# Anti-inflammatory Exploration of Sulfonamide Containing Diaryl Pyrazoles with Promising COX-2 Selectivity and Enhanced Gastric Safety Profile

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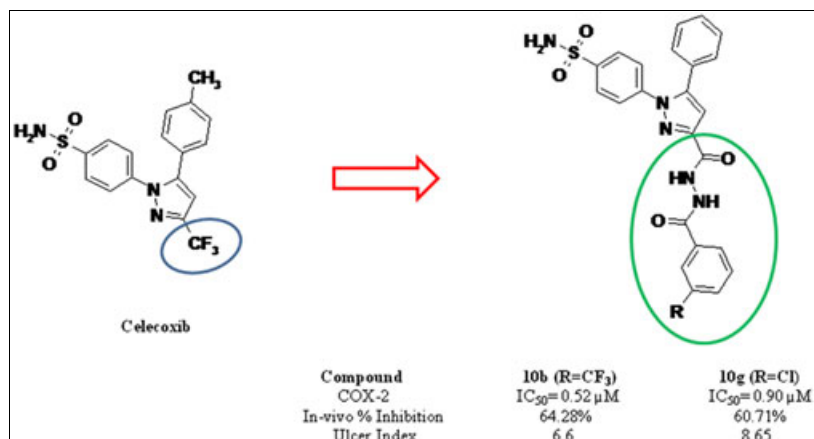[a]Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, MS, India
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| Compound | 10b (R=CF$_3$) | 10g (R=Cl) |
|---|---|---|
| COX-2 | IC$_{50}$= 0.52 μM | IC$_{50}$= 0.90 μM |
| In-vivo % Inhibition | 64.28% | 60.71% |
| Ulcer Index | 6.6 | 8.65 |

Novel sulfonamide containing diaryl pyrazoles were synthesized and were subsequently tested for their *in vitro* cyclooxygenase inhibitory assay. Compounds that showed promising *in vitro* COX-2 IC$_{50}$ values and selectivity indices were then evaluated for their *in vivo* anti-inflammatory inhibition assay using standard carrageenan-induced rat paw edema method. Two promising inhibitors were evaluated for ulcerogenic liability. X-ray crystal structure of COX-2 was taken from PDB entry COX-2 (3LN1) having a resolution of 2.80 Å (Angstroms). Structural preparations for docking studies were accomplished using protein preparation wizard in Maestro 9.0. Compound **10b** displayed reasonable COX-2 inhibition (COX-2 IC$_{50}$ = 0.52 μM) and COX-2 selectivity index (SI = 10.73) when compared with celecoxib (COX-2 IC$_{50}$ = 0.78 μM) and (SI = 9.51). *In vivo* anti-inflammatory studies demonstrated 64.28% inhibition for **10b** in comparison with the 57.14% for that of celecoxib itself. The results of ulcerogenic liability were also found comparable with standard celecoxib. Molecular docking studies revealed that all the designed molecules showed good interactions with receptor active site with glide scores in the range −13.130 to −10.624.

## INTRODUCTION

Fast and effective relief of pain and inflammation in the human being is continued to be a major task for the medicinal chemist. Non-steroidal anti-inflammatory drugs (NSAIDs) are important therapeutic agents for the alleviation of pain and inflammation associated with a number of pathological conditions [1]. NSAIDs bestow their effect by inhibiting the catalytic activity of cyclooxygenase (COX), which results in a blockage of the formation of prostaglandins (PGs) and thromboxane (TXs) [2,3]. The cyclooxygenase exists as two distinct isoforms (COX-1 and COX-2) [4]. The maintenance of physiological functions such as protection of gastric mucosa, vascular homeostasis, and platelet aggregation is governed by the constitutively expressed COX-1 isoform as organization enzyme while the upregulation of the

COX-2 is observed in acute and chronic inflammation [5,6]. Thus, inhibition of COX-2 accounts for the anti-inflammatory effects of NSAIDs, whereas interruption of COX-1 leads to gastrointestinal toxicity ranging from ulcers to perforation and bleeding [7]. Time-honored non-selective NSAIDs such as indomethacin, ibuprofen, and aspirin interact with both forms (COX-1 and COX-2), accounting for their anti-inflammatory activity in addition to their pronounced side effects, resulting from the inhibition of gastroprotective PGs synthesized through COX-1 pathway [8]. Hence, a number of selective COX-2 inhibitors such as celecoxib I, rofecoxib II, and valdecoxib III (coxibs) have been developed and approved for marketing by virtue of their fewer gastrointestinal side effects compared with traditional NSAIDs (Fig. 1). Celecoxib, in the 1,5-diarylpyrazole class of compound, was the first launched selective COX-2 inhibitor with
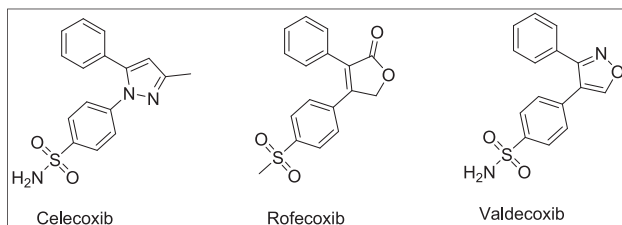
**Figure 1.** Representative examples of COX- 2 inhibitors.

excellent selectivity and potent anti-inflammatory activity, having advantage of not associating with increased cardiovascular complications [9] but known to have gastrointestinal side effects [10].

The pyrazole nucleus is known to exhibit wide range of biological activities such as antimicrobial [11,12], antiviral [13], antitumor [14], anti-depressant [15], and anti-inflammatory [8,16–19] activity. Among these, four functionalized pyrazoles occupy a distinctive position in medicinal chemistry. The archeology of research pertaining to the pyrazoles and their anti-inflammatory activity can be studied at ones by referring recent reviews [20,21].

The pharmacophoric structural features of the selective COX-2 inhibitors possess a central heterocyclic five-member ring system bearing two vicinal aryl moieties, such as pyrazole (celecoxib), 2(5*H*) furanone (rofecoxib), and isoxazole (valdecoxib). The main part of our research has been devoted to synthetic methods containing the pyrazole nucleus, as a pharmacophoric moiety for potential drugs. Also, sulfonamides [22] and hydrazide with their heterocyclic analogs showed evidence of diverse biological activities including anticancer [23] and anti-inflammatory [24] properties. In particular, the pyrazole nucleus represents a very attractive scaffold to obtain new molecules endowed with anti-inflammatory activities [25,26]. On the basis of these considerations, and in view of the reported COX-2 inhibitory activities of

certain 4-(3-hydrazinocarbonyl-5-phenylpyrazol-1-yl)-benzenesulfonamide derivatives bearing two aryl moieties at 1- and 5-positions of the pyrazole ring and carrying different substituent on the 5-amino and 3-hydrazinocarbony residue was synthesized. The synthesized compounds have a characteristic molecular pattern and bulk volume to fulfill the pharmacophoric requirements for better recognition at the COX-2 binding active site. The newly synthesized analogs were evaluated for their COX selectivity and their *in vivo* anti-inflammatory activity.

Although the synthesis of coxibs is engrained in recent years, the challenge of exploring the anti-inflammatory activity with promising COX-2 selectivity and safe gastric profile is still in need of investigative accomplishments. In furterance with our quest associated with synthesis of safe anti-inflammatory agents [25], authors here wish to report an investigation about synthesis, *in vitro* evaluation of COX selectivity, *in vivo* anti-inflammatory (AI) activity, and evaluation of ulcerogenic liability for two new groups of hydrazide 1,5-diaryl and amide containing 1,3-diaryl pyrazoles with promising results.

## RESULTS AND DISCUSSION

**Chemistry.** The present study focuses on the synthesis of novel amide compounds, *N*-[5-phenyl-2-(4-sulfamoylphenyl)-2*H*-pyrazol-3-yl]-amide (**5a**–**f**) and hydrazide compounds, 4-[3-(*N′*-alkyloyl/aryloyl-hydrazinocarbonyl)-5-phenylpyrazol-1-yl]-benzenesulfonamide (**10a**–**j**).

