



# International Journal of **Biological Chemistry**

ISSN 1819-155X



Academic  
Journals Inc.

[www.academicjournals.com](http://www.academicjournals.com)

## Synthesis and Spectral Characterization of Some Novel N-Substituted 2, 4-Thiazolidinedione

L.V. Sonawane and S.B. Bari

R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Dist-Dhule, Maharashtra 425 405, India

*Corresponding Author: Mr. Lalit Vijay Sonawane, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Dist-Dhule, Maharashtra 425 405, India Tel: +919881409073*

### ABSTRACT

In the present study, a series of novel N-substituted thiazolidine-2,4-dione was designed and further synthesized from their corresponding aldehydes according to Knoevenagel's condensation method. The resulting 5-arylidinethiazolidine-2,4-dione was reacted with substituted aromatic acid to give 3-substituted 5-arylidinethiazolidine-2,4-dione. The structural elucidation of the compounds was based on the various spectral data viz., IR, <sup>1</sup>HNMR, Mass and elemental analysis. The structure of acid was assigned on the basis of their IR spectrum which shows a very broad band at 3200-2500 cm<sup>-1</sup> attributable to the stretching of carboxylic OH group. Fragmentation pattern was also studied which gave different fragment with their corresponding mass to charge ratio. The synthesized compounds are under investigation for their insulinotropic activities.

**Key words:** Aldehydes, <sup>1</sup>HNMR, mass spectra, Knoevenagel's condensation, insulinotropic

### INTRODUCTION

Diabetes mellitus, long considered diseases of minor significance to the world, is now taking its place as the main threats to human health in the 21st century. The incidence of the disease is estimated to reach 210 million by the year 2010 and 300 million by the year 2025 (Rotella, 2004; Borkar *et al.*, 2009). Diabetes mellitus (Madhavan *et al.*, 2002) is a heterogeneous group of diseases characterized by a state of chronic hyperglycemia (Turner, 1996), resulting from a diversity of etiologies, environmental and genetic, acting jointly. It 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 body 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.

Thiazolidines and thiazolidinediones were the first parent compounds in which thiazole ring was recognized (Pattan *et al.*, 2004). Brown (1961) reported a brief review on the close structural relationship among the various 4-thiazolidinones (Elderfield, 1961). These compounds were found to be biologically active (Cecchetti *et al.*, 1987).

The thiazolidinediones are currently licensed for use in oral combination therapy (Fujita *et al.*, 1983; Saltiel and Olefsky, 1996). The first compound described was Ciglitazone, which produces dramatic decrease in the glycemic level but showed poor clinical efficacy. In 1997 troglitazone was launched in market but withdrawn in 2000 due to liver failure. Since 1999, rosiglitazone and Pioglitazone are available as second line drugs restricted to combination therapy (Peters, 2001).

The structure activity relationship studies on thiazolidine-2,4-diones showed structural requirements for these type of compounds (Kulkarni *et al.*, 1999).

In this study, we report the synthesis of several novel analogues of 3-substituted thiazolidine-2,4-dione and characterization of the synthesized compounds with the help of spectral data viz., IR, NMR, mass and elemental analysis. The synthesized compounds are under investigation for their insulinotropic activities.

## MATERIALS AND METHODS

This research project was conducted from 30/07/2007 to 28/10/2009.

Initially thiazolidine-2,4-dione (1) was synthesized by reacting chloroacetic acid and thiourea in the presence of water (Sohda *et al.*, 1982). The 5-arylidine-2,4-thiazolidines (Bruno *et al.*, 2002) (2) were synthesized by the condensation of some commercially available substituted benzaldehydes with thiazolidinedione according to Knoevenagel using piperidine as base. In refluxing ethanol, according to a known procedure (Momose *et al.*, 1991).

