European Journal of Medicinal Chemistry 53 (2012) 308–315

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis, hypoglycemic and hypolipidemic activities of novel thiazolidinedione derivatives containing thiazole/triazole/oxadiazole ring

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ARTICLE INFO

Article history:
Received 17 December 2011
Received in revised form
5 April 2012
Accepted 12 April 2012
Available online 21 April 2012

Keywords:
Thiazolidinediones
Pioglitazone analogs
Hypoglycemic activity
Hypolipidemic activity

ABSTRACT

Novel thiazolidinedione derivatives were synthesized by incorporating pharmacologically significant heterocycles viz, substituted thiazole, triazole, and oxadiazole moieties linked to the central phenyl ring via heteroatomlinkage with one/two carbon spacer as the structural analogs of Pioglitazone by employing multistep synthetic protocols. Structures of all the newly synthesized intermediates and target molecules were established by analytical and spectral data. These newly synthesized compounds were screened for their *invivo* hypoglycemic and hypolipidemic activities in male wistar rats. Some of the synthesized compounds demonstrated good activity.

1. Introduction

Thiazolidinediones are synthetic, high-affinity ligands of peroxisome proliferator activated receptor-gamma (PPARγ), which are members of a super family of nuclear receptors that include steroid, retinoid, and thyroid hormone receptors [1–3]. These receptors play a pivotal role in regulating the expression of a large number of genes involved in lipid metabolism and energy balance [4]. It has been shown that PPARγ located in nucleus is able to increase the insulin sensitivity, promote the differentiation of lipocytes, and retard the occurrence of complications.

Pioglitazone (Fig. 1) was identified as the first high-affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ) [5,6]. Thiazolidinedione compounds are predicted to be promising compounds, capable of ameliorating non-insulin-dependent diabetes mellitus (NIDDM) by improving insulin resistance without inducing hypoglycemia. However these drugs are found to have undesirable side effects including weight gain and edema [7,8]. These observations prompted us to undertake the synthesis of structural analogs of Pioglitazone with a hope of getting compounds with improved hypoglycemic activity and least side effects. Our strategies to accomplish these goals were to pursue modifications in the composition and nature of the linker that joins the central phenyl ring and the lipophilic tail, we replaced the 5-ethyl-pyridine moiety of Pioglitazone with pharmacologically important substituted thiazole, triazole and oxadiazole which were connected to the central phenyl ring via oxymethyl and thioethyloxy linkage with one/two carbon spacer.

2. Results and discussion

2.1. Chemistry

The general strategy for the synthesis of target molecules is shown in Schemes 1 and 2. The required starting material, 4-chloromethyl-2-methyl/phenyl thiazoles **2**(**a**–**b**) were prepared in good yields from the reaction of thioacetamide/thiobenzamide and 1,3-dichloroacetone (Scheme 1) [9,10]. This on coupling with *p*-hydroxybenzaldehyde in presence of anhydrous potassium carbonate in dry acetone furnished the intermediate 4-(2-methyl/phenyl-thiazol-4-ylmethoxy)-benzaldehyde **3**(**a**–**b**). The structure of these intermediates **3**(**a**–**b**) were confirmed by their IR spectra, which exhibited $\nu_{C=O}$, $\nu_{C=N}$ and ν_{C-O} bands around 1680, 1610 and 1210 cm^{-1} respectively. The ^1H NMR spectra of these compounds displayed characteristic aldehydic proton at δ 10.00

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doi:10.1016/j.ejmech.2012.04.015

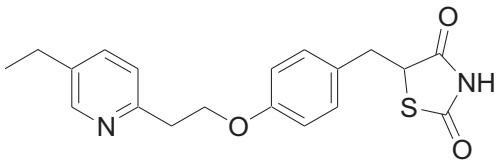


Fig. 1. Pioglitazone.

and rest of the protons resonated in the expected region. The reaction of **3**(**a**–**b**) with thiazolidine-2,4-dione in toluene with catalytic amount of piperidine-acetate afforded the target molecule **4**(**a**–**b**) . The structures of thus obtained thiazolidine-2,4-dione derivatives (**4 a**–**b**) were ascertained by their spectral and analytical data. The IR spectra of these compounds showed the presence of $\nu_{C=O}$ for two carbonyl groups around 1730 cm^{-1} and 1695 cm^{-1} along with $\nu_{N-H,}$ $\nu_{C=N}$ and ν_{C-O} in their respective regions. The ^1H NMR spectra displayed the absence of aldehyde proton and the presence of vinylic proton around δ 7.80, confirming the formation of condensed product. These compounds **3**(**a**–**b**) and **4**(**a**–**b**) were further confirmed by their ^{13}C NMR and mass spectra.

Substituted 2-mercaptotriazoles (**5**) and **2**-mercaptooxadiazole (**6**) required for the synthesis of second class of compounds depicted in Scheme 2 were synthesized according to the literature methods [11–16]. Synthon 7, which provided the bromoethyloxy part of the target molecule, was prepared by condensation of dibromoethane with p-hydroxybenzaldehde in DMF with potassium carbonate [17].

The base catalyzed nucleophilic substitution reaction of bromoethyloxybenzaldehyde **7** with 2-mercaptotriazoles (**5**) and 2-mercaptooxadiazoles (**6**) at room temperature yielded compound **8**(**a**–**h**) and **9**(**a**–**d**) respectively. The intermediate **8** and **9** were confirmed by their IR spectra where, aldehyde $\nu_{C=O}$ appeared around 1680 cm^{-1} and the ^1H NMR spectra displayed the aldehydic proton around δ 9.7, along with the triplet–triplet pattern for $-CH_2CH_2-$ group i; e δ 3.67(t, 2H, SCH_2) and δ 4.37(t, 2H, OCH_2).These intermediate **8** and **9** when refluxed with thiazolidine-2,4-dione in toluene, along with catalytic amount of piperidine acetate results in the formation of the target molecules **10**, **11**in good yields. They displayed the bands in the IR spectra for carbonyl group of thiazolidinedione around 1735 cm^{-1} and 1690 cm^{-1}, for derivatives **8**, ν_{N-H} was observed around 3100 cm^{-1}. The ^1H NMR showed the vinylic proton around δ 7.70 and the other protons resonated at expected regions. The absence of aldehydic proton also confirmed the formation of these compounds.

The configuration of the title compounds were established based on ^1H NMR analysis (olefinic C–H around δ 7.70–7.90) [18,19], theoretical calculations [20–23] and thermodynamic stability [24,25]. All these observation support the Z configuration. Hence the Z configuration was confirmed for the thiazolidinedione derivatives.

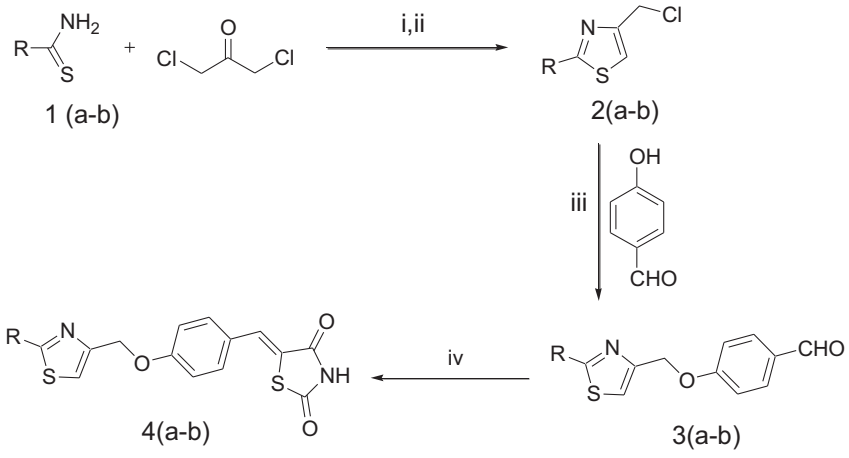
2.2. Hypoglycemic and hypolipidemic activities

All the synthesized thiazolidinedione analogs were screened *invivo* for their plasma glucose (PG) and triglyceride (TG) lowering activities in alloxan induced diabetic male wistar rats after oral treatment for 15 days with different doses. Acute toxicity studies were performed and doses were fixed. Pioglitazone was used as a standard drug for comparison. The hypoglycemic and hypolipidemic effects after oral administration of all the synthesized compounds in alloxan-induced model are summarized in terms of percentage reduction of PG and TG levels, obtained from samples of blood collected on final day of treatment.

