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Design and synthesis of novel oxazole containing 1,3-Dioxane-2-carboxylic acid derivatives as PPAR α/γ dual agonists ☆

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ABSTRACT

A few novel 1,3-dioxane carboxylic acid derivatives were designed and synthesized to aid in the characterization of PPAR α/γ dual agonists. Structural requirements for PPARα/γ dual agonism of 1,3-dioxane carboxylic acid derivatives included the structural similarity with potent glitazones in fibric acid chemotype. The compounds with this pharmacophore and substituted oxazole as a lipophilic heterocyclic tail were synthesized and evaluated for their in vitro PPAR agonistic potential and in vivo hypoglycemic and hypolipidemic efficacy in animal models. Lead compound 2-methyl-*c*-5-[4-(5-methyl-2-(4-methylphenyl)-oxazol-4-ylmethoxy)-benzyl]-1,3-dioxane-*r*-2-carboxylic acid **13b** exhibited potent hypoglycemic, hypolipidemic and insulin sensitizing effects in *db/db* mice and Zucker *fa/fa* rats.

1. Introduction

Type 2 diabetes is a complex metabolic disorder characterized by hyperglycemia, insulin resistance, and defects in insulin secretion and is usually associated with dyslipidemia, hypertension and obesity. Detailed pathophysiology of this disease remains incompletely understood. However, the probable reasons for the development of this disease are metabolic defects in the liver, pancreatic β-cells, adipose tissue and skeletal muscle. Though it was thought to be mainly a disorder of carbohydrate metabolism. Since hyperglycemia being the main symptom of this disease, it is evident from the advanced research that abnormalities in fat metabolism play a central role in the pathogenesis of this disease.[1–3] The peroxisome proliferation-activated receptors (PPARs) are ligand-activated transcription factors belonging to nuclear hormone receptor superfamily.[4,5] Three distinct PPAR subtypes (PPARα, PPARγ and PPARδ) have been identified in most mammalian species and their physiological roles in glucose homeostasis, fatty acid metabolism and cellular differentiation have been reviewed extensively.[6–10] PPARγ is well known for its role in adipogenesis at a cellular level and insulin sensitization.[11,12] PPARγ agonists, such as thiazolidinediones (TZDs or glitazones) have proven to be efficacious as insulin sensitizing agents in the treatment of type 2 diabetes.[13–15] Rosiglitazone and Pioglitazone (Fig. 1) belong to this class and are currently available in the market. PPARα is known to play an important role in fatty acids oxidation and lipoprotein metabolism.[16] Fibrates (**Fenofibrate, Clofibrate, and Bezafibrate**) and similar compounds like **WY-14643** (Fig. 2) show effects such as lowering triglycerides and elevating HDL levels through activation of PPARα.[17–23] The majority of type 2 diabetes patients suffer from atherogenic lipid abnormalities in addition to insulin resistance, termed as metabolic syndrome,[24] and given the importance of controlling both glucose and lipid levels in metabolic syndrome. This gave rise to the concept of identifying dual agonists, which can activate both PPARα and PPARγ. In addition to their hypolipidemic effects, fibrates reduce body weight gain in rodents without affecting food intake[25,26] and led to a hypothesis that probably activation of PPARα may mitigate the weight gain induced by PPARγ activation in humans. This hypothesis that PPARα/γ dual agonism would provide synergistic pharmacological effects has encouraged many research groups to develop these agents (Fig. 3) but none of these dual agonists including Farglitazar,[27] Ragaglitazar,[28] Tesaglitazar,[29] and Muraglitazar[30–32] has been marketed. These facts made the development of PPARα/γ dual agonists with distinct biological and safety profiles a challenge among the drug discovery groups around the world as the medical need for metabolic disorders is largely remain unmet. In continuation of our research in the field of PPARs to develop novel therapeutic agents to treat metabolic disorders[33–35] we herein report an initial SAR of novel 1,3-dioxane carboxylic acid derivatives which are shown to be potent PPARα/γ dual agonist.

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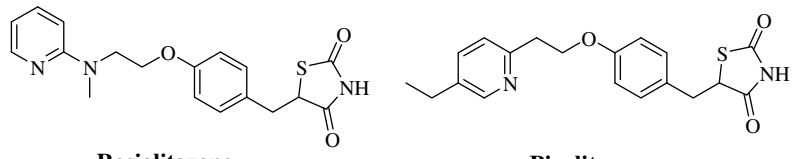
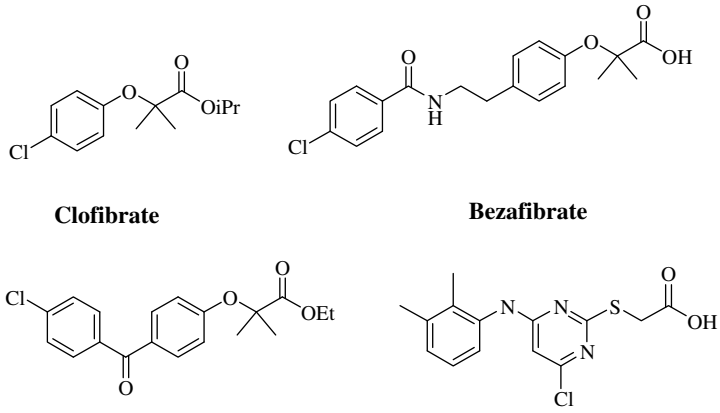


