Molecular Design, Synthesis, and Hypoglycemic Activity of a Series of Thiazolidine-2,4-diones

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Received October 18, 1999

A series of imidazopyridine thiazolidine-2,4-diones were designed and synthesized from their corresponding pyridines. These compounds represent conformationally restricted analogues of the novel hypoglycemic compound rosiglitazone (**5**). The series was evaluated for its effect on insulin-induced 3T3-L1 adipocyte differentiation in vitro and its hypoglycemic activity in the genetically diabetic KK mouse in vivo. The structure−activity relationships are discussed. On the basis of the in vivo potency, 5-[4-(5-methoxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (**19a**) was selected as the candidate for further studies in a clinical setting.

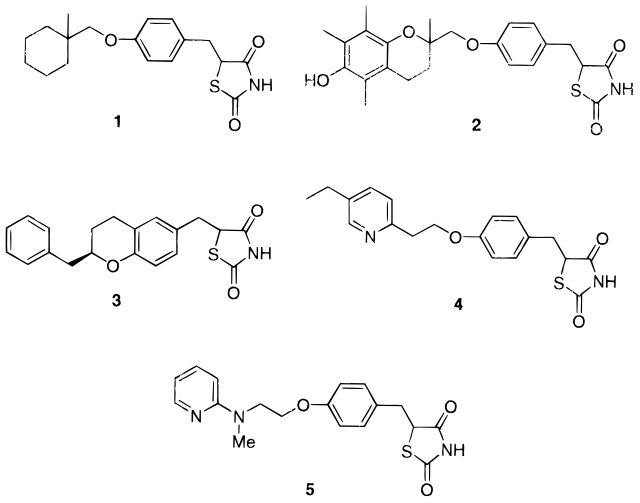
Introduction

Resistance to the metabolic actions of insulin is one of the salient features of impaired glucose tolerance and non-insulin-dependent diabetes mellitus (NIDDM). Insulin resistance is characterized by impaired uptake and utilization of glucose in insulin-sensitive target organs, such as adipocytes and skeletal muscle, and by impaired inhibition of hepatic glucose output.[1] As exercise enhances tissue responsiveness to insulin, the combination of diet and exercise is the primary treatment for NIDDM patients.[2] However, due to difficulties inherent in lifestyle changes and the rapid reversal of the positive effects of exercise,[3] an increasing number of NIDDM patients receive oral hypoglycemic therapy to control blood glucose levels.[4] The most widely used hypoglycemic agent is sulfonylurea.[5] A major drawback of this therapy is the occurrence of potentially life-threatening hypoglycemia due to hyperinsulinemia. Several new approaches to the treatment of the disease are being investigated.[6]

The discovery of compounds which improve insulin resistance enables the continued treatment of NIDDM patients without inducing hypoglycemia. Clofibrate is the first such compound found to improve insulin resistance.[7] It was followed by the discovery of thiazolidinedione compounds, typically represented by ciglitazone (**1**).[8] Of the thiazolidinedione compounds, ciglitazone, troglitazone (**2**),[9] englitazone (**3**),[10] pioglitazone (**4**),[11] and rosiglitazone (**5**)[12] are potential antidiabetic compounds that have been clinically examined.

Troglitazone was found to prevent the inhibitory effect of inflammatory cytokines such as TNF-α, which induce peripheral insulin resistance in glucose uptake[13,14] in insulin-induced adipocyte differentiation of 3T3-L1 cells.[14] Scientists at Glaxo identified rosiglitazone as the first high-affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ), a receptor subtype selectively expressed in adipocytes and shown to induce adipocyte differentiation.[15] It was also reported that there is a significant positive relationship between PPARγ agonism in vitro and hypoglycemic activity of thiazolidinedione compounds in genetically diabetic mice.[16] These studies are predicting the thiazolidinedione compounds to be promising compounds, capable of ameliorating NIDDM by improving insulin resistance without inducing hypoglycemia. Troglitazone, pioglitazone, and rosiglitazone were shown to be potentially active compounds in clinical trials. In other studies, it was also reported that cardiac hypertrophy remains the major obstacle for therapeutic use of thiazolidinediones.[17]

Chart 1



In this paper we describe the discovery of novel imidazopyridine thiazolidinedione compounds with potent hypoglycemic activity obtained from the modification of rosiglitazone by applying the assay method of

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10.1021/jm990522t CCC: $19.00
Published on Web 07/26/2000

adipocyte differentiation in 3T3-L1 cells in vitro and assaying the hypoglycemic effect in genetically diabetic KK mice in vivo. Cardiac hypertrophy was also considered in a series of candidate compounds selected for a clinical trial.

Biological Procedure

Measurement of in Vitro Adipocyte Differentiation Activity. A mouse preadipocyte cell line (3T3-L1) was obtained from the American Type Culture Collection. For the preparation of adipocytes, cells were grown in a basal medium [Dulbecco's modified Eagle medium (DMEM) containing 4.5 g/L glucose, 50 mg/L streptomycin sulfate, 100 000 units/L penicillin-G, 0.584 g/L L-glutamine, 4 mg/L pantothenate, 8 mg/L D-biotin, and 10 mM HEPES (pH 7.2)] supplemented with 10% FBS. Cells were plated at $1.5 \times 10^4/cm^2$ in a 96-well tissue culture plate (view plate, 96 white, Packard) coated with type 1 collagen. After the cells had reached confluence, the cells were further cultured with differentiation medium [basal medium supplemented with 5% FBS, 100 ng/mL insulin, 0.1 mM isobutylmethylxanthine (IBMX), and 1 mM dexamethasone] supplemented with various concentrations of compounds for 4 days. Compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration 1000 times higher than the final concentration and added to the differentiation medium at a concentration of 0.1% (v/v). DMSO was also present in the control culture at a concentration of 0.1% (v/v). The medium was replaced with maintenance medium (basal medium supplemented with 5% of FBS and 100 ng/mL of insulin), and the cells were cultured for 2 more days.

Activity of stimulation of adipogenesis was determined by [1-^{14}C]acetic acid uptake. The maintenance medium was exchanged for fresh maintenance medium supplemented with 7.4 kBq/mL [1-^{14}C]acetic acid. After 1 h of incubation, the maintenance medium was discarded and the cells were washed twice with PBS(−). The cells were air-dried, and 200 mL of scintillation cocktail (Microscint-20, Packard) was added to the wells. Scintillation counts were then measured with a Packard TopCount microplate scintillation counter. Stimulation of adipogenesis is expressed as concentrations equivalent to the [1-^{14}C] uptake counts in the treatment with 0.2 μg/mL troglitazone.

Measurement of in Vivo Hypoglycemic Activity. The hypoglycemic activity of the test compounds in diabetic KK mice ($n = 3$) was measured by the following method. Test compounds were administered to diabetic KK mice at 1 mg/kg immediately and 18 h after the first blood sampling in a nonfasting state. Blood samples were collected 18 and 21 h after first administration of the test compounds. Blood samples were collected from the tail vein of KK mice, placed in a hematocrit centrifuge tube, and centrifuged to obtain plasma. Plasma glucose in the collected plasma was measured by Glucororder F (A & T, Japan). The hypoglycemic activity of the test compounds was calculated as follows:

$$\text{hypoglycemic activity (\%)} = (\text{PG in C} - \text{PG in T})/\text{PG in C} \times 100$$

where "PG in C" is plasma glucose in control mice and "PG in T" is plasma glucose in the mice treated with test compounds.

Measurement of ED_{25} (mg/kg/day) in KK Mice After Oral Administration for 1 Week. Test compounds were administered to diabetic KK mice for 1 week as a food admixture at several predetermined doses. Control KK mice ($n = 5-6$) were given powdered chow not containing any test compound. Blood samples were collected from the tail vein of KK mice before and after drug administration, and the plasma glucose level was measured by a glucose autoanalyzer. The dose of test compounds was calculated from the food intake and body weight of mice. ED_{25} of each compound, defined as the dose at which a plasma glucose-lowering effect is seen, was calculated from the sigmoidal dose−response regression curve, which reveals any decrease in plasma glucose with respect to control mice after drug administration.

Two-Week Oral Toxicity Test in Rats. Seven-week-old male F_{344}/DuCrj rats were assigned to the control and treatment groups ($n = 5$ rats/group). Test compounds suspended in 0.5% carboxymethylcellulose sodium in water were given by gavage for 2 weeks at a dose of 50 mg/kg, and the control group received the vehicle alone. At termination, rats were anesthetized with ether and exsanguinated via the abdominal aorta. After death, all animals were examined macroscopically and major organs including the heart were excised and weighed. Relative organ weight was calculated as absolute organ weight/100 g final body weight. Data are expressed as mean ± standard error (SE). Statistical analysis was done on the treatment groups with respect to the control using Student's *t*-test ($p < 0.01$).

Chemistry

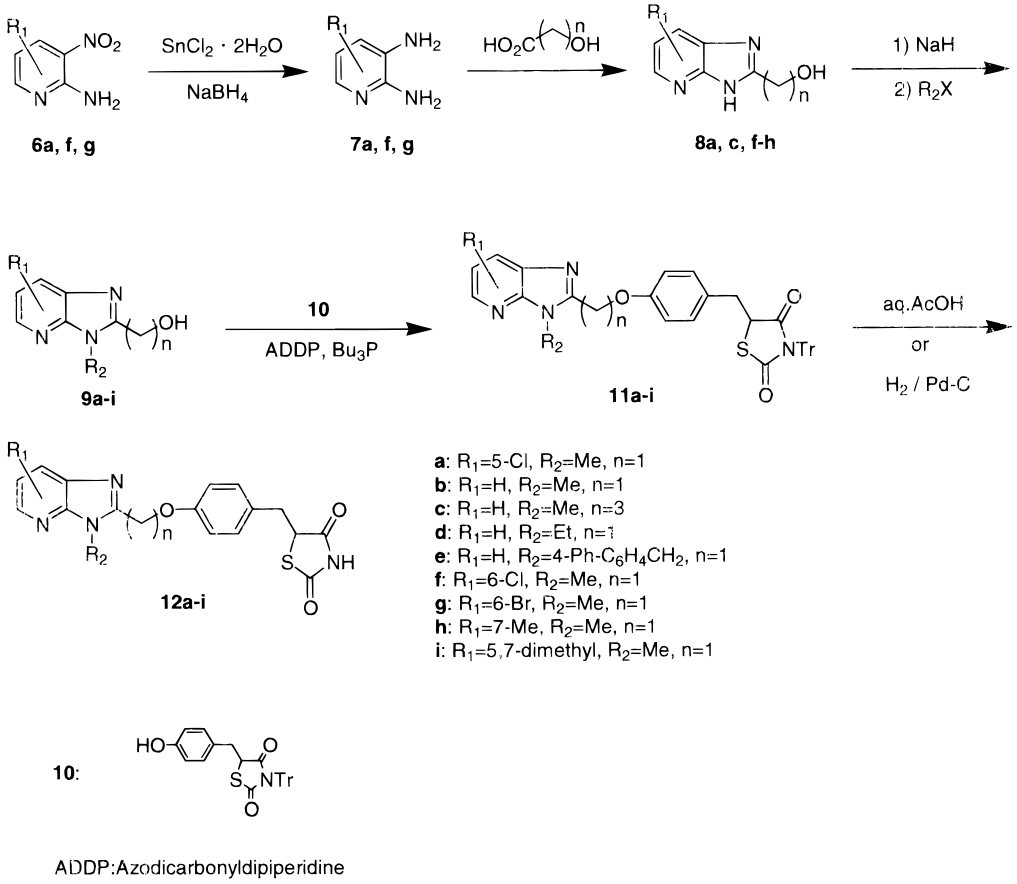
Compounds of type **12a**−**i** were prepared as follows. Pyridine derivative **6** was reduced to diaminopyridine **7**. Cyclization of **7** with glycolic acids[18] yielded imidazopyridine **8**, followed by alkylation at the 3-position to give the imidazopyridine derivative **9**. Mitsunobu reaction[19] of **9** with compound **10** gave compound **11**. Removal of the protecting group, trityl, of **11** yielded the desired product **12** (method A, Scheme 1).

Compounds of type **19a**−**g** were prepared as shown in Scheme 2. First, selective substitution at the 2-position of 2,6-dichloro-3-nitropyridine by methylamine gave 6-chloro-2-methylamino-3-nitropyridine (**14**). Compound **14** was reacted with sodium alkoxide or sodium alkylthioxide to give **15**, and then **15** was reduced to **16**. Cyclization of **16** with glycolic acid yielded imidazopyridine **17**. Mitsunobu reaction of **17** with **10** gave compound **18**. The desired product **19** was obtained by removal of the trityl group of **18** by acid-catalyzed hydrolysis or catalytic hydrogenation (method B).

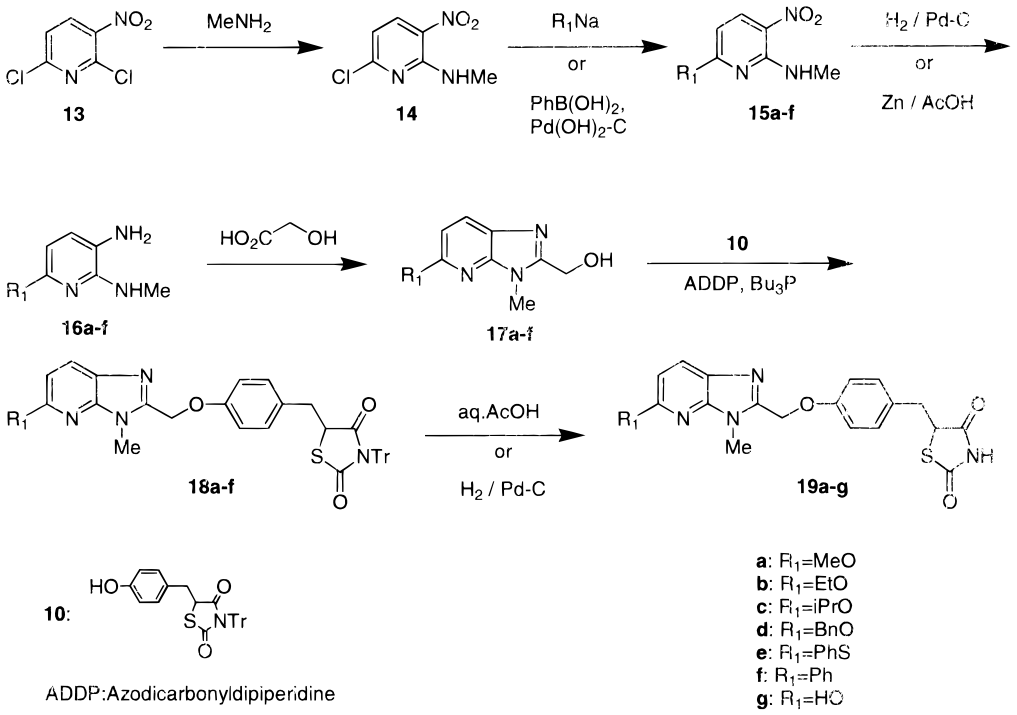
Compounds **24a**−**d** were prepared via an alternative route. The reaction of 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (**20**) with 2-bromoalkyl-1,3-dioxolanes yielded compound **21**; this was followed by deprotection of the ethylene acetal group to give aldehyde **22**. Cyclization of 3-amino-2-(monosubstituted amino)pyridine **23** with **22** followed by oxidation with iodine[20] gave the desired product **24** (method C, Scheme 3).

