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BRIEF ARTICLE

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Synthesis and Biological Evaluation of Novel Thiazolidinedione Analogues as 15-Hydroxyprostaglandin Dehydrogenase Inhibitors

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ABSTRACT: Novel thiazolidinedione analogues as 15-hydroxyprostaglandin dehydrogenase (15-PGDH) inhibitors were synthesized. Compounds **2**, **3**, and **4** exhibited IC_{50} of 25, 8, and 19 nM, respectively. They also significantly increased levels of PGE_2 in A549 cells. To assess the influence of 15-PGDH inhibitor on cochlear blood flow (CBF), **2** was applied intravenously to guinea pigs. It increased their CBFs. Scratch wounds were also analyzed in confluent monolayers of HaCaT cells. Cells exposed to **4** showed significantly improved wound healing with respect to a control.

INTRODUCTION

Naturally occurring prostaglandins, mainly prostaglandin E_1 (PGE_1) and prostaglandin E_2 (PGE_2), are important mediators in the gastric mucosa, renal medulla, and microvascular endothelium and in controlling other physiological functions. PGE_1, a potent vasodilator and inhibitor of platelet aggregation, is well-known as a useful drug for peripheral arterial disease such as Raynaud's and Burerger's diseases and diabetic neuropathy.[1] PGE_2 is crucial to the control of various physiological functions. Recent clinical studies have demonstrated that the prostaglandin analogue latanoprost causes the growth of body hair and eyelashes in humans and animals.[2] In humans, trials carried out on the scalp have shown that PGE_2 could increase hair density.[3] PGE_2 has been identified as an important mediator of gastric ulcer healing,[4] bone formation,[5] and dermal wound healing.[6] Both these prostaglandins are also potent stimulants of human uterine contractility at any stage of pregnancy and also cause cervical ripening and dilatation. These characteristics have been found clinically useful for different purposes during pregnancy. However, local administration of prostaglandin is an unacceptable therapeutic option for human diseases because of the limited knowledge of the potential changes caused by it on the tissue at cellular level and the biological instability of prostaglandins. Therefore, a number of prostaglandin analogues that are resistant to rapid inactivation have been developed for clinical use. Misoprostol, (11α,13*E*)-11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oic acid methyl ester, is a PGE_1 analogue used for the treatment and prevention of peptic ulcers caused by nonsteroidal anti-inflammatory drugs.[7] Misoprostol has more recently been used to induce labor and to treat postpartum hemorrhage.[8] The only parent prostaglandin still in extended clinical use is PGE_2, mainly for cervical ripening at term and for induction of labor.

Prostaglandins have a short lifetime in vivo because they are metabolized rapidly by oxidation to 15-ketoprostaglandins catalyzed by the cytosolic enzyme NAD^+-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH).[9] This enzyme is ubiquitous in mammalian tissue and is responsible for the biological inactivation of prostaglandins because 15-ketoprostaglandins is significantly less biologically active.[10] Therefore, inhibitors of 15-PGDH will be valuable for the therapeutic management of diseases requiring elevated prostaglandin levels.

Previous work has shown that the antidiabetic drug ciglitazone and its analogue 5-(4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione **1** (CT-8) (Chart 1) are potent inhibitors of 15-PGDH.[11−13] Because of this, a series of thiazolidinedione analogues with different substituents on phenyl rings were prepared in order to investigate the relationship between structure and 15-PGDH inhibition. Furthermore, human lung adenocarcinoma A549 cells were used as a model system to show that the inhibition of 15-PGDH may lead to increased accumulation of PGE_2, indicating that 15-PGDH inhibitors may be valuable for the therapeutic management of diseases in which elevated prostaglandin levels are needed.

