# Solid-Phase Synthesis of BRL 49653

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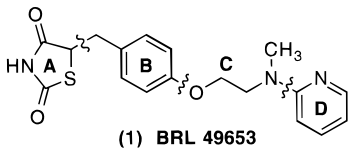
## Introduction

Obesity, a disease characterized by an excessive accumulation of adipose tissue, is affecting an increasing portion of the American population. This accumulation of excess adipose tissue has serious consequences because it also has been associated with other disease states such as hypertension, atherosclerosis, and non-insulin-dependent diabetes mellitus (NIDDM), more commonly referred to as type II diabetes. Unfortunately, little is known about the proteins that mediate the nutritional signals for gene control of lipid metabolism. Recently, an important class of proteins, the peroxisome proliferator activated receptors (PPARs) have been identified.[1] PPARs are members of a nuclear hormone receptor superfamily which respond in varying degrees to a variety of molecules, including peroxisome proliferators (such as clofibrate),[2] thiazolidinediones (such as BRL 49653),[3] long-chain fatty acids (such as linoleic acid),[4] and prostaglandins.[5] The activation of some PPARs by these compounds is an exciting discovery because this represents the first family of lipid-activatable transcription factors.[6] The mechanism by which PPARs induce gene activation is relatively well understood, but the factors that govern their selective activation by the small molecules mentioned above have not been elucidated. Increased knowledge in this area could result in the identification of new signaling pathways that regulate energy balance and may ultimately provide new therapeutic agents.[7]

Significant activation of the mPPAR$\gamma$ protein is obtained with the antidiabetic thiazolidinedione, BRL 49653 (**1**). This substrate has been found to bind to this




**(1) BRL 49653**

PPAR isoform with a $K_d$ of 40 nM.[3] Thus, the development of a structure activity model of BRL 49653 and its analogues would be useful in understanding PPARs, with the potential of synthesizing therapeutically useful compounds. Toward this end, it was reasoned that the preparation of analogues of BRL 49653 (**1**) could be effected most efficiently using solid-phase organic chemistry. This molecule can be divided up into four subunits, the 2,4-thiazolidinedione (subunit A), a substituted benzyl moiety (subunit B), an amino-alcohol moiety (subunit C) and a pyridine moiety (subunit D). This dissection strategy makes the preparation of analogues of BRL 49653 (**1**) particularly appealing, given the ready accessibility of a variety of substrates that could be used for each subunit.[8]

To determine the feasibility of the preparation of a combinatorial library of BRL 49653 analogues, using solid-phase organic synthesis, the preparation of the title compound on the solid support and subsequent cleavage from the support need to be demonstrated. Toward this end, we would like to report the successful development of a method for the preparation of BRL 49653 (**1**) on the solid support.

## Results and Discussion

Initially, direct attachment of the 2,4-thiazolidinedione moiety to the Merrifield resin was employed. As evidenced by infrared spectroscopy, the attachment was successful, but attempts to cleave this molecule from the support were unproductive. Alternatively, it has been reported that 4-formyl-3,5-dimethoxyphenol (**2**)[9] has been used as a linker to attach an amide[10] and amino[11] functionality to a solid support via a reductive amination process. Attachment of 4-formyl-3,5-dimethoxyphenol (**2**) to the Merrifield resin (NaH, DMF) was effected to afford resin-bound aldehyde **3** (Scheme 1). Because our substrate could not be attached using the reductive amination method, reduction of the formyl moiety ($NaBH_4$) was then effected to give benzyl alcohol **4**. This alcohol was in turn coupled with the 2,4-thiazolidinedione moiety to give thiazolidinedione **6**, using a modified Mitsunobu protocol (betaine **5**).[12] The standard Mitsunobu conditions using $Ph_3P$ and DEAD gave inferior results in the related

