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ORIGINAL RESEARCH

Pyridazine and its related compounds. Part 34. Hypoglycemic and hypolipidemic activity of some novel condensed pyridazine sulfonamides

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Abstract A novel class of sulfonylurea and thiourea derivatives substituted with pyridazine and triazolopyridazine were designed and synthesized. The target compounds were assayed for their effects on the insulin release of alloxan-induced diabetic rats. The results showed that derivatives **4a**, **4c**, **8a**, **11a**, and **11b** have significant antihyperglycemic effect in an experimental model of diabetes mellitus. No significant differences in cholesterol levels were observed between the diabetic group and diabetic groups that received the test compounds. However, the triglycerides level was reduced significantly by compound **8a** when compared with the diabetic group.

Keywords Pyridazine · Triazolopyridazine · Sulfonamide · Sulfonylurea · Hypoglycemic activity · Hypolipidemic activity

Introduction

Non-insulin-dependent diabetes mellitus (NIDDM, type 2 diabetes) is a condition characterized by chronic hyperglycemia and a relative insulin deficiency. The kinetics of insulin secretion are changed with reduced or absent acute insulin release in response to stimulation by meals or glucose (Defronzo *et al.*, 1983), NIDDM has also been associated with an increased risk for premature arteriosclerosis due to increase in triglycerides and low-density lipoprotein levels and increased levels of alkaline phosphate and transaminases (Shanmugasundaram *et al.*, 1983).

About 70–80 % of deaths in diabetic patients are due to vascular disease. An ideal treatment of diabetes would be a drug that not only controls the glycemic levels but also prevents the development of arteriosclerosis and other complications of diabetes (Haliwell and Gutteridge, 1985).

Over the last forty years oral therapy for type 2 diabetes has focused on sulfonylureas and biguanides (Defronzo, 1999; Kecskemeti *et al.*, 2002). Sulfonylurea drugs improve glucose levels by stimulating insulin secretion by the pancreatic β-cells (Jawale *et al.*, 2012). Also, several studies have focused on changing the urea group with its bioisosterist thiourea to check the change of hypoglycemic activity (Zhang *et al.*, 2009; Faidallah *et al.*, 2011). Recently, compounds containing the pyridazine nucleus have been reported as aldose reductase (AR) inhibitors (Coudert *et al.*, 1991; Costantino *et al.*, 2000). It has been considered worthwhile to attach a pyridazine ring to sulfonylurea derivatives.

In the present study, some novel pyridazine and triazolopyridazine substituted sulfonylurea and thiourea derivatives were synthesized from corresponding sulfonamide derivatives. These were characterized by elemental analysis and various spectroscopic methods. Oral antihyperglycemic and hypolipidemic activities were assessed for some derivatives in normal and alloxan-induced rats.

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Materials and methods

Chemistry

All melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded on a BRUKER Vector 22 Germany spectrometer (KBr). ^{1}H-NMR spectra were recorded on Varian Gemini 200 MHz spectrometer and ^{13}C-NMR spectra on JMS-AX500 (125 MHz), using tetramethylsilane (TMS) as an internal reference. The Electron Impact mass spectra were obtained at 70 eV using Shimadzu QP-2010 Plus mass spectrometer. The reactions were followed up by thin layer chromatography (TLC) on silica gel F_{254} aluminum sheets (Merck), the spots were detected by UV lamp at 254–365 nm. The synthesis of 4,5,6-triphenylpyridazine-3(2H)-thione (**1a**) (Deeb and Said, 1990), ethyl 5,6-diphenylpyridazine-3(2H)-thione (**1b**) (Radwan and Bakhite, 1990), and 6,7,8-triphenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-3-thiol (**5**) (Deeb *et al.*, 2005) were conducted according to known procedure.

*Preparation of pyridazine-3-sulfonylchloride derivatives (**2a, b**)*

To a solution of 3-mercapto derivatives (**1a, b**) (2.9 mmol) in acetic acid (19 mL) and water (1 mL), chlorine gas was bubbled at 0 °C for 1 h. The reaction mixture was poured into water (250 mL) portion-wise with stirring, the precipitate was filtered, washed with water several times and dried to give 3-sulfonylchloride derivatives (**2 a, b**) yield 92 and 84 %, respectively. The respective crude sulfonylchloride, was used in the next step without further purification.

*Preparation of pyridazine-3-sulfonamide derivatives (**3a, b**)*

A mixture of 3-sulfonylchloride (**2a, b**) (2.46 mmol) and ammonium hydroxide (20 mL), was stirred at room temperature for 12 h then refluxed for 30 min. The solution was filtered on hot and the filtrate was neutralized with 6 N HCl. The solid product formed was filtered, washed with water, and recrystallized from ethanol.

*4,5,6-Triphenylpyridazine-3-sulfonamide (**3a**)* White crystals, yield 40 %, mp 198–200 °C; IR (KBr, cm^{-1}): 3,393, 3,239 (NH_2), 3,038 (CH_{arom}), 1,338, 1,144 (SO_2), MS *m/z* (%): 387 [M^+] (75.61), 323 [M^+ –SO_2] (40.0), 307 [M^+ –SO_2NH_2] (32.0), ^{1}H-NMR (DMSO-d_6), $\delta = 7.8–7.5$ (m, 15H, 3Ph), 2.7 (s, 2H, NH_2), ^{13}C-NMR (DMSO-d_6): δ (ppm): 158.9 (C-6), 157.9 (C-3), 135.4 (C-4′), 134.7(C-5), 134.5(C-6′), 133.7(C-5′), 132(C-4), 128.2, 127.7, 126.5(3Ph). Anal. Calcd. for $C_{22}H_{17}N_3O_2S$; C, 68.20; H, 4.42; N, 10.85. Found: C, 68.05; H, 4.30; N, 10.70.

