Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 12 (2004) 5857–5864
Bioorganic & Medicinal Chemistry

Synthesis and antihyperglycemic activity profiles of novel thiazolidinedione derivatives☆

Bashir A. Bhat,[a] Shashikanth Ponnala,[a] Devi Prasad Sahu,[a,*] Priti Tiwari,[b] Brajendra K. Tripathi[b] and Arvind K. Srivastava[b]

[a]*Division of Medicinal and Process Chemistry, Central Drug Research Institute, Lucknow 226001, India*
[b]*Biochemistry Division, Central Drug Research Institute, Lucknow 226001, India*

Received 23 June 2004; revised 23 August 2004; accepted 23 August 2004
Available online 15 September 2004

Abstract—A number of thiazolidine-2,4-diones derivatives having carboxylic ester appendage at N-3 were synthesized and their antihyperglycemic activity was evaluated. Many of these derivatives as well as their corresponding carboxylic acid showed significant improvement on post-prandial hyperglycemia in normal rats, in contrast to their poor agonist activity at PPARγ.

1. Introduction

Diabetes mellitus, long considered a disease of minor significance to world health, is now taking its place as one of the main threats to human health in the 21st century.[1] The incidence of the disease currently is estimated to reach 210 million by the year 2010 and 300 million by the year 2025.[2] Most cases will be of type 2 diabetes, which is strongly associated with a sedentary life style and obesity.[3] Early stages of type 2 diabetes mellitus (Type 2 DM) are characterized by tissue resistance to the effects of insulin secreted by pancreatic beta cells. The ability of pancreatic beta cells to continue increased production of insulin diminishes over time. When insulin production declines in the face of insulin resistance, glucose disposal from the muscle is diminished and suppression of hepatic glucose output is decreased. The disease is often associated with obesity, dyslipidemia, and hypertension leading to cardiovascular risks.[4] The macrovascular (atherosclerotic) complications of Type 2 DM are less closely linked to hyperglycemia but contribute to substantial morbidity. The large vessel complications directly result from the altered metabolic milieu in Type 2 DM.[5]

When recommended dietary medication and exercise fail to control elevated blood glucose levels, pharmacological therapy is required to restore normoglycemia, reduce the attendant sequelae, and delay the need for insulin therapy. Pharmacological agents, currently available or under investigation, include drugs that improve insulin resistance or increase insulin secretion. Metformin, a biguanides, acts primarily by decreasing hepatic glucose output and increasing peripheral glucose utilization.[6] It is a first line therapeutic option for Type 2 DM. Another class of drugs, that is, sulfonylureas stimulate insulin secretion by blocking ATP-dependent potassium channels[7] but are associated with a significant risk of hypoglycemia. Since the pioneer thiazolidinedione compound, ciglitazone, was reported improving blood glucose level by increasing insulin sensitivity, several new thiazolidine-2,4-diones such as pioglitazone, rosiglitazone,[8] were launched into market since 1997.

Thiazolidinedione derivatives though effective therapeutic agents some of them have been reported to have hepatotoxicity.[9] There exist the need for efficient antidiabetic agents devoid of hepatotoxicity.

We were interested in developing a series of thiazolidine-2,4-diones having carboxylic ester appendage at N-3 and benzyl and heteroaryl substituents at C-5, which might surmount the hepatic toxicity encountered with the some of the glitazones. Epalrestat, a 5-cinnamylidene-2-thioxo-4-thiazolidinone *N*-acetic acid derivative is the only aldose reductase inhibitor available currently

Keywords: Antihyperglycemic activity; Thiazolidinedione; Diabetes; SLM; PPARγ.
☆CDRI Communication No 6534.
* Corresponding author. Tel.: +91 522 2212411 18 4378; fax: +91 522 223405/223938; e-mail: dpsahu@rediffmail.com

0968-0896/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2004.08.031

on the market, which is devoid of hepatic toxicity.[10] The aldose reductase inhibitory activity of 5-benzylidenethiazolidine-2,4-dione-3-acetic acid is found to be higher than that of N-unsubstituted analogues.[11] *N*-Carboalkoxymethylthiazolidine-2,4-diones (**A**) was selected as core structure with substituted benzylidene and benzyl and heteroaryl derivatives of (**A**) were synthesized and their hypoglycemic activity were evaluated. We present herein the hypoglycemic activity evaluated SLM (sucrose-loaded model) in mice.

2. Chemistry

The synthetic protocol of thiazolidinedione derivatives presented here is shown in Scheme 1. N-Alkylation of thiazolidine-2,4-dione **1** with alkyl bromoacetate furnished alkyl 2,4-dioxothiazolidin-3-ylacetate **2**, which on Knoevenagel condensation with various aromatic aldehydes yielded 5-arylidene-2,4-thiazolidinedione derivative **3**. Catalytic hydrogenation of **3** afforded saturated thiazolidinedione **4**. Compound **3a** is then alkylated with various alkylating agents to give **7**. Compounds **3**, **5**, **7**, **9**, and **11a** were hydrogenated to furnish **4**, **6**, **8**, **10**, and **12**.

