ELSEVIER

Methanesulfonamide group at position-4 of the C-5-phenyl ring of 1,5-diarylpyrazole affords a potent class of cyclooxygenase-2 (COX-2) inhibitors☆

Sunil Kumar Singh,[a,][*] Saibaba Vobbalareddy,[a] Samala Shivaramakrishna,[a] A. Krishnamraju,[a] Shaikh Abdul Rajjak,[a] Seshagiri Rao Casturi,[b] Vangoori Akhila[b] and Yeleswarapu Koteswar Rao[a,][*]

[a]*Discovery Chemistry, Discovery Research-Dr. Reddy's Laboratories Ltd, Bollaram Road, Miyapur, Hyderabad 500 049, India*
[b]*Discovery Biology, Discovery Research-Dr. Reddy's Laboratories Ltd, Bollaram Road, Miyapur, Hyderabad 500 049, India*

Abstract—The effect of methanesulfonamide ($MeSO_2NH$) group on COX-2 inhibitory activity of 1,5-diarylpyrazole is described. While this group being at position-4 of the N^1-phenyl ring was found to be ineffective, its installation at position-4 of the C-5 phenyl ring offered several potent and selective inhibitors of COX-2 with IC_{50} as low as 30 nM.
© 2004 Elsevier Ltd. All rights reserved.

Two isoforms of prostaglandin synthase (cyclooxygenase) are COX-1 and COX-2.[1] These two isozymes have tissue specific expression and regulation, and entirely different biochemical roles to play.[2] The COX-1, a constitutive enzyme, expressed mainly in gastrointestinal (GI) tract, is responsible for the biosynthesis of prostaglandins (PGs) required for cytoprotection and platelet aggregation.[3] Therefore, interference with its normal function for a long time, leads to GI toxicity such as ulceration, bleeding and perforation.[4] In contrast, the COX-2, induced by pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukines, mitogens and endotoxins present in inflammatory cells during injury, plays a major role in the biosynthesis of PGs required for inflammatory cells to cause inflammation, pain and fever.[5] The conventional NSAIDs being effective inhibitors of both COX-1 and COX-2, down regulate the biosynthesis of both kinds of PGs (cytoprotective and inflammatory) in most of the tissues, and exhibit anti-inflammatory activity along with above described side effects.[6] Thus, the selective inhibi-

tion of the inducible COX-2 (the main cause of inflammation), sparing COX-1 (involved in house keeping function of cells and tissues), emerged as the basis of inventing new anti-inflammatory agents with greater GI safety. This new approach has created a new avenue for inflammation research. Several COX-2 inhibitors were discovered in this process, but the proof of concept came into act on humans only with the launch of two blockbuster drugs celecoxib[7] and rofecoxib[8] by Pfizer and Merck for the chronic treatment of rheumatoid and osteoarthritis. Recently, two more effective drugs viz. valdecoxib[9] and etoricoxib[10] have been launched in this area further validating the new concept of inflammatory medication. Apart from inflammation, COX-2 has become a target for other ailments like cancer[11] and Alzheimer's disease.[12] However, a recent report has appeared as a caution regarding the use of COX-2 inhibitors in cardiac patients.[13] But, by and large, this new concept of treating inflammatory diseases with COX-2 inhibitors has a great clinical advantage over the conventional NSAIDs, and still warrants a search for more efficacious drugs in this area. Additionally, the recent discovery of COX-3, is bringing a challenge ahead in this area.[14]

In contrast to the diverse chemical structures of conventional NSAIDs, the selective COX-2 inhibitors belong to only two major chemical classes: (a) the

Figure 1.

Scheme 1.

