Synthesis and Biological Activity of Metabolites of the Antidiabetic, Antihyperglycemic Agent Pioglitazone

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Pioglitazone (5-(4-(2-(5-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione, **2**) is a prototypical antidiabetic thiazolidinedione that had been evaluated for possible clinical development. Metabolites **6**−**9** have been identified after dosing of rats and dogs. Ketone **10** has not yet been identified as a metabolite but has been added to the list as a putative metabolite by analogy to alcohol **6** and ketone **7**. We have developed improved syntheses of pioglitazone (**2**) metabolites **6**−**9** and the putative metabolite ketone **10**. These entities have been compared in the KKA^{y} mouse model of human type-II diabetes to pioglitazone (**2**). Ketone **10** has proven to be the most potent of these thiazolidinediones in this *in vivo* assay. When **6**−**10** were compared *in vitro* in the 3T3-L1 cell line to **2**, for their ability to augment insulin-stimulated lipogenesis, **10** was again the most potent compound with **6**, **7**, and **9** roughly equivalent to **2**. These data suggest that metabolites **6**, **7**, and **9** are likely to contribute to the pharmacological activity of pioglitazone (**2**), as had been previously reported for ciglitazone (**1**).

Introduction

Non-insulin-dependent diabetes mellitus (NIDDM) is a metabolic disease characterized by a reduction in the response of the peripheral target tissues to insulin and the inability of pancreatic insulin reserves to overcome this reduced response.[1,2] The incidence of the disease has been estimated to be approximately 5% of the population and to contribute in excess of 105 billion dollars to the health care costs (approximately 15% of the total health care cost) in the United States.[3] Current opinion holds that although there may be many genetic factors involved and pancreatic dysfunction is a prequisite for the clinical expression of NIDDM, the trigger for the development of NIDDM is the reduced responsiveness of the peripheral tissues to insulin, or insulin resistance. Thus, there is reason to believe that improvement of insulin sensitivity of the target tissues may not only reduce the consequences of established disease but actually prevent the development of NIDDM.[4,5] A successful therapy of this modality would likely have a substantial impact on health care costs.[6,7]

Although the biochemical basis for insulin resistance remains to be defined, thiazolidinediones and related analogs have been identified which either prevent or protect against experimental insulin resistant states which occur genetically or are induced by dietary or hormonal means.[8−12] These compounds appear to augment the insulin-signaling cascade, although the mechanism by which these compounds exert their effects on the sensitivity of target cells to insulin also remains to be elucidated.[9−14] Several studies have shown that analogs of this class, in addition to augmenting the insulin-signaling cascade in insulin target cells, increase the rate of differentiation of preadipocytes in culture.[15] Hence, it is possible to evaluate the biological activity of these compounds *in vivo* in animals exhibiting reduced insulin sensitivity and *in vitro* using cell models for adipocyte differentiation.

Most productive has been the use of murine models of insulin resistance which have given rise to the discovery of compounds such as the thiazolidinedione ciglitazone (**1**).[7,16−17] Analysis of the structure−activity relationship of related compounds has given rise to at least four entities that are or have been in clinical development: pioglitazone (**2**)[18] (Takeda Chemical Industries, Inc./Upjohn), troglitazone (**3**)[19] (Sankyo and Parke-Davis), englitazone (**4**)[20,21] (Pfizer), and BRL 49653 (**5**)[22] (SmithKline Beecham).

Pioglitazone (5-(4-(2-(5-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione, **2**) is a prototypical antidiabetic thiazolidinedione that has been evaluated for possible clinical development (*vide supra*). In the course of characterizing this compound, the metabolic fate of pioglitazone in laboratory animals was investigated.[23−25] Metabolites **6**−**9** (Figure 2) have been identified after the dosing of rats and dogs. Ketone **10** (Figure 2) has not yet been identified as a metabolite but has been added to the list as a putative metabolite by analogy to alcohol **6** and ketone **7**. We wished to develop improved syntheses of compounds **6**−**10**[26] in order to evaluate their biological profile *in vitro* and *in vivo*. These data would be of value as they would aid in the interpretation of the *in vivo* activity of pioglitazone (**2**). That is, is there a portion of the antihyperglycemic activity and duration of action of **2** which might be more appropriately attributed to its metabolites? These studies might also serve as a prelude to the possible selection of a metabolite of pioglitazone (**2**) as a second-generation thiazolidinedione clinical candidate. Such a compound might have an improved half-life and a simpler metabolic pattern and fate when compared to **2**.

Chemistry

We elected to pursue the synthesis of metabolites **6**−**8** from a common pyridine precursor, methyl 6-methylnicotinate, to maximize the utility of common precursors. In order to minimize the impact of an increase in the

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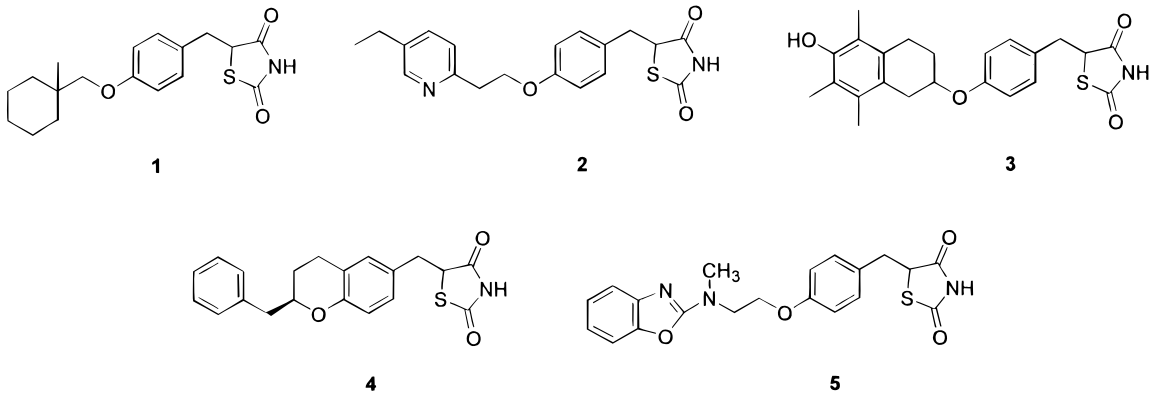


Figure 1. Representative thiazolidinedione antihyperglycemic agents **1**−**5**.

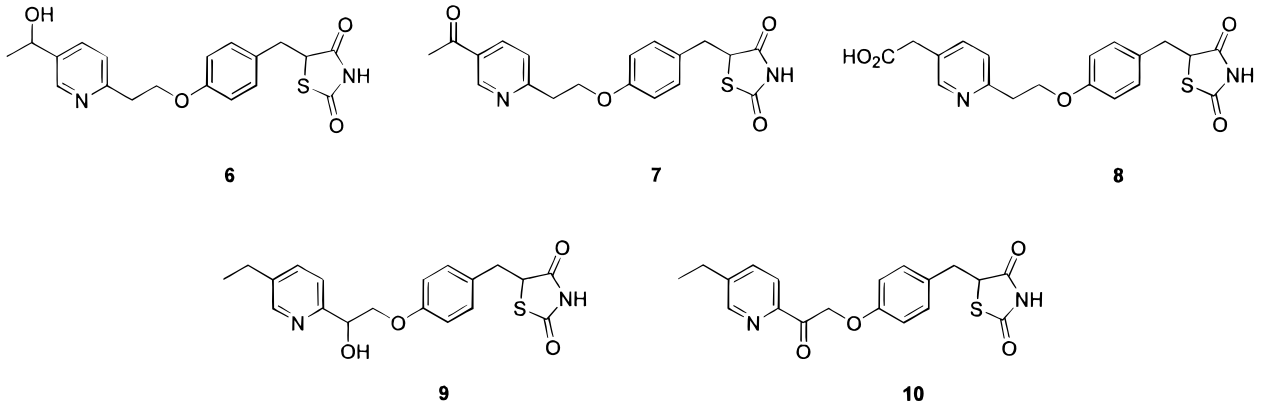
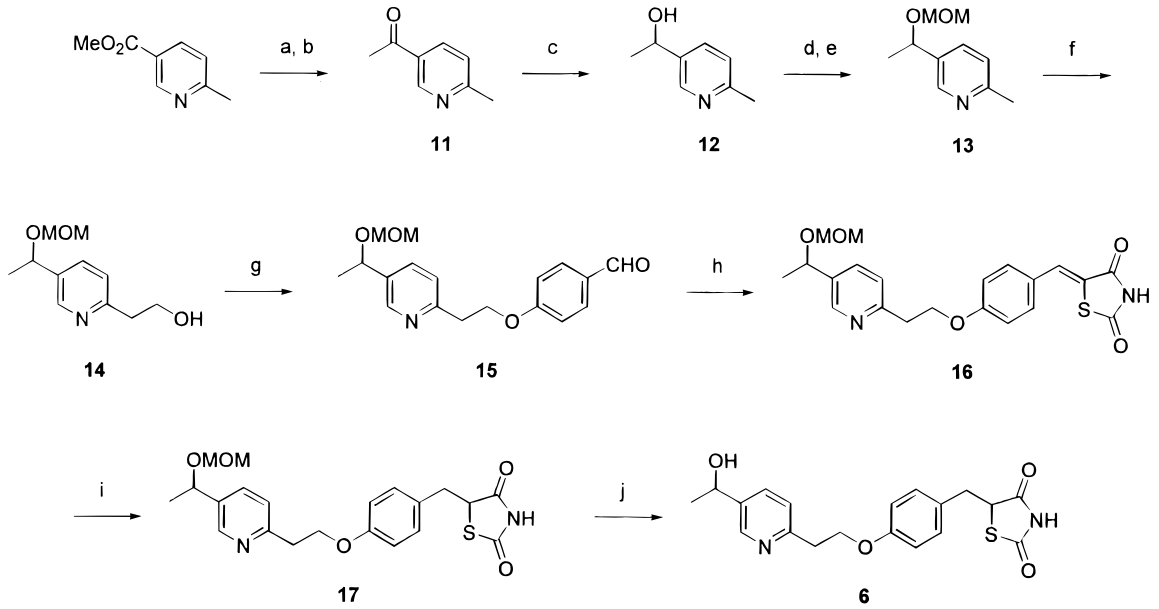


Figure 2. Rat and dog metabolites **6**−**9** of pioglitazone (**2**) and putative metabolite (**10**).

