Bioorganic & Medicinal Chemistry Letters 21 (2011) 3103–3109

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Revisiting glitazars: Thiophene substituted oxazole containing α-ethoxy phenylpropanoic acid derivatives as highly potent PPARα/γ dual agonists devoid of adverse effects in rodents ☆

Preeti Raval [a,b,*], Mukul Jain [a], Amitgiri Goswami [a], Sujay Basu [a], Archana Gite [a], Atul Godha [a], Harikishore Pingali [a], Saurin Raval [a], Suresh Giri [a], Dinesh Suthar [a], Maanan Shah [a], Pankaj Patel [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

Article history:
Received 19 August 2010
Revised 17 February 2011
Accepted 7 March 2011
Available online 11 March 2011

Keywords:
Metabolic syndrome
PPARα/γ dual agonist
Oxazole
Type 2 diabetes

ABSTRACT

In an effort to develop safe and efficacious compounds for the treatment of metabolic disorders, novel thiophene substituted oxazole containing α-alkoxy-phenylpropanoic acid derivatives are designed as highly potent PPARα/γ dual agonists. These compounds were found to be efficacious at picomolar concentrations. Lead compound **18d** has emerged as very potent PPARα/γ dual agonist demonstrating potent antidiabetic and lipid lowering activity at a very low dose and did not exhibit any significant signs of toxicity in rodents.

Last decade and a half had witnessed a rapid advancement in the biological roles of Peroxisome proliferator-activated receptors (PPARs) in metabolic syndrome, a cluster of disturbance of glucose & lipid metabolism and tremendous efforts towards the development of PPAR ligands for the treatment of this complex syndrome. Hyperglycemia, dyslipidemia and obesity are the major manifestations of metabolic syndrome and these abnormalities individually or in combination can lead to a high risk of developing type 2 diabetes and cardiovascular desease.[1]

Peroxisome proliferator-activated receptors (PPAR) are members of group of nuclear receptor super family and till date three subtypes (PPAR α, γ, and δ) are identified and cloned in several species including humans. The distinct tissue distribution and physiological roles of PPARs are well documented.[2] PPARα mainly controls the expression of genes involved in β-oxidation of fatty acids[3] and activation of PPARα with endogenous or synthetic ligands reduces triglycerides (TG) and elevates high density lipoprotein cholesterol (HDL-c) levels. Activation of PPARγ is known to improve insulin sensitivity and thereby control glucose homeostasis.[4] Two classes of compounds namely thiazolidinediones (popularly known as glitazones, e.g., Rosiglitazone and Pioglitazone) (Fig. 1) as antidiabetic agents[5] and fibrates as antihyperlipedimic agents[6] (Fig. 1) are currently marketed and are PPARγ and α agonists, respectively. However treatment with glitazones is associated with adverse effects such as weight gain and edema whereas fibrates are poor activators of PPARα and high dose is needed to be administered to exert therapeutic effect. As the metabolic syndrome is associated with defects in glucose as well as lipid metabolism, the concept of discovering dual agonists, which can activate both PPARα and PPARγ simultaneously has emerged as a fascinating target by a logical hypothesis that these dual agonists may not only control both glucose and lipid levels but also mitigate the weight gain induced by PPARγ activation based on the observation that fibrates in addition to their hypolipidemic effects, reduce body weight gain in rodents without affecting food intake.[7] Several PPARα/γ dual agonists, commonly termed as glitazars (Fig. 1) were developed by many pharmaceutical companies.

As reported by Agnes et al.[8] typical PPAR agonists have following skeleton (Fig. 2).

Oxazole group as lipophilic tail and α-alkoxy carboxylic acid as acidic pharmacophore are extensively studied during the development of PPAR agonists. Few PPARα/γ dual agonists containing oxazole group as lipophilic tail and non-α-alkoxy carboxylic acid group as acidic head have been advanced to clinical trials, for example, Imiglitazar **1**, muraglitazar **2**, Farglitazar **3** (Fig. 3) and several other compounds having oxazoles as cyclic tail are also reported to be potent dual agonists.[9] Further non oxazole α-Alkoxy carboxylic acid derivatives like Tesaglitazar (**4**) and Naveglitazar (**5**) (Fig. 3) have proven to be efficacious in animal models and in humans.[10]

☆ ZRC Communication # 315.

* Corresponding author. Tel.: +91 2717 665555; fax: +91 2717 250606.
E-mail address: preetiraval@zyduscadila.com (P. Raval).

