SYNTHETIC APPROACHES TO BENZOFURAN CONTAINING INSULIN SENSITIVITY ENHANCER COMPOUNDS FOR TREATMENT OF TYPE II DIABETES

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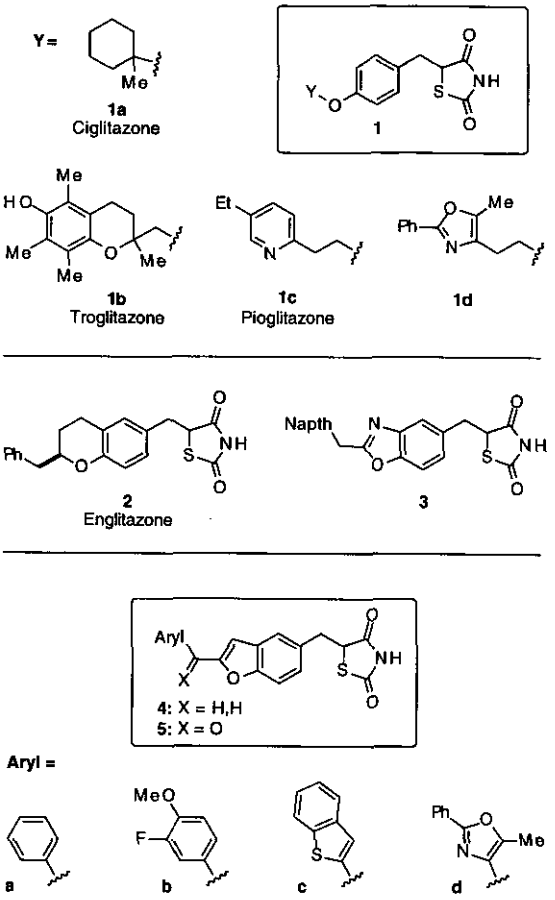
Abstract - The search for Insulin Sensitivity Enhancer (ISE) compounds, for potential use in the treatment of Type II diabetes, has led to the synthesis of compounds that contain a benzofuran spacer between an aryloyl substituent and a 2,4-thiazolidinedione pharmacophore. Sequential combination of haloacetyl aryl substrates with 5-formylsalicylaldehyde gave the desired 2-aryloyl-5-formylbenzofuran intermediates. A related class of compounds, those with a methylene tether between the aromatic moiety and the benzofuran spacer, were also prepared through this strategy.

INTRODUCTION

Approximately 5% of the population in the United States has diabetes mellitus, a chronic, progressive disease that can lead to severe physiological problems.[1] These complications include macrovascular disease, which results in cardiovascular and cerebrovascular disturbances, and microvascular disease, that can result in renal failure and retinopathy.[2] Approximately 90% of patients with diabetes mellitus do not have an absolute deficiency in insulin, but instead exhibit a reduced response to the insulin and are categorized as non-insulin dependent (NIDDM, Type II).[3] In addition to peripheral insulin resistance, patients exhibit obesity and hyperglycemia.[4] Current treatment for Type II diabetes involves maintenance of body physiology through diet and exercise,[5] and therapeutic intervention with sulfonylurea compounds for improved glycemic control.[6] The primary role of the sulfonylurea compounds is to stimulate insulin secretion, and as a result, the potential to induce fatal hypoglycemia exists.[7]

An important advance in the treatment of Type II diabetes was made with the introduction of the 2,4-thiazolidinedione compound Ciglitazone (**1a**).[8] In contrast to the action of the sulfonylurea compounds, 2,4-thiazolidinedione compounds were found to function as insulin sensitivity enhancers in the peripheral tissue and did not act through modulation of insulin levels. Importantly, even when given to nondiabetic animal models, 2,4-thiazolidinedione tyrosine analogs did not lower plasma glucose levels or promote

hypoglycemia.[9] The therapeutic potential of these 2,4-thiazolidinedione compounds has led to significant research efforts in this area.[10]



Many other 2,4-thiazolidinedione compounds have been prepared, and this class of compounds has evolved through several developmental stages. Since the introduction of **1a**,[8] the need for an oxygen para to the thiazolidinedionylmethyl substituent and an aromatic group tethered to this oxygen became apparent (**1b**,[11] **1c**,[12] and **1d**[13]). Further studies revealed that restricted rotation of the side chain C-O-Ph linkage, through the synthesis of bicyclic dihydrobenzopyran (**2**),[14] dihydrobenzofuran,[14] and benzoxazole (**3**)[15] groups, provided promising pharmacological profiles. A conformationally restricted derivative of **1b** has also displayed enhanced biological activity.[16]

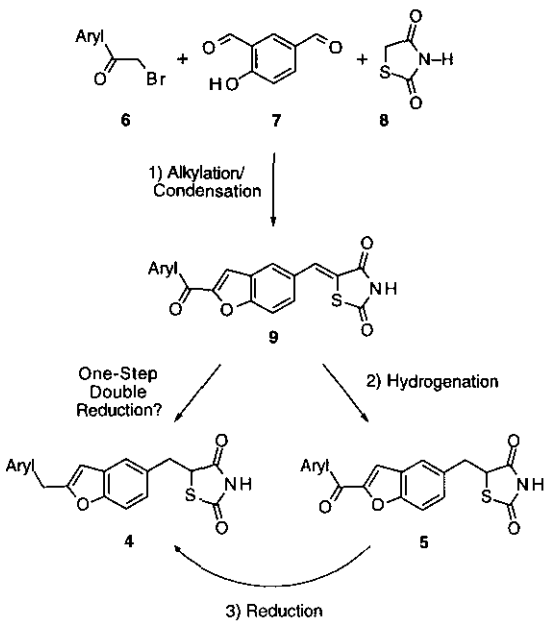
More recently, the use of benzofuran functionality has led to compounds with improved pharmacological activity. Compounds which contained a methylene tether, **4c** and **4d**, as well as those with a carbonyl linker, **5a-d**, have been prepared.[17] The focus of this paper is to report the efficient general synthesis of compounds with the structural features of **4** and **5**. Of particular interest are compounds (**5b**) and (**5c**), developed through a collaborative effort between Tanabe Seiyaku Co., Ltd. and Eli Lilly and Co.

RESULTS AND DISCUSSION

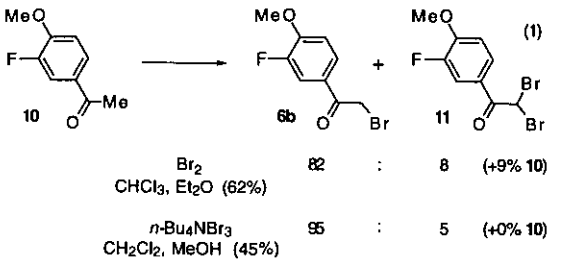
Our primary approach to the efficient construction of **4** and **5** was through the convergent combination of three fragments (Scheme 1). Combination of a bromoacetyl aromatic derivative (**6**) with 5-formylsalicylaldehyde (**7**) would generate the required benzofuran moiety, while condensation of the resultant aldehyde with 2,4-thiazolidinedione (**8**) would introduce the acidic pharmacophore.[17] Use of this strategy to access **9** would allow subsequent synthesis of either **4** or **5**, as desired, through divergent pathways.

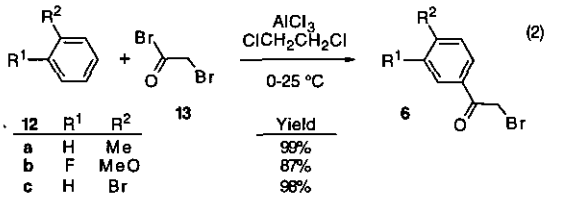
Formation of α-Halomethyl Aryl Ketones. The initial synthesis of **6b** was performed by bromination of the corresponding acetophenone, but this method was hampered by incomplete conversion and over bromination of the methyl ketone (eq. 1). Under typical bromination reaction conditions, crude product was obtained in a ratio of 9:82:8 (**10**:**6b**:**11**), and purification of the resultant solid by recrystallization led to an improved ratio of 3:97:0 (**10**:**6b**:**11**) in 62% overall yield. In order to avoid problems encountered with incomplete reaction selectivity, an alternative approach was investigated.

Direct Friedel-Craft acylation of aryl groups with α-bromoacetyl bromide (**13**) led to the more cost effective and synthetically efficient synthesis of compound (**6**) (eq. 2). Combination of **12** with $AlCl_3$ in 1,2-dichloroethane followed by the addition of **13** provided significant advantages to the standard use of CS_2 as solvent.[18] Several substrates were examined in this reaction, and these conditions gave complete regioselective formation of monoacylated product (**6**) in excellent yields with facile work up.[18]



Scheme 1.

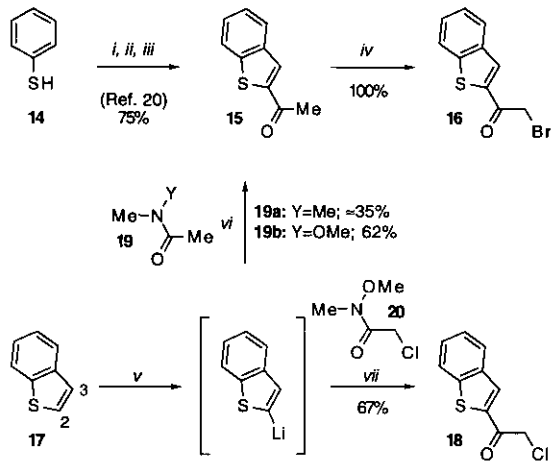




12	R^1	R^2	Yield
a	H	Me	99%
b	F	MeO	87%
c	H	Br	98%

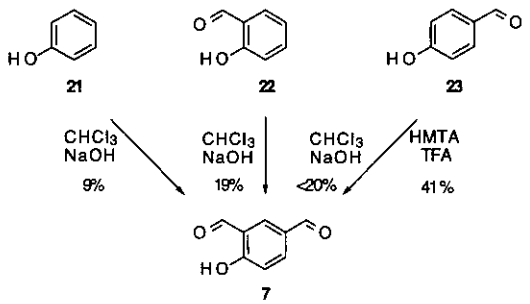
As an approach to **4c** and **5c**, the corresponding Freidel-Craft acylation of **17** with **13** did not result in selective formation of **16**. Instead, treatment of **17** with **13** under optimized conditions for the conversion of **12** to **6** led to a mixture of products that included both **16** and the isomeric 3-acylated species.[19] Regioselective preparation of **16** was accomplished through two alternative routes (Scheme 2). Established procedure was used to convert **14** to **15** in 75% yield; however, this route suffered from difficult product isolation.[20] Subsequent bromination proceeded selectively to give **16** in excellent yield without evidence for formation of the corresponding dibromide species.[21] An alternative route to **15** employed **17** as the substrate. Standard 2-lithiation[22] of **17** followed by treatment with **19a** led to generation of **15** in low yield, and the use of Weinreb's amide derivative (**19b**) greatly enhanced product formation (62%).[23] More direct synthesis of a 2-(2'-haloacetyl)benzothiophene species was accomplished by deprotonation of **17** and subsequent acylation with **20**, which led to the generation of **18** in 67% yield from **17**.