CHEMISTRY

The thiazolidine-2,4-dione derivatives listed in Table 1 were prepared by the method shown in Scheme 1. The connection of cyclohexylalcohol to the central arylaldehyde was accomplished via Mitsunobu coupling to produce an intermediate aldehyde with a yield of 60−80%. Knoevenagel condensation between intermediate aldehyde and 2,4-thiazolidinedione in refluxing toluene, containing a catalytic amount of piperidinium acetate, gave the benzylidenethiazolidine-2,4-dione, which crystallized from the reaction mixture in high purity. *p*-Hydroxybenzaldehyde, as a starting material, was reacted with various substrates to produce an intermediate substituted benzaldehyde in good yield. The intermediate was then used in the coupling reaction with thiazolidine-2,4-dione to afford the

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Chart 1. Structures of Ciglitazone and Compound 1 (CT-8)

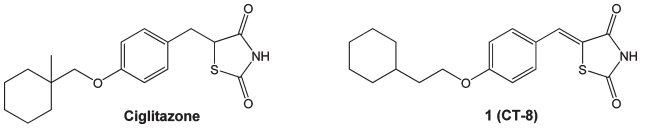
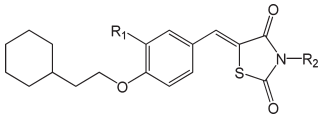


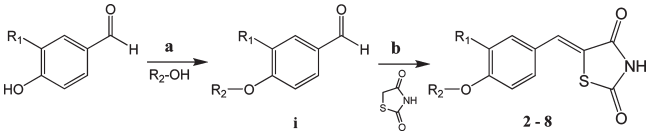
Table 1. Inhibitory Potency of Various Synthetic Thiazolidine-2,4-diones[a]



compd	R_1	R_2	IC_{50} (μM)
1	H	H	0.051
2	OCH_3	H	0.025
2a	OCH_3	CH_3	>50
3	Cl	H	0.008
4	Br	H	0.019

[a] The enzyme was assayed fluorometrically as described in the text. IC_{50} values were determined using NAD^+ (250 μM) as coenzyme and PGE_2 (21 μM) as substrate. 15-PGDH was expressed as a GST fusion enzyme using pGEX-2T vector as described in the text.

Scheme 1. Synthesis of Compounds 2−8[a]



[a] Reagents and conditions: (a) PPh_3, DEAD, THF, 25 °C, 18 h; (b) piperidine, AcOH, reflux, 12 h.

appropriate thiazolidinedione derivatives. Finally, control compound **2a** was synthesized from **2** with methyl iodide in the presence of a catalytic amount of NaH. All the compounds were characterized by ^{1}H NMR. Molecular weights of all compounds were identified using an Agilent Technologies series 1100 LC/MSD VL system (Palo Alto, CA, U.S.) with flow injection analysis using 50% acetonitrile in water containing 0.1% formic acid. The mass spectrometer was operated in negative ion mode. The purity of all compounds was determined using reversed-phase HPLC with a Hypersil Gold C-18 column (250 mm × 4.6 mm i.d., 5 μm, Thermo Scientific, Bellefonte, PA, U.S.). Samples were eluted by isocratic elution using 55% acetonitrile in water containing 0.1% trifluoroacetic acid at a flow rate of 1.0 mL/min. UV absorbance was monitored at 320 nm. Purity of all compounds was ≥95%.

BIOLOGICAL EVALUATION

Inhibition of 15-PGDH. The new compounds were tested for the inhibition of human 15-PGDH expressed in *Escherichia coli*. Inhibitory effects were observed using a fluorescence spectrophotometer that monitored the formation of NADH by measuring emission at 468 nm following excitation at 340 nm. Compounds were also tested in cellular situations: A549 cells were stimulated with IL-1β (1 ng/mL) overnight (18 h) to generate PGE_2. The compounds were then added, and incubation continued for 5 h. The medium was collected, and the level of PGE_2 was analyzed by enzyme immunoassay.

Effect on Cochlear Blood Flow (CBF). Compound **2** was administered intravenously to guinea pigs. Healthy males each weighing 250 g were used for CBF analysis. The animals were housed at a constant 22 °C with 50% humidity. Ambient noise levels were below 40 dB. Compound **2** was applied at the indicated concentrations, and CBF was measured by a computer equipped with a data acquisition program (PowerLab, AD Instruments).

