

# Heteroaromatic analogues of 1,5-diarylpyrazole class as anti-inflammatory agents

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Received: 18 February 2011 / Accepted: 8 November 2011 / Published online: 6 December 2011  
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**Abstract** A novel series of heteroaromatic analogues of known anti-inflammatory (AI) drug celecoxib replacing the benzenesulfonamide moiety with 6-sulfonamidobenzothiazol-2-yl moiety was synthesized. Regioselective synthesis of the target compounds **2a–i** having 1,5-diaryl relationship was achieved by exploring reaction conditions. All the newly synthesized compounds (**2a–i** and **8**) were screened for their in vivo AI activity using carrageenan-induced rat paw edema assay. Five compounds (**2c–f** and **2i**) were found to possess good AI activity ( $\geq 60\%$  inhibition), 3 h after the carrageenan injection when compared to that of standard drug indomethacin (78%), whereas the remaining four compounds (**2a–b** and **2g–h**) with 1,5-diaryl relationship have shown moderate activity with 49–56% inhibition after 3 h. However, pyrazole **8** having 1,3-diaryl relationship failed to show appreciable AI activity.

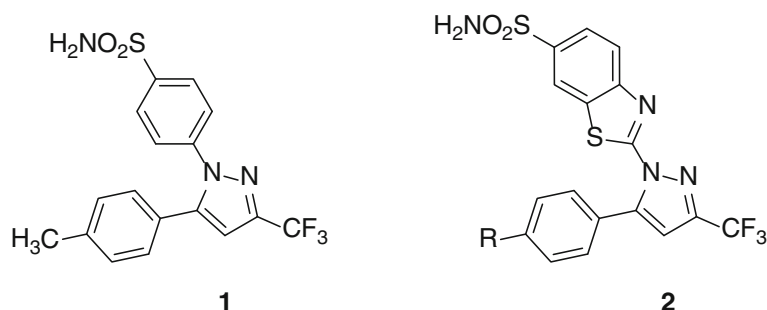
**Keywords** 1,5-Diarylpyrazoles ·  
Benzothiazolesulfonamide · Anti-inflammatory activity ·  
Inflammation · NSAID

## Introduction

The development of an effective therapeutic agent for the management of inflammation has undergone continual evolution leading to the emergence of more efficacious classes of drugs. Since the discovery of aspirin, much efforts have been devoted to the development of non-steroidal anti-inflammatory (AI) drugs (NSAIDs). Their mechanism of action involves the inhibition of the production of prostaglandins (PGs) by the enzyme cyclooxygenase (COX) (Vane, 1971). PGs are important biological mediators of inflammation originating from biotransformation of arachidonic acid catalyzed by COX (Cashman, 1996). It has been well established that the enzyme exists in two isoforms, one constitutive (COX-1) and the other inducible (COX-2) (Xie *et al.*, 1991). COX-1 is constitutively present in platelets and all tissues and produces PGs involved in physiological functions, such as gastric mucosal cytoprotection, renal homeostasis, and platelet aggregation (Ormrod *et al.*, 2002). Although constitutive in a few tissues, COX-2 isozyme is transiently induced by proinflammatory stimuli to generate PGs that mediate the inflammatory response (Kanapure and Letts, 2004). Conventional NSAIDs owing to their indiscriminate inhibition of both isoforms of COX, are associated with well-known side effects at the gastrointestinal (GI) level as well as at the renal level (Meyer-Irchrath and Schror, 2000). Therefore, currently, there is a considerable therapeutic interest in developing selective COX-2 inhibitors based on the hypothesis that these compounds will reduce pain, fever, and inflammation without causing GI injury (Dannhardt and Keifer, 2001). This drug design concept has been validated by the induction of a blockbuster drug celecoxib (Penning *et al.*, 1997) (**1**) which has shown excellent AI activity with reduced GI side effects.

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Thiazoles and their derivatives are also known to exhibit AI activity (Kalkhambkar *et al.*, 2007; Kouatly *et al.*, 2009; Giri *et al.*, 2009). Since the combination of pharmacophores on the same scaffold is a well-established approach to the synthesis of more potent drugs (Pillai *et al.*, 2003; Venkatachalam *et al.*, 2006), coupled with our ongoing interest (Kumar *et al.*, 2011; Sharma and Sawhney, 1993, 1997; Sharma *et al.*, 1998, 2010, 2011a, b; Sawhney and Sharma, 1993) in the synthesis of novel heterocyclic analogues as AI agents led us to focus our attention on the modification of the most celebrated drug celecoxib (**1**) belonging to the 1,5-diarylpyrazole class. Thus, we decided to study the effects on the AI activity of replacing the benzenesulfonamide moiety with benzothiazolesulfonamide moiety in the 1,5-diarylpyrazole class. We now report the synthesis and in vivo AI activity data for some heteroaromatic analogues (**2**) of celecoxib.

## Results and discussion

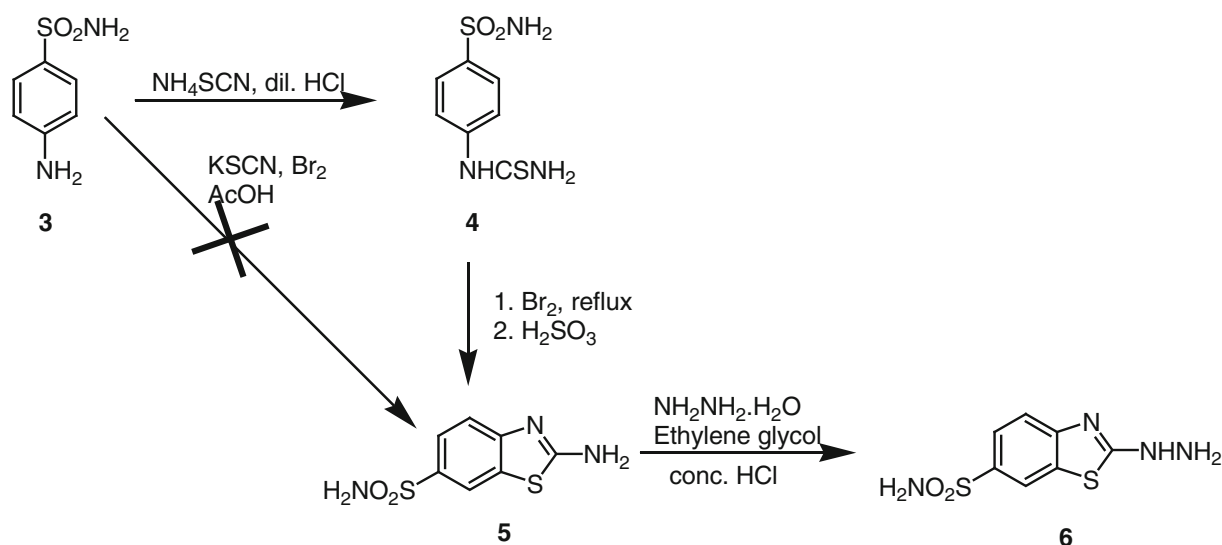
### Chemistry

The basic requirement for the synthesis of these pyrazoles was the availability of hitherto unknown 2-hydrazino-6-

