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Synthesis and biological evaluation of 2,3-diarylpyrazines and quinoxalines as selective COX-2 inhibitors☆,★

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Abstract—Several 2,3-diaryl pyrazines and quinoxalines with 4-sulfamoyl (SO_2NH_2)/methylsulfonyl (SO_2Me)-phenyl pharmacophores have been synthesized and evaluated for the cyclooxygenase (COX-1/COX-2) inhibitory activity. Smaller groups such as methoxy, methyl and fluoro when substituted at/around position-4 of the adjacent phenyl ring, have great impact on the selective COX-2 inhibitory activity of the series. Many potential compounds were obtained from a brief structure–activity relationship (SAR) study. Two of these, compounds **11** and **25** exhibited excellent in vivo activity in the established animal model of inflammation. Since compound **25** possessed an amenable sulfonamide group, two of its prodrugs **48** and **49** were also synthesized. Both of them have excellent in vivo potential, and represent a new class of COX-2 inhibitor.

1. Introduction

The discovery of two isoforms of prostaglandin synthase and their entirely different roles created a new window for the pharmaceutical research.[1] These isozymes, COX-1 and COX-2, are reported to exhibit a tissue dependent expression and regulation.[2] The constitutive COX-1, mainly expressed in gastrointestinal tract, is responsible for the biosynthesis of PGs required for the cytoprotection and platelet aggregation.[3] So, any interference with its normal activity for long time leads to severe gastrointestinal toxicity such as ulceration, bleeding and perforation.[4] The COX-2, induced during injury by the pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukines, plays a major role in the biosynthesis of PGs required for inflammatory cells such as monocytes and macrophages causing swelling, pain and fever.[5] The conventional NSAIDs causing nonselective inhibition of these differently acting COX-1 and COX-2 enzymes, down regulate the biosynthesis of PGs (cytoprotective as well as inflammatory) in most of the cells and tissues, and accounts for the anti-inflammatory activity along with side effects.[6] Thus, the selective inhibition of the inducible COX-2, sparing constitutive COX-1, formed the basis of designing COXIBs to have anti-inflammatory agents with minimal degree of ulcerogenic risk. This new concept of treating inflammation related disease came into effect with the consecutive launch of celecoxib[7] and rofecoxib.[8] The latter efforts in this direction introduced second generation drugs viz. valdecoxib,[9] parecoxib sodium[10] and etoricoxib[11] (Fig. 1). While these COX-2 inhibitors have been successful in treating inflammatory diseases like acute pain, rheumatoid arthritis and osteoarthritis, a few of them are also being studied for treating different types of cancer,[12] and Alzheimer's disease.[13] Despite a few latest cautionary reports,[14] the COXIB treatment has a high degree of benefit over risk.

Unlike traditional NSAIDs which have diverse class of chemical structures, the COX-2 inhibitors can structurally be restricted to only two classes, (1) the acidic methane sulphonamide containing diphenyl ethers, represented by nimesulide[15] and NS-398,[16] and (2) the vicinal diaryl heterocycles having essentially either sulfamoyl (SO_2NH_2) or methylsulfonyl (SO_2Me) substition at position-4 of one of the phenyl ring, represented by celecoxib, rofecoxib, valdecoxib, parecoxib sodium and

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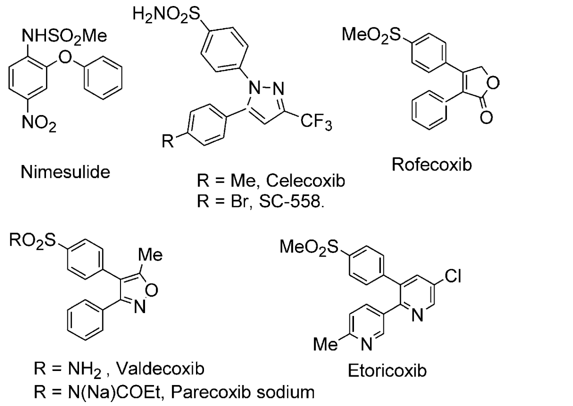


Figure 1.

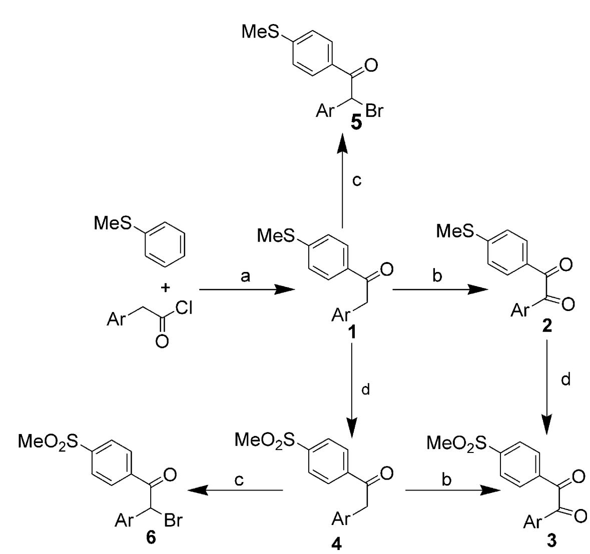
etoricoxib (Fig. 1). The two adjacent phenyl rings of these COX-2 inhibitors orient in rigid *cis*-stilbene geometry and the phenyl ring having SO_2NH_2/SO_2Me group extends towards hydrophilic region of COX-2 secondary pocket. This feature has thus been proposed to be the primary determinant for the COX-2 selectivity.[17] During the rational design, many diaryl carbocycles and heterocycles were identified which could adopt this favorable geometry to explicit the desired activity.[18] In other words, lack of this rigid geometry can also be reasoned for conventional NSAIDs to be nonselective. Though many COXIBs have been launched in the market during a short span of time, there still remains a need to develop more efficacious drugs with high degree of patient acceptability as an alternative to the steroidal and narcotic drugs used in severe surgical as well as postoperative pain which can check the initial process of inflammation. To the best of our knowledge, parecoxib sodium is only such COX-2 inhibitor, derived from valdecoxib, available in its water soluble form (injectable) which acts fast against the pain induced after surgical incisions.[10] The active ingradient of this prodrug is released immediately after injection to cause the desired action. This approach is very common way to get water soluble prodrug which releases the active ingradient in systemic circulation to cause the desired effect. Though we have also reported a water soluble form of celecoxib acting similarly in animal model,[19] it is still high time requirement for such type of drug in this segment which can be used in the above situations including ocular inflammation.[20]

Out of many six-membered heterocycles studied as central ring so far,[21] etoricoxib has recently entered the market as second generation therapy addressing many long standing problems associated with the first generation COX-2 inhibitors.[11] The possible reason for its excellent performance in clinic is the presence of two pyridyl rings improving its pharmacokinetic profile to the maximum extent leading to high degree of bioavailability and efficacy. Therefore, despite being involved in the design of five-membered vicinal diaryl structural motif,[22] we decided to ventured into six membered nitrogen containing heterocycles such as pyrazine and quinoxalines which could be envisioned as bringing the two nitrogen atoms of the two pyridyl rings of etoricoxib in one. During investigation, we came across a similar compound which was reported to be inactive in COX-2 assay.[23] But, the scanty report on these heterocycles provided us an opportunity to explore them further. Therefore, a few suitably substituted 2,3-diarylpyrazines and quinoxalines, their dihydro and tetrahydro analogues were synthesized and studied for their COX-1/COX-2 inhibitory activity. Herein, we wish to report the synthesis and a brief SAR on these two diarylheterocycles, their in vivo activity and a model of prodrug approach improving their potency and water solubility.

2. Results and discussion

2.1. Chemistry

Synthesis of important intermediates required for methylsulfonylphenyl containing pyrazines and quinoxalines is depicted in Scheme 1. The methylsulfanylphenyl ethanones **1**, were synthesized by Friedel–Crafts acylation of thioanisole with substituted phenyl acetyl chlorides. Methylsulfanylphenyl-1,2-diarylethanediones (benzils) **2**, were synthesized from **1** by simple SeO_2 oxidation carried out in dioxane–water under reflux condition whereas the corresponding methylsulfonylphenyl-1,2-diarylethanediones **3** were either obtained from **2** by H_2O_2 oxidation or from **1** by reversing the order of two oxidations mentioned above via **4** in almost equal yields (50–60% starting from **1**). The methylsulfanylphenyl and methylsulfonylphenyl α-bromoethanones **5** and **6** were prepared from the corresponding ethanones **1** and **4** by electrophilic bromination using liquid Br_2, catalysed by HBr in dichloromethane. The conversion of methylsulfanyl (SMe) to methylsulfonyl (SO_2Me) was detected by the δ shift from 2.03 to 3.08 for CH_3 protons, that of ethanone to ethanedione by the complete disappearance of CH_2 protons from 4.20 and that of ethanone to α-bromoethanones by the



Scheme 1. Reagents and conditions: (a) $AlCl_3$, CH_2Cl_2, 0–35 °C, 2–4 h (b) SeO_2, 1,4-Dioxane–H_2O, reflux, 1–2 h. (c) Br_2/HBr, CH_2Cl_2, AcOH, 0–35 °C, 4–5 h. (d) H_2O_2/AcOH, 50–60 °C, 3–4 h.

shift of CH_2 protons at 4.2 to 6.3 ppm for CH protons in ^1H NMR.