*Ethyl 5,6-diphenyl-3-sulfamoylpyridazine-4-carboxylate (**3b**)* White crystals, yield 45 %, mp 190–192 °C, IR (KBr, cm^{-1}): 3,420, 3,320 (NH_2), 2,922 (CH_{aliph}), 3,055($CH_{arom.}$), 1,723 (C=O), 1,375, 1,110 (SO_2), MS *m/z* (%): 382 [M^+] (1.27), 368[M^+ –NH_2] (1.47), 264 (100), ^{1}H-NMR (DMSO-d_6), $\delta = 7.8–7.5$ (m, 10H, 2Ph), 3.9 (q, 2H, CH_2), 2.7 (s, 2H, NH_2), 1.8 (t, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ (ppm): 166.9 (C=O), 159.7 (C-3), 159 (C-6), 139 (C-5′), 136.1(C-5), 134(C-6′), 129.2, 128.7, 127.5 (2Ph), 124.3 (C-4), 61.9(CH_2), 14.1(CH_3).

Anal. Calcd for $C_{19}H_{17}N_3O_4S$: C, 59.52; H, 4.47; N, 10.96. Found: C, 59.40; H, 4.32; N, 10.80.

*General procedure for the preparation of substituted pyridazine-3-sulfonylureas (**4a, c**)*

To a solution of sulfonamide derivatives **3a, b** (2.6 mmol) in benzene (20 mL), phenyl isocyanate (0.31 g, 2.6 mmol) and potassium hydroxide (0.146 g, 2.6 mmol) were added, the reaction mixture was refluxed for 5 h. The solvent was evaporated under reduced pressure; the residue was dissolved in water and neutralized with HCl. The solid product was filtered, dried, and recrystallized from ethanol.

*4,5,6-Triphenylpyridazine-3-sulfonyl-N-phenyl urea (**4a**)* Yellow crystals, yield 84.6 %, mp 262–264 °C, IR (KBr, cm^{-1}): 3,317, 3,450 (NH), 1,642 (C=O), 1,339, 1,107 (SO_2), MS *m/z* (%): 506 [M^+] (0.51), 429 [M^+ –Ph] (0.01), 369[M^+ –urea] (0.45), 55 (100); ^{1}H-NMR (DMSO-d_6) $\delta = 8.4$(s, 2H, NHCONH), 7.53–7.32 (m, 15H, 3Ph), 7.06–7.01 (m, 5H, NHPh). ^{13}C-NMR (DMSO-d_6) δ (ppm): 158.9 (C-6), 157.9 (C-3), 151(C=O), 138.4 (NHC_6H_5), 135.4 (C-4′), 134.7 (C-5), 134.5 (C-6′), 133.7 (C-5′), 132 (C-4), 128.2, 127.9, 127.7, 127, 126.5 (4Ph), 120.6 (C-2′, NHPh). Anal. Calcd for $C_{29}H_{22}N_4O_3S$: C, 68.76; H, 4.38; N, 11.06. Found: C, 68.60; H, 4.20; N, 10.87.

*Ethyl 3-(sulfonyl-N-phenyl urea)-5,6-diphenylpyridazine-4-carboxylate (**4c**)* White crystals, yield 76.9 %, mp 241–242 °C, IR(KBr, cm^{-1}): 3,390, 3,274 (2NH), 3,030 (CH_{arom}), 2,918 (CH_{aliph}), 1,783 (C=O ester), 1,680 (C=O amide), 1,310, 1,144 (SO_2), MS *m/z* (%): 502 [M^+] (65.22), 501 [M^+-1] (63.39),455 [M^+ –OC_2H_5] (67.51), 173 (100), ^{1}H-NMR (DMSO-d_6), $\delta = 8.72$(s, 2H, NHCONH), 7.5–7.3(m, 10H, 2Ph), 7.06–7.01(m, 5H, NHPh), 3.38(q, 2H, CH_2), 1.3(t, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ (ppm): 164.9 (C=O, ester), 157.7 (C-3), 157 (C-6), 151 (C=O, amide), 138.4 (C-1, NHPh), 137(C-5′), 134.1(C-5), 132 (C-6′), 128.2, 127.9, 127.7, 127, 126.5 (3Ph), 123.3(C-4), 120.6 (C-2, NHPh), 61.9 (CH_2), 15.1

(CH_3). Anal. Calcd for $C_{26}H_{22}N_4O_5S$: C, 62.14; H, 4.41; N, 11.15. Found: C, 62.01; H, 4.26; N, 10.90.

*Preparation of 4,5,6-triphenyl pyridazine-3-sulfonyl-N-ethyl thiourea (**4b**)*

Sulfonamide derivative **3a** (1.0 g, 2.6 mmol), ethyl isothiocyanate (0.23 g, 2.6 mmol), and potassium hydroxide(0.146 g, 2.6 mmol) were refluxed in benzene for 5 h, the solvent was evaporated under reduced pressure, and the residue was dissolved in water and neutralized with HCl. The solid product was filtered, dried, and recrystallized from ethanol to give (**4b**). Yellow crystals, yield 75.0 %, mp 286–288 °C, IR (KBr, cm^{-1}): 3,404, 3,350 (NH), 3,080 ($CH_{arom.}$), 2,917 (CH_{aliph}), 1,368, 1,150 (SO_2), 1,246 (C=S), MS *m/z* (%): 474 [M^+] (0.02), 387 [M^+ –C_2H_5NCS] (0.10), 339 (100), ^{1}H-NMR (DMSO-d_6), δ = 7.48–7.23 (m, 10H, 2Ph), 4.43 (q, 2H, NH$\underline{CH_2}CH_3$), 4.3 (q, 2H, $\underline{CH_2}CH_3$), 3.5 (s, 2H, NHCSNH), 1.8–1.75 (m, 6H, $2CH_3$), ^{13}C-NMR (DMSO-d_6) δ (ppm): 186.2 (C=S), 161.9 (C-6), 160.9 (C-3), 138.4 (C-4′), 137.7 (C-5), 137.5 (C-6′), 136.7 (C-5′), 135 (C-4), 131.2, 130.7, 129.5 (3Ph), 42 (CH_2), 17.2 (CH_3). Anal. Calcd for $C_{25}H_{22}N_4O_2S_2$: C, 63.27; H, 4.67; N, 11.80. Found: C, 63.10; H, 4.50; N, 11.65.

