Synthesis and Antiproliferative Evaluation of 2′-Arenesulfonyloxy-5-benzylidene-thiazolidine-2,4-diones

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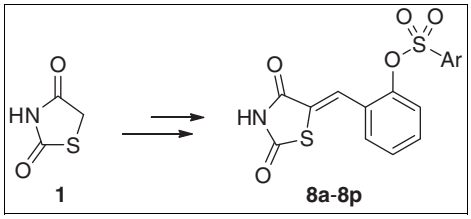
Received November 13, 2010
DOI 10.1002/jhet.859
View this article online at wileyonlinelibrary.com.



A series of 2′-arenesulfonyloxy-5-benzylidene-thiazolidine-2,4-diones (TZDs) were synthesized and examined for their antiproliferative effects on a panel of carcinoma cell lines. Our results indicated that initial synthesis of 5-[2′-hydroxybenzylidene]-2,4-thiazolidinone (9) by Knoevenagel condensation followed by nucleophilic substitution with arylsulfonyl chlorides exhibited superior efficiency to the alternative synthetic route. Among tested compounds, only 8c and 8e showed significant antiproliferative activity against PC-3 and BT474 cells with GI_{50} values of 8.4 and 20.6 μM, respectively. SKHep cells displayed interesting structure-activity relationships in response to TZD derivatives treatment. Alkyl group-substituted TZD analogs such as 8a (4-Me, GI_{50}, 9.4 μM) and 8k (4-*iso*-propyl, GI_{50}, 9.8 μM) revealed better antiproliferative activity than those with bulkier alkyl groups. On the other hand, halogen-substituted TZD analogs 8c, 8h, and 8i showed better antiproliferative activity against H460 cell line. Together, the new synthesized TZD derivatives **8a-8p** exhibited appreciable antiproliferative activity worth for further study.

J. Heterocyclic Chem., **49**, 792 (2012).

INTRODUCTION

Thiazolidinone (TZD) derivatives are reported to exhibit a variety of pharmacological activities such as antidiabetic [1], antioxidant [2], anti-inflammatory [3], antimicrobial [4], antiproliferative [5,6], antiviral [7], anticonvulsant [8], antifungal [9,10], and antibacterial activities [11]. In regard to its structural accessibility, TZD scaffold **1** can be modified to expand their diverse corresponding derivatives **2-4** (Fig. 1) [12]. Among all biological activities, the anticancer activity is of particular interest to us that we attempted to synthesize a new series of 2′-arenesulfonyloxy-5-benzylidene-thiazolidine-2,4-diones. To the best of our knowledge, the antiproliferative activity of above-mentioned TZD derivatives has not yet been examined. Herein, we employed two synthetic routes to prepare TZD derivatives by incorporating 2′-arylsulfonyloxy groups as well as to evaluate their antiproliferative effect on a panel of carcinoma cell lines.

RESULTS AND DISCUSSION

To prepare a series of 2′-arenesulfonyloxy-5-benzylidene-thiazolidine-2,4-diones, two synthetic pathways were utilized in the present work as shown in Scheme 1. As indicated, nucleophilic substitution of arylsulfonyl chlorides **5a-f** with 2-hydroxybenzaldehyde (**6**) in the presence of triethylamine in dichloromethane was carried out to afford arylsulfonates **7a-f** with good yields of 83–94% [13]. Arylsulfonates **7a-f** were subjected to undergo Knoevenagel condensation with thiazolidinone (**1**) in the presence of 0.5 equiv of piperidine in refluxed ethanol for 18–22 hr that afforded compounds **8a-f** with moderate yields of 43–56%. Accordingly, Knoevenagel condensation was poor in either strong bases such as sodium hydride and triethylamine or any bases more than 0.5 equiv. Moreover, the condensation reaction would not occur if no heat was charged.

We further turned our attention to employ the Method B in which the 5-[2′-hydroxybenzylidene]-2,4-thiazolidinone (**9**) was initially prepared as indicated in Scheme 1 [14]. Knoevenagel condensation of 2-hydroxybenzaldehyde **6** was expediently completed in the presence of sodium acetate in thiazolidinone **1** solution at 120°C in 10 min to give **9** with 85% isolated yield. With the intermediate **9** in hand, nucleophilic substitution of **9** with arylsulfonyl chlorides **5g-p** was taken place in the presence of triethylamine in acetone to give final products **8g-p** with moderate yields of 52–69%. Compared to Method A, Method B demonstrated to be more efficient in terms of time and overall yield (Table 1).

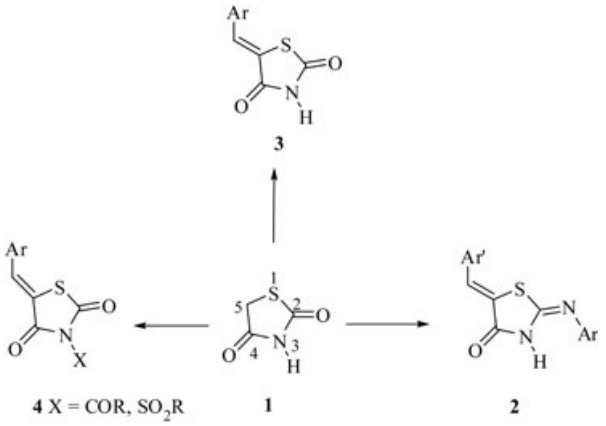


Figure 1. Thiazolidine-2,4-dione (**1**) and its derivatives **2**-**4**.