Synthesis of intermediates required for sulfamoylphenyl containing pyrazines and quinoxalines is outlined in Scheme 2. The 4-sulfamoylphenyl ethanediones (benzils) **9**, were obtained from diphenylethanones **7** (prepared by the Friedel–Crafts acylation of suitably substituted benzene using phenylacetyl chloride). The step wise chlorosulfonation and amination of **7** afforded 4-sulfamoylphenyl ethanones **8** which were converted to corresponding ethanediones **9** by SeO_2 oxidation. The sulfamoylphenyl α-bromoethanones **10** were prepared by the method described above for corresponding methylsulfanyl/sulfonyl derivatives **5** or **6** (Scheme 1).

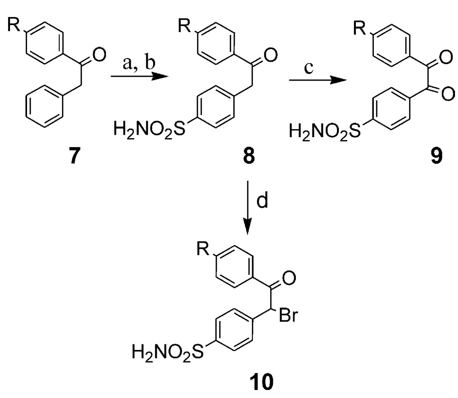
Synthesis of diarylpyrazines and quinoxalines, having sulfamoyl and methylsulfonyl groups **11–39** is depicted in Scheme 3. The 2,3-dihydropyrazines, obtained from coupling of diones (benzils) **2**, **3** and **9** (Schemes 1 and 2) with 1,2-diaminoethane and 1,2-diaminopropane in methanol, was further dehydrogenated to afford the fully aromatized pyrazines using Pd-C in ethanol under heating condition whereas coupling with phenylenediamine directly afforded aromatic quinoxalines. Coupling product of **3** and **9** in few cases directly afforded pyrazines due to the formation of energetically favored aromatic nucleus. The coupling product of **2** required further oxidation with H_2O_2 and suffered a comparative yield loss. The compounds obtained as a result of 1,2-diaminopropane coupling, were approximately a 60:40 mixture of regioisomers which could not be separated by column chromatography, and were screened as such in the COX-1/COX-2 in vitro assay. However, the two regioisomers of active compound **24**, are under separation by preparative HPLC and identification for deciding the correct isomer responsible for COX-2 inhibition.

Synthesis of tetrahydropyrazines **40–43** and dihydroquinoxalines **44–47** is depicted in Scheme 4. The coupling of α-bromoethanones **5**, **6** and **10** (Schemes 1 and 2) with 1,2-diaminoethane and 1,2-diaminopropane in methanol yielded tetrahydropyrazines **40** and **43** whereas with phenylenediamine afforded dihydroquinoxalines **44** and **47.** A few *N*-acylated derivatives of these compounds were also prepared for comparison sake using acetic anhydride and trifluoro acetic anhydride in presence of triethyl amine. In case of coupling using **5**, the oxidation of methylsulfanyl (SMe) to methylsulfonyl (SO_2Me) after acylation was observed to be higher yielding when compared to the oxidation followed by acylation process. These tetrahydropyrazines and dihydroquinoxalines were screened as racemic mixture.

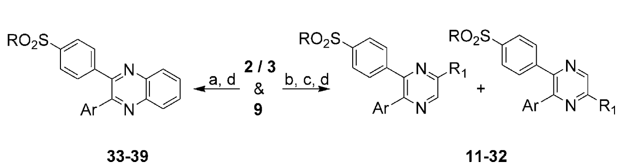
Synthesis of the prodrugs of compound **25** is depicted in Scheme 5. The *N*-propionylation of sulfamoyl group of **25** with propionic anhydride in presence of triethyl amine afforded its *N*-propionyl derivative **48** which on treatment with 0.95 equivalent of $NaHCO_3$ in methanol at room temperature afforded the desired water soluble sodium salt **49**.[10,19] The conversion of acyl derivative **48** to sodium salt **49** was characterized by the disappearance of NH signal in ^1H NMR spectra and dramatic increase in melting point. All the compounds reported herein were well characterized using spectroscopic methods such as IR, ^1H NMR and Mass and they were found to be highly pure (above 97%) by HPLC/C, H, N analysis.

2.2. Biology

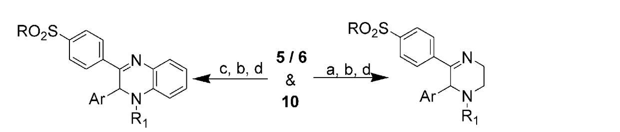
Initially, all the compounds were screened for their ability to inhibit the recombinant human COX-2 enzyme, expressed in sf-9 cells infected with baculovirus, and COX-1 enzyme, obtained from microsomal fraction



Scheme 2. Reagents and conditions: (a) $ClSO_3H$, CH_2Cl_2, 0–35 °C, 2–3 h, (b) aq. NH_3, 0–10 °C, 5–10 min. (c) SeO_2, 1,4-Dioxane–H_2O, reflux, 1–2 h. (d) Br_2/HBr, CH_2Cl_2, AcOH, 0–35 °C, 4–5 h.



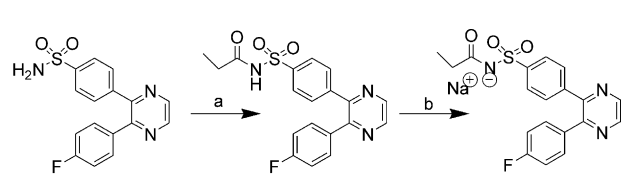
Scheme 3. Reagents and conditions: (a) *o*-Phenylenediamine, MeOH, 0–30 °C, 4–6 h. (b) 1,2-Diaminoethane or, 1,2-Diaminopropane, MeOH, 0–30 °C, 4–6 h. (c) Pd/C, EtOH, reflux, 12–14 h. (d) H_2O_2/AcOH, 50–60 °C, 3–4 h, in case of coupling with **2**.



44. Ar = Ph, R = Me, R_1 = H
45. Ar = Ph, R = Me, R_1 = Ac
46. Ar = Ph, R = Me, R_1 = $COCF_3$
47. Ar = 4-OMe-Ph, R = NH_2, R_1 = H

40. Ar = Ph, R = Me, R_1 = H
41. Ar = Ph, R = Me, R_1 = Ac
42. Ar = Ph, R = Me, R_1 = $COCF_3$
43. Ar = 4-OMe-Ph, R = NH_2, R_1 = H

Scheme 4. Reagents and conditions: (a) 1,2-Diaminoethane, MeOH, 0–30 °C, 4–6 h. (b) $(R_1CO)_2O$, TEA, CH_2Cl_2, reflux, 6–7 h. (c) *o*-Phenylenediamine, MeOH, 0–35 °C, 4–6 h. (d) H_2O_2/AcOH, 50–60 °C, 3–4 h, in case of coupling with **5**.

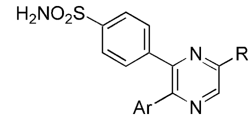


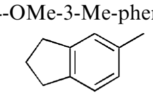
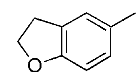
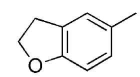
Scheme 5. Reagents and conditions: (a) $(C_2H_5CO)_2O$, TEA, CH_2Cl_2, reflux, 8–9 h. (b) $NaHCO_3$, MeOH, 0–35 °C, 4–5 h.

of Ram Seminal Vesicles at 100 μM concentration. Based on their initial in vitro efficacy, the promising compounds were tested further at lower concentrations. The enzyme activity was measurement by TMPD method and IC_{50}s for COX-1 and COX-2 were calculated using non-linear regression analysis of percent inhibitions.[24] Celecoxib and indomethacine were used as reference standard for COX-2 selective and nonselective inhibitors. Compounds were selected for in vivo screening[25] based on the higher ratio of IC_{50}s (COX-1/COX-2), known as selectivity index (SI).

The results of COX-1/COX-2 inhibition are summarized in Tables 1–3. The 4-methylsulfonylphenyl containing 2,3-diarylpyrazines with small groups on the adjacent phenyl ring with electron donating/electron withdrawing nature were preferred for the study. In few cases, a methyl group on the pyrazine nucleus was also tried. The electron withdrawing groups at position-4 were generally unfavorable, for example, nitro group was found totally inactive. But the activity started increasing with the introduction of electron donating groups, and 4-methoxy, 3-fluoro and 4-fluoro substituted phenyls and unsubstituted phenyl were found reasonably COX-2 selective. Particularly, these groups along with a methyl group at pyrazine nucleus showed highly improved activity, for example, 4-methoxy and 4-fluorophenyl analogues **13** and **15,** though screened as 60:40 mixture of regioisomers, respectively exhibited IC_{50}s of 1.62 and 5.43 μM when compared to their corresponding non-methylated poorly active analogues (Table 1).[23a] Out of four compounds **11**, **13**, **15** and **20** (in vitro active) studied in vivo in the carrageenan induced rat paw edema model of inflammation at 30 mg/kg (po), **11** and **13** showed 56% and 32% reduction in paw volume (Table 4). Recalling the lower potency exhibited by methylsulfonyl (SO_2Me) group when

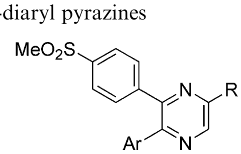
Table 2. In vitro activity of sulfonamide containing 2,3-diaryl pyrazines



Compd	Ar	R	% Inhibition[a,b] (IC_{50}, μM)[c]	
			COX-1	COX-2
21	4-Me-phenyl	H	0 (>1000)	43 (8.11±0.10)
22	4-Me-phenyl	Me	13 (>100)	63 (1.22±0.04)
23	4-OMe-phenyl	H	0 (131.4)	75 (1.93±0.06)
24	4-OMe-phenyl	Me	41 (97)	100 (0.46±0.01)
25	4-F-phenyl	H	0 (>300)	83 (1.07±0.03)
26	4-Cl-phenyl	H	0 (401)	67 (4.45±0.09)
27	4-Br-phenyl	H	31 (>300)	75 (7.26±0.08)
28	4-OMe-3-Me-phenyl	H	0 (>300)	75 (3.91±0.04)
29	4-OMe-3-Me-phenyl	Me	0 (285)	88 (1.62±0.03)
30		H	0 (251)	100 (1.01±0.02)
31		H	19 (190)	100 (4.42±0.08)
32		Me	38 (16)	100 (1.65±0.06)
48	—	—	0	67
49	—	—	0	25
Parecoxib Sodium	—	—	0	17

> Represents precipitation beyond this concentration and the IC_{50} for COX-1 can be much higher than the values mentioned here.
[a] At 10 μM concentration.
[b] Average of three determinations with experimental error of $< \pm 12\%$.
[c] Mean of two determinations with standard deviation of $< \pm 10\%$.

