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Full Paper

Synthesis and Biological Evaluation of New Diarylpyrazole and Triarylimidazoline Derivatives as Selective COX-2 Inhibitors

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New series of diarylpyrazoles **8a–f** and triarylimidazoline-5-ones **11a–g** were synthesized and evaluated for their *in vitro* cyclooxygenase-1 (COX-1) and COX-2 inhibitory activity and *in vivo* anti-inflammatory activity. The synthesized compounds showed good selectivity for COX-2; compounds **8a**, **8d**, **8f**, **11a**, and **11c** exhibited the highest COX-2 selectivity indexes (SI = 4.77–5.43) compared to the reference drug celecoxib (SI = 7.8). All compounds showed good *in vivo* anti-inflammatory activity, especially compounds **8a**, **8f**, **11c**, and **11d**, which also showed some similarities to the time interval pattern of celecoxib at all different time intervals (1, 3, and 6 h).

Keywords: Anti-inflammatory / Imidazoline / Pyrazole / Selective COX-2 inhibitor

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin (**1**) and indomethacin (**2**) are used to treat pain, inflammation, and fever [1]. All these agents produce their therapeutic effects through inhibition of cyclooxygenases enzyme (COX) which exists in two isozymes (COX-1 and COX-2) [2–4]. Inhibition of COX-1 isozyme leads to renal and gastrointestinal side effects, while isozyme COX-2 inhibition leads to therapeutic effects [5]. The classical NSAIDs like aspirin (**1**) and indomethacin (**2**) inhibit both COX-1 and COX-2 isozymes leading to undesirable side effects [6–10]. Celecoxib (**3**) is a selective COX-2 inhibitor that appeared on the world market as a safer replacement for the classical NSAIDs due to its less gastrointestinal complications [11–15]. After the launch of several selective COX-2 inhibitors as successful anti-inflammatory agents, rofecoxib (**4**) was withdrawn from the market with subsequent evidence of atherothrombotic cardiovascular side effects [16–18]. Fortunately, further studies revealed that cardiac adverse effects are related to certain drug structures and their metabolic products rather than COX-2 physiological role. For example, rofecoxib (**4**) was said to produce highly reactive oxidized metabolites leading to accumulation of oxidized LDL [19, 20]. Most of the reported selective COX-2 inhibitors possess two vicinal aryl groups attached to a heterocyclic core, one of the two aryl rings contains the essential pharmacophore for COX-2 selectivity: SO_2NH_2 or SO_2CH_3 [21–27]. In a recent study [28], we reported some triarylpyrazoline derivatives **5** with good anti-inflammatory activity and good safety profile (Fig. 1).

Our aim in this work is to continue our recent study to obtain other newly synthesized compounds with good anti-inflammatory activity. Accordingly, we now describe the synthesis, *in vitro* evaluation as COX-1/COX-2 inhibitors and *in vivo* anti-inflammatory (AI) activity for two new series of compounds: (i) diarylpyrazole compounds **8a–f** with vicinal

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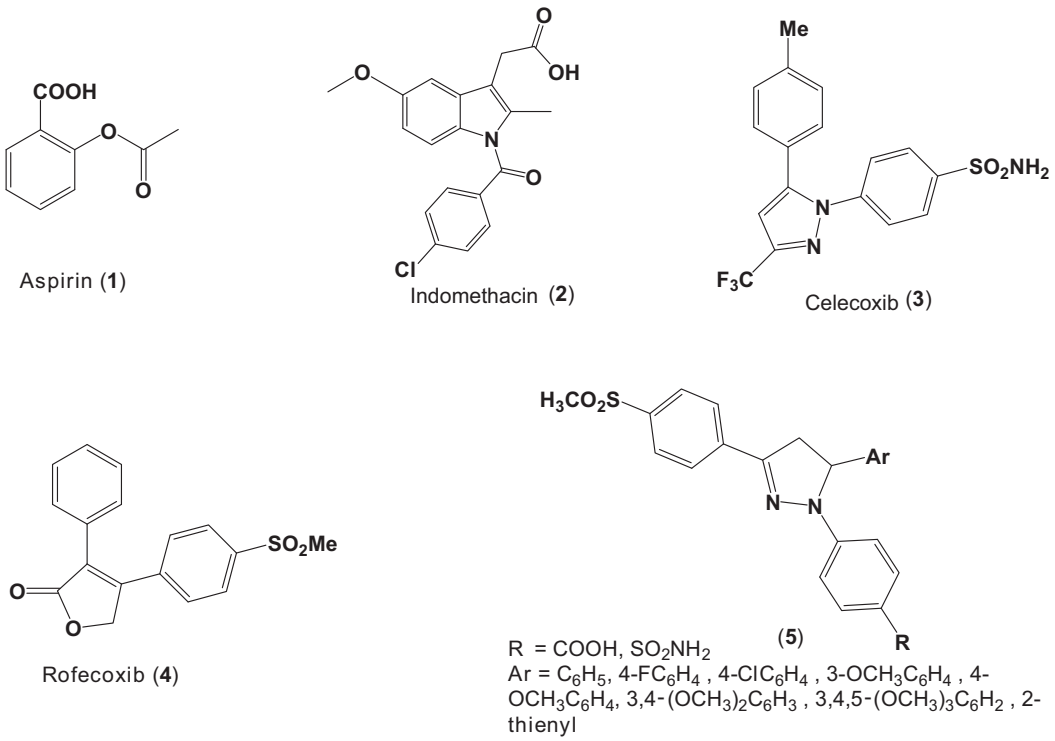


Figure 1. Chemical structures of aspirin (**1**), indomethacin (**2**), celecoxib (**3**), rofecoxib (**4**), and reported triarylpyrazoline derivatives (**5**).

diaryl rings containing SO_2CH_3 as an important pharmacophore for COX-2 selectivity, and (ii) triarylimidazoline derivatives **11a–g** which also have two vicinal diaryl rings, celecoxib CF_3 was replaced by a bulky lipophilic arylidene group and possess SO_2NH_2 moiety required for COX-2 selectivity (Fig. 2).

Results and discussion

Chemistry

The (*E*)-3-dimethylamino-1-(4-methylsulfonylphenyl)-prop-2-en-1-one (**6**) was prepared from *p*-methylsulfonylacetophenone and dimethylformamide-dimethylacetal (DMF-DMA) according to previously reported procedures [29]. Heating **6** with different substituted phenylhydrazine hydrochlorides **7a–f** in ethanol under reflux condition afforded the target diarylpyrazole compounds (**8a–f)** in good yields (55–77%) (Scheme 1).

Additionally, *p*-methoxybenzoylglycine **9** was synthesized via heating mixture of glycine in sodium hydroxide (10%) with 4-methoxybenzoyl chloride as reported before [30]. Cyclocondensation of **9** with different aromatic aldehydes in acetic anhydride containing catalytic amount of sodium acetate afforded (*E*)-4-arylmethylene-2-(4-methoxyphenyl)-oxazol-5(4*H*)-ones **10a–g** [29]. The triarylimidazoline-5-ones **11a–g** were obtained in good yields (60–85%) via heating oxazolones **10a–g** with sulfanilamide in glacial acetic acid (Scheme 2).

