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Synthesis and biological evaluation of thiazolidinedione derivatives of chalcones and flavones as antihyperglycemic and antidyslipidemic agents

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A series of chalcone and flavone derivatives (**6a-d, 9a-f**) based on 2,4-thiazolidinedione have been synthesized and evaluated for *in vivo* antihyperglycemic activity in sucrose loaded (SLM) and streptozotocin (STZ) induced diabetic animal models and also for antidyslipidemic activity in the triton model. Compounds **9d**, **9e**, and **9f** exhibited potent blood glucose-lowering activity in both SLM and STZ models. Compounds **6c**, **6d**, and **9c**, **9e**, and **9f** showed moderate lipid-lowering activity. The selected most potent compounds **6d** and **9e** were also studied in *db/db* mice for both antihyperglycemic and antidyslipidemic activity.

Keywords: Chalcones, flavones, thiazolidinedione, antihyperglycemic activity, antidyslipidemic activity, sucrose loaded model, streptozotocin model, *db/db* mice, glitazones

Type-II diabetes is a common disease worldwide and is defined by the presence of fasting hyperglycemia, insulin resistance, and hyperinsulinemia. The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [1]. The disease is often associated with obesity, dyslipidemia, and hypertension leading to cardiovascular risks[2]. The major chronic complications associated with untreated diabetes mellitus are neuropathy, retinopathy, nephropathy, and macrovasculopathy[3]. Therefore, it is important to maintain appropriate blood glucose levels, especially during the early stage of the disease. The therapy for type-II diabetes is often by a combination of diet, exercise, or pharmacological agents[4]. Thiazolidinediones generally referred to as glitazones are a new class of antidiabetic agents, identified as nuclear peroxisome proliferator activated receptor-gamma (PPAR-γ) ligands.

They are chemically and functionally different from the other classes of oral antihyperglycemic agents such as sulfonylureas and metformin. They exert their effects by binding to PPAR-γ, which in turn, activates insulin-sensitive genes that regulate carbohydrate and lipid metabolism[5,6]. However, among the first of the glitazones introduced, Troglitazone was withdrawn from the market because of its hepatotoxicity[7]. Several other glitazones were discontinued from clinical development because of their structure and/or mechanism of action[8]. Pioglitazone and Rosiglitazone are available in the market with safety warnings[9] (Figure 1). The associated problems with the existing glitazones prompt the development of safer new glitazones.

Flavones and chalcones are polyphenolic compounds, isolated from natural products and exhibit a broad range of biological activities including antimalarial[10], anticancer[11,12], antioxidant[13], antituberculosis[14], antileishmanial[15], anti-inflammatory[16], antiviral[17], antihypertensive[18], and antibacterial[19]. Chalcone and flavone derived propanolamines were synthesized as antihyperglycemic and antidyslipidemic agents[20-25]. The efforts towards the development of potent dual-acting hypoglycemic and hypolipidemic agents, the antioxidant property of flavonoids and chalcones attracted us, as oxidative stress plays an important role in diabetic patients leading to vascular complications[2,26]. The incorporation of a flavone or chalcone moiety as a lipophilic and antioxidant into

Abbreviations: PL, phospholipids; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; SLM, sucrose loaded model; STZ, streptozotocin.

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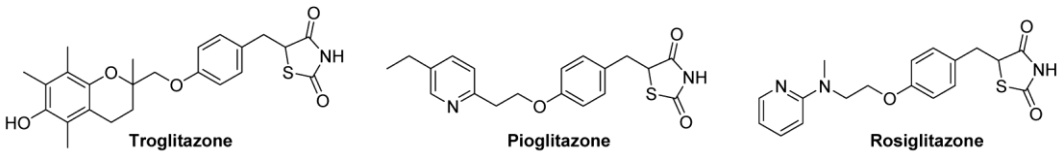
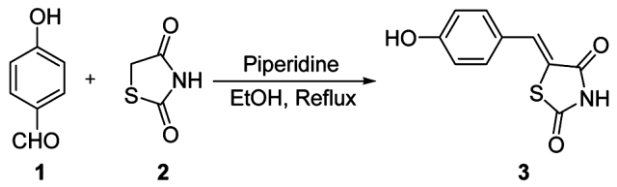


Figure 1 — Glitazone Drugs

glitazones may lead to a new set of compounds with enhanced activities. This led to the synthesis of 2,4-thiazolidinedione derivatives with various spacers linked to the 7- and 3'-hydroxy position of the flavones and chalcones respectively and evaluation as antihyperglycemic and antidyslipidemic agents.



Scheme I — Synthesis of compound **3**

Results and Discussion

Chemistry

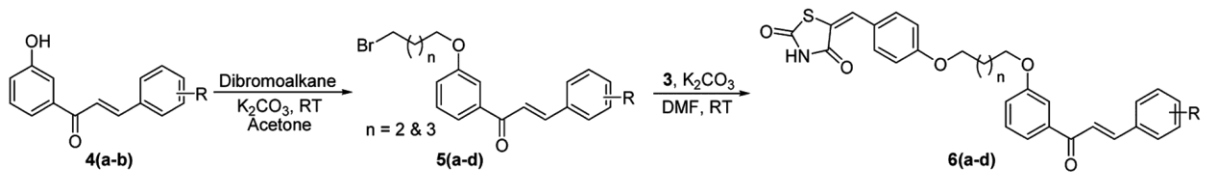
The synthetic strategies used to synthesize the required compounds are outlined in Scheme I, Scheme II and Scheme III. 5-(4-Hydroxy-benzylidene)-2,4-thiazolidinedione (**3**) has been synthesized by the condensation of commercially available 2,4-thiazolidinedione (**2**) with 4-hydroxybenzaldehyde (**1**) using piperidine as the base in refluxing ethanol, according to a known procedure (Scheme I)[27].

