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ORIGINAL RESEARCH

Synthesis and bioevaluation of new 5-benzylidenethiazolidine-2,4-diones bearing benzenesulfonamide moiety

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Abstract Two series of new 5-benzylidenethiazolidine-2,4-diones bearing benzenesulfonamide moiety were designed and synthesized. The synthesized compounds were evaluated for several biological activities, including cytotoxicity, histone deacetylation, and protein phosphatase 1B (PTP1B) inhibitory effects. It was found that those 5-benzylidenethiazolidine-2,4-diones with a chlorine substituent on the benzenesulfonamide moiety exhibited significant cytotoxicity, comparable to that of SAHA, which was used as a positive control. Several cytotoxic compounds also exhibited inhibitory effects against histone deacetylation, suggesting that these compounds might possess histone deacetylase inhibitory property. On the activity of PTP1B, however, these compounds displayed insignificant inhibitory effects.

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Introduction

Thiazolidine-2,4-dione is an important scaffold incorporated in many classes of chemical compounds with interesting biological properties, including antibacterial, antifungal (Aneja *et al.*, 2011; Mentese *et al.*, 2009; Bozdag-Dündar *et al.*, 2007; Desai *et al.*, 2014), antidiabetic (Jain *et al.*, 2013), cytotoxic (Romagnoli *et al.*, 2013; Barros *et al.*, 2012), and anti-inflammatory (Nastasă *et al.*, 2013) activities, to name a few. Several drugs bearing thiazolidine-2,4-dione moiety have been approved for clinical applications, for example pioglitazone and rosiglitazone (Baba, 2001; Cheng-Lai and Levine, 2000), which were approved for the treatment of type II diabetes mellitus. The two drugs rosiglitazone and pioglitazone (Fig. 1) act as potent ligands of PPAR-γ and show efficient insulin sensitization in type 2 diabetes patients (Bhattarai *et al.*, 2010; Patel *et al.*, 1999). Recently, a number of thiazolidine-2,4-dione incorporating compounds were also reported to be potent protein tyrosine phosphatase 1B (PTP1B) inhibitors (Bhattarai *et al.*, 2010; Maccari *et al.*, 2007), and in particular, some thiazolidinediones were also demonstrated to have histone deacetylase inhibitory effects (Mohan *et al.*, 2012) (Fig. 1).

In our continuing research to find new thiazolidine-2,4-dione derivatives with potential biological activities, we have designed and synthesized two series of new 5-benzylidenethiazolidine-2,4-diones bearing benzenesulfonamide moiety. The present paper describes the recent results we obtained from this investigation.

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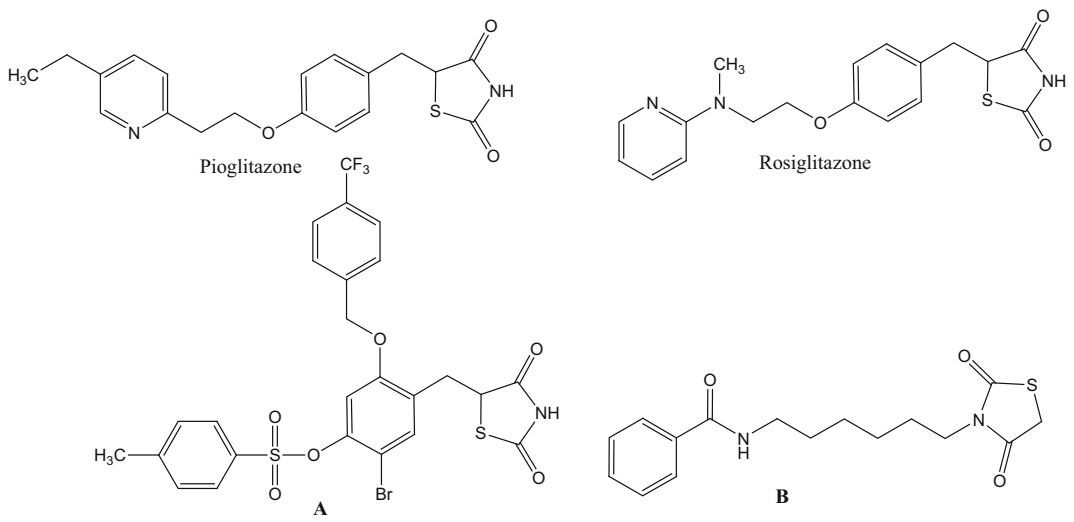


Fig. 1 Structures of thiazolidine-2,4-dione antidiabetic agents (pioglitazone, rosiglitazone), PTP1B inhibitor (**a**) and HDAC inhibitor (**b**)

Results and discussions

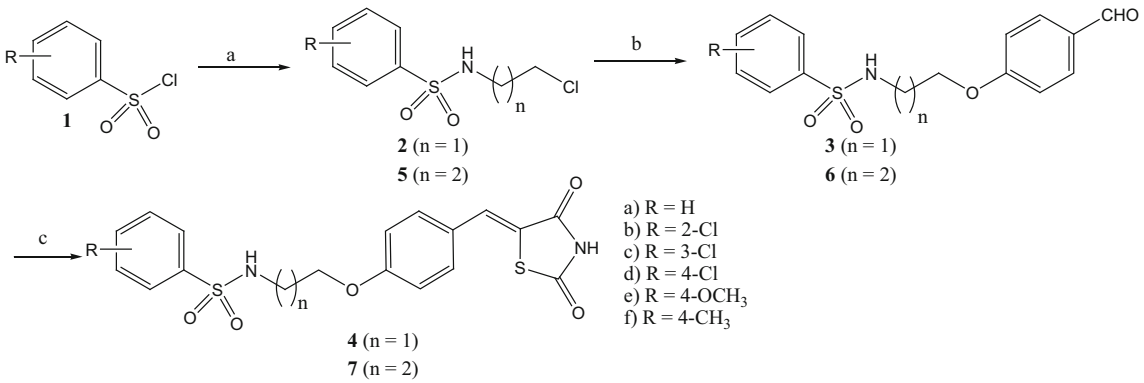
Chemistry

A series of new benzenesulfonamide-incorporated thiazolidine-2,4-diones (**4a–f**) was synthesized according to the pathway depicted in Scheme 1. Reaction of different benzenesulfonyl chlorides (**1**) with 2-chloroethylamine.HCl gave the intermediates **2a–f**. Nucleophilic substitution between **2a–f** and 4-hydroxybenzaldehyde under alkaline conditions resulted in 4-substituted benzaldehydes **3a–f** which were then condensed with thiazolidine-2,4-dione catalyzed by piperidine to afford the expected products **4a–f** in moderate-to-good overall yields.

