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Polar substitutions in the benzenesulfonamide ring of celecoxib afford a potent 1,5-diarylpyrazole class of COX-2 inhibitors☆

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Abstract—Several chemical modifications in the N^1-benzenesulfonamide ring of celecoxib are presented. The series with a hydroxymethyl group adjacent to the sulfonamide was found to be the most potent modification that yielded many compounds selectively active against COX-2 enzyme in vitro.

The conventional non-steroidal anti-inflammatory drugs (NSAIDs) exert their effect by inhibiting PGH synthase (Cyclooxygenase/COX, responsible for arachidonic acid metabolism) leading to synthesis of prostaglandin (PG), a major mediator of inflammation.[1] Two isoforms of this enzyme were identified early in the last decade. While constitutive COX-1 is responsible for the production of PGs involved in physiological functions such as gastric cytoprotection, renal homeostasis and platelate aggregation, the inducible COX-2 (produced by cytokines, mitogens and endotoxins in inflammatory cells) is responsible for the elevated production of prostaglandins during inflammation, causing pain, fever and inflammatory disorders.[2] The conventional NSAIDs, being non selective for these two differently acting enzymes, completely block the overall production of prostaglandins and elicit analgesic, antipyretic in addition to anti-inflammatory activities. But their long term use often disrupts the beneficial prostaglandin regulated processes[3] and causes life threatening gastrointestinal ulcers thereby limiting their therapeutic potential.[4]

Though the search for safer NSAIDs has continued over the years with little success, it took a new turn when selective COX-2 inhibition was thought to have exclusive control over inflammation process, leaving other tissues unharmed even during chronic treatment.[5] Proof of this new concept was soon realized when selective COX-2 inhibitors, celecoxib[6] and rofecoxib[7] were introduced on the market respectively by Pfizer and Merck. Soon after their success, other efficacious COX-2 inhibitors such as valdecoxib,[8] parecoxib sodium[9] and etoricoxib[10] entered the segment as second generation therapy. The popularity of COX-2 inhibitors as anti-inflammatory agents coupled with their increasing application in other ailments such as cancer (colon, lung, breast, prostate, bladder, pancreatic, skin and gastric),[11] and Alzheimer's disease[12] is still attracting fresh scientific input in this area.

The two major chemical classes of COX-2 inhibitors on the market are: the acidic methanesulfonamide ($MeSO_2NH$) containing diphenyl ethers such as nimesulide **1**[13] and sulfonamide (SO_2NH_2) or methylsulfonyl (SO_2Me) containing vicinal diarylheterocycles such as celecoxib **2a**,[6] valdecoxib **4**,[8] rofecoxib **3**[7] and etoricoxib **5**[10] (Fig. 1).

Though many diaryl heterocycles have been pursued by different research groups while designing COX-2 inhibitors, we focused our study on hitherto unreported chemical modification of the N^1-benzenesulfonamide core of celecoxib, a multi billion dollar drug in this area. By analogy with the enzyme-ligand co-crystal structure

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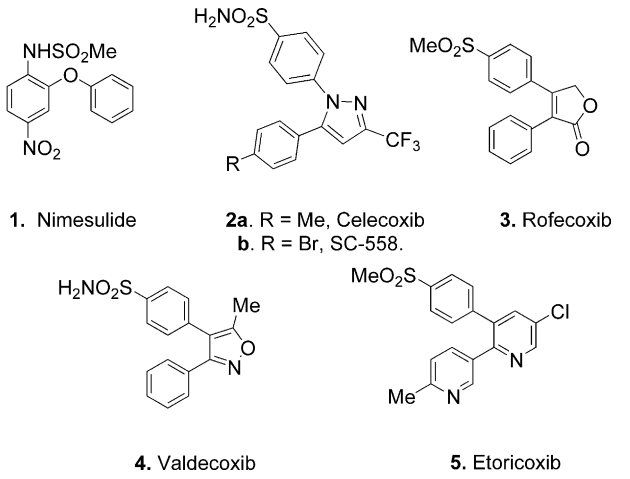
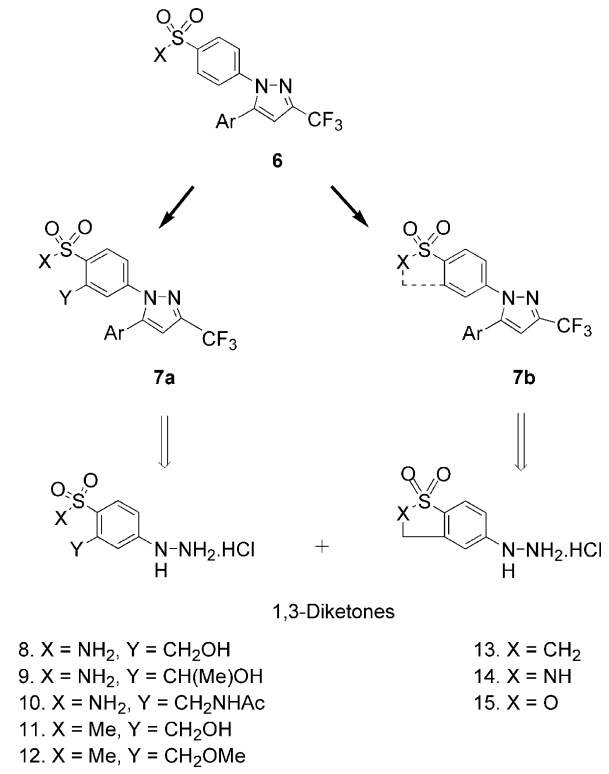