*Preparation of 6,7,8-triphenyl-[1,2,4]triazolo[4,3-b]pyridazine-3-sulfonylchloride (**6**)*

To a solution of 3-mercapto derivative (**5**) (1.0 g, 2.6 mmol) in acetic acid (19 mL) and water (1 mL), chlorine gas was bubbled at 0 °C for 1 h, then the reaction mixture was added to water drop wise with stirring, the formed precipitate was filtered, washed with water several times and dried, yield 90.5 %.

*Preparation of 6,7,8-triphenyl-[1,2,4]triazolo[4,3-b]pyridazine-3-sulfonamide (**7**)*

A mixture of sulfonylchloride **6** (1.0 g, 2.2 mmol) and ammonium hydroxide (20 mL), was stirred for 12 h then refluxed for 30 min. The reaction mixture was filtered while hot and the filtrate was neutralized with 6 N HCl. The solid product was filtered, washed with water and recrystallized from ethanol to give the corresponding sulfonamide **7**. Yield 60 %, mp 180–182 °C. IR(KBr, cm^{-1}): 3,361, 3,200 (NH_2), 3,038 ($CH_{arom.}$), 1,360, 1,168 (SO_2), MS *m/z* (%): 428 [M^+ +1] (16.83), 427 [M^+] (49.05), 347 [M^+ –SO_2NH_2] (21.38), 426 (100), ^{1}H-NMR (DMSO-d_6), δ = 7.8–7.5 (m, 15H, 3Ph), 2.72 (s, 2H, NH_2), ^{13}C-NMR (DMSO-d_6) δ (ppm): 158.7 (C-6), 153.1 (C-8′), 150 (C-3), 138.4 (C-8″), 138 (C-8), 137.4 (C-7), 136.7 (C-7′), 135 (C-6′), 131.2, 130.7, 129.5 (3Ph). Anal. Calcd for $C_{23}H_{17}N_5O_2S$: C, 64.62; H, 4.01; N, 16.38. Found: C, 64.48; H, 3.87; N, 16.24.

*Preparation of 6,7,8-triphenyl-[1,2,4]triazolo[4,3-b]pyridazine-3-sulfonyl-N-phenylurea (**8a**)*

To a solution of sulfonamide derivative **7** (1.0 g, 2.3 mmol) in benzene (20 mL), phenyl isocyanate (0.28 g, 2.3 mmol) and potassium hydroxide (0.131 g, 2.3 mmol) were added, the reaction mixture was refluxed for 6 h. The solvent was evaporated under reduced pressure, the residue was dissolved in water and neutralized with HCl. The solid product was filtered, dried, and recrystallized from ethanol to give **8a**. Yield 78.0 %, mp 236–238 °C, IR (KBr, cm^{-1}): 3,400, 3,335 (NH), 3,052 ($CH_{arom.}$), 1,627 (C=O), 1,273, 1,148 (SO_2), MS *m/z* (%): 546 [M^+] (0.06), 548 [M^+ –Ph], (0.02), 439 (100), ^{1}H-NMR (DMSO-d_6), δ = 7.8 (s, 2H, NHCONH), 7.09–6.8(m, 15H, 3Ph), 6.7–6.4(m, 5H, NH$\underline{Ph}$). ^{13}C-NMR (DMSO-d_6) δ (ppm): 157.7 (C-6), 153 (C=O), 152.1 (C-8′), 149 (C-3), 140.4 (C-1, NHPh), 137.4 (C-7), 137 (C-8), 136.4 (C-7), 135.7 (C-7′), 134 (C-6′), 130.2, 129.9, 129.7, 129, 128.5 (4-Ph), 122.6 (C-2, NHPh). Anal. Calcd for $C_{30}H_{22}N_6O_3S$: C, 65.92; H, 4.06; N, 15.38. Found: C, 65.78; H, 3.89; N, 15.20.

*Preparation of N-(ethylcarbamothioyl)-6,7,8-triphenyl-[1,2,4]triazolo[4,3-b]pyridazine-3-sulfonamide (**8b**)*

To a solution of sulfonamide derivative **7** (1.0 g, 2.3 mmol) in benzene ethyl isothiocyanate (0.31 g, 2.3 mmol) and potassium hydroxide (0.131 g, 2.3 mmol) were added, the reaction mixture was then refluxed for 6 h, then solvent was evaporated to dryness at reduced pressure, residue was triturated with water, neutralized with HCl, filtered, dried, and recrystalized from Ethanol to give **8b**. Yield (75.0 %), m.p. 198–200 °C, IR (KBr, cm^{-1}): 3,423, 3,257(NH), 3,073 (CH_{arom}), 2,929 ($CH_{aliph.}$), 1,333, 1,146 (–SO_2), 1,289 (–C=S), MS *m/z (%)*: 514 (M^+, 0.04), 437(M^+–Ph, 0.03), 486(M^+–CH_2CH_3, 0.03), 426(100), ^{1}H-NMR (DMSO-d_6), δ = 7.58–7.35 (m, 15H, 3Ph), 3.48 (s, 2H, NHCSNH), 4.43 (q, 2H, NH$\underline{CH_2}CH_3$), 1.8 (t, 3H, CH_3), ^{13}C-NMR (DMSO-d_6) δ (ppm): 185.2 (C=S), 157.7 (C-6), 152.1 (C-8′), 149 (C-3), 137.4 (C-8″), 137 (C-8), 136.4 (C-7), 135.7 (C-7′), 134 (C-6′), 130.2, 129.7, 128.5 (3Ph), 41 (CH_2), 16.2 (CH_3). Anal. Calcd for $C_{26}H_{22}N_6O_2S_2$: C, 60.68; H, 4.31; N, 16.33. Found: C, 60.50; H, 4.15; N, 16.18.