Formylation. The use of **6** to access 2-aryloyl-5-formyl-disubstituted benzofuran spacers required a method for consistent generation and isolation of 5-formylsalicylaldehyde (**7**) in significant quantities. Historically, formylation of electron deficient aromatic rings for the generation of diformylbenzene species has been problematic (Scheme 3). Established Reimer-Tiemann formylation of **21** was reported to generate a mixture of mono- and diformylated products, and isolation of **7** was accomplished through specialized chromatographic techniques to give 17% yield based on 53% consumption of **21** (9% actual yield).[24] Direct formylation of **22** was reported to give a more favorable mixture of products in which the ratio of **7** to the isomeric 3-formylsalicylaldehyde was 3:1.[25] Chromatographic separation of this mixture provided **7** in only 19% yield. Attempts to generate **7** from **23** through this method led to <20% formation of desired product in the crude mixture.



[a]Reaction conditions: i. 2 equiv. of *n*-BuLi, ii. DMF, iii. chloroacetone (75%, 3 steps). iv. $(n\text{-Bu})_4NBr_3$ (100%), v. *n*-BuLi, vi. **19a** (≈35%) or **19b** (62%). vii. **20** (67%).

Scheme 2.

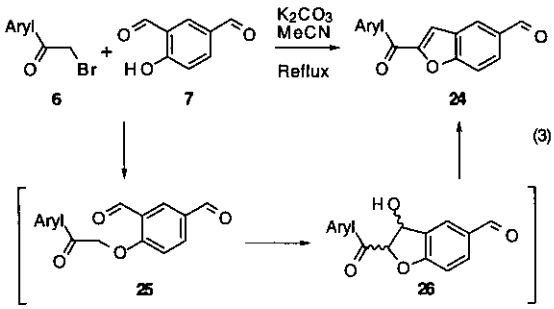


Scheme 3.

Use of the Duff reaction conditions proved to be a much more effective method for preparation of **7** (Scheme 3). Treatment of **23** with hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA) at reflux led to the formation of **7** as the major component of the crude mixture.[26] Of paramount importance to the success of this procedure were the conditions for reaction work up. Quench of the reaction with 3*N* HCl at >90 °C followed by slow cooling was essential for the efficient hydrolysis of excess reagent and imine intermediates. Extraction of the acidic solution with CH_2Cl_2 provided amine-free crude product, and treatment of the residue with EtOH led to crystalline material in 41% yield. Most importantly, this work up procedure avoided the need for chromatographic purification, and provided an economical and efficient method for generation of necessary quantities of **7**.

Benzofuran Formation. Construction of the benzofuran unit from **6** and salicylaldehyde derivatives promoted by K_2CO_3 has been reported for reactions performed in acetone,[27] 2-butanone,[17a] DMF,[27] and with phase transfer conditions.[28] However, combination of **6**, **7**, and K_2CO_3 in acetone generated **24** in only 65% yield (eq. 3).[29] Due to the minor complications that result from aldol chemistry of acetone, both

self condensation and reaction with **24**, MeCN was chosen as the solvent. In general, the use of MeCN as the solvent for benzofuran formation was found to give cleaner reaction profiles, accelerated reaction rates, easier product isolation, higher yields, and lower levels of residual solvent.



Although the overall reaction proceeded within 3-6 h, disappearance of either **6** or **7** could not be used to evaluate reaction progress. Alkylation of the phenol functionality occurred almost immediately to give **25**, and shortly thereafter the diastereomeric aldol condensation products (**26**) were observed. With time, the rate limiting aldol condensation and elimination of water generated the desired product (**24**).

The pK_a values for the different phenols associated with this project were obtained by titration of each compound as a 67% DMF/33% H_2O solution.[30] Interestingly, the pK_a values of **21**, **22**, **23**, and **7** were found to be 12.8, 9.9, 9.6, and 6.9, respectively. Apparently, the overall acidity of **22** and **23** in this solvent mixture was not affected significantly by inductive differences between ortho or para substitution or the potential differences due to intramolecular hydrogen bonding of the salicylaldehyde functionality. As expected, the additive effects of both formyl substituents substantially increased the acidity of the phenol functionality.

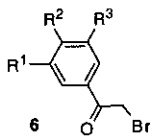
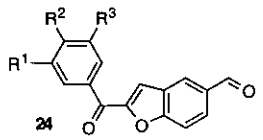
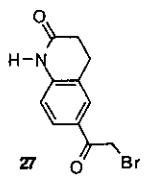
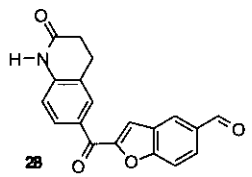
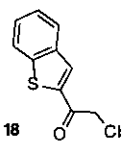
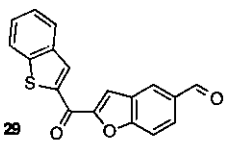
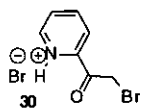
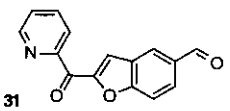
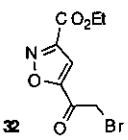
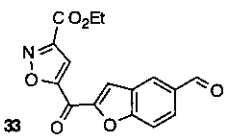
Various aryl substituents were examined to determine the general effectiveness of MeCN for benzofuran formation from the combination of **6** with **7** (Table 1). Unfunctionalized aromatic groups (**a** and **c**) and the aryl bromide (**d**), which has potential for use in a subsequent transition metal coupling reaction, each gave good yields.

The disubstituted aryl substituent (**6b**), an intermediate for one of the targeted ISE compounds, led to a 94% yield of **24b**. Under these reaction conditions, a hindered phenolic substituent on **6e** did not interfere with efficient formation of **24e**. Similarly, N-H functionality of lactam (**27**) did not adversely affect the outcome of the reaction, and was efficiently converted to **28**. Although reaction of this α-chloroketone with the phenol was slow, due to the nature of the halogen substituent, the addition of 1 equiv. of KI significantly accelerated the reaction and led to efficient generation of desired product in 78% yield.[31]

The use of heterocyclic aromatic species for the reaction of haloacetyl species (**18**) with **7** was equally as successful in the formation of **29**. However, benzofuran formation with **18** was very sluggish, as discussed for the chloro derivative (**27**), and the addition of 1 equiv. of KI was necessary to affect efficient product generation. The reaction of **7** with the pyridine derivative (**30**)[32] was performed with 2.0 equiv. of

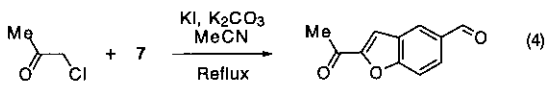
K_2CO_3 and provided the corresponding benzofuran product (**31**). Similarly, conversion of **32** to **33** was affected under these reaction conditions.

Table 1. Benzofuran Formation from **7**.[a]

substrate				product	yield[b]
					
	R^1	R^2	R^3		
a	H	H	H		84%
b	F	MeO	H		94%
c	H	Me	H		82%
d	H	Br	H		93%
e	*t*-Bu	HO	*t*-Bu		79%
					78%
					87%
					39%[c]
					61%

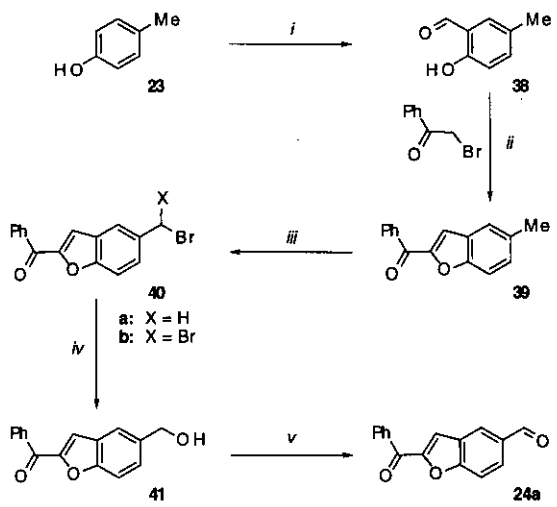
[a]Reaction conditions: 1.0 equiv. of K_2CO_3, MeCN, reflux (1.0 equiv. of KI was added to reactions with α-chloroketone substrate). [b]Isolated yield of crystalline compound. [c]An extra 1.0 equiv. of K_2CO_3 was added to free the amine salt.

As was observed for the reaction of the α-chloro species (**27**, **18**, and **32**), the reaction of **7** with chloroacetone (**34**) was slow in MeCN (eq. 4).[33] However, the reaction was accelerated when 1 equiv. of KI was added to the mixture, and **35** was isolated in 94% yield.



