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Design, synthesis and biological evaluation of new 2,5-diaryl-1,3,4-oxadiazole derivatives as selective cyclooxygenase-2 inhibitors

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Abstract:

Introduction: Non-steroidal anti-inflammatory drugs (NSAIDs) are common prescribed medications worldwide for the treatment of inflammatory conditions and pain. However, adverse effects of NSAIDs in long term use have led to investigation of selective cyclooxygenase-2 (COX-2) inhibitors with reduced adverse reactions, including gastrointestinal and cardiovascular side effects and nephrotoxicity.
Methods and Results: In this study, a series of 2,5-diaryl-1,3,4-oxadiazole derivatives as novel selective inhibitors of COX-2 were rationally designed, synthesized, and biologically evaluated. The structures of compounds were confirmed with LC-Mass, IR, and 1H NMR spectra. Based on our results, most of the compounds had proper inhibitory activity against COX-2 similar to celecoxib, and exhibited selectivity towards COX-2 than COX-1. In this series, compound **5f**, with nitro group in the R position, revealed the highest inhibitory activity and selectivity (IC_{50} = 19.6 µM, SI = 108.88) against COX-2. The docking study of compound **5a** showed that this structure had appropriate affinity to the active site of the enzyme forming multiple hydrogen bonds.
Conclusion: In summary, these structures will be a valuable lead scaffold to develop new potent and selective COX-2 inhibitors.

Keywords: Biological evaluation; 1,3,4-oxadiazole; COX-2 inhibitors; Selective

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1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed medications worldwide for the treatment of inflammatory conditions and pain [1,2]. These medications would act through the inhibition of cyclooxygenase (COX) enzymes, which are responsible for the synthesis of prostaglandins and other prostanoids in the human body [3].

The two isoforms of COX enzyme are presented as COX-1 and COX-2 illustrating near 60% structural similarity [4]. Despite this similarity the two isoforms hold different functions, and distribute in diverse tissues [5]. COX-1 is widely expressed in platelets, lung, prostate, brain, gastrointestinal tract, kidney, liver, and spleen, and is responsible for the protection of gastric mucosa, regulation of renal function, and platelet hemostasis. While COX-2 is an inducible form with producing role in enhanced prostanoid synthesis due to inflammatory stimuli and pain [6].

During recent decades, adverse effects of NSAIDs in long term consumption have led to investigation of selective COX-2 inhibitors with reduced adverse reactions, including gastrointestinal and cardiovascular side effects and nephrotoxicity [7-10]. Moreover, recent studies have indicated the prominent role of COX-2 inhibitors in the prevention of several cancers such as colon, breast, lung, and prostate cancer as well as neurodegenerative diseases such as Alzheimer's disease [11-15].

Selective COX-2 inhibitors can divide into three main classes, namely 1) tricyclics, 2) non-tricyclics, and (3) modified classical nonselective NSAIDs [12]. The category of tricyclic compounds contains 1,2-diarylsubstitution on a central heterocyclic or carbocyclic ring system with methanesulfonyl, sulfonamido, azido, methanesulfonamide or pharmacophore-based tetrazole groups on one of the aryl rings which possess significant role in COX-2 selectivity. Celecoxib and rofecoxib are two well-known selective COX-2 inhibitors belonging to this class (Figure 1) [12].

However, some coxibs such as rofecoxib have been withdrawn from the market due to cardiovascular side effects, thus encouraging the researchers to explore new selective COX-2 inhibitors with improved safety profiles [7,16]. Zarghi et al. developed a non-classic selective COX-2 inhibitors with a 1,3-diarylurea scaffold which illustrated suitable efficacy and selectivity [17].

In this regard, we have focused on designing some 2,5-diaryl-1,3,4-oxadiazole derivatives as selective COX-2 inhibitors with a methylsulfonyl group as a COX-2 pharmacophore at the para position of the phenyl ring (Figure 1). In this study, synthesis process, in vitro inhibitory evaluations and docking study were reported.

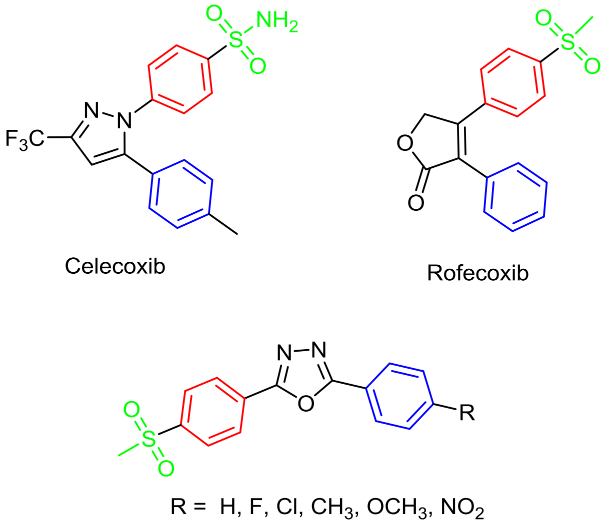


Figure 1. Chemical structures of some COX-2 inhibitors and general scaffold of the designed compounds **5a-f**.