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doi:10.1016/j.bmcl.2011.03.020

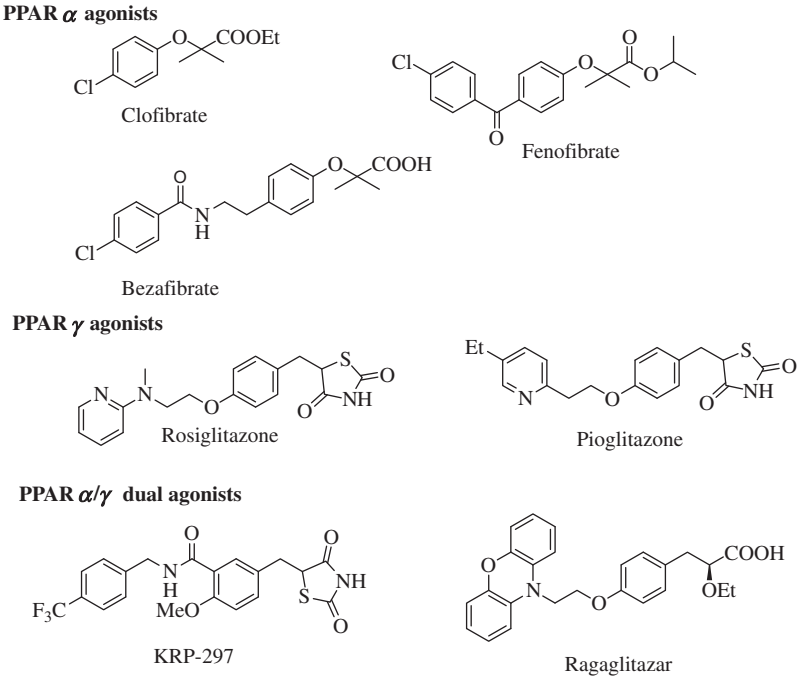


Figure 1. Structure of PPAR agonists.

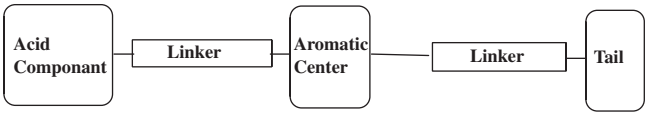


Figure 2. Common structural features of PPAR agonists.

In addition to this α-alkoxy arylpropanoic acids containing 2-phenyloxazole-4ylalkyl moiety are also reported to be potent dual agonists.[11] But none of the fore mentioned dual agonists has been marketed. The first dual agonist Farglitazar[12] which is a potent PPARγ agonist with a moderate PPARα activation was dropped in an advanced stage due to the emergence of edema. Two more dual agonists with substantial PPARα/γ activity Ragaglitazar[13] and Tesaglitazar[14] were also dropped from late clinical development due to carcinogenicity in rodent toxicity models and elevated serum creatinine & associated decrease in glomerular filtration rate, respectively. The only dual agonist that has been advanced to NDA filing, Muraglitazar[15] was also dropped very recently due to the higher incidence of edema, heart failure and cardiovascular deaths amongst the patients taking muraglitazar compared with those receiving placebo or treated with Pioglitazone.[16] These facts though appears to be discouraging to the scientists engaged in the development of PPAR agonists, the fact that the reasons for the failure of all these compounds are quite different from each other has left a ray of hope of developing new agents with modifications in these compounds in order to develop efficacious and relatively safer PPAR agonists as the medical need for metabolic disorders is largely remain unmet.

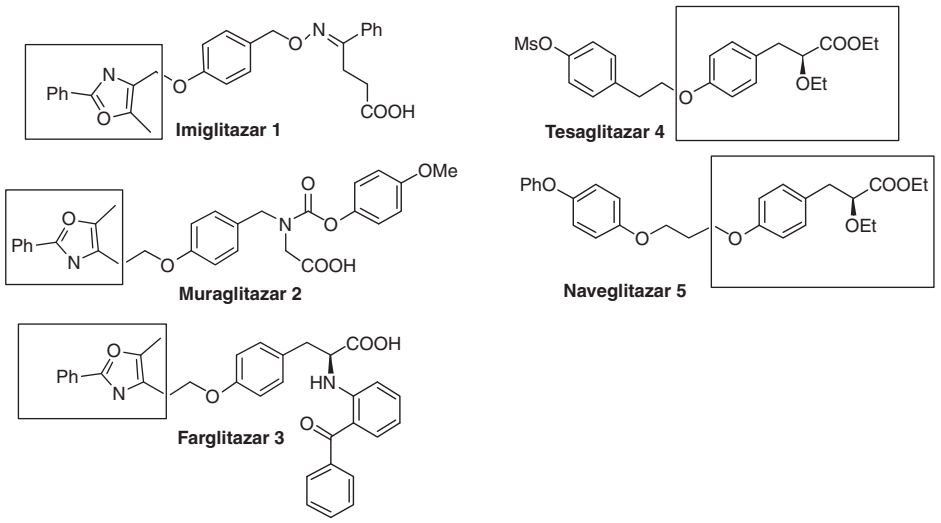


Figure 3. PPARα/γ dual agonists containing oxazole and α-alkoxy carboxylic acid groups.