The antiproliferative evaluation of newly synthesized 2′-arenesulfonyloxy-5-benzylidene-thiazolidine-2,4-diones **8a**-**p** was examined on a panel of five human carcinoma cell lines, including PC-3 (prostate carcinoma cell), H460 (lung large cell adenocarcinoma cell), SW620 (colorectal adenocarcinoma cell), BT474 (breast carcinoma cell) and SKHep (hepatocellular carcinoma cell). The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay was utilized for these antiproliferation studies and the GI_{50} values are summarized in Table 2 [15]. The compound concentration causing a 50% cell growth inhibition (GI_{50}) was determined by interpolation from dose-response curves. The maximal concentration of tested compounds was treated with 40 μM to all cell lines due to the solubility of tested compounds in the Dulbecco's modified eagle medium (DMEM).

As shown in Table 2, none of the tested compounds exhibited antiproliferative effect against SW620 cells. On the other hand, only **8c** and **8e** showed significant antiproliferative activity against PC-3 and BT474 cells with GI_{50} values of 8.4 and 20.6 μM, respectively. Nevertheless, both SKHep and H460 cells displayed appreciable sensitivity in response to TZD treatment. Exposure of SKHep cells to the tested compounds exhibited interesting structure-activity relationships. For instance, compared to **8b** (GI_{50}, 9.8 μM) without any substituents at 4-position, alkyl group-substituted analogs showed that methyl (**8a**, GI_{50}, 9.4 μM) and isopropyl (**8k**, GI_{50}, 9.8 μM) groups displayed better antiproliferative activity while the potency was counteracted as the bulky groups such as *t*-butyl (**8l**, GI_{50}, 15.7 μM) and phenyl (**8n**, GI_{50}, 23.1 μM) groups were introduced. Moreover, we found that neither electron-donating groups (**8f**, 3-OMe; **8g**, 4-OMe and **8j**, 3,4-*di*-OMe) nor electron-withdrawing groups (**8c**, 4-Cl; 8d, 4-NO_2; **8h**, 4-F; **8i**, 4-Br and **8m**, 4-OCF_3) at 3- and/or 4-position showed any antiproliferative activity against SKHep cells at maximal concentration treatment. Interestingly, **8e** bearing 2-nitro group exhibited the most potent activity among all tested compounds with a GI_{50} value of 8.7 μM against SKHep cells. In addition, replacement of benzene ring **8b** (GI_{50}, 9.8 μM) with naphthalene moiety (**8o** and **8p**) resulted in the loss of antiproliferative activity. As regard to the sensitivity of H460 cells in response to the compound treatment, we found that halogen-substituted analogs **8c** (4-Cl), **8h** (4-F), and **8i** (4-Br) exhibited better activity than others with GI_{50} values of 8.7, 16.5, and 18.9 μM, respectively. Except for **8a** (4-Me) without activity, analogs containing alky groups did not show substantial structure-activity relationships between **8k** (4-*iso*-propyl, GI_{50}, 22.3 μM), **8l** (4-*tert*-butyl, GI_{50}, 27.2 μM) and **8n** (4-biphenyl, GI_{50}, 18.9 μM).

MATERIALS AND METHODS

Synthesis. Chemical reagents and organic solvents were purchased from TCI, Acros, Aldrich and Alfa Aesar unless otherwise mentioned. Melting points were determined by Fargo MP-2D. Nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were measured on a Bruker AC-300 instrument. Chemical shifts (δ) are reported in ppm relative to the TMS peak. High resolution mass spectra (HRMS) were obtained by FAB on a Jeol JMS-700 instrument. Flash column chromatography was performed with

Scheme 1. Reagents and conditions: (a) 2-hydroxybenzaldehyde (**6**), DCM, TEA, r.t, 2–3 hr; (b) **1**, EtOH, piperidine, ref lux, 18–22 hr; (c) **1**, NaOAc, 120–140°C, 10 min; (d) arylsulfonyl chlorides **5g**-**p**, acetone, TEA, r.t, 18–22 hr.

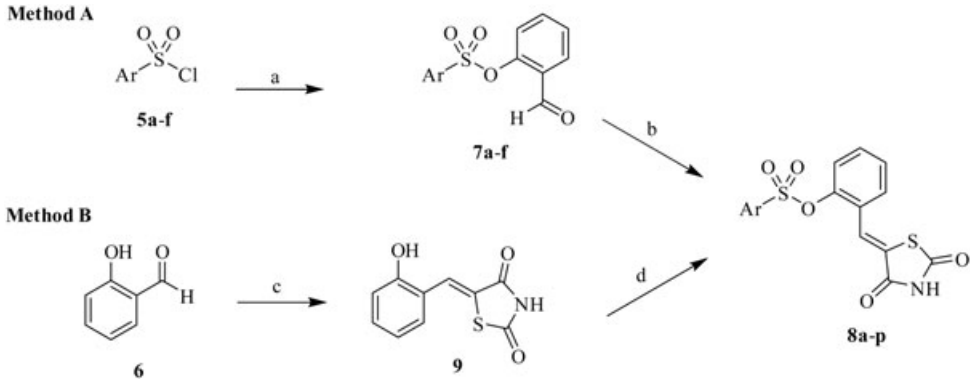


Table 1

Synthesis of 2′-arenesulfonyloxy-5-benzylidene-thiazolidine-2,4-diones **8a–p**.