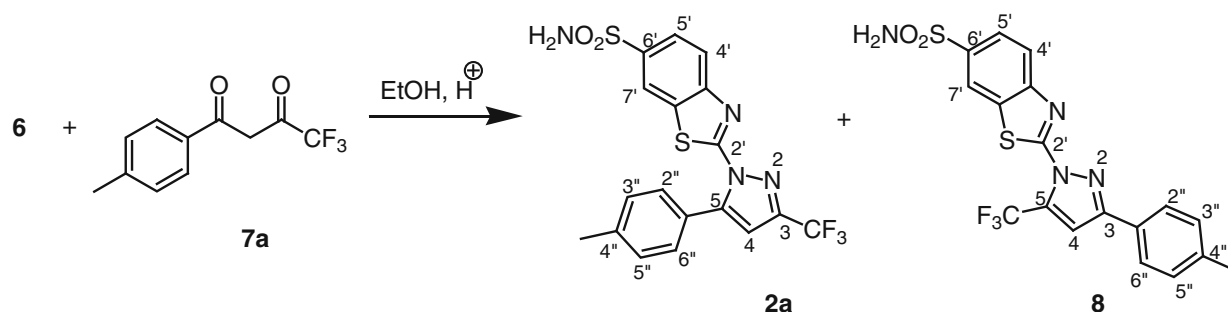
aminosulfonylbenzothiazole (**6**). Scheme 1 depicts the three-step conversion of 4-aminobenzenesulfonamide (**3**) into **6**. Unfortunately, the conventional method of preparing 2-aminobenzothiazoles in a single step (Kaufmann *et al.*, 1928) from appropriate anilines by treatment with  $\text{Br}_2/\text{KSCN}$  failed to give 2-amino-6-aminosulfonylbenzothiazole (**5**). Therefore, the required aminobenzothiazole (**5**) (Kaufmann and Buckmann, 1941) was prepared from **3** through the corresponding thiourea derivative (**4**). Oxidative cyclization of thiourea (**4**) with  $\text{Br}_2$  gave 2-amino-6-aminosulfonylbenzothiazole (**5**) which on treatment with hydrazine hydrate in ethylene glycol under acidic conditions afforded the required hydrazinobenzothiazole (**6**) in 53% overall yield from **3**.

The hydrazine **6** was then treated with unsymmetrical trifluoromethyl- $\beta$ -diketones (Singh *et al.*, 2005) in an effort to synthesize target 1,5-diarylpyrazoles (**2**) as shown in Scheme 2. First of all, the attempts were made toward the synthesis of **2a**, the closest analogue of celecoxib having a benzothiazolesulfonamide moiety in place of benzenesulfonamide moiety.

Accordingly, a solution of 2-hydrazinobenzothiazole-6-sulfonamide (**6**) and 4,4,4-trifluoro-1-(4-methylphenyl)butane-1,3-dione (**7a**) in ethanol containing a few drops of