34 94% Yield 35 (4)

An alternative route to aldehyde (**24a**) is illustrated in Scheme 4. Formylation of cresol (**23**) under established reaction conditions gave **38** as reported,[34] and subsequent benzofuran formation led to the generation of **39**. Activation of the methyl substituent was accomplished through bromination of the benzylic site with *N*-bromosuccinimide (NBS) and AIBN in $CCl_4/CHCl_3$ (2.5:1).[29]



[a]Reaction conditions: i. $SnCl_4$, paraformaldehyde, *n*-Bu_3N, toluene, 100 °C (80%). ii. K_2CO_3, acetone, reflux (79%). iii. *N*-bromosuccinimide, AIBN, $CCl_4/CHCl_3$, reflux (73%). iv. Na_2CO_3, H_2O/acetone. v. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 (75%, 2 steps).

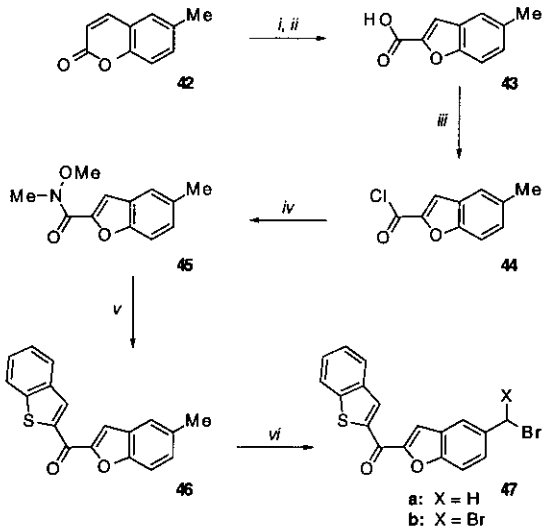
Scheme 4.

These conditions led to a 14:73:13 mixture of starting material (**39**), desired product (**40a**), and α,α-dibromo by-product (**40b**). Attempts to achieve complete consumption of **39** only led to increased amounts of **40b**. Crystallization of this crude mixture gave a 5:90:5 mixture of the three compounds (**39**:**40a**:**40b**), and this material could not be used to directly alkylate 2,4-thiazolidinedione and was taken on to the corresponding alcohol without further purification.[35] Alcohol (**41**) was prepared from **40b** most conveniently by the action of Na_2CO_3 in H_2O/acetone,[36] but potassium formate and Aliquot 336 could also be used.[37] Swern oxidation of this alcohol provided the desired aldehyde intermediate (**24a**).

Another approach to a benzylic bromide species (**47a**) was accomplished from **42** (Scheme 5). Conversion of **42** to the benzofurancarboxylic acid (**43**) was performed through a two-step process that involved bromination followed by treatment with base.[38] From this acid, the corresponding acid chloride (**44**) was prepared quantitatively. Preparation of the Weinreb's amide derivative (**45**) allowed selective conversion to **46** upon reaction with lithiated thianaphthene.

Direct treatment of **44** with 2-lithiothianaphthene (1.0 equiv.) resulted in reaction to give the tertiary alcohol as the major product, and the addition of two equivalents of the organometallic reagent allowed isolation of the corresponding tertiary alcohol in 87% yield. Subsequent bromination of **46** led to the formation of **47a**

in 63% yield, which contained 6% of the dibrominated product (**47b**). As was found for **40a**, direct alkylation of 2,4-thiazolidinedione was ineffective.[35]



[a]Reaction conditions: i. Br_2. ii. KOH, EtOH (81%, 2 steps). iii. $(COCl)_2$ (100%). iv. MeO(Me)NH, Et_3N, CH_2Cl_2 (100%). v. 2-lithiobenzo[*b*]thiophene (77%). vi. Br_2, $CHCl_3$, cat. AIBN, reflux, 24 h (63%).

Scheme 5.

Introduction of the 2,4-Thiazolidinedione Moiety. Conditions for condensation of the aldehyde intermediate (**24b**) with 2,4-thiazolidinedione (**8**) were designed around the insolubility of the product (**9b**). As the product was generated, **9b** precipitated from the reaction mixture and often entrained significant amounts of aldehyde substrate, which led to problems regarding incomplete conversion to product. Traditional solvents for this reaction,[12d] such as EtOH and *i*-PrOH, led to only 92% and 61% conversion of starting material to product, respectively. Instead, MeCN, which typically resulted in 96-97% conversion to product in 80-85% isolated yield, and DMF, which produced complete conversion to **9b** in 78% isolated yield, were the optimum solvents for conversion of **24b** to **9b**. Similar condensation of **24a** with **8** generated **9a** in 89% yield.

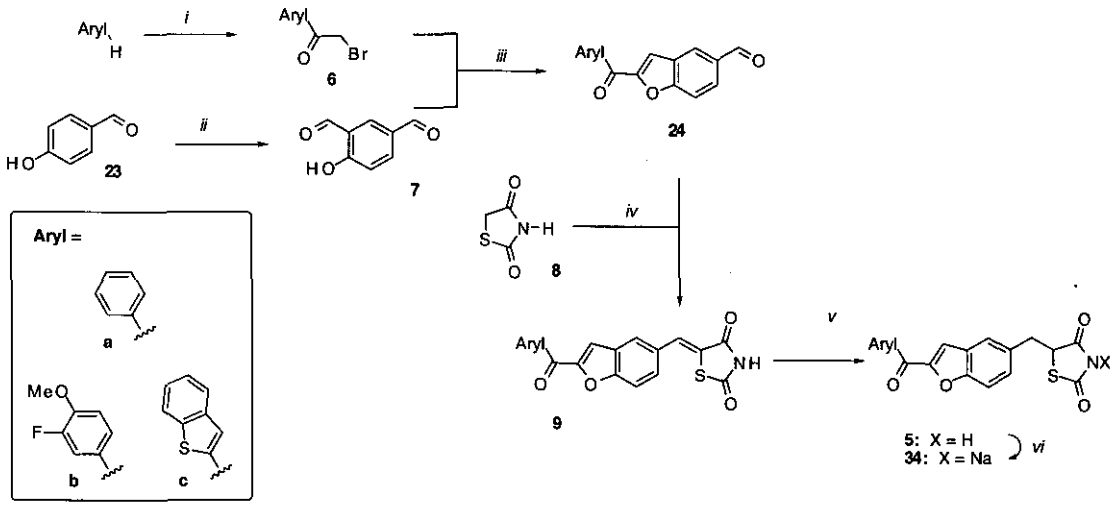
The analogous reaction of **24c** with **8** was complicated by the even greater insolubility of **9c** than **9b**. The use of greater amounts of DMF as the solvent was required to achieve reaction homogeneity, and when promoted by 0.1 equivalents of pyrrolidine under these conditions, the condensation reaction could be driven to only 85% conversion. Isolation of **9c** was accomplished in 55% yield.

Catalytic reduction of **9b** was attempted with a wide range of catalysts under a variety of conditions. Initially, 5% Pd/C at 45 °C and 1 atm. of H_2 in THF produced only 91% conversion after 24 h. Reduction with 5% Pd/C at 25 °C and 3 atm. of H_2 in THF with added HCO_2H gave only 57% conversion after 24 h. The use of 5% Pd on alumina at 50 °C and 3 atm. of H_2 in THF gave 90% conversion after 24 h. Of the many variables examined, the optimum reaction conditions for hydrogenation were the use of 10% Pd/C

(75 wt% catalyst loading [7.5 wt% of Pd metal]) in THF at 55 °C.[14] The reaction could be run at 50 psi of H_2 (16-20 h) or simply under 1 atm. of H_2 (balloon, 36-48 h).

The insolubility of **9b** played a key role in the problems encountered with the conversion of **9b** to **5b**, and performing the reaction at 55 °C in either THF or DMF helped to solubilize the alkene substrate. In all cases examined, reaction was sluggish in DMF, and overall conversion in DMF was lower (10% Pd/C, 75 wt% catalyst loading, 50 °C, 50 psi H_2, 24 h, 85% conversion) than when run in THF. Fortunately, generation of a site of asymmetry in this class of molecules, as in **5b**, significantly increased the solubility of these species during the course of the reaction. As a result, a suspension of **9b** could be converted to a solution of **5b** in reaction volumes as low as 50:1 volume:weight of substrate/THF. These conditions were used to achieve >98% conversion to **5b**, which could be isolated in 70% yield. Due primarily to substrate insolubility, analogous reduction of **9c** to **5c** could not be affected.

The direct conversion of a salt derivative of **9b** by hydrogenation to **34b** could not be accomplished. Exposure of the potassium salt of **9b** to these same reaction conditions led to <10% conversion to the potassium salt of **5b** after 48 h (10% Pd/C, 50 °C, 3 atm. of H_2, THF). In part, the pK_a values for the 2,4-thiazolidinedione species provide insight into inhibition of hydrogenation process. Although **9b** was too insoluble to obtain an accurate pK_a, the value for **5b** was 7.5 (Table 2).[30] In an analogous system, the values for the acidic NH protons of **49** and **48** were 7.7 and 6.8, respectively. If the same trend occurs for **5b** and **9b**, compound **9b** would be approximately ten times more acidic, and acid/base equilibration between **9b** and **5b** would tend to prevent opportunity for the hydrogenation of protonated **9b**. Thus, removal of base (K_2CO_3, $KHCO_3$, or pyrrolidine) during work up of the two previous steps was imperative for successful hydrogenation.



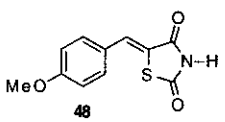
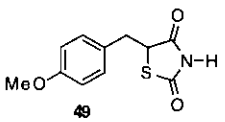
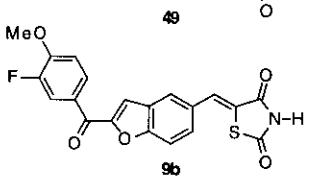
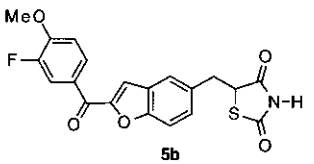
[a]Reaction conditions: i. $AlCl_3$, **13**, $ClCH_2CH_2Cl$, 25 °C (**b:** 87%). ii. HMTA, TFA, reflux (41%). iii. K_2CO_3, MeCN, reflux (**a:** 84%, **b:** 94%, **c:** 87%). iv. 0.05 equiv. pyrrolidine, MeCN, reflux (**a:** 89%, **b:** 84%, **c:** 55%). v. 3 atm of H_2, 10% Pd/C, THF, 50 °C (**b:** 70%). vi. NaOMe, MeOH (**b:** 87%).