Five other compounds (**7a, 7b, 7d–f**) were synthesized by similar procedures. The structures of synthesized compounds were straightforwardly confirmed by analysis of IR, MS, and NMR spectral data. All compounds showed chemical shifts of the olefinic protons (–CH=group), which appeared downfield as a singlet at 7.72–7.74 ppm. According to the literature (Bruno *et al.*, 2002), these chemical shifts of the olefinic proton should correspond to *Z*-configuration. For *E*-configuration, the chemical shifts of these olefinic protons should be around 6.52 ppm. The exclusive formation of Z-isomer in this condensation reaction has also been clearly demonstrated by X-ray analysis (Bruno *et al.*, 2002) and reported in many other similar studies (Alegaon and Alagawadi, 2012; da Rocha Junior *et al.*, 2013).

Bioactivity

The SRB (sulforhodamine B) cell proliferation assay was used to evaluate the antiproliferative activity of the synthesized compounds. The compounds were first screened at 100 μg/mL for cell growth inhibition against SW620

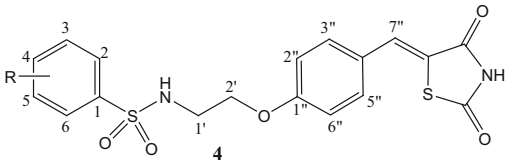


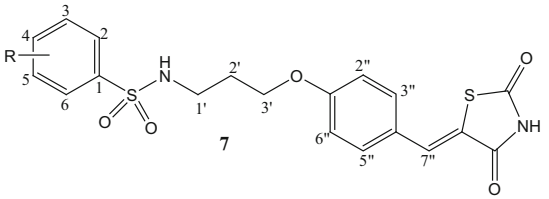
Scheme 1 Synthesis of (Z)-*N*-(2-(4-((2,4-dioxothiazolidine-5-ylidene)methyl)phenoxy)ethyl/propyl)benzenesulfonamide and derivatives. *Reagents and conditions: a* DMF, TEA, 2-chloroethylamine.HCl (for compounds **3**)/3-chloropropylamine.HCl (for compound **6**); *b* 4-hydroxybenzaldehyde, K_2CO_3, DMF, 45 °C; *c* ethanol, piperidine, thiazolidine-2,4-dione

(human colon cancer) cell line. It was found that all compounds synthesized (**4a–f, 7a**, **7b**, **7d–f**) completely inhibited the growth of SW620 cells at this concentration. Therefore, the compounds were subjected to further evaluation at five concentrations (30, 10, 3, 1, 0.3 μg/mL) in SW620 and two human cancer cell lines more, including PC-3 (prostate cancer) and NCI-H460 (lung cancer) cell lines. The IC_{50} (the concentration that causes 50 % of cell proliferation inhibition) values of each compound were determined and are summarized in Table 1. SAHA and ADR (adriamycin) were used as positive controls. Data from Table 1 clearly indicated that in overall, the compounds synthesized were more sensitive toward a lung cancer cell line NCI-H460 and less active against the colon cancer cells SW620. Introduction of substituents at position 4 on the benzenesulfonamide moiety was found to significantly influence cytotoxicity, but among substituents investigated, only chlorine group enhanced cytotoxic effects. Substituents at position 2 seemed more favorable than at position 3, which was in turn more favorable than at position 4 for cytotoxicity. Generally, lengthening the alkyl bridge connecting a benzenesulfonamide and 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione moiety seemed to decrease cytotoxicity in cell lines tested (**7a, 7b**, **7d** vs. **4a**, **4b**, **4d**). From these results, it is reasonable to postulate that although the synthesized compounds still retain acceptable lipophilicity and hydrophilicity balance, as manifested by logP values (Table 1), the increase in lipophilicity might not be favorable for cytotoxicity of these compounds series.

Among the two series synthesized, it was encouraging to note that several compounds (e.g., **4b**, **4c**) displayed comparable cytotoxicity to SAHA in some cell lines assayed (PC-3, NCI-H460) (Table 1). Although the cytotoxicity of these compounds was still lower than that of adriamycin (Table 1), the present results should warrant further interest and effort in these compounds' types to find more potent anticancer agents.

Table 1 Cytotoxicity of the compounds synthesized against several cancer cell lines





Cpd code	R	Molecular formula	Molecular weight	LogP	Cytotoxicity (IC_{50},[a] μg/mL)/cell lines[b]		
					SW 620	PC-3	NCI-H460
4a	H	$C_{18}H_{16}N_2O_5S_2$	404.46	2.32	>30	21.32	18.22
4b	2-Cl	$C_{18}H_{15}ClN_2O_5S_2$	438.91	2.97	7.45	4.26	2.57
4c	3-Cl	$C_{18}H_{15}ClN_2O_5S_2$	438.91	2.97	9.23	3.45	4.26
4d	4-Cl	$C_{18}H_{15}ClN_2O_5S_2$	438.91	2.97	12.36	6.15	5.41
4e	4-CH_3	$C_{19}H_{18}ClN_2O_5S_2$	418.49	2.87	>30	>30	16.53
4f	4-OCH_3	$C_{19}H_{18}ClN_2O_6S_2$	434.49	2.40	>30	17.26	16.51
7a	H	$C_{19}H_{18}N_2O_5S_2$	418.49	2.81	>30	19.11	21.36
7b	2-Cl	$C_{19}H_{17}ClN_2O_5S_2$	452.93	3.46	8.35	6.52	5.14
7d	4-Cl	$C_{19}H_{17}ClN_2O_5S_2$	452.93	3.46	10.89	5.42	4.24
7e	4-CH_3	$C_{20}H_{20}N_2O_5S_2$	432.51	3.36	>30	>30	24.58
7f	4-OCH_3	$C_{20}H_{20}N_2O_6S_2$	448.51	2.89	>30	15.23	15.47
SAHA[c]			264.32	1.44	6.42	4.31	2.77
ADR[d]					0.48	0.30	0.11

[a] The concentration (μg/mL) of compounds that produces a 50 % reduction in cell growth; the numbers represent the averaged results from triplicate experiments with deviation of less than 10 %

