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Synthesis of *N*-benzenesulfonamide-1*H*-pyrazoles bearing arylsulfonyl moiety: Novel celecoxib analogs as potent anti-inflammatory agents

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ABSTRACT

The reaction of arylsulfones **11a**–**d** with hydrazonoyl chloride derivative **13** furnished celecoxib analogs 4-(3-acetyl-5-aryl-4-(arylsulfonyl)-1*H*-pyrazol-1-yl)benzenesulfonamides **15a**–**d**, respectively. Oximes **16a**, **b** and hydrazones **17a**, **b** were prepared by reacting sulfones **11a**, **b** with hydroxyl amine and phenyl hydrazine, respectively. The anti-inflammatory activity of the synthesized compounds showed that, 5-(4-bromophenyl)-4-(phenylsulfonyl)pyrazole **15c** and 5-(4-bromophenyl)-4-(4-tolylsulfonyl)pyrazole **15d** exhibited excellent anti-inflammatory activity with $ED_{50} = 68 \pm 2.2$ and 51 ± 0.7 μM/kg, respectively, higher than that of celecoxib ($ED_{50} = 86 \pm 1.1$ μM/kg) after 3 h with acceptable ulcer index. In addition, the LD_{50} of **15c** and **15d** is 7.1 mM/kg for each, and 9.8 mM/kg for celecoxib. Compound **15d** appeared selectivity index (COX-2/COX-1) almost the half of celecoxib while **15c** is non-selective for COX-2. Compound **15c** with $ED_{50} = 80 \pm 2.8$ μM/kg showed a significant analgesic activity when compared with celecoxib ($ED_{50} = 70 \pm 3.9$ μM/kg) after 2 h whereas **15b** ($ED_{50} = 50 \pm 1.2$ μM/kg) and **15d** ($ED_{50} = 69 \pm 2.7$ μM/kg) seemed to be more potent than celecoxib ($ED_{50} = 156 \pm 4.8$ μM/kg) but with a shorter duration (0.5 h).

1. Introduction

The biotransformation of arachidonic acid *via* the enzyme cyclooxygenase (COXs) resulting in the formation of prostaglandin (PGs) which act as mediators and modulators in inflammation. PGD2 is involved in allergic reactions while PGE2 is involved in pain, fever and inflammation as in case of rheumatoid arthritis. Prostacyclin (PGI2) dilates blood vessels by inhibiting platelet aggregation while thromboxane A2 (TXA2) having vasoconstrictive and platelet aggregative effects [1–4]. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen having analgesic, antipyretic and anti-inflammatory effects usually indicated for the treatment of pain, fever and inflammatory diseases. NSAIDs inhibit the biosynthesis of the prostaglandins and thromboxanes by inhibiting COXs [5–7]. COXs isozymes are a membrane-associated proteins which exists in two isoforms, a constitutive

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form (COX-1) and an inducible form (COX-2). COX-1 enzyme is responsible for maintenance of gastric mucosal integrity, kidney function, and platelet aggregation whereas COX-2 induces inflammatory conditions. NSAIDs which act as inhibitors of both COX-1 and COX-2 have been found to cause gastric ulcers, GI bleeding and suppression of the renal functions [8,9]. SC-558 **1** (Fig. 1) a marvelous inhibitor with 1900-fold selectivity for COX-2 over COX-1 was found to be a potent anti-inflammatory agent [10]. COX-2 selective benzenesulfonamides rofecoxib **2**, valdecoxib **3** and celecoxib **4** (Fig. 1), used for treating pain and inflammation and they have been shown a much lower gastrointestinal side effects [11,12]. Market withdrawal of rofecoxib **2** and valdecoxib **3**, and FDA marketing alert for celecoxib **4** due to their adverse cardiovascular side effects [13,14] shows the need to discover novel scaffolds with COX-2 inhibitory activity and evaluate their anti-inflammatory effects [15–19]. On the other hand, several sulfones such as methionine derivative, L-methioninesulfone **5** [20] and austrasulfone derivative dihydroaustrasulfone alcohol **6** (Fig. 1) [21] are effective as anti-inflammatory agents. Moreover, arylsulfones PC-796 **7** [22] and 2-sulfonyl-*O*-aminoacetophenones **8** [23] (Fig. 1) exhibited a significant anti-inflammatory activity.

In this topic, keeping in mind the structure features of *N*-benzenesulfonamides **1**–**4**, the present study describes synthesis, anti-inflammatory activity, selectivity index (COX-2/COX-1), ulcerogenic activity and analgesic activity for *N*-benzenesulfonamide-1*H*-pyrazoles **15a**–**d** which bearing arylsulfonyl moiety in position 4 of pyrazole ring as analogs of SC-588 **1** and/or celecoxib **4** (Fig. 1). In this study, sulfones **11a**–**d** with structure features similar to that of sulfones **8** [23] used as starting materials in the synthesis of targeted pyrazoles **15a**–**d** in addition to oximes **16a**, **b** and hydrazones **17a**, **b** (Schemes 1 and 2). In continuation of our interest in the synthesis of novel bioactive compounds derived from hydrazonoyl chlorides [24–30], included *N*-arylpyrazoles with anti-inflammatory potency, herein we aimed to report the cyclization reaction of sulfones **11a**–**d** with hydrazonoyl chloride **13** to produce celecoxib analogs **15a**–**d**.