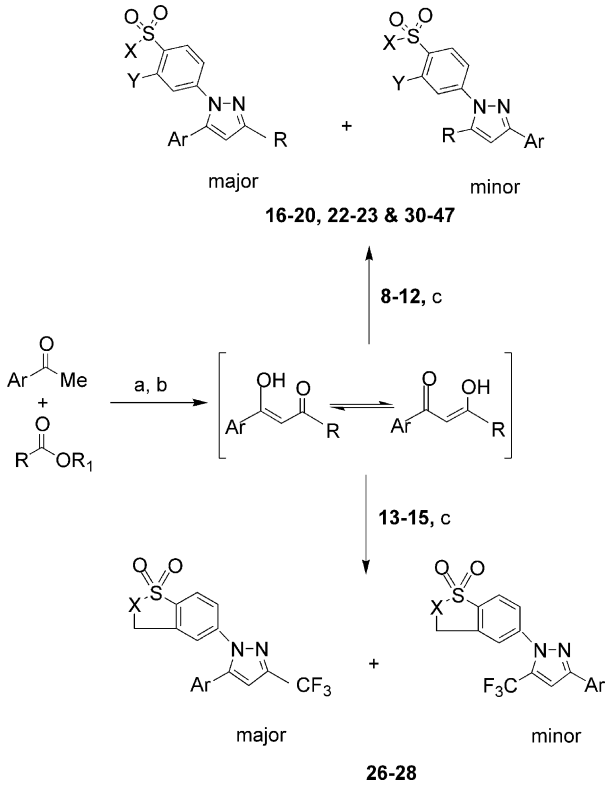
Figure 1.

describing the binding of the benzenesulfonamide group in the secondary COX-2 pocket,[14] we wished to study whether additional substitution on this group would lead to better COX-2 selectivity. To the best of our knowledge when we initiated the project, there was no such report wherein the benzenesulfonamide ring at N^1 was additionally substituted with polar groups such as hydroxyalkyl or acylaminoalkyl which could provide additional steric, electronic or even polar interactions with the amino acid residues of the COX-2 enzyme responsible for selectivity.[15] Nor did we come across any report where the entire benzenesulfonamide group had been replaced by fused heterocycles in which sulfonyl (–SO_2–) or sulfamoyl (–$HNSO_2$–) group forms a part of the ring. Taking these aspects into consideration, we synthesized two major classes of novel 1,5-diarylpyrazoles, one by introducing hitherto unreported groups such as CH_2OH, MeCHOH, CH_2NHAc and their derivatives adjacent to SO_2NH_2 and SO_2Me (**7a**) and the other by replacing the benzenesulfonamide group by fused heterocycles such as 1,1-dioxo 2,3-dihydrobenzo[*b*]thiophen-5-yl, 1,1-dioxo 2,3-dihydrobenzo[*d*]-isothiazol-5-yl and 1,1-dioxo-3*H*-benzo[*c*][1,2]oxathiol-5-yl (**7b**), keeping other substitutions intact as in celecoxib analogues (Scheme 1).