Rosiglitazone **Pioglitazone**

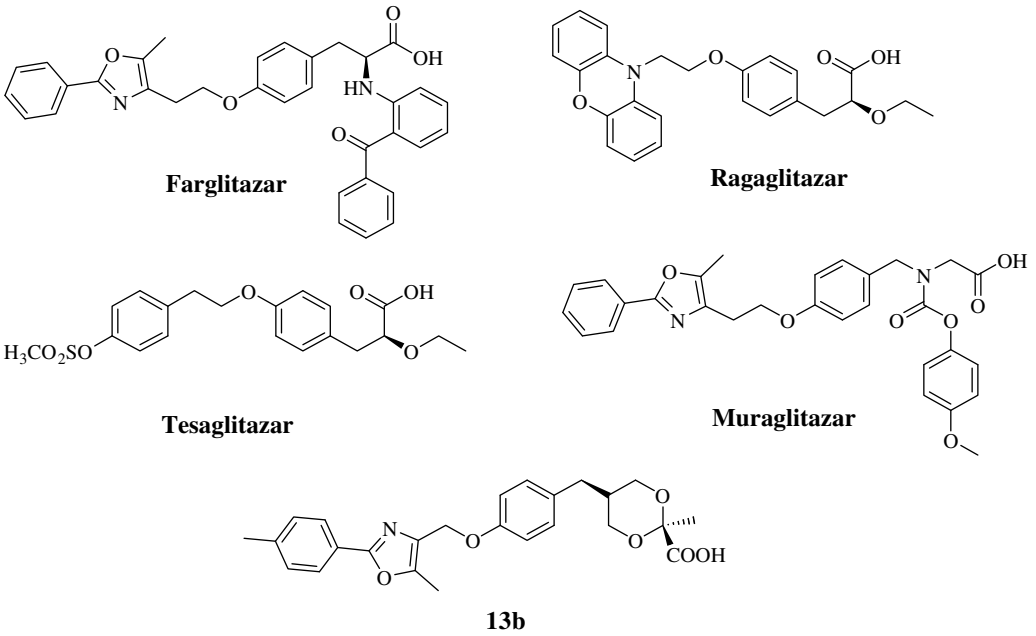
Figure 1. PPARγ agonists.



Clofibrate **Bezafibrate**

Fenofibrate **WY-14643**

Figure 2. PPARα agonists.



Farglitazar **Ragaglitazar**

Tesaglitazar **Muraglitazar**

13b

Figure 3. PPARα/γ dual agonists.

2. Design concept for 1,3-dioxane-2-carboxylic acids as PPAR α/γ dual agonists

Fibric acid is the key pharmacophore of PPARα ligands like **Fenofibrate**, **Clofibrate**, and **Bezafibrate** (Fig. 2). All the glitazone class of compounds possess 2,4-thiazolodinedione as key pharmacophore as in **Rosiglitazone** and **Pioglitazone** (Fig. 1). We intended to design compounds with a novel pharmacophore possessing the features of both fibric acid and glitazone hoping that these compounds can be developed as PPARα/γ dual agonists (Fig. 4). We started the structural design by introducing an oxygen atom on the carbon alpha to carboxylic acid of fibric acid chemotype and cyclizing with the aryl oxygen forming a 1,3-dioxane ring connected to phenyl ring either directly through a bond or with a methylene or ethylene group in-between forming the key pharmacophore of the novel compounds. The remaining part of the structure mimics the typical PPAR agonist comprising of a heterocyclic tail connected to a acidic head with a alkoxy spacer. The newly designed pharmacophore resembles glitazones structurally and possesses free carboxylic function resembling fibric acid pattern and