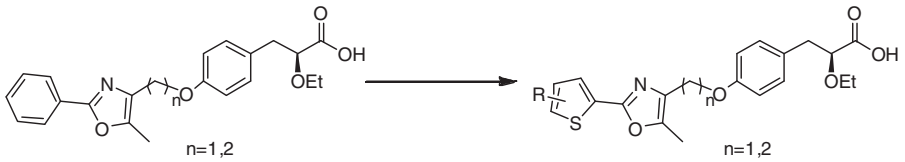


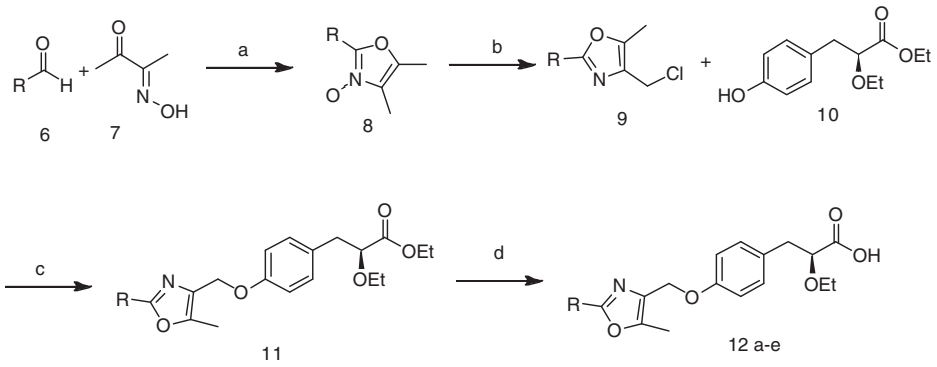
Figure 4. Designing PPARα/γ agonists containing thiophene substituted oxazole.

As a part of our research endeavor on PPARs[17] to develop efficacious and safe dual agonists, we hypothesized that administration of very low dose of potent compounds would probably a practical approach to minimise at least some of the adverse effects as these adverse effects exerted by this class of compounds are dose dependent. Our next goal obviously was to discover the compounds with very high invitro potency that translates to invivo efficacy. In order to achieve this 2-phenyloxazole containing α alkoxyphenylpropanoic acid derivative (Fig. 4) was chosen as chemical lead and we initially intended to study the effect of substitution on oxazole at 2-position and we eventually found by molecular modeling analysis (data not shown) that thiophene is the best fit. In the present Letter, we report few thiophene substituted oxazole containing α-alkoxyphenylpropanoic acid derivatives as potent PPARα/γ dual agonists and established our hypothesis of administering low dose of a potent dual agonist would minimize the adverse effects.

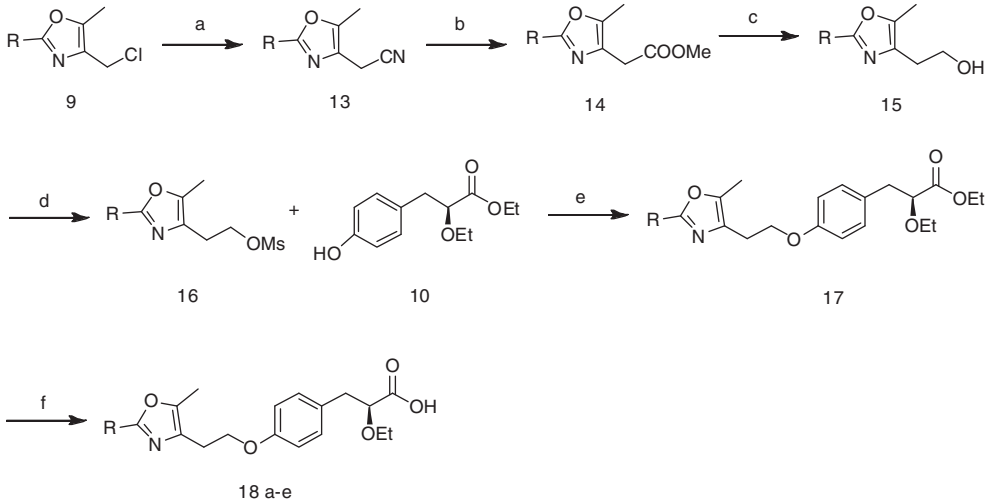
Two sets of thiophene substituted oxazole containing α-alkoxy acid derivatives**12a–e** and **18a–e** are reported as dual PPARα/γ agonists. Compounds **12a–e** contain methylene spacer between aromatic center and cyclic tail where as compounds **18a–e** represent corresponding analogues containing ethylene spacer (Fig. 4).

