

## Novel Group of Imidazole Derivatives as Atypical Selective Cyclooxygenase-2 Inhibitors: Design, Synthesis and Biological Evaluation

Azin Kiani, Elham Rezaee and Sayyed Abbas Tabatabai\*

*Department of Pharmaceutical Chemistry, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

---

### Abstract

In this study, a new series of 5-substituted 1-benzyl-2-(methylsulfonyl)-1-H-imidazole with atypical structure-activity relationship was designed, synthesized, and biological evaluated as selective cyclooxygenase-2 inhibitors. Docking studies revealed that although the pharmacophoric substitute of the compound 5b, methylsulfonyl group, has been directly attached to the central ring, it is in the same direction of the sulfonamide group of Celecoxib, a known selective cyclooxygenase-2 inhibitor. Therefore effective hydrogen binding with Arg513 is established. Also, additional hydrogen binding could form between NH of anilino moiety of the 5b and Arg120. All of the compounds had selective inhibitory activity against cyclooxygenase-2 in micromolar concentrations comparable with the reference, Celecoxibe. Finally, compound 5b with the selectivity index 115 and  $IC_{50}$  of 0.71  $\mu$ M against cyclooxygenase-2 was the most potent one.

**Keywords:** COX-2 inhibitor; Imidazole derivatives; Atypical; Synthesis; Docking.

---

### Introduction

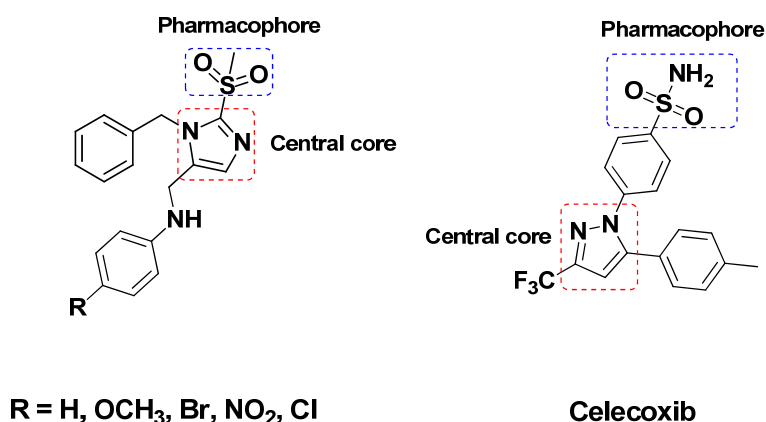
Cyclooxygenase (COX) is an endogenous enzyme that plays a central role in biosynthesis of the important biological mediators, prostaglandins, from Arachidonic acid (1). The two most known isoforms of COX (COX-1 and COX-2) share about 60% amino acid sequence but are encoded by different genes and have different biological roles (2, 3). The constitutive form, COX-1, is expressed in normal physiologic condition to maintain homeostasis, gastric, renal blood flow, and platelet aggregation while the inducible form, COX-2, is expressed in pain and inflammatory

conditions (4-6). Classic nonsteroidal anti-inflammatory drugs (NSAIDs) block both COX-1 and COX-2 non selectively and more tightly to COX-1 (7, 8) leading to the lack of the prostaglandins with normal physiological roles specially in long term use and consequently have several certain renal (9), gastrointestinal (10) and cardiovascular side effects (4, 11 and 12). These side effects prompted the development of selective COX-2 inhibitors with comparable efficacy and improved gastrointestinal safety (13, 14). The involvement of COX-2 in cancer development and neurodegenerative disease was previously evidenced. Therefore, selective COX-2 inhibitors are promising in the treatment of malignant and neurodegenerative disorders, such as adenocarcinoma, Alzheimer's, and Parkinson's disease (15-19). However, the cardiovascular risks such as myocardial infraction

---

\* Corresponding author:

E-mail: sa\_tabatabai@sbmu.ac.ir



**Figure 1.** Chemical structures of the designed compounds compared with Celecoxibe, a known COX-2 inhibitor.

and thrombosis related to selective inhibition of COX-2 due to the depression of the biosynthesis of atheroprotective prostaglandin (PGI<sub>2</sub>) and not the pro-aggregatory and vasoconstrictor mediator thromboxane A<sub>2</sub> derived from COX-1 (20) led to a withdrawal of Rofecoxib and Valdecoxib from the market (21, 22). Thus, the challenge persists to explore and evaluate selective COX-2 inhibitors with a mild tendency to COX-1 in order to reduce the cardiovascular side effects and enhance the safety profile along with addressing the unmet medical needs (22, 23). The majority of selective COX-2 inhibitors are diarylheterocycles with vicinal substitution attached to a mainly mono or bicyclic central ring (24-26). According to extent structure activity relationship (SAR) studies, the optimum COX-2 selectivity will be provided with a SO<sub>2</sub>NH<sub>2</sub> or a SO<sub>2</sub>Me substituent at the para position of one of the phenyl rings (27-29). In continuance of our previous studies on five member heterocycle rings (30-37), in this study, a new structure-activity relationship is presented with an imidazole cycle as the central heterocyclic ring and unlike classic COX-2 inhibitors the pharmacophore of methylsulfonyl is attached to the central core (Figure 1).

The docking study and biological evaluation were performed to clear the orientation of the synthesized compounds in the COX-2 active site and inhibitory activity of all compounds respectively.