Biological evaluation

In vitro COX inhibition assay

The *in vitro* COX-1/COX-2 isozyme inhibition studies measure the ability of target compounds to inhibit ovine COX-1 and human recombinant COX-2 using an enzyme immunoassay (EIA) [31]. The efficacy of the tested compounds is expressed as the concentration causing 50% inhibition (IC_{50}). *In vitro* COX-1 and COX-2 isozyme inhibition studies (Table 1) showed that all the tested compounds are weak inhibitors of COX-1 isozyme ($IC_{50} = 3.9–13.2\ \mu M$ range). In contrast, they have good COX-2 isozyme inhibitory activities ($IC_{50} = 0.74–4.74\ \mu M$) in comparison with the reference drug celecoxib ($IC_{50} = 0.87\ \mu M$). Additionally, the results showed COX-2 selectivity indexes (SI) – calculated as IC_{50} (COX-1)/IC_{50} (COX-2) – in the range of 2.58–5.43 in comparison with the selective COX-2 inhibitor, celecoxib (SI = 7.8). Within the diarylpyrazole compounds (**8a–f**), when the phenyl group attached to position 1 of the central pyrazole ring is unsubstituted (**8a**), *para* substituted with COOH (**8d**) or *para* substituted with SO_2NH_2 (**8f**), the potency against COX-2 isozyme was high ($IC_{50} = 1.52$, 1.27 and 1.11 μM, respectively) and consequently high COX-2 selectivity indexes

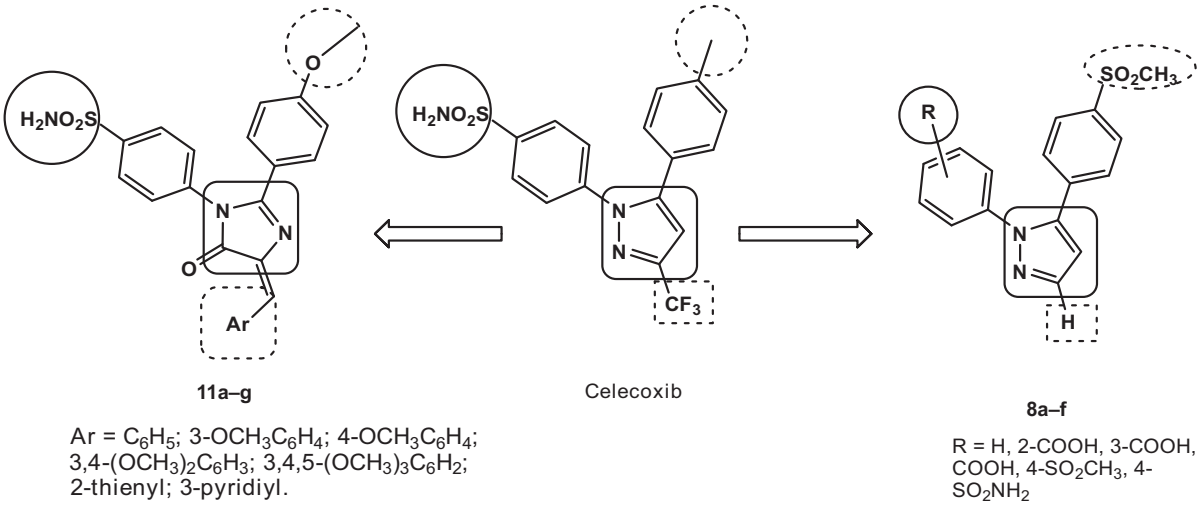


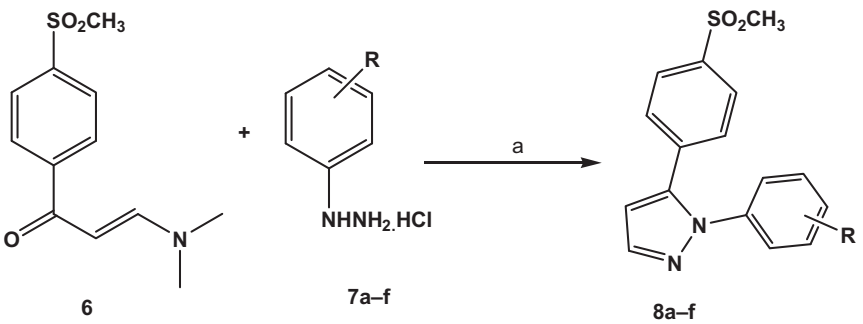
Figure 2. Representive examples of celecoxib (**3**) as selective COX-2 inhibitors and designed compounds **8a–f** and **11a–g**.

(SI = 4.80, 5.43 and 4.77, respectively) were obtained. Moreover, within the triarylimidazoline-5-ones **11a–g**, the unsubstituted phenyl derivative (**11a**), the *para* methoxyphenyl derivative (**11c**) and the dimethoxyphenyl derivative (**11d**) were the highest potent derivatives against COX-2 isozyme (IC_{50} = 0.87, 0.74 and 1.42 μM, respectively) and showed the highest COX-2 selectivity indexes (SI = 4.83, 5.27 and 3.59, respectively).

In vivo anti-inflammatory activity

The *in vivo* anti-inflammatory activity (AI) of diarylpyrazoles **8a–f**, triarylimidazoline-5-ones **11a–g**, and celecoxib was determined using carrageenan-induced rat paw edema assay according to the reported procedure [32] using a dose of 50 mg/kg body weight. The anti-inflammatory activity was then calculated based on paw-volume changes at 1, 3 and 6 h after carrageenan injection as presented in Table 1. A comparable study of the anti-inflammatory activity of the test compounds relative to celecoxib as a reference drug at the different time intervals revealed that, for pyrazole compounds **8a–f**, after 1 h they showed moderate anti-inflammatory activity (AI = 34–70%), and the most active compounds were **8a** (AI = 70%) and **8b** (AI = 69%) in comparison with celecoxib (AI = 42%). While after 3 h, compounds **8a–f** showed anti-inflammatory activity (AI = 29–63%), **8b** and **8f** showed the highest anti-inflammatory activity (63% for both). While after 6 h, **8a–f** showed anti-inflammatory activity (AI = 29–56%).

The imidazoline derivatives **11a–g** showed anti-inflammatory activity after 1 h of carrageenan injection (AI = 41–87%) and the most potent COX-2 derivatives (**11c** and **11d**) showed the highest



a, R = H; **b**, R = 2-COOH;
c, R = 3-COOH; **d**, R = 4-COOH;
e, R = 4-SO_2CH_3; **f**, R = 4-SO_2NH_2.

Scheme 1. Synthesis of compounds **8a–f**. Reagents and conditions: (a) Ethanol 95%, reflux, 24 h.

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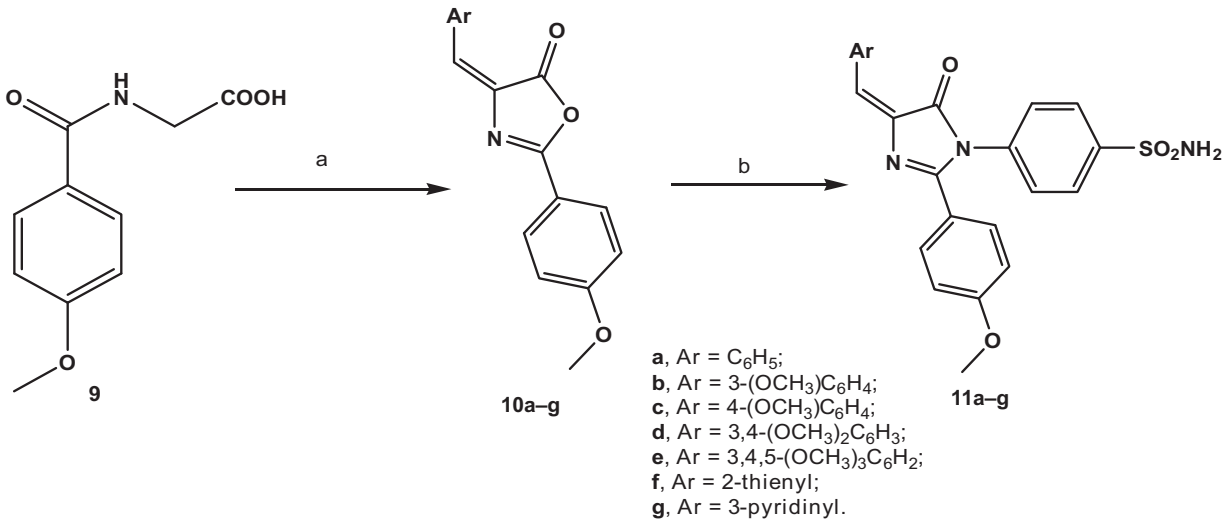

Scheme 2. Synthesis of compounds **11a–g**. Reagents and conditions: (a) Appropriate Ar-CHO, CH_3COONa, acetic anhydride, water bath, 100°C, 6 h. (b) $H_2NC_6H_4SO_2NH_2$, CH_3COONa, glacial acetic acid, reflux, 24 h.