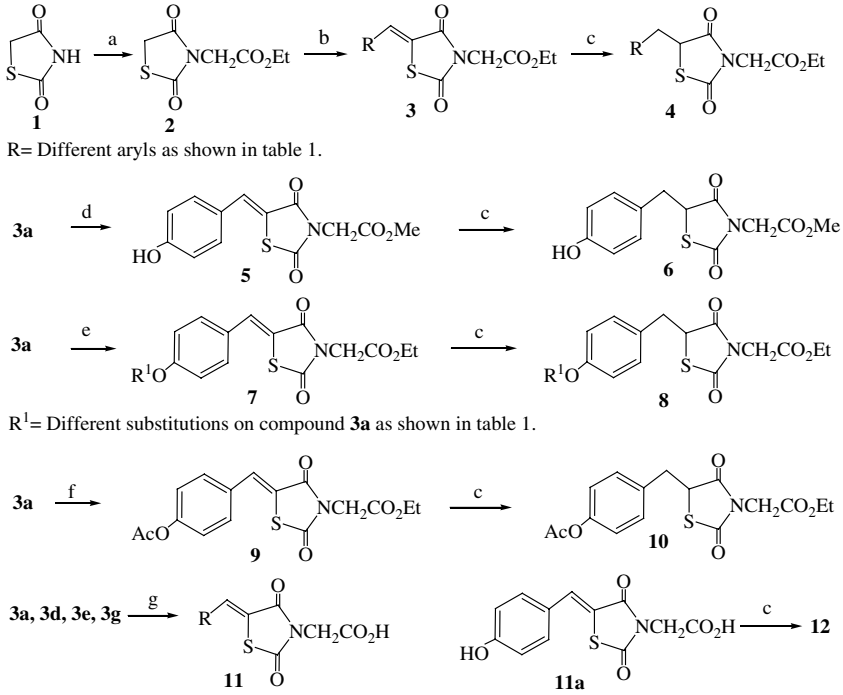
3. Results and discussion

The synthesized compounds were screened for antihyperglycemic activity in vivo by sucrose-loaded model (mice) and in vitro by PPARγ activation. The marketed, rosiglitazone and metformin were selected as positive control. The activity of all compounds is presented in Table 1 with reference to rosiglitazone and metformin.

Following pattern of hypoglycemic activity of the synthesized compounds was observed. The 5-arylmethyl thiazolidine-2,4-diones with various substituents displayed higher hypoglycemic activity than their corresponding precursor 5-arylidenethiazolidine-2,4-dione derivative. Surprisingly the ethyl ester of thiazolidine-2,4-dione-3-acetic acid **4a** exhibited higher antihyperglycemic activity (−26.7) than the corresponding methyl ester **6** (−9.5). The 5-(2-indolylmethylene)thiazolidine-2,4-dione **3h** and 5-(2-pyrrolylmethylene)thiazolidine-2,4-dione **3i** displayed hyperglycemic activity in contrast to marginal hypoglycemic activity shown by 5-benzylidenethiazolidine-2,4-dione derivatives.

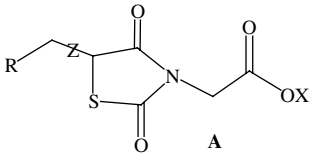
Correlation of electronic influence of the substituents on aryl group of thiazolidine-2,4-dione with the antihyperglycemic activity could not be well established as substituents such as methyl, methoxy, chloro, hydroxy, acetoxy at 3- or 4-position on the phenyl ring showed higher antihyperglycemic activity, where as trifluoromethyl, dimethylamino, substituent on the same position in phenyl ring exhibited low to moderate antihyperglycemic activity. As indicated in Table 1, compound **4a** and **10** having hydroxy and acetoxy substituent, 5-benzylthiazolidine-2,4-dione-3-acetic acid ethyl ester exhibited higher antihyperglycemic activity (−26.7 and −26.8, respectively). The activity of rosiglitazone and metformin were found to be −11.6 and −34.1, respectively.

There is moderate increase of hypoglycemic activity of thiazolidine-2,4-dione *N*-acetic acid (**11d**,**e**,**g**, and **12**)

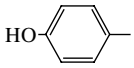
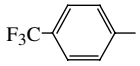
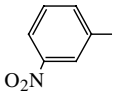
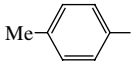
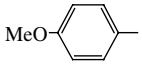
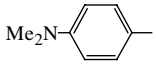
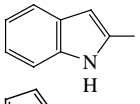
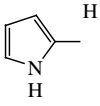
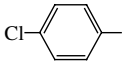
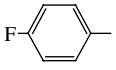
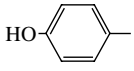
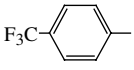
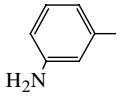
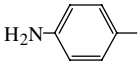
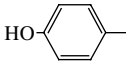
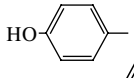
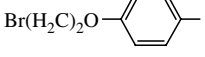
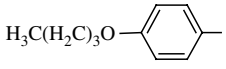


Scheme 1. Reagents: (a) NaH, ethyl bromoacetate, THF; (b) different aldehyde, CH_3CO_2H, pipyridine, toluene; (c) H_2–Pd/C, dioxane; (d) H_2SO_4, MeOH; (e) XR^1, K_2CO_3, DMF; (f) triethylamine, dichloromethane, AcCl, (g) AcOH, HCl.

Table 1. Antihyperglycemic activity profile of title compounds thiazolidine-2,4-dione derivatives

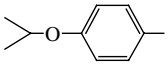
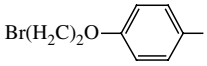
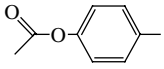
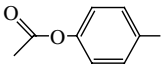
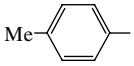
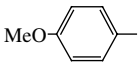
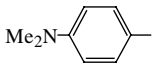
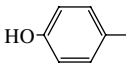


A

Entry	Compd	R	Z	X	Antihyperglycemic activity, **SLM**	PPARγ	
						10 nmol[a]	1000 nmol
	Standard	Rosiglitazone			−11.6	92	248
	Standard	Metformin			−34.1*		
1	**3a**		Double bond	$-CH_2CH_3$	+2.84[b]		
2	**3b**		Double bond	$-CH_2CH_3$	−3.30[c]	10	11
3	**3c**		Double bond	$-CH_2CH_3$	−2.69	11	11
4	**3d**		Double bond	$-CH_2CH_3$	−22.1	9	9
5	**3e**		Double bond	$-CH_2CH_3$	−22.2	7	8
6	**3f**		Double bond	$-CH_2CH_3$	−5.71		
7	**3g**		Double bond	$-CH_2CH_3$	−15.8		
8	**3h**		Double bond	$-CH_2CH_3$	+1.52		
9	**3i**		Double bond	$-CH_2CH_3$	+9.00		
10	**3j**		Double bond	$-CH_2CH_3$	−23.2	9	8
11	**3k**		Double bond	$-CH_2CH_3$	−6.80		
12	**4a**		Single bond	$-CH_2CH_3$	−26.7*	10	12
13	**4b**		Single bond	$-CH_2CH_3$	−12.3	9	11
14	**4c**		Single bond	$-CH_2CH_3$	−3.12		
15	**4d**		Single bond	$-CH_2CH_3$	−12.7	8	10
16	**5**		Double bond	$-CH_3$	−2.46	10	12
17	**6**		Single bond	$-CH_3$	−9.55	9	11
18	**7b**		Double bond	$-CH_2CH_3$	+3.07	11	14
19	**7c**		Double bond	$-CH_2CH_3$	−1.59		

