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Synthesis of fused sulfonamide (1,1-dioxoisothiazole)substituted 1,5-diarylpyrazoles as cyclooxygenase inhibitors[Ψ†]

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First synthesis of novel 1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazolyl substituted 1,5-diarylpyrazoles has been accomplished via oxidative cyclization of 4-fluoro-2-methyl benzenesulfonamide followed by the treatment with hydrazine and then with 1,3-dicarbonyl compounds. A number of 1,5-diarylpyrazoles were synthesized in good yields and some of them were of potential biological interest.

Cyclooxygenase-2 (COX-2) inhibitors are the topic of recent research due to their antiinflammatory activity with reduced side effects of traditional NSAIDs at the gastrointestinal level (mucosal damage, bleeding) and less frequently, at the renal level. Most of the COX-2 inhibitors belong to the vicinal diaryl heterocyclic class of compounds having an aminosulfonyl (SO_2NH_2) or a methanesulfone (SO_2Me) moiety attached to the *p*-position of one of the aryl ring. After the discovery of inducible isozyme (COX-2) in 1991, the methanesulfonanilide (NS398) and the diarylheterocycle (DUP-697) were first identified as non-ulcerogenic antiinflammatory agents (Fig. 1)[1,2]. Subsequent research and rational drug design resulted in a number of potent and selective COX-2 inhibitors which validated the initial concept that a selective COX-2 inhibitor would illicit effective anti-inflammatory activity without the adverse ulcerogenic effect associated with the use of NSAIDs that inhibit both COX-1 and COX-2. Accordingly celecoxib[3] and rofecoxib[4] followed by valdecoxib[5] and etoricoxib[6] became the first and second-generation selective COX-2 inhibitors (Fig. 1) to enter the market.

Celecoxib, a selective COX-2 inhibitor, belongs to a diaryl heterocyclic class where two aryl moieties are attached to the adjacent positions of the central pyrazole ring. The 4-benzenesulfonamide group attached to the nitrogen atom of the pyrazole ring is thought to be responsible for its efficacy and COX-2 selectivity in different models of inflammation. Recent study revealed that this class of compounds could be useful as dual COX-2/5-LO (5-lipooxygenase) inhibitors for the effective management of inflammatory diseases[7a]. Due to their interesting pharmacological and pharmacokinetic properties 1,5-diarylpyrazoles are in the focus for the development of selective COX-2 inhibitors by many research groups[7b-j]. In most of the these cases the Structure Activity Relationship (SAR) study was carried out with various possible modification of the central pyrazole ring, 1-(4-benzenesulfonamide) or 5-phenyl group individually keeping the SO_2NH_2 moiety intact. In connection with our effort on the development of cyclooxygenase inhibitors[8], we have reported synthesis and COX-2 inhibiting properties of a new class of 1,5-diaryl pyrazoles containing substituted benzenesulfonamide moiety as pharmacophore recently[9]. In further pursuance of our research on COX-2 inhibitors we anticipated that linking of the sulfonamide moiety with the adjacent benzene ring through a methylene bridge (Fig. 2)

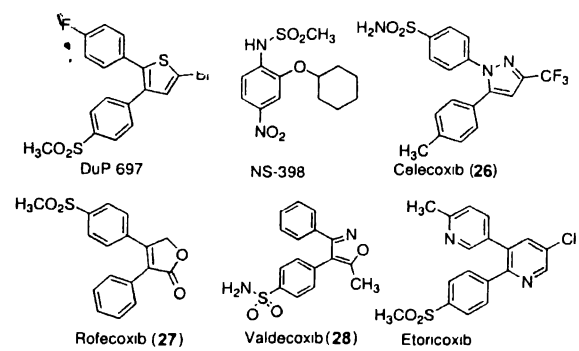

Fig. 1. Some selective COX-2 inhibitors.

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[†]Dedicated to Professor S. M. Mukherji.

could be a useful pharmacophore for COX-2 inhibition. Herein we describe the synthesis of a novel class of 1,5-diaryl pyrazoles (**A**) containing 1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazolyl-5-yl group as a possible pharmacophore.

