Studies on Antidiabetic Agents. X.[1] Synthesis and Biological Activities of Pioglitazone and Related Compounds

Yu MOMOSE, Kanji MEGURO, Hitoshi IKEDA, Chitoshi HATANAKA, Satoru OI, and Takashi SOHDA*

Research and Development Division, Takeda Chemical Industries, Ltd., 17–85, Jusohommachi 2-chome, Yodogawa-ku, Osaka 532, Japan.
Received December 17, 1990

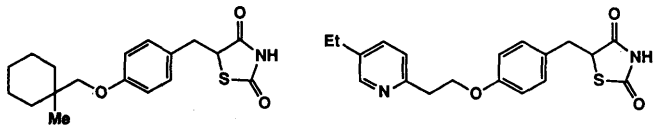
Various analogues of a new antidiabetic agent, pioglitazone (AD-4833, U-72107), were synthesized in order to study in more detail the structure–activity relationships of this class of drug. 5-(4-Pyridylalkylthiobenzyl)-2,4-thiazolidinediones (I), thia-analogues of pioglitazone, were prepared *via* Meerwein arylation of the alkylthioanilines (IV). 5-(4-Pyridylalkoxybenzylidene)-2,4-thiazolidinediones (IIa) and related heterocyclic analogues (IIb) were synthesized by Knoevenagel condensation of the aldehydes (VIII) with the corresponding azolidinones. Compounds I and II were evaluated for hypoglycemic and hypolipidemic activity in genetically obese and diabetic yellow KK (KK^{Ay}) mice. Several 5-[4-[2-(2-pyridyl)ethoxy]-benzylidene]-2,4-thiazolidinediones (IIa) were equipotent to pioglitazone. However, the thia-analogues (I) and the benzylideneheterocycles (IIb) had decreased activity. Catalytic hydrogenation of the 5-benzylidene analogue (14) was found to be a convenient new synthetic method for pioglitazone. The configuration of 14 is also discussed.

Keywords 5-benzyl-2,4-thiazolidinedione; 5-benzylidene-2,4-thiazolidinedione; hypoglycemic activity; hypolipidemic activity; pioglitazone; Knoevenagel condensation

In the course of our study aimed at developing a new oral agent for the treatment of non-insulin dependent diabetes mellitus (NIDDM), we found that a *p*-alkoxybenzyl-substituted thiazolidinedione derivative, ciglitazone,[2] showed hypoglycemic and hypolipidemic activity[3] in insulin-resistant animal models such as KKA^{y} mice[4] and Wistar fatty rats.[5] Further evaluation of this series of compounds led to the finding that the introduction of a 2-(2-pyridylethoxy) group as a *p*-alkoxy substituent remarkably potentiates the pharmacological effects. Among the compounds synthesized, pioglitazone[6] (AD-4833, U-72107), 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione, was selected as a candidate for further development. Pioglitazone is expected to effectively ameliorate the abnormal glucose and lipid metabolism associated with NIDDM or obesity and is currently under clinical evaluation.[6] Recently, several other studies based on ciglitazone as a prototype have been reported,[7] and drug development along this line is becoming one of the major concerns in the field of diabetes.

In this paper we describe the further modification of 5-(4-pyridylalkoxybenzyl)-2,4-thiazolidinediones such as replacement of the *p*-alkoxybenzyl portion with a *p*-alkoxybenzylidene or a *p*-alkylthiobenzyl moiety and replacement of the thiazolidinedione ring with other acidic heterocycles. In addition, an alternative method for the synthesis of pioglitazone involving catalytic hydrogenation of the 5-benzylidene-2,4-thiazolidinedione prepared by Knoevenagel condensation of the corresponding aldehyde with 2,4-thiazolidinedione is described. The stereochemistry of the benzylidene intermediate is also discussed.

Chemistry The 5-(4-alkylthiobenzyl)-2,4-thiazolidinediones (Ia: X=S) were synthesized as shown in Chart 2 from the 4-alkylthioanilines (IV) by a procedure similar to that previously described for the synthesis of their oxa-analogues (Ib: X=O).[2,6a] The requisite anilines (IV) were prepared by coupling the vinylarenes (III)[8] with 4-aminothiophenol and subjected to the Meerwein arylation. Radical coupling of the diazonium bromide of IV with methyl acrylate in the presence of cuprous oxide provided the α-bromopropionates (V). Subsequent cyclization of the intermediate (V) with thiourea followed by acid hydrolysis afforded the desired thiazolidinediones (Ia).