(*continued on next page*)

Table 1 (*continued*)

Entry	Compd	R	Z	X	Antihyperglycemic activity, **SLM**	PPARγ	
						10 nmol[a]	1000 nmol
20	**8a**		Single bond	$-CH_2CH_3$	−14.1		
21	**8b**		Single bond	$-CH_2CH_3$	−8.28	12	13
22	**9**		Double bond	$-CH_2CH_3$	+7.55		
23	**10**		Single bond	$-CH_2CH_3$	−26.8*		
24	**11d**		Double bond	H	−26.1*		
25	**11e**		Double bond	H	−33.4*		
26	**11g**		Double bond	H	−15.5		
27	**12**		Single bond	H	−18.3		

*Significant $p < 0.05$.
[a] Concn in nanomolar.
[b] + indicates further increase in blood glucose.
[c] − indicates decrease blood glucose.

compared to corresponding ester, which may be rationalized by assumption of the acids being the active principle rather than the respective esters.

In contrast to antihyperglycemic activity exhibited in vivo by the compounds **3d**,**e**,**g**,**i**, **4a**,**b**,**d**, **8a**, and **10** comparable or higher than rosiglitazone, these ligands have poor agonist activity at PPARγ in vitro estimated at 10 and 1000 nmol concentration (Table 1). The thiazolidinedione, netiglitezone undergoing phase-II clinical trials was reported to have poor potency at PPARγ in vitro than rosiglitazone.[12,13] NC-2100[14] and some of the (Δ^5-unsaturated) thiazolidinedione **13**[15] (Chart 1) are reported to have low or no activity at PPARγ but have high antidiabetic activity in vivo. These reports corroborate our observation presented herein, which raise the possibility that some thiazolidinediones mediate their antidiabetic activity through a mechanism other than PPARγ.

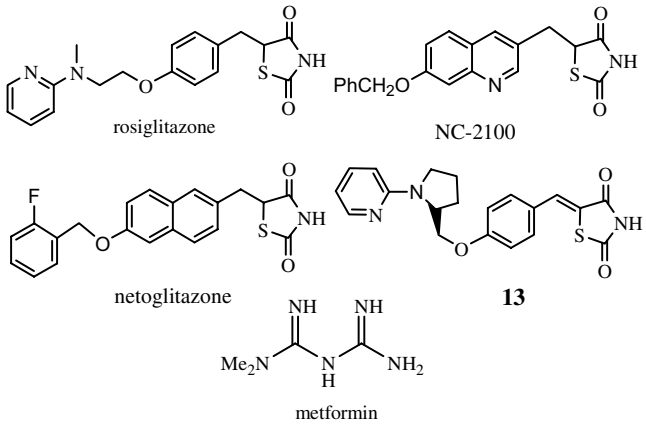


Chart 1.

4. Conclusion

The antihyperglycemic activity of 5-arylidenethiazolidine-2,4-dione-3-acetic acid ester, 5-arylmethylthiazolidine-2,4-dione-3-acetic acid ester and some of the corresponding acids were evaluated by SLM model. The 2,4-dioxo-5-(4-hydroxybenzyl)thiazolidin-3-ylacetic acid ester and its O-acylated derivatives showed comparable or higher antihyperglycemic activity than that of rosiglitazone and metformin, though they have poor PPARγ agonist activity. In the corresponding acids there is marginal enhancement of antihyperglycemic activity.

5. Experimental

5.1. Biology

Male albino rats of Charles Foster strain of average body weight 160 ± 20 g were selected for this study. The blood glucose of each animal was checked after 16 h starvation using glucose strips (Boehringer Mannheim, Germany). Animals showing blood glucose between 60 and 80 mg/dl (3.33 and 4.44 mM) were finally selected and divided into groups of five to six animals in each. Rats of experimental group were administered suspension of the desired compound orally (made in 1.0% gum acacia) at 100 mg/kg-body weight. Animals of control group were given an equal amount of 1.0%

gum acacia. A sucrose load (2.0 g/kg) was given to each animal orally exactly after 30 min post-administration of the test sample/vehicle. Blood glucose profile of each rat was again determined at 30, 60, 90, and 120 min post-administration by glucose strips. Food but not water was withheld from the cages during the course of experimentation. Quantitative glucose tolerance of each animal was calculated by Area under curve method. Comparing the AUC of experimental and control groups determined the percentage antihyperglycemic activity. Pairwise comparison was done by the one-tailed Student's *t* test. Probability values $p < 0.05$ were considered to be statistically significant. All results are expressed as the mean ± SEM ($n = 6$), and the sample size, *n*, represents the number of individual strips of ileum assayed.

5.1.1. PPARγ transactivation assay. Cells are transfected with an expression plasmid for PPARγ receptors and the ability of these to activate a luciferase gene is measured. Day one, human embryonic kidney (HEK) 293 cells grown in DMEM was inoculated in 96-well elisa plate 20,000 cells are added in each well. Day two, cells were infected with PPARγ expression plasmid. FuGene transfaction reagent (Boehringer Mannheim) is used for the transfactions. Day three, after transfaction the media is aspirated and media containing the ligand (drug) is added to the cells the concentration of the ligand are 10 and 1000 nm. Day four, approximately 48 h after transfaction the cells are harvested and assayed for expression of relevant gene. Luciferase is measured on luminescence counting instrument. Renilla assay is done to count the total number of cells; rosiglitazone is taken as standard compound.

5.2. Chemistry

Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in the indicated solvent on Bruker WM 200 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded in KBr on Perkin–Elmer AC-1 spectrometer. FAB mass spectra were recorded on JEOL SX 102/DA 6000 mass spectrometer. Microanalyses were performed on Carlo Erba EA-1108 element analyzer.