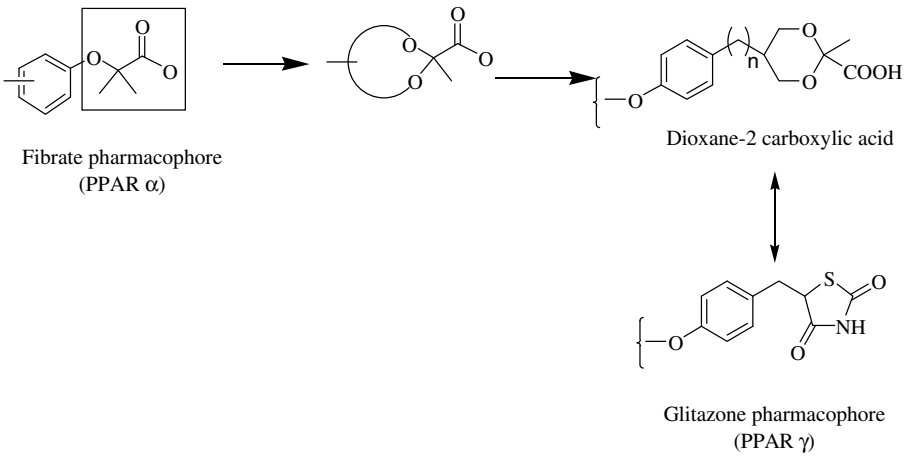
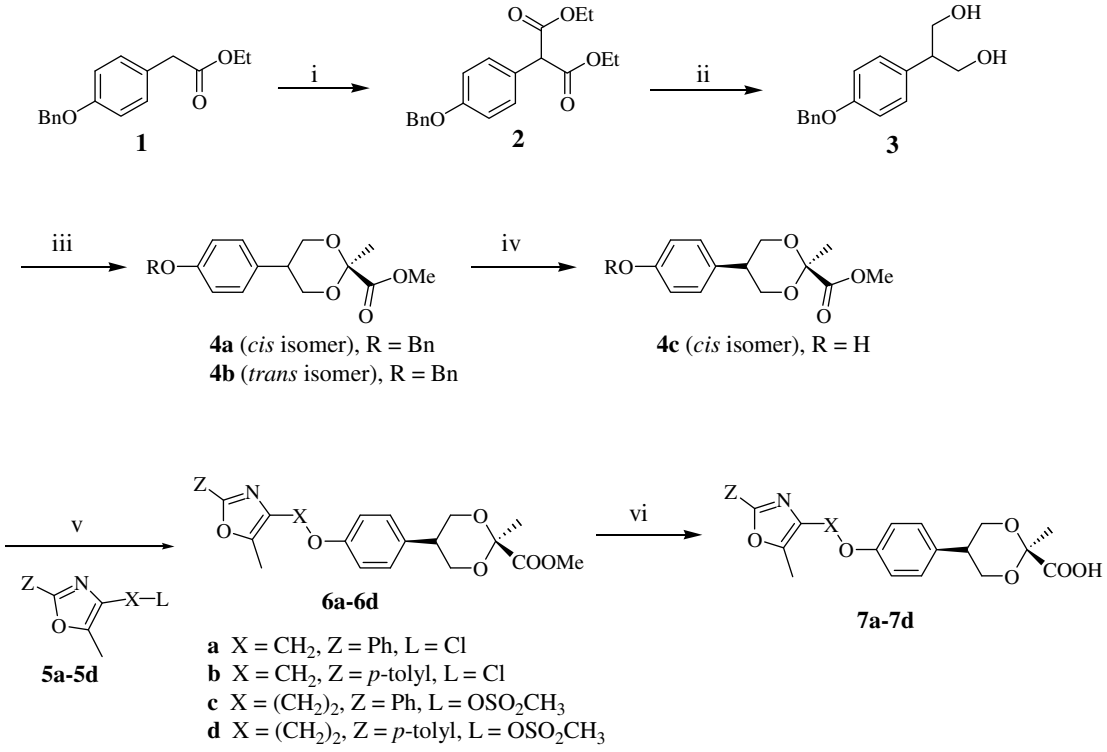


Figure 4. Design of dioxane carboxylic acids.

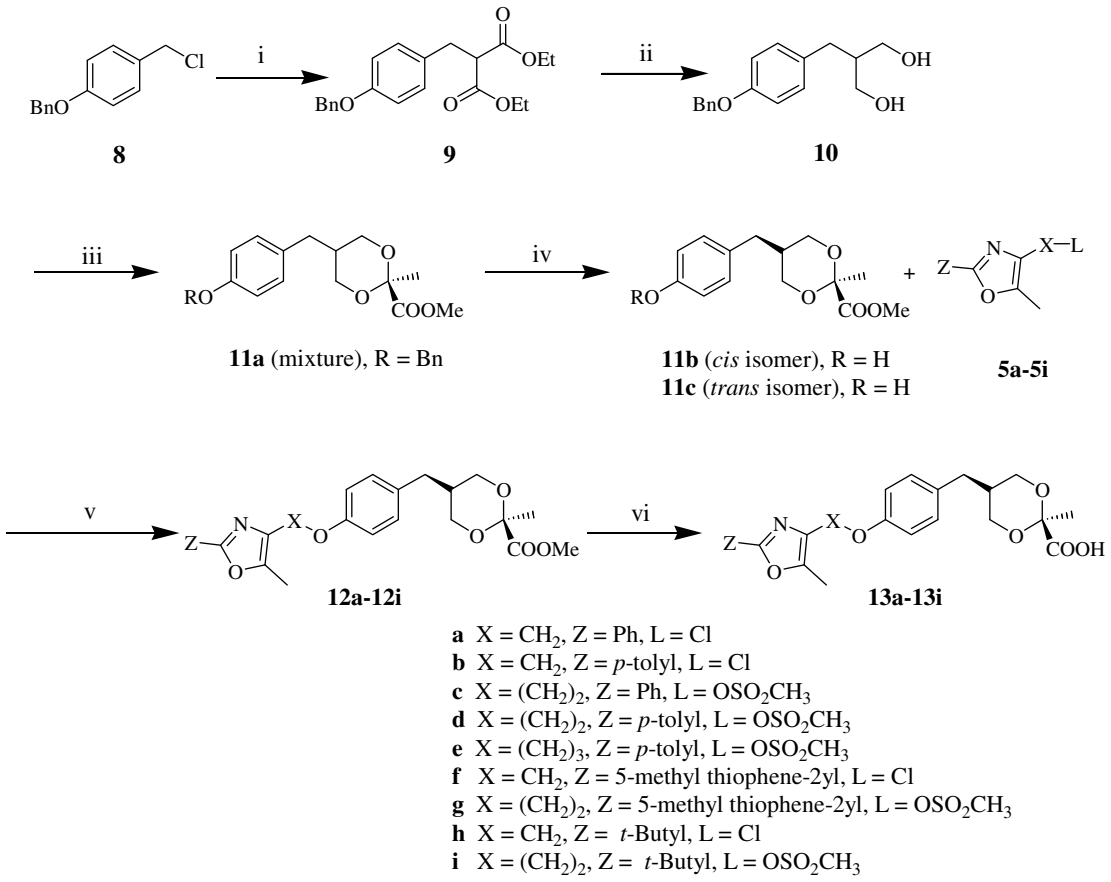
provides rationale to study these compounds as dual PPARα/γ agonists. Few compounds containing 1,3-dioxane carboxylic acid pharmacophore are reported earlier as selective PPARα agonists.[36,37]

