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Original article

Molecular design, synthesis, and hypoglycemic and hypolipidemic activities of novel pyrimidine derivatives having thiazolidinedione

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Abstract

We previously reported the synthesis and biological activity of novel substituted pyridines and purines having thiazolidinedione with hypoglycemic and hypolipidemic activities. We now report the synthesis and antidiabetic activity of novel substituted pyrimidines having thiazolidinedione moiety. These compounds (entry No. **5a–i**, **10a–d** and **16**) were evaluated for their glucose and lipid lowering activity in KKA^{y} mice. From the results, novel compounds, **5c** and **5g**, exhibited considerably more potent biological activity than that of the reference compounds, pioglitazone and rosiglitazone, respectively.

Keywords: Type 2 diabetes; PPARs; TZD compounds; Glucose and lipid lowering activity; Substituted pyrimidine derivatives

1. Introduction

Type 2 diabetes is growing epidemic, affecting an estimated 16 million people in the United States [1,2]. An additional 16 million people in the United States have the prediabetic condition of impaired glucose tolerance (IGT) [2]. Type 2 diabetes is a metabolic disorder characterized by hyperglycemia as well as insulin resistance and/or impaired insulin secretion. This increased risk of macrovascular disease in both type 2 diabetes and IGT is intricately associated with the presence of insulin resistance, which refers to an impaired ability for the body to respond appropriately to insulin and utilize glucose [3]. Insulin resistance and hyperinsulinemia are closely associated with a cluster of metabolic abnormalities termed the insulin resistance syndrome [3]. These metabolic disease not only include hyperglycemia and glucose intolerance, but also other cardiovascular risk factors, including dyslipidemia, hypertension, abnormal fibrinolysis, atherosclerotic disease [4]. Following the initial report of a novel antidiabetic agent ciglitazone [5] from Takeda laboratories, the PPARγ agonists have emerged a new class of antidiabetic agents to treat type 2 diabetes. These agents share a common partial chemical structure: thiazolidine-2,4-dione (TZD). The TZD are a group of pharmacological agents that enhance insulin action (insulin sensitizes) and promote glucose utilization in peripheral tissues. Between 1997 and 1999, a new class of drugs (Avandia and Actos) called glitazones [5,6] was approved by FDA for the treatment of type 2 diabetes (Fig. 1) [7,8]. Although their exact mechanism of action has not been completely elucidated, it has been demonstrated that TZD elicit their pharmacological actions by binding and activating nuclear receptor PPARγ [9,10]. It is hypothesized that their activation by TZDs affect the expression of a number of genes involved in lipid and glucose metabolism and preadipocyte differentiation [11,12]. Recently, several compounds have been reported to have both PPARα/γ dual agonistic activation. Among these compounds, KRP-297 (Kyorin/Merck) **C** [13,14], Netoglitazone (Mitsubishi/J & J) **D** [15] and AZ-242 (AstraZeneca) **E** [16] were comprised (Fig. 1).

Herein we describe our efforts to identify novel potent glucose and lipid lowering compounds. The design of a novel pyrimidine TZD derivatives structure came from the pyrrolidine series that had been studied earlier in our laboratories

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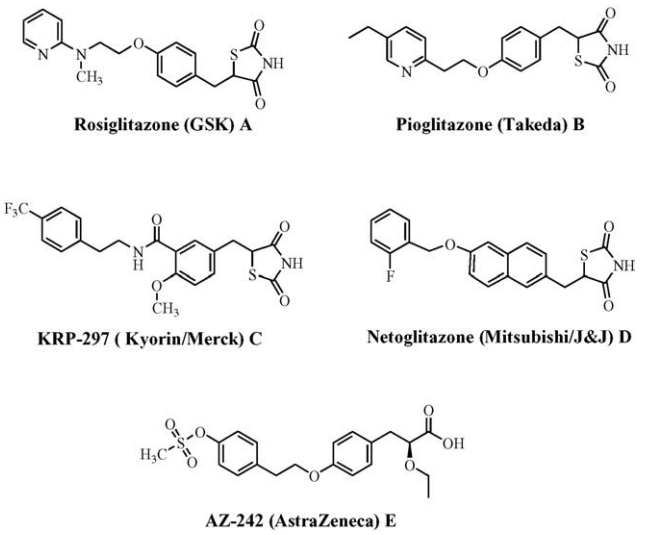

Fig. 1.

[17,18]. Some of the partial structure of substituted moiety were derived from recently reported a novel pyridine and purine TZD derivatives [19]. Considering their biological activity and structure of our previously reported compounds, we could infer that substituted pyrrolidines and pyridines containing TZD were more efficacious than reference compound, rosiglitazone. Therefore, in order to enhance glucose and lipid lowering activities, we focused our attention on the modification of pyrimidine moiety having TZD. As a result, we describe the design, synthesis and biological activities of novel substituted pyrimidine derivatives containing TZD, conceptually issued from modification of rosiglitazone.

The novel substituted pyrimidine analogues having TZD moiety (entry No. **5a–i, 10a–d**, **16**) were synthesized and evaluated their effect on triglyceride accumulation in 3T3-L1 cells. Also, their hypoglycemic and triglyceride lowering effects examined in KKA^{y} mice (Tables 1 and 2). Among synthesized analogues, 5-[4-{2-(6-[4-methoxyphenoxy]-pyrimidin-4-yl)methylaminoethoxy}benzyl]thiazolidine-2,4-dione (**5g**) showed the most excellent biological activity and is presently under further pharmacological studies.

2. Chemistry

Several novel substituted pyrimidines with TZD were designed and prepared as follows. General strategies to synthesize novel thiazolidinediones are shown in Figs. 2–4. First of all, 4-position substituted pyrimidine derivatives having TZD moiety **5a–i** were synthesized as depicted in Fig. 2. Treatment of 4,6-dichloropyrimidine and methanol, isopropanol, phenol, substituted phenol, or aniline in the presence of NaH in DMF generated the several 4-position substituted pyrimidine compounds **1a–i**, which were converted to substituted *N*-methylaminoalcohol compounds **2a–i** by amination with 2-methylaminoethanol. Compounds **2a–i** were then reacted with 4-fluorobenzaldehyde in the presence of NaH in DMF to furnish benzaldehyde compounds **3a–i** in good yield. Knoevenagel4s condensation [20] of benzaldehyde compounds **3a–i** with 2,4-thiazolidinedione in the presence of piperidine in EtOH gave unsaturated thiazolidinedione analogues **4a–i**. The desired compounds **5a–i** were prepared by reduction with 20 wt.% $Pd(OH)_2$ on carbon (Pearlman4s catalyst) under hydrogen atmosphere.

Secondly, 5-position substituted pyrimidine derivatives containing thiazolidinedione **10a–d** were synthesized as shown in Fig. 3. Amination of 5-bromo-2-chloropyrimidine with 2-methylaminoethanol gave the compound **6**. 5-Position substituted pyrimidine compounds **7a–d** were obtained through Stille coupling with the appropriately substituted (2-furanyl, phenyl, 2-pyridinyl and 2-thiophenyl) tri-*n*-butyl stannanes agent in the presence of $Pd(pph_3)_4$ [tetrakis(triphenylphosphine)palladium] catalyst [21,22]. Compounds **7a–d** were reacted with 4-fluorobenzaldehyde in the presence of NaH in DMF to furnish benzaldehyde compounds **8a–d**. Preparation of the desired 5-position substituted pyrimidine derivatives having TZD **10a–d** were obtained via catalytic hydrogenation with 20 wt.% $Pd(OH)_2$ under hydrogen atmo-

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

Compound	Effect on TG accumulation in 3T3-L1 cells (EC_{50}, μM)[a]	Cytotoxicity (TC_{25}, μM)[b]	Safety index (toxicity/activity)
5a	0.0012	77	35,045
5b	0.01	18	1760
5c	0.0012	59.4	49,500
5d	0.1	94	1085
5e	0.008	21	2625
5f	0.009	50	5555
5g	0.00041	35	85,122
5h	0.0012	75	62,833
5i	0.0045	40	8822
10a	0.0003	25	83,333
10b	0.002	90	45,000
10c	0.01	21	2100
10d	0.4	98	245
16	1.6	>200	121
Rosiglitazone	0.047	130	2766
Pioglitazone	0.015	200	13,333

[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
Glucose and triglyceride lowering effect in KKA^{Y} mice

Compound	ED_{25}[a] (mg kg^{-1} day^{-1}) plasma glucose	ED_{25}[a] (mg kg^{-1} day^{-1}) triglyceride
5c	2.0	7.4
5g	1.7	3.4
10a	5.6	>30
Rosiglitazone	4.1	>30
Pioglitazone	6.0	6.0

[a] Effective doses for 25% decrease in plasma and triglyceride levels were estimated from the dose–response curves obtained with three doses.

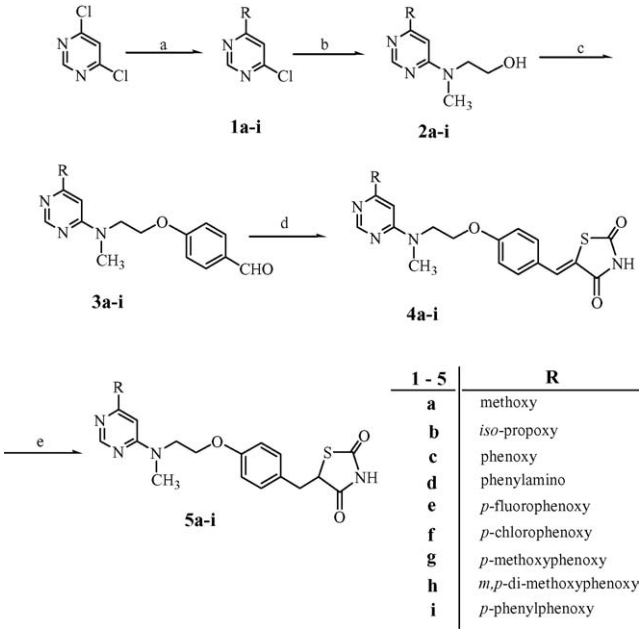

Fig. 2. (a) RH, NaH, DMF, RT, 5–10 h; (b) 2-methylaminoethanol, EtOH, reflux, 24 h; (c) 4-fluorobenzaldehyde, NaH, DMF, RT, 5 h; (d) 2,4-thiazolidinedione (TZD), piperidine, EtOH, reflux, 24 h; (e) 20% $Pd(OH)_2$, H_2, DMF, RT, 24–36 h.