5.2.1. Representative procedure for (3a–k). [5-(4-Methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (3e). To a solution of 4-methoxybenzaldehyde (0.34 g, 2.5 mmol) and 2,4-thiazolidinedione acetic acid ethyl ester **2** (0.507 g, 2.5 mmol) in toluene (5 mL), three drops of piperidine and two drops of acetic acid were added. The mixture was refluxed for 10 h, cooled to ambient temp and evaporated at reduced pressure. The solid residue was extracted twice with hot methanol (10 mL each) and was filtrated to furnish **3e** (0.62 g, 80%). Mp 129–131 °C; IR (KBr) *ν* 3445, 2987, 2317, 1744, 1689, 1596, 1512, 1382, 1259, 1156 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 1.29 (t, $J = 7.2$ Hz, 3H, C*H*$_3$), 3.86 (s, 3H, C*H*$_3$), 4.24 (q, $J = 7.2$ Hz, 2H, C*H*$_2$), 4.46 (s, 2H, C*H*$_2$), 6.99 (d, $J = 8.6$ Hz, 2H, Ar*H*), 7.46 (d, $J = 8.6$ Hz, 2H, Ar*H*), 7.88 (s, 1H, C*H*); MS-FAB *m/z*: 322 $(M+H)^+$; Anal. Calcd for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.70; N, 4.36; S, 9.98. Found: C, 56.40; H, 4.47; N, 3.92.

5.2.2. [5-(4-Hydroxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (3a). Yellow solid mp 160–162 °C; IR (KBr) *ν* 3452, 2996, 2367, 1727, 1669, 1578, 1505, 1381, 1213, 1144 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 1.17 (t, $J = 7.12$ Hz, 3H, C*H*$_3$), 4.11 (q, $J = 7.12$ Hz, 2H, C*H*$_2$), 4.35 (s, 2H, C*H*$_2$), 6.86 (d, $J = 6.6$ Hz, 2H, Ar*H*), 7.46 (d, $J = 6.6$ Hz, 2H, Ar*H*), 7.68 (s, 1H, C*H*); MS-FAB *m/z*: 308 $(M+H)^+$; Anal. Calcd for $C_{14}H_{13}NO_5S$: C, 54.71; H, 4.26; N, 4.56; S, 9.71. Found: C, 54.76; H, 4.22; N, 4.60.

5.2.3. [2,4-Dioxo-5-(4-trifluoromethyl-benzylidene)-thiazolidin-3-yl]-acetic acid ethyl ester (3b). Mp 155–157 °C; IR (KBr) *ν* 3416, 2997, 1741, 1686, 1325, 1163, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 1.30 (t, $J = 7.2$ Hz, 3H, C*H*$_3$), 4.25 (q, $J = 7.2$ Hz, 2H, C*H*$_2$), 4.49 (s, 2H, C*H*$_2$), 7.62 (d, $J = 8.4$ Hz, 2H, Ar*H*), 7.74 (d, $J = 8.4$ Hz, 2H, Ar*H*), 7.93 (s, 1H, C*H*); MS-FAB *m/z*: 360 $(M+H)^+$; Anal. Calcd for $C_{15}H_{12}F_3NO_4S$: C, 50.14; H, 3.37; F, 15.86; N, 3.90; S, 8.92.

5.2.4. [5-(3-Nitro-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (3c). Mp 134–136 °C; IR (KBr) *ν* 3415, 2996, 1737, 1690, 1381, 1347, 1231 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 1.32 (t, $J = 7.2$ Hz, 3H, C*H*$_3$), 4.26 (q, $J = 7.2$ Hz, 2H, C*H*$_2$), 4.5 (s, 2H, C*H*$_2$), 7.6 (t, $J = 8$ Hz, 1H, Ar*H*), 7.84 (d, $J = 8$ Hz, 1H, Ar*H*), 7.96 (s, 1H, C*H*), 8.29 (d, $J = 8$ Hz, 1H, Ar*H*), 8.37 (s, 1H, Ar*H*); MS-FAB *m/z*: 337 $(M+H)^+$; Anal Calcd for $C_{14}H_{12}N_2O_6S$: C, 50.00; H, 3.60; N, 8.33; S, 9.53. Found: C, 50.40; H, 3.23; N, 8.71.

5.2.5. [5-(4-Methyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (3d). Mp 119–121 °C; IR (KBr) *ν* 3464, 2991, 1735, 1683, 1599, 1407, 1382, 1222 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 1.29 (t, $J = 7.2$ Hz, 3H, C*H*$_3$), 2.40 (s, 3H, C*H*$_3$), 4.24 (q, $J = 7.2$ Hz, 2H, C*H*$_2$), 4.47 (s, 2H, C*H*$_2$), 7.28 (d, $J = 8.0$ Hz, 2H, Ar*H*), 7.41 (d, $J = 8.0$ Hz, 2H, Ar*H*), 7.91 (s, 1H, C*H*); MS-FAB *m/z*: 306 $(M+H)^+$; Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.0; H, 4.95; N, 4.59; S, 10.50. Found: C, 58.77; H, 5.34; N, 4.85.

5.2.6. (5-Benzylidene-2,4-dioxo-thiazolidin-3-yl)-acetic acid ethyl ester (3f). Mp 75–77 °C; IR (KBr) *ν* 3435, 2991, 2367, 1742, 1685, 1606, 1405, 1219, 1152 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 1.29 (t, $J = 7.2$ Hz, 3H, C*H*$_3$), 4.23 (q, $J = 7.2$ Hz, 2H, C*H*$_2$), 4.47 (s, 2H, C*H*$_2$), 7.48 (m, 5H, Ar*H*), 7.92 (s, 1H, C*H*); MS-FAB *m/z*: 292 $(M+H)^+$; Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81; S, 11.01. Found: C, 58.11; H, 4.86; N, 4.47.