Scratch Wound Test. Scratch wound analysis was performed in confluent monolayers of HaCaT cells. HaCaT cells were plated in a six-well plate at ∼5 × 10^5 cells per well and maintained in DMEM medium supplemented with 10% fetal bovine serum and 10 μg/mL mitomycin in a humidified atmosphere containing 5% CO_2 at 37 °C. The cells were incubated until ∼80% confluence was reached. The cells cultured in the six-well plate were mechanically scratched with a sterile 200 μL pipet tip and incubated under control conditions in the presence of 5 μM **4**. The width of the wound was measured upon wounding and after treatment using an inverted microscope equipped with a digital camera.

Quantitative Real-Time PCR. A549 cells were plated in a six-well plate at ∼5 × 10^5 cells per well and maintained in RPMI medium supplemented with 10% fetal bovine serum and 100 μg/mL penicillin in a humidified atmosphere containing 5% CO_2 at 37 °C overnight. 15-PGDH inhibitors were added at 5 μM, and incubation continued for 25 h. Levels of gene expression were then assayed by real-time PCR.

RESULTS AND DISCUSSION

Thiazolidinediones are well-known synthetic chemical entities that have been found to have several important biological activities. Ciglitazone was the first thiazolidinedione found to exhibit antihyperglycemic activity.[14] Previous studies have shown that the antidiabetic drug ciglitazone and its derivatives are potent inhibitors of 15-PGDH by a noncompetitive and an uncompetitive inhibition mechanism with NAD^+ and PGE_2 substrates, respectively.[11] The structures of these thiazolidinediones are shown in Chart 1. On the basis of this, a series of thiazolidinediones analogues with different substituents on the phenyl ring were prepared in order to investigate the structure−activity relations of 15-PGDH inhibition.

The substituents were introduced at the phenyl moiety of **1** described in Scheme 1. The introduction of a chlorine atom at the C3 of **1** showed a great increase in inhibitory potency with IC_{50} of 8 nM, as shown in Table 1. The introduction of a bromine atom at the C3 of **1** also showed a great increase in inhibitory potency with an IC_{50} of 19 nM. For structure−activity analysis, cyclohexyl was introduced with different chain lengths to the hydroxyl group of 5-(3-chloro-4-hydroxybenzylidene)thiazolidine-2,4-dione, and the effects of these derivatives were tested. Deletion of the methylene group between cyclohexyl ring and the oxygen of 5-(3-chloro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione (**3**) decreased inhibitory potency, as shown in Table 2. Further addition of a methylene group significantly decreased the inhibitory potency, as indicated by **8**. It also appears that two methylene groups between the cyclohexyl ring and oxygen of 5-(3-chloro-4-hydroxybenzylidene)-thiazolidine-2,4-dione are optimal for inhibitory activity. The most potent inhibitor of this series of compounds is **3**, (5-(3-chloro-4-(2-cyclohexylethoxy)benzyl)thiazolidine-2,4-dione), with

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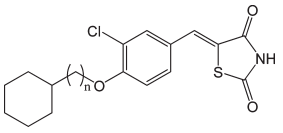
Table 2. Inhibitory Potency of Various Synthetic Thiazolidine-2,4-diones[a]



compd	*n*	IC_{50} (μM)
5	0	0.047
6	1	0.028
3	2	0.008
7	3	0.010
8	4	0.024

[a] The enzyme was assayed fluorometrically as described in the text. IC_{50} values were determined using NAD^+ (250 μM) as coenzyme and PGE_2 (21 μM) as substrate. 15-PGDH was expressed as a GST fusion enzyme using pGEX-2T vector as described in the text.

