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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design and synthesis of new 1,2-diaryl-4,5,6,7-tetrahydro-1H-benzo[d] imidazoles as selective cyclooxygenase (COX-2) inhibitors

A. Zarghi · H. Reihanfard · S. Arfaei · B. Daraei · M. Hedayati

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Abstract A new series of 1,2-diaryl-4,5,6,7-tetrahydro-1H-benzo[d]imidazoles, possessing a methylsulfonyl pharmacophore, were synthesized to evaluate their biological activities as selective cyclooxygenase-2 (COX-2) inhibitors. In vitro COX-1 and COX-2 isozyme inhibition studies were carried out to acquire structure–activity relationship data with respect to the point that molecular modeling studies showed that designed compounds bind in the primary binding site such that the SO_2Me substituent at *para*-position of C-2 phenyl ring inserts into the 2° pocket present in COX-2 enzyme. COX-1 and COX-2 inhibition studies showed that all compounds were selective inhibitors of the COX-2 isozyme with IC_{50} values in the highly potent 0.34–0.69 μM range, and COX-2 selectivity indexes in the 52.3–163.8 range. 1-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4,5,6,7-tetrahydro-1H-benzo[d] imidazole was identified as the most potent (IC_{50} = 0.34 μM), and selective (SI = 163.8), COX-2 inhibitor among the synthesized compounds.

Keywords Imidazoles · COX-1 · COX-2

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Introduction

Prostaglandins act as potent mediators of pain, fever, and inflammation. Cyclooxygenase (COX) catalyzes the conversion of arachidonic acid to the prostaglandin endoperoxide PGG2 then PGH2, which serves as the precursor for the formation of PGs and thromboxanes (Fu *et al*., 1990). Nowadays, it is well established that there are at least two COX isozymes, COX-1 and COX-2 (Vane and Botting, 1998). The constitutive COX-1 isozyme is produced in a variety of tissues and appears to be important to the maintenance of physiological functions such as gastro protection and vascular homeostasis (Smith and Dewitt, 1996). Alternatively, the COX-2 isozyme is induced by mitogenic and proinflammatory stimuli linking its involvement to inflammatory processes (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. In addition to role of COX-2 in rheumatoid arthritis and osteoarthritis, it is also implicated in cancer and angiogenesis (Kawamori *et al*., 1998; Katori and Majima, 2000; Srinath *et al*., 2003; Takkouche *et al*., 2008). Recent studies have also shown that selective COX-2 inhibitors may slow the progress of Alzheimer's disease without causing gastrointestinal damage (Nivsarkar *et al*., 2008). 1,2-Diarylheterocycles have been extensively studied as selective COX-2 inhibitors (Ghodsi *et al*., 2010; Penning *et al*.,1997; Prasit *et al*., 1999; Riendeau *et al*., 2002; Navidpour *et al*., 2006; Salimi *et al*., 2007; Zarghi *et al*., 2009). All these tricyclic molecules possess 1,2-diaryl substitution on a central hetero or carbocyclic ring system (Fig. 1). Celecoxib and rofecoxib are two typical COX-2 inhibitors in this class. However, the recent withdrawal of some diarylheterocyclic selective COX-2 inhibitors such as

