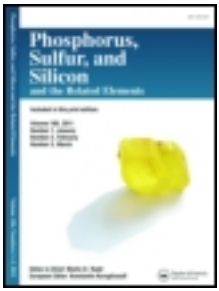

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Synthesis and Blood Glucose Lowering Activity of Novel Benzenesulfonyl-Urea Derivatives

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Synthesis and Blood Glucose Lowering Activity of Novel Benzenesulfonyl-Urea Derivatives

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*Treatment of the pyridazinone derivatives (**1a**, **1b**) with ethyl chloroformate afforded novel carbamates (**2a**, **2b**). Subsequent treatment of **2a**, **2b** with appropriate amines gave novel benzenesulfonylurea derivatives (**3a–i**). All these compounds were characterized on the basis of ^{1}H NMR, IR, Mass spectral data and elemental analysis results. Preliminary biological testing of urea derivatives revealed that some compounds possess significant blood sugar lowering activity. Four compounds (**3c**, **3f**, **3g**, and **3h**) were found to have promising blood glucose lowering activity and may be used as lead compounds for developing new antidiabetic drugs.*

Keywords Benzenesulfonylurea; carbamates; diabetes; pyridazinones

INTRODUCTION

Diabetes mellitus is one of the most daunting challenges posed by chronic diseases. Recent data show that approximately 135 million people suffer from diabetes mellitus worldwide, and that this number will rise to almost 300 million by the year 2025. Thus, a more than twofold rise is projected to occur because of population ageing, unhealthy diets, obesity, and a sedentary lifestyle. Though the rise will be of the order of 45% in developed countries, it will be almost 200% in developing countries.[1] India has 35 million diabetics. As per World Health Organization data, the number will reach 50 million in 2020.[2] Diabetes mellitus is generally classified as Type-I insulin-dependent diabetes mellitus (IDDM), caused by low or insufficient secretion of

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insulin by the pancreas, and Type-II non-insulin-dependent diabetes mellitus (NIDDM), caused due to insufficient utilization of insulin.[1,3] NIDDM is the most common form of diabetes, constituting nearly 90% of the diabetic population in any country.

Chronic diabetes is accompanied by complications such as neuropathy, nephropathy, cataracts, and retinopathy, which are not controlled by insulin. These complications are caused by accumulation of sorbitol, which is produced from glucose by aldose reductase (AR) in polyol pathway.[4,5] Over the last 40 years, oral therapy for Type-2 DM has focused on sulfonylureas and biguanides.[6] Sulfonylureas, which are widely used as hypoglycemic agents for NIDDM, strongly inhibit ATP-sensitive K+ channel activity by binding to sulfonylurea receptors in pancreatic β-cells.[7,8] The result of clinical trials justifies the importance of improved glycemic control in diabetic patients in order to prevent or at least delay long-term complications. There is need to develop antidiabetic agents provided with aldose reductase inhibitor (ARI).

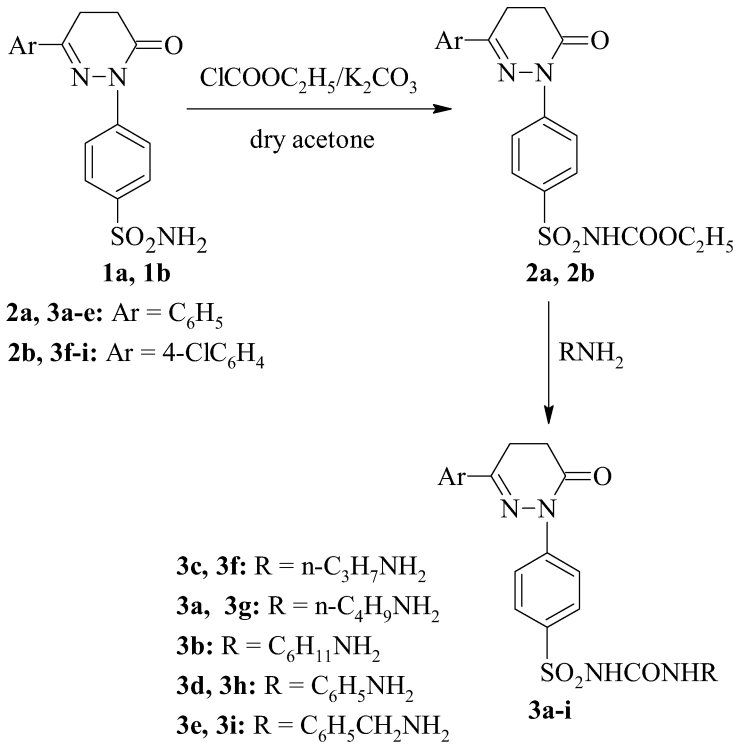
Recently, compounds containing pyridazine nucleus have been reported as AR inhibitors.[9–11] Therefore, it has been considered worthwhile to attach a pyridazinone ring to benzenesulfonylurea derivatives. In the present study, nine novel pyridazinone-substituted benzenesulfonylurea derivatives and six novel carbamates were synthesized. These were characterized by elemental analysis and various spectroscopic methods, viz. IR, ^{1}H NMR, and MS. Oral antihyperglycemic efficacy of sulfonylurea derivatives were assessed using an oral glucose tolerance test in a normal rat model.

