Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Medicinal Chemistry 39 (2004) 433–447
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
www.elsevier.com/locate/ejmech

Original article

Synthesis and biological activity of novel substituted pyridines and purines containing 2,4-thiazolidinedione

Bok Young Kim [a], Joong Bok Ahn [a], Hong Woo Lee [a,*], Sung Kwon Kang [a], Jung Hwa Lee [a], Jae Soo Shin [a], Soon Kil Ahn [a], Chung Il Hong [a], Seung Soo Yoon [b,*]

[a] *New Drug Research Laboratories, Chong Kun Dang Research Institute, Cheonan P.O. Box 74, Cheonan 330-831, South Korea*
[b] *Department of Chemistry, Sung Kyun Kwan University, Natural Science Campus, Suwon 440-764, South Korea*

Received 17 October 2003; received in revised form 2 February 2004; accepted 1 March 2004

Abstract

A series of substituted pyridines and purines containing 2,4-thiazolidinedione were designed and synthesized from their corresponding pyridines and purines. These synthesized compounds (entry no. **6a–d, 12a–e, 18a–d, 23a–c**) were evaluated for their effect on triglyceride accumulation in 3T3-L1 cells in vitro and their hypoglycemic and hypolipidemic activity in the genetically diabetic KKA^{y} mice in vivo. On the basis of their biological activities, 5-(4-{2-[*N*-methyl-(5-phenyl-pyridin-2-yl)amino]ethoxy}benzyl)thiazolidine-2,4-dione (**6d**) was selected as a candidate for further pharmacological studies.

Keywords: Substituted pyridines and purines containing 2,4-thiazolidinedione; 5-(4-{2-[*N*-methyl-(5-phenyl-pyridin-2-yl)amino]ethoxy}benzyl)thiazolidine-2,4-dione; Triglyceride accumulation; Hypoglycemic activity; Hypolipidemic activity

1. Introduction

Type 2 diabetes (non-insulin dependent diabetes mellitus; NIDDM) is characterized by high level of blood glucose and insulin and impaired insulin action [1]. Treatment for type 2 diabetes is currently performed with a combination of exercise and restriction of calorie in-take [2] or drug therapy. The most commonly used oral hypoglycemics for the disease are sulfonylurea drugs. These agents, however, induce serious hypoglycemia [3] and exhibit primary or secondary failure, which is presumably due to their characteristics as insulin secretagogues. Thus, use of the non-sulfonylurea class of hypoglycemics, which do not increase insulin secretion but enhance the action of insulin (insulin sensitizer), is required [4]. In recent years, the treatment of type 2 diabetes has been revolutionized with the advent of thiazolidinedione (TZD) class of molecules that ameliorate insulin resistance and thereby normalize elevated blood glucose, lipid, and insulin levels in rodent models of Type 2 diabetes and obesity [5–8], and recent clinical data support their efficacy in obese diabetic patients [9]. In the mid-1990s, the molecular target of TZD's moiety was reported to be the peroxisome proliferator activated receptor gamma (PPARγ). Although their exact mechanism of action has not been completely elucidated, it has been demonstrated that TZD's structure elicit its pharmacological actions by binding and activating nuclear receptor PPARγ. The PPARγ are a group of nuclear receptors that act as transcription factor which play a major role in the regulation of lipid metabolism and storage [10–12]. The first TZD's drug, troglitazone (Rezulin), was marketed in 1995, was withdrawn due to severe toxicity [13,14]. It was reported that troglitazone's toxicity had been associated with enterohepatic circulation of a metabolite, quinone moiety [15–17]. Between 1997 and 1999, two new TZD's drugs, pioglitazone **A** (Actos) [18] and rosiglitazone **B** (Avandia) [19] were approved by the FDA for the treatment of Type 2 diabetes (Fig. 1). To date, a large number of compounds containing TZD's moiety or without containing TZD's have been synthesized and clinical studies [20–26]. Recently, we reported the synthesis and anti-hyperglycemic activity of a novel erythrose, ribose and substituted pyrrolidine thiazolidinedione derivatives [27,28]. From the results, we found that substituted pyrrolidine compounds containing TZD's were more efficacious than a simple erythrose or ribose TZD's compounds. Therefore, in order to enhance glucose utiliza-

* Corresponding author.
E-mail address: hwlee@ckdpharm.com (H.W. Lee).

doi:10.1016/j.ejmech.2004.03.001

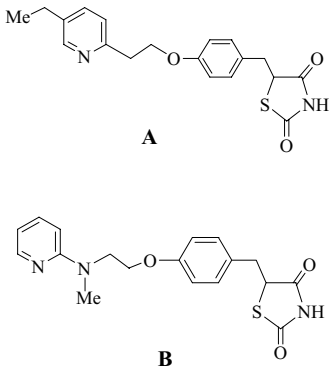

Fig. 1. Currently marketed TZD's anti-diabetic drugs.

tion properties, we focused our attention on the modification of marketed TZD's drugs. As a result, we describe in this paper the synthesis and biological activities of a novel substituted pyridines and purines TZD's compounds, and these compounds conceptually issued from substitution or cyclization in the pyridine moiety of rosiglitazone including incorporation of carbon or heteroatoms.

The novel substituted pyridine and purine analogues with TZD moiety (entry no. **6a–d, 12a–e, 18a–d, 23a–c**) and evaluated their effect on triglyceride accumulation in 3T3-L1 cells and their in vivo activity in KKA^y mice (Tables 1 and 2). Among the synthesized analogues, 5-[4-(2-{*N*-methyl-[5-phenyl-pyridin-2-yl]amino}ethoxy)benzyl]thiazolidine-2,4-dione (**6d**) showed the most excellent biological activity and is presently under further pharmacological studies.

Table 1
Effect on triglyceride accumulation in 3T3-L1 cells, cytotoxicity and safety index for the substituted pyridine and purine derivatives

Compound	Effect on TG accumulation in 3T3-L1 cells (EC_{50}μM) [a]	Cytotoxicity (TC_{25}μM) [b]	Safety index (TC_{25}/EC_{50})
6a	0.001	25	25000
6b	0.02	13	625
6c	0.009	27	3000
6d	0.00054	24	44444
12a	0.0097	55	5670
12b	0.009	50	5555
12c	0.0027	29	10740
12d	0.04	23	575
12e	0.025	18	720
18a	2.4	>200	83
18b	4.2	>200	47
18c	11	>200	18
18d	15	>200	13
23a	1.6	>200	121
23b	0.51	>200	392
23c	0.23	>200	869
Rosiglitazone	0.047	130	2766
Pioglitazone	0.15	200	1333

[a] Effective concentration for 50% enhancement of insulin-induced triglyceride accumulation in 3T3-L1 cells.

[b] Toxic concentration (TC_{25}) means increase 25% of neutral red uptake in cultured rat hepatocytes.

Table 2
Hypoglycemic and triglyceride lowering effect in KKA^y mice

Compound	ED_{25} [a] (mg/kg/day)	
	Blood glucose	Triglyceride
6a	0.056	25
6d	0.020	2.5
12c	0.084	15
Rosiglitazone	4.1	>30
Pioglitazone	8.1	30

[a] Effective doses for 25% decreases of blood glucose and triglyceride levels were estimated from the dose–response curves obtained with three doses.

2. Chemistry

Several novel substituted pyridines and purines with TZD's moiety were designed and prepared as follows. General strategies to synthesize novel thiazolidinediones are shown in Figs. 2–6. First of all, 4- or 5-position substituted pyridine derivatives having a thiazolidinedione moiety **6a–d** and **12a–e** were synthesized as depicted in Figs. 2 and 3. First, treatment of 5-amino-2-chloropyridine and 5-methylfurane, *N*-methylpyrrole, thiophene, or benzene in the presence of isoamyl nitrite and copper (I) oxide (Cu_2O) generated the several 5-position substituted pyridine compounds **2a–d**, which were converted to substituted aminoalcohol compounds **3a–d** by amination with 2-methylaminoethanol. Compounds **3a–d** were then reacted with 4-fluorobenzaldehyde in the presence of NaH in DMF to furnish benzaldehyde compounds **4a–d** in good yield. Knoevenagel's condensation [29] of benzaldehyde compounds **4a–d** with 2,4-thiazolidinedione in the presence of piperidine gave unsaturated thiazolidinedione analogues **5a–d**. The desired compounds **6a–d** were prepared by reduction with 20 wt.% $Pd(OH)_2$ on carbon (Pearlman's catalyst) under hydrogen atmosphere as depicted in Fig. 2.

The 4-position substituted pyridine derivatives containing thiazolidinedione **12a–e** were synthesized as shown in Fig. 3. Nucleophilic aromatic substitution of 4-nitro-2-chloropyridine **7** with methanol, isopropanol, phenol, aniline, or thiophenol containing sodium hydride gave the 4-position substituted 2-chloropyridines **8a–e**, respectively, which were transformed into aminoalcohol compounds **9a–e** by amination of *N*-methylaminoethanol under reflux condition. Compounds **9a–e** were reacted with 4-fluorobenzaldehyde in the presence of base to give compounds **10a–e**.

Preparation of the desired 4-position substituted pyridine derivatives containing TZD's **12a–e** was obtained via catalytic hydrogenation with 20 wt.% $Pd(OH)_2$ under hydrogen atmosphere from compounds **11a–e**, which were converted by the Knoevenagel's condition of compounds **10a–e** with 2,4-thiazolidinedione as shown in Fig. 3.

The reaction of 6-chloropurine **13** and methyl bromoacetate in the presence of *tetra*-butylammonium iodide as a catalyst yielded the methyl ester compound **14**, which was converted into the corresponding substituted purine ester compounds **15a–d** by using methanol, phenol, aniline, or

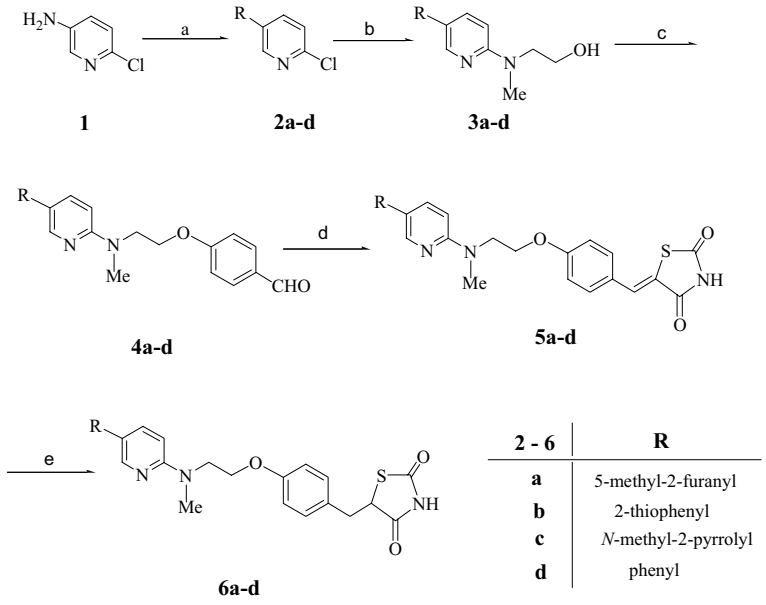

Fig. 2. (a) RH, isoamyl nitrite, Cu_2O, reflux, 10 h; (b) 2-methylaminoethanol, reflux, 24 h; (c) 4-fluorobenzaldehyde, NaH, DMF, rt, 5 h; (d) 2,4-thiazolidinedione, piperidine, EtOH, reflux, 24 h; (e) 20% $Pd(OH)_2$, H_2, rt, 36 h.

