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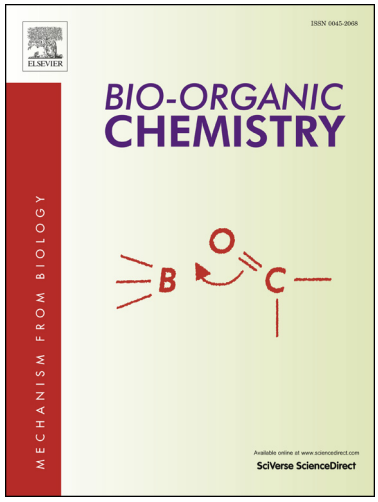

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Khaled R.A. Abdellatif, Heba A.H. Elshemy, Amany A. Azoz

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1-(4-Methane(amino)sulfonylphenyl)-3-(4-substituted-phenyl)-5-(4-trifluoromethylphenyl)-1H-2-pyrazolines/ pyrazoles as potential anti-inflammatory agents

Khaled R. A. Abdellatif[1,*], Heba A. H. Elshemy[1] Amany A. Azoz[2]

[1]Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt, [2]Pharmacology Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt

**To whom correspondence should be addressed.*

Khaled R. A. Abdellatif, Ph.D. Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Beni-Suef University, Beni-Suef 62514, Egypt.

Tel.: (002)-0100-2535444

Fax: (002)-082-2317958

E-mail address: khaled.ahmed@pharm.bsu.edu.eg

Abstract

2-Pyrazolins **14a-l** and pyrazoles **15a-l** were designed as celecoxib analogs for the evaluation of their *in vitro* COX-1/COX-2 inhibitory activity and the *in vivo* anti-inflammatory activity. Compounds **14i**, **15a**, **15d** and **15f** were the most COX-2 selective derivatives (S.I = 5.93, 6.08, 5.03 and 5.27 respectively) while the pyrazoline derivatives **14g** and **14i** exhibited the highest AI activity (ED_{50} = 190.5 and 160.1 μmol/kg po, respectively).

Keywords: Celecoxib analogs; Pyrazoline; Pyrazole; Cyclooxygenase-2; Anti-inflammatory activity.

1. Introduction:

The anti-inflammatory activity of non-steroidal anti-inflammatory drugs (NSAIDs) results from enzymatic inhibition of cyclooxygenase (COX)-mediated production of pro-inflammatory prostaglandins (PGs) and thromboxanes (TXs) [1–3]. Cyclooxygenase enzyme exists in two distinct isoforms, a constitutive form (COX-1) and an inducible form (COX-2); the constitutive COX-1 plays an important role in the maintenance of physiological functions such as protection of gastric mucosa, vascular homeostasis, and platelet aggregation. While, the inducible COX-2 is over expressed during acute and chronic inflammation [4]. Traditional NSAIDs as aspirin, ibuprofen and indomethacin interact with both forms (COX-1 and COX-2) and therefore their long term administration even at low prophylactic doses resulting in gastro intestinal side effects ranging from ulcers to perforation and bleeding. For this reason, synthesis of selective COX-2 inhibitor drugs (coxibs) takes much consideration in recent years that achieve the same anti-inflammatory activity as traditional NSAIDs but with minimal risk of undesirable gastrointestinal side effects [5]. Celecoxib (**1**), rofecoxib (**2**), and valdecoxib (**3**) are the most common coxibs approved for marketing, but adverse biochemical changes in the COX pathway are believed to be responsible for the increased incidences of high blood pressure and myocardial infarction that caused the withdrawal of rofecoxib and valdecoxib [6,7]. Although, celecoxib is not associated with an increased incidence of cardiovascular events compared with placebo and with nonselective NSAIDs and still one of the most important highly marketed COX-2 selective drugs, there are some characteristics of celecoxib that could be improved. For example, celecoxib is not effective in all patients and has some gastrointestinal side effects [8]. In this regard; we reported some celecoxib derivatives (**4-8**) [9–14] of comparable activity with celecoxib as COX-2 selective compounds (Figure 1).

[Please insert Figure 1 about here]

Celecoxib belongs to a tricyclic class of COX-2 inhibitors in which, two vicinal (adjacent) aryl substituents attached to a five-membered ring acts as a scaffold. SAR studies of this class showed that *para*-substituents on the adjacent aryl rings that provide optimal COX-2 selectivity, potency and oral activity are usually a COX-2 pharmacophore on one ring ($-SO_2Me$, $-SO_2NH_2$) and Me substituent on the other ring [15]. Also several reports suggested that the bioisosteric substitution of fluorine in place of hydrogen in many biologically active molecules has led to more potent compounds without extensive stereochemical changes due to its small size. Moreover, such substitution modulates the overall reactivity and stability of the compounds due to resistance of the

carbon-fluorine bond toward metabolic transformations and changes in acidity due to electronegativity differences between the two atoms [16]. Based on these observations and in continuation with our work related to the synthesis of safe anti-inflammatory agents, we now describe the synthesis, *in vitro* evaluation as COX-1/COX-2 inhibitors, and *in vivo* anti-inflammatory (AI) activity for two groups of celecoxib analogs **14a-l**, **15a-l** in which; i) the scaffold consisting of two adjacent aryl rings attached to a five-membered ring with COX-2 pharmacophore (-SO_2Me in **14a-f** and **15a-f**, -SO_2NH_2 in **14g-l** and **15g-l**) on one aryl ring was maintained, ii) Me group on the second aryl ring was replaced with trifluoromethyl moiety iii) trifluoromethyl moiety at C-3 of the central five-membered ring was replaced with substituted aryl moiety since it was reported that the substituent at C-3 of the central ring has very few steric restrictions with respect to COX-2 binding [17]. This replacement is expected to maximize the interaction with hydrophobic residues within COX-2 active site and enhances COX-2 selectivity, as the new compounds will be too large to fit into the smaller COX-1 active site (Figure 2).

[Please insert Figure 2 about here]

2. Results and discussion

2.1. Chemistry:

As shown in **scheme 1**, two groups of celecoxib analogs **14a-l** and **15a-l** were synthesized using the reaction sequence illustrated in Scheme 1. Accordingly, reaction of 4'-hydroxyactophenone (**9a**), 4'-methylactophenone (**9b**), 4'-methoxyactophenone (**9c**), or 4'-ethoxyactophenone (**9d**) with 4-trifluoromethylbenzaldhyde (**10**) in the presence of sodium hydroxide at room temperature for 2 hours provided the corresponding chalcones **11a-d.** While, when the reaction for 4'-fluoroactophenone (**9e**) was done for the same period (2 hours), 1,5-dicarbonyl derivative **12** was formed *via* an addition reaction for further molecule of 4'-fluoroactophenone on the non separated chalcone. So, for preparation of chalcones **11e** and **11f** from 4'-fluoroactophenone (**9e**) and 3',4'-difluoroactophenone (**9f**), the reaction time was decreased to 0.5 hour only. Cyclization of the chalcones **11a-f** with (4-methane/aminosulphonylphenyl)hydrazine hydrochloride (**13a-b**) in ethanol under reflux conditions gave the respective 3,5-diaryl-4,5-dihydropyrazoles (**14a-l)** in high yields (75-90%). Oxidation of 4,5-dihydropyrazoles (2-pyrazolines) **14a-l** using glacial acetic acid yielded the corresponding pyrazoles **15a-l** in good yields (65-90%). Also, trials for direct conversion of the chalcones **11a-f** to the respective pyrazoles **15a-l** were done by performing the reaction in acetic acid 96% and increasing reflux time till 36 h, a complete conversion had been

achieved for compounds **15b**, **15d**, **15h** and **15j** while mixture of 2-pyrazolines and the corresponding pyrazoles of close polarity on TLC sheets for the other compounds were obtained.

[Please insert Scheme 1 about here]

All the prepared compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, mass spectra and elemental analyses. The IR spectra of chalcone compounds **11a-f** showed sharp peak at 1667-1661 cm^{-1} corresponding to C=O while, the IR spectra for 1,5-dicarbonyl derivative **12** displayed the carbonyl sharp peak at 1672 cm^{-1}. The IR spectra of the 2-pyrazolines **14a-l** and pyrazoles **15a-l** showed the appearance of two sharp peaks at 1327-1320 and 1169-1132 cm^{-1} corresponding to SO_2 with disappearance of C=O peak of chalcones. The ^{1}H NMR spectra of **11a-f** displayed two doublets, each of one proton intensity, one at δ 7.55-7.73 and the second at δ 7.81-8.04 with high *J* value (15.6-16.8 Hz) indicating the 2 olefinic protons in *E* form. While, the ^{1}H NMR spectra of 1,5-dicarbonyl derivative **12** showed two characteristic signals as doublet of doublet (dd), each of two protons intensity, one at δ 3.31, second at δ 3.48 with two different *J* values (16.8, 7.2 Hz) corresponding to four protons of the two equivalent methylene, in addition to a multiplet of one proton intensity at δ 4.06-4.13 corresponding to C*H* of pentane-1,5-dione. The ^{1}H NMR spectra of dihydropyrazole compounds **14a-l** showed three signals dd, each of one proton intensity, one at δ 3.14-3.27, second at δ 3.93-4.01 and the third at δ 5.41-5.85 with three different *J* values (16.8-17-6, 12.0-12.4, 4.8-5.6 Hz) corresponding to three protons of the dihydropyrazole (2-pyrazoline) ring. Additionally, The ^{1}H NMR spectra of pyrazole compounds **15a-l** showed a singlet of one proton intensity in the range δ 6.87-7.45 corresponrding to pyrazole H-4. The ^{13}C NMR spectra of **11a-f** confirmed the presence of α, β-unsaturated carbonyl system of chalcones by presence of three peaks at δ 123.00-125.21, 141.16-143.67 and 187.23-189.48 corresponding to propenone C-2, propenone C-3 and propenone C-1 respectively. While the ^{13}C NMR spectra of **12** confirmed the presence of pentane-1,5-dione derivative by presence of three peaks at δ 36.76, 44.34 and 196.34 corresponding to C-3, 2C (C-2, C-4) and 2C=O respectively. Also ^{13}C NMR spectra of **14a-l** confirmed the presence of the pyrazoline ring due to presence of three peaks at δ 43.18-43.64, 61.89-63.70 and 147.71-151.38 corresponding to pyrazoline C-4, C-5 and C-3 respectively. While, these values are extremely changed in the respective pyrazoles **15a-l** (106.62-108.23, 142.89-143.97 and 150.74-153.39 corresponding to pyrazole C-4, C-5 and C-3 respectively).

2.2. Pharmacological screening

2.2.1. *In vitro* cyclooxygenase (COX) inhibition assay

In vitro COX-1/COX-2 enzyme inhibition studies (Table 1) showed that these pyrazoline **14a-l** and pyrazole derivatives **15a-l** are weak inhibitors of the COX-1 isozyme (IC_{50} = 5.6 – 24.1 μM range) but are moderate to good inhibitors of the COX-2 isozyme (IC_{50} = 0.97 – 10.8 μM range). All compounds were more selective COX-2 inhibitors (S.I = 2.23 – 6.08) than aspirin (S.I = 0.017) and ibuprofen (S.I = 1.05) but were less COX-2 selective than celecoxib (S.I = 7.70). Compounds **14i**, **15a**, **15d** and **15f** were the most COX-2 selective derivatives with close S.I to celecoxib (S.I = 5.93, 6.08, 5.03 and 5.27 respectively).

2.2.2. *In vivo* anti-inflammatory activity

The AI activities exhibited by the pyrazolines **14a-l** and pyrazoles **15a-l** were determined using a carrageenan-induced rat foot paw edema model (see data in Table 1). The ethoxy derivatives (**14d**, **14J**, **15d** and **15j**) and pyrazoline derivatives having a sulphamoyl (SO_2NH_2) substituent (**14g**, **14i** and **14k**) exhibited higher AI activities (38.8, 33.8, 33.3, 42.5, 41.3, 41.3 and 38.8 % inhibition of inflammation, respectively) than the other compounds for the same oral dose (50 mg/kg). Another AI evaluation for the seven aforementioned most potent AI compounds at another 2 oral doses were done to determine ED_{50} (the concentration causing 50% edema inhibition). The pyrazoline derivatives (**14g** and **14i**) exhibited AI activity (ED_{50} = 190.5 and 160.1 μmol/kg po, respectively) that was about 4-fold more potent than aspirin (ED_{50} = 710 μmol/kg po), 2-fold more potent than ibuprofen (ED_{50} = 327 μmol/kg po), but less active than celecoxib (ED_{50} = 30.9 μmol/kg po). The other five compounds (**14d**, **14J**, **14k**, **15d** and **15j**) exhibited an AI activity (ED_{50} = 239.6 – 312.0 μmol/kg po) between that observed for the reference drugs ibuprofen and celecoxib.

[Please insert Table 1 about here]

3. Conclusions:

Two groups of pyrazoline and pyrazole derivatives **14a-l** and **15a-l** were synthesized for evaluation as COX-1/COX-2 isozyme inhibitors, and as AI agents. Structure-activity and biological studies showed that i) all the compounds were more selective COX-2 inhibitors than aspirin and ibuprofen but were of comparable COX-2 selectivity to celecoxib, ii) twenty one compounds from the twenty four synthesized derivatives showed *in vivo* anti-inflammatory activity at 50 mg/kg dose and iii) The pyrazoline derivatives (**14g** and **14i**) exhibited AI activity about 4-fold more potent than aspirin, 2-fold more potent than ibuprofen, but less active than celecoxib.