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(8) This work was first presented at the 215th National Meeting of the American Chemical Society, Dallas, Texas, April, 1998. During our investigation toward the preparation of BRL 49653 on the solid support, another study involving the preparation of a library of thiazolidinedione−fatty acid PPAR$\gamma$ ligands was reported. This approach assembled subunits A, B, and C, using standard solution-phase techniques, and then attached the functionalized thiazolidinedione to a 2-chlorotrityl chloride resin. This functionalized thiazolidinedione (TZD) was then diversified on the support by coupling the supported TZD with a variety of straight-chain alkyl- and alkenyl-carboxylic acids. Tomkinson, N. C. O.; Sefler, A. M.; Plunket, K. D.; Blanchard, S. G.; Parks, D. J.; Willson, T. M. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 2491. In addition, the polymer-supported synthesis of 4-thiazolidinones derived from amino acids has been reported, and a library of analogues have been prepared. Holmes, C. P.; Chinn, J. P.; Look, G. C.; Gordon, E. M.; Gallop, M. A. *J. Org. Chem*. **1995**, *60*, 7328.

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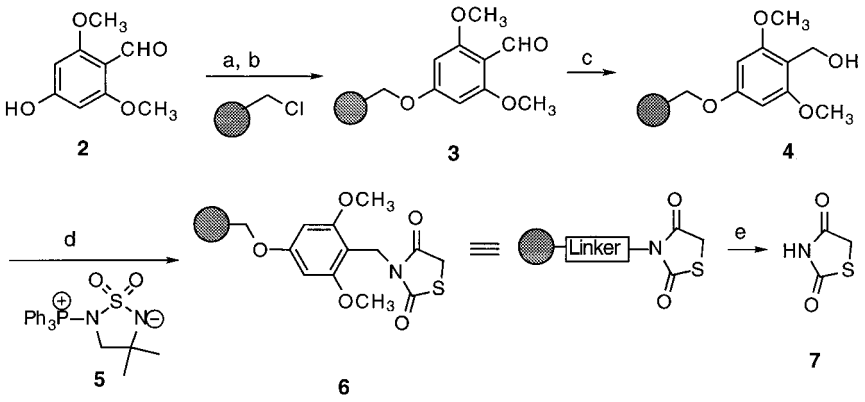
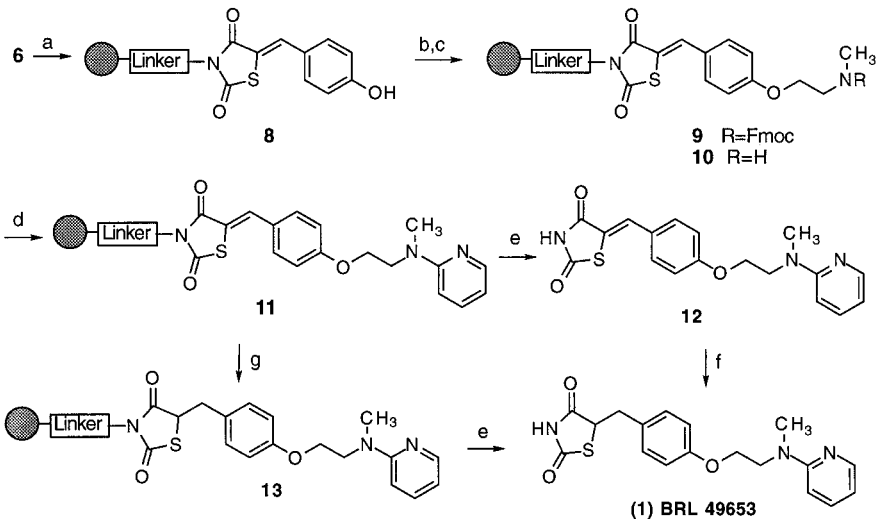
**Scheme 1**



Key: (a) NaH/DMF; (b) Merrifield resin, 50 °C, 36 h; (c) $NaBH_4$/THF/rt/24 h; (d) 2,4-thiazolidinedione, betaine (**5**), $CH_2Cl_2$/rt; (e) TFA/$H_2O$/triisopropylsilane (TIS).

