

## Note

### Synthesis and antidiabetic activity of 2-amino [5'(4-sulphonylbenzylidene)-2,4- thiazolidinedione]-7-chloro-6- fluorobenzothiazole

S R Pattan\*, Ch Suresh, V D Pujar, V V K Reddy,  
V P Rasal & B C Koti

Department of Medicinal Chemistry, KLES's College of  
Pharmacy, Belgaum 590 010, India

E-mail: [shashipattan@yahoo.com](mailto:shashipattan@yahoo.com)

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A new series of 2-amino[5'(4-sulphonylbenzylidene)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole were synthesized. The structures of the compounds were confirmed by UV-Vis, IR and NMR spectroscopy. The title compounds were screened for their antidiabetic activity on albino rats.

**Keywords:** antidiabetic activity, sulphonylbenzylidene, fluorobenzothiazole

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Diabetes mellitus<sup>1</sup> is a heterogeneous group of diseases, characterized by a state of chronic hyperglycemia<sup>2</sup>, 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 manifestation and progression. Chronic hyperglycemia leads to a number of disorders including cardiovascular, renal, neurological as well as ophthalmic infections<sup>3-5</sup>.

Diabetes mellitus<sup>6</sup> is a condition in which the pancreas no longer produces enough insulin or body 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 change in diet, oral medication and in some cases daily injection of insulin.

Thiazolidones and thiazolidinediones were the first parent compounds in which thiazole ring was recognized<sup>7</sup>. Frances E. Brown reported in 1961 a brief review on the close structural relationship

among the various 4-thiazolidinones<sup>8</sup>. These compounds were found to be biologically active<sup>9</sup>. In the present work, we have synthesized 2-amino[5'(4-sulphonylbenzylidene)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole and screened them for their antidiabetic activity on diabetes induced albino rats.

The thiazolidinediones<sup>10,11</sup> are currently licensed for use in oral combination therapy in management of patients with type-2 diabetes who have insufficient glycaemic control despite maximal tolerated dose of oral mono-therapy with either Metformin or Sulphonylurea. It is generally recommended that thiazolidinediones are used in combination with Metformin only in obese patients.

Rosiglitazone<sup>12-14</sup>, a member of the thiazolidinediones class of antidiabetic agents improves glycaemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferators activator receptor Gamma (PPAR)<sup>11-15</sup>. In humans, PPAR receptors are formed within the kidney and target tissues for insulin action such as adipose, skeletal muscle and liver tissues. Activation of PPAR nuclear receptors regulates the transcription of insulin responsive genes involved in the control, production, transport and utilization of glucose.

### Experimental Section

Melting points are uncorrected. The IR spectra were recorded on Nicolet FT-IR spectrometer and <sup>1</sup>H NMR spectra (DMSO-*d*<sub>6</sub>) were recorded on VXRO-300 MHz instrument using TMS as internal standard.

**General procedure for synthesis of 2-amino-6-fluoro-7-chlorobenzothiazole 1<sup>16</sup>.** To gl. acetic acid (20 mL) cooled to 20°C, was added 8 g (0.08 mole) of potassium thiocyanate and 1.45 g (0.01 mole) of 3-chloro-4-fluoroaniline. The mixture was placed in freezing mixture of ice-salt and mechanically stirred. 1.6 mL of bromine in 6 mL of glacial acetic acid was added from a dropping funnel at such a rate that the temperature never rose beyond 0°C. After all the bromine was added (105 min), the solution was stirred for 2 hr below rt and at rt for 10hr. It was then allowed to stand overnight, during which period an orange precipitate settled at the bottom. Water (6 mL)

was added quickly and the slurry was heated to 85°C on a steam-bath and filtered hot. The orange residue was placed in reaction flask and treated with 10 mL of gl. acetic acid heated again to 85°C and filtered. The combined filtrate was cooled and the precipitate was collected. Recrystallization from benzene:ethanol (1:1) after treatment with charcoal gave yellow crystals of 2-amino-6-fluoro-7-chloro-1,3-benzothiazole. The compound was dried in an oven at 80°C, Yield 76%; m.p. 210-12°C.

