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Synthesis and Biological Activity of Novel Pyrimidinone Containing Thiazolidinedione Derivatives☆

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Abstract—A series of pyrimidinone derivatives of thiazolidinediones were synthesized. Their biological activity were evaluated in insulin resistant, hyperglycemic and obese db/db mice. In vitro PPARγ transactivation assay was performed in HEK 293T cells. PMT13 showed the best biological activity in this series. **PMT13** (5-[4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethyl]thiazolidine-2,4-dione) showed better plasma glucose, triglyceride and insulin-lowering activity in db/db mice than rosiglitazone and pioglitazone. PMT13 showed better PPARγ transactivation than the standard compounds. Pharmacokinetic study in Wistar rats showed good systemic exposure of PMT13. Twenty-eight day oral toxicity study in Wistar rats did not show any treatment-related adverse effects.

Introduction

Type 2 diabetes is characterised by high level of blood glucose, insulin and impaired insulin action.[1] 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 levels.[2] These TZDs are synthetic, high-affinity ligands of peroxisome proliferator activated receptor-gamma (PPARγ); a member of the nuclear receptor family that controls the expression of genes in the target tissues of insulin action.[3,4] Within a short time after the launch of the TZDs, several reports of treatment-related toxicity have been published. Troglitazone, the first TZD marketed, was withdrawn due to severe liver toxicity.[5] Rosiglitazone, the second TZD launched is a potent ligand of PPARγ[6] and shows efficient insulin sensitization in type 2 diabetes patients.[7] However, even rosiglitazone has been associated with liver, cardiovascular and hematological toxicity.[8]

In order to synthesize novel TZDs with better safety and efficacy, we modified the *N*-methyl-2-pyridyl moiety of rosiglitazone with different heterocycles. One of the promising analogues that resulted from this effort; a TZD with indole as the heterocycle (DRF-2189) has already been reported[9] by us. In our efforts to improve the biological profile of these analogues, we have replaced the indole ring with monocyclic heterocycles like pyrimidinone having amidine moiety in the ring (as shown in Fig. 1). Some angiotensin antagonists were reported with this heterocycle.[10] We report here the structure–activity relationship (SAR) studies of several TZDs featuring pyrimidinone moiety as shown in Figure 1.

Chemistry

A general strategy to synthesize thiazolidinediones **V** is shown in Scheme 1. The starting material, pyrimidinone was prepared according to the literature[10,11] as shown in Scheme 2. The pyrimidinones were treated with 4-(2-bromoethoxy) benzaldehyde[12] in the presence of NaH and LiBr at 80 °C in DMF for 16 h to give a mixture of *O*- and *N*-alkylated compounds in which the latter was the major product. Separation of mixtures by column chromatography yielded both the compounds whose structures were confirmed by NMR and IR and confirmed with the structurally-related series of pyrimidinones.[13] The IR of *N*-alkylated isomer showed distinct amide

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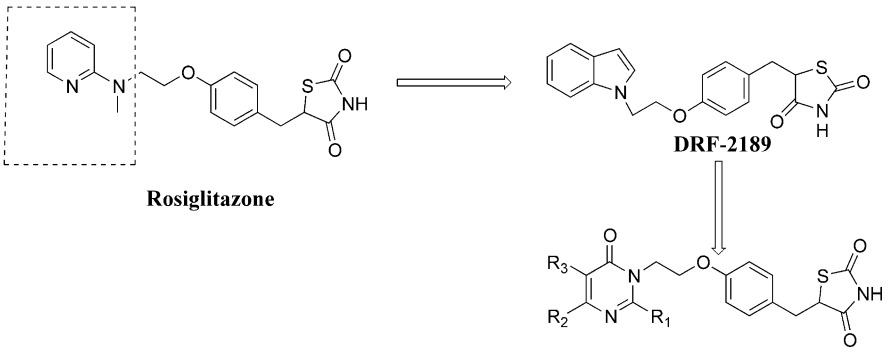
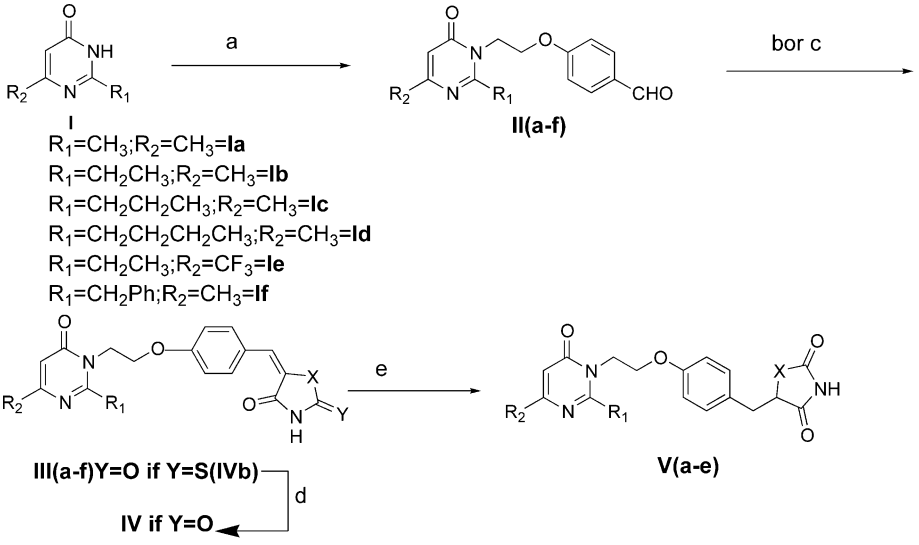
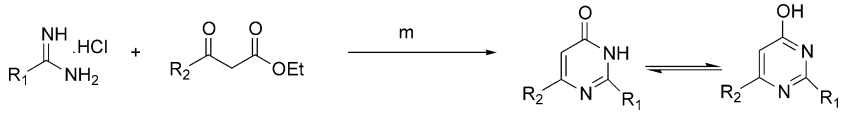


Figure 1. Modification of rosiglitazone to pyrimidinone derivatives of thiazolidinediones.



Scheme 1. (a) 4-[2-Bromoethoxy]benzaldehyde, NaH, LiBr, 80 °C, DMF, 16 h; (b) 2,4-thiazolidine dione, piperidine–$PhCO_2H$, toluene, reflux, 2–4 h; (c) rhodanine, NaOAc, 120 °C, 0.5 h; (d) *m*-CPBA, DMF, 0 °C–rt, 5 h; (e) 10% Pd/C, 1,4-dioxane, 60 psi H_2, RT, 24 h.



