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

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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 µM 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 infarction
and thrombosis related to selective inhibition of COX-2 due to the depression of the biosynthesis of atherosprotective prostaglandin (PGI₂) and not the pro-aggregatory and vasoconstrictor mediator thromboxane A₂ derived from COX-1 (20) leaded 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 diaryl heterocycles 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 SO₂NH₂ or a SO₂Me 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 1H NMR spectra; DMSO-d$_6$ 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; IR: (KBr) ν (cm$^{-1}$): 3200-3538 (O-H). The resulting precipitates were formed after acidifying of potassium iodide (5.44 g, 55.79 mmol) with NaOH 10% and extracted with chloroform. The Aqueous phase was alkalinized to give 6.66 g (54.1%) of compound 2 (1 g, 4.3 mmol) in THF.

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

A solution of compound 1 (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 refluxed overnight.

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 refluxed overnight.
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5-yl)methyl)benzamine (5a)
 Yield: 65%, mp: 114-115°C; IR: (KBr) ν (cm⁻¹): 3317 (N-H), 1127, 1308 (SO₂). ¹HNMR (DMSO, 400 MHz) δppm: 3.32 (s, 3H, SO₂CH₃), 4.11 (d, J = 5.6 Hz, 2H, CH₂-NH), 5.66 (s, 2H, benzyl), 6.10 (t, J = 5.6 Hz, 1H, NH), 6.50 (d, J = 7.2 Hz, 2H, H₂-phenyl), 6.56 (t, J = 7.2 Hz, 1H, H₂-phenyl), 7.04 (t, J = 7.2 Hz, 2H, H₂-phenyl), 7.11 (m, 3H, imidazole), 7.66 (t, J = 7.2 Hz, 1H, H₂-phenyl), 7.22 (t, J = 7.2 Hz, 1H, H₂-phenyl), 7.40 (t, J = 7.2 Hz, 2H, H₂-phenyl). LC-MS [M+1]: m/z 342, [M+23]: m/z 364. Anal. Calcld for C₁₈H₁₉N₃O₂S: C, 61.44; H, 5.61; N, 12.31. Found: C, 64.00; H, 5.56; N, 12.25.

N-((1-benzyl-2-(methylsulfonyl)-1H-imidazol-5-yl)methyl)-4-methoxybenzamine (5b)
 Yield: 10%, mp: 152 °C; IR: (KBr) ν (cm⁻¹): 3250 (N-H), 1150, 1360 (SO₂). ¹HNMR (DMSO, 400 MHz) δppm: 3.27 (s, 3H, SO₂CH₃), 3.76 (s, 3H, OCH₃), 4.10 (s, 2H, CH₂-NH), 5.70 (s, 2H, benzyl), 6.50 (d, J = 8.8 Hz, 2H, H₂-phenyl), 6.78 (d, J = 8.8 Hz, 2H, H₂-phenyl), 7.12 (d, J = 8.0 Hz, 1.6 Hz, 2H, H₂-phenyl), 7.14 (s, 1H, imidazole), 7.36 (m, 3H, H₃, H₂, H₁-benzyl). LC-MS [M+1]: m/z 372, [M+23]: m/z 394. Anal. Calcld for C₁₈H₁₇N₃O₃S: C, 63.32; H, 5.61; N, 11.23. Found: C, 64.00; H, 5.56; N, 12.25.

N-((1-benzyl-2-(methylsulfonyl)-1H-imidazol-5-yl)methyl)-4-bromobenzamine (5c)
 Yield: 16%, mp: 155 °C; IR: (KBr) ν (cm⁻¹): 3288 (N-H), 1136, 1329 (SO₂). ¹HNMR (DMSO, 400 MHz) δppm: 3.32 (s, 3H, SO₂CH₃), 4.10 (d, J = 6 Hz, 2H, CH₂-NH), 5.64 (s, 2H, benzyl), 6.32 (t, J = 6 Hz, 1H, NH), 6.47 (d, J = 8.8 Hz, 2H, H₂-phenyl), 7.06 (d, J = 8.8 Hz, 2H, H₂-phenyl), 7.10 (m, 3H, imidazole, H₃, H₂-benzyl), 7.32 (t, J = 7.2 Hz, 1H, H₂-phenyl), 7.38 (t, J = 7.2 Hz, 2H, H₂-phenyl). LC-MS [M+23]: m/z 398, [M+25]: m/z 400. Anal. Calcld for C₁₈H₁₇N₃O₂Br: C, 57.52; H, 4.83; N, 11.18. Found: C, 57.80; H, 4.79; N, 11.11.