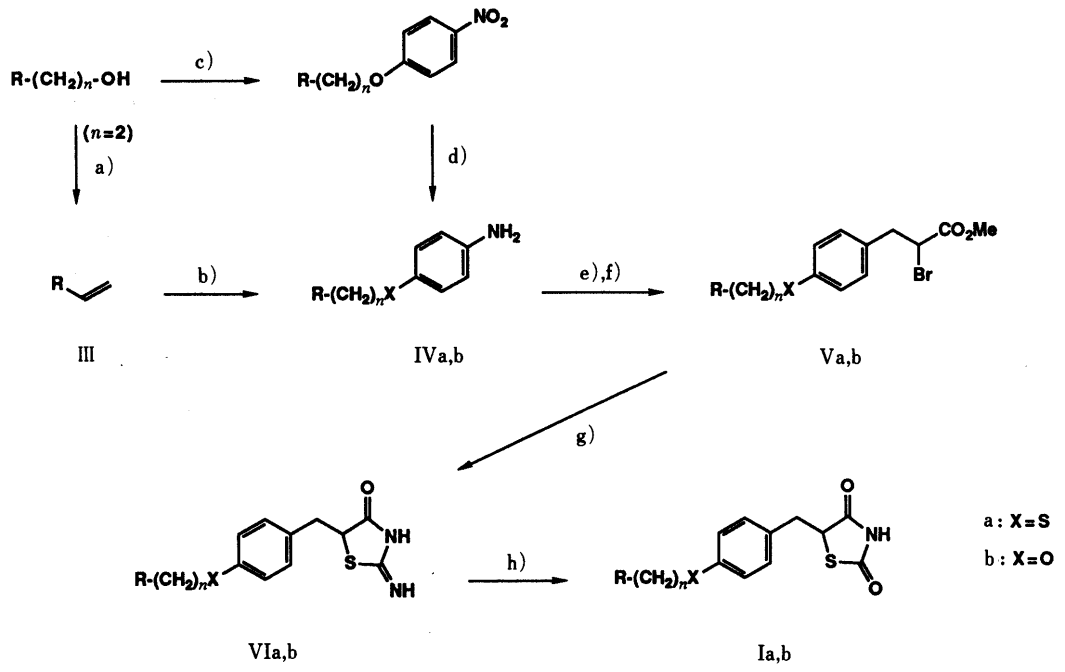
ciglitazone pioglitazone(AD-4833, U-72107)

Chart 1

The 5-benzylidene-2,4-thiazolidinediones (IIa) and their heterocyclic analogues (IIb) were synthesized by Knoevenagel condensation of the benzaldehydes (VIII) with various five-membered acidic heterocycles as shown in Chart 3. Although piperidine was generally used as the base in this condensation, pyrrolidine was more effective for the synthesis of benzylidenehydantoin (**19**). The requisite aldehydes (VIII) were obtained by a base mediate coupling of the pyridylethanols and 4-fluorobenzonitrile followed by treatment with Raney Ni alloy in aqueous formic acid.[9] An alternative and more efficient one-pot route to VIII was tosylation of the 2-pyridylethanols and subsequent coupling with 4-hydroxybenzaldehyde in the presence of benzyltributylammonium chloride as a phase transfer catalyst.[10]

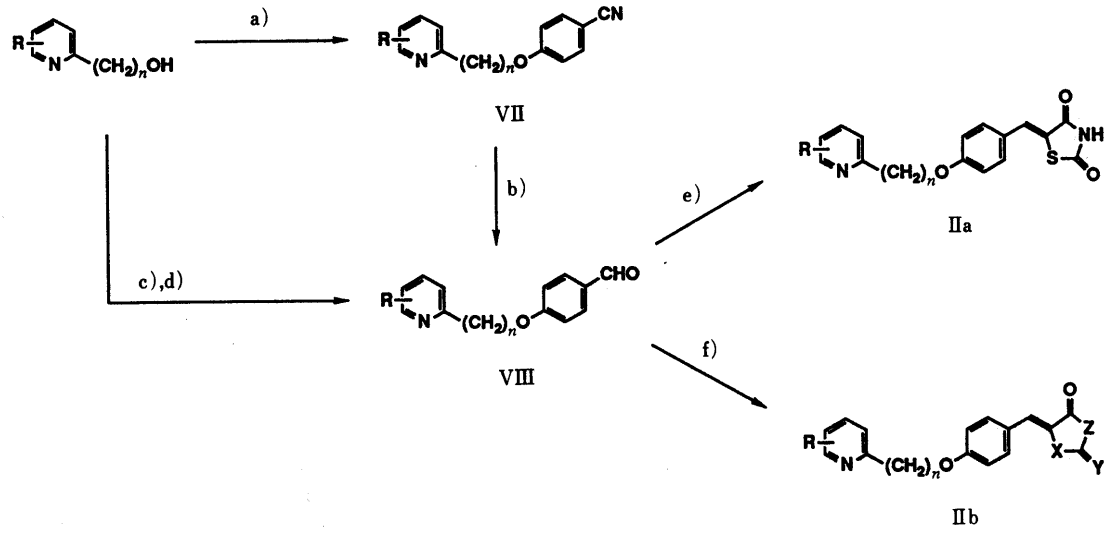
Catalytic hydrogenation of 5-[4-[2-(5-ethyl-2-pyridyl)-ethoxy]-benzylidene]-2,4-thiazolidinedione (**14**) gave pioglitazone in good yield (Chart 4).[10] This procedure, in combination with Knoevenagel condensation, provides a convenient method for large-scale synthesis of pioglitazone.

The configuration (*E* or *Z*) of the key intermediate (**14**) was determined as follows. Irradiation of **14** with a high pressure mercury-vapor lamp in acetonitrile gave an equilibrium mixture of **14** and **15** (ratio, *ca.* 3:2). The stereoisomer (**15**) was isolated using silica gel column chromatography. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **15** was very similar to that of **14** except for the signal due to the methine proton (H_a) in the benzylidene group. As shown in Chart 4, the methine proton of the starting **14** appeared at a lower field than that of the



a) KOH b) 4-aminothiophenol c) NaH, 4-fluoronitrobenzene d) H_2/Pd-C e) $NaNO_2$, aq.HBr f) $CH_2=CHCO_2Me$, Cu_2O g)$(H_2N)_2CS$, NaOAc h) aq.HCl

Chart 2



a) NaH, 4-fluorobenzonitrile b) Raney Ni, aq.HCO_2H c) TsCl, $PhCH_2NBu_3Cl$, aq.NaOH d) 4-hydroxybenzaldehyde, $PhCH_2NBu_3Cl$, aq. NaOH e) 2,4-thiazolidinedione, base f) heterocycles, base

Chart 3

photoisomerized compound (**15**). This suggests that the proton in **14** is on the same side as the carbonyl group at the 4-position of the thiazolidinedione ring while that in **15** is on the opposite side. In addition, Pascual and co-workers reported the prospective method to calculate the chemical shifts of the protons on variously substituted olefins.[11] The calculated values of the methine protons of *Z*-**14** and *E*-**15** by this method were δ 7.90 and δ 7.42, respectively, in good accordance with the observed values. Thus the configurations *Z*-**14** and *E*-**15** were determined.

