



Discovery of a potent G-protein-coupled receptor 119 agonist for the treatment of type 2 diabetes

Suresh Pola^{a,b,*}, Shailesh R. Shah^{b,*}, Harikishore Pingali^a, Pandurang Zaware^a, Baban Thube^a, Pankaj Makadia^a, Hoshang Patel^a, Debdutta Bandyopadhyay^a, Akshyaya Rath^a, Suresh Giri^a, Jitendra H. Patel^a, R.K. Ranvir^a, S.R. Sundar^a, Harilal Patel^a, Jeevan Kumar^a, Mukul R. Jain^a

^a Zydus Research Centre, Sarkhej-Bavla N.H 8A Moraiya, Ahmedabad 382210, India

^b Department of Chemistry, Faculty of Science, M. S. University of Baroda, Vadodara 390002, India

ARTICLE INFO

Keywords:

GPR119 agonist
Thiazolidinediones (TZDs)
Type 2 diabetes mellitus (T2DM)
Insulin sensitizers

ABSTRACT

The ever-growing prevalence of Type-2 diabetes in the world has an urgent need for multiple orally effective agents that can regulate glucose homeostasis. G-Protein coupled receptor 119 (GPR 119) agonists have demonstrated the glucose-dependent insulin secretion and showed beneficial effects on glycemic control in humans and/or relevant animal models. Herein, we describe our efforts towards identification of a potent and oral GPR 119 agonist **13c (ZY-G19)**, which showed *in vitro* potency in the cell-based assay and *in vivo* efficacy without exerting any significant signs of toxicity in relevant animal models.

1. Introduction

Diabetes is one of the major causes of death worldwide in this century after heart disease and cancer.¹ According to the International Diabetes Federation (IDF) data, 463 million individuals were suffering from diabetes world over in 2019, which is expected to significantly increase to 700 million by 2045.² If untreated, diabetes also leads to several other complications, such as cardiovascular disease, retinopathy, nephropathy, neuropathy, dental diseases and kidney related diseases.^{3–10} Type 2 diabetes mellitus (T2DM) is a complex chronic disease characterized by metabolic disorder and hyperglycemia due to insulin resistance, hepatic glucose overproduction and/or insufficient insulin secretion. In addition to genetic predisposition, obesity is an added risk factor associated with growing incidence of type 2 diabetes mellitus and many patients with T2DM are obese. These patients are often accompanied by increased cardiovascular risk factors. Innovative new therapies that could improve glucose metabolism and reduce body weight and excess food intake will provide benefits to such patients. Although there are a number of therapeutic options such as sulfonylureas, metformin, glitazones and glinides, they are unable to get satisfactory glycemic control without adverse side effects. Thus, there is an urgent need of novel therapeutic approaches for the treatment of T2DM by a good glycemic control without side effects.^{11,12}

G Protein-coupled receptor 119 (GPR119) is a member of class A

(rhodopsin-type) GPCR family and is highly expressed in pancreatic β -cells and the K and L cells of the gastrointestinal tract.^{13–15} It has also been shown to be expressed in peripheral tissues including skeletal muscles, cardiac muscles and liver. Coupling of GPR119 to $G\alpha$ stimulatory proteins induces adenylate cyclase activity to increase intracellular cyclic adenosine monophosphate (cAMP), which further regulates GPR119-mediated release of GLP-1. This GPR119-mediated release of GLP-1 from intestinal L-cells is shown *in vitro* to be protein kinase A (PKA) dependent. Recent work has indicated a potential signaling axis between GPR119 and 5-adenosine monophosphate-activated protein kinase alpha (AMPK α), a key regulator of cellular energy state in metabolically active tissues. The roles of GPR119 in regulating glucose homeostasis and appetite are substantiated by its pattern of expression. In pancreatic β -cell, activation of GPR119 is expected to potentiate glucose-stimulated insulin secretion similar to GLP-1 and GIP. The activation of GPR119 receptor expressed in enteroendocrine cells of intestine is shown to modulate incretin hormone release, a key function in maintaining glucose homeostasis. Thus the effects of GPR119 activation on glucose homeostasis are two fold, a direct action of glucose stimulated insulin secretion in pancreatic β -cell and an indirect action of stimulating the release of GLP-1 and GIP in enteroendocrine cells of intestine.^{16–20} This glucose-dependent dual mechanism of action makes GPR119 a promising target for discovery of anti-diabetic agents with low risk of hypoglycemia and body weight gain. Several phospholipids

* Corresponding authors at: Zydus Research Centre, Sarkhej-Bavla N.H 8A Moraiya, Ahmedabad 382210, India (S. Pola).

E-mail addresses: suresh.pola@zyduscadila.com (S. Pola), shailesh-chem@msubaroda.ac.in (S.R. Shah).

and lipid amides such as lysophosphatidylcholine (LPC), oleylethanolamide (OEA) and oleoyldopamine (OLDA) have been identified as endogenous ligands for GPR119. However, due to the low potency and poor selectivity of these endogenous agonists towards GPR119 receptor, many synthetic small molecule GPR119 agonists have been discovered and disclosed by several research groups over the years.^{21–24} These intense efforts led to the development of compounds till clinical phase as shown in Fig. 1.^{25,26} However, due to the tachyphylaxis, these compounds failed to show desired efficacy in the clinical trials^{27–29} and none could reach the market.

2. Designing

Arena compound (I) (Fig. 1) is reported to be a selective and potent agonist of the GPR119 receptor across several species (EC₅₀, melanophore: 2 nM, human; 1 nM, dog; 35 nM, cynomolgus monkey; 41 nM, mouse; 44 nM, rat) and possesses aqueous solubility with no appreciable inhibition of at least five cytochrome P450 enzymes (CYP2C9, 15 μ M; 1A2 2D6 3A4, >40 μ M; 2C19, 10 μ M). Compound (I) also demonstrated a dose-dependent inhibition of glucose excursion in the OGTT experiment in male SD rats (22%, 0.3 mg/kg p.o.; 24%, 3 mg/kg p.o.; 70%, 30 mg/kg p.o.).²⁹ However, further development of this compound has been suspended for reasons not disclosed. In our efforts to discover promising and safe GPR119 agonists, we replaced 2-methyl pyridine, a polar head of Arena compound with clinically proven pharmacophore benzylidenethiazolidinedione, as a novel heterocyclic head and identified this moiety as a pyridine surrogate (Fig. 2). Thiazolidinediones (TZDs) are insulin sensitizers having a pleiotropic pharmacology including reduction of insulin resistance, a root cause of diabetes. Importantly these agents also preserve pancreatic beta cell function or mass better than insulin secretagogues such as sulfonylureas. However The TZD class is reported to cause weight gain in animal models.³⁰ Herein, we report the synthesis and biological evaluation of novel thiazolidinedione derivatives as potent GPR119 agonists devoid of adverse side effects.

3. Results and discussion

3.1. Chemistry

The general synthetic procedure leading to the compounds **8a-e**, **9a-e**, **13a-e** and **14a-e** is outlined in Scheme 1. Coupling reaction of commercially available substituted 4,6-dichloropyrimidines **1a** and **1b** with various *N*-substituted hydroxy piperidines **2a-e** using *t*-BuOK as base in *N,N*-dimethylformamide produced piperidine intermediate **3a-e** and **4a-e**. Treatment of **3a-e** and **4a-e** with 4-hydroxybenzaldehyde **5** or 3-hydroxybenzaldehyde **10** in the presence of K₂CO₃ in *N,N*-dimethylacetamide gave *para* substituted benzaldehyde **6a-e** and **7a-e** or *meta* substituted benzaldehyde derivatives **11a-e** and **12a-e** respectively. The

Knoevenagel condensation of benzaldehyde intermediates **6a-e**, **7a-e**, **11a-e** and **12a-e** with thiazolidine-2,4-dione in the presence of piperidiniumbenzoate in toluene afforded the test compounds **8a-e**, **9a-e**, **13a-e** and **14a-e** in good yield with high chemical purity.³¹

3.2. In-vitro evaluation

GPR119 agonistic activity of the synthesized compounds were measured using a cAMP assay in the human GPR119 cell line. GPR119 agonist **AR231453** compound was used as the positive control and the results are shown in Table 1 and Table 2. cAMP stimulation is measured for all the synthesized compounds and the activity is reported as EC₅₀ values and %max of stimulation compared to maximal effect at 1 μ M of **AR231453**. As hypothesized, we synthesized compounds **8**, **9**, **13** and **14** by replacing pyridine ring of Arena compound with benzylidene thiazolidinedione. To start with compounds **8a-e** possessing methylpyrimidine as central ring were synthesized and evaluated for GPR119 agonistic activity. The results are represented in Table 1. Initial compound **8a**, methyl carbamate derivative showed weak GPR119 agonistic activity with EC₅₀ 1.4 μ M, while its homologue, the ethyl carbamate **8b** showed improvement in agonistic activity (EC₅₀: 157 nM; E_{max}: 141%). This 9 fold difference in the potency encouraged us to study the effect of various substitutions on piperidine nitrogen. We then synthesized compound **8c** and **8d** with *t*-butyl and *i*-butyl carbamates respectively. Both the compounds demonstrated significant improvement in potency compared to their lower homologues **8a** and **8b** with EC₅₀ of 88 nM (**8c**) and 75 nM (**8d**). Further increase in bulk at this position with benzyl carbamate found detrimental as evident from compound **8e** with EC₅₀ of 805 nM and E_{max} of 43.3%. Having done this, we then intended to know the role of methyl group on central pyrimidine ring and hence synthesized another series of compounds **9a-e** without methyl group on pyrimidine ring. Compound **9a** with methyl carbamate was found inactive whereas the ethyl carbamate **9b** showed moderate potency with EC₅₀ 790 nM. As expected, compound **9c** with *t*-butyl carbamate showed potent GPR119 agonistic activity with EC₅₀ of 130 nM and E_{max} of 121%. Surprisingly compound **9d** with *i*-butyl carbamate group found 10 fold inferior to its methylated counterpart **8d**. Interestingly a contrast trend was observed with benzyl carbamates. Compound **9e** with EC₅₀ of 107 nM and E_{max} of 88% found 8 fold potent than its methylated counterpart **8e**. Our next task in this endeavour was to optimise the position of thiazolidinedione on phenyl ring. To do so we have synthesized *meta*-benzylidene thiazolidinedione derivatives **13a-e** and **14a-e** with a similar substitution pattern as in compounds **8** and **9** and the results are presented in Table 2. Methyl carbamates **13a** and **14a** are found inactive and this is in line with our expectation as their corresponding *para*-substituted analogues also failed to show any activity. Compound **13b** with ethyl carbamate not showing activity unlike its *para* oriented counterpart **8b** is surprising. However compound **14b** with EC₅₀ of 819 nM found to be a weak agonist like its *para* substituted

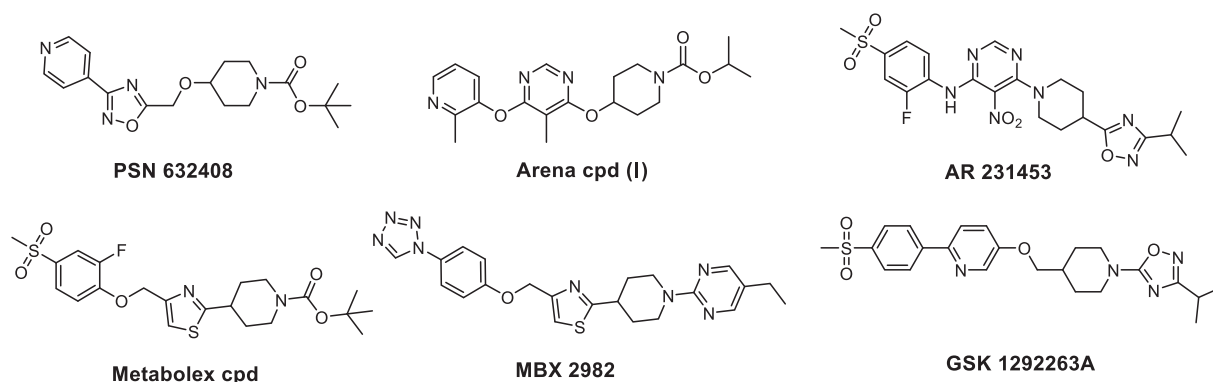


Fig. 1. The synthetic ligands of GPR119 Agonists.