[b] Cell lines: SW620, colon cancer; PC3, prostate cancer; NCI-H460, lung cancer

[c] SAHA, suberoylanilide acid, a positive control

[d] ADR, adriamycin, a positive control

These compounds possess a 5-benzylidenethiazolidine-2,4-dione scaffold, which contains an α,β-unsaturated carbonyl moiety. Therefore, one possible mechanism of cytotoxicity could be nucleophilic alkylation at the β position. Recently Mohan *et al.* (2012) demonstrated that several thiazolidine-2,4-dione compounds also exhibited histone deacetylase inhibition effects. Encouraged by this finding, we evaluated the effects of six compounds including **4a–f** on histone deacetylation using a Western blot analysis. It was found that compounds **4b**, **4c**, and **4d** at 10 μg/mL slightly inhibited deacetylation of histone H3 and histone H4 (Fig. 2). Meanwhile, the effects of compounds **4a**, **4e**, and **4f** on histone H3 and histone H4 deacetylation were not observed at this concentration. Though the inhibition effects of these compounds on histone deacetylation were still very weak, there seemed to exist a relative correlation between cytotoxicity and the ability of these compounds to inhibit histone deacetylation. To gain possible mode of binding of this type of compounds with histone deacetylase, we performed docking study with one compound **4b** using HDAC2 and HDAC8. We executed control docking experiments with SAHA to the crystal structures of HDAC2 and HDAC8 using AutoDock Vina program (Trott and Olson, 2010) after SAHA was removed from the complex structures, as described previously (Nam *et al.*, 2013; Tung *et al.*, 2013; Oanh *et al.*, 2011). It was found from docking experiments that compound **4b** was predicted to sit at the top and block the SAHA binding pocket (Fig. 3) with stabilization energy of −5.9 and −6.5 kcal/mol with HDAC2 and HDAC8, respectively. Meanwhile, the binding energy of SAHA with HDAC2 and HDAC8 was −7.4 and −7.0 kcal/mol, lower than that of compound **4b**. This docking study indicated that compound **4b** did bind to HDAC2 and HDAC8, though the binding affinities were lower than that of SAHA. Thus, collectively, it could be expected that the thiazolidine-2,4-dione scaffold might be interesting for further manipulation to obtain more potent histone deacetylase inhibitors.

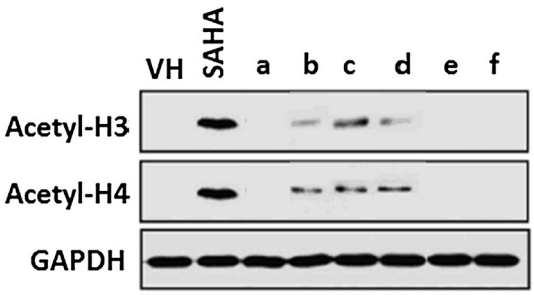


Fig. 2 Effect of compounds **4a–f** on histone acetylation in SW620 cells. Cells were treated with compounds (10 μg/mL) or SAHA (1 μg/mL, a positive control) for 24 h. Levels of acetylated histone H3 and H4 in total cell lysates were determined by Western immunoblot analysis

In addition to cytotoxicity and the effects on histone deacetylation, we also screened the synthesized compounds against the enzyme PTP1B. It was found, however, that these compounds exerted no significant inhibitory effects on the activity of PTP1B (Table 2), even when tested at the concentrations of 30 μM. Meanwhile, suramin, a positive control, inhibited the enzyme activity by approximately 55 % when tested at a concentration of 10 μM. Thus, the introduction of a bulky benzenesulfonamide moiety might not be favorable for binding to this enzyme. Nevertheless, these results should not discourage further effort in development of this type of compounds to obtain potent PTP1B inhibitors.

Conclusions

In conclusion, we have reported two new series of 5-benzylidenethiazolidine-2,4-diones bearing benzenesulfonamide moiety and evaluated their cytotoxicity, histone deacetylation, and PTP1B inhibitory effects. It was found that compounds with chlorine substituents on the benzene ring of the benzenesulfonamide moiety exhibited significant cytotoxicity against three human cancer cell lines tested, including SW620 (colon cancer), PC-3 (prostate cancer), and NCI-H460 (lung cancer). Several compounds (**4b–d**) exhibited cytotoxicity against PC-3 and NCI-H460 cell lines comparable to that of SAHA. In particular, these compounds also exhibited noted inhibition on histone deacetylation, suggesting that the compounds might possess histone deacetylase inhibitory property and are potential to serve as novel leads for design of histone deacetylase inhibitors. On the activity of PTP1B, however, these compounds displayed insignificant inhibitory effects.

Experimental protocols

Chemistry

All products were homogenous, as examined by thin-layer chromatography (TLC), performed on Whatman® 250 μm Silica Gel GF Uniplates, and visualized under UV light at 254 and 365 nm. Melting points were determined with a Gallenkamp Melting Point Apparatus (LabMerchant, London, UK) and are uncorrected. Chromatographic purification was done by the open flash silica gel column chromatography using Merck silica gel 60 (240–400 meshes). Nuclear magnetic resonance spectra (^{1}H NMR) were recorded using tetramethylsilane as an internal standard on a Bruker 500 MHz spectrometer with DMSO-d_6 as

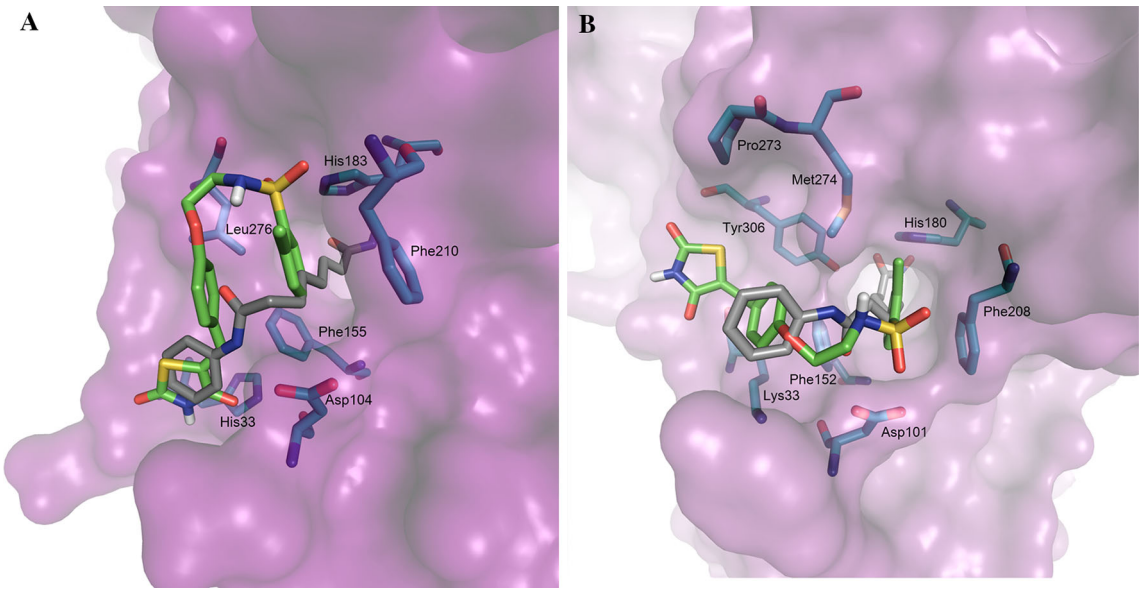
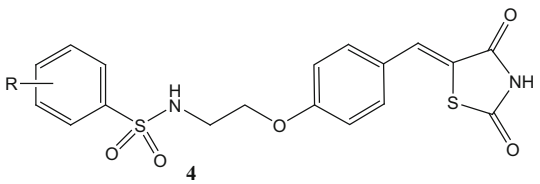