Synthetic route to compounds **12a–e** is outlined in Scheme 1. Synthesis of intermediate **9** was accomplished in two steps following the reported method.[18] Benzaldehydes **6** were reacted with diacetyl mono-oxime **7** in acetic acid in presence of dry HCl (gas) to afford N-Oxides **8**. Treatment of **8** with $POCl_3$ gave the corresponding chloromethyl oxazole **9**. Nucleophilic substitution of **9** with (*S*)-ethyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate **10**[19] using K_2CO_3 as base in DMF afforded precursor esters **11**. Hydrolysis of these ester compounds **11** under aqueous basic conditions yielded final acid derivatives **12a–e**.

The synthesis of compounds **18a–e** is outlined in Scheme 2. Intermediate mesylate derivatives **16** were prepared from their

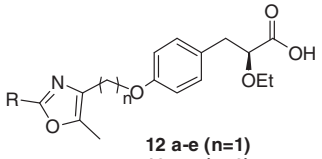


Scheme 1. Reagents and conditions: (a) AcOH/HCl gas, 0 °C, 1 h, 20–25%; (b) $POCl_3$, dichloroethane, reflux, 14 h, 50–70%; (c) K_2CO_3, DMF, 80–90 °C, 2 h, 40–50%; (d) NaOH/MeOH–H_2O, 20–25 °C, 16 h, 60–80%.

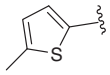
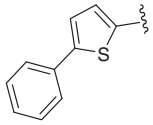
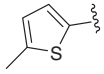
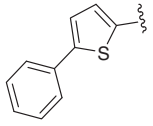


Scheme 2. Reagents and conditions: (a) NaCN, DMF, 25–30 °C, 4 h, 80–90%; (b) MeOH, H_2SO_4, catalytic H_2O, reflux, 16 h, 60–70%; (c) LAH, THF, 0–10 °C, 70–80%; (d) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 25 °C, 2 h, 85–90%; (e) K_2CO_3, DMF, 80–90 °C, 2 h, 40–50%; (f) NaOH/MeOH–H_2O, 20–25 °C, 16 h, 60–70%.

Table 1
In vitro hPPAR transactivation and TG lowering activity of compounds **12a–e and 18a–e**



12 a-e (n=1)
18 a-e (n=2)

Compd	R	hPPAR trans activation[a]		% Change TG[c]
		α EC_{50} (nM) (%max)[b]	γEC_{50} (nM) (%max)[b]	
12a		0.026 (134)	0.0015 (107)	−72
12b		3 (147)	2.7 (99)	−70
12c		0.00006 (106)	0.0003 (88)	−72
12d		0.00005 (151)	0.0002 (120)	−69
12e		20 (93)	3 (104)	−57
18a		0.1 (126)	0.05 (104)	−78
18b		1.9 (114)	0.6 (87)	−62
18c		0.00007 (96)	0.0001 (192)	−67
18d		0.00031 (116)	0.018 (165)	−88
18e		22	4.5	−62
WY-14643		4800 (100)	ND	ND
Rosiglitazone		ND	50 (100)	ND

[a] HepG2 cells transfected with pSG5 expression vector containing the cDNA of hPPARα or hPPARγ or hPPARδ and cotransfected with PPRE3-TK-luc. The Luciferase activity determined using commercial fire-fly luciferase assay and β-galactosidase activity determined in ELISA reader. None of the compound showed activation above basal level against PPARδ.

[b] Percent of maximal efficacy (%max) of all compounds compared to reference compounds (WY-14643 for α and Rosiglitazone for γ) normalized to 100%.

[c] The test compounds were administered orally at a dose of 10 mg/kg/day to male *swissalbino* mice (SAM) of 6–8 weeks of age for 6 days. Mean values ($n = 6$) are the % change in serum triglyceride (TG) concentration of the compound-treated mice versus vehicle controls. All values are the mean of $n = 6$. ND denotes not determined.

corresponding lower homologues **9** in four steps. Chloromethyl oxazoles **9** were converted to corresponding cyano derivatives **13** using NaCN in DMF at ambient temperature in good yields. Cyano derivatives **13** were refluxed in a mixture of methanol, sulfuric acid and water (catalytic amount) to yield corresponding esters **14** which were then reduced to alcohols **15** using $LiAlH_4$. Alcohols **15** were converted to corresponding mesylates **16**. Coupling of **16** with (*S*)-ethyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate as shown in Scheme 1 afforded ester compounds **17**. Aqueous basic hydrolysis of **17** gave the corresponding acids **18**. The structure of all the final compounds and intermediates are confirmed by their and spectral analysis and are found to be in conformity with the structures assigned.