Scheme 4 shows the formation of an imidazopyridine by the cyclization reaction of diaminopyridine **30** with

Scheme 1. Method A



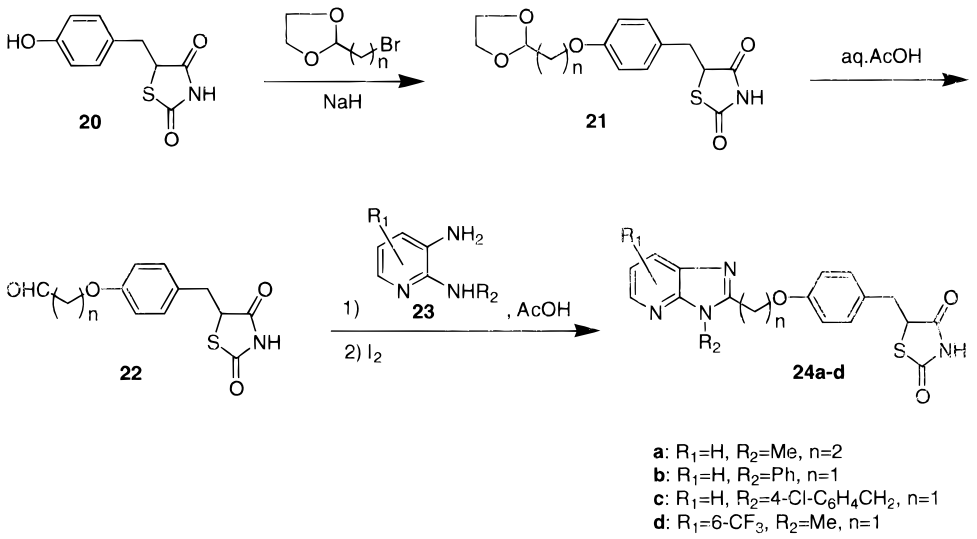
Scheme 2. Method B



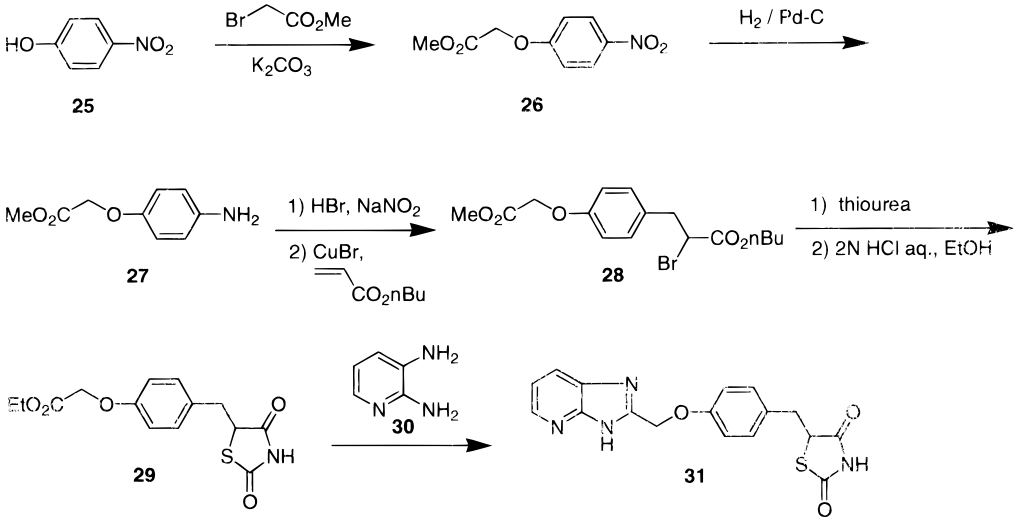
ester **29**. 4-Nitrophenol (**25**) was reacted with methyl bromoacetate to give *O*-acetic acid methyl ester (**26**), and then **26** was reduced to **27** by a method similar to the one described above. Meerwein arylation[21] was carried out on compound **27** to give bromoester ester **28**. Compound **28** gave thiazolidinedione derivative **29** by reaction with thiourea and subsequent hydrolysis in ethanolic hydrochloric acid. Then, **29** was reacted with 2,3-diaminopyridine (**30**) to give the desired product **31** (method D).

Compound **34** was prepared as follows. Mitsunobu reaction of **32** with **10** yielded compound **33**; removal of

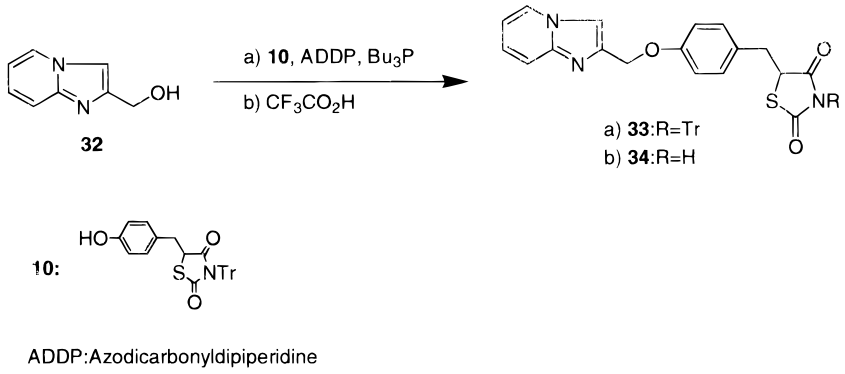
Scheme 3. Method C



Scheme 4. Method D



Scheme 5. Method E



the trityl group by treatment with trifluoroacetic acid produced **34** (method E, Scheme 5).Compound **38** was prepared as follows. 3-Amino-2-methylaminopyridine (**35**) was reacted with carbonyldiimidazole to give 3-methyl-1,3-dihydroimidazo[4,5-*b*]pyridin-2-one (**36**); this was followed by chlorination with $POCl_3$ to give chloride **37**. The reaction of **37** with **20** in the presence of sodium hydride yielded compound **38** (method F, Scheme 6).

Results and Discussion

Many thiazolidinedione derivatives, represented by compounds **1**−**5** described above, have been reported to possess very good hypoglycemic activity. Of these compounds, rosiglitazone (**5**) is reported to have the most potent agonism to PPARγ and a good hypoglycemic effect in genetically diabetic ob/ob mice.[12,15]

Considering the structure of rosiglitazone, we designed and synthesized imidazopyridine derivatives

Scheme 6. Method F

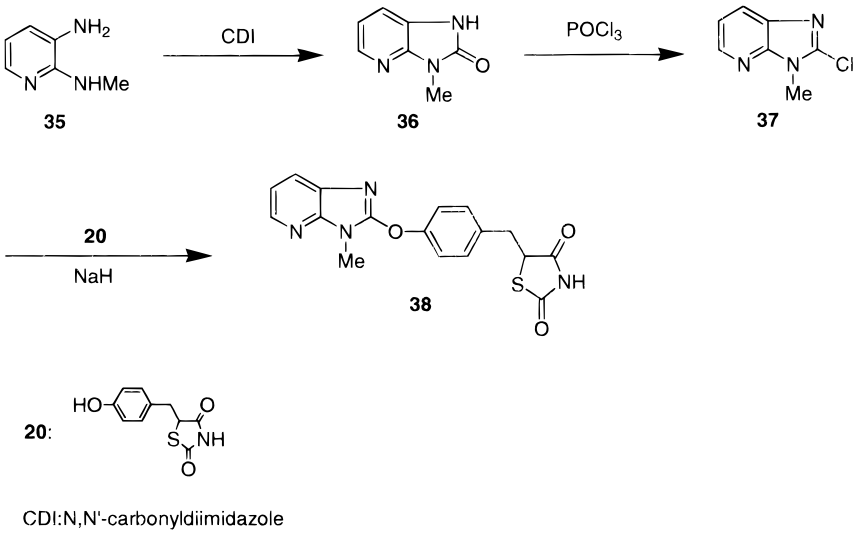
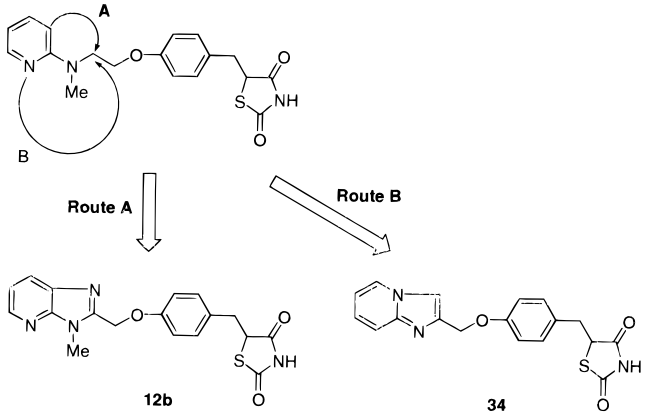


Chart 2



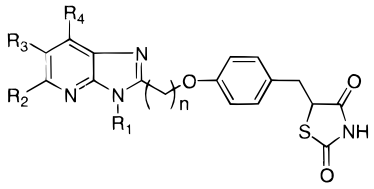
with a nitrogen-containing fused bicyclic ring system, as shown in Chart 2.

Imidazo[4,5-*b*]pyridine (**12b**) and imidazo[1,2-*a*]pyridine (**34**), designed by ring closure via routes A and B, respectively, were synthesized. Compound **12b** showed better adipocyte differentiation in 3T3-L1 cells and better hypoglycemic activity than compound **34** and rosiglitazone in genetically diabetic KK mice as shown in Table 1. Thus, we considered that compound **12b** could be a key compound in exploring hypoglycemic activity. First of all, the effect of the chain length between the imidazopyridine ring and the oxygen atom adjacent to the benzene ring was examined. The compounds bearing carbon chains of length 0−3 were synthesized. Their hypoglycemic and adipocyte differentiation effects were tested and are shown in Table 1 (**38**, **12b**, **24a**, and **12c**). The results revealed that the optimal number of methylene groups is 1, based on both the hypoglycemic and adipocyte differentiation effects. The trimethylene derivative **12c** showed a good adipocyte differentiation effect but no hypoglycemic activity. Possible reasons for the low in vivo activity of compound **12c** are due to poor oral absorption, rapid metabolism, and/or rapid excretion. Although the exact reason for the complete loss of in vivo efficacy of **12c** was not clear, it was not worth further consideration for the selection process. Next, the substituent on the nitrogen at the 3-position of the imidazopyridine ring was varied, where the carbon chain described above was fixed to methylene. The adipocyte differentiation and hypoglycemic effects of the synthesized compounds are shown in Table 1 (**12b**, **31, 12d**, **24b**, **24c**, and **12e**), which indicates that the methyl-substituted compound **12b** was the most potent. Furthermore, the substituent at the pyridine ring of compound **12b** was varied and the results are shown in Table 1 (**12a**, **19g**, **19a**, **19b**, **19c**, **19d**, **19e**, **19f**, **12f**, **12g**, **24d**, **12h**, and **12i**). The best position for substitution was at the 5-position (R_2); the chlorine atom followed by methoxy, ethoxy, isopropoxy, benzyloxy, and phenylthio groups were good substituents as indicated by their adipocyte differentiation activity. A chlorine substituent at the 5-position seemed to bring about the most potent hypoglycemic and adipocyte differentiation activity. Furthermore, substitution at the 6-position did not reduce the hypoglycemic activity compared to that at other positions. The substitution of the hydroxy group at the 5-position dramatically reduced the activity. The IR spectrum revealed that the proton of the hydroxy group tautomerized to the nitrogen atom at the 4-position to form an imidazopyridone structure. It is interesting to note that this imidazopyridine ring system should have an aromaticity to express higher hypoglycemic activity.

From the data on the hypoglycemic and adipocyte differentiation effects shown in Table 1, compounds **12a** and **12b** were designated as primary candidates for further examination. Compound **12a** showed the most potent hypoglycemic and adipocyte differentiation effects, and **12b** had potent hypoglycemic activity. However, these compounds caused cardiac hypertrophy in F_{344} rats after oral multiple administration at a dose of 50 mg/kg/day for 2 weeks as shown in Table 2. Furthermore, compound **12a** showed a tendency to accumulate in F_{344} rats under the above conditions. The concentration of **12b** in the blood increased over a course of time and at 24 h after administration, it reached ca. 30 μg/mL, which is a fairly high concentration, when orally administered to Zucker fatty rats at a single dose of 6.25 mg/kg. Normally, the multiple administration of low-clearance drugs such as **12b** would lead to an accumulation of drug in tissues and cause adverse effects.

One possible method to avoid such drug accumulation is to introduce a functional group which can be easily metabolized in vivo. Compounds with a methoxy group are metabolized relatively easily to their hydroxy derivatives and can be conjugated and excreted. These

Table 1. Hypoglycemic and Adipocyte Differentiation Activities of Imidazopyridine Derivatives and Rosiglitazone (**5**)



compd	R_1	R_2	R_3	R_4	*n*	% decrease in blood glucose[a,b] 18 h	% decrease in blood glucose[a,b] +3 h	adipocyte differentiation[c] EC (μM)
38	Me	H	H	H	0	−7.0 ± 4.8	3.6 ± 0.7	1.35
12b	Me	H	H	H	1	24.7 ± 9.1	27.6 ± 5.9	0.13
24a	Me	H	H	H	2	−5.6 ± 6.2	13.0 ± 9.3	0.65
12c	Me	H	H	H	3	−3.0 ± 6.1	−9.3 ± 18.3	0.081
31	H	H	H	H	1	13.9 ± 12.7	7.4 ± 3.0	8.18
12d	Et	H	H	H	1	−19.5 ± 8.7	2.4 ± 8.3	1.07
24b	Ph	H	H	H	1	3.9 ± 5.6	−3.4 ± 22.4	2.56
24c	4-Cl-$C_6H_4CH_2$	H	H	H	1	24.5 ± 8.2	−8.5 ± 19.0	0.71
12e	4-Ph-$C_6H_4CH_2$	H	H	H	1	3.8 ± 13.4	11.4 ± 6.0	0.92
12a	Me	Cl	H	H	1	37.1 ± 7.7	47.6 ± 6.9	0.0009
19g	Me	OH	H	H	1	−30.6 ± 3.9	−3.2 ± 4.0	1.98
19a	Me	OMe	H	H	1	3.6 ± 5.4	2.9 ± 12.8	0.080
19b	Me	OEt	H	H	1	29.7 ± 7.4	23.6 ± 7.2	0.078
19c	Me	OiPr	H	H	1	14.6 ± 9.7	−0.2 ± 12.2	0.075
19d	Me	OBn	H	H	1	20.3 ± 10.8	18.8 ± 12.8	0.067
19e	Me	SPh	H	H	1	−21.2 ± 6.5	14.7 ± 6.2	0.067
19f	Me	Ph	H	H	1	15.5 ± 15.6	38.1 ± 10.8	0.36
12f	Me	H	Cl	H	1	21.7 ± 8.8	49.7 ± 8.5	0.16
12g	Me	H	Br	H	1	10.2 ± 5.3	6.2 ± 10.4	0.34
24d	Me	H	CF_3	H	1	−0.7 ± 10.3	−26.4 ± 8.5	0.073
12h	Me	H	H	Me	1	−18.2 ± 15.7	−6.9 ± 10.2	0.37
12i	Me	Me	H	Me	1	9.5 ± 11.4	9.5 ± 7.6	0.22
34						5.9 ± 21.9	12.7 ± 22.4	5.09
HCl salt of **19a**	Me	OMe	H	H	1	14.8 ± 10.1	1.0 ± 9.5	0.11
rosiglitazone (**5**)						21.7 ± 18.5	14.6 ± 7.8	0.090

[a] The hypoglycemic activity of test compounds in diabetic KK mice was calculated as follows: hypoglycemic activity (%) = (PG in C − PG in T)/PG in C × 100 (PG in C: plasma glucose in control mice; PG in T: plasma glucose in mice treated with test compounds). Each value represents the mean ± SEM (n = 3). [b] Dose: 1 mg/kg. [c] Stimulation of adipogenesis is expressed as concentrations equivalent to the [1-^{14}C] uptake counts in the treatment with 0.2 μg/mL troglitazone.