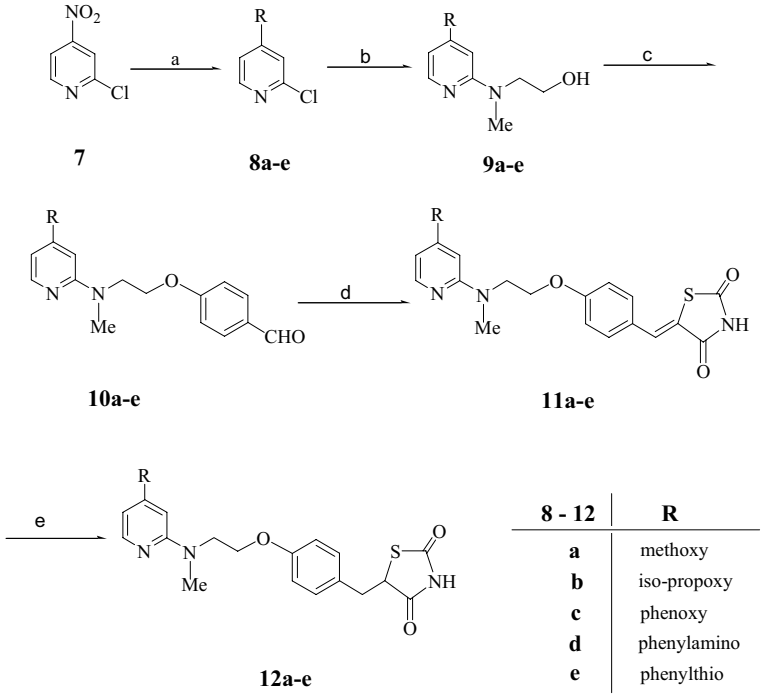

Fig. 3. (a) RH, NaH, DMF, rt, 24 h; (b) 2-methylaminoethanol, reflux, 24 h; (c) 4-fluorobenzaldehyde, NaH, DMF, rt, 6 h; (d) 2,4-thiazolidinedione, piperidine, EtOH, reflux, 24 h; (e) 20% $Pd(OH)_2$, H_2, rt, 36 h.

thiophenol in the presence of sodium hydride. The formation of 6-substituted purines containing benzyl thiazolidinedione **18a–d** was carried out as follows; reduction of compounds **15a–d** with DIBAL-H gave corresponding compounds **16a–d**, *O*-arylation of compounds **16a–d** with 4-fluorobenzaldehyde produced the benzaldehyde compounds **17a–d**. Preparation of the desired 6-position substituted purine derivatives containing thiazolidinedione moiety **18a–d** was obtained via the Knoevenagel's condition of compounds **17a–d** with 2,4-thiazolidinedione and catalytic hydrogenation with 20 wt.% $Pd(OH)_2$ under hydrogen atmosphere as shown in Fig. 4. Finally, *N*-9-substituted purine thiazolidinedione derivatives **23a–c** were prepared by using the general procedure described in Fig. 5. *N*-methyl hydroxyethylamino purine compounds **20a–c** were synthesized via *N*-9 alkylation of 6-chloropurine **13** with iodomethane, 2-iodopropane, benzyl bromide, and by amination of compounds **19a–c** with *N*-methylaminoethanol. The desired compounds **23a–c** were prepared by *O*-arylation, Knoevenagel's reaction, and reduction, respectively (Fig. 5).

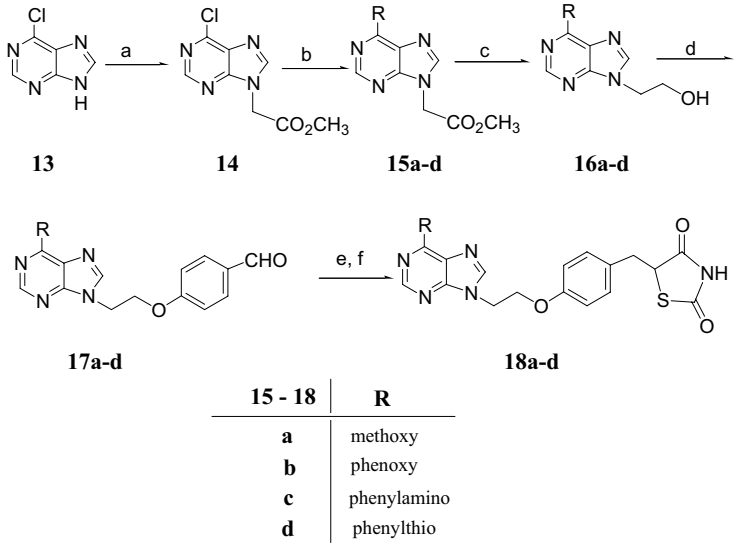

Fig. 4. (a) Methyl bromoacetate, NaH, *n*-Bu_4N^+I, DMF, rt, 6 h; (b) NaH, RH, reflux, 4 h; (c) DIBAL-H, CH_2Cl_2, 0 °C, 2 h; (d) 4-fluorobenzaldehyde, NaH, DMF, rt, 5 h; (e) 2,4-thiazolidinedione, piperidine, EtOH, reflux, 24 h; (f) 20% $Pd(OH)_2$, H_2, rt, 36 h.

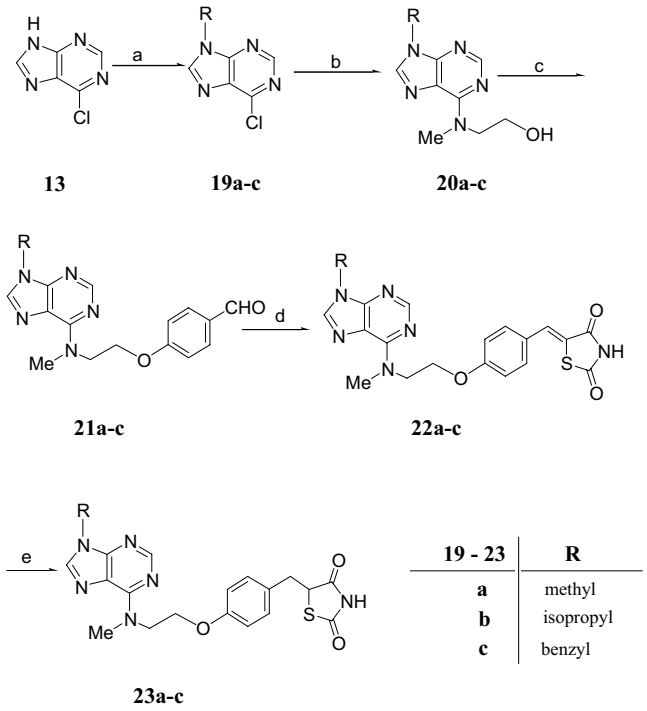

Fig. 5. (a) NaH, RI, DMF, rt to heat, 4 h; (b) 2-methylaminoethanol, EtOH reflux, 24 h; (c) 4-fluorobenzaldehyde, NaH, DMF, rt, 5 h; (d) 2,4-thiazolidinedione, piperidine, EtOH, reflux, 24 h; (f) 20% $Pd(OH)_2$, H_2, rt, 36 h.

3. Biology

Insulin-sensitizing activity was evaluated from the hypoglycemic and hypolipidemic activity in genetically diabetic KKA^y mice [30] and by the effect on insulin-regulated differentiation, which was monitored from the rate of triglyceride accumulation in 3T3-L1 cells [31]. In vitro cytotoxicity of the compounds was evaluated in cultured rat hepatocytes and neutral red uptake was used as a cytotoxicity end point [32,33]. Pioglitazone **A** and rosiglitazone **B** were synthesized in house by the reported procedure and used as reference compounds in our biological studies.

4. Results and discussion

In the case of rosiglitazone, derived from pioglitazone, modification of ethyl ether linkage containing nitrogen atom between the pyridine group and thiazolidinedione moiety has dramatically improved hypoglycemic activity compared to pioglitazone in ob/ob and db/db mice [19,35]. Considering

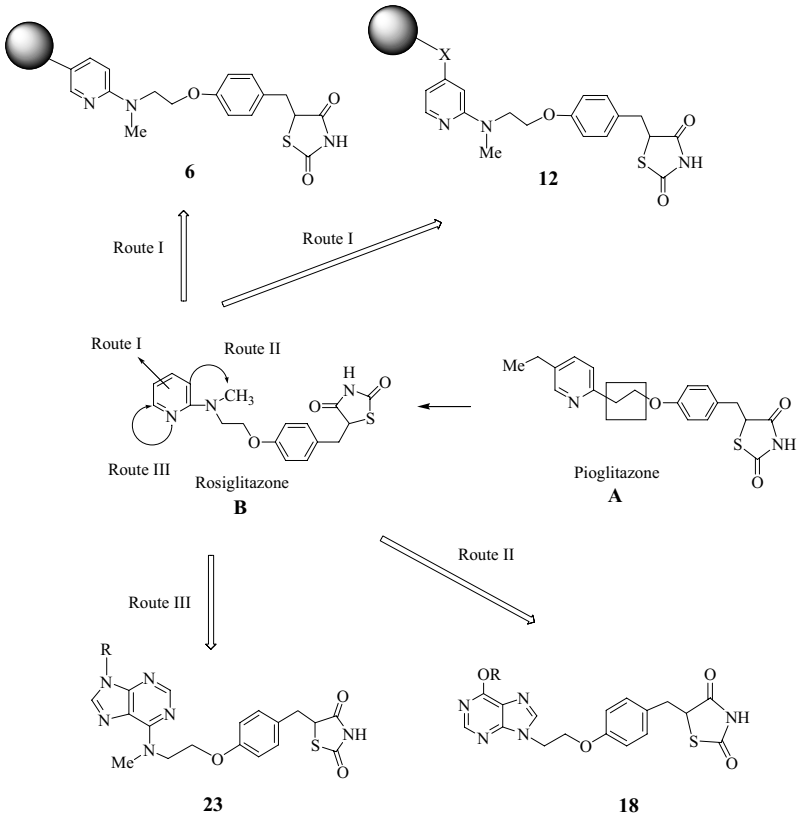

Fig. 6.

these results, we designed and synthesized substituted pyridine and purine derivatives with TZD's in order to increase hydrophobic properties as designed in Fig. 6. That is, these compounds, **6, 18**, and **23**, were designed by modification of rosiglitazone via routes **I, II** and **III**, respectively. All of them were synthesized and evaluated for their biological activities. First of all, in order to examine the effect of pharmacophore site, two differently oriented substituted pyridines with TZD's moiety **6a–d** and **12a–e** were synthesized and evaluated their biological activities. Almost substituted pyridine derivatives **6a–d** and **12a–e** showed a better triglyceride accumulation activity in 3T3-L1 cells than that of reference compounds (rosiglitazone and pioglitazone) (Table l). These results suggest that increased hydrophobicity and orientation of the substituent of the pyridine moiety showed a more potent activity in 3T3-L1 cells assay. Position of the substituent of pyridine derivatives containing TZD's was also considerably influenced for their activity. Although, the exact reason for relatively high triglyceride accumulation activity was not clear, 5-position substituted pyridine derivatives with TZD's, **6a, c**, and **d**, except for *N*-methyl pyrrolyl pyridine derivative **6b**, not only showed an excellent hypoglycemic activity but also had better safety index than 4-position substituted pyridine derivatives **12a–e**. Next, to explore the effect of lipophilicity of the substituent, 6-position substituted purine derivatives **18a–d** and 9-position substituted-9H-purines **23a–c** with a nitrogen-containing fused bicyclic ring system designed via routes II and III, respectively, were prepared, and evaluated for their triglyceride accumulation activity in 3T3-L1 cells as shown in Table 1. Almost 6-position substituted purines with TZD's **18a–d** dramatically reduced the activity than rosiglitazone but 9-position substituted-9H-purin-6-yl derivatives **23a–c** exhibited moderate triglyceride accumulation activity in 3T3-L1 cells (Table 1). From these results, compounds with TZD's **6a, 6d** and **12c**, were selected as primary candidates in order to examine the hypoglycemic and hypolipidemic activity in KKA^y mice [30] in vivo. Substituted pyridine derivatives **6a, 6d** and **12c** caused a 25% decrease of blood glucose in KKA^y mice at an oral dose of 0.056, 0.020, and 0.084 mg/kg/day, respectively, while reference compounds, rosiglitazone and pioglitazone, caused a 25% decrease of blood glucose at 4.1 and 8.1 mg/kg/day, respectively, as shown in Table 2. In particularly, 5-phenyl substituted pyridine compound **6d** exhibited an approximately 205-fold and 405-fold increase in hypoglycemic activity than rosiglitazone and pioglitazone, respectively (Table 2). In KKA^y mice, the oral hypolipidemic ED_{25}% values of **6a, 6d** and **12c** also were 25, 2.5 and 15 mg/kg/day, respectively, while ED_{25}% values of rosiglitazone and pioglitazone were >30, 30 mg/kg/day, respectively. The data reviewed herein indicate that the hypoglycemic and hypolipidemic activity of the compound **6d** was more potent than **6a** or **12c** and reference compounds.