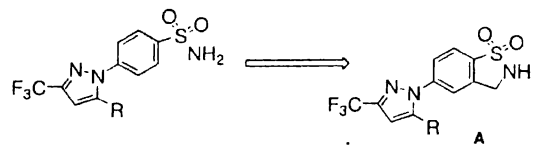
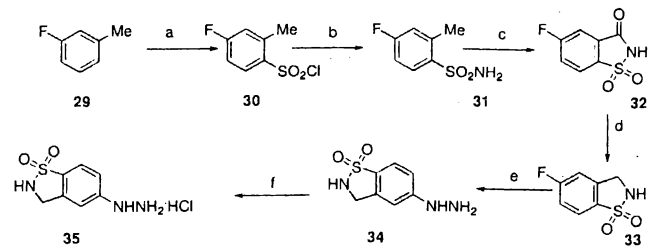


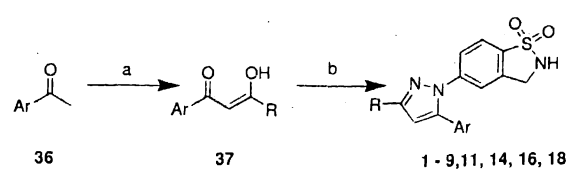
Fig. 2. Design of novel 1,5-diarylpyrazole derivatives.

While a number of methods are available for the synthesis of various pyrazole derivatives[7-9] none has been reported for the synthesis of 1,1-dioxo-2,3-dihydrobenzo[*d*] isothiazolyl substituted 1,5-diarylpyrazoles (**A**). We therefore decided to explore their synthesis starting from the 4-hydrazino-2-methyl-1-benzenesulfonamide, which on treatment with appropriate dicarbonyl compound yielded corresponding pyrazole having methyl group at the *o*-position of the sulfonamide moiety[9]. We expected that the oxidation of the methyl group followed by cyclization involving the sulfonamide moiety according to the procedure described in the lierature[10a] would result in pyrazole derivative that could be reduced to give the expected product **A**. However, we failed to isolate the desired product after this oxidative cyclization reaction presumably due to the decomposition of the products under the strong reaction condition employed. This forced us to change our strategy for the synthesis of **A** and thus the desired diaryl pyrazoles were synthesized according to the Schemes 1–4. 1,1-Dioxo-2,3-dihydrobenzo [*d*]isothiazole-5-yl hydrazine **34** was used as a common intermediate for the synthesis of most of the compounds (Scheme 1). Synthesis[10a,b] of **34** was carried out using 3-fluorotoluene **29** as starting material. Chlorosulfonation of **29** at low temperature using chlorosulfonic acid followed by ammonolysis using aqueous ammonia in dioxane led to the formation of 4-fluoro-2-methyl benzenesulfonamide **31** in good yield. Oxidative cyclization of **31** was carried out using alkaline potassium permanganate solution followed by the treatment with dilute hydrochloric acid to furnish benzo[*d*]isothiazine derivative **32**. The amidic carbonyl group of **32** was then reduced to a methylene group according to the procedure that is not documented well in the literature. Thus, **32** was treated with zinc powder in the presence of hydrochloric acid in ethanol to afford **33** in good yield. The fluorine atom of **33** was then replaced by hydrazine moiety using anhydrous hydrazine in acetonitrile under refluxing condition to provide **34**. This was then converted to a hydrochloride salt **35** in order to minimize the formation of side products in the next step.



Scheme 1. *Reagents and conditions* : (a) $ClSO_3H$, 0°, 4 h, 75% yield; (b) NH_3, dioxane, 0°, 6 h, 79% yield; (c) NaOH, H_2O, $KMnO_4$, 6 h, dilute HCl, 46% yield; (d) EtOH, conc. HCl, Zn powder, 0–25°, 2 h, 33% yield; (e) NH_2NH_2, CH_3CN, reflux, 6 h, yield 68%; (f) HCl, EtOH, quantitative yield.

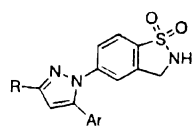
The dicarbonyl derivatives **37** were synthesized[10c-e] (Scheme 2) by Claisen condensation of an appropriate acetophenone **36** with either ethyl trifluroacetate or ethyl difluoroacetate in the presence of sodium hydride as a base in dimethylformamide (DMF). Reaction of **37** with hydrochloride salt **35** in ethanol under refluxing condition led to the formation of expected 1,5-diaryl pyrazoles (**1–9, 11, 14, 16, 18**) as major product along with the trace amount of other regio-isomer. The latter was removed by using chromatographic separation technique. Yields of the pure products isolated have been listed in Table 1. Except in few cases (e.g. compound **7** and **8**) yields are generally good when a strong electron donating group is present at the C-4 position of the 5-aryl moiety (compound **6, 9, 11, 14, 16** and **18**, Table 1).