Scheme 1[a]

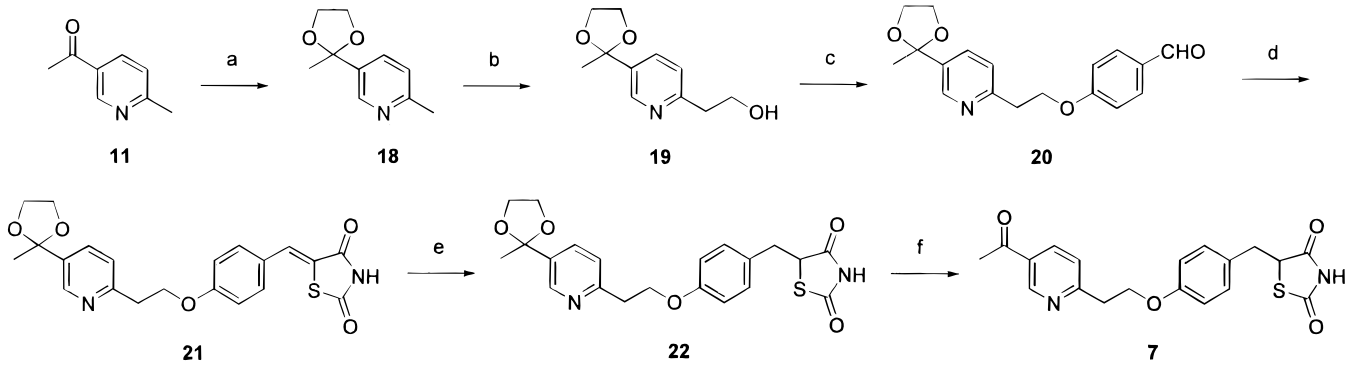


[a] (a) NaH, EtOAc; (b) 10% aqueous H_2SO_4, Δ; (c) $NaBH_4$; (d) NaH, (e) MOMCl; (f) 37% aqueous CH_2O, 170 °C; (g) DEAD, Ph_3P, 4-HOPhCHO; (h) 2,4-thiazolidinedione, piperidine, EtOH, Δ; (i) $NaBH_4$, $CoCl_2$, dimethylglyoxime; (j) 2 N aqueous HCl, Δ.

number of steps in the terminal stage of a linear synthesis, we planned to pursue three separate routes to the target metabolites. One each for alcohol **6** and ketone **7** and a third for acid **8**.

Our synthesis of **6** is presented in Scheme 1. Methyl 6-nicotinate was treated with sodium hydride and ethyl acetate to give the related β-keto ester which was immediately decarboxylated (aqueous H_2SO_4, Δ) to afford 6-methyl-3-acetylpyridine (**11**)[27] (48%). The ketone was smoothly reduced with sodium borohydride (EtOH, 0 °C), leading to the known pyridylethanol **12** in 90% yield.[26] Treatment of the pyridylethanol **12** with sodium hydride (DMF, 0 °C) formed the sodium salt. The mixture was cooled in a dry ice/2-propanol bath, chloromethyl methyl ether was added, and the reaction was then quenched at 0 °C to furnish **13** in 79% distilled yield. A mixture of methylpyridine **13** and 1.05 equiv of 37% aqueous formaldehyde was heated to 170 °C in a sealed (Teflon screw cap), thick walled glass tube (6 h) to give 27% of **14**[18,26,27] and 57% of recovered **13**. The

Scheme 2[a]



[a] (a) Ethylene glycol, pTsOH (1.25 equiv), toluene, Δ; (b) 37% aqueous CH_2O, 150 °C; (c) DEAD, Ph_3P, 4-HOPhCHO; (d) 2,4-thiazolidinedione, piperidine, EtOH, Δ; (e) $NaBH_4$, $CoCl_2$, dimethylglyoxime; (f) 2 N aqueous HCl, Δ.

connection of **13** to the central aryl ring was accomplished *via* a Mitsunobu coupling[28] between **14** and 4-hydroxybenzaldehyde to give **15** in reproducible 60−65% yields.

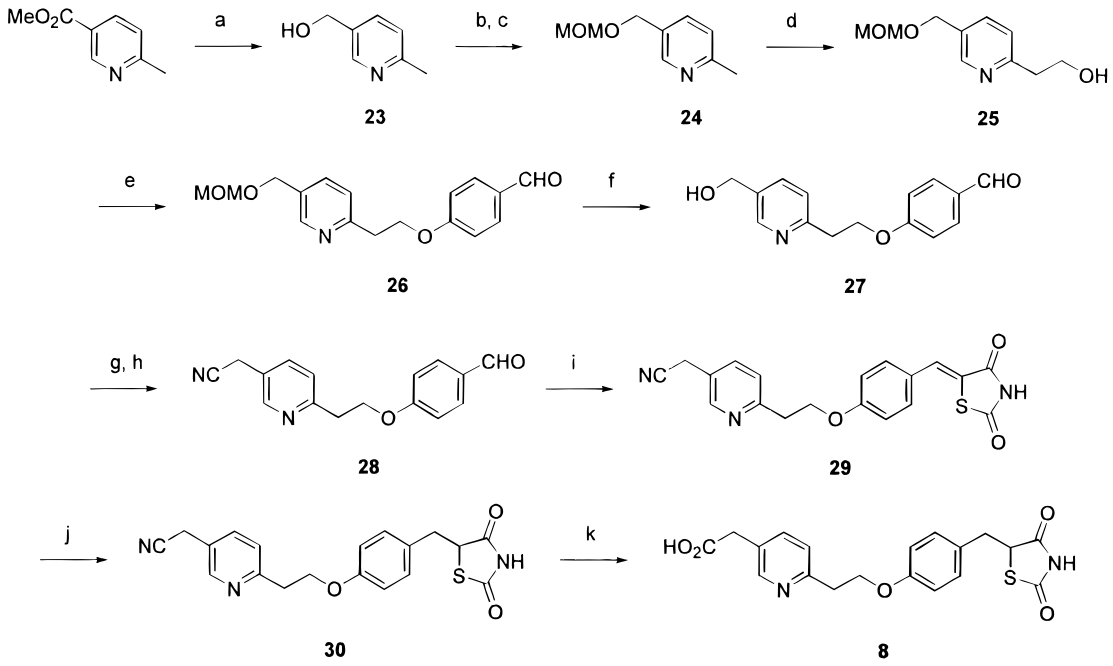
Aldehyde **15** was then subjected to "*standard*" Knoevenagel condensation conditions as defined by Takeda[18,26] (EtOH, piperidine (0.2 equiv), 2,4-thiazolidinedione (1.5 equiv)) to provide a 58% yield of the target protected dehydropioglitazone metabolite **17**. The completion of the synthesis endeavor required the selective reduction of the benzylidenethiazolidinedione, with preservation of the benzylic C−O bond, followed by deprotection to give **6**. Toward that end we utilized a modified conjugate reduction protocol[29] of Pfaltz[30] to reduce the double bond. A stirring mixture of $CoCl_2 \cdot 6H_2O$ and dimethylglyoxime in THF/H_2O containing aqueous NaOH was treated with $NaBH_4$ to produce a deep blue mixture. The reducing mixture was cooled in an ice-water bath and olefin **16** was added. The reaction mixture was carefully monitored by TLC, and the reaction was quenched upon the disappearance of olefin **16** (3 h) to give compound **17** (61%). The MOM ether was removed by treatment of a suspension of **17** in MeOH with 2 N aqueous HCl at reflux for 2 h, to give **6** in 98% yield.

Our next target, **7**, was prepared as outlined in Scheme 2. 6-Methyl-3-acetylpyridine (**11**) was treated with ethylene glycol and 1.25 equiv of pTsOH in toluene (Δ, H_2O) to give ketal **18** in 92% yield. The reaction of **18** with 1.0 equiv of 37% aqueous formaldehyde at 150 °C for 5 h afforded a 24% yield of **19** with 62% of **18** recovered. Pyridylethanol **19** was smoothly coupled (Ph_3P, DEAD) with 4-hydroxybenzaldehyde to provide **20** (55%) which readily underwent condensation with 2,4-thiazolidinedione to give the dehydro ketal **21** (56%). Reduction[29,30] as before ($CoCl_2$, $NaBH_4$, dimethylglyoxime) furnished **22** (96%), which led to **7** after ketal hydrolysis with 2 N aqueous HCl (98%).

Having successfully prepared quantities of **6** and **7**, we turned our attention to the preparation of the carboxylic acid metabolite **8**. As a result of the acid stability of **2** as well as the acid stability of the metabolites prepared to date (**6**, **7**), we designed a synthetic path to **8** which would unmask the terminal -COOH in an acid-mediated nitrile hydrolysis step. The synthesis of acid **8** is presented in Scheme 3. Methyl 6-methylnicotinate was reduced with LAH/THF to give pyridylmethanol **23** (85%) which was then protected as the related MOM ether **24** (MOMCl, NaH, DMF, −20 °C; 73%). Ether **24** was treated with 37% aqueous formaldehyde and heated in a glass tube in a 150 °C oil bath for 5 h to afford a 29% yield of (hydroxyethyl)-pyridine **25** and 60% of recovered pyridine **24**. Pyridine **25** was then coupled with 4-hydroxybenzaldehyde, in Mitsunobu fashion, to give aldehyde **26** in 58% yield. The MOM ether was removed by treatment of **26** with 2 N aqueous HCl in methanol to give **27**. Alcohol **27** could be transformed to nitrile **28** *via* the intermediacy of an unisolated (chloromethyl)pyridine, prepared according to the procedure of Carlson *et al.*[31] In the event, alcohol **27** was treated with thionyl chloride in refluxing chloroform to furnish the related chloride which was immediately reacted with KCN in DMF to provide a 61% yield of nitrile **28**. The condensation of **28** with 2,4-thiazolidinedione (piperidine, EtOH) was uneventful, leading to **29** in 65% yield. The reduction of benzylidenethiazolidinedione **29** proved to be somewhat problematic. When the reaction conditions which had been successfully employed in the preparations of **6** and **7** ($CoCl_2$, $NaBH_4$, dimethylglyoxime) were extended to the reduction of **29**, the results were poor or no double-bond reduction occurred. We finally resorted to a modification of these conditions[29] ($CoCl_2$, $NaBH_4$, 2,2′-dipyridyl) to obtain an acceptable 56% yield of **30**. Completion of the synthesis of **8** was realized after the exposure of **30** to refluxing 4 N aqueous HCl to give a 72% yield of the target metabolite **8**.

