PUBLICATIONS

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1. **Novel Oxazole containing phenylpropane derivatives as Peroxisome Proliferator Activated Receptor agonists with hypolipidemic activity.** *Pharmazie 63: 2008, 497–502.* Harikishore Pingali, Saurin Raval, ***Preeti Raval***, Pankaj Makadia, Pandurang Zaware, Asish Goel, Dinesh Suthar, Mukul Jain and Pankaj Patel.

2. **Revisiting glitazars : Thiophene substituted oxazole containing α-ethoxy phenyl propanoic acid derivatives as highly potent PPARα/γ dual agonists devoid of adverse effects in rodents.** *Bioorganic & Medicinal Chemistry Letters 21, 2011, 3103–3109.* ***Preeti Raval,*** Mukul Jain, Amitgiri Goswami, Sujay Basu, Archana Gite, Atul Godha, Harikishore Pingali, Saurin Raval, Suresh Giri, Dinesh Suthar, Maanan Shah, Pankaj Patel.

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Novel oxazole containing phenylpropane derivatives as peroxisome proliferator activated receptor agonists with hypolipidemic activity

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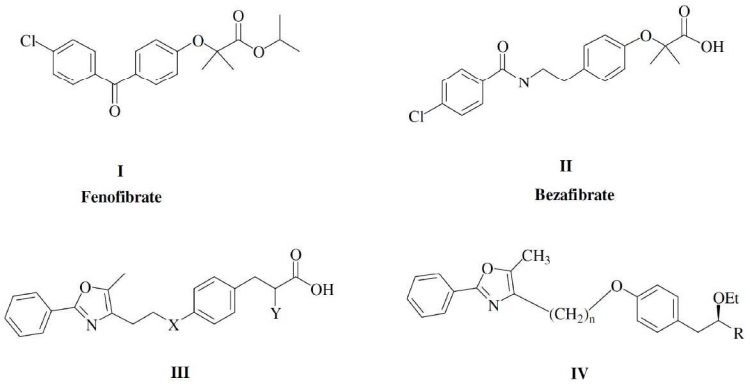
α-Alkoxy arylpropanoic acids containing 2-phenyloxazole-4yl-alkyl moiety are found to be potent hypolipidemic agents. These compounds were potent activators of the peroxisome proliferator activated receptor γ (PPARγ), with moderate PPARα activity and known to cause adverse effects such as weight gain and edema, which are essentially attributed to PPARγ activation. Although extensive work has been done on the phenylpropanoic acid class of compounds, other phenyl propane derivatives such as alcohols, amines, ethers etc. have not received much attention. In order to develop predominant PPARα agonists as hypolipidemic agents with minor chemical modifications on compound **III,** we have synthesised few (2S)-ethoxyphenylpropane derivatives containing a 2-phenyl-5-methyloxazole-4ylalkoxy moiety of the general formula **IV** and evaluated by PPARα and γ transactivation assay in conjugation with *in vivo* studies in male Swiss albino mice model. Compounds **3c** and **3d** showed the desired predominant PPARα activity and excellent tryiglyceride reduction *in vivo* and were selected as lead compounds for further development as hypolipidemic agents.

1. Introduction

Increasing evidence suggests that lipid accumulation in non adipose tissue, such as pancreatic islet cells and skeletal muscle is related to the development of type 2 diabetes in obese individuals (Kelly and Goodpaster 2001). High LDL-cholesterol, elevated levels of triglycerides (TG) and low HDL-cholesterol were identified as factors contributing to coronary artery disease. The presently available therapy for the above indications includes the use of statins which are effective in lowering LDL-cholesterol and increasing HDL-cholesterol and also found to be safe (La Rosa et al. 1999). However these drugs are not effective in lowering triglycerides. The scope of improving the potency of these drugs may be limited in view of recent reports of undesirable side effects of some super statins (Evans and Rees 2002). Fibrate compounds such as feno