*General procedure for the preparation of sulfonylurea derivatives (**11a, b**)*

To a solution of sulfonamide derivatives **10a**, **b** (2.3 mmol) in benzene (20 mL), phenyl isocyanate (2.3 mmol) and potassium hydroxide (2.3 mmol) were added. The reaction mixture was refluxed for 6 h. The solvent was evaporated under reduced pressure, the residue was dissolved in water (10 mL) and neutralized with HCl. The solid product

was filtered, dried, and recrystallized from ethanol to give (**11a**, **b**).

*4-((4-Cyano-5,6-diphenylpyridazin-3-yl)amino)-N-(phenylcarbamoyl)benzenesulfonamide (**11a**)* Yellow crystals, yield 86.6 %, mp 220–222 °C, IR (KBr, cm^{-1}): 3,404, 3,259, 3,117 (NH), 3,055($CH_{arom.}$), 2,215 (CN), 1747 (C=O), 1,338, 1,149 (SO_2); MS *m/z* (%): 547 [M^+ +1] (9.6), 453 [M^+ –PhNH] (13.73), 427 [M^+ –CONHPh] (41.49), 57 (100), ^{1}H-NMR (DMSO-d_6), δ = 3.8(s, 1H, NH), 8.4(s, 2H, NHCONH),7.89–7.8(m, 10H, 2Ph), 7.73–7.43(m, 5H, NHPh), 7.42–7.26(m, 4H, C_6H_4). ^{13}C-NMR (DMSO-d_6) δ (ppm): 164.4 (C-3), 153 (C=O), 152 (C-6), 145.1(C-5), 140.4(C-1″, NHCONHPh), 134 (C-6′), 133.2 (C-5′), 131(C-3′, NHC_6H_4), 130.2, 129.9, 129.7, 129, 128.5, 122.6, 114.8 (4Ph), 113.7 (CN), 98.8 (C-4). Anal. Calcd for $C_{30}H_{22}N_6O_3S$: C, 65.92; H, 4.06; N, 15.83. Found: C, 65.77; H, 3.91; N, 15.20.

*Ethyl 5,6-diphenyl-3-((4-(N-(phenylcarbamoyl)sulfamoyl) phenyl)amino)pyridazine-4-carboxylate (**11b**)* Yellow crystals, yield 72 %, mp 278–280 °C, IR (KBr, cm^{-1}): 3,330, 3,250 (NH), 3,055 (CH_{arom}), 2,920 (CH_{aliph}), 1,711 (C=O ester), 1,662 (C=O amide), 1,394, 1,152 (SO_2), MS *m/z* (%): 592[M^+ −1] (0.21), 564 [M^+ –C_2H_5] (0.21), 472 [M^+ –CONHPh] (0.24), 457 [M^+ –NHCONHPh] (0.22),57 (100); ^{1}H-NMR (DMSO-d_6), δ = 8.74(s, 2H, NHCONH), 7.38–7.33 (m, 10H, 2Ph), 7.06–7.01(m, 5H, NHPh), 3.42 (q, 2H, CH_2), 1.9 (t, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ (ppm): 164.9 (C=O, ester), 158.2 (C-3), 151(C=O, amide), 143.2 (C-6), 143.1(C-1′, NHC_6H_4), 138.4 (C-1″, NHCONHPh), 137 (C-5′), 136.1 (C-5), 132(C-6′), 129.8, 129, 128.2, 127.9, 127.7,127, 126.5, 120.6 (4Ph), 111.6 (C-4), 60.9(CH_2), 14.1(CH_3). Anal. Calcd for $C_{32}H_{27}N_5O_5S$: C, 64.74; H, 4.58; N, 11.80. Found: C, 64.60; H, 4.43; N, 11.65.

*General procedure for the preparation of sulfonylthiourea derivatives (**11c**, **d**)*

To a solution of sulfonamide derivatives **10a**, **b** (2.3 mmol) in benzene (20 mL), ethyl isothiocyanate (0.25 g, 2.3 mmol) and potassium hydroxide (0.12 g, 2.3 mmol) were added; the reaction mixture was refluxed for 6 h.; the solvent was evaporated under reduced pressure; and the residue was dissolved in water and neutralized with HCl. The solid product was filtered, dried, and recrystallized from ethanol to give (**11c**, **d**).

*4-((4-cyano-5,6-diphenylpyridazin-3-yl)amino)-N-(ethylcarbamothioyl) benzenesulfonamide (**11c**)* White crystals, yield 80.4 %, mp 208–210 °C, IR (KBr, cm^{-1}): 3,396, 3,329, 3,281 (NH), 2,215 (CN), 1,327, 1,145 (SO_2), 1,217 (C=S), MS *m/z* (%): 482 [M^+] (19.93), 452 [M^+ –CH_2CH_3] (15.24), 426 [M^+ –CN, –CH_2CH_3] (100.0), ^{1}H-NMR (DMSO-d_6), δ = 7.58–7.43 (m, 10H, 2Ph), 7.48–7.35 (m, 4H, C_6H_4), 4.4 (s, 1H, NH), 4.43 (q, 2H, $NHCH_2CH_3$), 3.5 (s, 2H, NHCSNH), 1.82 (t, 3H, CH_3), ^{13}C-NMR (DMSO-d_6) δ (ppm): 183.2 (C=S), 162.4(C-3), 150 (C-6), 143.1 (C-1′), 132 (C-6′), 131.2 (C-5′), 129, 128.2, 127.7, 126.5 (4Ph), 112.8 (CN), 96.8 (C-4), 41 (CH_2), 16.2 (CH_3). Anal. Calcd for $C_{26}H_{22}N_6O_2S_2$: C, 60.68; H, 4.31; N, 16.33. Found: C, 60.50; H, 4.15; N, 16.17.