4. Experimental protocol

4.1. Chemistry

4.1.1. General

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded as films on NaCl plates using a Nicolet 550 Series II Magna FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AM-400 spectrometer in $CDCl_3$ with TMS as the internal standard, where *J* (coupling constant) values are estimated in Hertz (Hz). Mass spectra (MS) were recorded on a Water's Micromass ZQ 4000 mass spectrometer using the electrospray (ES) ionization mode. Microanalyses were performed for C, H and N by The Regional Centre for Mycology and Biotechnology, Al-Azhar University, cairo, Egypt and were within ± 0.4% of theoretical values for all elements listed. Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70-230 mesh). (4-Methanesulphonylphenyl)hydrazine hydrochloride (**13a**) and (4-aminosulphonyl-phenyl)hydrazine hydrochloride (**13b**) were prepared according to the reported procedure [18].

4.1.2. General method for preparation of (*E*)-1,3-diarylprop-2-en-1-ones ***(11a-f).*** To a solution of the appropriate substituted acetophenone (**9a-f**, 2.0 mmol) in ethanol (10 mL), an aqueous sodium hydroxide solution (2 mL, 10%) was added slowly with continuous stirring. 4-Trifluoromethyl benzaldehyde (**10**, 2.0 mmol, 0.35 g) was added and the resulting mixture was stirred at 25 °C for 2 h (**11a**, **11b**, **11c**, **11d**), or for 0.5 h (**11e, 11f**). The obtained solid was filtered, washed with water (5 mL) and then EtOH (5 mL) followed by crystallization from absolute ethanol to give analytically pure compounds **11a-f**. Physical and spectral data are listed below.

*4.1.2.1. (E)-1-(4-Hydroxyphenyl)-3-(4-trifluoromethyl-phenyl)propenone (**11a**):* 74% yield; white powder; mp 189-190 °C; IR (KBr disk) 3407 (OH), 3013 (C-H aromatic), 1662 (CO); ^{1}H NMR (DMSO-d_6) δ 6.93 (d, *J* = 8.4 Hz, 2H, hydroxyphenyl H-3, H-5), 7.73 (d, *J* = 16.8 Hz, 1H, COC*H*=CH), 7.76 (d, *J* = 8.8 Hz, 2H, trifluoromethylphenyl H-2, H-6), 8.04 (d, *J* = 16.8 Hz, 1H, COCH=C*H*), 8.07 (d, *J* = 8.8 Hz, 2H, trifluoromethylphenyl H-3, H-5), 8.11 (d, *J* = 8.4 Hz, 2H, hydroxyphenyl H-2, H-6), 10.52 (s, 1H, O*H*, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ 115.56 (hydroxyphenyl C-3, C-5), 124.50 (q, *J* = 270 Hz, *C*F_3), 125.21 (propenone C-2), 126.07 (d, *J* = 4 Hz, trifluoromethylphenyl C-2, C-6), 129.32 (hydroxyphenyl C-1), 129.72 (d, *J* = 14 Hz, trifluoromethylphenyl C-3, C-5), 130.27 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 131.82 (hydroxyphenyl C-2, C-6), 139.35 (trifluoromethylphenyl C-1), 141.16 (propenone C-3), 162.91 (hydroxyphenyl C-4), 187.41 (propenone C-1); MS (m/z): 292 ($M^{+\cdot}$, 88.3%), 93 (100%); Anal. Calcd for $C_{16}H_{11}F_3O_2$: C, 65.76; H, 3.79; Found: C, 65.71; H, 3.87.

*4.1.2.2. (E)-1-p-Tolyl-3-(4-trifluoromethyl-phenyl)propenone (**11b**):* 80% yield; white crystals; mp 134-135 °C; IR (KBr disk) 3039 (C-H aromatic), 2938 (C-H aliphatic), 1661 (CO); ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H, CH_3), 7.34 (d, *J* = 8.0 Hz, 2H, tolyl H-3, H-5), 7.62 (d, *J* = 15.6 Hz, 1H, COC*H*=CH), 7.68 (d, *J* = 8.4 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.75 (d, *J* = 8.4 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.82 (d, *J* = 15.6 Hz, 1H, COCH=C*H*), 7.97 (d, *J* = 8.0 Hz, 2H, tolyl H-2, H-6); ^{13}C NMR (CDCl3) δ 21.72 (*C*H_3), 123.9 (q, *J* = 270 Hz, *C*F_3), 124.23 (propenone C-2), 125.88 (d, *J* = 4 Hz, trifluoromethylphenyl C-2, C-6), 128.48 (d, *J* = 4 Hz, trifluoromethylphenyl C-3, C-5), 128.73 (tolyl C-3, C-5), 129.47 (tolyl C-2, C-6), 131.78 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 135.22 (tolyl C-1), 138.39 (trifluoromethylphenyl C-1), 142.30 (propenone C-3), 144.12 (tolyl C-4), 189.48 (propenone C-1); MS (m/z): 290 ($M^{+\cdot}$, 77.1), 91 (100%); Anal. Calcd for $C_{17}H_{13}F_3O$: C, 70.34; H, 4.51; Found: C, 70.63; H, 4.59.

*4.1.2.3. (E)-1-(4-Methoxyphenyl)-3-(4-trifluoromethylphenyl)propenone (**11c**):* 77% yield; white crystals; mp 137-138 °C; IR (KBr disk) 3067 (C-H aromatic), 2921 (C-H aliphatic), 1667 (CO); ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H, OC*H*$_3$), 7.00 (d, *J* = 8.8 Hz, 2H, methoxyphenyl H-3, H-5), 7.63 (d, *J* = 15.6 Hz, 1H, COC*H*=CH), 7.68 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.75 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.81 (d, *J* = 15.6 Hz, 1H, COCH=C*H*), 8.07 (d, *J* = 8.8 Hz, 2H, methoxyphenyl H-2, H-6); ^{13}C NMR (CDCl3) δ 55.54 (O*C*H_3), 114.40 (methoxyphenyl C-3, C-5), 124.07 (propenone C-2), 125.30 (q, *J* = 270 Hz, *C*F_3), 125.87 (d, *J* = 4 Hz, trifluoromethylphenyl C-2, C-6), 128.43 (trifluoromethylphenyl C-3, C-5), 130.69 (methoxyphenyl C-2, C-6), 130.94 (methoxyphenyl C-1), 131.70 (q, *J* = 32 Hz, (trifluoromethylphenyl C-4), 138.49 (trifluoromethylphenyl C-1), 141.90 (propenone C-3), 163.71 (methoxyphenyl C-4), 188.18 (propenone C-1); MS (m/z): 306 ($M^{+\cdot}$, 97.2%), 107 (100%); Anal. Calcd for $C_{17}H_{13}F_3O_2$: C, 66.67; H, 4.28; Found: C, 66.84; H, 4.42.

*4.1.2.4. (E)-1-(4-Ethoxyphenyl)-3-(4-trifluoromethylphenyl)propenone (**11d**):* 75% yield; white crystals; mp 130-131 °C; IR (KBr disk) 3073 (C-H aromatic), 2966 (C-H aliphatic), 1667 (CO); ^{1}H NMR ($CDCl_3$) δ 1.48 (t, *J* = 6.8 Hz, 3H, CH_2CH_3), 4.15 (q, *J* = 6.8 Hz, 2H, CH_2CH_3), 7.00 (d, *J* = 8.4 Hz, 2H, ethoxyphenyl H-3, H-5), 7.63 (d, *J* = 15.6 Hz, 1H, COC*H*=CH), 7.68 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.75 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.81 (d, *J* = 15.6 Hz, 1H, COCH=C*H*), 8.06 (d, *J* = 8.4 Hz, 2H, ethoxyphenyl H-2, H-6); ^{13}C NMR (CDCl3) δ 14.68 (CH_2CH_3), 63.85 (CH_2CH_3), 114.39 (ethoxyphenyl C-3, C-5), 124.09 (propenone C-3), 125.20 (q, *J* = 270 Hz, *C*F_3), 125.88 (d, *J* = 4 Hz, trifluoromethylphenyl C-2, C-6), 128.42 (trifluoromethylphenyl C-3, C-5),, 130.50 (ethoxyphenyl C-2, C-6), 130.94 (ethoxyphenyl C-1) 131.70 (q, *J* = 32 Hz, *C*-CF_3), 138.5 (trifluoromethylphenyl C-1) (trifluoromethylphenyl C-1),

141.80 (propenone C-3), 163.2 (methoxyphenyl C-4), 188.20 (propenone C-1); MS (m/z): 320 ($M^{+\cdot}$, 91.8), 121 (100%); Anal. Calcd for $C_{18}H_{15}F_3O_2$: C, 67.50; H, 4.72; Found: C, 67.84; H, 4.92.

*4.1.2.5. (E)-1-(4-Fluorophenyl)-3-(4-trifluoromethylphenyl)propenone (**11e**):* 64% yield; white powder; mp 99-100 °C; IR (KBr disk) 3013 (C-H aromatic), 1664 (CO); ^{1}H NMR ($CDCl_3$) δ 7.13-7.23 (m, 2H, fluorophenyl H-3, H-5), 7.59 (d, *J* = 15.6 Hz, 1H, COC*H*=CH), 7.69 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.75 (d, *J* = 8.8 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.83 (d, *J* = 15.6 Hz, 1H, COCH=C*H*), 8.07-8.19 (m, 2H, fluorophenyl H-2, H-6); ^{13}C NMR ($CDCl_3$) δ 115.90 (d, *J* = 22 Hz, fluorophenyl C-3, C-5), 123.69 (propenone C-2), 123.81 (q, *J* = 270 Hz, *C*F_3), 125.93 (q, *J* = 4 Hz, trifluoromethylphenyl C-3, C-5), 128.54 (trifluoromethylphenyl C-2, C-6), 131.20 (d, *J* = 10 Hz, fluorophenyl C-2, C-6), 131.97 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 134.12 (fluorophenyl C-1), 138.12 (trifluoromethylphenyl C-1), 142.94 (propenone C-3), 165.81 (d, *J* = 254 Hz, fluorophenyl C-4), 188.31 (propenone C-1); MS (m/z): 294 ($M^{+\cdot}$, 83.7%), 115 (100%); Anal. Calcd for $C_{16}H_{10}F_4O$: C, 65.31; H, 3.43; Found: C, 65.53; H, 3.27.

*4.1.2.6. (E)-1-(3,4-Difluorophenyl)-3-(4-trifluoromethyl-phenyl)-propenone (**11f**):* 61% yield; white powder; mp 129-130 °C; IR (KBr disk) 3013 (C-H aromatic), 1665 (CO); ^{1}H NMR ($CDCl_3$) δ 7.26-7.37 (m, 1H, difluorophenyl H-5), 7.55 (d, *J* = 15.6 Hz, 1H, COC*H*=CH), 7.69 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.75 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.86 (d, *J* = 15.6 Hz, 1H, COCH=C*H*), 7.86-7.93 (m, 2H, difluorophenyl H-2, H-6); ^{13}C NMR ($CDCl_3$) δ 117.68 (d, *J* = 23 Hz, difluorophenyl C-5), 117.95 (d, *J* = 18 Hz, difluorophenyl C-2), 123.00 (propenone C-2), 123.76 (q, *J* = 270 Hz, *C*F_3), 125.44 (dd, *J* = 8, 3 Hz, difluorophenyl C-6), 126.00 (q, *J* = 4 Hz, trifluoromethylphenyl C-3, C-5), 128.63 (trifluoromethylphenyl C-2, C-6), 131.97 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 134.82 (d, *J* = 5 Hz, difluorophenyl C-1), 137.87 (trifluoromethylphenyl C-1), 143.67 (propenone C-3), 150.61 (dd, *J* = 250, 13 Hz, difluorophenyl C-3), 153.73 (dd, *J* = 256, 13 Hz, difluorophenyl C-4), 187.23 (propenone C-1); MS (m/z): 312 ($M^{+\cdot}$, 78.2%), 153 (100%); Anal. Calcd for $C_{16}H_9F_5O$: C, 61.55; H, 2.91; Found: C, 61.71; H, 2.87.

4.1.3. 1,5-Bis-(4-fluorophenyl)-3-(4-trifluoromethylphenyl)-pentane-1,5-dione (12). The title compound **12** was prepared, using a similar procedure that described for the preparation of **11a-d**, in 60% yield as a white powder; mp 138-139 °C; IR (KBr disk) 3039 (C-H aromatic), 2945 (C-H aliphatic), 1672 (CO); ^{1}H NMR ($CDCl_3$) δ 3.31 (dd, *J* = 16.8, 7.2 Hz, 2H, 2 C*H*H), 3.48 (dd, *J* = 16.8, 7.2 Hz, 2H, 2 CH*H*), 4.06-4.13 (m, 1H, C*H*), 7.08-7.12 (m, 4H, 2 fluorophenyl H-3, H-5), 7.39 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.52 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.93-7.97 (m, 4H, 2 fluorophenyl H-2, H-6); ^{13}C NMR ($CDCl_3$) δ

36.76 (C-3), 44.34 (2C, C-2, C-4), 115.82 (d, *J* = 21 Hz, 2 fluorophenyl C-3, C-5), 124.10 (q, *J* = 270 Hz, *C*F_3), 125.65 (q, *J* = 4 Hz, trifluoromethylphenyl C-3, C-5), 127.91 (trifluoromethylphenyl C-2, C-6), 129.05 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 131.76 (d, *J* = 10 Hz, 2 fluorophenyl C-2, C-6), 133.08 (2 fluorophenyl C-1), 147.77 (trifluoromethylphenyl C-1), 165.87 (d, *J* = 254 Hz, 2 fluorophenyl C-4), 196.34 (2*C*=O); ^{19}F NMR ($CDCl_3$) δ -62.46, -109.39; MS (m/z): 432 ($M^{+\cdot}$, 2.1%), 123 (100%); Anal. Calcd for $C_{24}H_{17}F_5O_2$: C, 66.67; H, 3.96; Found: C, 66.48; H, 3.87.