Fig. 3 Binding poses of the highest affinity binding modes from each docking experiment between compound **4b** and HDAC2 (**a**) or HDAC8 (**b**). Compound **4b** shown as *green* and SAHA as *gray color frames*. Compound **4b** is represented as a stick model with carbon, nitrogen, and oxygen atoms in *yellow*, *blue*, and *red*, respectively. Residues that seem to interact with compound **4b** are presented as *cyan* (Color figure online)

Table 2 Effects of the compounds **4a–f** on the activity of PTP1B



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Cpd code	R	Molecular formula	Molecular weight	Assay concentration (μM)	OD	PTP1B inhibition percentage (EIP, %)
4a	H	$C_{18}H_{16}N_2O_5S_2$	404.46	30	1.081 ± 0.020	−2.270
4b	2-Cl	$C_{18}H_{15}ClN_2O_5S_2$	438.91	30	1.061 ± 0.024	−0.363
4c	3-Cl	$C_{18}H_{15}ClN_2O_5S_2$	438.91	30	1.057 ± 0.038	0.047
4d	4-Cl	$C_{18}H_{15}ClN_2O_5S_2$	438.91	30	1.024 ± 0.340	3.137
4e	4-CH_3	$C_{19}H_{18}ClN_2O_5S_2$	418.49	30	1.013 ± 0.053	4.209
4f	4-OCH_3	$C_{19}H_{18}ClN_2O_6S_2$	434.49	30	1.014 ± 0.031	4.131
Blank				–	1.057 ± 0.034	
Suramin				10	0.473 ± 0.042	55.258

solvent unless otherwise indicated. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as internal standard. Electron ionization (EI), electrospray ionization (ESI) and high-resolution mass spectra were obtained using PE Biosystems API 200 (Perkin Elmer, Palo Alto, CA, USA) and Mariner® (Azco Biotech, Inc. Oceanside, CA, USA) mass spectrometers, respectively. Reagents and solvents were purchased from Aldrich or Fluka Chemical Corp. (Milwaukee, WI, USA) or Merck unless noted otherwise. Solvents were distilled and dried before use.

The synthesis of two series of (Z)-*N*-(2-(4-((2,4-dioxothiazolidine-5-ylidene)methyl)phenoxy)ethyl)benzenesulfonamides (**4a–f**) and (Z)-*N*-(3-(4-((2,4-dioxothiazolidine-5-ylidene)methyl)phenoxy)propyl)benzenesulfonamides (**7a, 7b, 7d–f**) was carried out as illustrated in

Scheme 1. For numbering, please refer to Table 1. Details are described as follows:

*(Z)-N-(2-(4-((2,4-dioxothiazolidine-5-ylidene)methyl)phenoxy) ethyl)benzenesulfonamide (***4a***)* Benzenesulfonyl chloride (525 mg, ~ 380 μL, 3 mmoL) was gradually added to a 50-mL round-bottom flask containing 2-chloroethylamine.HCl (116 mg, 3 mmol) in dimethyl formamide (5 mL) and triethylamine (TEA, 500 μL). The reaction mixture was stirred at room temperature for 3 h and then poured into a cold solution of HCl 5 % (50 mL). The precipitate was collected and dried under vacuum at 40 °C to give compound **2a**, which was used for the next step without further purification. Compound **2a** was then dissolved in DMF (6 mL). 4-Hydroxybenzaldehyde (366 mg, 3 mmoL) and K_2CO_3 (207 mg, 1.5 mmoL) were then added. The resulting mixture was warmed to 45 °C and stirred at this temperature for 12 h. The reaction mixture was poured into a cold solution of HCl 5 % (50 mL) to give white precipitates, which was dried to give **3a** (820 mg). *IR (KBr,* cm^{-1}*):* 3125 (NH), 3050 (C-H, aren), 2925, 2855 (CH, CH_2), 1745 (C = O), 1602, 1585 (C = C), 1350, 1180 (S=O), 1280 (C-O). *ESI–MS (*m/z): 304.4 $[M-H]^-$. Compound **3a** was dissolved in dry ethanol (25 mL), to which thiazolidine-2,4-dione (348 mg, 3 mmoL) and piperidine (300 μL) were added. The mixture was refluxed for 12 h, and then ethanol was evaporated. A cold solution of HCl 5 % (50 mL) was added and gently stirred to give precipitate, which was recrystallized from ethanol to afford white solids (**4a**, 900 mg). Yield: 74 %. mp: 212–215 °C. $R_f = 0.40$ (DCM/MeOH/AcOH = 90:5:1). *IR (KBr,* cm^{-1}*):* 3415, 3193 (NH), 3069 (C-H, aren), 2924, 2853 (CH, CH_2), 1736, 1693 (C = O), 1602, 1567 (C = C), 1323, 1160 (S = O), 1267 (C-O). *ESI–MS (*m/z): 402.9 $[M-H]^-$. *^{1}H-NMR (500 MHz, DMSO-d_6, ppm)*: δ 7.98 (1H, t, J = 6.0 Hz, sulfonamide), 7.83 (2H, dd, J = 7.0 Hz, J' = 1.5 Hz, H-2, H-6), 7.72 (1H, s, H-7″, olefinic proton), 7.63 (1H, tt, J = 7.0 Hz, J' = 1.5 Hz, H-4), 7.58 (2H, td, J = 7.0 Hz, J' = 1.5 Hz, H-3, H-5), 7.52 (2H, d, J = 8.75 Hz, H-3″, H-5″), 7.00 (2H, d, J = 8.75 Hz, H-2″, H-6″), 4.02 (2H, t, J = 5.25 Hz, H-2′), 3.16 (2H, td, J = 5.25 Hz, J' = 6.0 Hz, H-1′). *^{13}C NMR (125 MHz, DMSO-d_6, ppm)*: δ 168.1 (C-10″), 167.8 (C-9″), 159.8 (C-1″), 140.5 (C-1), 132.3 (C-7″), 131.9 (C-3″, C-5″), 131.4 (C-4), 129.6 (C-2, C-6), 126.4 (C-3, C-5), 125.7 (C-4″), 120.8 (C-8″), 115.3 (C-2″, C-6″), 66.7 (C-2′), 41.8 (C-1′). Anal. Calcd. For $C_{18}H_{16}N_2O_5S_2$ (404.46): C, 53.45; H, 3.99; N, 6.93. Found: C, 53.29; H, 3.95; N, 6.97.