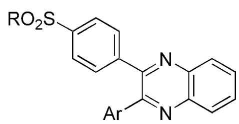
Table 1. In vitro activity of methylsulfonyl containing 2,3-diaryl pyrazines

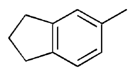


Compd	Ar	R	% Inhibition[a,b] (IC_{50}, μM)[c]	
			COX-1	COX-2
11	Phenyl	H	49	66
12	4-OMe-phenyl	H	29 (>100)	44 (11.81±0.12)
13	4-OMe-phenyl	Me	29 (>30)	75 (1.62±0.06)
14	4-F-phenyl	H	15	34
15	4-F-phenyl	Me	0 (>100)	71 (5.43±0.11)
16	4-NO_2-phenyl	H	0	0
17	4-Me-phenyl	H	22	37
18	4-Me-phenyl	Me	67	27
19	3-F-phenyl	H	43	19
20	3-F-phenyl	Me	22 (>300)	88 (4.4±0.10)
Celecoxib	—	—	11 (15.33±0.03)	100 (0.07±0.005)
Indomethacin	—	—	100 (0.067±0.001)	97 (7.80±0.11)

> Represents precipitation beyond this concentration and the IC_{50} for COX-1 can be much higher than the values mentioned here.
[a] At 10 μM concentration.
[b] Average of three determinations with experimental error of $< \pm 12\%$.
[c] Mean of two determinations with standard deviation of $< \pm 10\%$.

Table 3. In vitro activity of methylsulfonyl and sulfonamide containing 2,3-diaryl quinoxalines



Compd	R	Ar	% Inhibition[a,b] (IC_{50}, μM)[c]	
			COX-1	COX-2
33	Me	Phenyl	0	10
34	Me	4-Me-phenyl	12	0
35	NH_2	4-Me-phenyl	0	40
36	Me	4-OMe-phenyl	0 (>30)	81 (0.40±0.05)
37	Me	3-F-phenyl	0	19
38	NH_2	4-OMe-3-Me-phenyl	0 (30)	100 (2.10±0.07)
39	NH_2		47 (30)	100 (0.32±0.04)

> Represents precipitation beyond this concentration and the IC_{50} for COX-1 can be much higher than the values mentioned here.
[a] At 10 μM concentration.
[b] Average of three determinations with experimental error of <±12%.
[c] Mean of two determinations with standard deviation of <±10%.

Table 4. In vivo data for selected compounds

Compd	% Reduction in Paw Vol.[a] (30 mg / kg)[b,c]
11	56
13	32
24	20
25	63
30	37
39	22
48	73
49	48
Celecoxib	53
Parecoxib Sodium	45

[a] Carrageenan induced rat paw edema model, using six animal group of male Wistar rats on per oral dosing.
[b] Mean of two experiments.
[c] Experimental error <±20%.

compared to sulfonamide (SO_2NH_2) in general,[7] we synthesized a few sulfamoylphenyl containing pyrazines (Table 2). As expected, several potential COX-2 inhibitors with varying degree of potency were obtained from the series. The 4-methoxyphenyl analogue **24**, though screened as 65:35 mixture of regioisomers, was found to have excellent COX-2 selectivity (0.46 μM) in conjugation with a methyl group on the pyrazine ring. The 4-fluorophenyl analogue **25** topped in COX-2 potency (1.07 μM) and selectivity among halogens. The 4-methoxy-3-methylphenyl analogues **28** and **29**, the bicyclic indanyl analogue **30** and 2,3-dihydrobenzofuranyl analogue **31** showed very good in vitro potency. In almost every observation, a methyl group on the pyrazine nucleus was found to play a crucial role in increasing the selectivity and potency. But, the repeated in vivo study of these compounds indicated only **25** and **30** as potential candidates (Table 4). This was a quite surprising result because compound **24**, despite exhibiting excellent in vitro activity, could not perform well in animal model study. But, this observation was similar to that of 4-methoxyphenyl analogue **13** in animal model. Though the exact reason behind this abnormality is not known, the metabolic conversion of 4-methoxyphenyl group to 4-hydroxyphenyl can not be ignored. This possible explanation is based on the fact that COX-2 enzyme accepts only a hydrophobic group at this position.[26] In contrast, the 4-fluorophenyl analogue **25** which showed lesser COX-2 in vitro potency than **24** was found to be the best among all in the animal study. The possible reason for this fact could be a better metabolic stability of the 4-fluorophenyl group under physiological condition.[27] The in vitro study of quinoxalines, substituted with sulfamoyl (SO_2NH_2) and methylsulfonyl (SO_2Me) groups at position-4 of phenyl ring is summarized in Table 3. Like 4-methoxyphenyl substituted analogue of methylsulfonyl containing pyrazine **13** (Table 1), the corresponding quinoxaline **36** was also found to be potent. This similarity continued further and sulfamoyl containing quinoxalines such as 4-methoxy-3-methylphenyl analogue **38** and bicyclic indanyl analogue **39** showed very good in vitro COX-2 potency. But, the in vivo profile of these quinoxalines was quite discouraging as the two potent COX-2 inhibitors of the series **36** and **39** showed only ~22% reduction in paw volume even after repeated study at 30 mg/kg, po (Table 4). A number of dihydropyrazines, obtained during coupling reaction which are not reported here (Scheme 3), tetrahydropyrazines **40** and **43**, dihydroquinoxalines **44** and **47**, and a few of their acyl derivatives **41-42** and **45-46** (Scheme 4) were also screened for their COX-1/COX-2 activity but none of them showed significant COX-2 inhibition (less than 50% at 100 μM, not tabulated here). This showed the essentiality of an aromatic heterocyclic nucleus as central core providing suitable hydrophobic interaction with the similar pocket of COX-2 enzyme for its effective inhibition. Presumably, this is the reason why above hydrogenated central rings and their acyl derivatives failed to inhibit the COX-2 enzyme. Similarly, the relatively lesser potency of quinoxalines can be attributed to its larger size lacking effective accommodation in to COX-2 pocket.

We focused our attention to 4-fluorophenyl analogue **25**, a potent compound from benzenesulfonamide containing pyrazine class (Table 2) which showed excellent in vivo activity (63% at 30 mg/kg, po) in repeated study. As it was found to be fairly better than both celecoxib (53%) and parecoxib (45%), studied at same dose, we studied its prodrugs with a view to have a better drug candidate for animal study. While its *N*-propionyl derivative **48** showed reasonably good in vitro activity (67% at 10 μM), its sodium salt **49** was found to be poorly active (25%) at this concentration. But it was not surprising because salts generally fail to release the active ingredients in cell based assay, as parecoxib sodium was also found to be poorly active in this assay (17% at 10 μM). The compounds **48** and **49** showed excellent in vivo activity of 73% and 48% respectively at 30 mg/kg, po in repeated study and were found to be better than

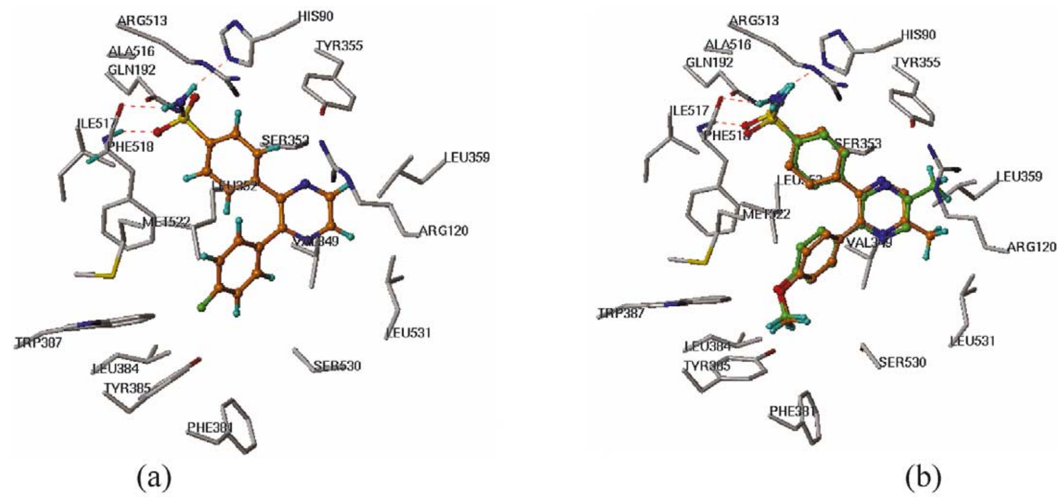


Figure 2. (a) Docking of **25** (orange). (b) Docking of **24a** (green) and **24b** (orange) in COX-2 pocket. Both the figures show that the sulfonamide group lies always in the close proximity of the hydrophilic pocket. All ligands are shown in ball and stick while amino acids residues in capped stick rendering. All hydrogens are removed for clarity.

the two reference compounds, celecoxib and parecoxib sodium (Table 4). But compound **49**, despite being less potent than **48** in this initial study, was preferred for further animal study due to its great water solubility (200 mg/mL) at ambient temperature and with the hope that it could be developed as an injectable like parecoxib sodium which can be used in postoperative and other similar conditions of inflammation. The results of further pharmacokinetic and pharmacodynamic studies will be reported elsewhere.