Scheme 1

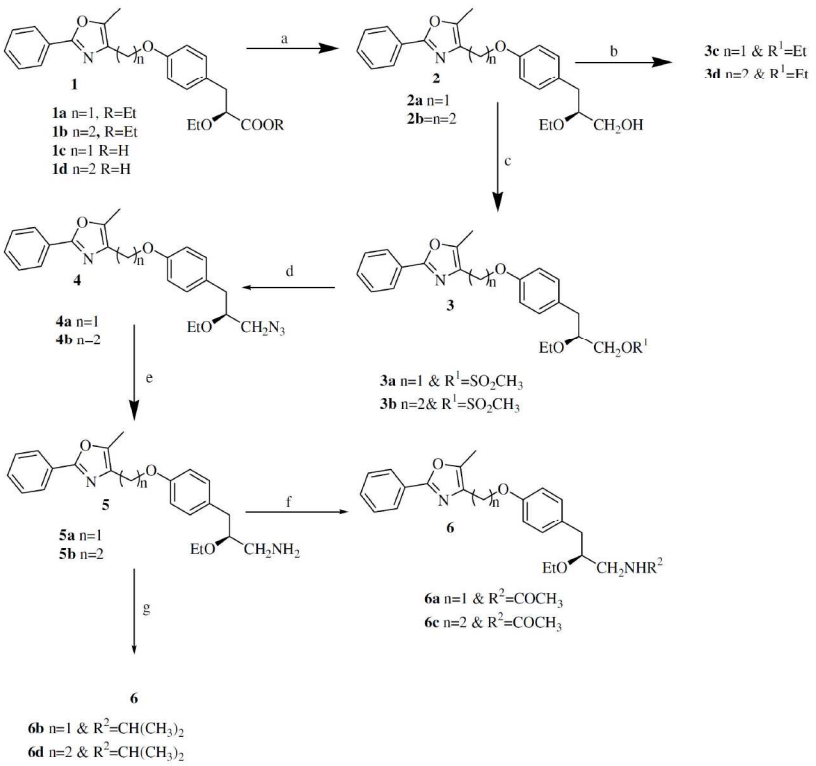


fibrate **I** and bezafibrate **II** used to treat hyperlipidemea are effective in reducing triglycerides, increasing HDL-cholesterol and lowering LDL-cholesterol are of poor efficacy and need high doses to show significant efficay (Stalcs et al. 1998). A combination of statins and fibratcs is found to show adverse effects (Evans and Rees 2002). These findings led to the discovery of several compounds in search for potent hypolipidemic agents such as α-alkoxy arylpropanoic acids containing 2-phenyloxazole-4yl-alkyl moiety as in compound **III** (Hulin et al. 1996) (e.g. **1c** and **1d**) and few other series of compounds containing 2S-ethoxyphenyl propanoic acid derivatives (Buckle et al. 1996; Cronet et al. 2001; Lohray et al. 2001; Sauerberg et al. 2002), which display potent hypolipidemic activity. These compounds were potent activators of the peroxisome proliferator activated receptor γ (PPARγ) with moderate PPARα activity and are known to cause adverse effects such as weight gain and edema. which are essentially attributed to PPARγ activation. Although extensive work has been done on the phenylpropanoic acid class of compounds, other phenyl propane derivatives such as alcohols, amines, ethers etc. have not received much attention except few compounds containing a phenylpropanol group which were reported as hypolipidemic and anti diabetic compounds (Fagerhag et al. 2001). In continuation of our anti-diabetic and hypolipidemic research (Lohray et al. 1999; Reddy et al. 1998; Tudor et al. 2007) and to develop predominant PPARα agonists as hypolipidemic agents by the chemical modifications on compound **III,** we have synthesised few (2S)-ethoxyphenylpropane derivatives containing a 2-phenyl-5-methyloxazole-4ylalkoxy moiety of general formula **IV** and evaluated by PPARα and γ transactivation assay in conjugation with *in vivo* studies in male *Swiss albino* mice model.

2. Investigations and results

Compounds **1**–**6** were synthesized as dipicted in the Scheme. Ethyl-(2S)-ethoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl) alkoxy]-phenyl}-propanoates **1a**–**b** were synthesized by reacting 5-methyl-2-phenyl-oxazol-4ylalkyl methane sulfonate (Goto et al. 1971) with ethyl-(2S)-ethoxy-3-(4-hydroxy-phenyl)-propanoate (Andersson and Lindstedt 1999) in the presence of potassium carbonate in dry DMF. These esters were hydrolysed under aqueous basic conditions to yield the carboxylic acids **1c** and **1d**. These esters **1a** and **1b** were treated with lithium aluminum hydride in dry THF to yield corresponding alcohols **2a** and **2b** which were converted to their corresponding ethylethers **3c** and **3d** and methanesulfonyl derivatives **3a** and **3b** by reacting with ethyl iodide in the presence of sodium hydride in DMF and with triethyl amine and methane sulfonyl chloride in dichloromethane respectively. The azide derivatives **4a** and **4b** obtained from **3a** and **3b**

Scheme 2



Reagents and condotions: (a) $LiAlH_4$, dry THF, 0–20 °C, 4 h; (b) NaH, EtI, DMF, 27–28 °C, 4 h; (c) Et_3N, CH_3SO_2Cl, $CH_2CH_2Cl_2$, 10 °C, 2 h; (d) NaN_3, DMF, 100 °C, 6 h; (e) Ph_3P, THF, 27–28 °C, 10 h, H_2O, 10 h; (f) Et_3N, CH_3COCl, CH_2Cl_2, 27–28 °C, 3 h; (g) NaH, $ICH(CH_3)_2$, DMF, 272–8 °C, 8 h

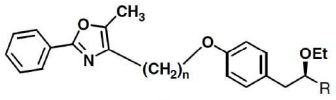
respectively by treating them with sodium azide in DMF at 100 °C were reduced to amines **5a** and **5b** by the treatment with triphenyl phosphine in THF followed by aqueous hydrolysis. Acetylation of amines **5a** and **5b** with aceticanhydride gave the respective amides **6a** and **6c** whereas the treatment of **5a** and **5b** with isopropyliodide gave the compounds **6b** and **6d** respectively.

3. Discussion

The newly synthesized compounds were screened for activity at human PPARα and γ subtypes by using an established cell-based transactivation assay. Rosiglitazone (which showed 6.2 fold activity at 0.2 μM concentration) and fenofibrate (which showed 4.4 fold activity at 10 μM concentration) were used as the reference standards for PPARγ and PPARα respectively in our studies. The moderate hypertriglyceridimic Swiss albino mice model was used for the assessment of plasma triglyceride (TG) lowering activity. Compounds **1**–**6** were evaluated for *in vitro* PPAR transactivation potential and subsequently administered orally to male *Swiss albino* mice at a dose of 3 mg/kg/day for six days and the reduction in plasma triglycerides (TG) was measured at the end. The results were summarized in the Table. The carboxylic acid derivatives **1c** and **1d** showed PPARα and γ activity and were twofold more potent towards γ than α and showed excellent TG reduction (78% and 74% respectively). The hydroxy derivative **2a** and its homologue **2b** showed equipotent induction (5.6 and 5.0 respectively) in the PPARγ transactivation assay, whereas they were found inactive towards PPARα and exhibited 71% and 57% TG reduction respectively. When the hydroxy group in compounds **2a** and **2b** were sulfonylated with the bulky methane sulfonyl group the resulting respective compounds **3a** and **3b** lost both *in vitro* and *in vivo* activities. Interestingly the conversion of hydroxy compound **2a** and **2b** to their respective ethyl ether derivatives **3c** and **3d** made them potent PPARα compounds with poor PPARγ activity. Both these compounds were found twofold more potent towards PPARα than γ and both compounds showed excellent triglyceride lowering (78% and 71% respectively) activity comparable to the lead compounds **1c** and **1d**. The azides **4a** and **4b** were found PPARγ selective compounds with moderate reduction in TG. The amines **5a** and **5b** found moderate and equipotent towards PPARα and γ with 61% and 54% TG reduction respectively. The amides **6a** and **6c** and the isopropyl amines **6b** and **6d** were found inactive towards PPARα and exhibited only PPARγ activity of the similar order. But surprisingly **6a** showed only 27% reduction in TG whereas its homologue **6c** reduced TG to an extent of 60%. The isopropyl amines **6b** and **6d** exhibited moderate reduction in TG. The standard fenofibrate showed 28% TG reduction at 30 mg/kg/day whereas bezafibrate showed 40% TG reduction at a dose of 300 mg/kg/day when administered for 6 days in male swiss albino mice. Rsosiglitazone did not show any significant TG reduction in this model.