Other compounds (**3b–f**, **7a, 7b, 7d–f**) were synthesized by a similar procedure as described for compound **4a.**

*(Z)-2-Chloro-N-(2-(4-((2,4-dioxothiazolidine-5-ylidene) methyl)phenoxy)ethyl)benzenesulfonamide (***4b***)* Yield: 72 %. mp: 215–217 °C. $R_f = 0.41$ (DCM/MeOH/AcOH = 90:5:1). *IR (KBr,* cm^{-1}*):* 3393, 3205 (NH), 3090 (C-H, aren), 2932 (CH, CH_2), 1741, 1696 (C=O), 1598, 1511, 1453 (C=C), 1326, 1160 (S=O), 1260 (C-O), 762 (C–Cl). *ESI–MS (*m/z): 437.6 $[M-H]^-$. *^{1}H-NMR (500 MHz, DMSO-d_6, ppm)*: δ 8.17 (1H, t, J = 5.5 Hz, sulfonamide), 7.99 (1H, d, J = 8.0 Hz, H-6), 7.72 (1H, s, H-7″, olefinic proton), 7.65 (1H, t, J = 8.0 Hz, H-4), 7.59 (2H, d, J = 8.0 Hz, H-3), 7.52 (1H, t, J = 8.0 Hz, H-5), 7.49 (2H, d, J = 9.0 Hz, H-3″, H-5″), 6.91 (2H, d, J = 9.0 Hz, H-2″, H-6″), 4.00 (2H, t, J = 5.5 Hz, H-2′), 3.31 (2H, td, J = 5.5 Hz, J' = 5.5 Hz, H-1′). *^{13}C NMR (125 MHz, DMSO-d_6, ppm)*: δ 167.9 (C-10″), 167.5 (C-9″), 159.7 (C-1″), 138.2 (C-1), 133.8 (C-7″), 132.0 (C-4), 131.9 (C-3″, C-5″), 131.7 (C-2), 130.7 (C-3), 130.1 (C-6), 127.5 (C-5), 125.6 (C-4″), 120.5 (C-8″), 115.1 (C-2″, C-6″), 66.5 (C-2′), 41.8 (C-1′). Anal. Calcd. For $C_{18}H_{15}ClN_2O_5S_2$ (438.91): C, 49.26; H, 3.44; N, 6.38. Found: C, 49.29; H, 3.55; N, 6.37.

*(Z)-3-Chloro-N-(2-(4-((2,4-dioxothiazolidine-5-ylidene)methyl) phenoxy)ethyl)benzenesulfonamide (***4c***)* Yield: 79 %. mp: 216–218 °C. $R_f = 0.41$ (DCM/MeOH/AcOH = 90:5:1). *IR (KBr,* cm^{-1}*):* 3449, 3185 (NH), 3067 (C-H, aren), 1737, 1693 (C=O), 1602, 1514, 1446 (C=C), 1327, 1159 (S=O), 1265 (C-O), 789 (C–Cl). *ESI–MS (*m/z): 437.1 $[M-H]^-$. *^{1}H-NMR (500 MHz, DMSO-d_6, ppm)*: δ 12.50 (1H, s, NH, thiazolidine-2,4-dione), 8.14 (1H, t, J = 5.5 Hz, sulfonamide), 7.82 (1H, t, J = 1.0 Hz, H-2), 7.78 (1H, dt, J = 7.75 Hz, J' = 1.0 Hz, H-6), 7.73 (1H, s, H-7″, olefinic proton), 7.69 (1H, dt, J = 7.75 Hz, J' = 1.0 Hz, H-4), 7.60 (1H, t, J = 8.0 Hz, H-5), 7.52 (2H, d, J = 8.85 Hz, H-3″, H-5″), 6.98 (2H, d, J = 8.85 Hz, H-2″, H-5″), 4.03 (2H, t, J = 5.5 Hz, H-2′), 3.22 (2H, td, J = 5.5 Hz, J' = 5.5 Hz, H-1′). *^{13}C NMR (125 MHz, DMSO-d_6, ppm)*: δ 167.9 (C-10″), 167.4 (C-9″), 159.7 (C-1″), 142.6 (C-1), 133.8 (C-7″), 132.3 (C-3), 132.0 (C-3″, C-5″), 131.7 (C-4), 131.2 (C-5), 126.0 (C-6), 125.7 (C-4″), 125.1 (C-2), 120.4 (C-8″), 115.2 (C-2″, C-6″), 66.6 (C-2′), 41.9 (C-1′). Anal. Calcd. For $C_{18}H_{15}ClN_2O_5S_2$ (438.91): C, 49.26; H, 3.44; N, 6.38. Found: C, 49.23; H, 3.54; N, 6.44.

*(Z)-4-Chloro-N-(2-(4-((2,4-dioxothiazolidine-5-ylidene)methyl) phenoxy)ethyl)benzenesulfonamide (***4d***)* Yield: 77 %. mp: 215–217 °C. $R_f = 0.41$ (DCM/MeOH/AcOH = 90:5:1). *IR (KBr,* cm^{-1}*):* 3412, 3118 (NH), 3066 (C-H, aren) 2940, 2875 (CH, CH_2), 1735, 1691 (C=O), 1602, 1541, 1440 (C=C), 1327, 1162 (S=O), 1267 (C-O), 824 (C–Cl). *ESI–MS (*m/z): 437.4 $[M-H]^-$. *^{1}H-NMR (500 MHz, DMSO-d_6, ppm)*: δ 12.52 (1H, s, NH, thiazolidine-2,4-dione), 8.10 (1H, t, J = 5.5 Hz, sulfonamide), 7.81 (2H, d, J = 8.5 Hz, H-3, H-5), 7.74 (1H, s, H-7″, olefinic proton), 7.63 (2H, d, J = 8.5 Hz, H-2, H-6), 7.52 (2H, d, J = 8.5 Hz, H-3″, H-5″), 6.98 (2H, d, J = 8.5 Hz, H-2″, H-6″), 4.02 (2H, t, J = 5.0 Hz, H-2′), 3.19 (2H, td, J = 5.0 Hz, J' = 5.5 Hz, H-1′). *^{13}C NMR (125 MHz, DMSO-d_6, ppm)*: δ 167.8 (C-

10″), 167.4 (C-9″), 159.7 (C-1″), 139.5 (C-1), 137.2 (C-7″), 131.9 (C-3″, C-5″), 131.7 (C-4), 129.3 (C-2, C-6), 128.3 (C-3, C-5), 125.7 (C-4″), 120.4 (C-8″), 115.2 (C-2″, C-6″), 66.6 (C-2′), 41.8 (C-1′). Anal. Calcd. For $C_{18}H_{15}ClN_2O_5S_2$ (438.91): C, 49.26; H, 3.44; N, 6.38. Found: C, 49.34; H, 3.55; N, 6.49.