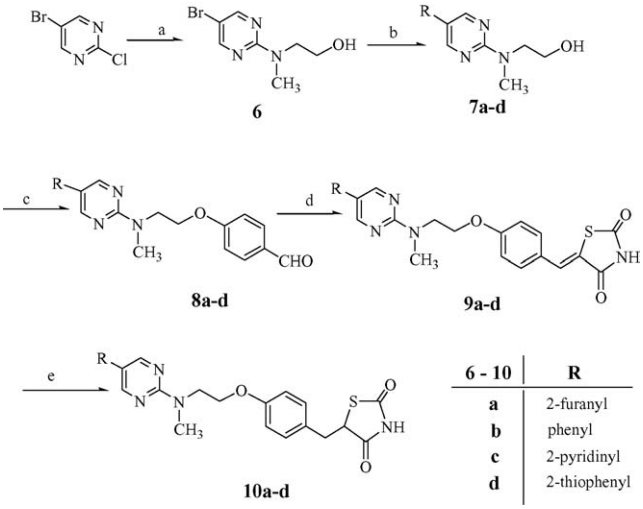

Fig. 3. (a) 2-Methylaminoethanol, RT, 1 h; (b) *n*-Bu_3Sn R, Pd $(pph_3)_4$, toluene, reflux, 9 h; (c) 4-fluorobenzaldehyde, NaH, DMF, RT, 6 h; (d) piperidine, acetic acid, 2,4-thiazolidinedione, toluene, reflux, 5 h; (e) 20% $Pd(OH)_2$, H_2, DMF, RT, 36 h.

sphere from compounds **9a–d**, which were obtained under Knoevenagel4s condition by reacting compounds **8a–d** with 2,4-thiazolidinedione as shown in Fig. 4.

Finally, 2-position substituted pyrimidine compound having thiazolidinedione **16** was synthesized as shown in Fig. 4. Treatment of 2-amino-4,6-dichloropyrimidine and benzene in the presence of isoamyl nitrite and copper (I) oxide (Cu_2O) generated the compound **11**, which was converted to *N*-methylaminoalcohol compound **12** by amination with 2-methylaminoethanol [20]. Compound **13** was obtained via catalytic palladium hydrogenolysis [23,24] of aryl chloride in the presence of Et_3N in EtOH under hydrogen atmosphere

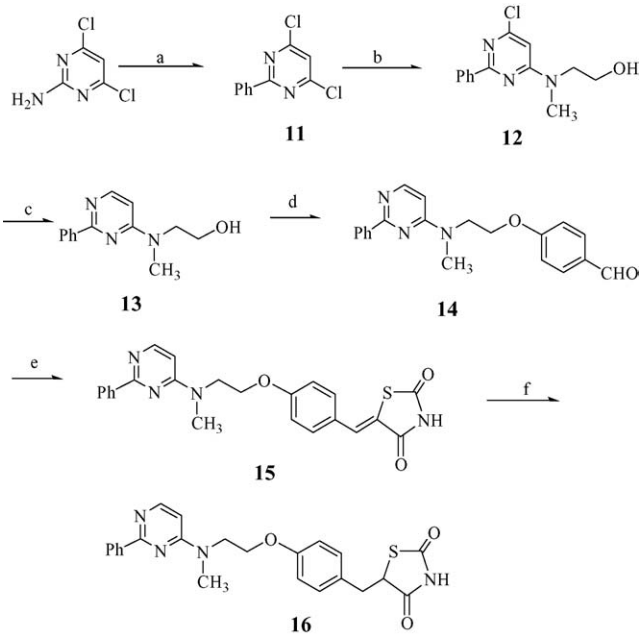

Fig. 4. (a) Isoamyl nitrite, Cu_2O, benzene, reflux, 3 h; (b) 2-methylaminoethanol, dichloromethane, reflux, 24 h; (c) 10% Pd/C, H_2, Et_3N, EtOH–EtOAc (1:1 v/v), 15 h; (d) 4-fluorobenzaldehyde, NaH, DMF, RT, 4 h; (e) 2,4-thiazolidinedione (TZD), piperidine, EtOH, reflux, 24 h; (f) 20% $Pd(OH)_2$, H_2, DMF/MeOH (1:2 v/v), RT, 4 days.

from compound **12**. The desired compound **16** was prepared by *O*-arylation, Knoevenagel4s reaction and reduction, respectively, using the described procedure in Figs. 2 and 3.

3. Biology

The glucose and lipid lowering activities of the compounds were tested using genetically diabetic KKA^y mice [25] and the effect on insulin-regulated differentiation was monitored from the rate of triglyceride accumulation in 3T3-L1 cells [26]. In vitro cytotoxicity of the compounds was evaluated in cultured rat liver hepatocytes and neutral red uptake was used as a cytotoxicity end point [27,28].

3.1. Materials

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

3.2. 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 Dulbecco4s modified Eagle4s medium/2% fetal bovine serum for 4 days with insu-

lin (10 μg ml^{-1}) 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, South Korea).

3.3. 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., South 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 to fed animals for 5 days. Animals in control groups received vehicle (0.5% Sodium CMC, 10 ml kg^{-1}). Blood samples were collected from fed animals under mild ether anesthesia from retro-orbital sinus 4 h after test compounds administration. The plasma glucose and triglyceride levels were determined by enzyme methods using the Glucose-E and TG kits (Young Dong Diagnostics, Seoul, South 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.

3.4. Cytotoxicity in cultured rat liver 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. Liver hepatocytes were isolated from male Sprague–Dawley rats weighing about 200 g by the collagenase perfusion method of Seglen [32]. 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 per cm^2), and cultured in DMEM containing 5 mM glucose, 10% heat-inactivated FBS, 10^{-7} M human insulin, and 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 with either 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 [31].

4. Results and discussion

In the course of our extensive and consecutive research program for searching more efficient and potent compounds

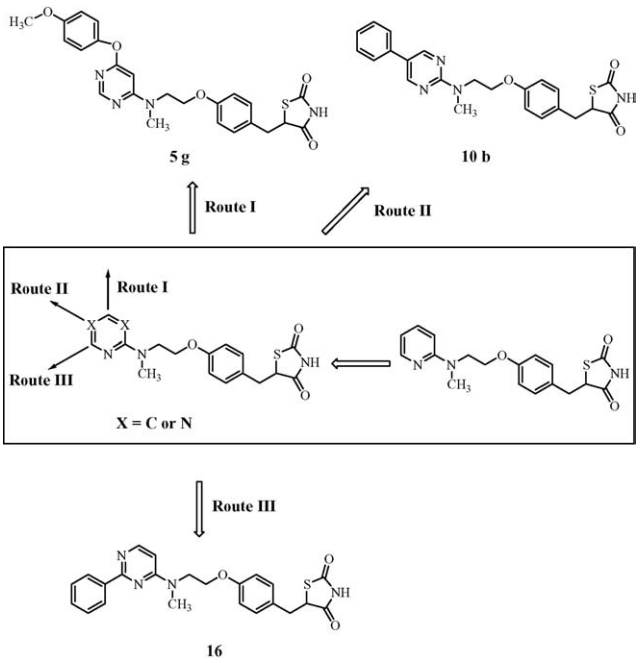

Fig. 5.

for antidiabetic agents to treat type 2 diabetes, we prepared several novel thiazolidinedione analogues containing substituted pyrimidine moiety as designed in Fig. 5 and evaluated their biological profiles for hypoglycemic and triglyceride lowering activities in KKA^y mice. Basically, these compounds are issued from rosiglitazone, itself derived from pioglitazone by modification of ethyl ether linkage containing nitrogen atom between the pyridine group and thiazolidinedione moiety. This modification has dramatically improved hypoglycemic activity compared to pioglitazone in KKA^y mice [29,30]. Thus, the pyrimidine analogues with three differently oriented substituents **5a–i**, **10a–i** and **16** were designed in order to examine the effect of pharmacophore sites by introduction of hydrophobic functional groups to rosiglitazone via routes **I–III**, respectively, synthesized and evaluated their biological activities. As a result, almost 4- or 5-position substituted pyrimidine derivatives showed a better triglyceride accumulation activity in 3T3-L1 cells than that of reference compounds (rosiglitazone and pioglitazone), except for compounds **5d** and **10d** as shown in Table 1. Especially, compounds **5a**, **5c**, **5g**, and **5h** not only showed an excellent hypoglycemic activity but also had better safety index than reference compounds. However, compounds **5b** and **10c** exhibited moderate triglyceride accumulation activity in 3T3-L1 cells (Table 1). Idiosyncratically, compounds **5d** and **10d**, introduced phenylamino and 2-thiophenyl group, respectively, showed relatively less triglyceride accumulation activity. Although the exact reason for relatively high triglyceride accumulation activity was not clear, these results indicate that hydrophobicity and orientation of substituent of the pyrimidine moiety affect the triglyceride accumulation activity in 3T3-L1 cells. But, 2-position substituted pyrimidine compound **16** dramatically reduced the activity com-