4.1.4. General method for preparation of 1-(4-amino(methane)sulfonylphenyl)-3-substituted-phenyl-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-pyrazoles (14a-l). A mixture of the appropriate chalcone (**11a-f**, 2.0 mmol) and the respective phenylhydrazine hydrochloride (**13a** or **13b**, 2.0 mmol) was heated under reflux in methanol (15 mL) for 24 h. After cooling, the formed solid was filtered off, dried and crystallized from methanol to give the respective dihydropyrazoles **14a-l**. Physical and spectral data are listed below.

*4.1.4.1. 1-(4-Methanesulfonylphenyl)-3-(4-hydroxyphenyl)-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-pyrazole (**14a**):* 75% yield; white powder; mp 295-296 °C; IR (KBr disk) 3407 (OH), 3056 (C-H aromatic), 2932 (C-H aliphatic), 1321, 1138 (SO_2); ^{1}H NMR (DMSO-d_6) δ 3.07 (s, 3H, SO_2CH_3), 3.20 (dd, *J* = 17.6, 4.8 Hz, 1H, pyrazole H-4), 3.97 (dd, *J* = 17.6, 12.0 Hz, 1H, pyrazole H'-4), 5.74 (dd, *J* = 12.0, 4.8 Hz, 1H, pyrazole H-5), 6.85 (d, *J* = 8.0 Hz, 2H, hydroxyphenyl H-3, H-5), 7.08 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6)), 7.48 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.65 (d, *J* = 8.4 Hz, 2H, hydroxyphenyl H-2, H-6), 7.66 (d, *J* = 8.0 Hz, 2H, methanesulphonylphenyl H-2, H-6), 7.74 (d, *J* = 8.0 Hz, 2H, methanesulphonylphenyl H-3, H-5), 9.96 (s, 1H, O*H*, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ 43.52 (pyrazole C-4), 44.63 (SO_2CH_3), 61.89 (pyrazole C-5), 112.25 (hydrxyphenyl C-3, C-5), 116.06 (methanesulphonylphenyl C-2, C-6), 122.82 (hydroxyphenyl C-1), 124.57 (q, *J* = 270 Hz, *C*F_3), 126.61 (d, *J* = 4 Hz, trifluoromethylphenyl C-3, C-5), 127.12 (methanesulphonylphenyl C-3, C-5), 128.57 (trifluoromethylphenyl C-2, C-6) , 128.75 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 129.16 (methanesulphonylphenyl C-4), 129.19 (hydroxyphenyl C-2, C-6), 146.73 (trifluoromethylphenyl C-1), 147.50 (methanesulphonylphenyl C-1), 151.38 (pyrazole C-3), 159.55 (hydroxyphenyl C-4); ^{19}F NMR (DMSO-d_6) δ -61.00; MS (m/z): 460 ($M^{+\cdot}$, 66.8%), 64 (100%); Anal. Calcd for $C_{23}H_{19}F_3N_2O_3S$: C, 59.99; H, 4.16; N, 6.08; Found: C, 59.71; H, 4.07; N, 6.18.

*4.1.4.2. 1-(4-Methanesulfonylphenyl)-3-(p-tolyl)-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-pyrazole (**14b**):* 87% yield; white crystals; mp 252-253 °C; IR (KBr disk) 3056 (C-H aromatic), 2932 (C-H aliphatic), 1325, 1132 (SO_2); ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 2.93 (s, 3H, SO_2CH_3), 3.14 (dd, *J* = 16.8, 5.6 Hz, 1H, pyrazole H-4), 3.93 (dd, *J* = 16.8, 12.0 Hz, 1H, pyrazole

H'-4), 5.48 (dd, *J* = 12.0, 5.6 Hz, 1H, pyrazole H-5), 7.02 (d, *J* = 7.6 Hz, 2H, methanesulphonylphenyl H-2, H-6), 7.16 (d, *J* = 7.2 Hz, 2H, tolyl H-3, H-5), 7.37 (d, *J* = 7.6 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.54-7.67 (m, 6H, tolyl H-2, H-6, trifluoromethylphenyl H-3, H-5, methanesulphonylphenyl H-3, H-5); ^{13}C NMR (DMSO-d_6) δ 21.47 (CH$_3$), 43.37 (pyrazole C-4), 44.60 (SO$_2C$H$_3$), 62.05 (pyrazole C-5), 112.51 (methanesulphonylphenyl C-2, C-6), 124.45 (q, *J* = 270 Hz, CF$_3$), 126.65 (d, *J* =4 Hz, trifluoromethylphenyl C-3, C-5), 126.76 (methanesulphonylphenyl C-3, C-5), 127.15 (trifluoromethylphenyl C-2, C-6), 129.12 (tolyl C-1), 129.17 (tolyl C-2, C-6), 129.65 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 129.81 (tolyl C-3, C-5), 133.19 (methanesulphonylphenyl C-4), 139.94 (tolyl C-4), , 146.62 (trifluoromethylphenyl C-1), 147.37 (methanesulphonylphenyl C-1), 151.20 (pyrazole C-3); ^{19}F NMR (DMSO-d_6) δ -61.47; MS (m/z): 458 (M$^{+\cdot}$, 100%); Anal. Calcd for $C_{24}H_{21}F_3N_2O_2S$: C, 62.87; H, 4.62; N, 6.11; Found: C, 62.90; H, 4.85; N, 5.93.

*4.1.4.3. 1-(4-Methanesulfonylphenyl)-3-(4-methoxyphenyl)-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-pyrazole (**14c**):* 81% yield; off-white powder; mp 262-263 °C; IR (KBr disk) 3057 (C-H aromatic), 2926 (C-H aliphatic), 1324, 1132 (SO$_2$); ^{1}H NMR (DMSO-d_6) δ 3.08 (s, 3H, SO$_2$CH_3), 3.23 (dd, *J* = 17.6, 4.8 Hz, 1H, pyrazole H-4), 3.81 (s, 3H, OCH_3), 4.00 (dd, *J* = 17.6, 12.0 Hz, 1H, pyrazole H'-4), 5.77 (dd, *J* = 12.0, 4.8 Hz, 1H, pyrazole H-5), 7.02 (d, *J* = 8.4 Hz, 2H, methoxyphenyl H-3, H-5), 7.09 (d, *J* = 8.4 Hz, 2H, methoxyphenyl H-2, H-6), 7.49 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.66 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.74-7.76 (m, 4H, methanesulphonylphenyl H-2, H-3, H-5, H-6); ^{13}C NMR (DMSO-d_6) δ 43.47 (pyrazole C-4), 44.61 (SO$_2C$H$_3$), 55.80 (OCH_3), 62.00 (pyrazole C-5), 112.35 (methoxyphenyl C-3, C-5), 114.69 (methanesulphonylphenyl C-2, C-6), 124.39 (methoxyphenyl C-1), 125.80 (q, *J* = 270 Hz, CF$_3$), 125.93 (trifluoromethylphenyl C-3, C-5), 126.66 (trifluoromethylphenyl C-2, C-6), 127.14 (methanesulphonylphenyl C-3, C-5), 128.70 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 128.87 (methanesulphonylphenyl C-4), 129.17 trifluoromethylphenyl C-1), 129.37 (methoxyphenyl C-2, C-6), 146.69 (trifluoromethylphenyl C-1), 147.43 (methanesulphonylphenyl C-1), 151.09 (pyrazole C-3), 160.69 (methoxyphenyl C-4); ^{19}F NMR (DMSO-d_6) δ -60.74; MS (m/z): 474 (M$^{+\cdot}$, 93.1), 107 (100%); Anal. Calcd for $C_{24}H_{21}F_3N_2O_3S$: C, 60.75; H, 4.46; N, 5.90; Found: C, 60.86; H, 4.72; N, 5.83.

*4.1.4.4. 3-(4-Ethoxyphenyl)-1-(4-methanesulfonylphenyl)-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-pyrazole (**14d**):* 83% yield; off-white crystals; mp 220-221 °C; IR (KBr disk) 3053 (C-H aromatic), 2926 (C-H aliphatic), 1326, 1134 (SO$_2$); ^{1}H NMR (CDCl$_3$) δ 1.45 (t, *J* = 6.8 Hz, 3H, CH$_2$CH_3), 3.01 (s, 3H, SO$_2$CH_3), 3.18 (dd, *J* = 17.2, 5.6 Hz, 1H, pyrazole H-4), 3.93 (dd, *J* = 17.2,

12.0 Hz, 1H, pyrazole H'-4), 4.09 (q, *J* = 6.8 Hz, 2H, C*H*$_2$CH$_3$), 5.41 (dd, *J* = 12.0, 5.6 Hz, 1H, pyrazole H-5), 6.94 (d, *J* = 8.4 Hz, 2H, ethoxyphenyl H-3, H-5), 7.06 (d, *J* = 8.4 Hz, 2H, ethoxyphenyl H-2, H-6), 7.40 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.62 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.68 (d, *J* = 7.2 Hz, 2H, methanesulphonylphenyl H-2, H-6), 7.70 (d, *J* = 7.2 Hz, 2H, methanesulphonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 14.75 (CH$_2$*C*H$_3$), 43.64 (pyrazole C-4), 44.95 (SO$_2$*C*H$_3$), 62.8 (*C*H$_2$CH$_3$), 63.70 (pyrazole C-5), 112.41 (ethoxyphenyl C-3, C-5), 114.70 (methanesulphonylphenyl C-2, C-6) , 123.90 (q, *J* = 270 Hz, *C*F$_3$), 123.95 (trifluoromethylphenyl C-3, C-5), 126.49 (ethoxyphenyl C-1), 126.52 (methanesulphonylphenyl C-3, C-5), 127.80 (trifluoromethylphenyl C-2, C-6) , 128.88 (methanesulphonylphenyl C-4), 128.99 (ethoxyphenyl C-2, C-6), 130.32 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 145.22 trifluoromethylphenyl C-1), 147.70 (methanesulphonylphenyl C-1), 149.83 (pyrazole C-3), 160.39 (ethoxyphenyl C-4); ^{19}F NMR ($CDCl_3$) δ -62.15; MS (m/z): 488 ($M^{+\cdot}$, 85.2%), 121 (100%); Anal. Calcd for $C_{25}H_{23}F_3N_2O_3S$: C, 61.47; H, 4.75; N, 5.73; Found: C, 61.71; H, 4.87; N, 5.83.

*4.1.4.5. 3-(4-Fluorophenyl)-1-(4-Methanesulfonylphenyl)-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-pyrazole (**14e**):* 85% yield; off-white crystals; mp 214-215 °C; IR (KBr disk) 3056 (C-H aromatic), 2932 (C-H aliphatic), 1325, 1137 (SO$_2$); ^{1}H NMR ($CDCl_3$) δ 3.01 (s, 3H, SO$_2$C*H*$_3$), 3.19 (dd, *J* = 17.2, 5.6 Hz, 1H, pyrazole H-4), 3.96 (dd, *J* = 17.2, 12.4 Hz, 1H, pyrazole H'-4), 5.46 (dd, *J* = 12.4, 5.6 Hz, 1H, pyrazole H-5), 7.09 (d, *J* = 8.8 Hz, 2H, methanesulphonylphenyl H-2, H-6), 7.14 (d, *J* = 8.4 Hz, 2H, fluorophenyl H-2, H-6), 7.41 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.64 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.71-7.77 (m, 4H, fluorophenyl H-3, H-5, methanesulphonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 43.56 (pyrazole C-4), 44.93 (SO$_2$*C*H$_3$), 63.00 (pyrazole C-5), 112.63 (methanesulphonylphenyl C-2, C-6), 114.70 (d, *J* = 22 Hz, fluorophenyl C-3, C-5), 123.82 (q, *J* = 270 Hz, *C*F$_3$), 126.08 (trifluoromethylphenyl C-3, C-5), 126.54 (trifluoromethylphenyl C-2, C-6), 127.81 (fluorophenyl, C-1), 128.12 (fluorophenyl C-2, C-6) , 129.04 (methanesulphonylphenyl C-3, C-5), 129.48 (methanesulphonylphenyl C-4), 130.40 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 144.91 trifluoromethylphenyl C-1), 147.51 (methanesulphonylphenyl C-1), 148.81 (pyrazole C-3), 163.63 (d, *J* = 249 Hz, fluorophenyl C-4); ^{19}F NMR (DMSO-d_6) δ -60.84, -110.11; MS (m/z): 462 ($M^{+\cdot}$, 92.7%), 64 (100%); Anal. Calcd for $C_{23}H_{18}F_4N_2O_2S$: C, 59.74; H, 3.92; N, 6.06; Found: C, 59.71; H, 3.87; N, 6.23.