Disconnection for synthesis of chemically modified 1,5-diarylpyrazoles is depicted in Scheme 1. The basic requirement for the synthesis of these pyrazoles was the availability of the suitably modified phenyl hydrazine hydrochlorides **8**–**15**. The multi step synthesis of these compounds will be discussed separately.[16] Simple coupling of the latter with appropriate 1,3-diketones in absolute ethanol under heating condition afforded the desired diarylpyrazoles (Scheme 2).[17] Though the regiomeric bias was normally in favor of 1,5-diarylpyrazoles, the minor undesired regio isomers were easily eliminated by triturating the product with a mixture of ethyl acetate–toluene after column chromatography. The 1,3-diketones were synthesized by Claisen condensation[18] using appropriate acetophenones and ethyl trifluoroacetate and slightly modified conditions involving sodium hydride in dry DMF at a temperature of −5–30 °C.[19] The 1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazole-

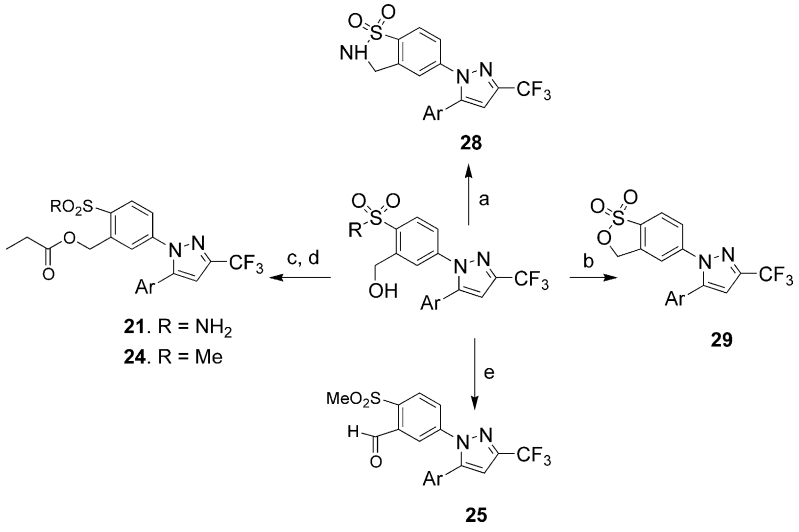


Scheme 1.



Scheme 2. (a) NaH/DMF, −5–30 °C, 4–5 h. (b) 2N HCl. (c) Absolute ethanol, 50–60 °C, 12 h.

5-yl pyrazole **28** was alternatively synthesized from compound **33** by sequential treatment with carbon tetrabromide-triphenyl phosphine[20] and aqueous $NaHCO_3$ (Scheme 3). The dioxo 3*H*-benzo[*c*][1,2]oxathiol-5-yl



Scheme 3. (a) (i) Ar = 4-OMe-phenyl, R=NH_2, TPP/CBr_4, CH_2Cl_2, room temperature, 14 h. (ii) aq $NaHCO_3$, room temperature, 0.5 h. (b) (i) Ar = 4-OMe-phenyl, R=NH_2, acetonyl acetone, $SOCl_2$, EtOH, reflux, 2–3 h. (ii) aq NaOH, Bu_4NBr, CH_2Cl_2–H_2O (75:25), room temperature, 2 h. (c) For **21**, Ar=4-Me-phenyl, R=NH_2, propionic anhydride, propionic acid, pyridine, room temperature, 12–14 h. (d) For **24**, Ar = 4-Me-phenyl, R=Me, propionic anhydride, TEA, CH_2Cl_2, reflux, 4–5 h. (e) Ar=4-OMe-phenyl, R= Me, PCC, CH_2Cl_2, room temperature, 2–3 h.

pyrazole **29** was prepared from **33** after converting to 2,5-dimethylpyrrole-1-sulfonyl derivative and treating it with aq NaOH in CH_2Cl_2–H_2O (75:25) in presence of Bu_4NBr (TBAB). While *O*-propionyl derivative **24** was prepared by refluxing a corresponding hydroxymethyl compound (not reported here) with propionic anhydride in CH_2Cl_2 in presence of TEA, compound **21** was synthesized by the selective O-acylation of **16** using propionic anhydride and pyridine in propionic acid solvent. Aldehyde **25** was obtained by PCC oxidation of hydroxymethyl group of compound **22** in CH_2Cl_2 at room temperature (Scheme 3). The methylsulfonyl (SO_2Me) derivative **38** was synthesized by H_2O_2 oxidation of methylsulfanyl (SMe) analogue **36** in acetic acid at 70–80 °C. All the compounds reported herein were characterized spectroscopically.[21] Additionally, the structure of the most potent series was confirmed by single crystal X-ray diffraction studies of one of the *O*-acylated derivative.[22]