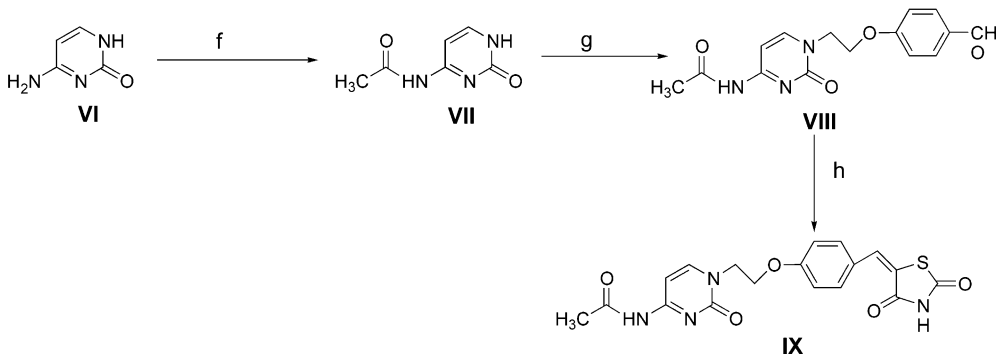
Scheme 2. (m) (i) EtOH, KOH, 0 °C–rt, 3 h; (ii) P_2O_5, 24 h.

carbonyl absorption near 1650 cm^{-1} that did not appear in *O*-alkylated isomers.The aldehyde **II** in the *N*-alkylated compound was condensed with 2,4-thiazolidine-dione to give unsaturated condensed product **III** in high yields. This unsaturated compound **III** was hydrogenated over Pd/C in dioxane as the solvent to give saturated thiazolidinedione **V** as a fluffy powder. In the case of cytosine derived thiazolidinedione **IX**, the cytosine amine was acylated with acetic anhydride in pyridine and the amine acylated cytosine **VII** was alkylated at lactam nitrogen with 4-(2-bromoethoxy) benzaldehyde, with potassium carbonate as base in DMF at 80 °C. The aldehyde **VIII** was condensed with 2,4-thiazolidinedione (Scheme 3).

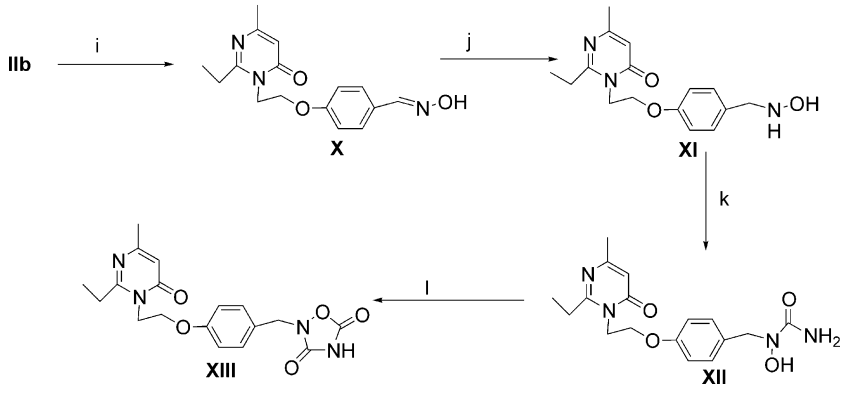
Oxazolidinone **IV** was prepared by condensation of pyrimidinone aldehyde (**IIb**) in the presence of NaOAc at 120 °C neat with 2-thio-1,3-oxazolidine 4-one (rhodanine) to give a condensed product (**IVb**), which in turn converted to oxazolidinedione **IV** by oxidation with *m*-CPBA. Oxadiazolidinedione compound was prepared from aldehyde (**IIb**) by converting it to oxime and then to the *N*-hydroxy uredo (Scheme 4)[14] and cyclizing it to the oxadiazolidinedione.

Results and Discussion

All the thiazolidinedione analogues of pyrimidinones were examined for their plasma glucose (PG) and triglyceride (TG) lowering activities in insulin-resistant and hyperlipidemic db/db mice after oral treatment for 6 days. Rosiglitazone at 30 mg/kg/day for 6 days showed 65% PG and 41% TG lowering activity and used as a standard for comparison. The results after 6



Scheme 3. (f) Ac_2O, pyridine; (g) K_2CO_3, DMF, 80 °C, 12 h; (h) 2,4-thiazolidinedione, piperidine–$PhCO_2H$, toluene, reflux, 4 h.



Scheme 4. (i) NH_2OH, NaOAc, EtOH, reflux, 3 h; (j) $NaCNBH_3$, 4 N HCl, dioxane; (k) KOCN, H_2O, AcOH, 30 °C, 1 h; (l) $ClCO_2Et$, 1 N NaOH, 30 °C, 1 h.

days of treatment (Table 1) revealed that compound **IIIb** showed 55% reduction in PG and 63% reduction in TG. Its saturated version, compound **Vb** (2-ethyl-4-methyl pyrimidinone derivative) (**PMT13**), showed 73% reduction in PG and 85% reduction in TG. Other derivatives like **Va** (2,4-dimethyl-pyrimidinone) showed less PG reduction compared to **PMT13** even at a dose of 100 mg/kg/day. The substitution at the 2-position of pyrimidinone has an effect on the efficacy of the compounds, PG reduction increased from methyl to ethyl derivatives in db/db mice and decreased towards *n*-propyl and *n*-butyl derivatives (**Vc** and **Vd**). Among these, the ethyl derivative was found to be the best compound (**Vb**, **PMT13**). When the alkyl group at the C-2 position of pyrimidinone was changed to benzyl group (**IIIf**) there was a significant reduction in the activity of the compound as compared to **IIIb**. This may be due to the electron withdrawing nature of the aromatic group. When the pyrimidinone **IIIb** was changed to cyclic urea (**IX**), it failed to show any activity at 30 mg/kg. The activity of the oxazolidinedione (**IV**) derivative of pyrimidinones was not better than that of thiazolidinedione **IIIb**. To improve the activity, we substituted CH_3 at C-4 position of the pyrimidinone ring with CF_3 (**Ve**), but did not show desirable effect.

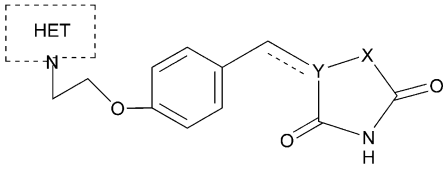
Compound (**XIII**) was prepared by cyclizing its oxime intermediate (Scheme 4), but it did not show any interesting activity. Our study showed that among thiazolidinedione, oxazolidinedione and diazolinedione series of compounds, only thiazolidinediones showed better activity than other two series. Based on the PG and TG lowering-activity in db/db mice, **PMT13** was selected for further studies.