Biological Methods The biological activities of the compounds prepared were tested using genetically obese and diabetic KKA^y mice[4] (8—11 weeks old). After being fed a laboratory chow (CE-2, Clea Japan Inc., Tokyo, Japan) for 3 d, the mice were divided into experimental groups of five mice each according to their blood glucose levels. The test compounds were given as a dietary admixture at 0.005% or 0.01% concentration in the CE-2 powdered diet. The mice were fed the experimental diet and water *ad libitum* for 4 d. Blood samples were taken from the orbital vein. Blood glucose was determined using the glucose oxidase method[12] and plasma triglyceride using

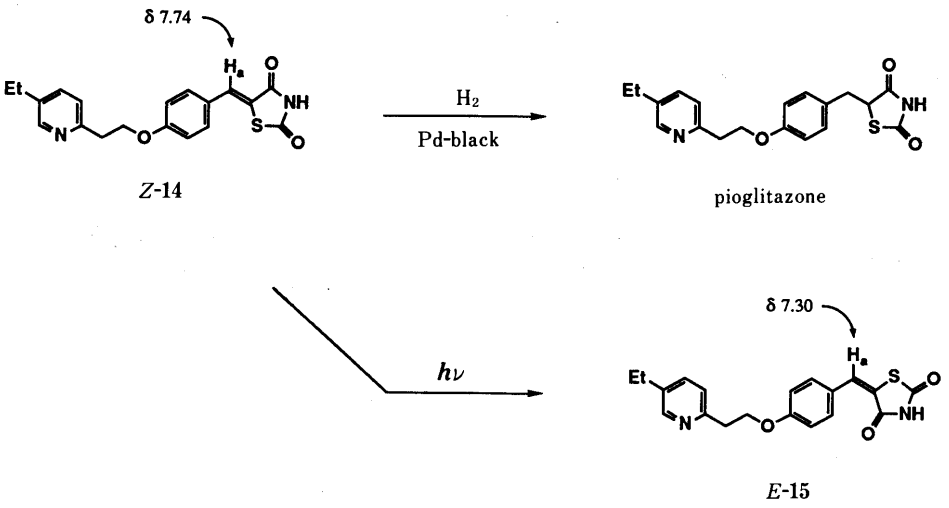
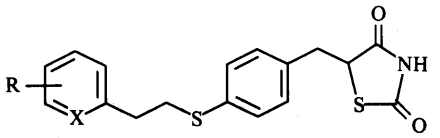


Chart 4

TABLE I. Physical and Biological Properties of 5-[4-(2-Arylethylthio)benzyl]-2,4-thiazolidinediones (I)



No.	R	X	Yield[a] (%)	mp (°C)	Recrystn. solvent	Formula[b]	Hypoglycemic activity[c]	Plasma triglyceride lowering activity[c]
1	H	CH	69	285—289[g]	EtOH	$C_{18}H_{16}NO_2S_2Na$	11	13
2	H	N	83	162—164	$CHCl_3$–EtOH	$C_{17}H_{16}N_2O_2S_2$	0	20[d]
3	3-Me	N	63	151—152	$CHCl_3$–EtOH	$C_{18}H_{18}N_2O_2S_2$	16	12
4	5-Me	N	79	154—155	CH_2Cl_2–EtOH	$C_{18}H_{18}N_2O_2S_2$	18	7
5	6-Me	N	95	146—147	EtOH	$C_{18}H_{18}N_2O_2S_2$	4	5
6	4,6-Me_2	N	84	162—163	CH_2Cl_2–EtOH	$C_{19}H_{21}N_2O_2S_2$	20[d]	9
7	5-Et	N	75	118—118.5	$CHCl_3$–EtOH	$C_{19}H_{20}N_2O_2S_2 \cdot 1/3EtOH$[h]	14	8
	Pioglitazone						54[f]	47[e]

a) Yield from the corresponding 5-[4-(2-arylethylthio)benzyl]-2-imino-4-thiazolidinone (VI). *b*) All compounds were analyzed for C, H, and N; analytical results obtained for these elements were within ±0.4% of calculated values. *c*) Maximum reduction in blood glucose and plasma triglyceride levels at the dosage of 0.01% diet were calculated as percentage reduction with respect to the control value. *d*) $p<0.05$. *e*) $p<0.02$. *f*) $p<0.001$. *g*) Decomposition. *h*) EtOH solvate.

a commercially available assay kit (Cleantech TG-S, Iatron Laboratories Inc., Tokyo, Japan). The maximum decreases in blood glucose and plasma triglyceride levels were calculated as percentage change from the control value.

