[1-(Quinolin-2-yl)-(2S)-pyrrolidin-2-yl]methoxy]-phenylmethyl]thiazolidine-2,4-dione (6f). The title compound (0.5 g, 63%) was prepared as a pale-yellow solid from ethyl 2-bromo-3-[4-[[1-(quinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]phenyl]propanoate (0.9 g, 1.9 mmol) and thiourea (0.21 g, 2.8 mmol) by a similar procedure to that described for the preparation of **6a**: mp 81−83 °C; $[\alpha]_D^{27} = -13.8$ (*c* 1.0, DMSO); IR ν_{max} (KBr) 1752, 1699, 1606, 1555, 1508 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.1 (m, 4 H), 3.1 (dd, $J = 14.0$ and 10.0 Hz, 1 H), 3.44 (m, 2 H), 3.69 (t, $J = 8.0$ Hz, 1 H), 3.94 (t, $J = 9.2$ Hz, 1 H), 4.5 (m, 2 H), 4.75 (s, 1 H), 6.78 (d, $J = 9.2$ Hz, 1 H), 7.15 (m, 5 H), 7.6 (m, 2 H), 7.73 (d, $J = 8.4$ Hz, 1 H), 7.87 (d, $J = 8.8$ Hz, 1 H); Mass *m/z* (relative intensity) 433 (M^+, 6.6), 211 (33.3), 197 (100), 170 (6.6). Anal. Calcd for $C_{24}H_{23}N_3O_3S$ ((433.53): C, 66.49; H, 5.36; N, 9.69. Found: C, 66.56; H, 5.29; N, 9.76.

5-[4-[[1-(Quinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethyl]thiazolidine-2,4-dione (6f) Sodium Salt. The title compound (0.27 g, 72%) was prepared as a pale-yellow solid from 5-[4-[[1-(quinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethyl]thiazolidine-2,4-dione (0.36 g, 0.83 mmol) and NaOMe (45 mg, 0.83 mmol) by a similar procedure to that described for the preparation of **6a** sodium salt: mp 248−250 °C; $[\alpha]_D^{27} = +1.4$ (*c* 1.0, DMSO); IR ν_{max} (KBr) 1664, 1606, 1562, 1508, 1233, 809 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2.1 (m, 4 H), 2.45−2.8 (m, 2 H), 3.4 (m, 1 H), 3.7 (m, 1 H), 3.88 (t, $J = 9.2$ Hz, 1 H), 4.15 (m, 1 H), 4.34 (d, $J = 7.6$ Hz, 1 H), 4.6 (s, 1 H), 6.9−7.3 (m, 6 H), 7.5−7.8 (m, 3 H), 8.05 (d, $J = 9.2$ Hz, 1 H); Mass *m/z* (relative intensity) 226 (1.7), 211 (100), 181 (12.2), 157 (5.2).

5-[4-[[1-(Quinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethyl]thiazolidine-2,4-dione (6f) Maleate. The title compound (0.85 g, 70%) was prepared as a yellow solid from 5-[4-[[1-(quinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]phenylmethyl]thiazolidine-2,4-dione (1 g, 2.3 mmol) and maleic acid (0.27 g, 2.3 mmol) by a similar procedure to that described for the preparation of **6a** maleate: mp 50−52 °C; $[\alpha]_D^{27} = -45.8$ (*c* 1.0, DMSO); IR ν_{max} (KBr) 2977, 1750, 1687, 1649, 1511 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.3 (m, 4 H), 3.0−3.4 (m, 2 H), 3.6−4.3 (m, 4 H), 4.41 (dd, $J = 8.0$ and 4.0 Hz, 1 H), 5.0 (bs, 1 H), 6.33 (s, 2 H), 6.8 (m, 2 H), 7.1 (m, 3 H), 7.5 (m, 1 H), 7.75 (m, 2 H), 8.2 (d, $J = 9.4$ Hz, 2 H); Mass *m/z* (relative intensity) 433 (3.6), 223 (5.4), 211 (54.5), 197 (80), 107 (100). Anal. Calcd for $C_{28}H_{27}N_3O_7S$ (549.60): C, 61.19; H, 4.95; N, 7.64. Found: C, 61.23; H, 4.88; N, 7.71.