## Experimental

### *Molecular Modeling Studies*

Docking simulation was performed to predict interaction of compounds (5a-f) with COX-2 binding site. The high resolution crystal structure of COX with Celecoxib as a cognate ligand was retrieved from RCSB Protein Data Bank (PDB code: 6COX). The structures of the compounds were investigated using the Lamarckian genetic algorithm search method implemented in AutoDock 4.0 software. The receptor was kept rigid and ligands were allowed to be flexible. Polar hydrogens and Kollman united atom partial charges were added to the individual protein atoms. The HyperChem 8 software was used for energy minimization of each structure under MM+ method and AutoDockTools 4.0 version 1.5.6rc3 for conversion of file formats to pdbqt. A docking grid box was built with 40, 40, and 40 points in 24.4370, 22.8660, and 48.5210 directions and the number of generations and maximum number of energy evaluations was set to 100 and 2,700,000, respectively. The docking results were clustered with a root mean square deviation (RMSD) of 0.5 Å and evaluated by Pymol software (38-40).

### *Chemistry*

All the chemicals and solvents were purchased from Merck or Aldrich Company and were used without further purification. Thin

layer chromatography (TLC) was performed on commercially available Merck precoated plates (silica gel 60 F254, 0.25 mm). Melting points were obtained using the Electrothermal 9100 apparatus and are uncorrected. Infrared spectra were acquired on a Perkin Elmer 843 spectrometer. A Bruker FT-400 MHz instrument (Bruker Biosciences, USA) was applied to obtain <sup>1</sup>HNMR spectra; DMSO-d<sub>6</sub> was used as solvents. LC Mass spectra and elemental analysis were achieved by HPLC Agilent system and Costech (Italy) elemental analyzer respectively.

*(1-benzyl-2-mercapto-1H-imidazol-5-yl) methanol (1)*

Potassium thiocyanate (5.44 g, 55.79 mmol), dihydroxyacetone (3.67 g, 40.74 mmol) and benzylamine (4 mL, 37.33 mmol) were refluxed at 55 °C for 18 h in 136 mL of water and glacial acetic acid (7/93). The mixture was alkalized with NaOH 10% and extracted with chloroform. The resulting precipitates were formed after acidifying of the aqueous phase with hydrochloric acid and recrystallized from ethanol 96% to give 6.66 g (54.1%) of **1**. mp: 127 °C; IR: (KBr) ν (cm<sup>-1</sup>) 2739-3200 (O-H). <sup>1</sup>HNMR (DMSO, 400 MHz) δppm: 4.14 (s, 2H, CH<sub>2</sub>OH), 5.29 (s, 1H, OH), 5.32 (s, 2H, benzyl), 6.87 (s, 1H, imidazole), 7.22 (d, *J* = 7.2 Hz, 2H, H<sub>2</sub>, H<sub>6</sub>-benzyl), 7.26 (t, *J* = 7.2 Hz, 1H, H<sub>4</sub>-benzyl), 7.32 (t, *J* = 7.2 Hz, 2H, H<sub>3</sub>, H<sub>5</sub>-benzyl), 12.04 (s, 1H, SH). LC-MS [M+1]<sup>+</sup>: m/z 221, [M+23]<sup>+</sup>: m/z 243, [M+39]<sup>+</sup>: m/z 259. Anal. Calcd for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>OS: C, 59.97; H, 5.49; N, 12.72. Found: C, 59.85; H, 5.51; N, 12.75.

*(1-benzyl-2-(methylthio)-1H-imidazol-5-yl) methanol (2)*

A solution of 1.1 g (5 mmol) intermediate **1** and 1.1 mL (5 mmol) sodium iodide in presence of 10 mL of NaOH 10% in ethanol was stirred at room temperature for one hour. The solvent was evaporated and the remnant was acidified and extracted with chloroform. The Aqueous phase was alkalized with NaOH 10% to participate 0.81 g (69%) of **2**. mp: 106 °C; IR: (KBr) ν (cm<sup>-1</sup>) 2850-3200 (O-H). <sup>1</sup>HNMR (DMSO, 400 MHz) δppm: 2.44 (s, 3H, SCH<sub>3</sub>), 4.33 (s, 2H, CH<sub>2</sub>OH), 5.21 (s, 3H, OH, 2H benzyl), 6.93 (s, 1H, imidazole), 7.07 (d, *J* = 7.2 Hz, 2H, H<sub>2</sub>, H<sub>6</sub>-benzyl), 7.26 (t, *J* = 7.2 Hz, 1H, H<sub>4</sub>-benzyl), 7.34 (t, *J* = 7.2 Hz,

2H, H<sub>3</sub>, H<sub>5</sub>-benzyl). LC-MS [M+1]<sup>+</sup>: m/z 235, [M+23]<sup>+</sup>: m/z 257. Anal. Calcd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>OS: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.75; H, 5.96; N, 11.93.