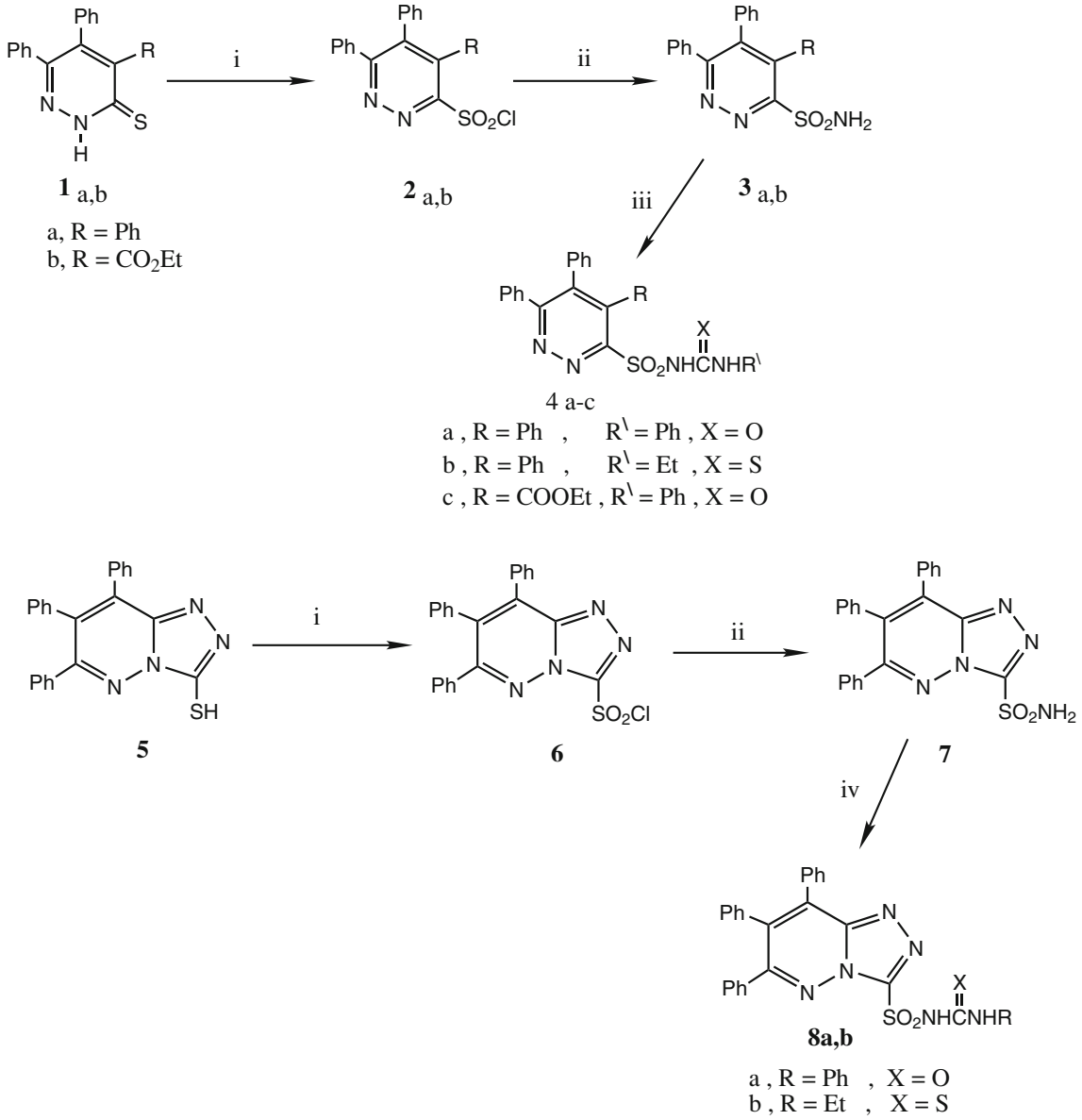
*Ethyl 3-((4-(N-(ethylcarbamothioyl)sulfamoyl)phenyl)amino)-5,6-diphenylpyridazine-4-carboxylate (**11d**)* White crystals, yield 67 %, mp 268–270 °C, IR (KBr, cm^{-1}): 3,561, 3,435 (NH), 3,061 ($CH_{arom.}$), 2,918 (CH_{aliph}), 1,712 (C=O ester), 1,400 (C=S), 1,360, 1,150 (SO_2), ^{1}H-NMR (DMSO-d_6), δ = 7.58–7.43 (m, 10H, 2Ph), 7.48–7.35 (m, 4H, C_6H_4), 4.4 (s, 1H, NH), 4.32 (q, 2H, $NHCH_2CH_3$), 4.25 (q, 2H, CH_2CH_3), 3.51 (s, 2H, NHCSNH) 1.83–1.75 (m, 6H, $2CH_3$), ^{13}C-NMR (DMSO-d_6) δ (ppm): 186.2 (C=S), 167.9 (C=O), 161.2 (C-3), 146.2 (C-6), 140 (C-5′), 139.1 (C-5), 135 (C-6′), 132, 131.2, 130.7, 129.5, 115.8(3Ph), 114.6 (C-4), 62.9 (OCH_2), 41 ($NHCH_2$), 16.2($NHCH_2CH_3$), 14.1(OCH_2CH_3). MS *m/z* (%): 560 [M^+ −1] (6.08), 43 (100), Anal. Calcd for $C_{28}H_{27}N_5O_4S$: C, 59.87; H, 4.85; N, 12.47. Found: C, 59.70; H, 4.71; N, 12.32.