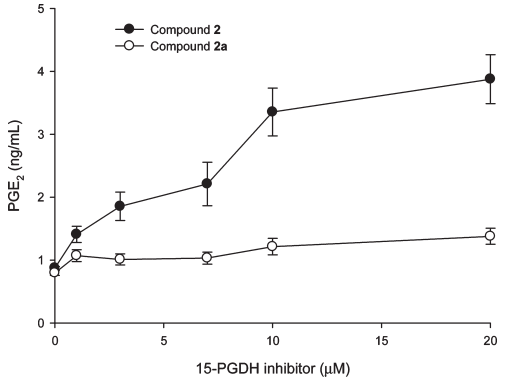


Figure 1. Inhibition of 15-PGDH in IL-1β-stimulated A549 cells. A single clone of 15-PGDH stably transfected A549 cell line was maintained in RPMI-1640 medium supplemented with 10% fetal calf serum (FBS) and 1 mg/100 mL gentamicin in a humidified atmosphere containing 5% CO_2 at 37 °C. Cells were plated in 24-well plate (0.5 mL per well) at about 10^5 cells per well in duplicate and grown for 24 h before stimulation with IL-1β (1 ng/mL) overnight (18 h) to generate PGE_2. Compounds **2** and **2a** were added at the indicated concentrations, and the incubation continued for 5 h. Medium was collected, and the level of PGE_2 was analyzed by enzyme immunoassay as described in the text. Data were analyzed from results of five independent experiments.

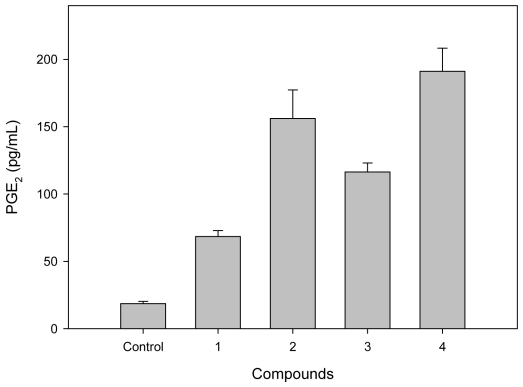


Figure 2. Inhibition of 15-PGDH in A549 cells. A549 cells were seeded in six-well culture plates in RPMI medium containing fetal bovine serum and antibiotic. They were incubated overnight at 5% CO_2 and 37 °C. A549 cells were treated by 15-PGDH inhibitors at 5 μM, and PGE_2 levels were assayed by PGE_2 enzyme immunoassay as described in the text. Data were analyzed from results of three independent experiments.

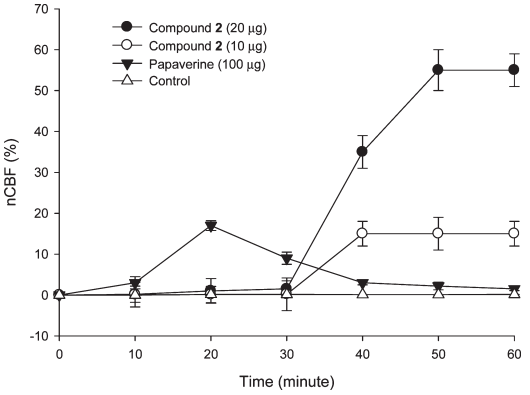


Figure 3. Cochlear blood flow (CBF) after intravenous administration of 15-PGDH inhibitor. Healthy male guinea pigs each weighing 250 g were used to measure CBF. The animals were housed at a constant 22 °C and 50% humidity. Ambient noise was below 40 dB. Compound **2** and papaverine as positive control were applied at the indicated concentrations, and CBF was measured by a computer equipped with a data acquisition program (PowerLab, AD Instruments) as described in the text. Data were analyzed from results of three independent experiments.

an IC_{50} of 8 nM. A summary of the inhibitory potencies of all these compounds is listed in Tables 1 and 2.

To evaluate the selectivity of **2** for inhibition of 15-PGDH in IL-1β-stimulated A549 cells, **2** and **2a** were added at various concentrations and incubated for 5 h. Medium was then collected, and the level of PGE_2 was analyzed by enzyme immunoassay. The results show that the level of PGE_2 was dose-dependently increased as shown in Figure 1. In addition, A549 cells were treated by **1**, **2**, **3**, and **4**, each at 5 μM, and PGE_2 levels were assayed by PGE_2 enzyme immunoassay. The results also show that levels of PGE_2 were significantly increased, as shown in Figure 2. These results suggest that thiazolidinedione derivatives as 15-PGDH inhibitors may have utility for the therapeutic management of diseases requiring elevated prostaglandin levels.