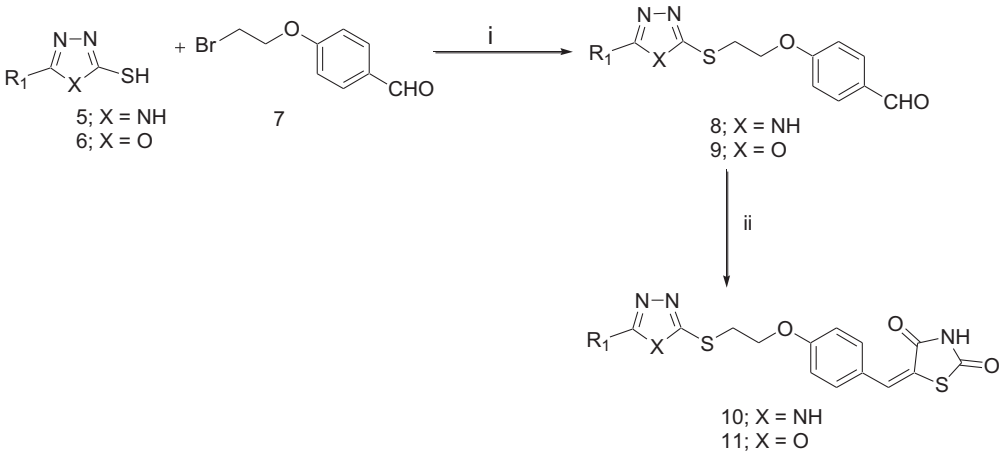
With our objective focused on improving insulin sensitivity to decrease the PG and TG level, initially we introduced methyl/phenyl substituted thiazole ring linked to the central phenyl ring via oxymethyl linkage with one carbon spacer **4**(**a**–**b**) which does not shown impressive results (Table 1).

Further we introduce the triazole and oxadiazole ring linked to the central phenyl ring via thioethyloxy linkage with two carbon spacer. We began our optimization work by exploring the SAR at the C-5 position of the triazole and oxadiazole. Introduction of benzyl moiety and introduction of both electron-donating and withdrawing groups at *para* and *ortho* position of the aromatic ring does not show any significant hypoglycemic and hypolipidemic activities. Further with introduction of methoxy group at para position of phenyl ring present at C-5 position of triazole ring (**10h**) caused a significant increase in insulin sensitivity. Similarly introduction of 3-pyridyl ring (**11c**) and 4-pyridyl ring (**11d**) at C-5 position of the oxadiazole ring displayed increased insulin sensitivity.

Hence the results after 15 days of treatment (Tables 1–3) revealed that incorporation of thioethyloxy linkage with two carbon spacer connecting to triazole derivative (**10h**) and



Scheme 1. Synthesis of 5-[4-(2-methyl/phenyl-thiazol-4-ylmethoxy)-benzylidine]-thiazol idine-2,4-dione **4**(**a**–**b**).



10(a-h): X = NH; R_1 = phenyl(a), benzyl(b), p-Me-phenyl(c), p-NO_2-phenyl(d), o-NO_2 – phenyl(e), p-Cl-Phenyl(f), p-Br-phenyl(g), p-OMe-phenyl(h).

11(a-d): X = O; R_1 = phenyl (a), benzyl (b), 3-pyridyl(c), 4-pyridyl (d).

Scheme 2. Synthesis of 5-(4-{2-[(5-aryl-4*H*-1,2,4-triazol-3-yl)thio]ethoxy}benzy lidene)-1,3-thiazolidine-2,4-dione **10**(**a**–**h**) and 5-(4-{2-[(5-aryl-1,3,4-oxadiazol-2-yl)thio]ethoxy} benzylidene)-1,3-thiazolidine-2,4dione **11**(**a**–**d**).

oxadiazole derivative (**11c**,**11d**) displayed good activities than the compounds having either thioethyloxy linkage connected to triazole/oxadiazole or oxymethyl linkage with one carbon spacer connected to thiazole.

3. Conclusions

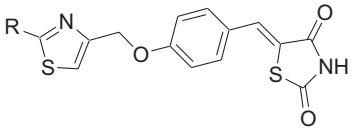
In this paper we have reported the design and synthesis of novel thiazole, triazole and oxadiazole containing thiazolidinedione derivatives. These compounds were screened for their *invivo* hypoglycemic and hypolipidemic activities which show interesting insulin sensitizing properties. Compound **10h**, **11c** and **11d** displayed comparable hypoglycemic and hypolipidemic efficacy that of standard. It is important to notice that **10h**, **11c** and **11d** significantly decreases plasma glucose and also lowers the triglyceride level, which is preferable for treatment of both hyperglcaemia and cardiovascular complication. Hence it's concluded that incorporation of thioethyloxy linkage connecting to triazole and oxadiazole may leads to development of novel potent drug candidate.

4. Experimental

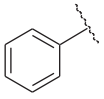
4.1. Chemistry – general aspects

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on Nicolet Impact 410 FTIR spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR were recorded on Bruker 300-MHz and 75-MHz FT NMR spectrometer in $CDCl_3$, C_6D_6 and TFA with TMS as internal standard. Mass spectra were recorded on Finnigan MAT (Model MAT8200) spectrometer and elemental analyses were carried out using Heraus CHN rapid

Table 1
Plasma glucose and triglyceride level at various drug doses of **4**(**a**–**b**).

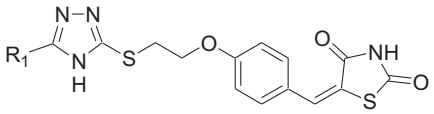


5-[4-(2-methyl/phenyl-thiazol-4-ylmethoxy)-benzylidine]-thiazolidine-2,4-dione.

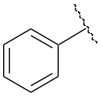
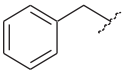
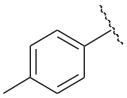
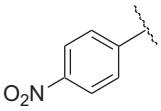
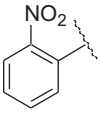
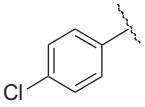
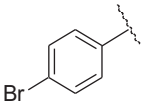
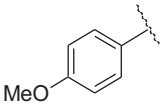
Compound	*R*	% Decrease in plasma glucose (PG) and triglyceride (TG) level at various doses (mg/kg body weight)				
			3 mg	10 mg	30 mg	100 mg
Pioglitazone	–	TG	41.60 ± 2.25	47.25 ± 5.50	64.59 ± 5.42	75.43 ± 3.40
		PG	47.02 ± 14.39	35.25 ± 20.42	40.96 ± 17.59	45.89 ± 2.24
4a	CH_3–	TG	18.62 ± 0.43	19.20 ± 2.01	26.40 ± 1.97	38.92 ± 1.46
		PG	10.42 ± 4.23	10.64 ± 1.18	14.73 ± 3.75	22.87 ± 1.73
4b		TG	25.24 ± 0.65	21.69 ± 1.73	40.26 ± 1.10	53.96 ± 0.66
		PG	17.75 ± 1.85	20.36 ± 1.20	22.64 ± 4.05	29.73 ± 1.39

Each value represents the mean ± SEM ($n = 6$). Percentage reduction was calculated according to the formula: [(PG in control–PG in treated)/PG in control] × 100; [(TG in control–TG in treated)/TG in control] × 100.

Table 2
Plasma glucose and triglyceride level at various drug doses of **10**(**a**–**h**).