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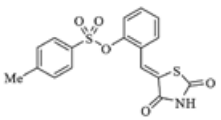
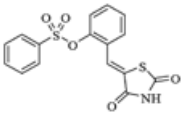
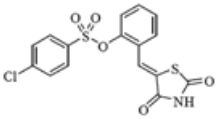
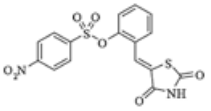
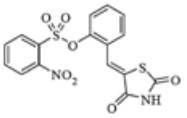
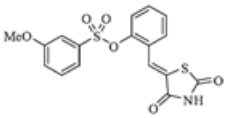
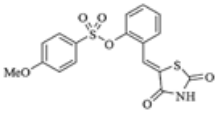
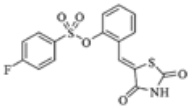
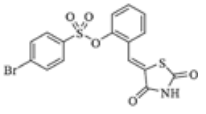
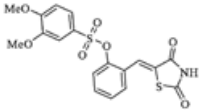
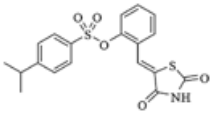
1		8a	39
2		8b	44
3		8c	46
4		8d	46
5		8e	45
6		8f	48
7		8g	44
8		8h	47
9		8i	46
10		8j	49
11		8k	53

(*Continued*)

Table 1

(Continued)

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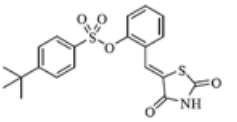
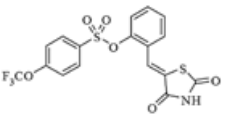
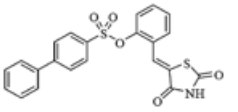
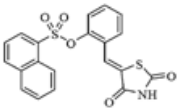
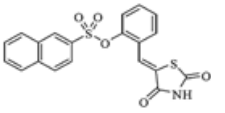
12		8l	57
13		8m	54
14		8n	57
15		8o	58
16		8p	58

[a]Two-step isolated yield.

silica gel (230–400 mesh). Elemental analysis was carried out on a Heraeus Vario EL-III C, H, N analyzer.

General procedure. *2-Formylphenyl 4-methylbenzenesulfonate (7a).* To a solution of 4-toluenesulfonyl chloride (0.59 g, 3.12 mmol) in dry dichloromethane (10 mL), 2-hydroxybenzaldehyde (0.38 g, 3.12 mmol) and triethylamine (0.35 g, 3.43 mmol) were added to the solution. The resulting mixture was stirred at room temperature for 2 hr. The reaction solution was extracted with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$. After filtration, solvent was removed under reduced pressure and the crude residue was purified by flash chromatography (hexane/ethyl acetate: 8/2) to afford **7a** (0.76 g, 88%). M.p 62.8°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45(s, 3H), 7.19(d, *J* = 8.0Hz, 1H), 7.32(d, *J* = 8.3 Hz, 2H), 7.39(dd, *J* = 7.5, 7.6 Hz, 1H), 7.58(dd, *J* = 7.6, 8.0 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.85(d, *J* = 7.5 Hz, 1H), 9.99(s, 1H) ppm ^{13}C NMR (75 MHz, $CDCl_3$) ° 21.93, 123.90, 127.70, 128.68, 128.83, 129.49, 130.31, 131.58, 135.48, 146.50, 151.41, 187.49 ppm.

2-Formylphenyl benzenesulfonate (7b). Compound **7b** was synthesized from the procedure described for Compound **7a**. Yield: 92%. M.p 54.8°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 7.9 Hz, 1H), 7.42(dd, *J* = 7.5, 7.7 Hz, 1H), 7.56(dd, *J* = 7.3, 7.5 Hz, 2H), 7.57(dd, *J* = 7.7, 7.9 Hz, 1H), 7.70(t, *J* = 7.5 Hz, 1H), 7.85(d, *J* = 7.3 Hz, 2H), 7.88(d, *J* = 7.5 Hz, 1H), 9.99(s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.83, 127.81, 128.64, 128.94, 129.47, 129.71, 134.60, 135.12, 135.50, 151.24, 187.35 ppm.

2-Formylphenyl 4-chlorobenzenesulfonate (7c). Compound **7c** was synthesized from the procedure described for Compound **7a**.

Table 2

Antiproliferative evaluation of 2′-arenesulfonyloxy-5-benzylidene-thiazolidine-2,4-diones **8a-p** against carcinoma cells.

	GI_{50} (μM)[a]				
No.	SKHep	H460	SW620	BT474	PC-3
8a	9.4 ± 2.7	>40	>40	>40	>40
8b	12.3 ± 2.6	21.9 ± 2.9	>40	>40	>40
8c	>40	8.7 ± 1.2	>40	>40	8.4 ± 0.8
8d	>40	17.9 ± 2.9	>40	>40	>40
8e	8.7 ± 0.9	>40	>40	20.6 ± 2.9	>40
8f	>40	>40	>40	>40	>40
8g	>40	>40	>40	>40	>40
8h	>40	16.5 ± 3.3	>40	>40	>40
8i	>40	18.9 ± 4.1	>40	>40	>40
8j	>40	>40	>40	>40	>40
8k	9.8 ± 1.3	22.3 ± 2.6	>40	>40	>40
8l	15.7 ± 1.5	27.2 ± 4.3	>40	>40	>40
8m	>40	>40	>40	>40	>40
8n	23.1 ± 2.2	18.9 ± 3.8	>40	>40	>40
8o	>40	>40	>40	>40	>40
8p	>40	>40	>40	>40	>40

[a]GI_{50} values are presented as the mean ± SEM (standard error of the mean) from three separated experiments.