Scheme 6.

With the similarities in reaction conditions for the conversion of **6b** to **24b**, and then the subsequent transformation of **24b** to **9b**, the opportunity to combine these steps was investigated. Addition of **8** directly to the reaction mixture without work up of the intermediate benzofuran required the addition of 1.2 equiv. of **8** and 0.1 equiv. of pyrrolidine for complete conversion of **24b** to **9b**. Precipitation of **9b** and removal of the inorganic potassium salts with an aqueous wash afforded the potassium salt of **9b** in 98% isolated yield. Suspension of this material in AcOH at 50 ℃ did not result in conversion of this salt to the corresponding acid due to the insoluble nature of **9b**. However, treatment of the potassium salt with 12 mM, pH 2.4 phosphate buffer and THF (50:50) at 50 ℃ followed by hydrogenation under optimum conditions generated **5b** in an overall yield of 50% for the three step process from **6b** to **7**.

Final formation of the sodium salt **34b** was performed by treatment of a suspension of **5b** in THF/MeOH with commercially available 25% NaOMe solution in MeOH. Upon addition of the NaOMe solution, the suspension dissolved to an extent of approximately 95%, and then product began to precipitate from solution. The resultant product was filtered and washed with EtOH to give a 94% yield of **34b** after drying so that only trace amounts of THF (0.2 wt%) and MeOH (0.3 wt%) remained after vacuum drying. Alternatively, the reaction could be performed in MeOH as the solvent to give 87% isolated product with 0.3 wt% residual solvent.

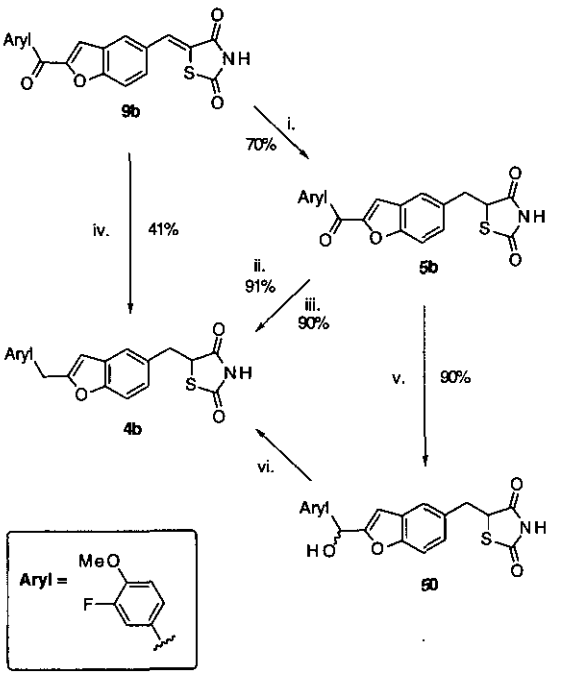
Table 2. Acidity Data for 2,4-Thiazolidinedione Compounds.[a]

compound	pK_a (N-H)
 **48**	6.8
 **49**	7.7
 **9b**	—
 **5b**	7.5

[a]Titrations were performed in 67% DMF/33% H_2O.

Synthetic routes from both **5b** and **9b** to **4b** were investigated (Scheme 7). Reduction of the carbonyl functionality of **5b** to a methylene group was initially approached in two steps. Formation of the intermediate alcohol (**50**) with $NaBH_4$ followed by catalytic hydrogenation did not result in complete removal of the hydroxyl functionality. However, two different methods were developed in which the

transformation of **5b** to **4b** was accomplished in a single step. Treatment with $NaBH_4$ followed by the addition of TFA led to the efficient formation of **4b**. Alternatively, reduction could be accomplished with BF_3•OEt_2/Et_3SiH in high yield. These same conditions allowed for direct reduction of **9b** to **4b**, but the yield was somewhat lower.



[a]Reaction conditions: i. 3.4 atm H_2, 10% Pd/C (70%), ii. $NaBH_4$ TFA (91%). iii. BF_3•OEt_2, Et_3SiH (90%). iv. BF_3•OEt_2, Et_3SiH (41%). v. $NaBH_4$ (90%). vi. 3.4 atm H_2, 10% Pd/C (incomplete conversion).

Scheme 7.

Summary. A convenient synthesis and isolation of **7** was established, and conditions were optimized for the effective utilization of **7** for the general synthesis of a variety of 2-aryloyl-5-formylbenzofuran products (**24**). Condensation of **24b** with **8** was used to introduce the 2,4-thiazolidinedione moiety for generation of **9b**. Catalytic hydrogenation led to the conversion of **9b** to **5b**. From **5b**, another class of insulin sensitivity enhancers, represented by **4b**, was accessed. When the longest linear sequence for the synthesis of **5b** was examined, the optimized overall yield was 20% (4 steps from **23**). When the cost-limiting sequence was examined, which included formation of **6b** from 2-fluoroanisole, an optimized overall yield of 45% was obtained (4 steps). Similarly, the general synthesis of **4b** was accomplished from **9b** in good yield.

EXPERIMENTAL SECTION

Reactions were carried out under positive nitrogen pressure. Microanalysis was obtained from Eli Lilly & Co. Physical Chemistry Department.

3'-Fluoro-4'-methoxy-2-bromoacetophenone (6b): Methyl ketone (**10**) (14.75 g, 87.7 mmol) was suspended in Et_2O (350 mL) and $CHCl_3$ (140 mL), and the mixture was cooled to 0 °C. A solution of Br_2 (14.16 g, 4.56 mL, 88.6 mmol) in $CHCl_3$ (70 mL) was added dropwise to the substrate over 2 h at 0 °C, and the colorless mixture was stirred an additional 2 h at 0 °C. HPLC of the crude reaction mixture showed a 9:82:8 ratio of **10**:**6b**:**11**. The mixture was washed with H_2O (150 mL), 2% $NaHCO_3$ (200 mL), saturated aqueous NaCl (100 mL), and was then dried over $MgSO_4$. After removal of inorganic salts by filtration, the filtrate was concentrated to a white solid. This solid was crystallized by dissolving the solid in 20 mL of EtOAc at 45-50 °C followed by the slow addition of 180 mL of hexane to the stirred solution. The resultant precipitate was collected by filtration to give 13.37 g of **6b** (62% yield), which was contaminated with 3% of methyl ketone (**10**): mp: 75.0-76.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.98 (s, 3 H), 4.39 (s, 2 H), 7.04 (t, J = 8.3 Hz, 1 H), 7.74 (dd, J = 11.2, 1.0 Hz, 1 H), 7.79 (dd, J = 8.3, 1.0 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$, includes peaks that result from ^{19}F coupling): δ 30.7, 56.8, 112.9, 116.8, 116.9, 126.92, 126.94, 127.47, 127.51, 151.5, 153.0, 153.1, 153.4, 189.6; IR ($CHCl_3$): 2940, 1679, 1612, 1519, 1440, 1285 cm^{-1}. Anal. Calcd for $C_9H_8O_2BrF$: C, 43.75; H, 3.26. Found: C, 43.84; H, 3.33.

General Procedure for Freidel-Crafts Acylation with Bromoacetyl Bromide: To a suspension of $AlCl_3$ (11.55 g, 86.6 mmol) in 1,2-dichlorethane (45 mL) at 0 °C was added bromobenzene (12.05 g, 76.0 mmol) in one portion. Bromoacetyl bromide (18.41 g, 91.2 mmol) was added over 10 min so that the reaction was maintained at a temperature between 0-10 °C. The mixture was warmed to ambient temperature, stirred for 4 h, the reaction was quenched by the slow addition to H_2O (76 mL) so as to maintain a temperature below 45 °C, the layers were separated, and the organic layer was washed sequentially with 1 *N* HCl (60 mL) and H_2O (60 mL). The organic layer was stripped to a crystalline solid and then dried *in vacuo* at 45 °C to give **6c** (20.74 g) in 98% yield:

4'-Methyl-2-bromoacetophenone (6a): (16.04 g, 99%); mp: 47.5-49.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.45 (s, 3 H), 4.45 (s, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 7.91 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 22.2, 31.5, 129.5, 130.0, 131.9, 145.4, 191.4; IR ($CHCl_3$): 1679, 1606, 1284, 1183 cm^{-1}.

3'-Fluoro-4'-methoxy-2-bromoacetophenone (6b): (16.3 g, 87%). Identified by direct comparison with product obtained by the method above.

4'-Bromo-2-bromoacetophenone (6c): (20.74 g, 98%); mp: 109.0-110.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.42 (s, 2 H), 7.63-7.67 (m, 2 H), 7.84-7.87 (m, 2 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 30.9, 129.7, 130.8, 132.6, 133.1, 190.8; IR ($CHCl_3$): 1685, 1587, 1398, 1280, 1072, 1008 cm^{-1}. Anal. Calcd for $C_8H_6OBr_2$: C, 34.57; H, 2.18. Found: C, 34.78; H, 2.34.

Conversion of 15 to 2-Bromoacetylbenzo[*b*]thiophene (16): To a solution of 2-acetylbenzo[*b*]thiophene (5.3 g, 30 mmol) in CH_2Cl_2 (360 mL) and MeOH (140 mL) was added (n-Bu)$_4$NBr$_3$ (16.0 g, 33 mmol) at 22 °C. The reaction mixture was stirred for 6 h, and was then evaporated under reduced pressure at 40 °C. The resultant solid was dissolved in Et_2O (200 mL), washed with H_2O (100 mL) and sat. aq. NaCl (100 mL), and then dried (Na_2SO_4). Concentration under reduced pressure gave a solid, which was crystallized from EtOH/H_2O (1:2) to give 7.27 g of product (**16**) (95%) in two crops: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (s, 2 H); 7.15-7.26 (m, 2 H); 7.60-7.69 (m, 2 H); 8.80 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 30.3, 123.0, 125.3, 126.3, 128.1, 130.9, 138.9, 140.1, 143.0, 186.0; IR (KBr) 2954, 1674, 1512 cm^{-1}.