5-(4-{2-[(5-aryl-4H-1,2,4-triazol-3-yl)thio]ethoxy}benzylidene)-1,3-thiazolidine-2,4-dione.

Compounds	R_1	% Decrease in plasma glucose (PG) and triglyceride (TG) level at various doses (mg/kg body weight)				
			3 mg	10 mg	30 mg	100 mg
Pioglitazone	–	TG	41.60 ± 2.25	47.25 ± 5.50	64.59 ± 5.42	75.43 ± 3.40
		PG	47.02 ± 14.39	35.25 ± 20.42	40.96 ± 17.59	45.89 ± 2.24
10a		TG	18.62 ± 0.43	19.20 ± 2.01	26.40 ± 1.97	38.92 ± 1.46
		PG	10.42 ± 4.23	10.64 ± 1.18	14.73 ± 3.75	22.87 ± 1.73
10b		TG	22.45 ± 0.55	22.81 ± 1.08	38.25 ± 2.78	41.87 ± 3.54
		PG	18.28 ± 1.68	19.36 ± 2.81	28.54 ± 3.08	34.38 ± 1.56
10c		TG	25.24 ± 0.65	21.69 ± 1.73	40.26 ± 1.10	53.96 ± 0.66
		PG	16.87 ± 1.01	20.36 ± 1.20	22.64 ± 4.05	29.73 ± 1.39
10d		TG	14.12 ± 2.06	15.32 ± 1.82	18.56 ± 1.82	22.08 ± 2.18
		PG	11.92 ± 1.04	13.85 ± 0.92	16.02 ± 3.08	18.04 ± 1.28
10e		TG	19.84 ± 1.24	20.91 ± 1.05	38.64 ± 1.83	49.12 ± 1.56
		PG	14.58 ± 0.85	15.28 ± 1.37	20.14 ± 2.12	26.84 ± 1.98
10f		TG	23.85 ± 0.52	24. 56 ± 2.26	32.92 ± 1.42	41.56 ± 1.08
		PG	16.04 ± 0.57	19.63 ± 1.58	23.68 ± 2.05	28.85 ± 1.28
10g		TG	28.35 ± 1.64	26.87 ± 0.82	39.45 ± 2.07	45.68 ± 3.12
		PG	13.15 ± 3.28	20.43 ± 1.58	19.52 ± 2.47	28.51 ± 1.83
10h		TG	43.14 ± 2.10	42.63 ± 3.21	59.46 ± 3.82	71.24 ± 1.30
		PG	41.28 ± 2.06	33.62 ± 2.13	40.04 ± 1.84	43.42 ± 0.50

Each value represents the mean ± SEM ($n = 6$). Percentage reduction was calculated according to the formula: [(PG in control−PG in treated)/PG in control] × 100; [(TG in control−TG in treated)/TG in control] × 100.

analyzer. Thin layer chromatography (TLC) was performed on silica gel plates (60 F254; Merck). Column chromatography was performed using silica gel (100–200 mesh size; Merck).

*4.1.1. Preparation of 4-chloromethyl-2-methyl/phenyl thiazole **2**(**a**–**b**)*

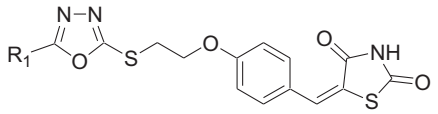
It was prepared in good yield from equimolar mixture of thioacetamide/thiobenzamide and 1,3-dichloroacetone according to previously described method [9,10].

*4.1.2. General procedure for preparation of 4-(2-methyl/phenyl-thiazol-4-ylmethoxy)-benzaldehyde **3**(**a**,**b**)*

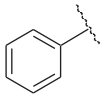
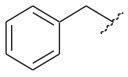
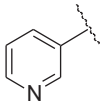
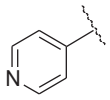
A mixture of **2**(**a**–**b**) (0.001 mol) and *p*-hydroxybenzaldehyde (1.22 g, 0.001 mol) was refluxed in dry acetone in presence of anhydrous potassium carbonate for 6–7 h monitored by TLC. The solid (K_2CO_3) was removed by filtration. Excess of solvent was removed under reduced pressure and the concentrated mass was kept for 5 h to afford pale yellow solid in moderate yield. It was purified by column chromatography with ethyl acetate–hexane (30:70v/v to 50:50v/v).

4.1.2.1. 4-(2-Methyl-thiazol-4-ylmethoxy)-benzaldehyde (3a). Yield 66%; Pale yellow granules (chloroform + pet ether); m.p. 92–94 °C; IR (KBr) υ cm^{-1}: 3044, 1675, 1608, 1535, 1208; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.73(s, 3H, CH_3), 5.26(s, 2H, CH_2), 6.84(s, 1H, H5, thiazole), 6.93(d, $J = 7.3$ Hz, 2H, H3, H5, Ar–H), 7.68(d, $J = 7.3$ Hz, 2H, H2, H6, Ar–H), 9.94(s, 1H, CHO); Anal calcd. for $C_{12}H_{11}NO_2S$, %: C, 61.78; H, 4.75; N, 6.00; Found, %: C, 62.05; H, 4.87; N, 5.86.

Table 3
Plasma glucose and triglyceride level at various drug doses of **11**(**a**–**d**).



5-(4-{2-[(5-Aryl-1,3,4-oxadiazol-2-yl)thio]ethoxy}benzylidene)-1,3-thiazolidine-2,4dione.

Compounds	R_1	% Decrease in plasma glucose (PG) and triglyceride (TG) level at various doses (mg/kg body weight)			
		3 mg	10 mg	30 mg	100 mg
Pioglitazone	–	TG 41.60 ± 2.25 PG 47.02 ± 14.39	47.25 ± 5.50 35.25 ± 20.42	64.59 ± 5.42 40.96 ± 17.59	75.43 ± 3.40 45.89 ± 2.24
11a		TG 21.56 ± 0.52 PG 11.62 ± 2.24	22.18 ± 3.24 14.64 ± 0.38	24.05 ± 1.97 16.13 ± 3.75	33.12 ± 1.46 20.08 ± 2.52
11b		TG 18.52 ± 1.26 PG 14.23 ± 3.05	20.54 ± 0.88 16.82 ± 2.04	28.02 ± 1.92 19.08 ± 2.14	34.56 ± 1.62 23.08 ± 1.68
11c		TG 40.66 ± 2.15 PG 24.35 ± 1.14	45.10 ± 1.62 33.16 ± 1.08	60.78 ± 2.27 39.34 ± 0.90	72.32 ± 4.27 50.09 ± 0.85
11d		TG 40.15 ± 2.10 PG 23.46 ± 0.65	42.17 ± 3.90 32.62 ± 2.16	58.48 ± 1.82 40.00 ± 1.86	69.72 ± 3.21 43.42 ± 0.55

Each value represents the mean ± SEM ($n = 6$). Percentage reduction was calculated according to the formula: [(PG in control−PG in treated)/PG in control] × 100; [(TG in control−TG in treated)/TG in control] × 100.

*4.1.2.2. 4-(2-Phenyl-thiazol-4-ylmethoxy)-benzaldehyde (**3b**).* Yield 73%; yellow granules (chloroform + pet ether); m.p.106–108 °C; IR (KBr) υ cm^{-1}: 3048, 1682, 1613, 1548, 1212; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.35(s, 2H, CH_2), 6.98(d, $J = 8.04$ Hz, 2H, Ar–H), 7.24(s, 1H, H5, thiazole), 7.46–7.97(m, 7H, Ar–H), 9.91(s, 1H, CHO). Anal calcd. for $C_{17}H_{13}N\,O_2S$, %: C, 69.13; H, 4.44; N, 4.74; Found, %: C, 69.28; H, 4.38; N, 4.82.