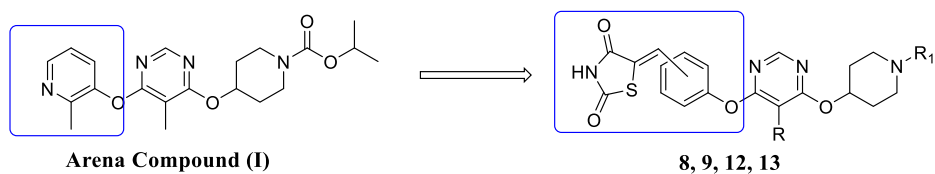
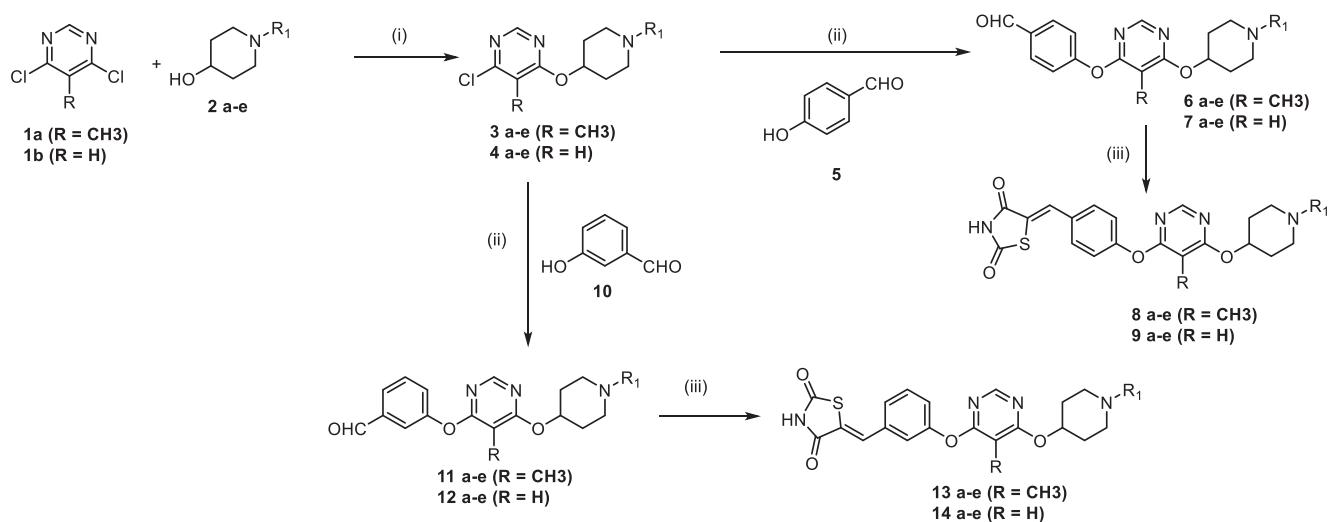


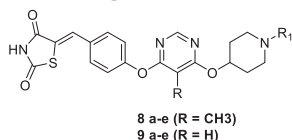
Fig. 2. Designing Strategy.



Scheme 1. Reagents and Conditions: (i) *t*-BuOK, THF, 0 °C, 30 min, (ii) K₂CO₃, DMA, 138 °C, 3 h, (iii) Thioazolidine-2,4-dione (TZD), Piperidine, benzoic acid, Toluene, Reflux, 7 h.

Table 1

GPR119 agonistic activities of compounds 8a-e and 9a-e.



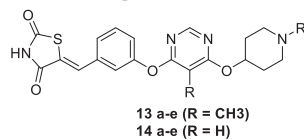
Comp. No.	R	R ₁	hGPR119 agonist Activity	
			EC ₅₀ (nM)	% max ^a
8a	CH ₃		1414.0	53.3
9a	H		IA	ND
8b	CH ₃		157.4	141.3
9b	H		790	51.84
8c	CH ₃		88	68.8
9c	H		130	121.6
8d	CH ₃		75.1	70.18
9d	H		745	51.0
8e	CH ₃		805	43.3
9e	H		107.4	88.3
AR231453			6.0	100

^a %max: cAMP stimulation % compared to maximal effect at 1 μM AR231453.

analogue **9b**. Interestingly, compound with *t*-butyl carbamate **13c** was found highly potent with EC₅₀ of 43 nM and E_{max} of 160% and came out as the most potent compound of this series. Compound **14c** was also found active but inferior to **13c** in terms of potency as well as efficacy. Surprisingly *i*-butyl carbamate **13d** failed to show activity however compound **14d** showed moderate potency comparable to its *para* analogue **9d**. Among benzyl carbamates **13e** found to be 8 fold potent than its corresponding *para* analogue (**8e**) with EC₅₀ of 105 nM and E_{max} 137% whereas compound **14e** found equipotent to **9e**. From the above

Table 2

GPR119 agonistic activities of compounds 13a-e and 14a-e.



Comp. No.	R	R ₁	hGPR119 agonist Activity	
			EC ₅₀ (nM)	% max ^a
13a	CH ₃		IA	ND
14a	H		1870	33.7
13b	CH ₃		IA	ND
14b	H		819	43.3
13c	CH ₃		43	160
14c	H		125.3	78.3
13d	CH ₃		IA	ND
14d	H		720	62.4
13e	CH ₃		105.7	137.5
14e	H		153.4	98.3
AR231453			6.0	100

^a %max: cAMP stimulation % compared to maximal effect at 1 μM AR231453.

in vitro GPR119 agonist structure activity relationship with different carbamate substitutions on piperidine ring compounds **8c**, **8d** and **13c** were selected for evaluation of efficacy in relevant animal models.

3.3. In-vivo studies

During oral glucose tolerance test (oGTT) an acute screening assay, blood glucose levels were monitored for 120 min after oral administration of glucose in C57 BL/N6 mice which are dosed with 50 mg/kg **8c**,

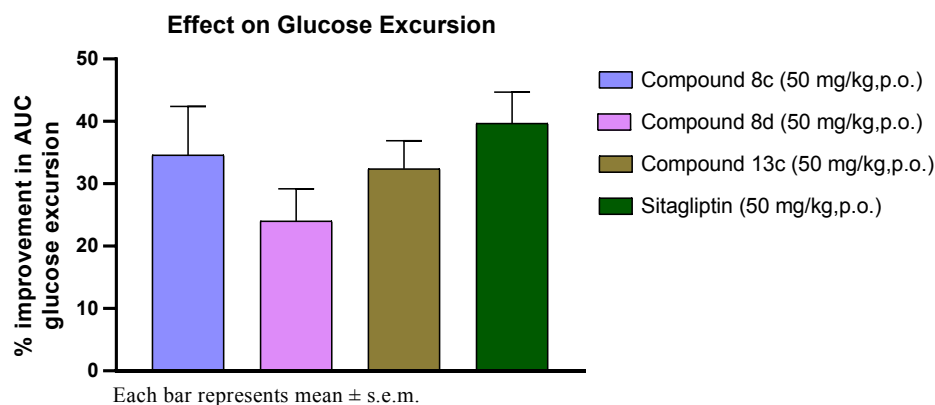


Fig. 3. The oGTT effect of compounds in C57 mice.

8d and **13c** along with Sitagliptin 30 min prior to the glucose challenge and data is presented in Figure 3. Compounds **8c** and **13c** significantly reduced plasma glucose levels showing 34.6% and 32.4% improvement in glucose excursion AUC respectively comparable sitagliptin, while Compound **8d** is found inferior with modest 24% improvement in glucose excursion AUC.

Having established primary *in-vitro* and *in-vivo* correlation, we then intended to study the pharmacokinetic parameters of **8c** and **13c** in *Sprague Dawley* rats at 25 mg/kg/day oral dose and the results are presented in Table 3. Based on impressive and superior pharmacokinetic parameters over **8c**, compound **13c** (C_{max} of 4956 ng/ml and AUC of 19,056 h.ng/ml) was chosen for evaluation of pharmacokinetic parameters in higher species.

13c, when dosed orally to *Male Wistar* rats and Beagle dogs at 10 mg/kg exhibited oral bioavailability of 21.67% and 5.17% respectively with decent exposure and good half-life in both the species as shown in Table 4.

Subsequently in an oGTT experiment in *db/db* mice, a diabetic disease model, **13c** showed a significant 69.1% improvement of in glucose excursion AUC when dosed orally at 50 mg/kg along with sitagliptin as positive control (Fig. 4).

Encouraged with the positive results, we then conducted an oGTT experiment to study time and dose dependent effects of compound **13c** on glucose excursion in *db/db* mice. Compound **13c** in doses ranging from 1 to 50 mg/kg and sitagliptin at 50 mg/kg were administered orally for 14 days and blood glucose levels were measured for 0–120 min after 30 min of the compound administration and AUC was calculated for Day1 and Day14. Compound **13c** showed significant and dose dependent reduction of glucose excursion compared to day 1 vs day 14 at

all the tested doses dose as shown in Fig. 5. The effect of compound **13c** on glucose dependent insulin secretion was also evaluated where 50 mg/kg/day dose of **13c** showed significant increase in secretion of insulin at 10 and 30 min after glucose administration (Fig. 6).

The effect of compound **13c** on plasma active GLP-1 secretion at various time points in male *db/db* mice after single dose oral administration was also evaluated. Treatment with **13c** at 50 mg/kg has increased active GLP-1 levels by an impressive 2.6 fold at 10 min after glucose administration. Further when co-administered with sitagliptin, a DPP-4 Inhibitor, **13c** showed a synergistic and significant elevation in the active GLP-1 levels compared to that caused by either **13c** or sitagliptin alone as shown in Fig. 7.

In order to investigate the potential to reduce body weight gain, **13c** was dosed to diet induced obese *Sprague Dawley* rats for 28 days. No significant effect on body weight gain was observed in the animals treated at 25 and 50 mg/kg/day (Fig. 8). However, the graph shows a trend of lowering in body weight towards the end of the treatment (50 mg/kg/day dose) which indicates that treatment if prolonged further may result in further reduction in body weight gain.

Having achieved the primary goal of identifying potent and efficacious GPR119 agonist, our next end point of this endeavour was to study the toxicity profile of the lead compound **13c** with repeated dose administration by oral gavage over the period of 28 days in *Wistar* rats. Groups of 10 animals of each male female rats were dosed orally with 100, 200 and 400 mg/kg compound **13c** once a day for 28 days. These doses corresponds to 50 \times , 100 \times and 200 \times of the ED₅₀ (considering ED₅₀ as ~2.0 mg) found from the efficacy study in *db/db* mice. There were no significant treatment related clinical manifestations noted in any of the treated group animals and there was no treatment mortality

Table 3
Pharmacokinetic parameters in fasted SD Rats at 25 mg/kg dose.

Compound	T _{max} (h)	C _{max} (ng/ml)	T _{1/2} (h)	K _{el} (h ⁻¹)	AUC _(0-t) (h.ng/ml)	AUC _(0-inf) (h.ng/ml)
8c	2.25 ± 0.63	834.78 ± 71.05	4.37 ± 0.33	0.16 ± 0.01	8108.40 ± 652.07	8310.72 ± 654.23
13c	1.75 ± 0.25	4955.84 ± 738.16	3.09 ± 0.99	0.33 ± 0.11	19055.89 ± 1167.41	19709.18 ± 1370.42

Table 4
Pharmacokinetic parameters of compound **13c** at 10 mg/kg oral dose.

Species	T _{max} (h)	C _{max} (ng/ml)	T _{1/2} (h)	K _{el} (h ⁻¹)	AUC _(0-t) (h.ng/ml)	AUC _(0-inf) (h.ng/ml)
Wistar Rat	1.50 ± 0.55	256.41 ± 106.37	12.30 ± 4.41	0.07 ± 0.05	1766.77 ± 299.26	1898.35 ± 352.46
Beagle Dog	3.00 ± 2.00	1047.88 ± 46.28	19.31 ± 5.66	0.04 ± 0.01	14868.45 ± 6253.72	15195.01 ± 6311.96

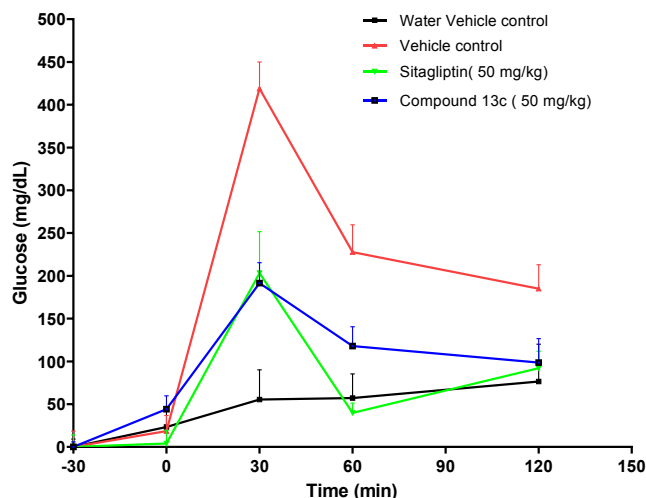


Fig. 4. The oGTT effect of compound 13c on serum glucose at various time points in *db/db* mice after single oral dose administration. Each line represents mean \pm s.e.m.

occurred in this study up to the dose level of 400 mg/kg. No treatment related adverse neurobehavioral changes were noticed in this study at 400 mg/kg. Food consumption was comparable to that of control groups throughout the study period in both the treated groups of both male and female animals. There were no findings of toxicological significance during ophthalmic examination at 400 mg/kg in both the sexes. Animals were sacrificed on day 29 and data analysis of blood biochemical parameters, organ weight ratios and histopathological findings.