*Preparation of 4-((4-cyano-5,6-diphenylpyridazin-3-yl) amino)-N-(phenylcarbamothioyl)benzenesulfonamide (**11e**)*

Sulfonamide derivative **10a** (1.0 g,2.3 mmol), phenyl isothiocyanate (0.31 g, 2.3 mmol), and potassium hydroxide (0.13 g, 2.3 mmol) were refluxed in benzene (20 mL) for 6 h. The solvent was evaporated under reduced pressure; the residue was dissolved in water and neutralized with HCl. The solid product was filtered, dried, and recrystallized from acetone to give **11e**, white crystals, yield 80.6 %, mp 203–205 °C, IR (KBr, cm^{-1}): 3,400, 3,350, 3,277 (NH), 2,215 (CN), 1,229 (C=S), 1,324, 1,147 (SO_2), ^{1}H-NMR (DMSO-d_6), δ = 7.8–6.81 (m, 19H, ArH), 4.4 (s, 2H, NHC_6H_4, NHPh), 3.5 (s, 1H, NHCSNHPh), ^{13}C-NMR (DMSO-d_6) δ (ppm): 182.2 (C=S), 161.4 (C-3), 149 (C-6), 142.1 (C-5), 136.5 (C-1″, NHCSNHPh), 131 (C-6′), 130.2 (C-5′), 129.8, 128, 127.2, 127, 126.7, 126.4, 125.5, 124.5 (4Ph), 111.7 (CN), 95.8 (C-4). MS *m/z* (%): 562 [M^+] (7.32), 426 [M^+ –CN, –Ph] (100.0), Anal. Calcd for $C_{30}H_{22}N_6O_2S_2$: C, 64.04; H, 3.49; N, 14.94. Found: C, 63.84; H, 3.81; N, 14.80.

Results and discussion

The sulfonylurea derivatives as the target compounds depicted in (Scheme 1) were obtained by allowing the



Scheme 1 Synthesis of derivatives $\mathbf{2}_{\mathbf{a,b}}$, $\mathbf{3}_{\mathbf{a,b}}$, $\mathbf{4}_{\mathbf{a–c}}$, **6**, **7**, and $\mathbf{8}_{\mathbf{a,b}}$. Reagents and conditions *i* Cl_2, AcOH, H_2O; *ii* NH_4OH; *iii* R′NCX, C_6H_6, KOH; and *iv* RNCX, C_6H_6, KOH

pyridazinethione derivatives (**1a**, **b**) (Deeb and Said, 1990; Radwan and Bakhite, 1990) to oxidatively chlorinate with chlorine gas in the presence of 90 % acetic acid at 0 °C, the corresponding sulfonyl chlorides (**2a**, **b**) were obtained. In the same manner, triazolopyridazine-3-sulfonyl chloride (**6**) was prepared starting from triazolopyridazine-3-thiol (**5**) (Deeb *et al.*, 2005).

Because of the instability of sulfonyl chlorides, the crude products of sulfonyl chloride derivatives **2a**, **b** and **6** were converted directly to the more stable sulfonamides **3** and **7** by treatment with aqueous ammonia. The sulfonyl chloride derivatives **2** and **6** were identified by their corresponding sulfonamides **3** and **7**. The IR spectra of **3** and **7** are characterized by bands at 3,300–3,200 cm^{-1}(NH), and characteristic absorption bands in the regions of 1,134–1,152 and 1,358–1,377 cm^{-1} corresponding to symmetrical and asymmetrical vibrations of SO_2 group. Compound **3b** shows an additional carbonyl band at 1,740–1,720 $cm^{-1,}$ these sulfonamide derivatives **3** and **7** on further treatment with phenyl isocyanate and with ethyl isothiocyanate in dry benzene containing KOH yield the desired substituted sulfonylureas (**4a–c**) and (**8a**, **b**). These were characterized by elemental analysis and various spectroscopic methods such as IR, 1H-NMR, and MS.

Finally, for further extension of SAR study, we aimed to synthesize a new series of sulfonylureas (**11a–e**) to

investigate the effect of the aniline group which is positioned *para* to the sulfone group and sulfonylurea derivatives to study the effect of this modification upon the required activity as antidiabetic agents.

The synthesis of 4-(4-cyano-5, 6-diphenylpyridazin-3-ylamino)benzene sulfonamide (**10a**) was prepared using a previously described method (El-Mariah *et al.*, 2009) wherein 4-aminobenzene sulfonamide was condensed with 3-chloro-4-cyano-5,6-diphenylpyridazine (**9a**).

Similarly, ethyl 3-chloro-5,6-diphenylpyridazine-4-carboxylate (**9b**) (Schmidt and Druey, 1954) reacted with 4-aminobenzene sulfonamide in refluxed 1-butanol to form ethyl 5,6-diphenyl-3-[(4-sulamoyl)phenyl amino]pyridazine-4-carboxylate (**10b**) in 83 % yield.

These sulfonamide derivatives **10a**, **b** on further treatment with phenyl isocyanate in dry benzene containing KOH yield the desired substituted sulfonylureas (**11a**, **b**) (Scheme 2). Similarly, refluxing compound (**10a**, **b**) with ethyl isocyanate in benzene/KOH produces substituted sulfonylthioureas (**11c**, **d**).

In the same manner, refluxing compounds **10a**, **b** with phenyl isothiocyanate in benzene/KOH produces substituted sulfonylthioureas **11a–e**. Elemental and spectral analyses of all prepared compounds described are consistent with the assigned structures.

Hypoglycemic activity

The hypoglycemic activity of sulfonylurea derivatives **4a**, **4c**, **8a**, **11a**, and **11b** was studied in diabetic rats and was induced by administration of alloxan at a dose of 150 mg/Kg. The reference drug was Gliclazide (Diamicron). Standard environmental conditions such as temperature (26 ± 2 °C) and relative humidity (45–55 %) were maintained. All the animals were fed with rodent pellet diet and water was allowed *ad-libtum* under strict hygienic conditions. Ethical clearance for performing the experiments on animals was obtained from Institutional Animal Ethics Committee.