*4.1.3. General procedure for preparation of 5-[4-(2-methyl/phenyl-thiazol-4-ylmethoxy)-benzylidine]-thiazol idine-2,4-dione **4**(**a**–**b**)*

A mixture of 4-(2-methyl/phenyl-thiazol-4-ylmethoxy)benzaldehyde **3**(**a**–**b**). (0.001 mol) and 1,3-thiazolidine-2,4-dione (0.11 g, 0.001 mol) was refluxed in toluene (25 mL) with catalytic amount of piperidine-acetate for 2–3 h. The yellow solid that separated was collected by filtration, washed with hot toluene, benzene and methanol successively. The products were recrystallized from dimethylformamide.

*4.1.3.1. 5-[4-(2-Methyl-thiazol-4-ylmethoxy)-benzylidene]-thiazolidine-2,4-dione (**4a**).* Yield 86%; pale yellow solid (DMF); m.p. 252–254 °C; IR (KBr) υ cm^{-1}: 3182, 2962, 1732, 1696, 1617, 1554, 1191; 1H NMR (300 MHz, CDCl3+TFA) δ: 2.77(s, 3H, CH_3), 5.31 (s, 2H, OCH_2), 6.95–7.13(m, 3H, H5, thiazole; H3, H5, Ar–H), 7.67(d, $J = 7.3$ Hz, H2, H6, Ar–H), 7.75(s, 1H, vinylic proton); Anal calcd. for $C_{15}H_{12}N_2O_3S_2$, %: C, 54.20; H, 3.64; N, 8.43; Found, %: C, 54.46; H, 3.75; N, 8.25, Mass, *m*/*z* (%) M+1, 333 (100).

*4.1.3.2. 5-[4-(2-Phenyl-thiazol-4-ylmethoxy)-benzylidene]-thiazolidine-2,4-dione (**4b**).* Yield 91%; pale yellow granules (DMF); m.p. 268–272 °C; IR (KBr) υ cm^{-1}: 3172, 2972, 1729, 1695, 1619, 1553, 1188; ^1H NMR (300 MHz, $CDCl_3$+TFA) δ: 5.42(s, 2H, CH_2), 7.07(d, $J = 8.87$ Hz, 2H, Ar–H), 7.11–7.76(m, 9H, H5, thiazole; Ar–H; vinylic proton); MS (ESI): 417.03 (M + Na); Anal. calcd. for $C_{20}H_{14}N_2O_3S_2$, %: C, 60.90; H, 3.58; N, 7.10; Found, %: C, 60.72; H, 3.62; N, 6.96.

*4.1.4. Preparation of 3-aryl-1,2,4-triazolin-5-thiones (**5a**–**h**)*

The required 3-aryl-1,2,4-triazolin-5-thiones were prepared by treating corresponding properly substituted thiosemicarbazide with aqueous sodium hydroxide under reflux according to previously described method [11–13].

*4.1.5. Preparation of p-(2-bromoethyloxy)benzaldehyde (**7**)*

It was prepared by condensation of dibromoethane with *p*-hydroxybenzaldehde in DMF with potassium carbonate according to previously described method [17].

*4.1.6. General procedure for preparation of 4-{2-[(5-aryl-4H-1,2,4-triazol-3-yl)thio]ethoxy}benzaldehyde (**8a**–**h**)*

To a solution of 5-aryl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **5**/5-aryl-1,3,4-oxadiazole-2(3*H*)-thione **6** (0.01 mol) in dimethylformamide (10 mL) was added potassium hydroxide (0.012 mol) and stirred for 20 min. A solution of *p*-(2-bromoethyloxy)benzaldehyde (0.01 mol) in DMF (8 mL) was then added and the reaction mixture was stirred at room temperature for 4 h (monitored by TLC). The mixture was then poured into water and extracted with chloroform (3×30 mL). The combined extracts were washed with water, dried over anhydrous sodium sulfate and solvent was removed under diminished pressure. The residue thus obtained was purified by column chromatography through silica using a mixture of hexane and ethyl acetate in required ratios, to obtain the title compounds.

*4.1.6.1. 4-{2-[(5-Phenyl-4H-1,2,4-triazol-3-yl)thio]ethoxy}benzaldehyde (**8a**).* Yield 66%; colorless crystalline solid (chloroform); m.p. 94–96 °C; IR (KBr) υ cm^{-1}, 3201, 2846, 1670, 1599; ^1H NMR

(300 MHz, $CDCl_3$) δ: 3.55 (t, $J = 6.3$ Hz, 2H, SCH_2), 4.40 (t, $J = 6.3$ Hz, 2H, OCH_2), 7.05 (d, $J = 8.1$ Hz, 2H, H3″, H5″, Ar–H), 7.43 (m, 3H, H3′, H4′, H5′, Ar–H), 7.78 (d, $J = 8.1$ Hz, 2H, H2′, H6′, Ar–H), 7.98 (m, 2H, H2″, H6″, Ar–H), 12.40 (s, br, 1H, NH, D_2O exchangeable), 9.84 (s, 1H, CHO); Anal. calcd. for $C_{17}H_{15}N_3O_2S$, %: C, 62.75; H, 4.65; N, 12.91; Found, %: C, 62.63; H, 4.79; N, 13.18.

*4.1.6.2. 4-{2-[(5-Benzyl-4H-1,2,4-triazol-3-yl)thio]ethoxy}benzaldehyde (**8b**).* Yield 64% colorless crystalline solid (chloroform); m.p. 84–86 °C; IR (KBr) υ cm^{-1} 3137, 2800, 1694, 1602; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.45 (t, $J = 6.6$ Hz, 2H, SCH_2), 4.15 (s, 2H, CH_2), 4.33 (t, $J = 6.6$ Hz, 2H, OCH_2), 6.99 (d, $J = 8.4$ Hz, 2H, H3″, H5″, Ar-H), 7.23 (s, 5H, Ar-H), 7.76 (d, $J = 8.4$ Hz, 2H, H2″, H6″, Ar-H), 9.80 (s, 1H, CHO); Anal. cacd. for C_{18} H_{17} N_3 O_2 S, %: C, 63.70; H, 5.05; N, 12.38; Found, %: C, 63.55; H, 5.10; N, 12.45.

*4.1.6.3. 4-(2-{[5-(4-Methylphenyl)-4H-1,2,4-triazol-3-yl] thio} ethoxy) benzaldehyde (**8c**).* Yield 72%; colorless needles (3:1 chloroform + benzene); m.p. 108–110 °C; IR (KBr) υ cm^{-1} 3158, 2877, 1700, 1599; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.41 (s, 3H, CH_3), 3.67 (t, $J = 5.7$ Hz, 2H, SCH_2), 4.42 (t, $J = 5.7$ Hz, 2H, OCH_2), 7.01 (d, $J = 8.4$ Hz, 2H, H3′, H5′, Ar–H), 7.37 (d, $J = 8.1$ Hz, 2H, H3″, H5″, Ar–H), 7.77 (d, $J = 8.4$ Hz, 2H, H2′, H6′, Ar–H), 7.85 (d, $J = 8.1$ Hz, 2H, H2″, H6″, Ar–H), 9.74 (s, 1H, CHO); Anal. calcd. for $C_{18}H_{17}N_3O_2S$, %: C, 63.70; H, 5.05; N, 12.38; Found, %: C, 63.99; H, 5.12; N, 12.93.

*4.1.6.4. 4-(2-{[5-(4-Nitrophenyl)-4H-1,2,4-triazol-3-yl]thio}ethoxy) benzaldehyde (**8d**).* Yield 65%; yellow color solid (chloroform); m.p. 156–59 °C; IR (KBr) υ cm^{-1}, 2827, 1697, 1601; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.75 (t, $J = 6$ Hz, 2H, SCH_2), 4.51 (t, $J = 6$ Hz, 2H, OCH_2), 7.06–7.87 (m, 8H, Ar–H), 9.89 (s, 1H, CHO); Anal. calcd. for $C_{17}H_{14}N_4O_4S$, %: C, 55.13; H, 3.7; N, 15; Found, % : C, 55.26; H, 3.8; N, 14.8.