5-[4-[[1-(Quinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethyl]thiazolidine-2,4-dione (6f) Hydrochloride. The title compound (0.09 g, 83%) was prepared as a yellow solid from 3-[4-[[1-(quinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenylmethyl]thiazolidine-2,4-dione (1 g, 2.3 mmol) by a similar procedure to that described for the preparation of **6a** hydrochloride: mp 140−142 °C; $[\alpha]_D^{27} = -100.6$ (*c* 1.0, DMSO); IR ν_{max} (KBr) 2974, 1748, 1695, 1648, 1511 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2.1 (m, 4 H), 2.9−4.3 (complex, 7 H), 4.9 (m, 1 H), 6.83 (d, $J = 8.0$ Hz, 2 H), 7.13 (d, $J = 8.6$ Hz, 2 H), 7.52 (m, 2 H), 7.9 (m, 1 H), 7.96 (d, $J = 7.6$ Hz, 1 H), 8.21 (d, $J = 8.0$ Hz, 1 H), 8.44 (d, $J = 9.6$ Hz, 1 H); Mass *m/z* (relative intensity) 433 (3.5), 279 (3.5), 223 (5.3), 211 (29.8), 197 (80.7), 167 (8.7). Anal. Calcd for $C_{24}H_{24}ClN_3O_3S$ (469.99): C, 61.33; H, 5.15; N, 8.94. Found: C, 61.25; H, 5.23; N, 8.81.

(*S*)-2-(Hydroxymethyl)-1-(4-methylquinolin-2-yl)pyrrolidine (3g). The title compound (22 g, 93.6%) was prepared as a brown-colored thick liquid from 2-chloro-4-methylquinoline (17.3 g, 100 mmol) and L-prolinol (59 g, 583 mmol) by a procedure analogous to that described for the preparation of **3a**: IR ν_{max} (neat) 2854, 1614, 1555 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.9−2.1 (m, 4 H), 2.60 (s, 3 H), 3.4−3.8 (m, 4 H), 4.4 (m, 1 H), 6.6 (s, 1 H), 7.2 (t, $J = 7.7$ Hz, 1 H), 7.5 (t, $J = 7.3$ Hz, 1 H), 7.6 (d, $J = 8.0$ Hz, 1 H), 7.7 (d, $J = 8.0$ Hz, 1 H); Mass *m/z* (relative intensity) 242 (M^+, 11.6), 211 (100), 183 (15), 142 (16), 115 (21.6). Anal. Calcd for $C_{15}H_{18}N_2O$ (242.32): C, 74.35; H, 7.48; N, 11.50. Found: C, 74.16; H, 7.53; N, 11.9.

(*S*)-4-[[1-(4-Methylquinolin-2-yl)pyrrolidin-2-yl]methoxy]nitrobnzene (7g). The title compound (10 g, 66.6%) was prepared as a yellow solid from (*S*)-2-(hydroxymethyl)-1-(4-methylquinolin-2-yl)pyrrolidine (10 g, 41.3 mmol) and 1-fluoro-4-nitrobenzene (5.26 mL, 49.5 mmol) by a similar procedure to that described for the preparation of **7a**: mp 96−98 °C; IR ν_{max} (KBr) 1611, 1553, 1501, 1418 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.04−2.2 (m, 4 H), 2.61 (s, 3 H), 3.4 (t, $J = 4.2$ Hz, 1 H), 3.6 (t, $J = 6.5$ Hz, 1 H), 4.0 (t, $J = 9.5$ Hz, 1 H), 4.6 (dd, $J = 2.8$ and 3.2 Hz, 1 H), 7.2 (t, $J = 7.3$ Hz, 1 H), 7.35−7.40 (d, $J = 9.2$ Hz, 2 H), 7.5 (t, $J = 7.6$ Hz, 1 H), 7.7 (t, $J = 8.6$ Hz, 2 H), 8.2 (d, $J = 9.2$ Hz, 2H); Mass *m/z* (relative intensity) 363 (M^+, 5.4), 211 (100),183 (9), 142 (14.5), 115 (16.3). Anal. Calcd

for $C_{21}H_{21}N_3O_3$ (363.41): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.35; H, 5.89; N, 11.64.