No significant change in body weights of animals of both the sex was observed. Analysis of organ to body weight ratios (Table 5) did not show evidence of toxicity attributed to compound treatment at least at 100 mg/kg dose, which is $50\times$ of ED_{50} . There was no changes in relative organ weight noted up to 400 mg/kg in male rats at the end of treatment periods. Although statistically significant changes such as higher weights of adrenals at 400 mg/kg, heart at 200 mg/kg, brain at 100 & 200 mg/kg, thymus at 400 mg/kg was noticed, none of these effects were clearly associated with any histomorphological changes during microscopic examination. No treatment related changes in relative organ weights were evident in female rats either at the end of treatment period or at post recovery termination. Similarly no significant alterations were observed in biochemical parameters (Table 6) except the decrease in urea levels in both sex animals and marginal decrease in glucose levels in male animals. No significant changes were observed in

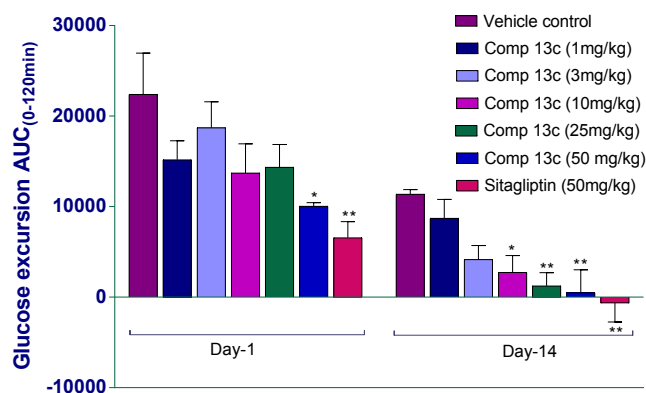


Fig. 5. The effect of compound 13c on AUC glucose (mg/dL.min) in male *db/db* mice single oral dose administration (glucose load was 2gm/kg/10 mL, p.o.) Each bar represents mean \pm s.e.m. * Significantly different from Vehicle control group ($p < 0.05$), ** ($p < 0.01$).

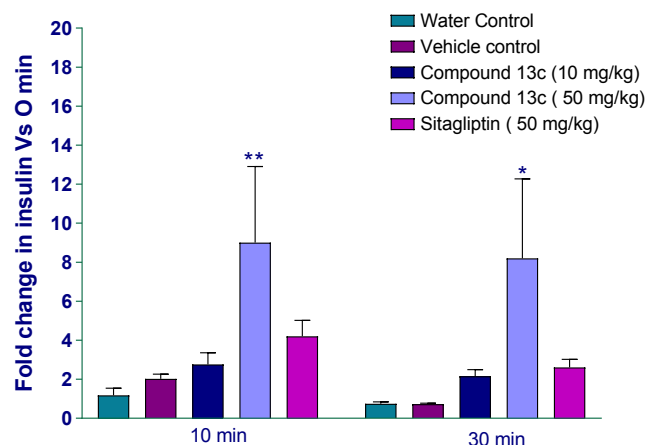


Fig. 6. Effect on glucose dependent insulin secretion of compound 13c using *db/db* model. * Significantly different from Vehicle control group ($p < 0.05$), ** ($p < 0.01$).

liver enzymes (ALP, AST, and ALT), hemoglobin, albumin and creatinine at any doses in both sex animals. Histopathological examination did not reveal any treatment related adverse effects up to 400 mg/kg in both the sexes. Although changes were noticed in liver, these were minimal and could not be attributed to adverse effects of the compound treatment. No evidence of local toxic effects noticed after repeated oral treatment with Compound 13c in the gastrointestinal tract of the animals. Oral administration of compound 13c for 28 days at the dose levels of 100, 200 and 400 mg/kg did not affect the survival of *Wistar* rats. No adverse changes were noticed during biochemical estimations, organ weights and histopathological examination. No observed adverse effect level (NOAEL) of Compound 13c was found to be more than 400 mg/kg in rats. These results clearly indicate that treatment with 13c on rodents did not exert any significant side effects even at 200 times higher dose than ED_{50} value.

4. Docking study

To explain the GPR119 agonistic activity of compound 13c, docking studies have been carried out using Glide,³² the automated docking program implemented in the Schrodinger package. The geometry of compound to be docked was subsequently optimized using the Lig-Prep.³³ The scoring function, binding mode and H-bonds were used to assess the binding affinity of the compounds. A homology model of GPR119 receptor was constructed based on template protein crystal structure (PDB ID: 2R4R) with sequence identity 26.94% using Prime module of Schrodinger,³⁴ which provided insight regarding the binding site and binding site residues. The grid file has been generated by specifying pocket identified by sitemap. The Arena molecule (AR231453) was docked into the homology model using the induced fit docking (IFD) protocol.³⁴ The IFD is based on the docking program Glide with the refinement module in Prime (Schrodinger, Inc.), which was reported to accurately predict the ligand binding modes and concomitant structural changes in the receptor. The results of docking have been shown in Fig. 9. AR231453 molecule fits snugly to binding site and adopts an extended conformation. The fluoro-phenyl ring forms pi-pi interaction with Phe 249 and 1, 2, 4-oxadiazole ring forms a pi-pi interaction with side chain of Tyr 271. This is also stabilized by cation-pi interaction between nitro group of AR231453 and Phe 168. These three interactions seem to stabilize the molecule in binding site. Compound 13c also adopts an extended conformation similar to AR231453 molecule in the binding site. 5-methyl pyrimidine forms a pi-pi interaction with the side chain of Phe 168. In addition to this interaction, compound 13c forms Van der Waals interactions with Phe 172, Phe 249, Arg 270, Tyr 271 and Gln 66. These interactions and similar

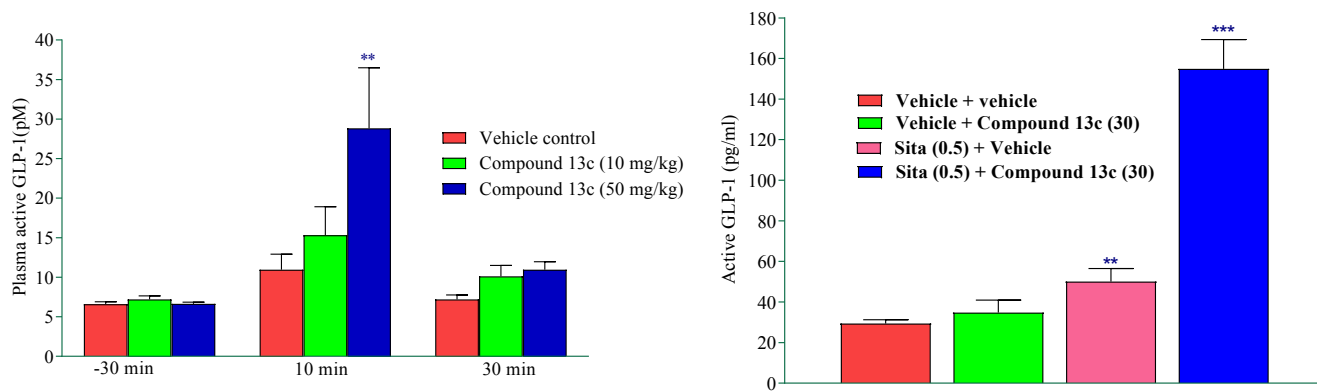


Fig. 7. (i) Effect on plasma active GLP-1 of compound **13c** using db/db model. Each bar represents mean \pm s.e.m. ** significantly different from Vehicle control group ($p < 0.01$), (ii) Plasma active GLP-1 (pg/ml) at 10 min after glucose load. ** Significantly different from Vehicle control group ($p < 0.001$), *** ($p < 0.0001$).

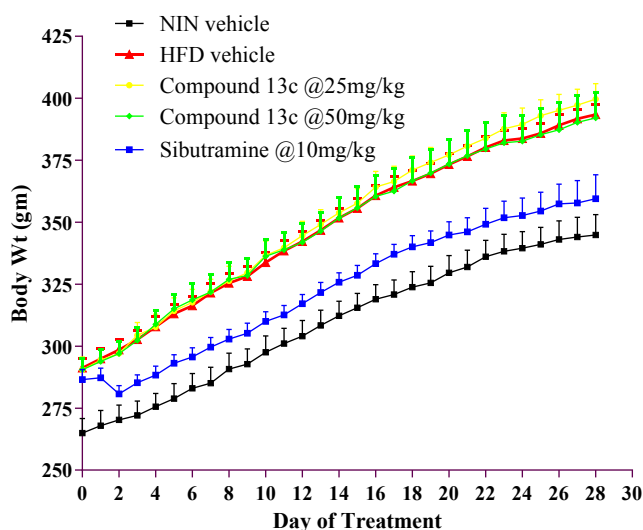


Fig. 8. The effect of compound **13c** on body weight (gm) in 28 days of treatment in DIO male SD Rats. Each line represents Mean \pm SEM.

binding mode with respect to **AR231453** molecule might be contributing to the potent agonistic activity of compound **13c**.

5. Conclusion

In conclusion, we have identified benzylidenethiazolidinedione as a novel polar head for discovering a new series of GPR119 agonists. The

efforts on SAR generation lead to the discovery of compound **13c** with potent *in vitro* activity, *in vivo* efficacy in various animal models and decent pharmacokinetic profile with no signs of toxicity at dose 200 times higher than efficacy dose. **13c** (**ZY-G19**) has been identified as a candidate for clinical development. Further follow-up of **ZY-G19** will be communicated in subsequent publication.

6. Experimental section

6.1. *In vitro* hGPR119 agonistic activity

Chinese Hamster Ovarian (CHO-K1) cells stably transfected with human GPR119 were grown at 37 °C, 95% O₂ and 5% CO₂ in 75 cm flasks containing DMEM/F12 (1:1) media with added 10% FBS (GibcoVR), Geneticin (GibcoVR) and grown until 90% confluent. Cells were then washed (PBS), lifted with cell dissociation solution (InvitrogenVR), counted and used for cAMP stimulation assays and/or passaging (1:10). Following the manufacturer's instructions for the LANCEVR Ultra cAMP assay (Perkin Elmer), cell transfected with hGPR119 were centrifuged (1000 rpm, 5 min), re-suspended in cAMP assay buffer (HBSS, 0.1% BSA, 0.5 mM IBMX and 5 mM HEPES) and seeded at 5000 cells/well in optiplate-384 (Perkin Elmer). The cells were treated with compounds or reference standard **AR231453** over a range of concentrations (10 nM–0.6 μM) and incubated for 1 h. The cells were then lysed and cAMP was quantified using Arbor Assay's DetectX® Enzyme immuno Assay kit for direct cAMP measurement. EC₅₀ of the compounds were calculated using Graph Pad Prism.

6.2. Pharmacokinetic studies

All the animals used in the study were procured from the Animal

Table 5

Relative organ weights^a of Wistar rats administered orally with **13c** for 28 days.

Dose (mg/kg)	Heart	Liver	Kidneys	Spleen	Adrenals	Brain	Testes	Epididymides	Thymus
Male									
Control	0.333 \pm 0.036	3.142 \pm 0.231	0.787 \pm 0.078	0.206 \pm 0.026	0.020 \pm 0.003	0.766 \pm 0.038	1.248 \pm 0.073	0.361 \pm 0.028	0.148 \pm 0.023
100	0.347 \pm 0.021	3.237 \pm 0.160	0.831 \pm 0.057	0.222 \pm 0.010	0.023 \pm 0.002	0.830* \pm 0.074	1.228 \pm 0.322	0.371 \pm 0.056	0.167 \pm 0.028
200	0.363* \pm 0.024	3.304 \pm 0.160	0.847 \pm 0.067	0.220 \pm 0.024	0.023 \pm 0.002	0.824* \pm 0.038	1.289 \pm 0.105	0.406 \pm 0.058	0.175 \pm 0.037
400	0.338 \pm 0.017	3.220 \pm 0.253	0.845 \pm 0.064	0.211 \pm 0.010	0.023* \pm 0.004	0.809 \pm 0.038	1.230 \pm 0.060	0.365 \pm 0.027	0.196* \pm 0.045
Female									
Control	0.380 \pm 0.037	3.219 \pm 0.221	0.801 \pm 0.071	0.244 \pm 0.032	0.045 \pm 0.007	1.100 \pm 0.078	0.091 \pm 0.009	0.335 \pm 0.108	0.260 \pm 0.025
100	0.410 \pm 0.030	3.243 \pm 0.268	0.875 \pm 0.125	0.241 \pm 0.027	0.046 \pm 0.007	1.103 \pm 0.066	0.089 \pm 0.013	0.345 \pm 0.103	0.241 \pm 0.022
200	0.394 \pm 0.016	3.285 \pm 0.262	0.840 \pm 0.057	0.242 \pm 0.033	0.044 \pm 0.010	1.114 \pm 0.036	0.089 \pm 0.011	0.330 \pm 0.142	0.257 \pm 0.048
400	0.367 \pm 0.044	3.172 \pm 0.301	0.806 \pm 0.093	0.228 \pm 0.029	0.042 \pm 0.006	1.069 \pm 0.051	0.081 \pm 0.007	0.429 \pm 0.142	0.244 \pm 0.043

* Significant from control group at 5% level ($p < 0.05$).

