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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and blood glucose lowering activity of some novel benzenesulfonylthiourea derivatives substituted with 6-aryl-4,5-dihyropyridazin-3(2H)-ones

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Abstract Some new benzenesulfonylthiourea derivatives substituted with pyridazinone (**2a**–**o**) were synthesized by refluxing the appropriate 6-aryl-2-(*p*-sulfamylphenyl)-4,5-dihydropyridazine-3(2H)-ones with isothiocyanate in dry acetone over anhydrous K_2CO_3. All the synthesized compounds were characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR, DEPT and MS data, and elemental analysis. These compounds at the dose of 20 mg/kg were tested for blood glucose lowering activity in glucose-fed hyperglycemic normal rats. Five compounds (**2a**, **2d**, **2l**, **2m**, and **2n**) markedly reduced the content of glucose in rat blood (by more than 25%). Compound **2d** showed the maximum reduction (38.8%).

Keywords Sulfonylthiourea · Pyridazinone · Diabetes · Antihyperglycemic

Introduction

Diabetes mellitus (DM) is a metabolic disorder, which affects the people of all age groups and from all walks of life. There are estimated 150 million people worldwide sufferings from diabetes (Marx, 2002), which is almost five times more than the estimated number 10 years ago. Generally DM is classified as Type I insulin dependent diabetes mellitus (IDDM) caused by low or insufficient secretion of insulin by pancreas and Type II non-insulin dependent diabetes mellitus (NIDDM) caused due to insufficient utilization of insulin (Sakurai, 2002; WHO, 1985). NIDDM is the most common form of diabetes constituting nearly 90% of the diabetes population in any country.

Over the last 40 years oral therapy for type II DM has focused on sulfonylureas (SU) and biguanides (Kecskemeti *et al*., 2002). SU drugs improve glucose levels by stimulating insulin secretion by the pancreatic β-cells. The SU were discovered accidentally. Some sulphonamides were demonstrated to induce hypoglycemia in experimental animals. This observation led to the development of a group of substituted arylsulphonylureas differing at the *para* position of the benzene ring at one nitrogen residue of the urea moiety. Some of these have been marketed for the treatment of NIDDM (Fig. 1).

Chronic diabetes is accompanied by complications such as neuropathy, cataracts, and retinopathy, which are not controlled by insulin. These complications are considerably caused by accumulation of sorbitol, which is produced from glucose by aldose reductase (AR) in polyol pathway. AR converts glucose to sorbitol only at high glucose levels in plasma and tissue in diabetes (Dvornik, 1987a, b; Kinoshita and Nishimura, 1988). Recently, compounds containing pyridazine nucleus have been reported as AR inhibitors (Courdert *et al*., 1991; Costantino *et al*., 1996, 2000). Therefore, it has been considered worthwhile to attach pyridazinone ring to benzenesulfonylthiourea derivatives (Fig. 2).

In the present study, 15 novel benzenesulfonylthiourea derivatives substituted with pyridazinone were synthesized by condensing appropriate 6-aryl-2-(*p*-sulfamylphenyl)-4,5-dihydropyridazine-3(2H)-one with isothiocyanate. These were characterized by elemental analysis and various spectroscopic methods viz. IR, ^{1}H NMR, ^{13}C NMR, DEPT, and MS. Oral antihyperglycemic activity of these compounds were assessed using an oral glucose tolerance test in normal rat model.

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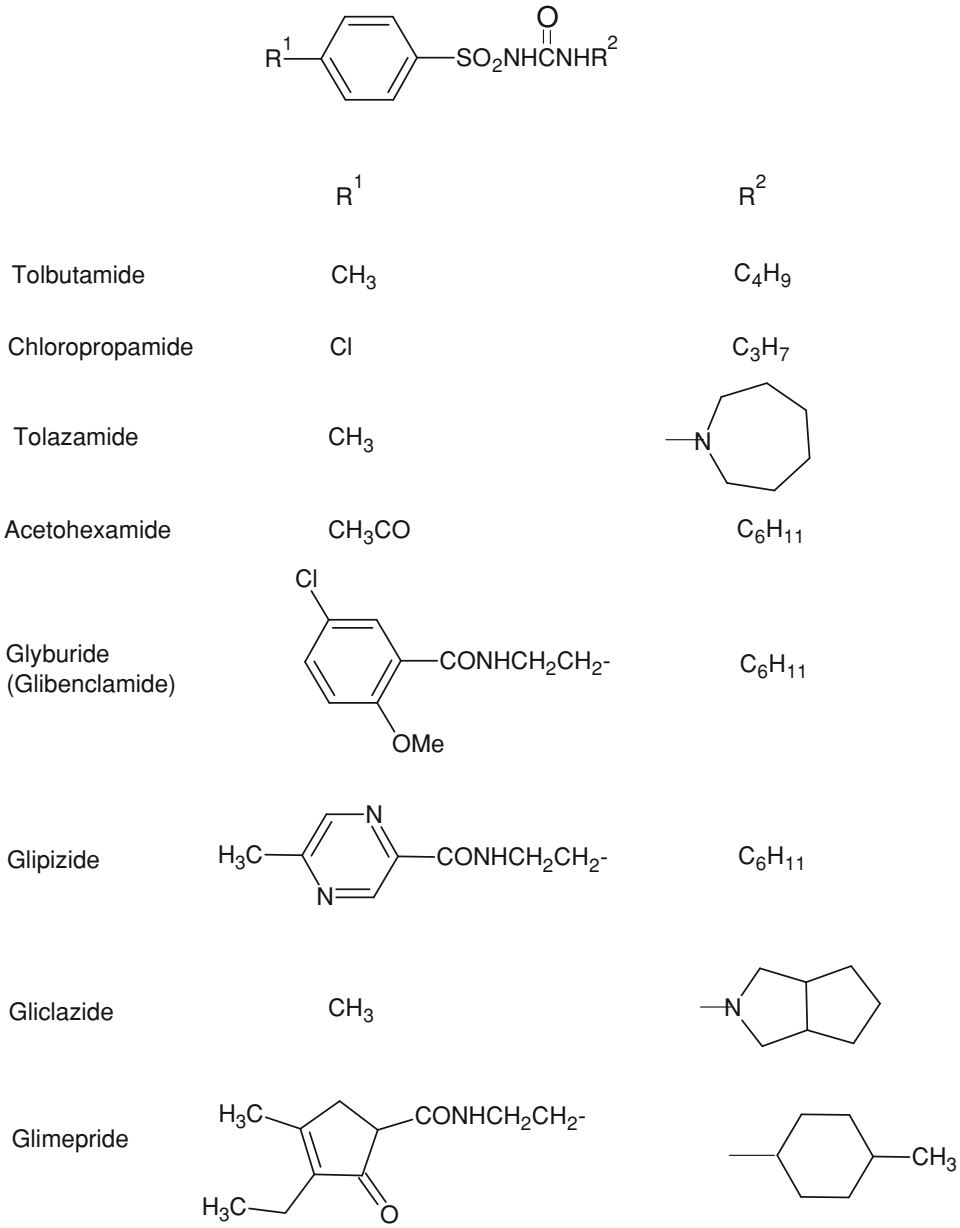
Fig. 1 Clinically used sulfonylureas