Yield: 94%. M.p 53.2°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 7.6 Hz, 1H), 7.45(dd, *J* = 7.2, 7.7 Hz, 1H), 7.53(d, *J* = 6.8 Hz, 2H), 7.62(dd, *J* = 7.2, 7.6 Hz, 1H), 7.79(d, *J* = 6.8 Hz, 2H), 7.90 (d, *J* = 7.7 Hz, 1H), 10.07(s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.69, 128.03, 129.39, 129.45, 130.10, 133.43, 135.60, 142.06, 151.41, 187.33 ppm.

2-Formylphenyl 4-nitrobenzenesulfonate (7d). Compound **7d** was synthesized from the procedure described for Compound **7a**. Yield: 83%. M.p 121.3°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20(d, *J* = 7.8 Hz, 1H), 7.47(dd, *J* = 6.3, 7.7 Hz, 1H), 7.62(dd, *J* = 6.3, 7.8 Hz, 1H), 7.91(d, *J* = 7.7 Hz, 1H), 8.11(d, *J* = 8.9 Hz, 2H), 8.41(d, *J* = 8.9 Hz, 2H), 10.07(s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.54, 124.83, 128.41, 129.34, 130.19, 135.74, 140.47, 150.26, 151.52, 187.11 ppm.

2-Formylphenyl 2-nitrobenzenesulfonate (7e). Compound **7e** was synthesized from the procedure described for Compound **7a**. Yield: 85%. M.p 102.6°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34(d, *J* = 8.1 Hz, 1H), 7.47(dd, *J* = 6.1, 7.1 Hz, 1H), 7.61(dd, *J* = 6.1, 8.1 Hz, 1H), 7.74(m, 1H), 7.89(d, *J* = 7.1 Hz, 1H), 7.93(m, 3H), 10.23(s, 1H) ppm.^{13}C NMR (75MHz, $CDCl_3$) δ 123.82, 125.40, 128.01, 128.32, 129.38, 132.19, 132.60, 135.73, 136.30, 148.90, 150.66, 187.80 ppm.

2-Formylphenyl 3-methoxybenzenesulfonate (7f). Compound **7f** was synthesized from the procedure described for Compound **7a**. Yield: 94%. M.p 50.6°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79(s, 3H), 7.18(d, *J* = 8.1 Hz, 1H), 7.20(dd, *J* = 7.2, 7.6 Hz, 1H), 7.28(s, 1H), 7.40(m, 3H), 7.57(dd, *J* = 7.2, 8.1 Hz, 1H), 7.86(d, *J* = 7.6 Hz, 1H), 10.00(s, 1H) ppm.^{13}C NMR (75 MHz, $CDCl_3$) δ 55.46, 112.87, 120.23, 120.95, 123.33, 127.47, 128.46, 129.13, 130.42, 135.03, 135.15, 150.71, 159.85, 186.96 ppm.

(Z)-2′-(4-Methylbenzenesulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8a). To a solution of 2,4-thiazolidinedione (0.32 g, 2.7 mmol) and piperidine, (0.11 g, 1.3 mmol) in dry ethanol (8 mL), the resulting mixture was stirred under reflux for 30 min, followed by the addition of 2-formylphenyl 4-methylbenzenesulfonate (**7a** , 0.75 g, 2.7 mmol) to stir for another 18 hr. The reaction solution was evaporated *in vacuo* and the crude product was purified by flash chromatography (hexane/ethyl acetate: 9/1 to 1/1) to afford Compound **8a** (0.46 g, 45 %). M.p 198.6°C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.33(s, 3H), 7.29(s, 1H), 7.35(dd, *J* = 7.9, 8.0 Hz, 1H), 7.36(d, *J* = 8.1 Hz, 2H), 7.41(d, *J* = 7.0 Hz, 1H), 7.48(dd, *J* = 7.0, 7.9 Hz, 1H), 7.55(d, *J* = 8.1 Hz, 2H), 7.57(d, *J* = 8.0 Hz, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.06, 124.08, 124.60, 126.70, 127.10, 128.20, 128.34, 128.40, 130.47, 130.47, 130.65, 131.87, 146.13, 166.50, 167.73 ppm. HRMS (M+1)+ calcd for $C_{17}H_{14}NO_5S_2$ 376.0313, found 376.0315. *Anal.* calcd. for $C_{17}H_{13}NO_5S_2$: C, 54.39; H, 3.49; N, 3.73. Found: C, 54.32; H, 3.54; N, 3.68.

(Z)-2′-Benzenesulfonyloxy-5-benzylidene-thiazolidine-2,4-dione (8b). Compound **8b** was synthesized from the procedure described for Compound **8a**. Yield: 48 %. M.p 224.5°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.30(d, *J* = 8.1 Hz, 1H), 7.39(s, 1H), 7.47(dd, *J* = 7.7, 8.4 Hz, 1H), 7.55(dd, *J* = 8.1, 8.4 Hz, 1H), 7.60(d, *J* = 7.7 Hz, 1H), 7.61(dd, *J* = 7.0, 7.2 Hz, 2H), 7.75(d, *J* = 7.2 Hz, 2H), 7.76(t, *J* = 7.0 Hz, 1H) ppm.^{13}C NMR (75 MHz, DMSO-d_6) δ 123.80, 124.28, 126.76, 126.99, 128.15, 128.38, 128.54, 130.00, 131.89, 133.76, 135.18, 147.50, 166.63, 167.54 ppm. HRMS (M+1)+ calcd for $C_{16}H_{12}NO_5S_2$ 362.0157, found 362.0158. *Anal.* calcd. for $C_{16}H_{11}NO_5S_2$: C, 53.18; H, 3.07; N, 3.88. Found: C, 53.23; H, 2.98; N, 3.78.