3. Chemistry

Compounds **7a**–**d** were synthesized as described in Scheme 1. Reaction of phenylacetate **1** with diethylcarbonate in presence of NaH gave the diester **2** which was reduced with $LiAlH_4$ to give the diol **3**. Dioxane ring formation was brought about by the Reaction of **3** with methyl pyruvate in presence of borontrifluoride diethylether complex which gave the cyclized compound as a mixture of diastereomeric isomers and the ratio of *cis*- to *trans*-isomers determined by HPLC was found to be 3:1. These isomers were separated by means of column chromatography to give *cis*-isomer **4a** and *trans*-isomer **4b**. Both of these isomers showed ^{1}HNMR chemical shifts identical with other 1,3-dioxane derivatives reorted.[37,38] Pure *cis*-isomer **4a** was subjected to debenzylation under hydrogenation conditions to obtain phenolic intermediate **4c**. Reaction of the intermediate **4c** with **5a–d** (Compounds **5a–i** were synthesized following the procedures reported.[39]) in presence of K_2CO_3 gave the esters **6a–d**, which upon hydrolysis under basic conditions gave the acids **7a–d**. Synthesis of compounds **13a–i** is illustrated in Scheme 2. Diester **9**, synthesized from **8** by reacting with diethylmalonate in presence of NaH was reduced to diol **10** with $LiAlH_4$. Transformation of **10** to dioxane **11a** (mixture of *cis*- and *trans*-isomers) was achieved by the treatment of **10** with methylpyruvate under the conditions described above, and the ratio of *cis*- to *trans*-isomer in this case as determined by HPLC was



Scheme 1. Reagents and conditions: (i) 60% NaH, diethyl carbonate, THF, 25 °C, 18 h; (ii) $LiAlH_4$, THF, 25 °C, 6 h; (iii) methyl pyruvate, 98% BF_3 ethyrate complex, CH_3CN, 25 °C, 4 h; (iv) 10% Pd/C, ammonium formate, MeOH, reflux, 2 h; (v) K_2CO_3, DMF, 60 °C, 18 h; (vi) $LiOH{\cdot}H_2O$, THF, H_2O, MeOH, 25 °C, 18 h.



Scheme 2. Reagents and conditions: (i) 60% NaH, diethyl malonate, THF, 25 °C, 14 h; (ii) $LiAlH_4$, THF, 25 °C, 6 h; (iii) methyl pyruvate, 98% BF_3 ethyrate complex, CH_3CN, 25 °C, 4 h; (iv) 10% Pd/C, ammonium formate, MeOH, reflux, 2 h; (v) K_2CO_3, DMF, 60 °C, 18 h; (vi) $LiOH{\cdot}H_2O$, THF, H_2O, MeOH, 25 °C, 18 h.

approximately 4:1. Surprisingly, the attempts to separate the *cis*- and *trans*-isomers of **11a** by column chromatography were unsuccessful. However, separation by recrystallization was successful after debenzylating the mixture of isomers **11a** under hydrogenation conditions using Pd/C and ammoniumformate. Pure *cis*-isomer **11b** was obtained quantitatively as first crop on recrystallization from a mixture of 1:2 ethyl acetate and hexane, whereas *trans*-isomer **11c** was obtained only after repeated crystallizations from a mixture of 1:1 ethyl acetate and hexane in minor quantity. Coupling of *cis* intermediate **11b** with **5a–i** in presence of potassium carbonate in DMF gave the esters **12a–i**, which were hydrolyzed under aqueous alkaline conditions to give the carboxylic acids **13a–i**.