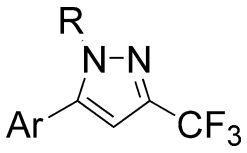
Initially, all the compounds were screened for their ability to inhibit recombinant human COX-2 enzyme, expressed in sf-9 cells infected with baculovirus, at 100 μM concentration. The compounds exhibiting more than 60% COX-2 inhibition were screened for inhibition of COX-1 enzyme, obtained from microsomal fraction of Ram Seminal Vesicles. The enzyme activity was measured by the TMPD method and IC_{50}s were calculated using non-linear regression analysis of percent inhibitions.[23]

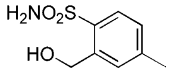
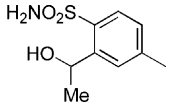
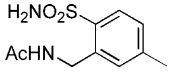
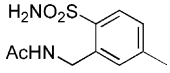
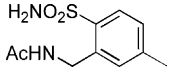
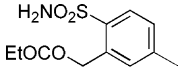
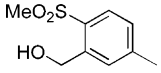
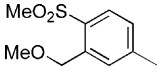
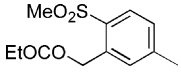
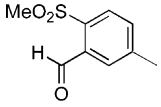
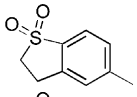
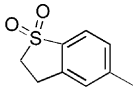
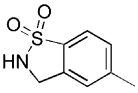
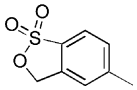
Compound **16**, incorporating our first modification wherein the hydroxymethyl group was introduced adjacent to sulfonamide in celecoxib (Table 1), was found to be COX-2 selective. Though the COX-2 inhibitory potency (0.76 μM) of this compound was not at par with celecoxib (0.036 μM), it was still considered sufficiently active to warrant further studies. A few other groups, e.g. in compounds **17**–**25** were also studied at this position but they were not as effective as compound **16**. It was observed that only such groups which were capable of forming additional hydrogen bonds (either donor or acceptor) with amino acid residues of the COX-2 secondary pocket, exhibited COX-2 selectivity, e.g. acetylaminomethyl derivatives **18**–**19**, ethoxycarbonylmethyl derivative **21** and hydroxymethyl derivative **22** showed considerable COX-2 selectivity whereas others, e.g. **23**–**25** were found almost inactive or nonselective. In the second series where benzenesulfonamide group was completely replaced by fused heterocycles such as 1,1-dioxo 2,3-dihydrobenzo[*b*]thiophen-5-yl in compounds **26**–**27**, 1,1-dioxo 2,3-dihydrobenzo[*d*]isothiazol-5-yl in compound **28** and 1,1-dioxo-3*H*-benzo[*c*][1,2]oxathiol-5-yl in compound **29** led to COX-1 selectivity. This is presumably because of the larger volume of these N^1-substituted groups which may not be able to enter the COX-2 pocket.

Since hydroxymethyl group introduction as observed in compound **16** was found to be an effective modification, a few analogues of this compound in which the C-5 phenyl substituent was varied, were also synthesized. The in vitro COX-1/COX-2 inhibitory activity of these analogues is depicted in Table 2. The 4-OMe analogue **33** and 4-SMe analogue **36** were found to be the most potent among ethers and thioethers. The COX-2 potency decreases with the introduction of either bulkier, hydrophilic or electron withdrawing groups at this position which is clearly shown by compounds **30**, **31**, **34**, **37**, **35** and **38**. The potency of compounds halogenated at this position was found to be in the reverse order of electronegativity and 4-Br analogue **41** was found to be the best among all. Compounds substituted at position-3 of this phenyl ring were observed to be almost equipotent to those substituted at position-4, e.g. 3-Me analogue **44** exhibited similar activity as compound **16**, but position-2 behaved quite differently as 2-OMe analogue **47** lost potency when compared to compound **33**.