**Scheme 1** Synthesis of hydrazine **6**

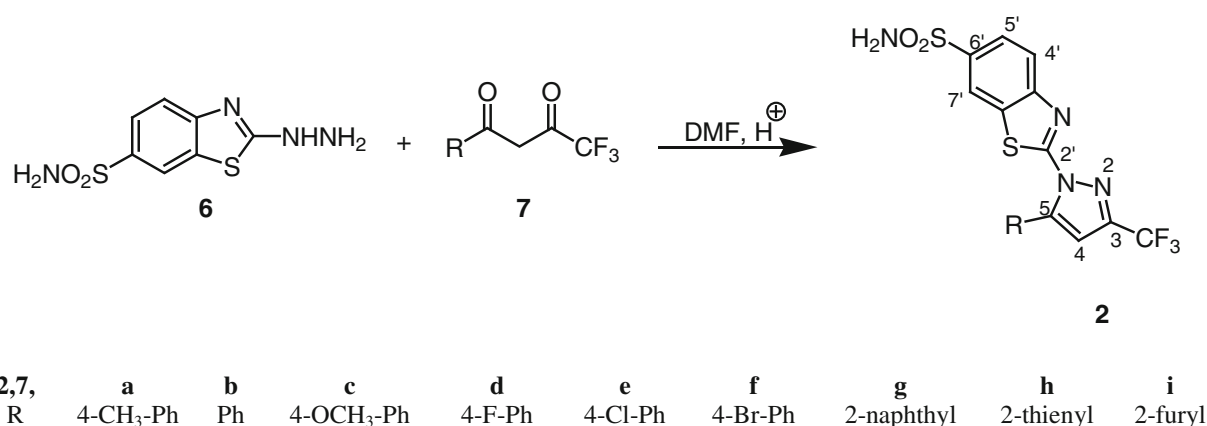


**Scheme 2** Attempted synthesis of target pyrazoles **2** in ethanol under acidic conditions

concentrated HCl was refluxed on water bath for 3 h following the procedure of Penning *et al.* (1997) for the synthesis of celecoxib. However, NMR of the isolated solid indicated a mixture of compounds presumably containing hydroxypyrazoline and pyrazole. Considering that the hydroxypyrazoline did not dehydrate completely under the reaction conditions used, the ethanolic solution of isolated mixture was refluxed in the presence of acetic acid and concentrated H<sub>2</sub>SO<sub>4</sub> to force dehydration (Singh *et al.*, 1997). After achieving the dehydration completely the reaction mixture was reduced to one-third of its original volume and allowed to cool to obtain a solid material which was characterized as **8** on the basis of its spectral data in 45% yield. <sup>19</sup>F NMR and <sup>13</sup>C NMR spectroscopy had been used as an elegant tool in the past to study the position of CF<sub>3</sub> on the pyrazole ring so as to distinguish between the regioisomeric pyrazole derivatives (Singh *et al.*, 1997, 1999, 2006; Song and Zhu, 2001). <sup>19</sup>F NMR spectrum of isolated product displayed a singlet at  $\delta -59.0$  which is characteristic for CF<sub>3</sub> located at C<sub>5</sub> of pyrazole ring (Singh *et al.*, 1997, 1999, 2006; Song and Zhu, 2001). <sup>13</sup>C NMR spectrum gave further credence to our assignment to the structure of the product as **8** by displaying a quartet due to the carbon bearing CF<sub>3</sub> group at  $\delta 132.5$  ( $^2J_{\text{CF}} = 41.8$  Hz) which is in the characteristic region for the C<sub>5</sub>-carbon of pyrazole ring bearing CF<sub>3</sub> group (Singh *et al.*, 1997, 1999, 2006; Song and Zhu, 2001). Low yield and isolation of unwanted isomer forced us to further investigate the reaction. In our next attempt, ethanolic solution of hydrazine **6** and  $\beta$ -diketone **7a** was refluxed for 12 h in the presence of concentrated H<sub>2</sub>SO<sub>4</sub>. On completion of reaction, solvents were removed, and the resulting crude was purified by using silica gel column chromatography to isolate both regioisomeric pyrazoles i.e., 1,3-diarylpyrazole (**8**) as the major product (60%) and the preferred 1,5-diarylpyrazole (**2a**) as minor product (11%). The structure of regioisomer **2a** was assigned on the basis of <sup>19</sup>F NMR and <sup>13</sup>C NMR spectroscopy. A signal at  $\delta -61.5$  in <sup>19</sup>F NMR spectrum and at  $\delta 144.4$  ( $^2J_{\text{CF}} = 38.4$  Hz) in <sup>13</sup>C NMR spectrum of **2a** indicate that the CF<sub>3</sub> is attached at C<sub>3</sub> of pyrazole ring (Singh *et al.*, 1997, 1999, 2006; Song and Zhu, 2001). This failure prompted us to search for appropriate conditions to synthesize **2** as major or exclusive product. We observed that

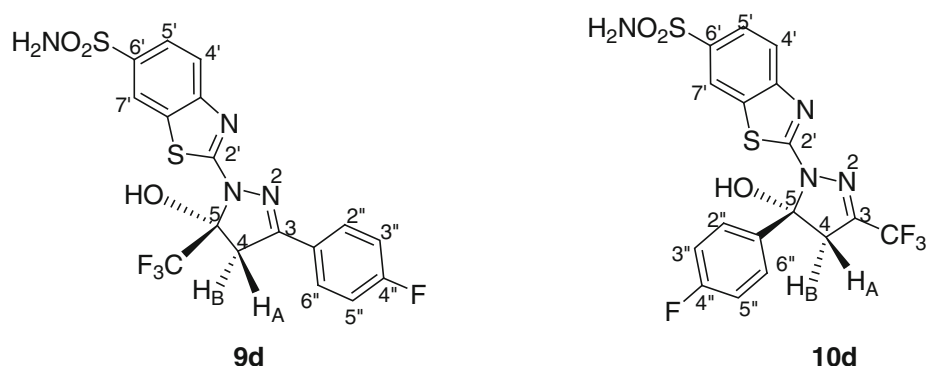
the solubility of our starting 2-hydrazinobenzothiazole **6** in ethanol was so poor that 100 ml of ethanol is required to dissolve only 500 mg of the hydrazine. This observation led us to try various other polar solvents. The solubility of our hydrazine was very poor in 1,4-dioxane, methanol, acetone, as well as acetonitrile, but the hydrazine **6** was reasonably soluble in DMF. Using DMF as the reaction solvent and following the procedure of Gosselin *et al.* (2006), we obtained the preferred 1,5-diarylpyrazole **2a** in 62% yield, and no 1,3-diarylpyrazole was obtained (Scheme 3). Although it is difficult to comment on the reasons for achieving regioselectivity in DMF, it can be ascribed to higher polarity of DMF. A proper investigation into the role of solvent polarity versus regioselectivity of the reaction could not be undertaken owing to the poor solubility of the starting hydrazine in other polar solvents. The other derivatives (**2b–i**) were synthesized in moderate-to-good yields following the same procedure.

Interestingly, in the case of reaction of hydrazine **6** with 4,4,4-trifluoro-1-(4-fluorophenyl)-1,3-butanedione (**7d**), a more polar product was also isolated, besides the preferred pyrazole **2d** (55%), which was assumed to be hydroxypyrazoline **9d** or **10d** (Fig. 1). We were able to fully assign the structure of this more polar product as **9d** on the basis of a rigorous spectral analysis. The IR spectrum of **9d** displayed an absorption band at 3,574 cm<sup>-1</sup> indicating the presence of O–H besides characteristic absorption bands at 3,371 and 3,271 cm<sup>-1</sup> (N–H stretch), and 1,319 and 1,157 cm<sup>-1</sup> (SO<sub>2</sub> stretch). The <sup>1</sup>H NMR spectrum of **9d** displayed a typical AB system of two sets of doublets of one proton each at  $\delta 3.70$  and  $\delta 4.12$  with a coupling constant of 19.2 Hz. This particular pattern is expected from the two methylene protons (CH<sub>A</sub>H<sub>B</sub>) at position-4 of 5-hydroxypyrazolines (Singh *et al.*, 1997). Compound **9d** also exhibited exchangeable signals at  $\sim \delta 7.40$  (NH<sub>2</sub>) and 8.39 (OH) indicating the presence of the NH<sub>2</sub> (SO<sub>2</sub>NH<sub>2</sub>) and OH protons. Further support for the structure of **9d** was provided by <sup>13</sup>C NMR spectrum, which exhibited signals at  $\delta 45.67$ , 93.45 (as a quartet,  $^2J_{\text{CF}} = 33.4$  Hz), and 154.7 ppm corresponding to carbons C<sub>4</sub>, C<sub>5</sub>, and C<sub>3</sub>, respectively. Appearance of a fluorine-coupled quartet at  $\delta 93.45$  is possible only for structure



**Scheme 3** Synthesis of target pyrazoles **2** in DMF under acidic conditions

**Fig. 1** Proposed structure of more polar product **9d** or **10d**



**9d** as it confirms the presence of CF<sub>3</sub> group at C<sub>5</sub> of 5-hydroxypyrazoline in conformity with literature reports where it has been unambiguously established that a structure like **10d** would show a quartet for C<sub>3</sub> around  $\delta$  140–142 (Singh *et al.*, 1997, 1999; Song and Zhu, 2001; Kumar *et al.*, 2006; Aggarwal *et al.*, 2009). Finally, the <sup>19</sup>F NMR spectrum gave further credence to structure **9d** as it displayed a signal at  $\delta$  –76.8, which is typical for a C<sub>5</sub>–CF<sub>3</sub> of 5-hydroxypyrazoline rather than a C<sub>3</sub>–CF<sub>3</sub> which should have appeared at  $\sim \delta$  –67 (Singh *et al.*, 1997, 1999; Song and Zhu, 2001; Kumar *et al.*, 2006; Aggarwal *et al.*, 2009).