*(Z)-N-(2-(4-((2,4-dioxothiazolidine-5-ylidene)methyl)phenoxy) ethyl)-4-methylbenzenesulfonamide (***4e***)* Yield: 81 %. mp: 224–225 °C. $R_f = 0.40$ (DCM/MeOH/AcOH = 90:5:1). *IR (KBr, cm^{-1}):* 3416, 3201 (NH), 3068 (C-H, aren) 2939, 2875 (CH, CH_2), 1736, 1693 (C=O), 1602, 1514, 1440 (C=C), 1322, 1160 (S=O), 1266 (C-O). *ESI–MS (*m/z): 417.2 $[M-H]^-$. *^{1}H-NMR (500 MHz, DMSO-d_6, ppm)*: δ 12.52 (1H, s, NH, thiazolidine-2,4-dione), 7.88 (1H, t, J = 5.5 Hz, sulfonamide), 7.74 (1H, s, H-7″, olefinic proton), 7.70 (2H, d, J = 8.25 Hz, H-2, H-6), 7.52 (2H, d, J = 8.75 Hz, H-3″, H-5″), 7.36 (2H, d, J = 8.25 Hz, H-3, H-5), 6.99 (2H, d, J = 8.75 Hz, H-2″, H-6″), 4.02 (2H, t, J = 5.5 Hz, H-2′), 3.13 (2H, td, J = 5.5 Hz, J' = 5.5 Hz, H-1′), 2.36 (3H, s, -CH_3). *^{13}C NMR (125 MHz, DMSO-d_6, ppm)*: δ 167.9 (C-10″), 167.3 (C-9″), 159.8 (C-1″), 142.6 (C-1), 137.7 (C-7″), 131.9 (C-3″, C-5″), 131.7 (C-4), 129.5 (C-2, C-6), 126.4 (C-3, C-5), 125.6 (C-4″), 120.4 (C-8″), 115.3 (C-2″, C-6″), 66.6 (C-2′), 41.8 (C-1′), 20.9 (CH_3). Anal. Calcd. For $C_{19}H_{18}ClN_2O_5S_2$ (418.49): C, 54.53; H, 4.34; N, 6.69. Found: C, 54.29; H, 4.49; N, 6.74.

*(Z)-N-(2-(4-((2,4-dioxothiazolidine-5-ylidene)methyl)phenoxy) ethyl)-4-methoxybenzenesulfonamide (***4f***)* Yield: 78 %. mp: 220–222 °C. $R_f = 0.39$ (DCM/MeOH/AcOH = 90:5:1). *IR (KBr, cm^{-1}):* 3418, 3207 (NH), 3067 (C-H, aren), 2932, 2848 (CH, CH_2), 1736, 1693 (C=O), 1602, 1575 (C=C), 1324, 1153 (S=O), 1265 (C-O). *ESI–MS (*m/z): 433.3 $[M-H]^-$. *^{1}H-NMR (500 MHz, DMSO-d_6, ppm)*: δ 12.50 (1H, s, NH, thiazolidine-2,4-dione), 7.81 (1H, t, J = 5.5 Hz, sulfonamide), 7.76–7.74 (3H, overlap, H-7″, olefinic proton, H-3, H-5), 7.53 (2H, d, J = 8.85 Hz, H-3″, H-5″), 7.08 (2H, dt, J = 7.0 Hz, J' = 2.0 Hz, H-2, H-6), 7.01 (2H, d, J = 8.85 Hz, H-2″, H-6″), 4.02 (1H, t, J = 5.5 Hz, H-2′), 3.81 (3H, s, -OCH_3), 3.12 (2H, td, J = 5.5 Hz, J' = 5.5 Hz, H-1′). *^{13}C NMR (125 MHz, DMSO-d_6, ppm)*: δ 167.9 (C-10″), 167.4 (C-9″), 162.1 (C-4), 159.8 (C-1″), 132.1 (C-1), 132.0 (C-3″, C-5″), 131.7 (C-7″), 128.6 (C-2, C-6), 125.6 (C-4″), 120.4 (C-8″), 115.3 (C-3, C-5), 114.3 (C-2″, C-6″), 66.6 (C-2′), 55.6 (C-OCH_3), 41.8 (C-1′). Anal. Calcd. For $C_{19}H_{18}ClN_2O_6S_2$ (434.49): C, 52.52; H, 4.18; N, 6.45. Found: C, 52.50; H, 4.29; N, 6.54.

*(Z)-N-(3-(4-((2,4-dioxothiazolidine-5-ylidene)methyl)phenoxy) propyl)benzenesulfonamide (***7a***)* Yield: 76 %. mp: 213–214 °C. $R_f = 0.42$ (DCM/MeOH/AcOH = 90:5:1). *IR (KBr, cm^{-1}):* 3519, 3243 (NH), 2937 (CH, CH_2), 1742, 1694 (C=O), 1604, 1569 (C=C), 1321, 1157 (S=O), 1264 (C-O). *ESI–MS (*m/z): 417.2 $[M-H]^-$. *^{1}H-NMR (500 MHz, DMSO-d_6, ppm)*: δ 12.50 (1H, s, NH, thiazolidine-2,4-dione), 7.80 (2H, d, J = 7.5 Hz, H-2 H-6), 7.73 (1H, s, H-7″, olefinic proton), 7.71 (1H, t, J = 6.25 Hz, NH, sulfonamide), 7.61 (1H, t, J = 7.0 Hz, H-4), 7.57 (2H, t, J = 7,5 Hz, H-3, H-5), 7.52 (2H, d, J = 8.75 Hz, H-3″, H-5″), 7.01 (2H, d, J = 8.75 Hz, H-2″, H-6″), 4.01 (2H, t, J = 6.5 Hz, H-3′), 2.92 (2H, td, J = 6.5 Hz, J' = 6.25 Hz, H-1′), 1.83 (2H, quintet, J = 6.5 Hz, H-2′) *^{13}C NMR (125 MHz, DMSO-d_6, ppm)*: δ 167.90 (C-10″), 167.38 (C-9″), 160.15 (C-1″), 140.37 (C-1), 132.33 (C-7″), 132.00 (C-2. C-6), 131.81 (C-4), 129.18 (C-3″. C-5″), 126.41 (C-3, C-5), 125.46 (C-4″), 120.27 (C-8″), 115.29 (C-2″, C-6″), 64.95 (C-3′), 28.70 (C-2′). Anal. Calcd. For $C_{19}H_{18}N_2O_5S_2$ (418.49): C, 54.53; H, 4.34; N, 6.69. Found: C, 54.45; H, 4.44; N, 6.71.

