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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

3-Aryl-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]-phenyl}-acrylic acid alkyl ester: synthesis and antihyperglycemic evaluation

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Abstract A number of 2,4-thiazolidinedione derivatives of aryl-substituted cinnamic acid were synthesized and studied for their antihyperglycemic activity in neonatal streptozotocin-induced diabetic Wister male rats. Substitution of the aryl ring resulted in higher activity. 3-(2,4-Dimethoxyphenyl)-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]-phenyl}-acrylic acid methyl ester (**Thz7**), was found to be most active compound in this series which showed that disubstitutions on aryl ring by electron releasing groups were found suitable for promising antihyperglycemic activity. Increase in the ester carbon chain length decreased the activity.

Keywords 2,4-Thiazolidinedione · PPARγ · Antihyperglycemic activity · Neonatal streptozotocin-induced diabetic rats

Introduction

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder characterized by hyperglycemia and/or insulin resistance. It is one of the most chronic metabolic disorders associated with co-morbidities, such as obesity, hypertension, hyperlipidemia, and cardiovascular disease, which taken together, constitute the "metabolic syndrome" (Staels and Fruchart, 2005; Bjork *et al*., 2003). T2DM chronic complications include vision damage due to retinopathy, renal failure due to nephropathy, loss of sensation or pain due to neuropathy-accelerated atherosclerosis, and premature cardiovascular mortality (Susman and Helseth, 1997).

Type 2 diabetes is usually first treated by attempts to change physical activity (generally an increase is desired), the diet (generally to decrease carbohydrate intake) and weight loss (Luna and Mark, 2001). The usual next step, if necessary, is treatment with oral antidiabetic drugs (John *et al*., 2003; Hardman *et al*., 2007). There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors. Currently available therapies for type 2 diabetes include insulin and various oral agents: sulfonylureas; alpha-glucosidase inhibitors, such as acarbose; biguanides; thiazolidinediones like troglitazone, rosiglitazone, and pioglitazone (Berger *et al*., 1996), which act by improving peripheral insulin sensitivity. Repaglinide is a recently launched non-sulfonylurea insulin secretagogue that works via a similar mechanism to sulfonylurea drugs (Zhang and Moller, 2000). When oral medications fail, insulin therapy will be necessary to maintain normal or near normal glucose levels (Liu *et al*., 2001).

However, current therapies to reduce plasma glucose levels have inherent problems, including poor compliance, ineffectiveness, and occurrence of hypoglycemic episodes with insulin and the sulfonylureas (Hara *et al*., 2006). Therefore, there is a need for more effective, orally active agents, particularly Thiazolidinediones (TZDs) that normalize both glucose and insulin levels (Adisakwattana *et al*., 2005). Thiazolidinedione (TZD) also known as "glitazone", are a unique new class of oral antidiabetic agents that exert direct effects on the mechanism of insulin resistance (Imoto *et al*., 2002). Chemically, the members of

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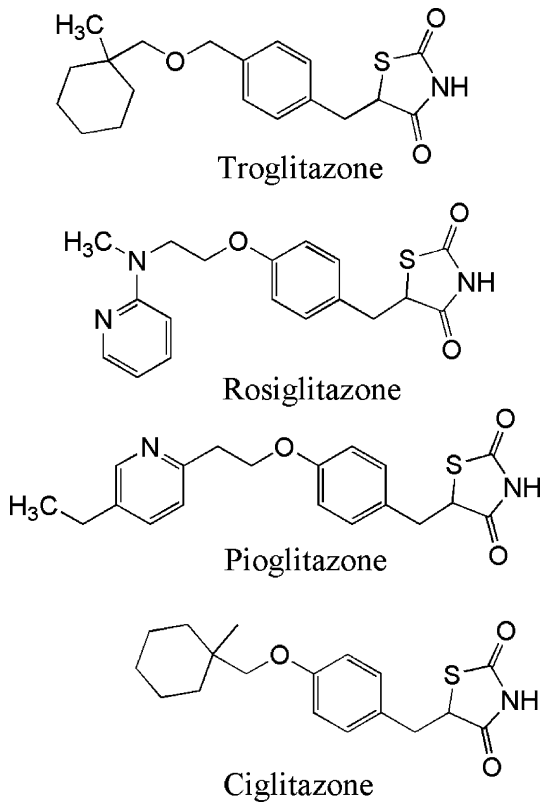