Docking the potent COX-2 inhibitors **33**, **36** and **2b** (SC-558)[14] into COX-2 active site (6COX) generated

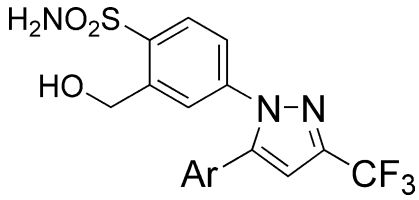
Table 1. 1,5-Diarylpyrazoles with additionally substituted benzenesulfonamide and methylsulfonyl groups



Compd	R	Ar	IC_{50} in μM[a]	
			COX-1	COX-2
16		4-Me-phenyl	278	0.76
17		4-SMe-phenyl	6[b]	50[b]
18		4-OMe-phenyl	100	2.8
19		4-Cl-phenyl	100	5
20		4-Me-phenyl	4.62	6.85
21		4-Me-phenyl	34.6	0.57
22		4-OMe-phenyl	300	3.2
23		4-SMe-phenyl	0[b]	45[b]
24		4-Me-phenyl	9[c]	0[c]
25		4-OMe-phenyl	92[b] [c,d]	100[b] 44[c]
26		4-OMe-phenyl	86[b]	36[b]
27		4-Me-phenyl	90[b]	10[b]
28		4-OMe-phenyl	85[b]	12[b]
29		4-OMe-phenyl	92[b]	36[b]
Celecoxib	—	—	10.7	0.036

[a] Mean of three determinations with standard deviation of $< \pm 10\%$.
[b] % Inhibition at 100 μM concentration (average of two experiments with standard deviation $< \pm 12\%$).
[c] % Inhibition at 10 μM concentration (average of two experiments with standard deviation $< \pm 12\%$).
[d] Not determined.

Table 2. 1,5-Diarylpyrazoles with hydroxymethyl group adjacent to sulfonamide



Compd	Ar	IC_{50} in μM[a]	
		COX-1	COX-2
16	4-Me-phenyl	278.0	0.760
30	4-Et-phenyl	500.0	1.380
31	4-iso-Butyl-phenyl	4[c]	14[c]
32	Phenyl	1085.0	3.450
33	4-OMe-phenyl	63.0	0.365
34	4-OEt-phenyl	135.0	0.901
35	4-OH-phenyl	0[b]	19[b]
36	4-SMe-phenyl	59.7	0.235
37	4-SEt-phenyl	300.0	51.200
38	4-SO_2Me-phenyl	68[c]	29[c]
39	4-F-phenyl	500.0	1.990
40	4-Cl-phenyl	336.0	0.712
41	4-Br-phenyl	230.0	0.592
42	3-F-phenyl	1000.0	7.050
43	3-Cl-phenyl	465.0	1.950
44	3-Me-phenyl	327.0	0.728
45	2-F-phenyl	500.0	3.300
46	2-Cl-phenyl	512.0	6.300
47	2-OMe-phenyl	1150.0	28.600

[a] Mean of three determinations with standard deviation of $< \pm 10\%$.
[b] % Inhibition at 10 μM concentration (average of two experiments with standard deviation $< \pm 12\%$).
[c] % Inhibition at 100 μM concentration (average of two experiments with standard deviation $< \pm 12\%$).

various structures with different orientations. The orientation and hydrogen bonding interaction of the most energetically favored conformation in the COX-2 complex is depicted in Figure 2. The hydroxymethyl substituted benzenesulfonamide group of compounds **33** and **36** enters the COX-2 secondary pocket in a similar manner as that of **2b** (SC-558) showing little variation in hydrogen bonding pattern (Fig. 2b). While hydrogen bonding interactions of the sulfonamide in **2b** (SC-558) with COX-2 residues are His^{90} (NH....O=S, 3.370 Å), Gln^{192} (C=O....H–N, 3.174 Å) and Phe^{518} (NH....O=S, 2.947 Å), that for compound **33** are His^{90} (N....H–O, 2.880 Å), Gln^{192} (C=O....H–N, 3.069 Å) and Phe^{518} (NH. . ..O=S, 2.921 Å) and for compound **36** are Ser^{353} (NH. . ..H–O, 2.804 Å) and Leu^{352} (C=O. . ..N–H, 2.919 Å). Though there is no intramolecular hydrogen bond observed in compound **36** in the free state, it becomes significant between the hydroxyl group of CH_2OH and one of the oxygens of the sulfonamide in its complex (Fig. 2a). In addition, one of the nitrogen atoms of its pyrazole ring also forms a hydrogen bond with Arg^{120} (NH. . .N^2, 3.649 Å). In general, the hydroxymethyl group introduced in these inhibitors competes with SO_2NH_2 in forming hydrogen bonds with His^{90} and binds in the polar region formed by His^{90}, Gln^{192} and Arg^{513} through electrostatic interaction. The fluorine atoms of CF_3 act as acceptors and form hydrogen bonds with the side chain of Arg^{120}. The CF_3 group of