2. Materials & Methods

2.1. Chemistry

All reagents were purchased from Aldrich or Merck Company without further purification. We afforded ^{1}H NMR spectra at 500 MHz by a Bruker Avance II spectrophotometer using $CDCl_3$, as a solvent and tetramethylsilane, as an internal standard. We reported Chemical shifts in parts per millions (ppm). All mass spectra were obtained using HPLC Agilent 1100 spectrometer. Melting points were taken with an Electrothermal 9100 apparatus and were not corrected. We utilized a Perkin Elmer 834 spectrometer to record infrared spectra, and expressed the absorptions on the wavenumber (cm^{-1}) scale in 400 to 4000cm^{-1}.

2.2. Synthesis of 4-(methylsulfonyl) benzoic acid (1)

A mixture of 4-(methylthio) benzaldehyde (1 ml, 7.5 mmol) and potassium peroxymonosulfate (11 g, 17.9 mmol) in 45 ml of H_2O/THF (2:1) was stirred at room temperature for 24 hours. After the completion of the reaction, the mixture was alkalinized with NaOH 5% and filtered. The filtrate was acidified with diluted HCl 12%. The resulting precipitate was filtered, washed with water, and recrystallized from methanol to afford compound **1**. Yield: 1.4g (93%); mp: 235-237 ºC; IR (KBr, cm^{-1}): 1159, 1327 (SO_2), 1695 (C=O), 2600-3200 (O-H); LC-MS (ESI) m/z: 199 (M-1).

2.3. Synthesis of ethyl 4-(methylsulfonyl) benzoate (2)

A mixture of compound **1** (3.5 g,17.5 mmol) and concentrated sulfuric acid 18M (1.2 ml) in 70 ml absolute ethanol was refluxed for 24 hours. Then the mixture was concentrated in vacuum and the precipitate was washed with NaOH 1% in ice bath to afford compound **2**. Yield: 3.48 g (87%). mp: 93-94 ºC; IR (KBr, cm^{-1}): 1170, 1328 (SO_2), 1728 (C=O); LC-MS (ESI) m/z: 229 (M + 1), 251 (M+23).

2.4. Synthesis of 4-(methylsulfonyl)benzohydrazide (3)

Compound **2** (3.2 g, 14 mmol) was dissolved in 10 ml DMF and hydrazine hydrate (3ml, 59 mmol) was added to the medium and stirred at room temperature for 18 hours. Then 30 ml chloroform/n-hexane (2:1) was added to the reaction mixture and cooled in ice-bath. The resulting oily precipitate was filtered, washed with boiling water, and recrystallized from methanol to obtain compound **3**. Yield: 2.2 g (73%); mp: 174-176 ºC; IR (KBr, cm^{-1}): 1150, 1293 (SO_2), 1678 (C=O), 3346, 3378 (N-H); LC-MS (ESI) m/z: 214 (M+1).

2.5. General procedure for the synthesis of substituted N'- benzoyl-4-(methylsulfonyl)benzohydrazides (4a-f)

A mixture of compound **3** (3 equiv), 4-substituated benzoyl chlorides (5 equiv) and sodium carbonate (2 equiv) in 40 ml dried 1,4-dioxane was stirred at room temperature for 8 hours. After evaporation of the solvent, the precipitate was washed with water, filtered, and recrystallized from methanol to afford compound **4a-f**.

2.5.1. *N'*-benzoyl-4-(methylsulfonyl) benzohydrazide (4a)

Yield: 0.89g (85%); mp: 214-216 °C; IR (KBr, cm^{-1}): 1169, 1320 (SO_2), 1675, 1690 (C=O), 3262 (N-H); LC-MS (ESI) m/z: 319.1 (M+1), 341 (M+23).

2.5.2. 4-Chloro-N'-(4-(methylsulfonyl) benzoyl) benzohydrazide (4b)

Yield: 0.96g (87%); mp: 264-266 °C; IR (KBr, cm^{-1}): 1140, 1293 (SO_2), 1600 (C=O), 3209 (N-H); LC-MS (ESI) m/z: 353 (M+1), 355 (M+3), 375 (M+23), 377 (M+25).