## Biological evaluation

### *In vivo* AI activity

All the newly synthesized compounds **2a–i** and **8** were evaluated for their *in vivo* AI activity by carrageenan-induced rat paw edema method (Winter *et al.*, 1962). The protocol of animal experiments has been approved by the Institutional Animal Ethics Committee. Each test compound was dosed orally (50 mg/kg body weight) 30 min before induction of inflammation by carrageenan injection. Indomethacin was used as a reference AI drug at a dose of

10 mg/kg, i.p. The AI activity was then calculated at hourly intervals 1–4 h after induction, and the results are presented in Table 1 as the mean paw volume (ml) as well as the percentage AI activity (AI%).

Among ten compounds (**2a–i** and **8**) tested, five compounds (**2c–f** and **2i**) showed consistently good AI activity ( $\geq 60\%$  inhibition) 3 h after the carrageenan injection compared to that of the standard drug indomethacin (78%), whereas the remaining compounds have shown moderate activity with 49–56% inhibition after 3 h. However, none of the compound showed appreciable AI activity 4 h after the carrageenan injection. All the compounds containing a halogen substituent (**2d–f**) showed better activity as compared to non-halogen-containing compounds. The best compound **2d** in terms of AI activity after 3 h contains a fluoro (F) substituent at position-4 of the phenyl ring that is attached to the C-5 of the pyrazole moiety. Compound **2c** containing a methoxy substituent also showed good AI activity (60% inhibition) after 3 h. These results are in accordance with our earlier observations (Sharma and Sawhney, 1997; Sharma *et al.*, 1998) that the compounds with halogen and methoxy substituents show higher activity. Loss of AI activity after 4 h suggests that these compounds get easily metabolized in the system. The

**Table 1** In vivo AI of compounds **2a–i**

Compound <sup>a</sup>	Volume of edema (ml) <sup>b</sup> and %AI <sup>c</sup>			
	1 h	2 h	3 h	4 h
<b>Control</b>	0.68 ± 0.14	0.96 ± 0.02	1.86 ± 0.03	1.95 ± 0.02
<b>Indomethacin</b>	0.20 ± 0.01** (70) <sup>c</sup>	0.21 ± 0.02** (78)	0.40 ± 0.03** (78)	0.49 ± 0.02** (75)
<b>2a</b>	0.44 ± 0.07 (35)	0.60 ± 0.14 (38)	0.81 ± 0.08** (56)	0.94 ± 0.06** (52)
<b>2b</b>	0.46 ± 0.06 (32)	0.50 ± 0.02* (48)	0.85 ± 0.13** (54)	1.61 ± 0.17 (17)
<b>2c</b>	0.39 ± 0.05 (42)	0.66 ± 0.03 (31)	0.75 ± 0.07** (60)	0.91 ± 0.04** (53)
<b>2d</b>	0.31 ± 0.07* (54)	0.49 ± 0.15* (48)	0.66 ± 0.02** (64)	0.96 ± 0.20** (50)
<b>2e</b>	0.38 ± 0.04 (44)	0.56 ± 0.17 (42)	0.73 ± 0.06** (61)	1.13 ± 0.19** (42)
<b>2f</b>	0.37 ± 0.05 (45)	0.42 ± 0.09* (56)	0.74 ± 0.02** (60)	1.11 ± 0.24** (43)
<b>2g</b>	0.47 ± 0.11 (30)	0.70 ± 0.04 (27)	0.87 ± 0.16** (53)	1.58 ± 0.03 (20)
<b>2h</b>	0.64 ± 0.13 (05)	0.71 ± 0.2 (26)	0.95 ± 0.15** (49)	1.65 ± 0.13 (15)
<b>2i</b>	0.48 ± 0.08 (27)	0.52 ± 0.03 (46)	0.73 ± 0.06** (61)	0.88 ± 0.16** (54)

\* Significantly different compared to respective control values,  $P < 0.05$

\*\* Significantly different compared to respective control values,  $P < 0.01$

<sup>a</sup> Dose levels: test compounds (50 mg/kg body wt.), indomethacin (10 mg/kg body wt.)

<sup>b</sup> Values are expressed as mean ± SEM and analyzed by ANOVA

<sup>c</sup> Values in parentheses (percentage AI activity, AI%)

pyrazole **8** with 1,3-diaryl relationship failed to show any appreciable AI activity. 1,5-diarylpyrazole **2a**, the closest relative of celecoxib failed to show the expected AI potential. A plausible reason for this might be the bulky nature of the benzothiazole moiety at N-1 position of pyrazole which prevents it from binding in the secondary pocket of COX-2.

## Conclusion

Ten new compounds including nine 1,5-diarylpyrazoles (**2a–i**) and one 1,3-diarylpyrazole (**8**) were synthesized and evaluated for their in vivo AI activity. Five (**2c–f**, **2i**) of the nine 1,5-diarylpyrazoles (**2a–i**) showed moderate AI activity ( $\geq 60\%$  inhibition) 3 h after the carrageenan injection when compared with the standard drug indomethacin with 78% inhibition. 1,3-diarylpyrazole **8** failed to show any appreciable AI activity. It can be concluded from the present study that increasing the bulkiness at N-1

position is detrimental to the AI properties of 1,5-diarylpyrazole class.

## Experimental protocols

Melting points were determined in open capillaries in electrical apparatus and are uncorrected. IR spectra were recorded on a Buck Scientific IR M500 instrument. The <sup>1</sup>H NMR, <sup>13</sup>C NMR, and <sup>19</sup>F NMR spectra were recorded on a Bruker instrument at 300, 75.5 and 282.4 MHz, respectively. Numbering of carbons and protons in the spectral assignment of newly synthesized compounds is as mentioned in Schemes 2 and 3. However, the aromatic protons of the 'R' group in compounds **2a–i** and **9d** are indicated by double primes. The  $\delta$  values are given in ppm relative to tetramethylsilane as internal standard (for <sup>1</sup>H and <sup>13</sup>C NMR). Mass spectra (direct analysis in real time, DART-MS) were recorded on a JEOL-AccuTOF JMS-T100LC Mass spectrometer having a DART source in ES<sup>+</sup> mode.