Fig. 1 Structures of some glitazones

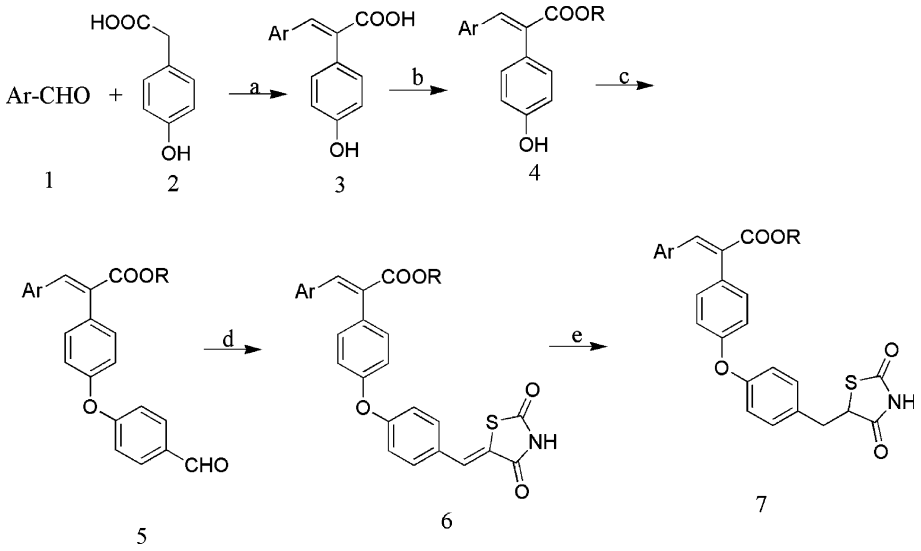
this class are derivatives of the parent compound thiazolidinedione. Three thiazolidinediones have been used in clinical practice: Troglitazone, Rosiglitazone and Pioglitazone as shown in Fig. 1. However, the first of these agents to be introduced (troglitazone) has been withdrawn from use because it was associated with severe hepatic toxicity (Evans, 1988; Cantello *et al*., 1994).

Thiazolidinediones do not stimulate the secretion of insulin but rather enhance the effects of circulating insulin by improving insulin sensitivity in muscle and adipose tissue and by inhibiting hepatic gluconeogenesis. Thiazolidinediones (TZDs) work by stimulating certain peroxisome proliferator-activated receptor γ (PPARγ) in the nucleus of the cells (Koyama *et al*., 2003). Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily. The normal ligands for these receptors are free fatty acids (FFAs) and eicosanoids. Thiazolidinedione activate transcription by binding to the PPARγ i.e. also a transcription factor and, when activated, binds to another transcription factor known as the retinoid X receptor (RXR) (Brooks *et al*., 2001). The PPAR/RXR complex can be activated by ligands of either receptors and the simultaneous binding of both ligands is more efficient. When these two proteins are complexed, a specific set of genes becomes activated and this active form of the receptor then binds to the PPRE and initiate transcription of insulin sensitive genes (Mannucci *et al*., 2008). Activation of insulin-responsive genes enhances the production of mRNAs of insulin dependent enzymes that regulate carbohydrate and lipid metabolism (Feige *et al*., 2006).

Chemistry

A general strategy for the synthesis of thiazolidine-2,4-diones is shown in Scheme 1. Perkin condensation (Lee *et al*., 2005) of aryl aldehyde **1** with 4-hydroxyphenyl acetic acid **2** in the presence of acetic anhydride and triethylamine yielded 3-Aryl-2-(4-hydroxyphenyl)-acrylic acid **3**. Esterification of this substituted acid followed by condensation with 4-fluorobenzaldehyde in the presence of

Scheme 1 Reagents and conditions: **a** acetic anhydride.Et3N, 6 h, 130°C, **b** ROH.H_2SO_4, 15 h, reflux, **c** 4-fluorobenzaldehyde, NaH, DMF. 18 h, 80°C, **d** 2,4-thiazolidinedione, piperidine. benzoic acid, toluene. 5 h reflux, **e** PD/C (10%), AcOH-$HCOONH_4$, 15 h, 125°c



sodium hydride in dimethyl formamide at 80°C for 18 h yielded 3-Aryl-2-[4-(4-formylphenoxy)-phenyl]-acrylic acid alkyl ester **5**. Knovenagel condensation (Prabhakar *et al*., 1998; Duendar *et al*., 2006) of this ester with 2,4-thiazolidinedione in the presence of piperidinium benzoate followed by hydrogenation using 10% Pd/C (3.52 g) in glacial acetic acid gave a good yield of final compound 3-Aryl-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)-phenoxy]-phenyl}-acrylic acid alkyl ester **7** (**Thz1**–**24**).