Synthesis of novel amide derivative was prepared as depicted in Scheme 1. Reaction of sulfanilide **1** with SnCl$_2$ and NaNO$_2$ in water under cooling condition gave 4-hydrazino-benzenesulfonamide hydrochloride salt **2**. This was transformed into the corresponding amino

**Scheme 1.** Synthetic route for *N*-[5-phenyl-2-(4-sulfamoylphenyl)-2*H*-pyrazol-3-yl]-amide (**5a**–**f**). Reagents and conditions: (a) SnCl$_2$, NaNO$_2$, water, HCl 3 h; (b) ethanol, reflux 4 h; (c) R-acid, *N*,*N*-dimethylformamide, EDC.HCl/HOBt, TEA, 25°C, 5 h.
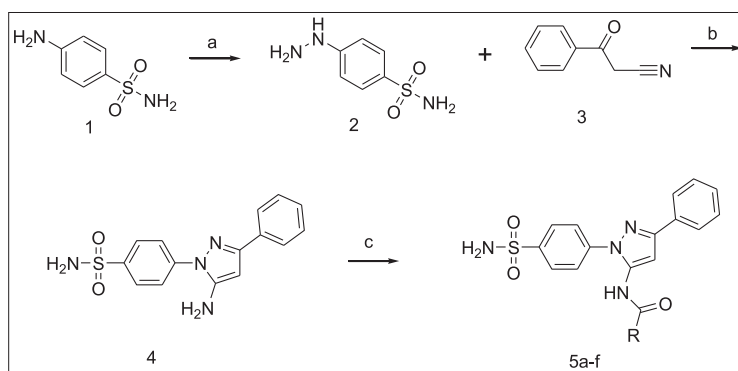
pyrrole derivative **4** by reaction with 3-oxo-3-phenylpropionitrile **3** in ethanol at reflux condition. At the last step, 4-(5-amino-3-phenylpyrazol-1-yl)-benzenesulfonamide amide derivatives **5a–e** were obtained in 60–70% yield through coupling of amine intermediate **4** with selected acid side chains. $^1$H NMR spectrum of **2** revealed the presence of broad singlet signal at δ 10.43 ppm corresponding to two protons of hydrazine (—NH$_2$) forming hydrochloride salt. It also showed singlet proton at δ 8.86 corresponding to hydrazine (—NH—). ES-MS spectrum showed m/z 188.1 (M + H)$^+$. Intermediate **4** was characterized by the singlet proton at δ 8.86 ppm corresponding to pyrazole ring and a broad singlet at δ 5.71 ppm for 5-amino pyrazole, mutilate for five protons at δ 7.33–7.42 was appeared for the newly added phenyl ring from the intermediate **3**. ES-MS spectrum showed m/z 315.1 (M + H)$^+$ for the amine core **4**. Novel amide derivatives **5a–f** were prepared by coupling selected acid with the amine core **4**. Substituted aromatic, aliphatic, and heterocyclic aromatic acids were selected to evaluate the structure activity relationship among the novel analogue.

The second series of targeted compounds **10a–j** were prepared as outlined in Scheme 2. The starting material, ethyl-2,4-dioxo-4-phenylbutanoate **7**, was prepared from acetophenone **6** and diethyl oxalate in toluene using sodium hydride at 0 to 50°C. Cyclization of ester intermediate **7** to pyrazole **8** was achieved using (4-sulfamoylphenyl)hydrazine hydrochloride in ethanol under reflux condition. Reaction of hydrazine hydrate with the cyclized pyrazole **8** converts its ester group to corresponding hydrazide intermediate **9** in ethanol with reflux condition. Coupling hydrazide intermediate **9** with substituted acid side chains using EDC.HCl and HOBt in DMF resulted into proposed compounds in 60–70%

yield. $^1$H NMR spectrum of ester intermediate **7** revealed the presence of triplet signal at δ 1.28 ppm (J = 7 Hz), and quartet signal at δ 4.32 ppm (J = 7 Hz) corresponds to ethyl group, and two aromatic protons at δ 8.06 ppm (J = 8 Hz) correspond to phenyl ring. Similarly, $^1$H NMR spectrum of pyrazole **8** showed shift in triplet signals of ester intermediate **7** to δ 1.32 ppm (J = 7 Hz) and quartet signal to δ 4.34 ppm (J = 7 Hz), an aromatic protons shifted to δ 7.85 ppm (J = 8 Hz), singlet of pyrazolyl proton was found at δ 7.13 ppm. Hydrazide intermediate **9** was confirmed by the disappeared signal of ester and by the shift of pyrazolyl proton to at δ 7.05 ppm.

**Molecular docking studies.** Molecular docking studies were carried out in order to identify the correlations of novel synthesized compounds with the targeted enzymes COX-2 to predict its selectivity. Synthesized compounds **5a–f** and **10a–j** were subjected for docking studies along with standard celecoxib using crystal structure of COX-2 (3LN1) [26]. An advanced grid-based ligand docking program, GLIDE (Schrodinger Inc., USA) version 4.5, was used to estimate binding affinities of docked compounds. This will approximate the algorithm energetics to systematic positions, orientations, and conformations. Elimination of unwanted conformations was performed by scoring the enzyme pocket via a series of hierarchical filters. Finally, the conformations were refined via Monte Carlo sampling of pose conformation [27,28]. X-ray crystal structure of COX-2 was taken from PDB entry COX-2 (3LN1) having resolution of 2.80 Å (Angstroms).

Structural preparations for docking studies were accomplished using protein preparation wizard in Maestro 9.0. Protein preparation wizard of Maestro 9.0 accomplished the structural preparation of docking studies in two steps, *viz*. preparation and refinement. In a

**Scheme 2.** Synthetic route for 4-[3-(*N′*-alkyloyl/aryloyl-hydrazinocarbonyl)-5-phenylpyrazol-1-yl]-benzenesulfonamide (**10a–j**). Reagents and conditions: (a) NaH/toluene, N$_2$, 0 to 50°C 4 h, yield 89%; (b) (4-sulfamoylphenyl) hydrazine hydrochloride, EtOH, refluxed for 6 h, yield 84%; (c) hydrazine hydrate/EtOH, refluxed for 4 h yield 83%; (d) R-acid, EDC.HCl, HOBt, DIPEA, DMF, RT, 4 h, yield 60–70%.
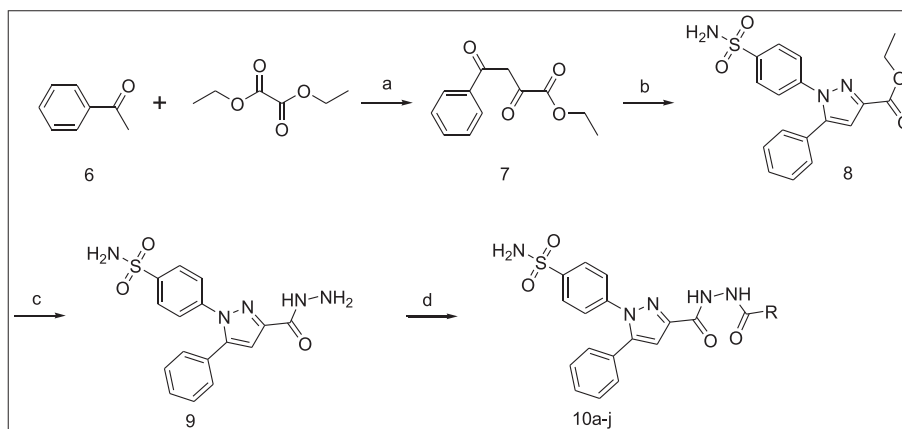
crystal structure of ligand protein, chemical correctness was ensured, water molecules were deleted, and hydrogen atoms were added at missing positions. Bond order for crystal ligand and protein was adjusted and minimized up to 0.30 Å RMSD. Low energy conformations of ligand using OPLS 2005 force field was produced from the Ligprep 2.2 module in Maestro 9.0 build panel. Glide provides three different levels of docking precisions *viz*. high throughput virtual screening, standard precision, and extra precision. We carried out our calculations using extra precision docking mode as the tool is designed for better refinement in ligands. Molecular docking studies revealed that all the designed molecules showed good interactions with receptor active site with glide scores in the range − 13.130 to −10.624. Molecules **10b** and **10g**, the most potent COX-2 inhibitors in current series, showed good interactions with the receptor active site (Fig. 2). Sulfonamide group of **10b** showed hydrogen bonding with Leu 338, Ser 339, Arg 499, and Phe 504. Pyrazole ring of **10b** showed pi stacking with Arg 106. Compound **10g** showed similar interactions with the receptor. All these interactions are also shown by celecoxib (Fig. 3). Thus, it can be concluded that these interactions contribute to the inhibitory activity of these molecules.