(Z)-2′-(4-Chlorobenzenesulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8c). Compound **8c** was synthesized from the procedure described for Compound **8a**. Yield: 43 %. M.p 187.7°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.24(s, 1H), 7.38(d, *J* = 7.9 Hz, 1H), 7.46

(dd, *J* = 7.7, 8.0 Hz, 1H), 7.52(dd, *J* = 7.7, 7.9 Hz, 1H), 7.57(d, *J* = 8.0 Hz, 1H), 7.64(d, *J* = 8.8 Hz, 2H), 7.70(d, *J* = 8.8 Hz, 2H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 123.95, 124.16, 127.02, 127.18, 128.47, 128.55, 130.04, 130.28, 131.91, 132.20, 140.57, 147.33, 166.84, 167.65 ppm. HRMS (M+1)+ calcd for $C_{16}H_{11}ClNO_5S_2$ 395.9767, found 395.9738. *Anal.* calcd. for $C_{16}H_{10}ClNO_5S_2$: C, 48.55; H, 2.55; N, 3.54. Found: C, 48.59; H, 2.46; N, 3.59.

(Z)-2′-(4-Nitrobenzenesulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8d). Compound **8d** was synthesized from the procedure described for Compound **8a**. Yield: 56 %. M.p 213.7°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.12(s, 1H), 7.28(m, 1H), 7.47(m, 3H), 8.02(d, *J* = 8.8 Hz, 2H), 8.36(d, *J* = 8.8 Hz, 2H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 119.04, 123.60, 125.06, 128.33, 128.47, 128.54, 129.99, 130.66, 133.51, 139.16, 147.05, 150.87, 171.03, 174.20 ppm. HRMS (M+1)+ calcd for $C_{16}H_{11}N_2O_7S_2$ 407.0008, found 407.3997. *Anal.* calcd. for $C_{16}H_{10}N_2O_7S_2$: C, 47.29; H, 2.48; N, 6.89. Found: C, 47.36; H, 2.53; N, 6.78.

(Z)-2′-(2-Nitrobenzenesulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8e). Compound **8e** was synthesized from the procedure described for Compound **8a**. Yield: 53 %. M.p 184.7°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.38(m, 1H), 7.56(m, 4H), 7.83(d, *J* = 8.2 Hz, 1H), 7.84(dd, *J* = 7.9, 8.5 Hz, 1H), 8.01(dd, *J* = 8.2, 8.5 Hz, 1H), 8.11(d, *J* = 7.9 Hz, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 123.71, 124.28, 125.97, 126.26, 127.09, 127.71, 128.65, 128.80, 131.55, 131.94, 133.46, 136.89, 147.45, 147.59, 167.10, 167.68 ppm. HRMS (M+1)+ calcd for $C_{16}H_{11}N_2O_7S_2$ 407.0008, found 407.0005. *Anal.* calcd. for $C_{16}H_{10}N_2O_7S_2$: C, 47.29; H, 2.48; N, 6.89. Found: C, 47.25; H, 2.52; N, 6.83.

(Z)-2′-(3-Methoxybenzenesulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8f). Compound **8f** was synthesized from the procedure described for Compound **8a**. Yield: 51 %. M.p 136.4°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.76(s, 3H), 7.15(s, 1H), 7.20(d, *J* = 7.8 Hz, 1H), 7.27(d, *J* = 8.0 Hz, 1H), 7.32(s, 1H), 7.38(d, *J* = 8.1 Hz, 1H), 7.42 (dd, *J* = 7.7, 7.9 Hz, 1H), 7.46(d, *J* = 7.9 Hz, 1H), 7.49(dd, *J* = 8.0, 8.1 Hz, 1H), 7.57(dd, *J* = 7.7, 7.8 Hz, 1H) ppm.^{13}C NMR (75 MHz, DMSO-d_6) δ 55.67, 112.13, 120.35, 121.41, 123.99, 124.29, 126.57, 127.03, 128.37, 131.13, 131.89, 134.67, 147.49, 159.85, 166.51, 167.54 ppm. HRMS (M+1)+ calcd for $C_{17}H_{14}NO_6S_2$ 392.0263, found 392.0262. *Anal.* calcd. for $C_{17}H_{13}NO_6S_2$: C, 52.16; H, 3.35; N, 3.58. Found: C, 52.15; H, 3.39; N, 3.49.

(Z)-5-(2-Hydroxybenzylidene)thiazolidine-2,4-dione (9). To a solution of 2,4-thiazolidinedione (0.44 g, 3.75 mmol) and sodium acetate (0.3 g, 3.75 mmol), 2-hydroxybenzaldehyde (0.46 g, 3.75 mmol) was added and the resulting mixture was stirred under reflux for 10 min. The reaction was cooled and the precipitate was washed with water to afford the crude product. The crude product was recrystallized with water and DMF to give **9** (0.71 g, 85 %). M.p 196.5°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.89(d, *J* =8.0 Hz, 1H), 6.93(dd, *J* = 7.1, 7.6 Hz, 1H), 7.26(dd, *J* = 7.6, 8.0 Hz, 1H), 7.39(d, *J* = 7.1 Hz, 1H), 8.18(s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 116.16, 119.69, 120.01, 121.96, 127.06, 128.33, 132.23, 157.30, 167.58, 168.22 ppm.