A major challenge was selective hydrogenation of one of the double bond. Hydrogenation with 10% palladium on carbon as catalyst yielded mixture of products (Bhat *et al*., 2004], and the separation of desired compound (**7**) from this mixture was possible only by reverse-phase chromatography on C-18 silica. This problem was overcome by using ammonium formate as hydrogen donor in the presence of palladium catalyst produced minimal amounts of other products, and isolation of desired compounds in high purity was possible by repeated crystallization from methanol (Ebdrup *et al*., 2003; Acton *et al*., 2005; Chittiboyina *et al*., 2006).

Pharmacology

Antidiabetic compounds of the thiazolidinedione class, increase peripheral tissue sensitivity to insulin via PPARγ receptor activation. Neonatal streptozotocin diabetic Wistar male rats (commonly used animal model of NIDDM), were used to assess the plasma glucose lowering activity of synthesized compounds and rosiglitazone was used as reference drug in this study (Adisakwattana *et al*., 2005).

Experimental animals

Wistar rats (2–4 days old pups with mother) were purchased from Disease Free Small Animal House, Chaudhary Charan Singh Haryana Agriculture University (CCSHAU), Hisar (Haryana). These mothers were housed separately one in a single cage with pups under laboratory conditions with alternating light and dark cycle of 12 h each. The animals had free access to food and water. All experimental procedures were approved by Institutional Animals Ethics Committee (IAEC) and animals care was taken as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India.

Induction of experimental neonatal streptozotocin diabetes

For induction of experimental diabetes, Wistar rats (5 days old pups) were injected with streptozotocin (90 mg/Kg, i.p.) freshly diluted in citrate buffer (0.1 mol, sodium citrate, pH 4.5). After 21 days, male rats were selected and were kept in groups of six in each cage. Male rats (9 weeks old) with fasting PGL of $\geq$200 mg/dl were considered as diabetic and selected for further pharmacological study. Blood samples were collected from retro-orbital sinus (Henke *et al*., 1999).

Dose selection and administration of synthesized compounds

The animals were kept under fasting state for 2 h before and 2 h after drug administration (Nomura *et al*., 1999). The effective dose to reduce plasma glucose level was determined using results of dose selection experiment. All compounds were given orally to 9 weeks old male rats, suspended in 0.25% carboxy methyl cellulose (CMC). Two compounds (**Thz4** and **Thz15**) were selected randomly for dose selection study, in which four different doses (15, 20, 25, and 30 μmol/kg) were tested at interval of 3, 7, 10, and 15 days. Plasma glucose level (PGL) (mg/dl) was measured by commercial supplied biological kit—Erba Glucose Kit (GOD-POD Method) using Chem 5 Plus-V_2 Auto-analyzer (Erba Mannhein Germany).

On the basis of this study, 25 μmol/kg dose was found most effective and this dose of all compounds was given for 15 days. Rosiglitazone (25 μmol/kg) as a reference and CMC (0.25% w/v) as a control were also given for 15 days (Dundar *et al*., 2008; Kuhn *et al*., 2006). Blood samples were collected from fasting animals under mild ether anesthesia from retro-orbital sinus, after 15 days of continuous dosing. The plasma glucose level was determined by enzymatic method using glucose kit and autoanalyzer.

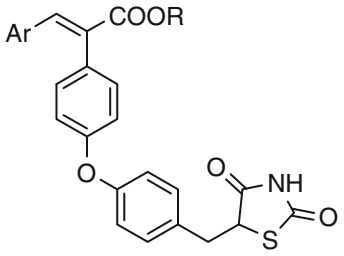
Data analysis

All the results were expressed as mean ± standard error mean (SEM). The data of all the groups were analyzed using one-way ANOVA followed by Dunnett's *t*-test (Madhavan *et al*., 2002) using the software SPSS 7.5.