2.3. Molecular modeling

Docking the potent COX-2 inhibitors **24a**, **24b**, **25** and SC-558 into COX-2 active site (6COX)[17] generated various structures with different orientations. The orientations and the hydrogen bonding interactions of the most energetically favored conformations in the COX-2 complex is depicted in Figure 2. The binding site of COX-2 enzyme is roughly divided into three small pockets. One of these pockets which is constituted by the hydrophilic amino acid residues His-90, Gln-192, Ser-353, Leu-352 and backbone of Phe-518, accommodates the benzenesulfonamide group of these representative ligands **24a** (regioisomer in which the methyl group is nearer to benzenesulfonamide), **24b** (regioisomer in which the methyl group is farther) and **25**. The various hydrogen bond interactions responsible for this binding are through different atoms of sulfonamide group and resemble the binding pattern of SC-558. Similarly, the second pocket of COX-2, constituted by several hydrophobic amino acid residues Phe-381, Leu-384, Tyr-385, Trp-387, Leu-517, Phe-518, Met-522 and Gly-526, accommodates the adjacent phenyl ring. Size of this pocket being large, can accommodate both the 4-methoxyphenyl as well as a 4-fluorophenyl groups. Due to the larger differential volume (calculated using SYBYL 6.9), the 4-methoxy group ($\sim$80 Å^3) of **24a** and **24b** fits better than the 4-fluoro ($\sim$15 Å^3) of **25** into this pocket. The third pocket, formed by the amino acid residues Arg-120, Val-349, Leu-359 and Leu-531, can

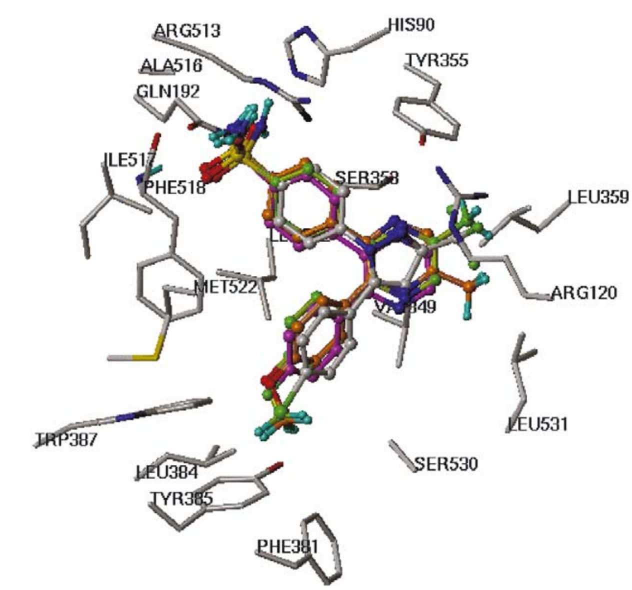


Figure 3. Superimposition of four ligands in the COX-2 binding pocket. SC-558 is shown by grey colored carbon, **25** (orange), **24a** (magenta) and **24b** (green). All the ligands are shown in ball and stick while amino acid residues in capped stick rendering. All hydrogens are removed for clarity. Results indicate that CH_3 group of **24a** binds to the same pocket as CF_3 group of SC-558.

accommodate the groups like CH_3, CF_3, Cl, F and even smaller ones. But, the steric interactions observed due to groups like CH_3 and CF_3 in **24** and SC-558 are relatively favorable. Thus, the molecular modeling studies of the representative analogues of the series demonstrated that the novel COX-2 inhibitors **24a**, **24b** (though not studied separately in vitro) and **25** have very good binding affinity with the COX-2 enzyme which confirms their in vitro potency.

Superimposition of these potent ligands **24a**, **24b** and **25** on SC-558 in the COX-2 pocket, also showed a high degree of similarity in the binding mode and further supported the rational design of the new class of COX-2 inhibitors (Fig. 3).

3. Conclusion

In this report, we have described the synthesis and (COX-1/COX-2) inhibitory activity of a few newly discovered 2,3-diarylpyrazines and quinoxalines having 4-methylsulfonyl (SO_2Me)/sulfonamide (SO_2NH_2)-phenyl pharmacophores. A few of them, substituted at adjacent phenyl ring with smaller hydrophobic groups at/around position-4, such as **13**, **24**, **25**, **30** and **39** were found to be potent COX-2 inhibitors. Of these, compound **25** and two of its prodrugs **48** and **49** have shown excellent in vivo activity and have the potential for further development. The prodrug **49**, which is exceptionally water soluble, has an additional advantage of being developed as an injectable for the postoperative and similar inflammatory pains. In summary, we have identified novel series of diarylpyrazines and quinoxalines which represent a potential class of COX-2 inhibitors and have the ability to deliver an effective anti-inflammatory drug with minimal side effects.

4. Experimental

4.1. Chemistry protocols

Research chemicals and reagents such as thioanisole, phenylacetic acids, phenylacetyl chlorides, ethylenediamine, propylenediamine and *o*-phenylenediamine, were purchased from Lancaster Co. and used as such for the reactions. Solvents except LR grade, were distilled before use. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}; Merck), visualizing with ultraviolet light or iodine spray. Usually the flash column chromatographic purification was performed over 100–200 or 230–400 mesh silica gel using mixture of ethyl acetate and petroleum ether. The reference samples such as celecoxib,[7] and parecoxib sodium[10] were prepared according to literature procedure whereas indomethacin was extracted from the capsules bought from medical store. The yields reported here are un-optimized. Melting points were determined on Buchi melting point B-540 apparatus and are uncorrected. IR spectra were recorded on Perkin–Elmer FT-IR 1650 spectrometer. ^{1}H NMR experiments were performed at 200 MHz Varian Gemini 200 spectrometer and their chemical shifts are reported in δ units with respect to TMS as internal standard. Mass spectra were recorded on HP-5989A spectrometer. Elemental analysis were carried out for C, H, N using Perkin–Elmer 2400 series II CHN-O analyzer. All the analyses were performed by the Analytical Research Group of Discovery-Research, Dr. Reddy's Laboratories Ltd. The purity of the final compounds were determined by HPLC using 'System 1' which consisted column Hichrom RPB (250 mm), mobile phase 0.01 M KH_2PO_4/CH_3CN (50:50) and 'System 2' which comprised column Intersil ODS 3V (250 mm), mobile phase H_2O/CH_3CN (50:50), both running at 1.0 mL/min with UV detection at respective λ max.

4.2. Procedure A. General preparation of methylsulfonyl containing diaryl pyrazines 11–20 and quinoxalines 33–34, 36 and 37

Step 1. Representative preparation of 1-(4-methylsulfanylphenyl)-2-phenyl-1-ethanone 1 (Ar, Ph)

Phenylacetyl chloride (2.0 mL, 15.13 mmol) was introduced to a suspension of anhydrous aluminium chloride (2.1 g, 15.84 mmol) in dichloromethane (25 mL) under argon atmosphere at 0–5 °C. After stirring the reaction mixture for 0.5 h at this temperature, thioanisole (1.7 mL, 13.57 mmol) was slowly added for a period of 15 min. After maintaining the reaction mixture at this temperature for 2 h, it was allowed to stir at room temperature for 10–12 h and poured over crushed ice. It was extracted with dichloromethane (3×50 mL), and the combined organic layer after washing with water, was dried (anhydrous Na_2SO_4) and evaporated to get an oil which was purified by column chromatography using ethyl acetate–petroleum ether (5%) to afford a viscous liquid of the title compound (2.5 g, 75%) which was used in the next step without further purification. IR (KBr) 3443, 1681, 1587, 1333 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.92 (d, $J=8.4$ Hz, 2H), 7.31–7.22 (m, 7H), 4.23 (s, 2H), 2.50 (s, 3H). MS (CI method) 242 (M^+), 185, 165, 151.

Step 2. Representative preparation of 1-(4-methylsulfanylphenyl)-2-phenyl-1,2-ethanedione 2 (Ar, Ph)

Selenium dioxide (2.0 g, 18.02 mmol) was dissolved in a mixture of 1,4-dioxane-water (50 mL, 48:2) under heating, and cooled to room temperature. The 1,4-dioxane solution of 1-(4-methylsulfanylphenyl)-2-phenyl-1-ethanone (2.0 g, 8.26 mmol), prepared in step 1, was added to the reaction mixture and refluxed overnight. The precipitated selenium was filtered off and the filtrate was poured over ice water. After repeated extraction with ethyl acetate, the combined organic layer was washed with water, dried and evaporated to get yellow solid of the title compound (1.95 g, 92%) which was used in the next step without further purification. IR (KBr) 2957, 1677, 1582 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.10 (d, $J=8.2$ Hz, 2H), 7.41–7.12 (m, 7H), 2.63 (s, 3H). MS (CI method) 256 (M^+, 100%), 151, 104.