pared to 4- or 5-position substituted pyrimidine derivatives. Considering the biological activities, 4- or 5-position substituted pyrimidine derivatives **5c**, **5g** and **10a**, were selected as primary candidates in order to examine the hypoglycemic and hypolipidemic activities in KKA^y mice [31] in vivo. The substituted pyrimidine derivatives **5c**, **5g** and **10a** caused a 25% decrease of plasma glucose (ED_{25}%) at an oral dose of 2.0, 1.7 and 5.6 mg kg^{-1} day^{-1}, respectively, while reference compounds, rosiglitazone and pioglitazone, caused a 25% decrease of plasma glucose (ED_{25}%) at 4.1 and 6.0 mg kg^{-1} day^{-1}, respectively, as shown in Table 2. Particularly, compound **5g** having *para*-methoxyphenoxy group at the 4-position of the pyrimidine moiety, **5g** exhibited an approximately 2.4-fold and 3.5-fold increase in glucose lowering activity than rosiglitazone and pioglitazone, respectively (Table 2). Also, in KKA^y mice, the oral lipid lowering ED_{25}% values of **5c**, **5g** and **10a** also were 7.4, 3.4 and > 30 mg kg^{-1} day^{-1}, respectively, while ED_{25}% values of rosiglitazone and pioglitazone were > 30 and 6.0 mg kg^{-1} day^{-1}, respectively. The data reviewed herein indicate that the glucose and lipid lowering activities of the compound **5g** was more potent than reference compounds (rosiglitazone and pioglitazone).

5. Conclusion

We designed, synthesized and evaluated novel substituted pyrimidine derivatives having TZD moiety as glucose and lipid lowering agents. We obtained more potent compounds **5c** and **5g** in comparison with known reference compounds (pioglitazone and rosiglitazone). Among these compounds, **5g** was selected for further investigation because of its biological activity and synthetic feasibility.

6. Experimental

6.1. Synthesis

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 an 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 4-chloro-6-methoxypyrimidine (**1a**). General procedure*

To a suspension of sodium hydride (60% dispersion in mineral oil, 537 mg, 13.4 mmol) in DMF (30 ml) was added anhydrous methanol (0.27 ml, 6.71 mmol) and 4,6-dichloropyrimidine (1 g, 6.71 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 solution and extracted with EtOAc (100 ml). The organic layer was washed with water and 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 **1a** (464 mg, 45% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 3445, 2917, 1652. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.02 (s, 3H), 6.79 (s, 1H), 8.60 (s, 1H). MS (ESI) *m*/*z* (M + 1) 145.

The following compounds **1b–i** were obtained by a similar procedure to that described for the preparation of **1a**.

*6.1.2. Preparation of 4-chloro-6-isopropoxypyrimidine (**1b**)*

Yield: 86%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2933, 1590, 1464. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.37, 5.29 (m, 1H), 6.71 (s, 1H), 8.56 (s, 1H). MS (ESI) *m*/*z* (M + 1) 173.

*6.1.3. Preparation of 4-chloro-6-phenoxypyrimidine (**1c**)*

Yield: 87%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2923, 2852, 1557, 1457. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.93 (s, 1H), 7.16 (m, 2H), 7.33 (m, 1H), 7.48 (m, 2H), 8.61 (s, 1H). MS (ESI) *m*/*z* (M + 1) 207.

*6.1.4. Preparation of (6-chloropyrimidin-4-yl)phenylamine (**1d**)*

Yield: 36%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2955, 1745, 1689. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.72 (s, 1H), 7.32 (m, 3H), 7.43 (m, 2H), 7.65 (bs, NH), 8.46 (s, 1H). MS (ESI) *m*/*z* (M + 1) 206.

*6.1.5. Preparation of 4-chloro-6-(4-fluorophenoxy)pyrimidine (**1e**)*

Yield: 73%. IR ($CHCl_3$) ν_{max} cm^{-1}: 1562, 1546, 1505, 1444. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.93 (s, 1H), 7.12 (m, 4H), 8.58 (s, 1H). MS (ESI) *m*/*z* (M + 1) 225.

*6.1.6. Preparation of 4-chloro-6-(4-chlorophenoxy)pyrimidine (**1f**)*

Yield: 90%. IR ($CHCl_3$) ν_{max} cm^{-1}: 1557, 1485, 1444. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.95 (s, 1H), 7.10 (m, 2H), 7.42 (m, 2H), 8.58 (s, 1H). MS (ESI) *m*/*z* (M + 1) 241.

*6.1.7. Preparation of 4-chloro-6-(4-methoxyphenoxy)pyrimidine (**1g**)*

Yield: 81%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3355, 2935, 1592, 1548. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.89 (s, 1H), 6.98 (m, 2H), 7.07 (m, 2H), 8.60 (s, 1H). MS (ESI) *m*/*z* (M + 1) 237.

*6.1.8. Preparation of 4-chloro-6-(3,4-dimethoxyphenoxy)-pyrimidine (**1h**)*

Yield: 82%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2936, 1559, 1508, 1442. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.88 (s, 3H), 3.92 (s,

3H), 6.71 (m, 2H), 6.89 (m, 2H), 8.61 (s, 1H). MS (ESI) *m/z* (M + 1) 267.

*6.1.9. Preparation of 4-(biphenyl-4-yloxy)-6-chloropyrimidine (**1i**)*

Yield: 70%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3064, 1565, 1485, 1448. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.99 (s, 1H), 7.24 (m, 2H), 7.41 (m, 1H), 7.48 (m, 2H), 7.61 (m, 2H), 7.69 (m, 2H), 8.64 (s, 1H). MS (ESI) *m/z* (M + 1) 283.

*6.1.10. Preparation of 2-[(6-methoxypyrimidin-4-yl)methylamino]ethanol (**2a**). General procedure*

To the stirred solution of **1a** (460 mg, 3.18 mmol) in anhydrous ethanol (30 ml) was added 2-methylaminoethanol (0.76 ml, 9.54 mmol), and the mixture was refluxed for 24 h under N_2 atmosphere. The reaction mixture was cooled to room temperature, quenched with NH_4Cl solution (50 ml), and extracted with EtOAc (120 ml). The extracted organic layers were washed with water and brine (50 ml), respectively, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography over SiO_2 using a mixture of *n*-hexane/EtOAc (2:3 v/v) as eluent to get the title compound **2a** as a foam (580 mg, 99% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2917, 16647, 1595, 1550. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.07 (s, 3H), 3.80 (m, 2H), 3.87 (m, 2H), 5.79 (s, 1H), 8.32 (s, 1H). MS (ESI) *m/z* (M + 1) 184.

The following compounds **2b–i** were obtained by a similar procedure to that described for the preparation of **2a**.

*6.1.11. Preparation of 2-[(6-isopropoxypyrimidin-4-yl)methylamino]ethanol (**2b**)*

Yield: 73%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2978, 2933, 1594, 1504. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.34 (d, J = 6.22 Hz, 6H), 3.03 (s, 3H), 3.74 (m, 2H), 3.84 (m, 2H), 4.10 (bs, OH), 5.31 (m, 1H), 5.71 (s, 1H), 8.24 (s, 1H). MS (ESI) *m/z* (M + 1) 212.

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

Yield: 85%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2955, 1725, 1571, 1505. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.05 (s, 3H), 3.78 (m, 2H), 3.85 (m, 2H), 5.87 (s, 1H), 7.13 (m, 2H), 7.26 (m, 1H), 7.42 (m, 2H), 8.27 (s, 1H). MS (ESI) *m/z* (M + 1) 246.

*6.1.13. Preparation of 2-[methyl-(6-phenylaminopyrimidin-4-yl)amino]ethanol (**2d**)*

Yield: 98%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3240, 2985, 1659, 1585. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.99 (s, 3H), 3.74 (m, 2H), 3.84 (m, 2H), 5.84 (s, 1H), 6.83 (bs, NH), 7.18 (m, 1H), 7.32 (m, 2H), 7.41 (m, 2H), 8.20 (s, 1H). MS (ESI) *m/z* (M + 1) 245.

*6.1.14. Preparation of 2-[6-(4-fluorophenoxy)pyrimidin-4-yl]methylaminoethanol (**2e**)*

Yield: quantitative. IR ($CHCl_3$) ν_{max} cm^{-1}: 2919, 1594, 1501, 1417. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.07 (s, 3H), 3.78 (m, 2H), 3.87 (m, 2H), 5.88 (s, 1H), 7.11 (m, 4H), 8.25 (s, 1H). MS (ESI) *m/z* (M + 1) 264.

*6.1.15. Preparation of 2-[6-(4-chlorophenoxy)pyrimidin-4-yl]methylaminoethanol (**2f**)*

Yield: 95%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3367, 2934, 1605, 1584, 1486. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.17 (s, 3H), 4.07 (m, 2H), 4.30 (m, 2H), 5.93 (s, 1H), 7.09 (m, 2H), 7.37 (m, 2H), 8.31 (s, 1H). MS (ESI) *m/z* (M + 1) 280.

*6.1.16. Preparation of 2-[6-(4-methoxyphenoxy)pyrimidin-4-yl]methylaminoethanol (**2g**)*

Yield: quantitative. IR ($CHCl_3$) ν_{max} cm^{-1}: 3355, 2935, 1592, 1546, 1504, 1441. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.05 (s, 3H), 3.65 (bs, OH), 3.78 (m, 2H), 3.85 (m, 5H), 5.84 (s, 1H), 6.93 (m, 2H), 7.06 (m, 2H), 8.27 (s, 1H). MS (ESI) *m/z* (M + 1) 276.