All the compounds synthesized[20] were screened for human PPARα, PPARγ and PPARδ transactivation assay using hPPAR receptor transfected HEPG2 cells as per the procedure described in our earlier publication.[21] WY14643, Rosiglitazone and GW501516 were used as control for PPARα, γ and δ, respectively. In vitro transactivation activities and triglyceride (TG) lowering potential of compounds **12** and **18** are presented in Table 1. In general in vitro potency of all the test compounds are in the range of low nM to pM and subtype selectivity ranges between 1- and 15-folds. The initial compound **12a** possessing unsubstituted thiophene linked through 2nd position to oxazole showed 26 and 1.5 pM potency towards PPAR α and γ, respectively, whereas its higher homologue **18a** is found detrimental in terms of in vitro potency as compared to **12a**. Both the compounds demonstrated significant TG lowering effect. When the linkage of thiophene was changed to 3rd position, resulting compounds **12b** and **18b** showed relatively poor in vitro potency but still exhibited comparable TG reduction

Table 2
In vivo glucose lowering effect of **12d** and **18d** in db/db mice[a]

Compd	Dose (mg/kg/day)	% change in glucose[a]
12d	3	−67
18d	3	−72
Tesaglitazar	3	−55

[a] Male db/db mice of 6–8 weeks old were dosed with test compounds daily for 6 days and Plasma glucose, triglycerides were measured. Values reported are % change of compound-treated mice versus vehicle controls.

to their 2nd position analogues **12a** and **18a**. These results indicate that linkage of thiophene through its 2nd position is favorable over 3rd position. Then we intended to substitute 3rd & 5th position of thiophene and synthesized compounds **12c–e** and **18c–e**. Compound **12c** bearing methyl group at 3rd position of thiophene showed remarkable increase in potency (0.06 pM for α and 0.3 pM for γ) and also reduced TG by 72%. When the methyl group was introduced at 5th position of thiophene, the resulting compound **12d** demonstrated similar in vitro potency as well as TG lowering effect. When chain length of the spacer of **12c** was increased to ethylene group the resulting compound **18c** showed similar profile as exhibited by **12c**. But compound **18d** which is higher homologue of **12d** though showed marginally inferior PPAR potency as compared to **12d**, demonstrated 88% of TG reduction and emerged as a lead compound in the series. To know the effect of bulkier substituent, we have introduced phenyl group at 5th position of thiophene and synthesized compounds **12e** and **18e**. Both the compounds are found detrimental in terms of in vitro potency with respect to other compounds of the series. Based on in vitro activity and TG lowering results, compound **18d** and its methylene analogue **12d** were selected for further in vivo evaluation.

Compounds **12d** and **18d** were subjected for glucose lowering effect in db/db mice and the results are summarized in Table 2. Compounds **12d** and **18d** produced excellent glucose reduction of 67% and 72%, respectively, when dosed orally at 3 mg/kg/day dose. Finally **18d** is selected as the lead compound of the series and its pharmacokinetic parameters were determined (Table 3) where this compound exhibited excellent profile with a C_{max} of 91.7 μg/mL and 455.8 h μg/mL of AUC. This compound exhibited extended $T_{1/2}$ of 7.4 h.

Subsequently **18d** was then evaluated for its dose dependent hypolipidemic and anti-hyperglycemic activity in *swissalbino* mice (SAM) and db/db mice and the data is presented in Table 4. In SAM model **18d** reduced TG by 41.5% at a dose of 0.003 mg/kg and the

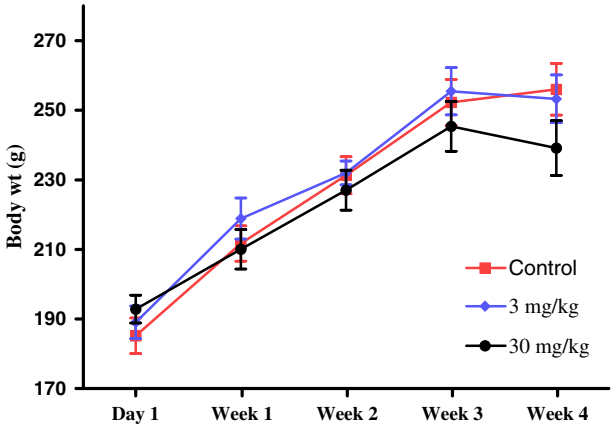


Figure 5. Body weight values of male *Wistar* rats treated with **18d** for 28 days.

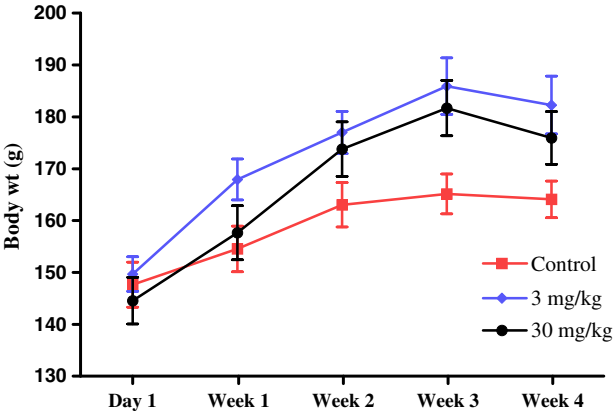


Figure 6. Body weight values of female *Wistar* rats treated with **18d** for 28 days.