** Significant from control group at 1% level ($p < 0.01$).

^a Presented as organ-to-body weight percent ratio.

Table 6Biochemical Parameters of Wistar rats administered orally with **13c** for 28 days.

Dose (mg/kg)	Globulin (g/dl)	Glucose (mg/dl)	Creatinine (mg/dl)	ALP (U/L)	AST (U/L)	ALT (U/L)	Albumin (g/dl)	Urea (mg/dl)
Male								
Control	2.62 ± 0.12	89.02 ± 13.41	0.61 ± 0.04	174.77 ± 25.42	119.40 ± 9.30	30.47 ± 2.63	3.56 ± 0.08	58.14 ± 9.13
100	2.50 ± 0.11	87.56 ± 12.75	0.57 ± 0.03	152.22 ± 24.91	114.13 ± 24.86	28.90 ± 3.98	3.47 ± 0.08	55.36 ± 10.27
200	2.64 ± 0.11	75.19* ± 9.02	0.57 ± 0.06	164.68 ± 37.51	116.98 ± 15.65	30.15 ± 2.96	3.61 ± 0.07	55.62 ± 10.44
400	2.53 ± 0.15	82.17 ± 10.39	0.57 ± 0.05	177.44 ± 46.84	116.36 ± 16.65	29.60 ± 4.46	3.54 ± 0.07	51.15 ± 6.00
Female								
Control	2.44 ± 0.18	78.40 ± 8.36	0.60 ± 0.04	100.14 ± 21.98	128.84 ± 21.42	21.28 ± 2.31	3.57 ± 0.14	48.09 ± 5.30
100	2.39 ± 0.11	79.83 ± 8.27	0.63 ± 0.05	103.72 ± 28.12	120.42 ± 23.17	22.37 ± 1.82	3.59 ± 0.11	47.84 ± 4.89
200	2.42 ± 0.11	82.10 ± 7.81	0.66 ± 0.07	91.73 ± 23.20	128.19 ± 23.17	22.20 ± 2.31	3.65 ± 0.08	46.42 ± 5.37
400	2.42 ± 0.13	76.54 ± 8.67	0.60 ± 0.07	100.97 ± 26.55	123.93 ± 14.28	23.30 ± 3.22	3.57 ± 0.14	43.20 ± 7.38

* Significant from control group at 5% level ($p < 0.05$).

Breeding Facility of Zydus Research Center. All animal studies were conducted according to protocols reviewed and approved by the Institutional Animal Care and Ethics Committee at the Zydus Research Centre.

The goal of these studies was to evaluate the Pharmacokinetic profile of compounds **8c** and **13c** in Sprague-Dawley rats following a single oral gavage (po; 25 mg/kg). Sprague Dawley (SD) rats (8 adult males), were obtained from Zydus Research Centre, Ahmedabad India, AAALAC Accreditation. All animals were housed in temperature-controlled rooms with appropriate light/dark cycles. The animals were fasted overnight before oral gavage dosing but were given access to water *ad libitum*. Food was provided at 4 h after dosing. Compounds **8c** and **13c** were dosed as solutions in 10% NMP and 10% solutol in normal Saline (i.v.) and homogenous suspension (p.o.) in 0.5% Tween 80 in 0.5% Na-CMC as a single dose in rats. Blood samples were collected at 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h post-dose in Na-heparin coated micro centrifuge tubes. Blood samples were centrifuged to separate plasma and were then stored at -70°C until analysis. PK parameters were calculated by non-compartmental analysis using WinNonlin program, version 5.3 (Pharsight Corp., Mountain View, California). A model was selected based on the vascular (i.v. bolus) or extravascular (p.o.) routes of administration. For the p.o. route, the concentration at time zero was assumed to be zero. Plasma concentrations below the limit of quantitation were treated as zero concentration for the purpose of calculating the mean plasma concentration values.

6.3. In vivo experiments

6.3.1. Oral glucose tolerance tests (OGTT) in C57/BL6 mice

C57/BL6 mice of 6–8 week age were used for this experiment. Animals were grouped based on non-fasting serum glucose levels and were kept on fasting overnight (day before OGTT). On the experiment day, each animal received a single dose of vehicle/test compounds (50 mg/kg) administered orally, 30 min post dosing animals were bled for basal glucose level estimation and at the same time glucose load (3gm/kg) was administered orally. Blood was collected at time points corresponding to 20, 40, 60 and 120 min after glucose load administration. Serum was separated for determination of glucose levels and change in area under curve for glucose was calculated and provided in Fig. 3.

6.3.1.1. Oral glucose tolerance tests (OGTT) in db/db mice. db/db Mice of 5–7 week age were used for this experiment. Animals were kept on fasting and were grouped based on fasting serum glucose levels and after grouping OGTT was performed. Each animal received a single dose of vehicle/test compounds (50 mg/kg) administered orally, 30 min post dosing animals were bled for basal glucose level estimation and at the same time glucose load (2 g/kg) was administered per orally. Blood was collected at time points corresponding to 30, 60 and 120 min after glucose load administration. Serum is separated for determination of glucose levels and change in area under curve for glucose and glucose excursion is calculated from Vehicle control with glucose load vs water control group without glucose load and provided in the above figure as % reduction in AUC glucose excursion vs vehicle control is calculated.

6.3.1.2. Body weight changes in diet induced obesity (DIO) rats. The high fat diet induced obesity (DIO) in rats exhibits various features of metabolic syndrome in humans. The metabolic syndrome is characterized by abdominal obesity, high triglycerides, impaired fasting glucose and hyperinsulinemia. Animals with uniform body weight were divided into two groups. The first group was provided with normal chow diet (NIN) and the 2nd group was provided with High Fat diet (HFD) for a period of 12 weeks. After 12 weeks diet feeding, the HFD fed animals were divided into 4 treatment groups. Formulations were prepared using vehicle {PG450, Twin 80 and 0.1% sodium CMC (5:5:90)} and body weight was recorded daily for 28 days.

6.4. Chemistry experiments

6.4.1. Synthetic materials and methods

All the solvents and reagents were obtained from commercial suppliers and were used without further purification or were prepared according to published procedures. The melting points were recorded on a scientific melting point apparatus and are uncorrected. NMR spectra were measured on a Bruker's 400 UltraShield NMR spectrometer and the chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS). Mass spectra were recorded on Perkin-Elmer Sciex API 3000. ESI-Q-TOF-MS measurements were performed on a

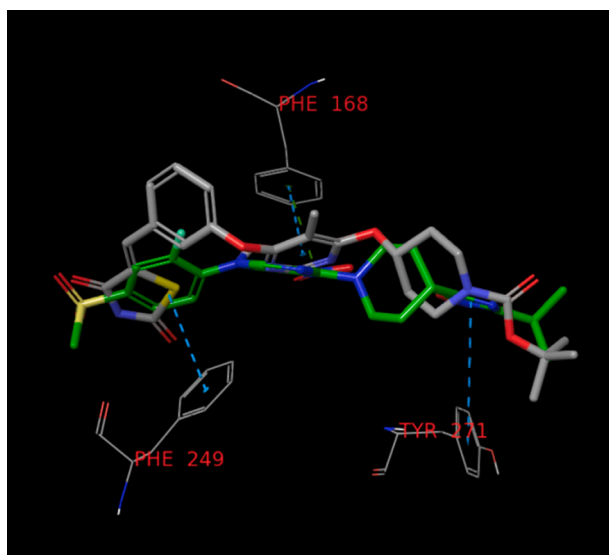


Fig. 9. AR 231453 (green) superposed with **13c** (grey) in the GPR119 binding site. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

microTOF-Q II (Bruker Daltonics) mass spectrometer. IR spectra were recorded as neat (for oils) or as KBr pellet (for solid) on FT-IR 8300 Shimadzu spectrophotometer and the values are reported in wavenumbers ν (cm^{-1}). Purity was determined by UPLC (Acquity Waters) via the following conditions. Column: YMC-Triart C18 (100×2.0 mm). Flow: 0.4 mL/min. Mobile phase: 0.05% TFA in Water: ACN (Gradient). Detector: UV at 254 nm. Reactions were monitored using thin layer silica gel chromatography (TLC) using 0.25 mm silica gel 60F plates from Merck. Plates were visualized by treatment with UV, acidic p-anisaldehyde stain, KMnO_4 stain with gentle heating. Products were purified by column chromatography using silica gel 100–200 mesh and the solvent systems indicated. All final compounds were obtained with over 95% purity as indicated by UPLC.

6.4.2. General procedure for the preparation of carbamates 2a–e

To a solution of 4-hydroxy piperidine (1.0 equivalent) in dichloromethane, triethylamine (1.5 equivalent) was added at 0°C followed by dropwise addition of chloroformates (methyl, ethyl, isobutyl and benzyl) (1.2 equivalent). After stirring for 30 min at 0°C , the reaction mixture was poured into water and extracted with dichloromethane. The organic extracts were washed with water, brine and dried over sodium sulfate. Then organic extract was concentrated under reduced pressure to yield product with quantitative yield.

6.4.2.1. Methyl 4-hydroxypiperidine-1-carboxylate (2a). Colorless oil; Yield: 73%; ^1H NMR (CDCl_3 , 400 MHz): δ 1.45–1.54 (m, 2H), 1.86–1.91 (m, 3H), 3.28–3.39 (m, 2H), 3.79–3.84 (m, 2H), 4.63 (s, 3H), 4.85 (d, J = 8.0 Hz, 1H); ESI/MS m/z : 160.1 ($\text{M}+\text{H}$) $^+$.

6.4.2.2. Ethyl 4-hydroxypiperidine-1-carboxylate (2b). Pale yellow oil; Yield: 84%; ^1H NMR (CDCl_3 , 400 MHz): δ 1.13 (t, J = 11.2 Hz, 3H), 1.43–1.52 (m, 2H), 1.84–1.89 (m, 3H), 3.07–3.13 (m, 2H), 3.26–3.36 (m, 2H), 3.85–3.90 (m, 2H), 4.84–4.88 (m, 1H); ESI/MS m/z : 173.8 ($\text{M}+\text{H}$) $^+$.

6.4.2.3. Isobutyl 4-hydroxypiperidine-1-carboxylate (2d). Pale yellow oil; Yield: 81%; ^1H NMR (CDCl_3 , 400 MHz): δ 0.97 (d, J = 8.0 Hz, 6H), 1.44–1.53 (m, 2H), 1.59–1.64 (m, 2H), 1.85–1.98 (m, 3H), 3.08–3.14 (m, 2H), 3.84–3.92 (m, 3H); ESI/MS m/z : 201.9 ($\text{M}+\text{H}$) $^+$.

6.4.2.4. Benzyl 4-hydroxypiperidine-1-carboxylate (2e). Colorless oil; Yield: 65%; ^1H NMR (CDCl_3 , 400 MHz): δ 1.47–1.49 (m, 2H), 1.55–1.62 (m, 2H), 3.11–3.17 (m, 2H), 3.83–3.92 (m, 3H), 5.12 (s, 2H), 7.30–7.38 (m, 5H); ESI/MS m/z : 258.1 ($\text{M}+\text{Na}$) $^+$.

6.4.3. General procedure for the preparation of 3a–e and 4a–e

Potassium *tert*-butoxide (0.9 equivalents) was added to a solution of intermediate **2a–e** (1 equivalent) and 4, 6-dichloropyrimidine **1a–b** (1 equivalent) in dry Tetrahydrofuran at 0°C and the reaction mixture was stirred for 15–20 h at 30°C . The reaction mixture was poured into ice cold water and extracted with ethyl acetate. The organic extract was washed with water, brine, dried over sodium sulfate and concentrated under reduced pressure to yield the desired product with good yield and high purity.

6.4.3.1. Methyl 4-((6-chloro-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (3a). The title compound was synthesized from **2a** and commercially available **1a**, according to the general procedure described above; White solid; Yield: 72%; Purity by UPLC: 99.29%; IR: 2993, 2864, 1716, 1556, 1442, 1359, 1313, 1228, 1049, 1022, 823, 765 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.76–1.82 (m, 2H), 1.97–2.02 (m, 2H), 2.29 (s, 3H), 3.40–3.46 (m, 2H), 3.71 (s, 3H), 3.73–3.77 (m, 2H), 5.33–5.37 (m, 1H), 8.38 (s, 1H); ESI/MS m/z : 285.8 (M) $^+$.