*6.1.17. Preparation of 2-[6-(3,4-dimethoxyphenoxy)pyrimidin-4-yl]methylamino-ethanol (**2h**)*

Yield: quantitative. IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1590, 1578, 1507, 1438. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.05 (s, 3H), 3.65 (bs, OH), 3.78 (m, 2H), 3.85 (m, 5H), 5.84 (s, 1H), 6.93 (m, 2H), 7.06 (m, 2H), 8.27 (s, 1H). MS (ESI) *m/z* (M + 1) 306.

*6.1.18. Preparation of 2-[6-(biphenyl-4-yloxy)pyrimidin-4-yl]methylaminoethanol (**2i**)*

Yield: 100%. IR ($CHCl_3$) ν_{max} cm^{-1}: 1591, 1545, 1485, 1441. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.09 (s, 3H), 3.65 (bs, OH), 3.81 (m, 2H), 3.89 (m, 2H), 5.95 (s, 1H), 7.21 (m, 2H), 7.36 (m, 1H), 7.48 (m, 2H), 7.63 (m, 4H), 8.30 (s, 1H). MS (ESI) *m/z* (M + 1) 322.

*6.1.19. Preparation of 4-{2-[(6-methoxypyrimidin-4-yl)methylamino]ethoxy}benzaldehyde (**3a**). General procedure*

To a suspension of sodium hydride (60% in mineral oil, 253 mg, 6.33 mmol) in anhydrous DMF (30 ml) was added compound **2a** (580 mg, 3.16 mmol) and the mixture was stirred for 30 min. And then 4-fluorobenzaldehyde (0.68 ml, 6.33 mmol) was added slowly in the reaction mixture under N_2 atmosphere at room temperature. After stirring at the same temperature for 3 h, the reaction mixture was quenched with aqueous NH_4Cl solution (10 ml), poured into ice-water solution (25 ml), and extracted with EtOAc (80 ml). The extract was washed with water and brine (50 ml), dried over Na_2SO_4, and concentrated by evaporation under reduced pressure. The concentrate thus obtained was purified by column chromatography on SiO_2 using a mixture of *n*-hexane/EtOAc (1:1, v/v) as eluent to give a title compound **3a**. (370 mg, 41% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2945, 2796, 1696, 1593, 1543, 1507. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.13 (s, 3H), 3.93 (s, 3H), 4.03 (m, 2H), 4.27 (m, 2H), 5.76 (s, 1H), 7.01 (m, 2H), 7.84 (m, 2H), 8.33 (s, 1H), 9.89 (s, 1H). MS (ESI) *m/z* (M + 1) 288.

The following compounds **3b–i** were obtained by a similar procedure to that described for the preparation of **3a**.

*6.1.20. Preparation of 4-{2-[(6-isopropoxypyrimidin-4-yl)-methylamino]ethoxy}benzaldehyde (**3b**)*

Yield: 24%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2940, 1691, 1601, 1584, 1507. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.36 (d, J = 6.16 Hz, 6H), 3.16 (s, 3H), 4.07 (m, 2H), 4.29 (m, 2H), 5.34 (m, 1H), 6.97 (m, 2H), 7.84 (m, 2H), 8.35 (s, 1H), 9.89 (s, 1H). MS (ESI) *m/z* (M + 1) 316.

*6.1.21. Preparation of 4-{2-[(6-phenoxypyrimidin-4-yl)-methylamino]ethoxy}benzaldehyde (**3c**)*

Yield: 85%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2932, 1691, 1599, 1501. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.15 (s, 3H), 4.06 (m, 2H), 4.29 (m, 2H), 5.90 (s, 1H), 7.01 (m, 2H), 7.14 (m, 2H), 7.26 (m, 1H), 7.42 (m, 2H), 7.86 (m, 2H), 8.33 (s, 1H), 9.91 (s, 1H). MS (ESI) *m/z* (M + 1) 350.

*6.1.22. Preparation of 4-{2-[methyl(6-phenylaminopyrimidin-4-yl)amino]ethoxy}benzaldehyde (**3d**)*

Yield: 33%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2932, 1691, 1599, 1501. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.08 (s, 3H), 4.02 (m, 2H), 4.27 (m, 2H), 5.87 (s, 1H), 6.76 (bs, NH), 7.01 (m, 2H), 7.17 (m, 1H), 7.29 (m, 2H), 7.37 (m, 2H), 7.84 (m, 2H), 8.27 (s, 1H), 9.89 (s, 1H). MS (ESI) *m/z* (M + 1) 349.

*6.1.23. Preparation of 4-{2-[6-(4-fluorophenoxy)pyrimidin-4-yl]methylaminoethoxy} benzaldehyde (**3e**)*

Yield: 79%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2917, 1684, 1589, 1506. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.16 (s, 3H), 4.07 (m, 2H), 4.30 (m, 2H), 5.91 (s, 1H), 7.02 (m, 2H), 7.09 (m, 4H), 7.85 (m, 2H), 8.31 (s, 1H), 9.91 (s, 1H). MS (ESI) *m/z* (M + 1) 368.

*6.1.24. Preparation of 4-{2-[6-(4-chlorophenoxy)pyrimidin-4-yl]methylaminoethoxy} benzaldehyde (**3f**)*

Yield: 79%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2939, 1691, 1599, 1583, 1485. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.17 (s, 3H), 4.08 (m, 2H), 4.30 (m, 2H), 5.93 (s, 1H), 7.01 (m, 2H), 7.10 (m, 2H), 7.36 (m, 2H), 7.84 (m, 2H), 8.31 (s, 1H), 9.90 (s, 1H). MS (ESI) *m/z* (M + 1) 384.

*6.1.25. Preparation of 4-(2-{[6-(4-methoxyphenoxy)pyrimidin-4-yl]methylamino} ethoxy)benzaldehyde (**3g**)*

Yield: 68%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2947, 2834, 1692, 1590, 1506, 1440. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.14 (s, 3H), 3.83 (s, 3H), 4.30 (m, 2H), 4.67 (m, 2H), 5.86 (s, 1H), 6.94 (m, 2H), 7.02 (m, 2H), 7.08 (m, 2H), 7.84 (m, 2H), 8.32 (s, 1H), 9.90 (s, 1H). MS (ESI) *m/z* (M + 1) 380.

*6.1.26. Preparation of 4-(2-{[6-(3,4-dimethoxyphenoxy)pyrimidin-4-yl]methylamino} ethoxy)benzaldehyde (**3h**)*

Yield: 76%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1689, 1588, 1508, 1438. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.14 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.07 (m, 2H), 4.29 (m, 2H), 5.86 (s, 1H), 6.69 (m, 2H), 6.89 (m, 1H), 7.00 (m, 2H), 7.84 (m, 2H), 8.34 (s, 1H), 9.90 (s, 1H). MS (ESI) *m/z* (M + 1) 410.

*6.1.27. Preparation of 4-(2-{[6-(biphenyl-4-yl-oxy)pyrimidin-4-yl]methylamino} ethoxy)benzaldehyde (**3i**)*

Yield: 84%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1693, 1586, 1544, 1507, 1485, 1440. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.17 (s, 3H), 4.08 (m, 2H), 4.31 (m, 2H), 5.97 (s, 1H), 7.01 (d, J = 1.77 Hz, 2H), 7.21 (m, 2H), 7.36 (m, 1H), 7.45 (m, 2H), 7.63 (m, 4H), 7.86 (m, 2H), 8.36 (s, 1H), 9.90 (s, 1H). MS (ESI) *m/z* (M + 1) 426.

*6.1.28. Preparation of 5-(4-2-[(6-methoxypyrimidin-4-yl)methylamino]ethoxybenzyl idene)thiazolidine-2,4-dione (**4a**). General procedure*

A mixture of an aldehyde compound **3a** (370 mg, 1.29 mmol), 2,4-thiazolidinedione (196 mg, 1.68 mmol), and piperidine (0.17 ml, 1.68 mmol) in anhydrous ethanol (80 ml) was refluxed for 24 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 column chromatography on SiO_2 with *n*-hexane/EtOAc (3:1, v/v) as eluent to give the title compound **4a** as an off-white solid (356 mg, 73% yield). M.p.: 151–153 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2964, 1727, 1697, 1611, 1592, 1513. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.07 (s, 3H), 3.82 (s, 3H), 3.94 (m, 2H), 4.22 (m, 2H), 5.93 (s, 1H), 7.10 (m, 2H), 7.55 (m, 2H), 7.73 (s, 1H), 8.24 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 41.4, 56.0, 58.8, 71.3, 99.2, 114.1, 120, 126.5, 126.8, 142, 154.9, 158.0, 166.3, 167.1, 169.8, 174.0. MS (ESI) *m/z* (M + 1) 387.

The following compounds **4b–i** were obtained by a similar procedure to that described for the preparation of **4a**.

*6.1.29. Preparation of 5-(4-2-[(6-isopropoxypyrimidin-4-yl)methylamino]ethoxybenzyl idene)thiazolidine-2,4-dione (**4b**)*

Yield: 48%. M.p.: 170–172 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2977, 1735, 1699, 1593, 1508, 1456. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.31 (d, J = 6.12 Hz, 6H), 3.13 (s, 3H), 3.99 (m, 2H), 4.25 (m, 2H), 5.13 (m, 1H), 5.78 (s, 1H), 7.01 (m, 2H), 7.45 (m, 2H), 7.62 (s, 1H), 8.11 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 22.6, 41.7, 58.3, 70.6, 71.7, 99.4, 114.1, 121, 125.5, 126.9, 142.5, 154.3, 158.2, 167.5, 169.3, 174.3. MS (ESI) *m/z* (M + 1) 415.