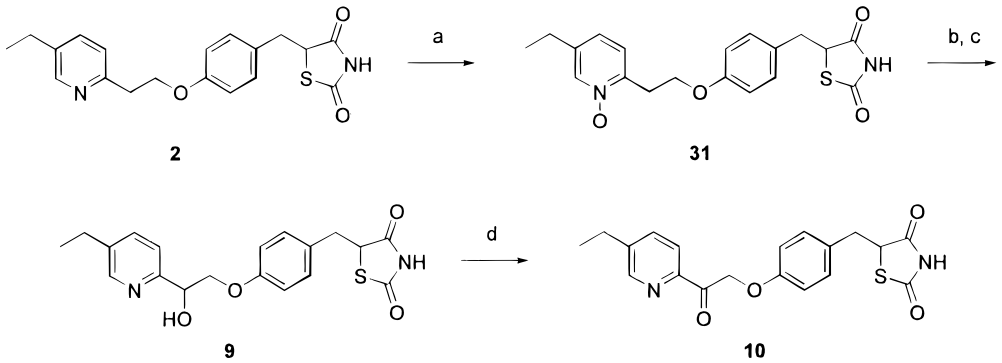
The remaining two targets, **9** and the putative metabolite **10**, were synthesized as described in Scheme 4. Pioglitazone (**2**) was oxidized (MCPBA) to give the related *N*-oxide **31** in 96% yield. *N*-Oxide **31** was then submitted to a modification of the procedure of Boekelheide[32] to effect the desired rearrangement. Toward that end, pioglitazone *N*-oxide (**31**) was treated with trifluoracetic anhydride (TFAA) in refluxing methylene chloride for 2 h. After cooling to room temperature, the solvent, trifluoroacetic acid, and excess TFAA were removed *in vacuo*, and the residue was dissolved in THF. To the resulting solution was added saturated aqueous $NaHCO_3$ until CO_2 evolution ceased to give **9** in 74% yield. The putative metabolite **10** would be realized upon oxidation of alcohol **9**. After considerable experimentation, we settled on a modified DMSO oxidation reported by Taber[33] for the conversion of **9** to **10**. A solution of **6** in DMSO and methylene chloride was cooled in an ice-water bath and treated in order with P_2O_5 and triethylamine to give **10** (crude) as a light yellow solid which required simple chromatographic

Scheme 3[a]



[a] (a) LAH, THF; (b) NaH; (c) MOMCl; (d) 37% aqueous CH_2O, 150 °C; (e) DEAD, Ph_3P, 4-HOPhCHO; (f) 2 N aqueous HCl, MeOH; (g) $SOCl_2$, $CHCl_3$, Δ; (h) KCN, DMF; (i) 2,4-thiazolidinedione, piperidine, EtOH, Δ; (j) $NaBH_4$, $CoCl_2$, 2,2′-dipyridyl; (k) 4 N aqueous HCl, Δ.

Scheme 4[a]



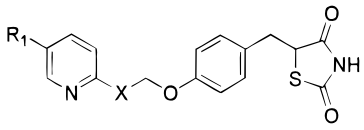
[a] (a) MCPBA, CH_2Cl_2; (b) TFAA, CH_2Cl_2, Δ; (c) aqueous $NaHCO_3$, THF; (d) DMSO, P_2O_5, Et_3N, CH_2Cl_2.

purification (88% purified yield). With the target metabolites in hand, we proceeded to evaluate their activity as potential antihyperglycemic agents in the KKA^y mouse model of type-II diabetes[34] and the facility with which they enhance the insulin-regulated differentiation of 3T3-L1 cells to adipocytes.[15]

Results and Discussion

Antihyperglycemic activity was determined in obese, hyperglycemic, hyperinsulinemic, insulin resistant KKA^y mice.[18,34] These mice are a cross between glucose intolerant black KK female mice and obese yellow male A^y mice. Animals were grouped into treatment and control groups (n = 6) through pretest blood glucose measurements by bleeding from the retroorbital sinus with glucose levels measured with an Alpkem glucose autoanalyzer.[35] Treatment groups had the selected compound administered as a food admixture at 100 mg/kg for 4 days. The glucose level for the treated group (T) over the control group (C) was utilized to determine the antihyperglycemic activity of the test compounds. Pioglitazone (**2**) was dosed at 100 mg/kg as the positive control, and results are reported as a T/C value. A compound with a T/C value of 0.85 is considered active in this model of diabetes.

Table 1. Antihyperglycemic Activity of Compounds **2** and **6**−**10**



no.	R_1	X	antihyperglycemic assay in KKA^y mice T/C
2	CH_2CH_3	CH_2	0.49
6	$CH(OH)CH_3$	CH_2	0.74
7	$COCH_3$	CH_2	0.74
8	CH_2CO_2H	CH_2	0.91
9	CH_2CH_3	CHOH	0.78
10	CH_2CH_3	CO	0.39

Metabolites **6**−**9** and pioglitazone (**2**) were examined in the KKA^y mouse as a measure of their ability to function as antihyperglycemic agents. These results are presented in Table 1. Pioglitazone (**2**), the positive control, effectively lowered blood glucose in the KKA^y mice providing a T/C = 0.49. Carboxylic acid **8** is

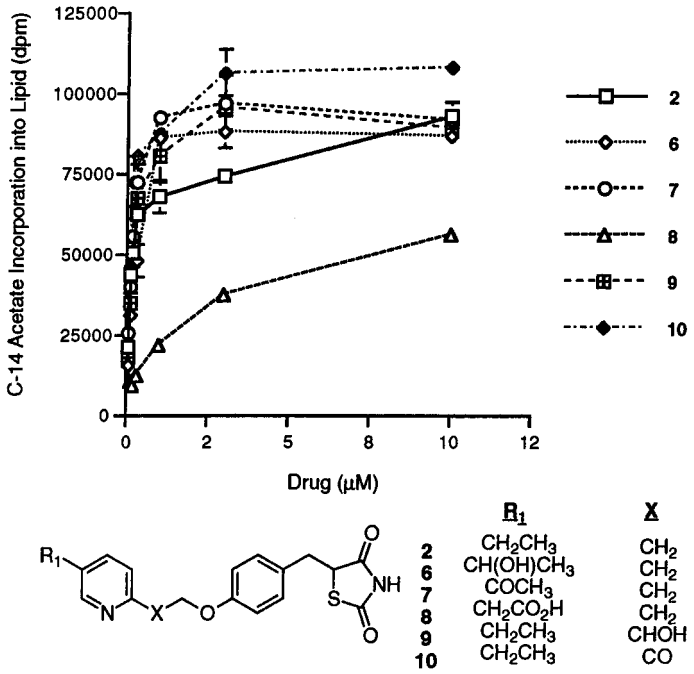


Figure 3. Thiazolidinedione-mediated augmentation of insulin-stimulated lipogenesis *in vitro*; [^{14}C]acetate incorporation into lipid in 3T3-L1 cells.

inactive as an antihyperglycemic agent in the KKA^{y} mouse, exhibiting a T/C = 0.91. The hydroxylated metabolites **6** and **9** and ketone **7** behaved similary in this assay, providing T/C values of 0.74, 0.78, and 0.74, respectively, an indication of modest antihyperglycemic activity. By comparison, ketone **10** exhibited antihyperglycemic activity in the KKA^{y} mice, with a T/C = 0.39. A perusal of these results does not immediately provide a rationale for this activity based upon position of metabolism, polarity, or electronic effects.

As a second measure of activity, we examined the ability of thiazolidinediones **6**−**10** to augment insulin-stimulated lipogenesis *in vitro*. The 3T3-L1 cell line, in the presence of the appropriate hormonal signals, undergoes differentiation from a fibroblastic adipoblast to a mature adipocyte capable of carrying out insulin-regulated lipogenesis.[15] Pioglitazone (**2**) has been reported to markedly enhance the insulin-regulated differentiation of 3T3-L1 adipocytes.[15] 3T3-L1 cells were staged to differentiate by incubation for 48 h in medium containing 1 μM dexamethasone and 0.5 mM 3-isobutyl-1-methylxanthine. Confluent cells were then incubated in Dubelco's modified Eagle's medium containing 5% fetal calf serum with insulin (150 nM) with and without added thiazolidinedione (0−10 μM). Forty-eight hours after time 0 (addition of insulin and compound), the cells received a 1 h pulse of [^{14}C]acetate and were then harvested. The ability of the target metabolites **6**−**9**, and the putative metabolite **10**, to enhance insulin-regulated differentiation of 3T3-L1 was measured versus pioglitazone (**2**) as a positive control utilizing the incorporation of [^{14}C]acetate into lipid (Figure 3) as the determinant of activity. Lipogenesis in the 3T3-L1 cells was measured, as this is the index of the fully differentiated phenotype of the adipocyte and pioglitazone (**2**) has been previously shown[15] to enhance the rate of insulin-stimulated lipogenesis in these cells. Figure 3 presents these results.

Pioglitazone (**2**) produced an augmentation of insulin-stimulated lipogenesis in a dose-dependant fashion which resulted in a ^{14}C incorporation of *ca.* 92 000 dpm at 10 μM **2**. As might have been expected from the results in the KKA^{y} mouse model, compounds **6**, **7**, and **9** were active in the 3T3-L1 cell assay. At the highest dose (10 μM) they were virtually indistinguishable from pioglitazone (**2**). However these metabolites were much more efficient than **2** in stimulating lipid synthesis at the 3 μM dose. Carboxylic acid **8** was quite poor in its ability to stimulate lipid synthesis at all drug levels. Ketone **10** provided high levels of [^{14}C]acetate incorporation into lipid at 1 μM (87 000 dpm), 3 μM (106 000 dpm), and 10 μM (108 000 dpm).

The *in vitro* activities of **2**, **8**, and **10** can be favorably compared with their *in vivo* activity in KKA^{y} mice in that **10** is more potent than **2** and **8** is essentially inactive. The comparison of alcohols **6** and **9** and ketone **7** with pioglitazone (**2**) and ketone **10** are more difficult to make, and perhaps these *in vivo* data reflect differences in biodistribution and pharmacokinetics in the mouse model.

In conclusion, we have developed improved syntheses of pioglitazone (**2**) metabolites **6**−**9**. We have also prepared the putative metabolite ketone **10**. These entities have been compared to pioglitazone (**2**) in the KKA^{y} mouse model of human type-II diabetes for their ability to serve as insulin-sensitizing antihyperglycemic agents. Ketone **10** has proven to be the most potent of these thiazolidinediones in this *in vivo* assay. When **6**−**10** were compared *in vitro* in the 3T3-L1 cell line to **2** for their ability to augment insulin-stimulated lipogenesis, **10** was again the most potent compound with **6**, **7**, and **9** roughly equivalent to **2** in prolipogenetic activity. These data suggest that metabolites **6**, **7**, and **9** are likely to contribute to the pharmacological activity of pioglitazone (**2**), as had been previously reported for the metabolites of ciglitazone,[37] provided that the metabolic profile of **2** in the mouse resembles that reported for the rat and dog.[23−25] The *in vitro* and *in vivo* biological activities presented for ketone **10** suggest its potential as a pioglitazone antihyperglycemic con-

gener with somewhat greater potency and the possibility of a simpler metabolic profile.

Experimental Section

All reagents were used as received unless otherwise stated. All reactions were performed under a blanket of nitrogen, in oven (150 °C)-dried glassware with rigid exclusion of moisture from all reagents and glassware unless otherwise mentioned. Melting points were determined on a Mettler FP62 melting point apparatus and are uncorrected. Proton magnetic resonance spectra (^{1}H-NMR) were recorded on a Bruker AM-300 instrument at 300 MHz in deuteriochloroform unless otherwise indicated. Chemical shifts are reported in parts per million (δ scale) from internal tetramethylsilane. Data are reported as follows: chemical shifts (multiplicity (s = singlet, brs = broad singlet, dd = doublet of doublets, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration). ^{13}C-NMR spectra were recorded on a Bruker AM-300 instrument at 75.4 MHz as solutions in deuteriochloroform unless otherwise indicated. Thin layer chromatography (TLC) was performed on E. Merck silica gel GF254 plates. Spots were made visible with UV light and/or exposure to I_2 vapors and/or dipping into a solution of ammonium molybdate (75 g) and ceric sulfate (2.5 g) in water and concentrated sulfuric acid (500 mL; 9:1, v/v) followed by heating. Flash column chromatography was performed according to the procedure of Still *et al*.[38] and eluted with the solvents specified.