*(Z)-2-Chloro-N-(3-(4-((2,4-dioxothiazolidine-5-ylidene)methyl) phenoxy)propyl)benzenesulfonamide (***7b***)* Yield: 77 %. mp: 210–211.5 °C. $R_f = 0.38$ (DCM/MeOH/AcOH = 90:5:1). *IR (KBr, cm^{-1}):* 3441, 3248 (NH), 2928, 2847 (CH, CH_2), 1736, 1693 (C=O), 1600, 1570 (C=C), 1318, 1157 (S=O), 1262 (C-O). *ESI–MS (*m/z): 451.7 $[M-H]^-$. *^{1}H-NMR (500 MHz, DMSO-d_6, ppm)*: δ 7.97 (1H, t, J = 6.0 Hz, NH, sulfonamide), 7.96 (1H, dd, J = 8.0 Hz, J' = 1,75 Hz, H-6), 7.73 (1H, s, H-7″, olefinic proton), 7.60 (1H, td, J = 8.0 Hz, J' = 2.0 Hz, H-4), 7.58 (1H, td, J = 8.0 Hz, J' = 2.0 Hz, H-5), 7.51 (2H, d, J = 8.5 Hz, H-3″, H-5″), 7.49 (1H, dd, J = 8.0 Hz, J' = 2.0 Hz, H-3), 6.98 (2H, d, J = 8.5 Hz, H-2″, H-6″), 4.01 (2H, t, J = 6.0 Hz, H-3′), 3.02 (2H, td, J = 6.5 Hz, J' = 6.0 Hz, H-1′), 1.84 (2H, quintet, J = 6.5 Hz, H-2′). *^{13}C NMR (125 MHz, DMSO-d_6, ppm)*: δ 168.00 (C-10″), 167.52 (C-9″), 160.12 (C-1″), 137.77 (C-7″), 133.92 (C-1), 132.00 (C-3″. C-5″), 131.79 (C-4), 131.74 (C-2), 130.56 (C-3), 130.46 (C-6), 127.64 (C-5), 125.48 (C-4″), 120.36 (C-8″), 115.27 (C-2″, C-6″), 64.83 (C-3′), 39.34 (C-1′), 28.76 (C-2′). Anal. Calcd. For $C_{19}H_{17}ClN_2O_5S_2$ (452.93): C, 50.38; H, 3.78; N, 6.18. Found: C, 50.31; H, 3.75; N, 6.27.

*(Z)-4-Chloro-N-(3-(4-((2,4-dioxothiazolidine-5-ylidene)methyl) phenoxy)propyl)benzenesulfonamide (***7d***)* Yield: 79 %. mp: 212–213 °C. $R_f = 0.37$ (DCM/MeOH/AcOH = 90:5:1). *IR (KBr, cm^{-1}):* 3446, 3274 (NH), 3036 (C-H, aren), 2929 (CH, CH_2), 1741, 1695 (C=O), 1596, 1571 (C=C), 1328, 1156 (S=O). *ESI–MS (*m/z): 450.5 $[M-2H]^-$. *^{1}H-NMR (500 MHz, DMSO-d_6, ppm)*: δ 7.82 (1H, t, J = 6,0 Hz, NH, sulfonamide), 7.79 (2H, d, J = 8,5 Hz, H-2, H-6), 7.72 (1H, s, H-7″, olefinic proton), 7.62 (2H, d, J = 8.25 Hz, H-3, H-5), 7.51 (2H, d, J = 8.5 Hz, H-3″, H-5″), 7.99 (2H, d, J = 8.5 Hz, H-2″, H-6″), 3.99 (2H, t, J = 6.0 Hz, H-3′), 2.94 (2H, td, J = 6.0 Hz, J' = 6.0 Hz, H-1′), 1.83 (2H, quintet, J = 6.0 Hz, H-2′). *^{13}C NMR (125 MHz, DMSO-d_6, ppm)*: δ 167.98 (C-10″), 167.56 (C-

9″), 160.07 (C-1″), 139.26 (C-7″), 137.22 (C-1), 131.97 (C-3″, C-5″), 131.69 (C-4), 129.30 (C-3, C-5), 128.37 (C-2, C-6), 125.50 (C-4″), 120.41 (C-8″), 115.23 (C-2″, C-6″), 64.79 (C-3′), 39.24 (C-1′), 28.62 (C-2′). Anal. Calcd. For $C_{19}H_{17}ClN_2O_5S_2$ (452.93): C, 50.38; H, 3.78; N, 6.18. Found: C, 50.29; H, 3.65; N, 6.27.

*(Z)-N-(3-(4-((2,4-Dioxothiazolidine-5-ylidene)methyl)phenoxy) propyl)-4-methylbenzenesulfonamide (***7e***)* Yield: 75 %. mp: 210–211 °C. $R_f = 0.42$ (DCM/MeOH/AcOH = 90:5:1). *IR (KBr, cm^{-1}):* 3445, 3291 (NH), 3121 (C-H, aren), 2970, 2875 (CH, CH_2), 1735, 1691 (C=O), 1594, 1568 (C=C), 1332, 1156 (S=O), 1266 (C-O). *ESI–MS* (m/z): 430.5 [M-2H]$^-$. *^{1}H-NMR (500 MHz, DMSO-d_6, ppm)*: δ 7.73 (1H, s, H-7″, olefinic proton), 7.67 (2H, d, J = 8.0 Hz, H-2, H-6), 7.61 (1H, s, J = 5.5 Hz, NH, sulfonamide), 7.51 (2H, d, J = 9.0 Hz, H-3″, H-5″), 7.35 (2H, d, J = 9.0 Hz, H-3, H-5), 7.00 (2H, d, J = 9.0 Hz, H-2″, H-6″), 3.99 (2H, t, J = 6.25 Hz, H-3′), 2.90 (2H, td, J = 6.25 Hz, J' = 6.25 Hz, H-1′), 1.82 (2H, quintet, J = 6.25 Hz, H-2′). δ *^{13}C NMR (125 MHz, DMSO-d_6, ppm)*: δ 167.94 (C-10″), 167.45 (C-9″), 160.15 (C-1″), 142.55 (C-7″), 137.51 (C-1), 131.99 (C-3″. C-5″), 131.78 (C-4), 129.59 (C-3, C-5), 126.48 (C-2, C-6), 125.46 (C-4″), 120.30 (C-8″), 115.28 (C-2″, C-6″), 64.92 (C-3′), 39.26 (C-1′), 28.65 (C-2′), 20.92 (-CH_3). Anal. Calcd. For $C_{20}H_{20}N_2O_5S_2$ (432.51): C, 55.54; H, 4.66; N, 6.48. Found: C, 55.42; H, 4.55; N, 6.57.