6.4.3.2. Ethyl 4-((6-chloro-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (3b). The title compound was synthesized from **2b** and commercially available **1a**, according to the general procedure described above; Yellow Oil; Yield: 52%; Purity by UPLC: 98.57%; IR: 3018, 2933, 2872, 1739, 1685, 1554, 1435, 1274, 1136 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.27 (t, J = 7.2 Hz, 3H), 1.77–1.80 (m, 2H), 1.96–2.04 (m, 2H), 2.22 (s, 3H), 3.39–3.45 (m, 2H), 3.73–3.75 (m, 2H), 4.14 (q, J = 8.4 & d 7.2 Hz, 2H), 5.30–5.36 (m, 1H), 8.40 (s, 1H); ESI/MS m/z : 299.9 ($\text{M}+\text{H}$) $^+$.

6.4.3.3. *t*-butyl 4-((6-chloro-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (3c). The title compound was synthesized from commercially available **2c** and **1a**, according to the general procedure described above; off white solid; Yield: 73%; m.p: 84–85 $^\circ\text{C}$; Purity by UPLC: 99.79%; IR: 3433, 3416, 2997, 1691, 1560, 1421, 1253, 771 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.47 (s, 9H), 1.73–1.80 (m, 2H), 1.94–2.0 (m, 2H), 2.22 (s, 3H), 3.32–3.39 (m, 2H), 3.68–3.74 (m, 2H), 5.31–5.35 (m, 1H), 8.38 (s, 1H); ESI/MS m/z : 328.0 ($\text{M}+\text{H}$) $^+$.

6.4.3.4. Isobutyl 4-((6-chloro-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (3d). The title compound was synthesized from **2d** and commercially available **1a**, according to the general procedure described above; Pale yellow oil; Yield: 61%; Purity by UPLC: 96.21%; ^1H NMR (CDCl_3 , 400 MHz): δ 0.94 (d, J = 6.8 Hz, 6H), 1.74–1.80 (m, 2H), 1.93–2.00 (m, 2H), 2.23 (s, 3H), 3.40–3.46 (m, 2H), 3.73–3.79 (m, 2H), 3.88 (d, J = 6.4 Hz, 2H), 5.32–5.37 (m, 1H), 8.38 (s, 1H); ESI/MS m/z : 327.9 ($\text{M}+\text{H}$) $^+$.

6.4.3.5. Benzyl 4-((6-chloro-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (3e). The title compound was synthesized from **2e** and commercially available **1a**, according to the general procedure described above; Yellow oil; Yield: 40%; Purity by UPLC: 90.84%; IR: 3433, 3416, 3018, 2958, 1691, 1554, 1433, 1205, 680 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.99 (s, 2H), 2.04 (d, J = 3.6 Hz, 2H), 2.22 (s, 3H), 3.75–3.81 (m, 2H), 4.09–4.15 (m, 2H), 5.15 (s, 2H), 5.32–5.38 (m, 1H), 7.26–7.39 (m, 5H), 8.38 (s, 1H); ESI/MS m/z : 384.0 ($\text{M}+\text{Na}$) $^+$.

6.4.3.6. Methyl 4-((6-chloropyrimidin-4-yl) oxy) piperidine-1-carboxylate (4a). The title compound was synthesized from **2a** and commercially available **1b**, according to the general procedure described above; Thick oil; Yield: 73%; Purity by UPLC: 97.37%; IR: 3016, 2958, 2870, 1745, 1697, 1568, 1452, 1276, 1238, 1141, 1085, 985, 756 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.75–1.79 (m, 2H), 1.97–2.01 (m, 2H), 3.29–3.39 (m, 2H), 3.71 (s, 3H), 3.73–3.77 (m, 2H), 5.30–5.36 (m, 1H), 6.76 (s, 1H), 8.55 (s, 1H); ESI/MS m/z : 271.8 ($\text{M}+\text{H}$) $^+$.

6.4.3.7. Ethyl 4-((6-chloropyrimidin-4-yl) oxy) piperidine-1-carboxylate (4b). The title compound was synthesized from **2b** and commercially available **1b**, according to the general procedure described above; White solid; Yield: 67%; Purity by UPLC: 99.54%; IR: 3014, 2978, 2868, 1685, 1568, 1460, 1425, 1352, 1234, 1130, 1085, 1028, 981, 775 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.27 (t, J = 7.2 Hz, 3H), 1.71–1.79 (m, 2H), 1.96–2.01 (m, 2H), 3.32–3.39 (m, 2H), 3.78–3.81 (m, 2H), 4.16 (q, J = 14.2 & 7.2 Hz, 2H), 5.30–5.36 (m, 1H), 6.76 (s, 1H), 8.55 (s, 1H); ESI/MS m/z : 285.9 ($\text{M}+\text{H}$) $^+$.

6.4.3.8. *tert*-butyl 4-((6-chloropyrimidin-4-yl) oxy) piperidine-1-carboxylate (4c). The title compound was synthesized from commercially available **2c** and **1b**, according to the general procedure described above; Thick oil; Yield: 30%; Purity by UPLC: 99.74%; IR: 3392, 3019, 2979, 2935, 1680, 1569, 1216, 758 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.47 (s, 9H), 1.70–1.76 (m, 2H), 1.95–2.00 (m, 2H), 3.25–3.31 (m, 2H), 3.75 (t, J = 12.4 Hz, 2H), 5.28–5.32 (m, 1H), 6.75 (s, 1H), 8.54 (s, 1H); ESI/MS m/z : 313.0 (M) $^+$.

6.4.3.9. Isobutyl 4-((6-chloropyrimidin-4-yl) oxy) piperidine-1-carboxylate (4d). The title compound was synthesized from **2d** and commercially available **1b**, according to the general procedure described above; Thick oil; Yield: 65%; Purity by UPLC: 97.38%; IR: 3012, 2962, 2874, 1691, 1568, 1454, 1350, 1230, 1085, 1030, 756 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 0.96 (d, J = 7.6 Hz, 6H), 1.71–1.80 (m, 2H), 1.89–2.03 (m, 3H), 3.33–3.40 (m, 2H), 3.77–3.83 (m, 2H), 3.88 (d, J = 6.8 Hz, 2H), 5.30–5.36 (m, 1H), 6.76 (s, 1H), 8.55 (s, 1H); ESI/MS m/z : 314.0 ($\text{M}+\text{H}$) $^+$.

6.4.3.10. Benzyl 4-((6-chloropyrimidin-4-yl) oxy) piperidine-1-carboxylate (4e). The title compound was synthesized from **2e** and commercially available **1b**, according to the general procedure described above; Thick oil; Yield: 54%; Purity by UPLC: 98.57%; IR: 3016, 2960, 2872, 1685, 1570, 1541, 1452, 1350, 1226, 1217, 1087, 1030, 985, 756 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.75–1.77 (m, 2H), 1.98–2.04 (m, 2H), 3.37–3.43 (m, 2H), 3.79–3.85 (m, 2H), 5.14 (s, 2H), 5.30–5.36 (m, 1H), 6.75 (s, 1H), 7.30–7.37 (m, 5H), 8.54 (s, 1H); ESI/MS m/z : 347.9 ($\text{M}+\text{H}$) $^+$.

6.4.4. General procedure for preparation of 6a-e, 7a-e, 11a-e and 12a-e

To a solution of intermediate **3a-e** and **4a-e** (1 equivalent) and *p*-hydroxybenzaldehyde (**5**) or *m*-hydroxybenzaldehyde (**10**) (1 equivalent) in *N,N*-dimethylformamide, cesium carbonate (2 equivalent) was added at 30 °C and then reaction mixture was stirred at 70 °C for 24 h. Then reaction mixture was cooled to 30 °C and poured to ice cold water and extracted with ethyl acetate. Then organic layer was washed with water, brine, dried over sodium sulfate and concentrated under reduced pressure to obtained crude product. Then crude product was purified through column chromatography using 15–20% ethyl acetate in hexane to give the desired intermediates **6a-e**, **7a-e**, **11a-e** and **12a-e**.

6.4.4.1. Methyl 4-((6-(4-formylphenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (6a). The title compound was synthesized from **3a** and *p*-hydroxybenzaldehyde (**5**), according to the general procedure described above; Thick oil; Yield: 92%; Purity by UPLC: 96.55%; IR: 3375, 2955, 2862, 1701, 1685, 1566, 1411, 1259, 1215, 1109, 1026, 844, 763 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.77–1.85 (m, 2H), 1.98–2.04 (m, 2H), 2.18 (s, 3H), 3.42–3.48 (m, 2H), 3.71 (s, 3H), 3.75–3.77 (m, 2H), 5.33–5.39 (m, 1H), 7.29 (d, J = 6.8 Hz, 2H), 7.94 (d, J = 8.8 Hz, 2H), 8.25 (s, 1H), 9.99 (s, 1H); ESI/MS m/z : 371.9 ($\text{M}+\text{H}$) $^+$.

6.4.4.2. Ethyl 4-((6-(4-formylphenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (6b). The title compound was synthesized from **3b** and *p*-hydroxybenzaldehyde (**5**), according to the general procedure described above; Thick Oil; Yield: 36%; Purity by UPLC: 96.51%; ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 1.27 (t, J = 7.2 Hz, 3H), 1.63–1.69 (m, 2H), 1.92–1.97 (m, 2H), 2.11 (s, 3H), 3.32–3.38 (m, 2H), 3.61–3.67 (m, 2H), 4.05 (q, J = 10.0 Hz & 2.8 Hz, 2H), 5.30–5.32 (m, 1H), 7.38 (d, J = 6.8 Hz, 2H), 7.95 (d, J = 4.4 Hz, 2H), 8.29 (s, 1H), 9.98 (s, 1H); ESI/MS m/z : 385.9 ($\text{M}+\text{H}$) $^+$.

6.4.4.3. tert-butyl 4-((6-(4-formylphenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (6c). The title compound was synthesized from intermediate **3c** and *p*-hydroxybenzaldehyde (**5**), according to the general procedure described above; Thick oil; Yield: 66%; Purity by UPLC: 98.27%; IR: 3018, 2980, 2870, 1685, 1570, 1425, 1261, 1217, 1112, 1026, 758 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.48 (s, 9H), 1.75–1.81 (m, 2H), 1.96–2.01 (m, 2H), 2.18 (s, 3H), 3.34–3.41 (m, 2H), 3.70–3.76 (m, 2H), 5.32–5.36 (m, 1H), 7.28 (d, J = 6.4 Hz, 2H), 7.94 (d, J = 6.8 Hz, 2H), 8.25 (s, 1H), 9.99 (s, 1H); ESI/MS m/z : 414.0 ($\text{M}+\text{H}$) $^+$.

6.4.4.4. Isobutyl 4-((6-(4-formylphenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (6d). The title compound was synthesized from intermediate **3d** and *p*-hydroxybenzaldehyde (**5**), according to the

general procedure described above; Thick oil; Yield: 63%; Purity by UPLC: 92.56%; ^1H NMR (CDCl_3 , 400 MHz): δ 0.94 (d, J = 6.8 Hz, 6H), 1.77–1.85 (m, 2H), 1.92–2.04 (m, 3H), 2.18 (s, 3H), 3.42–3.48 (m, 2H), 3.75–3.81 (m, 2H), 3.89 (d, J = 6.8 Hz, 2H), 5.30–5.38 (m, 1H), 7.28 (d, J = 6.8 Hz, 2H), 7.94 (d, J = 9.2 Hz, 2H), 8.25 (s, 1H), 9.99 (s, 1H); ESI/MS m/z : 413.9 ($\text{M}+\text{H}$) $^+$.

6.4.4.5. Benzyl 4-((6-(4-formylphenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (6e). The title compound was synthesized from intermediate **3e** and *p*-hydroxybenzaldehyde (**5**), according to the general procedure described above; Thick oil; Yield: 46%; Purity by UPLC: 93.54%; ^1H NMR (CDCl_3 , 400 MHz): δ 1.77–1.83 (m, 2H), 2.01–2.04 (m, 2H), 2.17 (s, 3H), 3.45–3.52 (m, 2H), 3.77–3.83 (m, 2H), 5.15 (s, 2H), 5.35–5.38 (m, 1H), 7.27–7.38 (m, 7H), 7.94 (d, J = 9.2 Hz, 2H), 8.25 (s, 1H), 9.99 (s, 1H); ESI/MS m/z : 447.9 ($\text{M}+\text{H}$) $^+$.