2. Results and discussion

2.1. Chemistry

1-Aryl-2-(arylsulfonyl)ethanones **11a**–**d** were prepared by the reaction of bromo-1-arylethanones **9a**–**d** with sodium arylsulfinate **10a**, **b** (Scheme 1) according to the reported methods [31–33]. Sulfones **11a**–**d** reacted with **13** in ethanolic sodium ethoxide solution at room temperature to furnish 4-(3-acetyl-5-aryl-4-(arylsulfonyl)-1*H*-pyrazol-1-yl)benzenesulfonamides **15a**–**d**, respectively (Scheme 1). The IR spectra of the latter pyrazoles showed, in each case, the appearance of absorption band in the region 1706–1702 cm^{-1} corresponding to the carbonyl function. Their ^1H NMR spectra showed the disappearance of CH_2 protons signal and displayed the signals of NH_2 protons around δ 7.5 in addition to the singlet signal of acetyl protons in the region δ 2.58–2.60. Mass spectra (ESI) of **15a**–**d** showed $m/z = M^+ - 1$ in each case.

In the light of reported anti-inflammatory activity of oximes and hydrazones [34,35], we aimed to synthesize oximes **16a**, **b** and hydrazones **17a**, **b** (Scheme 2) to evaluate their anti-inflammatory activity. Thus, 1-(aryl)-2-(phenylsulfonyl)ethanone oximes **16a**, **b** were prepared by reacting sulfones **11a**, **b** with hydroxyl amine in the presence of sodium acetate (Scheme 2) [31,36]. The IR spectra of oximes **16a**, **b** showed the appearance of OH absorption band in 3246–2922 cm^{-1} region, whereas their ^1H NMR revealed the D_2O exchangeable singlet signal of OH proton around δ 11.66–11.79 in addition to the methylene protons in the region δ 4.92–4.95.

Furthermore, the reaction of sulfones **11a**, **b** with phenyl hydrazine in the presence of acetic acid afforded the corresponding 1-(1-(aryl)-2-(phenylsulfonyl)ethylidene)-2-phenylhydrazines **17a**, **b** (Scheme 2). The IR spectra of hydrazones **17a**, **b** showed the appearance of NH absorption band in 3344–3349 cm^{-1} region. The ^1H NMR spectra of these compounds revealed the appearance of D_2O exchangeable singlet signal due to NH of hydrazone in the region δ 9.64–9.75 in addition to the singlet signals of methylene protons in the region δ 5.17–5.19 integral to two protons.

2.2. Biological evaluations

2.2.1. Anti-inflammatory activity

The anti-inflammatory activity was performed to get ED_{50} for each tested compound after 1, 2 and 3 h, and to compare it with the reference drug celecoxib, however, the significant decreasing in the activity of all compounds was noticed after 6 h (Table 1). Regard to the intermediates **11a**–**d**, they gave anti-inflammatory lower than that of celecoxib ($ED_{50} = 86 \pm 1.1$ μM/kg) varied from 133 ± 1.1 μM/kg for **11b** and 327 ± 2.2 μM/kg for **11c** after 3 h. However, the substitution in both X and Ar affect ED_{50} values of **11a**–**d**, for