*(1-benzyl-2-(methylsulfonyl)-1H-imidazol-5-yl) methanol (3)*

Compound **2** (1 g, 4.3 mmol) in THF was added to a solution of Oxon (6.22 g, 51.3 mmol) in water. The mixture was stirred at room temperature overnight and after evaporating THF, 0.62 g (54.1%) of compound **3** was participated. mp: 127 °C; IR: (KBr) ν (cm<sup>-1</sup>) 2848-3538 (O-H), 1144, 1327 (SO<sub>2</sub>). <sup>1</sup>HNMR (DMSO, 400 MHz) δppm: 3.28 (s, 3H, SO<sub>2</sub>CH<sub>3</sub>), 4.35 (s, 2H, CH<sub>2</sub>OH), 5.47 (s, 1H, OH), 5.62 (s, 2H, benzyl), 7.10 (d, *J* = 7.2 Hz, 2H, H<sub>2</sub>, H<sub>6</sub>-benzyl), 7.30 (m, 2H, imidazole, H<sub>4</sub>-benzyl), 7.36 (t, *J* = 7.2 Hz, 2H, H<sub>3</sub>, H<sub>5</sub>-benzyl). LC-MS [M+1]<sup>+</sup>: m/z 267, [M+23]<sup>+</sup>: m/z 289. Anal. Calcd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>S: C, 54.12; H, 5.30; N, 10.52. Found: C, 53.96; H, 5.34; N, 10.60.

*1-benzyl-5-(chloromethyl)-2-(methylsulfonyl)-1H-imidazole (4)*

Compound **3** (400 mg, 1.5 mmol) was refluxed in 2 mL (16.8 mmol) of thionyl chloride for 4 h. After evaporating thionyl chloride, 0.21 g of compound **4** (57%) was obtained. mp: 127 °C; IR: (KBr) ν (cm<sup>-1</sup>) 1154, 1347 (SO<sub>2</sub>). <sup>1</sup>HNMR (DMSO, 400 MHz) δppm: 3.33 (s, 3H, SO<sub>2</sub>CH<sub>3</sub>), 4.78 (s, 2H, CH<sub>2</sub>OH), 5.66 (s, 2H, benzyl), 7.10 (d, *J* = 7.2 Hz, 2H, H<sub>2</sub>, H<sub>6</sub>-benzyl), 7.31 (t, *J* = 7.2 Hz, 1H, H<sub>4</sub>-benzyl), 7.34 (t, *J* = 7.2 Hz, 2H, H<sub>3</sub>, H<sub>5</sub>-benzyl), 7.40 (s, 1H, imidazole). LC-MS [M+1]<sup>+</sup>: m/z 285, [M+23]<sup>+</sup>: m/z 307. Anal. Calcd for C<sub>12</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>2</sub>S: C, 50.61; H, 4.60; N, 9.84. Found: C, 50.74; H, 4.56; N, 9.79.

*General procedure for the synthesis of the compounds 5a-5e*

A solution of compound **4** (1.5 mmol) and proper amine (1.5 mmol) in 5 mL ACN, in presence of catalytic amount of potassium iodide and potassium carbonate was reflux overnight. The solvent was evaporated and the residue was purified with column chromatography to give final products **5a-5e**.

*N-((1-benzyl-2-(methylsulfonyl)-1H-imidazol-*

**5-yl)methyl)benzamine (5a)**

Yield: 65%, mp: 114-115 °C; IR: (KBr)  $\nu$  (cm<sup>-1</sup>): 3317 (N-H), 1127, 1308 (SO<sub>2</sub>). <sup>1</sup>HNMR (DMSO, 400 MHz)  $\delta$ ppm: 3.32 (s, 3H, SO<sub>2</sub>CH<sub>3</sub>), 4.11 (d,  $J$  = 5.6 Hz, 2H, CH<sub>2</sub>-NH), 5.66 (s, 2H, benzyl), 6.10 (t,  $J$  = 5.6 Hz, 1H, NH), 6.50 (d,  $J$  = 7.2 Hz, 2H, H<sub>2</sub>, H<sub>6</sub>-phenyl), 6.56 (t,  $J$  = 7.2 Hz, 1H, H<sub>4</sub>-phenyl), 7.04 (t,  $J$  = 7.2 Hz, 2H, H<sub>3</sub>, H<sub>5</sub>-phenyl), 7.11 (m, 3H, imidazole, H<sub>2</sub>, H<sub>6</sub>-benzyl), 7.22 (t,  $J$  = 7.2 Hz, 1H, H<sub>4</sub>-benzyl), 7.40 (t,  $J$  = 7.2 Hz, 2H, H<sub>3</sub>, H<sub>5</sub>-benzyl). LC-MS [M+1]<sup>+</sup>: m/z 342, [M+23]<sup>+</sup>: m/z 364. Anal. Calcd for C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>S: C, 63.32; H, 5.61; N, 12.31. Found: C, 64.00; H, 5.56; N, 12.25.

***N*-((1-benzyl-2-(methylsulfonyl)-1*H*-imidazol-5-yl)methyl)-4-methoxybenzamine (5b)**

Yield: 10%, mp: 152 °C; IR: (KBr)  $\nu$  (cm<sup>-1</sup>): 3250 (N-H), 1150, 1360 (SO<sub>2</sub>). <sup>1</sup>HNMR (DMSO, 400 MHz)  $\delta$ ppm: 3.27 (s, 3H, SO<sub>2</sub>CH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 4.10 (s, 2H, CH<sub>2</sub>-NH), 5.70 (s, 2H, benzyl), 6.50 (d,  $J$  = 8.8 Hz, 2H, H<sub>2</sub>, H<sub>6</sub>-phenyl), 6.78 (d,  $J$  = 8.8 Hz, 2H, H<sub>3</sub>, H<sub>5</sub>-phenyl), 7.12 (dd,  $J$  = 8.0 Hz, 1.6 Hz, 2H, H<sub>2</sub>, H<sub>6</sub>-benzyl), 7.14 (s, 1H, imidazole), 7.36 (m, 3H, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>-benzyl). LC-MS [M+1]<sup>+</sup>: m/z 372, [M+23]<sup>+</sup>: m/z 410. Anal. Calcd for C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S: C, 61.44; H, 5.70; N, 11.31. Found: C, 61.52; H, 5.72; N, 11.23.