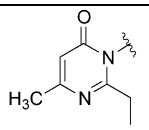
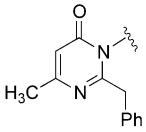
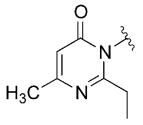
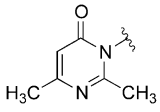
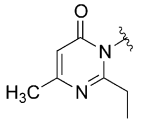
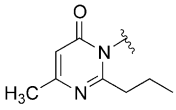
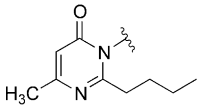
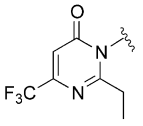
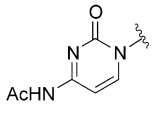
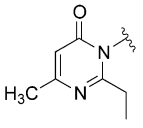
PMT13 was compared with rosiglitazone and pioglitazone, two marketed thiazolidinedione insulin sensitizers. A comparative concentration dependent study was performed in HEK 293T cells to evaluate the PPARγ transactivation potential. **PMT13** showed better activation than pioglitazone. At higher concentration, **PMT13** and rosiglitazone showed similar transactivation potential, but, at lower concentrations **PMT13** showed better activation (Table 2). In the in vivo dose–response study in db/db mice, **PMT13** showed better reduction in plasma triglyceride, glucose and insulin levels than rosiglitazone and pioglitazone (Table 3). These results indicate that **PMT13** is more potent and efficacious than the standard compounds.

Generally, thiazolidinediones have shown hemotoxicity and hepatotoxicity in both animal and clinical studies.[5,8] A 28-day probe toxicity study for **PMT13** was performed in Wistar rats. **PMT13** at 100 mg/kg dose showed no mortality, clinical signs of toxicity or changes in body weight or food consumption. However, mild changes in hemoglobin (−7%) and liver weight (+7%) were observed. The biochemical and histological findings are not suggestive of any treatment-related adverse effects.

To evaluate the pharmacokinetic profile of **PMT13**, a single dose (10 mg/kg) oral study was performed in

Table 1. SAR studies of pyrimidinones **1**–**IX**



Compd	Heterocycles (HET)	X	Y	Double bond	Dose (mg/kg/day)	% Redn. in PG	% Redn. in TG
IIIb		S	C	Yes	30	55	63
IIIf		S	C	Yes	100	27	NE
IV		O	C	Yes	30	10	NE
Va		S	CH	No	100	56	76
Vb (PMT13)		S	CH	No	30	73	85
Vc		S	CH	No	30	40	48
Vd		S	CH	No	30	29	15
Ve		S	CH	No	30	53	43
IX		S	C	Yes	30	NE	NE
XIII		O	N	No	30	14	NE
	Rosiglitazone	S	CH	No	30	65	41

Male db/db mice were treated orally with the compounds for 6 days and plasma glucose and triglyceride levels were measured. Percentage reduction was calculated according to the formula: $1-[(TT/OT)/(TC/OC)]\times 100$; TT: test day treated, OT: zero day treated, TC: test day control, OC: Zero day control; NE: no effect; PG: plasma glucose; TG: plasma triglyceride.

Table 2. Effect of PMT13, rosiglitazone and pioglitaone in PPAR transactivation assay

Concentration (μM)	PMT13 (Fold activation)	Rosiglitazone (Fold activation)	Pioglitazone (Fold activation)
0.010	0.92	0.80	0.1
0.050	2.58	1.80	0.3
0.200	7.79	4.46	1.2
1.0	16.66	15.04	3.8
5.0	20.04	19.33	6.0

HEK 293T cells were transfected with GAL4-PPARγ1 and pgl2-gal4X5-Luc plasmids. Transfected cells were treated with the compounds at the concentrations mentioned. Each data point represents mean of two experiments.

Table 3. Comparative effect of PMT13, rosiglitazone and pioglitazone in db/db mice

Compd	Dose (mg/kg/day)	Plasma glucose (Percent Reduction)	Triglyceride (% reduction)	Insulin (% reduction)
PMT13	0.3	31.1±2.5	31.5±3.1	16.7±1.2
PMT13	3.0	57.5±1.2	53.8±2.5	69.2±3.1
PMT13	10.0	72.2±0.9	59.4±1.8	77.3±2.4
Rosigltazone	0.3	18.5±5.6	NE	NE
Rosigltazone	3.0	42.3±3.4	23.6±2.5	30.5±3.1
Rosigltazone	10.0	47.1±2.7	40.5±1.12	41.7±4.4
Pioglitazone	0.3	19.4±3.5	14.7±1.9	12.2±2.1
Pioglitazone	3.0	38.5±2.4	36.1±1.7	45.6±2.3
Pioglitazone	10.0	46.2±2.9	46.9±1.6	57.8±1.3

Male db/db mice were treated for 15 days orally with the compounds at the doses mentioned. Values are mean±SE ($n=5$). Percentge reduction was calculated as mentioned in Table 1.

Wistar rats. The compound showed good oral exposure and pharmacokinetic profile as shown in Table 4.

Conclusion

Untreated insulin resistance not only leads to hyperglycemia, but also hyperlipidemia. Insulin-sensitizing thiazolidinediones, marketed recently, are known to act through PPARγ. In this communication, we have shown that pyrimidinone derivatives of thiazolidinedione have an interesting insulin-sensitizing property. **PMT13**, the best compound in this series is a potent PPARγ activator and showed plasma glucose, insulin and triglyceride-lowering activity. In both in vivo and in vitro studies, the compound showed better efficacy than the reference thiazolidinediones (i.e., pioglitazone and rosiglitazone). Subchronic oral toxicity study in Wistar rats did not show any treatment-related adverse effects. The compound has also shown good systemic exposure in rats after oral administration. It is important to note that a drug that ameliorates insulin resistance and also lowers triglyceride is preferable for treatment of both hyperglycemia and cardiovascular complications of type 2 diabetes patients. Therefore, by virtue of its potent PPARγ activation, antidiabetic and triglyceride lowering activity **PMT13** is a potential drug candidate for the treatment of the metabolic syndrome. Further development work on this compound is in progress.