ED_{50} was found to be 0.01 mg/kg. In db/db mice the ED_{50} values for the reduction of PG and TG were 0.1657 and 0.0188 mg/kg, respectively.

Having achieved the primary goal of identifying potent and efficacious PPARα/γ dual agonist, our next end point of this endeavor is to study the toxicity profile of the lead compound **18d**. Oral acute toxicity of this molecule was studied in male and female *wistar* rats at 3, 30 mg/kg for 28 days. 15x and 150x doses were se-

Table 3
Mean pharmacokinetic parameters[a] of **18d** in fasted male *Wistar* rat

Compd	Route	Dose (mg/kg)	T_{max} (h)	C_{max} (μg/mL)	$T_{1/2}$ (h)	AUC(0–α) (h μg/mL)
18d	Oral	30	0.667	91.7	7.4	455.8

[a] Values indicate mean ± SD for $n = 3$.

Table 4
Dose dependent effect of **18d** on TG and PG in SAM and db/db mice

Dose (mg/kg)	SAM		db/db			
	% change in TG	ED_{50} (mg/kg)	% change in PG	ED_{50} (mg/kg)	% change in TG	ED_{50}
0.003	−41.5	0.01	−47.1	0.1657	−7.2	0.0188
0.01	−61.9		−52.7		−6.6	
0.03	−65.6		−52.1		−25.9	
0.1	−71.8		−51.7		−49.4	
0.3	−80.8		−58.2		−51.8	
1	−82.0		−59.7		−64.2	
3	−83.1		−62.2		−55.1	

Table 5
Relative organ weights[a] of *wistar* rats administered orally with **18d** for 28 days

Dose (mg/kg)	Heart	Liver	Kidney	Spleen	Adrenal	Brain	Testes	Epididymine	Thymus	% change in body wt.
Males										
Control	0.383 ± 0.012	3.257 ± 0.069	0.745 ± 0.012	0.215 ± 0.007	0.018 ± 0.001	0.658 ± 0.015	1.075 ± 0.106	0.391 ± 0.017	0.081 ± 0.013	38.25
3	0.412 ± 0.006	7.505 ± 0.151	0.807 ± 0.007	0.223 ± 0.004	0.015 ± 0.001	0.720 ± 0.024	1.152 ± 0.033	0.360 ± 0.018	0.089 ± 0.013	33.99
30	0.479 ± 0.007	8.099 ± 0.124	0.955 ± 0.024	0.252 ± 0.005	0.018 ± 0.001	0.757 ± 0.021	1.356 ± 0.043	0.432 ± 0.016	0.075 ± 0.008	24.01
Females							*Ovary*	*Uterus*		
Control	0.403 ± 0.010	3.091 ± 0.087	0.733 ± 0.007	0.237 ± 0.012	0.028 ± 0.001	0.970 ± 0.023	0.039 ± 0.005	0.233 ± 0.041	0.094 ± 0.01	11.13
3	0.460 ± 0.010	6.221 ± 0.165	0.804 ± 0.024	0.257 ± 0.024	0.020 ± 0.001	0.947 ± 0.034	0.020 ± 0.002	0.176 ± 0.011	0.101 ± 0.013	21.77
30	0.501 ± 0.009	7.075 ± 0.314	0.915 ± 0.037	0.260 ± 0.011	0.022 ± 0.001	0.939 ± 0.050	0.024 ± 0.002	0.189 ± 0.029	0.066 ± 0.005	21.71

[a] Presented as organ-to-body weight percent ratio.

Table 6
Biochemical parameters of *wistar* rats administered orally with **18d** for 28 days

Dose (mg/kg)	HGB (g/dl)	Glu (mg/dl)	CREA (mg/dl)	ALP (U/L)	SGOT (U/L)	SGPT (U/L)	ALB (g.dl)	Urea (mg/dl)
Males								
Control	13.66 ± 0.23	70 ± 3.49	0.47 ± 0.03	243.88 ± 20.34	135.14 ± 6.89	34.24 ± 2.13	3.66 ± 0.10	30.52 ± 0.79
3	12.20 ± 0.18	75.74 ± 2.65	0.36 ± 0.04	470.50 ± 23.93	193.51 ± 9.76	28.54 ± 0.89	3.91 ± 0.15	31.24 ± 1.19
30	12.46 ± 0.21	83.28 ± 2.90	0.37 ± 0.02	679.13 ± 59.03	245.24 ± 26.13	33.03 ± 3.19	4.12 ± 0.10	34.58 ± 1.14
Females								
Control	11.90 ± 0.19	69.94 ± 2.30	0.42 ± 0.04	172.38 ± 7.18	155.70 ± 6.56	30.44 ± 1.59	3.92 ± 0.18	33.05 ± 2.02
3	11.84 ± 0.18	91.88 ± 5.71	0.36 ± .03	248.13 ± 18.00	157.09 ± 10.32	22.46 ± 0.77	4.03 ± 0.10	29.19 ± 1.48
30	11.83 ± 0.19	91.79 ± 9.14	0.41 ± 0.03	248.38 ± 32.75	224 ± 41.94	35.21 ± 4.41	4.12 ± 0.12	37.39 ± 7.93