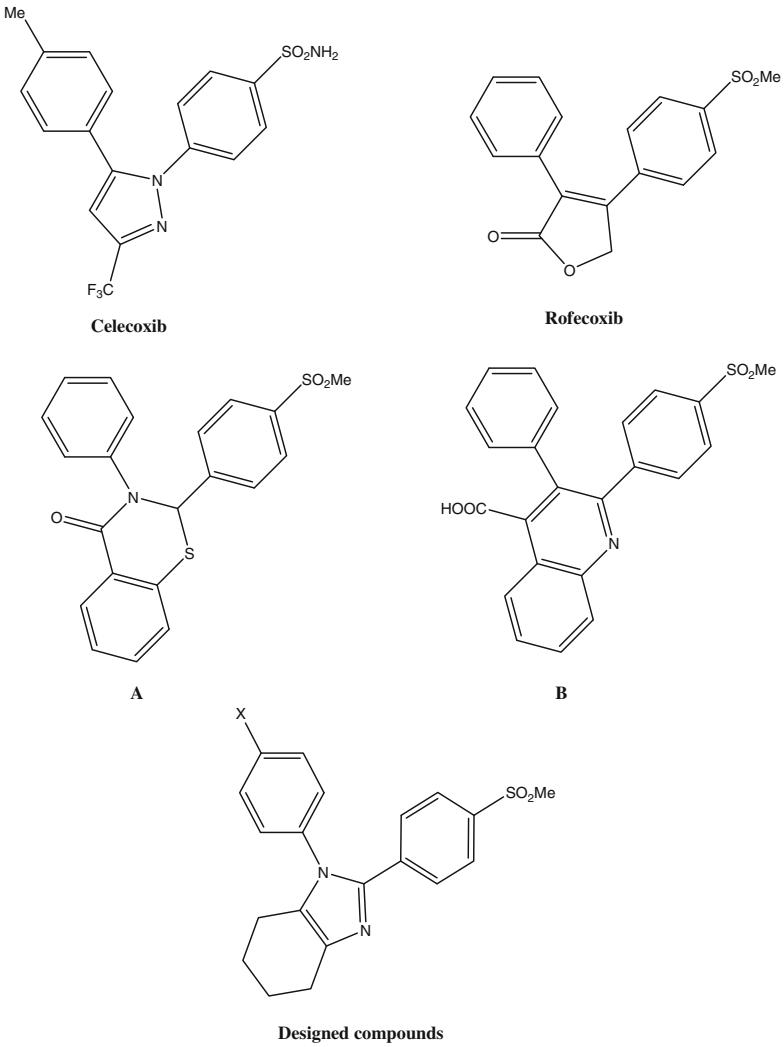


Fig. 1 Some representative examples of COXIBs (celecoxib and rofecoxib), 1,3-benzthiazine-4-one (**a**), quinoline-4-carboxylic acid (**b**) lead compounds and our 4,5,6,7-tetrahydro-1H-benzo[d] imidazole scaffolds

rofecoxib due to its adverse cardiovascular side effects (Dogné *et al*., 2005; Solomon, 2005) encourages the researchers to explore and evaluate new structural ring templates possessing COX inhibitory activity. In addition, recent studies have suggested that rofecoxib's adverse cardiac events may not be a class effect but rather related to its particular chemical structure (Dogne *et al*., 2006). For this reason novel scaffolds with high COX-2 inhibitory activity need to be found and evaluated for their biological activities. Recently, we reported a group of new diaryl-heterocyclic COX-2 inhibitors possessing a bicyclic central ring which exhibited highly selectivity for COX-2 inhibition. (Ghodsi *et al*., 2010; Zarghi *et al*., 2009). As part of our ongoing program to design new types of tricyclic selective COX-2 inhibitors, we now report the design, synthesis, cyclooxygenase inhibitory, and some molecular modeling studies of a new group of 1,2-diarylheterocycles possessing a 4,5,6,7-tetrahydro-1H-benzo[d]imidazole central ring and a COX-2 SO_2Me pharmacophore at the *para*-position of C-2 phenyl ring.