4. Results and discussion

Compounds **7a–d** and **13a–i** were screened for hPPAR α, γ, and δ agonistic activity on full length PPAR receptor transfected in HepG2 cells. **WY-14643** (Fig. 2), **Rosiglitazone** (Fig. 1), and **GW-501516**[40] were used as controls for PPARα, and δ, respectively, and the results are summarized in Table 1 where the activities were reported as fold induction as well as EC_{50}. A typical chemical structural design of PPAR ligands comprises of an acidic head as pharmacophore which is connected to an aromatic ring mostly the phenyl ring which inturn connected to a lipophilic tail group through a teether-like alkoxy group. Initially to start with the synthesis of novel compounds we chose phenyl dioxane carboxylic acid as pharmacophore which contained acidic head connected to phenyl ring mimicking a typical pharmacophore chemotype of PPAR agonist. Then we have selected 5-methyl-2-phenyl-oxazole group as lipophilic tail for the reason that this heterocycle being used extensively in PPAR drug discovery research. With this plan we have synthesized compounds **7a–d**. Both compounds **7a** and **7c** containing phenyl ring at 2-position on oxazole with a teether of methylene and ethylene, respectively, showed moderate PPARα activity. When the phenyl ring at 2-position on oxazole was substituted with a methyl group at metabolically susceptible *para* position compound **7b** with methylene teether showed similar activity as **7a** but the compound **7d** did not show any PPAR activity. But none of the compounds showed superior activity than the control compounds in terms of their fold induction and hence these compounds were not evaluated for their EC_{50} values. Then we intended to synthesize compounds **13a–i**, which resembles glitazone structure more closely. Compound **13a** with phenyl ring at 2-position of oxazole and a methylene teether showed 0.096 μM activity on PPARγ and 1 μM activity on PPARα, whereas the compound **13c** with ethylene spacer showed inferior and contradictory results with 0.27 μM activity on PPARα and 4 μM on PPARγ. When the phenyl ring in compounds **13a** and **13c** was substituted with a methyl group at *para* position the respective resulting compounds **13b** and **13d** exhibited superior activity compared to parent compounds and surprisingly compound **13b** was found equipotent towards PPARα and γ with 0.07 and 0.015 μM EC_{50}, respectively. The further elongation of the teether to propylene group as in compound **13e** found detrimental to PPAR affinities. Having done this we then wanted to replace the phenyl ring on oxazole with 5-methyl thiophene which was selected from a lead compound of our in-house library and the resulting compounds **13f** and **13g** showed interesting PPAR activity. **13f** found to be 30-fold more selective towards PPARγ whereas **13g** was 8-fold more selective

Table 1
In vitro data of compounds **7** and **13**

Compound	X	Z	hPPAR transactivation[a]				
			α (10 μM)[b]	γ (0.2 μM)[b]	δ (10 μM)[b]	$EC_{50}\alpha$ (μM)	$EC_{50}\gamma$ (μM)
7a	Methylene	Phenyl	3.0	1.6	1.4	ND	ND
7b	Methylene	4-methylphenyl	2.7	1.5	1.2	ND	ND
7c	Ethylene	Phenyl	3.0	1.5	1.3	ND	ND
7d	Ethylene	4-methylphenyl	IA	1.6	1.5	ND	ND
13a	Methylene	Phenyl	6.5	11.4	1.7	1.09	0.096
13b	Methylene	4-methylphenyl	8.2	12.7	IA	0.072	0.015
13c	Ethylene	Phenyl	5.3	3.9	IA	0.272	4.096
13d	Ethylene	4-methylphenyl	6.3	3.4	IA	0.089	1.385
13e	Propylene	4-methylphenyl	1.8	1.8	IA	ND	ND
13f	Methylene	5-methyl thiophene-2yl	5.6	11.5	1.0	0.6	0.0198
13g	Ethylene	5-methyl thiophene-2yl	6.8	8.9	1.1	0.03	0.239
13h	Methylene	*tert*-Butyl	2.3	3.2	IA	ND	ND
13i	Ethylene	*tert*-Butyl	5.8	4.2	1.2	4.2	5.01
Vehicle			1.0	1.0	1.0	–	–
WY-14643			4.4	ND	ND	4.8	ND
Rosiglitazone			ND	11.6	ND	ND	0.05
GW-501516@2 nM			ND	ND	4.3	ND	ND

[a] IA denotes inactive where compounds did not shows any fold induction above the basal level shown by vehicle and ND denotes not determined.
[b] Activities are presented as fold induction of PPAR α, γ and δ activation.

