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ORIGINAL RESEARCH

Synthesis and pharmacological evaluation of some novel 2-pyrazolines bearing benzenesulfonamide as anti-inflammatory and blood glucose lowering agents

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Abstract A series of novel pyrazolines (**2a–l**) bearing benzenesulfonamide moiety were synthesized by condensing appropriate chalcone (**1a–l**) with 4-hydrazinobenzenesulfonamide hydrochloride. Structure of all novel synthesized compounds was characterized on basis of elemental analysis data and spectral data (IR, ^{1}HNMR, MS). Compounds (**2a–l**) were screened for in vivo anti-inflammatory action in carrageenan-induced rat paw edema model and blood glucose lowering action in glucose fed hyperglycemic normal rats. Compounds **2a**, **2e**, and **2l** showed significant anti-inflammatory action (more than 75 %) at 5 h and also showed superior gastrointestinal safety profiles as compared to celecoxib. One compound (**2i**) was found to exhibit significant blood glucose lowering activity.

Keywords Pyrazoline · Sulfonamide · Anti-inflammatory · Anti-hyperglyceamic

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain, fever, and inflammation. Conventional NSAIDs act as nonselective inhibitors of cyclooxygenase (COX) enzymes, which catalyze the formation of prostaglandins (PGs) from arachidonic acid. There are at least two mammalian COX isoforms (Xie *et al.*, 1991; Kujubu *et al.*, 1991). COX-2 is induced in response to pro-inflammatory conditions, while COX-1 is constitutive and responsible for the maintenance of physiological homeostasis, such as gastrointestinal integrity and renal function. Traditional NSAIDs such as aspirin, indomethacin, and diclofenac are nonselective inhibitors and are associated with gastric ulceration, bleeding, and renal function suppression (Vane and Botting, 1998). Generally, prostacyclin and thromboxane normally balance each other's opposing effects.

Several selective inhibitors of COX-2 were shown to possess anti-inflammatory activity with little or no gastric side effects (Dannhardt and Kiefer, 2001). By far the greatest amount of research in the COX-2 area has been performed in the preparation and evaluation of carbocyclic or heterocyclic ring system bearing two vicinal aryl moieties. During the last few years a large number of compounds have been developed as potential candidates (Fig. 1). The introduction of COX-2 inhibitors, such as celecoxib, rofecoxib, and valdecoxib in the 1990s was viewed as a milestone triumph over human suffering of pain and inflammation with little or no damage to the gastric mucosa (Flower, 2003). Unfortunately, rofecoxib (Vioxx) was withdrawn from the market in the fall of 2004 after clinical reports of its linkage to elevated risk of cardiac stroke (Abramson and Greenberg, 2008).

Among the highly marketed COX-2 inhibitors that comprise the pyrazole nucleus, celecoxib is the one which is treated as a safe anti-inflammatory and analgesic agent. It is considered as a typical model of the diaryl heterocyclic template that is known to selectively inhibit the COX-2 enzyme. Some other examples of pyrazole derivatives as NSAIDs are mefobutazone, ramifenazone, famprofazone (Reynold, 1993; Amir and Kumar, 2005; Gursoy *et al.*,

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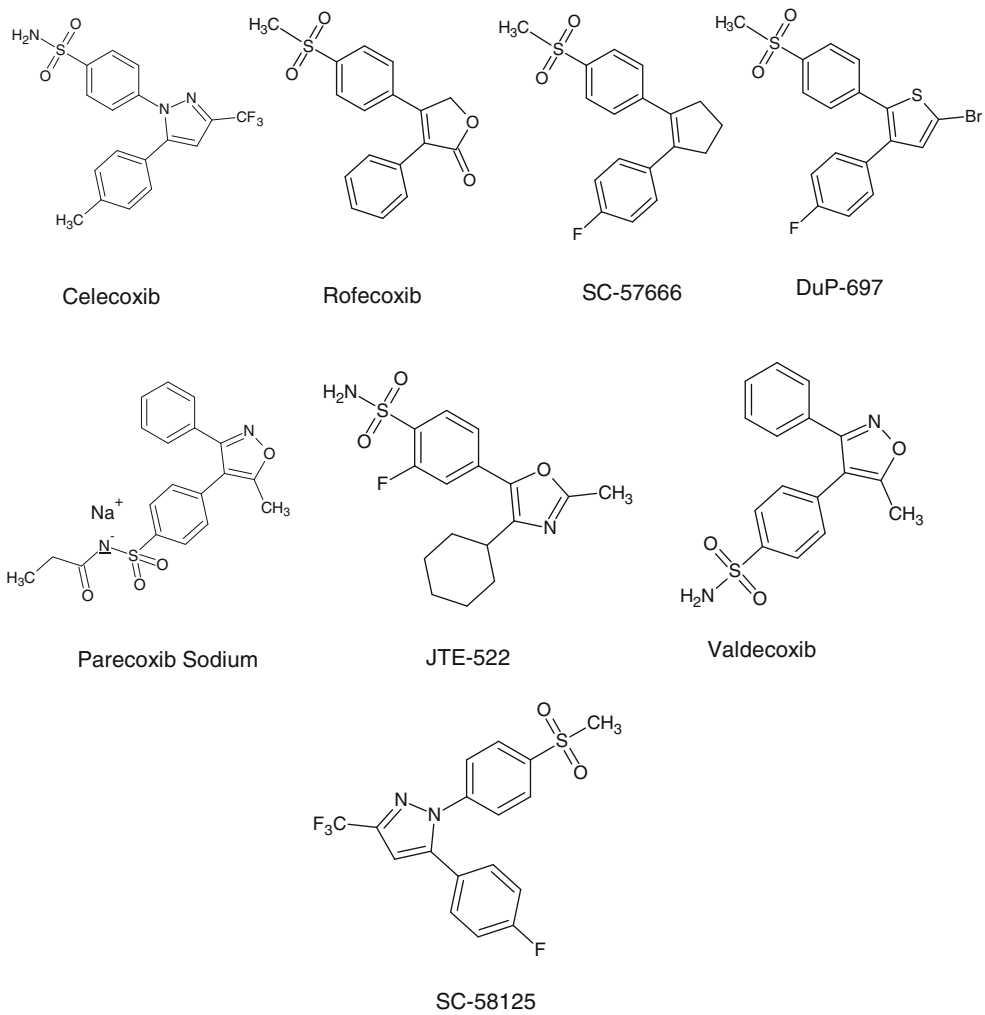

