Synthesis and evaluation of some novel 1,3,4-thiadiazoles for antidiabetic activity

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A new series of 1,3,4-thiadiazole derivatives are synthesized and the structures of these compounds have been established on the basis of spectral and elemental analysis. All the compounds are evaluated for antidiabetic activity on albino rats. Most of these compounds show promising antidiabetic activity.

Keywords: 1,3,4-Thiadiazole derivatives, antidiabetic activity.

Results and Discussion

The title compounds were screened for their antidiabetic activity by Alloxan induced Tail tipping method. The Albino rats of either sex weighing between 150-200 g were selected. The blood glucose level was induced and the study was carried out in six different groups.

Among the compounds synthesized, compounds B11, B14, B15, B17 and B18 have shown significant antidiabetic activity and compounds B2, B8, B9 and B16 have shown moderate antidiabetic activity (Scheme I). The results were calculated by measuring the mean SE ± and ‘P’ value.

Antidiabetic activity

The acclimatized animals were kept fasting for 24 hr with water ad libitum and alloxan monohydrate (120 mg/kg i.p.) in normal saline was administered. After 1 hr of alloxan administration the animals were given water ad libitum. The 5% dextrose solution was given in feeding bottle for a day to overcome the early hypoglycemic phase. The blood glucose regulator was monitored after alloxination by withdrawing a drop of blood from the tail vein by Tail tipping method. The blood was dropped on the dextrostrix reagent Pad. The strip was inserted into microprocessor digital Blood Gluco Meter and readings were noted.

After 72 hr, rats having blood glucose level beyond 150-mg/dL of blood were selected for the study and divided into 6 groups (n=6). The quantity of 1,3,4-thiadiazole derivatives equivalent to average human intake 200 mg/kg at a time was calculated for single dose 36 mg/kg (for acute study). The test compounds were administered orally by mixing with CMC (0.25%) solution. The blood glucose level was monitored at different times 0, 2, 4, 6 and 8 hr respectively.

1,3,4-Thiadiazoles are associated with diverse biocidal activities. A large number of 1,4-thiazolidiones have been reported to be antifungal, antibacterial and antileukemic agents. These observations prompted us to synthesise the title compound with the presumption that incorporation of aromatic aldehyde in 1,3,4-thiadiazoles nuclei would produce new compounds with significant antidiabetic activity.

Note

Diabetes mellitus is a heterogeneous group of diseases, characterized by a state of chronic hyperglycemia, resulting from a diversity of etiologies, environmental and genetic, acting jointly. The underlying causes of diabetes are the defective production or action of insulin, a hormone that controls carbohydrate, fat and protein metabolism. Characteristically diabetes is a long-term disease with variable clinical manifestations and progression, chronic hyperglycemia from whatever cause, leads to a number of complications including cardiovascular such as hypertension, renal, neurological such as anxiety, stress, ocular and other such inter-current infections.

Diabetes mellitus is a condition in which the pancreas no longer produces enough insulin or cells stop responding to insulin that is produced, so that glucose in the blood cannot be absorbed into the cells of the body. Symptoms include frequent urination, lethargy, excessive thirst, and hunger. The treatment includes changes in diet, oral medications and in some cases daily injection of insulin.
Experimental Section

All melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on Thermo Nicolet IR 200 spectrophotometer using KBr disc method. The $^1$H NMR spectra were recorded on sophisticated multinuclear FT-NMR spectrometer model Avance-II (Bruker) using DMSO-$d_6$ as solvent and tetramethylsilane as internal standard. Perkin Elmer 2400 CHN elemental analyzer was used to determine the percentages of C, H and N.

General procedure for synthesis of 2-amino-5-aryl-1,3,4-thiadiazole, I (ref. 9)

A mixture of thiosemicarbazide (0.01 mole), aryl carboxylic acid (0.01 mole), and conc. sulphuric acid (5 mL) was refluxed for 2 hr and poured onto crushed ice. The solid separated out was filtered, washed with water and recrystallized from ethanol to give compound I.

Synthesis of 2-(4-fluorobenzalamino)-5-phenyl-1,3,4-thiadiazole, B$_1$

A mixture of 2-amino-5-phenyl-1,3,4-thiadiazole (0.01 mole) and 4-flourobenzaldehyde (0.01 mole) were taken in a beaker. The mixture was irradiated in a microwave oven for 3 min with 40% power, at intervals of 30 s. After the completion of reaction, ice-cold water was added to the reaction-mixture and solid thus separated was filtered and dried to get 2-(4-flourobenzalamino)-5-phenyl-1,3,4-thiadiazole

![Scheme I](image-url)
recrystallized from ethanol. Yield 72%, m.p. 175-77°C. The compounds B1-B18 were synthesized following a similar procedure. The yields and m.p. are listed in Table I and antidiabetic activity in Table II.

### Spectral data

**B1**: IR (KBr): 3150 (Ar C-H str), 1596 (N=C str), 1224 (C-F str), 1148 cm\(^{-1}\) (C-S str); \(^1\)H NMR (DMSO-d\(_6\)): δ 8.6 (S, 1H, N=CH), 7.8-7.1 (m, 9H, Ar.CH).

**B2**: IR (KBr): 3294 (O-H str), 3050 (Ar C-H str), 1600 (C=N str), 1162 cm\(^{-1}\) (C-S str).

**B3**: IR (KBr): 2909 (Ar C-H str), 2830 (C-H str,CH\(_3\)), 1604 (C=N str), 1362 (Ar C-N str), 1226 (C-N str, aliphatic), 1171 cm\(^{-1}\) (C-S str); \(^1\)H NMR (DMSO-d\(_6\)): δ 8.49 (S, 1H, N=CH), 7.8-6.7 (m, 9H, Ar.CH), 3.05 (S, 6H (CH\(_3\)_2)).