enzyme. Following this principle, many vicinal diaryl carbocycles[17] and heterocycles[18] have been successfully discovered. Lack of this rigid geometry could be the reason for conventional NSAIDs to be non-selective. Though several COXIBs (COX-2 inhibitors) have been introduced in the market, there still remains a need for the best in class medication in a view to completely eliminate the use of steroidal and narcotic drugs in severe to moderate inflammatory pains. Being involved in the design and synthesis of novel COX-2 inhibitors, we have recently been successful to introduce a hydroxymethyl group adjacent to the sulfonamide group of celecoxib which fetched many compounds with improved efficacy.[19] Our idea of introducing this hydrophilic group adjacent to sulfonamide was based on the assumption that these groups might preferably bind to the hydrophilic pocket of the differentiating COX-2 enzyme and cause effective inhibition. In further pursuance in this area, we wished to study the effect of methanesulfonamide ($MeSO_2NH$) group taken from the most effective COX-2 inhibitor, nimesulide[15] on 1,5-diarylpyrazole scaffold (Scheme 1). Penning et al.[7] also studied this pharmacophore as replacement of sulfonamide at position-4 of the N^1-phenyl ring during the discovery of celecoxib. But, the modification was found to be ineffective for both the enzymes. We took up this group to study its effect on COX-2 inhibition by installing at position-4 of the C-5 phenyl ring in combination with a phenyl ring at N^1 and a CF_3 group at position-3. To our surprise, the group demonstrated a dramatic effect on COX-2 inhibition. Therefore, we wish to report herein our finding through a brief structure–activity relationship (SAR) as the preliminary observation.
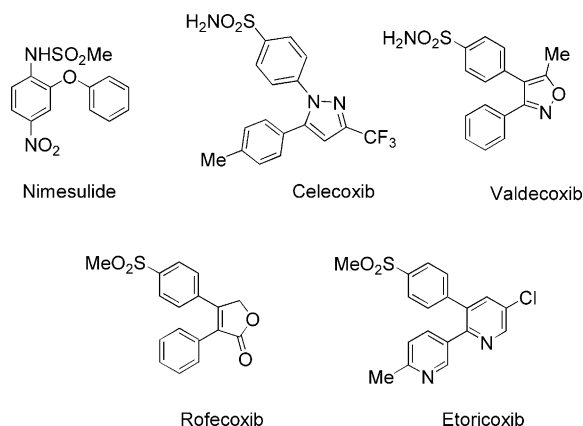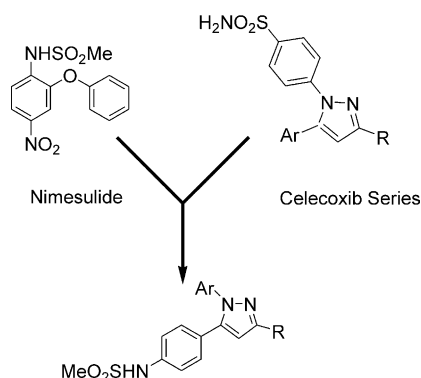
diphenyl ethers having acidic methanesulfonamide ($MeSO_2NH$) group as pharmacophore such as nimesulide,[15] and (b) the vicinal diarylheterocycles having 4-sulfamoyl (SO_2NH_2)/methanesulfonyl (SO_2Me)-phenyl as pharmacophore such as celecoxib,[7] valdecoxib,[9] rofecoxib[8] and etoricoxib[10] (Fig. 1).

The latter scaffold has become more acceptable due to the COX-2 enzyme–ligand co-crystal structure known for the structure based drug design[16] where two vicinal phenyl rings of the COX-2 inhibitors orient in a rigid cis-stilbene geometry and the 4-SO_2NH_2/SO_2Me-phenyl ring extends towards the hydrophilic pocket of COX-2

The synthetic route for the 1,5-diarylpyrazoles 3–43 reported here is depicted in Scheme 2. The essentially required 1-[4-(N-acetylaminophenyl)]-1,3-butanediones (1,3-diketones) 2 were synthesized in 95–98% yield by the Claisen condensation of 4-(N-acetylamino)acetophenone 1 with ethyl acetate/α-haloacetate using sodium hydride in dry DMF. This transformation was identified by the disappearance of the CH_3 protons of acetophenones present at ∼2.5 ppm and appearance of a D_2O exchangeable singlet at ∼6.5 ppm in the product. These 1,3-diketones 2 on coupling with appropriate
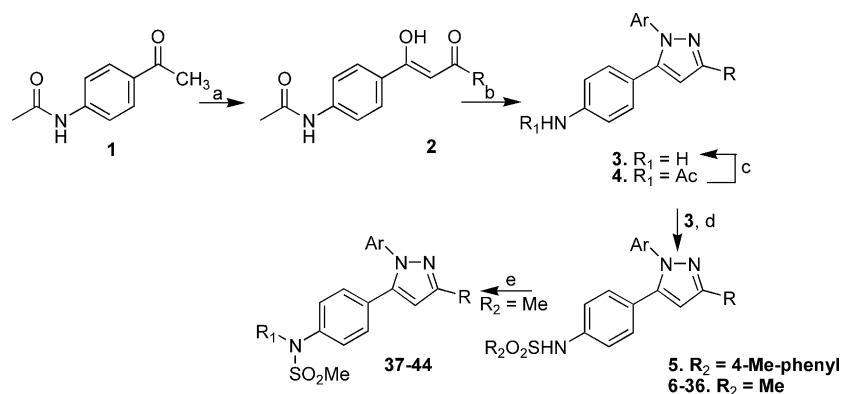
Scheme 2. Reagents and conditions: (a) RCO_2Et, NaH, DMF, −5–30 °C, 2–3 h. (b) $ArNHNH_2 \cdot HCl$, EtOH, reflux, 6–7 h. (c) 2N HCl, EtOH, reflux, 4–5 h. (d) For R_2 = 4-Me-phenyl, p-toluenesulfonylchloride and for R_2 = Me, methanesulfonylchloride, TEA, dichloromethane, 0–30 °C, 2–3 h. (e) Acid anhydride, TEA, dichloromethane, 0–5 °C, 1 h followed by reflux, 10–12 h.