*4.1.6.5. 4-(2-{[5-(2-Nitrophenyl)-4H-1,2,4-triazol-3-yl]thio}ethoxy) benzaldehyde (**8e**).* Yield 72%; yellow color solid (chloroform); m.p. 148–54 °C; IR (KBr) υ cm^{-1} 2827, 1697, 1601; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.75 (t, $J = 6$ Hz, 2H, SCH_2), 4.51 (t, $J = 6$ Hz, 2H, OCH_2), 7.00–7.85 (m, 8H, Ar–H), 9.89 (s, 1H, CHO); Anal. calcd. for $C_{17}H_{14}N_4O_4S$, %: C, 55.13; H, 3.7; N, 15; Found, %: C, 55.26; H, 3.8; N, 14.8.

*4.1.6.6. 4-(2-{[5-(4-Chlorophenyl)-4H-1,2,4-triazol-3-yl]thio}ethoxy) benzaldehyde (**8f**).* Yield 70%; yellow color crystalline solid (chloroform); m.p. 124–29 °C; IR (KBr) υ cm^{-1}, 3201, 2846, 1670, 1599; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.55 (t, $J = 6.3$ Hz, 2H, SCH_2), 4.40 (t, $J = 6.3$ Hz, 2H, OCH_2), 7.05–7.85(m, 8H, Ar–H), 12.40 (s, br 1H, NH, D_2O exchangeable), 9.84 (s, 1H, CHO); Anal. calcd. for $C_{17}H_{14}N_3O_2SCl$, %: C, 62.96; H, 4.32; N, 12.96; Found, %: C, 63.20; H, 4.29; N, 13.08.

*4.1.6.7. 4-(2-{[5-(4-Bromophenyl)-4H-1,2,4-triazol-3-yl]thio}ethoxy) benzaldehyde (**8g**).* Yield 65%; yellow color solid (chloroform); m.p. 134-39 °C; IR (KBr) υ cm^{-1} 2827, 1697, 1601; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.75 (t, $J = 6$ Hz, 2H, SCH_2), 4.51 (t, $J = 6$ Hz, 2H, OCH_2), 7.06–7.90(m, 8H, Ar–H), 9.89 (s, 1H, CHO); Anal. calcd. for $C_{17}H_{14}N_3O_2SBr$, %: C, 56.64; H, 3.84; N, 11.53; Found, %: C, 57.20; H, 4.04; N, 12.42.

*4.1.6.8. 4-(2-{[5-(4-Metoxyphenyl)-4H-1,2,4-triazol-3-yl]thio}ethoxy) benzaldehyde (**8h**).* Yield 70%; colorless needles (chloroform); m.p. 133–135 °C; IR (KBr) υ cm^{-1}, 3142, 1701, 1598; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.64 (t, $J = 5.7$ Hz, 2H, SCH_2), 3.87 (s, 3H, OCH_3), 4.41 (t, $J = 5.7$ Hz, 2H, OCH_2), 7.01 (d, $J = 8.4$ Hz, 2H, H3′, H5′, Ar–H), 7.01 (d, $J = 8.4$ Hz, 2H, H3″, H5″, Ar–H), 7.86 (d, $J = 8.4$ Hz, 2H, H2′, H6′, Ar–H), 7.86 (d, $J = 8.4$ Hz, 2H, H2″, H6″, Ar–H), 9.75 (s, 1H, CHO); Anal. calcd. for $C_{18}H_{17}N_3O_3S$, %: C, 60.83; H, 4.82; N, 11.82; Found, %: C, 60.75; H, 4.76; N, 11.70.

*4.1.7. Preparation of 5-(4-{2-[(5-aryl-4H-1,2,4-triazol-3-yl)thio] ethoxy}benzy lidene)-1,3-thiazolidine-2,4-dione (**10a**–**h**)*

The title compounds were prepared by procedure describe similar to **4**(**a**–**b**).

*4.1.7.1. 5-(4-{2-[(5-Phenyl-4H-1,2,4-triazol-3-yl)thio]ethoxy}benzylidene)-1,3-thiazolidine-2,4-dione (**10a**).* Yield 89%; pale yellow solid (DMF); m.p. 208–210 °C; IR (KBr) υ cm^{-1} 3249, 1751, 1692, 1594; ^1H NMR (300 MHz, C_6D_6+TFA) δ: 3.24 (t, $J = 5.1$ Hz, 2H, SCH_2), 3.94 (t, $J = 5.1$ Hz, 2H, OCH_2), 6.78 (d, $J = 8.4$ Hz, 2H, H3″, H5″, Ar–H), 7.22–7.30 (m, 5H, Ar–H), 7.61 (d, $J = 8.4$ Hz, 2H, H2″, H6″, Ar–H), 7.73 (s, 1H, vinylic proton); ^{13}C NMR (75 MHz, C_6D_6+TFA) δ: 32.1 (SCH_2), 66.4 (OCH_2), 109.2, 113.2, 115.61, 116.8, 119.3, 120.6, 126.3, 127.2, 130.1, 133.2, 134.9, 160.7, 169.7(C=O, C_4, thiazolidine) and 172.1(C=O, C_2, thiazolidine); Anal. calcd. for $C_{20}H_{16}N_4O_3S_2$, %: C, 56.59; H, 3.80; N, 13.20; Found, %: C, 56.52; H, 3.73; N, 13.25; Mass, *m*/*z* (%) M+1, 425 (100).

*4.1.7.2. 5-(4-{2-[(5-Benzyl-4H-1,2,4-triazol-3-yl)thio]ethoxy}benzylidene)-1,3-thiazolidine-2,4-dione (**10b**).* Yield 90%; pale yellow solid (DMF); m.p. 282–284 °C; IR(KBr) υ cm^{-1} 3125, 1737, 1691, 1593; ^1H NMR (300 MHz, C_6D_6+TFA) δ: 3.07 (t, $J = 5.1$ Hz, 2H, SCH_2), 3.77 (t, $J = 5.1$ Hz, 2H, OCH_2), 4.07 (s, 2H, CH_2), 6.65 (d, $J = 8.4$ Hz, 2H, H3″, H5″, Ar–H), 7.18–7.60 (m, 7H, Ar–H), 7.71 (s, 1H, vinylic proton); ^{13}C NMR (75 MHz, C_6D_6+TFA) δ: 30.7 (SCH_2), 31.8 (CH_2), 66.2 (OCH_2), 109.2, 113.0, 115.5, 116.8, 120.5, 126.2, 129.3, 129.9, 130.2, 133.2, 154.8, 169.5 (C=O, C_4, thiazolidine) and 172.1 (C=O, C_2, thiazolidine); Anal. calcd. for $C_{21}H_{18}N_4O_3S_2$, %: C, 57.52; H, 4.14; N, 12.78; Found, %: C, 57.45; H, 4.09; N, 12.84.

*4.1.7.3. 5-[4-(2-{[5-(4-Methylphenyl)-4H-1,2,4-triazol-3-yl]thio}ethoxy) benzylidene]-1,3-thiazolidine-2,4-dione (**10c**).* Yield 93%; pale yellow granules (DMF); m.p. 218–220 °C; IR (KBr) υ cm^{-1} 3245, 1754, 1692, 1593; ^1H NMR (300 MHz, C_6D_6+TFA) δ: 2.27 (s, 3H, CH_3), 3.33 (t, $J = 5.1$ Hz, 2H, SCH_2), 4.04 (t, $J = 5.1$ Hz, 2H, OCH_2), 6.85 (d, $J = 8.7$ Hz, 2H, H3′, H5′, Ar–H), 7.25 (d, $J = 8.1$ Hz, 2H, H3″, H5″, Ar–H), 7.29 (d, $J = 8.7$ Hz, 2H, H2′, H6′, Ar–H), 7.56 (d, $J = 8.1$ Hz, 2H, H2″, H6″, Ar–H), 7.79 (s, 1H, vinylic proton); ^{13}C NMR (75 MHz, C_6D_6+TFA) δ: 20.8 (CH_3), 31.9 (SCH_2), 66.3 (OCH_2), 109.2, 113.0, 115.6, 116.7, 120.5, 127.2, 130.9, 133.3, 138.4, 147.2, 154.3, 160.9, 169.6 (C=O, C_4, thiazolidine) and 172.5 (C=O, C_2, thiazolidine); Anal. calcd. for $C_{21}H_{18}N_4O_3S_2$, %: C, 57.52; H, 4.14; N, 12.78; Found, %: C, 57.61; H, 4.05; N, 13.14.