5.2.7. [5-(4-Dimethylamino-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (3g). Mp 170–171 °C; IR (KBr) *ν* 3385, 2946, 2363, 1735, 1676, 1589, 1531, 1377, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 1.30 (t, $J = 7.0$ Hz, 3H, C*H*$_3$), 3.05 (s, 6H, –(C*H*$_3$)$_2$), 4.23 (q, $J = 7.0$ Hz, 2H, C*H*$_2$), 4.45 (s, 2H, C*H*$_2$), 6.71 (d,

J = 9 Hz, 2H, Ar*H*), 7.39 (d, J = 9 Hz, 2H, Ar*H*), 7.84 (s, 1H, C*H*); MS-FAB *m/z*: 335 $(M+H)^+$; Anal. Calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38; S, 9.59. Found: C, 57.90; H, 4.91; N, 7.86.

5.2.8. [5-(1*H*-Indol-2-ylmethylene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (3h). Mp 201–202 °C; IR (KBr) ν 3309, 2986, 2364, 1720, 1664, 1595, 1381, 1225, 1149 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 7.0 Hz, 3H, CH_3), 4.24 (q, J = 7.0 Hz, 2H, CH_2), 4.46 (s, 2H, CH_2), 7.26 (br s, 4H, Ar*H*), 7.82 (s, 1H, C*H*), 8.90 (s, 1H, Ar*H*); MS-FAB *m/z*: 331 $(M+H)^+$; Anal. Calcd for $C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48; S, 9.71. Found: C, 58.48; H, 4.61; N, 8.96.

5.2.9. [2,4-Dioxo-5-(1*H*-pyrrol-2-ylmethylene)-thiazolidin-3-yl]-acetic acid ethyl ester (3i). Mp 174–176 °C; IR (KBr) ν 3343, 2989, 2362, 1729, 1681, 1604, 1376, 1223, 1141 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 7.0 Hz, 3H, CH_3), 4.24 (q, J = 7.0 Hz, 2H, CH_2), 4.46 (s, 2H, CH_2), 6.44 (d, J = 3.4 Hz, 1H, Ar*H*), 6.64 (s, 1H, Ar*H*), 7.08 (s, 1H, Ar*H*), 7.80 (s, 1H, C*H*), 9.20 (bs, 1H, N*H*); MS-FAB *m/z*: 381 $(M+H)^+$; Anal. Calcd for $C_{12}H_{12}N_2O_4S$: C, 51.62; H, 4.32; N, 9.9; S, 11.44. Found: C, 51.20; H, 4.89; N, 9.46.

5.2.10. [5-(4-Chloro-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (3j). Mp 120–122 °C; IR (KBr) ν 3461, 2992, 1736, 1691, 1586, 1401, 1225 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7.16 Hz, 3H, CH_3), 4.23 (q, J = 7.16 Hz, 2H, CH_2), 4.47 (s, 2H, CH_2), 7.46 (s, 4H, Ar*H*), 7.88 (s, 1H, C*H*); MS-FAB *m/z*: 326 $(M+H)^+$; Anal. Calcd for $C_{14}H_{12}ClNO_4S$: C, 51.62; H, 3.71; Cl, 10.88; N, 4.30; S, 9.84. Found: C, 51.20; H, 4.29; N, 4.96.

5.2.11. [5-(4-Fluoro-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (3k). Mp 110–112 °C; IR (KBr) ν 3408, 2994, 1741, 1665, 1593, 1507, 1405, 1220, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7.2 Hz, 3H, CH_3), 4.24 (q, J = 7.2 Hz, 2H, CH_2), 4.47 (s, 2H, CH_2), 7.2 (m, 2H, Ar*H*), 7.51 (m, 2H, Ar*H*), 7.89 (s, 1H, C*H*); MS-FAB *m/z*: 310 $(M+H)^+$; Anal. Calcd for $C_{14}H_{12}FNO_4S$: C, 54.36; H, 3.91; F, 6.14; N, 4.53; S, 10.37.

5.2.12. Representative procedure for (4a–d, 6a, 8a,b, 10, and 12). [5-(4-Hydroxy-benzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (4a). To a solution of [5-(4-hydroxy-benzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester **3a** (0.614 g, 2 mmol) in dioxane (50 mL) placed in an autoclave, palladium charcoal (10%, 0.6 g) was added and the mixture was hydrogenated at 300 psi at ambient temp with stirring for 8–10 h. The product mixture was filtered through bed of Celite and the filtrate was concentrated under vacuo to yield (0.602 g, 98%). Colorless solid mp 92–94 °C; IR (KBr) ν 3384, 2989, 2364, 1744, 1687, 1516, 1224 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H, CH_3), 3.01 (dd, J_1 = 14 Hz, J_2 = 10.2 Hz, 1H, C*H*), 3.53 (dd, J_1 = 14 Hz, J_2 = 4 Hz, 1H, C*H*), 4.22 (q, J = 7.2 Hz, 2H, CH_2), 4.31 (s, 2H, CH_2), 4.48 (dd, J_1 = 10.2 Hz, J_2 = 4 Hz, 1H, C*H*), 6.78 (d, J_1 = 8.4 Hz, 2H, Ar*H*), 7.1 (d, J_1 = 8.4 Hz, 2H, Ar*H*); MS-FAB *m/z*: 310 $(M+H)^+$; Anal. Calcd for $C_{14}H_{15}NO_5S$: C, 54.36; H, 4.48; N, 4.53; S, 10.37. Found: C, 54.0; H, 4.93; N, 4.16.

5.2.13. [2,4-Dioxo-5-(4-trifluoromethyl-benzyl)-thiazolidin-3-yl]-acetic acid ethyl ester (4b). Mp 99–101 °C; IR (KBr) ν 3414, 2999, 2371, 1740, 1685, 1598, 1411, 1328, 1164, 1113 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H, CH_3), 3.19 (dd, J_1 = 14 Hz, J_2 = 9.8 Hz, 1H, C*H*), 3.65 (dd, J_1 = 14 Hz, J_2 = 4 Hz, 1H, C*H*), 4.2 (q, J = 7.2 Hz, 2H, CH_2), 4.3 (s, 2H, CH_2), 4.5 (dd, J_1 = 9.8 Hz, J_2 = 4 Hz, 1H, C*H*), 7.1 (d, J_1 = 8 Hz, 2H, Ar*H*), 7.37 (d, J_1 = 8 Hz, 2H, Ar*H*); MS-FAB *m/z*: 362 $(M+H)^+$; Anal. Calcd for $C_{15}H_{14}F_3NO_4S$: C, 49.86; H, 3.91; F, 15.77; N, 3.88; S, 8.87.