RESULTS AND DISCUSSION

Synthesis of Compounds

The synthetic route used to prepare the title compounds (**3a–i**) is outlined in Scheme 1. The pyridazinone derivatives (**1a**, **1b**) were converted to the corresponding carbamates (**2a**, **2b**) by refluxing with ethyl chloroformate in dry acetone containing anhydrous K_2CO_3. The carbamates were subsequently condensed with the desired primary amines in toluene to give the corresponding pyridazinone-substituted benzenesulfonylurea derivatives (**3a–i**). The pyridazinone derivatives (**1a**, **1b**) were synthesized through a reported method.[12]

The structures of sulfonylurea derivatives were determined on the basis of their elemental analysis and various spectroscopic methods such as IR, ^{1}H NMR, and MS, whereas the carbamates were characterized by ^{1}H NMR, IR, and elemental analysis. Elemental analysis (C, H, N, and S) data were within $\pm$0.4% of the theoretical values.



SCHEME 1

Support for the structures **2a**, **2b** is evidenced by the presence of prominent bands in the IR spectra for C=O of carbamates (1754–1752 cm^{-1}), cyclic carbonyl (1681–1672 cm^{-1}), and $SO_2N <$ (1343–1338 cm^{-1} and 1164–1160 cm^{-1}). The ^1H NMR spectra revealed a triplet at δ 1.06 and a quartet at δ 4.36 for -OCH_2CH_3. Similarly, two triplets in the range of δ 2.78 and δ 3.16–3.17 can be attributed to the dihydropyridazinone ring protons. A broad singlet for NH at δ 4.10 was also observed. The aromatic protons were observed in the region of δ 7.36–7.90.

In the IR spectra of **3a–i** a band for NH (3385–3357 cm^{-1}) and two bands for carbonyl group of urea (1729–1687 cm^{-1}) and carbonyl function of pyridazinone (1680–1658 cm^{-1}) were identified. Two bands for $SO_2N <$ (1347–1310 cm^{-1} and 1161–1156 cm^{-1}) were also observed. The structures were further established by proton NMR spectral data. Two triplets at δ 2.78–2.83 and δ 3.10–3.18 were observed for dihydropyridazinone ring protons. A singlet for R-NH was observed at δ 6.08–8.93. The aromatic protons were observed in the region of δ

TABLE I Effect of Sulfonylurea Derivatives on Glucose Tolerance Test on Normal Rats

Group no.	Sample	0 Min	30 Min	60 Min
I	Control	84.3 ± 4.4	140.6 ± 6.6	164.0 ± 7.3
II	Standard	70.0 ± 3.2	102 ± 7.2 (43.2%)	115.5 ± 8.3 (42.9%)
III	(**3a**)	70.2 ± 6.1	139.3 ± 10.2 (0%)	135.8 ± 11.7 (17.7%)
IV	(**3c**)	78.2 ± 4.2	89.9* ± 5.7 (79.2%)	135.0 ± 9.4 (28.7%)
V	(**3e**)	67.7 ± 5.2	124.0 ± 7.9 (0%)	144.2 ± 11.7(4.0 %)
VI	(**3f**)	70.2 ± 3.2	88.0* ± 4.7 (68.4%)	142 ± 7.7 (9.9%)
VII	(**3g**)	73.7 ± 3.2	82.7* ± 6.7 (84.0%)	124.7 ± 8.8 (36.0%)
VIII	(**3h**)	72.4 ± 7.0	80.0* ± 2.3 (86.5%)	135 ± 7.7 (21.5%)

Values are mean ± SEM of six animals; values in parentheses indicate percentage reduction.

*Indicates statistical difference in respect to the vehicle ($P < 0.01$).

6.89–8.03. SO_2NH signal was observed in the case of two compounds **3f** (δ 10.17) and **3h** (δ 10.77).