Exchangeable (ex) protons were detected by disappearance of peaks upon D<sub>2</sub>O addition. The purity of the compounds was checked by <sup>1</sup>H NMR and thin layer chromatography (TLC). Iodine or UV lamp was used as a visualizing agent for TLC. All the newly synthesized compounds (**2a–2i**, **6**, **8**) were subjected to microanalysis and gave satisfactory analytical results (within ±0.4% of the calculated values).

#### Synthesis of 2-hydrazino-1,3-benzothiazole-6-sulfonamide (**6**)

The novel hydrazine (**6**) was prepared in three steps from sulfanilamide as per the procedure given below:

#### 4-[(Aminocarbothioyl)amino]benzenesulfonamide (**4**)

Sulfanilamide (34.4 g, 200.0 mmol) was dissolved in a mixture of conc. HCl (18 ml) and water (50 ml) by warming. The solution was cooled, and ammonium thiocyanate (15.2 g, 200.0 mmol) was added. The mixture was heated on water bath for 3 h and then cooled. The separated product was filtered, washed with water, and crystallized from aqueous ethanol. M.p. 190–191°C (Lit. m.p. 206°C) (Shingare and Ingole, 1977), yield 42.9 g (93%).

#### 2-Amino-1,3-benzothiazole-6-sulfonamide (**5**)

To a suspension of 4-aminosulfonylphenylthiourea (**4**, 29.0 g, 125.5 mmol) in chloroform (100 ml), bromine (10 ml) in chloroform (100 ml) was added dropwise for 1 h, and the resultant mixture was refluxed for 15 min. Chloroform (100 ml) was distilled off and the semi-solid product thus obtained was treated with sulfurous acid till the brown color was discharged. The solution was refluxed and treated with aqueous ammonia. The precipitated solid was filtered, washed with water, dried, and crystallized from ethanol. M.p. 268–270°C (Lit. m.p. 277°C) (Kaufmann and Buckmann, 1941), yield 19.8 g (69%).

#### 2-Hydrazino-1,3-benzothiazole-6-sulfonamide (**6**)

To hydrazine hydrate (10 g, 200.0 mmol) was added conc. HCl (10 ml) dropwise with stirring at 5–10°C. Ethylene glycol (40 ml) was then added followed by 2-Amino-1,3-benzothiazole-6-sulfonamide (**5**, 11.5 g, 50.2 mmol) in portions to the above reaction mixture and the resulting mixture was heated under reflux for 4 h. A fine crystalline solid, which separated out on cooling, was filtered, washed with water, and crystallized from ethanol. M.p. 250–253°C, yield 8.86 g (83%); IR (KBr) cm<sup>−1</sup>: 3,346 and 3,254 (N–H stretch), 1,552 (N–H bend); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.08 (d, 1H, *J* = 1.80 Hz, Ar), 7.64 (dd, 1H,

*J* = 1.80, 8.24 Hz, Ar), 7.57 (s, 2H, NH<sub>2</sub>), 7.36 (d, 1H, *J* = 8.24 Hz, Ar), 7.05 (s, 1H, NH), 6.70 (s, 2H, NH<sub>2</sub>); *m/z* 245 ([M + H]<sup>+</sup>, C<sub>7</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> H<sup>+</sup> calcd. 245).

Attempted synthesis of target pyrazoles in ethanol under acidic conditions

2-Hydrazino-1,3-benzothiazole-6-sulfonamide (**6**, 500 mg, 2.0 mmol) was dissolved in ethanol (100 ml) by warming, and 1-(4-methylphenyl)-4,4,4-trifluoromethyl-1,3-butanedione (**7a**, 510 mg, 2.2 mmol) was added to it while stirring. To the resulting mixture, a few drops of concentrated sulfuric acid were added and the contents were refluxed for 12 h whereupon solvents were evaporated off to afford the crude which was purified by silica gel chromatography (0–20% EtOAc in pet ether) to afford **8** (0.54 g, 60%) and **2a** (100 mg, 11%).

#### 2-[3-(4-Methylphenyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl]-1,3-benzothiazole-6-sulfonamide (**8**)

M.p. 284–285°C, yield 60%; IR (KBr) cm<sup>−1</sup>: 3,370 and 3,248 (N–H stretch), 1,541 (N–H bend), 1,316 and 1,150 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.67 (d, 1H, *J* = 1.50 Hz, H-7'), 8.10 (d, 1H, *J* = 8.70 Hz, H-4'), 7.99 (s, 1H, pyrazole H-4), 7.97 (dd, 1H, *J* = 1.50, 8.70 Hz, H-5'), 7.91 (d, 2H, *J* = 8.10 Hz, H-2'', H-6''), 7.51 (s, ex, 2H, SO<sub>2</sub>NH<sub>2</sub>), 7.35 (d, 2H, *J* = 8.10 Hz, H-3'', H-5''), 2.37 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (75.5 MHz, DMSO-*d*<sub>6</sub>): δ 161.4, 153.5, 152.1, 141.0, 139.8, 133.0, 132.5 (q, <sup>2</sup>*J*<sub>CF</sub> = 41.8 Hz, C-5), 129.7, 126.7, 126.1, 124.6, 123.0, 120.9, 119.1 (q, <sup>1</sup>*J*<sub>CF</sub> = 264.6 Hz, C<sub>5</sub>–CF<sub>3</sub>), 111.9, 20.9 (CH<sub>3</sub>); <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 282.4 MHz) −δ 59.0 (C<sub>5</sub>–CF<sub>3</sub>); *m/z* 439 ([M + H]<sup>+</sup>, C<sub>18</sub>H<sub>13</sub>F<sub>3</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> H<sup>+</sup> calcd. 439).

#### 2-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-1,3-benzothiazole-6-sulfonamide (**2a**)

M.p. 238–240°C, yield 11%; IR (KBr) cm<sup>−1</sup>: 3,371 and 3,271 (N–H stretch), 1,535 (N–H bend), 1,319 and 1,157 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.66 (d, 1H, *J* = 1.50 Hz, H-7'), 7.94 (dd, 1H, *J* = 1.80, 8.70 Hz, H-5'), 7.88 (d, 1H, *J* = 8.70 Hz, H-4'), 7.52 (d, 2H, *J* = 8.40 Hz, H-2'', H-6''), 7.49 (s, ex, 2H, SO<sub>2</sub>NH<sub>2</sub>), 7.28–7.30 (m, 3H, pyrazole H-4, H-3'', H-5''), 2.35 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (75.5 MHz, DMSO-*d*<sub>6</sub>): δ 162.4, 151.9, 147.4, 144.4 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.4 Hz, C-3), 141.6, 139.9, 133.9, 129.8, 129.0, 125.2, 124.8, 123.6, 121.1, 120.9 (q, <sup>1</sup>*J*<sub>CF</sub> = 265.8 Hz, C<sub>3</sub>–CF<sub>3</sub>), 109.0, 21.2 (CH<sub>3</sub>); <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 282.4 MHz) −δ 61.5 (C<sub>3</sub>–CF<sub>3</sub>); *m/z* 439 ([M + H]<sup>+</sup>, C<sub>18</sub>H<sub>13</sub>F<sub>3</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> H<sup>+</sup> calcd. 439).