These results showed that derivatives of (2S)-ethoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-alkoxy]-phenyl}-propionic acid such as alcohols, ethers, amines, azides, amides etc were useful to modulate the activity towards PPARα and γ subtype and were found to be excellent hypolipidemic agents, which lowered plasma triglycerides to a very significant extent. A most interesting finding is that hydroxy compounds (**2a** and **2b**) were found active towards PPARγ with no activity towards PPARα, whereas the ethyl ether derivatives **3c** and **3d** were twofold as po-

Table: PPAR Transactivation and plasma triglyceride lowering activity of compounds 1–6



(I)

Compd.	n	R	PPAR Transactivation[a]		*In vivo* efficacy
			α (10 μM)	γ (0.2 μM)	% Reduction in TG[b]
2a	1	CH_2OH	IA	5.6	71
3a	1	$CH_2OSO_2CH_3$	IA	1.8	24
3c	1	CH_2OEt	5.6	2.8	78
4a	1	CH_2N_3	1.9	6.2	51
5a	1	CH_2NH_2	3.8	3.1	61
6a	1	$CH_2NHCOCH_3$	IA	4.2	27
6b	1	$CH_2NHCH(CH_3)_2$	IA	3.5	44
2b	2	CH_2OH	IA	5.0	57
3b	2	$CH_2OSO_2CH_3$	IA	1.0	10
3d	2	CH_2OEt	5.5	2.7	71
4b	2	CH_2N_3	1.5	6.0	67
5b	2	CH_2NH_2	2.1	3.8	54
6c	2	$CH_2NHCOCH_3$	IA	4.8	60
6d	2	$CH_2NHCH(CH_3)_2$	IA	3.9	24
1c	1	COOH	4.8	11.0	78
1d	2	COOH	5.2	10.6	74
Rosiglitazone			IA	6.2	IA
Fenofibrate			4.4	IA	28
Bezafibrate (300 mg/kg/day)					40

a Activities are presented by fold induction of PPAR α and γ activation. IA indicates inactive.
b Values (mean ± SE) are the % reduction in plasma triglyceride (TG) concentration of the drug-treated mice relative to vehicle controls. All values are the mean of n = 6. IA indicates inactive.

tent towards PPARα than γ. On contrary to these results the parent acids (**1c** and **1d**) had twofold activity potent towards γ than α. These results clearly demonstrate that minor chemical modifications in the functional region of the compounds lead to significant changes in the *in vitro* activity even though they exhibit a similar *in vivo* profile. Compounds **3c** and **3d** which showed the desired predominant PPARα activity were selected as initial lead compounds for further development as hypolipidemic agents.

4. Experimental

4.1. In vitro PPAR transactivation assay

4.1.1. Cell culture

HepG2 cells (ATCC, USA) were maintained in growth medium composed of minimal essential medium (MEM, Sigma) supplemented with 10% fetal bovine serum (FBS, Hyclone), 1 × MEM non-essential amino acid (Sigma) and 1 mM sodium pyruvate and 1% penicillin and streptomycin (Sigma).

4.1.2. Transient transfection

HepG2 cells were seeded in 24 well plates at a density of 400000 cells/well in 1 mL of medium per well. Cells were transfected using the transfection reagent Superfect (Qiagen). Cells were transfected with 0.08 μg of the pSG5 expression vector containing the cDNA of PPARα or 0.08 μg of the pSG5 expression vector containing the cDNA of PPARγ was cotransfected with PPRE3-TK-luc. Cells were incubated at 37 °C, 5% CO_2 for 3 h after which 1.0 mL of the medium containing the respective ligands to the respective wells were added. The cells were then incubated at 37 °C, 5% CO_2 for 20–22 h. After the incubation period, cells were first washed with PBS, lysed and the supernatant was collected. Supernatant was then assayed for luciferase and β-galactosidase activity. The luciferase activity was determined using a commercial fire-fly luciferase assay according to the suppliers's instructions [Promega] in white 96-well plate [Nunc]. β-Galactosidase activity was determined in an ELISA reader at 415 nm.

4.2. In vivo screenig

An inbred colony of *Swiss albino* mice (SAM) of 20–30 g body weight with serum triglyceride levels in the range of 80–120 mg/dl have been used for screening the compounds. The study protocol was approved by the institutional animal ethics committee. The test compounds were administered orally at a dose of 3 mg/kg/day (fenofibrate at 30 mg/kg/day) to male *Swiss albino* mice for 6 days. The blood samples were collected in fed state one hour after drug administration on the 6th day of treatment and triglyceride levels were measured. Reduction of serum triglycerides was calculated according to the formula,

$$\% \text{ Reduction} = 1\text{-}\{(TT/OT)/(TC/OC)\}\ TT \times 100$$

where,
TT = serum TG level on test day of treated group, OT = serum TG level on day 0 of treatment of treated group, TC = serum TG level on test day of control group, OC = serum TG level on day 0 of treatment of control group.

4.3. Synthesis

Reagents and solvents were obtained from commercial suppliers and used without further purification. Flash chromatography was performed using commercial silica gel (230–400 mesh). Melting points were determined on a capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT IR 8300 spectrophotometer (V_{max} in cm^{-1}, using KBr pellets or Nujol). The ^{1}H NMR spectra were recorded on a Brucker Avanc-300 spectrometer (300 MHz). The chemical shifts (δ) are reported in parts per million (ppm) relative to TMS, either in $CDCl_3$ or DMSO-d_6 solution. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), bs (broad singlet), and m (multiplet). Mass spectra (ESI-MS) were obtained on Shimadzu LCMS 2010-A spectrometer. HPLC analysis were carried out at λ_{max} 220 nm using column ODS C-18, 150 nm × 4.6 nm × 4 μ on AGILENT 1100 series.