**Scheme 2**



Key: (a) 4-hydroxybenzaldehyde, piperidinium acetate, benzene, reflux, 24 h; (b) *N*-Fmoc-*N*-methyl-2-aminoethanol, betaine (**5**); (c) 20% piperidine, DMF; (d) 2-fluoropyridine, tri-*n*-butylamine, 105-110 °C; (e) TFA/$H_2O$/DMS; (f) Mg, $CH_3OH$; (g) $[(Ph_3P)CuH]_6$, toluene.

solution-phase synthesis.[13] Furthermore, all attempts to prepare thiazolidinedione **6** by nucleophilic substitution of the potassium salt of 2,4-thiazolidinedione to the bromide, mesylate, or tosylate derivative of benzyl alcohol **4** were not realized because the requisite benzyl alcohol derivatives could not be prepared, presumably as a result of the electron-rich nature of the aromatic system. Once the attachment of the thiazolidinedione was achieved, release of this substrate from the solid support was demonstrated and loading levels were determined using the standard acidic cleavage conditions TFA/$H_2O$/TIS (90:5:5). The loading level was found to be 0.55 mmol/g. To our knowledge, this is the first successful example using a memory free linker strategy to attach an imide moiety to the solid support.[8]

Next, we proceeded to the assembly of BRL 49653 by the introduction of subunit B. Treatment of thiazolidinedione **6** with 4-hydroxybenzaldehyde and piperidinium acetate resulted in the Knoevenagel condensation product **8** (Scheme 2). The incorporation of the amino alcohol motif (subunit C) was accomplished by the treatment of phenol **8** and *N*-Fmoc-*N*-methyl-2-aminoethanol under the modified Mitsunobu conditions (betaine **5**). Initially, this coupling process was attempted with the Cbz- and Boc-protected amino alcohols. In the case of the Cbz-protected amino alcohol, problems were experienced during the hydrogenolysis of the Cbz group, presumably caused by the sulfur moiety on the thiazolidinedione ring, and in the case of the Boc-protected amino alcohol, very low yields were obtained for the Mitsunobu coupling reaction as a result of the formation of unidentifiable side-products. Deprotection of the amine **9** (20% piperidine in DMF) afforded the secondary amine **10**, which was subsequently treated with 2-fluoropyridine in the presence of tri-*n*-butylamine, resulting in nucleophilic aromatic substitution product **11**. The solvent choice for this reaction proved to be critical to its success, because at the temperatures required to effect the substitution, DMF gave significant amounts of a byproduct arising from addition of dimethylamine to 2-fluoropyridine and *N*-methyl-2-pyrrolidinone gave significantly lower yields.

(13) Lower chemical yields were obtained as a result of the formation of significant amounts of byproducts resulting from the coupling reaction between the substrate and DEAD.

Finally, treatment of compound **11** to cleavage conditions (TFA/$H_2O$/DMS, 80 °C) and subsequent flash chromatography on silica gel gave the BRL 49653 precursor **12**, which was subjected to magnesium in refluxing methanol[14] to furnish the desired compound **1**. Alternatively, the polymer-bound substrate **10** was selectively reduced using copper(I) hydride complex $[(Ph_3P)CuH]_6$[15] to give **13**, which was cleaved from the solid support to give BRL 49653 (**1**) directly.

In conclusion, we have shown for the first time that the 4-formyl-3,5-dimethoxyphenol linker can be employed for the attachment and cleavage of an imide nitrogen to/from a solid support. This strategy was successfully applied to the solid-phase organic synthesis of BRL 49653. The preparation of a library containing structurally diversified analogues of BRL 49653 is currently underway in our laboratory.