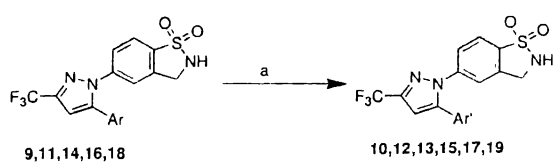
Scheme 2. *Reagents and conditions* : (a) NaH, DMF, 0°–room temp., RCO_2Et, 24 h; (b) **35**, EtOH, reflux.

The methylsulfoxide (**12**) and methylsulfone derivatives (**10, 13, 15, 17, 19**) were prepared (Scheme 3) by controlled oxidation of the appropriate 4-methylsulfanylphenyl derivatives (**11, 14, 16, 18**) using oxone ($2KHSO_5.KHSO_4.K_2SO_4$) in aqueous acetone at room temperature. Yields of the products (compound **10** and **17**, Table 2) are generally good to excellent when extra substituent is absent in the 5-aryl ring. Scheme 4 describes acylation and alkyl or arylsulfonation at the nitrogen atom of **6** using appropriate halides. Reactions were carried out smoothly in the presence of triethylamine as a base and catalytic amount of 4-

Table 1. Synthesis of 1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazolyl substituted 1,5-diarylpyrazoles from dicarbonyl compounds **37**

Compd. no.			% Yield[a]
	Ar=	R=	
1	4-Fluorophenyl	CF_3	20
2	4-Chlorophenyl	CF_3	28
3	4-Bromophenyl	CF_3	23
4	4-Methylphenyl	CF_3	18
5	3-Fluoro-4-methylphenyl	CF_3	26
6	4-Methoxyphenyl	CF_3	60
7	3-Fluoro-4-methoxyphenyl	CF_3	33
8	3,4-Dimethoxyphenyl	CF_3	30
9	4-Methylsulfanylphenyl	CF_3	62
11	3-Methyl-4-methylsulfanylphenyl	CF_3	50
14	2-Fluoro-4-methylsulfanylphenyl	CF_3	58
16	4-Methylsulfanylphenyl	CHF_2	44
18	2-Fluoro-4-methylsulfanylphenyl	CHF_2	65

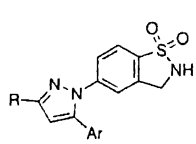
[a]Isolated yield of pure product.



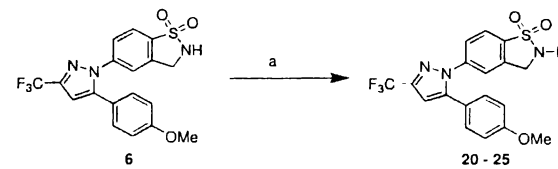
9,11,14,16,18 **10,12,13,15,17,19**

Scheme 3. *Reagents and conditions* : (a) oxone, acetone–H_2O (1 : 1), room temp., 3 h.

Table 2. Synthesis of 1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazolyl substituted 1,5-diarylpyrazoles via oxidation of the corresponding methylsulfanyl analogues

Compd. no.			% Yield[a]
	Ar=	R=	
10	4-Methylsulfonylphenyl	CF_3	67
12	3-Methyl-4-methylsulfinylphenyl	CF_3	28
13	3-Methyl-4-methylsulfonylphenyl	CF_3	28
15	2-Fluoro-4-methylsulfonylphenyl	CF_3	69
17	4-Methylsulfonylphenyl	CHF_2	80
19	2-Fluoro-4-methylsulfonylphenyl	CHF_2	35

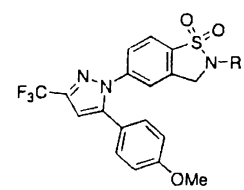
[a]Isolated yield of pure product.



6 **20 - 25**

Scheme 4. *Reagents and conditions* : (a) RCl, Et_3N, CH_2Cl_2, 4-(*N,N*-dimethylamino)pyridine, 1 h.

Table 3. Synthesis of *N*-substituted 1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazolyl substituted 1,5-diarylpyrazoles from **6**

Compd. no.		% Yield[a]
	R=	
20	Acetyl	70
21	Methylsulfonyl	33
22	*p*-Tolylsulfonyl	44
23	4-Fluorobenzenesulfonyl	65
24	4-Fluoro-2-methylbenzenesulfonyl	39
25	Trifluoromethylsulfonyl	19

[a]Isolated yield of pure product.