lected based on the ED_{50} (considering as ~0.2 mg) values in SAM and db/db mice. There were no significant treatment related clinical manifestations noted in any of the treated group animals and there was no treatment related mortality occurred. Food consumption was comparable to that of control groups throughout the study period in both the treated groups of both male and female animals. Animals were sacrificed on day 29 and data analysis of blood biochemical parameters, organ weight ratios and histopathological findings.

Body weights were recorded weekly and the data is presented in Figure 5 (male) and Figure 6 (female). No increase in body weight was observed due to compound treatment in male animals while in female animals an increase in body weight was observed till week 3 and thereafter marginal decrease was observed by the end of the treatment. These results clearly indicate that **18d** does not cause significant weight gain, the main side effect of PPAR class of compounds even at a dose of 15x and 150x of ED_{50} values. Analysis of organ to body weight ratios (Table 5) did not show evidence of toxicity attributed to compound treatment at least at 3 mg/kg dose, which is 15x of ED_{50}, except the liver weights. The results clearly indicate the hepatomegaly (liver enlargement) in both male and female animals treated with **18d** at 3 and 30 mg/kg. However it is well established by now that this phenomenon is specific to rodents and the literature precedence clearly established that such an effect does not occur in non-rodents.[22] There was marginal increase (7%) in heart weight at 3 mg dose and significant increase (25%) at 30 mg dose which is 150 times of ED_{50} was observed, Similarly no significant alterations were observed in biochemical parameters (Table 6) except the increase in liver enzymes (ALP, SGOT, SGPT) which are in correlation with rodent specific hepatomegaly. No significant changes were observed in hemoglobin, albumin urea and creatinine at 3 mg/kg while at 30 mg/kg dose an increase in urea levels was observed. More interestingly a marginal decrease in creatinine was observed at both the doses in male and female animals, while elevation of creatinine is common side effect of PPAR agonists. These results clearly indicate that treatment with **18d** in rodents did not exert any significant side effects even at 150 times higher dose than ED_{50} value. The evaluation of the toxicity of this molecule in non-rodent species will be carried out and the results will be published subsequently.

In summary we have designed a series of highly potent and efficacious PPARα/γ dual agonists and the lead candidate **18d** showed excellent anti-hyperglycemic, hypolipidemic effects than Rosiglitazone and Tesaglitazar. Further evaluation of the lead compound for its toxicity profile in rodents was encouraging the further development of this compound for the treatment of metabolic syndrome.

Acknowledgments

Authors are thankful to Pankaj Makadia for his help in preparing the manuscript, management of the Zydus Group for encouragement and the analytical department for support.