**General procedure for the synthesis of 2,4-thiazolidinedione 2<sup>17</sup>.** In a 250 mL three-necked flask was placed, a solution containing 56.5 g (0.6 M) of chloroacetic acid in 60 mL of water and 45.6 g (0.6M) of thiourea dissolved in 60 mL of water. The mixture was stirred for 15 min to obtain a white precipitate, accompanied by considerable cooling. To the contents of the flask was then added slowly 60 mL of concentrated hydrochloric acid from a dropping funnel. The flask was then connected with a reflux condenser and gentle heat applied to effect complete dissolution, after which the reaction mixture was stirred and refluxed for 8-10 hr at 100-10°C. On cooling, the contents of the flask solidified into a cluster of white needles. The product was filtered and washed with water to remove traces of hydrochloric acid and dried. It was purified by recrystallization from ethyl alcohol. Yield 85%; m.p. 123-25°C.

**Synthesis of 5-benzylidene 2,4-thiazolidinedione 3<sup>18</sup>.** In a 250 mL 3-necked round-bottomed flask provided with a Dean-Stark apparatus, benzaldehyde (20 g, 0.188 mole) and 2,4-thiazolidinedione (22 g, 0.188 mole) were together suspended in dry toluene. To this a catalytic amount of piperidine (1 mL) was added. The mixture was refluxed with stirring. After the complete removal of water and when the temperature crossed 110°C the reaction mixture was stirred for a further 1 hr. On cooling, the product precipitated out from toluene. The compound was filtered and washed with cold, dry toluene and dry ethanol. Yield 89-93%; m.p. 240-42°C.

**Synthesis of 4'-chlorosulphonylbenzylidene 2,4-thiazolidinedione 4<sup>18</sup>.** Benzylidene-2,4-thiazolidinedione (8 g, 0.0388 mole) was placed in a 100 mL round-bottomed flask equipped with a condenser and a dropping funnel. Chlorosulphonic acid (18.08 g, 0.155 mole) was added at rt using the dropping funnel. The reaction was found to be exothermic. After addition of chlorosulfonic acid was over the

reaction mixture was refluxed for 1 hr on a water-bath. The reaction mass was cooled and poured in a thin stream with stirring into crushed ice contained in a 1L beaker. It was filtered and dried and purified by recrystallization from ethanol. Yield 68%; m.p. 180-81°C.

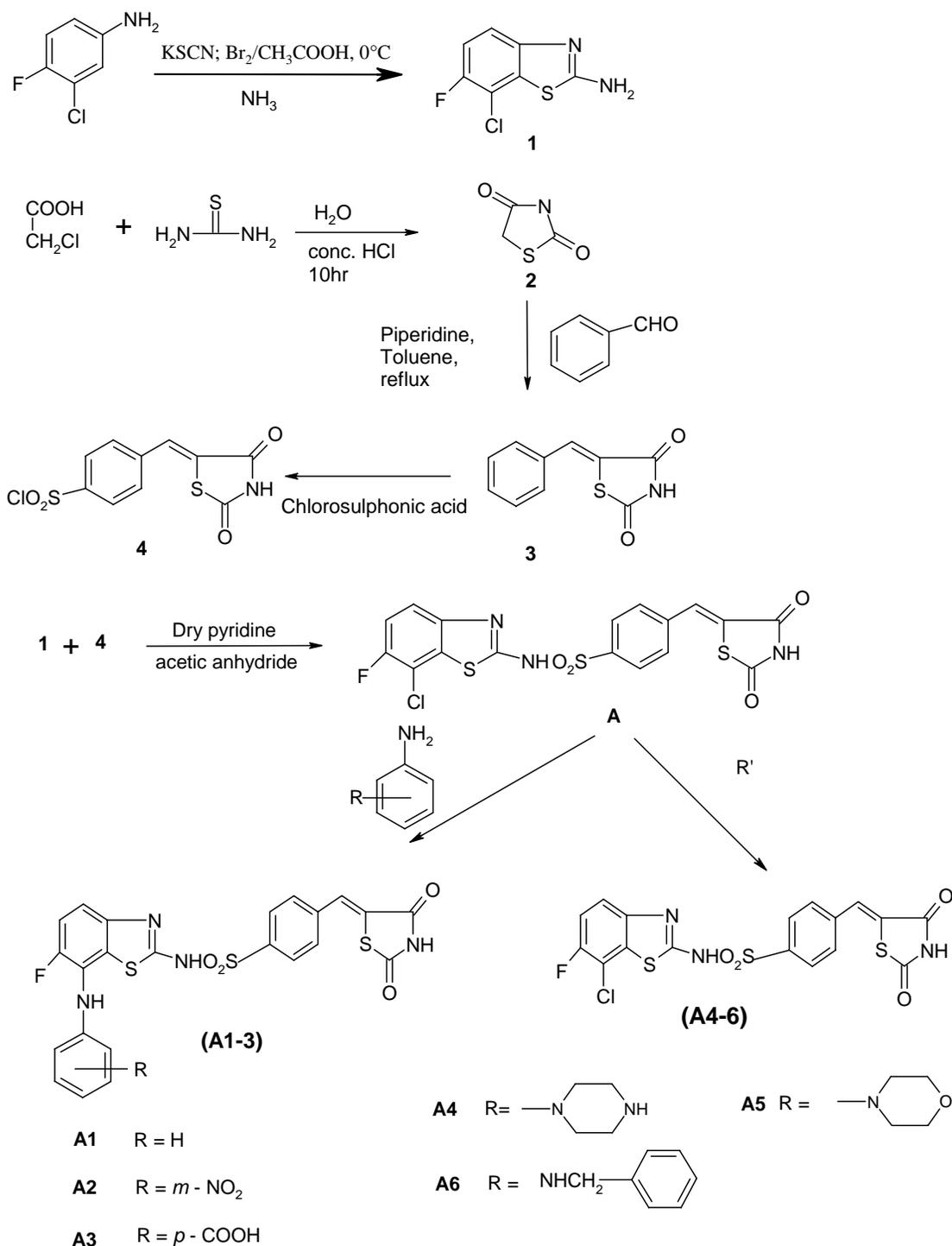
**Synthesis of 2-amino[5'(4-sulphonylbenzylidene)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole A.** 2-Amino-6-fluoro-7chlorobenzothiazole **1** (0.1 mole) and 4'-chlorosulphonylbenzylidene-2,4-thiazolidine dione **4** (0.1 mole) were added to a mixture of 4 mL of dry pyridine and 20 mL of acetic anhydride<sup>5</sup>. The mixture was refluxed for 2 hr, reaction mixture was then poured into 20 mL of ice-water and the solid obtained was filtered and purified by recrystallization from ethanol to give A as a crystalline solid, m.p. 195°C.