(*N,N*-dimethylamino)pyridine in dichloromethane to give the expected products in moderate to good yields (Table 3).

All the 1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-5-yl substituted 1,5-diarylpyrazoles synthesized were well characterized by the spectral (^{1}H NMR, MS and IR) data. Appearance of a peak at 6.9 ± 0.2 and 4.9 ± 0.5 δ in their ^{1}H NMR spectra was assigned to the C-4 proton signal of pyrazole ring and -NH of sulfonamide moiety, respectively. The methylene group of 1,1-dioxo-2,3-dihydrobenzo [*d*]isothiazol-5-yl moiety was typically characterized by the signal at 4.5 ± 0.3 δ. Many of these 1,5-diarylpyrazoles were tested against Human COX-2 (expressed in *sf*9 insect cells using baculovirus) and COX-1 (Ram Seminal vesicles) enzyme[11a] for their cyclooxygenase inhibiting properties. Some of them showed inhibition against both COX-1 and COX-2[11b]. Compound **15** showed more than 100 fold selectivity in COX-2 inhibition over COX-1 and therefore was identified as a novel COX-2 inhibitor.

Conclusion :

Thus we have described an efficient synthesis of a novel class of 1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazolyl substituted 1,5-diarylpyrazole derivatives of potential biological

interest. All the compounds described have been synthesized by using simple synthetic methods and the methodology utilized here does not involve the use of any costly reagents or chemicals. We also have demonstrated that 1,5-diarylpyrazoles possessing *N*-substitution on the sulfonamide ($-SO_2NH_2$) moiety have potential to be used as COX-2 specific inhibitor and therefore our present investigation would provide some insight on further designing as well as on biological activities of pyrazole based anti-inflammatory agents.

Experimental

Genreal methods : ^{1}H NMR spectra were determined in $CDCl_3$, DMSO-d_6 or MeOH-d_4 solution on Varian Gemini 200 MHz spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a Perkin-Elmer 1650 FT-IR spectrometer. Melting points were determined using a scientific capillary melting point apparatus and are uncorrected. Mass spectra were obtained on a HP-5989A mass spectrometer. HPLC was performed on Water IC Module 1 plus apparatus. Thin layer chromatography was performed on silica gel plates (60 F254; Merck). Flash chromatography was performed on silica gel (SRL 230-400 mesh). All the solvents used were commercially available and was distilled before use. Acetophenones were either purchased or prepared according to the procedure described in literature.

Preparation of 4-fluoro-2-methyl-1-benzenesulfonyl chloride (**30**)[10b] : To a cooled solution (0°) of chlorosulfonic acid (57.0 g, 450 mmol) was added 3-fluorotoluene (10 g, 90 mmol) slowly at 0°. The mixture was then stirred for 4 h at 0° and allowed to stand for overnight at same temperature. The reaction mixture was poured into crushed ice. Oily layer separated was collected and washed with water to yield the desired compound as liquid (14 g, 75%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10 (1H, m), 7.10 (2H, m), 2.79 (3H, s, CH_3).

Preparation of 4-fluoro-2-methyl-1-benzenesulfonamide (**31**)[12a] : To a cooled solution of **30** (14 g, 67.0 mmol) in dioxane (30 ml) was added 25% aqueous solution of ammonia (140 ml) with vigorous stirring. The stirring continued for 6 h at 0° and separated solid was filtered, washed with water (2 × 50 ml) to give the title compound as white solid (10 g, 79%); m.p. 171–172°; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.9 (1H, m), 7.4 (2H, s, exchangeable with D_2O), 7.2 (2H, m), 2.59 (3H, s).

Preparation of 5-fluoro-1,1,3-trioxo-2,3-dihydrobenzo[d]isothiazine (**32**)[12b] : To a mixture of **31** (10 g, 67 mmol) and aqueous sodium hydroxide (28 g, 70.3 mmol) solution (100 ml) was added potassium permanganate (18 g, 114 mmol) in small portions over a period of 5 h with vigorous stirring. The mixture was then stirred for 6 h and filtered through celite. The filtrate was collected and neutralized with cold dilute hydrochloric acid and the separated solid was filtered off. The filtrate was collected again and treated with concentrated hydrochloric aicd until the pH was 2.0. The separated solid was filtered and dired to afford the expected compound (4.3 g, 46%) as white solid, m.p. > 200°; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.9 (1H, bs, exchangeable with D_2O), 8.2 (1H, m), 7.8 (2H, m).