4.3.1. Ethyl (2S)-ethoxy-3-[4-[5-methyl-2-phenyl-oxazol-4-yl-methoxy]-phenyl]-propanoate (**1a**)

To a solution of ethyl (2S)-ethoxy-3-(4-hydroxy-phenyl)-propanoate (1.15 g, 4.83 mmol) and 4-chloromethyl-5-methyl-2-phenyl-oxazole (1.0 g, 4.83 mmol) in dry DMF (10 mL), K_2CO_3 (1.33 g, 9.66 mmol) was added and the reaction mixture was stirred at 60–70 °C for 20 h. The reaction mixture was poured into ice cold water (20 mL) and extracted with ethylacetate (3 × 20 mL). The organic layer was washed with water and brine, dried over sodium sulfate and evaporated *in vacuo*. The crude product was purified by flash column chromatography using 8% ethyl acetate in hexane as eluent to give 1.79 g of title compound **1a** as thick liquid; yield: 91%, purity: 98% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1 (3 H, t, J = 7.1 Hz), 1.2 (3 H, t, J = 7.0 Hz), 2.4 (3 H, s), 3.0 (2 H, m), 3.5 (2 H, m), 4.0 (1 H, dd, J = 7.4 & 4.3 Hz), 4.2 (2 H, q, J = 7.1 Hz), 4.9 (2 H, s), 6.8 (2 H, dd, J = 6.7 & 2.0 Hz), 7.1 (2 H, d, J = 1.9 Hz), 7.4 (3 H, m), 8.0 (2 H, dd, J = 5.1 & 1.8 Hz); IR (Nujol) 2881, 1741, 1720, 1587, 1515, 1341, 1251, 1160, 1071, 820 cm^{-1}; ESI/MS m/z: 410 $(M + H)^+$.

4.3.2. Ethyl (2S)-ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propanoate (**1b**)

Title compound was prepared from ethyl (2S)-ethoxy-3-(4-hydroxy-phenyl)-propanoate and 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl methanesulfonate following the procedure described for compound **1a**. Thick liquid; yield: 93%; purity: 99% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1 (3 H, t, J = 7.1 Hz), 1.2 (3 H, t, J = 7.0 Hz), 2.4 (3 H, s), 3.0 (4 H, m), 3.5 (2 H, m), 4.0 (1 H, dd, J = 7.4 & 4.3 & Hz), 4.1 (2 H, q, J = 7.1 Hz), 4.2 (2 H, t, J = 6.7 Hz), 6.8 (2 H, dd, J = 6.7 & 2.0 Hz), 7.1 (2 H, d, J = 1.9 Hz), 7.4 (3 H, m), 8.0 (2 H, dd, J = 5.1 & 1.8 Hz); IR (Nujol) 2877, 1744, 1583, 1513, 1344, 1245, 1176, 1064, 821 cm^{-1}; ESI/MS m/z: 424 $(M + H)^+$.

4.3.3. (2S)-Ethoxy-3-[4-[5-methyl-2-phenyl-oxazol-4-yl-methoxy]-phenyl]-propanoic acid (**1c**)

To a solution of ethyl (2S)-ethoxy-3-[4-[5-methyl-2-phenyl-oxazol-4-yl-methoxy]-phenyl]-propanoate (**1a**) (1.5 g, 3.66 mmol) in EtOH (10 mL), a solution of NaOH (0.29 g, 7.3 mmol) in H_2O (5 mL) was added and stirred at 25 °C for 18 h. The reaction mixture was concentrated *in vacuo*, diluted with 20 mL water, acidified by HCl and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with water and brine solution, dried over Na_2SO_4 and evaporated *in vacuo* to give 1.27 g of title compound **1c** as white solid. m.p. 103–104 °C; yield: 91%, purity: 99% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.2 (3 H, t, J = 7.0 Hz), 2.4 (3 H, s), 3.0 (2 H, m), 3.5 (2 H, m), 4.0 (1 H, dd, J = 7.4 & 4.3 & Hz), 4.9 (2 H, s), 6.8 (2 H, dd, J = 6.7 & 2.0 Hz), 7.1 (2 H, d, J = 1.9 Hz), 7.4 (3 H, m), 8.0 (2 H, dd, J = 5.1 & 1.8 Hz); IR (KBr) 3411, 2880, 1717, 1622, 1589, 1515, 1340, 1251, 1160, 1071, 820 cm^{-1}; ESI/MS m/z: 382 $(M + H)^+$.

4.3.4. (2S)-Ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propanoic acid (**1d**)

Title compound was prepared from **1b** following the procedure described for compound **1c**. White solid; m.p. 97–98 °C; yield: 93%; purity: 99% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2 (3 H, t, J = 7.0 Hz), 2.4 (3 H, s), 3.0 (4 H, m), 3.5 (2 H, m), 4.0 (1H , dd, J = 7.4 & 4.3 & Hz), 4.2 (2 H, t, J = 6.7 Hz), 6.8 (2 H, dd, J = 6.7 & 2.0 Hz), 7.1 (2 H, d, J = 1.9 Hz), 7.4 (3 H, m), 8.0 (2 H, dd, J = 5.1 & 1.8 Hz); IR (KBr), 3409, 2877, 1706, 1612, 1583, 1512, 1342, 1245, 1176, 1064, 821 cm^{-1}; ESI/MS m/z: 396 $(M + H)^+$.