5. Conclusion

In conclusion, on the basis of both triglyceride accumulation activity in 3T3-L1 cells and hypoglycemic and hypo-

lipidemic effect in KKA^y mice animal models, 5-(4-{2-[*N*-methyl-(5-phenyl-pyridin-2-yl)amino]ethoxy}benzyl)thiazolidine-2,4-dione (**6d**) showed more potent activity than the reference compounds (i.e. pioglitazone and rosiglitazone) in both in vitro and in vivo studies. Therefore, we have selected for further evaluation and are presently under further pharmacological studies.

6. Experimental

6.1. Chemistry

All reactions were conducted under anhydrous condition in solvents dried over molecular sieves type 4 Å under nitrogen atmosphere and performed using oven dried glassware. Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. IR spectra were recorded on a Bruker Vector 22 FT-IR spectrometer. NMR spectra were recorded on a Bruker DPX 400 MHz instrument operating at 400 MHz for proton and 100 MHz for carbon NMR and were performed in DMSO-d_6 solutions using tetramethylsilane as the internal reference except where indicated otherwise. The coupling constants (J) are reported in Hz. Mass spectra were recorded on a HP 5989B instrument. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh) according to the published procedure.

*6.1.1. Preparation of 2-chloro-5-(5-methylfuran-2-yl)pyridine (**2a**)*

General procedure: To a suspension of isoamyl nitrite (44.0 ml, 327.52 mmol) and copper (**I**) oxide (12.67 g, 88.52 mmol) in 2-methylfuran (40 ml, 483 mmol) was added 2-chloro-5-aminopyridine **1** (11.38 g, 88.52 mmol) over N_2 atmosphere, the resulting mixture was refluxed for 10 h. Insoluble materials were filtered away and the filtrate was concentrated by evaporation under reduced pressure. The concentrate thus obtained was purified by column chromatography through silica gel with *n*-hexane and ethyl acetate (5:1 to 9:1, v/v) as elution solvent to give the title compound **2a** as a yellowish foam (8.2 g, 48% yield), IR ($CHCl_3$) ν_{max} cm^{-1}: 2980, 2938, 1742, 1457. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.65 (m, 1H), 7.85 (m, 1H), 7.31 (m, 1H), 6.64 (m, 1H), 6.11 (m, 1H), 2.39 (s, 3H).

The following compounds **2b–d** were prepared by following above described procedure.

*6.1.2. Preparation of 2-chloro-5-(thiophen–2-yl)pyridine (**2b**)*

Yield: 4.6 g, 68%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2918, 1554, 1462, 1106. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.14 (m, 1H), 7.36 (m, 2H), 7.41 (m, 1H), 7.85 (m, 1H), 8.65 (m, 1H).

*6.1.3. Preparation of 2-chloro-5-(*N*-methylpyrrol-2-yl)pyridine (**2c**)*

Yield: 2.7 g, 52%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 2850, 1689, 1601. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.98 (s, 3H), 6.35 (m, 1H), 6.80 (m, 1H), 7.03 (m, 1H), 7.41 (m, 1H), 8.04 (m, 1H), 8.83 (m, 1H).

*6.1.4. Preparation of 2-chloro-5-(1-phenyl)pyridine (**2d**)*

Yield: 7.0 g, 47%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2923, 2850, 1455. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.41 (m, 2H), 7.52 (m, 2H), 7.58 (m, 2H), 7.87 (m, 1H), 8.63 (d, J = 2.6 Hz, 1H).

*6.1.5. Preparation of 2-{methyl-[5-(5-methylfuran-2-yl) pyridin-2-yl]amino}ethanol (**3a**)*

General procedure: The compound **2a** (700 mg, 3.69 mmol) was added *N*-methyl aminoethanol (30 ml), and the mixture was refluxed for 24 h. The reaction mixture was quenched with aqueous NH_4Cl (20 ml) and extracted with EtOAc (50 ml). The residue was washed with water and brine. The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo to leave a white foam which was purified by column chromatography on SiO_2 with CH_2Cl_2/MeOH (20:1, v/v) to give the title compound **3a** (900 mg, quantitative yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 3300, 2980, 2857, 1739, 1604. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 3.11 (s, 3H), 3.75 (m, 2H), 3.88 (m, 2H), 6.03 (m, 1H), 6.36 (m, 1H), 6.56 (m, 1H), 7.74 (m, 1H), 8.38 (m, 1H).

The following compounds **3b–d** were prepared by following above described procedure.

*6.1.6. Preparation of 2-{5-(thiophen-2-yl)pyridin-2-yl} amino}ethanol (**3b**)*

Yield: 1.2 g, 94%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3383, 2926, 1612, 1507, 1401. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.13 (s, 3H), 3.77 (m, 2H), 3.89 (m, 2H), 6.59 (m, 1H), 7.07 (m, 1H), 7.16 (m, 1H), 7.23 (m, 1H), 7.71 (m, 1H), 8.36 (m, 1H).

*6.1.7. Preparation of 2-{5-(*N*-methylpyrrol-2-yl) pyridin-2-yl}amino}ethanol (**3c**)*

Yield: 1.32 g, 90%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3362, 2925, 1597, 1506, 1396. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.17 (s, 3H), 3.81(m, 2H), 3.93 (m, 5H), 6.26 (m, 2H), 6.61(m, 2H), 6.87 (dd, J = 2.5 Hz, 3.0 Hz, 1H), 7.98 (m, 1H), 8.59 (d, J = 2.5 Hz, 1H).

*6.1.8. Preparation of 2-{5-(1-phenyl)pyridin-2-yl} amino}ethanol (**3d**)*

Yield: 1.64 g, 92%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3286, 2923, 1608, 1491. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.14 (s, 3H), 3.78 (m, 2H), 3.90 (m, 2H), 6.64 (d, J = 2.4 Hz, 1H), 7.32 (m, 1H), 7.42 (m, 2H), 7.51 (m, 2H), 7.75 (m, 1H), 8.34 (m, 1H).

*6.1.9. Preparation of 4-(2-{methyl-[5-methylfuran-2-yl] pyridin-2-yl}amino)ethoxy)-benzaldehyde (**4a**)*

General procedure: To a suspension of sodium hydride (60% in paraffin liquid, 240 mg, 5.91 mmol), in DMF (20 ml) was added compound **3a** (900 mg, 3.94 mmol), and 4-fluorobenzaldehyde (0.64 ml, 5.91 mmol) over N_2 atmosphere at room temperature. After stirring at the same temperature for 2 h, quenched with aqueous ammonium chloride

(10 ml), and the reaction mixture was poured into ice-water and extracted with EtOAc (100 ml). The extract was washed with water, brine, respectively, and dried ($MgSO_4$), and concentrated under reduced pressure. To leave a white foam which was purified by column chromatography on silica gel with *n*-hexane/EtOAc (5:1, v/v) to give the title compound **4a**. Yield: 840 mg, 68.4%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3058, 2984, 2935, 1739, 1701, 1596. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 3.20 (s, 3H), 4.06 (m, 2H), 4.31 (m, 2H), 6.04 (m, 1H), 6.37 (m, 1H), 6.54 (m, 1H), 7.02 (m, 2H), 7.72 (m, 1H), 7.83 (m, 2H), 8.47 (m, 1H), 9.89 (s, 1H).

The following compounds **4b–d** were prepared by following above described procedure.

*6.1.10. Preparation of 4-(2-{methyl-[5-(thiophen-2-yl) pyridin-2-yl]amino}ethoxy)-benzaldehyde (**4b**)*

Yield: 2.75 g, 66%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2932, 2738, 1688, 1602, 1503. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.20 (s, 3H), 4.06 (m, 2H), 4.32 (m, 2H), 6.57 (d, J = 8.48 Hz, 1H), 7.02–7.24 (m, 5H), 7.70 (m, 1H), 7.83 (m, 2H), 8.46 (m, 1H), 9.89 (s, 1H).

*6.1.11. Preparation of 4-(2-{methyl-[5-(*N*-methyl-pyrrol-2-yl)pyridin-2-yl]amino}-ethoxy)benzaldehyde (**4c**)*

Yield: 1.98 g, 83.2%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2940, 1684, 1595, 1506. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.26 (s, 3H), 3.95 (s, 3H), 4.13 (m, 2H), 4.36 (m, 2H), 6.28 (m, 1H), 6.62 (m, 2H), 6.87 (m, 1H), 7.03 (m, 2H), 7.83 (m, 2H), 7.99 (m, 1H), 8.69 (d, J = 2.5 Hz, 1H), 9.89 (s, 1H).

*6.1.12. Preparation of 4-(2-{methyl-[5-(1-phenyl) pyridin-2-yl]amino}ethoxy)-benzaldehyde (**4d**)*

Yield: 1.45 g, 92%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2921, 1692, 1601, 1490, 1394. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.22 (s, 3H), 4.09 (m, 2H), 4.35 (m, 2H), 6.65 (d, J = 2.5 Hz, 1H), 7.05 (m, 2H), 7.28 (m, 1H), 7.42 (m, 2H), 7.53 (m, 2H), 7.73 (m, 1H), 7.84 (m, 2H), 8.45 (d, J = 3.0 Hz, 1H), 9.89 (s, 1H).

*6.1.13. Preparation of 5-[4-(2-{methyl-[5-(5-methylfuran-2-yl)pyridin-2-yl]amino}-ethoxy)benzylidene]thiazolidine-2,4-dione (**5a**)*

General procedure: A mixture of aldehyde compound **4a** (7.93 g, 28.12 mmol), 2,4-thiazolidinedione (3.94 g, 33.74 mmol), piperidine (0.36 g, 4.2 mmol) in ethanol (80 ml) was refluxed for 24 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane, and washed with water (100 ml) and brine (200 ml), and dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was chromatography on SiO_2 with CH_2Cl_2/MeOH (10:1, v/v) to give the title compound **5a** as a yellowish solid (2.90 g, 42% yield). m.p.: 160–162 °C, IR ($CHCl_3$) ν_{max} cm^{-1}: 3446, 1751, 1700. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.29 (s, 3H), 3.09 (s, 3H), 3.94 (m, 2H), 4.23 (m, 2H), 6.11 (m, 1H), 6.55 (m, 1H), 6.70 (d, J = 9.2 Hz, 1H), 7.09 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.7 Hz, 2H), 7.73 (m, 2H), 8.37 (m, 1H).

The following compounds **5b–d** were synthesized by a similar procedure to that described for the preparation of **5a**.

*6.1.14. Preparation of 5-[4-(2-{methyl-[5-(thiophen-2-yl) pyridin-2-yl]amino}-ethoxy)benzylidene]thiazolidine-2,4-dione (**5b**)*

Yeld: 2.18 g, 53%. m.p.: 158–160 °C IR ($CHCl_3$) ν_{max} cm^{-1}: 2360, 1697, 1596, 1506. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.12 (s, 3H), 3.97 (m, 2H), 4.25 (m, 2H), 6.74 (d, J = 8.5 Hz, 2H), 7.10 (m, 3H), 7.33 (m, 1H), 7.41 (m, 1H), 7.54 (m, 2H), 7.72 (s, 1H), 7.79 (m, 1H), 8.40 (d, J = 4.0 Hz, 1H).