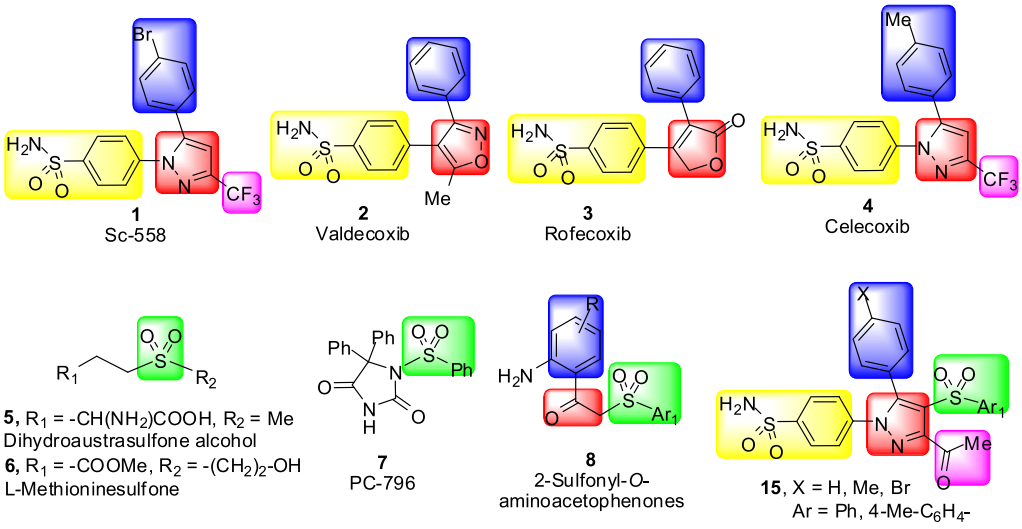
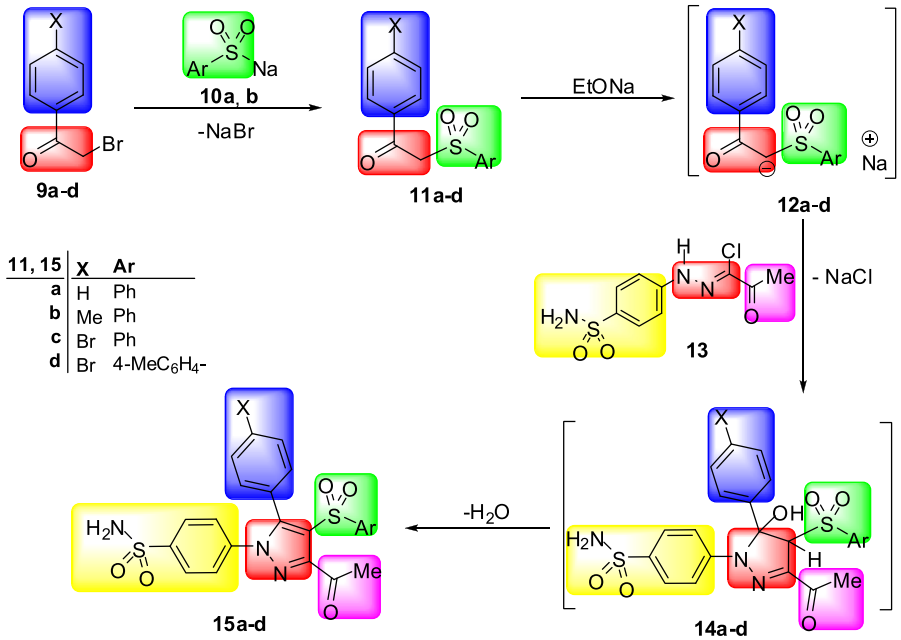
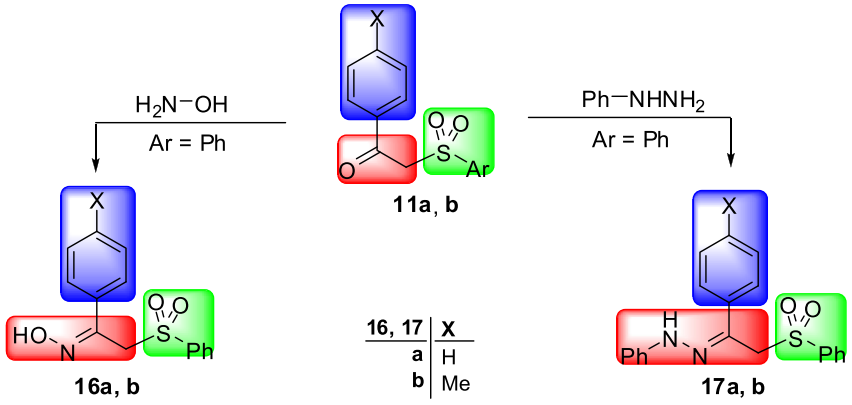


Fig. 1. Structure of compounds **1**–**8** and **15**.



Scheme 1. Synthesis of *N*-benzenesulfonamide-1*H*-pyrazoles **15a**–**d** as analogs of SC-588 **1** and/or celecoxib **4**.



Scheme 2. Synthesis of oximes **16a**, **b** and hydrazones **17a**, **b** as analogs of sulfones **8**.

Table 1
The anti-inflammatory activity, ED_{50} (μM/kg), LD_{50} (mM/kg) for the test compounds, percentage of inhibition of COX-1 and COX-2, selectivity index (COX-2/COX-1) of most active compounds at concentration of 5.0 μM and ulcer index of most active compounds.