5.2.14. [5-(3-Amino-benzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (4c). Thick liq; IR (neat) ν 3377, 2982, 2362, 1745, 1687, 1217, 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H, CH_3), 2.93 (dd, J_1 = 14 Hz, J_2 = 10.6 Hz, 1H, C*H*), 3.52 (dd, J_1 = 14 Hz, J_2 = 3.8 Hz, 1H, C*H*), 4.2 (q, J = 7.2 Hz, 2H, CH_2), 4.3 (s, 2H, CH_2), 4.5 (dd, J_1 = 10.6 Hz, J_2 = 3.8 Hz, 1H, C*H*), 6.51 (m, 3H, Ar*H*), 6.59 (s, 1H, Ar*H*); MS-FAB *m/z*: 309 $(M+H)^+$; Anal. Calcd for $C_{14}H_{16}N_2O_4S$: C, 54.53; H, 5.23; N, 9.08; S, 10.40. Found: C, 54.86; H, 5.51; N, 9.55.

5.2.15. [5-(4-Amino-benzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (4d). Mp 73–75 °C; IR (KBr) ν 3432, 2933, 2367, 1725, 1680, 1519, 1407, 1219 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3H, CH_3), 2.86 (dd, J_1 = 13.9 Hz, J_2 = 10.3 Hz, 1H, C*H*), 3.4 (dd, J_1 = 13.9 Hz, J_2 = 3.8 Hz, 1H, C*H*), 4.10 (q, J = 7.2 Hz, 2H, CH_2), 4.21 (s, 2H, CH_2), 4.38 (dd, J_1 = 10.3 Hz, J_2 = 3.8 Hz, 1H, C*H*), 6.53 (d, J_1 = 8.2 Hz, 2H, Ar*H*), 7.1 (d, J_1 = 8.2 Hz, 2H, Ar*H*); MS-FAB *m/z*: 309 $(M+H)^+$; Anal. Calcd for $C_{14}H_{16}N_2O_4S$: C, 54.53; H, 5.23; N, 9.08; S, 10.40. Found: C, 54.11; H, 4.85; N, 9.43.

5.2.16. [5-(4-Hydroxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid methyl ester (5). To the solution of [5-(4-hydroxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester **3a** (0.921 g, 3 mmol) in methanol (30 mL), concd H_2SO_4 (0.3 mL) was added and refluxed for 16 h. It was evaporated under vacuo. The solid mass obtained was washed with water and filtered. The filterate was extracted in methanol (2 × 10 mL) and filtered to yield **5** (0.856 g, 93%). Mp 150–152 °C; IR (KBr) ν 3506, 2363, 1734, 1680, 1599, 1512, 1386, 1284, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (s, 3H, CH_3), 4.39 (s, 2H, CH_2), 6.87 (d, J = 8.4 Hz, 2H, Ar*H*), 7.31 (d, J = 8.4 Hz, 2H, Ar*H*), 7.77 (s, 1H, C*H*); MS-FAB *m/z*: 294 $(M+H)^+$; Anal. Calcd for $C_{13}H_{11}NO_5S$: C, 53.24; H, 3.78; N, 4.78; S, 10.93. Found: C, 53.64; H, 3.36; N, 5.13.

5.2.17. [5-(4-Hydroxy-benzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid methyl ester (6). Mp 87–89 °C; IR (KBr) ν 3425, 2956, 2365, 1741, 1680, 1518, 1382, 1239, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.02 (dd, J_1 = 9.5 Hz, J_2 = 6.7 Hz, 1H, C*H*), 3.49 (dd, J_1 = 9.5 Hz,

J_2 = 2.6 Hz, 1H, C*H*), 3.74 (s, 3H, CH_3), 4.31 (s, 2H, CH_2), 4.47 (dd, J_1 = 6.7 Hz, J_2 = 2.6 Hz, 1H, C*H*), 6.76 (d, J_1 = 5.6 Hz, 2H, Ar*H*), 7.06 (d, J_1 = 5.6 Hz, 2H, Ar*H*) MS-FAB *m/z*: 296 $(M+H)^+$; Anal. Calcd for $C_{13}H_{13}NO_5S$: C, 52.87; H, 4.44; N, 4.74; S, 10.86. Found: C, 52.32; H, 4.09; N, 4.66.

5.2.18. Representative procedure for (7b,c). {5-[4-(2-Bromo-ethoxy)-benzylidene]-2,4-dioxo-thiazolidin-3-yl}-acetic acid ethyl ester (7b). To a solution of [5-(4-hydroxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester **3a** (0.614 g, 2 mmol) in dry DMF (30 mL), anhyd K_2CO_3 (0.552 g, 4 mmol) and 1,2-dibromoethane (1.87 g, 10 mmol) were added and the mixture was stirred at 110–120 °C for 12 h. The reaction mixture after cooling to ambient temp was diluted with ice water (100 mL) and was extracted with $CHCl_3$ (20 × 2 mL). The combined organic layer after drying over anhyd Na_2SO_4 was concentrated under vacuo. The crude compd thus obtained was recrystallized from methanol (6 mL) to yield **7b** (0.738 g, 89%). Mp 118–120 °C; IR (KBr) *v* 3449, 2989, 2363, 1732, 1677, 1592, 1512, 1383, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7.2 Hz, 3H, CH_3), 3.66 (t, J = 6.2 Hz, 2H, CH_2), 4.22 (q, J = 7.2 Hz, 2H, CH_2), 4.32 (t, J = 6.2 Hz, 2H, CH_2), 4.47 (s, 2H, CH_2), 7.00 (d, J = 8.8 Hz, 2H, Ar*H*), 7.48 (d, J = 8.8 Hz, 2H, Ar*H*), 7.88 (s, 1H, C*H*); MS-FAB *m/z*: 414 $(M+H)^+$; Anal. Calcd for $C_{16}H_{16}BrNO_5S$: C, 46.39; H, 3.89; Br, 19.29; N, 3.38; S, 7.74. Found: C, 46.78; H, 4.21; N, 3.84.