Results and discussion

Physicochemical characteristics of the synthesized 2,4-thiazolidinedione derivatives are presented in Table 1. The synthesized compounds were screened for in vivo antihyperglycemic activity by using streptozotocin-induced neonatal diabetic rats model of type 2 diabetes. Rosiglitazone (25 μmol/kg) was used as a reference drug and reduced plasma glucose level up to 56.73%. The effective dose of synthesized compounds was determined by dose selection study which has been shown in Table 2. The effective dose

Table 1 Physicochemical characteristics of synthesized 3-Aryl-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]-phenyl}-acrylic acid alkyl esters



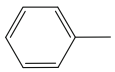
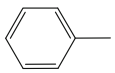
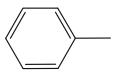
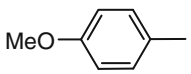
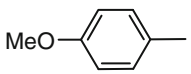
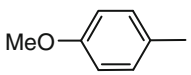
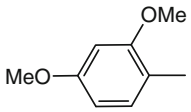
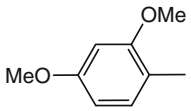
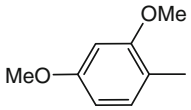
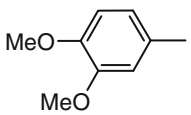
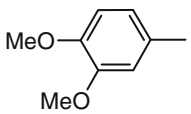
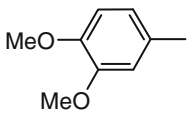
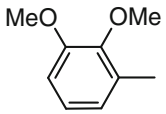
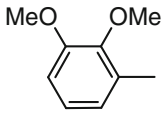
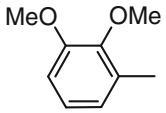
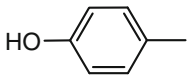
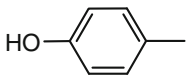
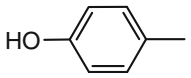
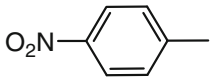
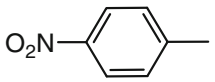
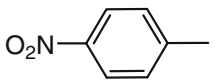
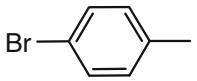
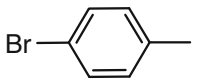
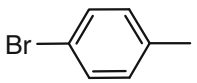
Compounds	–Ar	–R	Molecular formula	Molecular weight (g)	M.P. (°C)	R_f	% yield
Thz1		$-CH_3$	$C_{26}H_{21}NO_5S$	459.51	134–136	0.55	48.51
Thz2		$-C_2H_5$	$C_{27}H_{23}NO_5S$	473.54	141–143	0.62	34.10
Thz3		$-C_3H_7$	$C_{28}H_{25}NO_5S$	487.57	149–151	0.51[a]	52.09
Thz4		$-CH_3$	$C_{27}H_{23}NO_6S$	489.54	117–119	0.57	38.34
Thz5		$-C_2H_5$	$C_{28}H_{25}NO_6S$	503.57	127–129	0.49	42.80
Thz6		$-C_3H_7$	$C_{29}H_{27}NO_6S$	517.59	121–123	0.58	29.21
Thz7		$-CH_3$	$C_{28}H_{25}NO_7S$	519.57	112–114	0.64	47.40
Thz8		$-C_2H_5$	$C_{29}H_{27}NO_7S$	533.59	128–130	0.71	41.70
Thz9		$-C_3H_7$	$C_{30}H_{29}NO_7S$	547.62	123–125	0.59	33.28
Thz10		$-CH_3$	$C_{28}H_{25}NO_7S$	519.57	92–94	0.65	54.08
Thz11		$-C_2H_5$	$C_{29}H_{27}NO_7S$	533.59	97–99	0.56	46.90
Thz12		$-C_3H_7$	$C_{30}H_{29}NO_7S$	547.62	103–105	0.47[a]	53.45

Table 1 continued

Compounds	–Ar	–R	Molecular formula	Molecular weight (g)	M.P. (°C)	R_f	% yield
Thz13		$-CH_3$	$C_{28}H_{25}NO_7S$	519.57	99–101	0.54	32.58
Thz14		$-C_2H_5$	$C_{29}H_{27}NO_7S$	533.59	111–113	0.42	27.17
Thz15		$-C_3H_7$	$C_{30}H_{29}NO_7S$	547.62	106–108	0.45	41.52
Thz16		$-CH_3$	$C_{26}H_{21}NO_6S$	475.51	90–92	0.72	25.36
Thz17		$-C_2H_5$	$C_{27}H_{23}NO_6S$	489.54	96–98	0.67	37.49
Thz18		$-C_3H_7$	$C_{28}H_{25}NO_7S$	503.57	105–107	0.74	34.64
Thz19		$-CH_3$	$C_{26}H_{20}N_2O_7S$	504.51	101–103	0.46	39.60
Thz20		$-C_2H_5$	$C_{27}H_{22}N_2O_7S$	518.54	114–116	0.37	57.26
Thz21		$-C_3H_7$	$C_{28}H_{24}N_2O_7S$	532.56	109–111	0.41	42.81
Thz22		$-CH_3$	$C_{26}H_{20}BrNO_5S$	538.41	139–141	0.61	52.57
Thz23		$-C_2H_5$	$C_{27}H_{22}BrNO_5S$	552.44	147–149	0.48[a]	35.20
Thz24		$-C_3H_7$	$C_{28}H_{24}BrNO_5S$	566.46	154–156	0.32[a]	38.40