The 5-arylidine-2, 4-thiazolidines (2) was considered for N-arylation. So, it was converted in potassium salt at N3 position with the help of alcoholic solution of potassium hydroxide with continuous stirring (3). The 3 was then allowed to react with 4-chlorobenzoic acid having active halo group in the presence of dry acetone to give N-arylated product of 5-arylidine-2, 4-thiazolidines (4) (Table 1). The overall reaction sequence is shown in Fig. 1.

The structures of all synthesized intermediated as well as final compounds were assigned on the basis of IR, <sup>1</sup>HMR, Mass and elemental analysis. The structure of acid was assigned on the basis of their IR spectra which shows a very broad band at 3200-2500 cm<sup>-1</sup> attributable to the stretching of carboxylic OH group.

**Experimental:** Melting points were uncorrected and recorded on Scientific melting point apparatus. The TLC controls were carried out on glass plates coated with Silica gel G. The IR spectra was obtained with a Shimadzu FTIR 8400S. <sup>1</sup>HNMR spectra were recorded on a Varian 300 MHz spectrometer; chemical shifts are given in δ units (ppm) relative to internal standard Me<sub>4</sub>Si and refer to CDCl<sub>3</sub> or DMSO-d<sub>6</sub> solutions. Mass spectra were recorded on a Shimadzu GC17A/MSQP5050 spectrometer.

**General procedure for the synthesis of 2,4-thiazolidinedione (Sohda *et al.*, 1982; Bozdag *et al.*, 1999; Pattan *et al.*, 2005):** In a 100 mL round bottom flask, 10 g (0.106 mol) of chloroacetic acid in 10 mL of water was placed. 8.055 g (0.106 mol) of thiourea was added and the reaction mixture was stirred for 15 min to obtain a white precipitate accompanied by considerable

Table 1: Substituents present on benzene ring

Sr. No.	R
1	Bn
2	2-Cl
3	4-OCH <sub>3</sub>
4	4-OH
5	4-N(CH <sub>3</sub> ) <sub>2</sub>
6	4-Cl
7	4-F
8	4-NO <sub>2</sub>

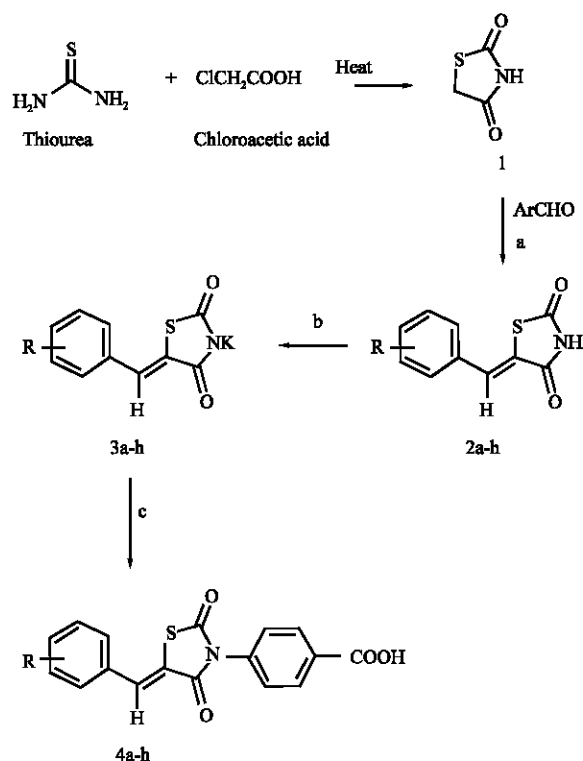


Fig. 1: Route of synthesis of 4a-h from thiazolidinedione. (a) Piperidine, EtOH, reflux (b) KOH, EtOH and (c) ClC<sub>6</sub>H<sub>4</sub>COOH, dry acetone, reflux

cooling. The flask was then connected with a reflux and gentle heat is applied to effect complete dissolution and refluxed for 40 h at 100-110°C. On cooling the contents of the flask solidified into a cluster of white needles. The product was filtered and washed with sufficient water to remove traces of unreacted species. It was then dried and purified by recrystallization from appropriate solvent to get 2,4-thiazolidinedione 1. Yield 89%; m.p. 122-124°C (L mp 126°C).