***In vitro cyclooxygenase inhibition assay***.    The *in vitro* COX-1/COX-2 isoenzyme inhibition studies measure the ability of tested compounds to inhibit ovine COX-1 and human recombinant COX-2 using an enzyme immunoassay. The obtained results (Table 1) showed that all the tested diaryl pyrazole are found to be weak
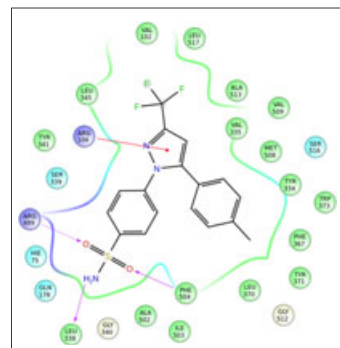


**Figure 3.** Docking interactions of celecoxib with COX-2. [Color figure can be viewed at wileyonlinelibrary.com]

inhibitors for COX-1 isoenzyme ($IC_{50}$ = 3.01–30.18 µM) and exhibited moderate COX-2 isoenzyme ($IC_{50}$ = 0.52–22.25 µM) with COX-2 selectivity's in the range of 0.68–10.31. The acquired data for the two different diaryl series showed that when the two phenyl rings attached to the central pyrazole moiety are not vicinal (**5a–e**), lower inhibitory activities against both COX-1 ($IC_{50}$ = 7.40–30.18 µM) and COX-2 ($IC_{50}$ = 10.18–22.25 µM).

While when the two phenyl rings attached to the central heterocyclic pyrazole nucleus are vicinal (**10a–j**) comparable inhibitory activities against both COX-1 ($IC_{50}$ = 3.01–10.42 µM) and COX-2 ($IC_{50}$ = 0.52–3.70 µM) with celecoxib. In this series, we replaced the trifluoromethyl group of the celecoxib with hydrazide and attached different alkyl and aryl carboxylic
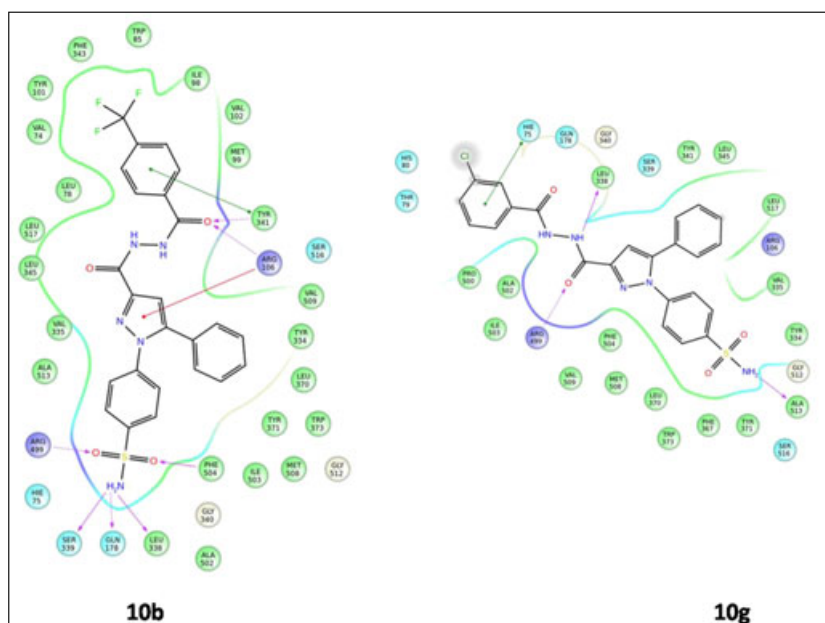


**Figure 2.** Interactions of **10b** and **10g** with the receptor. [Color figure can be viewed at wileyonlinelibrary.com]

**Table 1**

*In vitro* anti-inflammatory COX-1 and COX-2 activities of diaryl sulfonamides.

| Compound | R | COX-1 IC$_{50}$ (μM)[a] | COX-2 IC$_{50}$ (μM)[a] | SI[b] |
|---|---|---|---|---|
| **5a** | phenyl | 7.40 | 10.18 | 0.68 |
| **5b** | 3-pyridyl | 18.23 | 12.40 | 1.47 |
| **5c** | cyclohexyl | 30.18 | 22.25 | 1.35 |
| **5d** | 2-thienyl | 18.30 | 16.20 | 1.12 |
| **5e** | 2-furyl | 24.12 | 15.32 | 1.31 |
| **10a** | methyl | 9.75 | 2.08 | 4.68 |
| **10b** | 3-trifluoromethyl phenyl | 5.58 | 0.52 | 10.73 |
| **10c** | phenyl | 6.51 | 0.82 | 7.93 |
| **10d** | 2-thienyl | 4.21 | 0.62 | 6.79 |
| **10e** | 2,6-dimethoxy phenyl | 10.42 | 2.80 | 3.72 |
| **10f** | cinnamyl | 9.58 | 3.20 | 2.99 |
| **10g** | 3-chloro phenyl | 7.52 | 0.90 | 8.36 |
| **10h** | cyclohexyl | 9.23 | 3.70 | 2.49 |
| **10i** | 3-pyridyl | 3.357 | 0.43 | 8.30 |
| **10j** | 2-furyl | 5.92 | 1.62 | 3.65 |
| Celecoxib | | 7.42 | 0.78 | 9.51 |
| Ibuprofen | | 3.2 | 1.40 | 2.28 |

[a]IC$_{50}$ values represent concentration of test compound required to produce 50% inhibition; the result is the mean of two values obtained by assay of enzyme kits obtained from Cayman Chemicals Inc., Ann Arbor, MI, USA.
[b]Selectivity index (COX-1 IC$_{50}$/COX-2 IC$_{50}$).

acid side chains. Within the biologically active series (**10a**–**j**), the trifluoromethyl (**10b**) and chloro (**10g**) analogs were more selective COX-2 inhibitors (selectivity indices = 10.73 and 8.36, respectively) than unsubstituted phenyl (**10c**), 3-pyridyl (**10i**), and 2-thienyl (**10d**) analogs (selectivity indices = 7.93, 8.30, and 6.79, respectively) in comparison with celecoxib selectivity index = 9.51. Aliphatic acid side chain compounds (**10a** and **10h**) were stand inferior both in activity and COX-2 selectivity. In the active series, it was observed that the aromatic acid compounds substituted with halogen at third position (**10b** and **10g**) were most active. Heterocyclic acid side

chains (**10d** and **10i**) also contributed towards the activities and COX-2 selectivity than the benzoic acid derivative **10c**.

***In vivo* anti-inflammatory activity.**     The anti-inflammatory activities exhibited by selected five compounds (**10b**, **10c**, **10d**, **10g**, and **10i**) using dose 50 mg/kg are listed in Table 2. The phenyl analog **10c**, 2-thienyl analog **10d**, and 3-pyridyl analog **10i** were found to possess anti-inflammatory activity (35.71%, 42.85%, and 35.71% reduction in inflammation after 3 h) less than celecoxib (57.14% reduction in inflammation after 3 h).

While substituted phenyl derivatives **10b** (3-trifluoromethyl) and **10g** (3-chloro), which showed COX-2 activities *in vitro* comparable with celecoxib, showed *in vivo* activity (edema inhibition %: 64.28 and 60.71%, respectively, after 3 h) higher than reference drug celecoxib (edema inhibition %: 57.14% after 3 h).