*4.1.4.6. 3-(3,4-Difluoroluorophenyl)-1-(4-methanesulfonylphenyl)-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-pyrazole (**14f**):* 82% yield; off-white powder; mp 207-208 °C; IR (KBr disk) 3046 (C-

H aromatic), 2922 (C-H aliphatic), 1322, 1133 (SO_2); ^{1}H NMR (DMSO-d_6) δ 3.09 (s, 3H, SO_2CH_3), 3.27 (dd, *J* = 17.2, 5.6 Hz, 1H, pyrazole H-4), 4.01 (dd, *J* = 17.2, 12.4 Hz, 1H, pyrazole H'-4), 5.85 (dd, *J* = 12.4, 5.6 Hz, 1H, pyrazole H-5), 7.16 (d, *J* = 8.8 Hz, 2H, methanesulphonylphenyl H-2, H-6), 7.50 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.55-7.57 (m, 1H, difluorophenyl H-5), 7.64-7.66 (m, 1H, difluorophenyl H-2), 7.69 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.75 (d, *J* = 8.8 Hz, 2H, methanesulphonylphenyl H-3, H-5),7.84-7.89 (m, 1H, difluorophenyl H-6); ^{13}C NMR (DMSO-d_6) δ 43.18 (pyrazole C-4), 44.54 (SO_2CH_3), 62.51 (pyrazole C-5), 112.82 (methanesulphonylphenyl C-2, C-6), 115.63 (d, *J* = 19 Hz, difluorophenyl C-5), 118.49 (d, *J* = 17 Hz, difluorophenyl C-2), 123.94 (dd, *J* = 8, 3 Hz, difluorophenyl C-6), 124.55 (q, *J* = 270 Hz, CF_3), 126.67 (trifluoromethylphenyl C-3, C-5), 127.16 (trifluoromethylphenyl C-2, C-6), 127.70 (difluorophenyl, C-1), 128.85 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 129.15 (methanesulphonylphenyl C-3, C-5), 130.25 (methanesulphonylphenyl C-4), 146.34 trifluoromethylphenyl C-1), 147.16 (methanesulphonylphenyl C-1), 149.34 (pyrazole C-3), 150.04 (dd, *J* = 244, 13 Hz, difluorophenyl C-3), 150.64 (dd, *J* = 244, 13 Hz, difluorophenyl C-4); ^{19}F NMR (DMSO-d_6) δ -60.52, -136.37, -138.01; MS (m/z): 480 ($M^{+\cdot}$, 100%); Anal. Calcd for $C_{23}H_{17}F_5N_2O_2S$: C, 57.50; H, 3.57; N, 5.83; Found: C, 57.71; H, 3.87; N, 5.89.

*4.1.4.7. 1-(4-Aminosulfonylphenyl)-3-(4-hydroxyphenyl)-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-pyrazole (**14g**):* 76% yield; pale yellow powder; mp 197-198 °C; IR (KBr disk) 3427- 3374 (OH, NH_2), 3050 (C-H aromatic), 2932 (C-H aliphatic), 1325, 1137 (SO_2); ^{1}H NMR (DMSO-d_6) δ 3.18 (dd, *J* = 17.6, 4.8 Hz, 1H, pyrazole H-4), 3.95 (dd, *J* = 17.6, 12.0 Hz, 1H, pyrazole H'-4), 5.72 (dd, *J* = 12.0, 4.8 Hz, 1H, pyrazole H-5), 6.83 (d, *J* = 8.0 Hz, 2H, hydroxyphenyl H-3, H-5), 7.02-7.04 (m, 4H, trifluoromethylphenyl H-2, H-6, NH_2 (D_2O exchangeable)), 7.47 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.58 (d, *J* = 8.4 Hz, 2H, hydroxyphenyl H-2, H-6), 7.64 (d, *J* = 8.0 Hz, 2H, aminosulphonylphenyl H-2, H-6), 7.73 (d, *J* = 8.0 Hz, 2H, aminosulphonylphenyl H-3, H-5), 9.92 (s, 1H, O*H*, D_2O exchangeable) ; ^{13}C NMR (DMSO-d_6) δ 43.39 (pyrazole C-4), 61.94 (pyrazole C-5), 112.08 (hydrxyphenyl C-3, C-5), 116.02 (aminosulphonylphenyl C-2, C-6), 123.00 (hydroxyphenyl C-1), 124.59 (q, *J* = 270 Hz, CF_3), 126.54 (d, *J* = 4 Hz, trifluoromethylphenyl C-3, C-5), 127.18 (aminosulphonylphenyl C-3, C-5), 127.72 (trifluoromethylphenyl C-2, C-6) , 128.41 (hydroxyphenyl C-2, C-6), 128.75 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 133.15 (aminosulphonylphenyl C-4), 146.34 (trifluoromethylphenyl C-1), 146.88 (aminosulphonylphenyl C-1), 150.54 (pyrazole C-3), 159.35 (hydroxyphenyl C-4); ^{19}F NMR (DMSO-d_6) δ -60.71; MS

(m/z): 461 ($M^{+\cdot}$, 88.3%), 93 (100%); Anal. Calcd for $C_{22}H_{18}F_3N_3O_3S$: C, 57.26; H, 3.93; N, 9.11; Found: C, 57.51; H, 3.87; N, 9.01.

*4.1.4.8. 1-(4-Aminosulfonylphenyl)-3-(p-tolyl)-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-pyrazole (**14h**):* 90% yield; white crystals; mp 228-229 °C; IR (KBr disk) 3428 (NH_2), 3067 (C-H aromatic), 2933 (C-H aliphatic), 1327, 1134 (SO_2);^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H, CH_3), 3.20 (dd, *J* = 16.8, 4.8 Hz, 1H, pyrazole H-4), 3.95 (dd, *J* = 16.8, 12.0 Hz, 1H, pyrazole H'-4), 4.62 (s, 2H, NH_2, D_2O exchangeable), 5.44 (dd, *J* = 12.0, 4.8 Hz, 1H, pyrazole H-5), 7.06 (d, *J* = 8.8 Hz, 2H, aminosulphonylphenyl H-2, H-6), 7.24 (d, *J* = 7.6 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.41 (d, *J* = 7.6 Hz, 2H, tolyl H-3, H-5), 7.63 (d, *J* = 7.6 Hz, 2H, tolyl H-2, H-6), 7.65 (d, *J* = 7.6 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.73 (d, *J* = 8.8 Hz, 2H, aminosulphonylphenyl H-3, H-5); ^{13}C NMR (DMSO-d_6) δ 21.46 (*C*H_3), 43.23 (pyrazole C-4), 62.11 (pyrazole C-5), 112.34 (aminosulphonylphenyl C-2, C-6), 124.69 (q, *J* = 270 Hz, *C*F_3), 126.55 (trifluoromethylphenyl C-3, C-5), 126.62 (aminosulphonylphenyl C-3, C-5), 127.18 (trifluoromethylphenyl C-2, C-6), 127.73 (tolyl C-2, C-6), 128.65 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 129.28 (tolyl C-1), 129.78 (tolyl C-3, C-5), 133.60 (aminosulphonylphenyl C-4), 139.68 (tolyl C-4), , 146.17 (trifluoromethylphenyl C-1), 146.74 (aminosulphonylphenyl C-1), 150.32 (pyrazole C-3); ^{19}F NMR (DMSO-d_6) δ -60.73; MS (m/z): 459 ($M^{+\cdot}$, 73.5%), 64 (100%); Anal. Calcd for $C_{23}H_{20}F_3N_3O_2S$: C, 60.12; H, 4.39; N, 9.14; C, 60.31; H, 4.67; N, 9.11.

*4.1.4.9. 1-(4-Aminosulfonylphenyl)-3-(4-methoxyphenyl)-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-pyrazole (**14i**):* 87% yield; off-white powder; mp 246-247 °C; IR (KBr disk) 3422 (NH_2), 3057 (C-H aromatic), 2922 (C-H aliphatic), 1323, 1134 (SO_2);^{1}H NMR (DMSO-d_6) δ 3.22 (dd, *J* = 17.6, 4.8 Hz, 1H, pyrazole H-4), 3.80 (s, 3H, OCH_3), 3.98 (dd, *J* = 17.6, 12.0 Hz, 1H, pyrazole H'-4), 5.74 (dd, *J* = 12.0, 4.8 Hz, 1H, pyrazole H-5), 7.02 (d, *J* = 8.4 Hz, 2H, methoxyphenyl H-3, H-5), 7.05-7.07 (m, 4H, trifluoromethylphenyl H-2, H-6, NH_2 (D_2O exchangeable)), 7.48 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.61 (d, *J* = 8.4 Hz, 2H, methoxyphenyl H-2, H-6), 7.73-7.75 (m, 4H, aminosulphonylphenyl H-2, H-3, H-5, H-6); ^{13}C NMR (DMSO-d_6) δ 43.35 (pyrazole C-4), 55.76 (O*C*H_3), 62.09 (pyrazole C-5), 112.21 (methoxyphenyl C-3, C-5), 114.66 (aminosulphonylphenyl C-2, C-6), 124.58 (methoxyphenyl C-1), 124.59 (q, *J* = 270 Hz, *C*F_3), 126.53 (d, *J* = 3 Hz, trifluoromethylphenyl C-3, C-5), 127.18 (aminosulphonylphenyl C-3, C-5), 127.73 (trifluoromethylphenyl C-2, C-6) , 128.17 (methoxyphenyl C-2, C-6), 128.64 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 133.38 (aminosulphonylphenyl C-4), 146.29 (trifluoromethylphenyl C-1), 146.81 (aminosulphonylphenyl C-1), 150.21 (pyrazole C-3), 160.82 (methoxyphenyl C-4); ^{19}F

NMR (DMSO-d_6) δ -60.74; MS (m/z): 475 ($M^{+\cdot}$, 55.0%), 64 (100%); Anal. Calcd for $C_{23}H_{20}F_3N_3O_3S$: C, 58.10; H, 4.24; N, 8.84; Found: C, 57.81; H, 4.37; N, 8.89.

*4.1.4.10. 1-(4-Aminosulfonylphenyl)-3-(4-ethoxyphenyl)-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-pyrazole (**14j**):* 89% yield; white crystals; mp 22-223 °C; IR (KBr disk) 3427 (NH_2), 3066 (C-H aromatic), 2926 (C-H aliphatic), 1325, 1132 (SO_2); ^{1}H NMR (DMSO-d_6) δ 1.45 (t, *J* = 6.8 Hz, 3H, CH_2CH_3), 3.18 (dd, *J* = 17.6, 4.8 Hz, 1H, pyrazole H-4), 3.96 (dd, *J* = 17.6, 12.0 Hz, 1H, pyrazole H'-4), 4.07 (q, *J* = 6.8 Hz, 2H, CH_2CH_3), 5.74 (dd, *J* = 12.0, 4.8 Hz, 1H, pyrazole H-5), 6.99 (d, *J* = 8.4 Hz, 2H, ethoxyphenyl H-3, H-5), 7.05 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.47 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.60 (d, *J* = 8.4 Hz, 2H, ethoxyphenyl H-2, H-6), 7.71-7.74 (m, 4H, aminosulphonylphenyl H-2, H-3, H-5, H-6); ^{13}C NMR (DMSO-d_6) δ 15.01 (CH_2CH_3), 43.33 (pyrazole C-4), 62.07 (CH_2CH_3), 63.70 (pyrazole C-5), 112.19 (ethoxyphenyl C-3, C-5), 115.06 (aminosulphonylphenyl C-2, C-6), 124.42 (trifluoromethylphenyl C-3, C-5), 124.58 (q, *J* = 270 Hz, CF_3), 127.18 (ethoxyphenyl C-1), 127.73 (aminosulphonylphenyl C-3, C-5), 128.48 (trifluoromethylphenyl C-2, C-6) , 128.64 (ethoxyphenyl C-2, C-6), 128.95 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 133.34 (aminosulphonylphenyl C-4), 146.29 (trifluoromethylphenyl C-1), 146.81 (aminosulphonylphenyl C-1), 150.22 (pyrazole C-3), 160.10 (ethoxyphenyl C-4); ^{19}F NMR (DMSO-d_6) δ -60.74; MS (m/z): 489 ($M^{+\cdot}$, 100%); Anal. Calcd for $C_{24}H_{22}F_3N_3O_3S$: C, 58.89; H, 4.53; N, 8.58; Found: C, 58.81; H, 4.87; N, 8.80.