5.2.19. [5-(4-Butoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (7c). Mp 98–100 °C; IR (KBr) *v* 3415, 2942, 1740, 1690, 1599, 1382, 1249, 1179 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 3H, CH_3), 1.30 (t, J = 7.2 Hz, 3H, CH_3), 1.48 (m, J = 7.3 Hz, 2H, CH_2), 1.77 (m, J = 7.3 Hz, 2H, CH_2), 4.02 (t, J = 7.3 Hz, 2H, CH_2), 4.24 (q, J = 7.2 Hz, 2H, CH_2), 4.46 (s, 2H, CH_2), 6.97 (d, J = 8.6 Hz, 2H, Ar*H*), 7.45 (d, J = 8.6 Hz, 2H, Ar*H*), 7.87 (s, 1H, C*H*); MS-FAB *m/z*: 364 $(M+H)^+$; Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 59.49; H, 5.82; N, 3.85; S, 9.71. Found: C, 58.90; H, 6.40; N, 4.40.

5.2.20. [5-(4-Isopropoxy-benzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (8a). Mp 51–53 °C; IR (KBr) *v* 3423, 2979, 2363, 1748, 1690, 1510, 1381, 1217, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6.4 Hz, 6H, –(CH_3)$_2$), 1.30 (t, J = 8.0 Hz, 3H, CH_3), 3.01 (dd, J_1 = 14 Hz, J_2 = 10 Hz, 1H, C*H*), 3.50 (dd, J_1 = 14 Hz, J_2 = 4 Hz, 1H, C*H*), 4.20 (q, J = 8.0 Hz, 2H, CH_2), 4.29 (s, 2H, CH_2), 4.45 (dd, J_1 = 10 Hz, J_2 = 4 Hz, 1H, C*H*), 4.55 (m, 1H, C*H*), 6.83 (d, J_1 = 8.6 Hz, 2H, Ar*H*), 7.13 (d, J_1 = 8.6 Hz, 2H, Ar*H*); MS-FAB *m/z*: 352 $(M+H)^+$; Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99; S, 10.37. Found: C, 58.57; H, 6.46; N, 3.63.

5.2.21. {5-[4-(2-Bromo-ethoxy)-benzyl]-2,4-dioxo-thiazolidin-3-yl}-acetic acid ethyl ester (8b). Mp 75–77 °C; IR (KBr) *v* 3422, 2993, 2365, 1736, 1686, 1513, 1232, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7.0 Hz, 3H, CH_3), 3.04 (dd, J_1 = 14.2 Hz, J_2 = 10 Hz, 1H, C*H*), 3.53 (dd, J_1 = 14.2 Hz, J_2 = 4 Hz, 1H, C*H*), 3.63 (t, J = 6.2 Hz, 2H, CH_2), 4.16 (t, J = 6.2 Hz, 2H, CH_2), 4.25 (q, J = 7.0 Hz, 2H, CH_2), 4.3 (s, 2H, CH_2), 4.5 (dd, J_1 = 10 Hz, J_2 = 4 Hz, 1H, C*H*), 6.87 (d, J_1 = 8.6 Hz, 2H, Ar*H*), 7.22 (d, J_1 = 8.6 Hz, 2H, Ar*H*); MS-FAB *m/z*: 416 $(M+H)^+$. Anal. Calcd for $C_{16}H_{18}BrNO_5S$: C, 46.16; H, 4.36; Br, 19.19; N, 3.36; S, 9.84. Found: C, 46.57; H, 4.71; N, 2.93.

5.2.22. [5-(4-Acetoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (9). To a solution of [5-(4-hydroxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester **3a** (0.767 g, 2.5 mmol) in CH_2Cl_2 (15 mL) triethylamine (0.303 g, 3 mmol) was added and to this mixture, acetyl chloride (5 mmol) was added while stirring. The reaction mixture was further stirred for 16 h and the product mixture was concentrated in vacuo. After usual work up the crude product thus obtained was recrystallized from methanol to yield **9** (0.761 g, 87%). Mp 139–141 °C; IR (KBr) *v* 3412, 2993, 2364, 1740, 1689, 1411, 1195 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 4.24 (q, J = 7.2 Hz, 2H, CH_2), 4.48 (s, 2H, CH_2), 7.25 (d, J = 8.6 Hz, 2H, Ar*H*), 7.54 (d, J = 8.6 Hz, 2H, Ar*H*), 7.91 (s, 1H, C*H*); MS-FAB *m/z*: 350 $(M+H^+)$; Anal. Calcd for $C_{16}H_{15}NO_6S$: C, 55.01; H, 4.33; N, 4.01; S, 9.18. Found: C, 55.58; H, 3.91; N, 3.74.

5.2.23. [5-(4-Acetoxy-benzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester (10). Colorless solid mp 116–118 °C; IR (KBr) *v* 3421, 2989, 2924, 1735, 1691, 1508, 1411, 1377, 1227, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.08 (dd, J_1 = 14 Hz, J_2 = 10.2 Hz, 1H, C*H*), 3.63 (dd, J_1 = 14 Hz, J_2 = 3.8 Hz, 1H, C*H*), 4.22 (q, J = 7.2 Hz, 2H, CH_2), 4.31 (s, 2H, CH_2), 4.51 (dd, J_1 = 10.2 Hz, J_2 = 3.8 Hz, 1H, C*H*), 7.06 (d, J = 8.4 Hz, 2H, Ar*H*), 7.25 (d, J = 8.4 Hz, 2H, Ar*H*); MS-FAB *m/z*: 352 $(M+H)^+$; Anal. Calcd for $C_{16}H_{17}NO_6S$: C, 54.69; H, 4.88; N, 3.99; S, 9.13. Found: C, 54.14; H, 4.37; N, 4.37.