Compound	ED_{50} (μM/kg)			LD_{50} (mM/kg)	% Inhibition COX-1[a]	% Inhibition COX-2[a]	Selectivity Index	Ulcer index
	1 h	2 h	3 h					
11a	238 ± 1.9	232 ± 0.9	242 ± 1.7	19.7	–	–	–	–
11b	145 ± 2.7	137 ± 3.1	133 ± 1.1	14.3	–	–	–	–
11c	550 ± 9.7	350 ± 0.9	327 ± 2.2	12.4	–	–	–	–
11d	213 ± 0.9	213 ± 2.7	200 ± 2.7	12.7	–	–	–	–
15a	363 ± 12.3	376 ± 11.3	372 ± 3.6	10.1	–	–	–	–
15b	112 ± 3.1	102 ± 1.1	95 ± 0.9	10.1	18	33	1.83	2.25 ± 0.5
15c	87 ± 3.1	64 ± 1.9	68 ± 2.2	7.1	34	27	0.79	2.86 ± 0.6
15d	75 ± 1.3	54 ± 1.3	51 ± 0.7	7.1	3	39	13.0	0.98 ± 0.3
16a	285 ± 1.1	245 ± 1.9	256 ± 1.0	17.4	–	–	–	–
16b	271 ± 6.9	238 ± 2.3	237 ± 2.1	9.0	–	–	–	–
17a	270 ± 12.1	248 ± 3.1	256 ± 1.4	14.6	–	–	–	–
17b	280 ± 7.5	181 ± 1.5	169 ± 1.5	11.5	–	–	–	–
Celecoxib	89 ± 1.3	89 ± 0.8	86 ± 1.1	9.8	2	61	30.5	0.92 ± 0.2

[a] Values represents means of two determinations acquired using an ovine COX-2/COX-1 assay kits.

example, X = Me as in compound **11b** get the best result among **11a**–**d** with ED_{50} = 133 ± 1.1 μM/kg after 3 h, but it still not good related to the reference drug. Upon the deep view in the anti-inflammatory activity of compounds **15a**–**d**, we discovered the incorporation of substitution in position 5 of pyrazole moiety in their activity, for example, the 5-phenyl pyrazole **15a** showed the lowest anti-inflammatory activity among **15a**–**d** with ED_{50} = 372 ± 3.6 μM/kg after 3 h while 5-(4-tolyl)pyrazole **15b** exhibited a moderate activity with ED_{50} = 95 ± 0.9 μM/kg after 3 h. 5-(4-Bromophenyl)pyrazole **15c** exhibited excellent anti-inflammatory activity (ED_{50} = 64 ± 1.9 and 68 ± 2.2 μM/kg after 2 and 3 h, respectively) which is higher than that of celecoxib (ED_{50} = 89 ± 0.8 and 86 ± 1.1 μM/kg after 2 and 3 h, respectively). Interestingly, the activity of **15c** increased when phenylsulfonyl (X = H) in position 4 replaced by 4-tolylsulfonyl group (X = Me) to give compound **15d** with a marvelous anti-inflammatory activity (ED_{50} = 54 ± 1.3 and 51 ± 0.7 μM/kg after 2 and 3 h, respectively) (Table 1). In addition, LD_{50} of **15c** and **15d** showed a low LD_{50} (LD_{50} = 7.1 μM/kg for each) related to celecoxib (LD_{50} = 9.8 μM/kg). The anti-inflammatory activity showed a moderate activity for sulfones **11a**–**d** and it showed high potency for **15a**–**d**. This findings stimulated our interest to synthesize oximes **16a**, **b** and hydrazones **17a**, **b** (Scheme 2) as analogs of sulfones **8** to evaluate their anti-inflammatory activity in an attempt to improve the activity of sulfones **11a**, **b** in the light of reported anti-inflammatory activity of oximes and hydrazones [34,35]. However, the oximes **16a**, **b** and hydrazones **17a**, **b** gave weak anti-inflammatory activity when they compared with the reference drug which indicate that oxime and hydrazone functions have not a positive change in their activity.

2.2.2. *In vitro cyclooxygenase inhibitory activity*

Percentage of inhibition of COX-1 and COX-2 and selectivity (COX-2/COX-1) of test compounds at concentration of 5.0 μM were illustrated in Table 1. Compounds **15b** and **15c** are non-selective for COX-2 inhibitors whereas compound **15d** showed good selectivity towards COX-2. Its COX-2/COX-1 selectivity is 13.0, almost the half of selectivity of celecoxib (COX-2/COX-1 = 30.5) (Table 1). These results indicate that, mechanism of action of test compounds need further investigations.

2.2.3. *Ulcerogenic activity*

Compounds **15b**–**d** that showed the highest anti-inflammatory activity were subjected to ulcerogenic activity against celecoxib as reference drug (Table 1). Compound **15d** revealed a good ulcer index (0.98 ± 0.3) when compared with that of celecoxib (0.92 ± 0.2) while compounds **15b** and **15c** showed ulcer indexes = 2.25 ± 0.5 and 2.86 ± 0.6, respectively (Table 1).