Step 3. Representative preparation of 1-(4-methylsulfonylphenyl)-2-phenyl-1,2-ethanedione 3 (Ar, Ph)

30% Hydrogen peroxide solution (3.5 mL, 29.41 mmol) was slowly added to a mixture of 1-(4-methylsulfanylphenyl)-2-phenyl-1,2-ethanedione (1.9 g, 7.85 mmol, prepared in step 2) in glacial acetic acid (10 mL). The reaction mixture was heated at 50 °C for 5 h. The cooled mass was poured over ice-water and extracted with dichloromethane. The combined organic layer was washed with water, dried and evaporated. The crude solid was triturated with dichloromethane–petroleum ether mixture to get a light brown solid of the title compound (1.87 g, 87%) which was used in the next step without further purification. IR (KBr) 3442, 1666, 1595, 1398 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.18–8.00 (m, 3H), 7.98 (d, $J=7.4$ Hz, 2H), 7.70–7.00 (m, 4H), 3.08 (s, 3H). MS (CI method) 289 $(M+H)^+$, 183, 151, 121.

Step 4. Representative preparation of 5-(4-methylsulfonylphenyl)-6-phenyl-2,3-dihydropyrazine

Mixture of 1-(4-methylsulfonylphenyl)-2-phenyl-1,2-ethanedione, prepared in step 3 (280 mg, 0.97 mmol) and ethylenediamine (97 μL, 1.45 mmol) dissolved in methanol (2 mL) was stirred overnight at room temperature. The reaction mixture was poured over ice-water and extracted with ethyl acetate. The crude product isolated after evaporation was purified by column chromatography using ethyl acetate–petroleum ether (10%) to get a white solid of the title compound (115 mg, 38%) which was used in the next step without further purification. IR (KBr) 3431, 1560, 1310, 1150 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.83 (d, $J=8.2$ Hz, 2H), 7.59 (d, $J=7.8$ Hz, 2H), 7.33–7.27 (m, 5H), 3.74 (s, 4H), 3.01 (s, 3H). MS (CI method) 313 $(M+H)^+$.

Step 5. Representative preparation of 2-(4-methylsulfonylphenyl)-3-phenylpyrazine 11

10% Pd-C (5 mg) was added to a 2 mL ethanolic solution of 5-(4-methylsulfonylphenyl)-6-phenyl-2,3-dihydropyrazine (100 mg, 0.32 mmol), prepared in step 4 and refluxed the mixture for 5 h. The reaction mixture was filtered on celite bed and the filtrate after concentration was purified by column chromatography using ethyl acetate–petroleum ether (20%) to get a white solid of the title product (55 mg, 55%). Mp 142–144 °C. IR (KBr) 3437, 2919, 1599, 1390, 1309 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.66 (d, $J=6.2$ Hz, 2H), 7.90 (d, $J=8.4$ Hz, 2H), 7.67 (d, $J=8.2$ Hz, 2H), 7.44–7.20 (m, 5H), 3.05 (s, 3H). MS (CI Method) 311 $(M+H)^+$, 231 (100%), 204, 176, 150, 119, 103. HPLC (Method 1) 98.8%. Anal. calcd ($C_{17}H_{14}N_2O_2S$) C, H, N.

4.3. Compound 12

Yield 65%. Mp 183–185 °C. IR (KBr) 3427, 2915, 1592, 1385, 1302 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.42 (d, $J=6.8$ Hz, 2H), 7.78 (d, $J=8.0$ Hz, 2H), 7.56–7.35 (m, 4H), 7.00 (d, $J=6.8$ Hz, 2H), 3.85 (s, 3H), 3.07 (s, 3H). MS (CI Method) 341 $(M+H)^+$, 325, 231, 203, 151. HPLC (Method 1) 97.9%. Anal. calcd ($C_{18}H_{16}N_2O_3S$) C, H, N.

4.4. Compound 13

Yield 72%. Mp 208–210 °C. IR (KBr) 3422, 2921, 1609, 1512, 1437, 1311 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.50 (d, $J=11.2$ Hz, 1H), 7.91–7.87 (m, 2H), 7.69–7.63 (m, 2H), 7.37–7.26 (m, 2H), 6.86–6.82 (m, 2H), 3.81 (s, 3H), 3.04 (s, 3H), 2.66 (s, 3H). MS (CI Method) 355 $(M+H)^+$, 275, 133. HPLC (Method 1) 98.2% (Mixt. of regioisomers, 60:38.2). Anal. calcd ($C_{19}H_{18}N_2O_3S$) C, H, N.

4.5. Compound 14

Yield 57%. Mp 142–144 °C. IR (KBr) 3050, 2923, 1598, 1506, 1390, 1319 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.67 (t, $J=8.1$ Hz, 2H), 7.90 (d, $J=8.3$ Hz, 2H), 7.67 (d, $J=8.3$ Hz, 2H), 7.45–7.39 (m, 2H), 7.08 (t, $J=8.2$ Hz, 2H), 3.07 (s, 3H). MS 329 $(M+H)^+$. HPLC (Method 1) 99.6%. Anal. calcd ($C_{17}H_{13}FN_2O_2S$) C, H, N.

4.6. Compound 15

Yield 64%. Mp 148–150 °C. IR (KBr) 3025, 2915, 1588, 1510, 1385, 1311 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.54–8.51 (d, $J=5.37$ Hz, 1H), 7.92–7.86 (m, 2H), 7.67–7.60 (m, 2H), 7.44–7.34 (m, 2H), 7.06–6.97 (m, 2H), 3.05 (s, 3H), 2.68 (s, 3H). MS (CI Method) 343 $(M+H)^+$, 342 (M^+), 262, 194, 121, 102, 90. HPLC (System 1) 99.5% (Mixt. of regioisomers, 62:37.5). Anal. calcd ($C_{18}H_{15}FN_2O_2S$) C, H, N.

4.7. Compound 16

Yield 59%. Mp 250–252 °C. IR (KBr) 3426, 2926, 2360, 1597, 1513, 1388, 1346, 1312 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.74 (s, 2H), 8.21 (d, $J=8.8$ Hz, 2H), 7.93 (d, $J=8.4$ Hz, 2H), 7.68–7.61 (m, 4H), 3.08 (s, 3H). MS (CI Method) 356 $(M+H)^+$, 340, 326, 325. HPLC (Method 1) 97.9%. Anal. calcd ($C_{17}H_{13}N_3O_4S$) C, H, N.

4.8. Compound 17

Yield 63%. Mp 148–150 °C. IR (KBr) 3441, 3023, 2920, 1390, 1300 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.67–8.61 (m, 2H), 7.89 (d, $J=8.3$ Hz, 2H), 7.68 (d, $J=8.3$ Hz, 2H), 7.32–7.11 (m, 4H), 3.06 (s, 3H), 2.37 (s, 3H). MS (CI Method) 325 $(M+H)^+$, 309 (100%), 245, 230, 117. HPLC (Method 2) 97.5%. Anal. calcd ($C_{18}H_{16}N_2O_2S$) C, H, N.

4.9. Compound 18

Yield 68%. Mp 178–180 °C. IR (KBr) 3433, 2921, 1437, 1309, 1151 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.53–8.48 (d, $J=10.2$ Hz, 1H), 7.90–7.84 (m, 2H), 7.68–7.61 (m, 2H), 7.31–7.10 (m, 4H), 3.04 (s, 3H), 2.68 (s, 3H), 2.35 (s, 3H). MS (CI Method) 338 (M^+, 100%), 337, 259, 244, 189, 117, 102, 90. HPLC (Method 2) 98.7% (Mixt. of regioisomers, 65:33.7). Anal. calcd ($C_{19}H_{18}N_2O_2S$) C, H, N.

4.10. Compound 19

Yield 64%. Mp 200–202 °C. IR (KBr) 3425, 2917, 1730, 1575, 1442, 1362, 1310 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.56 (d, $J=8.0$ Hz, 2H), 7.92–7.75 (m, 4H), 7.55–7.35 (m, 2H), 7.10–6.95 (m, 2H), 3.01 (s, 3H). MS (CI Method) 329 $(M+H, 100\%)^+$, 248, 192. HPLC (Method 1) 97.7%. Anal. calcd ($C_{17}H_{13}FN_2O_2S$) C, H, N.

4.11. Compound 20

Yield 53%. Mp 210–212 °C. IR (KBr) 3429, 2919, 1733, 1585, 1446, 1422, 1365, 1312 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.56–8.54 (m, 1H), 7.92–7.87 (m, 2H), 7.68–7.61 (m, 2H), 7.26–7.18 (m, 2H), 7.10–7.02 (m, 2H), 3.01 (s, 3H), 2.70 (s, 3H). MS (CI Method) 343 $(M+H)^+$, 262, 261, 194, 121, 102, 97. HPLC (Method 2) 99.0% (Mixt of regioisomers, 65:34). Anal. calcd ($C_{18}H_{15}FN_2O_2S$) C, H, N.