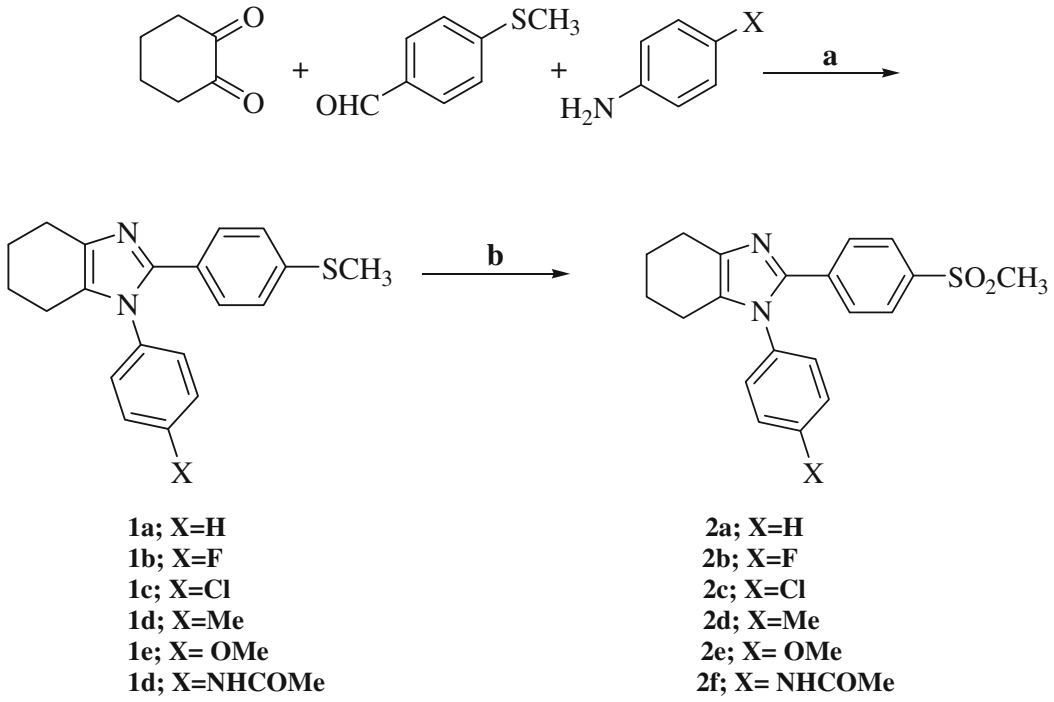
Results and discussions

Chemistry

The target 4,5,6,7-tetrahydro-1H-benzo[d]imidazole derivatives were synthesized via the route outlined in Scheme 1. Accordingly, 1,2-cyclohexanedione, 4-methylthiobenzaldehyde and aniline derivatives in the presence of excess amount of ammonium acetate were treated in microwave reactor at 180 watt power to obtain 1,2-diaryl-4,5,6,7-tetrahydro-1H-benzo[d]imidazoles (**1a–f**). Oxidation of the crude products **1a–f** using Oxone in THF/water afforded the 1-(4-substituted-phenyl)-2-(4-(methylsulfonyl)phenyl)-4,5,6,7-tetrahydro-1H-benzo[d] imidazoles **2a–f** (Yields: 12.7–15.5%).

Enzyme inhibitory activity

It is well established for the diarylheterocyclic class of COX-2 inhibitors that a *para*-methylsulfone substituent on



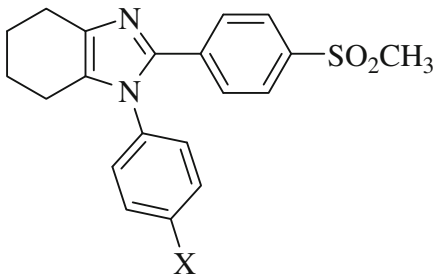
1a; X=H
1b; X=F
1c; X=Cl
1d; X=Me
1e; X= OMe
1d; X=NHCOMe

2a; X=H
2b; X=F
2c; X=Cl
2d; X=Me
2e; X= OMe
2f; X= NHCOMe

Scheme 1 Reagents and conditions: **a** NH_4OAc, ACOH, $CHCl_3$, microwave 180 watt, 20 min. **b** Oxone, THF, water, 25°C, 2 h

one of the phenyl rings is a requirement for good COX-2 potency and selectivity. Accordingly, a group of 1,2-diaryl-4,5,6,7-tetrahydro-1H-benzo[d]imidazoles (**2a–f**) containing a variety of substituents (H, F, Cl, Me, OMe, and NHCOMe) at the *para*-position of the N-1 phenyl ring, were synthesized to investigate the effect of these substituents on COX-2 selectivity and potency. The ability of the synthesized compounds to inhibit the COX-1 and COX-2 isozymes was determined using chemiluminescent enzyme assays (Table 1). In vitro COX-1/COX-2 inhibition studies showed that all compounds were selective inhibitors of the COX-2 isozyme with IC_{50} values in the highly potent 0.34–0.69 μM range, and COX-2 selectivity indexes (SI) in the 61.2–163.8 range. SAR data (IC_{50} μM 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 nature and size of substituent attached to N-1 phenyl ring influenced both selectivity and potency for COX-2 inhibitory activity. Our results indicated that the introduction of suitable substituents such as F (**2b**) and OMe (**2e**) at the *para*-position of N-1 phenyl ring increased both selectivity and potency for COX-2 inhibitory activity. However, compounds having Cl or NHCOMe substituents (**2c** and **2f**) showed less potency for COX-2 isozyme that may be explained by steric parameter. Based upon, compound **2a** containing unsubstituted N-1 phenyl ring showed better COX-2 inhibitory activity compared to compounds **2c** and **2f**. According to these results, 1-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4,5,6,7-tetrahydro-1H-benzo[d] imidazole (**2b**) was the most potent (IC_{50} = 0.34 μM), and selective (SI = 163.8), COX-2 inhibitor among the synthesized compounds. However, it was less selective than