## Experimental Section

**General.** THF and $Et_2O$ were distilled from sodium/benzophenone ketyl before use. Thin-layer chromatography was performed on silica gel Kieselgel-60 F-254 glass plates, and components were visualized by illumination with UV light or by staining with phosphomolybdic acid (5% in methanol) or *p*-anisaldehyde (2%) in ethanol containing 2% $H_2SO_4$. Flash chromatography was performed using Baker Flash silica gel 60 (40 $\mu$). Melting points were determined using a Mel-Temp Laboratory Device and are uncorrected. The glassware was oven and/or flame dried, assembled hot, and cooled under a stream of dry nitrogen or argon before use. Reactions involving air-sensitive materials were carried out using standard syringe techniques.

$^1$H NMR was recorded on a 270 MHz spectrometer. $^{13}$C NMR were recorded on a 67.9 MHz spectrometer, using broad band proton decoupling. IR spectra were obtained on a 1600 Series FT-IR spectrophotometer. Elemental analyses were performed by Atlantic Microlab Inc., P.O. Box 2288, Norcross, GA 30091-9990.

**General Procedure A for Cleavage of Substrate from Resin.** To a 10 mL round-bottom flask equipped with a condenser were added 0.30 g of resin and a freshly prepared solution containing $H_2O$ (0.25 mL), triisopropylsilane (TIS) (0.25 mL), and TFA (4.5 mL). The resultant suspension was stirred in an oil bath at 80−85 °C (bath temperature) for 12 h. The reaction mixture was cooled to room temperature, and the resin was filtered and washed with $CH_3OH$ (3 × 5 mL) and $CH_2Cl_2$ (3 × 5 mL). The filtrate was then concentrated by distillation at atmospheric pressure. The residue was diluted with $CH_2Cl_2$ (5 mL) and filtered through a pad of silica gel, which was washed with EtOAc (5 mL) and $CH_2Cl_2$ (5 mL). To ensure complete elution of the product, the silica gel was washed with $CH_3OH$ (5 mL) and checked by TLC. The combined organics were concentrated in vacuo. The crude product was purified by silica gel column chromatography, and analytically pure samples were obtained by preparative TLC.

**General Procedure B for Cleavage of Substrate from Resin.** To a 10 mL round-bottom flask equipped with a condenser were added 0.30 g resin and a freshly prepared solution containing TFA (3.0 mL), $H_2O$ (0.15 mL), and dimethyl sulfide (0.15 mL). The resultant suspension was stirred at 80−85 °C for 12 h in an oil bath. The reaction mixture was then cooled to room temperature. The resin was filtered and washed with $CH_3OH$ (3 × 5 mL) and $CH_2Cl_2$ (3 × 5 mL), and then the filtrate was concentrated by distillation at atmospheric pressure. The resulting dark residue was diluted with $H_2O$ (5 mL) and $CH_2Cl_2$ (5 mL). The pH value of the aqueous layer was adjusted to 7.5−8.0 with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with $CH_2Cl_2$ (4 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated in vacuo. The dark residue was filtered through a pad of silica gel with the aid of $CH_2Cl_2$ (5 mL), and the pad was washed with $CH_2Cl_2$ (3 × 5 mL) and $CH_3OH$ (5 mL) and monitored by TLC to ensure complete removal of substrate from the silica gel. The filtrate was concentrated in vacuo, and the crude yellow concentrate was purified by silica gel column chromatography. Analytically pure samples were obtained by using preparative TLC.

**Resin-Bound Benzaldehyde 3.** The resin-bound benzaldehyde was prepared according to a modified literature procedure.[10] To a flame-dried 250 mL round-bottom flask were added 4-formyl-3,5-dimethoxy phenol (6.35 g, 34.9 mmol) and anhydrous DMF (200 mL) under Ar. The contents of the flask were stirred mechanically at room temperature until a solution formed and then cooled to 0 °C. NaH (0.86 g, 95% in mineral oil, 33.9 mmol) was added in two portions, and the reaction mixture was stirred at room temperature for 1 h. Next, Merrifield resin (chloromethylated styrene/2% divinylbenzene, Aldrich, 2.0 mmol/g, 5.0 g) was added in one portion at room temperature. The resultant suspension was then mechanically stirred at 50 °C for 36 h. The reaction was cooled to room temperature, and then the resin was filtered and washed successively with $H_2O$ (2 × 50 mL), acetone (2 × 50 mL), $CH_3OH$ (2 × 50 mL), and $CH_2Cl_2$ (2 × 50 mL). The resultant yellow resin was dried in a vacuum oven to a constant weight (5.5 g) at 50 °C for 16 h in the presence of $P_2O_5$. IR (KBr): 1677, 1600, 1574 cm$^{-1}$ (lit. 1690 cm$^{-1}$).[10]