AI activities (AI = 87 and 75%, respectively). After 3 h, **11a–g** showed anti-inflammatory activity (AI = 32–51%), compounds **11a** and **11f** showed the highest activity (AI = 51.49%). After 6 h, compounds **11a–g** showed moderate anti-inflammatory activity (AI = 35–64%), the most active compounds were **11c** and **11d** (AI = 64 and 60%, respectively). Additionally, it was noted that all compounds **8a–f** and **11a–g** significantly decreased inflammation as compared with carragenan at alltime intervals and were significantly different from each other. Compounds **8a, 8f**, **11c**, and **11d** along the different time intervals (1, 3, and 6 h)

Table 1. ***In vitro*** **COX-1 ($IC_{50\%}$), COX-2 (IC_{50}) inhibition, SI and** ***in vivo*** **anti-inflammatory activity (% inhibition) of diarylpyrazoles 8a–f and triarylimidazoline-5-ones 11a–g in comparison with reference drug celecoxib.**

Compound no.	COX-1 ($IC_{50\%}$ μM)[a]	COX-2 ($IC_{50\%}$ μM)[a]	SI[b]	% Inhibition[c]		
				1 h	3 h	6 h
8a	7.3	1.52	4.80	70	49	54
8b	4.9	1.42	3.45	69	63	56
8c	10.9	4.23	2.58	38	53	38
8d	6.9	1.27	5.43	34*	44*	29*
8e	11.4	3.22	3.54	34*	29*	28*
8f	5.3	1.11	4.77	66	63	55
11a	4.2	0.87	4.83	41	51	35
11b	9.8	3.51	2.79	71	43	36
11c	3.9	0.74	5.27	87	35	64
11d	5.1	1.42	3.59	75	41	60
11e	13.2	4.74	2.78	71	33	35
11f	8.6	2.33	3.69	45	49	38
11g	10.1	2.87	3.52	50*	34*	26*
Celecoxib	7.7	0.87	7.8	42	51	63

[a] The concentration of test compound that produces 50% inhibition of COX-1, COX-2 enzyme; the result is the mean of two values obtained by assay of enzyme kits obtained from Cayman Chemicals Inc., Ann Arbor, MI, USA.
[b] The *in vitro* COX-2 selectivity index (COX-1/COX-2).
[c] Inhibitory activity of compounds determined at 1, 3, 6 h after carrageenan injection. The results were expressed using two-way ANOVA followed by post-hoc Tukey's test for multiple pairwise comparison between different compounds at $P < 0.01$.
* `Significantly different from celecoxib.

showed some similarities to the time interval pattern of celecoxib (Fig. 3).

A common structural feature of the most active diarylpyrazoles **8a** and **8f** and triarylimidazolines **11c** and **11d** is the occurrence of a central five—membered heterocyclic ring attached to two vicinal aryl rings. Also, presence of lipophilic group's methanesulfonyl (SO_2CH_3) and/or sulfonamide (SO_2NH_2) moieties attached to aryl groups at position-4 which is important for COX-2 selectivity. Additionally, the presence of methoxy group at *para* position of arylidine moiety in **11c** and **11d** is essential for anti-inflammatory activity.

Conclusion

The present study describes the synthesis of two new series of diarylpyrazoles **8a–f** and triarylimidazoline-5-ones **11a–g** for evaluation as selective COX-2 inhibitors and anti-inflammatory agents. The newly prepared compounds were tested for their *in vitro* COX-1/COX-2 inhibitory activity and *in vivo* anti-inflammatory activity. Structure–activity relationship and biological studies revealed that (i) all compounds were more selective COX-2 than COX-1 inhibitors, (ii) most of the evaluated compounds showed good anti-inflammatory activity especially compounds **8a**, **8f**, **11c**, and **11d** which along the different time intervals (1, 3, and 6 h) showed also some similarities to the time interval pattern of celecoxib, and (iii) within each series, the most potent COX-2 inhibitor derivatives had good anti-inflammatory activity (**8a**, **8d**, and **8f** for diarylpyrazoles **8a–f**, **11a**, **11c**, and **11d** for triarylimidazoline-5-ones **11a–g**).

Experimental

Chemistry

General

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded as films on KBr plates using a Nicolet 550 Series II Magna FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra

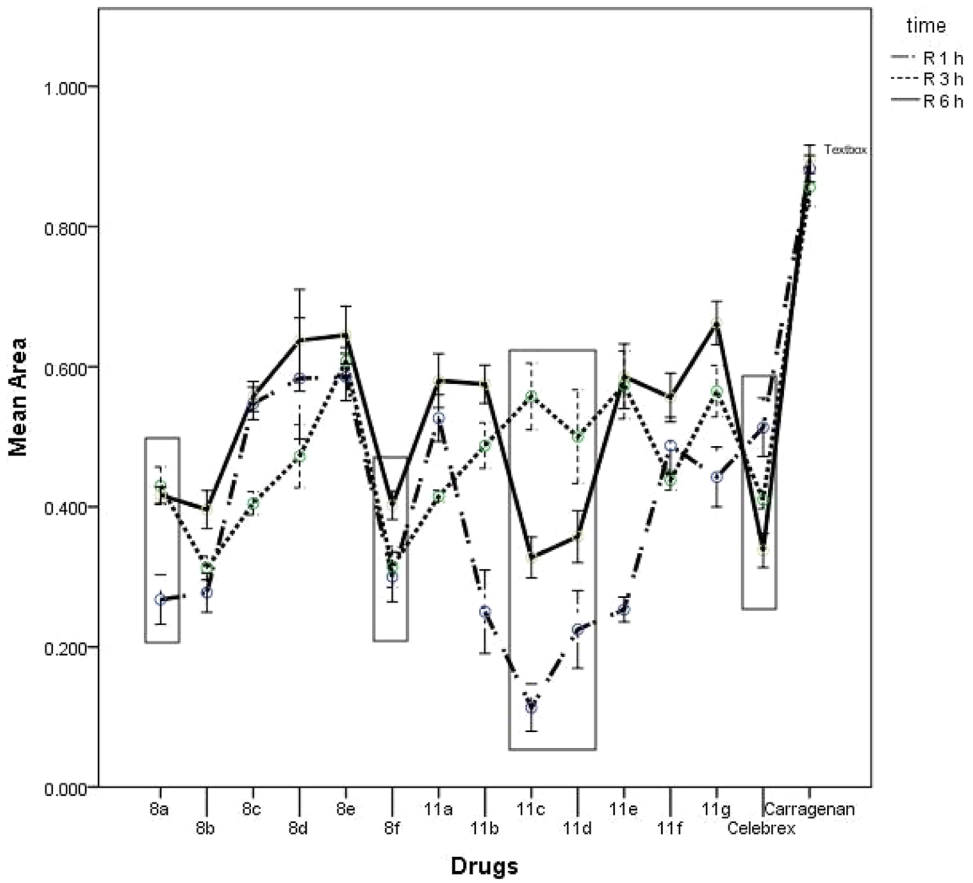

Figure 3. Line graph of two-way ANOVA analysis for diarylpyrazoles **8a–f** and triarylimidazoline-5-ones **11a–g** in comparison with reference drug celecoxib.

were measured on a Bruker Avence III 400 MHz spectrophotometer, Faculty of Pharmacy, Beni-Suef University, Egypt in $CDCl_3$ or DMSO-d_6, where *J* (coupling constant) values are estimated in Hertz (Hz). Microanalyses were performed for C, H, and N and were carried out on a PerkinElmer 2400 analyzer (PerkinElmer, Norwalk, CT, USA) at the Regional Center for Mycology and Bio-Technology, Al-azhar University, Egypt. All data were within +0.4% of the theoretical values. The propene-1-one (**6**) [29], *p*-methoxybenzoylglycine **9** and oxazolones **10a–c** [30] were prepared according to the previously reported procedures.

The InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

*General procedure for synthesis of 5-(4-methylsulfonylphenyl)-1-aryl-1H-pyrazoles (**8a–f**)*

A mixture of (*E*)-3-dimethylamino-1-(4-methylsulfonylphenyl)-prop-2-en-1-one **6** (3 mmol) and the appropriate substituted phenylhydrazine hydrochloride **7a–f** (3 mmol) in ethanol 95% was refluxed for 24 h. The reaction was monitored by TLC. After the reaction was completed, reaction mixture was poured onto crushed ice; the resulting precipitate was filtered, crystallized from ethanol to give compounds **8a–f** in good yield (60–70%).

*5-(4-Methylsulfonylphenyl)-1-phenyl-1H-pyrazole (**8a**)*

Yield 65%; dark yellow powder; mp 117–119°C; IR (KBr): 3103 (C–H aromatic), 2924 (C–H aliphatic), 1597 (C=N), 1305, 1149 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.24 (s, 3H, SO_2CH_3), 6.83 (s, 1H, pyrazole H-4), 7.29 (d, $J = 6.8$ Hz, 2H, phenyl H-3, H-5), 7.38–7.51 (m, 5H, methylsulfonylphenyl H-3, H-5, phenyl H-2, H-4, H-6), 7.83 (s, 1H, pyrazole H-3), 7.91 (d, $J = 7.2$ Hz, 2H, methylsulfonylphenyl H-2, H6); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 43.67 (CH_3, methanesulphonylcarbon), 109.6 (CH, pyrazole C-4), 125.8 (CH, phenyl C-2, C-6), 127.6 (CH, phenyl C-4), 128.5 (CH, methylsulfonylphenyl C-2, C-6), 129.6 (CH, methylsulfonylphenyl C-3, C-5), 129.7 (CH, phenyl C-3, C-5), 135.3 (C, methylsulfonylphenyl C-1), 139.9 (C, phenyl C-1), 140.6 (C, methylsulfonylphenyl C-4), 140.9 (CH, pyrazole C-3), 141.3 (C, pyrazole C-5); MS *m/z* (ES^+) 298 (M^+, 100%). Anal. calcd. for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39: Found; C, 64.58; H, 4.89; N, 9.48.

*2-[5-(4-Methylsulfonylphenyl)-1H-pyrazol-1-yl]benzoic acid (**8b**)*

Yield 60%; pale yellow powder; mp 227–229°C; IR (KBr): 3430 (COOH), 3072 (C–H aromatic), 2926 (C–H aliphatic), 1683 (C=O), 1603 (C=N), 1311, 1154 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.20 (s, 3H, SO_2CH_3), 6.80 (s, 1H, pyrazole H-4), 7.25 (m, 1H, benzoic acid H-5), 7.45 (d, $J = 7.2$ Hz, 2H, methylsulfonylphenyl H-3, H-5), 7.48–7.52 (m, 2H, benzoic acid H-4, H-6), 7.75 (s, 1H, pyrazole H-3), 7.86 (d, $J = 7.2$ Hz, 3H, methylsulfonylphenyl H-2, H-6, benzoic acid H-3), 12.95 (s, 1H, COO*H*, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 43.7 (CH_3, methanesulfonylcarbon), 108.3 (CH, pyrazole C-4), 127.6 (methylsulfonylphenyl C-2, C-6), 128.9 (CH, benzoic acid C-3), 129.2 (CH, methylsulfonylphenyl C-3, C-5), 129.6 (CH, benzoic acid C-5), 130.8 (C, benzoic acid C-1), 130.9 (CH, benzoic acid C-6), 132.7 (CH, benzoic acid C-4), 135.1 (C, methylsulfonylphenyl C-1), 138.8 (C, methylsulfonylphenyl C-4), 140.4 (C, benzoic acid C-2), 140.6 (CH, pyrazole C-3), 142.1 (C, pyrazole C-5), 167.2 (C, COOH); MS *m/z* (ES^+) 342 (M^+, 87.06%). Anal. calcd. for $C_{17}H_{14}N_2O_4S$; C, 59.64; H, 4.12; N, 8.18: Found; C, 59.83; H, 4.16; N, 8.34.

*3-[5-(4-Methylsulfonylphenyl)-1H-pyrazol-1-yl]benzoic acid (**8c**)*

Yield 55%; pale yellow powder; mp 273–275°C; IR (KBr): 3433 (COOH), 3073 (C–H aromatic), 2927 (C–H aliphatic), 1684 (C=O), 1604 (C=N), 1310, 1154 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.25 (s, 3H, SO_2CH_3), 6.86 (s, 1H, pyrazole H-4), 7.42 (d, $J = 8.4$ Hz, 2H, methylsulfonylphenyl H-3, H-5), 7.53 (d, $J = 7.2$ Hz, 2H, benzoic acid H-4, H-5), 7.89 (s, pyrazole H-3), 7.92 (d, $J = 7.6$ Hz, 2H, methylsulfonylphenyl H-2, H-6), 7.98 (d, $J = 8.0$ Hz, 2H, benzoic acid H-2, H-6), 13.4 (s, 1H, COOH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 43.7 (CH_3, methylsulfonylcarbon), 110.4 (CH, pyrazole C-4), 125.3 (CH, benzoic acid C-2, C-4), 127.8 (CH, benzoic acid C-5, C-6), 129.7 (CH, methylsulfonylphenyl C-2, C-6), 130.8 (C, benzoic acid C-1), 131.4 (CH, methylsulfonylphenyl C-3, C-5), 135.0 (C, methylsulfonylphenyl C-1), 140.9 (C, benzoic acid C-3), 141.6 (C, methylsulfonylphenyl C-4), 141.6 (CH, pyrazole C-3), 143.1 (C, pyrazole C-5), 167.0 (C, COOH); MS *m/z* (ES^+) 342 (M^+, 100%). Anal. calcd. for $C_{17}H_{14}N_2O_4S$; C, 59.64; H, 4.12; N, 8.18: Found; C, 59.87; H, 4.19; N, 8.30.