*4.1.7.4. 5-[4-(2-{[5-(4-Nitro-phenyl)-4H-1,2,4-triazol-3-yl]thio} ethoxy)benzylidene]-1,3-thiazolidine-2,4-dione (**10d**).* Yield 80%; pale yellow solid (DMF); m.p. 197–199 °C; IR (KBr) υ cm^{-1} 3143, 1738, 1686, 1588; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.33 (t, $J = 6$ Hz, 2H, SCH_2), 4.02 (t, $J = 6$ Hz, 2H, OCH_2), 6.82–7.86(m, 8H, Ar–H), 7.76 (s, 1H, vinylic proton); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.0 (SCH_2), 65.8 (OCH_2), 109.4, 113.1, 115.5, 116.9, 118.1, 119.7, 120.7, 126.1, 129.7, 113.3, 134.7, 138.1, 169.6 (C=O, C_4, thiazolidine) and 172.0 (C=O, C_2, thiazolidine); Anal. calcd. for $C_{20}H_{15}N_5O_5S_2$, %: C, 51.17; H, 3.19; N, 14.92; Found, %: C, 52.14; H, 3.42; N, 15.32.

*4.1.7.5. 5-[4-(2-{[5-(2-Nitro-phenyl)-4H-1,2,4-triazol-3-yl]thio}ethoxy) benzylidene]-1,3-thiazolidine-2,4-dione (**10e**).* Yield 72%; pale yellow color solid (DMF); m.p. 229–32 °C; IR (KBr) υ cm^{-1} 3143, 1738, 1686, 1588; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.33 (t, $J = 6$ Hz, 2H, SCH_2), 4.02 (t, $J = 6$ Hz, 2H, OCH_2), 6.82–7.70 (m, 8H, Ar–H), 7.76 (s, 1H, vinylic proton); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.0 (SCH_2), 65.8 (OCH_2), 109.4, 113.1, 115.5, 116.9, 118.1, 119.7, 120.7, 126.1, 129.7, 113.3, 134.7, 138.1,

169.6 (C=O, C_4, thiazolidine) and 172.0 (C=O, C_2, thiazolidine); Anal. calcd. for $C_{20}H_{15}N_5O_5S_2$, %: C, 51.17; H, 3.19; N, 14.92; Found, %: C, 51.97; H, 4.08; N, 15.12.

*4.1.7.6. 5-[4-(2-{[5-(4-Chloro-phenyl)-4H-1,2,4-triazol-3-yl]thio}ethoxy)benzylidene]-1,3-thiazolidine-2,4-dione (**10f**).* Yield 89%; pale yellow solid (DMF); m.p. 186–188 °C; IR (KBr) υ cm^{-1} 3249, 1751, 1692, 1594; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.24 (t, J = 5.1 Hz, 2H, SCH_2), 3.94 (t, J = 5.1 Hz, 2H, OCH_2), 6.78–7.70 (m, 8H, Ar–H), 7.73 (s, 1H, vinylic proton); ^{13}C NMR (75 MHz, C_6D_6+TFA) δ: 32.1 (SCH_2), 66.4 (OCH_2), 109.2, 113.2, 115.61, 116.8, 119.3, 120.6, 126.3, 127.2, 130.1, 133.2, 134.9, 160.7, 169.7(C=O, C_4, thiazolidine) and 172.1(C=O, C_2, thiazolidine); Anal. calcd. for $C_{20}H_{15}N_4O_3S_2Cl$, %: C, 56.20; H, 3.5; N, 13.11; Found, %: C, 56.62; H, 3.92; N, 12.98.

*4.1.7.7. 5-[4-(2-{[5-(4-Bromo-phenyl)-4H-1,2,4-triazol-3-yl]thio}ethoxy)benzylidene]-1,3-thiazolidine-2,4-dione (**10g**).* Yield 72%; pale yellow color solid (DMF); m.p. 232–235 °C; IR (KBr) υ cm^{-1} 3143, 1738, 1686, 1588; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.33 (t, J = 6 Hz, 2H, SCH_2), 4.02 (t, J = 6 Hz, 2H, OCH_2), 6.82–7.75 (m, 8H, Ar–H), 7.76 (s, 1H, vinylic proton); ^{13}C NMR (75 MHz, $CDCl_3$+TFA) δ: 32.0 (SCH_2), 65.8 (OCH_2), 109.4, 113.1, 115.5, 116.9, 118.1, 119.7, 120.7, 126.1, 129.7, 113.3, 134.7, 138.1, 169.6 (C=O, C_4, thiazolidine) and 172.0 (C=O, C_2, thiazolidine); Anal. calcd. for $C_{20}H_{15}N_4O_3S_2Br$, %: C, 51.83; H, 3.23; N, 12.09; Found, %: C, 52.1; H, 3.46; N, 11.96.

*4.1.7.8. 5-[4-(2-{[5-(4-Methoxyphenyl)-4H-1,2,4-triazol-3-yl]thio}ethoxy)benzylidene]-1,3-thiazolidine-2,4-dione (**10h**).* Yield 93%; pale yellow solid (DMF); m.p. 226–228 °C; IR (KBr) υcm^{-1} 3131, 1740, 1686, 1596; ^1H NMR (300 MHz, C_6D_6+TFA) δ: 3.34 (t, J = 5.1 Hz, 2H, SCH_2), 3.60 (s, 3H, OCH_3), 4.06 (t, J = 5.1 Hz, 2H, OCH_2), 6.86 (d, J = 8.4 Hz, 2H, H3′, H5′, Ar-H), 7.00 (d, J = 8.7 Hz, 2H, H3″, H5″, Ar-H), 7.29 (d, J = 8.4 Hz, 2H, H2′, H6′, Ar-H), 7.64 (d, J = 8.7 Hz, 2H, H2″, H6″, phenyl), 7.79 (s, 1H, vinylic proton); ^{13}C NMR (75 MHz, C_6D_6+TFA) δ: 31.8 (OCH_3), 55.3 (SCH_2), 66.2 (OCH_2), 109.3, 113.0, 115.6, 115.8, 116.8, 120.6, 129.4, 133.3, 138.4, 153.8, 160.5, 165.1, 169.6 (C=O, C_4, thiazolidine) and 172.7 (C=O, C_2, thiazolidine); Anal. calcd. for $C_{21}H_{18}N_4O_4S_2$, %: C, 55.49; H, 3.99; N, 12.33; Found, %: C, 55.71; H, 4.31; N, 12.61; Mass, m/z (%) M+1, 455 (100).

*4.1.8. Preparation of 5-aryl-1,3,4-oxadiazole-2(3H)-thione **6**(**a**–**d**)*

The required 5-aryl-1,3,4-oxadiazole-2(3*H*)-thione were prepared by refluxing Acid hydrazide in ethanolic potassium hydroxide solution and carbon disulfide according to previously described method [14–16].

*4.1.9. Preparation of 4-{2[(5-aryl-1,3,4–oxadiazol-2-yl)thio] ethoxy}benzaldehyde (**9a**–**d**)*

The title compounds were prepared by procedure describe similar to **8**(**a**–**h**).