towards PPARα. Replacing phenyl ring with *tert*-butyl group made the compounds **13h** and **13i** inactive towards PPARα and γ. In all of the above compounds except **13b** methylene teether made the compound more potent towards PPARγ whereas the ethylene group made the compounds more selective towards PPARα. Compound **13b** which was found equally potent towards PPARα and γ was selected as a lead compound and its pharmacokinetic behaviour was studied in male *Wistar* rats and the results are summarized in Table 2. Based on the cell-based activities and pharmacokinetic behaviour we then wished to evaluate compound**13b** in *db/db* mice and Zucker *fa/fa* rats for its hypolipidemic and hypoglycemic activities. When dosed orally to *db/db* mice at a dose of 3 mg/kg/day for 6 days **13b** reduced plasma glucose (PG) by 57% and triglycerides (TG) by 50% as depicted in Table 3. Subsequently compound **13b** when administered orally to male Zucker *fa/fa* rats at a dose of 3 mg/kg/day for 14 days normalized glucose tolerance and significantly reduced fasted insulin to an extent of 77%. Additionally, **13b** reduced plasma TG by 71% and total cholesterol (TC) by 30% (Table 4). The above results indicate that compound **13b** showed hypoglycemic, hypolipidemic and insulin sensitizing comparable to **Rosiglitazone** and **Tesaglitazar**.

Table 2
Mean pharmacokinetic parameters[a] of **13b** in fasted male *Wistar* rat

Compd.	Route	Dose (mg/kg)	T_{max} (h)	C_{max} (μg/mL)	$T_{1/2}$ (h)	AUC(0–∞) (h·μg/mL)
13b	Oral	30	1.7 (±0.06)	54 (±4.6)	2.7 (±0.2)	351 (±51)

[a] Values indicate mean ± SD for $n = 6$.

Table 3
In vivo efficacy of the compound **13b** in *db/db* mice

Compound	Dose (mg/kg/day)	% Change	
		TG	PG
13b	3	−50	−57
Rosiglitazone	30	−41	−54
Tesaglitazar	3	−60	−54

Table 4
In vivo efficacy of the compound **13b** in Zucker *fa/fa* rats

Compound	Dose (mg/kg/day)	% Change			% Improvement in glucose AUC
		TG	TC	Fasted insulin	
13b	3	−71	−30	−77	51
Rosiglitazone	30	−57	−17	−78	49
Tesaglitazar	3	−67	−16	−91	51

5. Conclusion

We discovered a novel series of oxazole containing 1,3-dioxane-2-carboxylic acid which are PPARα/γ dual agonists as exemplified by the lead compound **13b**. The pharmacophore was designed by incorporating structural features of glitazones in fibric acid chemotype and optimized using oxazole tail. Lead compound **13b** was found to be a potent PPARα/γ dual agonist and reduced plasma glucose and triglycerides significantly in *db/db* mice. The same compound normalized glucose tolerance and reduced fed insulin in Zucker *fa/fa* rats and exhibited favourable pharmacokinetic parameters in rodent model. Further work in the development of SAR of this lead series based on the benzyl dioxane carboxylic acid core will be described in a subsequent publication.

6. Experimental Section

6.1. In vitro PPAR transactivation assay

6.1.1. Cell culture

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

6.1.2. Transient transfection

HepG2 cells were seeded in 24-well plates at a density of 400,000 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 this, 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 supernatant collected. Supernatant was then

assayed for luciferase and β-galactosidase activity. The luciferase activity was determined using commercial fire-fly luciferase assay according to the suppliers's instructions [Promega] in white 96-well plate [Nunc]. β-Galactosidase activity was determined in ELISA reader at 415 nm.

6.2. In vivo studies (mice and rats)

All animals were used from inbred colony which are maintained on standard laboratory rodent chow ad libitum, and the study protocols were approved by Institutional Animal Ethics Committee.

6.2.1. *db/db* Mice and Zucker *fa/fa* rats experiments

Male *db/db* mice of 12–14 weeks age and 30–40 g body weight and male Zucker *fa/fa* rats of 13–15 weeks age and body weight of 450–470 g were selected for the study. The animals were weighed and tail-bled prior to the start of study. Plasma was analyzed for glucose (PG), triglyceride (TG) levels in *db/db* mice and PG, TG and cholesterol (TC) levels in Zucker *fa/fa* rats. The animals were arranged into the appropriate number of groups with each group having 6 animals of the same mean PG, TG and TC levels prior to dosing. All animals then were orally dosed once daily with vehicle (0.5% methylcellulose in water) and test compounds for 6 days in *db/db* mice and for 14 days in Zucker *fa/fa* rats. All animals were fed ad libitum throughout the study. Approximately, 1 h after the last dose, the animals were bled and the plasma was analyzed for glucose and triglycerides (also cholesterol in Zucker *fa/fa* rats) to calculate percent change due to drug treatment (This takes into account any changes that may have occurred in the vehicle-treated animals during the study).

6.2.2. Glucose tolerance experiments

On day 15 Zucker *fa/fa* rats were fasted overnight, insulin levels were measured and given a 2 g/kg oral glucose load. Blood glucose was measured just prior to the glucose load and after 30, 60 and 120 min by collecting blood from tail tip. The glucose area-under-the-curve (AUC) was calculated over 0 to 120 min using the trapezoidal method and result was reported as percent improvement in glucose AUC versus vehicle treated control group.