*6.1.15. Preparation of 5-[4-(2-{methyl-[5-(*N*-methyl-pyrrol-2-yl)pyridin-2-yl]-amino}ethoxy)benzylidene]thiazolidine-2,4-dione (**5c**)*

Yield: 1.96 g, 62%. m.p.: 162–164.5 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2924, 2854, 1737, 1698, 1595. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.26 (s, 3H), 3.88 (s, 3H), 4.03 (m, 2H), 4.29 (m, 2H), 6.28 (m, 1H), 6.46 (m, 1H) 6.82 (m, 1H), 7.11 (m, 3H), 7.53 (m, 2H), 7.73 (s, 1H), 7.99 (m, 1H), 8.55 (d, J = 2.5 Hz, 1H).

*6.1.16. Preparation of 5-[4-(2-{methyl-[5-(1-phenyl) pyridin-2-yl]amino}ethoxy)benzylidene]thiazolidine-2,4-dione (**5d**)*

Yield: 2.85 g, 74%. m.p.: 158–160 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 3350, 2980, 1741, 1700, 1594, 1509. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.22 (s, 3H), 4.09 (m, 2H), 4.32 (m, 2H), 6.65 (d, J = 2.5 Hz, 1H), 7.01 (d, J = 3.5 Hz, 2H), 7.28 (m, 1H), 7.44 (m, 3H), 7.53 (m, 2H), 7.74 (m, 1H), 7.80 (s, 1H), 8.45 (d, J = 4.5 Hz, 1H).

*6.1.17. Preparation of 5-[4-(2-{methyl-[5-(5-methylfuran-2-yl)pyridin-2-yl]amino}-ethoxy)benzyl]thiazolidine-2,4-dione (**6a**)*

General procedure: A stirred solution of **5a** (0.5 g, 0.82 mmol) in MeOH (15 ml) was added $Pd(OH)_2$ on carbon (10.5 g) under hydrogen atmosphere at room temperature for 72 h. After removal of the catalyst by filtration, the filtrate was concentrated in vacuo. The concentrate thus obtained was purified by column chromatography on SiO_2 with dichloromethane and methanol (20:1, v/v) to give the title compound **6a** as a pale yellowish solid (0.17 g, 78% yield). m.p.: 181–183 °C. IR (KBr) ν_{max} cm^{-1}: 2921, 1743, 1699, 1500. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.29 (s, 3H), 3.05 (m, 1H), 3.11 (s, 3H), 3.29 (m, 1H), 3.91 (m, 2H), 4.12 (m, 2H), 4.84 (m, 1H), 6.12 (d, J = 2.04 Hz, 1H), 6.56 (d, J = 2.05 Hz, 1H), 6.70 (d, J = 8.88 Hz, 1H), 6.87 (m, 2H), 7.10 (m, 2H), 7.72 (m, 1H), 8.38 (s, 1H), 11.99 (brs, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 13.8, 36.7, 37.5, 49.0, 53.4, 65.7, 104.3, 106.1, 108.2, 114.7, 115.9, 129.1, 130.8, 132.9, 143.2, 150.6, 150.8, 157.3, 157.9, 172.1, 176.1. MS (ESI) *m/z* (M+1) 438.

The following compounds **6b–d** were prepared by a similar procedure to that described for the preparation of **6a**.

*6.1.18. Preparation of 5-[4-(2-{methyl-[5-(thiophen-2-yl) pyridin-2-yl]amino}ethoxy)benzyl]thiazolidine-2,4-dione (**6b**)*

Yield: 0.92 g, 72%. m.p.: 165–166 °C. IR (KBr) ν_{max} cm^{-1}: 2924, 1750, 1697, 1605, 1507. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.04 (m, 1H), 3.11 (s, 3H), 3.29 (m, 1H), 3.93 (m, 2H), 4.13 (m, 2H), 4.85 (m, 1H), 6.72 (d, J = 2.5 Hz, 1H), 6.88 (d, J = 3.0 Hz, 2H), 7.08 (m, 1H), 7.11 (m, 2H), 7.32 (m, 1H), 7.40 (m, 1H), 7.76 (m, 1H), 8.40 (m, 1H), 11.99 (br s 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 36.6, 37.5, 49.1, 53.4, 65.7, 106.2, 114.7, 118.7, 122.1, 124.2, 128.7, 129.1, 130.8, 135.2, 141.5, 144.9, 157.7, 157.9, 172.1, 176.1. MS (ESI) *m/z* (M+1) 440.

*6.1.19. Preparation of 5-[4-(2-{methyl-[5-(N-methylpyrrol-2-yl)pyridin-2-yl]-amino}ethoxy)benzyl] thiazolidine-2,4-dione (**6c**)*

Yield: 1.42 g, 68%. m.p.: 167–170 °C. IR (KBr) ν_{max} cm^{-1}: 2923, 1750, 1698, 1596, 1510. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.97 (m, 1H), 3.19 (s, 3H), 3.29 (m, 1H), 3.86 (s, 3H), 3.99 (m, 2H), 4.16 (m, 2H), 4.85 (m, 1H), 6.21 (m, 1H), 6.45 (m, 1H), 6.82 (d, J = 9.6 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.13 (m, 3H), 7.94 (m, 1H), 8.55 (s, 1H), 11.99 (brs, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 33.2, 36.7, 37.8, 49.3, 53.5, 65.8, 98.3, 106.9, 109.8, 114.7, 126.6, 126.9, 129.2, 130.8, 140.9, 146.3, 147.5, 157.8, 158.8, 172.1, 176.2. MS (ESI) *m/z* (M+1) 437.

*6.1.20. Preparation of 5-[4-(2-{methyl-[5-(1-phenyl) pyridin-2-yl]amino}ethoxy)benzyl]thiazolidine-2,4-dione (**6d**)*

Yield: 2.5 g, 83%. m.p.: 172–173 °C. IR (KBr) ν_{max} cm^{-1}: 2927, 1741, 1696, 1616, 1514. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.04 (m, 1H), 3.12 (s, 3H), 3.28 (m, 1H), 3.94 (m, 2H), 4.14 (m, 2H), 4.85 (m, 1H), 6.75 (d, J = 2.5 Hz, 1H), 6.89 (d, J = 3.0 Hz, 2H), 7.14 (d, J = 7.5 Hz, 2H), 7.28 (m, 1H), 7.40 (m, 2H), 7.60 (m, 2H), 7.83 (m, 1H), 8.43 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 36.7, 37.6, 49.0, 53.5, 65.8, 106.2, 114.7, 123.9, 125.9, 126.8, 129.1, 129.3, 130.8, 136.0, 138.2, 145.9, 157.8, 157.9, 172.2, 176.2. MS (ESI) *m/z* (M+1) 434.

*6.1.21. Preparation of 2-chloro-4-methoxypyridine (**8a**)*

General procedure: To a suspension of sodium hydride (60% dispersion in paraffin liquid, 504 mg, 12.6 mmol) in DMF (20 ml) was added anhydrous methanol (1.1 ml, 6.75 mmol) and 2-chloro-4-nitro-pyridine (1.1 g, 6.31 mmol) under N_2 atmosphere at room temperature for 1 h. After stirring at room temperature for 3 h, the reaction mixture was poured into ice-water and extracted with EtOAc (100 ml). The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo to leave a colorless oil residue which was purified by column chromatography on SiO_2 with *n*-hexane/EtOAc (10:1, v/v) to give the title compound **8a** (1.05 g, 81% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 3014, 2976, 2942, 1596, 1480. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.81 (s, 3H), 6.71 (m, 1H), 6.78 (d, J = 2.28 Hz, 1H), 8.14 (d, J = 5.8 Hz, 1H).

The following compounds **8b–e** were obtained by a similar procedure to that described for the preparation of **8a**.

*6.1.22. Preparation of 2-chloro-4-isopropoxypyridine (**8b**)*

Yield: 0.85 g, 75%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2981, 1590, 1464. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.31 (d, J = 5.97 Hz, 6H), 4.56 (m, 1H), 6.56 (m, 1H), 6.73 (d, J = 5.80 Hz, 1H), 8.10 (d, J = 5.81 Hz, 1H).

*6.1.23. Preparation of 2-chloro-4-phenoxypyridine (**8c**)*

Yield: 1.84 g, 90%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3310, 2890, 1695. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.81 (m, 2H), 7.12 (m, 2H), 7.30 (m, 1H), 7.47 (m, 2H), 8.23 (m, 1H).

*6.1.24. Preparation of 2-chloro-4-phenylaminopyridine (**8d**)*

Yield: 1.35 g, 68%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2955, 1745, 1689. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.92 (m, 2H), 7.12 (m, 1H), 7.31 (m, 2H), 7.79 (m, 2H), 8.13 (m, 1H).

*6.1.25. Preparation of 2-chloro-4-phenylthiopyridine (**8e**)*

Yield: 1.49 g, 79%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3057, 1566, 1453, 1367. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.83 (m, 1H), 6.88 (s, 1H), 7.46 (m, 3H), 7.54 (m, 2H), 8.10 (m, 1H).

*6.1.26. Preparation of 2-[methyl-(4-methoxypyridin-2-yl)amino]ethanol (**9a**)*

General procedure: The compound **8a** (1.05 g, 3.71 mmol) was added *N*-methyl aminoethanol (20 ml), and the mixture was refluxed for 24 h under N_2 atmosphere. The reaction mixture was cooled to room temperature and quenched with NH_4Cl solution (20 ml), and extracted with EtOAc (120 ml). The extracted organic layers were washed with water, brine (50 ml), respectively, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography over SiO_2 using a mixture of dichloromethane/MeOH (30:1, v/v) as eluent to get the title compound **9a** as an oil (0.96 g, 77% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2936, 1605, 1560. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.00 (s, 3H), 3.66 (m, 2H), 3.79 (m, 5H), 5.93 (d, J = 2 Hz, 1H), 6.19 (m, 1H), 7.85 (d, J = 3.0 Hz, 1H).

The following compounds **9b–e** were obtained by a similar procedure to that described for the preparation of **9a**.

*6.1.27. Preparation of 2-[methyl-(4-isopropoxypyridin-2-yl)amino]ethanol (**9b**)*

Yield: 1.45 g, 62%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3332, 2977, 2932, 1604. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.38 (d, J = 6.02 Hz ,6H), 3.05 (s, 3H), 3.70 (m, 2H), 3.84 (m, 2H), 4.64 (m, 1H), 5.99 (s, 1H), 6.22 (m, 1H), 7.92 (d, J = 5.93 Hz, 1H).

*6.1.28. Preparation of 2-[methyl-(4-phenoxypyridin-2-yl)amino]ethanol (**9c**)*

Yield: 1.21 g, 73%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3320, 2890, 1630, 1600. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.00 (s, 3H),

3.74 (m, 2H), 3.85 (m, 2H), 6.07 (s, 1H), 6.23 (m, 1H), 7.11 (m, 2H), 7.25 (m, 1H), 7.44 (m, 2H), 7.94 (m, 1H).

*6.1.29. Preparation of 2-[methyl-(4-phenyaminopyridin-2-yl)amino]ethanol (**9d**)*

Yield: 1.85 g, 74%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3240, 2985, 1659, 1585. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.17 (s, 3H), 3.54 (m, 2H), 3.70 (m, 2H), 6.02 (s, 1H), 6.23 (m, 1H), 6.73 (m, 2H), 6.90 (m, 1H), 7.11 (m, 2H), 7.95 (m, 1H).

*6.1.30. Preparation of 2-[methyl-(4-phenylthiopyridin-2-yl)amino]ethanol (**9e**)*

Yield: 1.30 g, 68%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3345, 2917, 1578, 1532, 1475. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.99 (s, 3H), 3.72 (m, 2H), 3.86 (m, 2H), 6.29 (s, 1H), 6.34 (m, 1H), 7.49 (m, 3H), 7.61 (m, 2H), 7.89 (m, 1H).

