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Design and synthesis of new 1,3-benzthiazinan-4-one derivatives as selective cyclooxygenase (COX-2) inhibitors

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ABSTRACT

A new group of 1, 3-benthiazinan-4-ones, possessing a methyl sulfonyl pharmacophore, were synthesized and their biological activities were evaluated for cyclooxygenase-2 (COX-2) inhibitory activity. In vitro COX-1/COX-2 inhibition studies identified 3-(*p*-fluoropheny)-2-(4-methylsulfonylphenyl)-1,3-benzthiazinan-4-one (**7b**) as a potent (IC_{50} = 0.05 μM) and selective (selectivity index = 259) COX-2 inhibitor.

1. Introduction

The non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly medications in the world. The mechanism of action of these drugs is the inhibition of cyclooxygenase (COX) enzyme, which catalyzes the first step of the biosynthesis of PGG_2 from arachidonic acid.[1] A major factor limiting their use is gastrointestinal toxicity, ranging from ulcer to perforation and bleeding.[2] COX isozymes exist at least in two isoforms, COX-1 and COX-2.[3] The COX isoforms are heme containing enzymes that exhibit distinct expression roles in several physiological processes. The constitutive COX-1 isozyme is found in platelets, kidneys, and the gastrointestinal tract and is believed to be responsible for the maintenance of physiological functions such as gastro protection and vascular homeostasis.[4] In contrast, the COX-2 enzyme is the inducible isoform that is produced by various cell types upon exposure to cytokines, mitogens, and endotoxins released during injury and therefore molecules that inhibit its enzymatic activity would be of therapeutic value.[5,6] The gastrointestinal side effects associated with NSAIDs are due to the inhibition of gastroprotective PGs synthesized through the COX-1 pathway.[7] Thus, selective inhibition of COX-2 over COX-1 is useful for the treatment of inflammation and inflammation-associated disorders with reduced gastrointestinal toxicities when compared with NSAIDs. Moreover, recent studies indicating the place of COX-2 inhibitors in cancer chemotherapy[8] and neurological diseases such as Parkinson[9] and Alzheimer's[10] diseases still continue to attract investigations on development of COX-2 inhibitors. The majority of selective COX-2 inhibitors belong to a class of diarylheterocycles that possess vicinal diaryl substitution attached to a mono or bicyclic central ring system.[11–18] In this regard, many classes of selective COX-2 inhibitors such as coxibs have been developed with desired selectivity. The coxibs (e.g., celecoxib and rofecoxib, Fig. 1)[11,12] for treating pain and inflammation associated with arthritis have been shown to be well tolerated and reduce GI side effects. The recent market withdrawal of some coxibs such as rofecoxib and valdecoxib due to their adverse cardiovascular side effects[19] clearly delineates the need to develop alternative structures with COX-2 inhibitory activity. In addition, some studies have suggested that rofecoxib adverse cardiac events may not be a class effect but rather an intrinsic chemical property related to its metabolism.[20] For this reason novel scaffolds with high selectivity for COX-2 inhibition need to be found and evaluated for their anti-inflammatory effects. Recently, we reported several investigations describing the design, synthesis and molecular modeling studies for 1,3-thiazolidine-4-ones[17] and 1,3-thiazinan-4-ones[18] possessing a five or six membered central ring and methylsulfonyl COX-2 pharmacophore at the *para*-position of C-2 phenyl ring in conjunction with different substituents at the N-3 of the central ring. For example, 3-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazolidine-4-one and 3-benzyl-2-(4-methyl sulfonylphenyl)-1,3-thiazinan-4-one (see structures **1** and **2**) exhibited highly selectivity for COX-2 inhibition. As a part of our ongoing program to design new types of selective COX-2 inhibitors, we now report the design, synthesis, cyclooxygenase inhibitory and some molecular modeling studies