2.2.4. *Analgesic activity*

From the analgesic activity of synthesized compounds (Table 2), the highest analgesic activity in **11a**–**d** was recorded for compound **11d** with ED_{50} = 69 ± 4.5 and 66 ± 3.8 μM/kg when compared with celecoxib (ED_{50} = 72 ± 1.2 and 70 ± 3.9 μM/kg) after 1 and 2 h, respectively, this might be contributed to the presence of 4-bromophenyl (*X* = Br) and 4-tolyl (Ar = Me–C_6H_4-) moieties. With regard to the analgesic activity of **15a**–**d**, compound **15c** with ED_{50} = 80 ± 2.8 μM/kg showed a significant analgesic activity when compared with celecoxib (ED_{50} = 70 ± 3.9 μM/kg) after 2 h whereas **15b** (ED_{50} = 50 ± 1.2 μM/kg) and **15d** (ED_{50} = 69 ± 2.7 μM/kg) seemed to be more potent than celecoxib (ED_{50} = 156 ± 4.8 μM/kg) but with a shorter duration (after 0.5 h) (Table 2). However, **16a**, **b** and **17a**, **b** appeared poor analgesic activity comparing with reference drug.

Table 2
The analgesic activity, ED_{50} (μM/kg) for the test compounds.

Compound	ED_{50} (μM/kg)		
	0.5 h	1 h	2 h
11a	250 ± 1.6	158 ± 5.2	145 ± 3.6
11b	168 ± 3.7	408 ± 8.7	434 ± 4.4
11c	218 ± 6.1	318 ± 4.2	318 ± 5.0
11d	73 ± 1.3	69 ± 4.5	66 ± 3.8
15a	311 ± 6.9	261 ± 9.8	261 ± 3.4
15b	50 ± 1.2	147 ± 4.8	147 ± 4.9
15c	57 ± 1.6	81 ± 3.1	80 ± 2.8
15d	69 ± 2.7	195 ± 6.3	204 ± 5.2
16a	320 ± 11.3	265 ± 6.5	244 ± 6.1
16b	212 ± 8.4	203 ± 7.9	200 ± 4.0
17a	285 ± 9.1	319 ± 8.5	345 ± 5.8
17b	220 ± 1.2	260 ± 4.6	288 ± 4.7
Celecoxib	156 ± 4.8	72 ± 1.2	70 ± 3.9

3. Conclusion

In conclusion, *N*-benzenesulfonamide-1*H*-pyrazoles/arylsulfones hybrid **15c**, **d** were found to have excellent anti-inflammatory activity with ED_{50} = 68 ± 2.2 and 51 ± 0.7 μM/kg, respectively, higher than that of celecoxib (ED_{50} = 86 ± 1.1 μM/kg) after 3 h with acceptable ulcer index. Compound **15d** appeared COX-2/COX-1 selectivity almost the half of celecoxib while **15c** is non-selective for COX-2. These results invite to further investigations for the mechanism of action of this class of pyrazoles and/or to combine their promising activity with high COX-2 selectivity through variation of substitutions in positions 4 and 5 of pyrazole moiety. On a broad basis compounds **15c**, **d** seemed to be a promising anti-inflammatory agents and a new addition to the exciting group of NSAIDs.

4. Experimental

4.1. *Chemistry*

4.1.1. *General*

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared (IR) Spectra were recorded as KBr disks using the Perkin Elmer FT-IR Spectrum BX apparatus. NMR Spectra were scanned in DMSO-d_6 on a Brucker NMR spectrophotometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts are expressed in δ-values (ppm) relative to TMS as an internal standard. Coupling constants (*J*) are expressed in Hz. D_2O was added to confirm the exchangeable protons. Mass spectra were measured on an Agilent Triple Quadrupole 6410 QQQ LC/MS equipped with an ESI (electrospray ionization) source. Elemental analyses were carried out at the Microanalytical Center of Cairo University. 2-Bromo-1-arylethanones **9a**–**d** [37], sodium arylsulfinate **10a**, **b** [38] and 2-oxo-*N*′-(4-sulfamoylphenyl)propanehydrazonoyl chloride (**13**) [39] were prepared according to the reported method.

4.1.2. *Synthesis of 1-aryl-2-arylsulfonyl ethanones **11a**–**d***

These compounds were synthesized according to the reported method [31–33]. To a solution of 2-bromo-1-arylethanone **9a**–**d** (10 mmol) in absolute ethanol (50 mL), the appropriate sodium arylsulfinate dihydrate **10a**, **b** (12 mmol) was added. The mixture was refluxed for 3 h, then left to cool. The reaction mixture was poured into cold water and the solid product filtered off, washed with water, dried and finally recrystallized from EtOH to afford compounds **11a**–**d**, respectively.

*4.1.3. Synthesis of 4-(3-acetyl-5-aryl-4-(arylsulfonyl)-1H-pyrazol-1-yl)benzenesulfonamides **15a–d***

The appropriate 1-aryl-2-(arylsulfonyl) ethanones **11a–d** (10 mmol) was added to a stirred ethanolic sodium ethoxide solution [prepared from sodium metal (0.23 g, 10 mmol) and 50 mL of absolute ethanol]. After stirring for 20 min, 2-oxo-*N*′-(4-sulfamoylphenyl)propanehydrazonoyl chloride (**13**) (2.76 g, 10 mmol) was added and the reaction mixture was left to stir at room temperature for 12 h. Then added to cold water, the solid product was collected by filtration, washed with water and dried. Recrystallization from ethanol afforded 1*H*-pyrazoles **15a–d**.