Results and Discussion

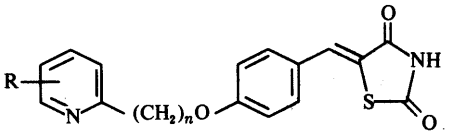
The structures and the biological data on the compounds prepared are shown in Tables I, II and III. The 5-(4-alkylthiobenzyl)-2,4-thiazolidinediones (**1**—**7**) were inactive or less potent than pioglitazone as shown in Table I. For example, compound **7**, the thia-analogue of pioglitazone, was inactive which indicates that the oxygen atom at the 4-position of the 5-benzyl moiety plays an important role in the pharmacological activity. Among the benzylidene-type analogues (II), the 5-[4-(2-pyridylalkoxy)-benzylidene]-2,4-thiazolidinediones (**8**, **9**, **11**, and **14**) had potent hypoglycemic and hypolipidemic activities (Table II) that were comparable to those of pioglitazone. However, 2-(4-pyridyl)ethoxy derivative (**16**) was inactive. The distance between the benzene ring and the pyridine ring appeared to influence the activity (**14** > **13**). Introduction of alkyl substituent(s) to the pyridine ring did not potentiate the activities. These structure–activity relationships are similar to those of the previously reported 5-(4-alkoxybenzyl)-2,4-thiazolidinediones.[2,6a] No significant difference was observed between the activities of compound **14** and the stereoisomer (**15**). However, replacement of the 2,4-thiazolidinedione in **11** with other heterocycles, such as a rhodanine, hydantoin, thiohydantoin, and 2-thioxo-5-thiazolidinone, resulted in a complete loss of activity as seen in compounds (**17**—**21**) (Table III).

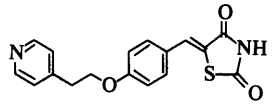
The above mentioned results indicate that the 2,4-thiazolidinedione moiety and the 4-oxybenzyl group are essential for the compound to exert favorable hypoglycemic and hypolipidemic activity. It also appeared that the methine portion is effective as a linker between the benzene and the thiazolidinedione rings, and its configuration does not affect the activity.

Conclusion

We synthesized 5-(4-arylalkylthiobenzyl)-2,4-thiazolidinediones (I) and 5-(4-pyridylalkoxybenzylidene)-substituted heterocycles (II) and evaluated them for hypoglycemic and hypolipidemic activity. Among them, several 5-[4-(2-

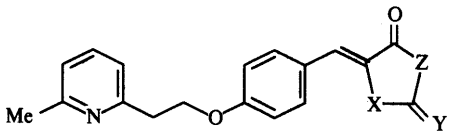
TABLE II. Physical and Biological Properties of 5-[4-[2-(2-Pyridyl)ethoxy]benzylidene]-2,4-thiazolidinediones (IIa)



No.	R	n	Yield[a] (%)	mp (°C)	Recrystn. solvent	Formula[b]	Hypoglycemic activity[c]	Plasma triglyceride lowering activity[c]
8	H	2	73	212—213	DMF–H_2O	$C_{17}H_{14}N_2O_3S$	44[e]	31[d]
9	3-Me	2	65	204—205	DMF–H_2O	$C_{18}H_{16}N_2O_3S$	48[e]	26[d]
10	5-Me	2	79	201—202	DMF–H_2O	$C_{18}H_{16}N_2O_3S$	31[d]	37
11	6-Me	2	78	181—182	MeOH	$C_{18}H_{16}N_2O_3S$	41[f]	41[d]
12	4,6-Me_2	2	45	181—182	EtOH	$C_{19}H_{18}N_2O_3S$	14	6
13	5-Et	1	71	223—224	DMF–H_2O	$C_{18}H_{16}N_2O_3S$	12	6
14	5-Et	2	64	165.5—167	AcOEt	$C_{19}H_{18}N_2O_3S$	38[d]	24[d]
15	5-Et(*E*)[h]	2		181—182	CH_2Cl_2–EtOH	$C_{19}H_{18}N_2O_3S$	47[f]	58[f]
16			83	219—220	DMF–H_2O	$C_{18}H_{16}N_2O_3S$	−1	8
	Pioglitazone						54[g]	47[e]

a) Yield from the corresponding benzaldehydes (VIII). *b*) All compounds were analyzed for C, H, and N; analytical results obtained for these elements were within ±0.4% of calculated values. *c*) Maximum reduction in blood glucose and plasma triglyceride levels at the dosage of 0.01% diet were calculated as percentage reduction with respect to the control value. *d*) $p<0.05$. *e*) $p<0.02$. *f*) $p<0.01$. *g*) $p<0.001$. *h*) *E*-Isomer of **14**.

TABLE III. Physical and Biological Properties of the Benzylidene-Type Analogues (IIb)



No.	X	Y	Z	Yield[a] (%)	mp (°C)	Recrystn. solvent	Formula[b]	Hypoglycemic activity[c]	Plasma triglyceride lowering activity[c]
11[e]	S	O	NH					31[d]	16
17	S	S	NH	89	197—198	$CHCl_3$–EtOH	$C_{18}H_{16}N_2O_2S_2$	16	4
18	S	S	NCH_2CO_2H	75	206—207	$CHCl_3$–MeOH	$C_{20}H_{18}N_2O_4S_2$	−20	−10
19	NH	O	NH	67	195—196	CH_2Cl–EtOH	$C_{18}H_{17}N_3O_3$	7	−15
20	NH	S	NH	85	183—185	Acetone–hexane	$C_{18}H_{17}N_3O_2S$	−2	5
21	NH	S	S	50	173—175	Acetone–hexane	$C_{18}H_{16}N_2O_2S_2$	0	21

a) Yield from the corresponding benzaldehyde. *b*) All compounds were analyzed for C, H, and N; analytical results obtained for these elements were within ±0.4% of calculated values. *c*) Maximum reduction in blood glucose and plasma triglyceride levels at the dosage of 0.005% diet were calculated as percentage reduction with respect to the control value. *d*) $p<0.05$. *e*) See Table II.