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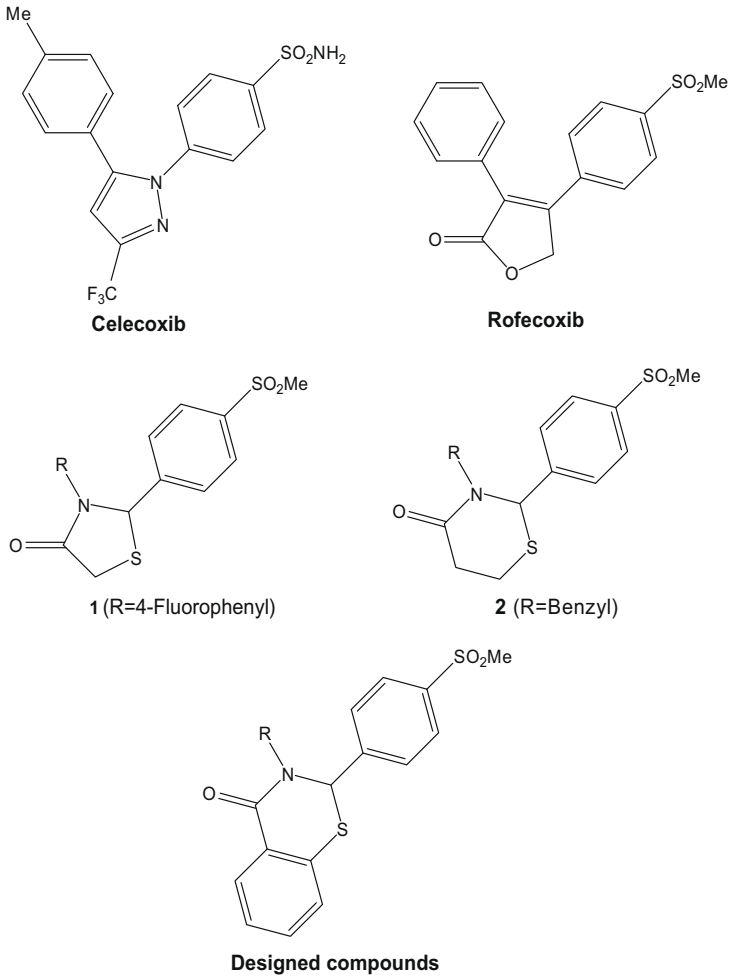


Figure 1. Some representative examples of COXIBs (celecoxib and rofecoxib), 1,3-thiazolidine-4-one (**1**), 1,3-thiazinan-4-one (**2**) lead compounds and our 1,3-benz thiazinan-4-one scaffolds.

of a group of 1,3-benzthiazinan-4-one derivatives having a new bicyclic central ring scaffold and different substituents at the N-3 in order to find the effect of these substituents on the inhibition of COX-2 activity.

2. Chemistry

The target 1,3-benzthiazinan-4-one derivatives (**7a–f**) were synthesized via the route outlined in Scheme 1. Accordingly, 4-methylsulfonylbenzaldehyde (**4**) was treated with an appropriate amine (**5a–f)** and thiosalicylic acid (**6**) in dry toluene in the presence of *p*-toluenesulfonic acid under reflux to give 2-(4-methylsulfonylphenyl)-3-substituted-1,3-benzthiazinan-4-one (**7a–f**, 33–73%).[18] The purity of all products was determined by thin layer chromatography using several solvent systems of different polarity. All compounds were pure and stable. The compounds were characterized by ^{1}H nuclear magnetic resonance, infrared, mass spectrometry and CHN analysis.