4.3.5. (2S)-Ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propan-1-ol (**2a**)

To a solution of ethyl (2S)-ethoxy-3-[4-[5-methyl-2-phenyl-oxazol-4-yl-methoxy]-phenyl]-propanoate (**1a**) (2.0 g, 4.89 mmol) in THF (10 mL), $LiAlH_4$ (0.185 g, 4.89 mmol) was added in small portions at 0 °C over a period of 30 min under nitrogen atmosphere and stirred at 20 °C for 4 h. Excess $LiAlH_4$ was quenched by drop-wise addition of saturated aqueous Na_2SO_4 solution at 0–10 °C. Solid residue was filtered and washed with ethyl acetate. Filtrate was evaporated *in vacuo* to give 1.74 g of title compound **2a** as thick liquid. yield: 97%; purity: 98% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (3 H, t, J = 6.99 Hz), 2.4 (3 H, s), 2.6–2.8 (2 H, m), 3.4–3.6 (5 H, m), 4.9 (2 H, s), 6.94 (2 H, d, J = 8.64 Hz), 7.12 (2 H, d, J = 8.58 Hz), 7.42–7.46 (3 H, m), 8.0–8.03 (2 H, m); IR (Nujol), 3622, 2927, 1515, 1461, 1341, 1250, 1159, 1070, 835 cm^{-1}; ESI/MS m/z: 368 $(M + H)^+$.

4.3.6. (2S)-Ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propan-1-ol (**2b**)

Title compound was prepared from **1b** following the procedure described for compound **2a**. Off white solid; m.p. 45–47 °C; yield: 84%; Purity: 97% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1 (3 H, t, J = 6.9 Hz), 2.3 (3 H, s), 2.5 (1 H, dd, J = 13.5 & 6.7 Hz), 2.7 (1 H, dd, J = 12.9 & 6.9 Hz), 2.9 (2 H, t, J = 6.69 Hz), 3.5 (5 H, m), 4.2 (2 H, t, J = 6.69 Hz), 6.8 (2 H, d, J = 8.55 Hz), 7.1 (2 H, d, J = 8.5 Hz), 7.2–7.4 (3 H, m), 7.9 (2 H, m); IR (KBr) 3290, 2862, 1581, 1448, 1286, 1178, 1056, 835 cm^{-1}; ESI/MS m/z: 382 $(M + H)^+$.

4.3.7. (2S)-Ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propyl methanesulfonate (**3a**)

To a solution of (2S)-ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propan-1-ol (**2a**) (1.0 g, 2.72 mmol) in CH_2Cl_2 (10 mL), Et_3N (0.42 g, 4.08 mmol) was added followed by drop-wise addition of CH_3SO_2Cl (0.37 mg, 3.26 mmol) at 0–10 °C under nitrogen atmosphere and stirred at the same temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water, $NaHCO_3$ solution, dil HCl and brine, dried over Na_2SO_4 and evaporated *in vacuo* to give 1.18 g of title compound **3a** as thick liquid; yield: 98%; purity: 98% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (3 H, t, J = 6.99 Hz), 2.4 (3 H, s), 2.7–2.8 (2 H, m), 3.0 (3 H, s), 3.4–3.6 (2 H, m), 3.6–3.7 (1 H, m), 4.0–4.2 (2 H, m), 4.9 (2 H, s), 6.95 (2 H, d, J = 8.61 Hz), 7.14 (2 H, d, J = 8.61 Hz), 7.41–7.46 (3 H, m), 8.0–8.03 (2 H, m); IR (Nujol): 3122, 2929, 1530, 1345, 1250, 1215, 1159, 1095, 1069, 828 cm^{-1}; ESI/MS m/z: 446 $(M + H)^+$.

4.3.8. (2S)-Ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propyl methanesulfonate (**3b**)

Title compound was prepared from **2b** following the procedure described for compound **3a**. White solid; m.p. 62–64 °C; yield: 84%, purity: 96% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1 (3 H, t, J = 7.0 Hz), 2.3 (3 H, s), 2.8 (2 H, m), 2.9 (2 H, t, J = 6.7 Hz), 3.0 (3 H, s), 3.5 (2 H, m), 3.6 (1 H, m), 4.0 (1 H, dd, J = 10.9 & 5.6 Hz), 4.2 (3 H, m), 6.8 (2 H, d, J = 8.6 Hz), 7.1 (2 H, d, J = 8.5 Hz), 7.4 (3 H, m), 7.9 (2 H, dd, J = 7.9 & 2.2 Hz); IR (KBr) 3110, 2924, 1529, 1350, 1250, 1216, 1150, 1071, 835 cm^{-1}; ESI/MS m/z: 460 $(M + H)^+$.

4.3.9. 4-[4-(2S,3-Diethoxy-propyl)-phenoxymethyl]-5-methyl-2-phenyl-oxazole (**3c**)

To an ice cold suspension of NaH (60%) (81.7 mg, 2.04 mmol) in DMF (1 ml), a solution of (2S)-ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-yl-methoxy)-phenyl]-propan-1-ol (**2a**) (500 mg, 1.36 mmol) in DMF (1 ml) was added drop wise at 10 °C under nitrogen atmosphere and stirred at 25 °C for 0.5 h. Ethyl iodide (254 mg, 1.63 mmol) was added at 27 °C and the reaction mixture was stirred at 27 °C for 4 h. The reaction mixture was poured into ice cold water (20 ml) and extracted with ethyl acetate (20 ml × 3). The organic extract was washed with water and brine solution, dried over Na_2SO_4 and evaporated *in vacuo* to give 408 mg of title compound **3c** as thick liquid. Yield: 76%; purity: 95% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (3 H, t, J = 6.9 Hz), 1.19 (3 H, t, J = 6.9 Hz), 2.43 (3 H, s), 2.77 (2 H, m), 3.37–3.63 (7 H, m), 4.97 (2 H, s), 6.9 (2 H, d, J = 8.6 Hz), 7.17 (2 H, d, J = 8.6 Hz), 7.42–7.47 (3 H, m), 8.0–8.03 (2 H, m); IR (Nujol) 3119, 2901, 1610, 1488, 1380, 1295, 1250, 1210, 1119, 757 cm^{-1}; ESI/MS m/z: 396 $(M + H)^+$.