To assess the effect of 15-PGDH inhibitor on CBF, **2** was applied intravenously to healthy male guinea pigs. The CBF values were expressed relative to the baseline value, which was set at 100% for each condition. CBF began to increase after 30 min, reaching plateaus of 22% 40 min after the intravenous application of 10 μg and 65% 50 min after the application of 20 μg. The plateau levels were maintained for at least 10 min (Figure 3).

Re-epithelialization is an important part of wound healing. The healing of wounds is complex and involves the formation of a clot, an inflammatory response, accumulation of granulation tissue, and the deposition and remodeling of an extracellular matrix.[15] It also requires the interaction of cells in the epidermis and the dermis and mediators released from inflammatory cells, fibroblasts, and keratinocytes.[16] Many factors influence wound healing, including growth factors, cytokines, metalloproteinases, and extracellular matrix (ECM) proteins,[16] and the exogenous application of some of these factors has been shown to aid healing.[17] Many studies have reported that PGE_2 is an important mediator of dermal wound healing with specific effects on fibroblast behavior. Kolodsick et al.[18] reported that PGE_2 can inhibit the differentiation of fibroblast into myofibroblasts

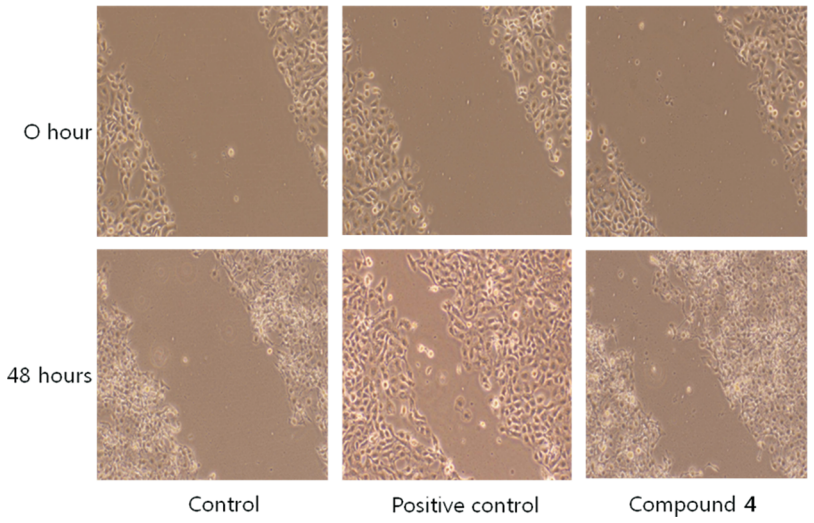


Figure 4. Scratch wound healing of HaCaT confluent monolayers. HaCaT cells were plated in a 6-well plate at ~5×10^5 cells per well and maintained in DMEM medium supplemented with 10% fetal bovine serum and 10 μg/mL mitomycin in a humidified atmosphere containing 5% CO_2 at 37 °C. The cells were incubated until ~80% confluence was reached. The cells were mechanically scratched with a sterile 200 μL pipet tip and incubated under control conditions in the presence of 1 ng of TGF-β1 as positive control and in the presence of 5 μM **4** and observed 48 h after wounding.

via the EP2 receptor pathway through the up-regulation of cAMP. To study wound healing, a scratch was made using a sterile 200 μL pipet tip in a HaCaT cell line. Confluent monolayers of HaCaT were scratch wounded as described in the methods section and then allowed to re-epithelialize for 48 h at 37 °C in the presence or absence of **4** at 5 μM. Cells exposed to **4** showed significantly improved wound healing after 48 h with respect to a control (Figure 4).

To evaluate the effect of 15-PGDH inhibitors on the regulation of COX-1/2, MRP4, and PGT in cells, real time PCR was studied against COX-1/2, MRP4, and PGT in A549 cell lines. The real time PCR data showed that **2** and **3** inhibited COX-1 expression; they induced hPGT expression and had no significant effect on COX-2 or MRP4 expression. These data suggest a decrease of PGE_2 level in extracellular. However, the results show that the levels of PGE_2 in extracellular were significantly increased, as shown in Figure 2. These results suggest that the compounds have major biological roles as 15-PGDH inhibitors, resulting in increased extracellular levels of PGE_2.