3. Results and discussion

A group of 1,3-benzthiazinan-4-one derivatives having different substituents at the N-3 of central ring (**7a–f**) were prepared to investigate the effect of different substituents on COX-2 selectivity and potency. The ability of the 1,3-benzthiazinan-4-ones **7a–f** to inhibit the COX-1 and COX-2 isozymes was determined using chemiluminescent enzyme assays (see enzyme inhibition data in Table 1.) according to our previously reported method.[17] In vitro COX-1/COX-2 inhibition studies showed that all compounds **7a–f** were selective inhibitors of the COX-2 isozyme with IC_{50} values in the highly potent 0.05–0.12 μM range, and COX-2 selectivity indexes (SI) in the 134.9–259.0 range. These data showed that the nature and size of substituent attached to N-3 of 1,3-benzthiazinan-4-one ring influenced both selectivity and potency for COX-2 inhibitory activity. However, compound **7f** showed less selectivity and potency for COX-2 isozyme compared with compound **7e** that may be explained by steric parameter. Our results indicated that the introduction of suitable substituents such as F (**7b**) and Me (**7c**) at the *para*-position of N-3 phenyl ring increased both selectivity and potency for COX-2 inhibitory activity. According to these results, 3-fluorophenyl-2-(4-methylsulfonyl phenyl)-1,3-benzthiazinan-4-one **7b** was the most potent (IC_{50} = 0.05 μM), and selective (SI = 259), COX-2 inhibitor among the synthesized compounds. It was more potent than celecoxib (IC_{50} = 0.06 μM; SI = 405) in terms of COX-2 inhibitory activity but showed less selectivity. These data suggest that the compound **7b** should inhibit the biosynthesis of prostaglandins via the cyclooxgenase pathway at sites of inflammation and be devoid of ulcerogenicity due to the absence of COX-1 inhibition. The orientation of the highly potent and selective COX-2 inhibitor, 3-fluorophenyl-2-(4-methylsulfonyl phenyl)-1,3-benzthiazinan-4-one **7b** in the COX-2 active site

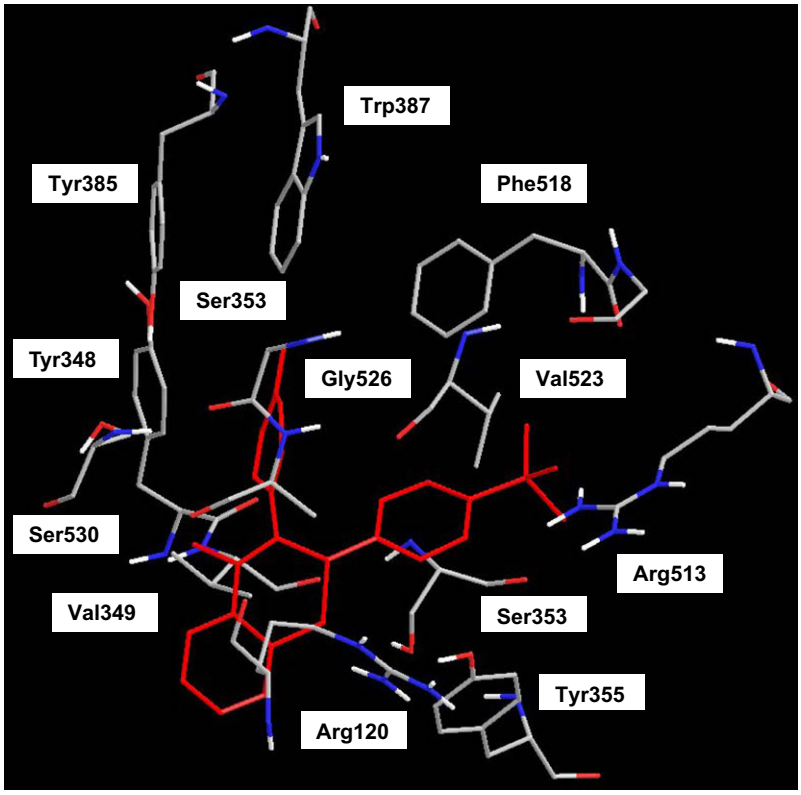
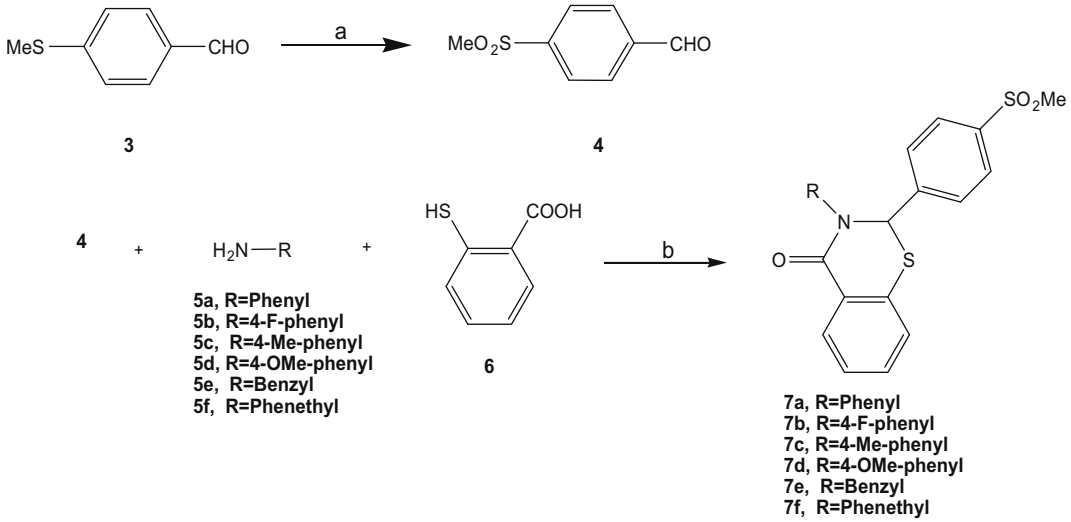