***N*-((1-benzyl-2-(methylsulfonyl)-1*H*-imidazol-5-yl)methyl)-4-bromobenzamine (5c)**

Yield: 16%, mp: 155 °C; IR: (KBr)  $\nu$  (cm<sup>-1</sup>): 3288 (N-H), 1136, 1329 (SO<sub>2</sub>). <sup>1</sup>HNMR (DMSO, 400 MHz)  $\delta$ ppm: 3.32 (s, 3H, SO<sub>2</sub>CH<sub>3</sub>), 4.10 (d,  $J$  = 6 Hz, 2H, CH<sub>2</sub>-NH), 5.64 (s, 2H, benzyl), 6.37 (t,  $J$  = 6 Hz, 1H, NH), 6.43 (d,  $J$  = 8.8 Hz, 2H, H<sub>2</sub>, H<sub>6</sub>-phenyl), 7.10 (m, 3H, imidazole, H<sub>2</sub>, H<sub>6</sub>-benzyl), 7.17 (d,  $J$  = 8.8 Hz, 2H, H<sub>3</sub>, H<sub>5</sub>-phenyl), 7.32 (t,  $J$  = 7.2 Hz, 1H, H<sub>4</sub>-benzyl), 7.38 (t,  $J$  = 7.2 Hz, 2H, H<sub>3</sub>, H<sub>5</sub>-benzyl). LC-MS [M+1]<sup>+</sup>: m/z 420, [M+3]<sup>+</sup>: m/z 423, [M+23]<sup>+</sup>: m/z 442, [M+25]<sup>+</sup>: m/z 444. Anal. Calcd for C<sub>18</sub>H<sub>18</sub>BrN<sub>3</sub>O<sub>2</sub>S: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.48; H, 4.30; N, 9.76.

***N*-((1-benzyl-2-(methylsulfonyl)-1*H*-imidazol-5-yl)methyl)-4-nitrobenzamine (5d)**

Yield: 10%, mp: 177 °C; IR: (KBr)  $\nu$  (cm<sup>-1</sup>): 3310 (N-H), 1110-1308 (SO<sub>2</sub>), 1324-1528 (NO<sub>2</sub>).

<sup>1</sup>HNMR (DMSO, 400 MHz)  $\delta$ ppm: 3.32 (s, 3H, SO<sub>2</sub>CH<sub>3</sub>), 4.30 (d,  $J$  = 6 Hz, 2H, CH<sub>2</sub>-NH), 5.65 (s, 2H, benzyl), 6.56 (d,  $J$  = 8.8 Hz, 2H, H<sub>2</sub>, H<sub>6</sub>-phenyl), 7.07 (d,  $J$  = 7.2 Hz, 2H, H<sub>2</sub>, H<sub>6</sub>-benzyl), 7.17 (s, 1H, imidazole), 7.31 (t,  $J$  = 7.2 Hz, 1H, H<sub>4</sub>-benzyl), 7.36 (t,  $J$  = 7.2 Hz, 2H, H<sub>3</sub>, H<sub>5</sub>-benzyl), 7.66 (t,  $J$  = 6 Hz, 1H, NH), 7.96 (d,  $J$  = 8.8 Hz, 2H, H<sub>3</sub>, H<sub>5</sub>-phenyl). LC-MS [M+23]<sup>+</sup>: m/z 409. Anal. Calcd for C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub>S: C, 55.95; H, 4.70; N, 14.50. Found: C, 55.91; H, 4.74; N, 14.43.

***N*-((1-benzyl-2-(methylsulfonyl)-1*H*-imidazol-5-yl)methyl)-4-chlorobenzamine (5e)**

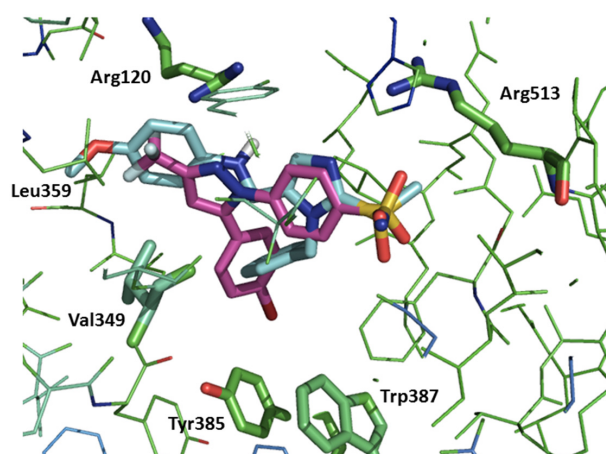
Yield: 25%, mp: 142 °C; IR: (KBr)  $\nu$  (cm<sup>-1</sup>): 3298 (N-H), 1140, 1333 (SO<sub>2</sub>). <sup>1</sup>HNMR (DMSO, 400 MHz)  $\delta$ ppm: 3.32 (s, 3H, SO<sub>2</sub>CH<sub>3</sub>), 4.10 (d,  $J$  = 6 Hz, 2H, CH<sub>2</sub>-NH), 5.64 (s, 2H, benzyl), 6.32 (t,  $J$  = 6 Hz, 1H, NH), 6.47 (d,  $J$  = 8.8 Hz, 2H, H<sub>2</sub>, H<sub>6</sub>-phenyl), 7.06 (d,  $J$  = 8.8 Hz, 2H, H<sub>3</sub>, H<sub>5</sub>-phenyl), 7.10 (m, 3H, imidazole, H<sub>2</sub>, H<sub>6</sub>-phenyl), 7.32 (t,  $J$  = 7.2 Hz, 1H, H<sub>4</sub>-benzyl), 7.38 (t,  $J$  = 7.2 Hz, 2H, H<sub>3</sub>, H<sub>5</sub>-benzyl). LC-MS [M+23]<sup>+</sup>: m/z 398, [M+25]<sup>+</sup>: m/z 400. Anal. Calcd for C<sub>18</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>2</sub>S: C, 57.52; H, 4.83; N, 11.18. Found: C, 57.80; H, 4.79; N, 11.11.