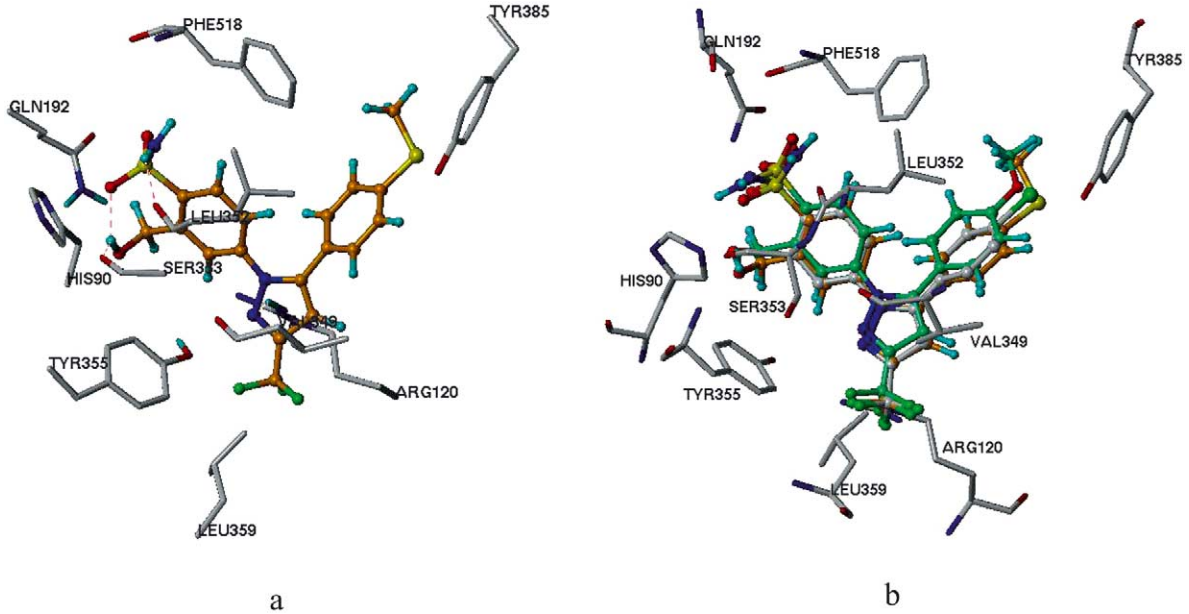


Figure 2. (a) Compound **36**-COX-2 complex. The hydrogen bonding interactions are shown as broken lines. The ligand is shown in ball and stick rendering (C-Orange). (b) Superposition of compound **33** (C-Green), **36** (C-Orange) and **2b** (SC-558, C-gray) in the binding site of COX-2. All protein hydrogens are removed for clarity.

all these compounds invariably lies in a pocket formed by Met^{113}, Val^{116}, Arg^{120}, Val^{349}, Tyr^{355}, Leu^{359}, Val^{523} and Leu^{531} through hydrophobic interactions. Similarly, the substituted phenyl ring at C-5 of these compounds lies in a hydrophobic cavity formed by Phe^{381}, Leu^{384}, Tyr^{385}, Trp^{387}, Phe^{513} and Ser^{530}. Thus, the reason why hydroxymethyl substituted compounds are COX-2 selective may be related to their ability to form favorable Van der Waals and electrostatic interactions with COX-2 amino acid residues. And the superior COX-2 selectivity of compound **36** over **33** can be attributed apart from above facts to their respective interaction energy of −395.000 kcal/mol and −393.937 kcal/mol perhaps due to the higher polarizability of the sulfur atom giving rise to stronger Van der Waals interactions with side chain of Tyr^{385}, Trp^{387} and Phe^{513}.

