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

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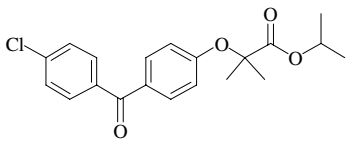
α-Alkoxy arylpropanoic acids containing 2-phenyloxazole-4yl-alkyl moiety are found to be potent hypolipidemic agents. These compounds were potent activators of the peroxisome proliferator activated receptor γ (PPARγ), with moderate PPARα activity and known to cause adverse effects such as weight gain 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.

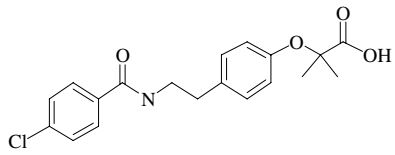
1. Introduction

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-

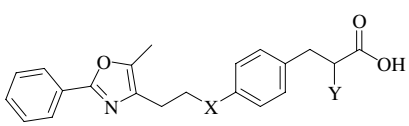
Scheme 1



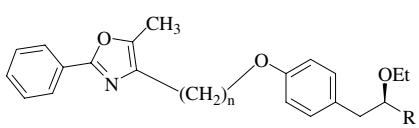
I
Fenofibrate



II
Bezafibrate



III



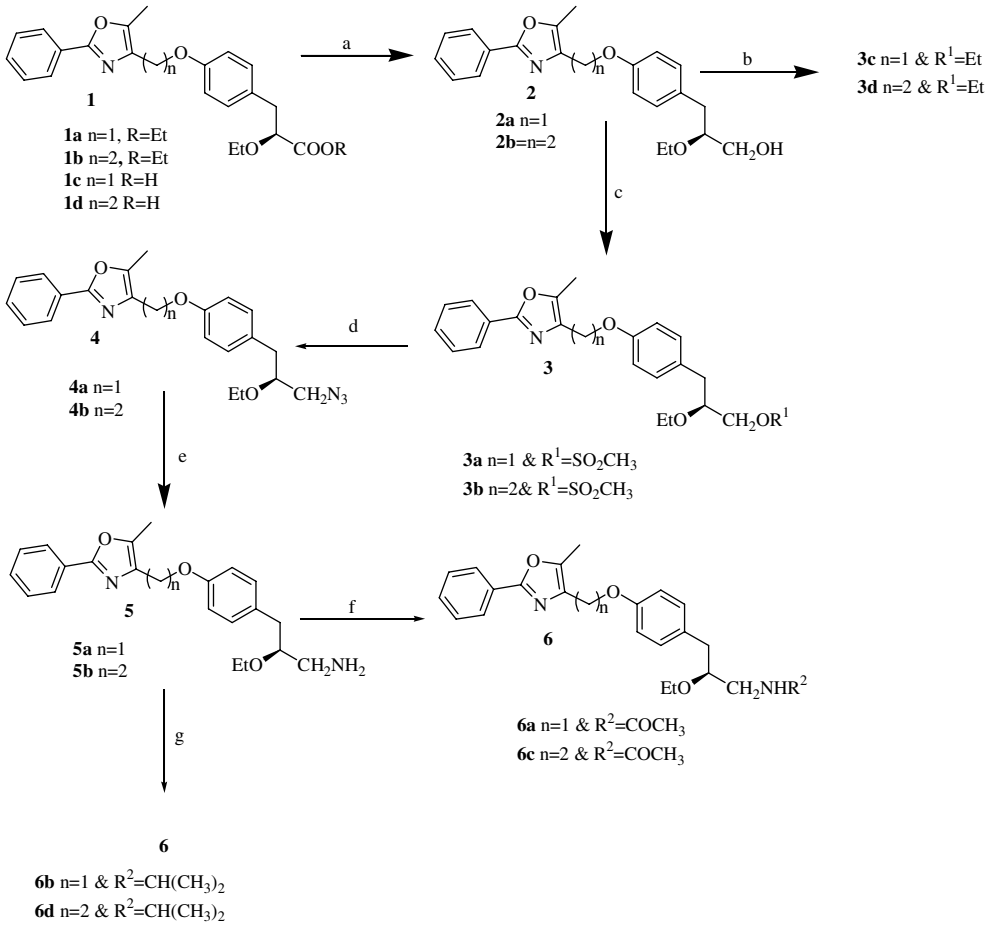
IV

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 (Stales et al. 1998). A combination of statins and fibrates 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

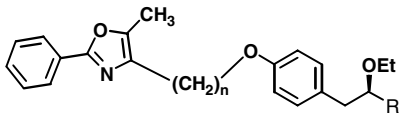
respectively by treating them with sodium azide in DMF at 100 °C were reduced to amines **5a** and **5b** by the treatment with triphenyl phosphine in THF followed by aqueous hydrolysis. Acetylation of amines **5a** and **5b** with aceticanhydride gave the respective amides **6a** and **6c** whereas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