Fig. 1 Some potent COX-inhibitors

2000; Kumar *et al.*, 2003). But due to serious adverse effects such as bone marrow depression (Inman, 1977), water and salt retention and carcinogenesis (Leonard, 1953), the use of pyrazole derivatives is limited. This limitation has led to the investigation of new pyrazole derivatives with more potent activity and less toxicity.

Motivated by aforesaid findings, and pursuing our studies on pyrazoline moiety (Rathish *et al.*, 2009; Bashir *et al.*, 2011). Some novel pyrazoline derivatives were synthesized by replacing pyrazole moiety with a dihydro-pyrazole nucleus linked in C3 and C5 with phenyl group and evaluated for anti-inflammatory activity.

Recently pyrazolines have also been reported as dipeptidyl peptidase-IV (DP-IV) inhibitors (Ahn *et al.*, 2004). Inhibition of DP-IV increases the level of circulating glucagon-like peptidase-1 (GLP-1) and thus, increases insulin secretion (Pospisilik *et al.*, 2002; Sudre *et al.*, 2002) which could ameliorate hyperglycemia in type 2 diabetes. It gave us immense confidence to evaluate the anti-hyperglycemic effect of these synthesized compounds.

Experimental

Melting points were determined by open capillary tubes and are uncorrected. Purity of the compounds was checked on TLC plates (silica gel G) which were visualized by exposing to iodine vapors. Infrared (IR) spectra were recorded (in KBr) on a BIO-RAD FTS-135 spectrophotometer and ^{1}HNMR spectra were recorded on a Bruker Spectrospin DPX 400 MHz spectrometer using deuterated DMSO as solvent and tetramethyl silane (TMS) as an internal standard. Chemical shifts are given in δ (ppm) scale and coupling constants (J values) are expressed in Hz. Mass spectra (MS) were recorded on ESI Q-TOF Water. Elemental analysis was carried out on CHNS Elementar (Vario EL III).

General procedure for the synthesis of chalcones (**1a–l**)

To a cold solution (below 10 °C) of 1-(3-hydroxy-phenyl)-ethanone (0.01 mol) and desired aromatic aldehyde (0.01 mol) in ethanol (20 ml) was added a chilled solution of

sodium hydroxide (10 ml of 30 % solution). The reaction mixture was covered with a layer of petroleum ether (60–80 °C) and left at room temperature for a period of 12 h. It was poured on crushed ice (100 ml) and acidified with concentrated HCl. The product obtained was filtered, washed with water and dried residue was crystallized from chloroform.

General procedure for the preparation of pyrazolines (**2a–l**)

A mixture of appropriate chalcone (**1a–l**) (0.01 mol) and 4-hydrazinobenzenesulfonamide hydrochloride (0.01 mol) in ethanol (95 %) (20–150 ml) was refluxed for 6–12 h. The reaction mixture was concentrated to a small volume and left at room temperature when a solid mass separated out, which were filtered, dried and crystallized from appropriate solvent.

4-[3-(3-Hydroxy-phenyl)-5-phenyl-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2a**)

This compound was obtained as light brown crystals when recrystallized from methanol in 35 % yield, m.p. 141–143 °C, $R_f = 0.51$, (toluene:ethyl acetate:formic acid, 7.5:2:0.5). IR υ_{max} (KBr): 3404 cm^{-1} and 3270 cm^{-1} (NH_2), 1591 cm^{-1} (C=N), 1306 cm^{-1} and 1144 cm^{-1} ($SO_2N<$). ^{1}HNMR (400 MHz, DMSO, δ): 3.13 [1H, dd, $J = 5.6$ Hz, $J = 16.8$ Hz, H-4 *trans* (pyrazoline)], 3.92 [1H, dd, $J = 12.4$ Hz, $J = 17.6$ Hz, H-4 *cis* (pyrazoline)], 5.59 [1H, dd, $J = 4.8$ Hz, $J = 12.0$ Hz, H-5 (pyrazoline)], 6.79 (1H, d, H-4′, $J = 7.6$ Hz), 6.97 (2H, s, SO_2NH_2), 7.02 (2H, d, $J = 8.8$ Hz, H-3″, H-5″), 7.14 (1H, d, $J = 6.8$ Hz, H-6′), 7.21–7.33 (7H, m, H-2′, H-5′, H-2, H-3, H-4, H-5, H-6), 7.55 (2H, d, $J = 8.4$ Hz, H-2″, H-6″), 9.56 (1H, s, OH). ESI–MS (*m/z*): 393 [M^+], 392 [M^+-1], 394 [M^++1]. CHNS analysis: found (calculated): C: 64.10 (64.12), H: 4.87 (4.83), N: 10.68 (10.68), S: 8.14 (8.15). Molecular formula: $C_{21}H_{19}N_3O_3S$.