*6.1.31. Preparation of 4-{2-[methyl-(4-methoxypyridin-2-yl)amino]ethoxy}-benzaldehyde (**10a**)*

General procedure: To a suspension of sodium hydride (60% in mineral oil, 313 mg, 7.83 mmol) in dry DMF (30 ml) was added compound **10a** (0.96 g, 3.91 mmol) and 4-fluorobenzaldehyde (0.63 ml, 5.86 mmol) under N_2 atmosphere at room temperature. After stirring at the same temperature for 3 h, quenched with aqueous NH_4Cl solution (10 ml), and the reaction mixture was poured into ice-water (25 ml) and extracted with EtOAc (80 ml). The extract was washed with water, brine (50 ml), respectively, and dried over Na_2SO_4, and concentrated by evaporation under reduced pressure. The concentrate thus obtained was purified by column chromatography with SiO_2, using a mixture of *n*-hexane/EtOAc (1:2, v/v) as eluent to give a title compound **10a** (1.12 g, 83% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2932, 1691, 1599, 1501. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.12 (s, 3H), 3.81 (s, 3H), 4.01 (m, 2H), 4.27 (m, 2H), 5.96 (d, J = 2 Hz, 1H), 6.22 (m, 1H), 7.01 (d, J = 8.7 Hz, 2H), 7.80 (d, J = 8.7 Hz, 2H), 8.00 (d, J = 5.79 Hz, 1H), 9.86 (s, 1H).

The following compounds **10b–e** were obtained by a similar procedure to that described for the preparation of **10a**.

*6.1.32. Preparation of 4-{2-[methyl-(4-isopropoxypyridin-2-yl)amino]ethoxy}-benzaldehyde (**10b**)*

Yield: 1.43 g, 78%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3052, 2979, 2929, 1692, 1599. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.34 (d, J = 6.06 Hz, 6H), 3.10 (s, 3H), 3.99 (m, 2H), 4.26 (m, 2H), 4.59 (m, 1H), 5.95 (d, J = 2 Hz, 1H), 6.18 (m, 1H), 7.00 (d, J = 8.69 Hz, 2H), 7.81 (d, J = 8.67 Hz, 2H), 7.99 (d, J = 5.82 Hz, 1H), 9.86 (s, 1H).

*6.1.33. Preparation of 4-{2-[methyl-(4-phenoxypyridin-2-yl)amino]ethoxy}-benzaldehyde (**10c**)*

Yield: 1.02 g, 87%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3250, 2985, 1765. 1600. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.09 (s, 3H), 4.02 (m, 2H), 4.30 (m, 2H), 6.09 (s, 1H), 6.19 (m, 1H), 7.01 (m, 2H), 7.11 (m, 2H), 7.23 (m, 1H), 7.39 (m, 2H), 7.84 (m, 2H), 8.04 (d, J = 5.69 Hz, 1H), 9.89 (s, 1H).

*6.1.34. Preparation of 4-{2-[methyl-(4-phenylaminopyridin-2-yl)amino]ethoxy}-benzaldehyde (**10d**)*

Yield: 0.98 g, 78%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2915, 1740, 1610, 1584. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.00 (s, 3H), 3.74 (m, 2H), 3.85 (m, 2H), 6.07 (s, 1H), 6.23 (m, 1H), 7.11 (m, 2H), 7.25 (m, 1H), 7.44 (m, 2H), 7.49 (m, 2H), 7.88 (m, 2H), 8.05 (m, 1H), 9.90 (s, 1H).

*6.1.35. Preparation of 4-{2-[methyl-(4-phenylthiopyridin-2-yl)-amino]-ethoxy}-benzaldehyde (**10e**)*

Yield: 1.62 g, 85.4%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2925, 1692, 1577, 1262. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.02 (s, 3H), 3.95 (m, 2H), 4.22 (m, 2H), 6.23 (s, 1H), 6.28 (m, 1H), 6.98 (d, J = 8.68 Hz, 2H), 7.40 (m, 3H), 7.52 (m, 2H), 7.80 (d, J = 8.69 Hz, 2H), 7.93 (m, 1H), 9.87 (s, 1H).

*6.1.36. Preparation of 5-(4-{2-[methyl-(4-methoxypyridin-2-yl)amino]ethoxy}-benzylidene)thiazolidine-2,4-dione (**11a**)*

General procedure : A mixture of an aldehyde compound **10a** (1.12 g, 3.2 mmol), 2,4-thiazolidinedione (490 mg, 42.0 mmol), piperidine (0.48 ml, 4.8 mmol) in ethanol (80 ml) was refluxed for 2 h. The reaction mixture was cooled to room temperature, and diluted with EtOAc. The diluted mixture was washed with water (90 ml) and brine (200 ml), and dried over $MgSO_4$, and concentrated by evaporation under reduced pressure. The obtained residue was purified by chromatography over SiO_2 with CH_2Cl_2/MeOH (50:1, v/v) as eluent to give the title compound **11a** as a off white solid (0.93 g, 64% yield). m.p.: 151–153 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2925, 1753, 1693, 1604. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.99 (s, 3H), 3.69 (s, 3H), 3.85 (m, 2H), 4.14 (m, 2H), 6.02 (s, 1H), 6.16 (m, 1H), 7.04 (m, 2H), 7.48 (m, 2H), 7.66 (s, 1H), 7.82 (d, J = 5.73 Hz, 1H).

The following compounds **11b–e** were obtained by a similar procedure to that described for the preparation of **11a**.

*6.1.37. Preparation of 5-(4-{2-[methyl-(4-isopropoxypyridin-2-yl)amino]ethoxy}-benzylidene)thiazolidine-2,4-dione (**11b**)*

Yield: 1.48 g, 78%. m.p.: 148–149 °C. IR (KBr) ν_{max} cm^{-1}: 2976, 2932, 2881, 1693, 1596, 1509. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.18 (d, J = 6.0 Hz, 6H), 2.96 (s, 3H), 3.83 (m, 2H), 4.13 (m, 2H), 4.61 (m, 1H), 5.96 (d, J = 2 Hz, 1H), 6.15 (m, 1H), 7.04 (d, J = 8.82 Hz, 2H), 7.47 (d, J = 8.82 Hz, 2H), 7.65 (s, 1H), 7.82 (d, J = 5.8 Hz, 1H).

*6.1.38. Preparation of 5-(4-{2-[methyl-(4-phenoxypyridin-2-yl)amino]ethoxy}-benzylidene)thiazolidine-2,4-dione (**11c**)*

Yield: 1.27 g, 84%. m.p.: 153–155 °C. IR (KBr) ν_{max} cm^{-1}: 2890, 1745, 1630, 1600. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.09 (s, 3H), 4.03 (m, 2H), 4.27 (m, 2H), 6.09 (s, 1H), 6.21 (d, J = 3.0 Hz, 1H), 6.98 (m, 2H), 7.09 (m, 2H), 7.23 (m, 1H), 7.42 (m, 4H), 7.76 (s, 1H), 8.05 (d, J = 4.5 Hz, 1H).

*6.1.39. Preparation of 5-(4-{2-[methyl-(4-phenylaminopyridin-2-yl)amino]ethoxy}-benzylidene)thiazolidine-2,4-dione (**11d**)*

Yield: 1.19 g, 62%. m.p.: 160–161 °C. IR (KBr) ν_{max} cm^{-1}: 3350, 1748, 1720, 1234. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.02 (s, 3H), 3.95 (m, 2H), 4.22 (m, 2H), 6.03 (s, 1H), 6.28 (m, 1H), 6.98 (m, 2H), 7.11 (m, 2H), 7.28 (m, 1H), 7.45 (m, 4H), 7.80 (s, 1H) 7.93 (m, 1H).

*6.1.40. Preparation of 5-(4-{2-[methyl-(4-phenylthiopyridin-2-yl)amino]ethoxy}benzylidene)-thiazolidine-2,4-dione (**11e**)*

Yield: 1.50 g, 71%. m.p.: 152–154 °C. IR (KBr) ν_{max} cm^{-1}: 3163, 3052, 2937, 1745, 1697. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.02 (s, 3H), 3.93 (m, 2H), 4.18 (m, 2H), 6.53 (s, 1H), 6.58 (m, 1H), 6.98 (d, J = 8.4 Hz, 2H), 7.40 (m, 4H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.73 (s, 1H), 7.93 (m, 1H).

*6.1.41. Preparation of 5-(4-{2-[methyl-(4-methoxypyridin-2-yl)amino]ethoxy}-benzyl)thiazolidine-2,4-dione (**12a**)*

General procedure: To a stirred solution of **11a** (0.92 g, 2.1 mmol) in MeOH (50 ml) was added $Pd(OH)_2$ on carbon (0.9 g) under hydrogen atmosphere at room temperature for 48 h. The mixture was filtered using celite and washed with MeOH. The filtrate was condensed by evaporation under reduced pressure. The concentrate thus obtained was purified by column chromatography on SiO_2 with dichloromethane-methanol (20:1, v/v) as eluent to give the title compound **12a** as a yellowish solid (700 mg, 76% yield). m.p.: 148–150 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2920, 1750, 1690, 1600. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.11 (m, 4H), 3.41 (m, 1H), 3.80 (s, 3H), 3.96 (m, 2H), 4.13 (m, 2H), 4.48 (m, 1H), 5.96 (d, *J* = 2 Hz, 1H), 6.21 (m, 1H), 6.83 (d, *J* = 8.58 Hz, 2H), 7.12 (d, *J* = 8.56 Hz, 2H), 7.99 (d, *J* = 5.82 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.6, 38.0, 49.7, 53.6, 66.4, 69.6, 92.3, 99.8, 114.7, 127.4, 130.4, 148.5, 158.3, 160.1, 165.6, 171.2, 175.0. MS (ESI) *m/z* (M+1) 388.

The following compounds **12b–e** were synthesized by a similar procedure to that described for the preparation of **12a**.

*6.1.42. Preparation of 5-(4-{2-[methyl-(4-isopropoxypyridin-2-yl)amino]ethoxy}-benzyl)thiazolidine-2,4-dione (**12b**)*

Yield: 680 mg, 58%. m.p.: 140–141 °C. IR (KBr) ν_{max} cm^{-1}: 2976, 2929, 1753, 1699, 1603, 1510, 1246. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.33 (d, *J* = 6.03 Hz, 6H), 3.10 (m, 4H), 3.34 (m, 1H), 3.88 (m, 3H), 4.08 (m, 1H), 4.44 (m, 1H), 4.59 (m, 1H), 5.94 (d, *J* = 211 Hz, 1H), 6.17 (m, 1H), 6.80 (d, *J* = 8.50 Hz, 2H), 7.11 (d, *J* = 8.51 Hz, 2H), 7.94 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.9, 37.5, 38.1, 49.9, 53.7, 66.3, 69.6, 92.1, 100.7, 114.6, 127.5, 130.5, 148.4, 158.3, 159.9, 165.6, 171.1, 175.0. MS (ESI) *m/z* (M+1) 416.

*6.1.43. Preparation of 5-(4-{2-[methyl-(4-phenoxypyridin-2-yl)amino]ethoxy}-benzyl)thiazolidine-2,4-dione (**12c**)*

Yield: 690 mg, 67%. m.p.: 158–159 °C. IR (KBr) ν_{max} cm^{-1}: 2925,1749, 1698, 1587, 1247. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.08 (s, 3H), 3.11 (m, 1H), 3.44 (m, 1H), 3.96 (m, 2H), 4.16 (m, 2H), 4.52 (m, 1H), 6.08 (s, 1H), 6.18 (m, 1H), 6.83 (m, 2H), 7.12 (m, 4H), 7.21 (m, 1H), 7.42 (m, 2H), 8.04 (d, *J* = 3.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 36.6, 37.5, 49.0, 53.4, 65.8, 93.7, 101.9, 114.7, 120.6, 125.2, 129.1, 130.6, 130.8, 149.7, 154.6, 157.8, 160.4, 165.7, 172.1, 176.1. MS (ESI) *m/z* (M+1) 450.

*6.1.44. Preparation of 5-(4-{2-[methyl-(4-phenylaminopyridin-2-yl)amino]ethoxy}benzyl)-thiazolidine-2,4-dione (**12d**)*

Yield: 710 mg, 71%. m.p.: 160–163 °C. IR (KBr) ν_{max} cm^{-1}: 1745, 1730, 1625, 1235. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.02 (s, 3H), 3.15 (m, 1H), 3.45 (m, 1H), 3.95 (m, 2H), 4.22 (m, 2H), 4.51 (m, 1H), 6.23 (s, 1H), 6.28 (m, 1H), 6.85 (m, 2H), 7.10 (m, 4H), 7.21 (m, 1H), 7.40 (m, 2H), 8.05 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 35.0, 41.5, 49.2 57.6, 58.9, 71.5, 95.0, 99.1, 115.0, 118.4, 128.0, 132.4, 147.6, 150.1, 156.3, 157.2, 162.1, 165.3 171.5, 176.9. MS (ESI) *m/z* (M+1) 449.