**Synthesis of 5-arylidine-2,4-thiazolidinedione (Bruno *et al.*, 2002):** To 2,4-thiazolidinedione 1 (4 g, 20 mmol), was added substituted benzaldehydes (20 mmol), piperidine (1.4 g, 16 mmol) and EtOH (150 mL). The resultant was refluxed for 16-24 h. The reaction mixture was poured into H<sub>2</sub>O and acidified with AcOH to give 2a-2h as solids. The derivatives were recrystallized from methanol.

**Synthesis of potassium salt of 5-arylidine-2,4-thiazolidinedione (Lo and Shropshire, 1957):** In a 100 mL round bottom flask 5-arylidine-2,4-thiazolidinedione 2a-2h was dissolved in 50 mL of ethanol. To this hot solution was added a solution of potassium hydroxide (42 g) in ethanol (100 mL). The mixture was stirred without cooling for 2-3 h and then cooled. The crystalline solid was collected on a filter, washed and air-dried. The potassium salt of 5-arylidine-2,4-thiazolidinedione thus obtained 3a-3h, decomposed at 248-250°C and was analytically pure.

**Synthesis of 5-arylidine-2,4-thiazolidinedione-3-benzoic acid:** Potassium salt of 5-arylidine-2,4-thiazolidinedione 3a-3h was suspended in dry acetone in a 100 mL round bottom flask. To the resulting suspension 1.6 g of 4-chlorobenzoic acid was added. The suspension was connected with

a reflux and it is refluxed for 3-5 h. the reaction was monitored with the help of TLC. After completion of reaction the solution was filtered and excess of acetone was allowed to evaporate to give crystals of 5-arylidine-2, 4-thiazolidinedione-3-benzoic acid 4a-4h.

**5-benzylidene-2,4-thiazolidinedione-3-benzoic acid (4a):** Yield: 81%, m.p: 206-208°C, TLC-Benzene: Glacial acetic acid (8.5:1.5).

**IR(KBr):** 1869,1772,1683, 1541,1458,1396, 669. <sup>1</sup>HNMR (CDCl<sub>3</sub>) (δ ppm): 7.41-7.54 (m,9H, arom), 7.78 (s, CH arylidene), MS(ESI-m/z): 325.2, 326.2 (M+1), 208.5, 117.2, 105.2, 77.0. Anal. Calcd for C<sub>17</sub>H<sub>11</sub>O<sub>4</sub>SN: C, 56.87; H, 3.65; N, 3.09; S, 10.01. Found C, 56.27; H, 3.14; N, 2.97; S, 10.02.

**5-(2-chlorobenzylidene)-2,4-thiazolidinedione-3-benzoic acid (4b):** Yield: 79%, m.p: 222-224°C, TLC-Benzene: Glacial acetic acid (8.5:1.5).

**IR(KBr):** 1799,1683,1506, 1338,1174, 761, 669. <sup>1</sup>HNMR (CDCl<sub>3</sub>) (δppm): 7.79 (s, CH, arylidene), 7.0-7.13 (m, 8H, arom), MS(ESI-m/z): 359.4, 360.4 (M+1), 242.8, 117.2, 114.4, 105.1, 77.2. Anal. Calcd for C<sub>17</sub>H<sub>10</sub>O<sub>4</sub>SNCl: C, 56.16; H, 2.21; N, 3.84; S, 10.16. Found C, 55.91; H, 2.06; N, 3.20; S, 10.08.

**5-(4-methoxybenzylidene)-2,4-thiazolidinedione-3-benzoic acid (4c):** Yield: 82%, m.p: 218-220°C, TLC-Benzene: Glacial acetic acid (8.5:1.5).