Table 2. 2-Week Oral Toxicity Test of the HCl Salt of **19a**, **12a**, **12b**, and Rosiglitazone (**5**) in Male F_{344}/DuCrj Rats (heart weight)

	HCl salt of **19a**		**12a**		**12b**		rosiglitazone (**5**)	
	control	treated	control	treated	control	treated	control	treated
heart wt absolute (g)[a,b]	0.61 ± 0.01	0.68 ± 0.02	0.60 ± 0.01	0.74 ± 0.03	0.61 ± 0.02	0.78 ± 0.02	0.64 ± 0.02	0.76 ± 0.02
% of control		111*		123*		128*		119*
relative (g %)[a,b]	0.31 ± 0.01	0.33 ± 0.01	0.32 ± 0.01	0.37 ± 0.01	0.31 ± 0.01	0.36 ± 0.01	0.32 ± 0.01	0.36 ± 0.00
% of control		106		116*		116*		113*

[a] Each value represents the mean ± SEM (n = 5). [b] Dose: 50 mg/kg. *p < 0.01 vs control (Student's t-test).

types of compounds would not be accumulated in organ tissues. Such a compound with a methoxy group is **19a**.

Here we suspected that **19a** did not lower blood glucose in vivo despite its relatively high adipocyte differentiation activity in vitro. It was supposed that the poor in vivo activity of **19a** could be due to its low concentration in the blood. The single oral administration of compound **19a** revealed very low bioavailability (AUC, 11.9 ± 1.3 μg·h/mL at a dose of 25 mg/kg). The low bioavailability is possibly due to its poor oral absorption, rapid metabolism, and/or rapid excretion. However, when it was administered intravenously, its whole body clearance was 10.2 mL/h/kg suggesting that the reason for its low oral bioavailability was poor absorption from the digestive tract. It is well-known that diet sometimes affects the absorption. Therefore, **19a** was administered orally as an admixture of the diet to KK mice for 1 week, resulting in very good hypoglycemic effects (decrease in blood glucose = 55.8% at a dose of 2.4 mg/kg). On the other hand, a low dissolution rate of a drug can bring about poor absorption. Compound **19a** seems to have very low solubility in water. Therefore, to improve the dissolution rate, its salts with acids, such as hydrogen chloride and fumaric acid, were prepared and administered to examine their oral bioavailability. The results are shown in Table 3 indicating that the HCl salt of **19a** possessed higher bioavailability than the parent compound or its fumarate salt. A single oral administration of the HCl salt of **19a** to KK mice improved the hypoglycemic activity as shown in Table 1, and its multiple administration to KK mice for 1 week resulted in a remarkably excellent ED_{25} value of 0.02 mg/kg/day compared with that of 0.39 mg/kg/day for the

Table 3. Oral Bioavailability of **19a** and Its Salts in F_{344} Rats

compd	dose (mg/kg)	AUC (μg·h/mL)[a]
free	25	11.9 ± 1.3
HCl salt	25	141.1 ± 7.9
$^1/_3$fumarate salt	25	36.4 ± 1.5

[a] Each value represents the mean ± SEM (n = 3).

Table 4. ED_{25}[a] (mg/kg/day) in KK Mice after Oral Administration for 1 Week

HCl salt of **19a**	maleate salt of rosiglitazone (**5**)
0.02	0.39

[a] Amount of test compound needed to reduce blood glucose to 25% of the increased control glucose level.

maleate salt of rosiglitazone as shown in Table 4. From the above observation, the adipocyte differentiation activity of the series of compounds seems to be closely related to the hypoglycemic activity in KK mice.

The HCl salt of **19a** was selected as a candidate over rosiglitazone for a clinical study based on its superior hypoglycemic activity after a multiple administration in KK mice and its lower levels of cardiac hypertrophy, an adverse effect.

Experimental Section

Mass spectra were recorded using a JEOL JMS-700 or JEOL DU-20 mass spectrometer. Proton magnetic resonance (NMR) spectra were recorded using a JEOL JMN GSX-400 spectrometer and are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (Me_4Si); the abbreviation, nd, means that precise identification of the signal was not possible because of an overlap by other signals or absorption of solvent. All NMR spectra were consistent with the structures assigned. Column chromatography was performed on Merck-60 silica gel with a reported solvent. TLC analyses were performed on Merck reagent silica gel 60 F_{254} (0.25 mm thickness). Spots were visualized either by ultraviolet (UV) light or by iodine. Melting points were determined using a Yanaco micro melting point apparatus and are uncorrected.

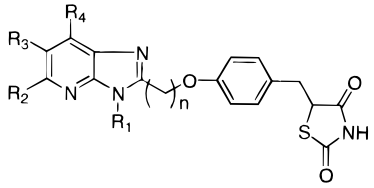
6-Chloro-2,3-diaminopyridine (7a). A mixture of 12.0 g (69.1 mmol) of 2-amino-6-chloro-3-nitropyridine (**6a**), 78.0 g (346 mmol) of tin(II) chloride dihydrate and 360 mL of ethyl acetate and 2-methyl-2-propanol (9:1, v/v) was stirred at 60 °C for 1 h, after which, 1.32 g (34.9 mmol) of sodium borohydride was added at 60 °C, and the mixture was stirred for another 3 h at the same temperature. The reaction mixture was freed from the solvent by distillation under reduced pressure. The resulting residue was diluted with water, neutralized by adding aqueous solution of potassium carbonate and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure. The residue thus obtained was crystallized with a mixture of ethyl acetate and hexane, to give 6.50 g (45.3 mmol) of **7a**: yield 66%; mp 120−122 °C; IR (KBr) 3354, 3175, 1651, 1466, 1242 cm^{-1}; MS *m/z* 143 (M^+); ^1H NMR (DMSO-d_6) δ 4.76 (2 H, s), 5.78 (2 H, s), 6.35 (1 H, d, J = 8.0 Hz), 6.69 (1 H, d, J = 8.0 Hz).

5-Chloro-2,3-diaminopyridine (7f). This compound was prepared using the same procedure as for the preparation of **7a**: mp 164−165 °C; IR (KBr) 3358, 3184, 1645, 1478, 863, 751 cm^{-1}; MS *m/z* 143 (M^+); ^1H NMR (DMSO-d_6) δ 5.02 (2 H, br s), 5.58 (2 H, br s), 6.69 (1 H, d, J = 2.2 Hz), 7.21 (1 H, d, J = 2.2 Hz).

5-Bromo-2,3-diaminopyridine (7g). This compound was prepared using the same procedure as for the preparation of **7a**: mp 135−137 °C; IR (KBr) 3361, 1475 cm^{-1}; MS *m/z* 187 (M^+); ^1H NMR (DMSO-d_6) δ 4.99 (2 H, br s), 5.59 (2 H, br s), 6.80 (1 H, d, J = 2.2 Hz), 7.27 (1 H, d, J = 2.2 Hz).

(5-Chloro-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (8a). A mixture of 6.60 g (86.8 mmol) of glycolic acid and 5.00 g (34.8 mmol) of **7a** was stirred at 150 °C for 4 h. The reaction mixture was treated with 3 N aqueous hydrochloric acid and subsequently made alkaline by the addition of aqueous ammonia. The aqueous mixture was evaporated to dryness, and the resulting residue was purified by column chromatography through silica gel, using a gradient elution method, with a mixture of ethyl acetate and methanol, in ratios ranging from

Table 5. Thiazolidine Compounds



compd	R_1	R_2	R_3	R_4	*n*	synthesis method	yield (%)	mp (°C)	anal. (formula)
38	Me	H	H	H	0	F	37	210−212	$(C_{17}H_{14}N_4O_3S)$ C,H,N,S
12b	Me	H	H	H	1	A	25	223−225	$(C_{18}H_{16}N_4O_3S\cdot{}^1/_5H_2O)$ C,H,N,S
24a	Me	H	H	H	2	C	3	96−100	$(C_{19}H_{18}N_4O_3S\cdot{}^2/_5C_4H_8O_2\cdot{}^3/_{10}H_2O)$ C,H,N,S
12c	Me	H	H	H	3	A	63	185−186	$(C_{20}H_{20}N_4O_3S)$ C,H,N,S
31	H	H	H	H	1	D	62	247−248	$(C_{17}H_{14}N_4O_3S\cdot{}^3/_{10}H_2O)$ C,H,N,S
12d	Et	H	H	H	1	A	46	210−212	$(C_{19}H_{18}N_4O_3S\cdot{}^3/_{20}H_2O)$ C,H,N,S
24b	Ph	H	H	H	1	C	6	88−91	$(C_{23}H_{18}N_4O_3S\cdot{}^3/_{10}H_2O)$ C,H,N,S
24c	4-Cl-$C_6H_4CH_2$	H	H	H	1	C	16	211−213	$(C_{24}H_{19}ClN_4O_3S)$ C,H,Cl,N,S
12e	4-Ph-$C_6H_4CH_2$	H	H	H	1	A	74	189−191	$(C_{30}H_{24}N_4O_3S\cdot{}^1/_4H_2O)$ C,H,N,S
12a	Me	Cl	H	H	1	A	53	222−223	$(C_{18}H_{15}ClN_4O_3S)$ C,H,Cl,N,S
19g	Me	OH	H	H	1	B	15	240−242	$(C_{18}H_{16}N_4O_4S\cdot{}^1/_5H_2O)$ C,H,N,S
19a	Me	OMe	H	H	1	B	77	258−260	$(C_{19}H_{18}N_4O_4S)$ C,H,N,S
19b	Me	OEt	H	H	1	B	91	245	$(C_{20}H_{20}N_4O_4S)$ C,H,N,S
19c	Me	OiPr	H	H	1	B	80	210−212	$(C_{21}H_{22}N_4O_4S\cdot{}^1/_{10}C_4H_8O_2\cdot{}^1/_{10}H_2O)$ C,H,N,S
19d	Me	OBn	H	H	1	B	95	210−211	$(C_{25}H_{22}N_4O_4S)$ C,H,N,S
19e	Me	SPh	H	H	1	B	97	166−168	$(C_{24}H_{20}N_4O_3S_2)$ C,H,N,S
19f	Me	Ph	H	H	1	B	72	211−213	$(C_{24}H_{20}N_4O_3S\cdot C_4H_8O_2\cdot{}^1/_3H_2O)$ C,H,N,S
12f	Me	H	Cl	H	1	A	77	203−205	$(C_{18}H_{15}ClN_4O_3S)$ C,H,Cl,N,S
12g	Me	H	Br	H	1	A	90	204−205	$(C_{18}H_{15}BrN_4O_3S)$ C,H,Br,N,S
24d	Me	H	CF_3	H	1	C	8	212−214	$(C_{19}H_{15}F_3N_4O_3S)$ C,H,F,N,S
12h	Me	H	H	Me	1	A	43	205−207	$(C_{19}H_{18}N_4O_3S)$ C,H,N,S
12i	Me	Me	H	Me	1	A	68	229−230	$(C_{20}H_{20}N_4O_3S)$ C,H,N,S
34						E	45	197−202	$(C_{18}H_{15}N_3O_3S\cdot{}^2/_5H_2O)$ C,H,N,S
HCl salt of **19a**	Me	OMe	H	H	1	B	77	258−260	$(C_{19}H_{18}N_4O_4S\cdot HCl\cdot{}^3/_{10}H_2O)$ C,H,N,S
fumarate salt of **19a**	Me	OMe	H	H	1	B	77	258−260	$(C_{19}H_{18}N_4O_4S\cdot{}^1/_3C_4H_4O_4)$ C,H,N,S

1:0 to 10:1 by volume, as the eluent. The product was then crystallized with ethyl acetate, to give 5.33 g (29.0 mmol) of **8a**: yield 83%; mp 224−226 °C; IR (KBr) 3114 (br), 1582, 1403, 1347, 1112, 1069 cm^{-1}; MS *m*/*z* 183 (M^+); ^1H NMR (DMSO-d_6) δ 4.73 (2 H, s), 5.83 (1 H, br s), 7.24 (1 H, d, J = 8.2 Hz), 7.92 (1 H, br s), 13.18 (br s) and 12.83 (br s) (1 H).

3-(3*H*-Imidazo[4,5-*b*]pyridin-2-yl)propan-1-ol (8c). This compound was prepared using the same procedure as for the preparation of **8a**: mp 151−153 °C; IR (KBr) 3139 (br), 1415, 1272, 788 cm^{-1}; MS *m*/*z* 177 (M^+); ^1H NMR (DMSO-d_6) δ 1.93 (2 H, m), 2.88 (2 H, t, J = 7.5 Hz), 3.49 (2 H, m), 4.60 (1 H, s), 7.15 (1 H, dd, J = 4.9 Hz), 8.0−7.7 (1 H, m), 8.4−8.1 (1 H, m), 12.76 (br s) and 12.44 (br s) (1 H).

(6-Chloro-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (8f). This compound was prepared using the same procedure as for the preparation of **8a**: mp 209−211 °C; IR (KBr) 3370, 3204 (br), 1680, 1656, 1079 cm^{-1}; MS *m*/*z* 183 (M^+); ^1H NMR (DMSO-d_6) δ 4.72 (2 H, s), 5.78 (1 H, br s), 8.00 (1 H, br s), 8.30 (1 H, s), 12.79 (br s) and 13.20 (br s) (1 H).