*6.1.45. Preparation of 5-(4-{2-[methyl-(4-phenylthiopyridin-2-yl)amino]ethoxy}-benzyl)thiazolidine-2,4-dione (**12e**)*

Yield: 1.22 g, 85%. m.p.: 162–165 °C. IR (KBr) ν_{max} cm^{-1}: 2924, 1752, 1698, 1577, 1511. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.02 (s, 3H), 3.10 (m, 1H), 3.42 (m, 1H), 3.89 (m, 2H), 4.05 (m, 2H), 4.47 (m, 1H), 6.22 (s, 1H), 6.25 (d, *J* = 5.4 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.38 (m, 3H), 7.52 (m, 2H), 7.91 (d, *J* = 5.4 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.7, 37.9, 49.6, 53.6, 66.2, 103.0, 110.2, 114.7, 127.6, 129.0, 129.5, 130.4, 130.7, 134.6, 147.5, 150.3, 170.2, 174.0. MS (ESI) *m/z* (M+1) 466.

*6.1.46. Preparation of (6-chloropurin-9-yl)acetic acid methyl ester (**14**)*

General procedure: A stirred suspension sodium hydride (60% in mineral oil, 1.03 g, 25.88 mmol) in DMF (50 ml) was added 6-chloro-9H-purine (2.0 g, 12.94 mmol) under N_2 atmosphere at room temperature for 2 h, after which methyl bromoacetate (2.45 ml, 25.88 mmol) and *tert*-butylammonium iodide (1.23 g, 2.58 mmol) were added to the mixture at the same temperature. The reaction mixture was then stirred at room temperature for 6 h, and quenched with aqueous NH_4Cl solution (25 ml). The reaction mixture was poured into water (50 ml), and extracted with EtOAc (100 ml). The organic layer was washed with brine, and dried over $MgSO_4$, after which the organic layer was condensed by evaporation under reduced pressure. To leave a yellowish oil which was purified by column chromatography on SiO_2 with CH_2Cl_2/MeOH (30:1, v/v) to give the title compound **14**. (2.06 g, 72.8% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2875, 1745, 1712, 1584. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.84 (s, 3H), 5.09 (s, 2H), 8.26 (s, 1H), 8.78 (s, 1H).

*6.1.47. Preparation of (6-methoxypurin-9-yl)acetic acid methyl ester (**15a**)*

General procedure: A mixture of methyl ester compound **14** (0.95 g, 4.35 mmol) and sodium methoxide (30 wt.% in MeOH, 1.1 g, 6.53 mmol) in dry methanol (10 ml) was stirred at reflux for 4 h under N_2 atmosphere. After cooling, the reaction mixture was poured into water, and neutralized with 2N AcOH. The reaction mixture was concentrated by evaporation under reduced pressure. The residue thus obtained was purified by column chromatography through SiO_2 using a mixture of CH_2Cl_2/MeOH (20:1, v/v) as eluent to give the title compound **15a**. (0.49 g, 50.6% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 3102, 1745, 1610, 1349. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.82 (s, 3H), 4.22 (s, 3H), 5.04 (s, 2H), 7.99 (s, 1H), 8.56 (s, 1H).

The following compounds **15b–d** were synthesized by a similar procedure to that described for the preparation of **15a**.

*6.1.48. Preparation of (6-phenoxypurin-9-yl)acetic acid methyl ester (**15b**)*

Yield: 1.08 g, 60%. IR ($CHCl_3$) ν_{max} cm^{-1}: 1740, 1710, 1630. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.82 (s, 3H), 5.06 (s, 2H), 7.29 (m, 3H), 7.46 (m, 2H), 8.08 (s, 1H), 8.50 (s, 1H).

*6.1.49. Preparation of (6-phenylaminopurin-9-yl)acetic acid methyl ester (**15c**)*

Yield: 0.98 g, 48%. IR ($CHCl_3$) ν_{max} cm^{-1}: 1770, 1745, 1610. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.81 (s, 3H), 4.99 (s, 2H), 7.11 (m, 1H), 7.40(m, 2H), 7.81 (m, 2H), 7.90 (s, 1H), 8.53 (s, 1H).

*6.1.50. Preparation of (6-phenylthiopurin-9-yl)acetic acid methyl ester (**15d**) Yield: 1.45 g, 77%*

IR ($CHCl_3$) ν_{max} cm^{-1}: 1748, 1564, 1474, 1436. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.78 (s, 3H), 5.02 (s, 2H), 7.46 (m, 3H), 7.66 (m, 2H), 8.06 (s, 1H), 8.60 (s, 1H).

*6.1.51. Preparation of 2-(6-methoxypurin-9-yl)ethanol (**16a**)*

General procedure: DIBAL-H (1.5 M in toluene, 8 ml, 8.1 mmol) was slowly added to a stirred solution to methyl ester compound **15a** (600 mg, 2.70 mmol) in dry CH_2Cl_2 (20 ml) at 0 °C. After stirring at the same temperature for 2 h, the reaction mixture was quenched with 2 N HCl and extracted with CH_2Cl_2 (50 ml). The residue was washed with water, dried over Na_2SO_4, and concentrated by evaporation under reduced pressure. The residue was purified by chromatography over SiO_2 with CH_2Cl_2/MeOH (10:1, v/v) as eluent to give the title compound **16a** as a yellowish oil (210 mg, 40% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 3241, 3081, 1598, 1346, 1315. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.77 (m, 2H), 4.09 (s, 3H), 4.30 (m, 2H), 5.01 (t, J = 2.5 Hz, 3.0 Hz, 1H), 8.31 (s, 1H), 8.52 (s, 1H).

The following compounds **16b–d** were prepared by a similar procedure to that described for the preparation of **16a**.

*6.1.52. Preparation of 2-(6-phenoxypurin-9-yl)ethanol (**16b**)*

Yield: 890 mg, 55%. IR (*Nujol*) ν_{max} cm^{-1}: 3268, 1605, 1575, 1453. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.33 (m, 2H), 3.52 (m, 2H), 4.82 (m, 1H), 6.46 (s, 1H), 7.19 (m, 5H), 7.59 (s, 1H).

*6.1.53. Preparation of 2-(6-phenylaminopurin-9-yl)ethanol (**16c**)*

Yield: 1.01 g, 74%. IR (*Nujol*) ν_{max} cm^{-1}: 2928, 1708, 1603, 1511. ^{1}H-NMR (400 MHz, CD_3OD) δ: 3.92 (m, 2H), 4.32 (m, 2H), 7.08 (m, 1H), 7.34 (m, 2H), 7.79 (m, 2H), 8.12 (s, 1H), 8.35 (s, 1H).

*6.1.54. Preparation of 2-(6-phenylthiopurin-9-yl)ethanol (**16d**)*

Yield: 920 mg, 63%. IR (*Nujol*) ν_{max} cm^{-1}: 3219, 1564, 1434, 1329. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.08 (m, 2H), 4.32 (m, 2H), 4.65 (s, 1H), 7.43 (m, 3H), 7.58 (m, 2H), 8.02 (s, 1H), 8.51 (s, 1H).

*6.1.55. Preparation of 4-[2-(6-methoxypurin-9-yl)ethoxy] benzaldehyde (**17a**)*

General procedure: To a suspension of sodium hydride (60% in mineral oil, 900 mg, 16.2 mmol) in dry DMF (300 ml) was added compound **16a** (2.11 g, 8.11 mmol) and 4-fluorobenzaldehyde (1.71 ml, 16.2 mmol) under N_2 atmosphere at room temperature. After stirring at the same temperature for 6 h, quenched with aqueous NH_4Cl solution (10 ml), and the reaction mixture was poured into ice-water (25 ml) and extracted with EtOAc (80 ml). The residue was washed with water, brine (50 ml), respectively, and dried over Na_2SO_4, and concentrated by evaporation under reduced pressure. The residue was purified by column chromatography through SiO_2 using a mixture of $CHCl_3$/MeOH (30:1, v/v) as eluent to give the title compound **17a** (1.8 g, 55.8% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 1684, 1598, 1477. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.21 (s, 3H), 4.45 (m, 2H), 4.71 (m, 2H), 6.99 (m, 2H), 7.82 (m, 2H), 8.09 (s, 1H), 8.55 (s, 1H), 9.87 (s, 1H).

The following compounds **17b–d** were synthesized by a similar procedure to that described for the preparation of **17a**.

*6.1.56. Preparation of 4-[2-(6-phenoxypurin-9-yl)ethoxy-]benzaldehyde (**17b**)*

Yield: 1.63 g, 64.1%. IR (KBr) ν_{max} cm^{-1}: 1685, 1600, 1450, 1303. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.42 (m, 2H), 4.69 (m, 2H), 6.95 (m, 2H), 7.03 (m, 3H), 7.52 (m, 2H), 7.82 (m, 2H), 8.08 (s, 1H), 8.55(s,1H), 9.87 (s, 1H).

*6.1.57. Preparation of 4-[2-(6-phenylaminopurin-9-yl)ethoxy]benzaldehyde (**17c**)*

Yield: 2.48 g, 47%. IR (KBr) ν_{max} cm^{-1}: 1738, 1690, 1581, 1498. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.42 (m, 2H), 4.67 (m, 2H), 6.98 (m, 2H), 7.10 (m, 1H) 7.40(m, 2H), 7.81 (m, 4H), 7.90 (s, 1H), 8.53 (s, 1H), 9.85 (s, 1H).

*6.1.58. Preparation of 4-[2-(6-phenylthiopurin-9-yl)ethoxy]benzaldehyde (**17d**)*

Yield: 1.25 g, 85%. IR (KBr) ν_{max} cm^{-1}: 1684, 1600, 1564, 1508. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.41 (m, 2H), 4.68 (m, 2H), 6.98 (m, 2H), 7.13 (m, 1H), 7.43 (m, 2H), 7.82 (m, 4H), 7.92 (s, 1H), 8.58 (s, 1H), 9.86 (s, 1H).

*6.1.59. Preparation of 5-{4-[2-(6-methoxypurin-9-yl)ethoxy]benzyl}thiazolidine-2,4-dione (**18a**)*

General procedure: A mixture of an aldehyde compound **17a** (1.80 g, 6.0 mmol), 2,4-thiazolidinedione (1.11 g, 9.1 mmol), piperidine (0.91 ml, 6.2 mmol) in dry ethanol (100 ml) was heated at reflux. After being cooled to room temperature, the reaction mixture was diluted with EtOAc, and washed with water (100 ml) and brine (150 ml), and dried over Na_2SO_4, and concentrated by evaporation to obtained crude material, and the residue was dissolved in dry DMF (10 ml). The reaction solution was added $Pd(OH)_2$ on carbon (0.45 g) under hydrogen atmosphere at room temperature for 96 h. After removal of the catalyst by filtration, the filtrate was concentrated in vacuo and purified by chromatography over SiO_2 with CH_2Cl_2/MeOH (10:1, v/v) as eluent to give the title compound **18a** as a yellowish solid (1.90 g, 78% yield). m.p.: 170–172 °C. IR (KBr) ν_{max} cm^{-1}: 2924, 1732, 1698, 1592. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.01 (m, 1H), 3.25 (m, 1H), 4.07 (s, 3H), 4.35 (m, 2H), 4.61 (m, 2H), 4.83 (m, 1H), 6.83 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 8.41 (s, 1H), 8.52(s, 1H), 12.0 (brs, NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 36.6, 43.3, 53.3, 54.3, 65.9, 114.8, 120.9, 129.6, 130.8, 144.8, 151.9, 152.5, 157.3, 160.6, 172.0, 176.1. MS (ESI) *m/z* (M+1) 400.