Figure 2. Compound **7b** 3-(*p*-fluoropheny)-2-(4-methylsulfonylphenyl)-1,3-benzthiazinan-4-one docked in the active site of murine COX-2 isozyme. Hydrogen atoms of the amino acid residues have been removed to improve clarity.



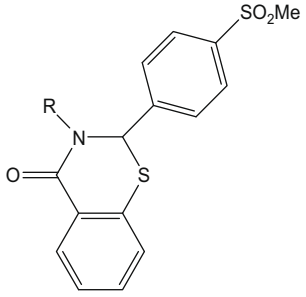
Scheme 1. Reagents and conditions: (a) oxone, methanol/H_2O, 2 h; (b) toluene, reflux, 48 h.

was examined by a docking experiment (Fig. 2).[21] This molecular modeling shows that it binds in the primary binding site such that the C-2 *para*-SO_2Me substituent inserts into the secondary pocket present in COX-2 isozyme. One of the O-atoms of *p*-SO_2Me forms a hydrogen bonding interaction with the amino group of Arg^{513} (distance = 1.7 Å) whereas the other O-atom is close to the other hydrogen of this amino acid (distance = 4.3 Å). The C=*O* of benzthiazinan-4-one ring is almost close to (distance = 5.8 Å) N*H* of Val^{349}. In addition, the phenyl moiety of the central ring is undergoing hydrophobic interactions with isopropyl group of Val^{349}. It was interesting to note that, the *para*-fluoro substituent of N-3 phenyl ring was forming a hydrogen bond with amide hydrogen (N*H*) of Gly^{526} (distance = 5.4 Å). These observations together with experimental results provide a good explanation for the potent and selective inhibitory activity of **7b**.

4. Conclusions

The results of this investigation indicate that (i) the 1,3-benzthiazinan-4-one moiety is a suitable scaffold (template) to design COX-2 inhibitors, (ii) in this class of compounds COX-1/-2 inhibi-

Table 1
In vitro COX-1/COX-2 enzyme inhibition assay data for 1,3-benzthiazinan-4-one derivatives **7a–f**



Compound	R	IC_{50}[a] (μM)		COX-2 SI[b]
		COX-1	COX-2	
7a	Phenyl	16.50	0.12	137.5
7b	4-F-phenyl	12.95	0.05	259.0
7c	4-Me-phenyl	16.12	0.06	252.1
7d	4-OMe-phenyl	14.84	0.11	134.9
7e	Benzyl	15.80	0.07	225.7
7f	Phenethyl	15.91	0.08	198.8
Celecoxib		24.30	0.06	405

[a] Values are means of two determinations acquired using an ovine COX-1/COX-2 assay kit and the deviation from the mean is <10% of the mean value.
[b] In vitro COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).

tion is sensitive to the nature of the N-3 substituents, and (iii) 3-(*p*-fluoropheny)-2-(4-methylsulfonylphenyl)-1,3-benzthiazinan-4-one (**7b**) exhibited high COX-2 inhibitory potency and selectivity.