*4.1.9.1. 4-{2-[(5-Phenyl-1,3,4-oxadiazol-2-yl)thio]ethoxy}benzaldehyde (**9a**).* Yield 65%; colorless solid (1:1 hexane–ethyl acetate); m.p. 78–80 °C; IR (KBr) υ cm^{-1} 2827, 1697, 1601; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.75 (t, J = 6 Hz, 2H, SCH_2), 4.51 (t, J = 6 Hz, 2H, OCH_2), 7.06 (d, J = 8.7 Hz, 2H, H3″, H5″, Ar–H), 7.53 (m, 3H, H3′, H4′, H5′, Ar–H), 7.86 (d, J = 8.7 Hz, 2H, H2′, H6′, Ar–H), 8.02 (m, 2H, H2″, H6″, Ar–H), 9.89 (s, 1H, CHO); Anal. calcd. for $C_{17}H_{14}N_2O_2S_2$, %: C, 59.63; H, 4.12; N, 8.18; Found, %: C, 59.89; H, 4.05; N, 8.62.

*4.1.9.2. 4-{2-[(5-Benzyl-1,3,4-oxadiazole-2-yl)thio]ethoxy}benzaldehyde (**9b**).* Yield 65% colorless semisolid; IR (CCl_4) υ cm^{-1} 2830, 1693, 1600; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.69 (t, J = 6.3 Hz, 2H, SCH_2), 4.39 (t, J = 6.3 Hz, 2H, OCH_2), 4.41(s, 2H, CH_2), 6.97–8.01 (m, 9H, Ar–H), 9.87 (s, 1H, CHO); Anal. calcd. for $C_{18}H_{16}N_2O_3S$: C, 63.51%; H, 4.74%; N, 8.23%; Found: C, 63.75%; H, 4.71%; N, 8.28%.

*4.1.9.3. 4-{2-[(5-Pyridin-3-yl-1,3,4-oxadiazol-2-yl)thio]ethoxy}benzaldehyde (**9c**).* Yield 71%; colorless solid (2:1 chloroform + ethyl acetate); m.p. 62–64 °C; IR (KBr) υ cm^{-1} 2485, 1698, 1601; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.72 (t, J = 6 Hz, 2H, SCH_2), 4.50 (t, J = 6 Hz, 2H, OCH_2), 7.30 (d, J = 8.4 Hz, 2H, H3″, H5″, Ar–H), 7.45 (dd, J_{H4H5} = 8.1 Hz, J_{H5H6} = 8.5 Hz, 1H, H5′, pyridine), 7.52 (d, J = 8.4 Hz, 2H, H2″, H6″, Ar–H), 8.25 (d, J = 8.1 Hz, 1H, H4′, pyridine), 8.75 (d, J = 8.5 Hz, 1H, H6′, pyridine), 9.19 (s, 1H, H2′, pyridine), 9.87(s, 1H, CHO); Anal. calcd. for $C_{16}H_{13}N_3O_2S_2$, %: C, 55.96; H, 3.82, N, 12.24; Found, %: C, 55.92; H, 3.79, N, 12.86.

*4.1.9.4. 4-{2-[(5-Pyridin-4-yl-1,3,4-oxadiazol-2-yl)thio]ethoxy}benzaldehyde (**9d**).* Yield 68%; colorless solid (1:1 hexane–ethyl acetate); m.p. 66–68 °C; IR (KBr) υ cm^{-1} 2844, 1692, 1600; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.77 (t, J = 6 Hz, 2H, SCH_2), 4.50 (t, J = 6 Hz, 2H, OCH_2), 7.02(d, J = 8.7 Hz, 2H, H3″, H5″, Ar–H), 7.82 (d, J = 8.7 Hz, 2H, H3′, H5′, pyridine), 7.85(d, J = 8.7 Hz, 2H, H2″, H6″, Ar–H), 8.81 (d, J = 8.7 Hz, 2H, H2′, H6′, pyridine), 9.86 (s, 1H, CHO); Anal. calcd. for $C_{16}H_{13}N_3O_2S_2$, %: C, 55.96; H, 3.82, N, 12.24; Found, %: C, 55.91; H, 3.89, N, 12.39.

*4.1.10. 5-(4-{2-[(5-Aryl-1,3,4-oxadiazol-2-yl)thio]ethoxy} benzylidene)-1,3-thiazolidine-2,4-dione (**11a**–**d**)*

The title compounds were prepared by procedure describe similar to **4**(**a**–**b**).

*4.1.10.1. 5-(4-{2-[(5-Phenyl-1,3,4-oxadiazol-2-yl)thio]ethoxy}benzylidene)-1,3-thiazolidine-2,4-dione (**11a**).* Yield 91%; pale yellow solid (DMF); m.p. 202–214 °C; IR (KBr) υ cm^{-1} 3143, 1738, 1686, 1588; ^1H NMR (300 MHz, $CDCl_3$+TFA) δ: 3.33 (t, J = 6 Hz, 2H, SCH_2), 4.02 (t, J = 6 Hz, 2H, OCH_2), 6.82 (d, J = 9 Hz, 2H, H3″, H5″, Ar–H), 7.29–7.32 (m, 5H, Ar–H), 7.73 (d, J = 9 Hz, 2H, H2″, H6″, Ar–H), 7.76 (s, 1H, vinylic proton); ^{13}C NMR (75 MHz, $CDCl_3$+TFA) δ: 32.0 (SCH_2), 65.8 (OCH_2), 109.4, 113.1, 115.5, 116.9, 118.1, 119.7, 120.7, 126.1, 129.7, 113.3, 134.7, 138.1, 169.6 (C=O, C_4, thiazolidine) and 172.0 (C=O, C_2, thiazolidine); Anal. calcd. for $C_{20}H_{15}N_3O_4S_2$, %: C, 56.46; H, 3.55; N, 9.88. Found, %: C, 56.25; H, 3.47; N, 10.00.

*4.1.10.2. 5-(4-{2-[(5-Benzyl-1,3,4-thiadiazol-2-yl)thio]ethoxy}benzylidene)-1,3-thiazolidine-2,4-dione (**11b**).* Yield 77%; pale yellow solid (DMF); m.p. 258–260 °C; IR (KBr) υ cm^{-1} 3147, 1736, 1697, 1592; ^1H NMR (300 MHz, $CDCl_3$ + TFA) δ: 3.71 (t, J = 5.4 Hz, 2H, SCH_2), 4.39 (t, J = 5.4 Hz, 2H, OCH_2), 4.48 (s, 2H, CH_2), 6.94–7.56 (m, 9H, Ar–H), 7.97 (s, 1H, vinylic proton); Anal. calcd. for $C_{21}H_{17}N_3O_4S_2$, %: C, 57.39; H, 3.90; N, 9.56; Found, %: C, 57.65; H, 3.77; N, 9.64, Mass, m/z (%) M+1, 456 (100).

*4.1.10.3. 5-(4-{2-[(5-Pyridin-3-yl-1,3,4-oxadiazol-2-yl)thio]ethoxy} benzylidene)-1,3-thiazoli dine-2,4-dione (**11c**).* Yield 89%; pale yellow granules (DMF); m.p. 246–248 °C; IR (KBr) υ cm^{-1} 3153, 1736, 1701, 1597; ^1H NMR (300 MHz, $CDCl_3$+TFA) δ: 3.83 (t, J = 5.1 Hz, 2H, SCH_2), 4.99 (t, J = 5.1 Hz, 2H, OCH_2), 7.04 (d, J = 8.7 Hz, 2H, H3″, H5″, Ar–H), 7.47 (d, J = 8.7 Hz, 2H, H2″, H6″, Ar–H), 7.91 (s, 1H, vinylic proton), 8.29 (dd, J_{H4H5} = 6 Hz, J_{H5H6} = 6.3 Hz, 1H, H5′, pyridine), 9.16 (d, J = 6 Hz, 1H, H4′, pyridine), 9.19 (d, J = 6 Hz, 1H, H6′, pyridine), 9.56 (s, 1H, H2′, pyridine); ^{13}C NMR (75 MHz, $CDCl_3$+TFA) δ: 32.2 (SCH_2), 66.0 (OCH_2), 109.1, 112.9, 115.8, 116.6, 118.3, 124.1, 126.2, 133.4, 138.2, 140.2, 144.2, 144.5, 169.7 (C=O, C_4, thiazolidine) and 171.6 (C=O, C_2, thiazolidine); Anal. calcd. for C_{19} $H_{14}N_4O_4S_2$, %: C, 53.51; H, 3.31; N, 13.14; Found, %: C, 53.39; H, 3.39; N, 13.51.