Biological Procedures. (1) *In Vivo* Antihyperglycemic Activity. Obese, hyperglycemic, insulin resistant male KKA^y mice, 10−12 weeks of age, were obtained from the Upjohn colony and used as a model for insulin resistant diabetes (type-II).[18,34] These mice are a cross between glucose intolerant black KK female mice and obese yellow male A^y mice. The yellow offspring KKA^y mice are obese, hyperglycemic, and insulin resistant at 10−12 weeks of age.[35] KKA^y mice were housed individually in shoebox cages and provided food (powdered laboratory chow) and water *ad libitum*. Animals were grouped into treatment and control groups (n = 6) through pretest blood glucose measurements, by bleeding from the retroorbital sinus with glucose levels measured with an Alpkem glucose autoanalyzer.[35] Treatment groups had the selected compound administered as a food admixture at 100 mg/kg for 4 days. Weights of the animals were measured and recorded on day 1 and at 0730 h on day 5. At 0800 h on day 5 from the start of treatment, animals were bled from the retroorbital sinus and glucose levels were measured. The glucose level for the treated group (T) over the control group (C) was utilized to determine the antihyperglycemic activity of the test compounds. Pioglitazone (**2**) was dosed at 100 mg/kg as the positive control, and results are reported as a T/C value.

(2) *In Vitro* Enhancement of Insulin-Regulated Differentiation of 3T3-L1 Cells to Adipocytes. The 3T3-L1 cell line, in the presence of the appropriate hormonal signals, undergoes differentiation from a fibroblastic adipoblast to a mature adipocyte capable of carrying out insulin-regulated lipogenesis.[15] Pioglitazone (**2**) has been reported to markedly enhance the insulin-regulated differentiation of 3T3-L1 adipocytes.[15] The 3T3-L1 cell line was from the American Type Culture Collection. Cells were maintained in Dubelco's modified Eagle's medium containing 5% fetal calf serum and 10 μg/mL gentamicin. Cells were staged to differentiate by incubation for 48 h in medium containing 1 μM dexamethasone and 0.5 mM 3-isobutyl-1-methylxanthine. Confluent cells were then incubated in Dubelco's modified Eagle's medium containing 5% fetal calf serum with insulin (150 nM) with and without added thiazolidinedione (0−10 μM) for 48 h. Cells were then incubated with [^{14}C]acetate for 1 h, and lipid was extracted into 2-propanol.[15] [^{14}C]Acetate incorporated into 2-propanol extractable material was quantitated by liquid scintillation counting.

3-Acetyl-6-methylpyridine (11). To a mechanically stirred suspension of sodium hydride (32.7 g of a 60%, w/w, oil dispersion, 818 mmol) in toluene (400 mL) and *N*,*N*-dimethylformamide (41 mL) was added approximately 10% of a solution of methyl 5-methyl-nicotinate (61.8 g, 408 mmol) in ethyl acetate (85 mL), and the mixture was heated at 80 °C for 30 min. The remainder of the solution was added slowly over 2 h while maintaining an internal temperature of approximately 80 °C. After cooling to room temperature, the reaction mixture was diluted with water (1 L) and thoroughly extracted with ethyl acetate (3 × 1 L) and methylene chloride (2 × 1 L). The combined organic extracts were evaporated *in vacuo*, and the residue was heated under reflux in 10% (v/v) sulfuric acid (300 mL) for 2 h. After cooling to 0 °C, the reaction mixture was neutralized with solid K_2CO_3 and extracted with ethyl acetate (1.5 L). The organic extract was dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give the crude ketone as a red-orange viscous liquid. The crude product was purified by distillation under reduced pressure to give 33.3 g (60%) of the desired methyl ketone **11** as a clear, pale yellow, viscous liquid: bp 58−60 °C (0.01 mmHg); TLC (Merck; acetone−CH_2Cl_2, 1:9, UV(+)) R_f = 0.31; ^{1}H-NMR ($CDCl_3$) δ 9.05 (d, J = 2.2 Hz, 1), 8.13 (dd, J = 8.1, 2.2 Hz, 1), 7.27 (d, J = 8.1 Hz, 1), 2.64 (s, 3), 2.62 (s, 3).

3-(1-Hydroxyethyl)-6-methylpyridine (12). To a stirring solution of ketone **11** (23.7 g, 175 mmol) in absolute EtOH (200 mL) at 0 °C was added $NaBH_4$ (3.32 g, 87.7 mmol) portionwise over 1 h. The reaction mixture was stirred at 0 °C for 1.5 h before warming to room temperature. The mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 450 g, 70 mm o.d., acetone−CH_2Cl_2, 1:3, 250 mL fractions), using the flash technique. Fractions 7−43 afforded 21.5 g (90%) of the target alcohol **12** as a clear, colorless oil: TLC (Merck; acetone−CH_2Cl_2, 1:3, UV(+)) R_f = 0.18; ^{1}H-NMR ($CDCl_3$) δ 8.30 (d, J = 2.2 Hz, 1), 7.63 (dd, J = 8.0, 2.3 Hz, 1), 7.11 (d, J = 8.0 Hz, 1), 4.87 (q, J = 6.5 Hz, 1), 4.01 (brs, 1), 2.48 (s, 3), 1.48 (d, J = 6.5 Hz, 3).

3-(1-(Methoxymethoxy)ethyl)-6-methylpyridine (13). A 60% (w/w) oil dispersion of NaH (3.35 g, 83.8 mmol) was washed with hexanes (3 × 10 mL) and suspended in DMF (40 mL). The suspension was cooled to 0 °C, and a solution of alcohol **12** (9.58 g, 69.8 mmol) in DMF (50 mL) was added over 1 h. The reaction mixture was stirred at 0 °C for 1.5 h and cooled to −78 °C, and chloromethyl methyl ether (6.4 mL, 83.8 mmol) was added over 15 min. After the mixture warmed to room temperature, the reaction was carefully quenched by the careful addition of H_2O. Then the mixture was partitioned between EtOAc (150 mL) and H_2O (150 mL). The aqueous phase was extracted with two additional portions of EtOAc (150 mL), and the combined organic extracts were washed with H_2O (3 × 150 mL) and brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 400 g, 70 mm o.d., acetone−CH_2Cl_2, 1:3, 250 mL fractions), using the flash technique. Fractions 4−9 were combined and evaporated *in vacuo* to give 10.05 g (79%) of the target compound **13** as a yellow oil: TLC (Merck; acetone−CH_2Cl_2, 1:9, UV(+)) R_f = 0.33; ^{1}H-NMR ($CDCl_3$) δ 8.46 (d, J = 2.1 Hz, 1), 7.60 (dd, J = 8.0, 2.3 Hz, 1), 7.16 (d, J = 8.0 Hz, 1), 4.77 (q, J = 6.6 Hz, 1), 4.57 (ABq, J = 20.8, 6.8 Hz, 2), 3.36 (s, 3), 2.57 (s, 3), 1.49 (d, J = 6.6 Hz, 3); IR (neat) 3408, 2976, 2889, 2823, 1603, 1571, 1492, 1450, 1404, 1374, 1220, 1156, 1106, 1039, 1025, 1001, 919, 861, 835, 739, 644 cm^{-1}; EI/MS (70 eV) 181 (M^+, 3.2), 166 (33.7), 149 (13.4), 136 (5.5), 120 (53.8), 45 (base); HRMS (EI) calcd for $C_{10}H_{15}NO_2$ (M^+) 181.1103, found 181.1101.

2-(5-(1-(Methoxymethoxy)ethyl)-2-pyridyl)ethanol (14). A stirring solution of the methylpyridine **13** (5.38 g, 29.7 mmol) and 37% aqueous formaldehyde (2.41 g, 29.7 mmol) was heated at 160 °C in a sealed glass tube for 5 h. After cooling to room temperature, the solvent was evaporated *in vacuo*. Residual H_2O was removed by azeotropic distillation of toluene (2×). The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 400 g, 70 mm o.d., packed and eluted with acetone−CH_2Cl_2, 25:75 (3 L), then MeOH−acetone−CH_2Cl_2, 2.5:25:72.5, 250 mL fractions), using the flash technique. Fractions 5−9 afforded 3.06 g (57%) of recovered starting methylpyridine **13**. Fractions 19−27 afforded 1.71 g

(27%) of the target (hydroxyethyl)pyridine **14** as a yellow oil: TLC (Merck; acetone−CH_2Cl_2, 25:75, UV(+)) R_f = 0.23; ^{1}H-NMR ($CDCl_3$) δ 8.46 (d, J = 2.1 Hz, 1), 7.66 (dd, J = 8.0, 2.3 Hz, 1), 7.20 (d, J = 8.0 Hz, 1), 4.79 (q, J = 6.6 Hz, 1), 4.5b (ABq, J = 23.6, 6.8 Hz, 2), 4.02 (t, J = 5.6 Hz, 2), 3.36 (s, 3), 3.04 (t, J = 5.6 Hz, 2), 1.49 (d, J = 6.6 Hz, 3); IR (neat) 3374, 2974, 2948, 2933, 1603, 1571, 1491, 1444, 1374, 1217, 1155, 1136, 1100, 1060, 1037, 998, 919, 850, 837 cm^{-1}; EI/MS (70 eV) 211 (M^+, 34.1), 194 (90.7), 181 (39.4), 166 (7.4), 150 (27), 134 (25.7), 120 (74), 45 (base); HRMS (EI) calcd for $C_{11}H_{17}NO_3$ (M^+) 211.1208, found 211.1213.

4-(2-(5-(1-(Methoxymethoxy)ethyl)-2-pyridyl)ethoxy)-benzaldehyde (15). To a stirring solution of the (hydroxyethyl)pyridine **14** (4.06 g, 19.2 mmol), *p*-hydroxybenzaldehyde (2.35 g, 19.2 mmol), and triphenylphosphine (5.54 g, 21.1 mmol) in THF (100 mL) at 0 °C was added diethyl azodicarboxylate (3.3 mL, 21.1 mmol) over 15 min. After stirring at room temperature for 18 h, the solvent was evaporated *in vacuo*. The resulting yellow oil was chromatographed on a column of silica gel (230−400 mesh, 300 g, 70 mm o.d., packed with acetone−CH_2Cl_2, 25:75, eluted with acetone−CH_2Cl_2, 35:65, 250 mL fractions), using the flash technique. Fractions 3−6 afforded an oily solid which consisted of the target compound **15** as a mixture with dicarbethoxyhydrazine. This material was treated with Et_2O−hexanes, 50:50, and the white solid (dicarbethoxyhydrazine) was removed by suction filtration. The mother liquor was evaporated *in vacuo*, and the residue was purified by chromatography on a column of silica gel (230−400 mesh, 500 g, 70 mm o.d., EtOAc−hexanes, 40:60, 250 mL fractions), using the flash technique. Fractions 13−30 were combined and evaporated *in vacuo* to give 3.75 g (62%) of the target compound **15** as a yellow oil: TLC (Merck; acetone−CH_2Cl_2, 10:90, UV(+)) R_f = 0.42; ^{1}H-NMR ($CDCl_3$) δ 9.87 (s, 1), 8.52 (d, J = 2.1 Hz, 1), 7.80 (m, 2), 7.64 (dd, J = 8.0, 2.3 Hz, 1), 7.28 (s, 1), 7.01 (d, J = 8.7 Hz, 2), 4.79 (q, J = 6.6 Hz, 1), 4.58 (ABq, J = 6.8 Hz, 2), 4.46 (t, J = 6.7 Hz, 2), 3.36 (s, 3), 3.30 (t, J = 6.6 Hz, 2), 1.49 (d, J = 6.6 Hz, 3); IR (Nujol) 2933, 2887, 2838, 2824, 1695, 1601, 1578, 1510, 1259, 1216, 1160, 1100, 1036, 1024 cm^{-1}; EI/MS (70 eV) 315 (M^+, 4.7), 284 (2.1), 270 (1.3), 254 (10.6), 224 (10.8), 210 (7.3), 194 (74.7), 181 (base); HRMS (EI) calcd for $C_{18}H_{21}NO_4$ (M^+) 315.1470, found 315.1479.