5. Experimental

All chemicals and solvents used in this study were purchased from Merck AG and Aldrich Chemical. Melting points were determined with a Thomas–Hoover capillary apparatus. Infrared spectra were acquired using a Perkin Elmer Model 1420 spectrometer. A Bruker FT-500 MHz instrument (Brucker Biosciences, USA) was used to acquire ^{1}H NMR spectra with TMS as internal standard. Chloroform-D and DMSO-d_6 were used as solvents. Coupling constant (*J*) values were estimated in hertz (Hz) and spin multiples were given as s (singlet), d (double), t (triplet), q (quartet), m (multiplet), and br (broad). Low-resolution mass spectra were acquired with a MAT CH5/DF (Finnigan) mass spectrometer that was coupled online to a Data General DS 50 data system. Electron-impact ionization was performed at an ionizing energy of 70 eV with a source temperature of 250 °C. Microanalyses, determined for C, H and N were within ±0.4% of the theoretical values.

5.1. Preparation of 4-(methylsulfonyl)benzaldehyde (4)

One milliliter of 2-(4-(methylthio)benzaldehyde dissolved in 5 ml of methanol and 5 g oxone in methanol/water (10 ml) was added. The mixture was stirred at room temperature for 2 h. After evaporation of methanol, the residue was extracted with ethyl acetate and dried with sodium sulfate and then evaporated. The obtained product was purified by column chromatography using chloroform/methanol (95:5 v/v) as mobile phase. Yield, 21%; yellow crystalline powder; IR (KBr): ν cm^{-1} 2850, 2750 (C–H), 1660(C=O), 1360, 1120 (SO_2); MS: *m/z* (%) 184.1 (M^+, 10), 169.1 (30), 122.2 (75), 105.1 (90), 77.1 (100); ^{1}H NMR($CDCl_3$): δ ppm 3.15 (S, 3H, SO_2Me), 8.14 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.4 Hz), 8.19 (d, 2H, 4-methylsulfonylphenyl H_3 and H_5, J = 8.4 Hz), 10.19 (s, 1H, CH); Anal. Calcd for $C_8H_8O_3S$: C, 52.16; H, 4.38. Found: C, 52.42; H, 4.60.

5.2. General procedure for preparation of 2-(4-methylsulfonylphenyl)-3-substituted-1,3-benzthiazinan-4-one (7a–f)

A mixture of 4-(methylsulfonyl)benzaldehyde **4** (20 mmol), an appropriate amine **5a–f** (30 mmol) and thiosalicylic acid (30 mmol) **6** in 50 ml anhydrous toluene in the presence of *p*-toluenesulfonic acid (100 mg) was refluxed for 48 h. After this time, the solvent was removed in vacuo and the residue was extracted with dichloromethane. The organic phase was washed with 2 M HCl, dilutes ammonium hydroxide and water and then dried (Na_2SO_4). After removing the solvent, the solid product was recrystallized in ethanol (yields: 33–73%). The physical and spectral data for **7a–f** are listed below.

5.2.1. 2-(4-Methylsulfonylphenyl)-3-phenyl-1,3-benzthiazinan-4-one (7a)

Yield, 33%; yellow crystalline powder, mp 218–219 °C; IR (KBr): ν cm^{-1} 1660 (C=O), 1310, 1150 (SO_2); MS: *m/z* (%) 395.5 (M^+,10), 340.0 (20), 310.0 (35), 221.0 (30), 175.0 (30), 136.0 (45), 106.1 (60), 91.1 (100); ^{1}H NMR (DMSO-d_6) δ ppm 3.26 (s, 3H, SO_2Me), 6.81 (s, 1H, CH), 6.87 (d, 1H, benzthiazinan H_8, J = 7.9 Hz), 7.17–7.47 (m, 5H, phenyl), 7.66 (m, 1H, benzthiazinan H_6), 7.85 (m, 1H, benzthiazinan H_7), 7.91 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 7.8 Hz), 8.06 (d, 4-methylsulfonylphenyl H_3 and H_5, J = 7.8 Hz), 8.33 (d, 1H, benzthiazinan H_5, J = 7.8 Hz); Anal. Calcd for $C_{21}H_{17}NO_3S_2$: C, 63.77; H, 4.33; N, 3.54. Found: C, 63.99; H, 4.61; N, 3.32.