Hydroxy chalcones (**4a-b**) and flavones (**7a-e**) were prepared according to literature procedures[20,23]. During the synthesis of flavones, Dowex-H^+ in 2-propanol has been used in place of AcOH-H_2SO_4, however, the rest of the procedure was similar as reported[28]. Flavones and chalcones thus obtained were alkylated at hydroxy groups with an excess of dibromoalkanes using K_2CO_3 and appropriate solvent at RT to afford **5a-d** and **8a-f**. Unwanted dimer was also obtained as a minor side product. The desired final products (**6a-d** and **9a-f**) were prepared by reacting compound **3** with bromoalkoxy chalcones and flavones in dry dimethylformamide (DMF) in presence of K_2CO_3 at RT (Scheme II and Scheme III).

Pharmacology

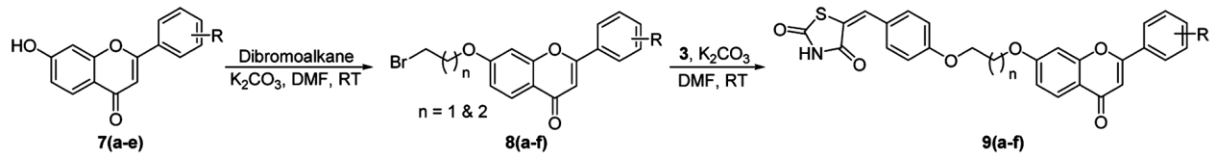
All the synthesized compounds (**6a-d** and **9a-f**) were evaluated for antihyperlipidemic activity in the triton model and antihyperglycemic activity in sucrose loaded (SLM) and streptozotocin (STZ) animal models. The potent selected compounds were also studied in *db/db* mice for both activities. Compound-**23** (S001-469)[20-22] is a chalcone based propanolamine, developed in our lab is a potent antidiabetic agent and used for comparison of the data. Metformin and Guggulipid were used as reference standards and the results are summarized in Table I. Methylenedioxy compound **6d** reduced the blood glucose levels by 13.4%, which is equipotent as the metformin (12.9%) in the SLM model. Chalcone derived thiazolidinediones (**6a-c**) have shown insignificant antidiabetic activity. Based on the antidiabetic activity of chalcone derivatives, while synthesizing flavone-based thiazolidinedione derivatives, the spacer was shortened from pentyl/butyl to ethyl/propyl, which is comparable to the chain length in the glitazone drugs and resulted in a significant increase in the activity. The 3',5'-dibenzyloxy compound with two carbon-spacer (**9a**) was found to be inactive whereas the 3',4'-dibenzyloxy compound (**9b**) significantly lowered the blood glucose by 26% in the SLM model. 3',4' and 3',5'-dimethoxy, and 3',4',5'-trimethoxy compounds with three-carbon spacer (**9d-f**) have shown the best antihyperglycemic activity by lowering glucose levels by 28.8%, 29.3%, 13.6%, respectively. Compounds **9d, 9e,** and **9f** have also significantly lowered the blood glucose levels in STZ induced diabetic animal model. Replacement of a three-carbon spacer with a two-carbon spacer resulted in the lowered antihyperglycemic activity as in trimethoxy compound (**9c**). In the triton model, chalcone and flavone derived thiazolidinedione derivatives showed moderate lipid-lowering activity. Compounds **6c**, **9c**, **9e** and **9f** lowered the TC by 23%, 20%, 20% and 28%, respectively. Compound **9c** lowered the PL and TG by ~25% and **6d** by ~20%.

Based on the preliminary results from SLM, STZ, and triton models, selected compounds **6d** and **9e** along with compound **23** were evaluated in obese *db/db* mice for antihyperglycemic and antidyslipidemic activities. The antihyperglycemic activity results are summarized in Table II (Figure 2, Figure 3). Compounds **6d** and **9e** significantly



6a, R = 4-OCH_3, n = 2; **6b**, R = 4-OCH_3, n = 3; **6c**, R = 3,4-methylenedioxy, n = 2; **6d**, R = 3,4-methylenedioxy, n = 3

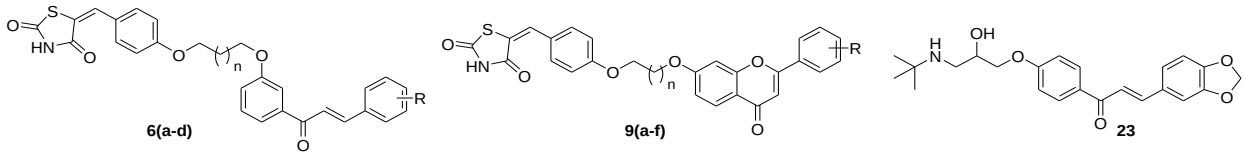
Scheme II — Synthesis of compounds **6(a-d)**



9a-c, n=1; **9a**, R = 3′,5′-dibenzyloxy; **9b**, R = 3′,4′-dibenzyloxy; **9c**, R = 3′,4′,5′-trimethoxy
9d-f, n=2; **9d**, R = 3′,5′-dimethoxy; **9e**, R = 3′,4′,5′-trimethoxy; **9f**, R = 3′,4′-dimethoxy

Scheme III — Synthesis of compounds **9(a-f)**

Table I — Antihyperglycemic and antidyslipidemic activity of thiazolidinedione derivatives of chalcones and flavones