***In-vitro* biological activity**

The inhibitory activity of the synthesized compounds was evaluated against COX-1 and COX-2 enzymes with Cayman colorimetric-based human cyclooxygenase assay kit (item number 701050). The enzyme was incubated with inhibitors for 2 min in 0.1 M Bis-Tris/HCl buffer (pH 8.0) at 25 °C. Arachidonic acid and Celecoxib were used as substrate and reference drug respectively. All test samples were dissolved in DMSO and absorbance was read at 590 nm. The IC<sub>50</sub> amounts of the novel compounds were analyzed using nonlinear regression with Dose-response inhibition parameter by the activity base software package (Program Prism, Graph Pad, San Diego, CA).

**Results and Discussion*****Molecular Modeling Studies***

To predict interaction of compounds (5a-e) with COX-2 binding site docking stimulation was performed. The orientation of the most potent



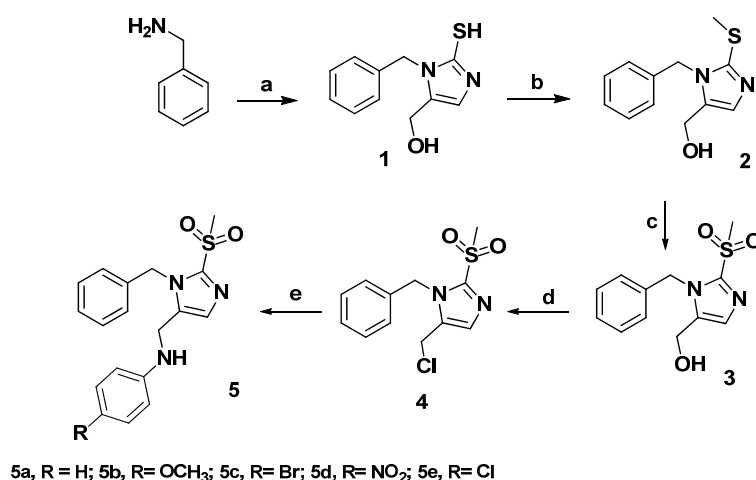
**Figure 2.** Overlay of 5b (blue) and Celecoxib (magenta) in the catalytic pocket of COX-2.

inhibitor **5b**, N-((1-benzyl-2-(methylsulfonyl)-1H-imidazol-5-yl)methyl)-4-methoxyaniline, along with Celecoxib in the active site of the COX-2 enzyme examined by a flexible docking experiment using AutoDock 4.0 software was observed in Figure 2. The pharmacophoric methylsulfonyl and sulfonamide groups of the **5b** and Celecoxib were in the same direction for hydrogen binding with Arg513 and also the phenyl ring of the **5b** may bind in a lipophilic

pocket formed by Trp387, Tyr385, and Val349 of the active site. Additional hydrogen binding could form between NH of anilino moiety of the **5b** and Arg120. Isobutyl moiety of Leu359 may form hydrophobic interaction with methyl group of methoxy substituent of the **5b**.

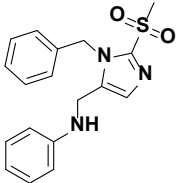
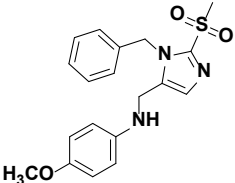
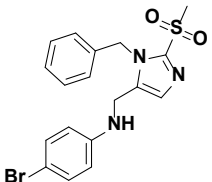
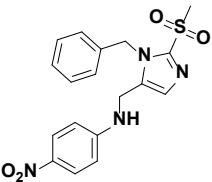
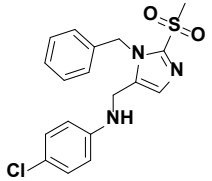
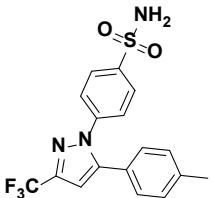
#### Chemistry

The designed compounds were synthesized according to Scheme 1. Benzylamine was



**Scheme 1.** Synthesis of compounds 5a-e Reagents and conditions: Reagents and conditions: (a) Potassium thiocyanate, dihydroxyacetone, acetic acid/ H<sub>2</sub>O (93/7), 55 °C, 18 h; (b) Sodium iodide, NaOH 10%, ethanol, rt, 1 h; (c) Oxone, THF/ H<sub>2</sub>O, rt, 24 h; (d) SOCl<sub>2</sub>, 70 °C, 4 h; (e) Proper amine, KI, K<sub>2</sub>CO<sub>3</sub>, ACN, 80 °C, 24 h.