The following compounds **18b–d** were synthesized by a similar procedure to that described for the preparation of **18a**.

*6.1.60. Preparation of 5-{4-[2-(6-phenoxypurin-9-yl)ethoxy]benzyl}thiazolidine-2,4-dione (**18b**)*

Yield: 1.46 g, 81%. m.p.: –175 °C. IR (KBr) ν_{max} cm^{-1}: 2923,1733, 1698, 1593. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.18 (m, 1H), 3.46 (m, 1H), 4.41 (m, 2H), 4.52 (m, 2H), 4.70 (m, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 7.36 (m, 3H), 7.51 (m, 2H), 8.23 (s, 1H), 8.57 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 37.1, 52.5, 59.1, 72.6, 112.5, 121.0, 123.5, 128.5, 129.1, 132.7, 145.2, 148.3, 153.3, 154.1, 155.9, 156.1, 171.4, 176.5. MS (ESI) *m/z* (M+1) 462.

*6.1.61. Preparation of 5-{4-[2-(6-phenylaminopurin-9-yl)ethoxy]benzyl}thiazolidine-2,4-dione (**18c**)*

Yield: 1.32 g, 68%. m.p.: 175–177 °C. IR (KBr) ν_{max} cm^{-1}: 3419, 1703, 1622, 1583. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.86 (m, 1H), 3.20 (m, 1H), 4.31 (m, 2H), 4.53 (m, 2H), 4.59 (m, 1H), 6.79 (d, J = 8.4 Hz, 2H), 6.96 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 7.25 (t, J = 7.8 Hz, 2H), 7.87 (d, J = 8.0 Hz, 2H), 8.29 (s, 1H), 8.34 (s, 1H), 9.77 (s, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ: 37.4, 43.1, 54.7, 66.0, 114.8, 120.1, 121.2, 122.9, 128.7, 130.4, 130.6, 140.1, 142.5, 150.2, 152.3, 152.4, 157.2. MS (ESI) *m/z* (M+1) 461.

*6.1.62. Preparation of 5-{4-[2-(6-phenylthiopurin-9-yl)ethoxy]benzyl}thiazolidine-2,4-dione (**18d**)*

Yield: 1.14 g, 80%. m.p.: 165–170 °C. IR (KBr) ν_{max} cm^{-1}: 1738, 1697, 1598, 1511. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.00 (m, 1H), 3.25 (m, 1H), 4.36 (m, 2H), 4.63 (m, 2H), 4.81 (m, 1H), 6.83 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.62 Hz, 2H) 7.47 (m, 3H), 7.61 (m, 2H), 8.38 (s, 1H), 8.52 (s, 1H), 12.45 (brs, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 35.1, 52.1, 56.3, 70.5, 112.1, 125.0, 128.9, 129.0, 129.2, 131.2, 132.1, 145.3, 148.4, 152.0, 152.1, 156.0, 172.4, 175.6. MS (ESI) *m/z* (M+1) 478.

*6.1.63. Preparation of 6-(chloro-9-methyl)-9H-purine (**19a**)*

General procedure: A stirred suspension of sodium hydride (60%, in mineral oil, 620 mg, 16.61 mmol) in DMF (30 ml) was treated with 6-chloro-9H-purine **13** (2.0 g, 12.94 mmol) under N_2 atmosphere at room temperature for 2 h. Methyl iodide (1.03 g, 16.54 mmol) was added to the reaction mixture, and the resultant was stirred at room temperature for 4 h, and quenched with aqueous NH_4Cl (25 ml). The mixture was poured into water (100 ml), and extracted with EtOAc (200 ml). The combined organic layer was washed with water and brine (50 ml), and dried over Na_2SO_4, and concentrated in vacuo to leave a yellowish oil residue which was purified by column chromatography on SiO_2 with CH_2Cl_2/MeOH (20:1, v/v) to give the title compound **19a** (1.14 g, 52% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2850, 1572, 1210. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.19 (s, 3H), 8.12 (s, 1H), 8.77 (s, 1H).

The following compounds **19b–c** were synthesized by a similar procedure to that described for the preparation of **19a**.

*6.1.64. Preparation of 6-(chloro-9-isopropyl)-9H-purine (**19b**)*

Yield: 1.58 g, 67%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2950, 1570. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.55 (d, J = 6.8 Hz, 6H), 4.81 (m, 1H), 7.78 (s, 1H), 8.30 (s, 1H).

*6.1.65. Preparation of 6-(chloro-9-benzyl)-9H-purine (**19c**)*

Yield: 1.75 g, 80%. IR ($CDCl_3$) ν_{max} cm^{-1}: 2920, 1745, 1215. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.55 (s, 2H), 7.40 (m, 2H), 7.45 (m, 3H), 8.19 (s, 1H), 8.89 (s, 1H).

*6.1.66. Preparation of 2-[methyl-(9-methyl-9H-purin-6-yl)amino]ethanol (**20a**)*

General procedure: A mixture of compound **19a** (1.01 g, 5.93 mmol) in ethanol (30 ml) was added *N*-methyl aminoethanol (0.71 ml, 8.89 mmol), and the mixture was refluxed for 24 h under N_2 atmosphere. The reaction mixture was cooled at room temperature, and quenched with water (20 ml), and concentrated by evaporation under reduced pressure. The residue was purified by column chromatography over SiO_2 using a mixture of CH_2Cl_2/MeOH (20:1, v/v) as eluent to give the title compound **20a** (1.09 g, 89% yield).

IR ($CHCl_3$) ν_{max} cm^{-1}: 3600, 1745, 1250. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.49 (br, s, 2H), 3.77 (s, 3H), 4.09 (br, s, 2H), 7.68 (s, 1H), 8.30 (s, 1H).

The following compounds **20b–c** were obtained by a similar procedure to that described for the preparation of **20a**.

*6.1.67. Preparation of 2-[methyl-(9-isopropyl-9H-purin-6-yl)amino]ethanol (**20b**)*

Yield: 1.69 g, 82%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3355, 2976, 2935, 1590, 1230, 1023. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.55 (d, J = 6.8 Hz, 6H), 3.50 (brs, 3H), 3.93 (m, 2H), 4.08 (m, 2H), 4.81 (m, 1H), 7.77 (s, 1H), 8.30 (s, 1H).

*6.1.68. Preparation of 2-[methyl-(9-benzyl-9H-purin-6-yl)amino]ethanol (**20c**)*

Yield: 1.45 g, 95%. IR ($CDCl_3$) ν_{max} cm^{-1}: 2920, 1745, 1215. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.56 (s, 3H), 3.99 (m, 2H), 4.12 (m, 2H), 5.38 (s, 2H), 7.29 (m, 2H), 7.38 (m, 3H), 7.72 (s, 1H), 8.38 (s, 1H).

*6.1.69. Preparation of 4-{2-[methyl-(9-methyl-9H-purin-6-yl)amino]ethoxy}-benzaldehyde (**21a**)*

General procedure: To a suspension of sodium hydride (60% in paraffin liquid, 1.16 g, 2.91 mmol) in dry DMF (30 ml) was added compound **20a** (500 mg, 2.42 mmol), 4-fluorobenzaldehyde (0.31 ml, 2.93 mmol) under N_2 atmosphere at room temperature. After stirring at the same temperature for 5 h, quenched with aqueous NH_4Cl solution (20 ml), and extracted with EtOAc (150 ml). The extract was washed with water, brine (50 ml), respectively, and dried over Na_2SO_4, and concentrated by evaporation under reduced pressure. The concentrate thus obtained was purified by chromatography through SiO_2, using CH_2Cl_2/MeOH (10:1, v/v) as eluent to give the title compound **21a** (480 mg, 63.5% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 1775, 1745, 1730. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.67 (br, s, 3H), 3.83 (s, 3H), 4.43 (br, s, 4H), 7.05 (d, J = 4.5 Hz, 2H), 7.73 (s, 1H), 7.84 (d, J = 2.5 Hz, 1H), 8.40 (s, 1H), 9.89 (s, 1H).

The following compounds **21b–c** were obtained by a similar procedure to that described for the preparation of **21a**.

*6.1.70. Preparation of 4-{2-[methyl-(9-isopropyl-9H-purin-6-yl)amino]ethoxy}-benzaldehyde (**21b**)*

Yield: 1.78 g, 74%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2976, 2936, 1693, 1587. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.57 (d, J = 6.8 Hz, 6H), 3.63 (brs, 3H), 4.39 (m, 4H), 4.84 (m, 1H), 7.00 (d, J = 8.4Hz, 2H), 7.79 (m, 3H), 8.35 (s, 1H), 9.85 (s, 1H).

*6.1.71. Preparation of 4-{2-[methyl-(9-benzyl-9H-purin-6-yl)amino]ethoxy}-benzaldehyde (**21c**)*

Yield: 1.05 g, 85%. IR ($CHCl_3$) ν_{max} cm^{-1}: 1750, 1725, 1525. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.76 (s, 3H), 4.43 (m, 4H), 5.38 (s, 2H), 7.03 (m, 2H), 7.29 (m, 2H), 7.34 (m, 3H), 7.72 (s, 1H), 7.81 (m, 2H), 8.42 (s, 1H), 9.87 (s, 1H).

*6.1.72. Preparation of 5-(4-{2-[methyl-(9-methyl-9H-purin-6-yl)amino]ethoxy}-benzylidene)thiazolidine-2,4-dione (**22a**)*

General procedure: A mixture of an aldehyde compound **21a** (400 mg, 1.54 mmol), 2,4-thiazolidinedione (220 mg, 1.85 mmol), piperidine (0.18 ml, 1.85 mmol) in ethanol (30 ml) was refluxed for 24 h. After being cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2, washed with water and brine (100 ml), and dried over Na_2SO_4, and concentrated by evaporation under reduced pressure. The obtained residue was purified by column chromatography over SiO_2 with CH_2Cl_2/MeOH (10:1, v/v) as eluent to give the title compound **22a** as a yellowish solid (140 mg, 52% yield). m.p.: 180–183 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2985, 1730, 1605, 1572, 1150. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.32 (br, s, 3H), 3.73 (s, 3H), 4.38 (m, 4H), 7.11 (d, J = 4.5 Hz, 2H), 7.54 (d, J = 3.8 Hz, 2H), 7.71 (s, 1H), 8.13 (s, 1H), 8.26 (s, 1H).

The following compounds **22b–c** were obtained by a similar procedure to that described for the preparation of **22a**.

*6.1.73. Preparation of 5-(4-{2-[methyl-(9-isopropyl-9H-purin-6-yl)amino]ethoxy}-benzylidene)thiazolidine-2,4-dione (**22b**)*

Yield: 1.84 g, 68%. m.p.: 158–160 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2936, 1739, 1702, 1592. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.45 (d, J = 6.8 Hz, 6H), 3.48 (brs, 3H), 4.28 (m, 4H), 4.68 (m, 1H), 7.03 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.64 (s, 1H), 8.17 (s, 1H), 8.19 (s, 1H).

*6.1.74. Preparation of 5-(4-{2-[methyl-(9-benzyl-9H-purin-6-yl)amino]ethoxy}-benzylidene)thiazolidine-2,4-dione (**22c**)*

Yield: 1.68 g, 72%. m.p.: 163–167 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 1745, 1575. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.30 (s, 3H), 4.37 (m, 4H), 5.39 (s, 2H), 7.11 (m, 2H), 7.35 (m, 5H), 7.51 (m, 2H), 7.71 (s, 1H), 8.26 (s, 1H), 8.31 (s, 1H).