S.No.	Compd	R	n	Fall in Blood Glucose Levels (%) SLM	Fall in Blood Glucose Levels (%) STZ-S 5h	Fall in Blood Glucose Levels (%) STZ-S 24h	Fall in Serum Lipid Profile (%) TC	Fall in Serum Lipid Profile (%) PL	Fall in Serum Lipid Profile (%) TG
1	**6a**	4-OCH_3	2	NIL	ND	ND	4	14	31
2	**6b**	4-OCH_3	3	NIL	ND	ND	6	13	19
3	**6c**	3,4-OCH_2O-	2	0.13	ND	ND	23	21	14
4	**6d**	3,4-OCH_2O-	3	13.4	11.8	7.18	13	20	20
5	**9a**	3,5-OCH_2Ph	1	NIL	ND	ND	15	15	18
6	**9b**	3,4-OCH_2Ph	1	26.0	ND	NIL	ND	ND	ND
7	**9c**	3,4,5-OCH_3	1	9.59	ND	ND	20	25	26
8	**9d**	3,5-OCH_3	2	28.8	18.9	20.2	ND	ND	ND
9	**9e**	3,4,5-OCH_3	2	29.3	16.1	11.0	20	6	3
10	**9f**	3,4-OCH_3	2	13.6	18.7	13.6	28	14	21
16	**23**	–	–	21.1	ND	23	26	20	18
17		Metformin		12.9	24.3	19.1			
18		Guggulipid					38	35	32

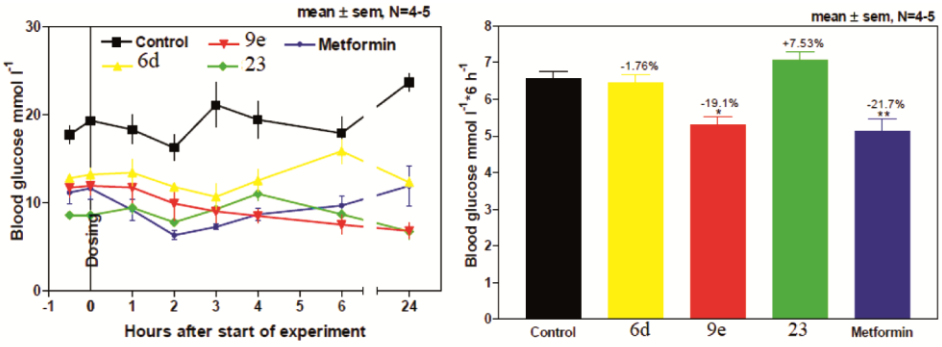
ND, Not Determined; NIL, Insignificant activity.
SLM, sucrose loaded model; STZ, streptozotocin; TC, total cholesterol; PL, phospholipids; TG, triglycerides

Table II — Antihyperglycemic activity of **6d**, **9e**, and **23** in *db/db* mice

S.No.	Compd	Fall of Blood Glucose Levels (%) STZ-S 6 days	Fall of Blood Glucose Levels (%) STZ-S 10 days
1	**6d**	1.76	23.1
2	**9e**	19.1	21.4
3	**23**	+7.53	32.0
4	Metformin	21.7	43.7

STZ, streptozotocin

lowered the blood glucose levels by 23.1% and 21.4% respectively after 10 days of dosing. Antihyperglycemic activity of **6d** after 6 days of dosing is very small in comparison with 10 days of dosing. At the same time, compound **9e** has almost reduced the blood glucose levels equally after 6 and 10 days of dosing. Compound **23** showed poor activity after 6 days of dosing, but it significantly lowered the blood glucose levels by 32% in

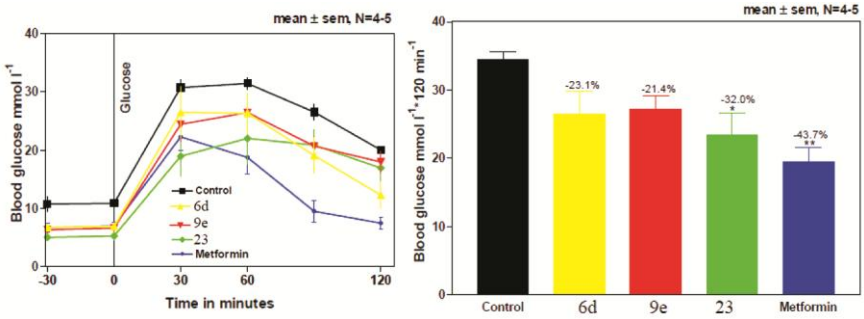


Postprandial blood glucose levels in *db/db* mice before and up to 24 h after 6 days of dosing with compounds **6d**, **9e** and **23**

Baseline subtracted 6 h area under the postprandial glucose curve in *db/db* mice after 6 days of dosing with compounds **6d**, **9e** and **23**

* p < 0.05, ** p < 0.01, *** p < 0.001

Figure 2 — Antihyperglycemic activity of compounds **6d**, **9e**, and **23** in *db/db* mice after 6 days of dosing



Blood glucose levels during OGTT in *db/db* mice after 10 days of dosing with compounds **6d**, **9e** and 23

Total area under the glucose curve during OGTT in *db/db* mice after 10 days of dosing with **6d**, **9e** and **23**

* p < 0.05, ** p < 0.01, *** p < 0.001

Figure 3 — Antihyperglycemic activity of compounds **6d**, **9e**, and **23** in *db/db* mice after 10 days of dosing

comparison with metformin (43.7%) after 10 days of dosing.

After 10 days of dosing, blood was withdrawn from *db/db* mice for analysis of serum lipid parameters, and the results are placed in Table III (Figure 4). Compound **23** lowered TC by 40.3% and raised the HDL level by 1.76%. All the compounds have shown an insignificant positive effect on HDL. Compounds **6d** and **9e** lowered the TG by 6.76% and 19.1% respectively, while compound **23** has raised the TG by 7.44%. The lowering of TC by compounds **6d** and **9e** has been insignificant. In summary, methoxy substituted compounds are superior to the benzylated compounds and thiazolidinedione derivatives with three-carbon spacers are the best for antihyperglycemic activity.