Result and discussion

Chemistry

The synthetic route used to synthesize title compounds (**2a**–**o**) is outlined in Scheme 1. The pyridazinone substituted benzenesulfonamide derivatives (**1a**–**f**) synthesized through reported method (Ahmad *et al.*, 2010, Bashir, 2010) were converted to sulfonylthioureas by refluxing with different isothiocyanates in dry acetone containing K_2CO_3.

The structures of sulfonylthiourea derivatives (**2a**–**o**) were determined on the basis of elemental analysis and various spectroscopic methods such as IR, ^{1}H NMR, ^{13}C NMR, DEPT, and MS. Elemental analysis (C, H, N, and S) data were within ±0.4% of the theoretical values.

In the IR spectra of **2a**–**o**, five bands characteristic of sulfonylthiourea moiety out of which two bands for thioureido group were observed (1585–1490 cm^{-1} and

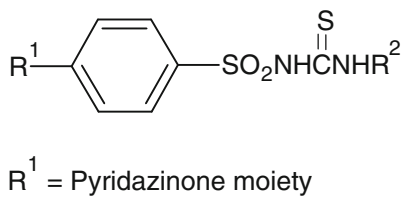
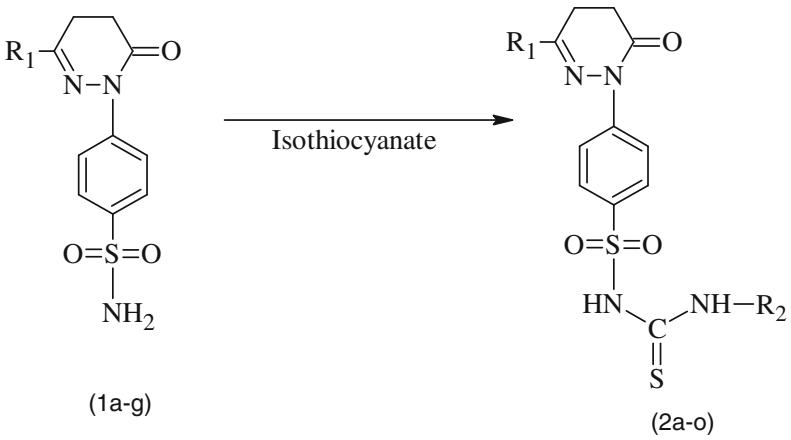


Fig. 2 Sulfonylthiourea

Scheme 1 Reagents and conditions: isothiocynate, K_2CO_3, dry acetone, reflux 24–72 h



1a, 2a, 2k: R_1= -C_6H_5

1b, 2b, 2l: R_1 = -$C_6H_5CH_3$

1c, 2c, 2h, 2m: R_1 = $C_6H_5OCH_3$

1d, 2d, 2i, 2n: R_1 = C_6H_5Cl

1e, 2e: R_1 = $C_6H_5C_2H_5$

1f, 2f, 2o: R_1 = $C_6H_5OC_6H_5$

1g, 2g, 2j: R_1 = $C_6H_5C_6H_5$

2a-2g: R_2 = $CH_2C_6H_5$

2h-2j: R_2 = C_6H_5

2k- 2o: R_2 = C_3H_7

1545–1488 cm^{-1}) and three bands for NH (3347–3040 cm^{-1}, 3287–2955 cm^{-1}, and 2964–2922 cm^{-1}). Apart from these a band for carbonyl of pyridazinone (1686–1588 cm^{-1}), a band for C=N of pyridazinone (1639–1586 cm^{-1}) and two bands for SO_2NH_2 (1378–1315 cm^{-1} and 1170–1136 cm^{-1}) were also observed. The structure was further established by proton NMR spectral data. The pyridazinone ring protons were appeared as two triplets at δ 2.70–2.83 and δ 3.05–3.19. Proton attached with nitrogen of thioureido group appeared as singlet at δ 4.30–8.90. DEPT spectra indicate the presence of CH_3, CH_2, and CH carbons.