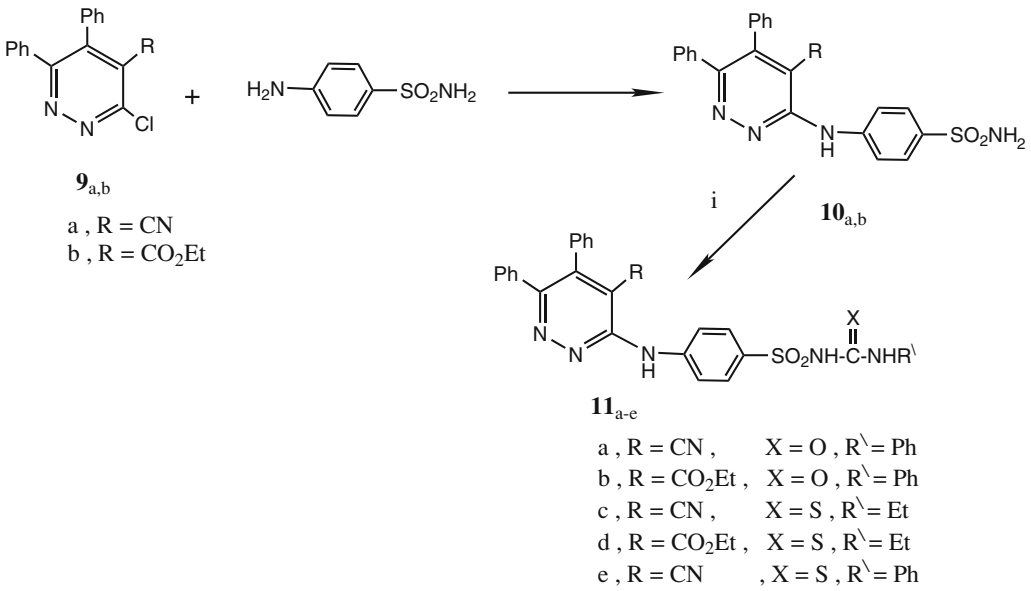
The animals fasted for 24 h before induction of diabetes. The induction of hyperglycemia involves the intra-peritoneal injection of freshly prepared alloxan monohydrate. Forty-eight hours later, blood sample were collected from 8 h fasted animals from the retro-orbital plexus in capillary tubes (Micro Hemocrit capillary, Mucaps) and serum was separated within 30 min. after collection using centrifuge at 2,000 rpm for 2 min for estimation of glucose and lipid profile.

The rats were randomly divided into seven groups and labeled. Drugs were orally administrated at a dose of 20 mg/kg daily for two weeks after diabetes induction as follows:

Group 1: received saline and served as diabetic group.

Group 2: received gliclazide and served as standard group.

Groups 3, 4, 5, 6, and 7: received compounds **4a**, **4c**, **8a**, **11a**, and **11b**, respectively. Following the administration of the drugs outlined above, blood was withdrawn from rats on day 15 and used for measurement of glucose (Trinder, 1969), triglycerides (Fassati and Prencipe, 1982), and cholesterol (Richmond, 1973). Glucose, triglycerides, and cholesterol were estimated by enzymatic methods using diagnostic kit (Biodiagnostic Company).



Scheme 2 Synthesis of derivatives $\mathbf{10_{a,b}}$ and $\mathbf{11_{a–e}}$. Reagents and conditions *i* R′NCX, benzene, KOH, reflux

The results of the present study indicate that the compounds were found to reduce the glucose levels in animals and demonstrated significant antidiabetic activity. The results also indicated that these compounds can reduce the levels of serum triglyceride which confirms the possibility that the major function of the compounds depends on the protection of vital tissues (liver) including the pancreas, thereby reducing the incidence of diabetes in the experimental animals.

It was found that compounds **4a**, **4c**, **8a**, **11a,** and **11b** in tests reduced the blood glucose content by 77.5, 84.93, 86.3, 83.4, and 81.4 %, respectively (Table 1; Fig. 1).

No significant differences in cholesterol levels were observed between the diabetic group and diabetic groups that received the test compounds (Table 2; Fig. 2).

Table 1 Hypoglycemic activity of compounds in rats with alloxan-induced diabetes

Groups	Day 2	Day 15
Diabetic rats	851.11 ± 20.23	294.05 ± 10.01
Gliclazide 20 mg/kg	501.15 ± 40.05	160.70 ± 3.52*
4a	662.15 ± 8.46	184.70 ± 3.52
4c	870.00 ± 100.05	131.10 ± 7.18*
8a	780.48 ± 37.58	129.4 ± 2.71*
11a	756.37 ± 15.65	140.50 ± 3.75*
11b	1037.05 ± 20.28	142.40 ± 5.94*

Glucose level: mg/dl

Values represent the mean ± s.e. of 6 rats for each group

* $P < 0.05$ versus diabetic control using one way ANOVA followed by Dunnett's as post hoc test

Table 2 Cholesterol and triglycerides mg/dl

Groups	Cholesterol	Triglycerides
Diabetic rats	66.70 ± 5.05	167.20 ± 10.52
Gliclazide 20 mg/kg	48.65 ± 3.45	152.23 ± 12.26
4a	97.85 ± 7.76*	197.70 ± 9.01
4c	76.88 ± 7.22	121.50 ± 7.99
8a	66.77 ± 6.91	99.55 ± 5.19*
11a	66.61 ± 7.1	137.10 ± 4.99
11b	72.37 ± 6.28	161.30 ± 5.21

Values represent the mean ± s.e. of 6 rats for each group

* $P < 0.05$ versus diabetic control using one way ANOVA followed by Dunnett's as post hoc test

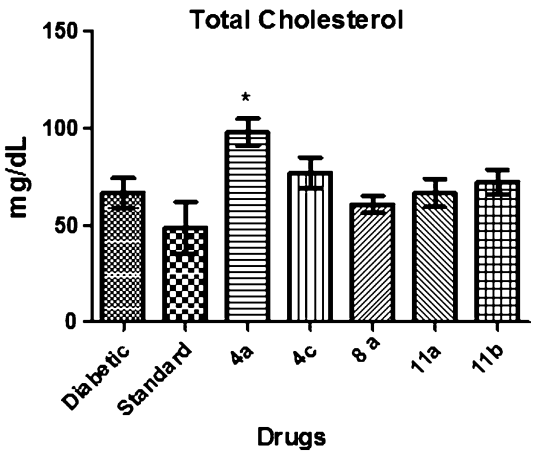


Fig. 2 Values represent the mean ± s.e. of 5–6 rats for each group. *$P < 0.05$ versus diabetic control using one way ANOVA followed by Dunnett's as post hoc test