Table III — Antidyslipidemic activity of **6d**, **9e**, and **23** in *db/db* mice

S.No.	Compd	Fall in Serum Lipid Profile (%)		
		TC	TG	HDL
1	**6d**	+18.9	6.76	21.4
2	**9e**	1.06	19.1	35.2
3	**23**	40.3	+7.44	+1.76
4	Metformin	28.5	11.1	24.7

TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein

Experimental Section

Melting points were determined on a capillary melting point apparatus and are uncorrected. Reaction progress was monitored by TLC and performed on aluminum precoated GF_{254} TLC plates. TLC spots were visualized by exposing to iodine vapors or in a UV chamber. ^{1}H and ^{13}C NMR spectra were recorded in the indicated solvent on Bruker WM 200 MHz spectrometer with TMS as an internal standard. Infrared spectra were recorded in KBr on Perkin–Elmer AC-1 spectrophotometer and FAB mass spectra on JEOL SX 102/DA 6000 mass spectrometer. Column chromatography was performed over silica gel (60-120 mesh).

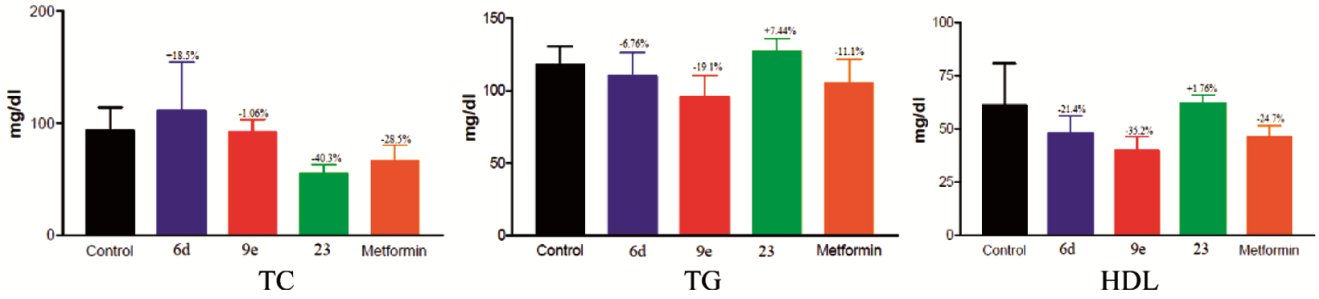


Figure 4 — Antidyslipidemic activity of compounds **6d**, **9e**, and **23** in *db/db* mice

4-(Thiazolidin-2,4-dione-5-ylidinemethyl)-phenol, 3 [27]

A mixture of 4-hydroxybenzaldehyde, **1** (3 g, 24.6 mmol), 2,4-thiazolidinedione, **2** (2.9 g, 24.8 mmol), and piperidine (2.5 mL) in methanol (100 mL) was refluxed for 18 h. The reaction mixture was poured into cold water and acidified with acetic acid. The separated solid was filtered, dried, and recrystallized from methanol to afford **3** (4.7 g, 86%); m.p. 296-298°C. IR (KBr): 3404, 3123, 1723, 1678 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 7.70 (s, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H); FAB-MS: *m/z* 222 (M^++1).

3'-(4-Bromo-butoxy)-4-methoxy-chalcone, 5a

Potassium carbonate (2.2 g, 15.8 mmol) was added to a stirred solution of 3'-hydroxy-4-methoxy-chalcone, **4a** (2 g, 7.87 mmol) in dry acetone (100 mL) at RT. After the mixture was stirred for 30 min, 1,4-dibromobutane (4.7 mL, 39.4 mmol) was added and the resulting mixture was stirred at RT for 12 h. The reaction mixture was filtered through celite and concentrated under reduced pressure. The residue was diluted with water and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulphate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with ethyl acetate/hexane to afford **5a** (2.8 g, 91%); m.p. 91-92°C. IR (KBr): 1654 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.79 (d, *J* = 15.6 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 15.6 Hz, 1H), 7.10 (dd, *J* = 8.1 Hz, 2.3 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 4.08 (t, *J* = 5.7 Hz, 2H), 3.86 (s, 3H), 3.50 (t, *J* = 6.3 Hz, 2H), 2.16-1.94 (m, 4H); FAB-MS: *m/z* 389/391 (M^++1).

3'-(5-Bromo-pentyloxy)-4-methoxy-chalcone, 5b

Compound **5b** was prepared from 3'-hydroxy-4-methoxy-chalcone, **4a** (2 g, 7.87 mmol), 1,5-dibromopentane (5.4 mL, 39.4 mmol) and potassium carbonate (2.2 g, 15.8 mmol) in dry acetone (100 mL) using the procedure as described for **5a** (2.7 g, 85%); m.p. 83-84°C. IR (KBr): 1650 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.78 (d, *J* = 15.6 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J*= 7.4 Hz, 1H), 7.52 (d, *J* = 2.2 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 15.6 Hz, 1H), 7.10 (dd, *J* = 8.0 Hz, 2.3 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.04 (t, *J* = 6.2 Hz, 2H), 3.85 (s, 3H), 3.44 (t, *J* = 6.7 Hz, 2H), 1.99-1.81 (m, 4H), 1.71-1.60 (m, 2H); FAB-MS: *m/z* 403/405 (M^++1).

3'-(4-Bromo-butoxy)-3,4-methylenedioxy-chalcone, 5c

Compound **5c** was prepared from 3'-hydroxy-3,4-methylenedioxy-chalcone, **4b** (2.7 g, 10 mmol), 1,4-dibromobutane (3.6 mL, 30 mmol) and potassium carbonate (2.76 g, 20 mmol) in dry acetone (100 mL) using the procedure as described for **5a** (3.6 g, 89%); m.p. 97-98°C. IR (KBr): 1654 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.73 (d, *J* = 15.6 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.51 (s, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 15.6 Hz, 1H), 7.16 (s, 1H), 7.14-7.07 (m, 2H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.02 (s, 2H), 4.07 (t, *J* = 5.6 Hz, 2H), 3.50 (t, *J* = 6.3 Hz, 2H), 2.16-1.94 (m, 4H); FAB-MS: *m/z* 403/405 (M^++1).