4.12. Compound 33

Yield 65%. Mp 254–256 °C. IR (KBr) 3442, 2359, 1347, 1301 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.25–8.17 (m, 2H), 7.95–7.73 (m, 3H), 7.70–7.51 (m, 3H), 7.52–7.40 (m, 2H), 7.37–7.27 (m, 3H), 3.07 (s, 3H). MS (CI Method) 361 $(M+H, 100\%)^+$, 281, 179, 151, 140. HPLC (Method 1) 99.7%. Anal. calcd ($C_{21}H_{16}N_2O_2S$) C, H, N.

4.13. Compound 34

Yield 72%. Mp 218–220 °C. IR (KBr) 3440, 1614, 1154 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.22–8.14 (m, 2H), 7.95–7.73 (m, 6H), 7.40–7.14 (m, 4H), 3.06 (s, 3H), 2.38 (s, 3H). MS (CI Method) 375 $(M+H)^+$, 359, 295, 280, 192, 178, 165, 116, 91. HPLC (Method 2) 99.2%. Anal. calcd ($C_{22}H_{18}N_2O_2S$) C, H, N.

4.14. Compound 36

Yield 66%. Mp 188–192 °C. IR (KBr) 3438, 2923, 1604, 1514, 1475, 1419, 1302 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.21–8.13 (m, 2H), 7.94 (d, $J=8.2$ Hz, 2H), 7.82–7.74 (m, 4H), 7.66 (d, $J=8.4$ Hz, 2H), 6.88 (d, $J=8.8$ Hz, 2H), 3.84 (s, 3H), 3.06 (s, 3H), MS (CI Method) 391 $(M+H)^+$, 376. HPLC (Method 1) 97.4%. Anal. calcd ($C_{22}H_{18}N_2O_3S$) C, H, N.

4.15. Compound 37

Yield 68%. Mp 158–160 °C. IR (KBr) 3435, 2915, 1735, 1577, 1445, 1365 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.55 (d, $J=7.8$ Hz, 2H), 7.88–7.76 (m, 6H), 7.45–7.38 (m, 2H), 7.05–6.90 (m, 2H), 3.02 (s, 3H). MS (CI Method) 379 $(M+H, 100\%)^+$, 364. HPLC (Method 2) 98.4%. Anal. calcd ($C_{21}H_{15}FN_2O_2S$) C, H, N.

4.16. Procedure B. General preparation of sulfonamide containing pyrazines 21–32 and quinoxalines 35, 38 and 39

Step 1. Representative procedure for 1-(4-fluorophenyl)-2-phenyl-1-ethanone 7 (R, F)

The title compound was prepared in 71% yield using fluorobenzene and phenylacetyl chloride following the general method described above (Procedure A, step 1), and was used in the next step without further purification. IR (KBr) 3361, 1689, 1598, 1452 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.07–8.00 (m, 2H), 7.44–7.26 (m, 5H), 7.12 (t, $J=8.8$ Hz, 2H), 4.26 (s, 2H), 3.06 (s, 3H). MS (EI Method) 215 $(M+H)^+$, 183, 165, 136.

Step 2. Representative procedure for 4-[2-(4-fluorophenyl)-2-oxoethyl]-1-benzenesulfonamide 8 (R, F)

1-(4-Fluorophenyl)-2-phenyl-1-ethanone 7 (2.0 g, 9.34 mmol), prepared above (Procedure B, step 1), was dissolved in dichloromethane (20 mL) and cooled to 0–5 °C. Chlorosulfonic acid (3.8 g, 32.7 mmol) was slowly added and the reaction mixture was allowed to stir at room temperature for 15 h. Poured the reaction mixture over ice-water, extracted with dichloromethane, dried the combined organic layer and evaporated. 25% aq ammonia solution (5 mL) was slowly added to the viscous mass maintained at 0–5 °C and reaction mixture stirred at room temperature for 10 min. The reaction mixture was poured over ice-water and extracted with ethyl acetate. The combined organic layer was washed with water, dried and evaporated to get a solid mass which upon trituration with ethyl acetate–petroleum ether afforded a white solid (1.1 g, 40%). This product was used in the next step without further purification. IR (KBr) 3315, 1669, 1597, 1343 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.18–8.11 (m, 2H), 7.77 (d, $J=8.2$ Hz, 2H), 7.46–7.39 (m, 4H), 4.53 (s, 2H). MS (EI Method) 294 $(M+H)^+$, 277, 255, 229.

Step 3. Representative procedure for 4-[2-(4-fluorophenyl)-2-oxoacetyl]-1-benzenesulfonamide 9 (R, F)

The title compound was obtained by the selenium dioxide oxidation of the above prepared 4-[2-(4-fluorophenyl)-2-oxoethyl]-1-benzenesulfonamide **8**, following procedure A, step 2, in 79% yield, and used in the next step without further purification. IR (KBr) 3370, 3253, 1674, 1598 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.17–8.01 (m, 6H), 7.48 (t, $J=8.4$ Hz, 2H). MS (CI Method) 308 $(M+H)^+$, 291, 243, 215, 184.

Step 4. Representative procedure for 4-[6-(4-fluorophenyl)-2,3-dihydro-5-pyrazinyl]-1-benzenesulfonamide

The title compound was obtained by the condensation of above prepared 4-[2-(4-fluorophenyl)-2-oxoacetyl]-1-benzenesulfonamide **9** and ethylenediamine, using the procedure A, step 4, in 68% yield, and used in the next step without further purification. IR (KBr) 3322, 3044, 1598, 1506 cm^{-1}. ^1H NMR (DMSO-d_6) δ 7.74 (d, $J=8.4$ Hz, 2H), 7.52 (d, $J=8.4$ Hz, 2H), 7.43–7.32 (m, 2H), 7.16 (t, $J=8.8$ Hz, 2H), 3.64 (s, 4H). MS (CI Method) 332, $(M+H)^+$, 315, 250, 183.

Step 5. Representative procedure for 4-[3-(4-fluorophenyl)-2-pyrazinyl]-1-benzenesulfonamide 25

The title compound was synthesized by the dehydrogenation of above prepared 4-[6-(4-fluorophenyl)-2,3-dihydro-5-pyrazinyl]-1-benzenesulfonamide (Procedure B, step 4) using general method described in procedure A, step 5. Yield 65%. Mp 178–180 °C. IR (KBr) 3381, 2926, 2361, 1726, 1601, 1511, 1389 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.66 (d, $J=2.4$ Hz, 2H), 7.88 (d, $J=8.2$ Hz, 2H), 7.60 (d, $J=6.6$ Hz, 2H), 7.45–7.39 (m, 2H), 7.08 (t, $J=3.9$ Hz, 2H), 4.98 (bs, 2H). MS (CI Method) 330 $(M+H)^+$. HPLC (Method 1) 98.9%. Anal. calcd ($C_{16}H_{12}FN_3O_2S$) C, H, N.

4.17. Compound 21

Yield 61%. Mp 222–224 °C. IR (KBr) 3365, 2924, 1609, 1389, 1325 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.61 (d, $J=4.8$ Hz, 2H), 7.86 (d, $J=8.2$ Hz, 2H), 7.58 (d, $J=8.4$ Hz, 2H), 7.34 (d, $J=2.6$ Hz, 2H), 7.12 (d, $J=7.8$ Hz, 2H), 6.2 (bs, 2H), 2.36 (s, 3H). MS (CI Method) 326 $(M+H)^+$, 310 (100%), 245, 230, 218, 189, 176, 117, 91.

HPLC (Method 1) 97.8%. Anal. calcd ($C_{17}H_{15}N_3O_2S$) C, H, N.

4.18. Compound 22

Yield 67%. Mp 180–182 °C. IR (KBr) 3349, 1728, 1612, 1554, 1437, 1337 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.50 (d, J = 8.7 Hz, 1H), 7.85–7.80 (m, 2H), 7.61–7.55 (m, 2H), 7.30–7.24 (m, 2H), 7.13–7.09 (m, 2H), 4.94 (bs, 2H), 2.67 (s, 3H), 2.34 (s, 3H). MS (CI Method) 340 $(M+H)^+$, 324, 259, 244, 189, 117, 91. HPLC (Method 1) 97.9% (Mixture of regioisomers, 60.1:37.8). Anal. calcd ($C_{18}H_{17}N_3O_2S$) C, H, N.

4.19. Compound 23

Yield 51%. Mp 174–176 °C. IR (KBr) 3430, 1607, 1514, 1344 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.73–8.68 (m, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.43 (s, 2H), 7.36 (d, J = 8.3 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 3.76 (s, 3H). MS (CI Method) 342 $(M+H)^+$, 325, 315, 261, 207, 133. HPLC (Method 2) 99.3%. Anal. calcd ($C_{17}H_{15}N_3O_3S$) C, H, N.

4.20. Compound 24

Yield 58%. Mp 142–144 °C. IR (KBr) 3366, 3064, 1655, 1609, 1513, 1342 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.49 (d, J = 10.7 Hz, 1H), 7.82 (d, J = 6.8 Hz, 2H), 7.61–7.55 (m, 2H), 7.36–7.26 (m, 2H), 6.83 (d, J = 7.8 Hz, 2H), 5.05 (s, 2H), 3.80 (s, 3H), 2.67 (s, 3H). MS (CI Method) 356 $(M+H)^+$, 339, 173. HPLC (Method 2) 98.9% (Mixture of regioisomers, 65.1:33.8). Anal. calcd ($C_{18}H_{17}N_3O_3S$) C, H, N.