TLC mobile phase—toluene:chloroform (1:2), [a] Ethyl acetate:benzene (1:2)

Table 2 Dose selection study: effect of different doses on % PGL reduction

Dose (μmol/kg)	%PGL reduction in days (**Thz4**)				%PGL reduction in days (**Thz15**)			
	3	7	10	15	3	7	10	15
15	2.12	5.39	8.27	10.26	8.38	11.49	15.53	18.47
20	3.42	4.94	9.51	11.73	10.91	14.56	17.26	21.76
25	6.38	9.28	11.34	16.30	18.06	21.34	25.53	37.24
30	7.15	9.86	11.17	15.82	19.42	20.87	24.68	35.47

Table 3 Antihyperglycemic activity of thiazolidinedione derivatives

Compounds	%PGL reduction	Compounds	%PGL reduction
Thz1	10.74 ± 2.23[a]	**Thz14**	36.53 ± 2.95[b]
Thz2	9.80 ± 2.58[a]	**Thz15**	37.24 ± 4.39[b]
Thz3	8.60 ± 3.64	**Thz16**	18.81 ± 3.02[b]
Thz4	16.30 ± 3.44[a]	**Thz17**	18.16 ± 2.07[b]
Thz5	14.61 ± 2.58[a]	**Thz18**	17.48 ± 2.92[b]
Thz6	13.00 ± 2.64[a]	**Thz19**	13.26 ± 1.93[a]
Thz7	46.13 ± 4.96[b]	**Thz20**	13.40 ± 2.75[a]
Thz8	46.03 ± 3.08[b]	**Thz21**	12.45 ± 2.39[a]
Thz9	45.91 ± 4.51[b]	**Thz22**	15.58 ± 2.5[b]
Thz10	38.11 ± 3.67[b]	**Thz23**	13.63 ± 2.74[a]
Thz11	37.15 ± 4.06[b]	**Thz24**	13.42 ± 3.01[a]
Thz12	35.85 ± 3.29[b]	Rosiglitazone	56.73 ± 3.09[b]
Thz13	37.05 ± 3.6[b]	Control	0.433 ± 1.17

One-way ANOVA followed by Dunnett's test. [a] $P < 0.05$ and [b] $P < 0.01$

Values are presented as mean ± S.E.M. ($n = 6$)

was found 25 μmol/kg which was given to all experimental diabetic rats. The results of antihyperglycemic activity of synthesized derivatives are given in Table 3. The following pattern of hypoglycemic activity of the synthesized compounds was observed.

Compounds **Thz1–3** has no substitution on aryl ring and has minimal activity (9–11% PGL reduction) among all synthesized compounds. Substitution of aryl ring by electron-withdrawing or electron-donating groups increases the activity. Compounds **Thz4–6** having mono methoxy substitution on aryl ring, were found more active (13–16% PGL reduction) than unsubstituted compounds, but were found less active than compounds having dimethoxy substitution (**Thz7–15**) on aryl ring. The substitution on aryl ring by electron-releasing group may be responsible for their higher activity, which is further evidenced by higher activities of hydroxy-substituted derivatives (**Thz16–18**) than nitro (**Thz19–21**) and bromo- (**Thz22–24**) substituted derivatives.

Compound **Thz7** exhibited highest antihyperglycemic activity within all synthesized compounds, which reduced PGL up to 46.13% in diabetic rats. Chemically compound **Thz7** is 3-(2,4-dimethoxyphenyl)-2-{4-[4-(2,4-thiazolidin-5-ylmethyl)phenoxy]-phenyl}-acrylic acid methyl ester. Compound **Thz7** was found most active among all other dimethoxy-substituted compounds, which indicates that dimethoxy substitutions at *ortho* and *para* position on aryl ring can enhance the binding of molecules with the target (receptor). In all compounds methyl ester have higher activity than ethyl and propyl ester, which means that heavy carbon chain ester decreases the activity. This may be due to hindrance developed by heavy ester groups between the interaction of compounds and target site.