3'-(5-Bromo-pentyloxy)-3,4-methylenedioxy-chalcone, 5d

Compound **5d** was prepared from 3'-hydroxy-3,4-methylenedioxy-chalcone, **4b** (2.7 g, 10 mmol), 1,5-dibromopentane (4.1 mL, 30 mmol) and potassium carbonate (2.76 g, 20 mmol) in dry acetone (100 mL) using the procedure as described for **5a** (2.7 g, 64%); m.p. 87-88°C. IR (KBr): 1652 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.73 (d, *J* = 15.6 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 15.6 Hz, 1H), 7.16 (s, 1H), 7.14-7.10 (m, 2H), 6.02 (s, 2H), 4.05 (t, *J* = 6.2 Hz, 2H), 3.50 (t, *J* = 6.7 Hz, 2H), 2.02-1.78 (m, 4H), 1.71-1.59 (m, 2H); FAB-MS: *m/z* 417/419 (M^++1).

4-Methoxy-3'-{4-[4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenoxy]-butoxy}-chalcone, 6a

A mixture of 3'-(4-bromo-butoxy)-4-methoxy-chalcone, **5a** (1.2 g, 3.1 mmol), 4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenol, **3** (1 g, 4.62 mmol) and potassium carbonate (600 mg, 4.34 mmol) in dry dimethylformamide (80 mL) was stirred at RT for 8 h. The reaction mixture was filtered through celite and diluted with water. The aqueous layer was acidified with dilute hydrochloric acid, filtered, and extracted with chloroform. The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated. The crude product was purified by column chromatography eluting with ethyl acetate/hexane to yield **6a** (800 mg, 49%); m.p. 186-187°C. IR (KBr): 3429, 1729, 1688, 1657 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.33 (s, 1H), 7.88 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 17.8 Hz, 1H), 7.75 (s, 1H), 7.75(d, *J* = 7.7 Hz, 1H), 7.62 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.54 (t, *J* = 9.3 Hz, 1H), 7.49 (d, *J* = 17.6 Hz, 1H), 7.25 (dd, *J* = 7.9 Hz, 2.1 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 4.16 (bs, 4H), 3.84 (s, 3H), 1.94 (bs, 4H); FAB-MS: *m/z* 530 (M^++1).

4-Methoxy-3'-{5-[4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenoxy]-pentyloxy}- chalcone, 6b

A mixture of 3'-(5-bromo-pentyloxy)-4-methoxy-chalcone, **5b** (1.4 g, 3.47 mmol), 4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenol, **3** (800 mg, 3.62 mmol) and potassium carbonate (500 mg, 3.62 mmol) in dry dimethylformamide (80 mL) were reacted in a similar way as described for **6a** to yield **6b** (970 mg, 52%); m.p. 182-183°C. IR (KBr): 3288, 1736, 1682, 1654 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.75 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 17.1 Hz, 1H), 7.63 (s, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.47 (s, 1H), 7.43 (d, *J* = 9.1 Hz, 2H), 7.40 (t, *J* = 9.6 Hz, 1H), 7.36 (d, *J* = 17.0 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 3.96 (bs, 4H), 3.72 (s, 3H), 1.71-1.33 (m, 6H); FAB-MS: *m/z* 544 (M^++1).

3,4-Methylenedioxy-3'-{4-[4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenoxy]-butoxy}-chalcone, 6c

A mixture of 3'-(4-bromo-butoxy)-3,4-methylenedioxy-chalcone, **5c** (3 g, 7.44 mmol), 4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenol, **3** (1.8 g, 8.14 mmol) and potassium carbonate (2.2 g, 16 mmol) in dry dimethylformamide (125 mL) were reacted in a similar way as described for **6a** to yield **6c** (800 mg, 20%); m.p. 173-175°C. IR (KBr): 3373, 1726, 1664 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 10.39 (s, 1H), 7.84 (s, 1H), 7.77 (s, 1H), 7.73 (d, *J* = 16.9 Hz, 1H), 7.70 (d, *J* = 6.2 Hz, 1H), 7.62 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.48 (t, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 16.7 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 6.5 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.12 (s, 2H), 4.10 (bs, 2H), 3.75 (bs, 2H), 1.78 (s, 4H); FAB-MS: *m/z* 544 (M^++1).

3,4-Methylenedioxy-3'-{5-[4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenoxy]-pentyloxy}-chalcone, 6d

A mixture of 3'-(5-bromo-pentyloxy)-3,4-methylenedioxy-chalcone, **5d** (2.5 g, 5.9 mmol), 4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenol, **3** (1.6 g, 7.24 mmol) and potassium carbonate (2.2 g, 16 mmol) in dry dimethylformamide (125 mL) were reacted in a similar way as described for **6a** to yield **6d** (1.4 g, 42%); m.p. 159-161°C. IR (KBr): 3316, 1736, 1679, 1655 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 10.41 (s, 1H), 7.85 (s, 1H), 7.74 (d, *J* = 16.7 Hz, 1H), 7.73 (s, 1H), 7.71 (d, *J* = 5.4 Hz, 1H), 7.63 (s, 1H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.48 (t, *J* = 8.9 Hz, 1H), 7.48 (d, *J* = 17.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 5.9 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.13 (s, 2H), 4.08 (t, *J* = 5.7 Hz, 2H), 3.70 (t, *J* = 6.6 Hz, 2H), 1.80-1.66 (m, 4H), 1.49-1.46 (m, 2H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 189.0, 167.9, 166.2, 160.5, 159.3, 149.9, 148.5, 144.5, 139.5, 133.8, 132.9, 130.2, 129.6, 126.4, 124.3, 121.2, 120.4, 119.6, 117.0, 116.7, 114.1, 108.9, 107.1, 102.0, 67.8, 41.7, 28.5, 27.3, 23.0; FAB-MS: *m/z* 558 (M^++1).