*4.1.4.11. 1-(4-Aminosulfonylphenyl)-3-(4-fluorophenyl)-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-pyrazole (**14k**):* 78% yield; off-white crystals; mp 209-210 °C; IR (KBr disk) 3430 (NH_2), 3062 (C-H aromatic), 2932 (C-H aliphatic), 1327, 1137 (SO_2); ^{1}H NMR (DMSO-d_6) δ 3.26 (dd, *J* = 17.6, 4.8 Hz, 1H, pyrazole H-4), 4.01 (dd, *J* = 17.6, 12.0 Hz, 1H, pyrazole H'-4), 5.80 (dd, *J* = 12.0, 4.8 Hz, 1H, pyrazole H-5), 7.08 (d, *J* = 8.4 Hz, 2H, aminosulphonylphenyl H-2, H-6), 7.28-7.32 (m, 2H, fluorophenyl H-3, H-5), 7.48 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.51 (s, 2H, NH_2, D_2O exchangeable), 7.61 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.74 (d, *J* = 8.4 Hz, 2H, aminosulphonylphenyl H-3, H-5), 7.83-7.86 (m, 2H, fluorophenyl H-2, H-6); ^{13}C NMR (DMSO-d_6) δ ^{13}C NMR δ 43.22 (pyrazole C-4), 62.33 (pyrazole C-5), 112.44 (aminosulphonylphenyl C-2, C-6), 116.23 (d, *J* = 21 Hz, fluorophenyl C-3, C-5) , 124.58 (q, *J* = 270 Hz, CF_3), 126.58 (d, *J* = 3 Hz, trifluoromethylphenyl C-3, C-5), 127.21 (trifluoromethylphenyl C-2, C-6), 127.73 (aminosulphonylphenyl C-3, C-5), 128.62 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 128.70 (fluorophenyl, C-1), 128.87 (d, *J* = 8 Hz, fluorophenyl C-2, C-6) , 133.81 (aminosulphonylphenyl C-4), 146.10 trifluoromethylphenyl C-1), 146.63 (aminosulphonylphenyl C-1), 149.42 (pyrazole C-3), 163.21 (d, *J* = 246 Hz, fluorophenyl C-4); ^{19}F NMR (DMSO-d_6) δ -

60.20, -110.06; MS (m/z): 463 ($M^{+\cdot}$, 67.8%), 115 (100%); Anal. Calcd for $C_{22}H_{17}F_4N_3O_2S$: C, 57.02; H, 3.70; N, 9.07; Found: C, 57.11; H, 3.87; N, 9.20.

*4.1.4.12. 1-(4-Aminosulfonylphenyl)-3-(3,4-difluorophenyl)-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-pyrazole (**14l**):* 82% yield; pale yellow powder; mp 235-236 °C; IR (KBr disk) 3432 (NH_2), 3067 (C-H aromatic), 2930 (C-H aliphatic), 1327, 1135 (SO_2); ^{1}H NMR ($CDCl_3$) δ 3.17 (dd, *J* = 17.2, 5.6 Hz, 1H, pyrazole H-4), 3.95 (dd, *J* = 17.2, 12.4 Hz, 1H, pyrazole H'-4), 5.49 (dd, *J* = 12.4, 5.6 Hz, 1H, pyrazole H-5), 7.09 (d, *J* = 9.2 Hz, 2H, aminosulphonylphenyl H-2, H-6), 7.19-7.26 (m, 1H, difluorophenyl H-5), 7.40 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.35-7.47 (m, 1H, difluorophenyl H-2), 7.65 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.65-7.68 (m, 1H, difluorophenyl H-6), 7.73 (d, *J* = 9.2 Hz, 2H, aminosulphonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 43.35 (pyrazole C-4), 63.25 (pyrazole C-5), 112.81 (aminosulphonylphenyl C-2, C-6), 115.03 (d, *J* = 19 Hz, difluorophenyl C-5), 117.71 (d, *J* = 18 Hz, difluorophenyl C-2), 122.52 (dd, *J* = 7, 4 Hz, difluorophenyl C-6), 123.78 (q, *J* = 270 Hz, CF_3), 126.04 (trifluoromethylphenyl C-3, C-5), 126.58 (trifluoromethylphenyl C-2, C-6), 128.74 (difluorophenyl, C-1), 129.04 (aminosulphonylphenyl C-3, C-5), 130.05 (aminosulphonylphenyl C-4), 130.64 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 144.67 trifluoromethylphenyl C-1), 147.32 (aminosulphonylphenyl C-1), 147.71 (pyrazole C-3), 150.51 (dd, *J* = 247, 13 Hz, difluorophenyl C-3), 151.16 (dd, *J* = 247, 13 Hz, difluorophenyl C-4); ^{19}F NMR (DMSO-d_6) δ -61.10, -136.37, -138.80; MS (m/z): 481 ($M^{+\cdot}$, 100%); Anal. Calcd for $C_{22}H_{16}F_5N_3O_2S$: C, 54.89; H, 3.35; N, 8.73; Found: C, 54.82; H, 3.49; N, 9.07.

4.1.5. General method for preparation of 1-(4-amino(methane)sulfonylphenyl)-3-substituted-phenyl-5-(4-trifluoromethyl-phenyl)-1*H*-pyrazoles (15a-l). Method 1: a solution of the appropriate dihydrropyrazole (**14a-l**, 2.0 mmol) in glacial acetic acid (10 mL) was heated under reflux for 24 h. After cooling, the reaction mixture was poured onto ice-water (20 mL) and the formed solid was filtered off, dried and crystallized from ethanol to yield the respective pyrazoles **15a–l**.

Method 2 (for **15b**, **15d**, **15h** and **15j**): To a solution of the appropriate chalcone (**11b** or **11d**, 2.0 mmol) in acetic acid 96% (10 mL), the respective phenylhydrazine hydrochloride (**13a** or **13b**, 2.0 mmol) was added. The reaction mixture was heated under reflux for 36 h. After cooling, the reaction mixture was poured onto ice-water (20 mL); the formed solid was filtered, dried and crystallized from aqueous ethanol to yield the corresponding pyrazoles **15b**, **15d**, **15h** and **15j**. Physical and spectral data for **15a–l** are listed below.

*4.1.5.1. 1-(4-Methanesulfonylphenyl)-3-(4-hydroxyphenyl)-5-(4-trifluoromethylphenyl)-1H-pyrazole (**15a**):* 69% yield; yellow powder; mp 187-188 °C; IR (KBr disk) 3407 (OH), 3073 (C-H aromatic), 2926 (C-H aliphatic), 1321, 1147 (SO_2); ^{1}H NMR (DMSO-d_6) δ 3.28 (s, 3H, SO_2CH_3), 6.87 (d, *J* = 8.8 Hz, 2H, hydroxyphenyl H-3, H-5), 7.23 (s,1H, pyrazole H-4), 7.57 (d, *J* = 8.8 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.59 (d, *J* = 8.8 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.77 (d, *J* = 8.8 Hz, 2H, hydrxyphenyl H-2, H-6), 7.82 (d, *J* = 8.4 Hz, 2H, methanesulphonylphenyl H-2, H-6), 7.99 (d, *J* = 8.4 Hz, 2H, methanesulphonylphenyl H-3, H-5), 9.71 (s, 1H, O*H*, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ 43.87 (SO_2CH_3), 107.53 (pyrazole C-4) , 115.81 (hydroxyphenyl C-3, C-5), 123.40 (hydroxyphenyl C-1), 124.48 (q, *J* = 270 Hz, CF_3), 125.61 (methanesulphonylphenyl C-2, C-6), 126.24 (d, *J* = 4 Hz, trifluoromethylphenyl C-3, C-5), 127.48 (trifluoromethylphenyl C-2, C-6), 128.74 (methanesulphonylphenyl C-3, C-5), 129.34 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 129.81 (hydroxyphenyl C-2, C-6), 134.22 (methanesulphonylphenyl C-4), , 139.66 (trifluoromethylphenyl C-1), 143.23 (methanesulphonylphenyl C-1), 143.65 (pyrazole C-5), 152.92 (pyrazole C-3), 158.38 (hydroxyphenyl C-4); ^{19}F NMR (DMSO-d_6) δ -61.00; MS (m/z): 458 ($M^{+\cdot}$, 67.2%), 93 (100%); Anal. Calcd for $C_{23}H_{17}F_3N_2O_3S$: C, 60.26; H, 3.74; N, 6.11; Found: C, 60.41; H, 3.87; N, 6.08.

*4.1.5.2. 1-(4-Methanesulfonylphenyl)-3-(p-tolyl)-5-(4-trifluoromethylphenyl)-1H-pyrazole (**15b**):* 79% yield; off-white crystals; mp 218-219 °C; IR (KBr disk) 3069 (C-H aromatic), 2924 (C-H aliphatic), 1320, 1152 (SO_2); ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H, CH_3), 3.05 (s, 3H, SO_2CH_3), 6.90 (s,1H, pyrazole H-4),7.29 (d, *J* = 8.0 Hz, 2H, tolyl H-3, H-5), 7.43 (d, *J* = 7.6 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.57 (d, *J* = 8.4 Hz, 2H, methanesulphonylphenyl H-2, H-6), 7.66 (d, *J* = 8.0 Hz, 2H, tolyl H-2, H-6), 7.82 (d, *J* = 7.6 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.95 (d, *J* = 8.4 Hz, 2H, methanesulphonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 21.38 (CH_3), 44.50 (SO_2CH_3), 107.39 (pyrazole C-4) , 123.79 (q, *J* = 270 Hz, CF_3), 125.16 (methanesulphonylphenyl C-2, C-6), 125.91 (methanesulphonylphenyl C-3, C-5), 125.98 (trifluoromethylphenyl C-3, C-5), 128.56 (trifluoromethylphenyl C-2, C-6), 129.05 (tolyl C-2, C-6), 129.47 (tolyl C-1), 129.56 (tolyl C-3, C-5), 130.85 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 133.59 (methanesulphonylphenyl C-4), 138.70 (tolyl C-4), , 138.85 trifluoromethylphenyl C-1), 143.13 (methanesulphonylphenyl C-1), 143.91 (pyrazole C-5), 153.39 (pyrazole C-3); ^{19}F NMR (DMSO-d_6) δ -60.89; MS (m/z): 456 ($M^{+\cdot}$, 100%); Anal. Calcd for $C_{24}H_{19}F_3N_2O_2S$: C, 63.15; H, 4.20; N, 6.14; Found: C, 63.36; H, 4.37; N, 6.10.

*4.1.5.3. 1-(4-Methanesulfonylphenyl)-3-(4-methoxy)-5-(4-trifluoromethylphenyl)-1H-pyrazole (**15c**):* 90% yield; yellow powder; mp 192-193 °C; IR (KBr disk) 3066 (C-H aromatic), 2927 (C-H

aliphatic), 1322, 1150 (SO_2); ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 1H, SO_2CH_3), 3.89 (s, 1H, OCH_3), 6.87 (s, 1H, pyrazole H-4), 7.01 (d, *J* = 8.0 Hz, 2H, methoxyphenyl H-3, H-5), 7.45 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.58 (d, *J* = 8.0 Hz, 2H, methanesulphonylphenyl H-2, H-6), 7.68 (d, *J* = 8.0 Hz, 2H, methoxyphenyl H-2, H-6), 7.87 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.96 (d, *J* = 8.0 Hz, 2H, methanesulphonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 44.55 (SO_2CH_3), 55.37 (OCH_3), 107.18 (pyrazole C-4) , 114.23 (methoxyphenyl C-3, C-5), 123.75 (q, *J* = 270 Hz, CF_3), 124.71 (methoxyphenyl C-1), 125.01 (methanesulphonylphenyl C-2, C-6), 125.94 (trifluoromethylphenyl C-3, C-5), 127.21 (trifluoromethylphenyl C-2, C-6), 128.57 (methanesulphonylphenyl C-3, C-5), 129.04 (methoxyphenyl C-2, C-6), 130.94 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 133.63 (methanesulphonylphenyl C-4), , 138.76 trifluoromethylphenyl C-1), 143.14 (methanesulphonylphenyl C-1), 143.96 (pyrazole C-5), 153.21 (pyrazole C-3), 160.12 (methoxyphenyl C-4); ^{19}F NMR ($CDCl_3$) δ -62.49; MS (m/z): 472 ($M^{+\cdot}$, 54.7%), 107 (100%); Anal. Calcd for $C_{24}H_{19}F_3N_2O_3S$: C, 61.01; H, 4.05; N, 5.93; Found: C, 61.13; H, 4.17; N, 6.01.

*4.1.5.4. 3-(4-Ethoxy)1-(4-methanesulfonylphenyl)-5-(4-trifluoromethylphenyl)-1H-pyrazole (**15d**):* 88% yield; orange powder; mp 150-151 °C; IR (KBr disk) 3069 (C-H aromatic), 2930 (C-H aliphatic), 1321, 1155 (SO_2); ^{1}H NMR ($CDCl_3$) δ 1.47 (t, *J* = 6.8 Hz, 3H, CH_2CH_3), 3.10 (s, 1H, SO_2CH_3), 4.11 (q, *J* = 6.8 Hz, 2H, CH_2CH_3), 6.86 (s, 1H, pyrazole H-4), 7.00 (d, *J* = 8.0 Hz, 2H, ethoxyphenyl H-3, H-5), 7.45 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.58 (d, *J* = 8.0 Hz, 2H, methanesulphonylphenyl H-2, H-6), 7.68 (d, *J* = 8.0 Hz, 2H, ethoxyphenyl H-2, H-6), 7.85 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.96 (d, *J* = 8.0 Hz, 2H, methanesulphonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 14.85 (CH_2CH_3), 44.55 (SO_2CH_3), 63.54 (CH_2CH_3) 107.17 (pyrazole C-4) , 114.74 (ethoxyphenyl C-3, C-5), 123.79 (q, *J* = 270 Hz, CF_3), 124.53 (ethoxyphenyl C-1), 124.99 (methanesulphonylphenyl C-2, C-6), 125.94 (trifluoromethylphenyl C-3, C-5), 127.19 (trifluoromethylphenyl C-2, C-6), 128.57 (methanesulphonylphenyl C-3, C-5), 129.03 (ethoxyphenyl C-2, C-6), 130.74 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 133.64 (methanesulphonylphenyl C-4), , 138.73 trifluoromethylphenyl C-1), 143.12 (methanesulphonylphenyl C-1), 143.97 (pyrazole C-5), 153.26 (pyrazole C-3), 159.52 (ethoxyphenyl C-4); ^{19}F NMR ($CDCl_3$) δ -62.33; MS (m/z): 486 ($M^{+\cdot}$, 47.9%), 121 (100%); Anal. Calcd for $C_{25}H_{21}F_3N_2O_3S$: C, 61.72; H, 4.35; N, 5.76; Found: C, 61.83; H, 4.57; N, 5.88.

