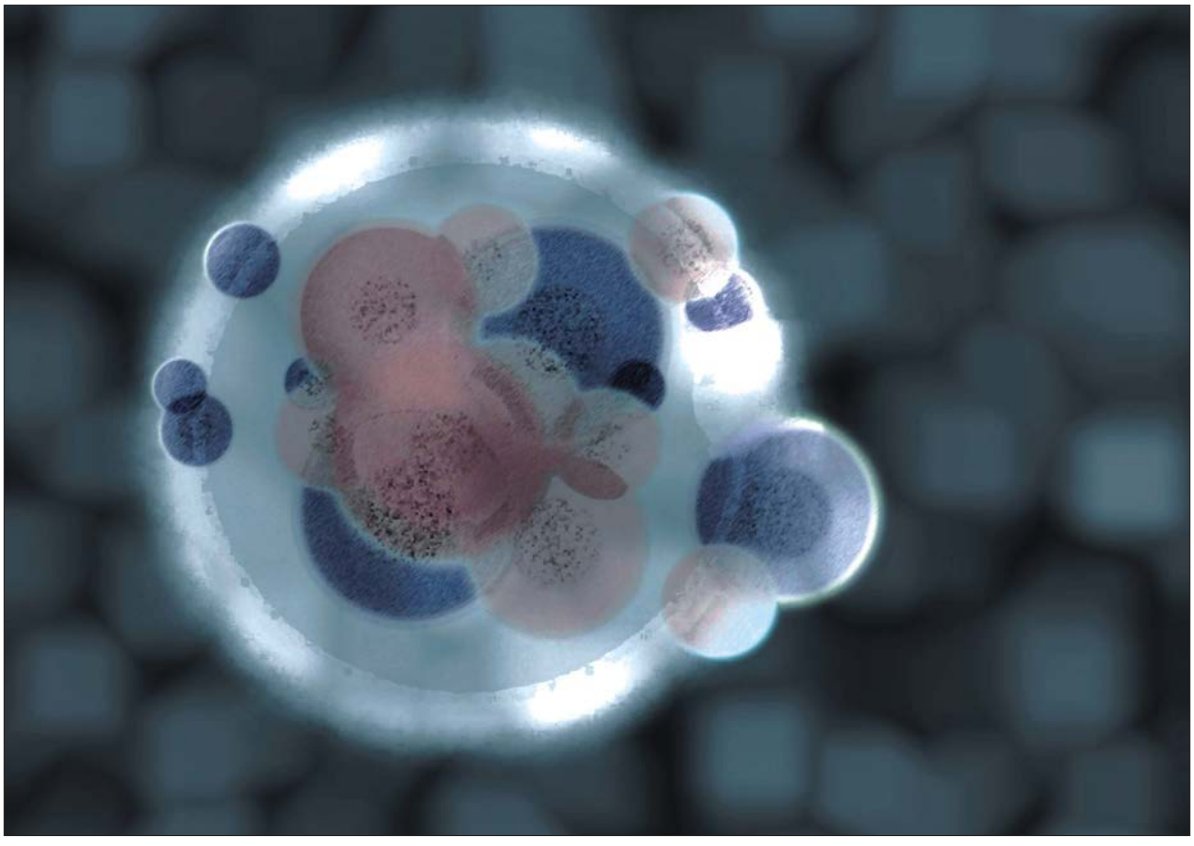

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New N-aryl-4-(methysulfony)aminobenzenesulfonamides as Selective COX-2 inhibitors

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Abstract: A group of N-aryl- 4-(methylsulfonyl)aminobenzenesulfonamides, possessing a (methylsulfonyl) amino pharmacophore at the para-position of the one phenyl ring, in conjunction with another substituted phenyl ring (4-F, 4-H, 4-Me, 4-OMe) were evaluated as selective cyclooxygenase-2 (COX-2) inhibitors. *In vitro* COX-2 isozyme inhibition structure–activity studies identified 6e with 4-OMe substituent as a potent COX-2 inhibitor (IC_{50} = 1.59 μM) with a high COX-2 selectivity index (SI = 51.7) comparable to the reference drug celecoxib (COX-2 IC_{50} = 9.59 μM; COX-2 SI = 25.62). The structure-activity data acquired indicate that the sulfonamido moiety constitutes a suitable scaffold to design new acyclic N-aryl- 4-(methysulfonyl)aminobenzenesulfonamides derivatives with selective COX-2 inhibitory activity.