Biological Activity

The blood glucose lowering effect of urea derivative was evaluated in glucose-fed hyperglycemic rats. As shown in Table I, blood glucose levels in control were increased after the administration of glucose up to 60 min. Test compounds **3c**, **3f**, **3g**, and **3h** significantly prevented the elevation of blood glucose level at 30 min after glucose loading, whereas test compounds **3a** and **3e** failed to inhibit the rise of blood glucose levels. Structure activity relationship studies (SARs) suggest that increment of carbon number at N^1 enhances the blood sugar lowering activity of the sulfonylureas derived from **2b**.

EXPERIMENTAL

Melting points were determined by open capillary tubes and are uncorrected. All Fourier transform infrared (FTIR) spectra were recorded on a Jasco FT/IR-55000 spectrophotometer using KBr pellets; ν_{max} values are given in cm^{-1}. ^1H NMR spectra were recorded on a Bruker Spectrospin DPX 300-MHz spectrometer using either $CDCl_3$ or DMSO as a solvent and trimethyl 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 using a FAB ionization JEOL-JMS-DX 303 system equipped with a direct inlet probe system. The m/z values of the more intense peaks are mentioned. Purity of the compounds was checked on TLC plates (silica gel G) that

were visualized by exposing to iodine vapors. Elemental analysis was carried out on a CHNS Elementar (Vario EL III).

General Procedure for the Preparation of Carbamates (2a, 2b)

A mixture of desired pyridazinone (**1a**, **1b**) (0.1 mol), ethyl chloroformate (0.13 mol), and anhydrous potassium carbonate (20 g) in dry acetone (150 mL) was refluxed for 18 h. Acetone was removed under reduced pressure, the residue was stirred in water (150 mL) and neutralized with acetic acid, and the product formed was separated and crystallized from methanol as colorless crystals.

Ethyl{[4-(6-oxo-3-phenyl-5,6-dihydropyridazin-1(4H)yl) phenyl]sulfonyl}Carbamate (2a)

mp 186°C; yield = 61%; IR υ_{max} (KBr): 1754 (C=O of carbamate), 1681 (cyclic carbonyl), 1338 and 1164 cm^{-1} (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 1.06 (3H, t, -O-CH_2- C$\underline{H}_3$), 2.78 and 3.17 (t each 2 x -CH_2-pyridazinone), 4.10 (1H, broad singlet, NH), 4.36 (2H, q, -O-C$\underline{H}_2$-CH_3), 7.36–7.89 (9H, m, Ar-H). FAB-MS (m/z): 402 [M+1], 401 [M^+].

Ethyl({4-[3-(4-chlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H) yl]phenyl}sulfonyl) Carbamate (2b)

mp 182°C; yield = 66%; IR υ_{max} (KBr): 1752 (C=O of carbamate), 1672 (cyclic carbonyl), 1343 and 1160 cm^{-1} (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 1.06 (3H, t, -O-CH_2- C$\underline{H}_3$), 2.78 and 3.16 (t each 2 x -CH_2-pyridazinone), 4.10 (1H, broad singlet, 4.36 (2H, q, -O-C$\underline{H}_2$-CH_3), NH), 7.53 (2H, d, J = 8.39 Hz, Ar-H), 7.78 (2H, d, J = 8.49 Hz, Ar-H), 7.87–7.90 (4H, m, Ar-H). FAB-MS (m/z): 435 [M^+].

General Method for the Preparation of Pyridazinone Substituted Benzenesulfonylurea (3a–i)

To a warm solution of carbamate (**2a**, **2b**) (0.02 mol) in toluene (75 mL), a solution of the desired amine (0.022 mol) in toluene (25 mL) was added dropwise with stirring. The mixture was refluxed for 3 h and then allowed to cool at room temperature. If the product crystallized out, it was separated; otherwise, the toluene was removed under reduced pressure. The product was then crystallized from methanol.

N-[(Butylamino)carbonyl]-4-(6-oxo-3-phenyl-5, 6-dihydropyridazin-1(4H)-yl) Benzenesulfonamide (3a)

mp 158°C; yield 58%; IR υ_{max} (KBr): 3385 (NH), 1716 (C=O of urea), 1658 (cyclic carbonyl), 1334 and 1156 cm^{-1} (SO_2N). ^1H NMR (400 MHz,

$CDCl_3$, δ): 0.89 (3H, t, CH_3), 1.30 (2H, q, -CH_2-C<u>H</u>$_2$-CH_2-CH_3) 1.47 (2H, m, -CH_2-CH_2-C<u>H</u>$_2$-CH_3), 2.81 and 3.11 (4H, t, each -CH_2-CH_2-/pyridazine ring), 3.21 (2H, q, HN-C<u>H</u>$_2$-CH_2-CH_2-CH_3), 6.55 (1H, s, NH-C_4H_9), 7.45 (3H, m, Ar-H), 7.79–7.94 (6H, m, Ar-H), signal for SO_2NH- could not be picked out. FAB-MS (m/z): 428 [M^+], 429 [M+1], 330, 313, 297, 266, 249.