Experimental

All reactions were monitored by thin layer chromatography (TLC) using silica gel G (Spectrochem Pvt. Ltd., Mumbai). The plates were developed by exposing to iodine chamber. Melting points (m.p.) were determined by decibel melting point apparatus and were uncorrected. Structures of the selected newly synthesized 2,4-thiazolidinedione derivatives have been ascertained on the basis of their consistent IR and ^{1}H NMR spectral assignments. The IR spectra were recorded on Perkin Elmer IR spectrophotometer using KBr pellets. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Brucker Avance II 400 NMR spectrophotometer using DMSO as solvent and TMS as internal standard and reported as chemical shift in δ values (ppm). C, H, N- analysis has been performed with Carlo Arba 1106 CHN analyzer.

General procedure for the synthesis of 3-Aryl-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]-phenyl}-acrylic acid alkyl ester (**Thz1–24**)

*3-Aryl-2-(4-hydroxyphenyl)–acrylic acid (**3**)*

To a mixture of aryl aldehyde (10 g, 0.06 mol) and 4-hydroxyphenylacetic acid (9.14 g, 0.06 mol) in a conical flask, acetic anhydride (20 ml, 0.212 mol) and triethylamine (8.4 ml, 0.06 mol) were added. The resulting mixture was heated at 130–140°C for 6 h with continuous stirring. Then, it was cooled to room temperature. Concentrated HCl (20 ml) was added to the reaction mixture slowly over 30 min, while keeping the temperature of the mixture between 20–30°C. The resulting precipitate was filtered and washed with water to give crude product (**3**) that was recrystallized from methanol–water (4:1) and dried at 40°C.

*3-Aryl-2-(4-hydroxyphenyl)–acrylic acid alkyl ester (**4**)*

Alkylalcohol (60 ml) was added to the completely dried compound **3** (8.55 g, 0.028 mol) in RBF. Concentrated sulfuric acid (2 ml) was added to the above suspension and the reaction mixture was refluxed for 15 h under nitrogen. The resulting mixture was filtered and residue was taken in ethyl acetate (60 ml) in separating funnel and washed sequentially with water (2 × 20 ml), saturated aqueous $NaHCO_3$ (2 × 20 ml) and brine (2 × 20 ml). The organic layer was passed through anhydrous magnesium sulfate to

remove any traces of water and filtered. Then, the solvent was evaporated to dryness at water bath and compound **4** was obtained.

*3-Aryl-2-[4-(4-formylphenoxy)-phenyl]-acrylic acid alkyl ester (**5**)*

Compound **4** (8.66 g, 0.027 mol) was taken in a conical flask and dissolved in dry DMF (32 ml). Sodium hydride (1.2 g, 0.03 mol) was added to the above solution. Then, 4-fluorobenzaldehyde (3.7 ml, 0.034 mol) was added to the resulting orange solution. The resulting solution was heated at 80°C for 18 h with continuous stirring. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (60 ml) and washed first with water (3 × 20 ml) and then with brine (1 × 20 ml). The organic layer was passed through anhydrous sodium sulfate, filtered and solvent was evaporated. The residue was suspended in methanol (60 ml) and then filtered to get compound **5** which was dried at 40°C.

*3-Aryl-2-{4-[4-(2,4-dioxothiazolidin-5-ylidenmethyl)-phenoxy]-phenyl}-acrylic acid alkyl ester (**6**)*

To a suspension of **5** (7.04 g, 0.016 mol) in anhydrous toluene (50 ml), 2,4-thiazolidinedione (1.97 g, 0.017 mol), benzoic acid (2.68 g, 0.022 mol), and piperidine (2.14 g, 0.025 mol) were added sequentially with continuous stirring. The resulting mixture was taken in a RBF and refluxed for 5 h. After refluxing, the reaction mixture was cooled to room temperature and the resulting compound was filtered and washed with water. The residue so obtained was recrystallized in a mixture of methanol–diethyl ether (1:1, 60 ml). The compound **6** was obtained and dried in oven at 40°C.