**Table 1.** Inhibitory activity of the imidazole derivatives against COX-1 and COX-2 enzymes.

Compound	Structure	IC <sub>50</sub> (μM)		COX-2 S.I. <sup>b</sup>
		COX-2 <sup>a</sup>	COX-1 <sup>a</sup>	
5a		3.2	87	27
5b		0.71	82	115
5c		2.8	78	28
5d		3	78	26
5e		3.6	138	38
Celecoxib		0.22	46	209

<sup>a</sup>The concentration of test compound produce 50% inhibition of COX-2, COX-1 enzyme, the result is the mean of two value obtained by assay of enzyme kits obtained from (Cayman colorimetric-based human cyclooxygenase assay kit Chemicals kit with item number 701050). <sup>b</sup>The *in-vitro* COX-2 selectivity index (COX-1/COX-2).

reacted with potassium thiocyanate and dihydroxyacetone in acetic acid/water to give imidazole ring. Methyl sulfonyl moiety was afforded after S-methylation and oxidation of the thiol group. Treatment of the compound **3** with

thionyl chloride followed by reaction with proper amine gave final products (**5a-5e**).

#### *In-vitro Biological activity*

As shown in Table 1, all of the designed

compounds have acceptable COX-2 inhibitory activity with  $IC_{50}$  values in the range of 0.7-3.6  $\mu$ M, while  $IC_{50}$  values of COX-1 inhibition were 78-138 $\mu$ M. The rank order for the contribution of substituents to the COX-2 inhibitory activity of the synthesized compounds is:  $OCH_3 > Br > NO_2 > H > Cl$ . Results reveal that the compound bearing methoxy (**5b**), shows the best inhibitory activity and selectivity against COX-2 with  $IC_{50}$  of 0.71  $\mu$ M and selectivity index of 115 due to additional hydrophobic interaction of methoxy with Leu359. The electron withdrawing substitutes and Hydrogen at the para position of anilino ring, despite selectivity to COX-2, show no considerable priority with each other.

### Conclusion

New imidazole-based compounds as non-classical selective cyclooxygenase-2 inhibitors were investigated by attaching the suitable pharmacophore directly to the central cyclic ring. The docking study shows the compounds fitted in the COX-2 catalytic pocket and interacted well with the active site residues. The synthesized compounds had comparable inhibitory activity to Celecoxib. Compound **5b** was found to be the most potent inhibitor with  $IC_{50}$  of 0.71  $\mu$ M and selectivity index of 115 in targeting COX-2 enzyme. Finally, these structures seem to be valuable leading scaffold to design and develop novel selective COX-2 inhibitors.

### Acknowledgement

This work was supported by a grant from the Research Council of Shahid Beheshti University of Medical Sciences.

### References

- (1) Dannhardt G and Kiefer W. Cyclooxygenase inhibitors-current status and future prospects. *Eur. J. Med. Chem.* (2001) 36: 109-26.
- (2) Bakhle YS. Structure of COX-1 and COX-2 enzymes and their interaction with inhibitors. *Drugs Today (Barc)* (1999) 35: 237-50.
- (3) Consalvi S, Alfonso S, Di Capua A, Poce G, Pirolli A, Sabatino M, Ragno R, Anzini M, Sartini S and La Motta C. Synthesis, biological evaluation and docking analysis of a new series of methylsulfonyl and sulfamoyl acetamides and ethyl acetates as potent COX-2 inhibitors. *Bioorg. Med. Chem.* (2015) 23: 810-20.
- (4) Murias M, Handler N, Erker T, Pleban K, Ecker G, Saiko P, Szekere T and Jäger W. Resveratrol analogues as selective cyclooxygenase-2 inhibitors: synthesis and structure-activity relationship. *Bioorg. Med. Chem.* (2004) 12: 5571-8.
- (5) Firke SD and Bari SB. Synthesis, biological evaluation and docking study of maleimide derivatives bearing benzenesulfonamide as selective COX-2 inhibitors and anti-inflammatory agents. *Bioorg. Med. Chem.* (2015) 23: 5273-81.
- (6) El-Sayed MA, Abdel-Aziz NI, Abdel-Aziz AA, El-Azab AS and ElTahir KE. Synthesis, biological evaluation and molecular modeling study of pyrazole and pyrazoline derivatives as selective COX-2 inhibitors and anti-inflammatory agents. *Bioorg. Med. Chem.* (2012) 20: 3306-16.
- (7) Abdellatif KRA, Abdelgawad MA, Labib MB and Zidan TH. Synthesis, cyclooxygenase inhibition, anti-inflammatory evaluation and ulcerogenic liability of novel triarylpyrazoline derivatives as selective COX-2 inhibitors. *Bioorg. Med. Chem. Lett.* (2015) 25: 5787-91.
- (8) Alanazi AM, El-Azab AS, Al-Suwaidan IA, ElTahir KE, Asiri YA, Abdel-Aziz NI and Abdel-Aziz AA. Structure-based design of phthalimide derivatives as potential cyclooxygenase-2 (COX-2) inhibitors: Anti-inflammatory and analgesic activities. *Eur. J. Med. Chem.* (2015) 92: 115-23.
- (9) Schneider V, Lévesque LE, Zhang B, Hutchinson T and Brophy JM. Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: a population-based, nested case-control analysis. *Am. J. Epidemiol.* (2006) 164: 881-9.
- (10) James MW and Hawkey CJ. Assessment of non-steroidal anti-inflammatory drug (NSAID) damage in the human gastrointestinal tract. *Br. J. Clin. Pharmacol.* (2003) 56: 146-55.
- (11) Sudano I, Flammer AJ, Roas S, Enseleit F, Noll G and Ruschitzka F. Nonsteroidal antiinflammatory drugs, acetaminophen, and hypertension. *Curr. Hypertens. Rep.* (2012) 14: 304-9.
- (12) Unsal-Tan O, Ozadali K, Piskin K and Balkan A. Molecular modeling, synthesis and screening of some new 4-thiazolidinone derivatives with promising selective COX-2 inhibitory activity. *Eur. J. Med. Chem.* (2012) 57: 59-64.
- (13) Dawood DH, Batran RZ, Farghaly TA, Khedr MA and Abdulla MM. New coumarin derivatives as potent selective COX-2 inhibitors: Synthesis, anti-inflammatory, QSAR, and molecular modeling studies. *Arch. Pharm.* (2015) 348: 875-88.
- (14) Ranatunge RR, Earl RA, Garvey DS, D Janero RL, Letts G, Martino AM, Murty MG, Richardson SK, Schwalb DJ and Young DV. 3-(2-Methoxytetrahydrofuran-2-yl)pyrazoles: a novel class of potent, selective cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med.*