5.2.24. Representative procedure for (11a, 11d, 11e, 11g). [5-(4-Methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid (11e). A mixture of acetate **3e** (1 mmol), glacial AcOH (10 mL), and HCl 12 N (3 mL) was refluxed for 5 h. After evaporation in vacuo, the solid residue thus obtained was washed with water and dried to give **11e** (0.258 g, 88%). Light yellow solid mp 214–216 °C; IR (KBr) *v* 3425, 2836, 2364, 1685, 1595, 1510, 1380, 1258, 1177, 1150 cm^{-1}; ^1H NMR (CD_3OD) δ 3.86 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 6.99 (d, J = 8.6 Hz, 2H, Ar*H*), 7.46 (d, J = 8.6 Hz, 2H, Ar*H*), 7.88 (s, 1H, C*H*); MS-FAB *m/z*: 294 $(M+H)^+$; Anal. Calcd for $C_{13}H_{11}NO_5S$: C, 53.24; H, 3.78; N, 4.78; S, 10.93. Found: C, 52.86; H, 4.17; N, 5.37.

5.2.25. [5-(4-Methyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid (11d). Dark brick solid mp 218–220 °C; IR (KBr) *v* 3402, 2924, 2854, 1735, 1664, 1602, 1510, 1375, 1238, 1148, 1089 cm^{-1}; ^1H NMR ($CDOD_3$) δ 2.40 (s, 3H, CH_3), 4.47 (s, 2H, CH_2), 7.28 (d, J = 8.0 Hz, 2H, Ar*H*), 7.41 (d, J = 8.0 Hz, 2H, Ar*H*), 7.91 (s, 1H, C*H*);

MS-FAB *m/z*: 278 $(M+H)^+$; Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05; S, 11.56. Found: C, 56.86; H, 4.57; N, 5.48.

5.2.26. [5-(4-Dimethylamino-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid (11g). Red solid mp 224–226 °C; IR (KBr) *v* 3410, 2924, 2362, 1725, 1675, 1588, 1526, 1374, 1243, 1194, 1097 cm^{-1}; ^1H NMR (CD_3OD) δ 3.21 (s, 6H, $-(CH_3)_2$), 4.42 (s, 2H, CH_2), 7.6 (m, 4H, Ar*H*), 7.8 (s, 1H, C*H*); MS-FAB *m/z*: 307 $(M+H^+)$; Anal. Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.6; N, 9.14; S, 10.47. Found: C, 54.42; H, 5.18; N, 9.57.

5.2.27. [5-(4-Hydroxy-benzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid (12). Colorless solid mp 159–161 °C; IR (KBr) *v* 3454, 2363, 1673, 1596, 1516, 1381, 1352, 1248, 1158 cm^{-1}; ^1H NMR (CD_3OD) δ 3.02 (dd, $J_1 = 9.5$ Hz, $J_2 = 6.7$ Hz, 1H, C*H*), 3.49 (dd, $J_1 = 9.5$ Hz, $J_2 = 2.6$ Hz, 1H, C*H*), 4.31 (s, 2H, CH_2), 4.47 (dd, $J_1 = 6.7$ Hz, $J_2 = 2.6$ Hz, 1H, C*H*), 6.76 (d, $J_1 = 5.6$ Hz, 2H, Ar*H*), 7.06 (d, $J_1 = 5.6$ Hz, 2H, Ar*H*); MS-FAB *m/z*: 282 $(M+H)^+$; Anal. Calcd for $C_{12}H_{11}NO_5S$: C, 51.24; H, 3.94; N, 4.98; S, 11.40. Found: C, 51.68; H, 3.37; N, 5.26.

Acknowledgements

One of us Bashir A. Bhat is thankful to CSIR for financial support, S.K.P. is thankful to ICMR for his financial support and RSIC, CDRI, Lucknow for providing spectroscopic data.

References and notes

1. Zimmet, P. *J. Int. Med.* **2000**, *247*(3), 301–310.
2. King, H.; Aubert, R.; Herman, W. *Diabetes Care* **1998**, *21*(9), 1414–1431.
3. Zimmet, P. *Diabetologia* **1999**, *42*, 499–518.
4. Ginsberg, H.; Plutzky, J.; Sobel, B. E. *J. Cardiovasc. Risk* **1999**, *6*(5), 337–346.
5. Grundy, S. M.; Benjamin, I. J.; Burke, G. L.; Chait, A.; Eckel, R. H.; Howard, B. W.; Mitch, W.; Smith, S. C. *Am. Heart Assoc. Circulation* **1999**, *100*, 1134–1146.
6. Bailey, C. J.; Turner, R. C. *N. Engl. J. Med.* **1996**, *334*(9), 574–579.
7. Groop, L. C. *Diabetes Care* **1992**, *15*, 737–754.
8. Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Du, P. T.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L. *J. Med. Chem.* **1994**, *37*, 3977.
9. Wilson, T. M.; Brown, P. J.; Strenbach, D. D.; Henke, B. R. *J. Med. Chem.* **2000**, *43*, 527–550.
10. Castaner, J.; Prous, J. *Drugs Future* **1987**, *12*, 336; Salah, Y. M. *Diabetes Rev.* **1999**, *7*, 55.
11. Bruno, G.; Costantino, L.; Curinga, C.; Maccari, R.; Monforte, F.; Nicono, F.; Ottana, R.; Vigorita, M. G. *Bioorg. Med. Chem.* **2002**, *10*, 1077–1084.
12. Reginato, M. J.; Bailey, S. T.; Krakow, S. L.; Minami, C.; Ishii, S.; Tanaka, H.; Lazar, M. A. *J. Biol. Chem.* **1998**, *273*, 32679–32684.
13. Pickavanc, L.; Widdowson, P. S.; King, P.; Ishii, S.; Tanaka, H.; Williams, G. *Br. J. Pharmacol.* **1998**, *125*, 767–770.
14. Fukui, Y.; Masui, S. I.; Osada, S.; Umesono, K.; Motojima, K. *Diabetes* **2000**, *49*, 759–767.
15. Lohary, B. B.; Bhushan, V.; Reddy, A. S.; Rao, P. B.; Reddy, N. J.; Harikishore, P.; Haritha, N.; Vikramadityan, R. K.; Chakrabarati, R.; Rajagopalan, R.; Katneni, K. *J. Med. Chem.* **1999**, *42*, 2569–2581.