7-(2-Bromo-ethoxy)-3',5'-dibenzyloxy-flavone, 8a

Compound **8a** was prepared from 3',5'-dibenzyloxy-7-hydroxy-flavone, **7a** (2.25 g, 5 mmol), 1,2-dibromoethane (5 mL, 58 mmol) and potassium carbonate (2.76 g, 20 mmol) in dry dimethylformamide (120 mL) using the procedure as described for **5a** (2.6 g, 93%); m.p. 157-159°C. IR (KBr): 1640 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.8 Hz, 1H), 7.43-7.34 (m, 10H), 7.10 (d, *J* = 2.1 Hz, 2H), 6.99 (dd, *J* = 8.8 Hz, 2.2 Hz, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 6.76 (s, 1H), 6.69 (s, 1H), 5.10 (s, 4H), 4.39 (t, *J* = 6.2 Hz, 2H), 3.69 (t, *J* = 6.2 Hz, 2H); FAB-MS: *m/z* 557/559 (M^++1).

7-(2-Bromo-ethoxy)-3',4'-dibenzyloxy-flavone, 8b

Compound **8b** was prepared from 3',4'-dibenzyloxy-7-hydroxy-flavone, **7b** (2.3 g, 5.1 mmol), 1,2-

dibromoethane (1.7 mL, 20.4 mmol) and potassium carbonate (3.5 g, 25.5 mmol) in dry dimethyl–formamide (90 mL) using the procedure as described for **5a** (2.1 g, 74%); m.p. 167-168°C. IR (KBr): 1626 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.8 Hz, 1H), 7.50-7.32 (m, 12H), 7.01 (d, *J* = 9.1 Hz, 1H), 6.92 (dd, *J* = 8.9 Hz, 2.2 Hz, 1H), 6.91 (s, 1H), 6.60 (s, 1H), 5.24 (s, 4H), 4.39 (t, *J* = 6.2 Hz, 2H), 3.69 (t, *J* = 6.3 Hz, 2H); FAB-MS: *m/z* 557/559 (M^++1).

7-(2-Bromo-ethoxy)-3',4',5'-trimethoxy-flavone, 8c

Compound **8c** was prepared from 7-hydroxy-3',4',5'-trimethoxy-flavone, **7c** (2.3 g, 7 mmol), 1,2-dibromoethane (3 mL, 35 mmol) and potassium carbonate (2.9 g, 21 mmol) in dry dimethylformamide (120 mL) using the procedure as described for **5a** (2.1 g, 68%); m.p. 184-185°C. IR (KBr): 1631 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.15 (d, *J* = 9.3 Hz, 1H), 7.10 (s, 2H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.99 (s, 1H), 6.71 (s, 1H), 4.43 (t, *J* = 6.2 Hz, 2H), 3.96 (s, 6H), 3.93 (s, 3H), 3.70 (t, *J* = 6.2 Hz, 2H); FAB-MS: *m/z* 435/437 (M^++1).

7-(3-Bromo-propoxy)-3',5'-dimethoxy-flavone, 8d

Compound **8d** was prepared from 3',5'-dimethoxy-7-hydroxy-flavone, **7d** (1.1 g, 3.7 mmol), 1,3-dibromopropane (1.9 mL, 18.5 mmol) and potassium carbonate (1.5 g, 11.1 mmol) in dry dimethylformamide (100 mL) using the procedure as described for **5a** (1.1 g, 74%); m.p. 173-174°C. IR (KBr): 1631 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 7.88 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.17 (d, *J* = 2.1 Hz, 2H), 7.02 (dd, *J* = 8.9 Hz, 2.2 Hz, 1H), 6.98 (s, 1H), 6.66 (s, 1H), 4.19 (t, *J* = 5.9 Hz, 2H), 3.79 (s, 6H), 3.64 (t, *J* = 6.4 Hz, 2H), 2.26 (q, *J* = 6.2 Hz, 2H); FAB-MS: *m/z* 419/421 (M^++1).

7-(3-Bromo-propoxy)-3',4',5'-trimethoxy-flavone, 8e

Compound **8e** was prepared from 7-hydroxy-3',4',5'-trimethoxy-flavone, **7c** (3.3 g, 10 mmol), 1,3-dibromopropane (3 mL, 30 mmol) and potassium carbonate (2.7 g, 20 mmol) in dry dimethylformamide (120 mL) using the procedure as described for **5a** (3.1 g, 69%); m.p. 156-157°C. IR (KBr): 1629 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.13 (d, *J* = 9.4 Hz, 1H), 7.11 (s, 2H), 7.01-6.97 (m, 2H), 6.70 (s, 1H), 4.25 (t, *J* = 5.8 Hz, 2H), 3.96 (s, 6H), 3.93 (s, 3H), 3.64 (t, *J* = 6.3 Hz, 2H), 2.39 (q, *J* = 6.1 Hz, 2H); FAB-MS: *m/z* 449/451 (M^++1).

7-(3-Bromo-propoxy)-3',4'-dimethoxy-flavone, 8f

Compound **8f** was prepared from 3',4'-dimethoxy-7-hydroxy-flavone, **7e** (3 g, 10 mmol), 1,3-dibromopropane (4 mL, 39.2 mmol) and potassium carbonate (2.8 g, 20 mmol) in dry dimethylformamide (150 mL) using the procedure as described for **5a** (3.4 g, 80%); m.p. 148-149°C. IR (KBr): 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.12 (d, *J* = 9.5 Hz, 1H), 7.53 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 7.36 (d, *J* = 1.9 Hz, 1H), 6.99-6.95 (m, 3H), 6.68 (s, 1H), 4.24 (t, *J* = 5.8 Hz, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 3.64 (t, *J* = 6.3 Hz, 2H), 2.39 (q, *J* = 6.1 Hz, 2H); FAB-MS: *m/z* 419/421 (M^++1).