(6-Bromo-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (8g). This compound was prepared using the same procedure as for the preparation of **8a**: mp 230−233 °C; MS, IR (KBr) 3112 (br), 1431, 1397, 1053 cm^{-1}; *m*/*z* 227 (M^+); ^1H NMR (DMSO-d_6) δ 4.72 (2 H, s), 5.83 (1 H, br s), 8.13 (1 H, s), 8.37 (1 H, d, J = 2.1 Hz), 10.5 (1 H, br s).

(5,7-Dimethyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (8h). This compound was prepared using the same procedure as for the preparation of **8a**: mp 244−246 °C; IR (KBr) 2600−3500 (br), 1625, 1444, 1382, 1365, 1041 cm^{-1}; MS *m*/*z* 177 (M^+); ^1H NMR (DMSO-d_6) δ 2.47 (6 H, s), 4.65 (2 H, d, J = 4.2 Hz), 5.65 (1 H, br s), 6.87 (1 H, s), 12.59 (1 H, br s).

(5-Chloro-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (9a). To a suspension of 0.71 g (16.3 mmol) of sodium hydride (as a 55 wt % dispersion in mineral oil, previously washed with hexane) and 60 mL of dimethylformamide was added 3.00 g (16.3 mmol) of **8a**, and the resulting mixture was stirred at room temperature for 1 h, after which 1.1 mL (17.3 mmol) of methyl iodide was added to the mixture, while ice cooling. The mixture was then stirred at room temperature for 2 h. The reaction mixture was freed from dimethylformamide by distillation under reduced pressure. The residue thus obtained was purified by column chromatography through silica gel, using a gradient elution method, with a mixture of ethyl acetate and methanol, in ratios ranging from 1:0 to 10:1 by volume, as the eluent, to give 1.60 g (8.10 mmol) of **9a**: yield 50%; mp 204−210 °C; IR (KBr) 3400, 3154 (br), 3074, 1491, 1407, 1383, 1261, 1069, 1007 cm^{-1}; MS *m*/*z* 197 (M^+); ^1H NMR (DMSO-d_6) δ 3.81 (3 H, s), 4.74 (2 H, d, J = 5.8 Hz), 5.71 (1 H, t, J = 5.8 Hz), 7.31 (1 H, d, J = 8.2 Hz), 8.07 (1 H, d, J = 8.2 Hz).

(3-Methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (9b). This compound was prepared using the same procedure as for the preparation of **9a**: mp 229−231 °C; IR (KBr) 3347 (br), 1493 cm^{-1}; MS *m*/*z* 163 (M^+); ^1H NMR (DMSO-d_6) δ 3.85 (3 H, s), 4.75 (2 H, d, J = 5.8 Hz), 5.66 (1 H, t, J = 5.8 Hz), 7.25 (1 H, dd, J = 4.4 and 8.1 Hz), 8.01 (1 H, dd, J = 1.4 and 8.1 Hz), 8.30 (1 H, dd, J = 1.4 and 4.4 Hz).

3-(3-Methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)propan-1-ol (9c). This compound was prepared using the same procedure as for the preparation of **9a**: IR (KBr) 3229 (br), 2956, 1399, 1043 cm^{-1}; MS *m*/*z* 191 (M^+); ^1H NMR (DMSO-d_6) δ 1.96 (2 H, m), 2.95 (2 H, t, J = 7.5 Hz), 3.54 (2 H, t, J = 6.2 Hz), 3.76 (3 H, s), 4.61 (1 H, s), 7.20 (1 H, dd, J = 5.1 and 8.0 Hz), 7.93 (1 H, dd, J = 1.3 and 8.0 Hz), 8.26 (1 H, dd, J = 1.3 and 5.1 Hz).

(3-Ethyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (9d). This compound was prepared using the same procedure as for the preparation of **9a**: mp 117−121 °C; IR (KBr) 3382 (br), 3249 (br), 1474, 1261, 1075, 774 cm^{-1}; MS *m*/*z* 177 (M^+); ^1H NMR (DMSO-d_6) δ 1.41 (3 H, t, J = 7.3 Hz), 4.37 (2 H, q, J = 7.3 Hz), 4.76 (2 H, d, J = 5.0 Hz), 5.71 (1 H, t, J = 5.0 Hz), 7.25 (1 H, dd, J = 4.4 and 8.0 Hz), 8.01 (1 H, dd, J = 1.3 and 8.0 Hz), 8.31 (1 H, dd, J = 1.3 and 4.4 Hz).

[3-(4-Phenylbenzyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanol (9e). This compound was prepared using the same procedure as for the preparation of **9a**: mp 163−165 °C; IR (KBr) 3181, 1487, 1475, 1403, 1041, 751, 693 m^{-1}; MS *m*/*z* 315 (M^+); ^1H NMR (DMSO-d_6) δ 4.74 (2 H, d, J = 5.8 Hz), 5.64 (2 H, s), 5.81 (1 H, t, J = 5.8 Hz), 7.2−7.4 (4 H, m), 7.44 (2 H, t, J = 7.7 Hz), 7.6−7.7 (4 H, m), 8.07 (1 H, dd, J = 1.3 and 7.5 Hz), 8.36 (1 H, dd, J = 1.3 and 4.4 Hz).

(6-Chloro-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (9f). This compound was prepared using the same procedure as for the preparation of **9a**: mp 141−142 °C; IR (KBr) 3277 (br), 1479, 1383, 1033, 893 cm^{-1}; MS *m*/*z* 197 (M^+); ^1H NMR (DMSO-d_6) δ 3.84 (3 H, s), 4.75 (2 H, d, J = 5.9 Hz), 5.73 (1 H, t, J = 5.9 Hz), 8.18 (1 H, d, J = 2.2 Hz), 8.37 (1 H, d, J = 2.2 Hz).

(6-Bromo-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (9g). This compound was prepared using the same procedure as for the preparation of **9a**: mp 142−144 °C; IR (KBr) 3274 (br), 1500, 1478, 1382, 1033, 889 cm^{-1}; MS *m*/*z* 241 (M^+); ^1H NMR (DMSO-d_6) δ 3.84 (3 H, s), 4.75 (2 H, s), 5.73 (1 H, br s), 8.30 (1 H, d, J = 2.0 Hz), 8.43 (1 H, d, J = 2.0 Hz).

(3,7-Dimethyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (9h). This compound was prepared using the same procedure as for the preparation of **9a**: mp >300 °C; IR (KBr) 3487, 3270 (br), 1618, 1395, 1344, 1052 cm^{-1}; MS *m*/*z* 177 (M^+); ^1H NMR (DMSO-d_6) δ 2.55 (3 H, s), 3.82 (3 H, s), 4.74 (2 H, d, J = 5.8 Hz), 5.62 (1 H, t, J = 5.8 Hz), 7.07 (1 H, d, J = 4.0 Hz), 8.18 (1 H, d, J = 4.0 Hz).

(3,5,7-Trimethyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (9i). This compound was prepared using the same procedure as for the preparation of **9a**: mp 178−179 °C; IR (KBr) 3386 (br), 1695, 1605, 1427, 1331, 1180 cm^{-1}; MS *m*/*z* 191 (M^+); ^1H NMR (DMSO-d_6) δ 2.49 (3 H, s), 2.52 (3 H, s), 3.78 (3 H, s), 4.71 (2 H, d, J = 5.8 Hz), 5.59 (1 H, t, J = 5.8 Hz), 6.94 (1 H, s).

5-[4-(5-Chloro-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]-3-triphenylmethylthiazolidine-2,4-dione (11a). To a mixture of 1.20 g (6.07 mmol) of **9a**, 2.83 g (6.08 mmol) of 5-(4-hydroxybenzyl)-3-triphenylmethylthiazolidine-2,4-dione (**10**), 1.53 g (6.06 mmol) of azodicarbonyldipiperidine and 25 mL of anhydrous toluene was added dropwise 1.51 mL (6.06 mmol) of tributylphosphine in anhydrous toluene (5 mL), and the resulting mixture was stirred at room temperature for 5 h. Insoluble materials were filtered away and the filtrate was concentrated by evaporation under reduced pressure. The concentrate thus obtained was purified by column chromatogaphy through silica gel, using a gradient elution method, with a mixture of hexane and ethyl acetate, in ratios ranging from 2:1 to 1:1 by volume, as the eluent, to give 1.29 g (2.00 mmol) of **11a**: yield 33%; mp 97−99 °C (softening); IR (KBr) 1691, 1511, 1450, 1299, 1251 cm^{-1}; MS *m*/*z* 645 (M^+); ^1H NMR (DMSO-d_6) δ 3.11 (1 H, dd, J = 8.1 and 14.2 Hz), 3.2−3.3 (1 H, m), 3.83 (3 H, s), 5.01 (1 H, dd, J = 4.6 and 8.1 Hz), 5.42 (2 H, s), 7.02 (2 H, d, J = 8.6 Hz), 7.1−7.4 (18 H, m), 8.14 (1 H, d, J = 8.6 Hz).

5-[4-(3-Methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)-benzyl]-3-triphenylmethylthiazolidine-2,4-dione (11b). This compound was prepared using the same procedure as for the preparation of **11a**: mp 97−102 °C; IR (KBr) 1688 cm^{-1}; MS *m*/*z* 610 (M^+); ^1H NMR (DMSO-d_6) δ 3.12 (1 H, dd, J = 8.1 and 14.2 Hz), 3.30 (1 H, dd, J = 4.7 and 14.2 Hz), 3.87 (3 H, s), 5.02 (1 H, dd, J = 4.7 and 8.1 Hz), 5.43(2 H, s), 7.03 (2 H, d, J = 8.7 Hz), 7.1−7.2 (5 H, m), 7.2−7.3 (6 H, m), 7.3−7.4 (7 H, m), 8.09 (1 H, d, J = 6.9 Hz), 8.39 (1 H, dd, J = 1.3 and 5.5 Hz).

5-[4-[3-(3-Methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)propoxy]-benzyl]-3-triphenylmethylthiazolidine-2,4-dione (11c). This compound was prepared using the same procedure as for the preparation of **11a**: mp 76−81 °C (softening); IR (KBr) 1689, 1511, 1298, 1249 cm^{-1}; MS *m*/*z* 638 (M^+); ^1H NMR (DMSO-d_6) δ 2.28 (2 H, m), 2.2−2.3 (3 H, m), 3.28 (1 H, dd, J = 4.6 and 14.2 Hz), 3.75 (3 H, s), 4.10 (2 H, dt, J = 2.7 and 6.8 Hz), 5.00 (1 H, dd, J = 4.6 and 7.9 Hz), 6.83(2 H, d, J = 8.6

Hz), 7.08 (2 H, d, J = 8.6 Hz), 7.15 (3 H, t, J = 7.1 Hz), 7.20−7.26 (7 H, m), 7.31 (6 H, m), 7.96 (1 H, dd, J = 1.2 and 7.5 Hz), 8.28 (1 H, dd, J = 1.2 and 4.5 Hz).

5-[4-(3-Ethyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)-benzyl]-3-triphenylmethylthiazolidine-2,4-dione (11d). This compound was prepared using the same procedure as for the preparation of **11a**: IR (KBr) 1690, 1510, 1299, 706 cm^{-1}; MS m/z 624 (M^+); ^1H NMR (DMSO-d_6) δ 1.37 (3 H, t, J = 7.2 Hz), 3.12 (1 H, dd, J = 8.0 and 14.3 Hz), 3.30 (1 H, dd, J = 4.5 and 14.3 Hz), 4.37 (2 H, q, J = 7.2 Hz), 5.02 (1 H, dd, J = 4.5 and 8.0 Hz), 5.43(2 H, d, J = 1.8 Hz), 7.03 (2 H, d, J = 8.7 Hz), 7.1−7.2 (5 H, m), 7.2−7.3 (6 H, m), 7.3−7.4 (7 H, m), 8.10 (1 H, dd, J = 1.2 and 7.5 Hz), 8.40 (1 H, dd, J = 1.2 and 5.1 Hz).

5-{4-[3-(4-Phenylbenzyl)-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy]benzyl}-3-triphenylmethylthiazolidine-2,4-dione (11e). This compound was prepared using the same procedure as for the preparation of **11a**: ^1H NMR ($CDCl_3$) δ 3.04 (1 H, dd, J = 8.9 and 14.1 Hz), 3.39 (1 H, dd, J = 3.9 and 14.1 Hz), 4.32 (1 H, dd, J = 3.9 and 8.9 Hz), 5.24 (2 H, s), 5.70 (2 H, s), 6.91 (2 H, d, J = 8.6 Hz), 7.1−7.6 (27H, m), 8.10 (1 H, dd, J = 1.3 and 8.0 Hz), 8.46 (1 H, dd, J = 1.4 and 4.8 Hz).

5-[4-(6-Chloro-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]-3-triphenylmethylthiazolidine-2,4-dione (11f). This compound was prepared using the same procedure as for the preparation of **11a**: mp 82−84 °C (softening); IR (KBr) 1689, 1511, 1299, 1232, 706 cm^{-1}; MS m/z 644 (M^+); ^1H NMR (DMSO-d_6) δ 3.12 (1 H, dd, J = 8.1 and 14.3 Hz), 3.31 (1 H, dd, J = 4.6 and 14.3 Hz), 3.86 (3 H, s), 5.02 (1 H, dd, J = 4.6 and 8.1 Hz), 5.44 (2 H, d, J = 0.9 Hz), 7.02 (2 H, d, J = 8.7 Hz), 7.1−7.2 (5 H, m), 7.2−7.3 (6 H, m), 7.3−7.4 (6 H, m), 8.27 (1 H, d, J = 2.2 Hz), 8.43 (1 H, d, J = 2.2 Hz).

5-[4-(6-Bromo-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]-3-triphenylmethylthiazolidine-2,4-dione (11g). This compound was prepared using the same procedure as for the preparation of **11a**: mp 97−100 °C (softening); IR (KBr) 1690, 1511, 1298 cm^{-1}; MS m/z 688 (M^+); ^1H NMR (DMSO-d_6) δ 3.12 (1 H, dd, J = 8.1 and 14.3 Hz), 3.31 (1 H, dd, J = 4.6 and 14.3 Hz), 3.86 (3 H, s), 5.02 (1 H, dd, J = 4.6 and 8.1 Hz), 5.44 (2 H, s), 7.02 (2 H, d, J = 8.7 Hz), 7.13 (2 H, d, J = 8.7 Hz), 7.1−7.2 (3 H, m), 7.2−7.3 (6 H, m), 7.3−7.4 (6 H, m), 8.38 (1 H, d, J = 2.0 Hz), 8.49 (1 H, d, J = 2.0 Hz).

5-[4-(3,7-Dimethyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]-3-triphenylmethylthiazolidine-2,4-dione (11h). This compound was prepared using the same procedure as for the preparation of **11a**: mp 92−105 °C (softening); IR (KBr) 1690, 1510, 1450, 1297, 1240 cm^{-1}; MS m/z 624 (M^+); ^1H NMR (DMSO-d_6) δ 2.58 (3 H, s), 3.12 (1 H, dd, J = 8.0 and 14.2 Hz), 3.30 (1 H, dd, J = 4.5 and 14.2 Hz), 3.84 (3 H, s), 5.02 (1 H, dd, J = 4.5 and 8.0 Hz), 5.41 (2 H, s), 7.03 (2 H, d, J = 8.7 Hz), 7.1−7.2 (6 H, m), 7.2−7.3 (6 H, m), 7.3−7.4 (6 H, m), 8.25 (1 H, d, J = 4.9 Hz).