In conclusion, among the several modifications in the N^1-benzenesulfonamide ring of celecoxib, the one with a hydroxymethyl group adjacent to the sulfonamide modifies the earlier belief that only *para* mono substituted arylsulfonamide or methylsulfonyl groups are necessary for COX-2 selectivity. An important outcome of the study was the observation that the smaller groups (hydrogen bond donors) which are capable of forming additional hydrogen bonds with amino acid residues of the secondary COX-2 pocket show COX-2 selectivity thereby providing ample scope for designing more efficacious COX-2 inhibitors involving benzenesulfonamide ring.

Acknowledgements

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16. Unpublished results.
17. Representative procedure for compound **16**. 4-Hydrazino-2-hydroxymethyl-1-benzenesulfonamide **8**[16] (2.0 g, 9.21 mmol) was dissolved in MeOH (10 mL) under argon atmosphere and acidified to pH 1–2 using IPA-HCl. The reaction mixture was stirred at room temperature for 0.5 h and solvent was completely removed under high vacuum at 40–50 °C. The solid obtained was dissolved in absolute alcohol (15 mL) and an ethanolic solution of 4,4,4-trifluoro-1-(4-methylphenyl)-1,3-butanedione (2.01 g, 8.75 mmol) was added at room temperature. After heating the reaction mixture at 50–60 °C for 10–12 h under argon atmosphere, it was cooled to room temperature and concentrated. The residue stirred with ice cold water was extracted with ethyl acetate and the combined organic layer was washed with brine and water. The organic layer was dried and the residue obtained after solvent evaporation was purified by column chromatography using ethyl acetate–petroleum ether (30:70). The product obtained was finally triturated with ethyl acetate-toluene to afford compound **16** as a colorless solid (2.50 g, 70%). Mp 178–180 °C. IR (KBr) 3326, 3250, 1605, 1476 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.00 (d, $J=8.6$ Hz, 1H), 7.65 (d, $J=2.0$ Hz, 1H), 7.26 (d, $J=4.8$ Hz, 1H), 7.20 (d, $J=5.2$ Hz, 2H), 7.16 (d, $J=7.8$ Hz, 2H), 6.75 (s, 1H), 5.45 (bs, 2H), 5.05 (d, $J=4.6$ Hz, 2H), 2.60 (bs, 1H), 2.40 (s, 3H). MS 411 (M^+), 393, 376, 330. HPLC (System 1) 98.3%. Anal. ($C_{18}H_{16}F_3N_3O_3S$) C, H, N.
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19. Representative procedure for 1, 3-Diketones. 4′-Methylacetophenone (5.0 g, 37.3 mmol) was dissolved in 25 mL of dry DMF under argon atmosphere and 60% NaH (1.86 g, 46.6 mmol) was added in three lots maintaining the temperature between −5 and 0 °C. After stirring at this temperature for 0.5 h, ethyl trifluoroacetate (6.62 g, 46.6 mmol) was injected and the reaction mixture was allowed to stir at ambient temperature for 4–5 h. The reaction mixture was poured into ice water, acidified with 2N HCl and extracted with ethyl acetate. The combined organic layer was washed with water, dried and evaporated leaving a residue which was washed with pet-ether, decanted, dried under high vacuum to provide a gummy mass of 4,4,4-trifluoro-1-(4-methylphenyl)-1,3-butanedione (7.72 g, 90%) which was used as such in the final step.[6] IR (Neat) 3340, 1611, 1407 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.84 (d, $J=8.2$ Hz, 2H), 7.30 (d, $J=8.0$ Hz, 2H), 6.54 (s, 1H), 2.43 (s, 3H). MS 230 (M^+), 215, 161, 119, 91.
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21. Melting points (uncorrected) were determined on Veego apparatus. IR, ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz), Mass spectra and Elemental analysis (C, H, N) were respectively obtained using Perkin–Elmer FT-IR 1650, Varian Gemini 200, HP-5989A and Perkin–Elmer 2400 series II CHN-O analyzer. The purity of the final compounds was determined by HPLC using either "System 1" consisting column, Hichrom RPB (250 mm) and mobile phase, 0.01 M KH_2PO_4/CH_3CN (50:50) or, "System 2" comprising column, Intersil ODS 3V (250 mm) and mobile phase, H_2O/CH_3CN (50:50), both running at 1.0 mL/min with UV detection at respective λ max.
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