Table 1 In vitro COX-1 and COX-2 enzyme inhibition data



Compound	X	IC_{50} (μM)[a]		COX-2 SI[b]
		COX-1	COX-2	
2a	H	56.5	0.55	102.7
2b	F	55.7	0.34	163.8
2c	Cl	61.6	0.67	91.9
2d	Me	40.1	0.62	64.6
2e	OMe	42.2	0.37	114.0
2f	NHCOMe	36.1	0.69	52.3
Celecoxib		24.3	0.06	405

[a] Values are mean values 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})

celecoxib (IC_{50} = 0.06 μM; SI = 405) in terms of COX-2 inhibitory activity. These data suggest that the compound **2b** should inhibit the synthesis of inflammatory prostaglandins via the cyclooxygenase pathway at sites of inflammation.

Docking study

The orientation of the highly potent and selective COX-2 inhibitors, 1-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4,5,6,7-tetrahydro-1H-benzo[d] imidazole **2b** in the COX-2 active site was examined by a docking experiment (Fig. 2). This molecular modeling showed that compound **2b** binds in the primary binding site such that the C-2 *para*-SO_2Me substituent inserts into the 2° pocket present in COX-2. One of the O-atoms of the SO_2Me moiety forms a H-bond with the NH of Arg^{513} (distance = 2.6 Å), whereas the other O-atom is close to the NH of His^{90} (distance = 3.8 Å). The N-3 atom of the central ring is also close to the NH of Arg^{120} and can form hydrogen bond (distance = 2.9 Å) with this amino acid. It was interesting to note that, the *para*-fluoro substituent of N-1 phenyl ring was forming a hydrogen bond with hydroxyl group (OH) of Tyr^{385} (distance < 5 Å which may explain the higher potency of compound **2b** compared with other analogs. These data also suggest that the compound **2b** should inhibit the synthesis of inflammatory prostaglandins via the cyclooxygenase pathway at sites of inflammation.

Conclusion

This study indicates that (i) the 4,5,6,7-tetrahydro-1H-benzo[d]imidazole moiety is a suitable scaffold (template) to design COX-1/-2 inhibitors, (ii) COX-1/-2 inhibition is sensitive to the type of substituent at C-2 phenyl ring, and (iii) 1-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4,5,6,7-tetrahydro-1H-benzo[d] imidazole (**2b**) exhibited good COX-2 inhibitory potency and selectivity.

Experimental

Materials

All reagents purchased from the Aldrich (USA) or Merck (Germany) Chemical Company and were used without further purifications.