(Z)-2′-(4-Methoxybenzenesulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8g). A mixture of (Z)-5-(2-Hydroxybenzylidene) thiazolidine-2,4-dione (**9**, 0.30 g, 1.36 mmol) and 4-methoxybenzenesulfonyl chloride (0.31 g, 1.5 mmol) was dissolved in dry acetone (10 mL), triethylamine (0.27 g, 2.72 mmol) was added to the solution and the mixture was stirred at room temperature for 18 hr. The reaction solvent was removed under reduced pressure and the crude residue was purified by flash chromatography (hexane/ethyl acetate: 8/2 to 1/1) to afford Compound **8g** (0.28 g, 52 %). M.p 211.2°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.79(s, 3H), 7.04(d, *J* = 8.6 Hz, 2H), 7.28(s, 1H), 7.35(d, *J* = 7.9 Hz, 1H), 7.41(d, *J* = 7.5 Hz, 1H), 7.49(dd, *J* = 7.2, 7.5 Hz, 1H), 7.56 (dd, *J* = 7.2, 7.9 Hz, 1H), 7.58(d, *J* = 8.6 Hz, 2H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.84, 115.15, 124.17, 124.53, 124.63, 126.48, 127.13, 128.25, 130.59, 131.79, 147.55, 164.18, 166.53, 167.55 ppm. HRMS (M+1)$^+$ calcd for $C_{17}H_{14}NO_6S_2$ 392.0263, found 392.0259. *Anal.* calcd. for $C_{17}H_{13}NO_6S_2$: C, 52.16; H, 3.35; N, 3.58. Found: C, 52.11; H, 3.41; N, 3.51.

(Z)-2′-(4-Fluorobenzenesulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8h). Compound **8h** was synthesized from the procedure described for Compound **8g**. Yield: 56 %. M.p 198.8°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32(s, 1H), 7.33(m, 1H), 7.45(m, 3H), 7.56(m, 2H), 7.81(m, 2H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 117.26, 117.57, 123.99, 124.22, 126.99, 128.46, 128.57, 129.99, 131.52, 131.65, 131.92, 147.41, 166.72, 167.54 ppm. HRMS (M+1)+ calcd for $C_{16}H_{11}FNO_5S_2$ 380.0063, found 380.0058. *Anal.* calcd. for $C_{16}H_{10}FNO_5S_2$: C, 50.65; H, 2.66; N, 3.69. Found: C, 50.61; H, 2.75; N, 3.65.

(Z)-2′-(4-Bromobenzenesulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8i). Compound **8i** was synthesized from the procedure described for Compound **8g**. Yield: 54 %. M.p 212.8°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.23(s, 1H), 7.39(d, *J* = 7.7 Hz, 1H), 7.43(dd, *J* = 7.3, 7.8 Hz, 1H), 7.52(dd, *J* = 7.3, 7.7 Hz, 1H), 7.56(d, *J* = 7.8 Hz, 1H), 7.59(d, *J* = 8.6 Hz, 2H), 7.78(d, *J* = 8.6 Hz, 2H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 124.13, 124.20, 126.79, 126.93, 128.44, 128.57, 129.81, 129.95, 131.98, 132.52, 133.25, 147.33, 166.41, 167.43 ppm. HRMS (M+1)+ calcd for $C_{16}H_{11}BrNO_5S_2$ 439.9262, found 439.9263. *Anal.* calcd. for $C_{16}H_{10}BrNO_5S_2$: C, 43.65; H, 2.29; N, 3.18. Found: C, 43.61; H, 2.32; N, 3.13.

(Z)-2′-(3,4-Dimethoxybenzenesulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8j). Compound **8j** was synthesized from the procedure described for Compound **8g**. Yield: 58 %. M.p 221.2°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.71(s, 3H), 3.77(s, 3H), 7.01(d, *J* = 8.6 Hz, 1H), 7.02(s, 1H), 7.12(d, *J* = 8.6 Hz, 1H), 7.21(s, 1H), 7.39(d, *J* = 7.4 Hz, 1H), 7.42(d, *J* = 7.8 Hz, 1H), 7.49(dd, *J* = 7.4, 7.6 Hz, 1H), 7.58(dd, *J* = 7.6, 7.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.60, 55.92, 109.62, 111.56, 122.82, 124.05, 124.22, 124.35, 126.44, 127.35, 128.12, 128.23, 131.77, 147.62, 149.11, 154.09, 166.83, 167.68 ppm. HRMS (M+1)+ calcd for $C_{18}H_{16}NO_7S_2$ 422.0368, found 422.0362. *Anal.* calcd. for $C_{18}H_{15}NO_7S_2$: C, 51.30; H, 3.59; N, 3.32. Found: C, 51.30; H, 3.59; N, 3.32.