4.21. Compound 26

Yield 62%. Mp 92–94 °C. IR (KBr) 3428, 1621, 1336 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.66 (s, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 7.2 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 3.85 (bs, 2H). MS (CI Method) 346 $(M+H)^+$, 313, 252, 217, 190, 180, 153. HPLC (Method 2) 99.6%. Anal. calcd ($C_{16}H_{12}ClN_3O_2S$) C, H, N.

4.22. Compound 27

Yield 59%. Mp 210–212 °C. IR (KBr) 3440, 2360, 1631, 1325 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.66 (s, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 7.2 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 3.85 (bs, 2H). MS (CI Method) 392 $(M+2, 100\%)^+$, 390, 312, 180, 153, 91. HPLC (Method 2) 98.9%. Anal. calcd ($C_{16}H_{12}BrN_3O_2S$) C, H, N.

4.23. Compound 28

Yield 68%. Mp 238–240 °C. IR (KBr) 3374, 1605, 1505, 1422, 1376, 1344 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.69 (d, J = 4.3 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.44 (bs, 2H), 7.33 (s, 1H), 7.10 (d, J = 6.8 Hz, 1H), 6.87 (d, J = 6.8 Hz, 1H), 3.78 (s, 3H), 2.11 (s, 3H). MS (CI Method) 356 $(M+H)^+$, 355, 340, 308, 275, 260, 245, 231, 147, 132, 102. HPLC (Method 2) 97.9%. Anal. calcd ($C_{18}H_{17}N_3O_3S$) C, H, N.

4.24. Compound 29

Yield 66%. Mp 216–218 °C. IR (KBr) 3316, 2924, 1607, 1505, 1438, 1345 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.57 (d, J = 5.8 Hz, 1H), 7.77 (d, J = 7.8 Hz, 2H), 7.57 (d, J = 7.8 Hz, 2H), 7.41 (bs, 2H), 7.32 (s, 1H), 7.06 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 3.77 (s, 3H), 2.59 (s, 3H), 2.11 (s, 3H). MS (CI Method) 370 $(M+H)^+$, 369, 354, 289, 274, 245, 132, 104, 91. HPLC (Method 1) 99.8% (Mixt. of regioisomers, 63.5:36.3). Anal. calcd ($C_{19}H_{19}N_3O_3S$) C, H, N.

4.25. Compound 30

Yield 49%. Mp 140–142 °C. IR (KBr) 3386, 3270, 1382, 1336 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.72 (s, 2H), 7.77 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 7.8 Hz, 2H), 7.40 (s, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 7.2 Hz, 1H), 2.84 (m, 4H), 2.05 (m, 2H). MS (CI Method) 352 $(M+H)^+$, 335, 323, 270. HPLC (Method 1) 97.5%. Anal. calcd ($C_{19}H_{17}N_3O_2S$) C, H, N.

4.26. Compound 31

Yield 65%. Mp 160–162 °C. IR (KBr) 3286, 1703, 1612, 1496 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.68 (d, J = 3.0 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.41 (s, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 4.56 (t, J = 8.4 Hz, 2H), 3.19 (t, J = 8.8 Hz, 2H). MS (CI Method) 353 (M^+), 272, 243, 145. HPLC (Method 1) 97.4%. Anal. calcd ($C_{18}H_{15}N_3O_3S$) C, H, N.

4.27. Compound 32

Yield 42%. Mp 85–87 °C. IR (KBr) 3293, 1608, 1495, 1446 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.56 (d, J = 5.0 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.4 (s, 1H), 7.98 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 4.55 (t, J = 8.8 Hz, 2H), 3.14 (t, J = 8.8 Hz, 2H), 2.58 (s, 3H). MS (CI Method) 368 $(M+H)^+$, 353. HPLC (Method 1) 99.3% (Mixt. of regioisomers, 65.1:34.2). Anal. calcd ($C_{19}H_{17}N_3O_3S$) C, H, N.

4.28. Compound 35

Yield 52%. Mp 220–222 °C. IR (KBr) 3356, 3034, 1612, 1345, 1162 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.20–8.15 (m, 2H), 7.91–7.88 (m, 3H), 7.81 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.40–7.38 (m, 3H), 7.20 (d, J = 7.8 Hz, 2H), 2.34 (s, 3H). MS (CI Method) 376 $(M+H)^+$, 360, 339, 295, 259, 192, 165, 112. HPLC (Method 1) 97.7%. Anal. calcd ($C_{21}H_{17}N_3O_2S$) C, H, N.

4.29. Compound 38

Yield 70%. Mp 202–204 °C. IR (KBr) 3341, 3256, 2927, 1731, 1602, 1504, 1440, 1341, 1315 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.17–8.13 (m, 2H), 7.90–7.86 (m, 2H), 7.82 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.45 (s, 2H), 7.19 (d, $J=8.7$ Hz, 2H), 6.89 (d, $J=8.7$ Hz, 1H), 3.80 (s, 3H), 2.14 (s, 3H). MS (EI Method) 406 $(M+H)^+$, 391, 376. HPLC (Method 1) 97.9%. Anal. calcd ($C_{22}H_{19}N_3O_3S$) C, H, N.

4.30. Compound 39

Yield 68%. Mp 134–136 °C. IR (KBr) 3221, 1557, 1324, 1163 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.16 (m, 2H), 7.90 (d, $J=8.4$ Hz, 2H), 7.78 (m, 2H), 7.69 (d, $J=8.4$ Hz, 2H), 7.51 (s, 1H), 7.11 (m, 2H), 2.92 (t, $J=7.4$ Hz, 4H), 2.10 (t, $J=7.4$ Hz, 2H). MS (EI Method) 401(M^+), 321, 254, 218. HPLC (Method 2) 98.9%. Anal. calcd ($C_{23}H_{19}N_3O_2S$) C, H, N.

4.31. Procedure C. General preparation of methylsulfonyl and sulfonamide containing tetrahydropyrazines 40 and 43, and dihydroquinoxalines 44 and 47

Step 1. Representative preparation of (2*RS*)-2-bromo-1-(4-methylsulfonylphenyl)-2-phenyl-1-ethanone 6 (Ar, Ph)

The corresponding 1-(4-methylsulfonylphenyl)-2-phenyl-1-ethanone 4 (3.0 g, 10.95 mmol), obtained in two steps by the Friedel–Crafts acylation of thioanisole using phenyl acetyl chloride followed by the H_2O_2 oxidation (Procedure A, step 1 and 3), was dissolved in dichloromethane (50 mL). Glacial acetic acid (3 mL) and HBr (0.5 mL) was added to this stirred solution at room temperature and cooled to 0–5 °C. Liquid bromine (0.51 mL, 9.85 mmol) was slowly introduced and the reaction mixture was allowed to stir at room temperature for 4–5 h. After pouring the reaction mixture to ice-water mixture, it was extracted with dichloromethane and the combined organic layer was washed with water. The dried layer on evaporation afforded a gummy mass which on purification by column chromatography using ethyl acetate–petroleum ether (3%) afforded viscous liquid of the title compound (1.5 g, 39%) which was used in the next step without further purification. IR (KBr) 3434, 1713, 1395, 1300 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.17 (d, $J=7.8$ Hz, 2H), 8.04 (d, $J=8.4$ Hz, 2H), 7.49–7.40 (m, 2H), 7.39–7.20 (m, 3H), 6.32 (s, 1H), 3.06 (s, 3H). MS (CI Method) 353 (M^+), 275, 183, 121.

Step 2. Representative procedure for (6*RS*)-5-(4-methylsulfonylphenyl)-6-phenyl-1,2,3,6-tetrahydropyrazine 40

Ethylenediamine (0.21 mL, 3.23 mmol) was drop-wise introduced to the solution of above prepared 2-bromo-1-(4-methylsulfonylphenyl)-2-phenyl-1-ethanone 6 (1.2 g, 3.4 mmol) in methanol (10 mL) and allowed to stir for 24 h at room temperature. After pouring to ice-water, the content was extracted with ethyl acetate, and the combined organic layer after washing with water was dried and evaporated to get a gummy mass which after trituration with dichloromethane–petroleum ether afforded a white solid of the title compound (410 mg, 38%). Mp 164–166 °C. IR (KBr) 3415, 1688, 1575, 1360, 1312 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.85 (d, $J=8.2$ Hz, 2H), 7.61 (d, $J=8.2$ Hz, 2H), 7.33–7.26 (m, 6H), 3.71 (s, 4H), 3.02 (s, 3H). MS (CI Method) 314 (M^+), 231, 183, 103. HPLC (Method 1) 97.6%. Anal. calcd ($C_{17}H_{18}N_2O_2S$) C, H, N.

4.32. Compound 43

Yield 52%. Mp 143–145 °C. IR (KBr) 3440, 1695, 1560, 1345 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.95 (d, $J=8.0$ Hz, 2H), 7.77 (d, $J=7.8$ Hz, 2H), 7.50 (bs, 3H), 7.26–7.14 (m, 3H), 6.82 (d, $J=7.6$ Hz, 2H), 3.85 (s, 3H), 3.75 (s, 4H). MS (CI Method) 345 (M^+), 223, 181, 103. HPLC (Method 1) 98.8%. Anal. calcd ($C_{17}H_{19}N_3O_3S$) C, H, N.