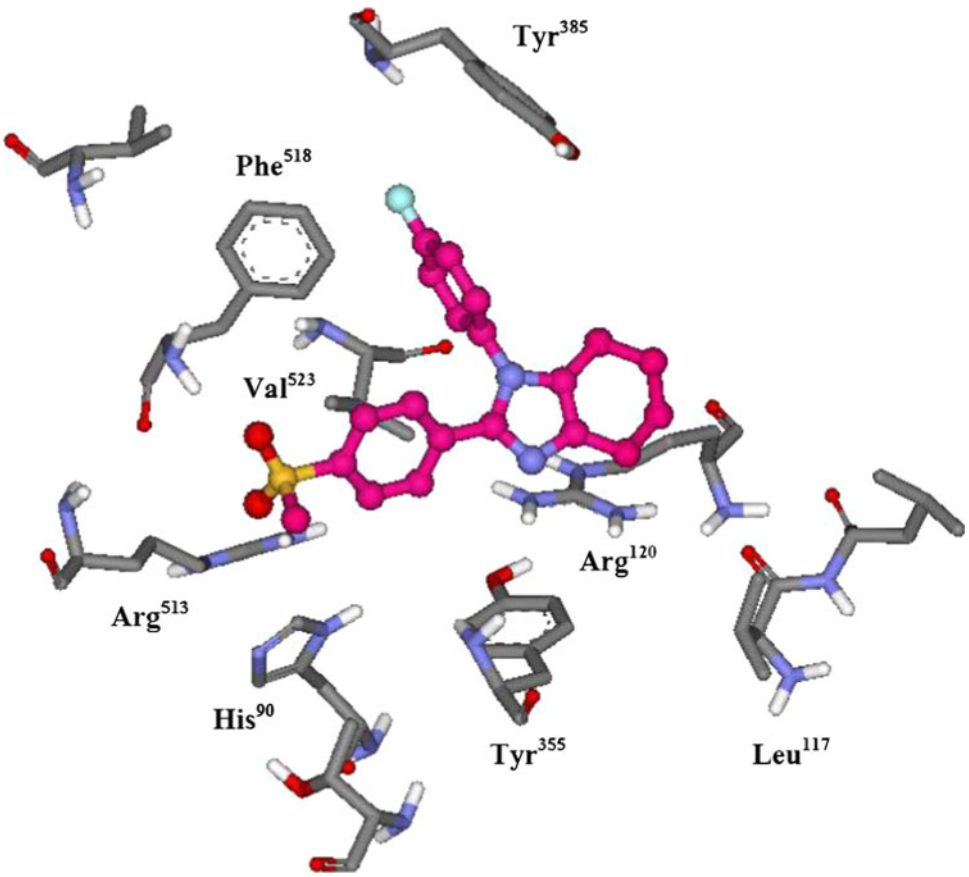


Fig. 2 Compound **2b**: 1-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4,5,6,7-tetrahydro-1H-benzo[d] imidazole docked in the active site of murine COX-2 isozyme. Hydrogen atoms of the amino acid residues have been removed to improve clarity

General

Melting points (mp) were determined using a Thomas Hoover capillary apparatus (Philadelphia, USA). Infrared spectra were acquired on a Perkin-Elmer 1420 ratio recording spectrometer. A Bruker FT-500 MHz instrument (Brucker Biosciences, Germany) was used to acquire ^{1}HNMR spectra; chloroform-D used as solvent. Coupling constant (*J*) values are estimated in hertz (Hz) and spin multiples are given as s (singlet), d (double), t (triplet), q (quartet), m (multiplet), and br (broad). The mass spectral measurements were performed on a 6410Agilent LCMS triple quadrupole mass spectrometer (LCMS) with an electrospray ionization (ESI) interface. Elemental analyses were carried out with a Perkin-Elmer Model 240-C apparatus (Perkin-Elmer, Norwalk, CT, USA). The results of the elemental analyses (C, H, N) were within ±0.4% of the calculated amounts.

General procedure for preparation of 1-(4-substituted-phenyl)-2-(4-(methyl sulfonyl) phenyl)-4,5,6,7-tetrahydro-1H-benzo[d] imidazoles (**2a–f**)

2 mmol 4-methylthiobenzaldehyde and 2.4 mmol of aniline derivatives were dissolved in 4 ml $CHCl_3$ and 6 ml glacial acetic acid and placed in microwave reactor with 180 watt power for 5 min. 2 mmol of 1,2-cyclohexanedione and excess amount of ammonium acetate were added subsequently and placed in microwave reactor for 15 min with 180 watt power. After cooling, aqueous ammonia solution was added to obtain neutral pH and then extraction with $CHCl_3$ was performed. The organic phase was washed three times with saturated sodium bicarbonate solution, dried with sodium sulfate, and evaporated in vacuo (Gelens *et al.*, 2006). The crude product was dissolved in THF and excess amount of Oxone in THF/water was added and stirred at room temperature overnight. THF was evaporated and the residue was extracted with chloroform. The organic phase was washed three times with saturated sodium bicarbonate solution and dried with sodium sulfate and concentrated in vacuo. The oily residue was purified by plate chromatography using ethyl acetate–hexane (5:1) as mobile phase (Yields: 12.7–15.5%).