*4-[5-(4-Methylsulfonylphenyl)-1H-pyrazol-1-yl]benzoic acid (**8d**)*

Yield 65%; pale yellow powder; mp 120–122°C; IR (KBr); 3428 (COOH), 3071 (C–H aromatic), 2923 (C–H aliphatic), 1686 (C=O), 1604 (C=N), 1294, 1148 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.23 (s, 3H, SO_2CH_3), 6.84 (s, 1H, pyrazole H-4), 7.26 (d, $J = 8.0$ Hz, 2H, benzoic acid H-3, H-5), 7.48 (d, $J = 8.0$ Hz, 2H, methylsulfonylphenyl H-3, H-5), 7.85 (s, 1H, pyrazole H-3), 7.90 (d, $J = 8.4$ Hz, 2H, methylsulfonylphenyl H-2, H-6), 7.98 (d, $J = 8.0$ Hz, 2H, benzoic acid H-2, H-6), 13.04 (s, 1H, COOH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 43.3 (CH_3, methanesulfonylcarbon), 109.8 (CH, pyrazole C-4), 124.8 (CH, benzoic acid C-3, C-5), 127.7 (CH, methylsulfonylphenyl C-2, C-6), 129.6 (CH, methylsulfonylphenyl C-3, C-5), 130.6 (CH, benzoic acid C-2, C-6), 135.2 (C, benzoic acid C-1), 136.5 (C, methylsulfonylphenyl C-1), 140.7 (C, methylsulfonylphenyl C-4), 141.1 (CH, pyrazole C-3), 141.2 (C, benzoic acid C-4), 141.4 (C, pyrazole C-5), 170.5 (C, COOH); MS *m/z* (ES^+) 342 (M^+, 100%). Anal. calcd. for $C_{17}H_{14}N_2O_4S$; C, 59.64; H, 4.12; N, 8.18: Found; C, 59.79; H, 4.21; N, 8.32.

*1,5-bis(4-Methylsulfonylphenyl)-1H-pyrazole (**8e**)*

Yield 77%; light brown powder; mp 165–167°C; IR (KBr): 3099 (C–H aromatic), 2926 (C–H aliphatic), 1594 (C=N), 1406, 1148;

1304, 1191, (2 SO_2CH_3) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.27 (s, 6H, $2SO_2CH_3$), 6.89 (s, 1H, pyrazole H-4), 7.55–7.58 (m, 4H, methylsulfonylphenyl H-2, H-3, H-5, H-6), 7.94 (s, 1H, pyrazole H-3), 7.98–8.02 (m, 4H, methylsulfonylphenyl H-2′, H-3′, H-5′ H-6′). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 43.7 (CH_3, methanesulfonylcarbon), 110.8 (CH, pyrazole C-4), 125.8 (CH, methylsulfonylphenyl C-2, C-6), 127.9 (CH, methylsulfonylphenyl C-2′, C-6′), 128.7 (CH, methylsulfonylphenyl C-3′, C-5′), 129.1 (CH, methylsulfonylphenyl C-3, C-5), 134.9 (C, methylsulphonylphenyl C-1′), 140.0 (C, methylsulfonylphenyl C-1), 141.1 (C, methylsulfonylphenyl C-4′), 141.8 (C, pyrazole C-5), 142.0 (CH, pyrazole C-3), 143.5 (C, methylsulfonylphenyl C-1); MS *m/z* (ES^+) 376 (M^+, 100%). Anal. calcd. for $C_{17}H_{16}N_2O_4S_2$; C, 54.24; H, 4.28; N, 7.44: Found; C, 54.4; H, 4.34; N, 7.53.

*4-[5-(4-Methylsulfonylphenyl)-1H-pyrazol-1-yl]-benzenesulfonamide (**8f**)*

Yield 70%; pale yellow powder; mp 208–210°C; IR (KBr): 3361, 3284 (NH_2), 3071 (C–H aromatic), 2929 (C–H aliphatic), 1595 (C=N), 1342, 1152; 1302, 1095 (SO_2CH_3, SO_2NH_2) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.26 (s, 3H, SO_2CH_3), 6.87 (s, 1H, pyrazole H-4), 7.28–7.35 (m, 6H, benzenesulfonamide H-2, H-3, H-5, H-6, D_2O exchangeable SO_2NH_2), 7.77–7.88 (m, 3H, pyrazole H-3, methylsulfonylphenyl H-3, H-5), 7.95 (d, $J = 8.0$ Hz, 2H, methylsulfonylphenyl H-2, H-6); ^{13}C NMR (DMSO-d_6 100 MHz, δ ppm): 43.7 (CH_3, SO_2CH_3), 110.5 (CH, pyrazole C-4), 125.8 (CH, benzene sulfonamide C-3, C-5), 127.3 (CH, benzene sulfonamide C-2, C-6), 127.8 (CH, methylsulfonylphenyl C-2, C-6), 129.8 (CH, methylsulfonylphenyl C-3, C-5), 135.0 (C, methylsulfonylphenyl C-1), 140.6 (C, methylsulfonylphenyl C-4), 141.7 (C, benzene sulfonamide C-1), 141.8 (CH, pyrazole C-3), 142.1 (C, benzene sulfonamide C-4), 143.2 (C, pyrazole C-5); MS *m/z* (ES^+) 377 (M^+, 100%). Anal. calcd. for $C_{16}H_{15}N_3O_4S_2$; C, 50.91; H, 4.01; N, 11.13: Found; C, 51.17; H, 4.06; N, 11.34.

*General procedure for the synthesis of (E)-4-arylidene-2-(4-methoxyphenyl)oxazol-5(4H)-ones (**10d–g**)*

A mixture of *p*-methoxy benzoyl glycine **9** (0.01 mol), the appropriate aromatic aldehyde (0.01 mol) and anhydrous sodium acetate (0.03 mol) in acetic anhydride (20 mL) was refluxed at 100°C for 6 h. The precipitated product obtained was filtered, washed with water, followed by aqueous ethanol and crystallized from ethanol to give oxazolone **10a–g** in excellent yield 70–90%.

*(E)-4-(3,4-Dimethoxybenzylidene)-2-(4-methoxyphenyl)-oxazol-5(4H)-one (**10d**)*

Yield 75%; yellow powder; mp 175–177°C; IR (KBr): 3092 (C–H aromatic), 2933 (C–H aliphatic), 1782 (C=O), 1602 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.93 (s, 3H, OCH_3, methoxyphenyl C-4), 3.99 (s, 3H, OCH_3, dimethoxyphenyl C-3), 4.05 (s, 3H, OCH_3, dimethoxyphenyl C-4), 6.95 (d, $J = 8.0$ Hz, 1H, dimethoxyphenyl H-5), 7.03 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-3, H-5), 7.08 (s, 1H, olefinic proton), 7.58 (d, $J = 8.0$ Hz, dimethoxyphenyl H-6), 8.10 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-2, H-6), 8.19 (s, 1H, dimethoxyphenyl H-2); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 55.5 (OCH_3, methoxyphenyl C-4), 55.9 (OCH_3, dimethoxyphenyl C-3), 56.0 (O-CH_3, dimethoxyphenyl C-4), 110.9 (CH, dimethoxyphenyl C-2), 113.3 (CH, dimethoxyphenyl C-5), 114.5 (CH, olefinic carbon), 118.1 (C, methoxyphenyl C-1), 127.0 (methoxyphenyl C-3, C-5), 127.3 (CH, dimethoxyphenyl C-6), 129.7 (oxazolone C-4), 130.5 (CH, methoxyphenyl C-2, C-6), 131.5 (C, dimethoxyphenyl C-1), 149.1 (C, dimethoxyphenyl C-4), 151.7 (C, dimethoxyphenyl C-3), 162.3 (C, oxazolone C-2), 163.6 (C, methoxyphenyl C-4), 168.1 (C, oxazolone, C-5); MS *m/z* 339 (M^+, 49.85 %). Anal. calcd. for $C_{19}H_{17}NO_5$; C, 67.25; H, 5.05; N, 4.13: Found; C; 67.43; H, 5.12; N, 4.18.