*4.1.3.1. 4-(3-Acetyl-5-phenyl-4-(phenylsulfonyl)-1H-pyrazol-1-yl) benzenesulfonamide(**15a**).* Yield (54%); m.p. 248–50 °C; IR ν 3272 (NH_2), 1705 (C=O) cm^{-1}; ^1H NMR (DSMO-d_6) δ 2.60 (s, 3H, CH_3), 7.42–7.47 (m, 5H, ArH), 7.49 (s, 2H, D_2O exchangeable, 2H, NH_2), 7.58 (d, J = 8.5 Hz, 2H, ArH), 7.61–7.62 (m, 2H, ArH), 7.67–7.73 (m, 1H, ArH), 7.80 (d, J = 8.5 Hz, 2H, ArH), 7.91 (d, J = 7.0 Hz, 2H, ArH); ^{13}C NMR (DSMO-d_6) δ 28.20, 121.04, 126.37, 126.87, 127.37, 127.99, 128.89, 129.97, 130.67, 133.35, 140.26, 141.75, 144.43, 147.93, 148.28, 192. MS (ESI) *m/z* 479.8 ($M^+ - 1$). Anal. Calcd for $C_{23}H_{19}N_3O_5S_2$ (481.54): C, 57.37; H, 3.98; N, 8.73. Found: C, 57.56; H, 4.07; N, 8.79.

*4.1.3.2. 4-(3-Acetyl-4-(phenylsulfonyl)-5-p-tolyl-1H-pyrazol-1-yl) benzenesulfonamide(**15b**).* Yield (58%); m.p. 260–2 °C; IR ν 3265 (NH_2), 1702 (C=O) cm^{-1}; ^1H NMR (DSMO-d_6) δ 2.34 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 7.22–7.23 (m, 2H, ArH), 7.30–7.34 (m, 2H, ArH), 7.51 (s, 2H, D_2O exchangeable, 2H, NH_2), 7.55–7.92 (m, 9H, ArH); ^{13}C NMR (DSMO-d_6) δ 20.97, 28.23, 120.97, 126.40, 126.88, 127.37, 127.97, 128.63, 128.88, 129.16, 129.20, 129.26, 129.65, 130.53, 133.31, 133.91, 139.56, 140.35, 141.83, 144.39, 144.87, 148.02, 148.37, 192.20; MS (ESI) *m/z* 493.1 ($M^+ - 1$). Anal. Calcd for $C_{24}H_{21}N_3O_5S_2$ (495.57): C, 58.17; H, 4.27; N, 8.48. Found: C, 58.36; H, 4.18; N, 8.33.

*4.1.3.3. 4-(3-Acetyl-5-(4-bromophenyl)-4-(phenylsulfonyl)-1H-pyrazol-1-yl)benzenesulfonamide(**15c**).* Yield (52%); m.p. 265–7 °C; IR ν 3270 (NH_2), 1706 (C=O) cm^{-1}; ^1H NMR (DSMO-d_6) δ 2.58 (s, 3H, CH_3), 7.45 (d, J = 8 Hz, 2H, ArH), 7.50 (s, 2H, D_2O exchangeable, 2H, NH_2), 7.60–7.76 (m, 7H, ArH), 7.84 (d, J = 8.5 Hz, 2H, ArH), 7.94 (d, J = 7.5 Hz, 2H, ArH); ^{13}C NMR (DSMO-d_6) δ 28.07, 121.25, 123.78, 126.36, 126.49, 127.01, 127.43, 128.90, 131.07, 132.81, 133.40, 140.12, 141.65, 144.58, 146.94, 148.10, 191.88; MS (ESI) *m/z* 558.9 ($M^+ - 1$). Anal. Calcd for $C_{23}H_{18}BrN_3O_5S_2$ (560.44): C, 49.29; H, 3.24; N, 7.50. Found: C, 49.24; H, 3.40; N, 7.37.

*4.1.3.4. 4-(3-Acetyl-5-(4-bromophenyl)-4-tosyl-1H-pyrazol-1-yl) benzenesulfonamide(**15d**).* Yield (57%); m.p. 271–3 °C; IR ν 3259 (NH_2), 1706 (C=O) cm^{-1}; ^1H NMR (DSMO-d_6) δ 2.39 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 7.42–7.43 (m, 3H, ArH), 7.50 (s, 2H, D_2O exchangeable, 2H, NH_2), 7.59–7.65 (m, 4H, ArH), 7.74–7.85 (m, 5H, ArH); ^{13}C NMR (DSMO-d_6) δ 21.05, 28.10, 121.70, 23.75, 126.40, 126.49, 126.98, 127.559, 128.05, 129.33, 129.64, 131.06, 131.78, 132.81, 138.80, 140.13, 143.96, 144.55, 146.63, 148.07, 191.92; MS (ESI) *m/z* 573.4 ($M^+ - 1$). Anal. Calcd for $C_{24}H_{20}BrN_3O_5S_2$ (574.47): C, 50.18; H, 3.51; N, 7.31. Found: C, 49.96; H, 3.46; N, 7.42.