N-((1-benzyl-2-(methylsulfonyl)-1H-imidazol-5-yl)methyl)-4-chlorobenzamine (5d)
 Yield: 25%, mp: 142 °C; IR: (KBr) ν (cm⁻¹): 3298 (N-H), 1140, 1333 (SO₂). ¹HNMR (DMSO, 400 MHz) δppm: 3.32 (s, 3H, SO₂CH₃), 4.10 (d, J = 6 Hz, 2H, CH₂-NH), 5.64 (s, 2H, benzyl), 6.32 (t, J = 6 Hz, 1H, NH), 6.47 (d, J = 8.8 Hz, 2H, H₂-phenyl), 7.06 (d, J = 8.8 Hz, 2H, H₂-phenyl), 7.10 (m, 3H, imidazole, H₃, H₂-benzyl), 7.32 (t, J = 7.2 Hz, 1H, H₂-phenyl), 7.38 (t, J = 7.2 Hz, 2H, H₂-phenyl). LC-MS [M+23]: m/z 398, [M+25]: m/z 400. Anal. Calcld for C₁₈H₁₇N₃O₂Cl: 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/HC1 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 IC₅₀ 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, SanDiego, 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
The designed compounds were synthesized according to Scheme 1. Benzylamine was 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 with thionyl chloride followed by reaction with proper amine gave final products (5a-5e).

As shown in Table 1, all of the designed compounds have acceptable COX-2 inhibitory activity with IC₅₀ values in the range of 0.7-3.6 µM, while IC₅₀ values of COX-1 inhibition were 78-138 µM. The rank order for the contribution of substituents to the COX-2 inhibitory activity of the synthesized compounds is: OCH₃ > Br > NO₂ > H > Cl. Results reveal that the compound bearing methoxy (5b), shows the best inhibitory activity and selectivity against COX-2 with IC₅₀ of 0.71 µM 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.

**Chemistry**

The designed compounds were synthesized according to Scheme 1. Benzylamine was reacted with potassium thiocyanate, dihydroxyacetone, acetic acid/water (93/7), 55 °C, 18 h; (b) Sodium iodide, NaOH 10%, ethanol, rt, 1 h; (c) Oxone, THF/H₂O, rt, 24 h; (d) SOCl₂, 70 °C, 4 h; (e) Proper amine, KI, K₂CO₃, ACN, 80 °C, 24 h.

**Scheme 1.** Synthesis of compounds 5a-e. Reagents and conditions: (a) Potassium thiocyanate, dihydroxyacetone, acetic acid/H₂O (93/7), 55 °C, 18 h; (b) Sodium iodide, NaOH 10%, ethanol, rt, 1 h; (c) Oxone, THF/H₂O, rt, 24 h; (d) SOCl₂, 70 °C, 4 h; (e) Proper amine, KI, K₂CO₃, ACN, 80 °C, 24 h.
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

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

| Compound | Structure | IC50 (µM) | COX-2 S.I.b |
|----------|-----------|-----------|-------------|
|          | COX-1     | COX-2     |             |
| 5a       | ![Structure](image_url) | 3.2       | 87          | 27          |
| 5b       | ![Structure](image_url) | 0.71      | 82          | 115         |
| 5c       | ![Structure](image_url) | 2.8       | 78          | 28          |
| 5d       | ![Structure](image_url) | 3         | 78          | 26          |
| 5e       | ![Structure](image_url) | 3.6       | 138         | 38          |
| Celecoxib| ![Structure](image_url) | 0.22      | 46          | 209         |

bThe 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). bThe in-vitro COX-2 selectivity index (COX-1/COX-2).
compounds have acceptable COX-2 inhibitory activity with IC_{50} values in the range of 0.7-3.6 µM, while IC_{50} values of COX-1 inhibition were 78-138µM. 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 µM 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 µM 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.

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