4.3.10. 4-[2-[4-(2S,3-Diethoxy-propyl)-phenoxy]-ethyl]-5-methyl-2-phenyl-oxazole (**3d**)

Title compound was prepared from **2b** following the procedure described for compound **3c.** Thick liquid; yield: 57%, purity: 99% by HPLC, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1 (3 H, t, J = 6.99 Hz), 1.2 (3 H, t, J = 6.99 Hz), 2.4 (3 H, s), 2.7 (2 H, t, J = 6.6 Hz), 3.0 (2 H, t, J = 6.69 Hz) 3.5 (7 H, complex), 4.2 (2 H, t, J = 6.69 Hz), 6.8 (2 H, dd, J = 1.87 & 6.65 Hz), 7.1 (2 H, d, J = 8.55 Hz), 7.4 (3 H, m) 7.9 (2 H, m); IR (Nujol) 3119, 2901, 1610, 1512, 1382, 1244, 1215, 1110, 756 cm^{-1}; ESI/MS m/z: 410 $(M + H)^+$.

4.3.11. 4-[4-(3-Azido-2S-ethoxy-propyl)-phenoxymethyl]-5-methyl-2-phenyl-oxazole (**4a**)

To a solution of (2S)-ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propyl methanesulfonate (**3a**) (1.0 g, 2.25 mmol) in dry DMF (2 mL), NaN_3 (0.73 g, 11.2 mmol) was added and the reaction mixture was stirred at 100 °C for 6 h. The reaction mixture was poured into ice cold water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic extract was washed with water and brine solution, dried over sodium sulfate and evaporated *in vacuo* to give 855 mg of title compound **4a** as thick liquid. Yield: 97%, purity: 98% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (3 H, t, J = 6.99 Hz), 2.4 (3 H, s), 2.7–2.85 (2 H, m), 3.2 (2 H, m), 3.45–3.65 (3 H, m), 4.9 (2 H, s), 6.95 (2 H, d, J = 8.6 Hz), 7.14 (2 H, d, J = 8.61 Hz), 7.41–7.46 (3 H, m), 8.0–8.03 (2 H, m); IR (Nujol) 2975, 2850, 1610, 1151, 1460, 1380, 1275, 1169, 1090, 973, 690 cm^{-1}; ESI/MS m/z: 392 $(M + H)^+$.

4.3.12. 4-[2-[4-(3-Azido-2S-ethoxy-propyl)-phenoxy]-ethyl]-5-methyl-2-phenyl-oxazole (**4b**)

Title compound was prepared from **3b** following the procedure described for compound **4a**. White solid: m.p. 60–63 °C; yield: 71%, purity: 99% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2 (3 H, t, J = 7.0 Hz), 2.3 (3 H, s), 2.7 (1 H, dd, J = 13.5 & 6.6 Hz), 2.8 (1 H, dd, J = 13.5 & 6.2 Hz), 2.9 (2 H, t, J = 6.7 Hz), 3.1 (2 H, m), 3.5 (3 H, m), 4.2 (2 H, t, J = 6.7 Hz), 6.8 (2 H, d, J = 9.5 Hz), 7.1 (2 H, d, J = 8.5 Hz), 7.4 (3 H, m), 7.9 (2 H, m); IR (KBr) 2979, 2854, 1610, 1510, 1463, 1384, 1278, 1170, 1091, 947, 690 cm^{-1}; ESI/MS m/z: 407 $(M + H)^+$.

4.3.13. (2S)-Ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propylamine (**5a**)

To a solution of (4-[4-(3-azido-2S-ethoxy-propyl)-phenoxymethyl]-5-methyl-2-phenyl-oxazole (**4a**) (1.2 g, 3.06 mmol) in dry THF (5 mL), Ph_3P (0.96 g, 3.67 mmol) was added and reaction mixture was stirred at 27 °C for 10 h. H_2O (5 ml) was added and the reaction mixture was stirred at 27 °C for 10 h. The reaction mixture was poured into ice cold water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic extract was washed with water and brine solution, dried over sodium sulfate and evaporated *in vacuo*. The crude product was purified by flash column chromatography using 1% MeOH in $CHCl_3$ as eluent to give 828 mg of title compound **4a** as thick liquid. Yield: 72%; purity: 94% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2 (3 H, t, J = 6.9 Hz), 2.45 (3 H, s), 2.68 (2 H, d, J = 5.3 Hz), 2.70–2.84 (2 H, m), 3.53–3.62 (2 H, m), 3.74–4.05 (1 H, m), 5.0 (2 H, s), 6.9 (2 H, d, J = 8.0 Hz), 7.1 (2 H, d, J = 8.58 Hz), 7.42–7.45 (3 H, m), 7.99–8.03 (2 H, m); IR (Nujol) 3411, 2979, 2360, 1510, 1466, 1388, 1179, 1089, 1089, 669 cm^{-1}; ESI/MS m/z: 367 $(M + H)^+$.

4.3.14. (2S)-Ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propylamine (**5b**)

Title compound was prepared from **4b** following the procedure described for compound **5a**. Thick liquid; yield: 76%; purity: 98% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1(3 H, t, J = 6.91 Hz), 2.3 (3 H, s), 2.6–2.8 (4 H, m), 2.9 (2 H, t, J = 6.69 Hz), 3.4–3.5 (3 H, m), 4.2 (2 H, t, J = 6.69 Hz), 6.8 (2 H, d, J = 8.5 Hz), 7.0 (2 H, d, J = 8.4 Hz), 7.4 (3 H, m), 7.9 (2 H, m); IR (Nujol) 3409, 2979, 2359, 1511, 1465, 1388, 1180, 1091, 927, 669 cm^{-1}; ESI/MS m/z: 381 $(M + H)^+$.