2.5.3. 4-Fluoro-N'-(4-(methylsulfonyl) benzoyl) benzohydrazide (4c)

Yield: 0.84g (77%); mp: 270-272 °C; IR (KBr, cm^{-1}): 1153, 1301 (SO_2), 1613 (C=O), 3202, 3262 (N-H); LC-MS (ESI) m/z: 337.1 (M+1).

2.5.4. 4-Methyl-N'-(4-(methylsulfonyl) benzoyl) benzohydrazide (4d)

Yield: 1g (92%); mp: 251-253 °C; IR (KBr, cm^{-1}): 1147, 1305 (SO_2), 1653, 1670 (C=O), 3221 (N-H); LC-MS (ESI) m/z: 333.2 (M+1), 355.1 (M+23).

2.5.5. 4-Methoxy-N'-(4-(methylsulfonyl) benzoyl) benzohydrazide (4e)

Yield: 1.1g (91%); mp: 257-258 °C; IR (KBr, cm^{-1}): 1152, 1301 (SO_2), 1680 (C=O), 3232 (N-H); LC-MS (ESI) m/z: 349 (M+1), 371 (M+23)

2.5.6. 4-(Methylsulfonyl)-N'-(4-nitrobenzoyl) benzohydrazide (4f)

Yield: 78%; mp: 294-296 °C; IR (KBr, cm^{-1}): 1152, 1347 (SO_2); 1664, 1689 (C=O), 3299 (N-H); LC-MS (ESI) m/z: LC-MS (ESI) m/z: 364 (M+1), 385.9 (M+23)

2.6. General procedure for the synthesis of 2,5-diaryl-1,3,4-oxadiazole derivatives (5a-f)

Compounds **4a-f** (2 equiv) and pyridine (0.6 ml, 6 equiv) were added to 10 ml thionyl chloride and the reaction mixture was refluxed for 24 hours. Then the solvent was concentrated under reduced pressure and the precipitate was washed with water and methanol. Compound **5a-f** was achieved through the recrystallization from chloroform.

2.6.1. 2-(4-(Methylsulfonyl) phenyl)-5-phenyl-1,3,4-oxadiazole (5a)

Yield: 0.53g (81%); mp: 195-197 °C; IR (KBr, cm^{-1}): 1147, 1353 (SO_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.1 (s, 3H, SO_2CH_3), 7.58-7.61 (m, 3H, H_3, H_4, H_5-phenyl,), 8.15 (d, 2H, J = 8.1 Hz, H_3, H_5- phenylene), 8.18 (d, 2H, J = 7.1 Hz, H_2, H_6- phenyl), 8.37 (d, 2H, J = 8.1 Hz, H_2, H_6- phenylene); LC-MS (ESI) m/z: 301.1 (M+1), 323 (M+23).

2.6.2. 2-(4-Chlorophenyl)-5-(4-(methylsulfonyl) phenyl)-1,3,4-oxadiazole (5b)

Yield: 0.49g (74%); mp: 262-263 °C; IR (KBr, cm^{-1}): 1169, 1328 (SO_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.15 (s, 3H, SO_2CH_3), 7.57 (d, 2H, J = 8.5 Hz, H_3, H_5- 4-chlorophenyl), 8.13 (d, 2H, J = 8.5 Hz, H_3, H_5-phenylene), 8.16 (d, 2H, J = 7.5 Hz, H_2, H_6-4-chlorophenyl), 8.37 (d, 2H, J = 8.5 Hz, H_2, H_6-phenylene); LC-MS (ESI) m/z: 335 (M+1), 337 (M+3).

2.6.3. 2-(4-Fluorophenyl)-5-(4-(methylsulfonyl) phenyl)-1,3,4-oxadiazole (5c)

Yield: 0.42g (74%); mp: 232-233 °C; IR (KBr, cm^{-1}): 1149, 1310 (SO_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.1 (s, 3H, SO_2CH_3), 7.28 (t, 2H, J = 8.05 Hz, H_3, H_5- 4–fluorophenyl), 8.15 (d, 2H, J = 8.1 Hz, H_3, H_5-phenylene), 8.19 (dd, 2H, J = 7.85, 5.35 Hz, H_2, H_6-4-fluorophenyl), 8.36 (d, 2H, J = 8.1 Hz, H_2, H_6-phenylene); LC-MS (ESI) m/z: 319.1 (M+1).