5-[4-(3,5,7-Trimethyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]-3-triphenylmethylthiazolidine-2,4-dione (11i). This compound was prepared using the same procedure as for the preparation of **11a**: mp 96−99 °C (softening); IR (KBr) 1692, 1510, 1299 cm^{-1}; MS m/z 639 $(M + H)^+$; ^1H NMR (DMSO-d_6) δ 2.52 (3 H, s), 2.54 (3 H, s), 3.12 (1 H, dd, J = 8.1 and 14.2 Hz), 3.30 (1 H, dd, J = 4.8 and 14.2 Hz), 3.80 (3 H, s), 5.02 (1 H, dd, J = 4.8 and 8.1 Hz), 5.37 (2 H, s), 6.99 (1 H, s), 7.02 (2 H, d, J = 8.7 Hz), 7.13 (2 H, d, J = 8.7 Hz), 7.1−7.2 (3 H, m), 7.2−7.3 (6 H, m), 7.3−7.4 (6 H, m).

5-[4-(5-Chloro-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (12a). In a mixture of 16 mL of acetic acid and water (3:1, v/v), 1.16 g (1.80 mmol) of **11a** was dissolved. The resulting mixture was stirred at 70 °C for 2 h. The reaction mixture was neutralized by the addition of sodium hydrogen carbonate, after which it was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure. The residue thus obtained was crystallized with ethyl acetate, to give 0.38 g (0.94 mmol) of **12a**: yield 53%; mp 222−223 °C; IR (KBr) 1694, 1511, 1396, 1237 cm^{-1}; MS m/z 402 (M^+); ^1H NMR (DMSO-d_6) δ 3.07 (1 H, dd, J = 9.2 and 14.1 Hz), 3.33 (1 H, dd, J = 4.3 and 14.1 Hz), 3.84 (3 H, s), 4.88 (1 H, dd, J = 4.3 and 9.2 Hz), 5.44 (2 H, s), 7.07 (2 H, d, J = 8.6 Hz), 7.20 (2 H, d, J = 8.6 Hz), 7.36 (1 H, d, J = 8.3 Hz), 8.15 (1 H, d, J = 8.3 Hz), 12.02 (1 H, s). Anal. ($C_{18}H_{15}ClN_4O_3S$) C, H, N, Cl, S.

5-[4-(3-Methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione (12b). A solution of 0.50 g (0.82 mmol) of **11b** in 100 mL of methanol was stirred under an atmosphere of hydrogen and in the presence of 1.00 g of 10% w/w palladium-on-charcoal, first at room temperature for 2 h then at 50 °C for 3 h. The reaction mixture was filtered to remove the catalyst and filtrate was concentrated by evaporation under reduced pressure. The concentrate thus obtained was purified by column chromatogaphy through silica gel, using a gradient elution method, with a mixture of ethyl acetate and ethanol, in ratios ranging from 1:0 to 10:1 by volume, as the eluent, to give 77 mg (0.21 mmol) of **12b**: yield 26%; mp 223−225 °C; IR (KBr) 1693 cm^{-1}; MS m/z 368 (M^+); ^1H NMR (DMSO-d_6) δ 3.06 (1 H, dd, J = 9.1 and 14.2 Hz), 3.32 (1 H, dd, J = 4.4 and 14.2 Hz), 3.87 (3 H, s), 4.88 (1 H, dd, J = 4.4 and 9.1 Hz), 5.44 (2 H, s), 7.08 (2 H, d, J = 8.7 Hz), 7.20 (2 H, d, J = 8.7 Hz), 7.30 (1 H, dd, J = 4.4 and 8.0 Hz), 8.08 (1 H, dd, J = 1.2 and 8.0 Hz), 8.39 (1 H, dd, J = 1.2 and 4.4 Hz), 12.02 (1 H, s). Anal. ($C_{18}H_{16}N_4O_3S\cdot{}^1/_5H_2O$) C, H, N, S.

5-{4-[3-(3-Methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)propoxy]benzyl}thiazolidine-2,4-dione (12c). This compound was prepared using the same procedure as for the preparation of **12a**: mp 185−186 °C; IR (KBr) 1697, 1512, 1248 cm^{-1}; MS m/z 396 (M^+); ^1H NMR (DMSO-d_6) δ 2.27 (2 H, m), 3.0−3.1 (3 H, m), 3.30 (1 H, dd, J = 4.4 and 14.3 Hz), 3.76 (3 H, s), 4.11 (2 H, m), 4.86 (1 H, dd, J = 4.4 and 8.8 Hz), 6.88 (2 H, d, J = 8.7 Hz), 7.15 (2 H, d, J = 8.7 Hz), 7.21 (1 H, dd, J = 5.1 and 8.0 Hz), 7.95 (1 H, dd, J = 1.4 and 8.0 Hz), 8.27 (1 H, dd, J = 1.4 and 5.1 Hz), 11.99 (1 H, s). Anal. ($C_{20}H_{20}N_4O_3S$) C, H, N, S.

5-[4-(3-Ethyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione (12d). This compound was prepared using the same procedure as for the preparation of **12a**: mp 210−212 °C; IR (KBr) 1695, 1513, 1405, 1250, 1228 cm^{-1}; MS m/z 382 (M^+); ^1H NMR (DMSO-d_6) δ 1.40 (3 H, t, J = 7.1 Hz), 3.07 (1 H, dd, J = 9.1 and 14.1 Hz), 3.32 (1 H, dd, J = 4.4 and 14.1 Hz), 4.38 (2 H, q, J = 7.1 Hz), 4.88 (1 H, dd, J = 4.4 and 9.1 Hz), 5.44 (2 H, s), 7.08 (2 H, d, J = 8.7 Hz), 7.21 (2 H, d, J = 8.7 Hz), 7.30 (1 H, dd, J = 5.1 and 8.0 Hz), 8.09 (1 H, dd, J = 1.4 and 8.0 Hz), 8.39 (1 H, dd, J = 1.4 and 5.1 Hz), 12.02 (1 H, s). Anal. ($C_{19}H_{18}N_4O_3S\cdot{}^3/_{20}H_2O$) C, H, N, S.

5-{4-[3-(4-Phenylbenzyl)-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy]benzyl}thiazolidine-2,4-dione (12e). This compound was prepared using the same procedure as for the preparation of **12a**: mp 189−191 °C; IR (KBr) 1699, 1511, 1239 cm^{-1}; MS m/z 520 (M^+); ^1H NMR (DMSO-d_6) δ 3.04 (1 H, dd, J = 9.1 and 14.2 Hz), 3.30 (1 H, dd, J = 4.3 and 14.2 Hz), 4.85 (1 H, dd, J = 4.3 and 9.1 Hz), 5.40(2 H, s), 5.66(2 H, s), 6.92 (2 H, d, J = 8.7 Hz), 7.15 (2 H, d, J = 8.7 Hz), 7.28 (2 H, d, J = 8.2 Hz), 7.3−7.4 (2 H, m), 7.44 (2 H, t, J = 7.4 Hz), 7.57 (2 H, d, J = 8.2 Hz), 7.61 (2 H, d, J = 7.4 Hz), 8.16 (1 H, dd, J = 1.4 and 8.1 Hz), 8.42 (1 H, dd, J = 1.4 and 5.6 Hz), 12.01 (1 H, s). Anal. ($C_{30}H_{24}N_4O_3S\cdot{}^1/_4H_2O$) C, H, N, S.

5-[4-(6-Chloro-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (12f). This compound was prepared using the same procedure as for the preparation of **12a**: mp 203−205 °C; IR (KBr) 1695, 1512, 1482, 1233 cm^{-1}; MS m/z 402 (M^+); ^1H NMR (DMSO-d_6) δ 3.07 (1 H, dd, J = 9.3 and 14.2 Hz), 3.32 (1 H, dd, J = 4.3 and 14.2 Hz), 3.87 (3 H, s), 4.88 (1 H, dd, J = 4.3 and 9.3 Hz), 5.45 (2 H, s), 7.07 (2 H, d, J = 8.6 Hz), 7.20 (2 H, d, J = 8.6 Hz), 8.28 (1 H, d, J = 2.2 Hz), 8.43 (1 H, d, J = 2.2 Hz), 12.02 (1 H, br s). Anal. ($C_{18}H_{15}ClN_4O_3S$) C, H, N, Cl, S.

5-[4-(6-Bromo-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (12g). This compound was prepared using the same procedure as for the preparation of **12a**: mp 204−205 °C; IR (KBr) 1695, 1513, 1238 cm^{-1}; MS *m*/*z* 446 (M^+); ^1H NMR (DMSO-d_6) δ 3.06 (1 H, dd, J = 9.1 and 14.2 Hz), 3.32 (1 H, dd, J = 4.4 and 14.2 Hz), 3.86 (3 H, s), 4.88 (1 H, dd, J = 4.4 and 9.1 Hz), 5.45 (2 H, s), 7.07 (2 H, d, J = 8.6 Hz), 7.20 (2 H, d, J = 8.6 Hz), 8.39 (1 H, d, J = 2.1 Hz), 8.49 (1 H, d, J = 2.1 Hz), 12.02 (1 H, br s). Anal. ($C_{18}H_{15}BrN_4O_3S$) C, H, N, Br, S.

5-[4-(3,7-Dimethyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (12h). This compound was prepared using the same procedure as for the preparation of **12a**: mp 205−207 °C; IR (KBr) 1703, 1514, 1240 cm^{-1}; MS *m*/*z* 382 (M^+); ^1H NMR (DMSO-d_6) δ 2.58 (3 H, s), 3.07 (1 H, dd, J = 9.1 and 14.2 Hz), 3.33 (1 H, dd, J = 4.3 and 14.2 Hz), 3.85 (3 H, s), 4.89 (1 H, dd, J = 4.3 and 9.1 Hz), 5.42 (2 H, s), 7.08 (2 H, d, J = 8.6 Hz), 7.12 (1 H, d, J = 5.0 Hz), 7.21 (2 H, d, J = 8.6 Hz), 8.24 (1 H, d, J = 5.0 Hz), 12.02 (1 H, br s). Anal. ($C_{19}H_{18}N_4O_3S$) C, H, N, S.

5-[4-(3,5,7-Trimethyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (12i). This compound was prepared using the same procedure as for the preparation of **12a**: mp 229−230 °C; IR (KBr) 1699, 1610, 1512, 1244 cm^{-1}; MS *m*/*z* 397 ($M + H)^+$; ^1H NMR (DMSO-d_6) δ 2.52 (3 H, s), 2.53 (3 H, s), 3.07 (1 H, dd, J = 9.1 and 14.2 Hz), 3.32 (1 H, dd, J = 4.3 and 14.2 Hz), 3.80 (3 H, s), 4.89 (1 H, dd, J = 4.3 and 9.1 Hz), 5.38 (2 H, s), 6.99 (1 H, s), 7.07 (2 H, d, J = 8.6 Hz), 7.20 (2 H, d, J = 8.6 Hz), 12.02 (1 H, br s). Anal. ($C_{20}H_{20}N_4O_3S$) C, H, N, S.

6-Chloro-2-methylamino-3-nitropyridine (14). To a mixture of 29.0 g (138 mmol) of 2,6-dichloro-3-nitropyridine (**13**), 300 mL of ethanol and 36.6 g (345 mmol) of sodium carbonate was added dropwise 20.0 mL (209 mmol) of a 30% w/w ethanolic solution of methylamine, while cooling on ice, and the resulting mixture was stirred at room temperature for 8 h. The reaction mixture was freed from ethanol by distillation. The residue was diluted with water, after which it was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure. The residue was crystallized with ethanol, to give 22.3 g (119 mmol) of **14**: yield 86%; mp 114 °C; IR (KBr) 3402, 1620, 1573, 1520, 1434, 1382, 1275, 1232, 762 cm^{-1}; MS *m*/*z* 187 (M^+); ^1H NMR (DMSO-d_6) δ 3.00 (3 H, d, J = 5.1 Hz), 6.77 (1 H, d, J = 8.1 Hz), 8.42 (1 H, d, J = 8.1 Hz), 8.72 (1 H, m).

6-Methoxy-2-methylamino-3-nitropyridine (15a). To a solution of 6.00 g (32.0 mmol) of **14** in 120 mL of methanol was added dropwise 19 mL (98.5 mmol) of a 28% w/w methanolic solution of sodium methoxide at room temperature, and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure. The residue was crystallized with ethanol, to give 5.34 g (29.2 mmol) of **15a**: yield 91%; mp 152−153 °C; IR (KBr) 3375, 1612, 1596, 1384, 1254, 1194 cm^{-1}; MS *m*/*z* 183 (M^+); ^1H NMR (DMSO-d_6) δ 3.07 (3 H, d, J = 4.5 Hz), 3.95 (3 H, s), 6.14 (1 H, d, J = 9.2 Hz), 8.29 (1 H, d, J = 9.2 Hz), 8.86 (1 H, m).

6-Ethoxy-2-methylamino-3-nitropyridine (15b). This compound was prepared using the same procedure as for the preparation of **15a**: mp 101 °C; IR (KBr) 3364, 1619, 1603, 1382, 1267 cm^{-1}; MS *m*/*z* 197 (M^+); ^1H NMR (DMSO-d_6) δ 1.34 (3 H, t, J = 7.1 Hz), 3.04 (3 H, d, J = 4.4 Hz), 4.42 (2 H, q, J = 7.1 Hz), 6.11 (1 H, d, J = 9.1 Hz), 8.27 (1 H, d, J = 9.1 Hz), 8.8−8.9 (1 H, m).

6-Isopropoxy-2-methylamino-3-nitropyridine (15c). This compound was prepared using the same procedure as for the preparation of **15a**: mp 75−76 °C; IR (KBr) 3367, 1602, 1441, 1387, 1282, 1166 cm^{-1}; MS *m*/*z* 211 (M^+); ^1H NMR (DMSO-d_6) δ 1.34 (6 H, d, J = 6.5 Hz), 3.04 (3 H, d, J = 4.8 Hz), 5.3−5.4 (1 H, m), 6.07 (1 H, d, J = 9.2 Hz), 8.26 (1 H, d, J = 9.2 Hz), 8.8−8.9 (1 H, m).

6-Benzyloxy-2-methylamino-3-nitropyridine (15d). This compound was prepared using the same procedure as for the preparation of **15a**: mp 149 °C; IR (KBr) 1619, 1593, 1449, 1395, 1271 cm^{-1}; MS *m*/*z* 259 (M^+); ^1H NMR (DMSO-d_6) δ 3.06 (3 H, d, J = 4.5 Hz), 5.46 (2 H, s), 6.19 (1 H, d, J = 9.0 Hz), 8.3−8.4 (3 H, m), 8.4−8.5 (2 H, m), 8.30 (1 H, d, J = 9.0 Hz), 8.85 (1 H, m).