*6.1.30. Preparation of 5-(4-2-[methyl-(6-phenoxypyrimidin-4-yl)amino]ethoxybenzyl idene)thiazolidine-2,4-dione (**4c**)*

Yield: 54%. M.p.: 180–182 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 3052, 2931, 1738, 1698, 1584, 1509, 1489, 1443. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.15 (s, 3H), 4.05 (m, 2H), 4.27 (m, 2H), 5.90 (s, 1H), 6.99 (m, 2H), 7.14 (m, 2H), 7.26 (m, 2H), 7.44 (m, 4H), 7.81 (s, 1H), 8.33 (s, 1H). ^{13}C-NMR (100 MHz,

DMSO-d_6) δ: 42.1, 58.3, 71.5, 94.5, 113.9, 120.5, 121.3, 124.4, 126.4, 126.9, 129.4, 141.9, 154.3, 154.7, 158.3, 166.1, 167.3, 171.9, 172.6. MS (ESI) *m/z* (M + 1) 449.

*6.1.31. Preparation of 5-(4-{2-[methyl-(6-phenylaminopyrimidin-4-yl)amino] ethoxy}benzylidene)thiazolidine-2,4-dione (**4d**)*

Yield: 68%. M.p.: 198–199 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1736, 1692, 1581, 1502, 1480. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.04 (s, 3H), 3.92 (m, 2H), 4.23 (m, 2H), 5.88 (s, 1H), 6.92 (m, 1H), 7.12 (m, 2H), 7.26 (m, 2H), 7.56 (m, 4H), 7.74 (s, 1H), 8.18 (s, 1H) 9.04 (s, NH), 12.51 (bs, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 40.6, 57.9, 72.1, 92.1, 113.9, 115.1, 118.5, 119.9, 126.3, 126.9, 129.5, 141.9, 146.7, 156.2, 157.9, 166.5, 167.4, 171.1. MS (ESI) *m/z* (M + 1) 448.

*6.1.32. Preparation of 5-[4-(2-{[6-(4-fluorophenoxy)pyrimidin-4-yl]methylamino} ethoxy)benzylidene]thiazolidine-2,4-dione (**4e**)*

Yield: 69%. M.p.: 190–192 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 1740, 1701, 1591, 1508, 1460, 1412. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.10 (s, 3H), 3.96 (m, 2H), 4.25 (m, 2H), 6.15 (s, 1H), 7.10 (d, J = 8.82 Hz, 2H), 7.16 (m, 2H), 7.23 (m, 2H), 7.56 (d, J = 8.82 Hz, 2H), 7.73 (s, 1H), 8.18 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 41.2, 58.3, 71.7, 94.5, 114.7, 116.5, 120.3, 122.7, 126.1, 126.9, 141.9, 149.9, 154.9, 157.8, 166.1, 167.1, 171.3, 172.6. MS (ESI) *m/z* (M + 1) 467.

*6.1.33. Preparation of 5-[4-(2-{[6-(4-chlorophenoxy)pyrimidin-4-yl]methyl amino}ethoxy)benzylidene]thiazolidine-2,4-dione (**4f**)*

Yield: 61%. M.p.: 188–192 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2949, 1740, 1702, 1597, 1509, 1486. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.11 (s, 3H), 3.96 (m, 2H), 4.26 (m, 2H), 6.19 (s, 1H), 7.10 (d, J = 8.82 Hz, 2H), 7.16 (m, 2H), 7.45 (m, 2H), 7.53 (d, J = 8.82 Hz, 2H), 7.73 (s, 1H), 8.19 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 41.1, 58.1, 71.3, 94.3, 114.3, 119.8, 122.5, 126.5, 126.8, 129.7, 129.9, 141.7, 152.4, 154.9, 157.9, 166.5, 166.9, 171.1, 172.6. MS (ESI) *m/z* (M + 1) 483.

*6.1.34. Preparation of 5-[4-(2-{[6-(4-methoxyphenoxy)pyrimidin-4-yl]methylamino} ethoxy)benzylidene]thiazolidine-2,4-dione (**4g**)*

Yield: 68%. M.p.: 194–195 °C. IR (KBr) ν_{max} cm^{-1}: 3428, 2948, 2748, 1741, 1704, 1591, 1508, 1292, 1257. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.07 (s, 3H), 3.75 (s, 3H), 3.94 (m, 2H), 4.23 (m, 2H), 6.05 (s, 1H), 6.95 (d, J = 8.84 Hz, 2H), 7.00 (m, 4H), 7.54 (d, J = 8.86 Hz, 2H), 7.73 (s, 1H), 8.16 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 37.3, 48.9, 56.2, 66.5, 86.4, 115.4, 116.2, 121.3, 123.3, 126.5, 132.5, 132.9, 146.9, 157.2, 158.1, 160.8, 164.5, 168.4, 168.8, 170.6. MS (ESI) *m/z* (M + 1) 479.

*6.1.35. Preparation of 5-[4-(2-{[6-(3,4-dimethoxyphenoxy-)pyrimidin-4-yl]methyl amino}ethoxy)benzylidene]thiazolidine-2,4-dione (**4h**)*

Yield: 57%. M.p.: 190–193 °C. IR (KBr) ν_{max} cm^{-1}: 3446, 2983, 1744, 1694, 1591, 1511, 1438. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.14 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 4.05 (m, 2H), 4.27 (m, 2H), 5.87 (s, 1H), 6.69 (m, 2H), 6.89 (m, 1H), 7.00 (d, J = 8.76 Hz, 2H), 7.47 (d, J = 8.76 Hz, 2H), 7.80 (s, 1H), 8.34 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 39.3, 56.2, 66.5, 86.4, 94.5, 107.7, 115.4, 116.2, 121.3, 123.3, 126.5, 132.5, 132.9, 146.9, 157.2, 158.1, 160.8, 164.5, 167.4, 169.8, 171.6. MS (ESI) *m/z* (M + 1) 509.

*6.1.36. Preparation of 5-[4-(2-{[6-(biphenyl-4-yl-oxy)pyrimidin-4-yl]methyl amino}ethoxy)benzylidene]thiazolidine-2,4-dione (**4i**)*

Yield: 77%. M.p.: 185–187 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 1741, 1704, 1591, 1509. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.10 (s, 3H), 3.99 (m, 2H), 4.23 (m, 2H), 5.87 (s, 1H), 6.95 (d, J = 8.76 Hz, 2H), 7.16 (m, 2H), 7.31 (m, 1H), 7.41 (m, 4H), 7.72 (s, 1H), 8.26 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 40.3, 56.2, 69.5, 86.4, 107.7, 115.4, 116.2, 127.3, 128.3, 129.5, 132.5, 136.9, 142.9, 157.2, 158.1, 160.8, 164.5, 167.4, 170.8, 171.6. MS (ESI) *m/z* (M + 1) 525.

*6.1.37. Preparation of 5-(4-{2-[(6-methoxypyrimidin-4-yl)methylamino]ethoxy} benzyl)thiazolidine-2,4-dione (**5a**). General procedure*

To a stirred solution of **4a** (365 mg, 0.944 mmol) in anhydrous DMF (100 ml) was added $Pd(OH)_2$ on carbon (360 mg) under hydrogen atmosphere at room temperature for 36 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 (30:1, v/v) as eluent to give the title compound **5a** as a yellowish solid. (100 mg, 27% yield). M.p.: 148–150 °C. IR (KBr) ν_{max} cm^{-1}: 2952, 1755, 1709, 1601, 1512. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.97 (m, 2H), 3.06 (s, 3H), 3.81 (s, 3H), 3.89 (m, 2H), 4.10 (m, 2H), 4.71 (m, 1H), 5.91 (s, 1H), 6.86 (d, J = 8.49 Hz, 2H), 7.14 (d, J = 8.45 Hz, 2H), 8.23 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 35.9, 39.1, 49.4, 54.8, 55.9, 70.6, 95.9, 115.0, 128.8, 131.8, 156.7, 170.8, 174.1, 175.3. MS (ESI) *m/z* (M + 1) 389.

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

*6.1.38. Preparation of 5-(4-{2-[(6-isopropoxypyrimidin-4-yl)methylamino]ethoxy} benzyl)thiazolidine-2,4-dione (**5b**)*

Yield: 30.8%. M.p.: 150–152 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2978, 1750, 1698, 1594, 1510, 1449, 1417. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.34 (m, 6H), 3.13 (s, 4H), 3.41 (m, 1H), 3.96 (m, 2H), 4.16 (m, 2H), 4.52 (m, 1H), 5.31 (m, 1H), 5.71 (s, 1H), 6.83 (m, 2H), 7.12 (m, 2H), 8.30 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 23.6, 35.2, 40.1, 54.8, 55.9, 70.6, 71.3, 99.3, 115.0, 128.8, 131.8, 154.7, 156.8, 167.1, 169.8, 174.1, 175.3. MS (ESI) *m/z* (M + 1) 417.

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

Yield: 65%. M.p.: 160–163 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 1753, 1698, 1604, 1584, 1510, 1489. ^{1}H-NMR (400 MHz,

$CDCl_3$) δ: 3.13 (m, 4H), 3.45 (dd, J = 3.98, 3.98 Hz, 1H), 4.02 (m, 2H), 4.18 (m, 2H), 4.51 (m, 1H), 5.88 (s, 1H), 6.85 (m, 2H), 7.16 (m, 4H), 7.22 (m, 1H), 7.40 (m, 2H), 8.31 (s, 1H), 8.33 (bs, NH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.0, 38.1, 54.8, 55.6, 66.2, 85.7, 115.8, 122.1, 128.4, 130.5, 146.6, 157.0, 157.3, 158.1, 164.2, 170.5, 171.2, 172.3, 175.1. MS (ESI) m/z (M + 1) 451.