*2-(4-(Methylsulfonyl)phenyl)-1-phenyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole (**2a**)*

Yield, 13.5%; white crystalline powder; mp 102–103°C; IR (KBr disk): υ (cm^{-1}) 1150, 1310 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 1.87–1.97 (m, 4H, CH_2), 2.40–2.43 (t, 2H, CH_2), 2.77–2.79 (t, 2H, CH_2), 3.06 (s, 3H, SO_2CH_3), 7.20–7.22 (m, 5H, phenyl), 7.58 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, $J = 8.6$ Hz), 7.80 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, $J = 8.6$ Hz); LC–MS (ESI) *m/z*: 353 (M + 1, 100); Anal. Calcd. for $C_{20}H_{20}N_2O_2S$: C, 68.16; H, 5.72; N, 7.95. Found: C, 68.25; H, 5.92; N, 8.01.

*1-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4,5,6,7-tetrahydro-1H-benzo[d] imidazole (**2b**)*

Yield, 13.5%; white crystalline powder; mp 117–118°C; IR (KBr disk): υ (cm^{-1}) 1150, 1310 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 1.87–1.95 (m, 4H, CH_2), 2.43 (t, 2H, CH_2), 2.78 (t, 2H, CH_2), 3.06 (s, 3H, SO_2CH_3), 7.19–7.22 (m, 4H, 4-fluorophenyl H_2–H_6), 7.58 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, $J = 8.6$ Hz), 7.80 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, $J = 8.6$ Hz); LC–MS (ESI) *m/z*: 371.1 (M + 1, 100); Anal. Calcd. for $C_{20}H_{19}FN_2O_2S$: C, 64.85; H, 5.17; N, 7.56. Found: C, 64.99; H, 5.01; N, 7.66.

*1-(4-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4,5,6,7-tetrahydro-1H-benzo[d] imidazole (**2c**)*

Yield, 14.7%; white crystalline powder; mp 135–136°C; IR (KBr disk): υ (cm^{-1}) 1160, 1320 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 1.87–1.93 (m, 4H, CH_2), 2.42 (t, 2H, CH_2), 2.77 (t, 2H, CH_2), 3.06 (s, 3H, SO_2CH_3), 7.16 (d, 2H, 4-chlorophenyl H_2 & H_6, $J = 8.6$ Hz), 7.47 (d, 2H, 4-chlorophenyl H_3 & H_5, $J = 8.6$ Hz), 7.57 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, $J = 8.6$ Hz), 7.81 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, $J = 8.6$ Hz); LC–MS (ESI) *m/z*: 387.4 (M + 1, 100); Anal. Calcd. for $C_{20}H_{19}ClN_2O_2S$: C, 62.09; H, 4.95; N, 7.24. Found: C, 62.25; H, 5.16; N, 7.22.

*1-(4-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4,5,6,7-tetrahydro-1H-benzo[d] imidazole (**2d**)*

Yield, 15.5%; white crystalline powder; mp 146–147°C; IR (KBr disk): υ (cm^{-1}) 1150, 1310 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 1.85–1.93 (m, 4H, CH_2), 2.42 (t, 2H, CH_2), 2.77 (t, 2H, CH_2), 3.05 (s, 3H, SO_2CH_3), 7.09 (d, 2H, 4-methylphenyl H_3 & H_5, $J = 8.3$ Hz), 7.29 (d, 2H, 4-methylphenyl H_2 & H_6, $J = 8.3$ Hz), 7.58 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, $J = 8.6$ Hz), 7.78 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, $J = 8.6$ Hz); LC–MS (ESI) *m/z*: 367.1 (M + 1, 100); Anal. Calcd. for $C_{21}H_{22}N_2O_2S$: C, 68.82; H, 6.05; N, 7.64. Found: C, 68.55; H, 6.12; N, 7.49.

*1-(4-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4,5,6,7-tetrahydro-1H-benzo [d] imidazole (**2e**)*

Yield, 13.3%; white crystalline powder; mp 108–109°C; IR (KBr disk): υ (cm^{-1}) 1150, 1300 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 1.86–1.94 (m, 4H, CH_2), 2.42 (t, 2H, CH_2),

2.83 (t, 2H, CH_2), 3.02 (s, 3H, SO_2CH_3), 3.91 (s, 3H, OCH_3), 7.01 (d, 2H, 4-methoxyphenyl H_3 & H_5, $J = 8.7$ Hz), 7.14 (d, 2H, 4-methoxyphenyl H_2 & H_6, $J = 8.7$ Hz), 7.66 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, $J = 8.6$ Hz), 7.82 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, $J = 8.6$ Hz); LC–MS (ESI) *m/z*: 383.1 (M + 1, 100); Anal. Calcd. for $C_{21}H_{22}N_2O_3S$: C, 65.94; H, 5.80; N, 7.32. Found: C, 66.15; H, 5.72; N, 7.65.