CONCLUSIONS

PGE_1, a strong vasodilator and platelet aggregation inhibitor, is clinically used to treat diseases such as peripheral arterial occlusive diseases and ductus arteriosus-dependent congenital heart disease. PGE_2 is also a physiologically important vasodilator in several vascular beds and is in extended clinical use for cervical ripening at term and to induce labor. However, they both have very short half-lives in blood, oxidizing to 15-ketoprostaglandins catalyzed by 15-PGDH. On the basis of the structures of previously synthesized thiazolidinedione analogues and their 15-PGDH inhibitory activities, a series of thiazolidinedione analogues with different substituents on the phenyl ring were prepared using a series of reactions and tested for 15-PGDH inhibitory activity. Novel derivatives of the 15-PGDH inhibitor **1** were developed that showed improved potency. These included **2**, **3**, and **4**, which showed IC_{50} of 25, 8, and 19 nM, respectively. These compounds also significantly increased levels of PGE_2 following IL-1β stimulation compared to inactive analogue in A549 cells. Compound **2** increased CBF in guinea pigs. Scratch wound testing showed that **4** could induce a significant increase of wound repair in HaCaT. Therefore, 15-PGDH inhibitors may be useful to treat diseases such as Raynaud's and Burerger's diseases, diabetic neuropathy, and wounds, which require elevated prostaglandin levels.

EXPERIMENTAL SECTION

General Procedures for the Synthesis of 2−8. To a stirring solution of 2-cyclohexylethanol (1.0 g, 7.80 mmol), 4-hydroxy-3-methoxybenzaldehyde (1.2 g, 7.80 mmol), and triphenylphosphine (2.25 g, 8.58 mmol) in THF (20 mL) was slowly added diethyl azodicarboxylate (40% in toluene, 3.74 g, 8.58 mmol) over 10 min at 0 °C. The mixture was then stirred at room temperature until the disappearance of starting materials (TLC analysis). The resulting solution was concentrated under reduced pressure and purified by column chromatography over silica gel (elution with hexane/ethyl acetate, 20:1) to produce 1.72 g of intermediate 4-(2-cyclohexylethoxy)-3-nitrobenzaldehyde (83.3%) as a yellow oil. A mixture of 4-(2-cyclohexylethoxy)-3-methoxybenzaldehyde (1.0 g, 3.8 mmol), 2,4-thiazolidinedione (445 mg, 3.6 mmol), piperidine (0.19 mL, 1.9 mmol), and acetic acid (0.11 mL, 1.9 mmol) in toluene (20 mL) was then added to a round-bottom flask fitted with a Dean−Stark water trap and stirred under reflux for overnight. After the mixture was cooled to room temperature, the precipitate was washed with hexane and dried to produce **2**.

5-(4-(2-Cyclohexylethoxy)-3-methoxybenzylidene)thiazolidine-2,4-dione (2). **2** was obtained by recrystallization from hexane/ethyl acetate as a yellow solid (1.12 g, 83% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.72 (s, 1H), 7.02 (d, J = 10.2 Hz, 2H), 6.92 (d, J = 10.2 Hz, 2H), 6.89 (s, 1H), 4.07 (t, J = 14.4 Hz, 2H), 3.84 (s, 3H), 1.71 (t, J = 14.4 Hz, 2H), 1.43−1.51 (m, 4H), 1.07−1.21 (m, 4H), 0.78−0.97 (m, 3H). MS (ESI): m/z 360 $[M - H]^-$.