**IR(KBr):** 1695, 1683, 1593, 1508, 1423, 1255, 1178, 682. <sup>1</sup>HNMR (CDCl<sub>3</sub>) (δppm): 3.81 (s, 3H, OCH<sub>3</sub>), 7.78 (s, CH, arylidene), 7.05-7.16 (m, 8H, arom), MS(ESI-m/z): 355.1, 356.1 (M+1), 238.5, 122.6, 117.3, 105.1, 77.2. Anal. Calcd for C<sub>18</sub>H<sub>13</sub>O<sub>5</sub>SN: C, 54.17; H, 5.30; N, 3.69; S, 10.13. Found C, 53.91; H, 5.01; N, 3.21; S, 10.11.

**5-(4-hydroxybenzylidene)-2,4-thiazolidinedione-3-benzoic acid (4d):** Yield: 76%, m.p: 278-280°C, TLC-Benzene: Glacial acetic acid (8.5:1.5).

**IR(KBr):** 3404, 1859, 1681, 1593, 1506, 1319, 1213, 1155, 1091, 696. <sup>1</sup>HNMR (CDCl<sub>3</sub>) (δppm): 8.11 (s, 1H, OH), 7.78 (s, CH, arylidene), 7.13-7.36 (m, 8H, arom), MS(ESI-m/z): 341.6, 342.6 (M+1), 224.6, 117.2, 107.5, 105.2, 77.3. Anal. Calcd for C<sub>17</sub>H<sub>11</sub>O<sub>5</sub>SN: C, 56.87; H, 3.65; N, 3.09; S, 10.12. Found C, 56.27; H, 3.14; N, 2.97; S, 10.09.

**5-(4-dimethylaminobenzylidene)-2,4-thiazolidinedione-3-benzoic acid (4e):** Yield: 86%, m.p: 228-230°C, TLC- Benzene: Glacial acetic acid (8.5:1.5).

**IR(KBr):** 1867,1683, 1558,1338,1190,1091,669. <sup>1</sup>HNMR (CDCl<sub>3</sub>) (δppm): 3.06 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>), 7.79 (s, CH, arylidene), 7.45-7.78 (m, 8H, arom), MS(ESI-m/z): 368.4, 369.4 (M+1), 251.0, 135.2, 117.0, 105.3, 77.1. Anal. Calcd for C<sub>19</sub>H<sub>16</sub>O<sub>4</sub>SN<sub>2</sub>: C, 55.07; H, 3.12; N, 3.15; S, 10.18. Found C, 54.85; H, 3.04; N, 2.80; S, 10.16.

**5-(4-chlorobenzylidene)-2,4-thiazolidinedione-3-benzoic acid (4f):** Yield: 78%, m.p: 268-270°C, TLC-Benzene: Glacial acetic acid (8.5:1.5).

**IR(KBr):** 1695, 1683, 1506, 1382, 1157, 933, 667. <sup>1</sup>HNMR (CDCl<sub>3</sub>) (δppm): 7.79 (s, CH, arylidene), 7.52-7.73 (m, 8H, arom), MS(ESI-m/z): 359.8, 360.8 (M+1), 249.2, 117.1, 114.3, 105.1, 77.2. Anal. Calcd for C<sub>17</sub>H<sub>10</sub>O<sub>4</sub>SNCl: C, 56.87; H, 2.16; N, 3.87; S, 10.08. Found C, 56.10; H, 2.00; N, 3.31; S, 10.07.

**5-(4-fluorobenzylidene)-2,4-thiazolidinedione-3-benzoic acid (4g):** Yield: A 82%, m.p: 202-204°C, TLC-Benzene: Glacial acetic acid (8.5:1.5).

**IR(KBr):** 1867, 1699, 1558, 1506, 1319, 1240, 1157, 761, 688. <sup>1</sup>HNMR (CDCl<sub>3</sub>) (δppm) 7.79 (s, CH, arylidene), 7.0-7.13 (m, 8H, arom), MS(ESI-m/z): 343.0, 344.0 (M+1), 300.2, 226.8, 117.2, 109.7, 105.3, 77.1. Anal. Calcd for C<sub>17</sub>H<sub>10</sub>O<sub>4</sub>SNF: C, 57.17; H, 3.45; N, 3.29; S, 10.12. Found C, 57.07; H, 3.40; N, 2.77; S, 10.08.