*4.1.5.5. 3-(4-Fluoro)-1-(4-methanesulfonylphenyl)-5-(4-trifluoromethylphenyl)-1H-pyrazole (**15e**):* 81% yield; pale yellow powder; mp 218-219 °C; IR (KBr disk) 3067 (C-H aromatic), 2924 (C-H aliphatic), 1325, 1150 (SO_2); ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 3H, SO_2CH_3), 6.89 (s,1H, pyrazole H-4), 7.15-7.19 (m, 2H, fluorophenyl H-3, H-5), 7.45 (d, *J* = 7.6 Hz, 2H, trifluoromethylphenyl H-2, H-

6), 7.58 (d, *J* = 7.6 Hz, 2H, methanesulphonylphenyl H-2, H-6), 7.69 (d, *J* = 7.6 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.89-7.93 (m, 2H, fluorophenyl H-2, H-6), 7.97 (d, *J* = 7.6 Hz, 2H, methanesulphonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 44.53 (SO_2CH_3), 107.27 (pyrazole C-4) , 115.84 (d, *J* = 22 Hz, fluorophenyl C-3, C-5), 123.79 (q, *J* = 270 Hz, CF_3), 125.09 (methanesulphonylphenyl C-2, C-6), 125.98 (trifluoromethylphenyl C-3, C-5), 127.66 (d, *J* = 8 Hz, fluorophenyl C-2, C-6), 128.27 (fluorophenyl C-1), 128.62 (trifluoromethylphenyl C-2, C-6), 129.05 (methanesulphonylphenyl C-3, C-5), 130.85 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 133.42 (methanesulphonylphenyl C-4), , 139.07 (trifluoromethylphenyl C-1), 143.37 (methanesulphonylphenyl C-1), 143.82 (pyrazole C-5), 152.48 (pyrazole C-3), 163.14 (d, *J* = 247 Hz, fluorophenyl C-4); ^{19}F NMR ($CDCl_3$) δ -61.99, 112.79; MS (m/z): 460 ($M^{+\cdot}$, 20.8%), 123 (100%); Anal. Calcd for $C_{23}H_{16}F_4N_2O_2S$: C, 60.00; H, 3.50; N, 6.08; Found: C, 60.11; H, 3.87; N, 6.15.

*4.1.5.6. 3-(3,4-Difluoro)-1-(4-methanesulfonylphenyl)-5-(4-trifluoromethylphenyl)-1H-pyrazole (**15f**):* 73% yield; pale yellow powder; mp 203-204 °C; IR (KBr disk) 3066 (C-H aromatic), 2925 (C-H aliphatic), 1324, 1157 (SO_2); ^{1}H NMR (DMSO-d_6) δ 3.28 (s, 3H, SO_2CH_3), 7.45 (s,1H, pyrazole H-4), 7.53-7.61 (m, 1H, difluorophenyl H-5), 7.58 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.64 (d, *J* = 8.0 Hz, 2H, methanesulphonylphenyl H-2, H-6), 7.79-7.81 (m, 1H, difluorophenyl H-2), 7.83 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.95-7.99 (m, 1H, difluorophenyl H-6), 8.01 (d, *J* = 8.0 Hz, 2H, methanesulphonylphenyl H-3, H-5); ^{13}C NMR (DMSO-d_6) δ 43.85 (SO_2CH_3), 108.23 (pyrazole C-4), 114.98 (d, *J* = 19 Hz, difluorophenyl C-5), 118.63 (d, *J* = 17 Hz, difluorophenyl C-2), 122.90 (dd, *J* = 7, 4 Hz, difluorophenyl C-6), 124.44 (q, *J* = 270 Hz, CF_3), 125.97 (methanesulphonylphenyl C-2, C-6), 126.30 (d, *J* = 4 Hz, trifluoromethylphenyl C-3, C-5), 128.80 (trifluoromethylphenyl C-2, C-6), 129.55 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 129.87 (methanesulphonylphenyl C-3, C-5), 130.15 (difluorophenyl, C-1), 133.82 (methanesulphonylphenyl C-4), 140.22 (trifluoromethylphenyl C-1), 143.36 (methanesulphonylphenyl C-1), 143.77 (pyrazole C-5), 149.64 (dd, *J* = 247, 13 Hz, difluorophenyl C-3), 149.91 (dd, *J* = 247, 13 Hz, difluorophenyl C-4), 150.74 (pyrazole C-3); ^{19}F NMR (DMSO-d_6) δ -61.10, -137.46, 138.80; MS (m/z): 478 ($M^{+\cdot}$, 100%); Anal. Calcd for $C_{23}H_{15}F_5N_2O_2S$: C, 57.74; H, 3.16; N, 5.86; Found: C, 57.71; H, 3.28; N, 6.00.

*4.1.5.7. 1-(4-Aminosulfonylphenyl)-3-(4-hydroxyphenyl)-5-(4-trifluoromethylphenyl)-1H-pyrazole (**15g**):* 65% yield; pale yellow powder; mp 229-230 °C; IR (KBr disk) 3391, 3250 (NH_2), 3075 (C-H aromatic), 1325, 1159 (SO_2); ^{1}H NMR (DMSO-d_6) δ 6.86 (d, *J* = 8.4 Hz, 2H, hydroxyphenyl H-3, H-5), 7.21 (s,1H, pyrazole H-4), 7.48 (s, 2H, NH_2, D_2O exchangeable), 7.53 (d, *J* = 8.4 Hz, 2H,

trifluoromethylphenyl H-2, H-6), 7.56 (d, *J* = 8.4 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.76 (d, *J* = 8.8 Hz, 2H, aminosulphonylphenyl H-2, H-6), 7.81 (d, *J* = 8.4 Hz, 2H, hydrxyphenyl H-2, H-6), 7.86 (d, *J* = 8.8 Hz, 2H, aminosulphonylphenyl H-3, H-5), 9.69 (s, 1H, O*H*, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ 107.16 (pyrazole C-4) , 116.03 (hydroxyphenyl C-3, C-5), 123.51 (hydroxyphenyl C-1), 124.48 (q, *J* = 270 Hz, *C*F_3), 125.52 (aminosulphonylphenyl C-2, C-6), 126.21 (trifluoromethylphenyl C-3, C-5), 127.27 (trifluoromethylphenyl C-2, C-6), 127.43 (aminosulphonylphenyl C-3, C-5), 129.34 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 129.79 (hydroxyphenyl C-2, C-6), 134.34 (aminosulphonylphenyl C-4), , 139.66 (trifluoromethylphenyl C-1), 142.24 (aminosulphonylphenyl C-1), 143.12 (pyrazole C-5), 152.67 (pyrazole C-3), 158.30 (hydroxyphenyl C-4); ^{19}F NMR (DMSO-d_6) δ -61.10; MS (m/z): 459 ($M^{+\cdot}$, 33.4%), 93 (100%); Anal. Calcd for $C_{22}H_{16}F_3N_3O_3S$: C, 57.51; H, 3.51; N, 9.15; Found: C, 57.79; H, 3.63; N, 9.08.

*4.1.5.8. 1-(4-Aminosulfonylphenyl)-3-(p-tolyl)-5-(4-trifluoromethylphenyl)-1H-pyrazole (**15h**):* 74% yield; off-white crystals; mp 194-195 °C; IR (KBr disk) 3355, 3260 (NH_2), 3085 (C-H aromatic), 2930 (C-H aliphatic), 1322, 1164 (SO_2); ^1H NMR (DMSO-d_6) δ 2.51 (s, 3H, C*H*$_3$), 7.28 (s, 1H, pyrazole H-4), 7.29 (d, *J* = 8.0 Hz, 2H, tolyl H-3, H-5), 7.51 (s, 2H, NH_2, D_2O exchangeable), 7.55 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.57 (d, *J* = 8.0 Hz, 2H, aminosulphonylphenyl H-2, H-6), 7.81 (d, *J* = 8.0 Hz, 2H, tolyl H-2, H-6), 7.85 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.89 (d, *J* = 8.0 Hz, 2H, aminosulphonylphenyl H-3, H-5); ^{13}C NMR (DMSO-d_6) δ 21.31 (*C*H_3), 107.59 (pyrazole C-4), 124.48 (q, *J* = 270 Hz, *C*F_3), 125.64 (methanesulphonylphenyl C-2, C-6), 125.92 (methanesulphonylphenyl C-3, C-5), 126.20 (trifluoromethylphenyl C-3, C-5), 127.29 (trifluoromethylphenyl C-2, C-6), 129.03 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 129.27 (tolyl C-1), 129.83 (tolyl C-2, C-6), 129.89 (tolyl C-3, C-5), 134.22 (methanesulphonylphenyl C-4), 138.34 (tolyl C-4), , 142.18 trifluoromethylphenyl C-1), 143.29 (methanesulphonylphenyl C-1), 143.39 (pyrazole C-5), 152.44 (pyrazole C-3); ^{19}F NMR (DMSO-d_6) δ -60.74; MS (m/z): 457 ($M^{+\cdot}$, 100%); Anal. Calcd for $C_{23}H_{18}F_3N_3O_2S$: C, 60.39; H, 3.97; N, 9.19; Found: C, 60.67; H, 3.84; N, 9.08.

*4.1.5.9. 1-(4-Aminosulfonylphenyl)-3-(4-methoxy)-5-(4-trifluoromethylphenyl)-1H-pyrazole (**15i**):* 83% yield; orange powder; mp 163-164 °C; IR (KBr disk) 3358, 3262 (NH_2), 3061 (C-H aromatic), 2924 (C-H aliphatic), 1325, 1158 (SO_2); ^1H NMR (DMSO-d_6) δ 3.82 (s, 1H, OC*H*$_3$), 7.05 (d, *J* = 8.8 Hz, 2H, methoxyphenyl H-3, H-5), 7.28 (s, 1H, pyrazole H-4), 7.48 (s, 2H, NH_2, D_2O exchangeable), 7.54 (d, *J* = 8.8 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.56 (d, *J* = 8.8 Hz, 2H, aminosulphonylphenyl H-2, H-6), 7.83 (d, *J* = 8.8 Hz, 2H, methoxyphenyl H-2, H-6), 7.87 (d, *J* = 8.8 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.89 (d, *J* = 8.8 Hz, 2H, aminosulphonylphenyl H-3,

H-5); ^{13}C NMR (DMSO-d_6) δ 55.66 (O*C*H$_3$), 107.32 (pyrazole C-4) , 114.73 (methoxyphenyl C-3, C-5), 123.75 (q, *J* = 270 Hz, *C*F$_3$), 125.12 (methoxyphenyl C-1), 125.60 (aminosulphonylphenyl C-2, C-6), 126.17 (trifluoromethylphenyl C-3, C-5), 127.28 (trifluoromethylphenyl C-2, C-6), 127.39 (aminosulphonylphenyl C-3, C-5), 129.82 (methoxyphenyl C-2, C-6), 130.94 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 134.29 (aminosulphonylphenyl C-4), 142.23 (trifluoromethylphenyl C-1), 143.28 (aminosulphonylphenyl C-1), 143.32 (pyrazole C-5), 152.33 (pyrazole C-3), 160.01 (methoxyphenyl C-4); ^{19}F NMR (DMSO-d_6) δ -60.89; MS (m/z): 473 ($M^{+\cdot}$, 53.2%), 107 (100%); Anal. Calcd for $C_{23}H_{18}F_3N_3O_3S$: C, 58.35; H, 3.83; N, 8.87; Found: C, 58.41; H, 3.87; N, 8.64.