Acylation of 17 to 2-acetylbenzo[*b*]thiophene (15): A solution of benzo[*b*]thiophene (1.34 g, 10.0 mmol) in dry THF (10.0 mL) was cooled to -78 °C, and n-BuLi (4.0 mL, 2.5 *N* in hexane, 10.0 mmol) was added slowly by syringe. The solution was stirred for 45 min at -78 °C and was then

transferred *via* cannula to a -78 °C solution of *N*-methoxy-*N*-methylacetamide (1.03 g, 10.0 mmol) in THF (10 mL). The mixture was stirred at -78 °C for 10 min, allowed to slowly warm to 22 °C, and then the reaction was quenched by the addition of sat. aq. NH_4Cl. The product was extracted into Et_2O (100 mL), the organic layer was washed with sat. aq. NaCl (100 mL), and then dried (Na_2SO_4). Concentration under reduced pressure gave 1.02 g of **15** (62%). Spectral data was in complete agreement with that reported in the literature.[20]

Conversion of 17 to 2-chloroacetylbenzo[*b*]thiophene (18): A solution of benzo[*b*]thiophene (2.95 g, 22.0 mmol) in dry THF (15.0 mL) was cooled to -78 °C, and *n*-BuLi (9.9 mL, 2.5 *N* in hexane, 24.7 mmol) was added slowly by syringe. The solution was stirred for 45 min at -78 °C and then 2-chloro-*N*-methoxy-*N*-methylacetamide (3.0 g, 22.0 mmol) was added. The mixture was stirred at -78 °C for 10 min, allowed to slowly warm to 22 °C, and then the reaction was quenched by the addition of sat. aq. NH_4Cl. The product was extracted into Et_2O (200 mL), the organic layer was washed with sat. aq. NaCl (100 mL), and then dried (Na_2SO_4). Concentration, followed by crystallization from CH_2Cl_2 and hexane gave 2.69 g of **18** (58%). An additional 0.40 g (9%) was obtained by chromatography (eluent: EtOAc/hexane, 15:85) to give a total yield of 67%: mp: 110-112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.24 (s, 2 H), 7.51 (bt, *J* = 7.2 Hz, 1 H), 7.57 (bt, *J* = 7.2 Hz, 1 H), 8.05 (d, *J* = 8.0 Hz, 1 H), 8.09 (d, *J* = 8.1 Hz, 1 H), 8.45 (s, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 47.5, 124.1, 126.4, 127.3, 129.0, 132.7, 139.8, 140.8, 142.5, 187.4; IR ($CHCl_3$): 2941, 1688, 1667, 1515 cm^{-1}. Anal. Calcd for $C_{10}H_7OClS$: C, 57.01; H, 3.35; Cl, 16.83. Found: C, 57.18; H, 3.40; Cl, 16.58.

5-Formylsalicylaldehyde (7): To a solution of **23** (527 g, 4.32 mol) in 4.35 L of TFA was added HMTA (605 g, 4.32 mol) in one portion under nitrogen. After the addition was complete, the solution temperature had reached 55 °C (mild exotherm), and then external heating was used to reflux (≈97 °C) the reaction mixture for 24 h. The reaction was then quenched by the addition of 6.82 L of 3*N* HCl, and the heat source was removed and the mixture was allowed to cool to ambient temperature over the course of 2 h. The mixture was extracted with 4 x 8.2 L of CH_2Cl_2, and the combined organic layers were concentrated to an oil. Addition of 557 mL of EtOH at 40 °C resulted in the crystallization of **7** as a light yellow solid. The mixture was then cooled to 0 °C overnight and then stirred at -10 to 0 °C for 1 h. The solids were isolated by filtration, washed with cold EtOH (2 x 220 mL), and dried to give **7** (264 g) in 41% yield. In general, second crops of crystalline material can be obtained in about 10% additional yield, but potency of the material was lower (≈90%): mp: 112-115 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.6 Hz, 1 H), 8.09 (dd, *J* = 8.5, 1.8 Hz, 1 H), 8.17 (d, *J* = 1.8 Hz, 1 H), 9.96 (s, 1 H), 10.03 (s, 1 H), 11.57 (s, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 119.3, 120.8, 129.7, 136.9, 137.6, 166.7, 189.7, 196.6; IR ($CHCl_3$): 2851, 2741, 1700, 1665, 1591, 1483, 1295, 1140 cm^{-1}. Anal. Calcd for $C_8H_6O_3$: C, 64.00; H, 4.03. Found: C, 64.13; H, 4.17.

General Procedure for Benzofuran Formation from 5-Formylsalicylaldehyde: A mixture of **6b** (376 g, 1.52 mol), **7** (229 g, 1.52 mol), and K_2CO_3 (211 g, 1.52 mol) was taken up in MeCN (5.4 L) and stirred with overhead mechanical stirring. The heterogeneous mixture was heated at reflux for 3 h under an atmosphere of N_2 until the transformation was complete (HPLC). After the heat source was removed, 10.8 L of H_2O was added to the 80°C reaction mixture, and the stirred mixture was allowed to cool to ambient temperature overnight (due to the reaction scale). In smaller scale reactions, the H_2O was added over the course of 2 h, and the mixture was cooled slowly over 90 min. The mixture was filtered, washed with H_2O/MeCN; 2:1 (2 x 1.5 L), MeCN (2 x 1.5 L), and then dried *in vacuo* at 50-60 °C overnight to give 2-(3-fluoro-4-methoxy)benzoyl-5-benzofurancarboxaldehyde **(24b)** (425 g) in 94% isolated yield as a white solid: mp: 171-172 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.03 (s, 3 H), 7.13 (t, *J* = 8.3 Hz, 1 H), 7.68 (s, 1 H), 7.79 (d, *J* = 8.7 Hz, 1 H), 7.93 (dd, *J* = 11.7, 2.3 Hz, 1 H), 8.00 (dt, *J* =

8.0, 1.4 Hz, 1 H), 8.08 (dd, J = 8.7, 1.3 Hz, 1 H), 8.31 (d, J = 1.3 Hz, 1 H), 10.12 (s, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$, includes peaks that result from ^{19}F coupling): δ 56.8, 113.0, 113.8, 116.0, 117.8, 117.9, 127.3, 127.66, 127.68, 127.8, 129.1, 129.67, 129.71, 133.6, 151.4, 152.7, 152.8, 153.3, 154.4, 159.2, 181.5, 191.5; IR ($CHCl_3$): 1699, 1650, 1613, 1519, 1284 cm^{-1}. Anal. Calcd for $C_{17}H_{11}O_4F$: C, 68.46; H, 3.72; F, 6.37. Found: C, 68.71; H, 3.63; F, 6.29.

2-Benzoyl-5-benzofurancarboxaldehyde (24a): (5.67 g, 84%); mp: 156.5-157.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (t, J = 7.7 Hz, 2 H), 7.65 (s, 1 H), 7.69 (m, 1 H), 7.78 (d, J = 8.7 Hz, 1 H), 8.06-8.10 (m, 3 H), 8.30 (d, J = 1.4 Hz, 1 H), 10.11 (s, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 113.8, 116.6, 127.3, 127.9, 129.1, 129.2, 129.9, 133.6, 133.7, 137.1, 154.2, 159.3, 184.3, 191.4; IR ($CHCl_3$): 3021, 1699, 1655, 1612, 1554, 1322, 1111 cm^{-1}. Anal. Calcd for $C_{16}H_{10}O_3$: C, 76.79; H, 4.03. Found: C, 76.64; H, 4.09.

2-(4-methyl)benzoyl-5-benzofurancarboxaldehyde (24c): (1.45 g, 82%); mp: 158.0-159.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.49 (s, 3 H), 7.38 (d, J = 8.0 Hz, 2 H), 7.63 (s, 1 H), 7.78 (d, J = 8.6 Hz, 1 H), 8.00 (d, J = 8.1 Hz, 2 H), 8.07 (dd, J = 8.5, 1.3 Hz, 1 H), 8.30 (s, 1 H), 10.11 (s, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 22.2, 113.8, 116.2, 127.2, 127.9, 129.1, 129.8, 130.1, 133.6, 134.5, 144.8, 154.4, 159.2, 183.9, 191.5; IR ($CHCl_3$): 3020, 1698, 1649, 1609, 1555, 1320, 1111 cm^{-1}. Anal. Calcd for $C_{17}H_{12}O_3$: C, 77.24; H, 4.58. Found: C, 76.85; H, 4.58.

2-(4-Bromo)benzoyl-5-benzofurancarboxaldehyde (24d): (2.04 g, 93%); mp: 177.0-178.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (s, 1 H), 7.72 (bd, J = 8.4 Hz, 2 H), 7.78 (d, J = 8.6 Hz, 1 H), 7.97 (bd, J = 8.4 Hz, 2 H), 8.09 (dd, J = 8.7, 1.4 Hz, 1 H), 8.31 (d, J = 1.1 Hz, 1 H), 10.12 (s, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 113.8, 116.7, 127.4, 127.8, 129.0, 129.4, 131.4, 132.5, 133.7, 135.7, 154.0, 159.3, 183.0, 191.4; IR ($CHCl_3$): 1699, 1654, 1588, 1553, 1111 cm^{-1}. Anal. Calcd for $C_{16}H_9O_3Br$: C, 58.39; H, 2.76; Br, 24.27. Found: C, 58.39; H, 3.11; Br, 23.79.