Antihyperglycemic activity

In the present study, oral antihyperglcemic effect of 15 compounds (**2a**–**o**) was assessed in glucose-fed hyperglycemic normal rats. The marketed sulfonylurea drug glibenclamide was selected as positive control. Five compounds (**2a**, **2d**, **2l**, **2m**, and **2n**) prevented the rise in the blood glucose level by 25% or more (Table 1). Compound **2d** showed maximum prevention (38.8%). With regard to the SAR it seems impossible to extract an obvious structure–activity relationship from the data shown in Table 1.

Experimental

Chemistry

Melting points were determined by open capillary tubes and are uncorrected. All the Fourier transform infra red (FTIR) spectra were recorded on a Brukers Vector 22 spectrophotometer in film; ν_{max} values are given in cm^{-1}. ^1H NMR spectra were recorded on a Bruker Spectrospin DPX 300-MHz spectrometer using deuterated DMSO as a 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 scanned by affecting FAB ionization JEOL-JMS-DX 303 system, equipped with direct inlet probe system and ESI Bruker Esquire 3000. The m/z values of the more intense peaks are mentioned. ^{13}C NMR and DEPT spectra were recorded on Bruker spectrospin DPX 400 MHz and 500 MHz using deuterated DMSO as a solvent and tetramthyl silane (TMS) as internal standard. Purity of the compounds was checked on TLC plates (silica gel G) which were visualized by exposing to iodine vapors. Elemental analysis was carried out on CHNS Elementar (Vario EL III).

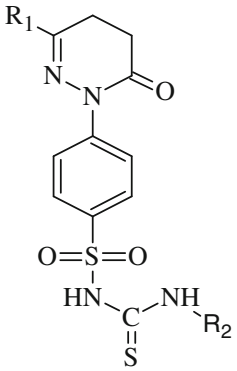
General procedure for the synthesis of sulfonylthiourea (**2a–o**)

A solution of appropriate pyridazinone (1 mmol) in dry acetone was refluxed over anhydrous K_2CO_3 for 1–1.5 h. At this temperature, a solution of the isothiocyanate (1.2 mmol) in dry acetone 5 mL was added in a drop wise manner. Refluxing was continued for 24–72 h. Acetone was removed under reduced pressure and the residue was suspended in water. The suspension acidified with acetic acid. It was filtered, washed and dried residue was crystallized by appropriate solvent.

4-(6-Oxo-3-phenyl-5,6-dihydropyridazin-1(4H)-yl)-*N*-(benzylcarbamothioyl) benzenesulfonamide (**2a**)

Yield = 50%, m.p 180–181°C, IR υ_{max}: 3330, 2955 and 2924 (NH–CS–NH), 1665 (C=O), 1589 (C=N), 1536 and 1492 (C=S of thioureido group), 1378 and 1157 cm^{-1} (SO_2N).^{1}H NMR: 2.75 (2H, t, $–CH_2–CH_2–$), 3.14 (2H, t, $–CH_2–CH_2–$), 4.39 (2H, s, $–CH_2–C_6H_5$), 7.01–8.15 (14H, m, *N*-phenyl, benzyl amine, 6-aryl protons), 10.00 (1H, s, NH). ESI–MS (*m*/*z*): 477 (M−1), 501 (M+Na). ^{13}C NMR: δ 22.72 ($–CH_2$ of pyridazinone), δ 28.03 ($–CH_2$ of pyridazinone), δ 48.15 ($–CH_2NH$), δ 153.89 (C=N of pyridazinone), δ 166.38

Table 1 Effect of sulfonylthiourea derivatives in glucose (3 g/kg) fed hyperglycemic normal rats



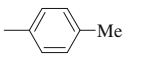
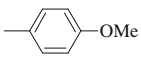
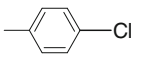
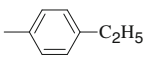
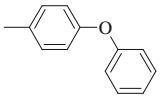
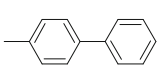
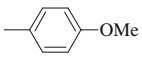
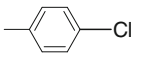
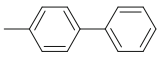
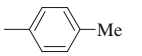
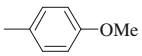
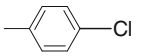
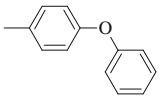
Compound	R_1	R_2	Blood glucose level (mg/dl) at zero hour	Blood glucose level (mg/dl) at one hour
Control	—		92.1 ± 4.1	149.3 ± 6.3
Glibanclamide	—		48.5 ± 5.3	94.3 ± 7.6*
2a			97.0 ± 5.6	139.0± 4.6 * (26.6%)
2b			91.5 ± 5.3	136.0± 6.1 * (21.3%)
2c			98.0± 5.6	152.0± 6.6 (5.6%)
2d			93.5± 4.6	128.5± 5.3 * (38.8%)
2e			93.0 ± 4.1	148.0± 6.6 (3.8%)
2f			92.0 ± 4.3	147.5± 7.1 (3.0%)
2g			94.5 ± 5.6	137.5± 6.1 * (24.8%)

Table 1 continued

Compound	R_1	R_2	Blood glucose level (mg/dl) at zero hour	Blood glucose level (mg/dl) at one hour
2h			91.5 ± 3.3	170.5± 4.1 (No activity)
2i			93.5± 5.1	148.0± 7.3 (4.7%)
2j			94.0± 3.1	166.0± 6.6 (No activity)
2k		C_3H_7	87.5 ± 9.3	160.0 ± 8.3 (No activity)
2l		C_3H_7	95.0 ± 6.5	134.5± 7.6* (30.9%)
2m		C_3H_7	96.0 ± 5.6	132.0± 3.6* (37.1%)
2n		C_3H_7	94.0 ± 4.3	132.5 ± 4.6* (32.7%)
2o		C_3H_7	91.0 ± 4.1	152.0± 5.6 (No activity)

* $P < 0.05$ compared to control (one-way ANOVA followed by Dunnett's test). Values are presented as mean ± S.E.M. ($n = 6$). Values in *parentheses* represent inhibition of the rise of blood glucose level in rats

(C=O), δ 179.04 (C=S). Anal. Calcd. for $C_{24}H_{22}N_4O_3S_2$: C = 60.23, H = 4.63, N = 11.71, S = 13.40. Found: C = 60.18, H = 4.60, N = 11.70, S = 13.37.