pyridylethoxy)benzylidene]-2,4-thiazolidinediones (IIa) were equipotent to pioglitazone, indicating that the *p*-alkoxybenzyl or *p*-alkoxybenzylidene moiety is essential for activity. We also arrived at an alternative method for the synthesis of pioglitazone using catalytic hydrogenation of the 5-benzylidene-2,4-thiazolidinedione derivative (**14**) prepared by Knoevenagel condensation of the corresponding aldehyde and 2,4-thiazolidinedione. In addition, we determined that the benzylidene intermediate (**14**) was *Z*-form.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi IR-260-10 or a Jasco IR-810 spectrophotometer. NMR spectra were recorded on a Varian EM-390 or a Varian Gemini-200 spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are given in ppm with tetramethylsilane as the internal standard, and the following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, td=triplet of doublets, br=broad.

5-[4-(2-Arylthioethyl)benzyl]-2,4-thiazolidinediones (I) A typical example to illustrate the general procedure is given below.

5-[4-[2-(2-Pyridyl)ethylthio]benzyl]-2,4-thiazolidinedione (2): A mixture of 2-imino-5-[4-[2-(2-pyridyl)ethylthio]benzyl]-4-thiazolidinone (5.00 g), 2 N HCl (40 ml), and EtOH (40 ml) was refluxed for 16 h. After removal of EtOH, the reaction mixture was neutralized with aq. $NaHCO_3$ to give **2** as crystals. Recrystallization from $CHCl_3$–EtOH gave colorless prisms (4.14 g, 83%), mp 162—164 °C. IR ν_{max}^{KBr} cm^{-1}: 3450, 1700, 1600. ^{1}H-NMR (DMSO-d_6) δ: 2.9—3.55 (6H, m), 4.88 (1H, dd, J=9, 4.5 Hz), 7.1—7.4 (6H, m), 7.68 (1H, td, J=8, 2 Hz), 8.49 (1H, dd, J=6, 2 Hz), 12.0 (1H, br s). *Anal.* Calcd for $C_{17}H_{16}N_2O_2S_2$: C, 59.28; H, 4.68; N, 8.13. Found: C, 59.17; H, 4.68; N, 7.86.

The other compounds (I) listed in Table I were prepared similarly.

5-Benzylidene-2,4-thiazolidinediones (IIa) A typical example to illustrate the general procedure is given below.

5-[4-[2-(6-Methyl-2-pyridyl)ethoxy]benzylidene]-2,4-thiazolidinedione (11): A mixture of 4-[2-(6-methyl-2-pyridyl)ethoxy]benzaldehyde (1.21 g), 2,4-thiazolidinedione (0.59 g), piperidine (0.33 g), and EtOH (50 ml) was refluxed for 16 h. The reaction mixture was poured into H_2O and acidified with AcOH to give **11** as crystals (1.34 g, 78%). Recrystallization from MeOH gave colorless prisms, mp 181—182 °C. IR ν_{max}^{KBr} cm^{-1}: 1730, 1695, 1685. ^{1}H-NMR (DMSO-d_6) δ: 2.43 (3H, s), 3.13 (2H, t, J=6.5 Hz), 4.40 (2H, t, J=6.5 Hz), 6.95—7.7 (7H, m), 7.71 (1H, s). *Anal.* Calcd for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23. Found: C, 63.40; H, 4.84; N, 8.30.

The other 5-benzylidene-2,4-thiazolidinediones (IIa) listed in Table II were prepared similarly.

5-[4-[2-(6-Methyl-2-pyridyl)ethoxy]benzylidene]rhodanine (17) A mixture of 4-[2-(6-methyl-2-pyridyl)ethoxyl]benzaldehyde (1.21 g), rhodanine (0.67 g), piperidine (0.39 g), and EtOH (50 ml) was refluxed for 40 min. The reaction mixture was poured into H_2O and acidified with AcOH to give **17** as crystals (1.60 g, 89%). Recrystallization from $CHCl_3$–EtOH gave pale yellow prisms, mp 197—198 °C. IR ν_{max}^{KBr} cm^{-1}: 3450, 1700. ^{1}H-NMR (DMSO-d_6) δ: 2.44 (3H, s), 3.15 (2H, t, J=6.5 Hz), 4.42 (2H, t, J=6.5 Hz), 6.95—7.7 (7H, m), 7.56 (1H, s). *Anal.* Calcd for $C_{18}H_{16}N_2O_2S_2$: C, 60.65; H, 4.52; N, 7.86. Found: C, 60.69; H, 4.72; N, 8.12.