(Z)-2′-(4-Isopropylbenzenesulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8k). Compound **8k** was synthesized from the procedure described for Compound **8g**. Yield: 62 %. M.p 222.4°C. ^{1}H NMR

(300 MHz, DMSO-d_6) δ 1.15(d, J = 6.9 Hz, 6H), 2.92(septet, J = 6.9 Hz, 1H), 7.32(s, 1H), 7.38(d, J= 8.1 Hz, 1H), 7.40(d, J = 7.1 Hz, 1H), 7.42(d, J = 8.5 Hz, 2H), 7.50(dd, J = 7.1, 7.5 Hz, 1H), 7.58(dd, J = 7.5, 8.1 Hz, 1H), 7.60(d, J = 8.5 Hz, 2H) ppm.^{13}C NMR (75 MHz, DMSO-d_6) δ 23.06, 33.43, 124.10, 124.20, 126.24, 126.85, 127.75, 128.33, 128.41, 130.94, 131.90, 147.58, 156.33, 166.48, 167.49 ppm. HRMS (M+1)+ calcd for $C_{19}H_{18}NO_5S_2$ 404.0626, found 404.0625. *Anal.* calcd. for $C_{19}H_{17}NO_5S_2$: C, 56.56; H, 4.25; N, 3.47. Found: C, 56.53; H, 4.31; N, 3.41.

(Z)-2′-(4-tert-Butylbenzenesulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8l). Compound **8l** was synthesized from the procedure described for Compound **8g**. Yield: 67 %. M.p 207.4°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.22(s, 9H), 7.32(s, 1H), 7.39(d, J = 8.3 Hz, 1H), 7.42(d, J = 7.0 Hz, 1H), 7.49(dd, J = 7.0, 7.9 Hz, 1H), 7.54(d, J = 8.7 Hz, 2H), 7.55(dd, J = 7.9, 8.3 Hz, 1H), 7.61(d, J = 8.7 Hz, 2H) ppm.^{13}C NMR (75 MHz, DMSO-d_6) δ 30.44, 35.05, 124.09, 124.12, 126.11, 126.59, 126.76, 128.16, 128.32, 130.62, 131.89, 147.56, 158.57, 166.44, 167.44 ppm. HRMS (M+1)+ calcd for $C_{20}H_{20}NO_5S_2$ 418.0783, found 418.0784. *Anal.* calcd. for $C_{20}H_{20}NO_5S_2$: C, 57.54; H, 4.59; N, 3.35. Found: C, 57.51; H, 4.62; N, 3.34.

(Z)-2′-(4-Trifluoromethxybenzenesulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8m). Compound **8m** was synthesized from the procedure described for Compound **8g**. Yield: 64 %. M.p 214.4°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.20(s, 1H), 7.43(d, J = 7.8 Hz, 1H), 7.45(d, J = 7.2 Hz, 1H), 7.53(dd, J = 7.2, 7.5 Hz, 1H), 7.61(dd, J = 7.5, 7.8 Hz, 1H), 7.93(m, 4H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 121.21, 123.88, 124.26, 124.83, 126.77, 127.15, 128.52, 128.71, 129.33, 132.10, 134.46, 137.45, 147.31, 166.33, 167.21 ppm. HRMS (M+1)+ calcd for $C_{17}H_{11}F_3NO_6S_2$ 445.9980, found 445.9982. *Anal.* calcd. for $C_{17}H_{10}F_3NO_6S_2$: C, 45.84; H, 2.26; N, 3.14. Found: C, 45.88; H, 2.31; N, 3.07.

(Z)-2′-(4-Biphenylsulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8n). Compound **8n** was synthesized from the procedure described for Compound **8g**. Yield: 67 %. M.p 168.7°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.21(m, 1H), 7.22(s, 1H), 7.39 (m, 3H), 7.47(t, J = 7.4 Hz, 1H), 7.52(dd, J = 7.4, 8.5 Hz, 2H), 7.67(d, J = 8.5 Hz, 2H), 7.81(m, 4H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 114.48, 122.79, 127.31, 127.72, 127.82, 128.15, 128.83, 128.96, 129.07, 129.87, 132.65, 138.10, 139.08, 146.53, 147.16, 174.92, 181.92 ppm. HRMS (M+1)+ calcd for $C_{22}H_{16}NO_5S_2$ 438.0470, found 438.0468. *Anal.* calcd. For $C_{22}H_{15}NO_5S_2$: C, 60.40; H, 3.46; N, 3.20. Found: C, 60.36; H, 3.52; N, 3.14.

(Z)-2′-(1-Naphthylsulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8o). Compound **8o** was synthesized from the procedure described for Compound **8g**. Yield: 68 %. M.p 173.2°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.10(m, 1H), 7.39(m, 1H), 7.43 (dd, J = 6.8, 8.2 Hz, 1H), 7.44(s, 1H), 7.45(dd, J = 6.8, 8.5 Hz, 1H), 7.64(dd, J = 7.4, 7.9 Hz, 1H), 7.73(m, 2H), 8.11(d, J = 7.4 Hz, 1H), 8.14(d, J = 7.9 Hz, 1H), 8.37(d, J = 8.2 Hz, 1H), 8.51 (d, J = 8.5 Hz, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 123.09, 123.65, 124.45, 124.61, 126.84, 127.18, 127.56, 127.64, 128.16, 128.63, 129.37, 131.47, 131.73, 133.80, 136.70, 147.57, 166.19, 167.42 ppm. HRMS (M+1)+ calcd for $C_{20}H_{14}NO_5S_2$ 412.0313, found 412.0311. *Anal.* calcd. for $C_{20}H_{13}NO_5S_2$: C, 58.38; H, 3.18; N, 3.40. Found: C, 58.34; H, 3.21; N, 3.37.