4-[5-(4-Chloro-phenyl)-3-(3-hydroxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2b**)

This compound was obtained as yellow crystals when recrystallized from methanol in 55 % yield, m.p. 84–86 °C, $R_f = 0.69$, (toluene:ethyl acetate:formic acid, 7.5:2:0.5). IR υ_{max} (KBr): 3471 cm^{-1} and 3304 cm^{-1} (NH_2), 1592 cm^{-1} (C=N), 1326 cm^{-1} and 1148 cm^{-1} ($SO_2N<$). ^{1}HNMR (400 MHz, DMSO, δ): 3.12 [1H, dd, J = 5.2 Hz, J = 18.8 Hz, H-4 *trans* (pyrazoline)], 3.92 [1H, dd, $J = 12$ Hz, $J = 17.2$ Hz, H-4 *cis* (pyrazoline)], 5.63 [1H, dd, $J = 4.4$ Hz, $J = 7.2$ Hz, H-5 (pyrazoline)], 6.79 (1H, d, $J = 7.6$ Hz, H-4′), 6.98 (2H, s, SO_2NH_2), 7.02 (2H, d, $J = 8.4$ Hz, H-3″, H-5″), 7.08–7.19 (3H, m, H-2′, H-5′, H-6′), 7.24 (2H, d, $J = 8.4$ Hz, H-2″, H-6″), 7.38 (2H, d, $J = 8.4$ Hz, H-3, H-5), 7.56 (2H, d, $J = 8.4$ Hz, H-2, H-6), 9.56 (1H, s, OH). ESI–MS (*m/z*): 427 [M^+], 426 [M^+-1], 428 [M^++1], 429 [M^++2], 430 [M^++3]. CHNS analysis: C: 59.01 (58.99), H: 4.21 (4.24), N: 9.83 (9.82), S: 7.49 (7.49). Molecular formula: $C_{21}H_{18}ClN_3O_3S$.

4-[3-(3-Hydroxy-phenyl)-5-(4-methoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2c**)

This compound was obtained as light brown crystals when recrystallized from methanol in 27 % yield, m.p. 131–133 °C, $R_f = 0.69$, (toluene:ethyl acetate:formic acid, 7.5:2:0.5). IR υ_{max} (KBr): 3390 cm^{-1} and 3256 cm^{-1} (NH_2), 1592 cm^{-1} (C=N), 1307 cm^{-1} and 1149 cm^{-1} ($SO_2N<$). ^{1}HNMR (400 MHz, DMSO, δ): 3.06 [1H, dd, $J = 4.8$ Hz, $J = 17.6$ Hz, H-4 *trans* (pyrazoline)], 3.67 (3H, s, OCH_3), 3.87 [1H, dd, $J = 12$ Hz, $J = 17.6$ Hz, H-4 *cis* (pyrazoline)], 5.54 [1H, dd, $J = 4.8$ Hz, $J = 11.6$ Hz, H-5 (pyrazoline)], 6.78 (1H, d, $J = 7.6$ Hz, H-4′), 6.86 (2H, d, $J = 8.8$ Hz, H-3, H-5), 6.97 (2H, s, SO_2 NH_2), 7.03 (2H, d, $J = 8.8$ Hz, H-2, H-6), 7.12–7.15 (3H, m, H-2′ H-3″, H-5″), 7.20–7.22 (2H, m, H-5′, H-6′), 7.55 (2H, d, $J = 8.8$ Hz, H-2″, H-6″), 9.52 (1H, s, OH). ESI–MS (*m/z*): 423 [M^+], 422 [M^+-1], 424 [M^++1]. CHNS analysis: C: 62.41 (62.40), H: 4.96 (5.00), N: 9.92 (9.92), S: 7.56 (7.57). Molecular formula: $C_{22}H_{21}N_3O_4S$.

4-[3-(3-Hydroxy-phenyl)-5-p-tolyl-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2d**)

This compound was obtained as yellow crystals when recrystallized from methanol in 29 % yield, m.p. 158–160 °C, $R_f = 0.85$, (toluene:ethyl acetate:formic acid, 7.5:2:0.5). IR υ_{max} (KBr): 3371 cm^{-1} and 3278 cm^{-1} (NH_2), 1591 cm^{-1} (C=N), 1327 cm^{-1} and 1146 cm^{-1} ($SO_2N<$). ^{1}HNMR (400 MHz, DMSO, δ): 2.20 (3H, s, CH_3), 3.10–3.14 [1H, m, H-4 *trans* (pyrazoline)], 3.85–3.92 [1H, m, H-4 *cis* (pyrazoline)], 5.53–5.56 [1H, m, H-5 (pyrazoline)], 6.78 (1H, d, $J = 7.2$ Hz, H-4′), 6.97 (2H, s, SO_2 NH_2), 7.01 (2H, d, $J = 8.8$ Hz, H-3″, H-5″), 7.11–7.21 (7H, m, H-2″, H-6″, H-2′, H-5′, H-6′, H-3, H-5), 7.54 (2H, d, $J = 8.8$ Hz, H-2, H-6), 9.58 (1H, s, OH). ESI–MS (*m/z*): 407 [M^+], 406 [M^+-1], 408 [M^++1], 409 [M^++2]. CHNS analysis: C: 64.86 (64.85), H: 5.16 (5.19), N: 10.32 (10.31), S: 7.86 (7.87). Molecular formula: $C_{22}H_{21}N_3O_3S$.