5.2.2. 3-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)-1,3-benzthiazinan-4-one (7b)

Yield, 55%;white crystalline powder, mp 221–223 °C; IR (KBr): ν cm^{-1} 1660 (C=O), 1310, 1145 (SO_2); MS: *m/z* (%) 413.1 (M^+, 20), 381.1 (40), 277.1 (100), 245.0 (80), 226.1 (20), 197.1 (40), 136.0 (50), 108.1 (30), 95.1 (30); ^{1}H NMR (DMSO-d_6) δ ppm 3.05 (s, 3H, SO_2Me), 6.30 (s, 1H, CH), 7.18 (t, 2H, 4-fluorophenyl H_3 and H_5), 7.46 (dd, 2H, 4-fluorophenyl H_2 and H_6, J_{HH} = 8.8 Hz, J_{HF} = 4.7 Hz), 7.51 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.3 Hz), 7.56 (d, 1H, benzthiazinan H_8, J = 7.5 Hz), 7.65 (m, 1H, benzthiazinan H_6), 7.78 (m, 1H, benzthiazinan H_7), 7.91 (d, 4-methyl sulfonylphenyl H_3 and H_5, J = 8.3 Hz), 8.42 (d, 1H, benzthiazinan H_5, J = 7.7 Hz); Anal. Calcd for $C_{21}H_{16}NO_3S_2F$: C, 61.00; H, 3.90; N, 3.39. Found: C, 61.29; H, 4.21; N, 3.12.

5.2.3. 3-(4-Methylphenyl)-2-(4-methylsulfonylphenyl)-1,3-benzthiazinan-4-one (7c)

Yield, 71%; yellow crystalline powder, mp 250–251 °C; IR (KBr): ν cm^{-1} 1660 (C=O), 1300, 1145 (SO_2); MS: *m/z* (%) 409.1 (M^+, 5), 289.0 (90), 273.1 (30), 183.1 (100), 121.1 (40), 104.1 (20), 76.1 (30); ^{1}H NMR (DMSO-d_6) δ ppm 2.14 (s, 3H, Me), 3.34 (s, 3H, SO_2Me), 5.26 (s, 1H, CH), 6.95 (d, 2H, 4-methylphenyl H_3 and H_5, J = 7.1 Hz), 7.18 (d, 1H, benzthiazinan H_8, J = 7.5 Hz), 7.31 (d, 2H, 4-methylphenyl H_2 and H_6, J = 7.1 Hz), 7.36 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.3 Hz), 7.44 (m, 1H, benzthiazinan H_6), 7.50 (m, 1H, benzthiazinan H_7), 7.76 (d, 4-methyl sulfonylphenyl H_3 and H_5, J = 8.3 Hz), 8.36 (d, 1H, benzthiazinan H_5, J = 7.7 Hz); Anal. Calcd for $C_{22}H_{19}NO_3S_2$: C, 64.52; H, 4.68; N, 3.42. Found: C, 64.19; H, 4.31; N, 3.58.

5.2.4. 3-(4-Methoxyphenyl)-2-(4-methylsulfonylphenyl)-1,3-benzthiazinan-4-one (7d)

Yield, 47%; brown crystalline powder, mp 203–205 °C; IR (KBr): ν cm^{-1} 1660 (C=O), 1300, 1150 (SO_2); MS: *m/z* (%) 425.1 (M^+, 5), 367.5 (10), 289.2 (100), 274.2 (90), 195.2 (60), 167.2 (50), 139.1 (40), 92.1 (30), 77.1 (50); ^{1}H NMR (DMSO-d_6) δ ppm 3.07 (s, 3H, SO_2Me), 3.85 (s, 3H, OMe), 5.96 (s, 1H, CH), 6.96 (d, 2H, 4-methoxyphenyl H_3 and H_5, J = 7.0 Hz), 7.28 (d, 2H, 4-methoxyphenyl H_2 and

H_6, J = 7.0 Hz), 7.36 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.4 Hz), 7.77–7.80 (m, 2H, benzthiazinan H_6 and H_8), 7.87 (m, 1H, benzthiazinan H_7), 7.93 (d, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.4 Hz), 8.42 (d, 1H, benzthiazinan H_5, J = 7.8 Hz); Anal. Calcd for $C_{22}H_{19}NO_4S_2$: C, 62.10; H, 4.50; N, 3.29. Found: C, 62.45; H, 4.81; N, 3.34.