N-[(Cyclohexylamino)carbonyl]-4-(6-oxo-3-phenyl-5, 6-dihydropyridazin-1(4H)-yl) Benzenesulfonamide (3b)

mp 190°C; yield = 56%; IR υ_{max} (KBr): 1679 (C=O), 1328 and 1159 cm^{-1} (SO_2NH). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.18–1.87 (10H, m, cyclohexane), 3.60 (1H, 2, axial-H at C-1 of cyclohexane), 2.80 and 3.10 (4H, t, each 2 x -CH_2-) 6.47 (1H, NH-C_6H_{11}), 7.45 (3H, m, Ar-H), 7.79–7.94 (6H, m, Ar-H). FAB-MS (m/z): 455 [M+1], 454 [M^+], 330, 313, 297, 266, 249.

N-[(Propylamino)carbonyl]-4-(6-oxo-3-phenyl-5, 6-dihydropyridazin-1(4H)-yl) Benzenesulfonamide (3c)

mp 188°C, yield = 49%; IR υ_{max} (KBr): 3368 (NH), 1680 (C=O), 1347 and 1161 cm^{-1} (SO_2N). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.91 (3H, t, CH_3), 1.54 (2H, m, N-CH_2-C<u>H</u>$_2$-CH_3) 2.83 and 3.13 (4H, t, each -CH_2-CH_2-/pyridazinone ring) 3.20 (2H, q, N-C<u>H</u>$_2$-CH_2-CH_3), 6.59 (1H, N<u>H</u>-C_3H_7), 7.47 (3H, closely packed multiplet, Ar-H), 7.82–7.93 (6H, m, Ar-H). FAB-MS (m/z): 415 [M+1], 414 [M^+].

N-[(Phenylamino)carbonyl]-4-(6-oxo-3-phenyl-5, 6-dihydropyridazin-1(4H)-yl) Benzenesulfonamide (3d)

mp 228–230°C, yield = 55%; IR υ_{max} (KBr): 3357 (NH), 1729 (C=O of urea), 1666 (cyclic carbonyl), 1342 and 1157 cm^{-1} (SO_2N). ^{1}H NMR (300 MHz, DMSO, δ): 2.79 and 3.17 (4H, t, each 2 x -CH_2-) 7.01 (1H, t, H-4 aniline unit), 7.23–7.36 (4H, m, aromatic protons of aniline unit), 7.48 (3H, compact multiplet, Ar-H), 7.89–8.03 (6H, m, Ar-H), 8.93 (1H, s, N<u>H</u>-Ar). FAB-MS (m/z): 448 [M^+].

N-[(Benzylamino)carbonyl]-4-(6-oxo-3-phenyl-5, 6-dihydropyridazin-1(4H)-yl) Benzenesulfonamide (3e)

mp 192–194°C, yield = 47%; IR υ_{max} (KBr): 1677 (C=O), 1335 and 1160 cm^{-1} (SO_2N). ^{1}H NMR (300 MHz, DMSO, δ): 2.79 and 3.18 (4H, t, each 2 x -CH_2-), 4.17 (2H, d, J = 5.76 Hz), 7.00 (1H, t, H-4 benzyl unit),

7.13–7.30 (4H, m, aromatic protons of benzyl unit), 7.48 (3H, compact multiplet, Ar-H), 7.83–7.97 (6H, m, Ar-H). FAB-MS (m/z): 462 [M^+].

4-[3-(4-Chlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)-yl]-N-[(propylamino) carbonyl]benzenesulfonamide (3f)

mp 184°C, yield = 53%; IR υ_{max} (KBr): 1726 (C=O of urea), 1666 (cyclic carbonyl), 1333 and 1158 cm^{-1} (SO_2N). ^1H NMR (300 MHz, $CDCl_3$, δ): 0.86 (3H, t, CH_3), 1.45 (2H, heptet, CH_2/C-2 of propyl chain), 2.83 (2H, t, -CH_2- of pyridazinone ring), 3.03–3.15 (4H, m, one CH_2 of pyridazinone and one CH_2/C-1 of propyl chain), 6.08 (1H, t, N<u>H</u>-C_3H_7), 7.42 (2H, d, J = 8.36 Hz, Ar-H), 7.78 (2H, d, J = 8.40 Hz, Ar-H), 7.84 (2H, d, J = 8.61 Hz, Ar-H), 8.02 (2H, d, J = 8.62, Ar-H), 10.17 (1H, broad singlet, SO_2NH-). FAB-MS (m/z): 448 [M^+].