(*S*)-4-[[1-(4-Methylquinolin-2-yl)pyrrolidin-2-yl]methoxy]aniline (10g). The title compound (6.5 g, 95.5%) was prepared as a thick liquid from (*S*)-4-[[1-(4-methylquinolin-2-yl)pyrrolidin-2-yl]methoxy]nitrobenzene (7.5 g, 20.6 mmol) and Fe (11.7 g 0.21 mol) by a similar procedure described for the preparation of **10a**: IR ν_{max} (neat) 2951, 1611, 1511 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.1 (m, 4 H), 2.6 (s, 3 H), 3.5 (m, 1 H), 3.6−3.9 (m, 2 H), 4.35 (dd, J = 9.8 and 3.2 Hz, 1 H), 4.7 (bs, 1 H), 6.7 (m, 3 H), 7.0 (d, J = 8.6 Hz, 2 H), 7.24 (m, 1 H), 7.5 (m, 1 H), 7.76 (t, J = 7.2 Hz, 2 H); Mass *m*/*z* (relative intensity) 334 (M^+, 4), 225 (100), 211 (75).

Ethyl 2-Chloro-3-[4-[[1-(4-methylquinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]phenyl]propanoate. The title compound (15 g, 85%) was prepared as a thick liquid from (*S*)-4-[[1-(4-methylquinolin-2-yl)pyrrolidinyl]methoxy]aniline (13.7 g, 41.1 mmol) and ethyl acrylate (2.5 g, 23.4 mmol) by a similar procedure to that described for the preparation of ethyl 2-bromo-3-[4-[[1-(pyridin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]-phenyl]propanoate, except HCl was used instead of HBr: IR ν_{max} (neat) 1743, 1611, 1553, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, J = 7.2 Hz, 3 H), 2.15 (m, 4 H), 2.6 (s, 3 H), 3.12 (dd, J = 14.0 and 7.6 Hz, 1 H), 3.32 (dd, J = 14.2 and 7.6 Hz, 1 H), 3.5 (m, 1 H), 3.7 (m, 1 H), 3.86 (t, J = 9.2 Hz, 1 H), 4.2 (q, J = 7.2 Hz, 2 H), 4.4 (m, 2 H), 4.7 (bs, 1 H), 6.65 (s, 1 H), 7.2 (m, 5 H), 7.6 (m, 1 H), 7.77 (t, J = 6.8 Hz, 2 H); Mass *m*/*z* (relative intensity) 452 (M^+, 2.5), 418 (3.5), 211 (100), 142 (10), 115 (10).

5-[4-[[1-(4-Methylquinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]-methoxy]phenylmethyl]thiazolidine-2,4-dione (6g). A mixture of ethyl 2-chloro-3-[4-[[1-(4-methylquinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]phenyl]propanoate (15 g, 33 mmol) and thiourea (5 g, 65 mmol) in sulfolane (20 mL) was stirred at 120−130 °C for 4 h under N_2 atmosphere. The reaction mixture was cooled to room temperature, and 2-methoxyethanol (192 mL), water (50 mL), and concentrated HCl (26 mL) were added. The temperature was raised to 80 °C and stirred for 15 h. The reaction mixture was cooled, diluted with EtOAc, and washed with aqueous NH_3 followed by water. The organic layer was dried (Na_2SO_4) and concentrated. The crude product was chromatographed on silica gel with 10−40% EtOAc in petroleum ether (gradient elution) as an eluent to afford the title compound (14 g, 95%) as a white solid: mp 95−97 °C; $[\alpha]_D^{27}$ = −31.5 (*c* 1.0, $CHCl_3$); IR ν_{max} (KBr) 1699, 1610, 1553, 1511 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.1 (m, 4 H), 2.1 (s, 3 H), 3.1 (m, 1 H), 3.5 (m, 2 H), 3.7 (m, 1 H), 3.9 (t, J = 9.0 Hz, 1 H), 4.5 (m, 2 H), 4.75 (bs, 1 H), 6.65 (s, 1 H), 7.2 (m, 5 H), 7.57 (t, J = 7.6 Hz, 1 H), 7.78 (t, J = 8.2 Hz, 2 H); Mass *m*/*z* (relative intensity) 447 (M^+, 6), 225 (24), 211 (100), 183 (7), 142 (12), 107 (20). Anal. Calcd for $C_{25}H_{25}N_3O_3S$ (447.55): C, 67.09; H, 5.63; N, 9.39. Found: C, 66.95; H, 5.54; N, 9.49.