2-Methylamino-3-nitro-6-phenylsulfanylpyridine (15e). This compound was prepared using the same procedure as for the preparation of **15a**: IR (neat) 3390, 1597, 1574, 1381, 1224 cm^{-1}; MS *m*/*z* 261 (M^+); ^1H NMR (DMSO-d_6) δ 2.81 (3 H, d, J = 4.9 Hz), 6.29 (1 H, d, J = 8.8 Hz), 8.5−8.6 (3 H, m), 8.6−8.7 (2 H, m), 8.22 (1 H, d, J = 8.8 Hz), 8.60 (1 H, m).

2-Methylamino-3-nitro-6-phenylpyridine (15f). A mixture of 5.00 g (26.7 mmol) of **14**, 3.90 g (32.0 mmol) of phenylboronic acid, 50 mL of 2 M aqueous solution of sodium carbonate and 80 mL of ethanol and toluene (1:1, v/v) was heated under reflux for 4.5 h in the presence of 0.34 g of 20% w/w palladium hydroxide-on-charcoal. The reaction mixture was filtered to remove the catalyst and the filtrate was concentrated by evaporation under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure. The residue was crystallized with ethanol, to give 4.75 g (20.7 mmol) of **15f**: yield 78%; mp 98−99 °C; ^1H NMR ($CDCl_3$) δ 3.29 (3 H, d, J = 4.7 Hz), 7.12 (1 H, d, J = 8.6 Hz), 7.4−7.6 (3 H, m), 8.1−8.2 (2 H, m), 8.30 (1 H, br s), 8.47 (1 H, d, J = 8.6 Hz).

3-Amino-6-methoxy-2-methylaminopyridine (16a). A solution of 3.45 g (18.8 mmol) of **15a** in 50 mL of dioxane was stirred under an atmosphere of hydrogen and in the presence of 0.70 g of 10% w/w palladium-on-charcoal, first at room temperature for 3 h and then at 80 °C for 5 h. The reaction mixture was filtered to remove the catalyst and the filtrate was concentrated by evaporation under reduced pressure, to give 2.66 g (17.4 mmol) of **16a** having R_f = 0.12 (on silica gel thin-layer chromatography using a 1:1 by volume mixture of hexane and ethyl acetate as the developing solvent): yield 92%; IR (neat) 3390 (br), 1609, 1509, 1475, 1416, 1255 cm^{-1}; MS *m*/*z* 153 (M^+); ^1H NMR (DMSO-d_6) δ 2.83 (3 H, d, J = 4.8 Hz), 3.69 (3 H, s), 4.04 (2 H, br s), 5.5−5.6 (1 H, m), 5.72 (1 H, d, J = 8.0 Hz), 6.71 (1 H, d, J = 8.0 Hz).

3-Amino-6-ethoxy-2-methylaminopyridine (16b). This compound was prepared using the same procedure as for the preparation of **16a**: IR (neat) 3390 (br), 1609, 1507, 1436, 1252 cm^{-1}; MS *m*/*z* 167 (M^+); ^1H NMR (DMSO-d_6) δ 1.25 (3 H, t, J = 6.9 Hz), 2.81 (3 H, d, J = 4.5 Hz), 4.05 (2 H, br s), 4.11 (2 H, q, J = 6.9 Hz), 5.5−5.6 (1 H, m), 5.70 (1 H, d, J = 7.9 Hz), 6.70 (1 H, d, J = 7.9 Hz).

3-Amino-6-isopropoxy-2-methylaminopyridine (16c). This compound was prepared using the same procedure as for the preparation of **16a**: IR (neat) 3379 (br), 2976, 1606, 1504, 1251 cm^{-1}; MS *m*/*z* 181 (M^+); ^1H NMR (DMSO-d_6) δ 1.22 (6 H, d, J = 6.1 Hz), 2.81 (3 H, d, J = 4.7 Hz), 4.04 (2 H, br s), 4.9−5.1 (1 H, m), 5.53 (1 H, q, J = 4.7 Hz), 5.67 (1 H, d, J = 8.0 Hz), 6.69 (1 H, d, J = 8.0 Hz).

3-Amino-6-benzyloxy-2-methylaminopyridine (16d). To a mixture of 0.50 g (1.93 mmol) of **15d**, 1.26 g (19.3 mmol) of zinc and 20 mL of methanol was added dropwise 0.5 mL of acetic acid at room temperature, and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was filtered to remove zinc and the filtrate was concentrated by evaporation under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure, to give 0.39 g (1.70 mmol) of **16d** having R_f = 0.63 (on silica gel thin-layer chromatography using ethyl acetate as the developing solvent): yield 88%; IR (neat) 3393 (br), 1609, 1505, 1432, 1250 cm^{-1}; MS *m*/*z* 229 (M^+); ^1H NMR (DMSO-d_6) δ 2.82 (3 H, d, J = 4.5 Hz), 4.15 (2 H, br s), 5.20 (2 H, s), 5.59 (1 H, m), 5.79 (1 H, d,

J = 7.8 Hz), 6.71 (1 H, d, J = 7.8 Hz), 7.2−7.3 (1 H, m), 7.3−7.4 (2 H, m), 7.40 (2 H, m).

3-Amino-2-methylamino-6-phenylsulfanylpyridine (16e). This compound was prepared using the same procedure as for the preparation of **16a**: IR (neat) 3405 (br), 1587, 1504, 1410, 1260 cm^{-1}; MS m/z 231 (M^+); ^{1}H NMR (DMSO-d_6) δ 2.76 (3 H, d, J = 4.5 Hz), 4.87 (2 H, s), 5.85 (1 H, q, J = 4.5 Hz), 6.43 (1 H, d, J = 7.6 Hz), 6.63 (1 H, d, J = 7.6 Hz), 7.1−7.2 (1 H, m), 7.2−7.3 (4 H, m).

3-Amino-2-methylamino-6-phenylpyridine (16f). This compound was prepared using the same procedure as for the preparation of **16a**: ^{1}H NMR ($CDCl_3$) δ 3.10 (3 H, s), 3.19 (2 H, br s), 4.15 (1 H, br s), 6.87 (1 H, d, J = 7.8 Hz), 7.02 (1 H, d, J = 7.8 Hz), 7.2−7.3 (1 H, m), 7.3−7.4 (2 H, m), 8.01 (2 H, d, J = 7.2 Hz).

(5-Methoxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)-methanol (17a). A solution of 2.20 g (14.4 mmol) of **16a** and 3.30 g (43.4 mmol) of glycolic acid in 40 mL of toluene was heated under reflux for 4 h. The reaction mixture was poured into water, after which it was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography through silica gel, using a 30:1 by volume mixture of ethyl acetate and methanol as the eluent, to give 620 mg (3.21 mmol) of **17a**: yield 22%; mp 138−140 °C; IR (KBr) 3161 (br), 1609, 1596, 1397, 1281, 1267, 1031 cm^{-1}; MS m/z 193 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.78 (3 H, s), 3.93 (3 H, s), 4.68 (2 H, d, J = 5.6 Hz), 5.56 (1 H, t, J = 5.6 Hz), 6.66 (1 H, d, J = 8.3 Hz), 7.90 (1 H, d, J = 8.3 Hz).

(5-Ethoxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (17b). This compound was prepared using the same procedure as for the preparation of **17a**: mp 161 °C; IR (KBr) 3193 (br), 1608, 1597, 1412, 1396, 1278, 1264, 1025 cm^{-1}; MS m/z 207 (M^+); ^{1}H NMR (DMSO-d_6) δ 1.36 (3 H, t, J = 7.1 Hz), 3.77 (3 H, s), 4.37 (2 H, q, J = 7.1 Hz), 4.67 (2 H, d, J = 5.6 Hz), 5.55 (1 H, t, J = 5.6 Hz), 6.63 (1 H, d, J = 8.6 Hz), 7.89 (1 H, d, J = 8.6 Hz).

(5-Isopropoxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl-)methanol (17c). This compound was prepared using the same procedure as for the preparation of **17a**: mp 125−127 °C; IR (KBr) 3139 (br), 1609, 1596, 1406, 1261, 1045 cm^{-1}; MS m/z 221 (M^+); ^{1}H NMR (DMSO-d_6) δ 1.34 (6H, d, J = 6.2 Hz), 3.76 (3H, s), 4.67 (2H, d, J = 5.7 Hz), 5.3−5.4 (1H, m), 5.55 (1H, t, J = 5.7 Hz), 6.58 (1H, d, J = 8.1 Hz), 7.87 (1H, d, J = 8.1 Hz).

(5-Benzyloxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)-methanol (17d). This compound was prepared using the same procedure as for the preparation of **17a**: mp 133−135 °C; IR (KBr) 3182 (br), 1606, 1407, 1262, 1030 cm^{-1}; MS m/z 269 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.79 (3 H, s), 4.68 (2 H, d, J = 5.6 Hz), 5.43 (2 H, s), 5.57 (1 H, t, J = 5.6 Hz), 6.71 (1 H, d, J = 8.7 Hz), 7.3−7.35 (1 H, m), 7.35−7.4 (2 H, m), 7.5−7.6 (2 H, m), 7.92 (1 H, d, J = 8.7 Hz).

(3-Methyl-5-phenylsulfanyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (17e). This compound was prepared using the same procedure as for the preparation of **17a**: mp 119−120 °C; IR (KBr) 3150 (br), 1397, 1257, 1033 cm^{-1}; MS m/z 271 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.76 (3 H, s), 4.71 (2 H, d, J = 5.8 Hz), 5.66 (1 H, t, J = 5.8 Hz), 6.92 (1 H, d, J = 8.4 Hz), 7.4−7.5 (3 H, m), 7.5−7.6 (2 H, m), 7.91 (1 H, d, J = 8.4 Hz).

(3-Methyl-5-phenyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)methanol (17f). This compound was prepared using the same procedure as for the preparation of **17a**: mp 174−177 °C; IR (KBr) 3162 (br), 1407, 1043, 762, 693 cm^{-1}; MS m/z 239 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.91 (3 H, s), 4.77 (2 H, d, J = 5.7 Hz), 5.69 (1 H, t, J = 5.7 Hz), 7.4−7.5 (1 H, m), 7.5−7.6 (2 H, m), 7.85 (1 H, d, J = 8.2 Hz), 8.07 (1 H, d, J = 8.2 Hz), 8.1−8.2 (2 H, m).

5-[4-(5-Methoxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]-3-triphenylmethylthiazolidine-2,4-dione (18a). To a mixture of 0.25 g (1.29 mmol) of **17a**, 0.66 g (1.42 mmol) of 5-(4-hydroxybenzyl)-3-triphenylmethylthiazolidine-2,4-dione (**10**), 0.36 g (1.43 mmol) of azodicarbonyldipiperidine and 10 mL of anhydrous toluene was added dropwise a solution of 0.35 mL (1.40 mmol) of tributylphosphine in 5 mL of anhydrous toluene, and the resulting mixture was stirred at room temperature for 4 h. Insoluble materials were filtered away and the filtrate was concentrated by evaporation under reduced pressure. The concentrate thus obtained was purified by column chromatogaphy through silica gel, using a 1:1 by volume mixture of hexane and ethyl acetate as the eluent, to give 0.70 g (1.09 mmol) of **18a**: yield 84%; mp 80−85 °C (softening); IR (KBr) 1690, 1606, 1510, 1299 cm^{-1}; MS m/z 640 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.11 (1 H, dd, J = 8.1 and 14.1 Hz), 3.29 (1 H, dd, J = 4.7 and 14.1 Hz), 3.80 (3 H, s), 3.94 (3 H, s), 5.02 (1 H, dd, J = 4.7 and 8.1 Hz), 5.35 (2 H, s), 6.71 (1 H, d, J = 8.3 Hz), 7.02 (2 H, d, J = 8.7 Hz), 7.12 (2 H, d, J = 8.7 Hz), 7.1−7.2 (3 H, m), 7.2−7.3 (6 H, m), 7.3−7.4 (6 H, m), 7.98 (1 H, d, J = 8.3 Hz).

5-[4-(5-Ethoxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]-3-triphenylmethylthiazolidine-2,4-dione (18b). This compound was prepared using the same procedure as for the preparation of **18a**: mp 88−100 °C (softening); IR (KBr) 1691, 1607, 1510, 1300, 1258 cm^{-1}; MS m/z 654 (M^+); ^{1}H NMR (DMSO-d_6) δ 1.36 (3 H, t, J = 7.1 Hz), 3.11 (1 H, dd, J = 8.1 and 14.2 Hz), 3.29 (1 H, dd, J = 4.7 and 14.2 Hz), 3.78 (3 H, s), 4.38 (2 H, q, J = 7.1 Hz), 5.02 (1 H, dd, J = 4.7 and 8.1 Hz), 5.34 (2 H, s), 6.68 (1 H, d, J = 8.3 Hz), 7.01 (2 H, d, J = 8.7 Hz), 7.12 (2 H, d, J = 8.7 Hz), 7.1−7.2 (3 H, m), 7.2−7.3 (6 H, m), 7.3−7.4 (6 H, m), 7.97 (1 H, d, J = 8.3 Hz).

5-[4-(5-Isopropoxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]-3-triphenylmethylthiazolidine-2,4-dione (18c). This compound was prepared using the same procedure as for the preparation of **18a**: mp 90−100 °C (softening); IR (KBr) 1692, 1607, 1510, 1299, 1258 cm^{-1}; MS m/z 668 (M^+); ^{1}H NMR (DMSO-d_6) δ 1.34 (6 H, d, J = 6.0 Hz), 3.12 (1 H, dd, J = 8.0 and 14.3 Hz), 3.29 (1 H, dd, J = 4.6 and 14.3 Hz), 3.78 (3 H, s), 5.02 (1 H, dd, J = 4.6 and 8.0 Hz), 5.3−5.4 (1 H, m), 5.34 (2 H, d, J = 1.0 Hz), 6.63 (1 H, d, J = 8.4 Hz), 7.02 (2 H, d, J = 8.7 Hz), 7.12 (2 H, d, J = 8.7 Hz), 7.1−7.2 (3 H, m), 7.2−7.3 (6 H, m), 7.3−7.4 (6 H, m), 7.95 (1 H, d, J = 8.4 Hz).

5-[4-(5-Benzyloxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]-3-triphenylmethylthiazolidine-2,4-dione (18d). This compound was prepared using the same procedure as for the preparation of **18a**: mp 88−92 °C (softening); IR (KBr) 1691, 1606, 1510, 1300, 1259, 1242 cm^{-1}; MS m/z 716 (M^+); ^{1}H NMR (DMSO-d_6) δ 3.11 (1 H, dd, J = 8.1 and 14.3 Hz), 3.30 (1 H, dd, J = 4.6 and 14.3 Hz), 3.81 (3 H, s), 5.02 (1 H, dd, J = 4.6 and 8.1 Hz), 5.35 (2 H, s), 5.44 (2 H, s), 6.76 (1 H, d, J = 8.7 Hz), 7.02 (2 H, d, J = 8.8 Hz), 7.12 (2 H, d, J = 8.8 Hz), 7.16 (3 H, m), 7.2−7.3 (6 H, m), 7.3−7.4 (7 H, m), 7.40 (2 H, m), 7.5−7.6 (2 H, m), 8.00 (1 H, d, J = 8.7 Hz).