Representative procedure for the synthesis of target pyrazoles in DMF under acidic conditions

To a solution of 2-Hydrazino-1,3-benzothiazole-6-sulfonamide (**6**, 500 mg, 2.0 mmol) and 1-(4-methylphenyl)-4,4,4-trifluoromethyl-1,3-butanedione (**7a**, 510 mg, 2.2 mmol) in DMF (15 ml) was added concentrated hydrochloric acid (1 ml). The reaction mixture was stirred at 50°C for 3 h, whereupon few drops of concentrated sulfuric acid were added, and the content was stirred again for 6 h at 90°C. The reaction mixture was allowed to cool and poured into ice-cold water to obtain a solid which was filtered and dried to afford crude material. The crude material was purified by silica gel chromatography (0–20% EtOAc in pet ether) to afford **2a** (560 mg, 62%).

2-[5-Phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-1,3-benzothiazole-6-sulfonamide (**2b**)

M.p. 234–236°C, yield 64%; IR (KBr)  $\text{cm}^{-1}$ : 3,370 and 3,268 (N–H stretch), 1,535 (N–H bend), 1,317 and 1,155 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.67 (d, 1H,  $J = 1.50$  Hz, H-7'), 7.91 (dd, 1H,  $J = 1.50$ , 8.70 Hz, H-5'), 7.83 (d, 1H,  $J = 8.70$  Hz, H-4'), 7.62–65 (m, 2H, H-2'', H-6''), 7.45–7.53 (m, 5H,  $\text{SO}_2\text{NH}_2$ , H-3'', H-4'', H-5''), 7.36 (s, 1H, pyrazole H-4);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  162.1, 152.1, 147.4, 144.0 (q,  $^2J_{\text{CF}} = 38.5$  Hz, C-3), 141.7, 134.0, 130.3, 130.1, 129.6, 128.6, 128.4, 126.6, 124.9, 123.7, 121.3, 121.0 (q,  $^1J_{\text{CF}} = 269.5$  Hz,  $\text{C}_3\text{-CF}_3$ ), 111.9;  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ , 282.4 MHz)  $-\delta$  61.5 ( $\text{C}_3\text{-CF}_3$ );  $m/z$  425 ( $[\text{M} + \text{H}]^+$ ,  $\text{C}_{17}\text{H}_{11}\text{F}_3\text{N}_4\text{O}_2\text{S}_2 \text{H}^+$  calcd. 425).

2-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-1,3-benzothiazole-6-sulfonamide (**2c**)

M.p. 236–238°C, yield 62%; IR (KBr)  $\text{cm}^{-1}$ : 3,394 and 3,286 (N–H stretch), 1,535 (N–H bend), 1,342 and 1,134 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.66 (d, 1H,  $J = 1.50$  Hz, H-7'), 7.88–7.91 (m, 2H, H-4', H-5'), 7.58 (d, 2H,  $J = 8.70$  Hz, H-2'', H-6''), 7.50 (s, ex, 2H,  $\text{SO}_2\text{NH}_2$ , Ar), 7.27 (s, 1H, pyrazole H-4), 7.03 (d, 2H,  $J = 8.70$  Hz, H-3'', H-5''), 3.83 (s, 3H,  $\text{OCH}_3$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  162.7, 160.9, 152.2, 147.4, 144.5 (q,  $^2J_{\text{CF}} = 37.8$  Hz, C-3), 141.7, 134.0, 131.7, 124.9, 123.7, 121.2, 120.4, 121.0 (q,  $^1J_{\text{CF}} = 271.8$  Hz,  $\text{C}_3\text{-CF}_3$ ), 114.0, 108.9, 55.7 ( $\text{CH}_3$ );  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ , 282.4 MHz)  $-\delta$  61.5 ( $\text{C}_3\text{-CF}_3$ );  $m/z$  453 ( $[\text{M} - \text{H}]^+$ ,  $\text{C}_{18}\text{H}_{13}\text{F}_3\text{N}_4\text{O}_3\text{S}_2 \text{H}^+$  calcd. 453).

2-[5-(4-Fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-1,3-benzothiazole-6-sulfonamide (**2d**)

M.p. 234–236°C, yield 55%; IR (KBr)  $\text{cm}^{-1}$ : 3,364 and 3,271 (N–H stretch), 1,535 (N–H bend), 1,319 and 1,157 (s,  $\text{SO}_2$

stretch);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.66 (d, 1H,  $J = 1.50$  Hz, H-7'), 7.84–7.92 (m, 2H, H-4', H-5'), 7.70–75 (m, 2H, H-2'', H-6''), 7.48 (s, ex, 2H,  $\text{SO}_2\text{NH}_2$ ), 7.37 (s, 1H, pyrazole H-4), 7.34 (m, 2H, H-3'', H-5'');  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  170.8, 163.4 (d,  $^1J_{\text{CF}} = 245.2$  Hz), 162.6, 152.1, 146.3, 144.5 (q,  $^2J_{\text{CF}} = 38.2$  Hz, C-3), 141.7, 133.8, 132.7 (d,  $^3J_{\text{CF}} = 9.0$  Hz), 124.9, 123.7, 121.2, 120.9 (q,  $^1J_{\text{CF}} = 269.5$  Hz,  $\text{C}_3\text{-CF}_3$ ), 115.6 (d,  $^2J_{\text{CF}} = 21.7$  Hz), 109.6;  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ , 282.4 MHz)  $-\delta$  61.5 ( $\text{C}_3\text{-CF}_3$ );  $m/z$  441 ( $[\text{M} - \text{H}]^+$ ,  $\text{C}_{17}\text{H}_{10}\text{F}_4\text{N}_4\text{O}_2\text{S}_2 \text{H}^+$  calcd. 441).