**Ulcerogenic liability.**     Compounds **10b** and **10g** with potential *in vitro* COX-2 inhibitory activity and showed higher *in vivo* anti-inflammatory activity than celecoxib were evaluated for their ulcerogenic liability according to a known method [29]. From the obtained results (Table 3), compound **10b** and **10g** were found to be less ulcerogenic (ulcer index: 6.6 and 8.65, respectively) than

**Table 3**

Ulcerogenic liability of compounds.

| Compound | Average severity | Average no. of ulcers | % Incidence | Ulcer index[a] |
|---|---|---|---|---|
| **10b** | 0.5 | 0.6 | 5.5 | 6.6 |
| **10g** | 0.65 | 1.5 | 6.5 | 8.65 |
| Celecoxib | 0.54 | 0.5 | 4.5 | 5.54 |
| Ibuprofen | 2.26 | 6.5 | 8.3 | 17.06 |

[a]Statistical analysis used was one-way ANOVA, followed by Dunnett's test, ($n$ = 6).

**Table 2**

*In vivo* anti-inflammatory activity employing carrageenan-induced paw edema method in mice.

| Compound | Change in paw volume in mL after drug treatment (±SEM) | | | | % Inhibition | | |
|---|---|---|---|---|---|---|---|
| | **0h** | **1h** | **2h** | **3h** | **1h** | **2h** | **3h** |
| Control | 0.38 ± 0.03* | 0.48 ± 0.04* | 0.57 ± 0.09* | 0.66 ± 0.04* | — | — | — |
| Celecoxib | 0.27 ± 0.10* | 0.33 ± 0.01* | 0.36 ± 0.10* | 0.39 ± 0.08* | 40 | 52.63 | 57.14 |
| **10b** | 0.34 ± 0.07* | 0.40 ± 0.05* | 0.42 ± 0.02* | 0.44 ± 0.07* | 40 | 57.89 | 64.28 |
| **10c** | 0.37 ± 0.02* | 0.44 ± 0.07* | 0.50 ± 0.07* | 0.55 ± 0.05* | 30 | 31.57 | 35.71 |
| **10d** | 0.30 ± 0.07* | 0.37 ± 0.08* | 0.41 ± 0.09* | 0.46 ± 0.07* | 30 | 42.10 | 42.85 |
| **10g** | 0.33 ± 0.06* | 0.38 ± 0.09* | 0.42 ± 0.08* | 0.44 ± 0.09* | 50 | 52.63 | 60.71 |
| **10i** | 0.35 ± 0.03* | 0.42 ± 0.08* | 0.47 ± 0.06* | 0.52 ± 0.09* | 30 | 36.84 | 35.71 |

Results of all parameters were expressed as mean ± standard error of mean for each group. Data were analyzed by one-way ANOVA followed by Dunnett's test, ($n$ = 6). Dose levels: Test compounds and celecoxib (50 mg/kg, b. w. p. o.).
*$P$ < 0.05 significant from control.

the ibuprofen (ulcer index: 17.06) and displayed comparable ulcerogenic potentials with the celecoxib (ulcer index: 5.54). Hence, **10b** and **10g** was found to be safe gastric profile.

## CONCLUSIONS

Two series containing novel amides (**5a**–**e**) and hydrazide (**10a**–**j**) with diaryl pyrazoles were synthesized and evaluated as selective COX-2 inhibitors, anti-inflammatory agents, and for the safety gastric profile. Molecular docking studies revealed that all the designed molecules showed good interactions with receptor active site with glide scores in the range $-13.130$ to $-10.624$. Biological studies showed that hydrazide analogs were most selective and potent anti-inflammatory agents as compared with the amide analogs. Among all the studied compounds, **10b** and **10g** showed >60% edema inhibition. These two compounds were found to exhibit less ulcerogenic than ibuprofen and showed ulceration effect comparable with that of celecoxib.

## EXPERIMENTAL

All the raw materials and reagents were procured commercially and used without further purification. All the newly synthesized compounds have been characterized by IR, $^1$H NMR, $^{13}$C NMR, mass spectra, and elemental analysis. Melting points were determined on a Veego melting point apparatus model VMP-D apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Varian 400-MHz spectrometer using CDCl$_3$ and DMSO-$d_6$ as solvent with tetramethylsilane as an internal standard, and $^{13}$C NMR spectra were measured on a Varian100 MHz spectrometer DMSO-$d_6$ with tetramethylsilane as the internal standard, where $J$ (coupling constant) values were estimated in hertz (Hz). Elecronspray ionization-mass spectra were obtained by using LC-MS/MS Waters (Aquity) TQ detector. Microanalyses for elemental composition were performed for C, H, and N using vario MICRO elemental instrument and were within ±0.4% of theoretical values. Diaryl sulfonamide derivatives were synthesized in three to four steps via coupling reaction with acids and hydrazides. All the products were soluble with DMSO and DMF. The postulated structures of the newly synthesized compounds (Table 1) were in good agreement with their $^1$H NMR, $^{13}$C NMR spectral data, and elemental analysis data.

**4-Hydrazinobenzenesulfonamide hydrochloride (2).** To a solution of sodium nitrate (3.1 g, 440 mmol) in 12.0-mL water was added into a mixture of sulphanilamide (6.9 g, 400 mol) in concd HCl (30 mL) over 15 min in ice-water bath. Then the mixture was rapidly added to a cooled (0°C) solution of tin (II) chloride dehydrate (27.1 g, 120 mmol) in concd HCl (30 mL). The resulting mixture was stirred at 0°C for 1 h and then warmed to ambient temperature to stir overnight. The precipitate was collected by filtration and successively washed with cool water and Et$_2$O to give the relatively pure compound, which was used directly without further purification. 4-Hydrazinylbenzenesulfonamide hydrochloride, white solid, (6.7 g, yield: 74.1%). $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 10.40 (br s, 3H, —N<u>H</u>$_2$.HCl), 8.86 (s, 1H, Ar—N<u>H</u>—NH$_2$), 7.68 (d, 2H, $J$ = 8 Hz, —SO$_2$—N<u>H</u>$_2$—), 7.18 (s, 1H, Ar—<u>H</u>), 7.03 (d, 2H, $J$ = 7.6 Hz, Ar—H); ESI-MS (M − HCl + H)$^+$: $m/z$ = 188.1.

**4-(5-Amino-3-phenylpyrazol-1-yl)-benzenesulfonamide (4).** To a clear solution of 3-oxo-3-phenylpropionitrile (10 g, 68 mmol) in ethanol (100 mL) at 25°C was added hydrochloride salt of 4-hydrazinylbenzenesulfonamide (15.4 g, 68 mmol) to form a suspension, which was then heated to refluxed temperature for 3 h to become a clear solution, and cooled the reaction mixture to 25°C. Obtained solid was collected by filtration and dried under vacuum to yield the desired intermediate **4** as a yellowish solid, (15 g, yield: 70%); $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 7.87–7.94 (m, 4H, Ar—<u>H</u>), 7.77–7.79 (m, 2H, Ar—<u>H</u>), 7.33–7.42 (m, 5H, Ar—<u>H</u>), 6.02 (s, 1H, Pyrazole-<u>H</u>), 5.72 (br s, Ar—N<u>H</u>$_2$—); ESI-MS (M + H)$^+$: $m/z$ = 315.1.

**General procedure for the synthesis of *N*-[5-phenyl-2-(4-sulfamoylphenyl)-2*H*-pyrazol-3-yl]-amide (5a–f).** To a solution of R-acid (32 mmol) in 5-mL DMF was added EDC.HCl (48 mmol) and 4-(5-amino-3-phenylpyrazol-1-yl)-benzenesulfonamide (32 mmol) followed by the addition of triethylamine (96 mmol) and HOBt (32 mmol) under nitrogen atmosphere. The reaction mixture was stirred for 6 h and quenched with water (50 mL), and adjust the pH = 4 of the reaction mixture with 1N HCl to obtained the solid, which was filtered at Buchner funnel and washed with diethyl ether then dried under vacuum to yield desired solid product (**5a**–**e**).