5-[4-[[1-(4-Methylquinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]-methoxy]phenylmethyl]thiazolidine-2,4-dione (6g) Sodium Salt. The title compound (0.28 g, 53%) was prepared as a pale-yellow solid from 5-[4-[[1-(4-methylquinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]phenylmethyl]thiazolidine-dione (0.5 g, 1.1 mmol) and NaOMe (62 mg, 1.3 mmol) by a similar procedure described for the preparation of **6a** sodium salt: mp 229 °C; $[\alpha]_D^{27}$ = −5.3 (*c* 1.0, DMSO); IR ν_{max} (KBr) 3425, 1665, 1612, 1561, 1511 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.1 (m, 4 H), 2.4−2.7 (m, 5 H), 3.4 (m, 1 H), 3.65 (m, 1 H), 3.85 (m, 1 H), 4.1 (m, 1 H), 4.3 (m, 1 H), 4.6 (bs, 1 H), 6.85 (s, 1 H), 7.0−7.3 (m, 5 H), 7.6 (m, 2 H), 7.82 (d, J = 8.4 Hz, 1 H); Mass *m*/*z* (relative intensity) 224 (100), 211 (18), 195 (19), 107 (20).

5-[4-[[1-(4-Methylquinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]-methoxy]phenylmethyl]thiazolidine-2,4-dione (6g) Hydrochloride. The title compound (0.2 g, 86%) was prepared as a white solid from 5-[4-[[1-(4-methylquinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]methoxy]phenylmethyl] thiazolidine-2,4-dione (0.215 g, 0.48 mmol) by a procedure analogous to that described for the preparation of **6a** hydrochloride: mp 170−172 °C; $[\alpha]_D^{27}$ = −120.5 (*c* 1.0, DMSO); IR ν_{max} (KBr) 3392, 1688, 1647, 1609, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.30 (m, 4 H), 2.7 (s, 3 H), 3.0−5.0 (complex, 8 H), 6.7−8.0 (complex, 9 H), 14.2 (bs, exchangeable with D_2O, 1 H); Mass *m*/*z* (relative intensity) 447 (free base M^+, 5), 211 (100). Anal. Calcd for $C_{25}H_{26}ClN_3O_3S$ (484.02): C, 62.04; H, 5.41; N, 8.60. Found: C, 61.91; H, 5.35; N, 8.68.

5-[4-[[1-(4-Methylquinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]-methoxy]phenylmethyl]thiazolidine-2,4-dione (6g) Maleate. The title compound (0.21 g, 78%) was prepared as a white solid from 5-[4-[[1-(4-methylquinolin-2-yl)-(2*S*)-pyrrolidin-2-yl]-methoxy]phenylmethyl]thiazolidine-2,4-dione (0.250 g, 0.48 mmol) and maleic acid (58 mg, 0.48 mmol) by a similar procedure described for the preparation of **6a** maleate: mp 68−70 °C; $[\alpha]_D^{27}$ = −72.0 (*c* 1.0, DMSO); IR ν_{max} (KBr) 1751, 1698, 1647, 1579, 1511, 1364, 1240, 1154, 1013, 864, 757, 713, 559 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.25 (m, 4 H), 2.7 (s, 3 H), 3.05−3.45 (m, 2 H), 3.8 (m, 1 H), 4.0 (m, 1 H), 4.2 (m, 2 H), 4.48 (dd, J = 8.0 and 4.2 Hz, 1 H), 5.0 (m, 1 H), 6.35 (s, 2 H), 6.9 (m, 3 H), 7.14 (d, J = 8.2 Hz, 2 H), 7.44 (t, J = 7.6 Hz, 1 H), 7.7 (t, J = 7.8 Hz, 1 H),7.84 (d, J = 8.4 Hz, 1 H), 8.1 (d, J = 8.2 Hz, 1 H); Mass *m*/*z* (relative intensity) 444 (free base M^+, 6), 211 (100), 142 (11), 107 (68). Anal. Calcd for $C_{29}H_{29}N_3O_7S$ (563.63): C, 61.79; H, 5.19; N, 7.45. Found: C, 61.63; H, 5.08; N, 4.56.

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