3',5'-Dibenzyloxy-7-{2-[4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenoxy]-ethoxy}-flavone, 9a

A mixture of 7-(2-bromo-ethoxy)-3',5'-dibenzyloxy-flavone, **8a** (2 g, 3.6 mmol), 4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenol, **3** (1.2 g, 5.4 mmol) and potassium carbonate (740 mg, 5.4 mmol) in dry dimethylformamide (120 mL) were reacted in a similar way as described for **6a** to yield **9a** (600 mg, 24%); m.p. 267-269°C. IR (KBr): 3451, 1736, 1696, 1618 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 7.92 (d, *J* = 8.9 Hz, 1H), 7.73 (s, 1H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.49-7.32 (m, 12H), 7.29 (s, 1H), 7.17 (s, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.03 (s, 1H), 6.89 (s, 1H), 5.19 (s, 4H), 4.49 (bs, 2H), 4.47 (bs, 2H); FAB-MS: *m/z* 698 (M^++1).

3',4'-Dibenzyloxy-7-{2-[4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenoxy]-ethoxy}-flavone, 9b

A mixture of 7-(2-bromo-ethoxy)-3',4'-dibenzyloxy-flavone, **8b** (2 g, 3.6 mmol), 4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenol, **3** (1.5 g, 6.8 mmol) and potassium carbonate (1.4 g, 10 mmol) in dry dimethylformamide (120 mL) were reacted in a similar way as described for **6a** to yield **9b** (300 mg, 12%); m.p. 239-241°C. IR (KBr): 3446, 1734, 1674, 1627 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 10.35 (s, 1H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.82 (s, 1H), 7.69 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.49-7.33 (m, 10H), 7.27 (d, *J* = 2.6 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 6.97 (dd, *J* = 8.8 Hz, 2.2 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.87 (s, 1H), 5.23 (s, 2H), 5.21 (s, 2H), 4.37 (bs, 2H), 4.05 (bs, 2H); FAB-MS: *m/z* 698 (M^++1).

7-{2-[4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenoxy]-ethoxy}-3',4',5'-trimethoxy-flavone, 9c

A mixture of 7-(2-bromo-ethoxy)-3',4',5'-trimethoxy-flavone, **8c** (2 g, 4.6 mmol), 4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenol, **3** (1.1

g, 5 mmol) and potassium carbonate (2.5 g, 18 mmol) in dry dimethylformamide (150 mL) were reacted in a similar way as described for **6a** to yield **9c** (380 mg, 14%); m.p. 237-238°C. IR (KBr): 3423, 1733, 1681, 1630 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.37 (s, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.86 (s, 1H), 7.49 (d, *J* = 9.0 Hz, 2H), 7.38 (d, *J* = 3.0 Hz, 1H), 7.36 (s, 2H) 7.06 (s, 1H), 7.02 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 4.41 (t, *J* = 4.5 Hz, 2H), 4.11 (t, *J* = 4.5 Hz, 2H), 3.91 (s, 6H), 3.75 (s, 3H); FAB-MS: *m/z* 576 (M^++1).

3',5'-Dimethoxy-7-{3-[4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenoxy]-propoxy}-flavone, 9d

A mixture of 7-(3-bromo-propoxy)-3',5'-dimethoxy-flavone, **8d** (1 g, 2.4 mmol), 4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenol, **3** (600 mg, 2.7 mmol) and potassium carbonate (1.3 g, 9.4 mmol) in dry dimethylformamide (80 mL) were reacted in a similar way as described for **6a** to yield **9d** (220 mg, 16%); m.p. 229-230°C. IR (KBr): 3229, 1733, 1678, 1632 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.34 (s, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.79 (s, 1H), 7.47 (d, *J* = 6.0 Hz, 2H), 7.30 (s, 1H), 7.20 (s, 2H), 7.02 (s, 1H), 6.98 (d, *J* = 9.0 Hz, 1H), 6.91 (d, *J* = 6.0 Hz, 2H), 6.71 (s, 2H), 4.20 (bs, 2H), 3.84 (bs, 2H), 3.84 (s, 6H), 2.14-2.12 (m, 2H); FAB-MS: *m/z* 560 (M^++1).

7-{3-[4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenoxy]-propoxy}-3',4',5'-trimethoxy-flavone, 9e

A mixture of 7-(3-bromo-propoxy)-3',4',5'-trimethoxy-flavone, **8e** (3 g, 6.7 mmol), 4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenol, **3** (1.7 g, 7.7 mmol) and potassium carbonate (3.7 g, 27 mmol) in dry dimethylformamide (150 mL) were reacted in a similar way as described for **6a** to yield **9e** (900 mg, 23%); m.p. 203-204°C. IR (KBr): 3401, 1733, 1683, 1626 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.33 (s, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.77 (s, 1H), 7.45 (d, *J* = 9.0 Hz, 2H), 7.32 (s, 1H), 7.28 (d, *J* = 3.0 Hz, 1H), 7.03 (s, 1H), 6.96 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 4.18 (t, *J* = 7.5 Hz, 2H), 3.88 (s, 6H), 3.85 (t, *J* = 7.5 Hz, 2H), 3.73 (s, 3H), 2.12-2.09 (m, 2H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 176.9, 168.0, 166.3, 163.3, 162.4, 160.4, 157.7, 153.6, 140.9, 133.7, 132.9, 126.8, 126.4, 124.2, 117.4, 117.1, 116.7, 115.0, 106.9, 104.2, 101.9, 66.9, 60.6, 56.6, 26.9; FAB-MS: *m/z* 590 (M^++1).

3',4'-Dimethoxy-7-{3-[4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenoxy]-propoxy}-flavone, 9f

A mixture of 7-(3-bromo-propoxy)-3',4'-dimethoxy-flavone, **8f** (2.5 g, 6 mmol), 4-(thiazolidin-2,4-dione-5-ylidinemethyl)-phenol, **3** (1.4 g, 6.33 mmol) and potassium carbonate (1 g, 7.24 mmol) in dry dimethylformamide (120 mL) were reacted in a similar way as described for **6a** to yield **9f** (600 mg, 18%); m.p. 240-241°C. IR (KBr): 3429, 1738, 1679, 1622 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 10.38 (s, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 7.82 (s, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.59 (s, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 1.9 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.96 (s, 1H), 6.94 (d, *J* = 8.5 Hz, 2H), 4.22 (bs, 4H), 3.90 (s, 3H), 3.87 (s, 3H), 2.25 (bs, 2H); FAB-MS: *m/z* 560 (M^++1).