Preparation of 1,1-dioxo-2,3-dihydrobenzo[d]-isothiazol-5-yl fluoride (**33**) : To a solution of **32** (2 g, 10 mmol) in ethanol (5 ml) was added concentrated hydrochloric acid (15 ml) at 0° followed by the portion wise addition of zinc powder. The reaction mixture was stirred for 2 h at 25° and then treated with cold sodium bicarbonate solution until the pH of the mixture became 9. The mixture was filtered through celite pad and the filtrate was extracted with EtOAc (3 × 50 ml). Combined organic layer was collected, washed with water (2 × 50 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the required compound (0.6 g, 33%); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.90 (2H, m, ArH and NH), 7.40 (2H, m), 4.40 (2H, d, J 4.0 Hz, CH_2); ^{13}C NMR (50 MHz, DMSO-d_6) δ 166.99, 162.04, 141.64, 141.44, 132.56, 123.28, 123.08, 117.04, 116.56, 112.61, 112.13, 44.70.

Preparation of 1,1-dioxo-2,3-dihydrobenzo[d]isothiazol-5-yl hydrazine (**34**) : A solution of **33** (0.55 g, 2.94 mmol) in acetonitrile (10 ml) was treated with anhydrous hydrazine (0.6 ml) and the mixture was refluxed for 6 h. The solvent was then removed under reduced pressure and the residue was treated with water (10 ml). The separated solid was filtered and washed with cold water (2 × 50 ml) to give the required product (0.4 g, 68%); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.60 (1H, s), 7.40 (2H, m), 6.70 (3H, m, NH), 4.20 (2H, d, J 5.0 Hz, CH_2).

Preparation of 1,1-dioxo-2,3-dihydrobenzo[d]isothiazol-5-yl hydrochloride (**35**) : To a solution of **34** (0.4 g) in ethanol (5 ml) was added *i*-propanol (3 ml) saturated with dry hydrochloric acid at 25° and the mixture was stirred for 1.5 h at the same temperature. The solvent was removed under low pressure to yield the required compound in quantitative yield and the residue was used directly for the next reaction without further purification.

General method for the preparation of 1,3-diketones (**37**) : To a solution of acetophenone (**36**, 2.7 mmol) in dimethylformamide was added 60% oil suspension of sodium hydride (3.24 mmol) at 10° under nitrogen atmosphere and the mixture was stirred for 10 minutes. To this mixture was added appropriate ethylacetate (3.24 mmol) at the same temperature and stirring was continued for 12 h. This mixture was then poured into ice-cold hydrochloric acid solution (100 ml) and was stirred for 10 minutes. Solid separated was extracted with ethyl acetate (2 × 50 ml). Combined organic layer was collected, washed with water (2 × 50 ml), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue isolated was purified by column chromatography using 5% EtOAc-petroleum ether to give the required compound **37**.

General method for the preparation of 1,5-diarylpyrazoles (**1–9**, **11**, **14**, **16**, **18**) : A mixture of hydrazine hydrochloride **35** and 1,3-diketone **37** in ethanol was heated to reflux with vigorous stirring under nitrogen atmosphere for 12 h. Ethanol was removed under low vacuum and the residue isolated was purified by column chromatography using EtOAc-petroleum ether (1 : 2) to give the expected product.

Spectral data for few compounds :

5-[5-(4-Bromophenyl)-3-trifluoromethyl-1H-1-pyrazolyl]-1,1-dioxo-2,3-dihydrobenzo[d]isothiazole (**3**): m.p. 240–242°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73 (2H, d, *J* 8.3 Hz), 7.51 (1H, s), 7.4–7.3 (4H, m), 7.19 (1H, d, *J* 8.3 Hz), 6.80 (1H, s), 4.45 (2H, d, *J* 4.6 Hz, CH_2); IR (nujol) cm^{-1} 1604, 1482; MS (CI, *i*-butane) 460 (M+2, 70), 469 (M+1, 70), 291 (100).