*(E)-2-(4-Methoxyphenyl)-4-(3,4,5-trimethoxybenzylidene)-oxazol-5(4H)-one (**10e**)*

Yield 78%; yellow solid; mp 168–170°C; IR (KBr); 3073 (C–H aromatic), 2940 (C–H aliphatic), 1784 (C=O), 1606 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.93 (s, 3H, O-CH_3, methoxyphenyl C-4), 3.96 (s, 3H, O-CH_3 trimethoxyphenyl C-4), 3.99 (s, 6H, 2-OCH_3, trimethoxyphenyl C-3, C-5), 7.04 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-3, H-5), 7.12 (s, 1H, olefinic proton), 7.56 (s, 2H, trimethoxyphenyl H-2, H-6), 8.10 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-2, H-6); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 55.5 (O-CH_3, methoxyphenyl C-4), 56.1 (2O-CH_3, trimethoxyphenyl C-3, C-5), 61.0 (O-CH_3, trimethoxyphenyl C-4), 109.3 (CH, trimethoxyphenyl C-2, C-6), 114. (CH, methoxyphenyl C-3, C-5), 117.9 (C, methoxyphenyl C-1), 129.1 (C, trimethoxyphenyl C-1), 129.7 (CH, olefinic CH), 130.7 (CH, methoxyphenyl C-2, C-6), 132.7 (C, oxazolone, C-4), 140.9 (C, trimethoxyphenyl C-4), 153.2 (C, trimethoxyphenyl C-3, C-5), 163.0 (C, oxazolone C-2), 163.8 (C, methoxyphenyl C-4), 167.8 (C, oxazolone C-5); MS *m/z* 369 (M^+, 100%). Anal. calcd. for $C_{20}H_{19}NO_6$; C, 65.03; H, 5.18; N, 3.79: Found; C; 65.17; H, 5.24; N, 3.85.

*(E)-2-(4-Methoxyphenyl)-4-(thiophen-2-ylmethylene)-oxazol-5(4H)-one (**10f**)*

Yield 76%; pale green solid; mp 198- 200°C; IR (KBr): 3100 (C–H aromatic), 2925 (C–H aliphatic), 1779 (C=O), 1602 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.89 (s, 3H, O-CH_3), 7.18 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-3, H-5), 7.26 (t, 1H, thienyl H-4), 7.65 (s, 1H, olefinic proton), 7.82 (d, $J = 3.2$ Hz, 1H, thienyl H-3), 8.02 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-2, H-6), 8.05 (d, $J = 4.8$ Hz, 1H, thienyl H-5). ^{13}C NMR (DMSO-d_6 100 MHz, δ ppm): 56.1 (O-CH_3, methoxyphenyl C-4), 115.4 (CH, methoxyphenyl C-3, C-5), 117.6 (C, methoxyphenyl C-1), 123.4 (CH, olefinic CH), 128.6 (CH, thienyl C-4), 130.4 (CH, methoxyphenyl C-2, C-6), 130.9 (C, oxazolone C-4), 136.1 (CH, thienyl C-3), 136.5 (CH, thienyl C-5), 137.7 (C, thienyl C-2), 162.0 (oxazolone C-2), 163.9 (C, methoxyphenyl C-4), 166.6 (C, oxazolone C-5); MS *m/z* 285 (M^+, 54.85%). Anal. calcd. for $C_{15}H_{11}NO_3S$; C, 63.14; H, 3.89; N, 4.9: Found; C, 63.32; H, 3.96; N, 5.02.

*(E)-2-(4-Methoxyphenyl)-4-(pyridin-3-ylmethylene)-oxazol-5(4H)-one (**10g**)*
Yield 78%; light brown solid; mp 216–218°C; IR (KBr): 3077 (C–H aromatic), 2928 (C–H aliphatic), 1783 (C=O), 1603 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.93 (s, 3H, O-CH_3), 7.1 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-3, H-5), 7.3 (s, 1H, olefinic proton), 7.5 (dd, $J = 4.8$, 7.2 Hz, 1H, pyridine H-5), 8.1 (d, $J = 8.0$ Hz, methoxyphenyl H-2, H-6), 8.63 (d, $J = 4.4$ Hz, 1H, pyridine H-6), 8.76 (d, $J = 7.2$ Hz, 1H, pyridine H-4), 9.26 (s, 1H, pyridine, H-2); ^{13}C NMR (DMSO-d_6 100 MHz, δ ppm): 56.2 (O-CH_3, methoxyphenyl), 115.4 (CH, olefinic proton), 117.6 (C, methoxyphenyl C-1), 124.5 (CH, methoxyphenyl C-3, C-5), 125.9 (CH, pyridine C-5), 130.2 (C, oxazolone C-4), 130.9 (CH, methoxyphenyl C-2, C-6), 133.2 (C, pyridine C-1), 138.6 (CH, pyridine C-6), 151.2 (CH, pyridine C-2), 153.0 (CH, pyridine C-4), 162.0 (oxazolone C-2), 163,9 (C, methoxyphenyl C-4), 166.6 (C, oxazolone C-5); MS *m/z* 280 (M^+, 100 %). Anal. calcd. for $C_{16}H_{12}N_2O_3$; C, 68.56; H, 4.32; N, 9.99: Found; C, 68.74; H, 4.39; N, 10.18.

*General procedure for the synthesis of (E)-4-[4-benzylidene-2-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide (**11a–g**)*
A mixture of the appropriate (*E*)-4-arylidene-2-(4-methoxyphenyl)oxazol-5(4*H*)-ones **10a–g** (0.01 mol) and sulfanilamide (0.01 mol) in glacial acetic acid (15 mL) containing anhydrous sodium acetate (0.03 mol) was heated on a boiling water bath with continuous stirring for the 24 h. The precipitated product was filtered off, washed with aqueous ethanol and crystallized from ethanol to give compounds **11a–g** in good yield (60–70%).

*(E)-4-[4-Benzylidene-2-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide (**11a**)*
Yield 60%; yellow powder; mp 277–279°C; IR (KBr): 3370; 3261 (NH_2), 3093 (C–H aromatic), 2928 (C–H aliphatic), 1695 (C=O), 1603 (C=N), 1342, 1166 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.79 (s, 3H, O-CH_3), 6.98 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-3, H-5), 7.41 (s, 1H, olefinic proton), 7.49–7.60 (m, 7H, methoxyphenyl H-2, H-6, phenyl H-2, H-3, H-4, H-5, H-6, SO_2NH_2, D_2O exchangeable), 7.80 (d, $J = 8.2$ Hz, 2H, benzenesulfonamide H-2, H-6), 7.92 (d, $J = 8.2$ Hz, 2H, benzenesulfonamide H-3, H-5); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 56.0 (O-CH_3, methoxyphenyl C-4), 114.6 (CH, methoxyphenyl C-3, C-5), 120.4 (C, methoxyphenyl C-1), 123.3 (CH, olefinic CH), 126.6 (C, oxazolone C-4), 127.2 (CH, benzene sulfonamide C-3, C-5), 128.7 (CH, phenyl C-4), 128.8 (CH, phenyl C-2, C-6), 131.5 (CH, phenyl C-3, C-5), 132.3 (CH, benzene sulfonamide C-2, C-6), 133.5 (C, phenyl C-1), 133.7 (CH, methoxyphenyl C-2, C-6), 137.8 (C, benzene sulfonamide C-1), 140.2 (C, benzene sulfonamide C-4), 161.9 (C, oxazolone C-2), 162.8 (C, methoxyphenyl C-4), 170.0 (C, oxazolone C-5); MS *m/z* 433 (M^+, 0.77%). Anal. calcd. for $C_{23}H_{19}N_3O_4S$; C, 63.73; H, 4.42; N, 9.69: Found; C, 63.94; H, 4.46; N, 9.82.