Biological Evaluation

The biological evaluation of the synthesized compounds was carried out in sucrose loaded rat model for primary screening followed by a streptozotocin-induced beta-cell damaged diabetic rat model for antihyperglycemic and triton model for antidyslipidemic activities. The compounds which exhibited significant activity repeatedly in the STZ model were subjected to screen in *db/db* mice for antihyperglycemic and antidyslipidemic activity.

Sucrose loaded rat model (SLM)

Male albino rats of Charles Foster/Wistar strain of average body weight 160 ±20 g were selected for the study. The blood glucose level of each animal was checked by glucometer using glucostrips (Boehringer Mannheim) after 16 h starvation. Animals showing blood glucose levels between 60 to 80 mg/dL were divided into groups of five to six animals each. Animals of the experimental group were administered suspension of the desired synthetic compound orally (made in 1.0% gum acacia) at a dose of 100 mg/kg body weight. Animals of the control group were given an equal amount of 1.0% gum acacia. A sucrose load (10.0 g/kg) was given to each animal orally exactly after 30 min post administration of the test sample/vehicle. The blood glucose profile of each rat was again determined by glucometer at 30, 60, 90, and 120 min after administration of sucrose. Food but not water was withheld from the cages during the experiment. The quantitative glucose tolerance of each animal was calculated by the area under the curve (AUC) method (Prism Software). Comparing

the AUC of experimental and control groups determined the percentage of antihyperglycemic activity. Statistical comparison was made by Dunnett's test.

Sucrose-challenged Streptozotocin-induced diabetic model (STZ-S)

Male albino rats of Sprague Dawley strain of average body weight 160±20 g were selected for the study. Streptozotocin[29] (Sigma, USA) was dissolved in 100 mM citrate buffer *p*H 4.5 and a calculated amount of the fresh solution was injected into overnight fasted rats (45 mg/kg) intraperitoneally. Blood glucose level was checked 48 h later by glucostrips and animals showing blood glucose values between 144 to 270 mg/dL were included in the experiment and termed diabetic. The diabetic animals were divided into groups consisting of five to six animals each group. Animals of experimental groups were administered suspension of the desired test samples orally (made in 1.0% gum acacia) at a dose of 100 mg/kg body weight. Animals of the control group were given an equal amount of 1.0% gum acacia. A sucrose load of 2.5 g/kg body weight was given after 30 minutes of compound administration. After 30 minutes of the post sucrose load, blood glucose level was again checked by glucostrips at 30, 60, 90, 120, 180, 240, 300 min, and 24 h, respectively. Food but not water was withheld from the cages during the experimentation. Comparing the AUC of experimental and control groups determined the percent antihyperglycemic activity. Statistical comparison between groups was made by Student's 't' test

Triton model

Male Charles foster rats weighing 200-225 g were divided into control, dyslipidemic, and dyslipidemic plus drug-treated groups containing six animals in each group. Dyslipidemia was induced by the administration of Triton WR-1339 (200 mg/kg i.p.). All animals were maintained on a special pellet diet and water *ad libitum*. Compounds and the standard drug were macerated with 0.2% aqueous gum acacia suspension. The suspension was fed orally at a dose of 100 mg/kg simultaneously with triton in the drug-treated group. The animals of the control group received the same amount of gum acacia by a similar route of administration. At the end of the experiment, after 18 h, blood was withdrawn from the retro-orbital plexus, and plasma was used for the assay of total cholesterol, phospholipid, and triglycerides using the assay kits as supplied by Roche[30-33].

Evaluation of antihyperglycemic and anti–dyslipidemic activity in *db/db* mice

C57BL/KsBom-*db/db* male mice of 12-18 weeks, 40-50 g, bred in the animal house of CDRI, Lucknow were used in the experiments. The mice were housed in groups of 5 individuals in a room controlled for temperature (23 ± 2°C) and 12/12 hours light/dark cycle (lights on at 6.00 am). Body weight was measured daily from day 1 to day 10. All animals had free access to freshwater and normal chow except on the days of the postprandial protocol day 6 and during the overnight fast before the oral glucose tolerance test (OGTT) on day 10. Blood glucose was checked every morning up till day 5. On day 6 postprandial protocol was employed, in this method blood glucose was checked at −0.30 min and 0 h. Test compounds were given to the treatment group whereas the control group received only gum acacia (1.0%); the blood glucose was again checked at 1, 2, 3, 4, and 6 h after test compound treatment. Finally, on day l0 an OGTT was performed after overnight fasting. Blood glucose was measured at −0.30 min and test drugs were fed, blood glucose was again measured at 0.0 min post-treatment, at this juncture, glucose solution was given at a dose of 3 gm/kg to all the groups including the control group; the profile of blood glucose was checked at 30 min, 60 min, 90 min, and 120 min after glucose administration. The quantitative glucose tolerance of each animal was calculated by the area under the curve (AUC) method (Prism Software). Comparing the AUC of experimental and control groups determined the percentage of antihyperglycemic activity[34]. Blood was withdrawn from the retro-orbital plexus of the mice for the estimation of plasma triglyceride, cholesterol, HDL cholesterol levels. Statistical comparison was made by Dunnett's test[35].

Conclusion

A new set of thiazolidinedione based chalcones and flavones were synthesized and evaluated *in vivo* in different animal models. The antihyperglycemic activity was assessed in SLM, STZ, and obese *db/db* mice and antidyslipidemic activity in the triton model. Compounds **6d**, **9e**, and **23** reduced the blood glucose levels significantly in *db/db* mice. In summary, methoxy substituted compounds are superior to the benzylated compounds, and thiazolidinedione derivatives with a three-carbon spacer are the best for antihyperglycemic activity.

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