*N-[5-Phenyl-2-(4-sulfamoylphenyl)-2H-pyrazol-3-yl]-benzamide (5a).* Off-white solid; (1.0 g, yield: 75%); mp = 132–134°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 8.11(d, 2H, $J$ = 8.4 Hz, Ar—<u>H</u>), 7.99 (d, 2H, $J$ = 8.8 Hz, Ar—<u>H</u>), 7.91 (d, 2H, $J$ = 7.2 Hz, Ar—<u>H</u>), 7.62 (d, 2H, $J$ = 7.2 Hz, Ar—<u>H</u>), 7.50 (t, 2H, $J$ = 8.0 Hz, $J$ = 7.2 Hz, Ar—<u>H</u>), 7.40 (t, 2H, $J$ = 7.6 Hz, Ar—<u>H</u>), 7.33–7.34 (m, 3H, Ar—<u>H</u>), 5.97 (s, 1H, Pyrazole-<u>H</u>), 5.77(br s, 2H, —SO$_2$—N<u>H</u>$_2$); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 94.7, 120.4 (2 × C), 127.4 (2 × C), 127.6 (2 × C), 127.8 (2 × C), 127.9, 128.8, 128.9 (2 × C), 129.4 (2 × C), 133.1, 134.2, 137.2, 142.9, 147.9, 151.3, 164.8; ES-MS: $m/z$ 420.3 (M + H)$^+$. *Anal*. Calcd for C$_{22}$H$_{18}$N$_4$O$_3$S; C, 63.14; H, 4.34; N, 13.39; found: C, 63.17; H, 4.33; N, 13.44.

*N-[5-Phenyl-2-(4-sulfamoylphenyl)-2H-pyrazol-3-yl]-nicotinamide (5b).* Brownish solid; (0.911 g, yield: 68%); mp = 130–132°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 9.04 (s, 1H, Py—H), 8.77–8.78 (m, 1H, Py—H), 8.28 (d, 2H, Py—H, $J$ = 8 Hz, Py–H), 8.11 (d, 2H, Py—H, $J$ = 8.8 Hz, Ar—H), 7.98 (d, 2H, $J$ = 8.4 Hz, Ar—H), 7.91 (d, 2H, $J$ = 7.2 Hz, Ar—H), 7.78 (d, 2H, J = 7.2 Hz, Ar—H), 7.72 (d, 2H, $J$ = 8.4 Hz, Ar—H), 5.98 (s,1H, Pyrazole-H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 94.8, 120.5 (2 × C), 125.2, 127.6 (2 × C), 127.8 (2 × C), 128.8, 129.3 (2 × C), 130.8, 138.1, 142.9, 148.0, 148.3, 151.3, 153.7, 164.8; ES-MS: $m/z$ 420.3 (M + H)$^+$. *Anal*. Calcd for C$_{21}$H$_{17}$N$_5$O$_3$S; C, 60.13; H, 4.09; N, 16.70; found: C, 60.13; H, 4.06; N, 16.74.

*Cyclohexanecarboxylic acid [5-phenyl-2-(4-sulfamoylphenyl)-2H-pyrazol-3-yl]-amide (5c).* Off-white solid; (0.976 g, yield: 72%); mp = 136–138°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 7.98–8.01(m, 2H, Ar—H), 7.95–7.99 (m, 2H, Ar—H), 7.39–7.43 (m, 4H, Ar—H), 7.31–7.34 (m, 2H, Ar—H), 5.98 (s,1H, Pyrazole-H), 3.00–3.04 (m, 1H, CH$_2$—CH$_2$—CH$_2$—), 2.23 (br s, 2H, CH$_2$—CH$_2$—CH$_2$—), 1.67–1.77 (m, 4H, —CH$_2$—CH$_2$—CH$_2$—), 1.15–1.19(m, 4H, —CH$_2$—CH$_2$—CH$_2$—); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 24.8 (2 × C), 27.4, 29.2 (2 × C), 43.1, 94.8, 120.4 (2 × C), 127.5 (2 × C), 127.9 (2 × C), 128.7, 129.3 (2 × C), 133.1, 137.2, 142.7, 148.0, 151.2, 173.2; ES-MS: $m/z$ 425.3 (M + H)$^+$. *Anal*. Calcd for C$_{22}$H$_{24}$N$_4$O$_3$S; C, 62.24; H, 5.70; N, 13.20; found: C, 62.28; H, 5.67; N, 13.24.

*Thiophene-2-carboxylic acid [5-phenyl-2-(4-sulfamoylphenyl)-2H-pyrazol-3-yl]-amide (5d).* Yellowish solid; (0.963 g, yield: 71%); mp = 142–144°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 8.11(d, 2H, $J$ = 8.8 Hz, Ar—H), 8.01 (d, 2H, $J$ = 8.8 Hz, Ar—H), 7.96 (d, 2H, $J$ = 8.8 Hz, Ar—H), 7.71–7.77 (m, 2H, Ar—H), 7.53–7.57 (m, 2H, Ar—H), 7.31–7.47 (m, 5H, Ar—H), 5.97 (s, 1H, Pyrazole-H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 94.9, 120.5 (2 × C), 127.4 (2 × C), 127.9 (2 × C), 128.7, 128.9, 129.2 (2 × C), 133.0, 137.2, 137.4, 137.7, 135.9, 142.9, 148.0, 151.3, 161.9; ES-MS: $m/z$ 425.2 (M + H)$^+$. *Anal*. Calcd for C$_{20}$H$_{16}$N$_4$O$_3$S$_2$; C, 56.59; H, 3.80; N, 13.20; found: C, 56.61; H, 3.83; N, 13.23.

*Furan-2-carboxylic acid [5-phenyl-2-(4-sulfamoylphenyl)-2H-pyrazol-3-yl]-amide (5e).* Brownish solid; (0.955 g, yield: 73%); mp = 138–140°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 8.13(d, 2H, $J$ = 8.4 Hz, Ar—H), 7.96 (d, 2H, $J$ = 8.4 Hz, Ar—H), 7.89 (d, 2H, $J$ = 8.8 Hz, Ar—H), 7.71–7.77 (m, 2H, Ar—H), 7.53–7.57 (m, 2H, Ar—H), 7.31–7.47 (m, 5H, Ar—H), 5.99 (s, 1H, Pyrazole-H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 94.8, 111.7, 113.4, 120.6 (2 × C), 127.5 (2 × C), 127.9 (2 × C), 128.7, 128.8, 129.2 (2 × C), 133.0, 142.7, 146.1, 147.2, 148.0, 151.3, 161.9; ES-MS: $m/z$ 409.1 (M + H)$^+$. *Anal*. Calcd for C$_{20}$H$_{16}$N$_4$O$_4$S$_2$; C, 58.81; H, 3.95; N, 13.72; found: C, 58.83; H, 3.97; N, 13.75.

*2-Phenyl-N-[5-phenyl-2-(4-sulfamoylphenyl)-2H-pyrazol-3-yl]-acetamide (5f).* (0.967 g, yield: 70%); mp = 136–138°C;$^1$H NMR (DMSO-$d_6$, 400 MHz): δ 10.14 (s, 1H, —CO—NH), 7.94 (d, 2H, $J$ = 8.4 Hz, Ar—H), 7.84–7.86 (m, 4H, Ar—H), 7.78 (d, 2H, $J$ = 8.0 Hz, Ar—H), 7.35–7.46 (m, 6H, Ar—H), 5.90 (s,1H, Pyrazole-H), 3.14 (s, 2H, Ar—CH$_2$—CO); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ 42.0, 88.32, 121.9, 125.2, 126.9, 128.0, 128.3, 128.5, 128.8 (3 × C), 128.9, 129.2, 129.3 (2 × C), 133.0, 133.8, 135.6, 143.4, 149.1, 149.1, 151.3, 169; ES-MS: $m/z$ 433.3 (M + H)$^+$. *Anal*. Calcd for C$_{23}$H$_{20}$N$_4$O$_3$S; C, 63.87; H, 4.66; N, 12.95; found: C, 63.83; H, 4.63; N, 12.94.