2.6.4. 2-(4-(Methylsulfonyl) phenyl)-5-(p-tolyl)-1,3,4-oxadiazole (5d)

Yield: 0.45g (68%); mp: 218-219 °C; IR (KBr, cm^{-1}): 1173, 1332 (SO_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.5 (s, 3H, CH_3-p–tolyl), 3.15 (s, 3H, SO_2CH_3), 7. 37 (d, 2H, J = 7. 45 Hz, H_3, H_5- p–tolyl), 8.06 (d, 2H, J = 7.5 Hz, H_3, H_5-phenylene), 8.13 (d, 2H, J = 7. 5, 5.35 Hz, H_2, H_6-p–tolyl), 8.36 (d, 2H, J = 7.7 Hz, H_2, H_6phenylene); LC-MS (ESI) m/z: 315 (M+1), 337 (M+23).

2.6.5. 2-(4-Methoxyphenyl)-5-(4-(methylsulfonyl) phenyl)-1,3,4-oxadiazole (5e)

Yield: 0.4g (53%); mp: 220-222 °C; IR (KBr, cm^{-1}): 1143, 1301 (SO_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.14 (s, 3H, SO_2CH_3), 3.92 (s, 3H, OCH_3), 7.06 (d, 2H, J = 8.45 Hz, H_3, H_5- 4-methoxyphenyl), 8.10-8.17 (m, 4H, H_3, H_5-phenylene, H_2, H_6- 4-methoxyphenyl), 8.35 (d, 2H, J = 7.95 Hz, H_2, H_6-phenylene); LC-MS (ESI) m/z: 349 (M+1), 371 (M+23).

2.6.6. 2-(4-(Methylsulfonyl) phenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (5f)

Yield: 2.5g (82.5%); mp: 279-280 °C; IR (KBr, cm^{-1}): 1148, 1346 (SO_2); LC-MS (ESI) m/z: 364 (M+1), 385 (M+23).

2.7. Biological evaluation

The inhibitory activity of the compounds was measured using Cayman colorimetric based human cyclooxygenase assay kit (item number 701050) against COX-1 and COX-2, based on the manufacturer's instructions [18]. 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_{50} values of the novel compounds were examined using nonlinear regression with dose response inhibition parameter by the activity base software package (Program Prism, Graph Pad, SanDiego, CA).

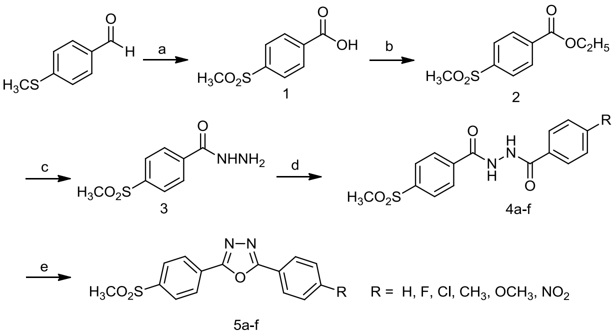
2.8. Docking study

The AutoDock Tools version 1.5.6rc3 (http://mgltools.scripps.edu) was applied for docking study of compound **5a**. The X-ray crystallographic structure of COX-2 (PDB code 6COX) was obtained from the Protein Data Bank. All water molecules in the PDB file were removed, hydrogen atoms were subsequently added to amino acid residues, and Gasteiger charges were assigned to all atoms of the enzyme. The structure of compound **5a** was optimized by the MM+ force field using HyperChem8 (http://www.hyper.com) and converted to pdbqt format file by AutoDock Tools. Each docked system was performed by 100 runs of the AutoDock search by the Lamarckian genetic algorithm (LGA). Finally, the lowest energy conformations were selected for analyzing the interactions between the enzyme and inhibitor. Graphic manipulations and visualizations were done by Pymol software version 1.5.0.1 (http://pymol.findmysoft.com).

3. Results

3.1. Chemistry

Synthesis of the target compounds **5a-f** is shown in Scheme **1**. The starting material 4-(methylthio) benzaldehyde was reacted with potassium peroxymonosulfate (oxone) in THF/H_2O to obtain compound **1**. Compound **1** was esterified through the reaction with ethanol and concentrated sulfuric acid as catalyst to furnish intermediate **2**. The hydrazide intermediate **3** was achieved via treating the intermediate **2** with hydrazine hydrate. The reaction of intermediate **3** with proper benzoyl chloride followed by the addition of thionyl chloride and pyridine led to closing 1,3,4-oxadiazole and affording final compounds **5a-f** [19].