6.2.3. Pharmacokinetics experiment

Pharmacokinetics of the test compound **13b** was studied *via* per-oral route of administration in *wistar* rats of 8 to 10 weeks of age. Animals were fasted for 18 hours and food was supplied after 4 hours of administration of the test compound. There was free access to water throughout the study. A homogenous suspension of the test substance was prepared in 0.5% w/v CMC in normal saline and a per-oral dose of 30 mg/kg was administered. After the administration of the test compounds, blood samples were withdrawn at various time intervals through retro-orbital plexus and collected into heparinized micro centrifuge tubes. Plasma was separated by centrifugation at 4000 rpm for 5 min at ambient temperature and analyzed immediately. Remaining samples were stored at −20 °C until analyzed.

Analysis was carried out by taking an aliquot of 180 μL plasma and 20 μL of internal standard (Atorvastatin), and was extracted with 2.5 mL of extracting solvent (ethyl acetate: acetonitrile 80:20, v/v) in glass test-tube by vortexing with spinix vortex mixture for a minute. This was then centrifuged at 2000 rpm for 2.0 min. The supernatant was transferred to another glass test-tube and the solvent was evaporated under nitrogen using Zymark evaporator at 40 °C. Finally, the tubes were reconstituted with 0.1 mL diluent (acetonitrile:methanol:water 40:40:20, v/v/v). The reconstituted samples were analyzed on Agilent 1100 Series HPLC system with a mobile phase of 0.05% v/v trifluoroacetic acid in water: acetonitrile (32:68, v/v); flowing at a flow rate of 1.0 mL/min through a Kromasil 250 mm × 4.6 mm × 5 μ column maintained at 30 °C. Chromatographic separation was achieved within 15 min. Agilent software version Chemstation Rev.A.09.01. (1206) was used to acquire and process all chromatographic data. Quantification was based on a series of calibrators ranging from 0.031 to 32 μg/mL, prepared by adding test compound to drug free rat plasma. Quality control samples were analyzed in parallel to verify that the system performs in control. Pharmacokinetic parameters namely maximum plasma concentration (C_{max}), time point of maximum plasma concentration (t_{max}), area under the plasma concentration-time curve from 0 h to infinity ($AUC_{0-\infty}$) and half-life of drug elimination during the terminal phase ($t_{1/2}$) were calculated from plasma concentration *versus* time data, by standard non-compartmental methods, using the WinNonLin software version 4.0.1 procured from Pharsight Corporation, USA.

6.3. Synthesis

6.3.1. Synthetic materials and methods

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 (Vmax in cm^{-1}, using KBr pellets or Nujol). The ^1H NMR spectra were recorded on a Brucker Avance-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), br s (broad singlet), and m (multiplet). ^{13}CNMR spectra were recorded on Brucker Avance-400 at 100 MHz either in $CDCl_3$ or in DMSO-d_6 solution. Mass spectra (ESI-MS) were obtained on Shimadzu LC–MS 2010-A spectrometer. HPLC analysis was carried out at λ_{max} 220 nm using column ODS C-18, 150 nm * 4.6 nm * 4 μ on AGILENT 1100 series.

6.3.2. Diethyl 2-(4-benzyloxyphenyl)malonate (2)

To an ice-cold suspension of NaH (60%) (4.4 g, 0.111 mol) in THF (30 mL), a solution of **1** (10.0 g, 0.037 mol) in THF (50 ml) was added drop wise over a period of 30 min at 0–10 °C and stirred at the same temperature for 30 min. Diethyl carbonate (18 mL, 0.148 mol) was added to the reaction mixture at 0–10 °C and stirred at 25 °C for 18 h. The reaction mixture was poured into ice-cold water (200 mL) and extracted with ethyl acetate (3× 100 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure to yield 15 g crude product as thick oil. The crude product was purified by column chromatography (10% ethyl acetate in hexane, 230–400 mesh silica gel) to give title compound **2** as off-white solid (6.5 g). Yield: 51%; mp: 58-60 °C; purity by HPLC: 90%; IR (KBr): 1743, 1726, 1247, 1226, 1177, 1010, 750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.25 (t, J = 7.11 Hz, 6H), 4.15–4.55 (m, 4H), 4.55 (s, 1H), 5.05 (s, 2H), 6.91 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 7.35-7.45 (m, 5H); ESI-MS m/z: 343.2 $(M+H)^+$.