5-[5-(4-Methoxyphenyl)-3-trifluoromethyl-1H-1-pyrazolyl]-1,1-dioxo-2,3-dihydrobenzo[d]isothiazole (**6**): m.p. 75–77°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (1H, d, *J* 8.0 Hz), 7.52 (1H, s), 7.33 (1H, d, *J* 8.0 Hz), 7.14 (2H, d, *J* 9.0 Hz), 6.89 (2H, d, *J* 9.0 Hz), 6.7 (1H, s), 4.98 (1H, bs, D_2O exchangeable), 4.49 (2H, d, *J* 5.0 Hz, CH_2), 3.8 (3H, s, OCH_3); IR (nujol) cm^{-1} 1610, 1470; MS (CI, *i*-butane) 410 (M+1, 100).

5-[5-(4-Methylsulfanylphenyl)-3-trifluoromethyl-1H-1-pyrazolyl]-1,1-dioxo-2,3-dihydrobenzo[d]isothiazole (**9**): m.p. 177–179°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74 (1H, d, *J* 8.3 Hz), 7.55 (1H, s), 7.35 (1H, d, *J* 8.8 Hz), 7.26–7.11 (4H, m), 6.79 (1H, s), 4.80 (1H, bs, D_2O exchangeable), 4.53 (2H, d, *J* 4.9 Hz, CH_2), 2.50 (3H, s, CH_3); IR (nujol) cm^{-1} 1604, 1465; MS (CI, *i*-butane) 426 (M+1, 100).

5-[5-(3-Methyl-4-methylsulfanylphenyl)-3-trifluoromethyl-1H-1-pyrazolyl]-1,1-dioxo-2,3-dihydrobenzo[d]isothiazole (**11**) : m.p. 159–160°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (1H, d, *J* 8.3 Hz), 7.55 (1H, s), 7.33 (1H, d, *J* 8.3 Hz), 7.08–7.04 (2H, m), 6.90 (1H, d, *J* 7.8 Hz), 6.73 (1H, s), 4.80 (1H, bs, D_2O exchangeable), 4.50 (2H, d, *J* 4.8 Hz, CH_2), 2.47 (3H, s, CH_3), 2.29 (3H, s, CH_3); IR (nujol) cm^{-1} 1606, 1464; MS (CI, *i*-butane) 440 (M+1, 100).

5-[5-(2-Fluoro-4-methylsulfanylphenyl)-3-trifluoromethyl-1H-1-pyrazolyl]-1,1-dioxo-2,3-dihydrobenzo[d]isothiazole (**14**) : m.p. 159–161°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71 (1H, d, *J* 8.3 Hz), 7.56 (1H, s), 7.32–6.89 (4H, m), 6.81 (1H, s), 4.94 (1H, bs, D_2O exchangeable), 4.52 (2H, d, *J* 3.4 Hz), 2.50 (3H, s); MS (CI, *i*-butane) 444 (M+1, 100).

General method for the preparation of 1,5-diarylpyrazoles (**10, 12, 13, 15, 17, 19**) : To a solution of methylsulfanylsubstituted 1,5-diarylpyrazole (0.36 mmol) in acetone-water (4 : 1, 40 ml) was added oxone (potassium monopersulphate triple salt, 0.73 mmol) at 25° and the mixture was stirred for 3 h at the same temperature. Acetone was removed under low vacuum and the residue was diluted with water (20 ml). Solid separated was filtered, washed with water (5 ml) followed by petroleum ether (5 ml) to give the required product.

Spectral data for selected compounds :

5-[5-(4-Methylsulfonylphenyl)-3-trifluoromethyl-1H-1-pyrazolyl]-1,1-dioxo-2,3-dihydrobenzo[d]isothiazole (**10**) : m.p. 228–230°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (2H, d, *J* 8.30 Hz), 7.78 (1H, d, *J* 8.3 Hz), 7.55 (1H, s), 7.47 (2H, d, *J* 8.3 Hz), 7.33 (1H, d, *J* 9.7 Hz), 6.90 (1H, s), 4.78 (1H, bs, D_2O exchangeable), 4.54 (2H, s, CH_3), 3.12 (3H, s, CH_3); IR (nujol) cm^{-1} 1607, 1496; MS (CI, *i*-butane) 458 (M+1, 100).