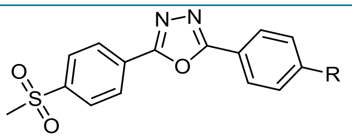


Scheme 1. Reagents and conditions: a) potassium peroxymonosulfate, THF/H_2O, rt, 24h, 93%; b) EtOH, H_2SO_4 18M, reflux, 24h, 87%; c) $NH_2NH_2.H_2O$, DMF, rt, 18h, 73%; d) corresponding benzoyl chloride, 1,4-dioxane, rt, 8h, 77-92%; e) $SOCl_2$, pyridine, reflux, 24h, 53-82.5%.

3.2. Biological evaluations

The inhibitory activity of the designed compounds against COX-1 and COX-2 was evaluated, and celecoxib was considered as a standard compound. As summarized in Table **1**, most of the compounds had proper inhibitory activity against COX-2 similar to celecoxib with desirable IC_{50} values (19.6 µM to 24.0 µM), and exhibited selectivity towards COX-2 than COX-1. In this series, compound **5f,** with nitro group in the R position, revealed the highest inhibitory activity and selectivity (IC_{50} = 19.6 µM, SI = 108.88) against COX-2. While compound **5e** with methoxy in this position showed the lowest activity (IC_{50} = 24.0 µM, SI = 25.53). The results showed that the presence of substitution in the R position had effect on inhibitory activity in the order of NO_2 > F> Cl > H> CH_3> OCH_3 methyl, indicating that the electron-withdrawing groups in these places would be in favor of anti-COX-2 activity.

Table 1. Inhibitory activities and selectivity index of the 1,3,4-oxadiazole derivatives **(5a-f).**



Compound	R	IC_{50} (µM)	Selectivity Index (SI)	
		COX-1	COX-2	
5a	H	0.50	21.70	43.4
5b	Cl	0.28	20.20	72.14
5c	F	0.22	21.00	95.45
5d	CH_3	0.67	20.90	31.19
5e	OCH_3	0.94	24.00	25.53
5f	NO_2	0.18	19.60	108.88
Celecoxib	-	0.10	20.00	200.0

3.3. Docking study

The docking study was conducted using AutoDock Tools software. The X-ray crystallographic structure of the COX-2 (PDB Code 6COX) was utilized as an enzyme structure. The docked binding mode was analyzed for the interactions between compound **5a** and COX-2. As revealed in Figure **2**, the compound **5a** was accommodated inside the active site properly. A hydrogen bond was observed between the sulfone group and Arg513 and His90 residues. The oxygen and nitrogen atoms of oxadiazole ring formed hydrogen bonds with Tyr355 and Arg120, respectively. Additionally, the phenyl rings adopted lipophilic interactions with Val523 and Val115.

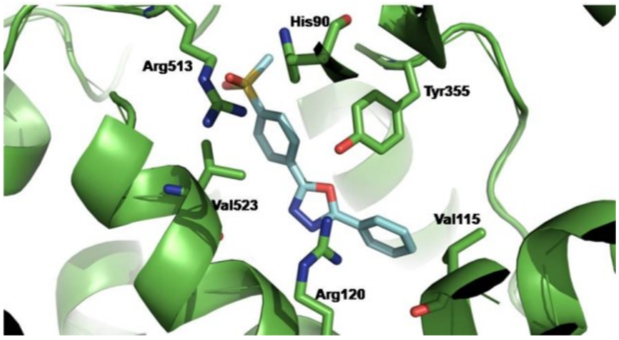


Figure 2. Compound **5a** (light blue sticks) in the catalytic pocket of COX-2 (PDB: 6COX). A hydrogen bond was observed between the sulfone group and Arg513 and His90 residues. The oxygen and nitrogen atoms of oxadiazole ring formed hydrogen bonds with Tyr355 and Arg120 respectively. Additionally, the phenyl rings adopted lipophilic interactions with Val523 and Val115.

4. Discussion and Conclusion

In this study, a series of 1,3,4-oxadiazole derivatives as novel selective inhibitors of COX-2 were rationally designed, synthesized, and biologically evaluated. Based on our results, most of the compounds had proper inhibitory activity against COX-2 similar to celecoxib, and exhibited selectivity towards COX-2 than COX-1. In this series, compound **5f,** revealed the highest inhibitory activity and selectivity (IC_{50} = 19.6 µM, SI = 108.88) against COX-2. Indeed, the presence of nitro group in the R position, promoted this selectivity. The docking study of compound **5a** showed that this structure had appropriate affinity to the active site of the enzyme forming multiple hydrogen bonds. In summary, these structures will be a valuable lead scaffold to develop new potent and selective COX-2 inhibitors.

Acknowledgements

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics

IR.SBMU.PHNM.1396.917
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