Key words: Benzenesulfonamides, COX-2 inhibitors

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen exhibit their anti-inflammatory effects by inhibiting Cyclooxygenase (COX) which catalyzes the conversion of arachidonic acid to prostaglandins. However, inhibition of COXs may lead to side effects such as gastric ulceration, bleeding and renal function suppression. Nowadays, it is well known that there are at least two COX isozymes, COX-1 and COX-2 (Zarghi *et al*., 2006). The isozyme COX-1 is constitutive and responsible for the physiological production of prostaglandins, the COX-2 isozyme is inducible and responsible for the elevated production of prostaglandins during inflammation (Herschman, 1996). 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 classic NSAIDs. In addition, to role of COX-2 in rheumatoid arthritis and osteoarthritis, it is also implicated in colon cancer and angiogenesis (Katori and Majima, 2000). Previous studies have shown that the progression of Alzheimer's disease is reduced among some users of NSAIDs. Chronic treatment with selective COX-2 inhibitors may therefore slow the progress of Alzheimer without causing gastrointestinal side effects (Vane and Botting, 1998). Diarylheterocycles and other central ring pharmacophore templates, have been extensively studied as selective COX-2 inhibitors. All these tricyclic molecules possess 1,2-diaryl substitution on a central hetero or carbocyclic ring system (structures 1-4 in Fig. 1) (Zarghi *et al*., 2007; Prasit *et al*., 1999).

COX-2 selective inhibitors are also known to suppress synthesis of prostacyclin, a potent vasodilator, act as gastroprotectant and platelet inhibitor via inhibition of endothelial COX-2. COX-2 selective inhibitors do not inhibit production of thromboxane, a vasoconstrictor and promoter of platelet aggregation, which is synthesized in platelets by COX-1 (Catella-Lawson and Crofford, 2001). Therefore, COX-2 inhibitors intrinsically lack anti-thrombotic activity and some cardiovascular liabilities have been associated preclinically with them (De Gaetano *et al*., 2003). Recently, some diarylheterocyclic selective COX-2 inhibitors such as rofecoxib and valdecoxib have been withdrawn from market due to their adverse cardiovascular side effects (Dogne *et al*., 2005; Solomon, 2005). Thus, there is still a need for novel, selective and potent COX-2 inhibitors with an improved profile and new structural ring templates (scaffolds). 1, 3-Diarylthiourea derivatives (structures 5 in Fig. 1), are among recently reported

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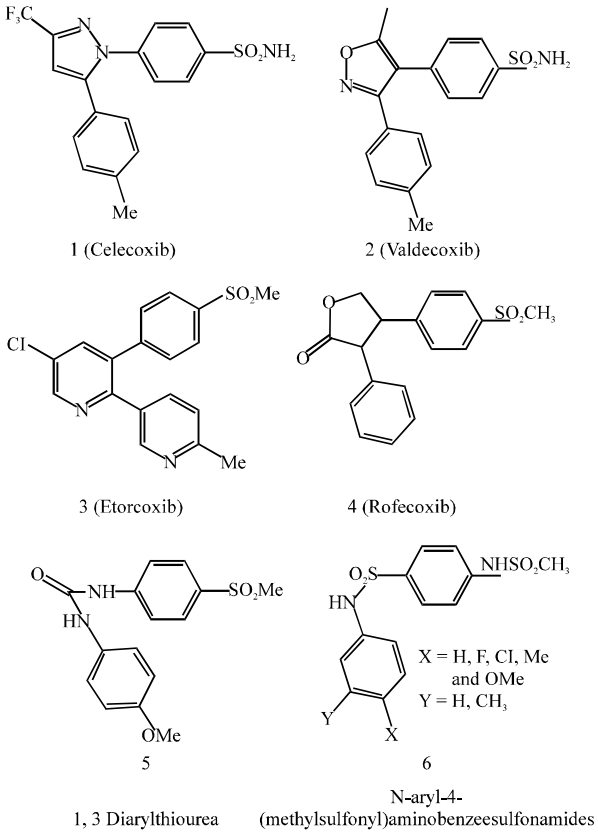