5.2.5. 3-Benzyl-2-(4-methylsulfonylphenyl)-1,3-benzthiazinan-4-one (7e)

Yield, 39%, yellow crystalline powder, mp 210–211 °C; IR (KBr): ν cm^{-1} 1695 (C=O), 1300, 1140 (SO_2); MS: m/z (%) 409.1 (M^+, 10), 377.1 (50), 272.1 (60), 193.1 (40), 152.1 (70), 136.1 (80), 105.1 (40), 91.1 (100); ^{1}H NMR (DMSO-d_6) δ ppm 3.23 (s, 3H, SO_2Me), 3.96 (d, 1H, CH_2, J = 15.2 Hz), 5.63 (s, 1H, CH), 5.92 (d, 1H, CH_2, J = 15.2 Hz), 7.12 (d, 1H, benzthiazinan H_8, J = 7.7 Hz), 7.26–7.31 (m, 5H, phenyl), 7.32–7.34 (m, 2H, benzthiazinan H_6 and H_7), 7.37 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 7.9 Hz), 7.41 (d, 4-methylsulfonylphenyl H_3 and H_5, J = 7.9 Hz), 8.28 (d, 1H, benzthiazinan H_5, J = 7.9 Hz); Anal. Calcd for $C_{22}H_{19}NO_3S_2$: C, 64.52; H, 4.68; N, 3.42. Found: C, 62.85; H, 4.96; N, 3.64.

5.2.6. 2-(4-Methylsulfonylphenyl)-3-phenethyl-1,3-benzthiazinan-4-one (7f)

Yield, 73%, white crystalline powder, mp 217–219 °C; IR (KBr): ν cm^{-1} 1665 (C=O), 1300, 1140 (SO_2); MS: m/z (%) 423.1 (M^+, 5), 391.1 (90), 376.1 (30), 312.1(90), 193.1 (40), 152.1 (70), 136.1 (80), 105.1 (40), 91.1 (100); ^{1}H NMR (DMSO-d_6) δ ppm 3.07 (s, 3H, SO_2Me), 3.10 (m, 2H, CH_2), 3.50 (m, 1H, CH_2), 4.45 (m, 1H, CH_2), 5.64 (s, 1H, CH), 7.24–7.33 (m, 6H, phenyl and benzthiazinan H_8), 7.41 (d, 2H, 4-methylsulfonyl phenyl H_2 and H_6, J = 8.4 Hz), 7.71–7.76 (m, 2H, benzthiazinan H_6 and H_7), 7.88 (d, 4-methylsulfonylphenyl H_3 and H_5, J = 8.4 Hz), 8.39 (d, 1H, benzthiazinan H_5, J = 7.9 Hz); Anal. Calcd for $C_{23}H_{21}NO_3S_2$: C, 65.22; H, 5.00; N, 3.31. Found: C, 64.95; H, 4.76; N, 3.60.

Satisfactory analysis for C, H, N was obtained for all the compounds within ±0.4% of the theoretical values.

6. Molecular modeling (docking) studies

Docking studies were performed using Autodock software Version 3.0.5. The coordinates of the X-ray crystal structure of the selective COX-2 inhibitor SC-558 bound to the murine COX-2 enzyme was obtained from the RCSB Protein Data Bank (1c×2) and hydrogens were added. The ligand molecules were constructed using the Builder module and were energy minimized for 1000 iterations reaching a convergence of 0.01 kcal/mol Å. The energy minimized ligands were superimposed on SC-558 in the PDB file 1cx2 after which SC-558 was deleted. The purpose of docking is to search for favorable binding configuration between the small flexible ligands and the rigid protein. Protein residues with atoms greater than 7.5 Å from the docking box were removed for efficiency. These docked structures were very similar to the minimized structures obtained initially. The quality of the docked structures was evaluated by measuring the intermolecular energy of the ligand-enzyme assembly.[21]

7. In vitro cyclooxygenase (COX) inhibition assays

The assay was performed using an enzyme chemiluminescent kit (catalog number 760101, Cayman chemical, MI, USA) according to our previously reported method.[17] The Cayman chemical chemiluminescent COX (ovine) inhibitor screening assay utilizes the heme-catalyzed hydroperoxidase activity of ovine cyclooxygenases to generate luminescence in the presence of a cyclic naphthalene hydrazide and the substrate arachidonic acid. Arachidonate-induced luminescence was shown to be an index of real-time catalytic activity and demonstrated the turnover inactivation of the enzyme. Inhibition of COX activity, measured by luminescence, by a variety of selective and nonselective inhibitors showed potencies similar to those observed with other in vitro and whole cell methods.