2-[3-(4-Fluorophenyl)-5-hydroxy-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl]-1,3-benzothiazole-6-sulfonamide (**9d**)

M.p. 254–256°C, yield 6%; IR (KBr)  $\text{cm}^{-1}$ : 3,573 (O–H), 3,364 and 3,271 (N–H stretch), 1,535 (N–H bend), 1,319 and 1,157 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.63 (d, 1H,  $J = 1.50$  Hz, H-7'), 8.39 (bs, 1H, 5-OH, exchangeable), 7.90–7.93 (m, 2H, H-2'', H-6''), 7.80–7.81 (m, 2H, H-3'', H-5''), 7.36–7.42 (m, 4H (exchangeable 2H),  $\text{SO}_2\text{NH}_2$ , H-4', H-5'), 4.12 ( $J_{\text{H}_A\text{-H}_B} = 19.2$  Hz, 4-H<sub>A</sub>), 3.70 (d, 1H,  $J_{\text{H}_A\text{-H}_B} = 19.2$  Hz,  $^4J_{\text{H}_B\text{-CF}_3} = 1.2$  Hz, 4-H<sub>B</sub>);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  164.93, 164.0 (d,  $^1J_{\text{CF}} = 249.1$  Hz), 154.7, 152.8, 138.6, 131.9, 129.6 (d,  $^3J_{\text{CF}} = 9.0$  Hz), 126.83, 126.7, 122.5 (q,  $^1J_{\text{CF}} = 271.8$  Hz,  $\text{C}_5\text{-CF}_3$ ), 120.0, 116.6 (d,  $^2J_{\text{CF}} = 21.7$  Hz), 93.5 (q,  $^2J_{\text{CF}} = 33.9$  Hz, C-5), 45.7 (C-4);  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ , 282.4 MHz)  $-\delta$  76.8 ( $\text{C}_3\text{-CF}_3$ ), 109(F);  $m/z$  461 ( $[\text{M} + \text{H}]^+$ ,  $\text{C}_{17}\text{H}_{12}\text{F}_4\text{N}_4\text{O}_3\text{S}_2 \text{H}^+$  calcd. 461).

2-[5-(4-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-1,3-benzothiazole-6-sulfonamide (**2e**)

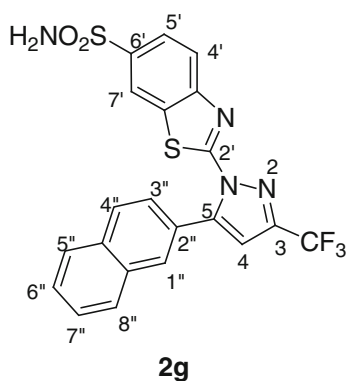
M.p. 236–238°C, yield 60%; IR (KBr)  $\text{cm}^{-1}$ : 3,365 and 3,271 (N–H stretch), 1,535 (N–H bend), 1,319 and 1,137 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.66 (d, 1H,  $J = 1.50$  Hz, H-7'), 7.88–7.90 (m, 2H, H-4', H-5'), 7.70 (d, 2H,  $J = 8.10$  Hz, H-2'', H-6''), 7.57 (d, 2H,  $J = 8.10$  Hz, H-3'', H-5''), 7.49 (s, ex, 2H,  $\text{SO}_2\text{NH}_2$ ), 7.40 (s, 1H, pyrazole H-4);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  162.6, 152.1, 146.1, 144.5 (q,  $^2J_{\text{CF}} = 38.2$  Hz, C-3), 141.7, 135.2, 133.8, 132.1, 129.7, 128.6, 128.4, 127.3, 124.9, 123.7, 121.2, 120.9 (q,  $^1J_{\text{CF}} = 269.5$  Hz,  $\text{C}_3\text{-CF}_3$ ), 109.9;  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ , 282.4 MHz)  $-\delta$  61.5 ( $\text{C}_3\text{-CF}_3$ );  $m/z$  458 ( $[\text{M} - \text{H}]^+$ ,  $\text{C}_{17}\text{H}_{10}\text{ClF}_3\text{N}_4\text{O}_2\text{S}_2 \text{H}^+$  calcd. 458).

2-[5-(4-Bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-1,3-benzothiazole-6-sulfonamide (**2f**)

M.p. 245–247°C, yield 65%; IR (KBr)  $\text{cm}^{-1}$ : 3,394 and 3,279 (N–H stretch), 1,528 (N–H bend), 1,335 and 1,165 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.65 (d,

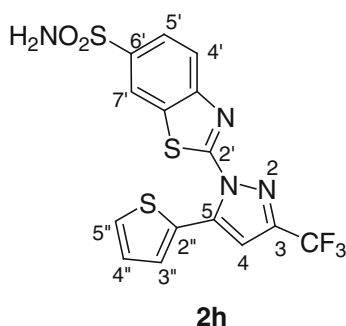
1H,  $J = 1.50$  Hz, H-7'), 7.87–7.91 (m, 2H, H-4', H-5'), 7.70 (d, 2H,  $J = 8.70$  Hz, H-2'', H-6''), 7.62 (d, 2H,  $J = 8.70$  Hz, H-3'', H-5''), 7.49 (s, ex, 2H, SO<sub>2</sub>NH<sub>2</sub>), 7.40 (s, 1H, pyrazole H-4); <sup>13</sup>C NMR (75.5 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  162.6, 152.1, 146.18, 144.5 (q, <sup>2</sup> $J_{CF} = 37.8$  Hz, C-3), 141.7, 133.8, 132.3, 131.5, 127.7, 124.9, 126.3, 123.9, 123.7, 121.2, 120.9 (q, <sup>1</sup> $J_{CF} = 268.5$  Hz, C<sub>3</sub>–CF<sub>3</sub>), 116.0, 109.9; <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 282.4 MHz)  $-\delta$  61.5 (C<sub>3</sub>–CF<sub>3</sub>);  $m/z$  503 ([M + H]<sup>+</sup>, C<sub>17</sub>H<sub>10</sub>BrF<sub>3</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> H<sup>+</sup> calcd. 503).

2-[5-(2-Naphthyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-1,3-benzothiazole-6-sulfonamide (**2g**)