aryl/heteroaryl hydrazine hydrochloride afforded a mixture of 1,5-diarylpyrazoles **3** and **4**.[19] The 1,3-diarylpyrazoles, formed in minor quantities, were easily eliminated by triturating the products with a mixture of ethyl acetate–toluene after column chromatography. In this transformation, the D_2O exchangeable singlet of the diketone became non-D_2O exchangeable C-4 proton of 1,5-diarylpyrazoles. The acetanilides **4** were hydrolyzed back to amines **3** by refluxing with ethanolic HCl which on treatment with *p*-toluenesulfonylchloride in presence of TEA afforded 1,5-diarylpyrazole **5** with a *p*-toluenesulfonamide group. Similarly, the treatment of **3** with methanesulfonyl chloride under above reaction condition yielded 1,5-diarylpyrazoles **6–36** having desired methanesulfonamide pharmacophore. While *N,N*-dimethanesulfonamide derivative **37** was obtained as a by-product during the synthesis of methanesulfonamide **10**, the *N*-acylated methanesulfonamides **38–43** were synthesized by the acylation of parent methanesulfonamide compounds **10** and **27** in very good yield (65–70%). All the compounds reported herein were characterized spectroscopically and their purity was assessed by HPLC/microanalyses.

All the 1,5-diarylpyrazoles, reported herein, were screened for the enzyme activity by TMPD method initially at 10 μM concentration. While source of COX-1 enzyme was the microsomal fraction of ram seminal vesicles, the COX-2 was obtained from the human recombinant, expressed in sf-9 cells infected with baculovirus. The promising compounds were further tested at lower concentrations, and the IC_{50}'s were calculated using non-linear regression analysis of the percent inhibitions.[20] Celecoxib and indomethacin were used as reference standards for COX-2 selective and non-selective inhibitors respectively. Compounds, selected on the basis of in vitro activity, were screened in the carrageenan-induced rat paw edema model at 30 mg/kg to assess their in vivo potency.[21]

As conceived, the 4-methanesulfonamide pharmacophore at position-4 of C-5 phenyl ring was normally maintained throughout the study. Diverse substitutions on the phenyl ring at N^1 along with a CF_3 group at C-3 were opted for the initial study and the in vitro data is presented in Table 1. The un-substituted N^1 phenyl ring was found to be less potent whereas 4-OMe-phenyl analogue **8**, though less COX-2 selective, was found to be highly potent (IC_{50}, 96 nM). Among halogens, 4-Cl-phenyl analogue **10** demonstrated the highest COX-2 potency (IC_{50}, 30 nM) and selectivity (SI, 520). While 3-F-phenyl analogue **16** showed reasonable COX-2 selectivity, 2-F-phenyl analogue **15** became non-selective and 3-Cl-phenyl analogue **17** turned out to be COX-1 selective. The 3,4-Cl_2-phenyl analogue **19** was found to be better than the corresponding 3,4-F_2-phenyl analogue **18**. Among amines, the 4-*N,N*-Me_2-phenyl **14** exhibited better potency and selectivity than 4-NHMe analogue

Table 1. In vitro activity of 1,5-diarylpyrazoles having methanesulfonamide pharmacophore