2-(3,5-Di-*t*-butyl-4-hydroxy)benzoyl-5-benzofurancarboxaldehyde (24e): (1.83 g, 79%); mp: 174.0-174.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53 (s, 18 H), 5.89 (s, 1 H), 7.60 (s, 1 H), 7.77 (d, J = 8.6 Hz, 1 H), 8.03 (s, 2 H), 8.07 (dd, J = 8.6, 1.0 Hz, 1 H), 8.33 (s, 1 H), 10.12 (s, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 30.6, 34.9, 113.7, 115.4, 127.2, 128.0, 128.7, 128.8, 133.5, 136.6, 155.0, 159.1, 159.4, 183.6, 191.6; IR ($CHCl_3$): 3625, 2965, 1697, 1641, 1612, 1591, 1304, 1110 cm^{-1}. Anal. Calcd for $C_{24}H_{25}O_4$: C, 76.17; H, 6.92. Found: C, 76.44; H, 7.11.

2-[(1,2,3,4-Tetrahydro-2-oxo-6-quinolyl)carbonyl]-5-benzofurancarboxaldehyde (28): (1.83 g, 78%); mp: 245.0-247.0 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.45-2.52 (m, 2 H), 2.94-3.00 (m, 2 H), 7.00 (d, J = 8.7 Hz, 1 H), 7.86-7.93 (m, 4 H), 8.03 (dd, J = 8.8, 1.1 Hz, 1 H), 8.40 (s, 1 H), 10.07 (s, 1 H), 10.50 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 24.5, 30.0, 113.1, 114.9, 116.2, 123.7, 127.2, 127.3, 128.3, 129.2, 129.4, 129.9, 132.8, 143.2, 153.0, 157.9, 170.4, 181.6, 192.2; IR (KBr): 1697, 1635, 1612, 1592, 1302, 1124 cm^{-1}. Anal. Calcd for $C_{19}H_{12}NO_4$: C, 71.47; H, 4.10; N, 4.39. Found: C, 71.33; H, 4.19; N, 4.63.

2-(Benzo[*b*]thien-2-ylcarbonyl)-5-benzofurancarboxaldehyde (29): (1.77 g, 87%); mp: 156.0-157.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (t, J = 7.5 Hz, 1 H), 7.60 (t, J = 7.5 Hz, 1 H), 8.02 (d, J = 8.6 Hz, 1 H), 8.08-8.18 (m, 3 H), 8.24 (s, 1 H), 8.48 (s, 1 H), 8.78 (s, 1 H), 10.12 (s, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 114.3, 116.9, 123.9, 126.4, 127.8, 128.1, 128.2, 129.1, 129.5, 133.6, 133.9, 140.1, 141.8, 142.5, 153.4, 159.0, 176.3, 193.1; Anal. Calcd for $C_{18}H_{10}O_3S$: C, 70.58; H, 3.29; S, 10.47. Found: C, 70.36; H, 3.41; S, 10.82.

2-(2-Pyridinylcarbonyl)-5-benzofurancarboxaldehyde (31): (0.600 g, 39%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 5.5 Hz, 1 H), 7.77 (d, J = 8.5 Hz, 1 H), 7.94 (t, J = 7.3 Hz, 1 H), 8.05 (d, J = 8.4 Hz, 1 H), 8.24 (d, J = 7.7 Hz, 1 H), 8.31 (s, 1 H), 8.60 (s, 1H), 8.80 (d, J = 3.5 Hz, 1 H), 10.09

(s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 113.2, 120.4, 123.8, 127.7, 127.9, 128.0, 129.0, 133.0, 138.0, 149.2, 151.9, 152.8, 158.0, 180.1, 192.2; IR ($CHCl_3$): 1690, 1654, 1579, 1551, 1327, 1108, 974 cm^{-1}. Anal. Calcd for $C_{15}H_9NO_3$: C, 71.71; H, 3.61; N, 5.57. Found: C, 71.79; H, 3.85; N, 5.82.

5-[(5-Formyl-2-benzofuranyl)carbonyl-3-isoxazolecarboxylic acid ethyl ester (33): (0.155 g, *61%*); *mp: 165.0-166.0* °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (t, *J* = 7.1 Hz, 3 H), 4.51 (q, *J* = 7.1 Hz, 2 H), 7.67 (s, 1 H), 7.80 (d, *J* = 8.7 Hz, 1 H), 8.13 (dd, *J* = 8.7, 0.8 Hz, 1 H), 8.23 (s, 1 H), 8.36 (s, 1 H), 10.11 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0, 62.7, 110.5, 113.5, 118.4, 127.2, 127.7, 129.7, 133.5, 151.3, 157.0, 158.7, 158.9, 166.3, 168.0, 190.6; IR (KBr): 1743, 1707, 1703, 1647, 1612, 1584, 1293, 1264 cm^{-1}. Anal. Calcd for $C_{16}H_{11}NO_6$: C, 61.35; H, 3.54; N, 4.47. Found: C, 61.18; H, 3.78; N, 4.69.

2-Acetyl-5-formylbenzofuran (35): A mixture of **34** (1.00 g, 6.66 mmol) and K_2CO_3 (0.92 g, 6.66 mmol) was taken up in MeCN (40 mL) and stirred with overhead mechanical stirring under an atmosphere of N_2. After 10 min, KI (1.22 g, 7.33 mmol) was added in one portion, and then chloroacetone (0.53 mL, 6.66 mmol) was added dropwise over the course of 2 min. The heterogeneous mixture was stirred at room temperature for 45 min, and was then heated to reflux for 3 h until the transformation was complete (HPLC). At reflux (≈83 °C), 28 mL of H_2O was added, and the stirred mixture was allowed to cool to ambient temperature to give an homogeneous solution. The mixture was concentrated *in vacuo* to give a slushy solid, which was suspended in CH_2Cl_2 (50 mL), filtered, and the solids were washed with CH_2Cl_2. The filtrate was washed with H_2O (50 mL), concentrated to a solid, and the solids were suspended in H_2O (8 mL). The mixture was stirred for 1 h, filtered, the solids were washed with H_2O, and dried *in vacuo* at 45 °C for *12 h to give* **35** *(1.18 g) in 94% isolated yield as a white solid: mp*: 169.0-171.0 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 2.64 (s, 3 H), 7.61 (s, 1 H), 7.70 (d, *J* = 8.7 Hz, 1 H), 8.04 (d, *J* = 8.7 Hz, 1 H), 8.26 (s, 1 H), 10.08 (s, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 27.0, 113.4, 113.7, 127.4, 127.9, 129.1, 133.5, 154.5, 159.0, 188.7, 191.5; IR ($CHCl_3$): 1690, 1612, 1562, 1294, 1110 cm^{-1}. Anal. Calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.29. Found: C, 70.21; H, 4.46.

5-Methyl-2-benzofuranyl phenyl ketone (39): α-Bromoacetophenone (51.8 g, 260 mmol) and 5-methylsalicylaldehyde (**38**, 35.5 g, 260 mmol) were dissolved in 320 mL of acetone in a 1 L three-necked flask, and the solution was mixed with overhead stirring. Freshly ground K_2CO_3 (108 g, 781 mmol) was added, and the mixture was heated for 10 h at an internal temperature of 55 °C. After the solution was cooled to ambient temperature, the mixture was filtered. The residual solids were dissolved in a minimum amount of H_2O, and this solution was extracted twice with EtOAc/Et_2O (1:1). Concentration of the filtrate gave a solid, which was dissolved in EtOAc/Et_2O (1:1) and was combined with the residual product extracted from the inorganic salts. The combined organic layers were washed with H_2O (2x), saturated aqueous NaCl, and dried (Na_2SO_4). Concentration of the filtrate gave a solid material, which was suspended in Et_2O and filtered to give **39** as a white powder (36.3 g, 59%). A second crop of **39** (7.78 g, 13%) was obtained as a solid from the mother liquor. Chromatography on SiO_2 (10% EtOAc/90% hexanes) led to a third sample of **39** (4.32 g, 7%) to give a combined 79% yield of **39**: *mp*: 94.5-95.5 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 2.50 (s, 3 H), 7.34 (d, *J* = 8.6 Hz, 1 H), 7.48 (s, 1 H), 7.52-7.58 (m, 4 H), 7.66 (t, *J* = 7.2 Hz, 1 H), 8.07 (d, *J* = 7.7 Hz, 2 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.7, 112.5, 116.7, 123.1, 127.5, 128.9, 129.9, 130.4, 133.2, 134.0, 137.8, 152.8, 155.0, 184.8; IR ($CHCl_3$): 3025, 3015, 1646, 1549, 1315, 1281, 975 cm^{-1}; Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.32; H, 5.07.

5-Bromomethyl-2-benzofuranyl phenyl ketone (40a): Benzofuran (**39**) (54.61 g, 231 mmol), *N*-bromosuccinimide (45.2 g, 254 mmol), and AIBN (1.2 g) were combined in a 2 L three-necked flask, and

were then dissolved in 1000 mL of CCl_4 and 400 mL of $CHCl_3$. The mixture was heated to 70 °C for 2.5 h to give a 25:68:7 ratio of **39**:**40a**:**40b**. Additional *N*-bromosuccinimide (4.5 g, 25.4 mmol), and AIBN (1.2 g) were added, and the mixture was heated an additional 1.5 h to give a 19:71:10 ratio of **39**:**40a**:**40b**. A final addition of *N*-bromosuccinimide (4.5 g, 25.4 mmol), and AIBN (1.2 g) was made, and the mixture was heated an additional 2.5 h to give a 14:73:13 ratio of **39**:**40a**:**40b**. After the reaction mixture was cooled to 25 °C, the mixture was then filtered through 100 g of silica gel and washed through with 1100 mL of CH_2Cl_2. Concentration of the combined filtrate and washings led to solid material, which was then taken up in a minimum amount of hexanes/CH_2Cl_2 (≈6:1). While stirring, the mixture was cooled to -50 °C with a dry ice/acetone bath. The resultant solid was removed by filtration to give a white powder (39.7 g). Concentration of the filtrate gave an oil, which was taken up in a minimum amount of Et_2O, cooled to -50 °C, and filtered to give an additional 13.1 grams of a white powder. The total amount of product obtained, 52.8 g, represented an ≈73% total yield that had a 5:90:5 final ratio of constituents **39**:**40a**:**40b**: mp: 87.0-88.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.65 (s, 2 H), 7.53 (s, 1 H), 7.54-7.58 (m, 3 H), 7.63-7.69 (m, 2 H), 7.78 (d, J = 1.0 Hz, 1 H), 8.07 (d, J = 7.2 Hz, 2 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 33.4, 113.1, 116.2, 123.7, 127.3, 128.6, 129.5, 129.7, 133.1, 133.9, 137.0, 153.0, 155.6, 184.2; IR ($CHCl_3$): 3016, 1723, 1648, 1552, 1324, 1280, 975 cm^{-1}; Anal. Calcd for $C_{16}H_{11}O_2Br$: C, 60.98; H, 3.52. Found: C, 60.00; H, 3.69.