4-(6-Oxo-3-(4′-methylphenyl)-5,6-dihydropyridazin-1(4H)-yl)-*N*-(benzylcarbamothioyl) benzenesulfonamide (**2b**)

Yield = 42%, m.p 190–191°C, IR υ_{max}: 3330 (NH–CS–NH), 1671 (cyclic carbonyl), 1589 (C=N), 1540 and 1490 (C=S of thiourea), 1322 and 1161 cm^{-1} (SO_2N). ^1H NMR: 2.35 (3H, s, CH_3), 2.77 (2H, t, $–CH_2–CH_2$), 3.05 (2H, t, $–CH_2–CH_2–$), 4.72 (2H, d, $J = 4.83$ Hz, $–CH_2–C_6H_5$), 7.65–8.00 (6H, m, aromatic protons system), 7.14–7.30 (7H, m, aromatic protons), 8.31 (1H, s, $–NH–CH_2–C_6H_5$). FAB-MS (*m/z*): 494 (M+2, base peak), 491 (M−1). Anal. Calcd. for $C_{25}H_{24}N_4O_3S_2$: C = 60.95, H = 4.91, N = 11.37, S = 13.02. Found: C = 60.90, H = 4.87, N = 11.36, S = 12.99.

4-(6-Oxo-3(4′-methoxyphenyl)-5,6-dihydropyridazin-1(4H)-yl)-*N*-(benzylcarbamothioyl) benzenesulfonamide (**2c**)

Yield = 52%, m.p 200–202°C; IR υ_{max}: 3322, 2956, and 2925 (NH–CS–NH), 1676 (cyclic carbonyl), 1588 (C=N), 1536 and 1513 (C=S of thiourea), 1315 and 1168 (SO_2N), 1084 cm^{-1} (OCH_3). ^1H NMR: 2.75 (2H, t, $–CH_2–CH_2–$),

3.12 (2H, t –CH_2–CH_2–), 3.79 (3H, s, OCH_3), 4.68 (2H, s, –CH_2–C_6H_5), 7.00–7.34 (7H, m, H-3′, H-5′, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴), 7.82–7.94 (6H, m, H-2″, H-3″, H-5″, H-6″, H-2′, H-6′), 8.90 (1H, s, NH–CH_2–C_6H_5). FAB-MS (*m/z*): 510 (M^++2), 509 (M^++1). ^{13}C NMR: δ 22.81 (–CH_2 of pyridazinone), δ 28.71 (–CH_2 of pyridazinone), δ 48.33 (–NH–CH_2), δ 55.85 (–OCH_3), δ 153.75 (C=N of pyridazinone), δ 166.35 (C=O), δ 179.20 (C=S). DEPT: δ 22.11 (–CH_2 of pyridazinone), δ 27.67 (–CH_2 of pyridazinone), δ 47.70 (–CH_2NH), δ 55.32 (–OCH_3). Anal. Calcd. for $C_{25}H_{24}N_4O_4S_2$: C = 59.04, H = 4.76, N = 11.02, S = 12.61. Found: C = 58.98, H = 4.72, N = 11.01, S = 12.58.

4-(6-Oxo-3-(4′-chlorophenyl)-5,6-dihydropyridazin-1 (4H)-yl)-*N*-(benzylcarbamothioyl) benzenesulfonamide (**2d**)

Yield = 45%, m.p 200–202°C; IR υ_{max}: 3320 (NH–CS–NH), 1671 (cyclic carbonyl), 1639 (C=N), 1585, 1545 (C=S of thiourea), 1335 and 1146 cm^{-1} (SO_2N). ^{1}H NMR: 2.79 (2H, t, –CH_2–CH_2–), 3.17 (2H, t, –CH_2–CH_2–), 4.67 (2H, d, –CH_2–C_6H_5), 7.10–7.95 (13H, m, *N*-phenyl, benzyl amine, 6-aryl protons), 8.90 (1H, s, –NH–CH_2–C_6H_5), 11.69 (1H, brs s, –NH–SO_2). ESI–MS (*m/z*): 511 (M^+−1), 536 (M^++Na). ^{13}C NMR (DMSO, δ): δ 22.16 (–CH_2 of pyridazinone), δ 27.35 (–CH_2 of pyridazinone), δ 47.67 (–CH_2NH), δ 152.24 (C=N of pyridazinone), δ 165.76 (C=O), δ 178.52 (C=S). DEPT (DMSO, δ): δ 22.15 (–CH_2 of pyridazinone), δ 27.35 (–CH_2 of pyridazinone), δ 47.67 (–CH_2NH). Anal. Calcd. for $C_{24}H_{21}ClN_4O_3S_2$: C = 56.19, H = 4.13, N = 10.92, S = 12.50. Found: C = 56.14, H = 4.09, N = 10.91, S = 12.47.