*(E)-4-[4-(3-Methoxybenzylidene)-2-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)benzenesulfonamide (**11b**)*
Yield 72%; pale yellow powder; mp 238–240°C; IR (KBr): 3415, 3262 (NH_2), 3073 (C–H aromatic), 2935 (C–H aliphatic), 1781 (C=O), 1601 (C=N), 1307, 1162 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.79 (s, 3H, O-CH_3, methoxyphenyl C-4), 3.83 (s, 3H, O-CH_3, methoxyphenyl C-3), 7.0 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-3, H-5), 7.06 (d, $J = 7.6$ Hz, 2H, methoxyphenyl H-4, H-5), 7.22 (s, 1H, olefinic proton), 7.41–7.50 (m, 7H, SO_2NH_2, D_2O exchangeable, methoxyphenyl H-2, H-6, benzenesulfonamide H-2, H-6, methoxyphenyl H-2), 7.84 (d, $J = 7.6$ Hz, 1H, methoxyphenyl H-6), 7.92 (d, $J = 8.2$ Hz, benzenesulfonamide H-3, H-5), 8.06 (s, 1H, methoxyphenyl H-2); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 55.6 (O-CH_3, methoxyphenyl C-4), 55.9 (O-CH_3, methoxyphenyl C-3), 114.6 (CH, methoxyphenyl C-3, C-5), 116.1 (CH, methoxyphenyl C-2), 117.3 (CH, methoxyphenyl C-4), 120.7 (C, 4-methoxyphenyl C-1), 120.8 (CH, olefinic carbon), 125.4 (CH, methoxyphenyl C-6), 127.2 (CH, benzene sulfonamide C-3, C-5), 128.7 (CH, benzene sulfonamide C-2, C-6), 130.3 (CH, methoxyphenyl C-5), 131.3 (CH, methoxyphenyl C-2, C-6), 135.8 (C, oxazolone C-4), 138.0 (C, benzene sulfonamide C-1), 138.9 (C, 3-methoxyphenyl C-1), 144.1 (C, benzene sulfonamide C-4), 159.7 (C, oxazolone C-2), 160.3 (C, 3-methoxyphenyl C-3), 162.4 (C, methoxyphenyl C-4), 170.0 (C, oxazolone C-5); MS *m/z* 463 (M^+, 19.74%). Anal. calcd. for $C_{24}H_{21}N_3O_5S$; C, 62.19; H, 4.57; N, 9.07: Found; C, 62.38; H, 4.65; N, 9.19.

*(E)-4-[4-(4-Methoxybenzylidene)-2-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1H-imidazol-1-yl]benzenesulfonamide (**11c**)*
Yield 70%; yellow powder; mp 247–249°C; IR (KBr); 3430, 3260 (NH_2), 3098 (C–H aromatic), 2932 (C–H aliphatic), 1687 (C=O), 1600 (C=N), 1313, 1164 (SO_2); ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.79 (s, 3H, O-CH_3, methoxybenzylidene), 3.85 (s, 3H, O-CH_3, methoxyphenyl), 6.98 (d, $J = 8.0$ Hz, 2H, methoxybenzylidene H-3, H-5), 7.11 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-3, H-5), 7.22 (s, 1H, olefinic proton), 7.47–7.49 (m, 6H, methoxyphenyl H-2, H-6, methoxybenzylidene H-2, H-6, SO_2NH_2, D_2O exchangeable), 7.90 (d, $J = 8.2$ Hz, 2H, benzenesulfonamide H-2, H-6), 8.35 (d, $J = 8.2$ Hz, 2H, benzenesulfonamide H-3, H-5); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 55.8 (O-CH_3, methoxyphenyl C-4), 55.9 (O-CH_3, methoxyphenyl C-4), 114.5 (CH, methoxybenzylidene C-3, C-5), 115.0 (CH, methoxyphenyl C-3, C-5), 121.0 (C, methoxyphenyl C-1), 127.1 (CH, benzene sulfonamide C-3, C-5), 127.4 (C, methoxybenzylidene), 127.7 (CH, olefinic carbon), 128.7 (CH, benzene sulfonamide C-2, C-6), 131.1 (CH, methoxybenzylidene C-2, C-6), 134.8 (CH, methoxyphenyl C-2, C-6), 136.7 (C, oxazolone C-4), 138.1 (C, benzene sulfonamide C-1), 144.02 (C, benzene sulfonamide C-4), 158.9 (C, oxazolone C-2), 161.7 (C, methoxybenzylidene C-4), 162.1 (C, methoxyphenyl C-4), 169.9 (C, oxazolone C-5); MS *m/z* 463 (M^+, 31.47%). Anal. calcd. for $C_{24}H_{21}N_3O_5S$; C, 62.19; H, 4.57; N, 9.07: Found; C, 62.43; H, 4.62; N, 9.23.

*(E)-4-[4-(3,4-Dimethoxybenzylidene)-2-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1H-imidazol-1-yl]-benzenesulfonamide (**11d**)*

Yield 65%; yellow powder; mp 280–282°C; IR (KBr): 3430, 3315 (NH_2), 3091 (C–H aromatic), 2941 (C–H aliphatic), 1684 (C=O), 1594 (C=N), 1348, 1163 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.79 (s, 3H, O-CH_3, dimethoxyphenyl C-3), 3.86 (s, 6H, 2O-CH_3, methoxyphenyl C-4, dimethoxyphenyl C-4), 6.98 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-3, H-5), 7.12 (d, $J = 8.0$ Hz, 1H, dimethoxyphenyl H-5), 7.21 (s, 1H, olefinic proton), 7.49–7.51 (m, 6H, methoxyphenyl H-2, H-6, benzenesulfonamide H-2, H-6, SO_2NH_2, D_2O exchangeable), 7.86 (d, $J = 8.0$ Hz, 1H, dimethoxyphenyl H-6), 7.92 (d, $J = 8.2$ Hz, 2H, benzene sulfonamide H-3, H-5), 8.24 (s, 1H, dimethoxyphenyl H-2); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 55.8 (O-CH_3, methoxyphenyl C-4), 56.1 (O-CH_3, dimethoxyphenyl C-3, C-4), 112.1 (CH, dimethoxyphenyl C-2), 114.6 (CH, methoxyphenyl C-3, C-5), 115.0 (CH, dimethoxyphenyl C-5), 121.0 (C, methoxyphenyl C-1), 127.2 (CH, benzene sulfonamide C-3, C-5), 127.5 (CH, olefinic carbon), 127.7 (C, oxazolone C-4), 128.0 (CH, dimethoxyphenyl C-6), 128.6 (CH, benzene sulfonamide C-2, C-6), 131.0 (CH, methoxyphenyl C-2, C-6), 136.7 (C, dimethoxyphenyl C-1), 138.2 (C, benzene sulfonamide C-1), 144.0 (C, benzene sulfonamide C-4), 149.1 (C, dimethoxyphenyl C-4), 151.6 (C, dimethoxyphenyl C-3), 158.7 (C, oxazolone C-2), 162.2 (C, methoxyphenyl C-4), 169.8 (C, oxazolone C-5); MS *m/z* 493 (M+2, 1.19%). Anal. calcd. for $C_{25}H_{23}N_3O_6S$; C, 60.84; H, 4.70; N, 8.51: Found; C, 61.02; H, 4.79; N, 8.59.