Fig. 1: Representative examples of selective COX-2 inhibitors 1-5 and novel N-aryl-4-(methylsulfonyl)aminobenzenesulfonamides 6

scaffolds (Zarghi *et al*., 2008). We now report some structure-activity relationship studies (SAR) for a group of N-aryl-4-(methylsulfonyl)aminobenzenesulfonamides (structures 6 in Fig. 1), possessing a COX-2 $NHSO_2Me$ pharmacophore at the para-position of one phenyl ring in conjunction with various substituents (H, F, Me and OMe) at the para-position of the other phenyl ring (Tabaraki and Zarghi, 2007).

MATERIALS AND METHODS

Molecular modeling: The compounds subjected to energy minimization using Force Field-MMFF94x by Molecular Operating Environment (MOE) software (http://www.chemcomp.com).

Source of target proteins: The crystal structure of murine COX-2 complexed with its inhibitor SC-558 (PDB ID code: 1cx2) was downloaded from the protein data bank and opened with MOE software. The complexed inhibitor was removed when using the synthesized compounds as ligands for docking. MOE-Dock is used to search for favorable binding configurations between the ligand and the macromolecular target.

Energy minimization procedure: Selected compounds for docking were drawn in mol format and all hydrogens were added, they were energy minimized using Hamiltonian-Force Field-MMFF94x and the partial charges were also calculated.

Docking procedure: Docking procedure of COX-2 was as following: (1) the cocrystallized SC-558 was identified; therefore, the binding site was identified with its residues. (2) Ligand interactions were computed for the X-ray co-crystallized SC-558 to reveal the different types of interaction as a validation for the coming docking procedure. (3) The co-crystallized SC-558 is then removed and the selected synthesized compound 6e is used instead. (4) The docking was done with the default settings of the MOE-DOCK as following: (a) the option: Rotate Bonds was selected to give flexible ligand-rigid receptor docking; (b) the scoring function was London dG with a replacement of Alpha Triangle; (c) 30 conformers of the ligand were retained with highest and best score by default; (d) the top score ligand-receptor docking was then demonstrated by 2D ligand-receptor interactions.

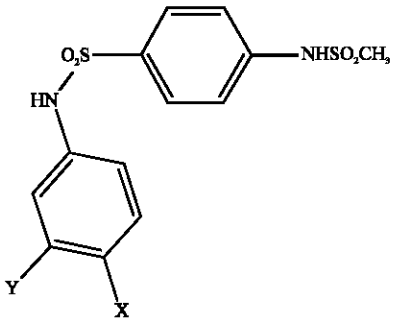
Biological evaluation

***In vitro* cyclooxygenase (COX) inhibition assay:** The ability of the test compounds 6a-e to inhibit ovine COX-1 and COX-2 was determined using a colorimetric COX (ovine) inhibitor screening assay kit (Cayman Chemical, Catalogue Number 760111) which utilizes the peroxidase component of cyclooxygenase. The peroxidase activity is assayed colorimetrically by monitoring the appearance of oxidized N, N, N', N'-tetramethyl-p-phenylenediamine (TMPD) at 590 nm.

RESULTS AND DISCUSSION

SAR data (IC_{50} values) acquired by determination of the *in vitro* ability of the title compounds to inhibit the COX-1 and COX-2 isozymes showed that the position and nature of the substituents on the phenyl ring was determinant of COX-2 inhibitory potency and selectivity. The ability of the N-aryl-4-amino-benzenesulfonamides derivatives 6a-e to inhibit the COX-1 and COX-2 isozymes was determined using colorimetric ovine COX inhibitor assay kit (Table 1). *In vitro* COX-1/COX-2 inhibition studies showed that all compounds 6a-e were selective inhibitors of the COX-2 isozyme with IC_{50} values in the potent 1.59-5.37 μM

Table 1: *In vitro* COX-2 enzyme inhibition data



Compound	X	Y	IC_{50} (μM) COX-2[a]	COX-2 SI[b]
6a	H	H	N/A	4.3
6b	CH_3	H	4.97	2.84
6c	CH_3	CH_3	5.37	11.18
6d	F	H	4.81	3.37
6e	OCH3	H	1.59	51.7
Celecoxib			9.59	25.62