4-(6-Oxo-3-(4′-ethylphenyl)-5,6-dihydropyridazin-1 (4H)-yl)-*N*-(benzylcarbamothioyl) benzenesulfonamide (**2e**)

Yield = 60%, m.p.: 201–202°C; IR υ_{max}: 3347, 3067 and 2962 (NH–CS–NH), 1653 (cyclic carbonyl), 1587 (C=N), 1547 (C=S of thiourea), 1330 and 1141 cm^{-1} (SO_2N). ^{1}H NMR: 1.18 (3H, t, –CH_2–CH_3), 2.64 (2H, q, –CH_2–CH_3), 2.76 (2H, t, –CH_2–CH_2–), 3.14 (2H, t, –CH_2–CH_2–), 4.67 (2H, d, J = 5.1 Hz, –CH_2–C_6H_5), 7.09–7.26 (5H, m, –CH_2–C_6H_5), 7.30 (2H, d, J = 8.1 Hz, H-2′, H-5′), 7.79 (2H, d, J = 8.1 Hz, H-3′, H-5′), 7.86 (d, J = 9.00, H-3″, H-5″), 7.94 (2H, d, J = 8.7 Hz, H-2″, H-6″), 8.90 (1H, t, –NH–CH_2–C_6H_5), 11.70 (1H, s, SO_2NH). FAB-MS (*m/z*): 506 (M^+), 508 (M^++2). ^{13}C NMR (DMSO, δ): δ 15.40 (–$CH_2\underline{C}H_3$), δ 22.25 (–CH_2 of pyridazinone), δ 27.63 (–$\underline{C}H_2CH_3$), δ 27.98 (–CH_2 of pyridazinone), δ 47.70 (–NH–CH_2), δ 146.19 (C=N of pyridazinone), δ 153.48 (C-4′), δ 165.90 (C=O of pyridazinone), δ 178.00 (C=S). DEPT (DMSO, δ): δ 15.92 (–$CH_2\underline{C}H_3$), δ 22.75 (–CH_2 of pyridazinone), δ 28.13 (–$\underline{C}H_2CH_3$), δ 28.49 (–CH_2 of pyridazinone), δ 48.21 (–CH_2NH). Anal. Calcd. for $C_{26}H_{26}N_4O_3S_2$: C = 61.64, H = 5.17, N = 11.10, S = 12.71. Found: C = 61.66, H = 5.14, N = 11.08, S = 12.67.

4-(6-Oxo-3-(4′-phenoxyphenyl)-5,6-dihydropyridazin-1 (4H)-yl)-*N*-(benzylcarbamothioyl) benzenesulfonamide (**2f**)

Yield = 50%, m.p 186–188°C; IR υ_{max}: 3330, 2955, and 2924 (NH–CS–NH), 1588 (cyclic carbonyl), 1490 (C=S of thiourea), 1377 and 1157 cm^{-1} (SO_2N). ^{1}H NMR: 2.78 (2H, t, –CH_2–CH_2), 3.05 (2H, t, –CH_2–CH_2–), 4.73 (2H, s, –CH_2–C_6H_5), 7.75-7.90 (6H, m, aromatic protons), 6.99-7.32 (12H, m, aromatic protons). FAB-MS (*m/z*): 411 (Base Peak). Anal. Calcd. for $C_{30}H_{26}N_4O_4S_2$: C = 63.14, H = 4.59, N = 9.82, S = 11.24. Found: C = 63.09, H = 4.56, N = 9.81, S = 11.22.

4-((6-Biphenyl-4-yl) 6-oxo-)-5,6-dihydropyridazin-1(4H)-yl)-*N*-(benzylcarbamothioyl) benzenesulfonamide (**2g**)

Yield = 52%, m.p 192–194°C; IR υ_{max}: 3316, 3095, and 2922 (NH–CS–NH), 1656 (cyclic carbonyl), 1586 (C=N), 1542 (C=S of thiourea), 1327 and 1137 cm^{-1} (SO_2N). ^{1}H NMR: 2.81 (2H, t, –CH_2–CH_2–), 3.21 (2H, t, –CH_2–CH_2–), 4.68 (2H, s, –CH_2–C_6H_5), 7.10–7.98 (18H, m, aromatic hydrogens), 8.90 (1H, s, NH–CH_2–C_6H_5), 11.75 (1H, s, SO_2NH). FAB-MS (*m/z*): 555 (M+1), 556 ((M+2), base peak).^{13}C NMR (DMSO, δ): δ 22.22 (–CH_2 of pyridazinone), δ 27.58 (–CH_2 of pyridazinone)), δ 47.71 (–NH–CH_2), δ 153.00 (C=N of pyridazinone), δ 165.87 (C=O), δ 178.55 (C=S). DEPT (DMSO, δ): δ 22.29 (–CH_2 of pyridazinone), δ 27.65 (–CH_2 of pyridazinone)), δ 47.78 (–CH_2NH). Anal. Calcd. for $C_{30}H_{26}N_4O_3S_2$: C = 64.96, H = 4.72, N = 10.10, S = 11.56. Found: C = 64.98, H = 4.69, N = 10.13, S = 11.58.

4-(6-Oxo-3-(4′-methoxyphenyl)-5,6-dihydropyridazin-1(4H)-yl)-*N*-phenylcarbamothioyl) benzenesulfonamide (**2h**)

Yield = 37%, m.p 184–186°C; IR υ_{max}: 3282 (NH–CS–NH), 1662 (cyclic carbonyl), 1590 (C=N), 1512 and 1494 (C=S of thiourea), 1322 and 1170 cm^{-1} (SO_2N). ^{1}H NMR: 2.73 (2H, t, –CH_2–CH_2–), 3.11 (2H, t, –CH_2–CH_2–), 3.79 (3H, s, OCH_3), 4.30 (1H, s, –NH–C_6H_5), 6.71–7.86 (14H, m, aromatic hydrogens), 6.68 (1H, s, SO_2NH). FAB-MS (*m/z*): 495 (M^++1), 493 (M^+−1). Anal. Calcd. for $C_{24}H_{20}N_4O_4S_2$: C = 58.28, H = 4.48, N = 11.33,

S = 12.97. Found: C = 58.29, H = 4.45, N = 11.34, S = 12.95.