Table 4. Pharmacokinetic profile of PMT13 in Wistar rats

Parameters	PMT13
$AUC_{(0-\infty)}$ (μg h/mL)	206.84±43.78
C_{max} (μg/mL)	39.23±4.55
t_{max} (h)	1.25±0.88
K_{el} (h^{-1})	0.26±0.09
$t_{1/2}$ (h)	3.02±1.12

Experimental

Animals and treatment

Male C57 BL/Ks J-db/db mice were from the breeding stock of DRF animal house generated from an original stock of Jackson Laboratories, Maine, USA. All animals were maintained under 12 h light and 12 h dark cycle at 25±1 °C. All animals were given standard chow (National Institute of Nutrition, India) and water ad libitum. All animal experiments were carried out in accordance with internationally valid guidelines. All experimental protocols were approved by DRF animal ethics committee.

In preliminary studies db/db mice (8–9 weeks) were treated with drugs orally at 30 or 100 mg/kg/day for 6 days. Animals in control groups received vehicle alone (0.25% CMC, 10 mL/kg). During dose response study, db/db mice were treated with **PMT13,** rosiglitazone and pioglitazone at 0.3, 3 and 10 mg/kg/day doses for 15 days. Blood samples were collected from animals, in fed state, under mild ether anesthesia from retro-orbital sinus 1 h after drug administration. Plasma samples were separated for glucose, triglycerides and insulin measurement.

For subacute toxicity study, 6–8-week old Wistar rats (obtained from National Institute of Nutrition, Hyderabad, India) of either sex (110–160 g) were divided randomly into two groups, each consisting of four males and four females. PMT13 was administered orally daily at 100 mg/kg dose, while the control group received the vehicle only. On the day of termination (28th day),

blood was collected from retro-orbital sinus under light ether anesthesia for clinical pathological parameters followed by autopsy and macroscopic examination.

PPAR transactivation assay

The response element (UASGAL4 X 5) is present upstream of pFR-Luc reporter (Promega, WI, USA) that contains Simian virus early promoter for luciferase assay. GAL4 fusions were made by fusing human PPARγ1 ligand binding domain (amino acids: 174–475) to the C-terminal end of yeast GAL4 DNA binding domain (amino acids: 1–147) of pM1 vector. pAdVantage vector was used to enhance luciferase expression. HEK 293T cells were transfected with relevant plasmids by superfect as per the supplier's instruction manual. Forty-two h after transfection, cells were treated for 18 h with the test compounds. DMSO (0.1%) was used as blank. Luciferase activity was determined as fold activation relative to untreated cells by using Luclite kit (Packard Instrument Co, Meriden, CT, USA) in a Packard Top Count (Packard Instrument Co.)

Pharmacokinetic studies

All studies were carried out in male Wistar rats obtained from National Institute of Nutrition (Hyderabad, India). The animals (200–225 gm) were fasted 12 h before starting the experiment and they had free access to water throughout the experiment period. Animals were fed 3 h after drug administration.

Single-dose pharmacokinetics. Animals were administered the drug at 10 mg/kg per orally as 0.5% CMC suspension and about 0.3 mL of blood sample was collected into heparinised microfuge tubes at different time points from retro-orbital sinus. To 0.1 mL of plasma, internal standard (another thiazolidinedione) was added and drugs were extracted with a suitable solvent mixture. Solvent was evaporated and residue was reconstituted with mobile phase and injected into HPLC system. The samples were analyzed by reverse-phase HPLC to generate plasma concentration time profiles.

Pharmacokinetic parameters such as $AUC_{(0-\infty)}$, K_{el}, half-life, C_{max} and t_{max} were calculated using non-compartmental model analysis. $AUC_{(0-\infty)}$ is the area under the plasma concentration versus time curve extrapolated to infinity, Kel is the elimination rate constant, C_{max} is the observed maximum plasma concentration and t_{max} is the time at which maximum concentration (C_{max}) is reached.

HPLC assay. The HPLC system includes a Waters LC Module-1, Millennium software and a Suplecosil C_{18} (ODS) column (5 μm, 4.6×250 mm). Analysis of **PMT13** was carried out using 0.05 M NaH_2PO_4 buffer (pH: 4.0)/methanol/acetonitrile (55:7:38; v/v) as mobile phase at a flow rate of 1 mL/min. Eluate from the column was monitored by UV detector (Waters LC Module) set at 275 nm. Under these conditions retention times for **PMT13** and IS were, respectively, 8.5 and 12.0 min. Absolute recovery was >95%, the limit of quantification was 0.2 μg/mL and response was linear up to 50 μg/mL.

Synthesis

Melting points were determined on Veego melting point apparatus and are uncorrected. Infra red spectra were recorded on Perkin-Elmer FT-IR 1600 spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini 200 MHz spectrometer with TMS as the internal standard. Mass spectra were recorded on HP-5989A mass spectrometer. Elemental analysis was performed with Perkin-Elmer, 2400 series II CHN-O analyzer. Column chromatography was performed by using silicagel (200–400 mesh, SRL) with the indicated solvent. 4-(2-Bromoethoxy) benzaldehyde[11] and pyrimidinones were prepared according to the general method[10,11] given in Scheme 2.

Preparation of 4-[2-[2,4-disubstituted-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] benzaldehyde (IIa–f)

Preparation of 4-[2-[4-methyl-2-propyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] benzaldehyde (IIc). To a stirred suspension of NaH (570 mg, 22.57 mmol) in dry DMF (35 mL) at 25 °C was added a solution of 4-methyl-2-propyl-1,6-dihydro-6-pyrimidinone (2.64 g, 17.36 mmol) in dry DMF. After the effervescence had ceased (about 15 min), anhydrous LiBr (3.51 g, 40 mmol) was added followed by 4-[2-bromoethoxy]benzaldehyde[12] (4.37 g, 19.08 mmol) in dry DMF at the same temperature. The reaction was continued at 80 °C for 16 h. The reaction mixture was cooled to room temperature, poured into water and extracted with ethyl acetate (EtOAc), the combined EtOAc extracts were washed with water, brine, dried over Na_2SO_4 and concentrated. The crude compound was chromatographed on silicagel using 3:7 EtOAc–petroleum ether, to yield 1.61 g (31%) of the title compound. IR (KBr) 1700, 1680 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 9.80 (s, 1H), 7.82 (d, J = 8.72 Hz, 2H), 6.95 (d, J = 8.72 Hz, 2H), 4.45 (t, J = 5.30 Hz, 2H), 4.35 (t, 5.30 Hz, 2H), 2.92 (t, J = 7.50 Hz, 2H), 2.25 (s, 3H), 1.92–1.70 (m, 2H), 1.20 (t, J = 7.50 Hz, 3H); CIMS m/z 301 $(M+H)^+$. Analysis calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.32. Found: C, 68.10; H, 6.52; N, 9.44%.