Compd	Ar	% Inhibition @ 10 μM[a] (IC_{50} in μM)[b]	
		COX-1[c]	COX-2[d]
6	Phenyl	0 (85.30)	100 (2.900)
7	4-NO_2-phenyl	34	0
8	4-OMe-phenyl	100 (0.40)	100 (0.096)
9	4-F-phenyl	6 (20.30)	65 (0.760)
10	4-Cl-phenyl	25 (15.60)	100 (0.030)
11	4-Br-phenyl	88 (4.90)	100 (0.230)
12	4-NH_2-phenyl	22 (31.60)	69 (2.640)
13	4-NHMe-phenyl	14	42
14	4-NMe_2-phenyl	85 (3.40)	100 (0.530)
15	2-F-phenyl	97	89
16	3-F-phenyl	49[b,e]	70[b,e]
17	3-Cl-phenyl	96	3
18	3,4-F_2-phenyl	32	59
19	3,4-Cl_2-phenyl	10[b,e]	70[b,e]
20		0	13
21		42	12
Celecoxib	—	0 (10.7)	100 (0.036)
Indomethacin	—	100 (0.067)	97 (7.810)

[a] Value from single experiment.
[b] Mean of three determinations with standard deviation of $< \pm 10\%$.
[c] COX-1 enzyme, obtained from the microsomal fraction of ram seminal vesicles.
[d] COX-2 enzyme, obtained from the human recombinant, expressed in sf-9 cells infected with baculovirus.
[e] Not determined.

13. Electron withdrawing phenyl, multisubstituted phenyl and heteroaryl rings at N^1, for example, **7**, **20** and **21** were found to be neither active nor selective. The effect of CHF_2 and CH_3 groups at C-3 is depicted in Table 2. The N^1 substituted analogues which were either inactive, poorly active or non-selective in conjugation with CF_3 (Table 1), did not show much improvement.

However, this change affected the activity of 4-Cl-phenyl derivative, for example, its CHF_2 (IC_{50}, 150 nM) and CH_3 (IC_{50}, 265 nM) analogues **27** and **28**, though slightly less potent, demonstrated very good COX-2 selectivity (SI, 420 and 377, respectively). Similarly, the 4-Br-phenyl analogue showed decrease in potency but increase in selectivity. Though the optimization of the

Table 2. In vitro activity of 1,5-diarylpyrazoles having methanesulfonamide pharmacophore

Compd	Ar	R	% Inhibition @ 10 μM[a] (IC_{50} in μM)[b]	
			COX-1[c]	COX-2[d]
22	Phenyl	CHF_2	22	31
23	Phenyl	CH_3	34	7
24	4-NO_2-phenyl	CH_3	40	0
25	4-F-phenyl	CHF_2	22[b,e]	62 (8.000)
26	4-F-phenyl	CH_3	0	25
27	4-Cl-phenyl	CHF_2	0 (63)	100 (0.150)
28	4-Cl-phenyl	CH_3	0 (100)	88 (0.265)
29	4-Br-phenyl	CH_3	10 (63)	100 (0.770)
30	2-F-phenyl	CHF_2	90[b,e]	89[b,e]
31	3-F-phenyl	CHF_2	97	67
32	2-Cl-phenyl	CHF_2	66	22
33	3,4-F_2-phenyl	CHF_2	11	36
34	3,4-Cl_2-phenyl	CHF_2	43[b,e]	71[b,e]
35		CH_3	0	13
36		CHF_2	100	0

[a–e] Same as in Table 1.

Table 3. In vitro activity of 1,5-diarylpyrazoles having other than methanesulfonamide pharmacophore