4-(6-Oxo-3-(4′-chlorophenyl)-5,6-dihydropyridazin-1(4H)-yl)-*N*-(phenylcarbamothioyl) benzenesulfonamide (**2i**)

Yield = 57%, m.p 187–188°C; IR υ_{max}: 3040 (NH–CS–NH), 1656 (cyclic carbonyl), 1587 (C=N), 1358 and 1166 cm^{-1} (SO_2N). ^1H NMR: 2.74 (2H, t, –CH_2–CH_2–), 3.13 (2H, t, –CH_2–CH_2–), 7.36–7.88 (13H, m, 6-aryl, *N*-phenyl, aniline protons). ESI–MS (*m/z*): 498 (M^+). Anal. Calcd. for $C_{23}H_{19}ClN_4O_3S_2$: C = 55.36, H = 3.84, N = 11.23, S = 12.85. Found: C = 55.31, H = 3.81, N = 11.22 S = 12.82.

4-((3-Biphenyl-4-yl) 6-oxo-)-5,6-dihydropyridazin-1 (4H)-yl)-*N*-(phenylcarbamothioyl) benzenesulfonamide (**2j**)

Yield = 36%, m.p 191–192°C; IR υ_{max} (Solvent, in cm^{-1}): 3362 and 3287 (NH–CS–NH), 1662 (cyclic carbonyl), 1588 (C=N), 1509 and 1496 (C=S of thiourea), 1326 and 1136 cm^{-1} (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 2.79 (2H, t, –CH_2–CH_2–), 3.19 (2H, t, –CH_2–CH_2–), 7.15–7.51 (8H, m, aromatic protons), 7.71–7.79 (4H, m, aromatic protons), 7.95–7.99 (5H, m, *N*-phenyl protons), 7.87 (2H, d, J = 8.70 Hz, H-2′, H-6′), 10.15 (1H, s, SO_2NH). FAB-MS (*m/z*): 476 (M^+-SO_2), 442 (base peak). ^{13}C NMR (DMSO, δ): δ 22.18 (–CH_2 of pyridazinone), δ 27.57 (–CH_2 of pyridazinone), δ 152.94 (C=N of pyridazinone), δ 165.86 (C=O), δ 177.49 (C=S). DEPT (DMSO, δ): δ 22.18 (-CH_2 of pyridazinone), δ 27.57 (–CH_2 of pyridazinone). Anal. Calcd. for $C_{29}H_{24}N_4O_3S_2$: C = 64.42, H = 4.47, N = 10.36, S = 11.86. Found: C = 64.44, H = 4.44, N = 10.37, S = 11.85.

4-(6-Oxo-3-(phenyl)-5,6-dihydropyridazin-1(4H)-yl)-*N*-(propylcarbamothioyl) benzene sulfonamide (**2k**)

Yield = 63.3%, m.p, 192-193°C; IR υ_{max} (Solvent, in cm^{-1}): 3335, 2958 and 2924 (NH–CS–NH), 1686 (cyclic carbonyl), 1543 and 1491 (C=S of thiourea), 1589 (C=N), 1318 and 1154 cm^{-1} (SO_2N). ^1H NMR (300 MHz, DMSO,δ) : 0.91 (3H, t, $\underline{C}H_3$–CH_2–CH_2–N), 1.58 (2H, m, CH_3–$\underline{C}H_2$–CH_2–N), 2.83 (2H, t, –CH_2–CH_2–), 3.16 (2H, t, –CH_2–CH_2–), 3.47 (2H, m, CH_3–CH_2–$\underline{C}H_2$–NH), 7.46–7.98 (9H, m, 6-aryl, *N*-phenyl protons), 8.21 (1H, t, –CO–$\underline{N}$H-propyl), 11.39 (1H, brs s, SO_2–$\underline{N}$H). ESI–MS (*m/z*): 429 (M−1), 453 (M^++Na). ^{13}C NMR (DMSO, δ): δ 10.97 (–$CH_2CH_2\underline{C}H_3$), δ 20.93 (–$CH_2\underline{C}H_2CH_3$), δ 22.48 (–CH_2 of pyridazinone), δ 27.66 (–CH_2 of pyridazinone), δ 145.27 (C=N of pyridazinone), δ 153.39 (C=O of pyridazinone), δ 165.78 (C=S). DEPT (DMSO, δ): δ 11.09 (–$CH_2CH_2\underline{C}H_3$), δ 20.93 (–$CH_2\underline{C}H_2CH_3$), δ 22.23 (–CH_2 of pyridazinone), δ 27.48 (–CH_2 of pyridazinone), δ 46.08 (–$NH\underline{C}H_2CH_2CH_3$). Anal. Calcd. for $C_{20}H_{22}N_4O_3S_2$: C = 55.79, H = 5.15, N = 13.01, S = 14.90. Found: C = 55.75, H = 5.13, N = 13.00, S = 14.88.

4-(6-Oxo-3-(4′-methylphenyl)-5,6-dihydropyridazin-1(4H)-yl)-*N*-(propylcarbamothioyl) benzenesulfonamide (**2l**)