(Z)-2′-(2-Naphthylsulfonyloxy)-5-benzylidene-thiazolidine-2,4-dione (8p). Compound **8p** was synthesized from the procedure described for Compound **8g**. Yield: 69 %. M.p 210.0°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.26(s, 1H), 7.33(d, J = 7.3 Hz, 1H), 7.41(d, J = 8.0 Hz, 1H), 7.46(dd, J = 7.5, 8.0 Hz, 1H), 7.56(dd, J = 7.3, 7.5 Hz, 1H), 7.63(dd, J = 6.8, 8.0 Hz, 1H), 7.66(dd, J = 6.8, 6.9 Hz, 1H), 7.75(d, J = 6.9 Hz, 1H), 8.00(d, J = 8.0 Hz, 1H), 8.06(d, J = 8.0 Hz, 1H), 8.11(d, J = 8.0 Hz, 1H), 8.45(s, 1H) ppm.^{13}C NMR (75 MHz, DMSO-d_6) δ 122.36, 123.62, 124.09, 126.97, 127.25, 127.78, 128.12, 128.30, 128.36, 129.73, 130.14, 130.25, 130.42, 131.54, 131.77, 135.21, 147.49, 166.87, 167.56 ppm. HRMS (M+1)+ calcd for $C_{20}H_{14}NO_5S_2$ 412.0313, found 412.0314. *Anal.* calcd. for $C_{20}H_{13}NO_5S_2$: C, 58.38; H, 3.18; N, 3.40. Found: C, 58.32; H, 3.23; N, 3.43.

Cell culture. Cancer cells were purchased from Bioresource Collection and Research Center in Taiwan. Each cell line was maintained in the standard medium and grown as a monolayer in Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum, 2 mM glutamine, 100 units/mL penicillin, and 100 g/mL streptomycin. Cultures were maintained at 37°C with 5 % CO_2 in a humidified atmosphere.

MTT assay for cell viability. Cells were plated in 96-well microtiter plates at a density of 5 × 10^3/well and incubated for 24 h. After that, cells were treated with vehicle alone (control) or compounds (drugs were dissolved in DMSO previously) at the concentrations indicated. Treated cells were further incubated for 48 h. Cell survival is expressed as percentage of control cell growth. The 3-[4, 5-Dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide (MTT, 2 mg/mL) dye reduction assay in 96-well microplates was used. The assay is dependent on the reduction of MTT by mitochondrial dehydrogenases of viable cell to a blue formazan product, which come be measured spectrophotometrically. Tumor cells were incubated in each well with serial dilutions of the tested compounds. After 2 days of incubation (37°C, 5 % CO_2 in a humid atmosphere) 100 μL of MTT (2 mg/mL in PBS) was added to each well and the plate was incubated for a further 2 h (37°C). The resulting formazan was dissolved in 100 μL DMSO and read at 570 nm. The percentage of growth inhibition was calculated by the following equation: percentage growth inhibition = $(1-At/Ac) \times 100$, where At and Ac represent the absorbance in treated and control cultures, respectively. The drug concentration causing a 50 % cell growth inhibition (GI_{50}) was determined by interpolation from dose-response curves. All determinations were carried out in four to six separated experiments.

Statistical analysis. Data are presented as the mean±sem (standard error of the mean) from four to six separated experiments. Statistical analyses were performed using Bonferroni t-test method after ANOVA for multigroup

comparison and Student's *t*-test method for two-group comparison. $P = 0.05$ was considered significant. Analysis of linear regression (at least five data within 20–80% inhibition) was used to calculate GI_{50} value.

CONCLUSIONS

In summary, we have successfully synthesized a series of 2′-arenesulfonyloxy-5-benzylidene-thiazolidine-2,4-diones by employing two synthetic pathways. We found that the optimal yield of Knoevenagel condensation was obtained in the presence of 0.5 equiv of piperidine in refluxed ethanol for 18–22 hr. In addition, we also found that initial preparation of 5-[2′-hydroxybenzylidene]-2,4-thiazolidinone (**9**) followed by nucleophilic substitution with arylsulfonyl chlorides exhibited better efficiency. Upon exposure of five carcinoma cells, none of test compounds exhibited antirpoliferative activity against SW620 cells. We found that only **8c** and **8e** showed significant antiproliferative activity against PC-3 and BT474 cells with GI_{50} values of 8.4 and 20.6 μM, respectively. We also obtained that SKHep exhibited some interesting structure-activity relationship results in response to TZD treatment. Among alkyl group-substituted TZD analogs, **8a** (4-Me, GI_{50}, 9.4 μM) and **8k** (4-*iso*-propyl, GI_{50}, 9.8 μM) revealed better antiproliferative activity than those of bulkier alkyl group-substituted TZD analogs such as *t*-butyl (**8l**, GI_{50}, 15.7 μM) and phenyl (**8n**, GI_{50}, 23.1 μM). On the other hand, we found that halogen-substituted analogs **8c** (4-Cl, GI_{50}, 8.7 μM), **8h** (4-F, GI_{50}, 16.5 μM) and **8i** (4-Br, GI_{50}, 18.9 μM) showed better antiproliferative activity than others against H460 cells. Taken together, we concluded that the new synthesized 2′-arenesulfonyloxy-5-benzylidene-thiazolidine-2,4-diones have shown to be antiproliferative agents deserved for further study.

Acknowledgments. This work was supported by the National Science Council of the Republic of China to A.Y.S.

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