| Compd	Ar	R	R_1	R_2	% Inhibition @ 10 μM[a] (IC_{50} in μM)[b]	
					COX-1[c]	COX-2[d]
3	4-OMe-phenyl	CF_3	H	H	100 (0.072)	100 (0.129)
4a	4-OMe-phenyl	CF_3	H	$COCH_3$	51[b,e]	64[b,e]
4b	4-Br-phenyl	CF_3	H	$COCH_3$	100 (3.5)	87 (0.07)
4c	4-Br-phenyl	CH_3	H	$COCH_3$	9 (13.3)	80 (0.55)
5	4-Cl-phenyl	CF_3	H	SO_2-C_6H_4-Me	0[b,e]	70[b,e]
37	4-Cl-phenyl	CF_3	SO_2Me	SO_2Me	14	13
38	4-Cl-phenyl	CF_3	$COCH_3$	SO_2Me	0[b,e]	63[b,e]
39	4-Cl-phenyl	CF_3	COC_2H_5	SO_2Me	18[b,e]	65[b,e]
40	4-Cl-phenyl	CF_3	COC_3H_7	SO_2Me	0[b,e]	62[b,e]
41	4-Cl-phenyl	CHF_2	$COCH_3$	SO_2Me	66	17
42	4-Cl-phenyl	CHF_2	COC_2H_5	SO_2Me	100	36
43	4-Cl-phenyl	CHF_2	COC_3H_7	SO_2Me	100	42
4d		CF_3	H	$COCH_3$	59	0

[a–e] Same as in Table 1.
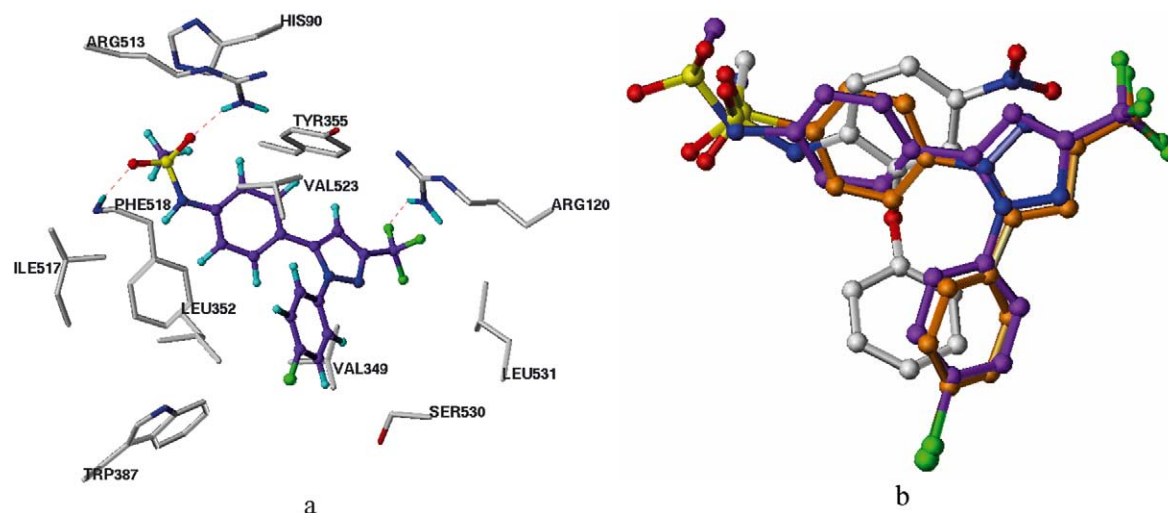
Figure 2. (a) Docking of compound **10** (ball and stick, carbon-violet) in the binding site of COX-2. The hydrogen bonding interactions are shown as broken lines. (b) Superposition of compound **10** (carbon-violet), SC-558 (carbon-orange) and nimesulide (carbon-gray) in the active site of COX-2. Ligands are shown in ball and stick rendering. Amino acid residues are not shown for clarity.

series with respect to substitutions at N^1 is in progress, we turned back to search few other similar groups as a substitute for the methanesulfonamide at position-4 of C-5 phenyl ring. The results are shown in Table 3. While the 4-aminophenyl analogue **3** was found to be highly potent but non-selective, its acetyl derivative **4a–c** (except **4d**) and 4-*p*-toluenesulfonamide derivative **5** were found to be reasonably active and moderately selective. The *N,N*-dimethanesulfonamide analogue **37**, in contrast, turned out to be inactive and non-selective. This could be due to the lack of H-bond donor feature in this molecule to bind the hydrophilic pocket of the COX-2 enzyme. While *N*-acylated methanesulfona-mides in conjugation with a CF_3 at position-3, for example, **38–40** were found to be COX-2 selective, their CHF_2 analogues **41–43** turned out to be COX-1 selec-tive. The preliminary in vivo activity of the potent compounds **10**, **27** and **28** in carrageenan-induced rat paw edema model at 30 mg/kg was found to be in the range of 45–65% whereas those of **38**, **39** and **40** was in the range of 60–67%. The higher in vivo potency of compounds **38**, **39** and **40** was explained by a pharma-cokinetic study performed on a model compound **38** which was proved to be the prodrug of compound **10**.[22]