5-[4-[2-(6-Methyl-2-pyridyl)ethoxy]benzylidene]rhodanine-3-acetic Acid (18) A mixture of 4-[2-(6-methyl-2-pyridyl)ethoxy]benzaldehyde (1.21 g), rhodanine-3-acetic acid (0.96 g), piperidine (0.85 g), and EtOH (50 ml) was refluxed for 1 h. The reaction mixture was poured into H_2O and acidified with AcOH to give **18** as crystals (1.57 g, 75%). Recrystallization from $CHCl_3$–MeOH gave pale yellow prisms, mp 206—207 °C. IR ν_{max}^{KBr} cm^{-1}: 3450, 1705. ^{1}H-NMR (DMSO-d_6) δ: 2.42 (3H, s), 3.14 (3H, t, J=6.5 Hz), 4.43 (2H, t, J=6.5 Hz), 4.71 (2H, s), 7.0—7.25 (4H, m), 7.5—7.7 (3H, m), 7.81 (1H, s). *Anal.* Calcd for $C_{20}H_{18}N_2O_4S_2$: C, 57.96; H, 4.38; N, 6.76. Found: C, 57.68; H, 4.25; N, 6.61.

5-[4-[2-(6-Methyl-2-pyridyl)ethoxy]benzylidene]hydantoin (19) A mixture of 4-[2-(6-methyl-2-pyridyl)ethoxy]benzaldehyde (1.00 g), hydantoin (0.42 g), pyrrolidine (0.15 g), and EtOH (50 ml) was refluxed for 24 h. The reaction mixture was poured into H_2O to give **19** as crystals (0.90 g, 67%). Recrystallization from CH_2Cl_2–EtOH gave colorless prisms, mp 195—196 °C. IR ν_{max}^{KBr} cm^{-1}: 3230, 1740, 1725, 1660, 1605. ^{1}H-NMR (DMSO-d_6) δ: 2.43 (3H, s), 3.10 (2H, t, J=6.5 Hz), 4.38 (2H, t, J=6.5 Hz), 6.34 (1H, s), 6.85—7.7 (7H, m), 10.37 (1H, br s), 11.09 (1H, br s). *Anal.* Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 67.03; H, 5.22; N, 13.30.

5-[4-[2-(6-Methyl-2-pyridyl)ethoxy]benzyl]-2-thiohydantoin (20) A mixture of 4-[2-(6-methyl-2-pyridyl)ethoxy]benzaldehyde (0.70 g), 2-thiohydantoin (0.35 g), piperidine (0.20 g), and EtOH (30 ml) was refluxed for 1.5 h. The reaction mixture was poured into H_2O to give **20** as crystals (0.84 g, 85%). Recrystallization from acetone–hexane gave pale yellow prisms, mp 183—185 °C. IR ν_{max}^{KBr} cm^{-1}: 3450, 1730, 1660, 1600. ^{1}H-NMR (DMSO-d_6) δ: 2.42 (3H, s), 3.12 (2H, t, J=6.5 Hz), 4.39 (2H, t, J=6.5 Hz), 6.43 (1H, s), 6.8—7.2 (4H, m), 7.5—7.8 (3H, m), 12.00 (1H, br s), 12.25 (1H, br s). *Anal.* Calcd for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.68; H, 4.96; N, 12.20.

4-[4-[2-(6-Methyl-2-pyridyl)ethoxy]benzylidene]-2-thioxo-5-thiazolidinone (21) A mixture of 4-[2-(6-methyl-2-pyridyl)ethoxy]benzaldehyde (3.75 g), 2-thioxo-5-thiazolidinone (2.09 g), piperidine (0.85 g), and AcOH (100 ml) was refluxed for 2 h. After removal of the solvent, the residue was treated with H_2O to give **21** as crystals (2.80 g, 50%). Recrystallization from acetone–hexane gave yellow prisms, mp 173—175 °C. IR ν_{max}^{KBr} cm^{-1}: 3450, 1705. ^{1}H-NMR (DMSO-d_6) δ: 2.46 (3H, s), 3.23 (2H, t, J=7 Hz), 3.75 (2H, t, J=7 Hz), 6.79 (2H, d, J=9 Hz), 6.96 (1H, s), 7.09 (2H, d, J=7.5 Hz), 7.60 (1H, d, J=7.5 Hz), 8.11 (2H, d, J=9 Hz), 10.34 (1H, br s). *Anal.* Calcd for $C_{18}H_{16}N_2O_2S_2$: C, 60.65; H, 4.52; N, 7.86. Found: C, 60.93; H, 4.52; N, 7.87.

4-(2-Arylethylthio)anilines (IV) A typical example to illustrate the general procedure is given below.

4-[2-(2-Pyridyl)ethylthio]aniline: A mixture of 2-vinylpyridine (4.32 g) and 4-aminothiophenol (4.63 g) was stirred at room temperature for 30 min. The reaction mixture was purified by column chromatography using silica gel and CH_2Cl_2 as the eluent to give an oil (7.96 g, 93%). IR ν_{max}^{neat} cm^{-1}: 3340, 3225, 1620. ^{1}H-NMR δ: 2.49 (3H, s), 2.8—3.3 (4H, m), 3.68 (2H, br s), 6.57 (2H, d, J=8.5 Hz), 7.24 (2H, d, J=8.5 Hz), 7.0—7.35 (2H, m), 7.56 (1H, td, J=7.5, 2 Hz), 8.51 (1H, dd, J=6, 2 Hz).

The other compounds (IV) listed in Table IV were prepared similarly.

5-[4-(2-Arylethylthio)benzyl]-2-imino-4-thiazolidinone (VI) A typical example to illustrate the general procedure is given below.