*(Z)-N-(3-(4-((2,4-Dioxothiazolidine-5-ylidene)methyl)phenoxy)propyl)-4-methoxybenzenesulfonamide (***7f***)* Yield: 74 %. mp: 213–214 °C. $R_f = 0.39$ (DCM/MeOH/AcOH = 90:5:1). *IR (KBr, cm^{-1}):* 3293, 3121 (NH), 2970, 2839 (CH, CH_2), 1736, 1690 (C=O), 1596, 1588, 1566 (C=C), 1154 (S=O), 1269 (C-O). *ESI–MS* (m/z): 446.6 [M-2H]$^-$. *^{1}H-NMR (500 MHz, DMSO-d_6, ppm)*: δ 7.73 (1H, s, H-7″, olefinic proton), 7.71 (2H, d, J = 9.0 Hz, H-2, H-6), 7.53 (1H, t, J = 5.5 Hz, NH, sulfonamide), 7.51 (2H, d, J = 8.75 Hz, H-3″, H-5″), 7.07 (2H, d, J = 9.0 Hz, H-3, H-5), 7.00 (2H, d, J = 8.75 Hz, H-2″, H-6″), 3.99 (2H, t, J = 6.0 Hz, H-3′), 3.80 (3H, s, OCH_3), 2.89 (2H, td, J = 6.5 Hz, J' = 6.0 Hz, H-1′), 1.82 (2H, quintet, J = 6.5 Hz, H-2′). *^{13}C NMR (125 MHz, DMSO-d_6, ppm)*: δ 167.92 (C-10″), 167.42 (C-9″), 162.05 (C-4), 160.16 (C-1″), 131.99 (C-3″, C-5″), 131.78 (C-7″), 128.60 (C-2, C-6), 125.45 (C-1), 120.27 (C-4″), 115.27 (C-3, C-5), 114.83 (C-8″), 114.27 (C-2″, C-6″), 64.94 (C-3′), 55.54 (-OCH-$_3$), 39.23 (C-1′), 28.62 (C-2′). Anal. Calcd. For $C_{20}H_{20}N_2O_6S_2$ (448.51): C, 55.54; H, 4.66; N, 6.48. Found: C, 55.63; H, 4.50; N, 6.53.

Cytotoxicity assays

Three human cancer cell lines including SW620 (colon cancer), PC-3 (prostate cancer), and NCI-H460 (lung cancer) were obtained from a cancer cell bank at the Korea Research Institute of Bioscience and Biotechnology (KRIBB). All media, sera, and other reagents used for cell culture were obtained from GIBCO Co., Ltd. (Grand Island, New York, USA). Compounds were initially dissolved in dimethyl sulfoxide (DMSO) to make stock solutions at concentrations of 1000-fold higher than the testing concentration. Right before assays, the stock solutions were serially diluted by 100-fold using cell culture medium. One hundred and eighty microliters of cell suspension (9×10^3 cells) was plated in each well in 96-well plates. The plates were incubated for 24 h, and then the cells in each well were treated with 20 μL of samples or positive controls (SAHA or adriamycin) at different concentrations as prepared above. To blank wells was added 20 μL of cell culture medium containing no sample. Cytotoxicity was measured by the method as described in the literature (Skehan *et al.*, 1990) with slight modifications (You *et al.*, 2004; Kim *et al.*, 2002). The IC_{50} values were calculated according to the probit method (Wu *et al.*, 1992). The values reported for these compounds are averages of three separate determinations.

Western blot assay

Total protein extracts were prepared by lysing cells in RIPA buffer (50 mM Tris–Cl [pH 8.0], 5 mM EDTA, 150 mM NaCl, 1 % NP-40, 0.1 % SDS, and 1 mM phenylmethylsulfonyl fluoride). Protein concentrations in the lysates were determined using a Bio-Rad protein assay kit (Bio-Rad Laboratories Inc., Hercules, CA, USA) according to the manufacturer's instructions. Samples were separated on SDS–polyacrylamide gels and transferred to nitrocellulose membranes. The membranes were incubated with blocking buffer (Tris-buffered saline containing 0.2 % Tween-20 and 3 % nonfat dried milk) and probed with the primary antibodies against acetyl histone H3, H4, and GAPDH). After washing, membranes were probed with horseradish peroxidase-conjugated secondary antibodies. Detection was performed using an enhanced chemiluminescent protein (ECL) detection system (Amersham Biosciences, Little Chalfont, UK).

PTP1B inhibition assay

The effect of the synthesized compounds on PTP1B was measured using a colorimetric assay kit purchased from Biomol International L.P., USA, consisting of recombinant enzyme, PTP1B substrate (IR5), Biomol Red reagent, and buffer. Before the assay, enzyme, substrate, and buffer were thawed on ice. A diluted solution of PTP1B enzyme (BML-SE332-9092) in cold 1X Assay Buffer, such that each 5 μL contains the desired amount (2.5 ng) of enzyme

per reaction well, was prepared. Following, a diluted solution of the 1.5 mM IR5 substrate stock at two times the desired assay concentration was prepared and warmed to assay temperature. To each reaction well was added 35 μL of 1X Assay Buffer and warmed to assay temperature, e.g., 30 °C. Following, 10 μL of a test sample 10X stocks was appropriately added to each well. For blank wells, 10 μL of 1X Assay Buffer was added instead and for positive control wells, 10 μL of a suramin solution (100 μM). Then, to each well, 5 μL of the cold PTP1B dilution was added to the 45 μL of warmed Assay Buffer. The reaction was initiated by mixing in 50 μL of the warmed 2X substrate. After incubation for 30 min, reactions were terminated by addition of 25 μL BIOMOL RED™ Reagent (BML-KI468). The reaction mixtures were mixed by pipetting (care should be taken to avoid producing bubbles). Color was allowed to develop for 20–30 min. ODs were read at 620 nm on a microplate reader. The enzyme inhibition percentage (EIP) was calculated by an equation: $EIP = (OD_{blk} - OD_s)/OD_{blk} \times 100$ (%), where OD_{blk} was the OD of the blank well and OD_s was the OD of the sample's well. All OD values were calibrated against the OD value at time zero.

Docking studies

AutoDock Vina program (The Scripps Research Institute, CA, USA) (Trott and Olson, 2010) was used in the docking studies. Initial structures of HDAC8 (Somoza *et al.*, 2004) and HDAC2 (Lauffer *et al.*, 2013) (complexed with SAHA) were obtained from the Protein Data Bank (PDB) (PDB ID: 1T69 and PDB ID: 4LXZ, respectively), and coordinates for the compounds were generated using the GlycoBioChem PRODRG2 Server (http://davapc1.bioch.dundee.ac.uk/prodrg/) (Schuttelkopf and van Aalten, 2004). The grid maps for docking studies were centered on the SAHA binding site and comprised 26 × 26 × 22 points with 1.0 Å spacing after SAHA was removed from the complex structure, as described previously. AutoDock Vina program was run with eight-way multithreading, and the other parameters were default settings in AutoDock Vina program.

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