In the same manner, the following compounds were obtained.

Preparation of 4-[2-[2,4-dimethyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] benzaldehyde (IIa). Yield = 30%; IR (KBr) 1742, 1710, 1685 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 9.90 (s, 1H), 7.80 (d, J = 8.70 Hz, 2H), 7.02 (d, J = 8.70 Hz, 2H), 6.20 (s, 1H), 4.50–4.30 (m, 4H), 2.70 (s, 3H); CIMS m/z 273 $(M+H)^+$. Analysis calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.28. Found: C, 66.36; H, 5.83; N, 10.40%.

Prepration of 4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] benzaldehyde (IIb). Yield = 42%; IR (KBr) 1700, 1681 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 9.90 (s, 1H), 7.80 (d, J = 8.70 Hz, 2H), 6.98 (d, J = 8.70 Hz, 2H), 6.20 (s, 1H), 4.52–4.25 (m, 4H), 3.02 (q, J = 7.40 Hz, 2H), 2.30 (s, 3H), 1.40 (t, J = 7.40 Hz, 3H); CIMS m/z 287 $(M+H)^+$. Analysis calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.33; N, 9.78. Found: C, 67.01; H, 6.25; N, 9.49%.

Preparation of 4-[2-[2-butyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl] ethoxy]benzaldehyde (IId). Yield = 31%; IR (KBr) 1701, 1692 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 9.90 (s, 1H), 7.84 (d, J = 8.72 Hz, 2H), 6.98 (d, J = 8.72 Hz, 2H), 6.20 (s, 1H), 4.52–4.30 (m, 4H), 2.96 (t, J = 7.47 Hz, 2H), 2.26 (s, 3H), 1.90–1.70 (m, 2H), 1.70–1.50 (m, 2H), 1.01 (t, J = 7.47 Hz, 3H); EIMS m/z 315 (M^+). Analysis calcd for $C_{18}H_{22}N_2O_3$: C, 68.76; H, 7.05; N, 8.91. Found: C, 68.54; H, 7.28; N, 8.59%.

Preparation of 4-[2-[2-ethyl-4-trifluoromethyl-6-oxo-1,6-dihydro-1-pyrimidinyl] ethoxy]benzaldehyde (IIe). Yield = 31%; IR (KBr) 1695, 1692 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 9.89 (s, 1H), 7.83 (d, J = 8.67 Hz, 2H), 6.95 (d, J = 8.67 Hz, 2H), 6.70 (s, 1H), 4.50 (t, J = 4.66 Hz, 2H), 4.39 (t, J = 4.66 Hz, 2H), 3.1 (q, J = 7.4 Hz, 2H), 1.4 (t, J = 7.4 Hz, 3H); CIMS m/z 341 $(M+H)^+$. Analysis calcd for $C_{16}H_{15}F_3N_2O_3$: C, 56.47; H, 4.44; N, 8.23. Found: C, 56.52; H, 4.23; N, 8.17%.

Preparation of 4-[2-[2-benzyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] benzaldehyde (IIf). Yield = 31%; IR (KBr) 1695, 1675 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 9.89 (s, 1H), 7.83 (d, J = 8.72 Hz, 2H), 7.45–7.15 (m, 5H), 6.98 (d, J = 8.72 Hz, 2H), 6.44 (s, 1H), 4.70 (t, J = 4.71 Hz, 2H), 4.30 (t, J = 4.71 Hz, 2H), 4.14 (s, 2H), 2.42 (s, 3H); EIMS m/z 348 (M^+). Analysis calcd for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.78; N, 8.04. Found: C, 72.48; H, 5.69; N, 7.94%.

Preparation of 4-[2-[4-*N*-acetylamino-2-oxo-1,2-dihydro-1-pyrimidinyl]ethoxy] benzaldehyde (VIII) (Scheme 3). To the N^4-acetyl cytosine [Aldrich sample or can be prepared from cytosine by acetylation with Ac_2O/pyridine (Scheme 3)] (1.8 g, 11.9 mmol) in DMF (30 mL) was added K_2CO_3 (3.28 g, 23.8 mmol) and 4-[2-bromoethoxy]benzaldehyde (2.72 g, 11.9 mmol), the mixture was heated at 80 °C for 14 h .The reaction mixture was cooled to RT, filtered and the filterate was worked up in a usual way to yield 1.8 g (66%) of the product. IR (KBr) 1651, 1695 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 9.90 (s, 1H), 8.70 (bs, 1H, D_2O exchangeable), 7.85 (d, J = 8.70 Hz, 2H), 7.75 (d, J = 7.80 Hz, 1H), 7.42 (d, J = 7.80 Hz, 1H), 6.95 (d, J = 8.70 Hz, 2H), 4.40–4.20 (m, 4H), 2.30 (s, 3H); EIMS m/z 301 (M^+). Analysis calcd for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.94. Found: C, 59.57; H, 4.85; N, 13.86%.

Prepration of 5-[4-[2-[2,4-disubstituted-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethylene]thiazolidine-2,4-dione [III(a–f)] and 5-[4-[2-[2,4-disubstituted-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy]phenylmethylene]-2-thio-1,3-oxazolidine-4-one (IV)

Preparation of 5-[4-[2-[4-methyl-2-propyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethylene]thiazolidine-2,4-dione (IIIc). A mixture of 4-[2-[4-methyl-2-propyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] benzaldehyde **IIc** (1.0 g, 2.45 mmol), thiazolidine-2,4-dione (0.35 g, 3 mmol), benzoic acid (38.8 mg,0.32 mmol) and piperidine (30.3 mg, 0.37 mmol) in toluene (10 mL) was refluxed for 2–4 h. with continuous removal of water. The reaction mixture was cooled to room temperature and the resultant crystalline compound was filtered and washed with water and dried to afford the title compound. Yield = 1.23 g, 99%; mp: 240–242 °C; IR (KBr) 1739, 1697, 1643; ^1H NMR (δ in $CDCl_3$) 12.40 (bs, 1H, D_2O exchangeable), 7.75 (s, 1H), 7.54 (d, J = 8.72 Hz, 2H), 7.02 (d, J = 8.72 Hz, 2H), 6.15 (s, 1H), 4.45–4.15 (m, 4H), 2.91 (t, J = 7.65 Hz, 2H), 2.20 (s, 3H), 1.90–1.65 (t, J = 7.65 Hz, 3H); CIMS m/z 400$(M+H)^+$. Analysis calcd for $C_{20}H_{21}N_3O_4S$: C, 60.13; H, 5.29; N, 10.52. Found: C, 60.00; H, 5.13; N, 10.46%.