**Resin-Bound Benzyl Alcohol 4.** A flame-dried 250 mL round-bottom flask was charged with resin-bound benzaldehyde **3** (5.51 g) and THF (150 mL), and the resin was allowed to swell at room temperature for 1 h. The suspension was then cooled to 0 °C, and $NaBH_4$ (2.08 g, 55.0 mmol) was added in portions while the mixture was stirred mechanically. The reaction mixture was stirred continually at 0 °C for 30 min and then at room temperature for 24 h. The reaction mixture was then cooled to 0 °C and quenched by the slow addition of saturated $NH_4Cl$ (20 mL). Upon completion of the addition, the reaction mixture was stirred for an additional 15 min and then 10% HOAc (50 mL) was added at 0 °C. After 10 min at 0 °C, the mixture was allowed to warm to room temperature and stirred an additional 30 min. The resin was filtered and washed successively with $H_2O$ (3 × 50 mL), $CH_3OH$ (3 × 50 mL), THF (2 × 50 mL), and $CH_3OH$ (2 × 50 mL) to give a yellow resin. The resin was dried to a constant weight (5.60 g) in a vacuum oven at 50 °C in the presence of $P_2O_5$. IR (KBr): 3446 (br), 1600 cm$^{-1}$.

**Resin-Bound 2,4-Thiazolidinedione 6.** Resin-bound benzyl alcohol **4** (5.60 g) was swelled in $CH_2Cl_2$ (150 mL) under Ar in a 250 mL round-bottom flask for 1 h. To the resultant suspension was added 2,4-thiazolidinedione (6.55 g, 56.0 mmol) with mechanical stirring, followed by the addition of the Mitsunobu reagent, betaine **5** (20.6 g, 50.4 mmol), which was added in four equal portions over 12 h. The resulting red reaction mixture was stirred mechanically at room temperature for an additional 24 h. The resin was filtered and washed with dilute $K_2CO_3$ (3 × 100 mL), $H_2O$ (3 × 100 mL), acetone (2 × 100 mL), THF (2 × 100 mL), and $CH_3OH$ (2 × 100 mL). The resultant light green resin was dried in a vacuum oven to a constant weight (6.01 g) at 50 °C in the presence of $P_2O_5$. IR (KBr): 1754, 1687, 1600 cm$^{-1}$. The loading level was determined to be 0.55 mmol/g by cleaving the 2,4-thiazolidinedione (**7**) from the support, and 12.8 mg of **7** was obtained by subjecting 200 mg of resin to general cleavage procedure A.

**Resin-Bound Phenol 8.** To a 250 mL round-bottom flask equipped with a mechanical stirrer and a Dean−Stark trap were added the resin-bound 2,4-thiazolidinedione **6** (6.0 g, 3.3 mmol), 4-hydroxybenzaldehyde (4.03 g, 33.0 mmol), and piperidinium acetate (0.48 g, 3.3 mmol) in benzene (150 mL). The suspension was refluxed for 24 h. The reaction mixture was cooled to room temperature, and the resin was filtered and washed successively with benzene (2 × 50 mL), $H_2O$ (4 × 50 mL), acetone (3 × 50 mL), THF (3 × 50 mL), and finally with $CH_3OH$ (3 × 50 mL). The resultant golden resin was dried in a vacuum oven to a

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constant weight (6.5 g) at 50 °C overnight in the presence of $P_2O_5$. IR (KBr): 3405 (br), 1744, 1682, 1595 $cm^{-1}$. The loading level was determined to be 0.39 mmol/g by subjecting **8** (250 mg) to general cleaving procedure A to give (*Z*)-5-[4-hydroxyphenyl]-methylene-2,4-thiazolidinedione (21.5 mg).