4-[3-(4-Chlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)-yl]-N-[(butylamino) carbonyl]benzenesulfonamide (3g)

mp 202°C; yield = 59%; IR υ_{max} (KBr): 3358 (NH), 1699 (C=O of urea), 1680 (cyclic carbonyl), 1310 and 1161 cm^{-1} (SO_2N). ^1H NMR (400 MHz, $CDCl_3$, δ): 0.91 (3H, t, CH_3), 1.30 and 1.46 (each multiplet 2 x -CH_2-/*n*-butyl chain), 3.27 (2H, quartet, CH_2/C-1/butyl chain) 2.83 and 3.10 (each t, 2 x CH_2-/pyridazinone ring), 7.42 (2H, d, J = 8.4 Hz, Ar-H), 7.75 (2H, d, J = 8.4 Hz, Ar-H), 7.89 (2H, d, J = 6.9 Hz, Ar-H) and 7.92 (2H, d, J = 6.9 Hz, Ar-H). FAB-MS (m/z): 462 [M^+].

4-[3-(4-Chlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)-yl]-N-[(phenylamino) carbonyl]benzenesulfonamide (3h)

mp 198–200°C; yield = 62%; IR υ_{max} (KBr): 3359 (NH), 1726 (C=O of urea), 1666 (cyclic carbonyl), 1334 and 1157 cm^{-1} (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 2.78 and 3.16 (4H, t, each 2 x -CH_2-), 7.02 (1H, t, H-4‴), 7.23–7.35 (4H, m, Ar-H), 7.53 (2H, d, J = 8.48 Hz, Ar-H), 7.86 (2H, d, J = 8.84 Hz, Ar-H), 7.90 (2H, d, J = 8.64 Hz, Ar-H), 8.00 (2H, d, J = 8.68 Hz, Ar-H), 8.86 (1H, s, N<u>H</u>-Ar), 10.77 (1H, broad singlet, SO_2NH). FAB-MS (m/z): 482 [M^+].

4-[3-(4-Chlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)-yl]-N-[(benzylamino)carbonyl]benzenesulfonamide (3i)

mp 204°C; yield = 57%; IR υ_{max} (KBr): 1687 (C=O of urea), 1663 (cyclic carbonyl), 1316 and 1161 cm^{-1} (SO_2N). ^1H NMR (400 MHz, $CDCl_3$, δ): 2.83 and 3.10 (4H, t, each 2 x -CH_2-), 4.41 (2H, d, J = 5.6 Hz, CH_2- of benzyl), 6.89 (1H, t, Ar-H), 7.17–7.29 (4H, m, Ar-H), 7.42 (2H, d, 8.4

Hz, Ar-H), 7.75 (2H, d, J = 8.8 Hz, Ar-H) 7.84 (2H, d, J = 7.2 Hz, Ar-H), 7.86 (2H, J = 6.9 Hz, Ar-H). FAB-MS (m/z): 496 [M^+].

Biological Activity

Albino rats of either sex (Wistar strain), weighing 150–200 g, that fasted overnight (16 h) were divided into eight groups. Group I was fed with vehicle (1% CMC in distilled water) in volume of 10 mL/kg and served as the control. The reference drug glibenclamide (10 mg/kg) and the test compounds (**3a**, **3c**, **3e–h**) in the dose of 20 mg/kg suspended in the vehicle were administered p.o. in volume of 10 mL/kg to groups II–VIII, respectively. All the animals were given glucose (2 g/kg, p.o.) 30 min after dosing. Blood samples were collected from the retro-orbital plexus just prior to and 30 and 60 min after the glucose loading and glucose levels were measured by Dubowski's method.[13]

Results of the blood glucose estimation are presented in the form of ±SEM and percentage reduction by the test drug (Table I). The percentage reduction was calculated by considering the difference between the blood glucose levels at 0 and 30 and 0 and 60 min of respective control animal as 100% rise in the blood sugar. A 100% reduction indicates that there is no rise in the level of blood sugar, whereas 0% reduction indicates that there is no reduction in the level of blood sugar.

CONCLUSION

The structures proposed to the synthesized compounds (**2a**, **2b**, and **3a–i**) are well supported by spectroscopic data and elemental analysis.

Four compounds (**3c**, **3f**, **3g**, and **3h**) were found to have promising blood glucose lowering activity and may be used as lead compounds for developing new antidiabetic drugs.

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