**2,4-Dioxo-4-phenylbutyric acid ethyl ester (7).** To a solution of acetophenone **6** (20 g, 166 mmol) in dry toluene (200 mL) at −10°C was added sodium hydride (11.95 g, 498 mmol) and stirred under nitrogen atmosphere for 1 h. Diethyl oxalate (43.32 g, 249 mmol) in toluene (100 mL) was added dropwise and allowed reaction mixture to room temperature. Reaction mixture then heated to 50°C for 4 h. Cooled reaction mixture to −10°C was added with water (100 mL), and crude product was extracted in toluene. Organic layers were collected, dried over sodium sulfate, and removed under vacuum to give crude intermediate, which was purified by column chromatography (5% EtOAc in Hexane as eluent) to furnish yellow liquid intermediate **7**. (28 g, yield: 76%); $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 8.04 (d, 2H, $J$ = 7.2 Hz, Ar—H), 7.93–7.94 (m, 1H, Ar—H), 7.67–7.70 (m, 1H, Ar—H), 7.54–7.58 (m, 2H, Ar—H), 7.10 (s, 1H, Ar—H), 4.32 (q, 2H, $J$ = 4.4 Hz, —OCH$_2$—CH$_3$), 1.31 (t, 3H, —OCH$_2$—CH$_3$,$J$ = 7.2 Hz); ES-MS: $m/z$ 221.1 (M + H)$^+$.

**5-Phenyl-1-(4-sulfamoylphenyl)-1H-pyrazole-3-carboxylicacid ethyl ester (8).** To a suspension of (4-sulfamoylphenyl) hydrazine hydrochloride (25.4 g, 113 mmol) in ethanol (100 mL) was added 2,4-dioxo-4-phenylbutyric acid ethyl ester **7** (25 g, 113 mmol) and refluxed the reaction mixture for 6 h. Reaction mixture becomes clear at the completion of the reaction under reflux. Cooled the content to room temperature, precipitated solid was filtered and washed with chilled ethanol (10 mL) and dried to obtain white solid as intermediate **8** (30 g, yield: 69%); mp = 192–194°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 7.84 (d, 2H, $J$ = 8.4 Hz, Ar—H), 7.49–7.51 (m, 4H, Ar—H), 7.38–7.39 (m, 2H, Ar—H), 7.27–7.29 (m, 2H, Ar—H), 7.13 (s, 1H, Pyrazole-H), 4.34 (q, 2H, $J$ = 6.8 Hz, —OCH$_2$—CH$_3$), 1.30 (t, 3H, —OCH$_2$—CH$_3$, $J$ = 7.2 Hz); ES-MS: $m/z$ 372.2 (M + H)$^+$.

**4-(3-Hydrazinocarbonyl-5-phenylpyrazol-1-yl)-benzenesulfonamide (9).** To a suspension of ester intermediate (10 g, 269 mmol) **8** in ethanol (50 mL) was added hydrazine hydrate (6.72 g, 134 mmol) and refluxed the reaction mixture for 6 h. Reaction mixture becomes clear at the completion of the reaction under reflux.

Cooled the content to room temperature, precipitated solid was filtered and washed with chilled ethanol (10 mL) and dried to obtain white solid as hydrazide intermediate **9** (8 g, yield: 83%); mp = 187–189°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 9.73 (s, 1H, —N$\underline{\text{H}}$—NH$_2$), 7.86 (d, 2H, $J$ = 8.4 Hz, Ar—$\underline{\text{H}}$), 7.54 (d, 2H, $J$ = 7.6 Hz, Ar—$\underline{\text{H}}$), 7.38–7.44 (m, 4H, Ar—$\underline{\text{H}}$), 7.27–7.29 (m, 2H, Ar—$\underline{\text{H}}$), 7.11 (s, 1H, Pyrazole-$\underline{\text{H}}$),4.64 (br s, 2H, —NH—N$\underline{\text{H}}_2$); ES-MS: $m/z$ 358.1 (M + H)$^+$.

**General procedure for the synthesis of 4-[3-($N'$-alkyloyl/ aryloyl-hydrazinocarbonyl)-5-phenylpyrazol-1-yl]-benzenesulfonamide (10a–j).** To a clear solution of R-acid (14 mmol) in dry dimethylformamide (5 mL) was added EDC.HCl (21 mmol) and 4-(3-hydrazinocarbonyl-5-phenylpyrazol-1-yl)-benzenesulfonamide (14 mmol), followed with the addition of HOBt (14 mmol). Reaction mixture was stirred for 6 h. Water was added (50 mL), and the product was extracted in EtOAc (2 × 50 mL), organic layers were washed with NaHCO$_3$ solution in water, 10% aq HCl, 25% aq NH$_4$Cl solution in water, brine, and dried over Na$_2$SO$_4$ and removed under vacuum to obtain crude residue, which was purified by column chromatography (2% MeOH in Chloroform as eluent) to furnish title solid product in 60–70% yield (**10a–j**).

*4-[3-($N'$-Acetylhydrazinocarbonyl)-5-phenylpyrazol-1-yl]-benzenesulfonamide (10a).* White solid; (0.52 g, yield: 72%); mp = 124–126°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 10.11 (s, 1H, —CO—N$\underline{\text{H}}$—), 9.78 (s, 1H, —CO—N$\underline{\text{H}}$—), 7.86 (d, 2H, $J$ = 9.2 Hz, Ar—$\underline{\text{H}}$), 7.54 (d, 2H, $J$ = 9.2 Hz, Ar—$\underline{\text{H}}$), 7.48–7.52 (m, 2H, Ar—$\underline{\text{H}}$), 7.41–7.43 (m, 3H, Ar—$\underline{\text{H}}$), 7.29–7.32 (m, 2H, Ar—$\underline{\text{H}}$), 7.09 (s, 1H, Pyrazole-$\underline{\text{H}}$), 2.24 (s, 3H, —C$\underline{\text{H}}_3$); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 25.4, 108.6, 125.5 (3 × C), 126.6 (3 × C), 128.7, 128.6, 129.2, 129.1, 141.5, 143.5, 144.3, 145.8, 162.3, 172.5; ES-MS: $m/z$ 400.3 (M + H)$^+$; *Anal*. Calcd for C$_{18}$H$_{17}$N$_5$O$_4$S: C, 54.13; H, 4.29; N, 17.53; found: C, 54.16; H, 4.32; N, 17.50.

*4-{5-Phenyl-3-[$N'$-(3-trifluoromethylbenzoyl)-hydrazinocarbonyl]-pyrazol-1-yl}-benzenesulfonamide (10b).* Greenish solid; (0.55 g, yield: 74%); greenish solid; mp = 136–138°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 10.81 (s, 1H, —CO—N$\underline{\text{H}}$—), 10.51 (s, 1H, —CO—N$\underline{\text{H}}$—), 8.27(s, 1H, Ar—$\underline{\text{H}}$), 8.23 (d, 1H, $J$ = 8 Hz, Ar—$\underline{\text{H}}$), 7.99 (d, 1H, $J$ = 7.6 Hz, Ar—$\underline{\text{H}}$), 7.88 (d, 2H, $J$ = 8.4 Hz, Ar—$\underline{\text{H}}$), 7.78 (t, 1H, $J$ = 7.6 Hz, Ar—$\underline{\text{H}}$), 7.57 (d, 2H, $J$ = 8.4 Hz, Ar—$\underline{\text{H}}$), 7.50 (s, 2H, Ar—SO$_2$—N$\underline{\text{H}}_2$), 7.32–7.34 (m, 2H, Ar—$\underline{\text{H}}$ 7.42–7.44 (m, 3H, Ar—$\underline{\text{H}}$), 7.34–7.35 (m, 2H, Ar—$\underline{\text{H}}$), 7.16 (s, 1H, Pyrazole-H), $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 108.7, 122.5, 125.2 (3 × C), 125.7, 126.7, 128.5, 128.8 (2 × C), 129.5, 129.9 (2 × C), 131.6 (2 × C), 133.3, 141.5, 143.6, 144.6, 146.0, 160.4, 164.3; ES-MS: $m/z$ 528.5 (M + H)$^+$; *Anal*. Calcd for C$_{24}$H$_{18}$F$_3$N$_5$O$_4$S: C, 54.44; H, 3.43; N, 13.23; found: C, 54.47; H, 3.45; N, 13.25.