Yield = 50%, m.p 188–189°C; IR υ_{max} (Solvent, in cm^{-1}): 3328, 3123, and 2965 (NH–CS–NH), 1669 (cyclic carbonyl), 1587 (C=N), 1542 and 1489 (C=S of thiourea), 1322 and 1154 cm^{-1} (SO_2N). ^1H NMR (400 MHz, DMSO,δ) : 0.80 (2H, t, –$\underline{C}H_2$–CH_2–CH_3), 1.49 (2H, m, –CH_2–$\underline{C}H_2$–CH_3), 2.31 (3H, s, –CH_3), 2.70 (2H, t, –CH_2–CH_2^-), 3.05 (2H, t, -CH_2-CH_2^-), 3.37 (2H, m, –CH_2–CH_2–$\underline{C}H_3$), 7.17 (2H, d, J = 8.00 Hz, H-2′, H-6′), 7.65 (2H, d, J = 8.00 Hz, H-3′, H-5′), 7.83 (2H, d, *N*-phenyl, J = 8.7 Hz, H-2″, H-6″), 7.88 (2H, d, *N*-phenyl, J = 8.8 Hz, H-3″, H-5‴), 8.17 (1H, t, NH–CH_2–CH_2–CH_3), 11.35 (1H, s, SO_2NH). FAB-MS (*m/z*): 443 (M^+-1), 445 (M^++1). ^{13}C NMR (DMSO, δ): δ 11.61 (–CH_2 $CH_2\underline{C}H_3$), δ 21.42 (–$CH_2\underline{C}H_2CH_3$, –CH_3), δ 22.63 (–CH_2 of pyridazinone), δ 28.02 (–CH_2 of pyridazinone), δ 46.66 (–$\underline{C}H_2CH_2CH_3$), δ 153.87 (C=N of pyridazinone), δ 166.39 (C=O), δ 178.41 (C=S). DEPT (DMSO,δ): δ 11.61 (–CH_2 $CH_2\underline{C}H_3$), δ 21.40 (–CH_3), δ 21.44 (–$CH_2\underline{C}H_2CH_3$), δ 22.63 (–CH_2 of pyridazinone), δ 28.02 (–CH_2 of pyridazinone), δ 46.66 (–$NH\underline{C}H_2CH_2CH_3$). Anal. Calcd. for $C_{21}H_{24}N_4O_3S_2$: C = 56.73, H = 5.44, N = 12.60, S = 14.43. Found: C = 56.69, H = 5.40, N = 12.59, S = 14.40.

4-(6-Oxo-3-(4′-methoxyphenyl)-5,6-dihydropyridazin-1(4H)-yl)-*N*-(propylcarbamothioyl) benzenesulfonamide (**2m**)

Yield = 78%, m.p 184–185°C; IR υ_{max} (Solvent, in cm^{-1}): 3323, 3126, 2964 (NH–CO–NH), 1668 (cyclic carbonyl), 1545 and 1514 (C=S of thiourea), 1588 (C=N), 1327 and 1155 cm^{-1} (SO_2N). ^1H NMR (300 MHz, DMSO,δ): 0.78 (3H, t, NH–CH_2–CH_2–CH_3), 1.46 (2H, q, NH–CH_2–CH_2–CH_3), 2.76 (2H, t, –CH_2–CH_2–), 3.11 (2H, t, –CH_2–CH_2–), 3.79 (3H, s, OCH_3), 7.01 (2H, d, J = 9.00 Hz, H-3′, H-5′), 7.82–7.94 (6H, m, H-2″, H-3″, H-5″, H-6″, H-2′, H-6′), 8.45 (1H, t, NH), 11.50 (1H, s, SO_2NH). FAB-MS (*m/z*): 461 (M+1). ^{13}C NMR (DMSO, δ): δ 10.98 (–CH_2 $CH_2\underline{C}H_3$), δ 20.96 (–$CH_2\underline{C}H_2CH_3$), δ 22.34 (–CH_2 of pyridazinone), δ 27.78 (–CH_2 of pyridazinone), δ 46.24

(–NHCH$_2$CH$_2$CH$_3$), δ 55.33 (–OCH$_3$), δ 153.22 (C=N of pyridazinone), δ 165.83 (C=O), δ 178.23 (C=S). DEPT (DMSO, δ): δ 11.08 (–CH$_2$CH$_2$CH$_3$), δ 20.93 (–CH$_2$CH$_2$CH$_3$), δ 22.10 (–CH$_2$ of pyridazinone), δ 27.66 (–CH$_2$ of pyridazinone), δ 46.16 (–NHCH$_2$CH$_2$CH$_3$), δ 55.30 (–OCH$_3$). Anal. Calcd. for $C_{21}H_{24}N_4O_4S_2$: C = 54.76, H = 5.25, N = 12.16, S = 13.92. Found: C = 54.72, H = 5.21, N = 12.16, S = 13.89.

4-(6-Oxo-3-(4′-chlorophenyl)-5,6-dihydropyridazin-1 (4H)-yl)-*N*-(propylcarbamothioyl) benzenesulfonamide (**2n**)

Yield = 52%, m.p 195–196°C; IR υ_{max} (Solvent, in cm^{-1}): 3326 and 3129 (NH–CS–NH), 1670 (cyclic carbonyl), 1587 (C=N), 1540 (C=S of thiourea), 1324 and 1154 cm^{-1} (SO_2N). ^{1}H NMR (300 MHz, DMSO,δ) : 0.78 (3H, t, CH$_3$–CH$_2$–CH$_2$–NH), 1.47 (2H, m, CH$_3$–CH$_2$–CH$_2$–NH), 2.79 (2H, t, –CH$_2$–CH$_2$–), 3.14 (2H, t, –CH$_2$–CH$_2$–), 7.53 (2H, d, H-3′, H-5′), 7.77–7.96 (6H, m, *N*-phenyl protons, H-2′, H-6′), 8.48 (1H, s, NH-propyl), 11.48 (1H, brs s, SO_2–NH–). ESI–MS (*m*/*z*): 464 (M^+), 487 (M^++Na). DEPT (DMSO, δ): δ 18.51 (–CH$_2$CH$_2$CH$_3$), δ 22.16 (–CH$_2$ of pyridazinone), δ 27.15 (–CH$_2$ of pyridazinone), δ 56.00 (–NHCH$_2$CH$_2$CH$_3$). Anal. Calcd. for $C_{20}H_{21}ClN_4O_3S_2$: C = 51.66, H = 4.55, N = 12.05, S = 13.79. Found: C = 51.62, H = 4.50, N = 12.04, S = 13.70.