*4.1.5.10. 1-(4-Aminosulfonylphenyl)-3-(4-ethoxy)-5-(4-trifluoromethylphenyl)-1H-pyrazole (**15j**):* 86% yield; off-white powder; mp 178-179 °C; IR (KBr disk) 3353, 3258 (NH_2), 3071 (C-H aromatic), 2934 (C-H aliphatic), 1325, 1169 (SO_2); ^{1}H NMR (DMSO-d_6) δ 1.37 (t, *J* = 6.8 Hz, 3H, CH$_2$C*H*$_3$), 4.02 (q, *J* = 6.8 Hz, 2H, C*H*$_2$CH$_3$), 6.82 (d, *J* = 8.0 Hz, 2H, ethoxyphenyl H-3, H-5), 6.89 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.06 (s, 1H, pyrazole H-4), 7.38 (s, 2H, NH_2, D_2O exchangeable), 7.45 (d, *J* = 8.0 Hz, 2H, aminosulphonylphenyl H-2, H-6), 7.57 (d, *J* = 8.0 Hz, 2H, ethoxyphenyl H-2, H-6), 7.75 (d, *J* = 8.0 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.87 (d, *J* = 8.0 Hz, 2H, aminosulphonylphenyl H-3, H-5); ^{13}C NMR (DMSO-d_6)δ 14.83 (CH$_2$*C*H$_3$), 63.44 (*C*H$_2$CH$_3$) 106.62 (pyrazole C-4) , 114.66 (ethoxyphenyl C-3, C-5), 123.75 (q, *J* = 270 Hz, *C*F$_3$), 124.67 (methanesulphonylphenyl C-2, C-6), 124.78 (ethoxyphenyl C-1), 125.71 (trifluoromethylphenyl C-3, C-5), 125.74 (trifluoromethylphenyl C-2, C-6), 127.09 (methanesulphonylphenyl C-3, C-5), 129.15 (ethoxyphenyl C-2, C-6), 130.71 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 133.86 (methanesulphonylphenyl C-4), , 138.73 trifluoromethylphenyl C-1), 142.14 (methanesulphonylphenyl C-1), 142.89 (pyrazole C-5), 152.52 (pyrazole C-3), 159.25 (ethoxyphenyl C-4); ^{19}F NMR (DMSO-d_6) δ -60.71; MS (m/z): 487 ($M^{+\cdot}$, 28.7%), 121 (100%); Anal. Calcd for $C_{24}H_{20}F_3N_3O_3S$: C, 59.13; H, 4.14; N, 8.62; Found: C, 59.31; H, 4.27; N, 8.53.

*4.1.5.11. 1-(4-Aminosulfonylphenyl)-3-(4-fluoro)-5-(4-trifluoromethylphenyl)-1H-pyrazole (**15k**):* 73% yield; yellow powder; mp 233-234 °C; IR (KBr disk) 3391, 3262 (NH_2), 3066 (C-H aromatic), 1325, 1160 (SO_2); ^{1}H NMR (DMSO-d_6) δ 7.31-7.36 (m, 2H, fluorophenyl H-3, H-5), 7.33 (s,1H, pyrazole H-4), 7.49 (s, 2H, NH_2, D_2O exchangeable), 7.53-7.62 (m, 4H, aminosulphonylphenyl H-2, H-6 , trifluoromethylphenyl H-2, H-6), 7.82 (d, *J* = 7.6 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.88 (d, *J* = 7.6 Hz, 2H, aminosulphonylphenyl H-3, H-5), 7.97-8.03 (m, 2H, fluorophenyl H-2, H-6); ^{13}C NMR (DMSO-d_6) δ 107.67 (pyrazole C-4) , 116.28 (d, *J* = 21 Hz, fluorophenyl C-3, C-5), 123.79 (q, *J* = 270 Hz, *C*F$_3$), 125.74 (aminosulphonylphenyl C-2, C-6), 126.22 (d, *J* = 4 Hz, trifluoromethylphenyl C-3, C-5), 127.31 (trifluoromethylphenyl C-2, C-6), 128.07 (d, *J* = 8 Hz,

fluorophenyl C-2, C-6), 129.13 (fluorophenyl C-1), 129.40 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 129.86 (aminosulphonylphenyl C-3, C-5), 134.10 (aminosulphonylphenyl C-4), 139.07 (trifluoromethylphenyl C-1), 142.07 (aminosulphonylphenyl C-1), 143.50 (pyrazole C-5), 151.50 (pyrazole C-3), 162.73 (d, *J* = 243 Hz, fluorophenyl C-4) ; ^{19}F NMR (DMSO-d_6) δ -61.11, -112.14; MS (m/z): 461 ($M^{+\cdot}$, 42.3%), 64 (100%); Anal. Calcd for $C_{22}H_{15}F_4N_3O_2S$: C, 57.27; H, 3.28; N, 9.11; Found: C, 57.33; H, 3.40; N, 9.08.

*4.1.5.12. 1-(4-Aminosulfonylphenyl)-3-(3,4-difluoro)-5-(4-trifluoromethylphenyl)-1H-pyrazole (**15l**):* 75% yield; pale yellow powder; mp 111-112 °C; IR (KBr disk) 3389, 3252 (NH_2), 3076 (C-H aromatic), 1324, 1162 (SO_2); ^{1}H NMR (DMSO-d_6) δ 7.42 (s,1H, pyrazole H-4), 7.50-7.55 (m, 1H, difluorophenyl H-5), 7.57 (d, *J* = 7.6 Hz, 2H, trifluoromethylphenyl H-2, H-6), 7.63 (d, *J* = 8.0 Hz, 2H, aminosulphonylphenyl H-2, H-6), 7.73-7.81 (m, 1H, difluorophenyl H-2), 7.82 (d, *J* = 7.6 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.94-7.98 (m, 1H, difluorophenyl H-6), 8.01 (d, *J* = 8.0 Hz, 2H, aminosulphonylphenyl H-3, H-5); ^{13}C NMR (DMSO-d_6) δ 108.18 (pyrazole C-4), 114.98 (d, *J* = 19 Hz, difluorophenyl C-5), 118.60 (d, *J* = 17 Hz, difluorophenyl C-2), 122.90 (dd, *J* = 7, 4 Hz, difluorophenyl C-6), 124.43 (q, *J* = 270 Hz, *C*F_3), 126.25 (aminosulphonylphenyl C-2, C-6), 126.67 (d, *J* = 4 Hz, trifluoromethylphenyl C-3, C-5), 128.78 (trifluoromethylphenyl C-2, C-6), 129.30 (q, *J* = 32 Hz, trifluoromethylphenyl C-4), 129.86 (aminosulphonylphenyl C-3, C-5), 130.20 (difluorophenyl, C-1), 133.81 (aminosulphonylphenyl C-4), 140.23 (trifluoromethylphenyl C-1), 143.38 (aminosulphonylphenyl C-1), 143.78 (pyrazole C-5), 150.02 (dd, *J* = 247, 13 Hz, difluorophenyl C-3), 150.29 (dd, *J* = 247, 13 Hz, difluorophenyl C-4), 150.76 (pyrazole C-3); ^{19}F NMR (DMSO-d_6) δ -60.52, -136.37, -138.80; MS (m/z): 479 ($M^{+\cdot}$, 93.7%), 64 (100%); Anal. Calcd for $C_{22}H_{14}F_5N_3O_2S$: C, 55.12; H, 2.94; N, 8.76; Found: C, 55.20; H, 3.11; N, 8.58.

4.2. Pharmacological screening

4.2.1. *In vitro* cyclooxygenase (COX) inhibition assay

The ability of the test compounds listed in Table 1 to inhibit ovine COX-1 and human recombinant COX-2 (IC_{50} value, μM) was determined using an enzyme immuno assay (EIA) kit (catalog no. 560131, Cayman Chemical, Ann Arbor, MI, USA) according to previously reported method [19].

4.2.2. *In vivo* anti-inflammatory activity

The test compounds **14a-l**, **15a-l**, and the reference drugs celecoxib, aspirin and ibuprofen were evaluated using the *in vivo* carrageenan-induced rat foot paw edema model reported previously [20]

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Declaration of interest

The authors have declared no conflict of interest.

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Tables, Figures and Schemes Legends:

Table 1: *In vitro* COX-1 and COX-2 inhibition, and anti-inflammatory (AI) data for 1-(4-amino(methane)sulfonylphenyl)-3-substituted-phenyl-5-(4-trifluoromethylphenyl)-4,5-dihydro-1*H*-pyrazoles (**14a-l**), 1-(4-amino(methane)sulfonylphenyl)-3-substituted-phenyl-5-(4-trifluoromethyl-phenyl)-1*H*-pyrazoles (**15a-l**), and the reference drugs celecoxib, aspirin and ibuprofen.

Figure 1: Chemical structures of the selective cyclooxygenase-2 (COX-2) inhibitors celecoxib (**1**), rofecoxib (**2**), and valdecoxib (**3**), and celecoxib analogs (**4-8**).

Figure 2: Chemical structures of the selective cyclooxygenase-2 (COX-2) inhibitor celecoxib (**1**), the designed dihydropyrazoles (pyrazolines) **14a-f**, **14g-l** and the designed pyrazoles **15a-f**, **15g-l**.

Scheme 1: Synthetic protocol for compounds **11a-f**, **12**, **14a-l**, **15a-l**.