**(*Z*)-5-[4-Hydroxyphenyl]-methylene-2,4-thiazolidinedione.** Mp 297−300 °C; $R_f$ 0.70 (50:50 hexane/EtOAc); $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 6.89 (d, $J$ = 9.5 Hz, 2H), 7.44 (d, $J$ = 9.5 Hz, 2H), 7.68 (s, 1H), 10.33 (bs, 1H), 12.44 (bs, 1H); $^{13}$C NMR (67.9 MHz, DMSO-$d_6$) $\delta$ 168.1, 167.6, 159.9, 132.4, 132.3, 123.9, 119.0, 116.3; IR (KBr) 3405 (b), 1723, 1677, 1595 $cm^{-1}$. Anal. Calcd for $C_{10}H_7NO_3S$: C, 54.29; H, 3.19; N, 6.33. Found: C, 54.41; H, 3.26; N, 6.44.

**Resin-Bound *N*-Fmoc Amino Alcohol 9.** To a 100 mL round-bottom flask equipped with a mechanical stirrer was added the resin-bound phenol **8** (2.8 g, 1.1 mmol). It was swelled in $CH_2Cl_2$ (50 mL) at room temperature for 30 min. *N*-Fmoc-*N*-methyl-2-aminoethanol (3.98 g, 13.3 mmol) was added at room temperature, followed by the addition of betaine **5** (4.90 g, 12.0 mmol) in three portions over 9 h. The resultant red mixture was stirred at room temperature for an additional 24 h. The reaction mixture was filtered, and the resin was washed with $CH_2Cl_2$ (2 × 20 mL), $CH_3OH$ (2 × 20 mL), dilute $K_2CO_3$ (2 × 100 mL), $H_2O$ (2 × 20 mL), acetone (2 × 20 mL), and $CH_3OH$ (20 mL). The resultant brown resin was dried in a vacuum oven to a constant weight (2.89 g) at 50 °C in the presence of $P_2O_5$. IR (KBr): 1737, 1685, 1596 $cm^{-1}$. After being subjected to general procedure A for cleavage, 307 mg of resin gave 32.3 mg of (*Z*)-5-[4-[2-(*N*-Fmoc-*N*-methylamino)ethoxy]phenyl]-methylene-2,4-thiazolidinedione, and the loading level was calculated to be 0.21 mmol/g.

**(*Z*)-5-[4-[2-(*N*-Fmoc-*N*-methylamino)ethoxy]phenyl]-methylene-2,4-thiazolidinedione.** Mp 171−173 °C; $R_f$ 0.42 (65:35 hexane/EtOAc); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 2.99 (s, 1.4H), 3.08 (s, 1.6H), 3.36 (t, $J$ = 5.2 Hz, 1H), 3.70 (dt, $J$ = 10.8, 5.2 Hz, 2H), 4.19 (t, $J$ = 5.2 Hz, 1H), 4.26 (t, $J$ = 7.1 Hz, 1H), 4.44 (d, $J$ = 6.9 Hz, 1H), 4.60 (d, $J$ = 5.0 Hz, 1H), 6.81 (d, $J$ = 8.7 Hz, 1H), 7.00 (d, $J$ = 8.7 Hz, 1H), 7.31−7.47 (m, 6H), 7.60 (d, $J$ = 6.8 Hz, 2H), 7.75 (d, $J$ = 2.8 Hz, 1H), 7.78 (d, $J$ = 2.8 Hz, 1H), 7.79 (s, 0.5H), 7.81 (s, 0.5H), 8.99 (s, 1H); $^{13}$C NMR (67.9 MHz, $CDCl_3$) $\delta$ 167.2, 166.7, 160.6, 160.4, 144.0, 143.9, 141.4, 141.3, 127.7, 127.1, 127.0, 125.8, 124.9, 124.6, 119.9, 119.4, 115.2, 67.5, 66.8, 66.7, 66.2, 48.7, 48.2, 47.3, 36.3, 36.0; IR (KBr) 3446 (b), 1739, 1697, 1672, 1589 $cm^{-1}$. Anal. Calcd for $C_{28}H_{24}N_2O_5S$: C, 67.19; H, 4.83; N, 5.60. Found: C, 66.93; H, 4.93; N, 5.58.