*4-[3-($N'$-Benzoylhydrazinocarbonyl)-5-phenylpyrazol-1-yl]-benzenesulfonamide (10c).* White solid; (0.540 g, yield: 83%); mp = 128–130°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 10.49 (s, 1H, —CO—N$\underline{\text{H}}$—), 10.36 (s, 1H, —CO—N$\underline{\text{H}}$—), 7.91(d, 3H, $J$ = 7.2 Hz, Ar—$\underline{\text{H}}$), 7.86 (d, 2H, $J$ = 8 Hz, Ar—$\underline{\text{H}}$), 7.54–7.58 (m, 6H, Ar—$\underline{\text{H}}$), 7.49 (s, 2H, Ar—SO$_2$—N$\underline{\text{H}}_2$), 7.40–7.41 (br s, 2H, Ar—$\underline{\text{H}}$), 7.31–7.32 (br s, 2H, Ar—$\underline{\text{H}}$), 7.13 (s, 1H, Pyrazole -H), $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 108.7, 125.7(3 × C), 126.7 (3 × C), 127.5 (3 × C), 128.5 (2 × C),128.1, 128.8, 128.9 (2 × C), 131.8, 132.5, 141.5, 143.5, 144.5, 146.1, 160.4, 165.7;ES-MS: $m/z$ 462.3 (M + H)$^+$, mp = 128–130°C, *Anal*. Calcd for C$_{23}$H$_{19}$N$_5$O$_4$S: C, 59.86; H, 4.15; N, 15.18; S, 6.95. Found: C, 59.83; H, 4.17; N, 15.16; S, 6.98.

*4-{5-Phenyl-3-[$N'$-(thiophene-2-carbonyl)-hydrazinocarbonyl]-pyrazol-1-yl}-benzenesulfonamide (10d).* Brownish solid; (0.52 g, yield: 79%); mp = 122–124°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 10.53 (s, 1H, —CO—N$\underline{\text{H}}$—), 10.41 (s, 1H, —CO—N$\underline{\text{H}}$—), 7.86–7.9 (m, 5H, Ar—$\underline{\text{H}}$), 7.56 (d, 2H, $J$ = 8.8 Hz, Ar—$\underline{\text{H}}$), 7.49 (s, 2H, Ar—SO$_2$—N$\underline{\text{H}}_2$), 7.41–7.43 (m, 2H, Ar—$\underline{\text{H}}$), 7.32–7.34 (m, 2H, Ar—$\underline{\text{H}}$), 7.21–7.23 (m, 1H, Ar—$\underline{\text{H}}$), 7.13 (s, 1H, Pyrazole-$\underline{\text{H}}$), $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 108.3, 125.4(2 × C), 126.3 (2 × C), 127.5, 128.5 (2 × C), 128.1, 128.8, 128.9 (2 × C), 131.8, 132.5(2 × C), 137.4 (2 × C), 141.5,143.5, 161.5, 163.5; ES-MS: $m/z$ 468.2 (M + H)$^+$. *Anal*. Calcd for C$_{21}$H$_{17}$N$_5$O$_4$S$_2$: C, 53.95; H, 3.67; N, 14.98; found: C, 53.93; H, 3.64; N, 14.96.

*4-{3-[$N'$-(2,6-Dimethoxybenzoyl)-hydrazinocarbonyl]-5-phenylpyrazol-1-yl}-benzenesulfonamide (10e).* White solid; (0.51 g, yield: 69%); mp = 132–134°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 10.29 (s, 1H, —CO—N$\underline{\text{H}}$—), 10.13 (s, 1H, —CO—N$\underline{\text{H}}$—), 7.86 (d,3H, $J$ = 9.2 Hz, Ar—$\underline{\text{H}}$), 7.56 (d, 3H, $J$ = 8.8 Hz, Ar—SO$_2$—N$\underline{\text{H}}_2$), 7.49 (m, 2H, Ar—SO$_2$—N$\underline{\text{H}}_2$), 7.43–7.44 (m, 4H, Ar—$\underline{\text{H}}$), 7.43–7.44 (m, 4H, Ar—$\underline{\text{H}}$), 7.31–7.36 (m, 5H, Ar—$\underline{\text{H}}$), 7.14 (s, 1H, Pyrazole-$\underline{\text{H}}$), 6.70 (d, 3H, $J$ = 8.8 Hz, Ar—$\underline{\text{H}}$), 3.77 (s, 6H, Ar—OC$\underline{\text{H}}_3$), $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 56.1, 56.3, 105.4, 107.3(2 × C), 108.4, 122.3, 125.7(2 × C), 126.4 (2 × C), 127.8, 128.5 (2 × C),128.1, 128.8, 128.9 (2 × C), 131.8, 132.5, 141.5, 144.5, 146.1, 160.4, 165.7; ES-MS: $m/z$ 522.4 (M + H)$^+$, *Anal*. Calcd for C$_{25}$H$_{23}$N$_5$O$_6$S: C, 57.57; H, 4.45; N, 13.43; found: C, 57.54; H, 4.43; N, 13.47.

*4-{5-Phenyl-3-[$N'$-(3-phenylacryloyl)-hydrazinocarbonyl]-pyrazol-1-yl}-benzenesulfonamide (10f).* White solid; (0.55 g, yield: 80%);mp = 128–130°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 10.38 (s, 1H, —CO—N$\underline{\text{H}}$—), 10.24 (s, 1H, —CO—N$\underline{\text{H}}$—), 7.89 (d, 2H, $J$ = 8 Hz, Ar—$\underline{\text{H}}$), 7.71 (br s, 2H, Ar—$\underline{\text{H}}$), 7.49–7.64 (m, 5H, Ar—$\underline{\text{H}}$), 7.49 (s,1H, Ar—SO$_2$—N$\underline{\text{H}}_2$), 7.41–7.45 (m, 2H, Ar—$\underline{\text{H}}$), 7.32–7.36 (m, 2H, Ar—$\underline{\text{H}}$), 7.14 (s, 1H, Pyrazole-$\underline{\text{H}}$), 6.77 (s, 1H, —CO—C$\underline{\text{H}}$=CH—), 6.73 (s, 1H, —CH=C$\underline{\text{H}}$—Ar); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 108.5, 119.1, 124.9 (2 × C), 125.3, 126.5 (2 × C), 126.7 (2 × C), 127.3 (2 × C), 128.4 (2 × C), 128.1, 128.8,

128.9 (2 × C), 131.8, 132.5, 141.5, 142.8, 144.5, 146.1, 160.4, 165.7; ES-MS: $m/z$ 488.2 (M + H)$^+$; *Anal*. Calcd for $C_{25}H_{21}N_5O_4S$: C, 61.59; H, 4.34; N, 14.36; found: C, 61.58; H, 4.37; N, 14.39.

*4-{3-[N′-(3-Chlorobenzoyl)-hydrazinocarbonyl]-5-phenylpyrazol-1-yl}-benzenesulfonamide (10g).* Yellowish solid; (0.53 g, yield: 76%); mp = 125–127°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 10.89 (s, 1H), 10.42 (s, 1H), 7.88 (d, 2H, $J$ = 8.4 Hz, Ar—<u>H</u>), 7.51–7.57 (m, 5H, Ar—<u>H</u>), 7.46 (s, 2H, Ar—SO₂—N<u>H</u>₂), 7.42–7.45 (m, 4H, Ar—<u>H</u>), 7.32–7.34 (m, 2H, Ar—<u>H</u>), 7.14 (s, 1H, Pyrazole-<u>H</u>), $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 108.5, 121.8, 125.2 (3 × C), 125.7, 127.3, 128.7, 128.5 (2 × C), 129.5, 131.2 (2 × C), 131.6 (2 × C), 133.4, 142.0, 143.6, 144.6, 146.2, 160.1, 164.2; ES-MS: $m/z$ 496.3 (M + H)$^+$; *Anal*. Calcd for $C_{23}H_{18}ClN_5O_4S$: C, 55.70; H, 3.66; N, 14.12; found: C, 55.68; H, 3.67; N, 14.10.