4-[5-(4-Hydroxy-phenyl)-3-(3-hydroxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2e**)

This compound was obtained as brown crystals when recrystallized from methanol in 27 % yield, m.p.

151–153 °C, $R_f = 0.58$, (toluene:ethyl acetate:formic acid, 7.5:2:0.5). IR υ_{max} (KBr): 3351 cm^{-1} and 3252 cm^{-1} (NH_2), 1591 cm^{-1} (C=N), 1326 cm^{-1} and 1136 cm^{-1} ($SO_2N<$). ^{1}HNMR (400 MHz, DMSO, δ): 3.02–3.14 [1H, m, H-4 *trans* (pyrazoline)], 3.81–3.88 [1H, m, H-4 *cis* (pyrazoline)], 5.46 [1H, dd, $J = 4.8$ Hz, $J = 11.6$ Hz, H-5 (pyrazoline)], 6.67 (2H, d, $J = 8.4$ Hz, H-3, H-5), 6.78 (1H, d, $J = 7.6$ Hz, H-4′), 6.96 (2H, s, SO_2NH_2), 7.01–7.03 (4H, m, H-3″, H-5″, H-2, H-6), 7.14 (1H, d, $J = 7.2$ Hz, H-6), 7.19–7.20 (2H, m, H-2′, H-6′), 7.54 (2H, d, $J = 8.8$ Hz, H-2″, H-6″), 9.37 (1H, s, OH), 9.55 (1H, s, OH). ESI–MS (*m/z*): 409 [M^+], 408 [M^+-1], 410 [M^++1], 411 [M^++1]. CHNS analysis: C: 61.61 (61.60), H: 4.65 (4.68), N: 10.26 (10.26), S: 7.82 (7.83). Molecular formula: $C_{21}H_{19}N_3O_4S$.

4-[5-(2-Chloro-phenyl)-3-(3-hydroxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfoamide (**2f**)

This compound was obtained as brown crystals when re-crystallized from methanol in 43 % yield, m.p. 258–260 °C, $R_f = 0.84$, (toluene:ethyl acetate:formic acid, 7.5:2:0.5). IR υ_{max} (KBr): 3348 cm^{-1} and 3284 cm^{-1} (NH_2), 1592 cm^{-1} (C=N), 1329 cm^{-1} and 1148 cm^{-1} ($SO_2N<$). ^{1}HNMR (400 MHz, DMSO, δ): 3.12 [1H, dd, $J = 11.6$ Hz, $J = 16.4$ Hz, H-4 *trans* (pyrazoline)], 4.02 [1H, dd, $J = 12.8$ Hz, $J = 17.6$ Hz, H-4 *cis* (pyrazoline)], 5.78 [1H, dd, $J = 8.4$ Hz, $J = 12$ Hz, H-5 (pyrazoline)], 6.79 (1H, d, $J = 7.6$ Hz, H-4′), 6.93–6.99 (5H, m, H-2″, H-6″, SO_2NH_2, H-6′), 7.15 (1H, $J = 7.6$ Hz, H-3), 7.16–7.31 (4H, m, H-2′, H-5′, H-4, H-5), 7.54 (1H, d, $J = 7.6$ Hz, H-6), 7.60 (2H, d, $J = 7.6$ Hz, H-3″, H-5″), 9.56 (1H, s, OH). ESI–MS (*m/z*): 428 [M^++1], 429 [M^++2], 430 [M^++3]. CHNS analysis: C: 59.01 (58.98), H: 4.22 (4.24), N: 9.83 (9.82), S: 7.49 (7.49). Molecular formula: $C_{21}H_{18}ClN_3O_3S$.

4-[5-(2-Hydroxy-phenyl)-3-(3-hydroxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2g**)

This compound was obtained as brown crystals when re-crystallized from chloroform in 32 % yield, m.p. 249–250 °C, $R_f = 0.55$, (toluene:ethyl acetate:formic acid, 7.5:2:0.5). IR υ_{max} (KBr): 3348 cm^{-1} and 3234 cm^{-1} (NH_2), 1591 cm^{-1} (C=N), 1305 cm^{-1} and 1135 cm^{-1} ($SO_2N<$). ^{1}HNMR (400 MHz, DMSO, δ): 3.02 [1H, dd, $J = 4.6$ Hz, $J = 12.0$ Hz, H-4 *trans* (pyrazoline)], 3.88 [1H, dd, $J = 12$ Hz, $J = 17.2$ Hz H-4 *cis* (pyrazoline)], 5.68 [1H, dd, $J = 4.4$ Hz, $J = 11.2$ Hz, H-5 (pyrazoline)], 6.66 (1H, d, $J = 7.2$ Hz, H-4′), 6.79 (2H, s, SO_2NH_2), 6.86 (1H, d, $J = 8.0$ Hz, H-3), 7.02–7.20 (8H, m, H-2′, H-3′, H-5′, H-4, H-5, H-6, H-2″, H-6″), 7.56 (2H, d, $J = 8.0$ Hz, H-3″, H-5″), 9.69 (1H, s, OH), 9.88 (1H, s, OH). ESI–MS (*m/z*): 409 [M^+], 408 [M^+-1], 410 [M^++1]. CHNS analysis: C: 61.62 (61.60), H: 4.64 (4.68), N: 10.27 (10.26), S: 7.82 (7.83). Molecular formula: $C_{21}H_{19}N_3O_4S$.