4-(6-Oxo-3-(4′-phenoxyphenyl)-5,6-dihydropyridazin-1(4H)-yl)-*N*-(propylcarbamothioyl) benzenesulfonamide (**2o**)

Yield = 42%, m.p 183–184°C; IR υ_{max} (Solvent, in cm^{-1}): 3327, 3019 and 2926 (NH–CS–NH), 1664 (cyclic carbonyl), 1536 and 1488 (C=S of thiourea), 1587 (C=N), 1326 and 1155 cm^{-1} (SO_2N). ^{1}H NMR (300 MHz, DMSO,δ) : 0.96 (3H, t, –NH–CH$_2$–CH$_2$–CH$_3$), 1.65 (2H, m, –NH–CH$_2$–CH$_2$–CH$_3$), 2.83 (2H, t, –CH$_2$–CH$_2$–), 3.11 (2H, –CH$_2$–CH$_2$–), 3.53 (2H, m, –NH–CH$_2$–CH$_2$–CH$_3$), 7.05–8.01 (13H, m, 6-phenoxy phenyl, *N*-phenyl), 8.17 (1H, brs s, NH-propyl). ^{13}C NMR (DMSO, δ): δ 11.09 (–CH$_2$–CH$_2$–CH$_3$), δ 20.90 (–CH$_2$–CH$_2$–CH$_3$), δ 22.23 (–CH$_2$ of pyridazinone), δ 27.60 (–CH$_2$ of pyridazinone), δ 46.14 (–NH–CH$_2$–CH$_2$–CH$_3$), δ 152.85 (C=N of pyridazinone)), δ 165.83 (C=O), δ 177.96 (C=S). DEPT (DMSO, δ): δ 11.09 (–CH$_2$–CH$_2$–CH$_3$), δ 20.93 (–CH$_2$–CH$_2$–CH$_3$), δ 22.22 (–CH$_2$ of pyridazinone), δ 27.59 (–CH$_2$ of pyridazinone), δ 46.16 (–NH–CH$_2$–CH$_2$–CH$_3$). Anal. Calcd. for $C_{26}H_{26}N_4O_4S_2$: C = 59.75, H = 5.01, N = 10.72, S = 12.27. Found: C = 59.70, H = 4.99, N = 10.71, S = 12.25.

Effect of synthesized compounds on oral glucose tolerance in normal rats

Albino rats (either sex) of Wistar strain weighing 150–200 g were fasted overnight and classified into groups of six animals each. Animals of group I received only vehicle (10 ml/kg) to serve as control, while animals of given II were given glibenclamide 20 mg/kg suspended in the vehicle. The test compounds in the dose of 20 mg/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 condition) just prior to and 60 min after the glucose loading and blood glucose levels were measured with an autoanalyser by using AccuCheck Advantage II glucose kit.

Statistics and calculation

All the results were expressed as mean ± standard error mean (SEM). The data of all the groups were analyzed using one-way ANOVA followed by Dunnett's *t*-test. Percent reduction was calculated by considering the differences between the sugar level at 0 and 60 min of control animals as 100% rise in the blood sugar. A 100% reduction indicates that there is no rise in the level of blood sugar, while 0% reduction indicates that there is no reduction in the level of blood sugar.

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References

Ahmad S, Rathish IG, Bano S, Alam MS, Javed K (2010) Synthesis and biological evaluation of some novel 6-aryl-2-(*p*-sulfamylphenyl)-4,5-dihydropyridazin-3(2H)-ones as anti-cancer, antimicrobial, and anti-inflammatory agents. J Enzym Inhib Med Chem 25(2):266–271

Bashir R (2010) Synthesis of novel heterocyclic compouns of pharmaceutical interest. Ph.D. Thesis, Jamia Hamdard, New Delhi, India

Costantino L, Rastelli G, Vescovini K, Cignarella G, Vianello P, Corso AD, Cappiello M, Mura U, Barlocco D (1996) Synthesis, activity, and molecular modeling of a new series of tricyclic pyridazinones as selective aldose reductase inhibitors. J Med Chem 36:4396–4405

Costantino L, Rastelli G, Vescovini K, Cignarella G, Barlocco D (2000) Synthesis and aldose reductase inhibitory activity of a new series of benzo[*h*]cinnolinone derivatives. Farmaco 55:544–552

Courdert P, Duroux E, Bastide P, Couquelet J (1991) Synthese at evaluation de I' activite Inhibitrice d' aldose redutase de Nouvelles Diaryl pyridazin-3-ones. J Pharm Belg 46:375–380

Dvornik D (1987) In: Porte D (ed) Aldose reductase inhibition: an approach to the prevention of diabetic complications. Mcgraw Hill, New York, pp 221–323

Dvornik D (1987) In: Porte D (ed) Aldose reductase inhibition: an approach to the prevention of diabetic complications. Mcgraw Hill, New York, pp 69–151

Kecskemeti V, Bagi Z, Pacher P, Posa I, Koesis E, Koltai MZ (2002) New trends in the development of oral antidiabetic drugs. Curr Med Chem 9:53–71

Kinoshita JH, Nishimura C (1988) The involvement of aldose reductase in diabetic complications. Diabetes Metab Rev 4:323–337

Marx J (2002) Unraveling the causes of diabetes. Science 296: 686–689

Sakurai H (2002) A new concept: the use of vanadium complexes in the treatment of diabetes mellitus. Chem Rec 2:237–248

World Health Organization (WHO) (1985) Diabetes mellitus, report of a WHO study group. WHO technical series (TRS) 727. WHO, Geneva, pp 7–98