6.4.4.6. Methyl 4-((6-(4-formylphenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (7a). The title compound was synthesized from intermediate **4a** and *p*-hydroxybenzaldehyde (**5**), according to the general procedure described above; Thick oil; Yield: 81%; Purity by UPLC: 97.23%; IR: 3375, 2955, 2862, 1701, 1685, 1566, 1411, 1259, 1215, 1109, 1026, 844, 763 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.72–1.80 (m, 2H), 1.98–2.02 (m, 2H), 3.33–3.40 (m, 2H), 3.71 (s, 3H), 3.78–3.81 (m, 2H), 5.30–5.35 (m, 1H), 6.24 (s, 1H), 7.30 (d, J = 6.8 Hz, 2H), 7.95 (d, J = 9.2 Hz, 2H), 8.42 (s, 1H), 9.99 (s, 1H); ESI/MS m/z : 380.0 ($\text{M}+\text{Na}$) $^+$.

6.4.4.7. Ethyl 4-((6-(4-formylphenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (7b). The title compound was synthesized from the intermediate **4b** and *p*-hydroxybenzaldehyde (**5**), according to the general procedure described above; Off-white solid; Yield: 72%; Purity by UPLC: 96.89%; IR: 3429, 2989, 2864, 1687, 1581, 1438, 1246, 1211, 1134, 1028, 854, 767 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.27 (t, J = 7.4 Hz, 3H), 1.71–1.80 (m, 2H), 1.97–2.04 (m, 2H), 3.32–3.38 (m, 2H), 3.78–3.83 (m, 2H), 4.15 (q, J = 14.2 and 6.8 Hz, 2H), 5.30–5.35 (m, 1H), 6.24 (s, 1H), 7.30 (d, J = 6.8 Hz, 2H), 7.96 (d, J = 7.2 Hz, 2H), 8.43 (s, 1H), 10.01 (s, 1H); ESI/MS m/z : 372.1 ($\text{M}+\text{H}$) $^+$.

6.4.4.8. tert-butyl 4-((6-(4-formylphenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (7c). The title compound was synthesized from intermediate **4c** and *p*-hydroxybenzaldehyde (**5**), according to the general procedure described above; Off-white solid product; Yield: 57%; Purity by UPLC: 98.84%; IR: 3383, 2970, 2868, 1687, 1581, 1469, 1421, 1253, 1215, 1161, 1024, 846, 765 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.47 (s, 9H), 1.71–1.77 (m, 2H), 1.96–2.01 (m, 2H), 3.25–3.31 (m, 2H), 3.76–3.79 (m, 2H), 5.28–5.32 (m, 1H), 6.24 (s, 1H), 7.30 (d, J = 6.4 Hz, 2H), 7.95 (d, J = 6.8 Hz, 2H), 8.42 (s, 1H), 10.01 (s, 1H); ESI/MS m/z : 400.0 ($\text{M}+\text{H}$) $^+$.

6.4.4.9. Isobutyl 4-((6-(4-formylphenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (7d). The title compound was synthesized from the intermediate **4d** and *p*-hydroxybenzaldehyde (**5**), according to the general procedure described above; colorless thick oil; Yield: 78%; Purity by UPLC: 97.71%; IR: 3464, 3018, 2964, 1687, 1581, 1460, 1251, 1217, 1161, 1035, 756 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 0.94 (d, J = 6.8 Hz, 6H), 1.72–1.80 (m, 2H), 1.91–1.96 (m, 1H), 1.98–2.04 (m, 2H), 3.33–3.39 (m, 2H), 3.79–3.85 (m, 2H), 3.88 (d, J = 6.4 Hz, 2H), 5.30–5.36 (m, 1H), 6.24 (s, 1H), 7.30 (d, J = 9.2 Hz, 2H), 7.95 (d, J = 9.2 Hz, 2H), 8.42 (s, 1H), 10.01 (s, 1H); ESI/MS m/z : 400.1 ($\text{M}+\text{H}$) $^+$.

6.4.4.10. Benzyl 4-((6-(4-formylphenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (7e). The title compound was synthesized from the intermediate **4e** and *p*-hydroxybenzaldehyde (**5**), according to the general procedure described above and the crude product was directly used for the next step.

6.4.4.11. Methyl 4-((6-(3-formylphenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (11a). The title compound was synthesized from the intermediate **3a** and *m*-hydroxybenzaldehyde (**10**), according to the general procedure described above and the crude product was directly used for the next step.

6.4.4.12. Ethyl 4-((6-(3-formylphenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (11b). The title compound was synthesized from the intermediate **3b** and *m*-hydroxybenzaldehyde (**10**), according to the general procedure described above and the crude product was directly used for the next step.

6.4.4.13. *tert*-butyl 4-((6-(3-formylphenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (11c). The title compound was synthesized from the intermediate **3c** and *m*-hydroxybenzaldehyde (**10**), according to the general procedure described above; Thick oil; Yield: 81%; Purity by UPLC: 98.57%; IR: 3010, 2978, 2866, 1701, 1585, 1570, 1425, 1365, 1261, 1232, 1143, 1026, 756 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.48 (s, 9H), 1.76–1.81 (m, 2H), 1.97–2.01 (m, 2H), 2.18 (s, 3H), 3.35–3.41 (m, 2H), 3.70–3.76 (m, 2H), 5.32–5.36 (m, 1H), 7.39–7.42 (m, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 4.0 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 8.23 (s, 1H), 10.01 (s, 1H); ESI/MS *m/z*: 414.0 (M+H)⁺.

6.4.4.14. Isobutyl 4-((6-(3-formylphenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (11d). The title compound was synthesized from the intermediate **3d** and *m*-hydroxybenzaldehyde (**10**), according to the general procedure described above and the crude product was directly used for the next step.

6.4.4.15. Benzyl 4-((6-(3-formylphenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (11e). The title compound was synthesized from the intermediate **3e** and *m*-hydroxybenzaldehyde (**10**), according to the general procedure described above and the crude product was directly used for the next step.

6.4.4.16. Methyl 4-((6-(3-formylphenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (12a). The title compound was synthesized from the intermediate **4a** and *m*-hydroxybenzaldehyde (**10**), according to the general procedure described above; Thick oil; Yield: 61%; Purity by UPLC: 98.25%; ¹H NMR (CDCl₃, 400 MHz): δ 1.74–1.78 (m, 2H), 1.97–2.01 (m, 2H), 3.33–3.42 (m, 2H), 3.71 (s, 3H), 3.78–3.80 (m, 2H), 5.30–5.33 (m, 1H), 6.21 (s, 1H), 7.40–7.43 (m, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 4.0 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 8.40 (s, 1H), 10.08 (s, 1H); ESI/MS *m/z*: 357.9 (M+H)⁺.

6.4.4.17. Ethyl 4-((6-(3-formylphenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (12b). The title compound was synthesized from the intermediate **4b** and *m*-hydroxybenzaldehyde (**10**), according to the general procedure described above; Thick oil; Yield: 57%; Purity by UPLC: 97.29%; ¹H NMR (CDCl₃, 400 MHz): δ 1.27 (t, *J* = 7.0 Hz, 3H), 1.71–1.79 (m, 2H), 1.97–2.01 (m, 2H), 3.32–3.38 (m, 2H), 3.80–3.83 (m, 2H), 4.16 (q, *J* = 14.2 & 6.8 Hz, 2H), 5.29–5.35 (m, 1H), 6.21 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 8.41 (s, 1H), 10.02 (s, 1H); ESI/MS *m/z*: 372.0 (M+H)⁺.

6.4.4.18. *tert*-butyl 4-((6-(3-formylphenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (12c). The title compound was synthesized from the intermediate **4c** and *m*-hydroxybenzaldehyde (**10**), according to the general procedure described above; Thick oil; Yield: 58%; Purity by UPLC: 98.45%; ¹H NMR (CDCl₃, 400 MHz): δ 1.47 (s, 9H), 1.71–1.76 (m, 2H), 1.96–2.01 (m, 2H), 3.24–3.31 (m, 2H), 3.76–3.79 (m, 2H), 5.28–5.32 (m, 1H), 6.20 (s, 1H), 7.40–7.43 (m, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 4.0 Hz, 1H), 7.78 (d, *J* = 6.4 Hz, 1H), 8.41 (s, 1H), 10.02 (s, 1H); ESI/MS *m/z*: 400.2 (M+H)⁺.

6.4.4.19. Isobutyl 4-((6-(3-formylphenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (12d). The title compound was synthesized from the intermediate **4d** and *m*-hydroxybenzaldehyde (**10**), according to the general procedure described above; Thick oil; Yield: 83%; Purity by UPLC: 98.96%; IR: 3016, 2962, 2874, 1701, 1581, 1460, 1450, 1251, 1230, 1170, 1035, 837, 756 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 0.94 (d, *J* = 6.8 Hz, 6H), 1.73–1.79 (m, 2H), 1.98–2.04 (m, 3H), 3.33–3.39 (m, 2H), 3.79–3.85 (m, 2H), 3.88 (d, *J* = 6.4 Hz, 2H), 5.29–5.34 (m, 1H), 6.21 (s, 1H), 7.41 (d, *J* = 6.8 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.66 (s, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 8.40 (s, 1H), 10.02 (s, 1H); ESI/MS *m/z*: 400.1 (M+H)⁺.

6.4.4.20. Benzyl 4-((6-(3-formylphenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (12e). The title compound was synthesized from the intermediate **4e** and *m*-hydroxybenzaldehyde (**10**), according to the general procedure described above and the crude product was directly used for the next step.

6.4.5. General procedure for the preparation of 8a-e, 9a-e, 13a-e and 14a-e

To a solution of intermediate **6a-e**, **7a-e**, **11a-e** and **12a-e** (1 equivalent), thiazolidine-2, 4-dione (0.9 equivalent) and benzoic acid (0.1 equivalent) in toluene, piperidine (1.5 equivalent) was added at 30 °C and the reaction mixture was refluxed for 7 h. Then reaction mixture was cooled to 30 °C and solid product was filtered, washed with ice cold toluene and dried to give desired product. In all final compounds **8a-e**, **9a-e**, **13a-e** and **14a-e**, the —CH= proton from the newly introduced benzylidene moiety appeared as a sharp singlet at 7.70–7.90 ppm. This value indicates that all final compounds **8a-e**, **9a-e**, **13a-e** and **14a-e** are in *Z* conformation which being the most thermodynamically stable isomer according to the literature.^{35–38}

6.4.5.1. Methyl-4-((6-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (8a). The title compound was synthesized from the intermediate **6a** according to the general procedure described above; Yellow solid; Yield: 66.6%; m.p: >200 °C; Purity by UPLC: 97.65%; IR: 3194, 3072, 2862, 2748, 1755, 1703, 1687, 1572, 1413, 1220 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.79–1.83 (m, 2H), 1.98–2.03 (m, 2H), 2.19 (s, 3H), 3.43–3.48 (m, 2H), 3.72 (s, 3H), 3.73–3.79 (m, 2H), 5.35–5.39 (m, 1H), 7.21–7.26 (m, 2H), 7.53 (dd, *J* = 6.8 and 2.0 Hz, 2H), 7.77 (s, 1H), 8.25 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 7.92, 30.63, 66.72, 71.72, 102.76, 122.86, 123.44, 128.19, 128.90, 130.31, 131.78, 137.43, 154.59, 155.00, 167.48, 167.81, 168.24, 168.30; HRMS ESI/MS *m/z* calcd for C₂₂H₂₂N₄O₆S 471.1260 (M+H)⁺, found 471.1251.

6.4.5.2. Ethyl-4-((6-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (8b). The title compound was synthesized from the intermediate **6b** according to the general procedure described above; Yellow solid; Yield: 37.7%; m.p: >200 °C; Purity by UPLC: 97.19%; IR: 3109, 2953, 2933, 2852, 2750, 1743, 1701, 1589, 1572, 1222, 1111 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.81 (t, *J* = 7.0 Hz, 3H), 1.62–1.69 (m, 2H), 1.91–1.96 (m, 2H), 2.11 (s, 3H), 3.31–3.37 (m, 2H), 3.60–3.66 (m, 2H), 4.03 (q, *J* = 7.2 Hz, 2H), 5.27–5.33 (m, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.80 (s, 1H), 8.26 (s, 1H), 12.6 (s, 1H); HRMS ESI/MS *m/z* calcd for C₂₃H₂₄N₄O₆S 485.1417 (M+H)⁺, found 485.1411.