*4.1.10.4. 5-(4-{2-[(5-Pyridin-4-yl-1,3,4-oxadiazol-2-yl)thio]ethoxy} benzylidene)-1,3-thiazoli dine-2,4-dione (**11d**).* Yield 92%; yellow solid(DMF); m.p. 268–270 °C; IR(KBr) υ cm^{-1} 3142, 1738, 1686, 1589; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.87 (t, J = 5.7 Hz, 2H, SCH_2), 4.51 (t, J = 5.7 Hz, 2H, OCH_2), 7.05 (d, J = 8.1 Hz, 2H, H3″, H5″, Ar–H), 7.49 (d, J = 8.1 Hz, 2H, H2″, H6″, Ar–H), 7.92 (s, 1H, vinylic proton), 8.62 (d, J = 5.1 Hz, 2H, H3′, H5′, pyridine), 9.10 (d, J = 5.1 Hz, 2H, H2′, H6′, pyridine); ^{13}C NMR (75 M Hz, $CDCl_3$+TFA) δ: 31.0 (SCH_2), 66.0 (OCH_2), 113.1, 115.9, 116.9, 118.7, 120.7, 124.2, 126.3, 133.3, 137.5, 139.3, 143.6, 160.9, 169.6 (C═O, C_4, thiazolidine) and 170.6 (C═O, C_2, thiazolidine); Anal. calcd. for $C_{19}H_{14}N_4O_4$, %: C, 53.51; H, 3.31; N, 13.14; Found, %: C, 53.79; H, 3.44; N,13.55.

4.2. Pharmacology

4.2.1. Hypoglycemic and hypolipidemic activities

Male Wistar rats weighing 150–200 g were used for this study [26]. All animals were maintained under 12 h light and 12 h dark cycle at 25 ± 1 °C. All animals were given standard chow (National Institute of Nutrition, India) and water ad libitum. The experiments were designed and conducted in accordance with the guidelines of institutional animal's ethics committee. The acclimatized animals were kept fasting for 24 h with water ad libitum and alloxan monohydrate (120 mg/kg i.p.) in normal saline was then administered. Serum glucose level was checked after 72 h. Animals with serum glucose levels >250 mg/dl were considered diabetic and were used for the study. The animals were divided in to two groups of six animals each. Group I animal was termed as control or untreated and group II animals was termed as treated. Group II animals were administered with compounds to be screened for euglycemic effect. The suspension of the compound was prepared in water with 1% carboxy methyl cellulose (CMC) as suspending agent. All the test compounds were orally administered at different doses (3, 10, 30, 100 mg/kg) for 15 days. Pioglitazone was used as standard drug. On the final day the blood samples were collected from the tail vein. Plasma was separated from whole blood of each group by centrifugation. Plasma glucose (PG) and triglyceride (TG) levels were estimated using commercial kits [27–29].

Acknowledgments

The authors thanks Karnatak University, Dharwad, University Grants Commission (UGC), New Delhi, India, for financial support [F.No: 36-138/2009 (SR)] and to the University Science Instruments Centre, Karnatak University, Dharwad, for providing the spectral data.

References

[1] I. Isseman, S. Green, Nature 347 (1990) 645–650.
[2] D.J. Mangelsdorf, R.M. Evans, Cell 83 (1995) 841–850.
[3] T.M. Willson, P.J. Brown, D.D. Sternbach, B.R. Henke, J. Med. Chem. 43 (2000) 527–550.
[4] I. Bogacka, H. Xie, G.A. Bray, S.R. Smith, Diabetes Care 27 (2004) 1660–1667.
[5] T.M. Willson, J.E. Cobb, D.J. Cowan, R.W. Wiethe, I.D. Correa, S.R. Prakash, K.D. Beck, L.B. Moore, S.A. Liewer, J.M. Lehmann, J. Med. Chem. 39 (1996) 665–668.
[6] V. Ribon, J.H. Johnson, H.S. Camp, A.R. Saltiel, Proc. Natl. Acad. Sci. U.S.A 95 (1998) 14751–14756.
[7] R.W. Nesto, D. Bell, R.O. Bonow, V. Fonseca, S.M. Grundy, E.S. Horton, M.L. Winter, D. Porte, C.F. Semenkovich, S. Smith, L.H. Young, R. Kahn, Diabetes Care 27 (2004) 256–263.
[8] H. Yki-Järvinen, N. Eng, J. Med. 351 (2004) 1106–1118.
[9] F.E. Hooper, T.B. Johnson, J. Am. Chem. Soc. 56 (1984) 484–485.
[10] W.S. Hinegardner, T.B. Johnson, J. Am. Chem. Soc. 52 (1930) 3742–3746.
[11] E. Hoggarth, J. Chem. Soc. (1949) 1163–1167.
[12] E. Hoggarth, J. Chem. Soc. (1949) 1918–1923.
[13] F. Kurzer, J. Chem. Soc. (1971) 2927–2931.
[14] E. Hoggarth, J. Chem. Soc. (1952) 4811–4817.
[15] R.W. Young, K.H. Wood, J. Am. Chem. Soc. 77 (1955) 400–403.
[16] C. Ainsworth, J. Am. Chem. Soc. 78 (1956) 4475–4478.
[17] R. Laudien, I. Yoshida, T. Nagamura, J. Chem. Soc. Perkin Trans. 2 (2002) 1772–1777.
[18] V. Patil, K. Tilekar, S. Mehendale-Munj, R. Mohan, C.S. Ramaa, Eur. J. Med. Chem. 45 (2010) 4539–4544.
[19] Y. Momose, K. Meguro, H. Ikeda, C. Hatanaka, S. Oi, T. Sohda, Chem. Pharm. Bull. 39 (6) (1991) 1440–1445.
[20] L.F.C. Costa Leite, R.H. Veras Mourao, M.C. Alves de Lima, S.L. Galdino, M.Z. Hernandes, F.A. Rocha Neves, S. Vidal, J. Barbe, I.R. Pitta, Eur. J. Med. Chem. 42 (2007) 1263–1271.
[21] V.L.M. Guarda, M.A. Pereira, C.A. De Simone, J.C. Albuquerque, S.L. Galdino, J. Chantegrel, M. Perrissin, C. Beney, F. Thomasson, I.R. Pitta, C. Luu-Duc, Sulfur Lett. 26 (2003) 17–27.
[22] S.F. Tan, K.P. Ang, Y.F. Fong, J. Chem. Soc. Perkin Trans. II (1986) 1941–1944.
[23] J.F.C. Albuquerque, A. Albuquerque, C.C. Azevedo, F. Thomasson, S.L. Galdino, J. Chantegrel, M.T.J. Catanho, I.R. Pitta, C. Luu-Duc, Pharmazie 50 (1995) 387–389.
[24] W. Heng, S. Tieu, Hautmann, K. Kuan, D.S. Pedersen, M. Pietsch, M. Gütschow, A.D. Abell, Bioorg. Med. Chem. 19 (2011) 7453–7463.
[25] T. Ishida, Y. In, M. Inoue, Y. Ueno, C. Tanaka, N. Hamanaka, 30 (1989) 959–962.
[26] R. Murugan, S. Anbazhagan, S.S. Narayanan, Eur. J. Med. Chem. 44 (2009) 3272–3279.
[27] A.St.G. Hugget, D.A. Nixon, The Lancet 270 (1957) 368–370.
[28] J.S. Annino, Clinical Chemistry: Principles and Procedures, fourth ed. Little Brown and Company, Boston, 1976, 184–188.
[29] C.S. Frings, T.W. Fendley, R.T. Dunn, C.A. Queen, Clin. Chem. 18 (1972) 673–674.