4.3.15. N-[(2S)-Ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propyl]-acetamide (**6a**)

To a solution (2S)-ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propylamine (**5a**) (500 mg, 1.37 mmol) in CH_2Cl_2 (5 mL), Et_3N (207 mg, 2.05 mmol) was added followed by drop-wise addition of CH_3COCl (125 mg, 1.64 mmol) at 0–10 °C under nitrogen atmosphere and stirred at the same temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water, $NaHCO_3$ solution, dil HCl and brine solution, dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was triturated with diethyl ether to give 247 mg of title compound **6a** as white solid. m.p. 111–112 °C; yield: 37%, purity: 97% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2 (3 H, t, J = 6.9 Hz), 2.1 (3 H, s), 2.43 (3 H, s), 2.69–2.77 (2 H, m), 2.78–3.44 (1 H, m), 3.45–3.53 (4 H, m), 4.97 (2 H, s), 5.73 (1 H, s), 6.93 (2H, d, J = 8.61 Hz), 7.12 (2 H, d, J = 8.58 Hz), 7.42–7.46 (3 H, m), 8.00–8.03 (2 H, m); IR (KBr) 3314, 2970, 2850, 1639, 1609, 1551, 1466, 1377, 1280, 1180, 1090, 829 cm^{-1}; ESI/MS m/z: 409 $(M + H)^+$.

4.3.16. {(2S)-Ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propyl}-isopropyl-amine (**6b**)

To an ice cold suspension of NaH (60%) (82 mg, 2.06 mmol) in DMF (1 ml), a solution of (2S)-ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-yl-methoxy)-phenyl]-propylamine (**5a**) (500 mg, 1.37 mmol) in DMF (1 ml) was added drop wise at 10 °C under nitrogen atmosphere and stirred at 25 °C for 30 min. Isopropyl iodide (279 mg, 1.64 mmol) was added at 25 °C and the reaction mixture was stirred below 27 °C for 8 h. The reaction mixture was poured into ice cold water (20 ml) and extracted with ethyl acetate (20 ml × 3). The organic extract was washed with water and brine solution, dried over Na_2SO_4 and evaporated *in vacuo* to give 475 mg of title compound **6b** as thick liquid. Yield: 85%; purity: 96% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (3 H, t, J = 6.8 Hz), 1.17 (6 H, d, J = 5.52 Hz), 2.77–2.92 (4 H, m), 2.43 (3 H, s), 3.25 (1 H, t, J = 6.16 Hz), 3.43–3.92 (2 H, m), 4.96 (2 H, s), 6.97 (2 H, d, J = 8.25 Hz), 7.17 (2 H, d, J = 8.19 Hz), 7.50–7.92 (5 H, m); IR (Nujol) 3421, 2979, 2880, 2359, 1551, 1466, 1388, 1188, 1099, 1010, 671 cm^{-1}; ESI/MS m/z: 409 $(M + H)^+$.

4.3.17. N-(2S-Ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propyl)-acetamide (**6c**)

Title compound was prepared from **5b** following the procedure described for compound **6a**. White solid; m.p. 101–102 °C; yield: 64%; purity: 98% by HPLC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1 (3 H, t, J = 7.0 Hz), 1.9 (3 H, s), 2.3 (3 H, s), 2.6 (2 H, m), 2.9 (2 H, t, J = 6.7 Hz), 3.1 (1 H, m), 3.5 (4 H, m), 4.2 (2 H, t, J = 6.7 Hz), 6.8 (2 H, d, J = 8.6 Hz), 7.0 (2 H, d, J = 8.5 Hz), 7.4 (3 H, m), 8.0 (2 H, dd, J = 7.9 & 2.3 Hz); IR (KBr) 3311, 2974, 2856, 1641, 1610, 1550, 1463, 1373, 1284, 1176, 1099, 829 cm^{-1}; ESI/MS m/z: 423 $(M + H)^+$.

4.3.18. (2S-Ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propyl)-isopropyl-amine (**6d**)

Title compound was prepared from **5b** following the procedure described for compound **6b**. White solid; m.p. 122–125 °C; yield: 82%; purity: 95% by HPLC; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.0–1.1 (9 H, m), 2.3 (3 H, s), 2.7 (3 H, m), 2.9 (3 H, m), 3.23 (1 H, m), 3.4–3.6 (3 H, complex), 4.1 (2 H, t, J = 6.0 Hz), 6.8 (2 H, d, J = 8.1 Hz), 7.1 (2 H, d, J = 8.1 Hz), 7.5 (3 H, m), 7.8 (2 H, m); IR (KBr) 3433, 2977, 2345, 1702, 1612, 1512, 1484, 1245, 1220, 1099, 1022, 692 cm^{-1}; ESI/MS m/z: 423 $(M + H)^+$.

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

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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]

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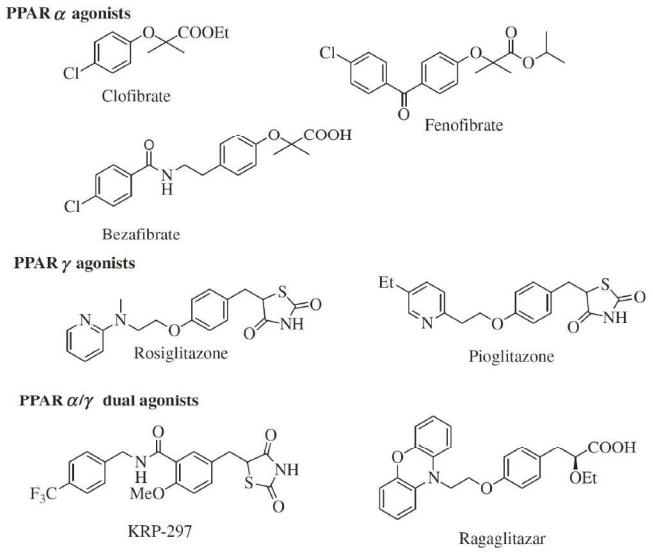


Figure 1. Structure of PPAR agonists.

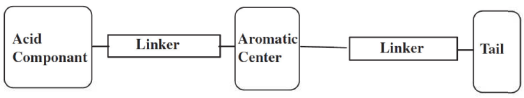


Figure 2. Common structural features of PPAR agonists.

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.