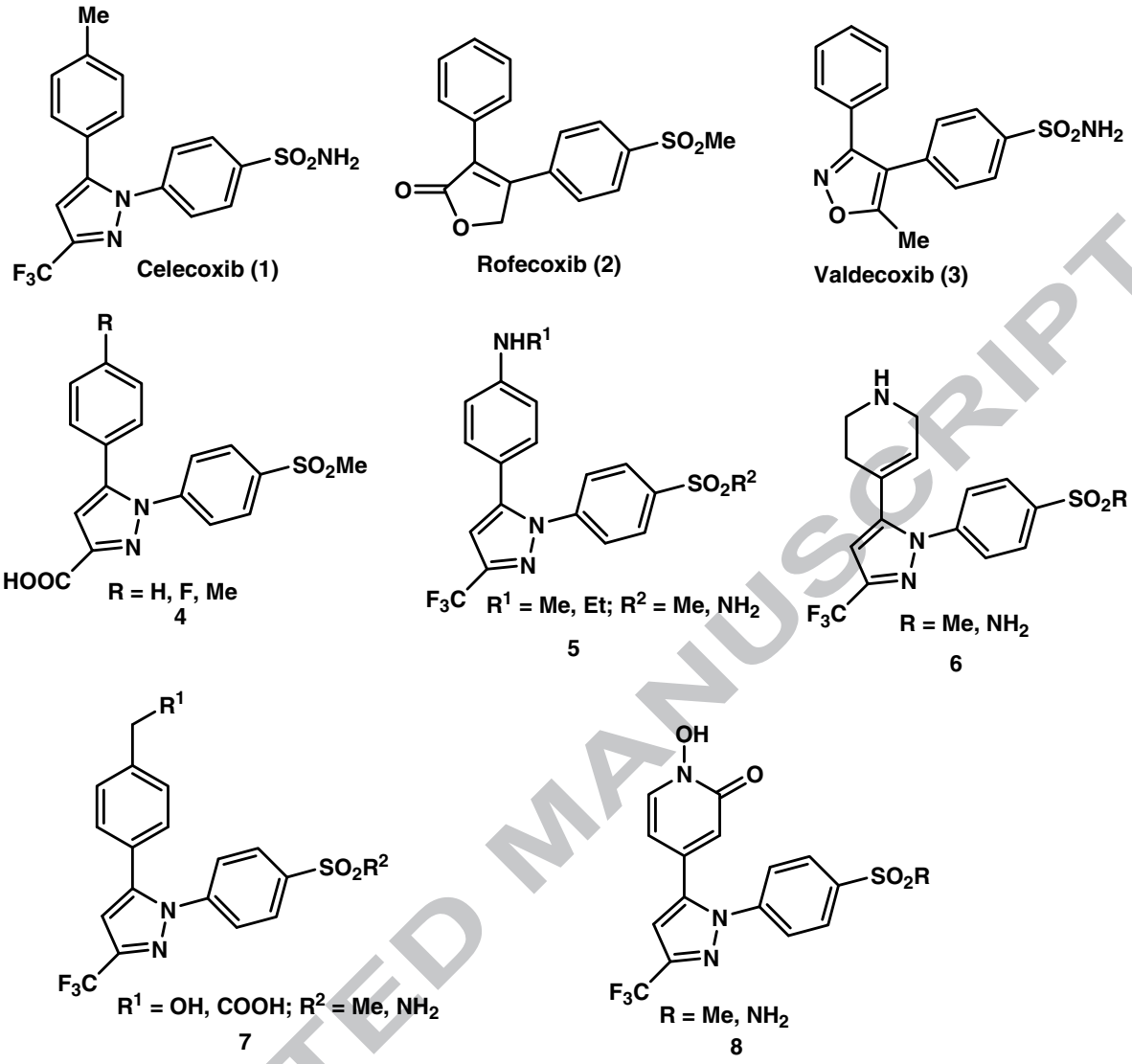
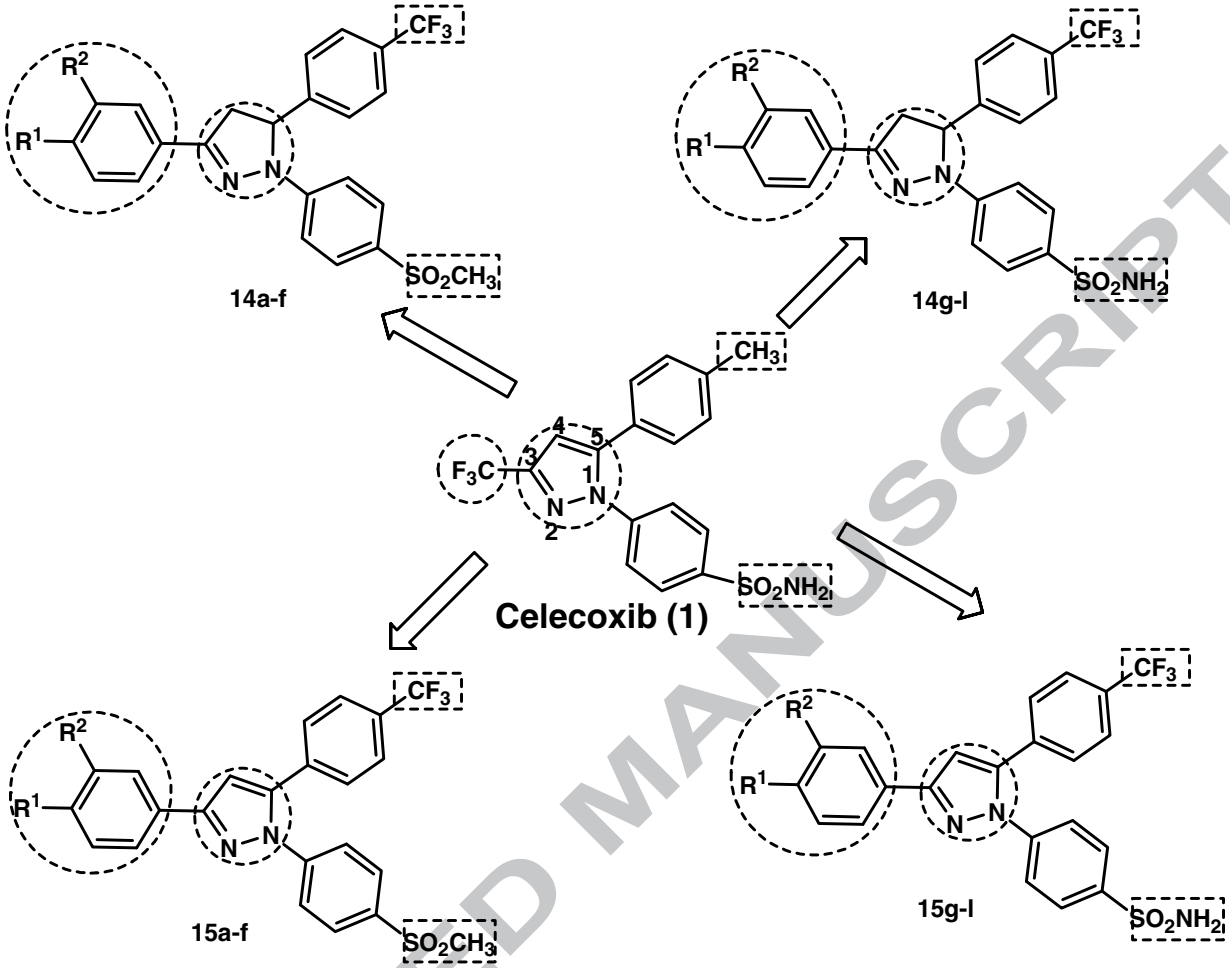
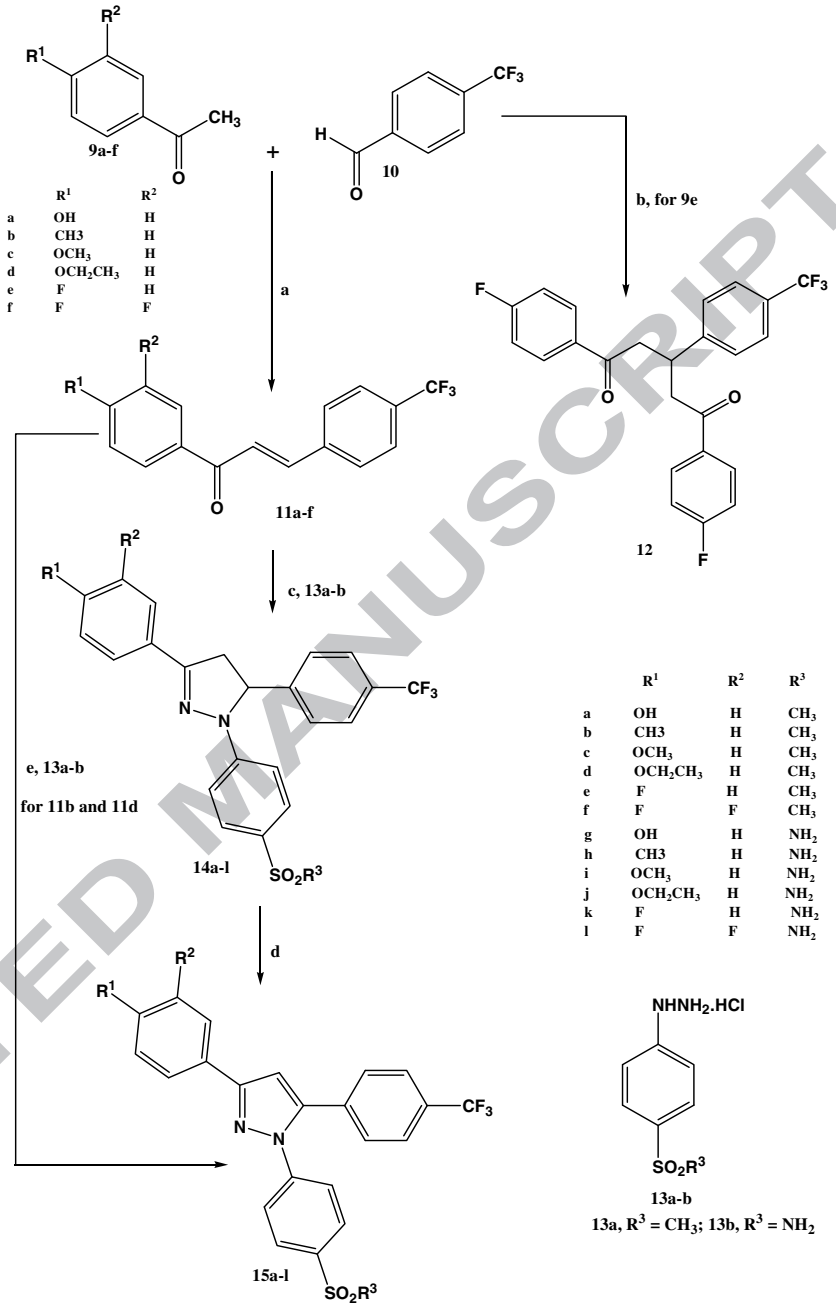


Figure 1.



R^1 = OH, CH_3, OCH_3, OCH_2CH_3, F; R^2 = H, F

Figure 2.

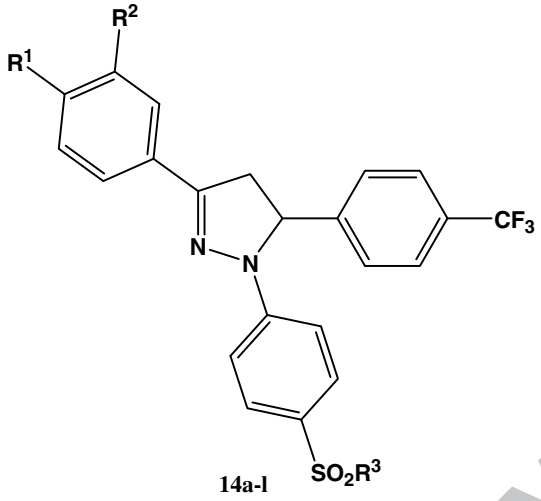


	R^1	R^2
a	OH	H
b	CH3	H
c	OCH_3	H
d	OCH_2CH_3	H
e	F	H
f	F	F

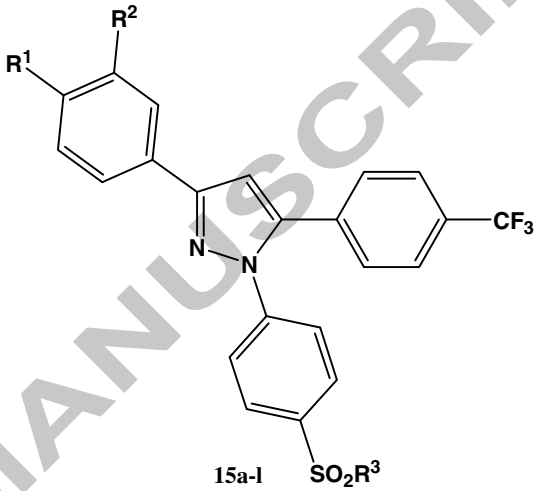
	R^1	R^2	R^3
a	OH	H	CH_3
b	CH3	H	CH_3
c	OCH_3	H	CH_3
d	OCH_2CH_3	H	CH_3
e	F	H	CH_3
f	F	F	CH_3
g	OH	H	NH_2
h	CH3	H	NH_2
i	OCH_3	H	NH_2
j	OCH_2CH_3	H	NH_2
k	F	H	NH_2
l	F	F	NH_2

Scheme 1. Reagents and conditions: (a) EtOH, 10% NaOH, RT, 2 h for **9a-d**, 0.5 h for **9e-f**; (b) EtOH, 10% NaOH, RT, 2 h for **9e**; (c) EtOH, reflux, 24 h; (d) glacial AcOH , reflux, 24 h; (e) AcOH (96%), reflux, 36 h.

Table 1. *In vitro* COX-1 and COX-2 inhibition, and anti-inflammatory (AI) data for 1-(4-amino(methane)sulfonylphenyl)-3-substituted-phenyl-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-1*H*-pyrazoles (**14a-l**), 1-(4-amino(methane)sulfonylphenyl)-3-substituted-phenyl-5-(4-trifluoromethylphenyl)-1*H*-pyrazoles (**15a-l**), and the reference drugs celecoxib, aspirin and ibuprofen.



14a-l



15a-l

Compd	R^1	R^2	R^3	IC_{50} (uM)[a]		COX-2 S.I.[b]	AI activity[c]	
				COX-1	COX-2		% inhibition (50 mg/kg)	ED_{50} (umol/kg)
14a	OH	H	Me	17.3	6.7	2.58	25.0	—
14b	Me	H	Me	6.6	1.11	5.95	16.3	—
14c	OMe	H	Me	24.1	10.8	2.23	30.0	—
14d	OEt	H	Me	5.6	0.97	5.77	38.8	296.0
14e	F	H	Me	16.4	4.8	3.42	31.3	—
14f	F	F	Me	23.1	9.4	2.46	Inactive	—
14g	OH	H	NH_2	5.8	1.9	3.05	41.3	190.5

14h	Me	H	NH_2	22.5	8.7	2.59	5.0	—
14i	OMe	H	NH_2	8.9	1.5	5.93	41.3	160.1
14j	OEt	H	NH_2	11.3	4.5	2.51	33.8	279.8
14k	F	H	NH_2	9.7	2.17	4.47	38.8	312.0
14l	F	F	NH_2	12.4	3.7	3.35	25.0	—
15a	OH	H	Me	5.9	0.97	6.08	2.5	—
15b	Me	H	Me	11.8	2.9	4.07	30.0	—
15c	OMe	H	Me	15.1	5.4	2.80	32.5	—
15d	OEt	H	Me	8.6	1.71	5.03	31.3	268.3
15e	F	H	Me	14.3	4.1	3.49	16.3	—
15f	F	F	Me	7.9	1.5	5.27	15.0	—
15g	OH	H	NH_2	9.6	3.1	3.10	Inactive	—
15h	Me	H	NH_2	18.1	5.7	3.18	Inactive	—
15i	OMe	H	NH_2	21.3	8.4	2.54	8.8	—
15j	OEt	H	NH_2	10.7	2.9	3.70	42.5	239.6
15k	F	H	NH_2	19.4	6.8	2.85	15.0	—
15l	F	F	NH_2	6.4	1.34	4.78	22.5	—
Celecoxib	—	—	—	6.7	0.87	7.70	—	30.9
Asprin	—	—	—	1.7	> 100	0.017	—	714.0
Ibuprofen	—	—	—	7.6	7.2	1.05	—	327.0

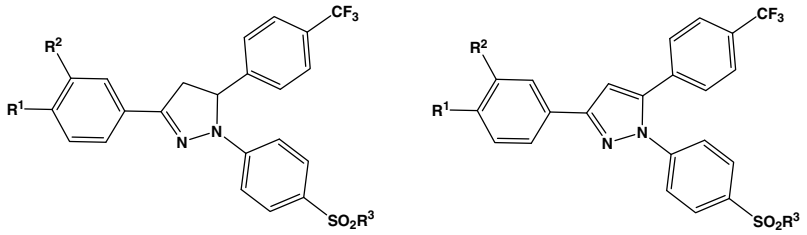
[a] The in vitro test compound concentration required to produce 50% inhibition of ovine COX-1 or human recombinant COX-2. The result (IC_{50}, μM) is the mean of two determinations acquired using

the enzyme immuno assay kit (Catalog No. 560131, Cayman Chemicals Inc., Ann Arbor, MI, USA) and the deviation from the mean is <10% of the mean value.

[b] In vitro COX-2 selectivity index (COX-1 IC_{50} / COX-2 IC_{50}).

[c] Inhibitory activity in a carrageenan-induced rat paw edema assay. The results are expressed as the % inhibition of inflammation at 3 hours after oral administration of the test compound at the specified dose (μmol/kg).

Graphical abstract



R^1 = OH, CH_3, OCH_3, OCH_2CH_3, F; R^2 = H, F; R^3 = CH_3, NH_2

Research Highlights:

Two groups of 2-pyrazoline and pyrazole derivatives were designed and synthesized.

All the compounds were more selective COX-2 inhibitors than aspirin and ibuprofen and were of comparable COX-2 selectivity to celecoxib.

Two pyrazoline derivatives (**14g** and **14i**) exhibited AI activity about 4-fold more potent than aspirin, 2-fold more potent than ibuprofen.

Compounds **14g** and **14i** could be used as a lead compound for developing new anti-inflammatory agents.