*(E)-4-[2-(4-Methoxyphenyl)-5-oxo-4-(3,4,5-trimethoxybenzylidene)-4,5-dihydro-1H-imidazol-1-yl]-benzenesulfonamide (**11e**)*

Yield 77%; yellow powder; mp 217–219°C; IR (KBr): 3424, 3305 (NH_2), 3103 (C–H aromatic), 2938 (C–H aliphatic), 1786 (C=O), 1604 (C=N), 1332, 1127 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.77 (s, 3H, O-CH_3, trimethoxyphenyl C-4), 3.79 (s, 3H, O-CH_3, methoxyphenyl), 3.86 (s, 6H, 2O-CH_3, trimethoxyphenyl C-3, C-5), 6.98 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-3, H-5), 7.16 (s, 1H, olefinic proton), 7.49–7.51 (m, 6H, methoxyphenyl H-2, H-6, benzene sulfonamide H-2, H-6, SO_2NH_2, D_2O exchangeable), 7.8 (s, 2H, trimethoxyphenyl H-2, H-6), 7.93 (d, $J = 8.2$ Hz, benzene sulfonamide, H-3, H-5); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 55.9 (O-CH_3, methoxyphenyl), 56.3 (O-CH_3, trimethoxyphenyl C-3, C-5), 60.7 (O-CH_3, trimethoxyphenyl C-4), 110.3 (CH, trimethoxyphenyl C-2, C-6), 114.6 (CH, methoxyphenyl C-3, C-5), 120.8 (C, methoxyphenyl C-1), 127.2 (CH, benzene sulfonamide C-3, C-5), 127.5 (CH, olefinic carbon), 128.7 (CH, benzene sulfonamide C-2, C-6), 130.1 (C, trimethoxyphenyl C-1), 131.1 (CH, methoxyphenyl C-2, C-6), 137.8 (C, oxazolone C-4), 138.1 (C, benzene sulfonamide C-1), 140.2 (C, trimethoxyphenyl C-4), 144.1 (C, benzene sulfonamide C-4), 153.2 (C, trimethoxyphenyl C-3, C-5), 159.5 (C, oxazolone C-2), 162.3 (C, methoxyphenyl C-4), 169.3 (C, oxazolone C-5); MS *m/z* 523 (M^+, 5.4%). Anal. calcd. for $C_{26}H_{25}N_3O_7S$; C, 59.65; H, 4.81; N, 8.03: Found; C, 59.87; H, 4.86; N, 8.16.

*(E)-4-[2-(4-Methoxyphenyl)-5-oxo-4-(thiophen-2-ylmethylene)-4,5-dihydro-1H-imidazol-1-yl]-benzenesulfonamide (**11f**)*

Yield 85%; brown powder; mp 254–256°C; IR (KBr): 3422, 3250 (NH_2), 3100 (C–H aromatic), 2926 (C–H aliphatic), 1724 (C=O), 1603 (C=N), 1324, 1163 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.80 (s, 3H, O-CH_3), 6.99 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-3, H-5), 7.23 (s, 1H, olefinic proton), 7.49–7.52 (m, 6H, methoxyphenyl H-2, H-6, benzene sulfonamide H-2, H-6, SO_2NH_2, D_2O exchangeable), 7.61 (t, 1H, thienyl H-4), 7.8 (d, $J = 3.2$ Hz, 1H, thienyl H-3), 7.91 (d, $J = 8.2$ Hz, 2H, benzene sulfonamide H-3, H-5), 7.97 (d, $J = 4.8$ Hz, 1H, thienyl H-5); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 55.9 (CH_3, OCH_3), 114.6 (CH, methoxyphenyl C-3, C-5), 120.8 (C, methoxyphenyl C-1), 121.7 (CH, olefinic carbon), 127.2 (CH, benzene sulfonamide C-3, C-5), 128.3 (CH, thienyl C-4), 128.7 (CH, benzene sulfonamide C-2, C-6), 131.1 (CH, methoxyphenyl C-2, C-6), 135.8 (CH, thienyl C-3), 136.0 (CH, thienyl C-5), 136.1 (C, oxazolone C-4), 138.2 (C, benzene sulfonamide C-1), 138.7 (C, thienyl C-2), 144.2 (C, benzene sulfonamide C-4), 158.2 (C, oxazolone C-2), 162 (C, methoxyphenyl C-4), 169.2 (C, oxazolone C-5); MS *m/z* 439 (M^+, 77.83%). Anal. calcd. for $C_{21}H_{17}N_3O_4S_2$; C, 57.39; H, 3.90; N, 9.56: Found; C, 57.52; H, 3.93; N, 9.67.

(E)-4-[2-(4-Methoxyphenyl)-5-oxo-4-(pyridin-3-ylmethylene)-4,5-dihydro-1H-imidazol-1-yl]-benzenesulfonamide (11g)

Yield 80%; pale brown powder; mp 241–243°C; IR (KBr): 3430, 3313 (NH_2), 3044 (C–H aromatic), 2925 (C–H aliphatic), 1725 (C=O), 1601 (C=N), 1344, 1164 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.8 (s, 3H, O-CH_3), 6.99 (d, $J = 8.0$ Hz, 2H, methoxyphenyl H-3, H-5), 7.29 (s, 1H, olefinic proton), 7.51–7.57 (m, 7H, methoxyphenyl H-2, H-6, pyridine H-5, benzenesulfonamide H-2, H-6, SO_2NH_2, D_2O exchangeable), 7.94 (d, $J = 8.2$ Hz, 2H, benzenesulfonamide H-3, H-5), 8.62 (d, $J = 4.0$ Hz, 1H, pyridine H-6), 8.85 (d, $J = 7.6$ Hz, 1H, pyridine H-4), 9.33 (s, 1H, pyridine H-2); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 55.9 (O-CH_3, methoxyphenyl C-4), 114.6 (CH, methoxyphenyl C-3, C-5), 120.5 (C, methoxyphenyl C-1), 123.5 (CH, olefinic carbon), 124.4 (CH, pyridine C-5), 127.2 (CH, benzene sulfonamide C-3, C-5), 128.8 (CH, benzene sulfonamide C-2, C-6), 130.8 (C, pyridine C-1), 131.4 (CH, methoxyphenyl C-2, C-6), 137.8 (C, oxazolone C-4), 138.7 (CH, pyridine C-6), 140.3 (C, benzene sulfonamide C-1), 144.2 (C, benzene sulfonamide C-4), 150.8 (CH, pyridine C-2), 153.2 (CH, pyridine C-4), 161.2 (C, oxazolone C-2), 162.6 (C, methoxyphenyl C-4), 169.6 (C, oxazolone C-5); MS *m/z* 434 (M^+, 100%). Anal. calcd. for $C_{22}H_{18}N_4O_4S$; C, 60.82; H, 4.18; N, 12.90: Found; C, 61.04; H, 4.24; N, 13.08.

Biological evaluation

COX-1/COX-2 inhibition colorimetric assay

The ability of the target compounds listed in Table 1 to inhibit ovine COX-1 and human recombinant COX-2 (IC_{50} value, μM) was determined using an enzyme immunoassay (EIA) kit

(catalog no. 560131, Cayman Chemical, Ann Arbor, MI, USA) according to the previously reported method [31].

In vivo anti-inflammatory activity

Adult male Wistar albino rats (100–150 g) were used in the pharmacological studies. The animals (five per cage) were maintained under standard laboratory conditions (light period of 12 h/day and temperature 27 ± 2°C), with access to food and water. The experimental procedures were carried out in strict compliance with the Institutional Animal Ethics Committee regulations. All experiments were performed in the morning according to the guidelines for the care of laboratory animals.

The anti-inflammatory activity of tested compounds **8a–f**, **11a–g** (50 mg/kg) and the reference drug celecoxib were evaluated using *in vivo* carrageenan-induced rat foot paw edema model. The paw thickness was measured 3 h after carrageenan injection according to the previously reported method [32].

The authors have declared no conflict of interest.

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