4.33. Compound 44

Yield 61%. Mp 248–250 °C. IR (KBr) 3399, 1605, 1484, 1454, 1319 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.12 (d, $J=8.8$ Hz, 2H), 7.93 (d, $J=8.4$ Hz, 2H), 7.47 (d, $J=7.8$ Hz, 1H), 7.27–7.20 (m, 5H), 7.03 (t, $J=6.8$ Hz, 1H), 6.80 (t, $J=6.6$ Hz, 1H), 6.50 (d, $J=7.8$ Hz, 1H), 4.45 (bs, 1H), 3.02 (s, 3H). MS (CI Method) 362 (M^+), 285, 281, 207, 179, 152, 140, 127, 102. HPLC (Method 1) 99.2%. Anal. calcd ($C_{21}H_{18}N_2O_2S$) C, H, N.

4.34. Compound 47

Yield 68%. Mp 233–235 °C. IR (KBr) 3430, 1610, 1510, 1422, 1325 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.10 (d, $J=8.0$ Hz, 2H), 7.90 (d, $J=8.0$ Hz, 2H), 7.40–7.20 (m, 6H), 7.10 (bs, 2H), 6.95 (t, $J=6.6$ Hz, 1H), 6.80 (d, $J=7.6$ Hz, 2H), 3.82 (s, 3H). MS (CI Method) 394 $(M+H)^+$, 378, 215, 205, 159. HPLC (Method 1) 98.6%. Anal. calcd ($C_{21}H_{19}N_3O_3S$) C, H, N.

4.35. Representative procedure for (2*RS*)-1-[3-(4-methylsulfonylphenyl)-2-phenyl-1,2-dihydro-1-quinoxalinyl]-1-ethanone 45

Triethyl amine (231 μL, 1.65 mmol) was added to the solution of 3-(4-methylsulfonylphenyl)-2-phenyl-1,2-dihydroquinoxaline **44** (400 mg, 1.10 mmol), prepared above (Procedure C, Step 2), in dichloromethane (20 mL). Acetic anhydride (167 μL, 1.64 mmol) was slowly added at room temperature and the reaction mixture was refluxed overnight. After pouring the reaction mixture to ice-water, it was extracted with dichloromethane. The combined organic layer was washed with water, dried and evaporated to get a gummy mass which on column purification using ethyl acetate–petroleum ether (25%) afforded a white solid of the titled compound (250 mg, 56%). Mp 238–240 °C. IR (KBr) 3431, 2920, 1662, 1611, 1478, 1320 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.27 (d, $J=8.2$ Hz, 2H), 8.02 (d, $J=8.8$ Hz, 2H), 7.64 (d, $J=7.4$ Hz, 1H), 7.31–7.10 (m, 5H), 7.05–7.00 (m, 4H), 3.06 (s, 3H), 2.40 (s, 3H). MS (CI Method) 404 (M^+), 361, 285, 282, 207, 180, 152, 104. HPLC (Method 1) 97.6%. Anal. calcd ($C_{23}H_{20}N_2O_3S$) C, H, N.

4.36. Compound 46

Yield 63%. Mp 152–154 °C. IR (KBr) 3432, 2923, 1689, 1485, 1322 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.26 (d, $J=8.2$ Hz, 2H), 8.05 (d, $J=8.2$ Hz, 2H), 7.66 (d, $J=7.2$ Hz, 1H), 7.42–7.10 (m, 5H), 7.05–7.00 (m, 4H), 3.07 (s, 3H).

MS (CI Method) 458 (M^+), 389, 381, 361, 282, 205, 178, 152. HPLC (Method 1) 97.3%. Anal. calcd ($C_{23}H_{17}F_3N_2O_3S$) C, H, N.

4.37. Compound 41

Yield 46%. Mp 180–182 °C. IR (KBr) 3320, 2925, 1675, 1465, 1319 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.24 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.0 Hz, 2H), 7.66–7.32 (m, 6H), 3.90 (s, 4H), 3.08 (s, 3H), 2.42 (s, 3H). MS (CI Method) 356 (M^+), 313, 280, 203, 175, 151. HPLC (Method 1) 99.3%. Anal. calcd ($C_{19}H_{20}N_2O_3S$) C, H, N.

4.38. Compound 42

Yield 55%. Mp 149–152 °C. IR (KBr) 3345, 2935, 1685, 1475, 1325 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.44 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 8.4 Hz, 2H), 7.70–7.45 (m, 6H), 3.98 (s, 4H), 3.10 (s, 3H). MS (CI Method) 410 (M^+), 313, 281, 151. HPLC (Method 2) 98.1%. Anal. calcd ($C_{19}H_{17}F_3N_2O_3S$) C, H, N.

4.39. *N*^{1}-Propionyl-4-[3-(4-fluorophenyl)-2-pyrazinyl]-1-benzenesulfonamide 48

A mixture of 4-[3-(4-fluoro phenyl)-2-pyrazinyl]-1-benzene sulfonamide **25** (2.0 g, 6.07 mmol), triethylamine (2.1 mL, 15.19 mmol) and propionic anhydride (1.18 mL, 9.10 mmol), dissolved in dichloromethane (30 mL), was refluxed for 12 h. The cooled reaction mixture was poured over ice-water, acidified with dil. HCl and extracted with dichloromethane. The combined organic layer was washed with water, dried and evaporated to get a gummy mass which after column purification using ethyl acetate–petroleum ether (15%) afforded a white solid of the title compound (1.5 g, 65%). Mp 100–102 °C. IR (KBr) 3250, 1724, 1601, 1501, 1413, 1344, 1159 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.65 (d, J = 4.0 Hz, 2H), 8.19 (bs, 1H), 8.02 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 7.45–7.38 (m, 2H), 7.00 (t, J = 8.7 Hz, 2H), 2.35–2.22 (m, 2H), 1.10 (t, J = 7.3 Hz, 3H). MS 386 $(M+H)^+$, 333 (100%). HPLC (Method 2) 99.5%. Anal. calcd ($C_{19}H_{16}FN_3O_3S$) C, H, N.

4.40. Sodium salt of *N*^{1}-propionyl-4-[3-(4-fluorophenyl)-2-pyrazinyl]-1-benzenesulfonamide 49

Powdered $NaHCO_3$ (310 mg, 3.69 mmol) was added to a stirred solution of *N*^{1} propionyl-4-[3-(4-fluorophenyl)-2-pyrazinyl]-1-benzenesulfonamide **48** (1.5 g, 3.89 mmol) in methanol (10 mL) at 0–5 °C. The reaction mixture was stirred for 5 h at room temperature. Solvent was evaporated completely to get a gummy mass which on trituration with ethyl acetate–petroleum ether afforded a white solid of the title compound (1.12 g, 75%). Mp 260–262 °C. IR (KBr) 3460, 2935, 1720, 1625, 1522 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.6 (s, 2H), 7.99 (d, J = 8.3 Hz, 2H), 7.39–7.38 (m, 4H), 7.00 (t, J = 8.3 Hz, 2H), 2.20 (q, J = 7.3 Hz, 2H), 1.06 (t, J = 7.3 Hz, 3H). MS 385 $(M-22)^+$, 322, 277, 266, 183, 102. HPLC (Method 2) 98.7%. Anal. calcd ($C_{19}H_{17}FN_3O_4SNa$) C, H, N.

4.41. In-vitro biochemical assay. Spectrophotometric assay for COX-1 and COX-2 inhibition[24]

Microsomal fraction of ram seminal vesicles were used as a source of COX-1 enzyme, and microsomes from *sf-9* cells infected with baculovirus containing human COX-2 c-DNA were used as a source of COX-2 enzyme.[24a] Enzyme activity was measured using a chromogenic assay based on oxidation of *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine (TMPD) during the reduction of PGG_2 to PGH_2. The assay mixture (1000 μL) contained 100 mM Tris pH 8.0, 3 mM EDTA, 15 μM hematin, 150 units of enzyme and 8% DMSO. The mixture was preincubated at 25 °C for 15 min before initiation of enzymatic reaction in presence of compound/vehicle. The reaction was initiated by the addition of 100 μM arachidonic acid and 120 μM TMPD. The enzyme activity was measured by estimation of the initial velocity of TMPD oxidation over the first 25 s of the reaction followed by tracking the increase in absorbance at 603 nM. The IC_{50} values were calculated using nonlinear regression analysis.[24b]

4.42. In vivo screening method. Carrageenan-induced rat paw edema[25]

Male Wistar rats (120–140 g) were fasted for 16 h before the experiment. Compounds were suspended in 0.25% carboxymethylcellulose (CMC) and administered orally in a volume of 10 mL/kg, 2 h before carrageenan injection. Paw edema was induced in rats by intradermal injection of 50 μL of 1% λ-carrageenan in saline into the plantar surface of the right hind paw. Paw volume was measured 3 h before and after carrageenan injection by plethysmometer (Ugo-Basile, Italy). Paw edema was compared with the vehicle control group and percent inhibition was calculated.

4.43. Molecular modeling

Energies of the diarylpyrazines **24** (regioisomers, **a** and **b**) and **25** were minimized using the MMFF94 force field and charges in SYBYL 6.9.[28] A co-crystal structure of COX-2 with the selective ligand SC-558[17] (PDB: 6COX)[29] was used for docking. '*Two-Stage Docking Method for Protein-Ligand Docking*' as described by Hoffmann et al.,[30] was adopted. FlexX[31] docked all the ligands including SC-558 in the same binding pocket as reported in the crystal structure. The best conformations, generated by FlexX based on CScore and Total Score, were selected and merged into the 6COX crystal structure to carry out the minimization. The energy-minimized complexes were analyzed for ligand-receptor interactions in the active site.

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