5-[4-(3-Methyl-5-phenylsulfanyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]-3-triphenylmethylthiazolidine-2,4-dione (18e). This compound was prepared using the same procedure as for the preparation of **18a**: mp 90−95 °C (softening); IR (KBr) 1690, 1510, 1299, 1242, 706 cm^{-1}; MS m/z 719 ($M + H$)$^+$; ^{1}H NMR (DMSO-d_6) δ 3.11 (1 H, dd, J = 8.1 and 14.2 Hz), 3.30 (1 H, dd, J = 4.6 and 14.2 Hz), 3.77 (3 H, s), 5.02 (1 H, dd, J = 4.6 and 8.1 Hz), 5.39 (2 H, s), 6.94 (1 H, d, J = 8.7 Hz), 7.01 (2 H, d, J = 8.7 Hz), 7.12 (2 H, d, J = 8.7 Hz), 7.1−7.2 (3 H, m), 7.2−7.3 (6 H, m), 7.3−7.4 (6 H, m), 7.4−7.5 (3 H, m), 7.5−7.6 (2 H, m), 7.98 (1 H, d, J = 8.7 Hz).

5-[4-(3-Methyl-5-phenyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]-3-triphenylmethylthiazolidine-2,4-dione (18f). This compound was prepared using the same procedure as for the preparation of **18a**: ^{1}H NMR ($CDCl_3$) δ 3.07 (1 H, dd, J = 8.9 and 14.2 Hz), 3.41 (1 H, dd, J = 3.8 and 14.2 Hz), 4.02 (3 H, s), 4.37 (1 H, dd, J = 3.8 and 8.9 Hz), 5.39 (2 H, s), 7.03 (2 H, d, J = 8.7 Hz), 7.1−7.4 (17 H, m), 7.4−7.5 (3 H, m), 7.72 (1 H, d, J = 8.4 Hz), 8.0−8.1 (3 H, m).

5-[4-(5-Methoxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (19a). In a mixture of 10 mL of acetic acid and water (3:1, v/v), 680 mg (1.06

mmol) of **18a** was dissolved. The resulting mixture was stirred at 60 °C for 2 h. The reaction mixture was neutralized by the addition of sodium hydrogen carbonate and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography through silica gel, using ethyl acetate as the eluent, to give 325 mg (0.82 mmol) of **19a**: yield 77%; mp 258−260 °C; IR (KBr) 1694, 1608, 1510, 1400, 1264 cm^{-1}; MS *m/z* 398 (M^+); ^1H NMR (DMSO-d_6) δ 3.06 (1 H, dd, J = 9.3 and 14.2 Hz), 3.32 (1 H, dd, J = 4.3 and 14.2 Hz), 3.81 (3 H, s), 3.94 (3 H, s), 4.88 (1 H, dd, J = 4.3 and 9.3 Hz), 5.36 (2 H, s), 6.71 (1 H, d, J = 8.5 Hz), 7.07 (2 H, d, J = 8.6 Hz), 7.19 (2 H, d, J = 8.6 Hz), 7.98 (1 H, d, J = 8.5 Hz), 12.02 (1 H, s). Anal. ($C_{19}H_{18}N_4O_4S$) C, H, N, S.

To 6 mL of 4 N solution of hydrogen chloride in ethyl acetate was added 100 mg (0.25 mmol) of **19a**, and the mixture was treated with ultrasound for 30 min. At the end of this time, the resulting crystals were collected by filtration and dried under reduced pressure, to give 87 mg (0.20 mmol) of the hydrochloride of **19a**: yield 80%; mp 255−262 °C. Anal. ($C_{19}H_{18}N_4O_4S \cdot HCl \cdot {}^3/_{10}H_2O$) C, H, N, S.

A mixture of 100 mg (0.25 mmol) of **19a**, 29 mg (0.25 mmol) of fumaric acid and 30 mL of methanol was treated with ultrasound for 30 min. At the end of this time, the resulting crystals were collected by filtration and dried under reduced pressure, to give 85 mg (0.19 mmol) of the fumarate of **19a**: yield 77%; mp 245−253 °C. Anal. ($C_{19}H_{18}N_4O_4S \cdot {}^1/_3C_4H_4O_4$) C, H, N, S.

5-[4-(5-Ethoxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (19b). This compound was prepared using the same procedure as for the preparation of **19a**: mp 245−246 °C; IR (KBr) 1701, 1608, 1512, 1410, 1261, 1243, 1229 cm^{-1}; MS *m/z* 412 (M^+); ^1H NMR (DMSO-d_6) δ 1.36 (3 H, t, J = 7.1 Hz), 3.06 (1 H, dd, J = 9.1 and 14.1 Hz), 3.32 (1 H, dd, J = 4.3 and 14.1 Hz), 3.79 (3 H, s), 4.38 (2 H, q, J = 7.1 Hz), 4.88 (1 H, dd, J = 4.3 and 9.1 Hz), 5.35 (2 H, s), 6.68 (1 H, d, J = 8.5 Hz), 7.06 (2 H, d, J = 8.6 Hz), 7.19 (2 H, d, J = 8.6 Hz), 7.97 (1 H, d, J = 8.5 Hz), 12.02 (1 H, s). Anal. ($C_{20}H_{20}N_4O_4S$) C, H, N, S.

5-[4-(5-Isopropoxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (19c). This compound was prepared using the same procedure as for the preparation of **19a**: mp 210−212 °C; IR (KBr) 1703, 1609, 1512, 1408, 1261, 1243 cm^{-1}; MS *m/z* 426 (M^+); ^1H NMR (DMSO-d_6) δ 1.34 (6 H, d, J = 6.3 Hz), 3.06 (1 H, dd, J = 9.3 and 14.2 Hz), 3.32 (1 H, dd, J = 4.3 and 14.2 Hz), 3.78 (3 H, s), 4.88 (1 H, dd, J = 4.3 and 9.3 Hz), 5.3−5.4 (1 H, m), 5.35 (2 H, s), 6.63 (1 H, d, J = 8.6 Hz), 7.07 (2 H, d, J = 8.6 Hz), 7.19 (2 H, d, J = 8.6 Hz), 7.95 (1 H, d, J = 8.6 Hz), 12.02 (1 H, s). Anal. ($C_{20}H_{20}N_4O_4S \cdot {}^1/_{10}CH_3CO_2C_2H_5 \cdot {}^1/_{10}H_2O$) C, H, N, S.

5-[4-(5-Benzyloxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (19d). This compound was prepared using the same procedure as for the preparation of **19a**: mp 210−211 °C; IR (KBr) 1698, 1607, 1511, 1409, 1254 cm^{-1}; MS *m/z* 474 (M^+); ^1H NMR (DMSO-d_6) δ 3.06 (1 H, dd, J = 9.2 and 14.2 Hz), 3.31 (1 H, dd, J = 4.3 and 14.2 Hz), 3.81 (3 H, s), 4.88 (1 H, dd, J = 4.3 and 9.2 Hz), 5.36 (2 H, s), 5.44 (2 H, s), 6.76 (1 H, d, J = 8.6 Hz), 7.07 (2 H, d, J = 8.6 Hz), 7.19 (2 H, d, J = 8.6 Hz), 7.32 (1 H, t, J = 7.3 Hz), 7.39 (2 H, m), 7.51 (2 H, d, J = 7.2 Hz), 8.00 (1 H, d, J = 8.6 Hz), 12.02 (1 H, s). Anal. ($C_{25}H_{22}N_4O_4S$) C, H, N, S.

5-[4-(3-Methyl-5-phenylsulfanyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (19e). This compound was prepared using the same procedure as for the preparation of **19a**: mp 166−168 °C; IR (KBr) 1698, 1511, 1397, 1239 cm^{-1}; MS *m/z* 476 (M^+); ^1H NMR (DMSO-d_6) δ 3.06 (1 H, dd, J = 9.1 and 14.2 Hz), 3.31 (1 H, dd, J = 4.3 and 14.2 Hz), 3.78 (3 H, s), 4.87 (1 H, dd, J = 4.3 and 9.1 Hz), 5.40 (2 H, s), 6.94 (1 H, d, J = 8.3 Hz), 7.06 (2 H, d, J = 8.6 Hz), 7.19 (2 H, d, J = 8.6 Hz), 7.4−7.5 (3 H, m), 7.5−7.6 (2 H, m), 7.98 (1 H, d, J = 8.3 Hz), 12.02 (1 H, br s). Anal. ($C_{24}H_{20}N_4O_3S_2$) C, H, N, S.

5-[4-(3-Methyl-5-phenyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (19f). This compound was prepared using the same procedure as for the preparation of **19a**: mp 211−213 °C; IR (KBr) 1705, 1511, 1406, 1232 cm^{-1}; MS *m/z* 444 (M^+); ^1H NMR (DMSO-d_6) δ 3.06 (1 H, dd, J = 9.1 and 14.2 Hz), 3.32 (1 H, dd, J = 4.3 and 14.2 Hz), 3.94 (3 H, s), 4.88 (1 H, dd, J = 4.3 and 9.1 Hz), 5.46 (2 H, s), 7.09 (2 H, d, J = 8.7 Hz), 7.21 (2 H, d, J = 8.7 Hz), 7.4−7.5 (1 H, m), 7.5−7.6 (2 H, m), 7.89 (1 H, d, J = 4.5 Hz), 8.1−8.2 (3 H, m), 12.05 (1 H, br s). Anal. ($C_{24}H_{20}N_4O_3S \cdot CH_3CO_2C_2H_5 \cdot {}^1/_3H_2O$) C, H, N, S.

5-[4-(5-Hydroxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (19g). A solution of 1.20 g (1.67 mmol) of **18d** in 50 mL of methanol was stirred under an atmosphere of hydrogen and in the presence of 1.80 g of 10% w/w palladium-on-charcoal, first at room temperature for 3 h then at 50 °C for 3 h. The reaction mixture was filtered to remove the catalyst and filtrate was concentrated by evaporation under reduced pressure. The concentrate thus obtained was purified by column chromatogaphy through silica gel, using a gradient elution method, with a mixture of ethyl acetate and methanol, in ratios ranging from 1:0 to 10:1 by volume, as the eluent, to give 0.10 g (0.26 mmol) of **19g**: yield 16%; mp 240−242 °C; IR (KBr) 1694, 1608, 1510, 1240, 1223 cm^{-1}; MS *m/z* 384 (M^+); ^1H NMR (DMSO-d_6) δ 3.06 (1 H, dd, J = 9.1 and 14.2 Hz), 3.31 (1 H, dd, J = 4.3 and 14.2 Hz), 3.74 (3 H, s), 4.88 (1 H, dd, J = 4.3 and 9.1 Hz), 5.33 (2 H, s), 6.54 (1 H, d, J = 8.6 Hz), 7.06 (2 H, d, J = 8.6 Hz), 7.19 (2 H, d, J = 8.6 Hz), 7.89 (1 H, d, J = 8.6 Hz), 10.87 (1 H, s), 12.02 (1 H, s). Anal. ($C_{18}H_{16}N_4O_4S \cdot {}^1/_5H_2O$) C, H, N, S.

5-{4-[2-(1,3-Dioxolan-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione (21). To a suspension of 8.80 g (202 mmol) of sodium hydride (as a 55 wt % dispersion in mineral oil, previously washed with hexane) in 180 mL of dimethylformamide was added 15.0 g (67.2 mmol) of 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (**20**), while cooling on ice, and the resulting mixture was stirred at room temperature for 2 h. To the mixture was added 17 mL (134 mmol) of 2-(2-bromoethyl)-1,3-dioxolane, while cooling on ice, and the resulting mixture was stirred at 50 °C for 5 h. The reaction mixture was freed from dimethylformamide by distillation under reduced pressure. The resulting residue was diluted with water, and the aqueous mixture was adjusted to a pH between 2 and 3 with the addition of 2 N aqueous hydrochloric acid, after which it was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure. The resulting residue was purified by column chromatogaphy through silica gel, using a 1:1 by volume mixture of hexane and ethyl acetate as the eluent, to give 6.67 g (20.6 mmol) of **21**: yield 31%; mp 102−104 °C; IR (KBr) 1742, 1690, 1674, 1517, 1257, 1144 cm^{-1}; MS *m/z* 323 (M^+); ^1H NMR (DMSO-d_6) δ 2.01 (2 H, dt, J = 5.0 and 6.5 Hz), 3.06 (1 H, dd, J = 9.1 and 14.2 Hz), 3.30 (1 H, dd, J = 4.3 and 14.2 Hz), 3.79 (2 H, m), 3.91 (2 H, m), 4.04 (2 H, t, J = 6.5 Hz), 4.87 (1 H, dd, J = 4.3 and 9.1 Hz), 4.98 (1 H, t, J = 5.0 Hz), 6.87 (2 H, d, J = 8.6 Hz), 7.15 (2 H, d, J = 8.6 Hz), 12.00 (1 H, s).

5-[4-(3-Oxopropoxy)benzyl]thiazolidine-2,4-dione (22). A solution of 6.30 g (19.5 mmol) of **21** in 50 mL of a 4:1 mixture of acetic acid and water was stirred at 60 °C for 6 h. The reaction mixture was freed from the solvent by distillation under reduced pressure. The resulting residue was purified by column chromatogaphy through silica gel, using a 1:1 by volume mixture of hexane and ethyl acetate as the eluent, to give 2.20 g (7.88 mmol) of **22**: yield 40%; mp 48−51 °C (softening); IR (KBr) 1750, 1686, 1513, 1247 cm^{-1}; MS *m/z* 279 (M^+); ^1H NMR (DMSO-d_6) δ 2.86 (2 H, dt, J = 1.5 and 5.9 Hz), 3.06 (1 H, dd, J = 8.9 and 14.1 Hz), 3.30 (1 H, dd, J = 4.4 and 14.1 Hz), 4.26 (2 H, t, J = 5.9 Hz), 4.87 (1 H, dd, J = 4.4 and 8.9 Hz), 6.88 (2 H, d, J = 8.6 Hz), 7.16 (2 H, d, J = 8.6 Hz), 9.73 (1 H, t, J = 1.4 Hz), 12.00 (1 H, s).