*4-[3-(N′-Cyclohexanecarbonyl-hydrazinocarbonyl)-5-phenylpyrazol-1-yl]-benzenesulfonamide (10h).* White solid; (0.50 g, yield: 76%); mp = 134–136°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 10.11 (s, 1H, —CO—N<u>H</u>—), 9.78 (s, 1H, —CO—N<u>H</u>—), 7.86 (d, 2H, $J$ = 9.2 Hz, Ar—<u>H</u>), 7.54 (d, 3H, $J$ = 9.2 Hz, Ar—<u>H</u>), 7.48 (s, 1H, Ar—SO₂—N<u>H</u>₂), 7.41–7.43 (m, 3H, Ar—<u>H</u>), 7.29–7.32 (m, 2H, Ar—<u>H</u>), 7.09 (s, 1H, Pyrazole-<u>H</u>), 2.24 (m, 1H, —C<u>H</u>₂—CH₂—), 1.62–1.90 (m, 5H, —C<u>H</u>₂—CH₂—), 1.15–1.41 (m, 5H, —C<u>H</u>₂—CH₂—),$^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 25.1(2 × C), 25.4, 29.0 (2 × C), 42.0, 108.6, 125.5 (3 × C), 126.6 (3 × C), 128.7, 128.8, 129.0, 129.1, 141.5, 143.5, 144.4, 146.1, 160.0, 174.5; ES-MS: $m/z$ 468.3 (M + H)$^+$; *Anal*. Calcd for $C_{23}H_{25}N_5O_4S$: C, 59.09; H, 5.39; N, 14.98; found: C, 59.06; H, 4.37; N, 14.99.

*4-{5-Phenyl-3-[N′-(pyridine-3-carbonyl)-hydrazinocarbonyl]-pyrazol-1-yl}-benzenesulfonamide (10i).* Yellowish solid (0.49 g, yield: 75%); mp = 148–150°C;$^1$H NMR (DMSO-$d_6$, 400 MHz) δ 10.49 (s, 1H, —CO—N<u>H</u>—), 10.36 (s, 1H, —CO—N<u>H</u>—), 9.08(s, 1H, Ar—H), 8.58–8.659 (m, 2H, Ar—H) 7.99 (d, 2H, $J$ = 8 Hz, Ar—<u>H</u>), 7.84 (d, 2H, $J$ = 8 Hz, Ar—<u>H</u>), 7.54–7.58 (m, 2H, Ar—<u>H</u>), 7.49 (s, 2H, Ar—SO₂—N<u>H</u>₂), 7.42–7.44 (m, 3H, Ar—<u>H</u>), 7.31–7.32 (br s, 2H, Ar—<u>H</u>), 7.13 (s, 1H, Pyrazole-<u>H</u>), $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ 108.7, 125.7(2 × C), 126.7 (2 × C), 127.5 (2 × C), 128.5 (2 × C),128.1, 128.7, 128.9 (2 × C), 131.8, 132.5, 141.5, 143.5, 144.5, 148.3, 153.7, 161.3, 165.6; ES-MS: $m/z$ 463.3 (M + H)$^+$, *Anal*. Calcd for $C_{22}H_{18}N_6O_4S$: C, 57.13; H, 3.92; N, 18.17; O, 13.84; found: C, 57.15; H, 3.95; N, 18.16.

*4-{3-[N′-(Furan-2-carbonyl)-hydrazinocarbonyl]-5-phenylpyrazol-1-yl}-benzenesulfonamide (10j).* Brownish solid (0.54 g, yield: 85%); mp = 138–140°C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 10.54 (s, 1H, —CO—N<u>H</u>—), 10.44 (s, 1H, —CO—N<u>H</u>—), 7.88–7.92 (m, 4H, Ar—<u>H</u>), 7.58 (d, 2H, $J$ = 8.0 Hz, Ar—<u>H</u>), 7.49 (s, 2H, Ar—SO₂—N<u>H</u>₂), 7.44–7.46 (m, 3H, Ar—<u>H</u>), 7.34–7.37 (m, 2H, Ar—<u>H</u>), 7.24–7.26 (m, 1H, Ar—<u>H</u>), 7.14 (s, 1H, Pyrazole-<u>H</u>), $^{13}$C NMR

(DMSO-$d_6$, 100 MHz) δ 108.5, 113.4, 113.7, 126.3 (2 × C), 127.4, 127.6 (2 × C), 128.1, 128.8, 128.9 (2 × C), 131.7, 133.5(2 × C), 136.5, 137.4 (2 × C), 141.5, 161.5, 163.5; ES-MS: $m/z$ 451.2 (M + H)$^+$, *Anal*. Calcd for $C_{21}H_{17}N_5O_5S$: C, 55.87; H, 3.80; N, 15.51. Found: C, 55.90; H, 3.84; N, 15.53.

**Determination of anti-inflammatory activity.** All the prepared target compounds **5a**–**e** and **10a**–**j** were screened for their anti-inflammatory activities against cyclooxygenase-1 and cyclooxygenase-2 at Deshpande Laboratories, Bhopal, M.P. Inhibition by test compounds **5a**–**e** and **10a**–**j** of ovine COX-1 and human recombinant COX-2 [IC$_{50}$ values (μM)] was assessed using a COX Fluorescent Inhibitor Screening Assay Kit (catalog number 700100, Cayman Chemical, Ann Arbor, MI, USA).

*In vitro* **cyclooxygenase inhibition assay.** Stock solutions of test compounds were prepared in a minimum volume of DMSO. Briefly, to a series of supplied reaction buffer solutions (150 mL, 100m*M* Trise-HCl, pH 8.0) with either COX-1 or COX-2 (10 mL) enzyme in the presence of Heme (10 mL) and fluorometric substrate (10 mL) were added 10 mL of various concentrations of the test compound solutions (final between 0.01 and 100m*M*). The reactions were initiated by quickly adding 10 mL of arachidonic acid solution and then incubated for 2 min at room temperature. Fluorescence of resorufin that is produced by the reaction between PGG2 and the fluorometric substrate, ADHP (10-acetyl-3,7-dihydroxyphenoxazine) was read with an excitation wavelength of 535 nm and an emission wavelength of 590 nm. The intensity of this fluorescence is proportional to the amount of resorufin, which is proportional to the amount of PGG2 present in the well during the incubation. Percent inhibition was calculated by comparison from the 100% initial activity sample value (no inhibitor). The concentration of the test compound causing 50% inhibition of COX-1 and COX-2 (IC$_{50}$, m*M*) was calculated from the concentration-inhibition response curve (triplicate determinations); results were tabulated in Table 1.

*In vivo* **anti-inflammatory activity.** Compounds with better *in vitro* anti-inflammatory activities (IC$_{50}$) were evaluated further for *in vivo* anti-inflammatory activity. Five compounds (**10b**, **10c**, **10d**, **10g**, and **10i**) were studied using carrageenan-induced rat paw edema method at a dose of 50 mg/kg. The sub planter region of right hind paw of each rat was injected with a freshly prepared aqueous suspension of carrageenan (1.0% *w/v*, 0.1 mL). Out of the two groups of animals, one group was kept as control, and other were pretreated with test drugs and standard drug 1 h before the carrageenan treatment. Results are reported in Table 2. Digital plethysmometer (UGO Basil, Italy) was used to measure the paw volume

of the all groups. Readings were taken before injection of carrageenan (0 min) and again at 1, 2, and 3 h after carrageenan injection. The edema was expressed as a mean reduction in paw volume (mL) and the percent of edema inhibition were obtained as follows: where $V_t$ is the volume of edema at specific time interval and $V_c$ is the volume of edema at zero time interval.

$$\%\text{inhibition} = \frac{(V_t - V_c)\,\text{control} - (V_t - V_c)\,\text{tested compound}}{(V_t - V_c)} \times 100$$

**Evaluation of ulcerogenicity index.** Compound **10b** and **10g** were studied further for ulcerogenicity index. Ulceration in rats was induced as described in known procedure [30]. Albino rats of the Wister strain weighing 150–200 g of either sex were divided into various groups, each of six animals. Control group of animals were administered only 1% carboxymethylcellulose solution in water. One group was administered with Ibuprofen at a dose of 100 mg/kg once daily for 4 days. The remaining group of animals was administered with test compound sat a dose of 100 mg/kg. On the fifth day, pylorus was legated as per the literature method [31]. Ten animals were fasted for 24 h before the pylorus ligation procedure. Four hours after the ligation, animals were sacrificed. The stomach was removed and opened along with the greater curvature. Ulcer index was determined by the method of [29] and is recorded in Table 3.

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### SUPPORTING INFORMATION

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