5-[5-(3-Methyl-4-methylsulfinylphenyl)-3-trifluoromethyl-1H-1-pyrazolyl]-1,1-dioxo-2,3-dihydrobenzo[d]isothiazole (**12**) : m.p. 130–132°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (1H, d, *J* 8.3 Hz), 7.75 (1H, d, *J* 7.8 Hz), 7.54 (1H, s), 7.36–7.25 (2H, m), 7.18 (1H, s), 6.83 (1H, s), 5.38 (1H, bs, D_2O exchangeable), 4.52 (2H, d, *J* 4.3 Hz, CH_2), 2.76 (3H, s, CH_3), 2.38 (3H, s, CH_3); IR (nujol) cm^{-1} 1610, 1455; MS (CI, *i*-butane) 455 (M^+, 100).

5-[5-(3-Methyl-4-methylsulfonylphenyl)-3-trifluoromethyl-1H-1-pyrazolyl]-1,1-dioxo-2,3-dihydrobenzo[d]isothiazole (**13**) : m.p. 134–136°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (1H, d, *J* 8.3 Hz), 7.76 (1H, d, *J* 8.3 Hz), 7.55 (1H, s), 7.32–7.15 (3H, m), 6.86 (1H, s), 4.92 (1H, bs, D_2O exchangeable), 4.54 (2H, d, *J* 4.8 Hz, CH_2), 3.13 (3H, s, CH_3), 2.72 (3H, s, CH_3); IR (nujol)

cm^{-1} 1608, 1481; MS (CI, *i*-butane) 472 (M+1, 100), 407 (10).

General procedure for the preparation of 1,5-diarylpyrazoles (**20–24**) : To a solution of **6** (0.24 mmol) in dichloromethane (4 ml) was added triethylamine (0.36 mmol) followed by acyl or sulfonyl halide (0.293 mmol) at 0°. 4-(*N,N*-Dimethylamino)pyridine (0.02 mmol) was also added to the mixture as a catalyst and the mixture was stirred for 1 h at 25°. Water (100 ml) was added to the mixture followed by extraction with EtOAc (2 × 50 ml). Organic layers collected, combined, washed with water (2 × 50 ml) and dired over anhydrous Na_2SO_4 and concentrated under vacuum. The residue isolated was purified by using column chromatography to give the expected product.

Spectral data for selected compounds :

1-[5-[4-Methoxyphenyl)-3-trifluoromethyl-1H-1-pyrazolyl]1, 1-dioxo-2,3-dihydro benzo[d]isothiazol-2-yl]-1-ethanone (**20**) : m.p. 69–74°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* 8.5 Hz), 7.57 (1H, s), 7.49 (1H, d, *J* 8.5 Hz), 7.17 (2H, d, *J* 8.5 Hz), 6.93 (2H, d, *J* 8.5 Hz), 6.75 (1H, s), 4.89 (2H, s, CH_2), 3.87 (3H, s, OCH_3), 2.63 (3H, s, CH_3); MS (CI, *i*-butane) 451 (M^+, 20), 408 (100).

5-[5-(4-Methoxyphenyl)-3-trifluoromethyl-1H-1-pyrazolyl]-1,1-dioxo-2-methylsulfonyl-2,3-dihydro-benzo[d]isothiazole (**21**) : m.p. 105–107°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72 (1H, d, *J* 8.3 Hz), 7.58 (1H, s), 7.41 (1H, d, *J* 8.5 Hz), 7.13 (2H, d, *J* 8.8 Hz), 6.89 (2H, d, *J* 8.6 Hz), 6.71 (1H, s), 4.85 (2H, s, CH_2), 3.82 (3H, s, CH_3), 3.27 (3H, s, CH_3); MS (CI, *i*-butane) 487 (M^+, 20), 408 (100).

5-[5-(4-Methoxyphenyl)-3-trifluoromethyl-1H-1-pyrazolyl]-1,1-dioxo-2-(4-methylphenylsulfonyl)-2,3-dihydrobenzo[d]isothiazole (**22**) : m.p. 161–163°; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97 (2H, d, *J* 8.3 Hz), 7.64 (1H, d, *J* 8.5 Hz), 7.49 (1H, s), 7.36–7.32 (3H, m), 7.07 (2H, d, *J* 8.8 Hz), 6.87 (2H, d, *J* 8.5 Hz), 6.67 (1H, s), 4.67 (2H, s, CH_2), 3.8 (3H, s, CH_3), 2.41 (3H, s, CH_3); MS (CI, *i*-butane) 564 (M^+, 100), 408 (40).

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