4-[5-(3,4-Dimethoxy-phenyl)-3-(3-hydroxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2h**)

This compound was obtained as yellow crystals when re-crystallized from methanol in 47 % yield, m.p. 217–219 °C, $R_f = 0.45$, (toluene:ethyl acetate:formic acid, 7.5:2:0.5). IR υ_{max} (KBr): 3403 cm^{-1} and 3277 cm^{-1} (NH_2), 1593 cm^{-1} (C=N), 1331 cm^{-1} and 1154 cm^{-1} ($SO_2N<$). ^{1}HNMR (300 MHz, DMSO, δ): 3.11 [1H, dd, $J = 12.3$ Hz, $J = 17.4$ Hz, H-4 *trans* (pyrazoline)], 3.69 (3H, s, OCH_3 at C-3), 3.72 (3H, s, OCH_3 at C-4), 3.88 [1H, dd, $J = 8.4$ Hz, $J = 14.8$ Hz, H-4 *cis* (pyrazoline)], 5.52 [1H, dd, $J = 6.0$ Hz, $J = 15.2$ Hz, H-5 (pyrazoline)], 6.67 (1H, d, $J = 8.4$ Hz, H-4′), 6.81 (1H, d, $J = 8.4$ Hz, H-5), 6.88 (1H, d, $J = 8.4$ Hz, H-6), 6.93 (1H, s, H-2), 7.02 (2H, s, SO_2NH_2), 7.07 (2H, d, $J = 8.7$ Hz, H-3″, H-5″), 7.16–7.26 (3H, m, H-2′, H-5′, H-6′), 7.59 (2H, d, $J = 8.7$ Hz, H-2″, H-6″), 9.61(1H, s, OH). ESI–MS (*m/z*): 453 [M^+], 452 [M^+-1], 454 [M^++1]. CHNS analysis: C: 60.92 (60.91), H: 5.07 (5.11), N: 9.27 (9.27), S: 7.06 (7.07). Molecular formula: $C_{23}H_{23}N_3O_5S$.

4-[3-(3-Hydroxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2i**)

This compound was obtained as yellow crystals when recrystallized from methanol in 44 % yield, m.p. 269–270 °C, $R_f = 0.38$, (toluene:ethyl acetate:formic acid, 7.5:2:0.5). IR υ_{max} (KBr): 3390 cm^{-1} and 3299 cm^{-1} (NH_2), 1591 cm^{-1} (C=N), 1329 cm^{-1} and 1138 cm^{-1} ($SO_2N<$). ^{1}HNMR (400 MHz, DMSO, δ): 3.13-3.14 [1H, m, H-4 *trans* (pyrazoline)], 3.59 (3H, s, OCH_3), 3.66 (6H, s, 2xOCH_3), 3.88 [1H, dd, $J = 17.6$ Hz, $J = 28.4$ Hz, H-4 *cis* (pyrazoline)], 5.45 [1H, dd, $J = 6.8$ Hz, $J = 12.8$ Hz, H-5 (pyrazoline)], 6.55 (2H, s, SO_2NH_2), 6.79 (1H, d, $J = 7.6$ Hz, H-4′), 7.00 (2H, s, H-2, H-6), 7.06 (2H, d, $J = 8.8$ Hz, H-3″, H- 5″), 7.15 (1H, d, $J = 7.2$ Hz, H-5′), 7.21–7.23 (2H, m, H-2′, H-6′), 7.59 (2H, d, $J = 8.8$ Hz, H-2″, H-6″), 9.57 (1H, s, OH). ESI–MS (*m/z*): 483 [M^+], 482 [M^+-1], 484 [M^++1]. CHNS analysis: C: 59.62 (59.61), H: 5.17 (5.21), N: 8.69 (8.68), S: 6.63 (6.62). Molecular formula: $C_{24}H_{25}N_3O_6S$.

4-[3-(3-Hydroxy-phenyl)-5-styryl-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2J**)

This compound was obtained as brown crystals when recrystallized from methanol in 29 % yield, m.p. 228–229 °C, $R_f = 0.67$, (toluene:ethyl acetate:formic acid, 7.5:0 2:0.5). IR υ_{max} (KBr): 3308 cm^{-1} and 3240 cm^{-1} (NH_2), 1591 cm^{-1} (C=N), 1326 cm^{-1} and 1143 cm^{-1}

($SO_2N<$). ^{1}HNMR (400 MHz, DMSO, δ): 3.14–3.20 [1H, m, H-4 *trans* (pyrazoline)], 3.70 [1H, dd, $J = 11.6$ Hz, $J = 17.2$ Hz, H-4 *cis* (pyrazoline)], 5.19-5.20 [1H, m, H-5 (pyrazoline)], 6.27 (1H, m, H-5′), 6.63 (1H, d, $J = 15.6$ Hz, β-H), 6.79 (1H, d, $J = 7.6$ Hz, H-4′), 6.98 (2H, s, SO_2NH_2), 7.15–7.28 (7H, m, H-3, H-4, H-α, H-3″, H-5″, H-2′, H-6′), 7.39 (2H, d, $J = 6.8$ Hz, H-2, H-6), 7.62 (2H, d, $J = 6.8$ Hz, H-2″, H-6″), 9.55 (1H, s, OH). ESI–MS (*m/z*): 419 [M^+], 420 [M^++1], 421 [M^++2]. CHNS analysis: C: 65.87 (65.85), H: 5.03 (5.05), N: 10.05 (10.02), S: 7.66 (7.64). Molecular formula: $C_{23}H_{21}N_3O_3S$.