**Resin-Bound Amino Alcohol 10.** To a 100 mL round-bottom flask equipped with a mechanical stirrer were added the resin-bound Fmoc-amino alcohol **9** (2.87 g), DMF (40 mL), and piperidine (8 mL). The suspension was stirred at room temperature for 10 h. The reaction mixture was filtered, and the resin was washed with 5% citric acid (3 × 20 mL), dilute $K_2CO_3$ (2 × 20 mL), $H_2O$ (3 × 20 mL), acetone (2 × 20 mL), and $CH_3OH$ (2 × 20 mL). The resultant brown resin was dried to a constant weight (2.50 g) in a vacuum oven at 50 °C overnight in the presence of $P_2O_5$ to afford **10**. IR (KBr): 3436 (b), 1744, 1682, 1595 $cm^{-1}$.

**Resin-Bound BRL 49653 Precursor 11.** To a 10 mL round-bottom flask were added the resin-bound amino alcohol **10** (0.31 g), a magnetic stirrer, 2-fluoropyridine (2.5 mL), and freshly distilled tri-*n*-butylamine (0.70 mL). The suspension was then stirred under Ar at 110 °C for 30 h. The resin was filtered and washed with $CH_3OH$ (2 × 10 mL), $H_2O$ (2 × 10 mL), acetone (2 × 10 mL), $CH_3OH$ (2 × 10 mL), and finally $CH_2Cl_2$ (2 × 10 mL). It was then dried in a vacuum oven at 50 °C overnight in the presence of $P_2O_5$ to give a brown resin (0.31 g). IR (KBr): 1744, 1687, 1594 $cm^{-1}$. After being subjected to general procedure B for cleavage, 0.30 g of resin gave 9.7 mg of (*Z*)-5-[[4-(2-methyl-2-pyridinyl(amino)ethoxy]phenyl]-methylene]-2,4-thiazolidinedione. The loading level for the resin was determined to be 0.09 mmol/g.

**(*Z*)-5-[[4-(2-Methyl-2-pyridinyl(amino)ethoxy]phenyl]-methylene]-2,4-thiazolidinedione.** The physical and spectroscopic data of the pure sample are identical to those reported:[14] light yellow powder, mp 194−196 °C; $R_f$ 0.50 (50:50 hexane/EtOAc); $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 3.07 (s, 3H), 3.92 (t, $J$ = 5.9 Hz, 2H), 4.22 (t, $J$ = 5.9 Hz, 2H), 6.58 (dd, $J$ = 7.0, 4.9 Hz, 1H), 6.67 (d, $J$ = 8.9 Hz, 1H), 7.09 (d, $J$ = 9.1 Hz, 2H), 7.48−7.55 (m, 3H), 7.73 (s, 1H), 8.06−8.08 (m, 1H), 12.51 (br s, 1H); $^{13}$C NMR (67.9 MHz, DMSO-$d_6$) $\delta$ 168.0, 167.5, 160.2, 132.1, 131.8, 125.6, 120.3, 115.3, 111.7, 99.5, 65.8, 48.4, 40.4, 38.6, 37.1.