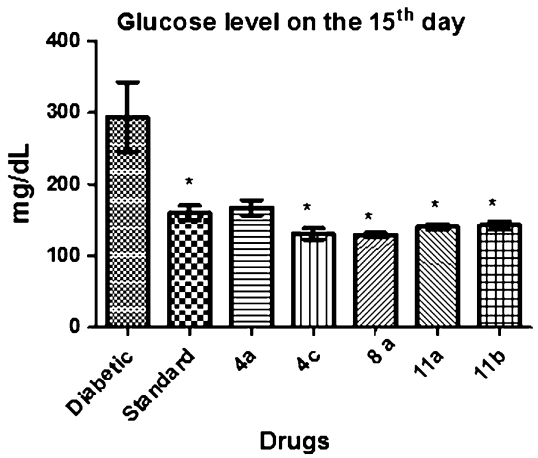


Fig. 1 Values represent the mean ± s.e. of 5–6 rats for each group. *$P < 0.05$ versus diabetic control using one way ANOVA followed by Dunnett's as post hoc test

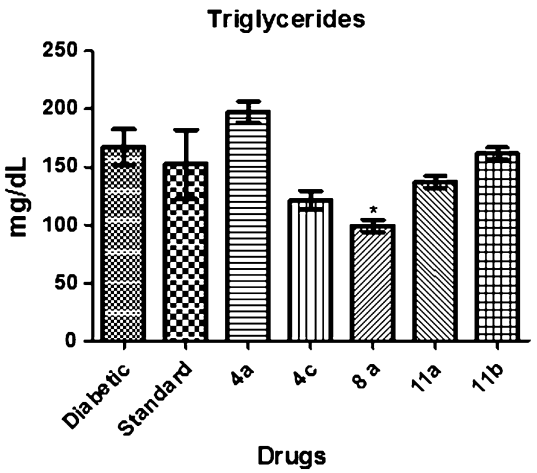


Fig. 3 Values represent the mean ± s.e. of 5–6 rats for each group. *$P < 0.05$ versus diabetic control using one way ANOVA followed by Dunnett's as post hoc test

However, the triglycerides level was reduced by compound **8a** by 40.5 % when compared with the diabetic group (Table 2; Fig. 3).

Conclusion

In summary, we have developed a novel class of sulfonylurea derivatives substituted with pyridazine and triazolopyridazine derivatives as potential hypoglycemic agents, these compounds increase the insulin release of rats in the alloxan-induced diabetes. Compound **8a** with triazole ring fused with pyridazine nucleus showed a remarkable antihyperglycemic activity than that of the non-condensed pyridazine nucleus in case of compound **4c**. Also, it is noticeable that when regarding substitutions at position 3 of the pyridazine nucleus in case of compounds **11a** and **11b**, it is clear that the presence of cyano group on the ring give higher activity than that in case of ester group, this in turn reveals that there is a significant relation between activity and substituent on the pyridazine nucleus.

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References

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

Coudert P, Duroux E, Bastide P, Couquelet J, Tronche P (1991) Synthesis and evaluation of the aldose reductase inhibitory activity of new diaryl pyridazine-3-ones. J Pharm Belg 46(6):375–380

Deeb A, Said S (1990) Studies on polyazaindenes synthesis of several new condensed pyridazine derivatives collect. Czech Chem Commun 55:2795–2799

Deeb A, Hassaneen M, Kotb M (2005) Pyridazine derivatives and related compounds, part 8: synthesis of different heterocycles from 3-hydrazinopyridazine. Heteroat Chem 12:278–282

DeFronzo RA (1999) Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med 131:281–303

DeFronzo RA, Ferrannini E, Koivisto V (1983) New concepts in the pathogenesis and treatment of noninsulin-dependent diabetes mellitus. Am J Med 74:52–81

El-Mariah F, Nassar E, Hosny M, Deeb A (2009) Pyridazine derivatives and related compounds, part 28.1 pyridazinesulfonamides: synthesis and antimicrobial activity phosphorus. Sulfur Silicon 184:92–102

Faidallah HM, Khan KA, Asiri AM (2011) Synthesis and biological evaluation of new 3-trifluoromethylpyrazolesulfonyl-urea and thiourea derivatives as antidiabetic and antimicrobial agents. J Fluor Chem 132(2):75–146

Fassati P, Prencipe L (1982) Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. Clin Chem 28:2077–2080

Haliwell B, Gutteridge JM (1985) Free radicals in biology and medicine, 2nd edn. Clarendon Press, Oxford

Jawale DV, Pratap UR, Rahuja N, Srivastava AK, Mane RA (2012) Synthesis and antihyperglycemic evaluation of new 2,4-thiazolidinediones having biodynamic aryl sulfonylurea moieties. Bioorg Med Chem Lett 22(1):436–439

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

Radwan S, Bakhite E (1990) Synthese neuer Thieno[2,3-*c*]pyridazine und verwandter Heterocyclen. Monatshefte Für Chemie 130(9):1117–1128

Richmond W (1973) Preparation and properties of a cholesterol oxidase from *Nocardia* sp. and its application to the enzymatic assay of total cholesterol in serum. Clin Chem 19:1350–1356

Schmidt P, Druey J (1954) Heilmittelchemische Studien in der heterocyclischen Reihe. 5. Mitteilung. Pyridazine II. Eine neue Pyridazinsynthese Helv. Chem Acta 37:134–139

Shanmugasundaram KR, Panneerselvam C, Samudram P, Shanmugasundaram ER (1983) Enzyme changes and glucose utilization in diabetic rabbits: the effect of *Gymnema sylvestre*. J Ethnopharmacol 7:205–234

Trinder P (1969) Enzymatic method of glucose estimation. Ann Clin Biochem 6:24–33

Zhang H-B, Zhang Y-A, Wu G-Z, Zhou J-P, Huang W-L, Hu X-W (2009) Synthesis and biological evaluation of sulfonylurea and thiourea derivatives substituted with benzenesulfonamide groups as potential hypoglycemic agents. Bioorg Med Chem Lett 19(6):1740–1744