Docking the potent COX-2 inhibitors **10**, **27**, **28** and nimesulide[15c] into COX-2 active site (6COX),[16] gener-ated various structures of different orientations.[23] The orientation and hydrogen bonding interactions of the most energetically favored conformation of **10** in COX-2 complex are shown in Figure 2a. The binding mode of these novel COX-2 inhibitors is similar to that of SC-558[16] and nimesulide[15c] and is shown in Figure 2b. The polar methanesulfonamide group of these compounds binds in a pocket formed by His-90, Arg-513, Gln-192 and Phe-518. The fluorine atoms of CF_3 acts as H-bond acceptor and form hydrogen bond with the side chain of Arg-120. Similarly, other substituted phenyl ring at N^1 of these compounds lie in a hydrophobic cavity lined by Tyr-385 and Trp-387. Thus, the reason for these com-pounds to be COX-2 selective, lies with their strong ability to form favorable van der Waals and electro-static interactions with COX-2 amino acid residues.

In conclusion, the 4-methanesulfonamide group at position-4 of the C-5 phenyl ring disclosed herein, serves as a novel pharmacophore to induce COX-2 inhibitory activity of 1,5-diarylpyrazoles, and has provided a few potent and selective inhibitors of COX-2 with IC_{50} up to 30 nM. This pharmacophore which is sensitive to the variations at different sites of 1,5-diarylpyrazoles, leaves an excellent opportunity for further studies to fetch many more potent COX-2 inhibitors. In addition, this group being amenable to suitable prodrugs, can play an important role during developmental studies.

Acknowledgements

References and notes

1. (a) Vane, J. R.; Bakhle, Y. S.; Botting, R. M. *Annu. Rev. Pharmacol. Toxicol.* **1998**, *38*, 97. (b) Picot, D.; Loll, P. J.; Garavito, R. M. *Nature* **1994**, *367*, 243.

2. (a) Wallace, J. L. *Am. J. Med.* **1999**, *107*, 11 S. (b) Xie, W.; Chipman, J. G.; Robertson, D. L.; Erikson, R. L.; Simmons, D. L. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 2692.

3. (a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature* **1976**, *263*, 663. (b) Whittle, B. J. R.; Higgs, G. A.; Eakins, K. E.; Moncada, S.; Vane, J. R. *Nature* **1980**, *284*, 271.

4. Allison, M. C.; Howatson, A. G.; Torrance, C. J.; Lee, F. D.; Russel, R. I. G. *N. Engl. J. Med.* **1992**, *327*, 749.

5. (a) Xie, W.; Robertson, D. L.; Simmons, D. L. *Drug Develop. Res.* **1992**, *25*, 249. (b) Vane, J. *Nature* **1994**, *367*, 215.

6. (a) Griswold, D. E.; Adams, J. L. Med. Res. Rev. 1996, 16, 181. (b) Meyer-irchrath, J.; Schror, K. Curr. Med. Chem. 2000, 7, 1121 and references cited therein.

7. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. M.; Zhang, Y. Y.; Isakson, P. C. J. Med. Chem. 1997, 40, 1347.

8. Prasit, P.; Wang, Z.; Brideau, C.; Chan, C.-C.; Charleson, S.; Cromlish, W.; Either, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y.; Gordon, R.; Guay, J.; Gresser, M.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Leger, S.; Mancini, J.; O'Neil, G. P.; Ouellet, M.; Percival, M. D.; Perrier, H.; Riendeau, D.; Rodger, I.; Tagari, P.; Therien, M.; Vickers, P.; Wong, E.; Xu, L.-J.; Young, R. N.; Zamboni, R.; Boyce, S.; Rupniak, N.; Forrest, M.; Visco, D.; Patrick, D. Bioorg. Med. Chem. Lett. 1999, 9, 1773.

9. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. J. Med. Chem. 2000, 43, 775.

10. Sorbera, L. A.; Castaner, R. M.; Silvestre, J.; Castaner, J. Drugs Fut. 2001, 26, 346.

11. (a) Vainio, H. Int. J. Cancer 2001, 94, 613. (b) Kalgutkar, A. S.; Zhao, Z. Curr. Drug. Targets 2001, 2, 79.