In the same manner, the following compounds were obtained.

Preparation of 5-[4-[2-[2,4-dimethyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethylene]thiazolidine-2,4-dione (IIIa). Yield = 95%; mp 235 °C; IR (KBr) 1743, 1703, 1672; ^1H NMR (δ in $CDCl_3$) 8.50 (bs, 1H, D_2O exchangeable), 7.80 (s, 1H), 7.48 (d, J = 8.40 Hz, 2H), 6.98 (d, J = 8.40 Hz, 2H), 6.21 (s, 1H), 4.52–4.30 (m, 4H), 2.70 (s, 3H), 2.25 (s,3H); CIMS m/z 372 $(M+H)^+$. Analysis calcd for $C_{18}H_{17}N_3O_4S$: C, 58.21; H, 4.61; N, 11.31. Found: C, 58.14; H, 4.47; N, 11.52%.

Preparation of 5-[4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethylene]thiazolidine-2,4-dione (IIIb). Yield = 92%; mp 248–250 °C; IR (KBr) 1751, 1692 cm^{-1}; ^1H NMR (δ in $CDCl_3$ + DMSO-d_6) 12.25 (bs, 1H, D_2O exchangeable), 7.78 (s, 1H), 7.40 (d, J = 7.40 Hz, 2H), 7.0 (d, J = 7.40 Hz, 2H), 6.20 (s, 1H), 4.48–4.24 (m, 4H), 3.0 (q, J = 6.4 Hz, 2H), 2.20 (s, 3H), 1.28 (t, J = 6.4 Hz, 3H); CIMS m/z 386 $(M+H)^+$. Analysis calcd for $C_{19}H_{19}N_3O_4S$: C, 59.20; H, 4.97; N, 10.90. Found: C, 59.08; H, 4.67; N, 10.55%.

Preparation of 5-[4-[2-[2-butyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethylene]thiazolidine-2,4-dione (IIId). Yield = 31%; IR (KBr) 1734, 1695, 1647 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 7.80 (s, 1H), 7.40 (d, J = 8.63 Hz, 2H), 6.95 (d, J = 8.63 Hz, 2H), 6.21 (s, 1H), 4.55–4.22 (m, 4H), 2.95 (t, J = 7.47 Hz, 2H), 2.25 (s, 3H), 1.85–1.60 (m, 2H), 1.60–1.40 (m, 2H), 0.99 (t, J = 7.10 Hz, 3H); CIMS m/z 414 $(M+H)^+$. Analysis calcd for $C_{21}H_{23}N_3O_4S$: C, 60.99; H, 5.60; N, 10.16. Found: C, 60.69; H, 5.62, N, 9.79%.

Preparation of 5-[4-[2-[2-ethyl-4-trifluoromethyl-6-oxo-1,6-dihydro-1-pyrimidinyl] ethoxy]phenylmethylene]thiazoline-2,4-dione (IIIe). Yield = 31%; mp > 250 °C IR (KBr) 1748, 1700, 1680 cm^{-1}; ^1H NMR (δ in $CDCl_3$ + DMSO-d_6) 7.70 (s, 1H), 7.45 (d, J = 8.3 Hz, 2H), 6.95 (d, J = 8.3 Hz, 2H), 6.69 (s, 1H), 4.50 (t, J = 4.5 Hz, 2H), 4.35 (t, J = 4.5 Hz, 2H), 3.11 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H); CIMS m/z 440 $(M+H)^+$. Analysis calcd for $C_{19}H_{16}F_3N_3O_4S$: C, 51.93; H, 3.67; N, 9.56. Found: C, 51.77; H, 3.63; N, 9.84%.

Preparation of 5-[4-[2-[2-benzyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethylene]thiazolidine-2,4-dione (IIIf). Yield = 66%; mp 223 °C; IR (KBr) 1733, 1701 cm^{-1}; ^1H NMR (δ in $CDCl_3$ + DMSO-d_6) 7.74 (s, 1H), 7.44 (d, J = 8.71 Hz, 2H), 7.40–7.10 (m, 5H), 6.95 (d, J = 8.71 Hz, 2H), 6.26 (s, 1H), 4.38 (s, 2H),

4.35–4.10 (m, 4H), 2.32 (s, 3H); CIMS m/z 448 $(M+H)^+$. Analysis calcd for $C_{24}H_{21}N_3O_4S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.52; H, 4.59; N, 9.03%.

Preparation of 5-[4-[2-[4-acetylamino-2-oxo-1,2-dihydro-1-pyrimidinyl]ethoxy] phenylmethylene]thiazolidine-2,4-dione (IX). Yield = 1.8 g, 81%; mp 274 °C; IR (KBr) 1720, 1681, 1630 cm^{-1}; ^1H NMR (δ in $CDCl_3$ + DMSO-d_6) 10.85 (s, 1H, D_2O exchangeable), 8.11 (d, J = 7.2 Hz, 1H),7.74 (s, 1H) 7.55 (d, J = 8.30, 2H), 7.17 (d, J = 7.20 Hz, 1H), 7.11 (d, J = 8.30 Hz, 2H), 4.40–4.05 (m, 4H), 2.08 (s, 3H); CIMS m/z 401$(M+H)^+$. Analysis calcd for $C_{18}H_{16}N_4O_5S$: C, 53.99; H, 4.03; N, 13.99. Found: C, 53.69; H, 3.66; N, 13.68%.

Preparation of 5-[4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethylene]-2-thio-1,3-oxazolidine-4-one (IVb). An immate mixture of 4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] benzaldehyde **IIb** (286 mg, 1.0 mmol), 2-thioxo-4-thiazolidinone (rhodanine) (175 mg, 1.5 mmol) and anhydrous sodium acetate (246 mg, 3.0 mmol) was heated at 120 °C under reduced pressure (2.0 torr) and stirred for 30 min. After cooling to room temperature the reaction mixture was poured in to ethyl acetate (80 mL) and water (20 mL) and stirred for 30 min, the aqueous layer was separated acidified to pH 4 with 2 N HCl. The solid separated, which was filtered and dried to yield the title compound, 207 mg, 54%; IR (KBr) 1710, 1645 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 7.76 (d, J = 8.62 Hz, 2H), 6.93 (d, J = 8.62 Hz, 2H), 6.59 (s, 1H), 6.17 (s, 1H), 4.50–4.30 (m, 4H), 2.98 (q, J = 7.47 Hz, 2H), 2.27 (s, 3H), 1.35 (t, J = 7.47 Hz, 3H); CIMS m/z 386 $(M+H)^+$. Analysis calcd for $C_{19}H_{19}N_3O_4S$: C, 59.20; H, 4.97; N, 10.90. Found: C, 59.01; H, 4.88, N, 10.61%.