- Chem. Lett.* (2004) 14: 6049-52.
- (15) Basile L, Álvarez S, Blanco A, Santagati A, Granata G, Pietro PD, Guccioneet S and Fernández A. Sulfonilamidothiopyrimidone and thiopyrimidone derivatives as selective COX-2 inhibitors: Synthesis, biological evaluation, and docking studies. *Eur. J. Med. Chem.* (2012) 57: 149-61.
- (16) Nivsarkar M, Banerjee A and Padh H. Cyclooxygenase inhibitors: a novel direction for Alzheimer's management. *Pharmacol. Rep.* (2008) 60: 692-8.
- (17) Anzini M, Rovini M, Cappelli A, Vomero S, Manetti F, Botta M, Sautebin L, Rossi L, Pergola C, Ghelardini C, Norcini M, Giordani A, Makovec F, Anzellotti P, Patrignani P and Biava M. Synthesis, biological evaluation, and enzyme docking simulations of 1, 5-diarylpyrrole-3-alkoxyethyl ethers as selective cyclooxygenase-2 inhibitors endowed with anti-inflammatory and antinociceptive activity. *J. Med. Chem.* (2008) 51: 4476-81.
- (18) Rizzo MT. Cyclooxygenase-2 in oncogenesis, *Clin. Chim. Acta* (2011) 412: 671-87.
- (19) Ye F, Wu J, Dunn T, Yi J, Tong X and Zhang D. Inhibition of cyclooxygenase-2 activity in head and neck cancer cells by genistein. *Cancer Lett.* (2004) 211: 39-46.
- (20) Zarghi A and Arfaei S. Selective COX-2 inhibitors: a review of their structure-activity relationships. *Iran. J. Pharm. Res.* (2011) 10: 655-83.
- (21) Banerjee AG, Das N, Shengule SA, Sharma PA, Srivastava RS and Shrivastava K. Design, synthesis, evaluation and molecular modeling studies of some novel 5,6-diphenyl-1,2,4-triazin-3(2H)-ones bearing five-member heterocyclic moieties as potential COX-2 inhibitors: A hybrid pharmacophore approach. *Bioorg. Chem.* (2016) 69: 102-20.
- (22) Abolhasani H, Dastmalchi S, Hamzeh-Mivehroud M, Daraei B and Zarghi A. Design, synthesis and biological evaluation of new tricyclic spiroisoxazoline derivatives as selective COX-2 inhibitors and study of their COX-2 binding modes via docking studies. *Med. Chem. Res.* (2016) 25: 858-69.
- (23) Black WC, Brideau C, Chan CC, Charleson S, Chauret N, Claveau D, Ethier D, Gordon R, Greig G, Guay J, Hughes G, Jolicoeur P, Leblanc Y, Nicoll-Griffith D, Ouimet N, Riendeau D, Visco D, Wang Z, Xu L and Prasit P. 2, 3-Diaryl cyclopentenones as orally active, highly selective cyclooxygenase-2 inhibitors. *J. Med. Chem.* (1999) 42: 1274-81.
- (24) Zebardast T, Zarghi A, Daraie B, Hedayati M and Dadrass OG. Design and synthesis of 3-alkyl-2-aryl-1,3-thiazinan-4-one derivatives as selective cyclooxygenase (COX-2) inhibitors. *Bioorg. Med. Chem. Lett.* (2009) 19: 3162-5.
- (25) Zarghi A, Zebardast T, Daraie B and Hedayati M. Design and synthesis of new 1,3-benzthiazinan-4-one derivatives as selective cyclooxygenase (COX-2) inhibitors. *Bioorg. Med. Chem.* (2009) 17: 5369-73.
- (26) Talley JJ, Brown DL, Carter JS, Graneto MJ, Koboldt CM, Masferrer JL, Perkins WE, Rogers RS, Shaffer AF, Zhang YY, Zweifel BS and Seibert K. 4-[5-Methyl-3-phenylisoxazol-4-yl]-benzenesulfonamide, valdecoxib: a potent and selective inhibitor of COX-2. *J. Med. Chem.* (2000) 43: 775-7.
- (27) Palomer A, Cabré F, J Pascual, Campos J, Trujillo MA, Entrena A, Gallo M, García L, Mauleón D and Espinosa A. Identification of novel cyclooxygenase-2 selective inhibitors using pharmacophore models. *J. Med. Chem.* (2002) 45: 1402-11.