The above product was treated with equimolar quantities of various substituted anilines, morpholine, piperazine and benzyl amine and in each case refluxed for 2 hr, in presence of DMF. The mixture was cooled and poured into crushed ice. The solid separated was filtered, washed with water and dried. It was purified by recrystallization from ethanol-benzene mixture (1:1).

#### Antidiabetic activity<sup>19</sup>

The acclimatized animals were kept fasting for 24 hr with water *ad libitem* and alloxan monohydrate (120 mg/Kg i.p.) in normal saline was then administered. After 1 hr of alloxan administration the animals were given *ad libitem*, 5% dextrose solution which was administered *via* 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 the 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 thiazolidinedione derivatives equivalent to average human intake of 200mg/kg at a time was calculated for a single dose of 36mg/kg (for acute study). The test compounds were administered orally by mixing with CMC (0.25 %) solution. The blood glucose level was monitored at 0 hr, 1 hr, 3 hr and 6 hr respectively.



Scheme I

### Results and Discussion

The title compounds were synthesized as shown in **Scheme I**. All the compounds were characterized by UV-Vis, NMR and IR (**Table I**). The compounds **A1-6** were screened for their antidiabetic activity by alloxan induced tail tipping method. The albino rats of

either sex weighing between 150 to 200 g were selected. The blood glucose level was induced and the study was carried out in six different groups.

All the six compounds **A1-6** showed good antidiabetic activity. Compounds **A1-3** showed the maximum antidiabetic activity. Compound **A4-6** also