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

Yield: 42%. M.p.: 178–181 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 1750, 1699, 1610, 1584, 1499. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.04 (s, 3H), 3.28 (m, 1H), 3.87 (m, 2H), 4.09 (m, 2H), 4.86 (m, 1H), 5.87 (s, 1H), 6.89 (m, 2H), 7.15 (d, J = 8.67 Hz, 2H), 7.26 (m, 2H), 7.58 (m, 2H), 8.17 (s, 1H), 9.03 (bs, NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 37.0, 38.1, 56.8, 58.6, 66.2, 91.7, 115.8, 119.1, 128.8, 130.7, 146.4, 156.0, 156.3, 158.9, 163.2, 170.5, 171.2, 172.6, 175.1. MS (ESI) m/z (M + 1) 450.

*6.1.41. Preparation of 5-(4-{2-[6-(4-fluorophenoxy)pyrimidin-4-yl]methylaminoethoxy} benzyl)thiazolidine-2,4-dione (**5e**)*

Yield: 72%. M.p.: 172–173 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 1751, 1700, 1591, 1500, 1441. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.15 (m, 4H), 3.45 (dd, J = 3.98, 3.96 Hz, 1H), 4.02 (m, 2H), 4.18 (m, 2H), 4.52 (m, 1H), 5.89 (s, 1H), 6.85 (m, 2H), 7.09 (m, 4H), 7.16 (m, 2H), 7.96 (bs, NH), 8.31 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 36.4, 40.1, 56.5, 58.7, 66.7, 91.3, 114.8, 120.1, 127.4, 129.9, 148.7, 155.8, 156.1, 159.8, 163.2, 170.5, 171.2, 172.6, 175.3. MS (ESI) m/z (M + 1) 469.

*6.1.42. Preparation of 5-(4-{2-[6-(4-chlorophenoxy)pyrimidin-4-yl]methylamino ethoxy}benzyl)thiazolidine-2,4-dione (**5f**)*

Yield: 75%. M.p.: 167–169 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 1751, 1699, 1605, 1584, 1509, 1485. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.98 (m, 1H), 3.16 (s, 3H), 3.45 (dd, J = 3.93, 3.97 Hz, 1H), 4.02 (m, 2H), 4.18 (m, 2H), 4.52 (m, 1H), 5.92 (s, 1H), 6.83 (m, 2H), 7.09 (m, 2H), 7.16 (m, 2H), 7.38 (m, 2H), 8.04 (bs, NH), 8.30 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 35.4, 39.1, 54.5, 58.8, 71.7, 94.3, 115.8, 121.1, 129.7, 130.9, 147.7, 154.6, 156.7, 158.8, 163.2, 170.4, 171.2, 172.3, 175.5. MS (ESI) m/z (M + 1) 485.

*6.1.43. Preparation of 5-(4-{2-[6-(4-methoxyphenoxy)pyrimidin-4-yl]methylamino ethoxy}benzyl)thiazolidine-2,4-dione (**5g**)*

Yield: 89%. M.p.: 165–167 °C. IR (KBr) ν_{max} cm^{-1}: 3427, 3112, 2924, 2835, 2752, 1749, 1693, 1590, 1545, 1506, 1444, 1363. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.12 (m, 4H), 3.45 (m, 1H), 3.83 (s, 3H), 4.00 (m, 2H), 4.16 (m, 2H), 4.50 (m, 1H), 5.84 (bs, 1H), 6.83 (m, 2H), 7.06 (m, 2H), 7.15 (m, 2H), 8.31 (s, 1H), 8.89(bs, NH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.9, 38.1, 49.7, 54.0, 55.9, 66.6, 85.9, 115.0, 122.8, 128.8, 130.7, 146.7, 157.3, 157.9, 158.4, 164.2, 170.8, 171.1, 174.9. MS (ESI) m/z (M + 1) 481.

*6.1.44. Preparation of 5-(4-{2-[6-(3,4-dimethoxyphenoxy-)pyrimidin-4-yl]methylamino ethoxy}benzyl)thiazolidine-2,4-dione (**5h**)*

Yield: 63%. M.p.: 160–163 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2933, 1750, 1699, 1590, 1509, 1483. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.13 (s, 3H), 3.16 (m, 1H), 3.46 (dd, J = 3.96, 4.00 Hz, 1H), 3.86 (s, 3H), 3.90 (s, 3H), 4.00 (m, 2H), 4.19 (m, 2H), 4.51 (m, 1H), 5.86 (s, 1H), 6.71 (m, 2H), 6.85 (m, 3H), 7.14 (m, 2H), 8.33 (s, 1H), 8.41 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 36.9, 38.8, 48.7, 54.5, 55.9, 56.3 68.6, 86.8, 115.5, 127.4, 128.9, 131.7, 148.7, 156.3, 157.4, 159.4, 164.2, 170.8, 171.1, 174.3. MS (ESI) m/z (M + 1) 511.

*6.1.45. Preparation of 5-(4{-2-[(6-biphenyl-4-yl-oxypyrimidin-4-yl)methylamino]ethoxy} benzyl)thiazolidine-2,4-dione (**5i**)*

Yield: 27%. M.p.: 180–183 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 1752, 1700, 1592, 1511, 1440. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.08 (m, 1H), 3.16 (s, 3H), 3.45 (m, 1H), 4.02 (bs, 2H), 4.19 (m, 2H), 4.50 (m, 1H), 5.95 (s, 1H), 6.86 (d, J = 8.72 Hz, 2H), 7.13 (m, 2H), 7.23 (m, 2H), 7.36 (m, 1H), 7.45 (m, 2H), 7.64 (m, 4H), 8.03 (s, 1H), 8.65(bs, NH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 36.9, 39.1, 56.6, 58.8, 69.7, 94.0, 114.9, 121.6, 127.4, 128.5, 129.8, 131.8, 132.7, 136.7, 153.3, 157.9, 158.4, 167.2, 170.8, 172.1, 175.2. MS (ESI) m/z (M + 1) 527.

*6.1.46. Preparation of 2-[(5-bromopyrimidin-2-yl)methylamino]ethanol (**6**)*

A suspension of 2-chloro-5-bromopyrimidine (1 g, 5.1 mmol) in 2-methylamino-ethanol (5 ml) was stirred for 1 h at room temperature. The reaction mixture was diluted with EtOAc (30 ml), washed with brine (100 ml), dried with $MgSO_4$, and evaporated under reduced pressure. The residue was dried in vacuo, and obtained the title compound **6** as colorless oil (1.2 g, quantitative yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2936, 1582, 1524, 1408. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.17 (s, 3H), 3.34 (t, OH), 3.72 (m, 2H), 3.84 (m, 2H), 8.25 (s, 2H), 4.50 (m, 1H), 5.95 (s, 1H), 6.86 (d, J = 8.72 Hz, 2H), 7.13 (m, 2H), 7.23 (m, 2H), 7.36 (m, 1H), 7.45 (m, 2H), 7.64 (m, 4H), 8.03 (s, 1H), 8.65 (bs, NH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 36.85, 52.70, 61.80, 105.58, 157.80, 160.68.

*6.1.47. Preparation of 2-[(5-furan-2-yl-pyrimidin-2-yl)methylamino]ethanol (**7a**). General procedure*

To a solution of **6** (1.1 g, 7.1 mmol) in anhydrous tetrahydrofuran (30 ml) was added tri-*n*-butyl tin 2-furan (2.24 ml, 7.1 mmol) and palladium tetrakis triphenylphosphine Pd $(pph_3)_4$ (approximately 3 mol% catalytic amount), and the mixture was refluxed for 9 h under argon atmosphere. The reaction mixture was diluted with EtOAc (50 ml), washed with H_2O (50 ml) and brine (50 ml), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on SiO_2 with EtOAc/*n*-hexane

(1:3, v/v) to give the title compound **7a** (980 mg, 95%) as a white solid. M.p.: 180–183 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 3345, 2943, 1600, 1549, 1406. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.28 (s, 3H), 3.83 (m, 2H), 3.91 (m, 2H), 6.47 (m, 2H), 7.46 (s, 1H), 8.59 (s, 2H).). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.9, 53.5, 62.7, 122.2, 125.6, 127.4, 129.8, 135.4, 155.3, 161.9.

The following compounds **7b–d** were obtained by a similar procedure to that described for the preparation of **7a**.

*6.1.48. Preparation of 2-[methyl-(5-phenyl-pyrimidin-2-yl)amino]ethanol (**7b**)*

Yield: 59%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3355, 2933, 1605, 1529, 1407. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.26 (s, 3H), 3.81 (m, 2H), 3.90 (m, 2H), 7.07 (m, 1H), 7.13 (m, 1H), 7.26 (m, 1H), 8.50 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 36.89, 5, 62.5, 117.5, 122.3, 124.3, 128.1, 138.1, 154.9, 161.6.

*6.1.49. Preparation of 2-[methyl-(5-pyridin-2-yl-pyrimidin-2-yl)amino]ethanol (**7c**)*

Yield: 67%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3331, 2932, 1603, 1534, 1402. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.28 (s, 3H), 3.83 (m, 2H), 3.91 (m, 2H), 4.03 (t, OH), 7.17 (m, 1H), 7.53 (d, J = 7.92 Hz, 1H), 7.70 (m, 1H), 8.62 (m, 1H), 8.89 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 36.9, 53.0, 62.4, 118.6, 121.2, 121.8, 136.9, 149.9, 153.3, 156.2, 162.4.

*6.1.50. Preparation of 2-[methyl-(5-thiophen-2-yl-pyrimidin-2-yl)amino]ethanol (**7d**)*

Yield: 49%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3320, 3239, 2959, 1604, 1538, 1517, 1408. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.28 (s, 3H), 3.83 (m, 2H), 3.92 (m, 2H), 4.02 (bs, OH), 7.34 (m, 1H), 7.45 (m, 1H), 8.53 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 36.8, 53.0, 62.7, 122.9, 125.8, 127.3, 129.1, 135.4, 155.8, 161.9.