5-(3-Chloro-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione (3). **3** was obtained by recrystallization from hexane/ethyl acetate as a yellow solid (1.21 g, 88% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.73 (s, 1H), 7.52 (s, 1H), 7.38 (d, J = 10.5 Hz, 1H), 7.01 (d, J = 10.5 Hz, 1H), 4.15 (t, J = 13.2 Hz, 2H), 1.80 (t, J = 13.2 Hz, 2H), 1.65−1.80 (m, 4H), 1.50−1.60 (m, 1H), 1.15−1.33 (m, 4H), 0.85−1.05 (m, 2H). MS (ESI): m/z 364 $[M - H]^-$.

5-(3-Bromo-4-(2-cyclohexylethoxy)benzylidene)thiazolidine-2,4-dione (4). **4** was obtained by recrystallization from hexane/ethyl acetate as a yellow solid (1.08 g, 82% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.57 (s, 1H), 7.84 (s, 1H), 7.83 (s, 1H), 7.57 (d, J = 10.8 Hz, 1H), 7.28 (d, J = 10.8 Hz, 1H), 4.17 (t, J = 12.6 Hz, 2H), 1.61−1.75 (m, 7H), 1.46−1.52 (m, 1H), 1.06−1.26 (m, 3H), 0.89−0.96 (m, 2H). MS (ESI): m/z 410 $[M - H]^-$.

5-(3-Chloro-4-(cyclohexyloxy)benzylidene)thiazolidine-2,4-dione (5). **5** was obtained by recrystallization from hexane/ethyl acetate as a yellow solid (1.30 g, 88% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.58 (s, 1H), 7.72 (s, 1H), 7.69 (s, 1H), 7.51 (d, J = 13.2 Hz, 1H), 7.37 (d, J = 13.2 Hz, 1H), 4.56−4.61 (m, 1H), 2.02−2.49 (m, 2H), 1.69−1.86 (m, 2H), 1.50−1.53 (m, 2H), 1.35−1.45 (m, 4H). MS (ESI): m/z 336 $[M - H]^-$.

5-(3-Chloro-4-(cyclohexylmethoxy)benzylidene)thiazolidine-2,4-dione (6). **6** was obtained by recrystallization from hexane/ethyl acetate as a yellow solid (1.30 g, 88% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.58 (s, 1H), 7.72 (s, 1H), 7.69 (s, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 3.94 (d, J = 6.0 Hz, 2H), 1.62−1.82 (m, 6H), 1.03−1.26 (m, 5H). MS (ESI): m/z 350 $[M - H]^-$.

5-(3-Chloro-4-(cyclohexylpropoxy)benzylidene)thiazolidine-2,4-dione (7). **7** was obtained by recrystallization from hexane/ethyl acetate as a yellow solid (1.29 g, 88% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.58 (s, 1H), 7.71 (s, 1H), 7.69 (s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 4.12 (t, J = 12.6 Hz, 2H), 1.62−1.77 (m, 7H), 1.07−1.34 (m, 6H), 0.83−0.91 (m, 2H). MS (ESI): m/z 378 $[M - H]^-$.

5-(3-Chloro-4-(cyclohexylbutoxy)benzylidene)thiazolidine-2,4-dione (8). **8** was obtained by recrystallization from hexane/ethyl acetate as a yellow solid (1.28 g, 87% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.58 (s, 1H), 7.73 (s, 1H), 7.69 (s, 1H), 7.53 (d, J = 9.0 Hz, 1H), 7.30 (d, J = 9.0 Hz, 1H), 4.14 (t, J = 12.3 Hz, 2H), 1.65−1.76 (m, 7H), 1.22−1.61 (m, 2H), 1.06−1.20 (m, 6H), 0.81−0.88 (m, 2H). MS (ESI): m/z 392 $[M - H]^-$.

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ABBREVIATIONS USED

PG, prostaglandin; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; PPARγ, peroxisome proliferator-activated receptor γ; NAD^+, nicotinamide adenine dinucleotide (oxidized form); NADH, nicotinamide adenine dinucleotide (reduced form); DTT, dithiothreitol; SDS, sodium dodecyl sulfate; EDTA, ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid; GST, glutathione *S*-transferase; TLC, thin layer chromatography; THF, tetrahydrofuran; DMSO, dimethylsulfoxide; DMF, *N*,*N*-dimethylformamide; CBF, cochlear blood flow

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