- (28) Ahmaditaba MA, Tehrani MH, Zarghi A, Shahosseini S and Daraei B. Design, synthesis and biological evaluation of novel peptide-like analogues as selective COX-2 inhibitors. *Iran. J. Pharm. Res.* (2018) 17: 87-92.
- (29) Shahrabi M, Azami Movahed M, Ghorban Dadrass O, Daraei B and Zarghi A. Design, synthesis and biological evaluation of new Imidazo [2, 1-B] thiazole derivatives as selective COX-2 inhibitors. *Iran. J. Pharm. Res.* (2018) 17: 1288-96.
- (30) Tabatabai SA, Lashkari SB, Zarrindast MR, Gholibeikian M and Shafiee A. Design, synthesis and anticonvulsant activity of 2-(2-phenoxy) phenyl-1, 3, 4-oxadiazole derivatives. *Iran. J. Pharm. Res.* (2013) 12: 105-11.
- (31) Faizi M, Sheikhha M, Ahangar N, Ghomi HT, Shafaghi B, Shafiee A and Tabatabai SA. Design, synthesis and pharmacological evaluation of novel 2-[2-(2-chlorophenoxy) phenyl]-1, 3, 4-oxadiazole derivatives as benzodiazepine receptor agonists. *Iran. J. Pharm. Res.* (2012) 11: 83-90.
- (32) Mahdavi M, Akbarzadeh T, Sheibani V, Abbasi M, Firoozpour L, Tabatabai SA, Shafiee A and Foroumadi A. Synthesis of two novel 3-amino-5-[4-chloro-2-phenoxyphenyl]-4H-1, 2, 4-triazoles with anticonvulsant activity. *Iran. J. Pharm. Res.* (2010) 9: 265-9.
- (33) Foroumadi A, Sheibani V, Sakhteman A, Rameshk M, Abbasi M, Farazifard R, Tabatabai SA and Shafiee A. Synthesis and anticonvulsant activity of novel 2-amino-5-[4-chloro-2-(2-chlorophenoxy) phenyl]-1,3,4-thiadiazole derivatives. *DARU* (2007) 15: 89-93.
- (34) Rad AA, Sheikhha M, Hosseini R, Tabatabai SA and Shafiee A. Synthesis and morphine enhancement activity of N-[5-(2-phenoxyphenyl)-1,3, 4-oxadiazole-2-yl]-N'-phenylurea derivatives. *Arch. Pharm.* (2004) 337: 193-200.
- (35) Foroumadi A, Tabatabai SA, Gitinezhad G, Zarrindast MR, Shafiee A. Synthesis and anticonvulsant activity of 5-aryl-1,3,4-thiadiazole derivatives. *Pharm. Pharmacol. Commun.* (2000) 6: 31-3.
- (36) Ghasemi M, Ghadbeighi S, Amirhamzeh A, Tabatabai SA, Ostad S N, Shafiee A and Amini M. Synthesis, molecular docking study, and cytotoxic activity of 1,3,5-triaryl pyrazole derivatives. *Lett. Drug Des. Discov.* (2016) 13: 121-28.
- (37) Faizi M, Jahani R, Ebadi SA, Tabatabai SA, Rezaee E, Lotfaliei M, Amini M and Almasirad A. Novel 4-thiazolidinone derivatives as agonists of benzodiazepine receptors: Design, synthesis and



- pharmacological evaluation. *EXCLI J.* (2017) 16: 52-62.
- (38) Faizi M, Dabirian S, Tajali H, Ahmadi F, Rezaee E, Shahhosseini S and Tabatabai SA. Novel agonists of benzodiazepine receptors: design, synthesis, binding assay and pharmacological evaluation of 1, 2, 4-triazolo [1, 5-a] pyrimidinone and 3-amino-1, 2, 4-triazole derivatives. *J. Bioorg. Med. Chem.* (2015) 23: 480-7.
- (39) Rezaee E, Hedayati M, Hoghooghi Rad L, Kiani A, Shahhosseini S, Faizi M and Tabatabai SA. Design, synthesis and biological evaluation of some oxadiazole derivatives as novel amide-based inhibitors of soluble epoxide hydrolase. *Lett. Drug Des. Discov.* (2014) 11: 721-30.
- (40) Zavareh ER, Hedayati M, Rad LH, Shahhosseini S, Faizi M and Tabatabai SA. Design, synthesis and biological evaluation of 4-benzamidobenzoic acid hydrazide derivatives as novel soluble epoxide hydrolase inhibitors. *Iran. J. Pharm. Res.* (2014) 13: 51-9.

---

This article is available online at <http://www.ijpr.ir>

---