5-(4-(2-(5-(1-(Methoxymethoxy)ethyl)-2-pyridyl)ethoxy)-benzylidene)-2,4-thiazolidinedione (16). A stirring solution of aldehyde **15** (3.67 g, 11.6 mmol), 2,4-thiazolidinedione (1.36 g, 11.6 mmol), and piperidine (0.50 g, 5.82 mmol) in absolute EtOH (25 mL) was heated under reflux for 18 h. After cooling to room temperature, the solvent was evaporated *in vacuo*. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 500 g, 70 mm o.d., packed with acetone−CH_2Cl_2, 10:90, eluted with acetone−CH_2Cl_2, 10:90 (3 L), 20% acetone−CH_2Cl_2, 20:80 (2 L), and MeOH−acetone−CH_2Cl_2, 2.5:25:72.5, 250 mL fractions) using the flash technique. Fractions 17−23 afforded 2.77 g (58%) of the target compound **16** as a yellow solid (mp 122−123 °C): TLC (Merck; acetone−CH_2Cl_2, 10:90, UV(+)) R_f = 0.30; ^{1}H-NMR ($CDCl_3$) δ 8.52 (d, J = 2.1 Hz, 1), 7.72 (dd, J = 8.0, 2.2 Hz, 1), 7.64 (s, 1), 7.39 (d, J = 8.8 Hz, 2), 7.32 (d, J = 8.0 Hz, 1), 6.96 (d, J = 8.8 Hz, 2), 4.81 (q, J = 6.5 Hz, 1), 4.59 (ABq, J = 6.8 Hz, 2), 4.48 (t, J = 6.2 Hz, 2), 3.37 (s, 3), 3.35 (t, J = 6.2 Hz, 2), 1.51 (d, J = 6.5 Hz, 3); IR (Nujol) 1730, 1696, 1597, 1508, 1291, 1272, 1240, 1229, 1184, 1109, 1056, 1046, 1033, 1017 cm^{-1}; EI/MS (70 eV) 414 (M^+, 11.0), 353 (5.9), 221 (47.9), 194 (68.2), 181 (33.9), 178 (34.6), 150 (base). Anal. ($C_{21}H_{22}N_2O_5S$) C, H, N.

5-(4-(2-(5-(1-(Methoxymethoxy)ethyl)-2-pyridyl)ethoxy)-benzyl)-2,4-thiazolidinedione (17). To a stirring solution of $CoCl_2 \cdot 6H_2O$ (10 mg, 0.04 mmol) and 2,2′-dipyridyl (24.7 mg, 0.158 mmol) in H_2O (10 mL) was added 1.0 N NaOH (0.13 mL) followed by $NaBH_4$ (568 mg, 15.0 mmol), and the resulting deep blue mixture was cooled to 0 °C. A solution of the olefin **16** (1.85 g, 4.46 mmol) in DMF (15 mL) was added over 0.5 h. The reaction mixture stirred for 18 h at room temperature, and then an additional portion of $NaBH_4$ (250 mg) was added. After stirring for 24 h, acetic acid was added until the pH of the mixture was approximately 6. The mixture was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The crude product was dissolved in hot acetone/CH_2Cl_2 and purified by chromatography on a column of silica gel (230−400 mesh, 300 g, 70 mm o.d., acetone−CH_2Cl_2, 25:75, 250 mL fractions), using the flash technique. Fractions 5−9 afforded 1.13 g (61%) of the target compound **17** as an off-white solid (mp 130−132 °C): TLC (Merck; acetone−CH_2Cl_2, 10:90, UV(+)) R_f = 0.17; ^{1}H-NMR ($CDCl_3$) δ 8.51 (d, J = 2.2 Hz, 1), 7.64 (d, J = 6.0 Hz, 1), 7.28 (d, J = 8.0 Hz, 1), 7.12 (d, J = 8.6 Hz, 2), 6.83 (d, J = 8.6 Hz, 2), 4.79 (q, J = 6.5 Hz, 1), 4.58 (ABq, J = 6.8 Hz, 2), 4.46 (dd, J = 9.3, 3.9 Hz, 1), 4.32 (t, J = 6.4 Hz, 2), 3.42 (dd, J = 14.1, 3.9 Hz, 1), 3.36 (s, 3), 3.27 (t, J = 6.4 Hz, 2), 3.09 (dd, J = 14.1, 9.3 Hz, 1), 1.49 (d, J = 6.5, 3); IR (Nujol) 1705, 1514, 1252, 1165, 1152, 1058, 1034, 1022 cm^{-1}; EI/MS (70 eV) 416 (M^+, 2.3), 355 (8.4), 346 (2.1), 194 (92.1), 181 (base). Anal. ($C_{21}H_{24}N_2O_5S$) C, H, N.

5-(4-(2-(5-(1-Hydroxyethyl)-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione (6). To a stirring suspension of **17** (0.50 g, 1.20 mmol) in MeOH (20 mL) was added 2 N aqueous HCl (1.5 mL), and the resulting solution was heated under reflux for 2 h. After cooling to room temperature, the reaction mixture was evaporated *in vacuo*. The residue was dissolved in H_2O (25 mL), and the solution was neutralized with saturated aqueous $NaHCO_3$. The resulting white precipitate was collected by filtration, washed with H_2O, and dried. The crude product was purified by chromatography on a small column of silica gel (acetone−CH_2Cl_2−MeOH) to afford 0.43 g (98%) of **6** as an off-white solid (mp 153−158 °C): TLC (Merck; MeOH−CH_2Cl_2, 5:95, UV(+)) R_f = 0.15; ^{1}H-NMR ($CDCl_3$) δ 8.49 (d, J = 2.1 Hz, 1), 7.70 (dd, J = 8.0, 2.3 Hz, 1), 7.33 (d, J = 8.0 Hz, 1), 7.16 (d, J = 8.6 Hz, 2), 6.89 (d, J = 8.6 Hz, 2), 4.86 (dd, J = 9.0 Hz, 4.3, 1), 4.78 (q, J = 6.5, 1), 4.33 (t, J = 6.6 Hz, 2), 3.42 (brs, 1), 3.32 (dd, J = 14.1, 4.3 Hz, 1), 3.17 (dd, J = 8.1, 6.6 Hz, 2), 3.06 (dd, J = 14.1, 9.0 Hz, 1), 1.36 (d, J = 6.5, 3); IR (Nujol) 1611, 1515, 1473, 1333, 1318, 1253, 1162, 1023 cm^{-1}; EI/MS (70 eV) 372 (M^+, 11.8), 193 (7.7), 166 (5.1), 150 (base); HRMS (EI) calcd for $C_{19}H_{20}N_2O_4S$ (M^+) 372.1144, found 372.1139.

3-(2-Methyl-1,3-dioxolan-2-yl)-6-methylpyridine (18). To a stirring mixture of the methylacetylpyridine **11** (14.4 g, 106 mmol) in toluene (100 mL) were added ethylene glycol (8.9 mL, 160 mmol) and *p*-toluenesulfonic acid monohydrate (22.3 g, 117 mmol). The mixture was heated under reflux for 8 h, and H_2O was removed from the system through the use of a Dean−Stark trap. After cooling to room temperature, the reaction mixture was neutralized with K_2CO_3. The mixture was diluted with H_2O (100 mL) and extracted with EtOAc (150 mL). The organic extract was washed with H_2O and brine (150 mL each), dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give the desired ketal **6** as a light yellow oil. Distillation afforded 17.4 g (92%) of **18** as a clear, colorless, viscous liquid (bp 67−68 °C, 0.06 mmHg): TLC (Merck; acetone−CH_2Cl_2, 10:90, UV(+)) R_f = 0.29; ^{1}H-NMR ($CDCl_3$) δ 8.61 (d, J = 2.1 Hz, 1), 7.66 (dd, J = 8.0, 2.3 Hz, 1), 7.13 (d, J = 8.0 Hz, 1), 4.06 (m, 2), 3.78 (m, 2), 2.56 (s, 3), 1.66 (s, 3); IR (Nujol) 3401, 3063, 3040, 1603, 1488, 1376, 1261, 1223, 1200, 1108, 1088, 1041, 1023, 949, 891, 873, 835, 738 cm^{-1}; EI/MS (70 eV) 164 (base), 120 (47.6), 87 (35.5), 42 (34.6). Anal. ($C_{10}H_{13}NO_2$) C, H, N.

2-(5-(2-Methyl-1,3-dioxolan-2-yl)-2-pyridyl)ethanol (19). A stirring solution of the ketal **18** (40.0 g, 223 mmol) and 37% aqueous formaldehyde (18.1 g, 223 mmol) was heated at 150 °C in a sealed glass tube for 5 h. After cooling to room temperature, the solvent was evaporated *in vacuo*, and residual H_2O was removed by azeotropic distillation with toluene (2 × 100 mL). The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 500 g, 70 mm o.d., packed and eluted with acetone−CH_2Cl_2, 25:75 (3 L), then MeOH−acetone−CH_2Cl_2, 2.5:25:72.5, 250 mL fractions), using the flash technique. Fractions 5−9 afforded 24.91 g (62%) of recovered starting material **18**. Fractions 12−30 afforded 11.36 g (24%) of the target (hydroxyethyl)pyridine **19** as a yellow oil: TLC (Merck; acetone−CH_2Cl_2, 25:75, UV(+)) R_f = 0.23; ^{1}H-NMR ($CDCl_3$) δ 8.62 (d, J = 2.2 Hz, 1), 7.74 (dd, J = 8.0, 2.3 Hz, 1), 7.17 (d, J = 8.0 Hz, 1), 4.05 (m, 4), 3.81 (m, 2), 3.03 (t, J = 5.5 Hz, 2), 1.66 (s, 3); IR (Nujol) 1600, 1567, 1488,

1448, 1260, 1203, 1103, 1092, 1052, 1044, 1029, 951, 868 cm^{-1}; EI/MS (70 eV) 209 (M^+, 60.7), 194 (46.5), 192 (base), 179 (48.8), 164 (72.2). Anal. ($C_{11}H_{15}NO_3$) C, H, N.