*4.1.4. Synthesis of 1-(aryl)-2-(phenylsulfonyl)ethanone oximes **16a**, **b***

A mixture of the appropriate 1-aryl-2-arylsulfonyl ethanones **11a**, **b** (10 mmol), hydroxyl amine hydrochloride (1.1 g, 15 mmol) and anhydrous sodium acetate (1.2 g, 15 mmol) in ethanol (50 mL) was refluxed for 1 h, then left to cool. The reaction mixture was poured into cold water and the solid product was filtered off, washed with water, dried and finally recrystallized from EtOH to afford compounds **16a**, **b**, respectively [31,36].

*4.1.4.1. 1-Phenyl-2-(phenylsulfonyl)ethanone oxime(**16a**).* Yield (73%); m.p. 120–2 °C; IR ν 3230–2940 (OH) cm^{-1}; ^1H NMR (DSMO-d_6) δ 4.95 (s, 2H, CH_2), 7.35–7.37 (m, 3H, ArH), 7.56–7.59 (m, 2H, ArH), 7.64–7.66 (m, 2H, ArH), 7.69–7.72 (m, 1H, ArH), 7.75–7.77 (m, 2H, ArH), 11.79 (s, D_2O exchangeable, 1H, OH); ^{13}C NMR (DSMO-d_6) δ 51.37, 126.34, 127.77, 128.18, 128.96, 129.01, 133.83, 134.50, 139.71, 145.54; MS (ESI) *m/z* 275.1 (M^+). Anal. Calcd for $C_{14}H_{13}NO_3S$ (275.32): C, 61.07; H, 4.76; N, 5.09. Found: C, 61.30; H, 4.85; N, 5.11.

*4.1.4.2. 1-(4-Methylphenyl)-2-(phenylsulfonyl)ethanone oxime(**16b**).* Yield (68%); m.p. 155–7 °C; IR ν 3246–2922 (OH) cm^{-1}; ^1H NMR (DSMO-d_6) δ 2.32 (s, 3H, CH_3), 4.92 (s, 2H, CH_2), 7.16 (d, J = 8 Hz, 2H, ArH), 7.54 (d, J = 8 Hz, 2H, ArH), 7.56–7.59 (m, 2H, ArH), 7.69–7.72 (m, 1H, ArH), 7.75–7.76 (m, 2H, ArH), 11.66 (s, D_2O exchangeable, 1H, OH); ^{13}C NMR (DSMO-d_6) δ 20.76, 51.38, 126.27, 127.76, 127.88, 128.15, 128.77, 131.75, 133.79, 138.53, 139.73, 145.42; MS (ESI) *m/z* 289.3 (M^+). Anal. Calcd for $C_{15}H_{15}NO_3S$ (289.35): C, 62.26; H, 5.23; N, 4.84. Found: C, 62.27; H, 5.17; N, 4.97.

*4.1.5. Synthesis of 1-(1-(aryl)-2-(phenylsulfonyl)ethylidene)-2-phenylhydrazines **17a**, **b***

To a solution of the appropriate 1-aryl-2-arylsulfonyl ethanones **11a**, **b** (10 mmol) in ethanol (50 mL) and phenyl hydrazine (1.08 g, 10 mmol), catalytic amount of acetic acid were added. The reaction mixture was refluxed for 1 h. After cooling, the precipitated product was filtered off, washed with ethanol and dried. Recrystallization from EtOH afforded compounds **17a**, **b**, respectively.

*4.1.5.1. 1-Phenyl-2-(1-phenyl-2-(phenylsulfonyl)ethylidene)hydrazine(**17a**).* Yield (66%); m.p. 160–2 °C; IR ν 3349 (NH) cm^{-1}; ^1H NMR (DSMO-d_6) δ 5.17 (s, 2H, CH_2), 6.82–6.84 (m, 1H, ArH), 7.13–7.14 (m, 2H, ArH), 7.23–7.30 (m, 5H, ArH), 7.51–7.54 (m, 2H, ArH), 7.59–7.60 (m, 1H, ArH), 7.70–7.72 (m, 2H, ArH), 7.88–7.90 (m, 2H, ArH), 9.75 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (DSMO-d_6) δ 51.75, 112.95, 119.85, 125.60, 127.34, 127.93, 128.10, 128.90, 128.96, 129.35, 133.89, 137.557, 139.38, 144.69; MS (ESI) *m/z* 349.5 ($M^+ - 1$). Anal. Calcd for $C_{20}H_{18}N_2O_2S$ (350.43): C, 68.55; H, 5.18; N, 7.99. Found: C, 68.59; H, 5.04; N, 8.12.