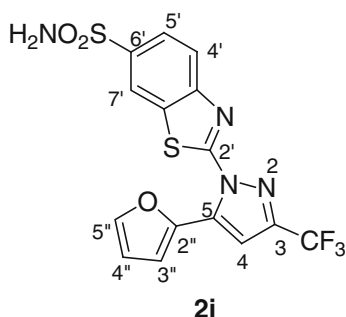
M.p. 238–240, yield 58%; IR (KBr) cm<sup>-1</sup>: 3,394 and 3,280 (N–H stretch), 1,531 (N–H bend), 1,335 and 1,157 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.67 (d, 1H,  $J = 1.50$  Hz, H-7'),  $\delta$  8.27 (s, 1H, H-1''), 7.97–8.02 (m, 3H, H-4'', H-5'', H-8''), 7.87 (dd, 1H,  $J = 1.50, 8.70$  Hz, H-5''), 7.76 (d, 1H,  $J = 8.70$  Hz, H-4'), 7.55–7.70 (m, 3H, H-3'', H-6'', H-7''), 7.50 (s, ex, 2H, SO<sub>2</sub>NH<sub>2</sub>), 7.47 (s, 1H, pyrazole H-4); <sup>13</sup>C NMR (75.5 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  162.7, 152.2, 147.4, 144.7 (q, <sup>2</sup> $J_{CF} = 38.5$  Hz, C-3), 141.7, 133.9, 133.65, 132.8, 129.8, 128.85, 128.2, 127.8, 127.7, 127.5, 127.2, 126.0, 124.9, 123.7, 122.8, 121.0 (q, <sup>1</sup> $J_{CF} = 271.8$  Hz, C<sub>3</sub>–CF<sub>3</sub>), 109.9; <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 282.4 MHz)  $-\delta$  61.5 (C<sub>3</sub>–CF<sub>3</sub>);  $m/z$  475 ([M + H]<sup>+</sup>, C<sub>21</sub>H<sub>13</sub>F<sub>3</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> H<sup>+</sup> calcd. 475).

2-[5-(2-Thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-1,3-benzothiazole-6-sulfonamide (**2h**)



M.p. 223–225°C, yield 64%; IR (KBr) cm<sup>-1</sup>: 3,393 and 3,276 (N–H stretch), 1,525 (N–H bend), 1,339 and 1,163 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.69 (d, 1H,  $J = 1.50$  Hz, H-5'), 8.07 (d, 1H,  $J = 8.70$  Hz, H-4'), 7.97 (dd, 1H,  $J = 1.50, 8.70$  Hz, H-5'), 7.84 (dd, 1H,  $J = 0.90$  Hz, 4.80 Hz, H-3''), 7.74 (dd, 1H,  $J = 0.90, 3.90$  Hz, H-5''), 7.52 (s, 2H, SO<sub>2</sub>NH<sub>2</sub>), 7.50 (s, 1H, pyrazole H-4), 7.22 (dd, 1H,  $J = 3.90, 4.80$  Hz, H-4''); <sup>13</sup>C NMR (75.5 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  161.9, 151.5, 144.2 (q, <sup>2</sup> $J_{CF} = 38.1$  Hz, C-3), 141.5, 140.7, 133.8, 131.8, 130.2, 127.5, 120.4 (q, <sup>1</sup> $J_{CF} = 269.7$  Hz, CF<sub>3</sub>), 124.6, 123.8, 123.4, 121.0, 109.1; <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 282.4 MHz):  $\delta$  –62.3 (C<sub>3</sub>–CF<sub>3</sub>); <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 282.4 MHz)  $-\delta$  61.5 (C<sub>3</sub>–CF<sub>3</sub>);  $m/z$  431 ([M + H]<sup>+</sup>, C<sub>15</sub>H<sub>9</sub>F<sub>3</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> H<sup>+</sup> calcd. 431).

2-[5-(2-Furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-1,3-benzothiazole-6-sulfonamide (**2i**)



M.p. 237–239, yield 57%; IR (KBr) cm<sup>-1</sup>: 3,394 and 3,278 (N–H stretch), 1,535 (N–H bend), 1,342 and 1,128 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.70 (d, 1H,  $J = 1.80$  Hz, H-7'), 8.18 (d, 1H,  $J = 8.70$  Hz, H-4'), 7.99 (dd, 1H,  $J = 1.80, 8.70$  Hz, H-5'), 7.97 (dd, 1H,  $J = 0.90, 3.60$  Hz, H-3''), 7.66 (dd, 1H,  $J = 0.90, 1.8$  Hz, H-5''), 7.53 (s, ex, 2H, SO<sub>2</sub>NH<sub>2</sub>, Ar), 7.50 (s, 1H, pyrazole H-4), 6.76 (dd, 1H,  $J = 1.8, 3.60$  Hz, H-4''); <sup>13</sup>C NMR (75.5 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  162.7, 152.2, 145.9, 144.75 (q, <sup>2</sup> $J_{CF} = 38.25$  Hz, C-3), 141.9, 141.6, 137.8, 133.9, 125.1, 123.9, 121.4, 120.9 (q, <sup>1</sup> $J_{CF} = 267.8$  Hz, C<sub>3</sub>–CF<sub>3</sub>), 115.6, 112.7, 107.8; <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 282.4 MHz)  $-\delta$  61.5 (C<sub>3</sub>–CF<sub>3</sub>);  $m/z$  415 ([M + H]<sup>+</sup>, C<sub>15</sub>H<sub>9</sub>F<sub>3</sub>N<sub>4</sub>O<sub>3</sub>S<sub>2</sub> H<sup>+</sup> calcd. 415).

## Biological evaluation

### In vivo AI activity

Male Wistar albino rats weighing 200–250 g were used throughout the study. They were kept in the animal house



under standard conditions of light and temperature with free access to food and water. Food was withdrawn 12 h before and during experimental hours. The animals were randomly divided into groups each consisting of six rats. One group of six rats was kept as control and received tween 80 (95:5). Another group received the standard drug indomethacin at a dose of 10 mg/kg body weight ip. Other groups of rats were administered the test compounds at a dose of 50 mg/kg body weight orally. A mark was made on the left hind paw just beyond the tibiotarsal articulation, so that every time the paw was dipped up to the fixed mark, a constant paw volume was ensured. Paw volumes were measured using a plethysmometer (model 7140, Ugo Basile, Italy). Thirty minutes after administration of test compounds and standard drug, 0.1 ml of 1% w/v of carrageenan suspension in normal saline was injected into sub planter region of the left hind paw of all the animals. The initial paw volume was measured within 30 s of the injection and remeasured again 1, 2, 3, and 4 h after administration of carrageenan. The edema was expressed as an increase in the volume of paw and the percentage of edema inhibition for each rat and each group was obtained as follows:

The edema was expressed as an increase in the volume of paw, and the percentage of edema inhibition for each rat and each group was obtained as follows:

$$\% \text{ Inhibition} = (V_t - V_0)_{\text{control}} - (V_t - V_0)_{\text{tested compound}} / (V_t - V_0)_{\text{control}} \times 100$$

where  $V_t$  is the volume of edema at specific time interval and  $V_0$  is the volume of edema at zero time interval.

**Acknowledgments** This research study was funded by the Defence Research and Development Organization (DRDO), Ministry of Defence, India (Grant no. ERIP/ER/0803739/M/01/1154). The authors thank the faculty of the Sophisticated Analytical Instrument Facility, Central Drug Research Institute, Lucknow, for assistance with Mass spectral facility.

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