4-(2-(5-(2-Methyl-1,3-dioxolan-2-yl)-2-pyridyl)ethoxy)-benzaldehyde (20). To a stirring solution of the (hydroxyethyl)pyridine **19** (3.58 g, 17.1 mmol), *p*-hydroxybenzaldehyde (2.30 g, 18.8 mmol), and triphenylphosphine (4.94 g, 18.8 mmol) in THF (75 mL) at 0 °C was added a solution of diethyl azodicarboxylate (3.0 mL, 18.8 mmol) in THF (10 mL) over a period of 0.5 h. After stirring at room temperature for 18 h, the solvent was evaporated *in vacuo*. The resulting yellow oil was purified by chromatography on a column of silica gel (230−400 mesh, 200 g, 70 mm o.d., packed with acetone−CH_2Cl_2, 1:3, eluted with acetone−CH_2Cl_2, 35:65, 250 mL fractions), using the flash technique. Fractions 3−6 afforded an oily solid which consisted of the target compound **20** as a mixture with dicarbethoxyhydrazine. This material was treated with Et_2O−hexanes (1:1, 100 mL), and the white solid (dicarbethoxyhydrazine) was removed by filtration. The solvent was evaporated *in vacuo*, and the residue was purified by chromatography on a column of silica gel (230−400 mesh, 500 g, 70 mm o.d., EtOAc−hexanes, 2:3, 250 mL fractions), using the flash technique. Fractions 13−30 were combined and evaporated *in vacuo* to give 2.98 g (55%) of **20** as a pale yellow oil: TLC (Merck; acetone−CH_2Cl_2, 10:90, UV(+)) R_f = 0.35; ^{1}H-NMR ($CDCl_3$) δ 9.87 (s, 1), 8.67 (d, J = 2.2 Hz, 1), 7.82 (m, 2), 7.73 (dd, J = 7.9, 2.3 Hz, 1), 7.25 (d, J = 9.3 Hz, 1), 7.01 (m, 2), 4.46 (t, J = 6.6 Hz, 2), 4.07 (m, 2), 3.76 (m, 2), 3.30 (t, J = 6.6 Hz, 2), 1.67 (s, 3); IR (Nujol) 1694, 1600, 1578, 1510, 1259, 1216, 1200, 1161, 1039, 1022, 834 cm^{-1}; EI/MS (70 eV) 313 (M^+, 14.1), 298 (10.6), 192 (82.6), 179 (base). Anal. ($C_{18}H_{19}NO_4$) C, H, N.

5-(4-(2-(5-(2-Methyl-1,3-dioxolan-2-yl)-2-pyridyl)ethoxy)-benzylidene)-2,4-thiazolidinedione (21). A stirring solution of the aldehyde **20** (3.60 g, 11.5 mmol), 2,4-thiazolidinedione (1.35 g, 11.5 mmol), and piperidine (0.49 g, 5.74 mmol) in absolute EtOH (100 mL) was heated under reflux for 18 h. Upon cooling to room temperature, a precipitate formed. The mixture was cooled to 0 °C, and the solid was collected by filtration, washed with Et_2O, and dried *in vacuo* to afford 2.67 g (56%) of **21** as a light yellow solid (mp 163−164 °C): TLC (Merck; acetone−CH_2Cl_2, 10:90, UV(+)) R_f = 0.22; ^{1}H-NMR (DMSO-d_6) δ 8.35 (d, J = 2.2 Hz, 1), 7.53 (m, 2), 7.33 (d, J = 8.8 Hz, 2), 7.16 (dd, J = 8.1 Hz, 1), 6.89 (d, J = 8.8 Hz, 2), 4.24 (t, J = 6.5 Hz, 2), 3.79 (m, 2), 3.51 (m, 2), 3.15 (brs, 1), 3.00 (t, J = 6.5 Hz, 2), 1.37 (s, 3); IR (Nujol) 1731, 1696, 1596, 1509, 1289, 1271, 1235, 1184, 1165, 1055, 1039, 1031, 1017, 824 cm^{-1}; EI/MS (70 eV) 412 (M^+, 15.0), 221 (4.2), 192 (base). Anal. ($C_{21}H_{20}N_2O_5S$) C, H, N.

5-(4-(2-(5-(2-Methyl-1,3-dioxolan-2-yl)-2-pyridyl)ethoxy)-benzyl)-2,4-thiazolidinedione (22). To a stirring solution of $CoCl_2 \cdot 6H_2O$ (7.45 mg, 0.025 mmol) and dimethylglyoxime (116 mg, 1.00 mmol) in H_2O (40 mL) was added 1.0 N NaOH (4 drops) followed by $NaBH_4$ (568 mg, 15.0 mmol), and the resulting deep blue mixture was cooled to 0 °C. A solution of the olefin **21** (2.06 g, 5.00 mmol) in THF−DMF (2:1, 30 mL) was added over 0.5 h. The reaction mixture was allowed to slowly warm to room temperature and stirred for 18 h. Acetic acid was added until the pH of the mixture was approximately 6. The mixture was then diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 300 g, 70 mm o.d., packed with acetone−CH_2Cl_2, 10:90, eluted with acetone−CH_2Cl_2, 15:85, 220 mL fractions), using the flash technique. Fractions 8−12 afforded 1.99 g (96%) of the target compound **22** as a white solid (mp 59−61 °C): TLC (Merck; acetone−CH_2Cl_2, 10:90, UV(+)) R_f = 0.30; ^{1}H-NMR ($CDCl_3$) δ 8.67 (d, J = 2.1 Hz, 1), 7.73 (dd, J = 8.0, 2.2 Hz, 1), 7.26 (d, J = 8.0 Hz, 1), 7.13 (d, J = 8.6 Hz, 2), 6.84 (d, J = 8.6 Hz, 2), 4.47 (dd, J = 9.3, 3.9 Hz, 1), 4.32 (t, J = 6.4 Hz, 2), 4.07 (m, 2), 3.79 (m, 2), 3.42 (dd, J = 14.1, 3.8 Hz, 1), 3.27 (t, J = 6.4 Hz, 2), 3.10 (ABq, J = 14.1, 9.3 Hz, 1), 1.66 (s, 3); IR (Nujol) 1752, 1698, 1611, 1512, 1247, 1039, 1032 cm^{-1}; EI/MS (70 eV) 414 (M^+, 1.9), 399 (1.6), 344 (1.7), 223 (2.8), 192 (base); HRMS (EI) calcd for $C_{21}H_{22}N_2O_5S$ (M^+) 414.1249, found 414.1258.

5-(4-(2-(5-(1-Oxoethyl)-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione (7). To a stirring solution of **22** (2.72 g, 6.56 mmol) in THF (50 mL) was added 4 N HCl (50 mL), and the solution was stirred at room temperature for 18 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ (pH ≈ 7) and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and evaporated *in vacuo* to afford a pale yellow oil. Trituration with CH_2Cl_2 gave 2.38 g (98%) of **7** as a white solid which was recrystallized from EtOAc−hexanes (mp 106−107 °C); TLC (Merck; acetone−CH_2Cl_2, 10:90, UV(+)) R_f = 0.13; ^{1}H-NMR ($CDCl_3$) δ 9.65 (brs, 1), 9.11 (d, J = 1.9 Hz, 1), 8.19 (dd, J = 8.1, 2.3 Hz, 1), 7.41 (d, J = 8.1 Hz, 1), 7.12 (d, J = 8.6 Hz, 2), 6.82 (d, J = 8.6 Hz, 2), 4.48 (dd, J = 9.3, 3.9 Hz, 1), 4.36 (t, J = 6.2 Hz, 2), 3.42 (dd, J = 14.1, 3.9 Hz, 1), 3.34 (t, J = 6.2 Hz, 2), 3.10 (dd, J = 14.1, 9.3 Hz, 1), 2.63 (s, 3); IR (Nujol) 1703, 1612, 1600, 1514, 1333, 1316, 1276, 1250, 1181, 1159, 1032, 1024 cm^{-1}; EI/MS (70 eV) 370 (M^+, 2.3), 254 (4.5), 223 (5.1), 148 (base); HRMS (EI) calcd for $C_{19}H_{18}N_2O_4S$ (M^+) 370.0987, found 370.0992.

(6-Methyl-3-pyridyl)methanol (23). To a stirring suspension of lithium aluminum hydride (3.80 g, 100 mmol) in dry THF (100 mL) at 10 °C was added a solution of methyl 5-methylnicotinate (30.23 g, 200 mmol) in THF (125 mL) over 1.5 h. After the mixture stirred at 0 °C for 30 min, the reaction was carefully quenched by the slow addition of H_2O (25 mL). The reaction mixture was filtered through a pad of Celite, and the pad was thoroughly rinsed with Et_2O. The solution was dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The resulting crude alcohol was purified by distillation under reduced pressure (bp 98−100 °C, 0.65 mmHg) to furnish 18.74 g (73%) of the known alcohol[26] **23** as a clear liquid which crystallized upon cooling (mp 37−39 °C): TLC (Merck; MeOH−CH_2Cl_2, 1:9, UV(+)) R_f = 0.32; ^{1}H-NMR ($CDCl_3$) δ 8.30 (d, J = 2.03 Hz, 1), 7.60 (dd, J = 7.93, 2.23 Hz, 1), 7.12 (d, J = 7.94 Hz, 1), 4.87 (brs, 1), 4.63 (s, 2), 2.49 (s, 3).

3-((Methoxymethoxy)methyl)-6-methylpyridine (24). NaH (4.80 g of a 60% oil dispersion, 120 mmol) was washed with three portions of hexanes and suspended in DMF (25 mL). To the mechanically stirred suspension at −10 °C was added a solution of alcohol **23** (12.32 g, 100 mmol) in DMF (50 mL) over 1 h. After stirring for 30 min, the reaction mixture was cooled to −15 °C, and MOMCl (9.1 mL, 120 mmol) was added over 30 min. After the mixture stirred for 30 min, the reaction was quenched by the careful addition of H_2O. The reaction mixture was allowed to warm to room temperature and partitioned between H_2O (150 mL) and EtOAc (150 mL). The organic phase was washed with three portions of H_2O (100 mL) and brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 400 g, 70 mm o.d., acetone−CH_2Cl_2, 20:80, 210 mL fractions). Fractions 5−16 were combined and evaporated *in vacuo* to afford 12.22 g (73%) of the target methoxy methyl ether **24** as a yellow oil: TLC (Merck; MeOH−CH_2Cl_2, 5:95, UV(+)) R_f = 0.21; ^{1}H-NMR ($CDCl_3$) δ 8.48 (d, J = 2.1 Hz, 1), 7.58 (dd, J = 7.9, 2.3 Hz, 1), 7.15 (d, J = 8.0 Hz, 1), 4.70 (s, 2), 4.57 (s, 2), 3.40 (s, 3), 2.55 (s, 3).