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20. Spectroscopic data of compounds **12a–e** and **18a–e**: **12a**: (*S*)-2-ethoxy-3-(4-((5-methyl-2-(thiophen-2-yl)oxazol-4-yl)methoxy)phenyl)propanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, J = 7.0 Hz, 3H), 2.40 (s, 3H), 2.91–2.98 (m, 2H), 3.35–3.49 (m, 1H), 3.54–3.64 (m, 1H), 4.03 (m, 1H), 4.95 (s, 2H), 6.93 (d, J = 8.5 Hz, 2H), 7.01 (t, J = 3.7 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 4.9 Hz, 1H), 7.65 (d, J = 3.4 Hz, 1H); ESI-MS: 387; **12b**: (*S*)-2-ethoxy-3-(4-((5-methyl-2-(thiophen-3-yl)oxazol-4-yl)methoxy)phenyl)propanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, J = 7.0 Hz, 3H), 2.4 (s, 3H), 2.90–2.97 (dd, J = 7.6 Hz, 1H), 3.03–3.09 (dd, J = 4.7 Hz, 1H), 3.39–3.44 (m, 1H), 3.57–3.62 (m, 1H), 4.01–4.05 (m, 1H), 4.94 (s, 2H), 6.93 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 7.35–7.38 (m, 1H), 7.59–7.61 (m, 1H), 7.91–7.92 (m, 1H); ESI-MS: 387; **12c**: (*S*)-2-ethoxy-3-(4-((5-methyl-2-(3-methylthiophen-2-yl)oxazol-4-yl)methoxy)phenyl) propanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, J = 7.0 Hz, 3H), 2.4 (s, 3H), 2.57 (s, 3H), 2.90–2.98 (m, 1H), 3.05–3.10 (m, 1H), 3.41–3.46 (m, 1H), 3.58–3.61 (m, 1H), 4.02–4.13 (m, 1H), 4.95 (s, 2H), 6.9 (d, J = 5.0 Hz, 1H), 6.94 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 4.9 Hz, 1H); ESI-MS: 401; **12d**: (*S*)-2-ethoxy-3-(4-((5-methyl-2-(5-methylthiophen-2-yl)oxazol-4-yl)methoxy)phenyl) propanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, J = 7.0 Hz, 3H), 2.38 (s, 3H), 2.51 (s, 3H), 2.90–2.97 (m, 1H), 3.03–3.09 (m, 1H), 3.38–3.43 (m, 1H), 3.57–3.62 (m, 1H), 4.00–4.04 (m, 1H), 4.92 (s, 2H), 6.73–6.75 (m, 1H), 6.92 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 3.6 Hz, 1H); ESI-MS: 401; **12e**: (*S*)-2-ethoxy-3-(4-((5-methyl-2-(5-phenylthiophen-2-yl) oxazol-4-yl)methoxy)phenyl) propanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, J = 7.0 Hz, 3H), 2.41 (s, 3H), 2.96 (d, J = 6.7 Hz, 2H), 3.32–3.63 (m, 2H), 3.97 (t, J = 6.7 Hz, 1H), 4.95 (s, 2H), 6.92 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H), 7.26–7.43 (m, 4H), 7.58 (d, J = 3.9 Hz, 1H), 7.63 (d, J = 7.14 Hz, 2H); ESI-MS: 463; **18a**: (*S*)-2-ethoxy-3-(4-(2-(5-methyl-2-(thiophen-2-yl)oxazol-4-yl)ethoxy)phenyl)propanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, J = 7.0 Hz, 3H), 2.35 (s, 3H), 2.92–2.97 (m, 1H), 2.95 (t, J = 6.6 Hz, 2H), 3.04–3.09 (m, 1H), 3.41–3.47 (m, 1H), 3.55–3.60 (m, 1H), 4.01–4.05 (m, 1H), 4.18 (t, J = 6.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 7.06–7.09 (m, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.37 (dd, J = 4.2 Hz, 1H), 7.48 (m, 1H); ESI-MS: 401; **18b** : (*S*)-2-ethoxy-3-(4-(2-(5-methyl-2-(thiophen-3-yl)oxazol-4-yl)ethoxy) phenyl)propanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, J = 7.0 Hz, 3H), 2.34 (s, 3H), 2.89–3.08 (m, 4H), 3.40–3.45 (m, 1H), 3.55–3.60 (m, 1H), 4.0–4.04 (m, 1H), 4.19 (t, J = 6.66 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 5.01 Hz, 1H), 7.14 (d, J = 8. 5 Hz, 2H), 7.23 (d, J = 5.0 Hz, 1H), 7.86 (d, J = 2.58 Hz, 1H); ESI-MS: 401; **18c**; (*S*)-2-ethoxy-3-(4-(2-(5-methyl-2-(3-methylthiophen-2-yl)oxazol-4-yl)ethoxy) phenyl) propanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, J = 7.0 Hz, 3H), 2.34 (s, 3H), 2.55 (s, 3H), 2.89–3.08 (m, 4H), 3.40–3.49 (m, 1H), 3.55–3.60 (m, 1H), 4.0–4.04 (m, 1H), 4.19 (t, J = 6.7 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 5.01 Hz, 1H), 7.14 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 5.01 Hz, 1H); ESI-MS: 415; **18d**: (*S*)-2-ethoxy-3-(4-(2-(5-methyl-2-(5-methyl thiophen -2-yl)oxazol-4-yl)ethoxy) phenyl) propanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, J = 7.0 Hz, 3H), 2.32 (s, 3H), 2.50 (s, 3H), 2.89–2.96 (m, 4H), 3.40–3.43 (m, 1H), 3.56–3.59 (m, 1H), 3.99–4.03 (m, 1H), 4.16 (t, J = 6.6 Hz, 2H), 6.72 (d, J = 3.54 Hz, 1H), 6.81 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8. 5 Hz, 2H), 7.39 (d, J = 3.6 Hz, 1H); ESI-MS: 415; **18e**: (*S*)-2-ethoxy-3-(4-(2-(5-methyl-2-(5-pheny lthiophen-2-yl)oxazol-4-yl)ethoxy) phenyl) propanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, J = 6.4 Hz, 3H), 2.89 (s, 3H), 2.93–3.05 (m, 4H), 3.41–3.58 (m, 2H), 4.01–4.05 (m, 1H), 4.20 (t, J = 6.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 7.26–7.42 (m, 4H), 7.54 (d, J = 3.9 Hz, 1H), 7.62 (d, J = 7.3 Hz, 2H); ESI-MS : 477.
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