**Table I** — Characterization data of compounds **A1-6**

Compd	Yield (%)	m.p. °C	Mol. wt.	Mol. formula	Calcd %			UV-Vis (nm)	<sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> )
					C	H	N		
<b>A1</b>	69	197	526	C <sub>23</sub> H <sub>15</sub> N <sub>4</sub> O <sub>4</sub> S <sub>3</sub> F	52.47	2.85	10.65	271.5, 310.5	2.5 (3H, t, 3NH), 7.5-7.35 (2H, m, Aryl-H), 7.50 (5H, m, Aryl-H), 7.74-7.7 (4H, m, Aryl-H), 2.25 (1H, d, C=H).
<b>A2</b>	72	194	571	C <sub>23</sub> H <sub>14</sub> N <sub>5</sub> O <sub>6</sub> S <sub>3</sub> F	48.33	2.45	12.25	272, 310	2.5 (3H, t, 3NH), 7.5-7.35 (2H, m, Aryl-H), 7.50 (4H, m, Aryl-H), 7.7-7.5 (4H, m, Aryl-H), 2.25 (1H, d, C=H).
<b>A3</b>	68	190	570	C <sub>24</sub> H <sub>15</sub> N <sub>4</sub> O <sub>6</sub> S <sub>3</sub> F	50.50	2.63	9.82	273, 309	2.5 (3H, t, 3NH), 7.4-7.35 (2H, m, Aryl-H), 7.5-7.6 (4H, m, Aryl-H), 7.7-7.5 (4H, m, Aryl-H), 7.47 (1H of COOH), 2.25 (1H, d, C=H).
<b>A4</b>	65	197	519	C <sub>21</sub> H <sub>18</sub> N <sub>5</sub> O <sub>4</sub> S <sub>3</sub> F	48.55	3.46	13.48	271, 310.5	2.5 (2H, s, 2NH), 1.6-0.8 (8H, n, CH <sub>2</sub> CH <sub>2</sub> NHCH <sub>2</sub> CH <sub>2</sub> ), 7.35 (1H, m, Aryl-H), 7.50 (1H, d, Aryl-H), 7.74-7.7 (2H, d, Aryl-H), 7.83 (1H, d, Aryl-H) 7.84-7.8 (1H, d, Aryl-H), 2.25 (1H, d, C=H).
<b>A5</b>	70	196	520	C <sub>21</sub> H <sub>17</sub> N <sub>4</sub> O <sub>5</sub> S <sub>3</sub> F	48.46	3.26	10.76	273, 309	2.5 (2H, s, 2NH), 1.6-0.8 (8H, of Morpholine), 7.35 (1H, m, Aryl-H), 7.50 (1H, d, Aryl-H), 7.74-7.7 (2H, d, Aryl-H), 7.83 (1H, d, Aryl-H) 7.84-7.8 (1H, d, Aryl-H), 2.25 (1H, d, C=H).
<b>A6</b>	56	187	540	C <sub>24</sub> H <sub>17</sub> N <sub>4</sub> O <sub>4</sub> S <sub>3</sub> F	53.55	3.14	10.37	272, 310	2.5 (3H, s, 3NH), 7.27 (5H, s, Aryl), 7.35 (1H, m, Aryl-H), 7.50 (1H, d, Aryl-H), 7.74-7.7 (2H, d, Aryl-H), 7.83 (1H, d, Aryl-H) 7.84-7.8 (1H, d, Aryl-H), 2.25 (2H, d, C-H)

**Table II** — Antidiabetic activity screening

Compd	Time in hr			
	0 hr	1 hr	3 hr	6 hr
<b>A1</b>	300.5 ± 10.12**	134.5 ± 2.723	123.5 ± 5.236	116.5 ± 5.90**
<b>A2</b>	320 ± 15.811**	145.5 ± 2.26	137 ± 3.80	123.5 ± 1.109*
<b>A3</b>	311 ± 10.496	134.5 ± 3.70	125.75 ± 4.36	116.2 ± 2.17**
<b>A4</b>	209 ± 8.81	134.5 ± 5.85	110 ± 4.96	104.75 ± 5.21**
<b>A5</b>	213.5 ± 18.78	140 ± 15.23	106 ± 6.91	95.75 ± 6.06**
<b>A6</b>	283 ± 43.76*	205.75 ± 49.7	166 ± 38.92	124.5 ± 13.16*
Control	184 ± 10.51	163 ± 6.51	155.5 ± 4.80	150.25 ± 4.008

\* P &lt; 0.05

\*\* P &lt; 0.01

The mean ± S.E. of the blood glucose level was calculated for each group and the results were analyzed by ANOVA and student t-test by comparing the results of 1, 3 and 6 hr with 0 hr. This test is applied to assess the statistical significance of difference between two independently drawn sample means.

The P < 0.05 indicates statistically significant.

P < 0.01 indicates statistically more significant.

showed good antidiabetic activity. The results were obtained by measuring the mean SE ± and 'p' values. The title compound and their derivatives were found to be promising antidiabetic agents (**Table II**).

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