[a]All Values are mean of two determinations acquired using an ovine COX-1/COX-2 assay kit, where 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})

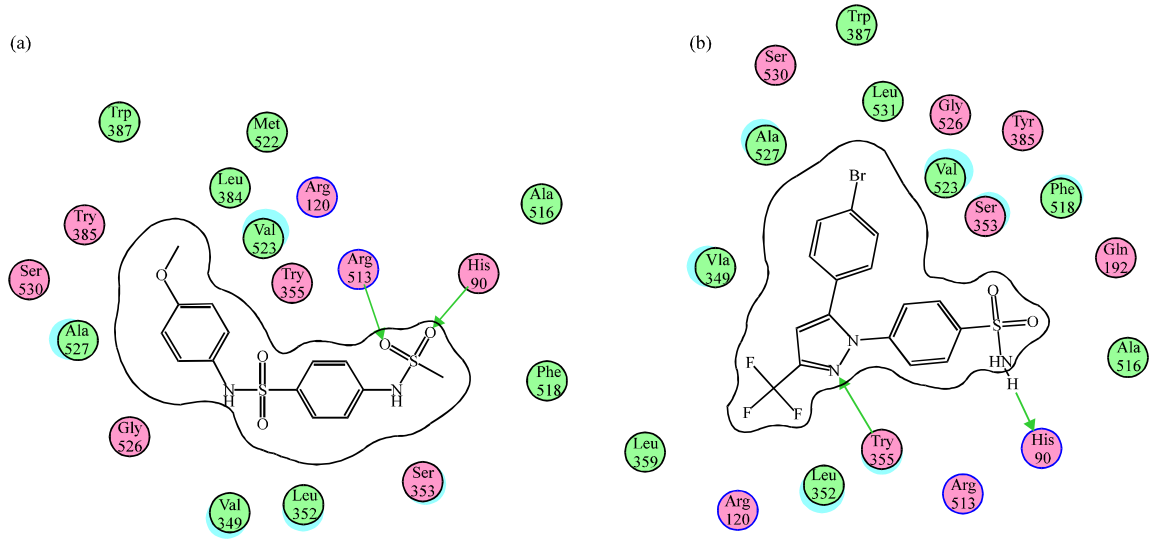


Fig. 2(a-b): Docking of COX-2 with compound 6e in 2D diagram (a) and SC-558 (b)

range and COX-2 selectivity indexes (SI) in the 2.84 to 51.7 range. According to these results, 6e with 4-OMe substituent was the most potent (IC_{50} = 1.59 μM) and the most selective (SI = 51.7) COX-2 inhibitor among the synthesized compounds. These results showed that the presence of a methoxy substituent at the para-position of the phenyl ring may improve potency and selectivity for COX-2 inhibition. All compounds were compared with celecoxib with IC_{50} = 9.59 μM and SI = 25.6 as positive control. DMSO which was the solvent of compounds was used as negative control.

The orientation of the most potent and selective COX-2 inhibitor 6e in the COX-2 active site was examined by a docking experiment (Fig. 2). This molecular modeling shows that it binds in the primary binding site such that one of the O-atoms of p-MeSO2NH forms a hydrogen bonding interaction with hydroxyl group (OH) of Arg513 (distance = 2.6) and the other O-atom forms a hydrogen bonding interaction with NH of His90 (distance = 2.8). In SC-558 on the other hand, there is only one hydrogen bond between p-SO_2NH_2 and His90. 4-Methoxyphenyl residue is placed within a hydrophobic pocket formed between hydrophobic amino acids Val523, Leu384 on one side and Ala527 and Gly526 on the other side of it. 4-Methoxy group is placed near to hydrogen bond donor groups Tyr385 and Ser530. These observations together with experimental results provide a good explanation for the potent and selective inhibitory activity of 6e.

CONCLUSION

The structure-activity data acquired indicate that the sulfonamido moiety constitutes a suitable scaffold to design new acyclic N-aryl-4-methysulfonyl aminobenzenesulfonamides derivatives with selective COX-2 inhibitory activity.

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