*4.1.5.2. 1-Phenyl-2-(2-(phenylsulfonyl)-1-p-tolylethylidene)hydrazine(**17b**).* Yield (70%); m.p. 147–9 °C; IR ν 3344 (NH) cm^{-1}; ^1H NMR (DSMO-d_6) δ 2.29 (s, 3H, CH_3), 5.19 (s, 2H, CH_2), 6.80–6.83 (m, 1H, ArH), 7.08–7.12 (m, 4H, ArH), 7.22–7.24 (m, 2H, ArH), 7.53–7.54 (m, 2H, ArH), 7.60–7.61 (m, 3H, ArH), 7.88–7.89 (m, 2H, ArH), 9.64 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (DSMO-d_6) δ 20.68, 51.79, 112.85, 119.68, 125.59, 128.08, 128.56, 128.90, 129.56, 133.85, 134.88, 136.74, 139.41, 144.78; MS (ESI) *m/z* 364.3 (M^+). Anal. Calcd for $C_{21}H_{20}N_2O_2S$ (364.46): C, 69.20; H, 5.53; N, 7.69. Found: C, 69.46; H, 5.55; N, 7.82.

4.2. Anti-inflammatory activity

Male Sprauge–Dawley rats weighing 250 g were purchased from local source and kept at room temperature (22 ± 2 °C) in a light-controlled room with an alternating 12 h light/dark cycle. They were fasted with free access to water at least 16 h prior to experiments. The tested compounds were prepared as suspension in vehicle (0.5% methyl cellulose) and celebrex (Celecoxib) was used as a standard drug. The positive control group animals received the reference drug while the negative control received only the vehicle. The anti-inflammatory activity was evaluated using *in vivo* rat carrageenan-induced foot paw edema model reported previously [40]. Edema was produced by injecting 0.2 mL of a solution of 1% λ-carrageenan in the hind paw. The rats were injected intraperitoneally with 1 mL suspension in 0.5% methyl

cellulose of the tested compounds and reference drug. Paw volume was measured by water displacement with a plethysmometer (UGO BASILE) before, 1 and 2 h after treatment. The percentage was calculated by the following equation: anti-inflammatory activity (%) = (1 − D/C) − 100, where *D* represents the difference in paw volume before and after drug was administered to the rats, and C stands for the difference of volume in the control groups [40]. Values reported as mean ± s.e.m., significant differences were calculated using ANOVA.

4.2.1. Determination of LD_{50} for the active anti-inflammatory compounds

Male mice were divided into various groups and test compounds were administered in various doses, intraperitoneally. Following treatments, the animals were observed for up to 6 h continuously and were then kept under observation for 72 h. All behavioral changes and death during the observation periods were recorded. The percentage of death at each dose level was then calculated, converted to probits and the LD_{50} (mM/kg) values were calculated [41].

4.2.2. In vitro cyclooxygenase inhibitory assay

The *in vitro* ability of test compounds and celecoxib to inhibit the COX-1 and COX-2 isozymes was carried out using Cayman colorimetric COX (ovine) inhibitor screening assay kit (Catalog no. 560131) supplied by Cayman chemicals, USA. The calculations were performed as per the kit guidelines [42,43].

4.3. Ulcerogenic activity

Male albino rats weighing 200–250 g were fasted for 12 h prior to drug administration. Water was supplied *adlibitum*. The animals were divided into seven equal groups (each of four). The first group received 7% gum acacia (suspending vehicle) orally once a day and was left as a control, whereas the other groups received the reference drugs and test compounds with a dose of 100 mmol/kg/day orally. The test compounds were administered once a day for three successive days. The animals were killed by an overdose of ether 6 h after the last dose. The stomachs were removed, opened along the greater curvature, and examined for ulceration. The number and diameter of discrete areas of damage in the glandular mucosa were scored (Table 1). The ulcer score was calculated according to the method of Vijaya and Mishra [44]: 0.0 − normal (no injury); 0.5 − latent injury; 1.0 − slight injury (two to three dotted lines); 2.0 − severe injury (continuous lined injury or five to six dotted injuries); 3.0 − very severe injury (several continuous lined injuries); 4.0 − widespread lined injury.

4.4. Analgesic activity

Male albino Swiss mice (25 g body weight) were divided into various groups ($N = 4$). Each mouse was initially placed on a hot plate thermostatically maintained at 58 °C (Colombus Co.) [45]. The mouse was watched carefully for the time in seconds in which it displays nociceptive responses exhibited as licking or blowing (fanning) its front paws. This time was considered as the control reaction time. A cut-off time of 60 s was used to avoid damage to the paws. To test the analgesic activity of the compounds each group of mice was treated with one dose of the test compounds (5–200 mg/kg i–p). The reaction time was then retested at 15, 30, 60, and 120 min after injection (each animal acted as its own control). The percentage changes in the reaction were then calculated. The ED_{50} for each compound was then calculated by linear regression.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2014.04.065. These data include MOL files and InChiKeys of the most important compounds described in this article.

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