**5-(4-nitrobenzylidene)-2,4-thiazolidinedione-3-benzoic acid (4g):** Yield: 71%, m.p: 226-228°C, TLC- Benzene: Glacial acetic acid (8.5:1.5).

**IR(KBr):** 1696, 1601, 1419, 1176, 852, 761. <sup>1</sup>HNMR (CDCl<sub>3</sub>) (δppm) 7.79 (s, CH, arylidene), 7.0-7.13 (m, 8H, arom), MS(ESI-m/z): 370.2 371.2 (M+1), 253.6, 238.1, 136.8, 117.3, 105.2, 77.1. Anal. Calcd for C<sub>17</sub>H<sub>10</sub>O<sub>6</sub>SN<sub>2</sub>: C, 56.17; H, 3.78; N, 3.21; S, 10.06. Found C, 56.00; H, 3.24; N, 2.21; S, 10.05.

## RESULTS AND DISCUSSION

The general method which is known as Knoevenagel condensation was used to synthesis 5-arylidene-2,4-thiazolidinedione from 2,4-thiazolidinedione. This type of reactions are generally carried out in basic medium for which piperidine was used. Alcohol was generally used in this condensation. The 5-arylidene-2,4-thiazolidinedione was then converted to its potassium salt by the action of alcoholic potassium hydroxide solution. The hydrogen from 3rd position in 2,4-thiazolidinedione is replaced by potassium with removal of water molecule. This salt was then treated with substituted benzoic acid in the presence of dry acetone to give final compounds.

The formula, melting points, yields, IR, <sup>1</sup>HNMR, mass spectral and elemental analysis values of the compounds are listed earlier. All spectral data were in accordance with the assumed structures. A very broad band at 3200-2500 cm<sup>-1</sup> attributable to the stretching of carboxylic OH in the IR spectra. The final compounds showed characteristic NMR pattern 7-7.5 for aromatic hydrogen, 7.78-7.79 for arylidene C-H bonding (Bruno *et al.*, 2002). Mass fragmentation pattern was also studied which gave idea about the fragmentation of the final compounds with their corresponding mass (Bruno *et al.*, 2002; Sohda *et al.*, 1982; Bozdogan *et al.*, 1999; Pattan *et al.*, 2005).

## CONCLUSIONS

In the present studies, a series of Novel N-substituted 2, 4-Thiazolidinedione were synthesized successfully in convenient steps in 52-80% yields. All compounds were characterized with the help of analytical techniques viz., IR, NMR, mass and elemental analysis. The synthesized compounds are under investigation for their possible insulinotropic property.

This kind of synthetic protocol shall be helpful in the design and development of some novel thiazolidinedione derivatives, which shows remarkable effect in Type-2 diabetes mellitus.

## ACKNOWLEDGMENTS

LVS gratefully acknowledge Department of Science and Technology, Govt. of India for awarding Young Scientist Fellowship (SR/FT/LS-161/2008). Authors would like to acknowledge Principal of the institute for providing necessary facilities during the research.