Preparation of 5-[4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethylene]oxazolidine-2,4-dione (IV). To a stirred solution of 5-[4-[2-[2ethyl-4methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethylene]-2-thio-1,3-oxazolidine-4-one (**IV b**) (100 mg, 0.259 mmol) in dry DMF (2 mL) was added 3-chloroperbenzoic acid (65%, 179 mg, 0.68 mmol) at 0 °C and stirred for 30 min at 0–10 °C and then at 30 °C for 5 h. The reaction mixture was diluted with ethyl acetate (10 mL), washed with water (5 mL) and then with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography to yield the title compound, 72 mg, 75%; IR (KBr) 1745, 1701, 1670 cm^{-1}; ^1H NMR (δ in $CDCl_3$ + DMSO-d_6) 7.68 (d, J = 8.72 Hz, 2H), 6.91 (d, J = 8.72 Hz, 2H), 6.61 (s, 1H), 6.16 (s, 1H), 4.50–4.38 (m, 2H), 4.38–4.00 (m, 2H), 3.12 (q, J = 7.47 Hz, 2H), 2.24 (s, 3H), 1.35 (t, J = 7.47 Hz, 3H); CIMS m/z 369 (M^+). Analysis calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.37. Found: C, 61.57; H, 5.08; N, 11.44%.

Preparation of 4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] benzaldehyde oxime (X) (Scheme 4). To a stirred solution of hydroxylamine hydrochloride (10 g, 143 mmol) and Sodium acetate (20 g, 146.9 mmol) in water (100 mL) at 30 °C was added a hot solution of 4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy]benzaldehyde **IIb** (5.72 g, 20 mmol) in ethanol (100 mL). The reaction mixture was refluxed at 95 °C for 3 h. The reaction mixture was then cooled to rt concentrated to a volume where crystals of oxime started separating out and the mixture was kept aside for 30 min to 1 h at 25 °C. The resultant crystals were filtered and washed with water and dried to obtain the title compound, 5.4 g, 90% yield. IR (KBr) 3430, 1680 cm^{-1}; ^1H NMR (δ in $CDCl_3$ + DMSO-d_6) 10.56 (s, 1H, OH, D_2O exchangeable), 8.08 (s, 1H), 7.55 (d, J = 8.56 Hz, 2H), 6.88 (d, J = 8.56 Hz, 2H), 6.20 (s, 1H), 4.51–4.40 (m, 2H), 4.40–4.28 (m, 2H), 3.05 (q, J = 7.06 Hz, 2H), 2.30 (s, 3H), 1.40 (t, J = 7.06 Hz, 3H); CIMS m/z 301 $(M+H)^+$. Analysis calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.35; N, 13.94. Found: C, 63.47; H, 6.05; N, 13.66%.

Preparation of 4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] benzyl hydroxyl amine (XI). To a solution of 4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] benzaldehyde oxime X (301 mg, 1.0 mmol) in a mixture of methanol (3 mL) was added 4 N HCl (2 mL) in dioxane at 30 °C was added $NaCNBH_3$ (0.508 mmol) and stirred for 10 min at the same temperature. The reaction mixture was made alkaline to pH = 9.0 with 1 N NaOH and extracted with EtOAc. The combined extracts were washed with brine and dried over Na_2SO_4 and concentrated to yeild the title compound. 272 mg; 90%; IR (KBr) 3400, 3240 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 7.23 (d, J = 8.72 Hz, 2H), 6.80 (d, J = 8.72 Hz, 2H), 6.18 (s, 1H), 4.45–4.35 (m, 2H), 4.35–4.20 (m, 2H), 3.98 (s, 2H), 3.01 (q, J = 7.56 Hz, 2H), 2.22 (s, 3H), 1.32 (t, J = 7.56 Hz, 3H); CIMS m/z 304 $(M+H)^+$. Analysis calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.97; N, 13.85. Found: C, 63.27; H, 7.02; N, 13.68%.

Preparation of 4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] benzyl]N-hydroxy urea (XII). To a stirred solution of 4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl] ethoxy] benzyl hydroxyl amine **XI** (303 mg, 1.0 mmol) in a mixture of water (2 mL) and acetic acid (0.5 mL) was added a solution of KOCN (343 mg, 3.0 mmol) in water (1 mL) and stirred for 1 h at 30 °C. The reaction mixture was diluted with water and extracted with ethyl acetate and the combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated to yield, 295 mg, 85%; IR (KBr) 3400, 3200 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 7.18 (d, J = 8.65 Hz, 2H), 6.90 (d, J = 8.65 Hz, 2H), 6.60 (bs, 1H, D_2O exchangeable), 6.15 (s, 1H), 5.85 (bs, 1H, D_2O exchangeable), 4.70 (s, 2H), 4.50 (bs, 1H, D_2O exchangeable), 4.40–4.30 (m, 2H), 4.22–4.10 (m, 2H), 2.92 (q, J = 7.56 Hz, 2H), 2.20 (s, 3H), 1.20 (t, J = 7.56 Hz, 3H); EIMS m/z 334 (M^+). Analysis calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.65; H, 7.33; N, 9.04%.

Prepration of 5-[4-[2-[2,4-disubstituted-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethyl]thiazolidine-2,4-dione (Va–e)

Preparation of 5-[4-[2-[4-methyl-2-propyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethyl]thiazolidine-2,4-dione (Vc). A solution of 5-[4-[2-[4-methyl-2-propyl-6-

oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethylene]thiazolidine-2,4-dione IIIc (5.0 g, 12.46 mmol) in dioxane (75 mL) was hydrogenated in the presence of 10%Pd/C (12.0 g) at 60 psi for 24 h. The mixture was filtered through a bed of Celite. The filtrate was evaporated under reduced pressure and purified by column chromatography using 2:1 EtOAc/petroleumether to afford the title compound as white fluffy solid. Yield = 4.6 g, 92%; mp 144–146 °C; IR (KBr) 1750, 1704, 1640 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 8.25 (bs, 1H, D_2O exchangeable), 7.12 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 7.48 Hz, 2H), 6.21 (s, 1H), 4.47 (dd, J = 9.36, 4.06 Hz, 1H), 4.41 (t, J = 4.47 Hz, 2H), 4.26 (t, J = 4.47 Hz, 2H), 3.41 (dd, J = 14.11, 4.06 Hz, 1H), 3.10 (dd, J = 14.11, 9.36 Hz, 1H), 2.92 (t, J = 7.63 Hz, 2H), 2.24 (s, 3H), 1.90–1.60 (m, 2H), 1.05 (t, J = 7.65 Hz, 3H); CIMS m/z 402 $(M+H)^+$. Analysis calcd for $C_{20}H_{23}N_3O_4S$: C, 59.83; H, 5.77; N, 10.46. Found: C, 59.68; H, 5.84; N, 10.18%.