*3-Aryl-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]-phenyl}-acrylic acid alkyl ester (**7**)*

To a solution of **6** (7.04 g, 0.013 mol) in glacial acetic acid (120 ml) in a conical flask, ammonium formate (47.06 g, 0.74 mol) was added and stirred for 30 min. Slurry of Pd on carbon (10%, dry, 3.52 g) in glacial acetic acid (5.8 ml) was added to the flask and heated at 125°C for 15 h with continuous stirring. The resulting mixture was filtered and the filtrate was poured slowly into water (140 ml) with vigorous stirring and the solid that separated, was filtered and dried. The resulting solid was recrystallized in a mixture of methanol and ethanol (2:1) to yield compound **7**.

*Analytical data for compound **Thz1***: mp (°C)—135; Yield—48.51%; ^{1}H NMR (DMSO): δ 1.06–1.13 (s, 3H, $COOCH_3$), 7.06–7.31 (m, 8H, ArH–O–ArH), 7.35–7.58 (m, 5H, ArH), 7.04–7.12 (s, 1H, CH of Ar–CH=C<), 8.26 (s, 1H, NH), 3.64–3.72 (d, 2H, CH_2 of Ar–CH_2–Thz); IR (KBr pellets): cm^{-1} 1706.6 (C=O str., ketonic), 1734.1 (C=O str., $COOCH_3$), 3029.1 (C–H str., aromatic), 2835.3 (C–H str., aliphatic), 3214.0 (NH str.), 1268.4 (Ar–O–SAr str.), 1494.2 (C=C str., aromatic). Anal. Calcd for $C_{26}H_{21}NO_5S$: C, 67.96; H, 4.61; N, 3.05. Found: C, 67.89; H, 4.67 N, 3.15.

*Analytical data for compound **Thz4***: mp (°C)—118; Yield—38.34%; ^{1}H NMR (DMSO): δ 1.34–1.57 (s, 3H, $COOCH_3$), 3.75–4.0 (s, 3H, OCH_3), 7.2–7.9 (m, 12H, Ar–H), 7.00 (s, 1H, CH of Ar–CH=C<), 8.5 (s, 1H, NH), 3.59 (d, 2H, CH_2 of Ar–CH_2–Thz); IR (KBr pellets): cm^{-1} 1694.7 (C=O str., ketonic), 1734.1 (C=O str., $COOCH_3$), 3030.1 (C–H str., aromatic), 2835.3 (C–H str., aliphatic), 3214.0 (NH str.), 1286.7 (Ar–O–Ar str.), 1507.6 (C=C str., aromatic). Anal. Calcd for $C_{27}H_{23}NO_6S$: C, 66.24; H, 4.74; N, 2.86. Found: C, 66.89; H, 4.88 N, 3.05.

*Analytical data for compound **Thz8***: mp (°C)—129; Yield—41.70%; ^{1}H NMR (DMSO): δ 1.14–1.18 (d, 5H, $COOC_2H_5$), 3.75–3.95 (s, 6H, OCH_3), 7.14–7.51 (m, 8H, ArH–O–ArH), 6.7–6.76 (m, 3H, ArH) 6.9–6.96 (s, 1H, CH of Ar–CH=C<), 8.21 (s, 1H, NH), 3.58 (d, 2H, CH_2 of Ar–CH_2–Thz); IR (KBr pellets): cm^{-1} 1673.0 (C=O str., ketonic), 1731.8 (C=O str., $COOC_2H_5$), 2941.0 (C–H str., aromatic), 2832.3 (C–H str., aliphatic), 3143.1 (NH str.), 1284.4 (Ar–O–Ar str.), 1461.8 (C = C str., aromatic). Anal. Calcd for $C_{29}H_{27}NO_7S$: C, 65.28; H, 5.10; N, 2.62. Found: C, 65.59; H, 4.87 N, 2.78.

*Analytical data for compound **Thz11***: mp (°C)—98; Yield—46.90 %; ^{1}H NMR (DMSO): δ 1.14–1.18 (d, 5H, $COOC_2H_5$), 3.92–3.94 (s, 6H, OCH_3), 7.22–7.38 (m, 11H, ArH), 7.14 (s, 1H, CH of Ar–CH=C<), 8.22 (s,1H, NH), 3.72 (d, 2H, CH_2 of Ar–CH_2–Thz); IR (KBr pellets): cm^{-1} 1706.6 (C=O str., ketonic), 1734.1 (C=O str., $COOC_2H_5$), 3053.8 (C–H str., aromatic), 2835.3 (C–H str., aliphatic), 3214.0 (NH str.), 1265.3 (Ar–O–Ar str.), 1449.6 (C=C str., aromatic). Anal. Calcd for $C_{29}H_{27}NO_7S$: C, 65.28; H, 5.10; N, 2.62. Found: C, 65.61; H, 4.97 N, 2.71.