6.4.5.3. *tert*-butyl-4-((6-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (8c). The title compound was synthesized from the intermediate **6c** according to the general procedure described above; White solid; Yield: 47%; m.p: 207–208 °C; Purity by UPLC: 99.48%; IR: 3500, 3070, 2928, 2750, 1743, 1705, 1685, 1589, 1566, 1506, 1415, 1220, 1020, 900; ¹H NMR (CDCl₃, 400 MHz): δ 1.46 (s, 9H), 1.76–1.83 (m, 2H), 1.97–2.02 (m, 2H), 2.18 (s, 3H), 3.35–3.41 (m, 2H), 3.71–3.75 (m, 2H), 5.33–5.37 (m, 1H),

7.22–7.25 (m, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.77 (s, 1H), 8.25 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 7.91, 28.53, 30.74, 71.93, 79.25, 102.73, 121.86, 122.84, 123.50, 130.32, 130.82, 131.52, 131.96, 154.35, 154.99, 167.46, 167.88, 168.30; HRMS ESI/MS m/z calcd for $\text{C}_{25}\text{H}_{28}\text{N}_4\text{O}_6\text{S}$ 513.1730 ($\text{M}+\text{H}$) $^+$, found 513.1728.

6.4.5.4. Isobutyl-4-((6-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (8d). The title compound was synthesized from the intermediate **6d** according to the general procedure described above; Yellow Solid; Yield: 40%; m.p.: >200 °C; Purity by UPLC: 98.77%; IR: 2962, 2750, 1745, 1705, 1589, 1570, 1417, 1219, 1112, 1022 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 0.89 (d, $J = 6.8$ Hz, 6H), 1.62–1.69 (m, 2H), 1.83–1.90 (m, 1H), 1.93–1.97 (m, 2H), 2.11 (s, 3H), 3.30–3.35 (m, 2H), 3.60–3.66 (m, 2H), 3.79 (d, $J = 6.4$ Hz, 2H), 5.30–5.33 (m, 1H), 7.31 (d, $J = 8.8$ Hz, 2H), 7.65 (d, $J = 8.8$ Hz, 2H), 7.81 (s, 1H), 8.27 (s, 1H), 12.61 (s, 1H); HRMS ESI/MS m/z calcd for $\text{C}_{25}\text{H}_{28}\text{N}_4\text{O}_6\text{S}$ 513.1730 ($\text{M}+\text{H}$) $^+$, found 513.1725.

6.4.5.5. Benzyl-4-((6-(4-((2,4-dioxothiazolidin-5-ylidene) methyl) phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (8e). The title compound was synthesized from the intermediate **6e** according to the general procedure described above; Yellow Solid; Yield: 58.3%; m.p.: >200 °C; Purity by UPLC: 97.59%; IR: 3435, 2951, 2748, 1745, 1708, 1587, 1570, 1504, 1419, 1220, 1112 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.63–1.71 (m, 2H), 1.93–1.98 (m, 2H), 2.11 (s, 3H), 3.31–3.37 (m, 2H), 3.60–3.66 (m, 2H), 5.08 (s, 2H), 5.30–5.33 (m, 1H), 7.31 (d, $J = 8.8$ Hz, 2H), 7.35–7.39 (m, 5H), 7.63–7.65 (d, $J = 8.8$ Hz, 2H), 7.81 (s, 1H), 8.27 (s, 1H), 12.61 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 7.92, 30.63, 41.12, 66.72, 71.72, 102.76, 122.86, 123.44, 128.19, 130.31, 131.58, 131.98, 137.43, 154.59, 155.00, 167.65, 168.24, 168.30; HRMS ESI/MS m/z calcd for $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_6\text{S}$ 547.1573 ($\text{M}+\text{H}$) $^+$, found 547.1568.

6.4.5.6. Methyl-4-((6-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (9a). The title compound was synthesized from the intermediate **7a** according to the general procedure described above; Yellow Solid; Yield: 69.7%; m.p.: 228–230 °C; Purity by UPLC: 95.31%; IR: 3427, 3109, 3041, 2958, 2764, 1745, 1705, 1583, 1460, 1253, 1174 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.68–1.80 (m, 2H), 1.98–2.03 (m, 2H), 3.34–3.40 (m, 2H), 3.71 (s, 3H), 3.73–3.79 (m, 2H), 5.30–5.36 (m, 1H), 6.25 (s, 1H), 7.23–7.26 (m, 2H), 7.53–7.56 (m, 2H), 7.81 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 30.54, 41.05, 52.75, 71.93, 93.00, 122.42, 122.63, 130.42, 131.96, 132.56, 137.43, 154.31, 157.75, 166.82, 167.25, 170.33, 170.96; HRMS ESI/MS m/z calcd for $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_6\text{S}$ 457.1104 ($\text{M}+\text{H}$) $^+$, found 457.1101.

6.4.5.7. Ethyl-4-((6-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (9b). The title compound was synthesized from the intermediate **7b** according to the general procedure described above; Yellow Solid; Yield: 63.0%; m.p.: 200–202 °C; Purity by UPLC: 99.62%; IR: 3429, 3119, 2949, 2748, 1745, 1701, 1601, 1589, 1554, 1502, 1475, 1435, 1253, 1174, 1155, 1132 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.27 (t, $J = 7.2$ Hz, 3H), 1.73–1.80 (m, 2H), 1.98–2.03 (m, 2H), 3.32–3.39 (m, 2H), 3.80–3.83 (m, 2H), 4.15 (q, $J = 7.2$ Hz, 2H), 5.30–5.35 (m, 1H), 6.25 (s, 1H), 7.24–7.26 (m, 2H), 7.55 (d, $J = 8.4$ Hz, 2H), 7.80 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.70, 30.55, 40.97, 61.54, 72.09, 93.09, 122.45, 130.35, 132.03, 132.64, 154.37, 155.61, 157.68, 166.64, 167.05, 170.29, 171.02; HRMS ESI/MS m/z calcd for $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_6\text{S}$ 471.1260 ($\text{M}+\text{H}$) $^+$, found 471.1254.

6.4.5.8. Tert-butyl-4-((6-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (9c). The title compound was synthesized from the intermediate **7c** according to the general procedure described above; Yellow Solid; Yield: 43.0%; m.p.:

180–182 °C; Purity by UPLC: 97.52%; IR: 2976, 2858, 2758, 1743, 1701, 1608, 1589, 1465, 1411, 1251, 1174, 1033 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.47 (s, 9H), 1.70–1.78 (m, 2H), 1.97–2.01 (m, 2H), 3.25–3.31 (m, 2H), 3.71–3.80 (m, 2H), 5.29–5.33 (m, 1H), 6.24 (d, $J = 8.0$ Hz, 1H), 7.23–7.26 (m, 2H), 7.53–7.56 (m, 2H), 7.81 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 28.51, 30.77, 72.48, 79.28, 92.78, 122.90, 123.71, 130.77, 131.44, 132.16, 154.30, 158.33, 167.81, 168.28, 170.54, 170.91; HRMS ESI/MS m/z calcd for $\text{C}_{24}\text{H}_{26}\text{N}_4\text{O}_6\text{S}$ 499.1573 ($\text{M}+\text{H}$) $^+$, found 499.1568.

6.4.5.9. Isobutyl-4-((6-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (9d). The title compound was synthesized from the intermediate **7d** according to the general procedure described above; Yellow Solid; Yield: 61.7%; m.p.: 168–170 °C; Purity by UPLC: 97.56%; IR: 2958, 2754, 1745, 1707, 1587, 1475, 1222, 1153, 1030 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 0.94 (d, $J = 6.4$, 6H), 1.72–1.81 (m, 2H), 1.90–2.03 (m, 3H), 3.34–3.40 (m, 2H), 3.81–3.85 (m, 2H), 3.88 (d, $J = 6.8$ Hz, 2H), 5.30–5.36 (m, 1H), 6.25 (d, $J = 0.8$ Hz, 1H), 7.23–7.26 (m, 2H), 7.53–7.56 (m, 2H), 7.80 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 19.35, 28.02, 30.71, 41.24, 71.17, 72.33, 92.80, 122.89, 123.70, 130.77, 131.44, 132.16, 154.25, 155.11, 158.33, 167.80, 168.27, 170.55, 170.90; HRMS ESI/MS m/z calcd for $\text{C}_{24}\text{H}_{26}\text{N}_4\text{O}_6\text{S}$ 499.1573 ($\text{M}+\text{H}$) $^+$, found 499.1570.

6.4.5.10. Benzyl-4-((6-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (9e). The title compound was synthesized from the intermediate **7e** according to the general procedure described above; Yellow Solid; Yield: 39.5%; m.p.: 190–192 °C; Purity by UPLC: 96.39%; IR: 3435, 3064, 2931, 2748, 1745, 1693, 1504, 1255, 1220 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.78–1.85 (m, 2H), 2.00–2.04 (m, 2H), 3.37–3.43 (m, 2H), 3.82–3.85 (m, 2H), 5.15 (s, 2H), 5.30–5.36 (m, 1H), 6.24 (s, 1H), 7.23–7.26 (m, 2H), 7.30–7.39 (m, 5H), 7.53–7.56 (m, 2H), 7.81 (s, 1H), 8.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 30.69, 41.34, 66.73, 72.28, 92.80, 122.90, 123.72, 128.20, 128.90, 130.77, 131.45, 132.17, 137.41, 154.25, 154.88, 158.33, 167.81, 168.29, 170.55, 170.90; HRMS ESI/MS m/z calcd for $\text{C}_{27}\text{H}_{24}\text{N}_4\text{O}_6\text{S}$ 533.1417 ($\text{M}+\text{H}$) $^+$, found 533.1411.

6.4.5.11. Methyl-4-((6-(3-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (13a). The title compound was synthesized from the intermediate **11a** according to the general procedure described above; Off White Solid; Yield: 50%; m.p.: 120–122 °C; Purity by UPLC: 97.43%; IR: 3435, 3064, 2958, 2754, 1753, 1705, 1589, 1568, 1413, 1234, 1112 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.79–1.85 (m, 2H), 1.98–2.03 (m, 2H), 2.19 (s, 3H), 3.44–3.48 (m, 2H), 3.72 (s, 3H), 3.75–3.76 (m, 2H), 5.35–3.38 (m, 1H), 7.18–7.21 (m, 2H), 7.26–7.28 (m, 1H), 7.36 (d, $J = 8.0$ Hz, 1H), 7.51 (t, $J = 5.2$ Hz, 1H), 7.80 (s, 1H), 8.24 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 7.91, 22.68, 52.83, 71.71, 102.50, 123.48, 124.08, 125.12, 126.71, 129.72, 130.97, 135.08, 153.99, 154.54, 155.55, 167.61, 168.18; HRMS ESI/MS m/z calcd for $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_6\text{S}$ 471.1260 ($\text{M}+\text{H}$) $^+$, found 471.1256.

6.4.5.12. Ethyl-4-((6-(3-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (13b). The title compound was synthesized from the intermediate **11b** according to the general procedure described above; Off White Solid; Yield: 48%; m.p.: 138–139 °C; Purity by UPLC: 99.34%; IR: 3169, 3068, 2947, 2754, 1753, 1708, 1585, 1570, 1425, 1236, 1157 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.26 (t, $J = 10.4$ Hz, 3H), 1.77–1.85 (m, 2H), 1.98–2.04 (m, 2H), 2.19 (s, 3H), 3.42–3.48 (m, 2H), 3.75–3.79 (m, 2H), 4.17 (q, $J = 6.8$ Hz, 2H), 5.34–3.39 (m, 1H), 7.18–7.21 (m, 1H), 7.26–7.28 (m, 1H), 7.36 (d, $J = 8$ Hz, 1H), 7.51 (t, $J = 5.2$ Hz, 1H), 7.79 (s, 1H), 8.24 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 7.90, 14.43, 15.07, 22.54, 30.64, 31.43, 61.21, 71.75, 102.50, 123.47,

124.08, 125.08, 126.71, 130.97, 131.33, 135.07, 153.99, 154.54, 155.11, 167.61, 167.67, 168.17; HRMS ESI/MS m/z calcd for $C_{23}H_{24}N_4O_6S$ 485.1417 (M+H)⁺, found 485.1412.

6.4.5.13. Tert-butyl-4-((6-(3-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (13c).

The title compound was synthesized from the intermediate **11c** according to the general procedure described above; Yellow Solid; Yield: 60%; m.p: 188–190 °C; Purity by UPLC: 98.27%; IR: 3429, 3138, 2964, 2848, 2773, 1741, 1695, 1585, 1564, 1417, 1288, 1240, 1112 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.48 (s, 9H), 1.76–1.83 (m, 2H), 1.97–2.03 (m, 2H), 2.19 (s, 3H), 3.36–3.42 (m, 2H), 3.70–3.75 (m, 2H), 5.33–5.37 (m, 1H), 7.19–7.21 (m, 2H), 7.26–7.28 (m, 1H), 7.36 (d, J = 8 Hz, 1H), 7.51 (t, J = 5.2 Hz, 1H), 7.80 (s, 1H), 8.24 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 7.91, 28.53, 30.75, 71.89, 79.25, 102.49, 123.47, 124.07, 125.13, 125.78, 126.71, 128.66, 129.36, 130.97, 131.29, 135.08, 153.99, 154.40, 167.65, 168.19; HRMS ESI/MS m/z calcd for $C_{25}H_{28}N_4O_6S$ 513.1730 (M+H)⁺, found 513.1726.