*6.1.51. Preparation of 4-2-[(5-furan-2-yl-pyrimidin-2-yl)methylamino]ethoxybenzaldehyde (**8a**). General procedure*

To a solution of aminoalcohol compound **7a** (980 mg, 4.47 mmol) in anhydrous DMF (20 ml) was added NaH (60% dispersion in mineral oil, 358 mg, 8.94 mmol), and the reaction mixture was stirred for 1 h at ice-bath temperature under N_2 atmosphere. And 4-fluorobenzaldehyde (0.72 ml, 0.7 mmol) was added dropwise over 15 min. The reaction mixture was stirred at room temperature for 5 h, added carefully to saturated ammonium chloride solution (100 ml), and extracted with ethyl acetate (2 × 50 ml). The combined organic layer was washed with brine (3 × 40 ml), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography on SiO_2 with EtOAc/*n*-hexane (1:4, v/v) to give the title compound **8a** (752 mg, 52% yield) IR ($CHCl_3$) ν_{max} cm^{-1}: 3355, 2933, 1605, 1529, 1407. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.36 (s, 3H), 4.10 (m, 2H), 4.33 (m, 2H), 6.48 (m, 2H), 7.03 (m, 2H), 7.47 (s, 1H), 7.84 (m, 2H), 8.64 (s, 2H), 9.90 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 36.5, 48.9, 65.6, 114.8, 117.4, 122.2, 124.3, 128.1, 130.0, 132.0, 138.4, 155.0, 160.7, 163.8, 190.8.

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

*6.1.52. Preparation of 4-{2-[methyl-(5-phenylpyrimidin-2-yl)amino]ethoxy}benzaldehyde (**8b**)*

Yield: 60%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2939, 1693, 1600, 1527, 1408. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.34 (s, 3H), 4.07 (m, 2H), 4.31 (m, 2H), 7.01 (m, 2H), 7.08 (m, 1H), 7.14 (m, 1H), 7.26 (m, 1H), 7.83 (m, 2H), 8.55 (s, 2H), 9.87 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.2, 49.0, 66.4, 114.8, 117.4, 122.2, 124.3, 128.1, 130.0, 132.0, 132.3, 138.4, 155.0, 160.7, 163.8, 190.8.

*6.1.53. Preparation of 4-{2-[methyl-(5-pyridin-2-yl-pyrimidin-2-yl)amino]ethoxy}benzaldehyde (**8c**)*

Yield: 57%. IR ($CHCl_3$) ν_{max} cm^{-1}: 2932, 1691, 1600, 1531, 1406. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.36 (s, 3H), 4.11 (m, 2H), 4.31 (m, 2H), 7.01 (m, 2H), 7.19 (m, 1H), 7.55 (m, 1H), 7.69 (m, 1H), 7.82 (m, 2H), 8.62 (m, 1H), 8.94 (s, 2H), 9.94 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.3, 49.0, 114.8, 118.6, 121.2, 121.7, 129.3, 130.0, 132.0, 136.8, 149.9, 153.6, 156.3, 161.5, 163.8, 190.8.

*6.1.54. Preparation of 4-{2-[methyl-(5-thiophen-2-yl-pyrimidin-2-yl)amino]ethoxy} benzaldehyde (**8d**)*

Yield: 66%. IR ($CHCl_3$) ν_{max} cm^{-1}: 3420, 3230, 2852, 1604, 1538, 1408. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.35 (s, 3H), 4.09 (m, 2H), 4.32 (m, 2H), 7.03 (m, 2H), 7.35 (m, 1H), 7.48 (m, 4H), 7.83 (m, 2H), 8.57 (s, 2H), 9.87 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 37.2, 49.0, 66.4, 114.8, 117.4, 122.2, 124.3, 128.1, 130.0, 132.0, 138.4, 155.0, 160.7, 163.8, 190.8.

*6.1.55. Preparation of 5-(4-{2-[(5-furan-2-yl-pyrimidin-2-yl)methylamino]ethoxy} benzylidene)thiazolidine-2,4-dione (**9a**). General procedure*

A mixture of benzaldehyde compound **8a** (750 mg, 2.32 mmol), piperidine (0.07 ml, 0.69 mmol), acetic acid (0.04 ml, 0.69 mmol) and 2,4-thiazolidinedione (300 mg, 2.55 mmol) in toluene (25 ml) was refluxed for 5 h with continuous removal of water through Dean-Stark apparatus. The reaction mixture then was cooled to room temperature, and the resultant crystalline compound was filtered, washed with methanol and dried to afford the title compound **9a** (860 mg, 88% yield). M.p.: 197–198 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 3320, 3239, 2959, 2852, 1604, 1538, 1408. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.24 (s, 3H), 4.02 (m, 2H), 4.28 (m, 2H), 6.57 (m, 1H), 6.81 (m, 1H), 7.13 (d, J = 8.85 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 7.73 (m, 2H), 8.70 (s, 2H). ^{13}C-NMR ($CDCl_3$) δ: 35.6, 47.9, 66.2, 116.5, 122.2, 125.7, 127.4, 132.1, 132.7, 134.9, 156.2, 160.2, 161.9, 168.8. MS (ESI) m/z (M + 1) 423.

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

*6.1.56. Preparation of 5-(4-{2-[methyl-(5-phenylpyrimidin-2-yl)amino]ethoxy} benzylidene)thiazolidine-2,4-dione (**9b**)*

Yield: 78%. M.p.: 195–196 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 3030, 2954, 1735, 1694, 1537. ^{1}H-NMR (400 MHz, DMSO-

d_6) δ: 3.23 (s, 3H), 4.02 (m, 2H), 4.28 (m, 2H), 7.12 (m, 3H), 7.40 (m, 1H), 7.49 (m, 3H), 7.73 (s, 1H), 8.66 (s, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 37.2, 49.0, 53.4, 66.4, 114.8, 122.8, 125.8, 127.2, 129.1, 129.3, 129.6, 130.0, 132.0, 132.3, 135.6, 155.9, 160.9, 162.2, 163.8, 190.8. MS (ESI) *m/z* (M + 1) 433.

*6.1.57. Preparation of 5-(4-{2-[methyl-(5-pyridin-2-yl-pyrimidin-2-yl)amino]ethoxy} benzylidene)thiazolidine-2,4-dione (**9c**)*

Yield: 70%. M.p.: 180–181 °C. IR (KBr) ν_{max} cm^{-1}: 3010, 2805, 1730, 1696, 1579. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.20 (s, 3H), 3.98 (m, 2H), 4.23 (m, 2H), 7.06 (d, J = 8.84 Hz, 2H), 7.24 (m, 1H), 7.48 (d, J = 8.86 Hz, 2H), 7.74 (m, 2H), 8.52 (m, 1H), 8.97 (s, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 36.8, 48.4, 66.0, 115.8, 119.1, 120.8, 120.8, 122.4, 126.0, 132.1, 132.5, 137.6, 150.0, 153.1, 156.5, 160.5, 161.6, 167.9, 168.4. MS (ESI) *m/z* (M + 1) 434.

*6.1.58. Preparation of 5-(4-{2-[methyl-(5-thiophen-2-yl-pyrimidin-2-yl)amino] ethoxy}benzylidene)thiazolidine-2,4-dione (**9d**)*

Yield: 70%. M.p.: 160–162 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 3108, 2975, 1735, 1684, 1580, 1505, 1402. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.18 (s, 3H), 3.96 (m, 2H), 4.21 (m, 2H), 7.03 (m, 2H), 7.27 (m, 1H), 7.37 (m, 2H), 7.44 (m, 2H), 7.54 (m, 2H), 7.57 (m, 2H), 7.61 (s, 1H), 8.63 (s, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 36.7, 48.4, 65.9, 115.8, 117.2, 120.9, 123.1, 125.1, 126.1, 128.7, 132.1, 132.5, 138.0, 155.1, 160.5, 160.8, 168.0, 168.4. MS (ESI) *m/z* (M + 1) 439.

*6.1.59. Preparation of 5-(4-{2-[(5-furan-2-yl-pyrimidin-2-yl)methylamino]ethoxy} benzyl)thiazolidine-2,4-dione (**10a**). General procedure*

To a stirred solution of **9a** (200 mg, 0.473 mmol) in anhydrous DMF (100 ml) was added $Pd(OH)_2$ on carbon (200 mg) under hydrogen atmosphere at room temperature for 36 h. The mixture was filtered through celite and washed with MeOH. The filtrate was condensed by evaporation under reduced pressure. The concentrate thus obtained was purified by column chromatography over SiO_2 using dichloromethane/methanol (100:1, v/v) as eluent to give the title compound **10a** as a yellowish solid. (136 mg, 68% yield). M.p.: 193–194 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2920, 1750, 1690, 1600. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.04 (m, 1H), 3.23 (s, 3H), 3.34 (m, 1H), 3.97 (m, 2H), 4.13 (m, 2H), 4.87 (m, 1H), 6.58 (m, 1H), 6.81 (m, 1H), 6.88 (m, 2H), 7.13 (m, 2H), 7.71 (s, 1H), 8.70 (s, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 35.8, 37.8, 48.3, 53.6, 65.0, 114.5, 121.5, 125.3, 127.7, 129.6, 129.9, 130.3, 135.9, 156.3, 157.6, 161.0, 172.5, 176.8. MS (ESI) *m/z* (M + 1) 425.