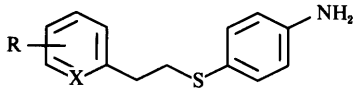
2-Imino-5-[4-[2-(2-pyridyl)ethylthio]benzyl]-4-thiazolidinone: A solution of $NaNO_2$ (2.31 g) in H_2O (10 ml) was added to a stirred and ice-cooled mixture of 4-[2-(2-pyridyl)ethylthio]aniline (7.00 g), 47% HBr (14.0 ml), and MeOH–acetone (1 : 1, v/v, 100 ml). The mixture was stirred at 5 °C for 30 min, and then methyl acrylate (15.5 g) was added to the mixture. The temperature was raised to 35 °C and Cu_2O (0.3 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated *in vacuo*, diluted with H_2O, neutralized with conc. NH_4OH, and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give crude methyl 2-bromo-3-[4-[2-(2-pyridyl)-ethylthio]phenyl]propionate as an oil. A mixture of the oil, thiourea (1.98 g), sodium acetate (2.13 g), and EtOH (50 ml) was refluxed for 2 h. The reaction mixture was poured into H_2O to give crystals which were collected by filtration and washed with Et_2O. Yield: 5.40 g (52%). Recrystallization from EtOH gave colorless prisms, mp 189—190 °C. IR ν_{max}^{KBr} cm^{-1}: 3400, 1700, 1620. ^{1}H-NMR (DMSO-d_6) δ: 2.88 (1H, dd, J=14, 9.5 Hz), 3.00 (2H, t, J=7.5 Hz), 3.2—3.5 (3H, m), 4.57 (1H, dd, J=9.5, 4 Hz), 7.15—7.3 (6H, m), 7.70 (1H, td, J=7.5, 2 Hz), 8.50 (1H, br d, J=5 Hz), 8.69 (1H, br s), 8.92 (1H, br s). *Anal.* Calcd for $C_{17}H_{17}N_3OS_2$: C, 59.45; H, 4.99; N, 12.23. Found: C, 59.60; H, 5.07; N, 11.86.

The other compounds (VI) listed in Table V were prepared similarly.

4-[2-(2-Pyridyl)ethoxy]benzonitriles (VII) A typical example to illustrate the general procedure is given below.

4-[2-(6-Methyl-2-pyridyl)ethoxy]benzonitrile: Sodium hydride (60% in oil, 29.0 g) was added gradually to a stirred and ice-cold solution of 6-methyl-2-pyridylethanol (97.2 g) and 4-fluorobenzonitrile (85.8 g) in tetrahydrofuran (THF 600 ml). After stirring for 2 h, the reaction mixture

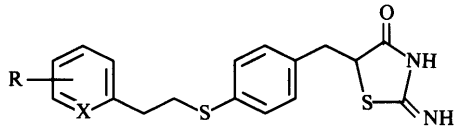
TABLE IV. 4-(2-Arylethylthio)anilines (IV)



R	X	Yield (%)[a]	Formula[b]
H	CH	91	$C_{14}H_{15}NS$
3-Me	N	90	$C_{14}H_{16}N_2S$
5-Me	N	76	$C_{14}H_{16}N_2S$
6-Me	N	96	$C_{14}H_{16}N_2S$
4,6-Me_2	N	66	$C_{15}H_{18}N_2S$
5-Et	N	95	$C_{15}H_{18}N_2S$

a) Yield from the corresponding vinylarenes (III). *b*) Oily compounds were used for the next reaction after silica gel column chromatography.

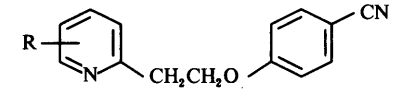
TABLE V. 5-[4-(2-Arylethylthio)benzyl]-2-imino-4-thiazolidinones (VI)



R	X	Yield (%)[a]	mp (°C)	Recrystn. solvent	Formula[b]
H	CH	50	Oil[c]	—	$C_{18}H_{18}N_2OS_2$
3-Me	N	58	207—208	$CHCl_3$–MeOH	$C_{18}H_{19}N_3OS_2$
5-Me	N	46	203—204	$CHCl_3$–EtOH	$C_{18}H_{19}N_3OS_2$
6-Me	N	34	169.5—171	Acetone–hexane	$C_{18}H_{19}N_3OS_2$
4,6-Me_2	N	28	Oil[c]	—	$C_{19}H_{21}N_3OS_2$
5-Et	N	59	185—187	EtOH	$C_{19}H_{21}N_3OS_2$

a) Yield from the corresponding anilines (IV). *b*) See foot note *b* of Table I. *c*) See footnote of *b* of Table IV.

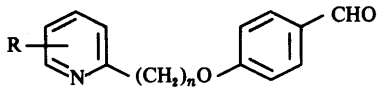
TABLE VI. 4-[2-(2-Pyridyl)ethoxy]benzonitriles (VII)

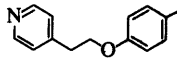


R	Yield (%)[a]	mp (°C)	Recrystn. solvent	Formula[b]
H	36	Oil[c]	—	$C_{14}H_{12}N_2O$
3-Me	49	98—99	AcOEt–hexane	$C_{15}H_{14}N_2O$
5-Me	53	74—75	AcOEt–hexane	$C_{15}H_{14}N_2O$
4,6-Me_2	29	87—88	AcOEt–hexane	$C_{16}H_{16}N_2O$
5-Et	67	Oil[c]	—	$C_{16}H_{16}N_2O$

a) Yield from the corresponding 2-pyridylethanols. *b*) See footnote *b* of Table I. *c*) See footnote *b* of Table IV.