4-[5-Furan-2-yl-3-(3-hydroxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2k**)

This compound was obtained as reddish brown crystals when recrystallized from methanol in 37 % yield, m.p. 259–260 °C, $R_f = 0.60$, (toluene:ethyl acetate:formic acid, 7.5:2:0.5). IR υ_{max} (KBr): 3340 cm^{-1} and 3250 cm^{-1} (NH_2), 1592 cm^{-1} (C=N), 1329 cm^{-1} and 1145 cm^{-1} ($SO_2N<$). ^{1}HNMR (400 MHz, DMSO, δ): 3.13–3.14 [1H, m, H-4 *trans* (pyrazoline)], 3.77 [1H, dd, $J = 13.6$ Hz, $J = 18.8$ Hz, H-4 *cis* (pyrazoline)], 5.72 [1H, dd, $J = 4.4$ Hz, $J = 12$ Hz, H-5 (pyrazoline)], 6.36 [1H, d, $J = 2.8$ Hz, (H-4 furan)], 6.45 [1H, d, $J = 2.8$ Hz, H-5 (furan)], 6.80 (1H, d, $J = 7.6$ Hz, H-4′), 7.01 (2H, s, SO_2NH_2), 7.16–7.25 (5H, m, H-2′, H-5′, H-6′, H-2″, H-6″), 7.53 (1H, s, H-2), 7.60 (2H, d, $J = 8.8$ Hz, H-3″, H-5″), 9.58 (1H, s, OH). ESI–MS (*m/z*): 383[M^+], 384 [M^++1], 385 [M^++2]. CHNS analysis: C: 59.54 (59.52), H: 4.43 (4.47), N: 10.97 (10.97), S: 8.35 (8.36). Molecular formula: $C_{19}H_{17}N_3O_4S$.

4-[5-Anthracen-9-yl-3-(3-hyroxy-pheyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2l**)

This compound was obtained as yellow crystals when re-crystallized from methanol in 27 % yield, m.p. 265–266 °C, $R_f = 0.77$, (toluene:ethyl acetate:formic acid, 7.5:2:0.5). IR υ_{max} (KBr): 3382 cm^{-1} and 3277 cm^{-1} (NH_2), 1588 cm^{-1} (C=N), 1314 cm^{-1} and 1145 cm^{-1} ($SO_2N<$). ^{1}HNMR (300 MHz, DMSO, δ): 3.07–3.14 [1H, m, H-4 *trans* (pyrazoline)], 3.46 [1H, dd, $J = 13.8$ Hz, $J = 7.5$ Hz, H-4 *cis* (pyrazoline)], 4.19–4.27 [1H, m, H-5 (pyrazoline)], 6.76–6.94 (4H, m, H-2″, H-6″, SO_2NH_2), 7.25–7.41 (7H, m, H-3/H-6, H-2′, H-6′, H-3″, H-5 ″, H- 4′, H-5′), 7.62 (1H, t, H-7/H-2), 7.72 (1H, t, H-7/H-2), 7.93 (1H, d, $J = 6.6$ Hz, H-5/H-4), 8.08 (1H, d, $J = 5.4$ Hz, H-5/H-4), 8.19 (1H, d, $J = 6.0$ Hz, H-8/H-1), 8.66 (1H, s, H-10), 8.79 (1H, d, $J = 7.2$ Hz, H-8/H-1), 9.63 (1H, s, OH). ESI–MS (*m/z*): 493 [M^+], 492 [M^+−1], 494 [M^++1], 495 [M^++2]. CHNS analysis: C: 70.56 (70.57), H: 4.68 (4.70), N: 8.50 (18.51), S: 6.51 (6.50). Molecular formula: $C_{29}H_{23}N_3O_3S$.

Biological activities

All the experiments were carried out in albino rats of Wistar strain (either sex) were procured from Central Animal House of Jamia Hamdard, New Delhi (Registration no. 173/CPCSEA). The experiments were performed in accordance with the guidelines for the care and use of laboratory animals, laid down by the Committee for the Purpose of Control and Supervision of Experiments in Animals (CPCSEA), Ministry of Social Justice and Empowerment, Govt. of India, Jan. 2000. Animals described as fasted were deprived of food for at least 16 h but allowed free access to water. CMC (1 % w/v) in distilled water was used as vehicle for dosing in all the experiments. All treatments were given orally.

Anti-inflammatory activity

Carrageenan-induced hind paw edema method was used for evaluating anti-inflammatory activity (Winter *et al.*, 1962). Fasted rats were divided into fourteen groups of 6 animals each. One group of rats, which served as control was given vehicle only (10 ml/kg), while animals of group II were given celecoxib 0.05 mmol/kg suspended in the vehicle and served as standard. Test compounds (**2a**–**l**) (0.05 mmol/kg) suspended in vehicle (10 ml/kg) were administered to respective groups. After 30 min, all animals were injected with 0.1 ml of 1 % carrageenan solution (prepared in normal saline) in the subplantar aponeurosis of left hind paw to induce inflammation and the volume of injected paw was measured by using plethysmometer immediately (at 0 h). The paw volume was again measured after 3 and 5 h (Table 1). The average paw volume in a group of treated rats was compared with vehicle (control group) and the percentage inhibition of edema was calculated by using the formula

$$\text{Percent inhibition} = (1 - \text{Vt}/\text{Vc}) \times 100$$

where Vt is the mean paw volume of the test drug treated rats and Vc is the mean paw volume of the control.