In the same manner, the following compounds were obtained.

Preparation of 5-[4-[2-[2,4-dimethyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethyl]thiazolidine-2,4-dione (Va). Yield 85%; mp = 170 °C; IR (KBr) 1750, 1697 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 8.15 (bs, 1H, D_2O exchangeable), 7.14 (d, J = 8.30 Hz, 2H), 6.80 (d, J = 8.30 Hz, 2H), 6.21 (s, 1H), 4.50 (dd, J = 9.13, 3.73 Hz, 1H), 4.48–4.20 (m, 4H), 3.41 (dd, J = 14.12, 3.73 Hz, 1H), 3.13 (dd, J = 14.12, 9.13 Hz, 1H), 2.70 (s, 3H), 2.25 (s, 3H); CIMS m/z 374 $(M+H)^+$. Analysis calcd for $C_{18}H_{19}N_3O_4S$: C, 57.89; H, 5.13; N, 11.25. Found: C, 57.68; H, 5.02; N, 11.32%.

Preparation of 5-[4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethyl]thiazolidine-2,4-dione (Vb). Yield = 82%; mp 155 °C; IR (KBr) 1749, 1708, 1670 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 8.65 (bs, 1H, D_2O exchangeable), 7.12 (d, J = 8.51 Hz, 2H), 6.79 (d, J = 8.51 Hz, 2H), 6.21 (s, 1H), 4.43 (dd, J = 9.27, 3.83 Hz, 1H), 4.42 (t, J = 4.57 Hz, 2H), 4.26 (t, J = 4.57 Hz, 2H), 3.41 (dd, J = 14.11, 3.83 Hz, 1H), 3.11 (dd, J = 14.11, 9.27 Hz, 1H), 2.99 (q, J = 7.47 Hz, 2H), 2.25 (s, 3H), 1.34 (t, J = 7.47 Hz, 3H); CIMS m/z 388 $(M+H)^+$. Analysis calcd for $C_{19}H_{21}N_3O_4S$: C, 58.90; H, 5.46; N, 10.84. Found: C, 58.69; H, 5.18; N, 10.67%.

Preparation of 5-[4-[2-[2-butyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethyl]thiazolidine-2,4-dione (Vd). Yield = 78%; mp 150–152 °C; IR (KBr) 1747, 1702, 1640 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 9.53 (bs, 1H, D_2O exchangeable), 7.13 (d, J = 8.40 Hz, 2H), 6.79 (d, J = 8.40 Hz, 2H), 6.22 (s, 1H), 4.45 (dd, J = 9.22, 3.83 Hz, 1H), 4.42 (t, J = 4.57 Hz, 2H), 4.26 (t, J = 4.57 Hz, 2H), 3.42 (dd, J = 14.12, 3.83 Hz, 1H), 3.09 (dd, J = 14.12, 9.22 Hz, 1H), 2.95 (t, J = 7.47 Hz, 2H), 2.24 (s, 3H), 1.85–1.65 (m, 2H), 1.58–1.32 (m, 2H), 0.98 (t, J = 7.38 Hz, 3H); CIMS m/z 416 $(M+H)^+$. Analysis calcd for $C_{21}H_{25}N_3O_4S$: C, 60.70; H, 6.06; N, 10.11. Found: C, 60.44; H, 6.08; N, 10.12%.

Preparation of 5-[4-[2-[2-ethyl-4-trifluoromethyl-6-oxo-1,6-dihydro-1-pyrimidinyl] ethoxy]phenylmethyl]thiazolidine-2,4-dione (Ve). Yield = 66%; mp 135 °C; IR (KBr) 1752, 1715, 1680 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 7.11 (d, J = 8.53 Hz, 2H), 6.77 (d, J = 8.53 Hz, 2H), 6.70 (s, 1H), 4.52–4.38 (m, 1H), 4.46 (t, J = 4.68 Hz, 2H), 4.28 (t, J = 4.68 Hz, 2H), 3.4 (dd, J = 14.21, 3.83 Hz, 1H), 3.20–2.98 (m, 3H), 1.38 (t, J = 7.33 Hz, 3H); CIMS m/z 441 (M^+). Analysis calcd for $C_{19}H_{18}F_3N_3O_4S$: C, 51.70; H, 4.11; N, 9.52. Found: C, 51.85; H, 3.88; N, 9.41%.

Preparation of 5-[4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl] ethoxy]phenylmethyl]-1,2,4-oxadiazolidine-3,5-dione (XIII). To a stirred solution of *N*-[4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl] ethoxy]benzyl]-*N*-hydroxyurea XII (346 mg, 1.0 mmol) in water (2 mL) was added 1 N NaOH (3 mL) followed by ethyl chloroformate (191 μL, 217 mg, 2.0 mmol) and stirred for 1 h at 30 °C. The reaction mixture was diluted with water, acidified to pH 3.0 and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to yield the title compound (283 mg, 76%); IR (KBr) 1745, 1650 cm^{-1}; ^1H NMR (δ in $CDCl_3$ + DMSO-d_6) 12.40 (bs, 1H, D_2O exchangeable), 7.25 (d, J = 8.72 Hz, 2H), 6.90 (d, J = 8.72 Hz, 2H), 6.15 (s, 1H), 4.70 (s, 2H), 4.40–4.25 (m, 2H), 4.25–4.12 (m, 2H), 2.91 (q, J = 7.56 Hz, 2H), 2.12 (s, 3H), 1.20 (t, J = 7.56 Hz, 3H); CIMS m/z 359 $(M+H)^+$. Analysis calcd for $C_{18}H_{20}N_4O_5$: C, 58.06; H, 5.41; N, 15.04. Found: C, 57.99; H, 5.48; N, 14.94%.

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