5-Hydroxymethyl-2-benzofuranyl phenyl ketone (41): A solution of **39** (2.1 g of 90% wt, 6.0 mmol) in 1:1 acetone:H_2O (50 mL) was treated with Na_2CO_3 (6.4 g, 60 mmol) and the reaction was heated at 50 °C for 25 h. The mixture was cooled and partitioned between water (20 mL) and EtOAc (40 mL). The organic phase was washed with sat. aq. NaCl, dried (Na_2SO_4) and concentrated *in vacuo*. The residue (yellow solid) was recrystallized from EtOAc/hexane to provide **41** (1.14 g, 75%) as off-white crystals: mp 108.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (br s, 1 H), 4.80 (s, 2 H), 7.25-7.71 (m, 7 H), 8.03 (d, J = 7.1 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 62.7, 111.8, 117.3, 121.0, 126.7, 127.7, 128.7, 129.1, 133.0, 136.8, 138.6, 151.6, 154.5, 183.4; FDMS *m/z* 252 (M+). Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.07; H, 4.85.

2-Benzoyl-5-benzofurancarboxaldehyde (24a): A solution of oxalyl chloride (123 μL, 1.51 mmol) in CH_2Cl_2 (2.0 mL) was cooled to -78 °C and treated dropwise with DMSO (215 μL, 3.02 mmol). The reaction was stirred at -78 °C for 10 min, and then was treated with a solution of **41** (318 mg, 1.26 mmol) in CH_2Cl_2 (2 mL) by cannulation. The reaction was stirred at -78 °C for 10 min then warmed to -25 °C and stirred at that temperature for 10 min. Triethylamine (843 μL, 6.05 mmol) was added by syringe and the reaction was warmed to ambient temperature, washed with 1N HCl (2 x 6 mL), dried (Na_2SO_4) and concentrated *in vacuo* to provide **24a** (317 mg, 100% yield, identical to authentic sample).

5-Methyl-2-benzofurancarboxylic acid (43): A solution of 6-methylcoumarin (**42**, 3.2 g, 20.0 mmol) in CH_2Cl_2 (10 mL) was treated dropwise with a solution of Br_2 in CH_2Cl_2 (3.2 g, 20.0 mmol in 4.0 mL CH_2Cl_2) over a 1 h. The reaction was stirred for an additional 1.5 h, and was then concentrated *in vacuo*. The residue (yellow oil, 5.66 g) was dissolved in EtOH (10 mL) and added to an ice-cold solution of KOH (12.9 g of 85 wt%, 195 mmol) in EtOH (30 mL) at such a rate that the reaction temperature did not exceed 15 °C. The reaction was heated to 77 °C and the resultant thick paste was dispersed by the addition of more EtOH (25 mL) to facilitate stirring. After 30 min at 77°C, the reaction was cooled in an ice-water bath, diluted with water (150 mL) and the solution concentrated *in vacuo* until ~100 mL of distillate was collected. The cloudy solution was washed with EtOAc (40 mL) and acidified with conc. HCl (13 mL). The mixture was extracted three times with EtOAc and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to provide **43** as light yellow crystals (2.84 g, 81%). An analytical sample was obtained by recrystallization from EtOH/water: mp 241.5 °C (decomp); ^{1}H NMR (300 MHz, DMSO-d_6) δ

2.40 (s, 3 H), 7.20-7.80 (m, 4 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ20.8, 111.6, 113.3, 122.4, 127.0, 128.9, 133.0, 146.3, 153.5, 160.2; FD MS *m/z* 176 (M+). Anal. Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.43; H, 4.71.

5-Methyl-2-benzofurancarbonyl chloride (44): A mixture of **43** (1.4 g, 7.95 mmol) and oxalyl chloride (901 μL, 10.3 mmol) in CH_2Cl_2 (20 mL) was added two drops of DMF. The reaction was stirred at rt for 2 h, concentrated *in vacuo*, and then was taken up in warm hexane (30 mL) and filtered. The filtrate was concentrated *in vacuo* to provide **44** (1.55 g, 100%) as an off-white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3 H), 7.36-7.48 (m, 3 H), 7.72 (d, *J* = 1.7 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.2, 112.1, 120.3, 123.0, 126.5, 131.6, 134.3, 146.4, 155.5, 157.1.

5-Methyl-2-(*N*-methoxy-*N*-methyl)benzofurancarbonyl (45): A solution of **44** (1.74 g, 8.94 mmol) in CH_2Cl_2 (30 mL) was treated with *N,O*-dimethylhydroxylamine hydrochloride (1.05 g, 10.7 mmol) and triethylamine (4.5 mL, 32.2 mmol). The reaction was stirred at rt for 30 min, and then was concentrated *in vacuo*. The residue was taken up in EtOAc (80 mL) washed with H_2O, 1 M HCl, dried (Na_2SO_4) and concentrated *in vacuo* to provide **45** as an amber oil (2.03 g, ~100%). The oil was dissolved in THF, concentrated *in vacuo*, and used directly in the preparation of **46**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3 H), 3.40 (s, 3 H), 3.80 (s, 3 H), 7.20-7.80 (m ,4 H).

5-Methyl-2-(benzo[*b*]thien-2-ylcarbonyl)-benzofurancarboxaldehyde (46): A solution of thianaphthene (1.20 g, 8.94 mmol) in THF (20 mL) was cooled to -78 °C and treated with *n*-BuLi (6.2 mL of a 1.6 M solution in hexane, 9.92 mmol) by syringe. The reaction was stirred at -78 °C for 1 h, and then was treated with a solution of **45** (2.00 g, 8.94 mmol) in THF (10 mL) by cannulation. The reaction was stirred at -78 °C for 15 min then quenched with sat.. aq. NH_4Cl (20 mL). The mixture was extracted with *t*BuOMe (30 mL) and the organic portion was washed with 1 M HCl (2 X 15 mL), brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was triturated in hexane and cooled to provide **46** as a light yellow solid, which was filtered, washed with hexane and dried (2.02 g, 77%). An analytical sample was obtained by recrystallization from EtOAc/hexane: mp 136.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3 H), 7.23-7.49 (m, 5 H), 7.60 (s, 1 H), 7.81-7.92 (m, 2 H), 8.48 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.2, 111.7, 114.6, 122.6, 124.9, 126.2, 126.9, 127.4, 129.8, 131.5, 133.6, 139.2, 141.8, 142.3, 152.4, 154.2, 175.9; FD MS *m/z* 293 (M+1); Anal. Calcd for $C_{18}H_{12}O_2S$: C, 73.95; H, 4.14. Found: C, 73.86; H, 4.17.

5-Bromomethyl-2-(benzo[*b*]thien-2-ylcarbonyl)benzofurancarboxaldehyde (47a): A solution of **46** (100 mg, 0.342 mmol) in $CHCl_3$ (3 mL) was treated with AIBN (≈1-3 mg), and the reaction was heated at reflux (63 °C). A solution of Br_2 in $CHCl_3$ (2.8 mL of a 5% v/v solution, ~2.7 mmol) was added dropwise over 23 h by syringe pump. Additional AIBN (≈1-3 mg) was added to the reaction after 7 h. Upon completion of the Br_2 addition, the reaction was cooled and concentrated *in vacuo*. The residue was triturated in EtOAc to provide **47a**, filtered, washed with EtOAc, and dried (80 mg, 63%). An analytical sample was obtained by recrystallization from EtOAc: mp 169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62 (s, 2 H), 7.42-7.98 (m, 8 H), 8.53 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 33.4, 112.9, 114.7, 122.7, 123.6, 125.1, 126.4, 127.1, 127.7, 129.6, 131.9, 134.0, 139.2, 141.7, 142.5, 153.2, 155.4, 176.0; FD MS *m/z* 370.372.

General Procedure for Condensation with 2,4-Thiazolidinedione (8): A suspension of **24b** (808 g, 2.71 mol) in MeCN (16 L) was stirred and heated to reflux until the mixture was homogeneous. Pyrrolidine (23 mL, 275 mmol) and 2,4-thiazolidinedione (**8**, 380.5 g, 3.25 mol) were added, and the product began to precipitate almost immediately. After the mixture was heated at reflux for 16 h, it was cooled to ambient temperature, filtered, and washed with MeCN (3 x 1 L), and dried *in vacuo* at 50-60 °C. The product was recrystallized from 16 volumes of DMF (8 L, 120 C to -10 C) to remove residual starting

material (7%), filtered, washed with cold DMF (500 mL), and dried *in vacuo* at 50-60 C to give 5-[[2-(3-fluoro-4-methoxybenzoyl)-5-benzofuranyl]methylene]-2,4-thiazolidinedione (**9b**) (852 g) in 78% yield: mp: 292-295 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.00 (s, 3 H), 7.41 (t, J = 8.6 Hz, 1 H), 7.82 (dd, J = 9.0, 1.8 Hz, 1 H), 7.89 (dd, J = 12.0, 2.0 Hz, 1 H), 7.92-7.95 (m, 3 H), 7.97 (dd, J = 8.1, 1.8 Hz, 1 H), 8.11 (d, J = 1.7 Hz, 1 H), 12.64 (bs, 1 H); ^{13}C NMR (125.8 MHz, DMF-d_7, includes peaks that result from ^{19}F coupling): δ 56.6, 113.6, 113.8, 116.6, 117.0, 117.1, 124.0, 125.83, 127.81, 127.84, 128.5, 129.78, 129.83, 130.2, 131.0, 131.9, 150.9, 152.4, 152.5, 152.9, 153.5, 156.4, 167.8, 168.2, 181.2; IR (KBr): 1740, 1698, 1579, 1548, 1513, 1289 cm^{-1}. Anal. Calcd for $C_{20}H_{12}NO_5FS$: C, 60.45; H, 3.04; F, 4.78; N, 3.52; S, 8.07. Found: C, 60.54; H, 2.99; F, 5.08; N, 3.65; S, 7.77.