Ulcerogenic activity

Acute gastric ulcerogenic effect of the compounds **2a**, **2e**, and **2l** were evaluated in Albino Wistar rats (Daidone *et al.*, 1994). Albino wistar rats (150–220 g) were fasted over 24 h and where randomly allotted into five groups of six animals each. Group I served as control and was administered vehicle 10 ml/kg (CMC 1 % w/v in distilled water) orally. Group II served as standard and was administered orally celecoxib (0.15 mmol/kg i.e., three times the dose given in anti-inflammatory activity) suspended in vehicle. Group III, IV, and V were administered orally compounds **2a**, **2e**, and **2l** (0.15 mmol/kg) suspended in vehicle,

respectively. They were sacrificed under deep anesthesia after 6 h of dosing. Their stomach were removed and opened through greater curvature for examining lesions or bleedings. Compounds **2a**, **2e**, and **2l** showed no ulcers.

Effect of synthesized compounds (**2a–l**) on oral glucose tolerance in normal rats

Fasted albino rats (150–200 g) were classified into fourteen groups of six animals each. Animals of group I received only vehicle (10 ml/kg) to serve as control, while animals of group II were given gliclazide 0.05 mmol/kg suspended in the vehicle and served as standard. The test compounds **(2a–l)** in the dose of 0.05 mmol/kg suspended in the vehicle were administered to respective groups. All the animals were given glucose (3 g/kg, p.o.) 30 min after dosing. Blood samples were collected from retro-orbital plexus (under mild anesthesia) just before and 60 min after the glucose loading, and blood glucose levels were measured with an auto analyzer AccuCheck Advantage II glucose kit (Table 2).

Results and discussion

Chemistry

The synthetic route used to synthesize title compounds (**2a–l**) is outlined in Scheme 1. Chalcones required for the synthesis of pyrazolines were synthesized through modified reported method (Ansari *et al.*, 2008) Structures of 2-pyrazolines (as given in scheme) were established on the basis of spectral (IR, NMR, and Mass) and CHNS analyses data.

The IR spectra showed absorption bands in the region 1588–1593 cm^{-1} corresponding to C=N stretching bands because of ring closure. Also, infrared spectra revealed NH_2 peak at 3403–3256 cm^{-1} and for SO_2NH_2 peak at 1305–1331 cm^{-1} and 1154–1135 cm^{-1}.

In the ^{1}HNMR spectra of 2-pyrazolines, the three hydrogen atoms attached to the C-4 and C-5 carbon atoms of the heterocyclic ring gave an ABX spin system. Measured chemical shift and coupling constant values (cf. 'Experimental' section) equivocally prove the 2-pyrazoline structure. The protons of the SO_2NH_2 group were observed at 6.76–7.02 ppm generally as a sharp peak. The hydroxyl and aromatic protons were observed at expected ppms. Elemental analysis (C, H, N, and S) data were within ±0.4 % of the theoretical values.

Anti-inflammatory activity

Anti-inflammatory activity of synthesized compounds was evaluated by using carrageenan-induced rat hind paw edema method. Synthesized compounds (**2a–l**) have structural resemblance with celecoxib because of this reason celecoxib was used as reference standard in this study. All the derivatives exhibited varying degree of anti-inflammatory activity (19.2–64.7 % at 3 h and 29.6–77.7 % at 5 h) (Table 1). Among these compound **2e** showed maximum activity (64.7 % at 3 h and 77.7 % at 5 h).

Table 1 Anti-inflammatory activity of tested compounds using carrageenan-induced hind paw edema in rats

Treatment (0.05 mol/kg)	Increase in paw volume ml ±SEM after carrageenan administration	
	3 h	5 h
Vehicle	0.416 ± 0.04	0.450 ± 0.04
Celecoxib	0.1 ± 0.02*** (75.9)	0.08 ± 0.02*** (82.2)
2a	0.26 ± 0.01** (35.8)	0.10 ± 0.03*** (77.7)
2b	0.33 ± 0.01 (19.2)	0.21 ± 0.02*** (51.8)
2c	0.15 ± 0.03*** (64.7)	0.16 ± 0.03*** (62.9)
2d	0.15 ± 0.04*** (64.7)	0.15 ± 0.02*** (66.0)
2e	0.15 ± 0.21*** (64.7)	0.10 ± 0.02*** (77.7)
2f	0.28 ± 0.04*** (32.6)	0.13 ± 0.04*** (70.3)
2g	0.26 ± 0.02** (35.4)	0.2 ± 0.02*** (55.5)
2h	0.18 ± 0.02*** (55.9)	0.15 ± 0.01*** (66.7)
2i	0.20 ± 0.04*** (51.9)	0.11 ± 0.05*** (74.4)
2j	0.25 ± 0.02** (39.9)	0.18 ± 0.02** (59.2)
2k	0.26 ± 0.02*** (35.8)	0.31 ± 0.01*** (29.6)
2l	0.16 ± 0.03*** (59.8)	0.10 ± 0.02*** (77.7)

Values are presented as mean ± SEM ($n = 6$); values in parentheses represent percent inhibitions

** $P < 0.01$, *** $P < 0.001$ compared to control (one-way ANOVA followed by Dunnett's test)

With regard to SAR we observed that replacement of benzenoid ring with heterocyclic ring (**2k**) causes remarkable reduction in the activity at both time points (3 and 5 h). Introduction of Cl atom at ortho or para position (C-2 or C-4) leads to decrease in the activity (**2a** vs **2b**, **2a** vs **2f**) at both time points. On the other hand introduction of OCH_3 or CH_3 at C-4 leads to significant increase in the activity at 3 h but reduce the activity at 5 h (**2a** vs **2c**, **2a** vs **2d**). It is interesting to note that introduction of more than one methoxyl group in the 5-phenyl ring of pyrazoline causes enhancement in the activity at 5 h and slight reduction in the activity at 3 h (**2c** vs **2h**, **2h** vs **2i**). Introduction of hydroxyl at C-4 causes an enhancement of the activity at 3 h (**2a** vs **2e**) but when the same group is introduced at ortho position (C-2), it diminishes the activity at 5 h (**2a** vs **2g**).