**5-[[4-[2-(Methyl-2-pyridinyl(amino)ethoxy]phenyl]-methyl]-2,4-thiazolinedione, BRL 49653 (1).** To a 10 mL round-bottom flask were added BRL 49653 precursor **12** (21 mg, 0.06 mmol) and $CH_3OH$ (6 mL), followed by the addition of Mg (23 mg, 0.95 mmol) and a crystal of iodine. The reaction mixture was stirred in an oil bath at reflux for 3 h. The reaction mixture was then added to ice (5 mL), and the pH value was adjusted to ca. 7.5 with 1 M HCl. The aqueous layer was extracted with $CH_2Cl_2$ (5 × 5 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography, eluting in 25% EtOAc/hexanes to afford BRL 49653 (16.7 mg) as a slightly yellow oil in 79% yield. The analytically pure sample was obtained by further purification of the product by preparative TLC, eluting with 50% $Et_2O$/hexanes to give a white crystalline compound. The physical and spectroscopic data of the pure sample are identical to those reported:[14] mp 151−153 °C; $R_f$ 0.32 (65:35 hexane/EtOAc); $^1$H NMR (270 MHz, DMSO-$d_6$) $\delta$ 3.03 (dd, $J$ = 14.4, 9.1 Hz, 1H), 3.05 (s, 3H), 3.28 (dd, $J$ = 14.4, 4.4 Hz, 1H), 3.88 (t, $J$ = 5.8 Hz, 2H), 4.09 (t, $J$ = 5.8 Hz, 2H), 4.85 (dd, $J$ = 9.1, 4.4 Hz, 1H), 6.53−6.57 (m, 1H), 6.63 (d, $J$ = 8.3 Hz, 1H), 6.86 (d, $J$ = 8.6 Hz, 2H), 7.12 (d, $J$ = 8.6 Hz, 2H), 7.45−7.49 (m, 1H), 8.05−8.08 (m, 1H), 11.99 (bs, 1H); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 3.11 (dd, $J$ = 14.2, 3.9 Hz, 1H), 3.15 (s, 3H), 3.41 (dd, $J$ = 14.2, 3.9 Hz, 1H), 3.92−3.98 (m, 2H), 4.01−4.19 (m, 2H), 4.49 (dd, $J$ = 9.2, 3.9 Hz, 1H), 6.53 (d, $J$ = 8.5 Hz, 1H), 6.56−6.59 (m, 1H), 6.83 (d, $J$ = 8.9 Hz, 2H), 7.13 (d, $J$ = 8.9 Hz, 2H), 7.46 (ddd, $J$ = 8.7, 7.7, 2.0 Hz, 1H), 8.14 (ddd, $J$ = 5.0, 2.0, 0.8 Hz, 1H); $^{13}$C NMR (67.9 MHz, $CDCl_3$) $\delta$ 174.1, 170.4, 158.3, 158.1, 147.6, 137.4, 130.4, 127.5, 114.6, 111.7, 105.8, 66.2, 53.6, 49.5, 37.9, 37.6; IR (KBr): 3200 (b), 1749, 1692, 1600 $cm^{-1}$.

**[CuH(PPh$_3$)]$_6$ Reduction of BRL 49653 Precursor.** To a 10 mL round-bottom flask was added 290 mg of compound **11**, followed by the addition of 500 mg of $[CuH(PPh_3)]_6$ in a glovebox. A solution of degassed THF (5 mL) and $H_2O$ (40 $\mu$L) was added, and the resulting red reaction mixture was stirred in an oil bath at 75 °C for 12 h. The mixture was allowed to cool, and the resin was filtered and washed with THF (2 × 5 mL), $CH_3OH$ (2 × 5 mL), $CH_2Cl_2$ (2 × 5 mL), $CH_2Cl_2$/THF 3:1 (2 × 5 mL), $H_2O$ (2 × 5 mL), acetone (2 × 5 mL), $CH_3OH$ (2 × 5 mL), and $CH_2Cl_2$ (2 × 5 mL). The resulting dark brown resin was briefly dried in a vacuum oven over $P_2O_5$ (30 min) and then subjected to general cleavage procedure B to afford 4.7 mg of BRL 49653 (**1**).

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**Supporting Information Available:** Copies of $^1$H NMR, $^{13}$C NMR, and IR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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