5-[[5-Benzoyl]methylene]-2,4-thiazolidinedione (9a): (1.25 g, 89%) Note: After reaction conversion was complete, H_2O was added to the hot reaction mixture in order to maximize product recovery upon cooling. mp: 286-288 °C (decomp); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.50-8.00 (m, 10 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) 113.8, 117.6, 123.9, 125.8, 128.2, 129.3, 129.7, 129.9, 131.4, 131.9, 133.8, 137.0, 152.9, 156.1, 168.1, 168.5, 183.8; IR (KBr): 1761, 1702, 1647, 1603, 1330, 1301 cm^{-1}; Anal. Calcd for $C_{19}H_{11}NO_4S$: C, 65.32; H, 3.17; N, 4.01; Found: C, 65.09; H, 3.34; N, 4.30.

5-[[5-(Benzo[*b*]thioen-2-ylcarbonyl)]methylene]-2,4-thiazolidinedione (9c): (0.51 g, 55%); mp: 322-325 °C (decomp); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (t, J = 7.4 Hz, 1 H), 7.61 (t, J = 7.4 Hz, 1 H), 7.85 (d, J = 8.6 Hz, 1 H), 7.94 (s, 1 H), 7.99 (s, 1 H), 8.12-8.19 (m, 3 H), 8.22 (s, 1 H), 8.80 (s, 1 H), 12.67 (bs, 1 H); IR (KBr): 3140, 3054, 1747, 1685, 1611, 1597, 1558, 1301 cm^{-1}. Anal. Calcd for $C_{21}H_{11}NO_4S_2$: C, 62.21; H, 2.74; N, 3.46; S, 15.81. Found: C, 62.14; H, 2.91; N, 3.46; S, 15.69.

5-[[2-(3-Fluoro-4-methoxybenzoyl)-5-benzofuranyl]methyl]-2,4-thiazolidinedione (5b): To a suspension of **9b** (421 g, 1.06 mol) in 20 L of THF was added 10% Pd/C (318 g, 7.5 wt% of Pd) in a 10 gal hydrogenation reactor, and the mixture was placed under 50 psi of H_2. The mixture was heated to 50 °C, and was stirred for 18 h.. Removal of the catalyst by filtration, followed by thorough rinsing of the catalyst with THF, gave a solution which was concentrated to 2.5 kg of net weight. EtOH (2 L, denatured with toluene) was slowly added to the mixture at 30-40 °C, and the mixture was placed in an ice bath to stir for 2 h. The product was filtered, washed with EtOH (1 L), and dried *in vacuo* at 50 °C to give **5b** (296 g) in 70% yield: mp: 184-186 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.30 (dd, J = 14.1, 8.8 Hz, 1 H), 3.52 (dd, J = 14.1, 4.5 Hz, 1 H), 3.98 (s, 3 H), 4.99 (dd, J = 8.8, 4.5 Hz, 1 H), 7.38 (t, J = 8.6 Hz, 1 H), 7.47 (dd, J =8.6, 1.3 Hz, 1 H), 7.71-7.75 (m, 2 H), 7.81 (s, 1 H), 7.87 (dd, J = 12.0, 1.8 Hz, 1 H), 7.95 (bd, J = 8.7 Hz, 1 H), 12.02 (br s, 1 H); ^{13}C NMR (125.8 MHz, DMSO-d_6, includes peaks that result from ^{19}F coupling): δ 37.7, 53.8, 57.3, 113.1, 114.4, 117.1, 117.4, 117.6, 125.0, 127.8, 128.2, 130.0, 130.1, 130.9, 133.6, 150.9, 152.3, 152.4, 152.8, 152.9, 155.3, 172.3, 176.4, 181.7. IR (KBr): 1749, 1700, 1641, 1612, 1552, 1283 cm^{-1}. Anal. Calcd for $C_{20}H_{14}NO_5FS$: C, 60.15; H, 3.53; N, 3.51; F, 4.76; S, 8.03. Found: C, 60.16; H, 3.57; N, 3.25; F, 4.93; S, 7.39.

5-[[2-(3-Fluoro-4-methoxybenzoyl)-5-benzofuranyl]methyl]-2,4-thiazolidinedione, sodium salt (34b): A suspension of **5b** (375 g, 0.94 mol) in MeOH (12.8 L) was stirred at ambient temperature under N_2, and a solution of NaOMe (203 g, 25 wt% in MeOH) was added. Upon addition, the reaction mixture appeared to approach approximately 98% homogeneity before significant amounts of precipitate were generated. After 4 h at ambient temperature, the mixture was filtered, rinsed with MeOH (1 L), and dried *in vacuo* at 50-60 °C to give **34b** (344 g) in 87% yield: mp: 296-298 °C (decomp); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.90 (dd, J = 13.9, 10.0 Hz, 1 H), 3.49 (dd, J = 13.9, 3.5 Hz, 1 H), 3.98 (s, 3 H), 4.25 (dd, J = 10.0, 3.5 Hz, 1 H), 7.39 (t, J = 8.5 Hz, 1 H), 7.44 (d, J =8.9 Hz, 1 H), 7.64-7.68 (m, 2 H), 7.78 (s, 1 H), 7.86 (dd, J = 11.9, 1.3 Hz, 1 H), 7.95 (bd, J = 8.5 Hz, 1 H); ^{13}C NMR (125.8

MHz, DMSO-d_6, includes peaks that result from ^{19}F coupling): δ 57.3, 59.7, 117.3, 117.4, 117.5, 124.3, 127.6, 128.2, 130.1, 130.2, 130.9, 136.9, 150.9, 152.3, 152.4, 152.5, 152.9, 155.0, 181.8, 182.0, 191.2; IR (KBr): 1662, 1639, 1614, 1558, 1542, 1520, 1327, 1288 cm^{-1}. Anal. Calcd for $C_{20}H_{13}NO_5FNaS$: C, 57.01; H, 3.11; N, 3.32; F, 4.51; S, 7.61. Found: C, 57.22; H, 3.06; N, 3.10; F, 4.58; S, 7.50.

Reduction of 5b to 4b with BF_3•OEt_2/Et_3SiH. A suspension of **5b** (0.80 g, 2.0 mol) in 15 mL of $Cl_2CH_2CH_2Cl$ was stirred at 0 °C during the addition of BF_3•OEt_2 (0.74 mL, 6.0 mmol) over a period of 2 min. After the resultant orange solid was stirred for 5 min at 0°C, Et_3SiH (0.96 mL, 6.0 mmol) was added at 0 °C, and the mixture was heated to 85 °C. The mixture was heated at 85 °C for 6 h (only 85% conversion), and additional Et_3SiH (0.32 mL, 2.0 mmol) was added. The mixture was heated an additional 12 h at 85 °C, cooled to ambient temperature, and the reaction was quenched by the addition of H_2O. The solution was extracted with CH_2Cl_2, washed with 1N HCl, sat. aq. NaCl, and dried ($MgSO_4$). Filtration through a pad of SiO_2 followed by concentrated to a solid and trituration with CH_2Cl_2 gave 5-[[2-(3-fluoro-4-methoxy)phenylmethyl)-5-benzofuranyl]methyl]-2,4-thizolidinedione (**4b**) (0.69 g) in 90% yield: mp: 126.0-127.0 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 3.18 (dd, J = 14.1, 9.3 Hz, 1 H), 3.45 (dd, J = 14.1, 4.1 Hz, 1 H), 3.82 (s, 3 H), 4.08 (s, 2 H), 4.93 (dd, J = 9.2, 4.3 Hz, 1 H), 6.57 (s, 1 H), 7.06-7.15 (m, 3 H), 7.17 (d, J = 12.7 Hz, 1 H), 7.39-7.44 (m, 2 H), 12.02 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$, includes peaks that result from ^{19}F coupling): δ 33.8, 37.9, 54.1, 56.8, 104.0, 111.5, 114.8, 117.1, 117.2, 122.0, 125.7, 125.77, 125.79, 129.4, 130.99, 131.04, 132.1, 146.7, 146.8, 151.2, 153.2, 154.3, 159.1, 172.5, 176.5; IR ($CHCl_3$): 3385, 2842, 1757, 1703, 1520, 1274, 1126 cm^{-1}. Anal. Calcd for $C_{20}H_{16}NO_4FS$: C, 62.33; H, 4.18; N, 3.63; S, 8.32. Found: C, 62.33; H, 4.27; N, 3.67; S, 7.90.

Reduction of 5b to 4b with $NaBH_4$/TFA. $NaBH_4$ (0.113 g, 3.0 mmol) and **5b** (0.80 g, 2.0 mmol) were loaded into a flask and purged with an atmosphere of N_2. THF (15 mL) was added, and the mixture was stirred at 0 °C for 10 min until the clear solution became cloudy with a white precipitate. The mixture was warmed to rt, stirred for 3 h, and then cooled to 0 °C. TFA (5 mL) was added at 0 °C, and the mixture became homogeneous. After 3 h at rt, the reaction was quenched by the addition of H_2O. The solution was extracted with CH_2Cl_2, washed with 1N HCl, sat. aq. NaCl, and dried ($MgSO_4$). Flash chromatography on SiO_2 (CH_2Cl_2/MeCN; 95:5) gave **4b** (0.704 g) in 91% yield.

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