2-(5-((Methoxymethoxy)methyl)-2-pyridyl)ethanol (25). A stirring solution of the methylpyridine **24** (40.0 g, 223 mmol) and 37% aqueous formaldehyde (18.1 g, 223 mmol) was heated at 150 °C (preheated oil bath) in a sealed glass tube for 5 h. After cooling to room temperature, the solvent was evaporated *in vacuo*, and residual H_2O was removed by azeotropic distillation with toluene (2 × 50 mL). The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 500 g, 70 mm o.d., packed and eluted with acetone−CH_2Cl_2, 25:75 (3 L), then MeOH−acetone−CH_2Cl_2, 2.5:25:72.5, 250 mL fractions), using the flash technique. Fractions 5−9 afforded 24.11 g (60%) of recovered **24**. Fractions 12−30 afforded 13.72 g (29%) of the target (hydroxyethyl)pyridine **25** as a yellow oil: TLC (Merck; MeOH−CH_2Cl_2, 10:90, UV(+)) R_f = 0.41; ^{1}H-NMR ($CDCl_3$) δ 8.62 (d, J = 2.2 Hz, 1), 7.74 (dd, J = 8.0, 2.3 Hz, 1), 7.17 (d, J = 8.0 Hz, 1), 4.05 (m, 4), 3.81 (m,

2), 3.03 (t, J = 5.5 Hz, 2), 1.66 (s, 3); IR (liquid) 3385, 3285, 2946, 2885, 1606, 1492, 1150, 1104, 1050, 1034, 920 cm^{-1}; EI/MS (70 eV) 197 (M^+, 16.5), 180 (42.5), 167 (21.1), 106 (39.4), 79 (base). Anal. ($C_{10}H_{15}NO_3$) C, H, N.

4-(2-(5-((Methoxymethoxy)methyl)-2-pyridyl)ethoxy)-benzaldehyde (26). To a stirring solution of (hydroxyethyl)-pyridine **25** (3.58 g, 17.1 mmol), *p*-hydroxybenzaldehyde (2.30 g, 18.8 mmol), and triphenylphosphine (4.94 g, 18.8 mmol) in THF (75 mL) at 0 °C was added a solution of diethyl azodicarboxylate (3.0 mL, 18.8 mmol) in THF (10 mL) over 15 min. After stirring at room temperature for 18 h, the solvent was evaporated *in vacuo* to furnish a yellow oil which was purified by chromatography on a column of silica gel (230−400 mesh, 200 g, 70 mm o.d., packed with acetone−CH_2Cl_2, 25:75, eluted with acetone−CH_2Cl_2, 35:65, 250 mL fractions), using the flash technique. Fractions 3−6 afforded an oily solid which consisted of the target compound **26** admixed with dicarbethoxyhydrazine. This material was treated with Et_2O−hexanes (1:1), and the white solid (dicarbethoxyhydrazine) was removed by filtration. The mother liquor was evaporated *in vacuo*, and the residue was purified by chromatography on a column of silica gel (230−400 mesh, 500 g, 70 mm o.d., EtOAc−hexanes, 2:3, 250 mL fractions), using the flash technique. Fractions 13−30 were combined and evaporated *in vacuo* to give 3.14 g (58%) of the target compound **26** as a clear, yellow oil: TLC (Merck; EtOAc−hexanes, 50:50, UV(+)) R_f = 0.20; ^{1}H-NMR ($CDCl_3$) δ 9.87 (s, 1), 8.67 (d, J = 2.2 Hz, 1), 7.82 (m 1), 7.73 (dd, J = 7.9, 2.3 Hz, 1), 7.25 (d, J = 9.3 Hz, 1), 7.01 (m, 2), 4.46 (t, J = 6.6 Hz, 2), 4.07 (m, 2), 3.76 (m, 2), 3.30 (t, J = 6.6 Hz, 2), 1.67 (s, 3); IR (Nujol) 1701, 1687, 1605, 1602, 1580, 1512, 1263, 1252, 1216, 1169, 1148, 1117, 1057, 1028, 1022, 837 cm^{-1}; EI/MS (70 eV) 301 (M^+, 3.6), 240 (2.6), 196 (9.8), 180 (71.7), 167 (base). Anal. ($C_{17}H_{19}NO_4$) C, H, N.

4-(2-(5-(Hydroxymethyl)-2-pyridyl)ethoxy)benzaldehyde (27). To a stirring solution of the MOM ether **26** (1.51 g, 5.00 mmol) in MeOH (5 mL) was added 2 N aqueous HCl (5 mL). The solution was heated under reflux for 2 h and then allowed to cool to room temperature, and the solvent was evaporated *in vacuo*. The residue was neutralized with saturated aqueous $NaHCO_3$ and then extracted with two portions (25 mL) of EtOAc. The combined extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 300 g, 70 mm o.d., packed and eluted with acetone−CH_2Cl_2, 20:80) using the flash technique. Fractions containing the desired alcohol **27** (as determined by TLC) were combined and evaporated *in vacuo* to afford 1.24 g (96%) of **27** as a white solid (mp 90−91 °C): TLC (Merck; MeOH−CH_2Cl_2, 5:95, UV(+)) R_f = 0.13; ^{1}H-NMR ($CDCl_3$) δ 9.84 (s, 1), 8.46 (d, J = 1.90 Hz, 1), 7.81 (dm, J = 8.76 Hz, 2), 7.68 (dd, J = 7.97, 2.20 Hz, 1), 7.26 (d, J = 7.97 Hz, 1), 6.97 (dm, J = 8.76 Hz, 2), 4.70 (s, 2), 4.41 (t, J = 6.53 Hz, 2), 3.47 (brs, 1), 3.26 (t, J = 6.53 Hz, 2); IR (Nujol) 3229, 1696, 1689, 1603, 1510, 1463, 1310, 1259, 1158, 1024, 825 cm^{-1}; EI/MS (70 eV) 257 (M^+, 3.8), 136 (base), 123 (97.1). Anal. ($C_{15}H_{15}NO_3$) C, H, N.

4-(2-(5-(Cyanomethyl)-2-pyridyl)ethoxy)benzaldehyde (28). To a stirring solution of the alcohol **27** (3.86 g, 15.0 mmol) in $CHCl_3$ (100 mL) was added $SOCl_2$ (11 mL, 150 mmol), and the solution was heated under reflux for 1 h. After cooling to room temperature, H_2O (100 mL) and $CHCl_3$ (100 mL) were added, and the mixture was neutralized with saturated aqueous $NaHCO_3$. The aqueous phase was separated and extracted with $CHCl_3$ (100 mL). The combined organic phases were washed with brine (200 mL), dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The resulting yellow oil was dissolved in DMF (75 mL), and KCN (1.47 g, 22.5 mmol) was added in one portion. The resulting reddish-brown mixture was stirred at room temperature for 16 h. The mixture was cast into H_2O (500 mL) and extracted with three portions of EtOAc (1 L total volume). The combined extracts were washed with H_2O (3 × 500 mL) and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 300 g, 70 mm o.d., packed with CH_2Cl_2, eluted with acetone−CH_2Cl_2, 10:90, 275 mL fractions), using the flash technique. Fractions 10−13 were combined and evaporated *in vacuo* to give 2.46 g (61%) of the target compound **28** as a yellow solid (mp 70−71 °C): TLC (Merck; acetone−CH_2Cl_2, 10:90, UV(+)) R_f = 0.31; ^{1}H-NMR ($CDCl_3$) δ 9.87 (s, 1), 8.52 (brd, J = 2.37 Hz, 1), 7.81 (dm, J = 6.76 Hz, 2), 7.67 (dd, J = 8.04, 2.37 Hz, 1), 7.33 (d, J = 8.04 Hz, 1), 6.99 (dm, J = 6.76 Hz, 2), 4.61 (t, J = 6.45 Hz, 2), 3.76 (s, 2), 3.31 (t, J = 6.45 Hz, 2); IR (Nujol) 3049, 3019, 2811, 1694, 1605, 1599, 1579, 1507, 1492, 1425, 1252, 1024, 833 cm^{-1}; EI/MS (70 eV) 266 (M^+, 6.1), 145 (base), 132 (65.5). Anal. ($C_{19}H_{17}N_3O_3S\cdot0.045CH_2Cl_2$) C, H, N.

5-(4-(2-(5-(Cyanomethyl)-2-pyridyl)ethoxy)benzylidene)-2,4-thiazolidinedione (29). A stirring solution of the aldehyde **28** (3.60 g, 11.5 mmol), 2,4-thiazolidinedione (1.35 g, 11.5 mmol), and piperidine (0.49 g, 5.74 mmol) in absolute EtOH (100 mL) was heated under reflux for 18 h. Upon cooling to room temperature, a precipitate formed. The mixture was cooled to 0 °C, and the solid was collected by filtration, washed with Et_2O, and dried to afford 3.10 g (65%) of the target compound **29** as a light yellow solid (mp 163−164 °C): TLC (Merck; acetone−CH_2Cl_2, 10:90, UV(+)) R_f = 0.24; ^{1}H-NMR (DMSO-d_6) δ 8.49 (d, J = 2.2 Hz, 2), 7.75 (s, 1), 7.74 (dd, J = 7.9, 2.2 Hz, 1), 7.53 (d, J = 8.8 Hz, 2), 7.42 (d, J = 7.9 Hz, 1), 7.09 (d, J = 8.8 Hz, 2), 4.44 (t, J = 6.5 Hz, 2), 4.07 (s, 2), 3.22 (t, J = 6.5 Hz, 2); IR (Nujol) 1731, 1695, 1597, 1512, 1256, 1181, 1160, 1017, 692 cm^{-1}; EI/MS (70 eV) 365 (M^+, 14.5), 221 (22.8), 150 (43.8), 145 (base). Anal. ($C_{19}H_{15}N_3O_3S\cdot0.28H_2O$) C, H, N.

5-(4-(2-(5-(Cyanomethyl)-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione (30). To a stirring solution of $CoCl_2\cdot6H_2O$ (8.4 mg, 0.028 mmol) and 2,2′-dipyridyl (176 mg, 1.12 mmol) in H_2O (40 mL) was added 1.0 N NaOH (4 drops) followed by $NaBH_4$ (568 mg, 15.0 mmol), and the resulting deep blue mixture was cooled to 0 °C. A solution of the olefin **29** (2.06 g, 5.00 mmol) in THF−DMF (2:1, 30 mL) was added over 0.5 h. The reaction mixture was allowed to slowly warm to room temperature and stirred for 18 h. Acetic acid was added until the pH of the mixture was *ca.* 6. The mixture was diluted with H_2O (25 mL) and extracted with two portions of CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 300 g, 70 mm o.d., packed with acetone−CH_2Cl_2, 10:90, eluted with acetone−CH_2Cl_2, 15:85, 220 mL fractions), using the flash technique. Fractions 8−12 afforded 1.03 g (56%) of the target compound **30** as a white solid (mp 128−129 °C): TLC (Merck; MeOH−CH_2Cl_2, 5:95, UV(+)) R_f = 0.20; ^{1}H-NMR (DMSO-d_6) δ 8.39 (d, J = 2.0 Hz, 1), 7.63 (dd, J = 8.0, 2.0 Hz, 1), 7.31 (d, J = 8.0 Hz, 1), 7.04 (d, J = 8.6 Hz, 2), 6.77 (d, J = 8.6 Hz, 2), 4.75 (dd, J = 9.1, 4.3 Hz, 1), 4.22 (t, J = 6.5 Hz, 2), 3.97 (s, 2), 3.20 (dd, J = 14.1, 4.3 Hz, 1), 3.08 (t, J = 6.5 Hz, 2), 2.94 (dd, J = 14.1, 9.1 Hz, 1); IR (Nujol) 3027, 3011, 2712, 2604, 1761, 1742, 1708, 1516, 1469, 1330, 1251, 1232, 1187, 1040, 1019, 828, 736 cm^{-1}; EI/MS (70 eV) 367 (M^+, 2.1), 251 (8.5), 223 (9.5), 145 (base), 132 (22.8); HRMS (EI) calcd for $C_{19}H_{17}N_3O_3S$ (M^+) 367.0991, found 367.0999.