*Analytical data for compound **Thz13***: mp (°C)—100; Yield—32.58%; ^{1}H NMR (DMSO): δ 1.14–1.18 (s, 3H, $COOCH_3$), 3.72–3.98 (s, 6H, OCH_3), 7.13–7.34 (m, 11H, ArH), 7.0–7.06 (s, 1H, CH of Ar–CH=C<), 8.22 (s, 1H, NH), 3.64 (d, 2H, CH_2 of Ar–CH_2–Thz); IR (KBr pellets): cm^{-1} 1701.6 (C=O str., ketonic), 1737.7 (C=O str., $COOCH_3$), 3028.8 (C–H str., aromatic), 2835.8 (C–H str., aliphatic), 3143.1 (NH str.), 1273.0 (Ar–O–Ar str.), 1454.0 (C=C str., aromatic). Anal. Calcd for $C_{28}H_{25}NO_7S$: C, 64.73; H, 4.85; N, 2.70. Found: C, 65.19; H, 4.87 N, 2.88.

*Analytical data for compound **Thz16***: mp (°C)—91; Yield—25.36%; ^{1}H NMR (DMSO): δ 1.13–1.32 (s, 3H, $COOCH_3$), 7.17–7.49 (m, 12H, ArH), 7.79–7.82 (s, 1H, CH

of Ar–CH=C<), 4.0 (s, 1H, OH), 8.3 (s, 1H, NH), 3.66–3.77 (d, 2H, CH_2 of Ar–CH_2–Thz).; IR (KBr pellets): cm^{-1} 1693.9 (C=O str., ketonic), 1751.0 (C=O str., $COOCH_3$), 3034.6 (C–H str., aromatic), 2835.8 (C–H str., aliphatic), 3028.8 (OH str.), 3143.1 (NH str.), 1215.7 (Ar–O–Ar str.), 1485.9 (C=C str., aromatic). Anal. Calcd for $C_{26}H_{21}NO_6S$: C, 65.67; H, 4.45; N, 2.95. Found: C, 65.44; H, 4.35 N, 3.06.

Analytical data for compound ***Thz19***: mp (°C)—102; Yield—39.60%; ^{1}H NMR (DMSO): δ 1.33 (s, 3H, CO-OCH_3), 7.16–7.32 (m, 4H, ArH), 7.34–7.52 (m, 8H, ArH–O–ArH), 7.83 (s, 1H, CH of Ar–CH=C<), 8.18 (s, 1H, NH), 3.66 (d, 2H, CH_2 of Ar–CH_2–Thz); IR (KBr pellets): cm^{-1} 1697.8 (C=O str., ketonic), 1734.1 (C=O str., CO-OCH_3), 3047.6 (C–H str., aromatic), 2835.8 (C–H str., aliphatic), 1525.3 (NO_2 str.), 3143.1 (NH str.), 1257.8 (Ar–O–Ar str.), 1505.9 (C=C str., aromatic). Anal. Calcd for $C_{26}H_{20}N_2O_7S$: C, 61.90; H, 4.00; N, 5.55. Found: C, 61.76; H, 4.32 N, 5.15.

Analytical data for compound ***Thz23***: mp (°C)—148; Yield—35.20%; ^{1}H NMR (DMSO): δ 1.17–1.31 (d, 5H, $COOC_2H_5$), 7.35–7.50 (m, 4H, ArH), 7.15–7.32 (m, 8H, ArH–O–ArH), 7.82 (s, 1H, CH of Ar–CH=C<), 8.2 (s, 1H, NH), 3.65 (d, 2H, CH_2 of Ar–CH_2–Thz); IR (KBr pellets): cm^{-1} 1678.9 (C=O str., ketonic), 1734.1 (C=O str., $COOC_2H_5$), 3032.3 (C–H str., aromatic), 2835.3 (C–H str., aliphatic), 698.5 (Br str.), 3214.0 (NH str.), 1254.2 (Ar–O–Ar str.), 1485.1 (C=C str., aromatic). Anal. Calcd for $C_{27}H_{22}NO_5SBr$: C, 58.7; H, 4.01; N, 2.54. Found: C, 58.43; H, 4.27 N, 2.78.

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