*1-(4-Acetamidopheny)-2-(4-(methylsulfonyl)phenyl)-4,5,6,7-tetrahydro-1H-benzo[d] imidazole (**2f**)*

Yield, 12.7%; white crystalline powder; mp 100–101°C; IR (KBr disk): υ (cm^{-1}) 1150, 1320 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 1.88–1.91 (m, 4H, CH_2), 2.22 (s, 3H, NHC-OCH_3), 2.41 (t, 2H, CH_2), 2.80 (t, 2H, CH_2), 3.06 (s, 3H, SO_2CH_3), 7.16 (d, 2H, 4-acetamidophenyl H_3 & H_5, $J = 8.6$ Hz), 7.60 (d, 2H, 4-acetamidophenyl H_2 & H_6, $J = 8.6$ Hz), 7.68 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, $J = 8.4$ Hz), 7.79 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, $J = 8.4$ Hz); LC–MS (ESI) *m/z*: 410.1 (M + 1, 100); Anal. Calcd. for $C_{22}H_{23}N_3O_3S$: C, 64.53; H, 5.66; N, 10.26. Found: C, 64.75; H, 5.32; N, 10.19.

In vitro COX inhibition assays

The ability of the test compounds listed in Table 1 to inhibit ovine COX-1 and COX-2 (IC_{50} value, μM) was determined using chemiluminescent enzyme assays kit (catalog number 560101, Cayman Chemical, Ann Arbor, MI, USA) according to our previously reported method (Zarghi *et al*., 2007).

Molecular modeling (docking) studies

Docking studies were performed using Autodock software Version 3.0. 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 (1cx2) and hydrogens were added. The ligand molecules were constructed using the Builder module and were energy minimized for 1,000 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. Searching is conducted within a specified 3D docking box using annealing based on the Monte Carlo method and MMFF94 molecular mechanics force field for 8,000 iterations. 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 (Kurumbail *et al*., 1996).

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References

Dogne JM, Hanson J, Supuran C, Pratico D (2006) Coxibs and cardiovascular side effects: from light to shadow. Curr Pharm Des 12:971–975

Dogné JM, Supuran CT, Pratico D (2005) Cardiovascular effects of the coxibs. J Med Chem 48:2251–2257

Fu JY, Masferrer JL, Seibert K, Raz A, Needleman P (1990) The induction and suppression of prostaglandin H_2 synthase (cyclooxygenase) in human monocytes. J Biol Chem 265:16737–16740

Gelens E, De Kanter FJJ, Schmitz RF, Sliedregt LAJM, Van Steen BJ, Kruse Chris G, Leurs R, Groen MB (2006) Efficient library synthesis of imidazoles using a multicomponent reaction and microwave irradiation. Mol Divers 10:17–22

Ghodsi R, Zarghi A, Daraie B, Hedayati M (2010) Design, synthesis and biological evaluation of new 2,3-diarylquinoline derivatives as selective cyclooxygenase-2 inhibitors. Bioorg Med Chem 18:1029–1033

Herschman HR (1996) Prostaglandin synthase 2. Biochem Biophys Acta 1299:125–140

Katori M, Majima M (2000) Cyclooxygenase-2: its rich diversity of roles and possible application of its selective inhibitors. Inflamm Res 49:367–392

Kawamori T, Rao CV, Seibert K, Reddy BS (1998) Chemopreventive activity of celecoxib, a specific cyclooxygenase-2 inhibitor, against colon carcinogenesis. Cancer Res 58:406–412

Kurumbail RG, Stevens AM, Gierse JK, McDonald JJ, Stegeman RA, Pak JY, Gildehaus D, Miyashiro JM, Penning TD, Seibert K, Isakson PC, Stallings WC (1996) Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents. Nature 384:644–648