12. Pasinetti, G. M. J. Neurosci. Res. 1998, 54, 1.

13. Mukherjee, D.; Nissen, S. E.; Topol, E. J. J. Am. Med. Assoc. 2001, 286, 954.

14. Chandrasekharan, N. V.; Dai, H.; Roos, K. L.; Evanson, N. K.; Tomsik, J.; Elton, T. S.; Simmons, D. L. Proc. Natl. Acad. Sci. U.S.A. 2002, 99, 13371.

15. (a) Xavier, R. Drugs Today 1996, 32, 365. (b) Cignarella, G.; Vianello, P.; Berti, F.; Rossoni, G. Eur. J. Med. Chem. 1996, 31, 359. (c) Garcia-Nieto, R.; Perez, C.; Checa, A.; Gago, F. Rheumatology 1999, 38, 14.

16. Kurumbail, R. G.; Stevens, A. M.; Gierse, J. K.; McDonald, J. J.; Stegeman, R. A.; Pak, J. Y.; Gildehaus, D.; Miyashiro, J. M.; Penning, T. D.; Seibert, K.; Isakson, P. C.; Stallings, W. C. Nature 1996, 384, 644.

17. (a) Pinto, D. J. P.; Batt, D. G.; Pitts, W. J.; Petraitis, J. J.; Orwat, M. J.; Wang, S.; Jetter, J. W.; Sherk, S. R.; Houghton, G. C.; Copeland, R. A.; Covington, M. B.; Trzaskos, J. M.; Magolda, R. L. Bioorg. Med. Chem. Lett. 1999, 9, 919. (b) Li, J. J.; Norton, M. B.; Reinhard, E. J.; Anderson, G. D.; Gregory, S. A.; Isakson, P. C.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Seibert, K.; Zhang, Y.; Zweifel, B. S.; Reitz, D. B. J. Med. Chem. 1996, 39, 1846.

18. (a) Joo, Y. H.; Kim, J. K.; Kang, S. H.; Noh, M. S.; Ha, J. Y.; Chio, J. K.; Lim, K. M.; Lee, C. H.; Chung, S. Bioorg. Med. Chem. Lett. 2003, 13, 413. (b) Praveen, R. P. N.; Amini, M.; Li, H.; Habeeb, G.; Knaus, E. E. Bioorg. Med. Chem. Lett. 2003, 13, 2205. (c) Li, C. S.; Brideau, C.; Chan, C. C.; Savoie, C.; Claveau, D.; Charleson, S.; Gordon, R.; Greig, G.; Gauthier, J. Y.; Lau, C. K.; Riendeau, D.; Therien, M.; Wong, E.; Prasit, P. Bioorg. Med. Chem. Lett. 2003, 13, 597.

19. Singh, S. K.; Reddy, P. G.; Rao, K. S.; Lohray, B. B.; Misra, P.; Rajjak, S. A.; Rao, Y. K.; Venkateswarlu, A. Bioorg. Med. Chem. Lett. 2004, 14, 499.

20. Chan, C. C.; Boyce, S.; Brideau, C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J.; Ford-Hutchinson, A. W.; Forrest, M. J.; Gauthier, J. Y.; Gordon, R.; Gresser, M.; Guay, J.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Leger, S.; Mancini, J.; O'Neill, G. P.; Ouellet, M.; Patrick, D.; Percival, M. D.; Perrier, H.; Prasit, P.; Rodger, I.; Tagari, P.; Therien, M.; Vickers, P.; Visco, D.; Wang, Z.; Webb, J.; Wong, E.; Xu, L. J.; Young, R. N.; Zamboni, R.; Riendeau, D. J. Pharmacol. Exp. Ther. 1999, 290, 551.

21. Winter, C. A.; Risley, E. A.; Nuss, G. W. Proc. Soc. Exp. Biol. Med. 1962, 111, 544.

22. Unpublished results.

23. All calculations were performed on Sybyl6.9 Octane 2 workstation. Molecules were sketched and minimized using MMFF94 force field and charges. Docking study was carried out using SC-558 bound 6COX (monomer) crystal structure with FlexX module of Sybyl. The active site was defined as 6.5 Å around the ligand. After docking, the ligands were merged in the binding site of COX-2, and energy minimization of this complex was performed using above method.