Ulcerogenic activity

Ulcerogenic activity of the compounds **2a**, **2e**, and **2l** was recorded at dose of 0.15 mmol/kg and compared with

Scheme 1 Synthesis is of pyrazo lines bearing benzenesulfonamide moiety. **1a**, **2a**; Ar = phenyl. **1b**, **2b**; Ar = 4-chlorophenyl. **1c**, **2c**; Ar = 4-methoxyphenyl. **1d**, **2d**; Ar = 4-methylphenyl. **1e**, **2e**; Ar = 4-hydroxyphenyl. **1f**, **2f**; Ar = 2-chlorophenyl. **1g**, **2g**; Ar = 2-hydroxyphenyl. **1h**, **2h**; Ar = 3,4-dimethoxyphenyl. **1i**, **2i**; Ar = 3,4,5-trimethoxyphenyl. **1j**, **2j**; Ar = ethylenephenyl. **1k**, **2k**; Ar = furyl (C-2). **1l**, **2l**; Ar = anthryl (C-9)

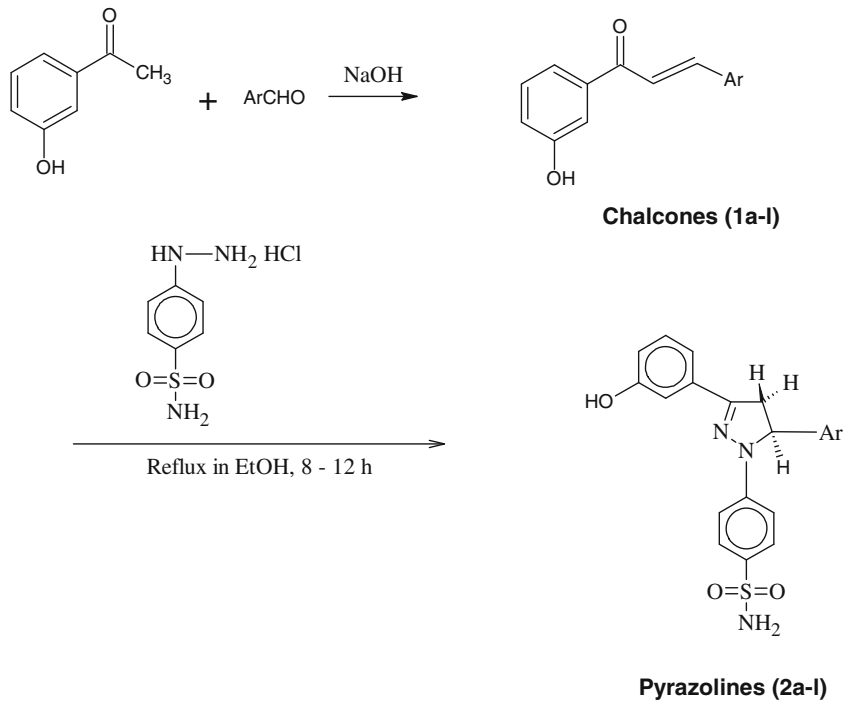

Table 2 Effect of synthesized compounds on oral glucose tolerance in normal rats

Treatment (0.05 mol/Kg)	Blood glucose level (mg/dl)	
	0 min	60 min
Control	74.0 ± 3.92	126.50 ± 3.80
Gliclazide	63.67 ± 2.51	85.83 ± 2.72
2a	78.3 ± 0.05	126.3 ± 2.44
2b	74.6 ± 1.14	134.0 ± 2.17
2c	70 ± 1.28	116.5 ± 1.31
2d	75.3 ± 2.10	138.6 ± 2.37
2e	78.0 ± 0.88	121 ± 1.23
2f	75 ± 1.78	121 ± 1.12
2g	77.3 ± 1.01	133 ± 3.89
2h	76.6 ± 1.47	111 ± 1.17
2i	76.0 ± 1.58	94.6 ± 0.80*
2j	75 ± 1.52	131 ± 1.71
2k	74.3 ± 1.00	133 ± 1.86
2l	76.3 ± 1.12	136.6 ± 0.87

Values are presented as mean ± SEM ($n = 6$)

* $P < 0.001$ compared to control (one-way ANOVA followed by Dunnett's test)

reference drug celecoxib (0.15 mmol/kg). All three active compounds were generally found safe from the point of view of ulcer induction.

Blood glucose lowering activity

All the synthesized compounds were evaluated for sugar lowering activity in glucose fed hyperglycemic normal rats. Only compound (**2i**) was found to exhibit significant blood glucose lowering activity. It has been observed that as the number of methoxyl groups are increased in the 5-phenyl of pyrazoline, the activity enhances gradually (**2a** vs **2c**, **2c** vs **2h**, **2h** vs **2i**).

Conclusion

The present study describes the synthesis of novel 2-pyrazolines bearing benzenesulfonamide moiety (**2a–l**). These synthesized compounds were evaluated for anti-inflammatory action in carrageenan-induced rat paw edema model and blood glucose lowering action in glucose fed hyperglycemic normal rats. Compounds **2a**, **2e**, and **2l** showed significant anti-inflammatory action at 5 h (more than 75 %) and proved to have superior gastrointestinal safety profiles as compared to standard drug celecoxib. The compound (**2i**) showed significant blood glucose lowering effect when compared to the standard drug gliclazide.

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