Navidpour L, Shafaroodi H, Abdi KH, Amini M, Ghahremani MH, Dehpour AR, Shafiee A (2006) Design, synthesis and biological evaluation of substituted 3-alkylthio-4,5-diaryl-4H-1,2,4-triazoles as selective COX-2 inhibitors. Bioorg Med Chem 14:2507–2517

Nivsarkar M, Banerjee A, Padh H (2008) Cyclooxygenase inhibitors: a novel direction for Alzheimer's management. Pharmacol Rep 60:692–698

Penning TD, Tally JJ, Bertenshaw SR, Carter JS, Collins PW, Docter S, Graneto MJ, Lee LF, Malecha JW, Miyashiro JM, Rogers R, Rogier DJ, Yu SS, Anderson GD, Burton EG, Cogburn JN, Gregory SA, Koboldt CM, Perkins WE, Seibert K, Veenhuizen AW, Zhang YY, Isakson PC (1997) Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (SC-b58635, celecoxib). J Med Chem 40:1347–1365

Prasit P, Wang Z, Brideau C, Chan CC, Charlson S, Cromlish W, Ethier D, Evans JF, Ford-Hutchinson AW, Gauthier JY, Gordon R, Guay J, Gresser M, Kargman S, Kennedy B, Leblanc Y, Leger S, Mancini JO, Neil GP, Quellet M, Percival MD, Perrier H, Riendeau D, Rodger I, Tagari P, Therien M, Vikers P, Wong E, Xu L, Young RN, Zamboni R, Boyce S, Rupniak N, Forrest M,

Visco D, Patrick D (1999) The discovery of rofecoxib, [MK 966, Vioxx, 4-(4′-methylsulfonylphenyl)-3-phenyl-2(5H)-furanone], an orally active cyclooxygenase-2-inhibitor. Bioorg Med Chem Lett 9:1773–1778

Riendeau D, Percival MD, Brideau C, Dube CS, Ethier D, Falgueyret JP, Friesen RW, Gordon R, Greig G, Guay J, Girard Y, Prasit P, Zamboni R, Rodger IW, Gresser M, Ford-Hutchinson A, Young RN, Chan CC (2002) Etoricoxib (MK-0663): preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. J Pharmacol Exp Ther 296:558–566

Salimi M, Ghahremani MH, Naderi N, Amini M, Salimi E, Amanlou M, Abidi Kh, Salehi R, Shafiee A (2007) Design, synthesis and pharmacological evaluation of 4-[2-alkylthio-5-(4)-4-substituted phenyl)imidazole-4(5)yl]benzene sulfonamides as selective COX-2 inhibitors. Acta Pharm Sinica 28:1254–1260

Scholz M, Ulbrich HK, Dannhardt G (2008) Investigations concerning the COX/5-LOX inhibiting and hydroxyl radical scavenging potencies of novel 4,5-diaryl isoselenazoles. Eur J Med Chem 43:1152–1159

Smith WL, DeWitt DL (1996) Prostaglandin endoperoxide H synthases-1 and -2. Adv Immunol 62:167–215

Solomon DH (2005) Selective cyclooxygenase 2 inhibitors and cardiovascular events. Arthritis Rheum 52:1968–1978

Srinath P, Rao PN, Knaus EE, Suresh MR (2003) Effect of cyclooxygenase-2 (COX-2) inhibitors on prostate cancer cell proliferation. Anticancer Res 23:3923–3928

Takkouche B, Regueira-Mendez C, Etminan M (2008) Breast cancer and use of nonsteroidal anti-inflammatory drugs: a meta-analysis. J Natl Cancer Inst 100:1439–1447

Vane JR, Botting RM (1998) Anti-inflammatory drugs and their mechanism of action. Inflamm Res 47:S78–S87

Zarghi A, Najafnia L, Daraie B, Dadrass OG, Hedayati M (2007) Synthesis of 2,3-diaryl-1,3-thiazolidine-4-one derivatives as selective cyclooxygenase (COX-2) inhibitors. Bioorg Med Chem Lett 17:5634–5637

Zarghi A, Zebardast T, Daraie B, Hedayati M (2009) Design and synthesis of new 1,3-benzthiazinan-4-one derivatives as selective cyclooxygenase (COX-2) Inhibitors. Bioorg Med Chem 17: 5369–5373