*6.1.75. Preparation of 5-(4-{2-[methyl-(9-methyl-9H-purin-6-yl)amino]ethoxy}-benzyl)-thiazolidine-2,4-dione (**23a**)*

General procedure: To a stirred solution of **22a** (1.40 g, 2.11 mmol) in DMF (50 ml) was added $Pd(OH)_2$ on carbon (1.4 g) under hydrogen atmosphere at room temperature. The reaction mixture was stirred for 72 h. After removal of the catalyst by filtration, the filterate was concentrated in vacuo. The concentrate residue was purified by column chromatography on SiO_2 with CH_2Cl_2/MeOH (8:1, v/v) as eluent to give the title compound **23a** as a yellowish solid (800 mg, 67% yield). m.p.: 175–177 °C. IR (KBr) ν_{max} cm^{-1}: 1750, 1725, 1595, 1210. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.03 (m, 1H), 3.24 (m, 1H), 3.40 (s, 3H), 3.73 (s, 3H), 4.25 (m, 4H), 4.84 (m, 1H), 6.89 (d, J = 4.0 Hz, 2H), 7.14 (d, J = 3.8 Hz, 2H), 8.13 (s, 1H), 8.25 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 35.9, 38.0, 42.5, 57.9, 58.8, 70.1,

114.1, 128.6, 132.1, 144.9, 148.1, 152.7, 155.3, 157.1, 173.1, 175.9. MS (ESI) *m/z* (M+1) 413.

The following compounds **23b–c** were obtained by a similar procedure to that described for the preparation of **23a**.

*6.1.76. Preparation of 5-(4-{2-[methyl-(9-isopropyl-9H-purin-6-yl)amino]ethoxy}-benzyl)thiazolidine-2,4-dione (**23b**)*

Yield: 850 mg, 67%. m.p.: 150–153 °C. IR (KBr) ν_{max} cm^{-1}: 1748, 1730, 1572, 1280. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.44 (d, J = 6.4 Hz, 6H), 2.99 (m, 1H), 3.20 (m, 1H), 3.30 (brs, 3H), 4.20 (m, 4H), 4.70 (m, 1H), 4.75 (m, 1H), 6.81 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 8.17 (s, 1H), 8.19 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 22.4, 36.7, 46.8, 53.5, 114.7, 119.9, 129.1, 130.8, 138.4, 151.9, 154.3, 157.8, 172.4, 176.5. MS (ESI) *m/z* (M+1) 441.

*6.1.77. Preparation of 5-(4-{2-[methyl-(9-benzyl-9H-purin-6-yl)amino]ethoxy}-benzyl)thiazolidine-2,4-dione (**23c**)*

Yield: 480 mg, 74%. m.p.: 168–171 °C. IR (KBr) ν_{max} cm^{-1}: 1745, 1725, 1575, 1270. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.74 (m, 1H), 2.99 (m, 1H), 3.17 (s, 3H), 4.37 (m, 2H), 4.41 (m, 2H), 4.85 (m, 1H), 5.39 (s, 2H), 7.10 (m, 2H), 7.32 (m, 5H), 7.52 (m, 2H), 8.52 (s, 1H), 8.31 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 35.1, 42.0, 57.1, 58.4, 59.0, 72.3, 114.5, 125.3, 127.0, 128.9, 132.0, 138.6, 144.5, 147.0, 151.9, 155.0, 157.6, 172.5, 177.0. MS (ESI) *m/z* (M+1) 489.

6.2. Biological procedures

6.2.1. Materials

The reference standard compounds, rosiglitazone and pioglitazone, were synthesized in house by the published procedure and were found to be 99% pure.

6.2.2. In vitro enhancement of triglyceride accumulation in 3T3-L1 cells

The effect of each compound on insulin-regulated differentiation 3T3-L1 cells was monitored by the rate of triglyceride accumulation. Confluent 3T3-L1 cells were incubated in 10% heat-inactivated fetal bovine serum with isobutylmethylxanthine (0.5 mM) and dexamethasone (0.25 μM) for 48 h. Cultures were then incubated in Dulbecco's Modified Eagle's Medium/2% fetal bovine serum for 4 days with insulin (10 μg/ml) and the test compounds (3×10^{-5}–3×10^{-11} M). Cellular triglycerides were extracted with isopropanol and assayed by the enzymatic method using a commercially available kit (TG kit, Young Dong Diagnostics, Seoul, Korea).

6.2.3. In vivo hypoglycemic activity

The hypoglycemic activity of each compound was evaluated using genetically diabetic KKA^y mice (male, 8 weeks old) purchased from Clea Japan Inc., Tokyo, Japan. All animals were maintained at 25 ± 2 °C on a 12-h light/12-h dark cycle. The animals were given standard laboratory chow (Jeil saryo Inc., Korea) and water ad libitum. The KKA^y mice were used for experiments at 9 weeks of age. The mice were divided into experimental groups of four or five animals each according to their blood glucose levels. The test compounds (1, 6, 30 mg kg^{-1}) were orally administrated for 5 days. Animals in control groups received vehicle (0.5% sodium CMC, 10 ml kg^{-1}). Blood samples were collected from animals under mild ether anesthesia from retro-orbital sinus 4 h after test compounds administration. The blood glucose and plasma triglyceride levels were determined using by enzyme methods using the glucose-E and TG kits (Young Dong Diagnostics, Seoul, Korea). The effective dose to reduce plasma glucose and triglyceride levels by 25% (ED_{25}) was determined using results of an experiment in which three different doses were tested.

6.2.4. Cytotoxicity in cultured rat hepatocytes

Primary cultures of hepatocytes isolated by collagenase perfusion of adult rat were used as an in vitro system for assessing cytotoxicity of the compounds. Hepatocytes were isolated from male Sprague–Dawley rats weighing about 200 g by the collagenase perfusion method of Seglen [35]. Cells with >85% viability (confirmed by trypan blue exclusion) were distributed onto collagen type I-coated 24 well plates at a subconfluent density (10^5 cells/cm^2), and cultured in DMEM containing 5 mM glucose, 10% Heat-inactivated FBS, 10^{-7} M human insulin, 10^{-6} M dexamethasone. After incubation for 24 h, the medium was collected and the cells were washed twice with phosphate-buffered saline. Then, hepatocytes were cultured in serum-free DMEM as described above. This medium was supplemented either with 12.5, 25, 50, 100 or 200 μm compounds or with the solvent (1% DMSO) only. Cells were exposed to the compounds and/or solvent for 24 h. All cultures were performed at 37 °C in an atmosphere of 5% CO_2 and 95% air with a relative humidity of 100%. Cytotoxicity of the compounds tested was determined by means of the Neutral Red uptake assay [30].

Acknowledgements

The authors like to thanks for the Research Grant (HMP-00-B-21500-014) from Ministry of Health and Welfare, Korea for financial support. The authors thank Dr. S.S. Lee for helpful discussion and Mr. K.S. Moon for biological activity in vitro and vivo assay and Miss K.H. Yang for typing the manuscript.

References

[1] R.A. Defronzo, Diabetologia 35 (1992) 389–391.
[2] N.B. Ruderman, S.H. Schneider, Diabetes Care 15 (1992) 1787–1793.
[3] J.E. Gerich, Engl. J. Med. 321 (1989) 1231–1245.

[4] G.M. Reaven, Am. J. Med. 74 (1983) 109–112.
[5] A.R. Saltiel, J.M. Olefsky, Diabetes 45 (1996) 1661–1668.
[6] T. Fujita, Y. Sugiyama, S. Taketomi, T. Sohda, Y. Kawamatsu, H. Iwatsuka, Z. Suzuoka, Diabetes 32 (1983) 804–810.
[7] A.Y. Chang, B.M. Wyse, B.J. Gilchrist, T. Peterson, A.R. Diani, Diabetes 32 (1983) 830–838.
[8] Y. Sugiyama, S. Taketomi, Y. Shimura, H. Ikeda, T. Fujita, Arzneim, Forsch/Drug Res 40 (1990) 263–267.
[9] J.J. Nolan, B. Ludvik, P. Beerdsen, M. Joyce, N. Olefsky, Engl. J. Med. 331 (1994) 1188–1193.
[10] B.M. Forman, P. Tonotonoz, J. Chem, R.P. Brun, B.M. Spiegelman, R.M. Evans, Cell 83 (1995) 803–812.
[11] J.M. Lehman, L.B. Moore, T.A. Smith-Oliver, W.O. Wilkison, T.M. Willson, J. Biol. Chem. 270 (1995) 12953–12956.
[12] T.M. Willson, J.E. Cobb, D.J. Cowan, R.W. Wiethe, I.D. Correa, S.R. Prakash, K.D. Beck, J. Med. Chem. 39 (1996) 665–668.
[13] Liver damage warnings for troglitazone, Scrip 21 (1997) 2282.
[14] NIH abandons Rezulin in diabetes trial, Scrip 20 (1998) 2342.
[15] T. Yoshloka, T. Fujita, T. Kanai, Y. Alzawa, T. Kurumada, K. Hasegawa, H. Horikoshi, J. Med. Chem. 32 (1989) 421–428.
[16] T. Fujiwara, S. Yoshioka, T. Yoshioka, I. Ushiyama, H. Horikoshi, Diabetes 37 (1988) 1549–1558.
[17] S.L. Suter, J.J. Nolan, P. Wallace, J.M. Gumbine, J.M. Olefsky, Diabetes Care 15 (1992) 193–203.
[18] Y. Momose, K. Meguro, H. Ikeda, C. Hatanaka, T. Sohda, Chem. Pharm. Bull. 39 (1991) 1440–1445.
[19] B.C.C. Cantello, M.A. Cawthorne, D. Haigh, R.M. Hindley, S.A. Smith, P.L. Thurlby, Bioorg. Med. Chem. Lett 4 (1994) 1181–1184.
[20] T. Fujiwara, S. Yoshioka, T. Yoshioka, I. Ushiyama, H. Horikoshi, Diabetes 37 (1988) 1549–1558.
[21] A.Y. Chang, B.M. Wyse, B.J. Gilchrist, T. Peterson, A.R. Diani, Diabetes 32 (1983) 830–838.
[22] Y. Iwamoto, T. Kuzuya, A. Matsuda, T. Awata, S. Kumakura, G. Inooka, I. Shiraishi, Diabetes Care 14 (1991) 1083–1086.
[23] R.R. Henry, Endocrinol. Metab. Clin. N. Am. 26 (1997) 553–573.
[24] K. Anji Reddy, B.B. Lohray, V. Bhushan, A. SekRar Reddy, N.V.S. Rao Mamidi, P. Papi Reddy, V. Saibaba, N. Jaipal Deddy, A. Suryaprakash, M. Parimal, R.K. Vikramadithyan, R. Rajagopalon, J. Med. Chem. 42 (1999) 3265–3278.
[25] H. Yamazadi, A. Shibata, M. Suzuki, M. Nakajima, N. Shimada, F.P. Guengerich, T. Yokoi, Drug Metab. Dispos. 27 (1999) 1260–1266.
[26] J.E. Cobb, S.G. Blanchard, E.G. Boswell, K.K. Brown, P.S. Charifson, J.P. Cooper, J.L. Collins, M. Dezube, B.R. Henke, J. Med. Chem. 41 (1998) 5020–5036.
[27] B.Y. Kim, J.B. Ahn, H.W. Lee, K.S. Moon, T.B. Sim, J.S. Shin, S.K. Ahn, C.I. Hong, Chem. Pharm. Bull. 51 (3) (2003) 276–285.
[28] H.W. Lee, B.Y. Kim, J.B. Ahn, H.J. Son, J.W. Lee, S.K. Ahn, C.I. Hong, Heterocycles 57 (11) (2002) 2163–2173.
[29] J.R. Johnson, Org. React. 1 (1942) 210.
[30] H. Iwatsuka, A. Shino, Z. Suzuoki, Endocrinol. Jpn. 17 (1970) 23–35.
[31] R.F. Kletzien, S.D. Clarke, R.G. Ulrich, Mol. Pharmacol. 41 (1991) 393–398.
[32] Y. Toyoda, A. Tsuchida, E. Iwami, I. Miwa, Life Sci. 68 (2001) 1867–1876.
[33] P. Olivier, P. Testard, D. Marzin, D. Abbott, Toxic. In Vitro 9 (1995) 133–138.
[34] J.M. Lehmann, L.B. More, T.A. Smith-Oliver, W.O. Wilkison, T.M. Wilson, S.A. Kliewer, J. Biol. Chem. 270 (1995) 12953–12956.
[35] P.O. Seglen, Methods in Soil Biology 13 (1976) 29–83.