6.4.5.14. Isobutyl-4-((6-(3-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (13d).

The title compound was synthesized from the intermediate **11d** according to the general procedure described above; Yellow Solid; Yield: 50%; m.p: 112–113 °C; Purity by UPLC: 98.94%; IR: 3435, 2960, 2756, 1753, 1707, 1589, 1566, 1431 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 0.95 (d, J = 6.4 Hz, 6H), 1.78–1.86 (m, 2H), 1.90–2.04 (m, 3H), 2.19 (s, 3H), 3.43–3.49 (m, 2H), 3.75–3.81 (m, 2H), 3.89 (d, J = 6.8 Hz, 2H), 5.34–5.40 (m, 1H), 7.19 (m, 1H), 7.26–7.35 (m, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.80 (s, 1H), 8.24 (s, 1H), 8.78 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 7.91, 19.36, 28.03, 30.67, 71.17, 71.74, 102.50, 123.48, 124.09, 125.07, 126.71, 130.97, 131.33, 135.07, 153.99, 154.54, 155.14, 167.61, 168.17; HRMS ESI/MS m/z calcd for $C_{25}H_{28}N_4O_6S$ 513.1730 (M+H)⁺, found 513.1731.

6.4.5.15. Benzyl-4-((6-(3-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (13e).

The title compound was synthesized from the intermediate **11e** according to the general procedure described above; Yellow Solid; Yield: 20%; m.p: 128–129 °C; Purity by UPLC: 98.48%; IR: 3433, 2951, 2764, 1751, 1705, 1587, 1568, 1431 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.87–1.95 (m, 2H), 2.08–2.16 (m, 2H), 2.16 (s, 3H), 2.49–2.60 (m, 2H), 2.79–2.81 (m, 2H), 3.63 (s, 2H), 5.20–5.24 (m, 1H), 7.17–7.20 (m, 1H), 7.26–7.30 (m, 2H), 7.31–7.38 (m, 5H), 7.51 (d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 8.22 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 7.92, 22.69, 30.63, 66.72, 71.67, 102.50, 123.43, 123.97, 125.68, 126.68, 128.02, 128.32, 128.90, 130.88, 130.94, 135.21, 137.43, 153.98, 154.54, 154.92, 167.61, 168.16, 168.40, 168.53; HRMS ESI/MS m/z calcd for $C_{28}H_{26}N_4O_6S$ 547.1573 (M+H)⁺, found 547.1569.

6.4.5.16. Methyl-4-((6-(3-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (14a). The title compound was synthesized from the intermediate **12a** according to the general procedure described above; Yellow Solid; Yield: 30%; m.p: 200–202 °C; Purity by UPLC: 92.97%; IR: 3433, 3130, 3026, 2958, 1747, 1695, 1593, 1456, 1255, 1182 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.74–1.80 (m, 2H), 1.98–2.02 (m, 2H), 3.34–3.40 (m, 2H), 3.71 (s, 3H), 3.75–3.81 (m, 2H), 5.30–5.34 (m, 1H), 6.20 (s, 1H), 7.18–7.23 (m, 1H), 7.26–7.28 (m, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.80 (s, 1H), 8.41 (s, 1H); HRMS ESI/MS m/z calcd for $C_{21}H_{20}N_4O_6S$ 457.1104 (M+H)⁺, found 457.1098.

6.4.5.17. Ethyl-4-((6-(3-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (14b). The title compound was synthesized from the intermediate **12b** according to the general procedure described above; Yellow Solid; Yield: 66%; m.p:

169–170 °C; Purity by UPLC: 96.27%; IR: 3455, 3126, 2929, 2777, 1743, 1691, 1599, 1570, 1462, 1330, 1247, 1178, 1134, 1024, 846 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.27 (t, J = 9.2 Hz, 3H), 1.72–1.80 (m, 2H), 1.98–2.04 (m, 2H), 3.33–3.39 (m, 2H), 3.80–3.83 (m, 2H), 4.13–4.18 (q, J = 7.2 Hz, 2H), 5.30–5.35 (m, 1H), 6.21 (s, 1H), 7.21–7.24 (m, 1H), 7.28–7.29 (m, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.81 (s, 1H), 8.42 (s, 1H), 8.77 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 15.05, 30.68, 41.19, 61.23, 72.32, 92.55, 123.51, 123.98, 125.40, 127.03, 131.10, 131.22, 135.36, 153.32, 155.06, 158.31, 167.84, 168.23, 170.72; HRMS ESI/MS m/z calcd for $C_{22}H_{22}N_4O_6S$ 471.1260 (M+H)⁺, found 471.1261.

6.4.5.18. Tert-butyl-4-((6-(3-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (14c). The title compound was synthesized from the intermediate **12c** according to the general procedure described above; White Solid; Yield: 55%; m.p: 170–171 °C; Purity by UPLC: 99.63%; IR: 3433, 3117, 3036, 2974, 2762, 1745, 1707, 1593, 1574, 1460, 1321, 1176, 1033 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.47 (s, 9H), 1.70–1.78 (m, 2H), 1.97–2.01 (m, 2H), 3.25–3.32 (m, 2H), 3.76–3.80 (m, 2H), 5.28–5.32 (m, 1H), 6.20 (s, 1H), 7.21–7.24 (m, 1H), 7.28–7.29 (m, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.82 (s, 1H), 8.41 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 28.52, 30.52, 72.45, 79.29, 92.56, 123.50, 123.96, 125.57, 127.03, 130.99, 131.23, 135.41, 153.33, 154.36, 158.41, 168.16, 170.80; HRMS ESI/MS m/z calcd for $C_{24}H_{26}N_4O_6S$ 499.1573 (M+H)⁺, found 499.1568.

6.4.5.19. Isobutyl-4-((6-(3-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (14d). The title compound was synthesized from the intermediate **12d** according to the general procedure described above; Yellow Solid; Yield: 33.6%; m.p: 136–138 °C; Purity by UPLC: 98.24%; IR: 3429, 3155, 3063, 2960, 1743, 1705, 1600, 1460, 1178 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 0.95 (d, J = 6.4 Hz, 6H), 1.78–1.86 (m, 2H), 1.90–2.04 (m, 3H), 2.19 (s, 3H), 3.43–3.49 (m, 2H), 3.75–3.81 (m, 2H), 3.89 (d, J = 6.8 Hz, 2H), 5.34–5.40 (m, 1H), 7.19 (m, 1H), 7.26–7.35 (m, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.80 (s, 1H), 8.24 (s, 1H), 8.78 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 19.35, 28.02, 30.73, 41.25, 71.17, 72.30, 92.57, 115.67, 123.52, 124.01, 125.28, 127.04, 129.82, 131.24, 131.24, 135.34, 153.33, 155.12, 158.32, 167.68, 168.15, 170.80; HRMS ESI/MS m/z calcd for $C_{24}H_{26}N_4O_6S$ 499.1573 (M+H)⁺, found 499.1570.

6.4.5.20. Benzyl-4-((6-(3-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (14e). The title compound was synthesized from the intermediate **12e** according to the general procedure described above; Yellow Solid; Yield: 40.7%; m.p: 178–180 °C; Purity by UPLC: 97.08%; IR: 3176, 3057, 2951, 2359, 1743, 1589, 1570, 1465, 1172 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.78–1.85 (m, 2H), 2.00–2.04 (m, 2H), 3.37–3.43 (m, 2H), 3.82–3.85 (m, 2H), 5.15 (s, 2H), 5.30–5.36 (m, 1H), 6.21 (s, 1H), 7.21–7.23 (m, 1H), 7.26–7.30 (m, 2H), 7.31–7.40 (m, 5H), 7.53 (d, J = 8.0 Hz, 1H), 7.81 (s, 1H), 8.41 (s, 1H), 8.61 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 30.74, 66.72, 72.24, 92.57, 123.51, 123.99, 125.38, 127.04, 128.08, 128.90, 131.13, 131.23, 135.36, 137.41, 153.32, 154.88, 158.31, 167.80, 168.21, 170.75; HRMS ESI/MS m/z calcd for $C_{27}H_{24}N_4O_6S$ 533.1417 (M+H)⁺, found 533.1420.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Authors are grateful to Dr. Rajiv Sharma, Dr. Sanjay Kumar and the management of Zydus Group for support and encouragement. Authors thank to the analytical department for providing analytical data.

References

- Singh VP. *Sci Technol J*. 2016;4:113–123.
- International Diabetes Federation. IDF DIABETES ATLAS, 9th ed; 2019.
- Bugger H, Abel ED. *Diabetologia*. 2014;57:660–671.
- Kostev K, Rathmann W. *Diabetologia*. 2013;56:109–111.
- Gray SP, Cooper ME. *Nat Rev Nephrol*. 2011;7:71–73.
- Martin CL, Albers JW. *Diabetes Care*. 2014;37:31–38.
- Wukich DK, Armstrong DG, Attinger CE, et al. *Diabetes Care*. 2013;36:2862–11871.
- Metzger BE, Lowe LP, Dyer AR, et al. *N Engl J Med*. 2008;358:1991–2002.
- National Diabetes Fact Sheet. Department of Health and Human Services, Centres for disease control and prevention; 2007.
- Dowarah J, Prakash Singh V. *Bioorg Med Chem*. 2020;28.
- (a) Tahrani AA, Bailey CJ, Prato SD, Barnett AH. *Lancet*. 2011;378:182. (b) UMHS Management of Type 2 Diabetes Mellitus, May 2014.
- Wild S, Roglic G, Green A, Sicree R, King H. *Diabetes Care*. 2004;27:1047.
- Wacker DA, Wang Y, Broekema M, et al. *J Med Chem*. 2014;57:7499–7508.
- Scott JS, Bowker SS, Brocklehurst KJ, et al. *J Med Chem*. 2014;57:8984–8998.
- Jang YK, Lee KM, Jung KY, et al. *Bioorg Med Chem Lett*. 2017;27:3909–3914.
- Overton HA, Fyfe MCT, Reynet C. *Br J Pharmacol*. 2010;153:S76–S81.
- Jones RM, Leonard JN. *Annu Rep Med Chem*. 2009;44:149–170.
- Hansen HS, Rosenkilde MM, Holst JJ, Schwartz TW. *Trends Pharmacol Sci*. 2012;33:374–481.
- Harada K, Mizukami J, Kadowaki S, et al. *Bioorg Med Chem Lett*. 2018;28:1228–1233.
- Zhu C, Wang LP, Zhu YP, et al. *Bioorg Med Chem Lett*. 2017;27:1124–1128.
- Dhayal S, Morgan NG. *Drug News Perspect*. 2010;23:418.
- Overton HA, Babbs AJ, Doel SM, et al. *Cell Metab*. 2006;3:167.
- Yore MM, Syed I, Moraes-Vieira PM, et al. *Cell*. 2014;159:318.
- Ritter K, Buning C, Halland N, et al. *J Med Chem*. 2015;59(8):3579–3592.
- Kang SU. *Drug Discov Today*. 2013;18:1309.
- Scott JS, Brocklehurst KJ, Brown HS, et al. *Bioorg Med Chem Lett*. 2013;23:3175.
- Fu SH, Xiang W, Chen JY, Ma L, Chen LJ. *Chem Biol Drug Des*. 2017;89:815.
- Gao J, Tian L, Weng G, O'Brien TD, Luo J, Guo Z. *Transplant Proc*. 2011;43:3217.
- Jones RM, Leonard JN, Buzard DJ, Lehmann J. *Expert Opin Ther Pat*. 2009;19:1339.
- Nanjan MJ, Mohammed Manal, Prashantha Kumar BR, Chandrasekar MJN. *Bioorg Chem*. 2018;77:548–567.
- Pingali, Harikishore, Zaware, Pandurang. WO 2012/046249 A1; 2012.
- Schrödinger Release 2018-4: Glide. New York, NY: Schrödinger, LLC; 2018.
- Schrödinger Release 2018-4: LigPrep. New York, NY: Schrödinger, LLC; 2018.
- Schrödinger Release 2018-4: Induced Fit Docking protocol; Glide. Schrödinger, LLC, New York, NY, 2019; Prime, Schrödinger, LLC, New York, NY; 2018.
- Marc Gabriel, Stana Anca, Oniga Smaranda Dafina, Pîrnu Adrian, Vlase Laurian, Oniga Ovidiu. *Molecules*. 2019;24:2060.
- Silva IM, Filho J, Santiago PBG, Egito MS, Souza CA, Gouveia FL. *Biomed Res Int*. 2014;2014:1–8.
- Pratap UR, Jawale DV, Waghmare RA, Lingampalle DL, Mane RA. *New J Chem*. 2011;35:49–51.
- Tuncbilek M, Altanlar N. *Arch Pharm (Weinheim)*. 2006;339:213–216.