5-(4-(2-(5-(Carboxymethyl)-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione (8). A stirring solution of **30** (0.404 g, 1.10 mmol) in 4 N aqueous HCl (20 mL) was heated under reflux for 18 h. The reaction mixture was cooled to room temperature, and the pH was adjusted to *ca.* 9 with 1 N aqueous NaOH. The solution was extracted with EtOAc (2 × 25 mL), the aqueous layer was retained, and the pH was adjusted to *ca.* 5 with acetic acid. The resulting cloudy solution was extracted with EtOAc−MeOH (9:1; 5 × 30 mL), and the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo* to provide 0.31 g (72%) of **8** as a white, powdery solid (mp 146−148 °C): TLC (Merck; MeOH−CH_2Cl_2, 5:95, UV(+)) R_f = 0.15; ^{1}H-NMR (DMSO-d_6) δ 8.53 (d, J = 2.0 Hz, 1), 7.76 (dd, J = 7.9, 2.0 Hz, 1), 7.46 (d, J = 7.9 Hz, 1), 7.29 (d, J = 8.6 Hz, 2), 7.02 (d, J = 8.6 Hz, 2), 4.99 (dd, J = 9.1, 4.3 Hz, 1), 4.47 (d, J = 6.6 Hz, 2), 3.75 (s, 2), 3.45 (dd, J = 14.1, 4.3 Hz, 1), 3.30 (t, J = 6.6 Hz, 2), 3.18 (dd, J = 14.1, 9.1 Hz, 1); IR (Nujol) 3438, 1693, 1641, 1581, 1515, 1252, 1165 cm^{-1}; FAB-MS 387 (M^++ 2H, base),

306 (6.0), 289 (8.5), 261 (6.0), 245 (6.5), 229 (22.7), 199 (9.9), 177 (17.6), 164 (54.7). Anal. ($C_{19}H_{18}N_2O_5S\cdot0.37H_2O$) C, H, N.

5-((4-(2-(5-Ethyl-2-pyridyl *N*-oxide)ethoxy)phenyl)-methyl)-2,4-thiazolidinedione (31). To a suspension of **2**·0.33dioxane (48.5 g, 0.125 mol) in CH_2Cl_2 (1.2 L) was added methanol (0.3 L) followed by the addition of MCPBA (60%, 41.9 g, 0.145 mol) in one portion. The mixture was allowed to stir overnight at room temperature, affording a clear solution. The solution was cast into saturated aqueous $NaHCO_3$ (1 L); the organic phase was separated, washed with 10% aqueous $Na_2S_2O_3$ (0.75 L), saturated aqueous $NaHCO_3$ (1 L), and brine (1 L), and dried (Na_2SO_4). Concentration *in vacuo* afforded the crude product as a clear, colorless oil which slowly crystallized to furnish **31** (45.25 g, 96%) after drying *in vacuo* (40 °C). A portion of this material was recrystallized from acetonitrile to give **31**·0.38CH_3CN as a white, highly crystalline solid (mp 160−161 °C): TLC (Merck; MeOH−CH_2Cl_2, 5:95, UV(+)) $R_f = 0.20$; ^{1}H-NMR ($CDCl_3$) δ 12.03 (brs, 1), 8.20 (d, J = 1.4 Hz, 1), 7.40 (d, J = 8.0 Hz, 1), 7.19 (dd, J = 8.0, 1.4 Hz, 1), 7.14 (d, J = 8.6 Hz, 2), 6.90 (d, J = 8.6 Hz, 2), 4.87 (dd, J = 9.1, 4.3 Hz, 1), 4.28 (t, J = 6.4 Hz, 2), 3.30 (dd, J = 14.2, 4.3 Hz, 1), 3.21 (d, J = 6.4 Hz, 2), 3.05 (dd, J = 14.2, 9.1 Hz, 1), 2.55 (q, J = 7.6 Hz, 2), 2.08 (s, CH_3CN), 1.16 (t, J = 7.6 Hz, 3); ^{13}C-NMR ($CDCl_3$) δ 175.0, 171.2, 157.6, 146.2, 140.9, 138.9, 130.1, 128.2, 127.7, 126.6, 114.5, 63.6, 53.7, 37.7, 34.0, 30.7, 25.4, 14.3. Anal. ($C_{19}H_{20}N_2O_4S\cdot0.38CH_3CN$) C, H, N.

5-((4-(2-(5-Ethyl-2-pyridyl)-1-hydroxyethoxy)phenyl)-methyl)-2,4-thiazolidinedione (9). A mixture of **31** (42.9 g, 115 mmol) and trifluoroacetic anhydride (81 mL, 121 g, 0.576 mol) in methylene chloride (0.5 L) was heated under reflux for 2 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in THF (0.25 L), and saturated aqueous sodium bicarbonate was added slowly until gas evolution was no longer evident. Ethyl acetate and brine were added (0.25 L each), and the organic phase was separated. The aqueous phase was extracted with THF−EtOAc (1:1, 0.25 L), and the combined organic layers were washed with brine (0.5 L), dried (Na_2SO_4), and concentrated *in vacuo* to give crude **9** as a sticky, yellow solid. The crude product was purified by chromatography on a column of silica gel (500 g, 230−400 mesh, 70 mm o.d., CH_2Cl_2−acetone, 90:10, 400 mL fractions) using the flash technique. Fractions 10−25 afforded 31.51 g (74%) of **9** as a free flowing white powder. Recrystallization from ethanol afforded **9**·$^1/_2$EtOH as white needles (mp 128.4−130.4 °C): TLC (Merck; MeOH−CH_2Cl_2, 10:90, UV(+)) $R_f = 0.25$; ^{1}H-NMR (DMSO-d_6) δ 12.02 (brs, 1), 8.39 (d, J = 1.9 Hz, 1), 7.66 (dd, J = 8.0, 1.9 Hz, 1), 7.51 (d, J = 8.0 Hz, 1), 7.14 (d, J = 8.6 Hz, 2), 6.87 (d, J = 8.6 Hz, 2), 5.74 (d, J = 5.3 Hz, 1), 4.91 (m, 1), 4.86 (dd, J = 9.1, 4.4 Hz, 1), 4.25 (dd, J = 10.0, 4.4 Hz, 1), 4.06 (dd, J = 10.0, 9.1 Hz, 1), 3.44 (brq, J = 6.9 Hz, 1, EtOH), 3.29 (dd, J = 14.2, 4.3 Hz, 1), 3.04 (dd, J = 14.2, 9.0 Hz, 1), 2.61 (q, J = 7.5 Hz, 2), 1.19 (t, J = 7.5 Hz, 3), 1.05 (t, J = 6.9 Hz, 1.5, EtOH); ^{13}C-NMR (DMSO-d_6) δ 175.6, 171.6, 158.5, 157.5, 147.8, 137.4, 135.7, 130.2, 128.5, 120.4, 114.3, 72.1, 71.8, 55.9, 52.9, 36.1, 24.9, 18.4, 15.3; IR (Nujol) 3530, 3030, 1760, 1737, 1705, 1513, 1332, 1241, 1231, 1180, 1160, 1106, 1053, 1038, 840, 732 cm^{-1}; EI/MS (70 eV) 372 (M^+, 5.0), 355 (10), 325 (0.5), 210 (7), 150 (30), 136 (base). Anal. ($C_{19}H_{20}N_2O_4S\cdot0.5C_2H_5OH$) C, H, N.

5-((4-(2-(5-Ethyl-2-pyridyl)-1-oxoethoxy)phenyl)methyl)-2,4-thiazolidinedione (10). To a solution of **9** (20.5 g, 55.0 mmol) in warm DMSO (50 mL) was added methylene chloride (450 mL), and the resulting solution was cooled in an ice-water bath. P_2O_5 (14.1 g, 99.0 mmol) was added in three portions over 0.5 h followed by the addition of triethylamine (19.5 g, 192 mmol, 27 mL) over 15 min. The mixture was allowed to stir for 2 h as it warmed to room temperature and then was concentrated *in vacuo* and the residue dissolved in THF (150 mL). The pH of the solution was adjusted to *ca.* 1 with 6 N aqueous HCl, and the mixture was allowed to stir for 1 h at room temperature. The solution was neutralized (pH *ca.* 7) with saturated aqueous sodium bicarbonate. The mixture was cast into ethyl acetate (0.5 L). The aqueous phase was extracted with EtOAc (0.5 L), and the combined organic layers were washed with brine (1.0 L) and dried (Na_2SO_4). Concentration *in vacuo* afforded the crude product **10** as a pale yellow foam which was purified by chromatography on a column of silica gel (500 g, 230−400 mesh, 70 mm o.d., CH_2Cl_2−acetone, 90:10, 400 mL fractions) using the flash technique. Fractions 5−15 afforded 17.97 g (88%) of **10** as a free flowing white powdery solid (mp 146−147 °C): TLC (Merck; MeOH−CH_2Cl_2, 5:95, UV(+)) $R_f = 0.21$; ^{1}H-NMR ($CDCl_3$) δ 8.95 (brs, 1), 8.52 (d, J = 2.0 Hz, 1), 8.02 (d, J = 8.0 Hz, 1), 7.70 (dd, J = 8.0, 2.0 Hz, 1), 7.16 (d, J = 8.7 Hz, 2), 6.94 (d, J = 8.7 Hz, 2), 5.62 (s, 2), 4.49 (dd, J = 9.7, 3.8 Hz, 1), 3.47 (dd, J = 14.2, 3.8 Hz, 1), 3.08 (dd, J = 14.2, 9.7 Hz, 1), 2.76 (q, J = 7.6 Hz, 2), 1.31 (t, J = 7.6 Hz, 3); ^{13}C-NMR ($CDCl_3$) δ 194.7, 174.1, 170.4, 157.7, 149.7, 148.9, 144.7, 136.3, 130.3, 128.4, 121.9, 115.2, 70.5, 53.7, 37.8, 26.4, 15.0; EI/MS (70 eV) 370 (M^+, 19.4), 341 (6.9), 254 (20.6), 148 (base). Anal. ($C_{19}H_{18}N_2O_4S$) C, H, N, S.

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