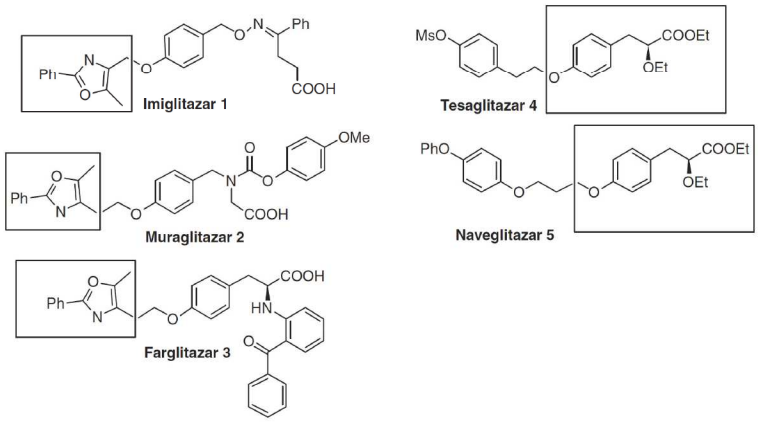


Figure 3. PPARα/γ dual agonists containing oxazole and α-alkoxy carboxylic acid groups.

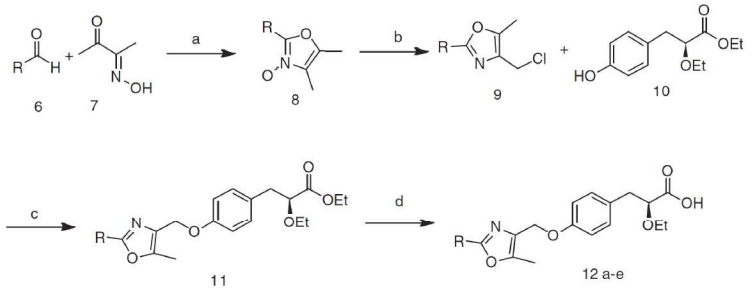
Figure 4. Designing PPARα/γ agonists containing thiophene substituted oxazole.

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.

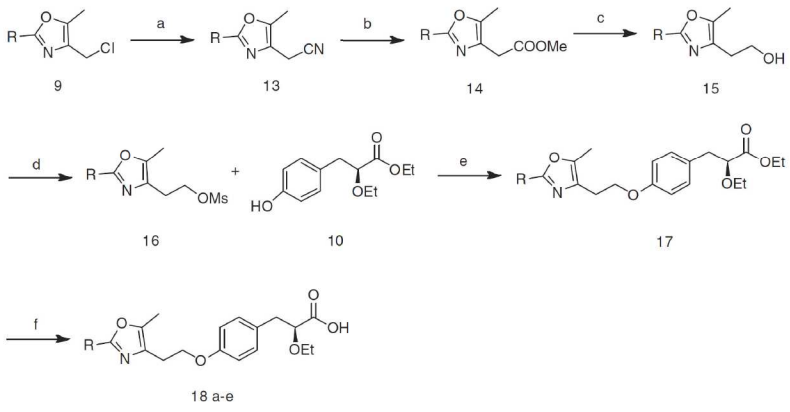
Two sets of thiophene substituted oxazole containing α-alkoxy acid derivatives**12a–e** and **18a–e** are reported as dual PPARα/γ agonists. Compounds **12a–e** contain methylene spacer between aromatic center and cyclic tail where as compounds **18a–e** represent corresponding analogues containing ethylene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

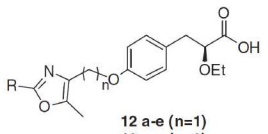


Scheme 1. Reagents and conditions: (a) AcOH/HCl gas, 0 °C, 1 h, 20–25%; (b) $POCl_3$, dichloroethane, reflux, 14 h, 50–70%; (c) K_2CO_3, DMF, 80–90 °C, 2 h, 40–50%; (d) NaOH/MeOH–H_2O, 20–25 °C, 16 h, 60–80%.

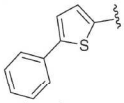
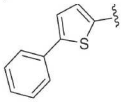


Scheme 2. Reagents and conditions: (a) NaCN, DMF, 25–30 °C, 4 h, 80–90%; (b) MeOH, H_2SO_4, catalytic H_2O, reflux, 16 h, 60–70%; (c) LAH, THF, 0–10 °C, 70–80%; (d) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 25 °C, 2 h, 85–90%; (e) K_2CO_3, DMF, 80–90 °C, 2 h, 40–50%; (f) NaOH/MeOH–H_2O, 20–25 °C, 16 h, 60–70%.

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

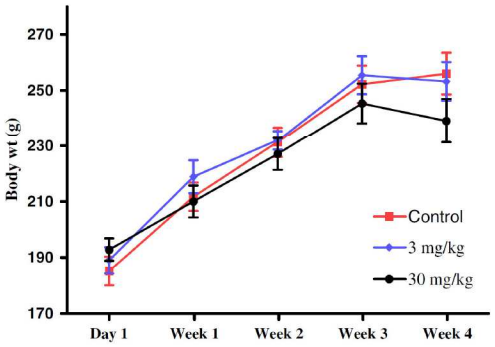


Figure 5. Body weight values of male *Wistar* rats treated with **18d** for 28 days.

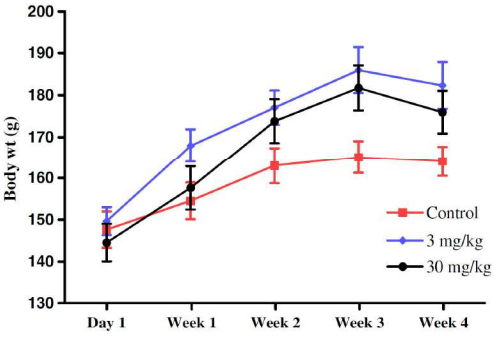


Figure 6. Body weight values of female *Wistar* rats treated with **18d** for 28 days.

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.

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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-phenyl thiophen-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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