5-{4-[2-(3-Methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione (24a). To a solution of 0.94 g (7.63 mmol) of 3-amino-2-methylaminopyridine (**23**) in a

mixture of 6 mL of ethanol and 3 mL of acetic acid was added 2.10 g (7.52 mmol) of **22**, and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was freed from the solvent by distillation under reduced pressure. To the residue were added 30 mL of 1,2-dimethoxyethane and 2.32 g (9.14 mmol) of iodine, and the resulting mixture was stirred at 60 °C for 1 day. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatogaphy through silica gel, using ethyl acetate as the eluent, to give 85 mg (0.22 mmol) of **24a**: yield 3%; mp 96−100 °C; IR (KBr) 1682, 1515, 1384 cm^{-1}; MS *m*/*z* 382 (M^+); ^1H NMR (DMSO-d_6) δ 2.94 (1 H, dd, J = 9.4 and 14.1 Hz), 3.09 (2 H, t, J = 7.4 Hz), 3.24 (1 H, dd, J = 4.3 and 14.1 Hz), 3.77 (3 H, s), 3.94 (2 H, dt, J = 3.7 and 7.4 Hz), 4.81 (1 H, dd, J = 4.3 and 9.4 Hz), 6.70 (2 H, dd, J = 8.5 Hz), 7.02 (2 H, d, J = 8.5 Hz), 7.23 (1 H, dd, J = 4.4 and 8.0 Hz), 7.98 (1 H, dd, J = 1.3 and 8.0 Hz), 8.30 (1 H, dd, J = 1.3 and 4.4 Hz), 9.36 (1 H, s). Anal. ($C_{19}H_{18}N_4O_3S\cdot{}^2/_5CH_3CO_2C_2H_5\cdot{}^3/_{10}H_2O$) C, H, N, S.

5-[4-(3-Phenyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione (24b). This compound was prepared using the same procedure as for the preparation of **24a**: mp 88−91 °C; IR (KBr) 1699, 1510, 1240 cm^{-1}; MS *m*/*z* 430 (M^+); ^1H NMR (DMSO-d_6) δ 3.03 (1 H, dd, J = 9.1 and 14.2 Hz), 3.29 (1 H, dd, J = 4.3 and 14.2 Hz), 4.84 (1 H, dd, J = 4.3 and 9.1 Hz), 5.27 (2 H, s), 6.85 (2 H, d, J = 8.6 Hz), 7.20 (2 H, d, J = 8.6 Hz), 7.38 (1 H, dd, J = 5.1 and 8.0 Hz), 7.5−7.6 (5 H, m), 8.20 (1 H, dd, J = 1.4 and 8.0 Hz), 8.35 (1 H, dd, J = 1.4 and 5.1 Hz), 12.01 (1 H, s). Anal. ($C_{23}H_{18}N_4O_3S\cdot{}^3/_{10}H_2O$) C, H, N, S.

5-{4-[3-(4-Chlorobenzyl)-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy]benzyl}thiazolidine-2,4-dione (24c). This compound was prepared using the same procedure as for the preparation of **24a**: mp 211−213 °C; IR (KBr) 1705, 1511, 1232 cm^{-1}; MS *m*/*z* 478 (M^+); ^1H NMR (DMSO-d_6) δ 3.05 (1 H, dd, J = 9.2 and 14.2 Hz), 3.31 (1 H, dd, J = 4.3 and 14.2 Hz), 4.87 (1 H, dd, J = 4.3 and 9.2 Hz), 5.38 (2 H, s), 5.60 (2 H, s), 6.88 (2 H, d, J = 8.6 Hz), 7.15 (2 H, d, J = 8.6 Hz), 7.20 (2 H, d, J = 8.6 Hz), 7.34 (2 H, d, J = 8.6 Hz), 7.3−7.4 (1 H, m), 8.15 (1 H, dd, J = 1.4 and 8.1 Hz), 8.40 (1 H, dd, J = 1.4 and 4.5 Hz), 12.01 (1 H, s). Anal. ($C_{24}H_{19}ClN_4O_3S$) C, H, N, Cl, S.

5-[4-(3-Methyl-6-trifluoromethyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (24d). This compound was prepared using the same procedure as for the preparation of **24a**: mp 212−214 °C; IR (KBr) 1698, 1513, 1336, 1241, 1121 cm^{-1}; MS *m*/*z* 436 (M^+); ^1H NMR (DMSO-d_6) δ 3.07 (1 H, dd, J = 9.0 and 14.2 Hz), 3.33 (1 H, dd, J = 4.4 and 14.2 Hz), 3.93 (3 H, s), 4.89 (1 H, dd, J = 4.4 and 9.0 Hz), 5.51 (2 H, s), 7.08 (2 H, d, J = 8.6 Hz), 7.20 (2 H, d, J = 8.6 Hz), 8.55 (1 H, d, J = 1.8 Hz), 8.78 (1 H, d, J = 1.8 Hz), 12.02 (1 H, br s). Anal. ($C_{19}H_{15}F_3N_4O_3S$) C, H, N, F, S.

Methyl 4-Nitrophenoxyacetate (26). A solution of 56 g (403 mmol) of 4-nitrophenol (**25**), 90 g (588 mmol) of methyl bromoacetate and 100 g (724 mmol) of potassium carbonate in 500 mL of dimethylformamide was stirred at room temperature for 2 days. The reaction mixture was freed from dimethylformamide by distillation under reduced pressure. The residue thus obtained was diluted with water and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure. The resulting residue was crystallized with hexane, to give 63.3 g (300 mmol) of **26**: yield 75%; mp 98−99 °C.

Methyl 4-Aminophenoxyacetate (27). A solution of 30.8 g (146 mmol) of **26** in 500 mL of methanol was stirred in an atmosphere of hydrogen and in the presence of 5.0 g of 10% w/w palladium-on-charcoal, at room temperature for 6 h. The reaction mixture was filtered to remove the catalyst and the filtrate was concentrated by evaporation under reduced pressure, to give 25.8 g (142 mmol) of **27**: yield 98%; R_f = 0.79 (on silica gel thin-layer chromatography using ethyl acetate as the developing solvent).

Methyl 4-(2-Bromo-2-*n*-butoxycarbonylethyl)phenoxyacetate (28). To a solution of 25.8 g (142 mmol) of **27** in 263 mL of a 2:5 by volume mixture of methanol and acetone was added dropwise 98 g (569 mmol) of 47% w/v aqueous hydrobromic acid and, subsequently, 33 mL of aqueous solution containing 12.8 g (186 mmol) of sodium nitrate, while cooling on ice, and the resulting mixture was stirred for 30 min while cooling on ice. Then, 18.2 g (142 mmol) of *n*-butyl acrylate was added. The mixture was then stirred for 30 min while cooling on ice, after which 3.2 g (22.4 mmol) of copper(I) bromide was added, and the resulting mixture was stirred overnight at room temperature. The reaction mixture was freed from the solvent by distillation under reduced pressure. The residue was diluted with brine and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure, to give 51.7 g of **28** as a crude product: R_f = 0.46 (on silica gel thin layer chromtography using a 5:1 by volume mixture of hexane and ethyl acetate as the developing solvent).

5-[4-(Ethoxycarbonylmethoxy)benzyl]thiazolidine-2,4-dione (29). A solution of 100 g (268 mmol) of **28** and 22 g (289 mmol) of thiourea in 200 mL of ethanol was heated under reflux for 2.5 h. After that, 2 N aqueous hydrochloric acid was added to the mixture, and the resulting mixture was heated under reflux for 5 h. The reaction mixture was freed from the solvent by distillation under reduced pressure. The resulting residue was diluted with water and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The resulting residue was purified by column chromatography through silica gel, using a 2:5 by volume mixture of ethyl acetate and hexane as the eluent, to give 19.4 g (62.7 mmol) of **29**: mp 105−106 °C; IR (KBr) 1751, 1738, 1707, 1513, 1231, 1151, 1086 cm^{-1}; MS *m*/*z* 309 (M^+); ^1H NMR (DMSO-d_6) δ 1.20 (3 H, t, J = 7.1 Hz), 3.06 (1 H, dd, J = 9.3 and 14.2 Hz), 3.31 (1 H, dd, J = 4.4 and 14.2 Hz), 4.16 (2 H, q, J = 7.1 Hz), 4.74 (2 H, s), 4.87 (1 H, dd, J = 4.4 and 9.3 Hz), 6.86 (2 H, d, J = 8.7 Hz), 7.16 (2 H, d, J = 8.7 Hz), 11.99 (1 H, br s).

5-[4-(3*H*-Imidazo[4,5-*b*]pyridin-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione (31). A mixture of 1.13 g (3.65 mmol) of **29** and 200 mg (1.83 mmol) of 2,3-diaminopyridine (**30**) was stirred at 110 °C for 2 days. The reaction mixture was treated with 3 N aqueous hydrochloric acid and subsequently made alkaline with the addition of aqueous ammonia. The aqueous mixture was evaporated to dryness under reduced pressure, and then the residue was purified by column chromatogaphy through silica gel, using a gradient elution method, with a mixture of ethyl acetate and methanol, in ratios ranging from 1:0 to 10:1 by volume, as the eluent. The product was crystallized with ethyl acetate, to give 400 mg (1.13 mmol) of **31**: yield 62%; mp 247−248 °C; IR (KBr) 1701, 1512, 1242 cm^{-1}; MS *m*/*z* 354 (M^+); ^1H NMR (DMSO-d_6) δ 3.07 (1 H, dd, J = 9.1 and 14.2 Hz), 3.32 (1 H, dd, J = 4.3 and 14.2 Hz), 4.88 (1 H, dd, J = 4.3 and 9.1 Hz), 5.30 (s) and 5.36 (s) (2 H), 7.04 (2 H, d, J = 8.5 Hz), 7.20 (2 H, d, J = 8.5 Hz), 7.24 (1 H, dd, J = 4.8 and 8.0 Hz), 7.8−8.1 (1 H, m), 8.3−8.4 (1 H, m), 12.01 (1 H, s), 12.90 (br s) and 13.30 (br s) (1 H). Anal. ($C_{17}H_{14}N_4O_3S\cdot{}^3/_{10}H_2O$) C, H, N, S.

5-[4-(Imidazo[1,2-*a*]pyridin-2-ylmethoxy)benzyl]-3-triphenylmethylthiazolidine-2,4-dione (33). A procedure similar to that described in preparation **11a** was repeated, except that 920 mg (6.21 mmol) of imidazo[1,2-*a*]pyridine-2-methanol (**32**), 2.9 g (6.23 mmol) of 5-(4-hydroxybenzyl)-3-triphenylmethylthiazolidine-2,4-dione (**10**), 1.4 g (6.92 mmol) of tributylphosphine, 1.65 g (6.54 mmol) of azodicarbonyldipiperidine and 60 mL of benzene were used, to give 3.1 g (5.20 mmol) of **33**: yield 84%; R_f = 0.71 (on silica gel thin-layer chromatography using a 10:1 by volume mixture of ethyl acetate and ethanol as the developing solvent).

5-[4-(Imidazo[1,2-*a*]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (34). A solution of 3.0 g (5.04 mmol) of **33** in 30 mL of trifluoroacetic acid was stirred at room temper-

ature for 1 h. The reaction mixture was freed from trifluoroacetic acid by distillation under reduced pressure. Aqueous solution of potassium carbonate and ethyl acetate were added to the residue, and the resulting precipitat of insoluble material was collected by filtration, dried over anhydrous sodium sulfate, and recrystallized with ethanol, to give 0.8 g (2.26 mmol) of **34**: yield 45%; mp 197−202 °C. Anal. ($C_{18}H_{15}N_3O_3S \cdot {}^2/_5H_2O$) C, H, N, S.

3-Methyl-1,3-dihydroimidazo[4,5-*b*]pyridin-2-one (36). A solution of 2.66 g (21.6 mmol) of 3-amino-2-methylaminopyridine (**35**) and 4.20 g (25.9 mmol) of carbonyldiimidazole in 40 mL of dichloromethane was stirred, first at room temperature for 1 h and then heated under reflux for 2 h. The reaction mixture was freed from dichloromethane by distillation under reduced pressure. The resulting residue was purified by column chromatography through silica gel, using a gradient elution method, with a mixture of hexane and ethyl acetate, in ratios ranging from 3:1 to 0:1 by volume, as the eluent, to give 2.16 g (14.5 mmol) of **36**: yield 67%; mp 233−235 °C; IR (KBr) 1721 cm^{-1}; MS *m*/*z* 149 (M^+); ^1H NMR (DMSO-d_6) δ 3.30 (3 H, s), 6.99 (1 H, dd, J = 5.3 and 7.6 Hz), 7.28 (1 H, dd, J = 1.3 and 7.6 Hz), 7.94 (1 H, m), 11.07 (1 H, br s).

2-Chloro-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (37). A solution of 1.95 g (13.1 mmol) of **36** in 10 mL of phosphoryl chloride was heated under reflux for 1.5 h. The reaction mixture was freed from phosphoryl chloride by distillation under reduced pressure. The resulting residue was diluted with ice water and the aqueous mixture was neutralized with saturated aqueous solution of sodium hydrogen carbonate, after which it was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure. The resulting residue was purified by column chromatogaphy through silica gel, using a 2:3 by volume mixture of hexane and ethyl acetate as the eluent, to give 0.64 g (3.82 mmol) of **37**: yield 29%; mp 65−67 °C; IR (KBr) 1484, 1359 cm^{-1}; MS *m*/*z* 167 (M^+); ^1H NMR (DMSO-d_6) δ 3.80 (3 H, s), 7.33 (1 H, dd, J = 5.1 and 8.1 Hz), 8.05 (1 H, dd, J = 1.3 and 8.1 Hz), 8.39 (1 H, dd, J = 1.3 and 5.1 Hz).

5-[4-(3-Methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yloxy)benzyl]thiazolidine-2,4-dione (38). To a suspension of 175 mg (4.01 mmol) of sodium hydride (as a 55 wt % dispersion in mineral oil, previously washed with toluene) in 15 mL of dimethylformamide was added 401 mg (1.80 mmol) of 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (**20**), while cooling on ice, and the resulting mixture was stirred at room temperature for 20 min. To the mixture was added 302 mg (1.80 mmol) of **37**, while cooling on ice, and the resulting mixture was stirred at 60 °C for 3 h. The reaction mixture was diluted with water and the aqueous mixture was treated with 3 N aqueous hydrochloric acid and subsequently neutralized with saturated aqueous solution of sodium hydrogen carbonate, after which it was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure. The resulting residue was washed with diisopropyl ether and hexane, to give 235 mg (0.66 mmol) of **38**: yield 37%; mp 210−212 °C; IR (KBr) 1702, 1524, 1489 cm^{-1}; MS *m*/*z* 354 (M^+); ^1H NMR (DMSO-d_6) δ 3.19 (1 H, dd, J = 9.1 and 14.1 Hz), 3.44 (1 H, dd, J = 4.4 and 14.1 Hz), 3.73 (3 H, s), 4.96 (1 H, dd, J = 4.4 and 9.1 Hz), 7.19 (1 H, dd, J = 5.1 and 8.0 Hz), 7.36 (2 H, d, J = 8.7 Hz), 7.41 (2 H, d, J = 8.7 Hz), 7.78 (1 H, dd, J = 1.4 and 8.0 Hz), 8.20 (1 H, dd, J = 1.4 and 5.1 Hz), 12.08 (1 H, br s). Anal. ($C_{18}H_{16}N_4O_3S$) C, H, N, S.

Acknowledgment. We thank Dr. Hiroaki Yanagisawa for his useful comments and encouragement and also Ms. Eiko Yorikane and Ms. Yuka Hagisawa for their technical assistance.

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JM990522T