## REFERENCES

- Borkar, M.R., N. Sachan, S.S. Kadam and V.M. Kulkarni, 2009. Synthesis of N-substituted 2,4-thiazolidinediones and their hypoglycemic activity and QSAR. *Indian J. Heterocyclic Chem.*, 18: 295-300.
- Bozdog, O., G. Ayhan-Kilicgil, M. Tuncbilek and R. Ertan, 1999. Studies on the synthesis of some substituted flavonyl thiazolidinedione derivatives-I. *Turk. J. Chem.*, 23: 163-169.
- Brown, F.C., 1961. 4-Thiazolidinones. *Chem. Rev.*, 61: 463-521.
- Bruno, G., L. Costantino, C. Curinga, R. Maccari and F. Monfort *et al.*, 2002. Synthesis and aldose reductase inhibitory activity of 5-arylidene-2,4-thiazolidinediones. *Bioorganic Med. Chem.*, 10: 1077-1084.
- Cecchetti, V., A. Fravolini, R. Fringuelli, G. Mascellani and P. Pagella *et al.*, 1987. Quinolonecarboxylic acids. 2. Synthesis and antibacterial evaluation of 7-oxo-2,3 dihydro-7H-pyrido[1,2,3-de][1,4]benzothiazine-6-carboxylic acids. *J. Med. Chem.*, 30: 465-473.
- Elderfield, R.C., 1961. *Heterocyclic Compounds 2,4-Dioxothiazolidines*. John Willey and Sons Inc., London.
- Fujita, T., Y. Sugiyama, S. Taketomi, T. Sohda, Y. Kawamatsu, H. Iwatsuka and Z. Suzuoki, 1983. Reduction of insulin resistance in obese and/or diabetic animals by 5-[4-(1-methylcyclohexylmethoxy) benzyl]-thiazolidine-2,4-dione (ADD-3878, U-63,287, ciglitazone), a new antidiabetic agent. *Diabetes*, 32: 804-810.
- Kulkarni, S.S., L.K. Gediya and V.M. Kulkarni, 1999. Three-dimensional quantitative structure activity relationships (3-D-QSAR) of antihyperglycemic agents. *Bioorganic Med. Chem.*, 7: 1475-1485.
- Lo, C.P. and E. Shropshire, 1957. Notes-alkylation of 2,4-thiazolidinedione. *J. Org. Chem.*, 22: 999-1001.
- Madhavan, G.R., R. Chakrabarti, R.K. Vikramadithyan, R.N.V.S. Mamidi and V. Balraju *et al.*, 2002. Synthesis and biological activity of novel pyrimidinone containing thiazolidinedione derivatives. *Bioorganic Med. Chem.*, 10: 2671-2680.
- Momose, Y., K. Meguro, H. Ikeda, C. Hatanaka, S. Oi and T. Sohda, 1991. Studies on antidiabetic agents. X. Synthesis and biological activities of pioglitazone and related compounds. *Chem. Pharm. Bull.*, 39: 1440-1445.
- Pattan, S.R., R.B. Patel, M.S. Ali, S.R. Butle and J.S. Pattan, 2004. Synthesis of some substituted 2-amino/acetamido 4-aryl thiazolyl-5-substituted sulphides and sulphones and their antibacterial and antifungal activity. *Indian J. Heterocyclic Chem.*, 13: 265-268.
- Pattan, S.R., C. Suresh, V.D. Pujari, V.V.K. Reddy, V.P. Rasal and B.C. Koti, 2005. Synthesis and antidiabetic activity of 2-amino [5'(4-sulphonylbenzylidene)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole. *Indian J. Chem.*, 44: 2404-2408.
- Peters, A.L., 2001. Using thiazolidinediones: Rosiglitazone and pioglitazone in clinical practice. *Am. J. Manage. Care*, 7: S87-S95.

- Rotella, D.P., 2004. Novel second-generation approaches for the control of type 2 diabetes. *J. Med. Chem.*, 47: 4111-4112.
- Saltiel, A.R. and J.M. Olefsky, 1996. Thiazolidinediones in the treatment of insulin resistance and type II diabetes. *Diabetes*, 45: 1661-1669.
- Sohda, T., K. Mizuno, E. Imamiya, Y. Sugiyama, T. Fujita and Y. Kawamatsu, 1982. Studies on antidiabetic agents. II. Synthesis of 5-[4-(1-methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and its derivatives. *Chem. Pharm. Bull. (Tokyo)*, 30: 3580-3600.
- Turner, N.C., 1996. New therapeutic agents for the treatment of insulin resistance and NIDDM. *Drug Discovery Today*, 1: 109-116.