**B4**: IR (KBr): 3011(Ar C-H str), 1628(C=N str), 1294 cm\(^{-1}\) (C-O-C str); MS: m/z 294 [M\(^+\)].

**B5**: IR (KBr): 3067(Ar C-H str), 1602(C=N str), 1180(C-S str), 933 cm\(^{-1}\) (Ar C-H str furan); \(^1\)H NMR (DMSO-d\(_6\)): δ 9.2 (S, 1H, N=CH), 8.04-8.01 (m, 3H, furan), 7.5-7.4 (m, 5H, Ar.CH); MS: m/z 255 [M\(^+\)].

**B6**: IR (KBr): 3060(Ar C-H), 1600(C=N), 1170 cm\(^{-1}\) (C-S).

**B7**: IR (KBr): 3200 (N-H str, NH\(_2\), 2909 (Ar C-H str), 1612 (C=N str), 1285(C-F str), 1134 cm\(^{-1}\) (C-S str); \(^1\)H NMR (DMSO-d\(_6\)): δ 7.9 (S,2H,NH\(_2\)),7.86 (S 1H,N=CH), 7.8-6.72 (m, 8H, Ar.CH).

**B8**: IR (KBr): 3000 (Ar C-H str), 1614 (C=N str), 1130 cm\(^{-1}\) (C-S str); \(^1\)H NMR (DMSO-d\(_6\)): δ 9.8 (s,1H, OH), 7.85 (s, 1H, N=CH), 6.75-6.73 (s, 2H, NH\(_2\)), 7.8-6.9 (m, 8H, Ar.CH); MS: m/z 296 [M\(^+\)].

**B9**: IR (KBr): 3433(N-H str,NH\(_2\)), 2926 (Ar C-H str), 2800 (C-H str,CH\(_3\)), 1655 (C=N str), 1353 (Ar C-N str), 1181 (C-N str aliphatic), 1116 cm\(^{-1}\) (C-S str).

**B10**: IR (KBr): 2892(Ar C-H str), 1611(C=N str), 1285(C-O-C str), 1134 cm\(^{-1}\) (C-S str).

**B11**: IR (KBr): 2971(Ar C-H str), 1698(C=N str), 1170(C-S str 1097 cm\(^{-1}\) (C-H str, furan).

**B12**: IR (KBr): 3000 (Ar C-H str), 1614(C=N str), 1130 cm\(^{-1}\) (C-S str); \(^1\)H NMR (DMSO-d\(_6\)): δ 7.864 (S, 1H, N=CH), 7.84- 7.4 (m, 8H Ar.CH) 6.74-6.72 (s, 2H, NH\(_2\)), 2.65- 2.58 (s, 3H, CH\(_3\)); MS: m/z 294 [M\(^+\)].

**B13**: IR (KBr): 3000 (Ar C-H str), 1620 (C=N str), 1221 (C-F str), 1153 cm\(^{-1}\) (C-S str); MS: m/z 315 [M\(^+\)].

**B14**: IR (KBr): 3300(N-H str NH\(_2\)), 3100(O-H str), 2938(Ar C-H str),1663 cm\(^{-1}\) (C-N str).
B15: IR (KBr): 3414 (N-H str, NH$_2$), 3100 (O-H str), 2924 (Ar C-H str), 2800 (C-H str, CH$_3$), 1610 (C=N str), 1367 (C-N str, Ar), 1228 cm$^{-1}$ (C-N str, N(CH$_3$)$_2$);

$^1$H NMR (DMSO-$d_6$): $\delta$ 9.7 (s, 1H, OH), 7.72 (s, 1H, N=CH), 7.71-6.7 (m, 7H, Ar.CH), 6.2 (s, 2H, NH$_2$);

MS: m/z 339 [M$^+$].

B16: IR (KBr): 3300 (N-H str, NH$_2$), 3126 (Ar C-H str), 1599 (C=N str), 1367 (C-N str, Ar), 1258 cm$^{-1}$ (C-N str, N(CH$_3$)$_2$); $^1$H NMR (DMSO-$d_6$): $\delta$ 9.8 (s, 1H, OH), 7.72 (s, 1H, N=CH), 7.71-6.7 (m, 7H, Ar.CH), 6.2 (s, 2H, NH$_2$); MS: m/z 339 [M$^+$].

B17: IR (KBr): 3250 (N-H str, NH$_2$), 3036 (Ar C-H str), 1605 cm$^{-1}$ (C-N str).

B18: IR (KBr): 3250 (N-H str, NH$_2$), 3036 (Ar C-H str), 1605 cm$^{-1}$ (C-N str).

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References
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Table II — Antidiabetic activity of thiadiazoles

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<tr>
<th>Drug</th>
<th>Blood glucose level mg/dL (Mean ± SE)</th>
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<tr>
<td>B1</td>
<td>280.5±3.969</td>
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<td>B2</td>
<td>272.8±2.955</td>
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<td>B3</td>
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<tr>
<td>Control</td>
<td>276.5±1.848</td>
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<td>Standard Drug: Glibenclamide.</td>
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Note: Statistical analysis is done by one-way ANOVA followed by Dunnet’s 't' test. ** P<0.01 (considered as significant), *P<0.05