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

*6.1.60. Preparation of 5-(4-{2-[methyl-(5-phenylpyrimidin-2-yl)amino]ethoxy}benzyl) thiazolidine-2,4-dione (**10b**)*

Yield: 70%. M.p.: 183–185 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1740, 1698, 1610, 1536. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.03 (m, 1H), 3.23 (s, 3H), 3.28 (m, 1H), 3.98 (m, 2H), 4.17 (m, 2H), 4.84 (m, 1H), 6.90 (m, 2H), 7.15 (m, 3H), 7.39 (m, 1H), 7.50 (m, 1H), 8.65 (s, 2H), 11.98 (bs, NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 36.6, 48.5, 53.4, 65.6, 114.7, 121.9, 125.8, 127.4, 129.1, 129.4, 130.8, 135.4, 156.1, 157.8, 161.1, 172.1, 176.1. MS (ESI) *m/z* (M + 1) 435.

*6.1.61. Preparation of 5-(4-{2-[methyl-(5-pyridin-2-yl-pyrimidin-2-yl)amino]ethoxy} benzyl)thiazolidine-2,4-dione (**10c**)*

Yield: 40%. M.p.: 168–170 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2937, 2709, 1742, 1699, 1607, 1533. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.98 (m, 1H), 3.19 (s, 3H), 3.24 (m, 1H), 3.95 (m, 2H), 4.11 (m, 2H), 4.79 (m, 1H), 6.83 (m, 2H), 7.08 (m, 2H), 7.21 (m, 1H), 7.77 (m, 2H), 8.53 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 36.6, 48.5, 53.4, 65.5, 114.7, 119.0, 120.7, 122.4, 129.1, 130.8, 137.6, 149.9, 153.1, 156.5, 157.8, 161.6, 172.1, 176.1. MS (ESI) *m/z* (M + 1) 436.

*6.1.62. Preparation of 5-(4-{2-[methyl-(5-thiophen-2-yl-pyrimidin-2-yl)amino]ethoxy} benzyl)thiazolidine-2,4-dione (**10d**)*

Yield: 68%. M.p.: 160–162 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2973, 1740, 1705, 1606, 1538. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.97 (m, 1H), 3.18 (s, 3H), 3.24 (m, 1H), 3.93 (m, 2H), 4.10 (m, 2H), 4.78 (m, 1H), 6.84 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 7.25(m, 1H), 7.35 (m, 2H), 7.57 (m, 2H), 8.63 (s, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 36.7, 48.5, 53.4, 65.5, 114.7, 117.1, 123.1, 125.0, 128.7, 129.1, 130.8, 138.1, 155.1, 157.8, 160.8, 172.1, 176.1. MS (ESI) *m/z* (M + 1) 441.

*6.1.63. Preparation of 4,6-dichloro-2-phenylpyrimidine (**11**)*

To a solution of 2-amino-4,6-dichloropyrimidine (1 g, 6.1 mmol) in anhydrous benzene (50 ml) was added isoamyl nitrite (3 ml, 22.57 mmol) and copper (I) oxide (872 mg, 6.1 mmol). The reaction mixture was refluxed for 3 h through monitoring using TLC. Insoluble materials were removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by column chromatography over silica gel using *n*-hexane/EtOAc (10:1, v/v) as eluent to give the title compound **11** (953 mg, 69% yield). M.p.: 150–152 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2935, 1740, 1698, 1610, 1536. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.29 (s, 1H), 7.54 (m, 3H), 8.46 (m, 2H). MS (ESI) *m/z* (M + 1) 225.

*6.1.64. Preparation of 2-[(6-chloro-2-phenylpyrimidin-4-yl)methylamino]ethanol (**12**)*

To the stirred solution of **11** (953 mg, 4.23 mmol) in anhydrous dichloromethane (30 ml) was added 2-methylaminoethanol (0.4 ml, 5.08 mmol), and the mixture was refluxed for 24 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature and quenched with saturated NH_4Cl solution (50 ml), and extracted with EtOAc (120 ml). The extracted organic layers were washed with water

and brine (50 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography over SiO_2 using a mixture of dichloromethane/methanol (50:1, v/v) as eluent to get the title compound **12** as yellowish oil (747 mg, 67% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 2936, 1605, 1560. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.09 (s, 3H), 3.81 (m, 2H), 3.88 (m, 2H), 6.34 (s, 1H), 7.46 (m, 3H), 8.32 (m, 2H). MS (ESI) *m/z* (M + 1) 264.

*6.1.65. Preparation of 2-[methyl-(2-phenylpyrimidin-4-yl)amino]ethanol (**13**)*

A solution of aminoalcohol compound **12** (747 mg, 2.83 mmol) in a mixture of anhydrous ethanol (20 ml) and ethyl acetate (20 ml) containing triethylamine (1.2 ml, 8.49 mmol) was added 10% palladium on carbon (50 mg) under hydrogen atmosphere (50–55 psi) at room temperature for 15 h. The suspension was filtered using celite and the filtrate was condensed in vacuo. The residue was purified by column chromatography over SiO_2 using a mixture of dichloromethane/methanol (20:1, v/v) as eluent to give the title compound **12** (377 mg, 59% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 3355, 2933, 1605, 1529, 1407. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.09 (s, 3H), 3.84 (m, 2H), 3.90 (m, 2H), 6.32 (d, J = 6.0 Hz, 1H), 7.46 (m, 3H), 8.26 (d, J = 6.1 Hz, 1H), 8.34 (m, 2H). MS (ESI) *m/z* (M + 1) 230.

*6.1.66. Preparation of 4-{2-[methyl-(2-phenylpyrimidin-4-yl)amino]ethoxy}benzaldehyde (**14**)*

To a solution of aminoalcohol **13** (380 mg, 1.67 mmol) in anhydrous DMF (20 ml) was added NaH (60% dispersion in mineral oil, 134 mg, 3.34 mmol), and the mixture was stirred for 1 h at 0 °C under N_2 atmosphere. And 4-fluorobenzaldehyde (0.27 ml, 2.5 mmol) was added dropwise over 15 min. The reaction mixture was stirred at room temperature for 3 h, added carefully to saturated ammonium chloride solution (100 ml), and extracted with ethyl acetate (2 × 50 ml). The combined organic phase was washed with brine (3 × 40 ml), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography on SiO_2 using EtOAc/*n*-hexane (1:1, v/v) as eluent to give the title compound **14** (381 mg, 68% yield). IR ($CHCl_3$) ν_{max} cm^{-1}: 3355, 2933, 1605, 1529, 1407. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.25 (s, 3H), 4.13 (m, 2H), 4.37 (m, 2H), 6.41 (d, J = 6.4 Hz, 1H), 7.02 (d, J = 9.2 Hz, 2H), 7.47 (m, 3H), 7.82 (d, J = 9.2 Hz, 2H), 8.38 (m, 3H), 9.88 (s, 1H). MS (ESI) *m/z* (M + 1) 334.

*6.1.67. Preparation of 5-(4-{2-[methyl-(2-phenylpyrimidin-4-yl)amino]ethoxy}benzyl idene)thiazolidine-2,4-dione (**15**)*

A mixture of an aldehyde compound **14** (200 mg, 0.6 mmol), 2,4-thiazolidinedione (105 mg, 0.9 mmol), and piperidine (0.09 ml, 0.9 mmol) in anhydrous ethanol (80 ml) was refluxed for 24 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), dried over $MgSO_4$, and concentrated by evaporation under reduced pressure. The obtained residue was purified by column chromatography over SiO_2 with *n*-hexane/EtOAc (1:1, v/v) as eluent to give the title compound **15** as a yellowish solid (250 mg, 96% yield). M.p.: 191–193 °C. IR ($CHCl_3$) ν_{max} cm^{-1}:2925, 1753, 1693, 1604. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.17 (bs, 3H), 4.09 (m, 2H), 4.33 (m, 2H), 6.70 (bs, 1H), 7.11 (d, J = 8.8 Hz, 2H), 7.45 (m, 3H), 7.52 (d, J = 8.8 Hz, 2H), 7.71 (s, 1H), 8.30 (m, 3H), 12.5 (bs, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 36.8, 44.1, 48.3, 65.4, 103.6, 114.5, 122.2, 125.4, 126.4, 127.4, 129.8, 135.4, 156.2, 158.0, 164.7, 166.3, 167.1, 169.2. MS (ESI) *m/z* (M + 1) 433.

*6.1.68. Preparation of 5-(4-{2-[methyl-(2-phenylpyrimidin-4-yl)amino]ethoxy} benzyl)thiazolidine-2,4-dione (**16**)*

To a stirred solution of **15** (260 mg, 0.6 mmol) in anhydrous DMF (25 ml) and dried methanol (25 ml) was added $Pd(OH)_2$ on carbon (100 mg) under hydrogen atmosphere at room temperature for 36 h. The mixture was filtered using celite and washed with cooled 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 (50:1, v/v) as eluent to give the title compound **16** as a yellowish solid (100 mg, 74% yield). M.p.: 178–180 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 2920, 1750, 1690, 1600. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.12 (dd, J = 14.4 Hz, 9.2 Hz, 1H), 3.25 (s, 3H), 3.44 (dd, J = 14 Hz, 3.6 Hz, 1H), 4.12 (m, 2H), 4.27 (m, 2H), 4.50 (dd, J = 9.6 Hz, 4.0 Hz, 1H), 6.41 (d, J = 6.0 Hz, 1H), 6.8 (d, J = 6.4 Hz, 2H), 6.86 (d, J = 6.4 Hz, 2H), 7.47 (m, 3H), 8.40 (m, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 36.6, 48.5, 53.4, 65.6, 114.5, 115.9, 121.2, 125.8, 126.4, 127.4, 129.1, 136.5, 156.2, 158.9, 164.7, 166.3, 172.1, 176.1. MS (ESI) *m/z* (M + 1) 435.

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