TABLE VII. 4-[2-(2-Pyridyl)alkoxy]benzaldehydes (VIII)



R	n	Yield (%)[a]	mp (°C)	Recrystn. solvent	Formula[b]
H	2	80	Oil[c]	—	$C_{14}H_{13}NO_2$
3-Me	2	78	69—70	Et_2O–hexane	$C_{15}H_{15}NO_2$
5-Me	2	83	73—74	AcOEt–hexane	$C_{15}H_{15}NO_2$
4,6-Me_2	2	73	69—70	Et_2O–hexane	$C_{16}H_{17}NO_2$
5-Et	1	75[d]	52—53	Et_2O–hexane	$C_{15}H_{15}NO_2$
5-Et	2	70	Oil[c]	—	$C_{16}H_{17}NO_2$
		82	Oil[c]	—	$C_{15}H_{15}NO_2$

a) Yield from the corresponding 4-(2-pyridylethoxy)benzonitriles (VII). *b*) See footnote *b* of Table I. *c*) See footnote *b* of Table IV. *d*) Prepared by alkylation of 4-hydroxybenzaldehyde with 2-chloromethyl-5-ethylpyridine.

was poured into H_2O and extracted with Et_2O. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residual crystals were recrystallized from hexane to give colorless prisms (85.9 g, 50%), mp 66—67 °C. IR ν_{max}^{KBr} cm^{-1}: 2215, 1600. ^{1}H-NMR δ: 2.52 (3H, s), 3.22 (2H, t, J=6.5 Hz), 4.39 (2H, t, J=6.5 Hz), 6.8—7.65 (7H, m). *Anal.* Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.62; H, 6.01; N, 11.73.

The other compounds (VII) listed in Table VI were prepared similarly.

4-[2-(2-Pyridyl)ethoxy]benzaldehydes (VIII) A typical example to illustrate the general procedure is given below.

4-[2-(6-Methyl-2-pyridyl)ethoxy]benzaldehyde: A mixture of 4-[2-(6-methyl-2-pyridyl)ethoxy]benzonitrile (9.62 g), Raney Ni alloy (10.0g), and 75% HCO_2H (150 ml) was refluxed for 1 h. After removal of the alloy by filtration, the filtrate was diluted with H_2O, made alkaline with 4 N KOH, and extracted with Et_2O. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residual crystals were recrystallized from Et_2O–hexane to give colorless prisms (6.20 g, 64%), mp 53—54 °C. IR ν_{max}^{KBr} cm^{-1}: 1695, 1600. ^{1}H-NMR δ: 2.52 (3H, s), 3.23 (2H, t, J=6.5 Hz), 4.42 (2H, t, J=6.5 Hz), 6.8—7.2 (4H, m), 7.49 (1H, t, J=7.5 Hz), 7.78 (2H, d, J=9 Hz), 9.87 (1H, s). *Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.74; H, 6.16; N, 5.65.

The other compounds (VIII) listed in Table VII were prepared similarly.

One-Pot Synthesis of 4-[2-(5-Ethyl-2-pyridyl)ethoxy]benzaldehyde: A mixture of 2-(5-ethyl-2-pyridyl)ethanol (15.0 g), benzyltributylammonium chloride (50%, 6.0 g), *p*-toluenesulfonyl chloride (23.0 g), and CH_2Cl_2 (100 ml) was added to a solution of NaOH (5.0 g) In H_2O (30 ml). After stirring at room temperature for 2 h, a mixture of 4-hydroxybenzaldehyde (12.0 g), NaOH (8.0 g), and H_2O (100 ml) was added to the mixture, and then the resultant mixture was stirred at 40—50 °C for 12 h. The organic layer was removed, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude oil, which was purified by column chromatography using SiO_2 to yield the title compound (15.8 g, 62%).

Catalytic Hydrogenation of 14 to Pioglitazone Pd-black (0.2 g) was added to a solution of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzylidene]-2,4-thiazolidinedione (**14**, 1.0 g) in dimethylformamide (DMF) (20 ml), and the resultant mixture was hydrogenated under 50 kg/cm^2 at 50 °C for 5 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo*. The residue was dissolved in 6 N HCl and neutralized with aq. $NaHCO_3$ to give crystals of pioglitazone (650 mg, 65%). *Anal.* Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86. Found: C, 63.73; H, 5.65; N, 7.84.

(*E*)-5-[4-[2-(5-Ethyl-2-pyridyl)ethoxy]benzylidene]-2,4-thiazolidinedione (15) A solution of **14** (800 mg) in acetonitrile (1.2 l) was irradiated for 45 min in a quartz tube with a 400W high pressure mercury-vapor lamp with continuous bubbling of N_2 gas. After removal of the solvent, the residue was purified by column chromatography and recrystallized from CH_2Cl_2–EtOH to yield pure **15** as colorless needles, mp 181—182 °C. IR ν_{max}^{KBr} cm^{-1}: 3420, 1710, 1690, 1605. ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7.5 Hz), 2.59 (2H, q, J=7.5 Hz), 3.17 (2H, t, J=6.5 Hz), 4.41 (2H, t, J=6.5 Hz), 6.98 (2H, d, J=9 Hz), 7.29 (1H, d, J=8 Hz), 7.30 (1H, s), 7.58 (1H, dd, J=8, 2 Hz), 8.02 (2H, d, J=9 Hz), 8.38 (1H, d, J=2 Hz), 12.24 (1H, br s). *Anal.* Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.12; N, 7.90. Found: C, 64.06; H, 5.15; N, 7.93.

Acknowledgement The authors are grateful to Drs. H. Iwatsuka, T. Fujita, and Y. Kawamatsu for encouragement throughout this work.

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