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References and notes

1. Otta, J. C.; Smith, W. L. *J. Lipid Mediators Cell Signalling* **1995**, *12*, 139.
2. Vane, J. R.; Bakhle, Y. S.; Botting, R. M. *Ann. Rev. Pharmacol. Toxicol.* **1998**, *38*, 9704.
3. Xie, W. L.; Chipman, J. G.; Robertson, D. L.; Erikson, R. L.; Simmons, D. L. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 2692.
4. Laneuville, O.; Breuer, D. K.; DeWitt, D. L.; Hla, T.; Funk, C. D.; Smith, W. L. *J. Pharmacol. Exp. Ther.* **1994**, *271*, 927.
5. Herschman, H. R. *Biochem. Biophys. Acta* **1996**, *1299*, 125.
6. Kanaoka, S.; Takai, T.; Yoshida, K. *Adv. Clin. Chem.* **2007**, *43*, 59.
7. Eberhart, C. E.; DuBois, R. N. *Gasteroenterology* **1995**, *109*, 285.
8. Kawamori, T.; Rao, C. V.; Seibert, K.; Reddy, B. S. *Cancer Res.* **1998**, *58*, 409.
9. Yasojima, K.; Tourtellotte, W. E.; McGeer, E. G.; McGeer, P. L. *Neurology* **2001**, *57*, 952.
10. Nivsarkar, M.; Banerjee, A.; Padh, H. *Pharmacol. Rep.* **2008**, *60*, 692.
11. Penning, T. D.; Tally, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.
12. Prasit, P.; Wang, Z.; Brideau, C.; Chan, C.-C.; Charlson, S.; Cromlish, W.; Ethier, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y.; Gordon, R.; Guay, J.; Gresser, M.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Leger, S.; Mancini, J.; O'Neil, G. P.; Ouellet, M.; Percival, M. D.; Perrier, H.; Riendeau, D.; Rodger, I.; Tagari, P.; Therien, M.; Vikers, P.; Wong, E.; Xu, L.-J.; Young, R. N.; Zamboni, R.; Boyce, S.; Rupniak, N.; Forrest, M.; Visco, D.; Patrick, D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773.
13. Riendeau, D.; Percival, M. D.; Brideau, C.; Dube, C. S.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Gordon, R.; Greig, G.; Guay, J.; Girard, Y.; Prasit, P.; Zamboni, R.; Rodger, I. W.; Gresser, M.; Ford-Hutchinson, A. W.; Young, R. N.; Chan, C. C. *J. Pharmacol. Exp. Ther.* **2002**, *296*, 558.
14. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775.
15. Zarghi, A.; Rao, P. N. P.; Knaus, E. E. *Bioorg. Med. Chem.* **2007**, *15*, 1056.
16. Zarghi, A.; Rao, P. N. P.; Knaus, E. E. *J. Pharm. Pharm. Sci.* **2007**, *10*, 159.
17. Zarghi, A.; Najafnia, L.; Daraee, B.; Dadrass, O. G.; Hedayati, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5634.
18. Zebardast, T.; Zarghi, A.; Daraie, B.; Hedayati, M.; Dadrass, O. G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3162.
19. Dogné, J. M.; Supuran, C. T.; Pratico, D. *J. Med. Chem.* **2005**, *48*, 2251.
20. Mason, R. P.; Walter, M. F.; McNulty, H. P.; Lockwood, S. F.; Byun, J.; Day, C. A.; Jacob, R. F. *J. Cardivasc. Pharmacol.* **2006**, *47*, S7.
21. Kurumbail, R. G.; Stevens, A. M.; Gierse, J. K.; McDonald, J. J.; Stegeman, R. A.; Pak, J. Y.; Gildehaus, D.; Miyashiro, J. M.; Penning, T. D.; Seibert, K.; Isakson, P. C.; Stallings, W. C. *Nature* **1996**, *384*, 644.