6.3.3. 2-(4-Benzyloxyphenyl)propane-1,3-diol (3)

To a solution of **2** (6.0 g, 0.0175 mol) in THF (100 mL), $LiAlH_4$ (1.33 g, 0.035 mol) was added in small portions at 0 °C over a period of 30 min. and stirred at 25 °C for 6 h. The excess $LiAlH_4$ was quenched by dropwise addition of saturated aqueous Na_2SO_4 solution at 0–10 °C. Solid residue was filtered and washed with ethyl acetate. Filtrate was evaporated under reduced pressure. Crude product was triturated in diisopropyl ether to give title compound **3** as white solid (1.76 g). Yield: 39%; mp: 130–132 °C; purity by HPLC: 93%; IR (KBr): 3278, 2943, 2292, 2868, 1514, 1226, 1026,

and 740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.01 (br s, 2H), 3.02–3.11 (m, 1H), 3.93–3.97 (m, 4H), 5.05 (s, 2H), 6.95 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 7.32–7.44 (m, 5H); ESI-MS m/z: 276.2 $(M+NH_4)^+$.

6.3.4. Methyl *c*-5-(4-benzyloxyphenyl)-2-methyl-1,3-dioxane-*r*-2-carboxylate (4a)

To a solution of **3** and methyl pyruvate (1.14 mL, 15.5 mmol) in acetonitrile (15 mL), BF_3 etherate (98%) (0.98 mL, 7.7 mmol) was added dropwise at 25 °C and stirred at the same temperature for 4 h. The reaction mixture was poured into an ice cold aqueous sodium bicarbonate solution (50 mL) and extracted with ethyl acetate (3× 20 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure to give mixture of *cis*- and *trans*-isomers which were separated by means of flash chromatography on a silicagel column using 10% ethylacetate in hexane as eluent to yield 0.55 g of title compound **4a** and 0.52 g of *trans*-isomer **4b** as white solids. Yield: 41%; mp: 84–86 °C; purity by HPLC: 98%; IR (KBr): 1739, 1514, 1236, 1218, 1195, 1139, 1043, and 748 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.58 (s, 3H), 3.15–3.24 (m, 1H), 3.82 (d, J = 11.8 Hz, 2H), 3.87 (s, 3H), 4.02–4.08 (dd, J = 11.8 and 4.7 Hz, 2H), 5.03 (s, 2H), 6.91 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H), 7.32–7.42 (m, 5H); ESI-MS m/z: 360.3 $(M+NH_4)^+$.

6.3.5. Methyl *t*-5-(4-benzyloxyphenyl)-2-methyl-1,3-dioxane-*r*-2-carboxylate (4b)

The latter fractions eluted from the column in previous experiment gave 0.52 g of *trans*-isomer **4b** as white solid. Yield: 39%; mp: 110–112 °C; purity by HPLC: 97%; IR (KBr): 1739, 1514, 1236, 1218, 1195, 1139, 1043, and 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.60 (s, 3H), 2.69–2.71 (m, 1H), 3.86 (s, 3H), 4.04–4.09 (dd, J = 11.9 and 2.3 Hz, 2H), 4.20–4.25 (dd, J = 12 and 3.6 Hz, 2H), 5.06 (s, 2H), 6.94 (d, J = 8.6 Hz, 2H), 7.29–7.44 (m, 7H); ESI-MS m/z: 360.3 $(M+NH_4)^+$.

6.3.6. Methyl *c*-5-(4-hydroxyphenyl)-2-methyl-1,3-dioxane-*r*-2-carboxylate (4c)

To a suspension of Pd/C (10%) (55 mg) in MeOH (5 mL), a solution of **4a** (550 mg, 1.6 mmol) in MeOH (10 mL) and ammonium formate (405 mg, 6.4 mmol) was added and refluxed for 2 h. The reaction mixture was filtered through Celite, and filtrate was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (50 mL), washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure to give title compound **4c** as white solid (400 mg). Yield: 99%; mp: 65–67 °C; purity by HPLC: 99%; IR (KBr): 1724, 1519, 1263, 1028, and 817 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.58 (s, 3H), 3.14–3.23 (m, 1H), 3.81 (d, J = 11.8 Hz, 2H), 3.88 (s, 3H), 4.02–4.13 (dd, J = 11.9 and 4.6 Hz, 2H), 4.98 (br s, 1H), 6.77 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H); ^{13}C NMR: (100 MHz, DMSO-d_6): δ 25.72, 38.43, 52.39, 67.48, 97.51, 115.39, 127.44, 128.56, 156.59, 170.43; ESI-MS m/z: 274.8 $(M+Na)^+$.

6.3.7. Methyl 2-methyl-*c*-5-[4-(5-methyl-2-phenyloxazol-4-ylmethoxy)phenyl]- 1,3-dioxane-*r*-2-carboxylate (6a)

To a solution of **4c** (600 mg, 2.38 mmol) and 4-chloromethyl-5-methyl-2-phenyl-oxazole **5a** (494 mg, 2.38 mmol) in dry DMF (10 mL), K_2CO_3 (657 mg, 4.76 mmol) was added and reaction mixture was stirred at 60 °C for 20 h. Reaction mixture was poured into ice-cold water (20 mL) and extracted with ethyl acetate (3× 20 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (8% ethyl acetate in hexane) to give title compound **6a** as white solid (850 mg). Yield: 84%; mp: 82–84 °C; purity by HPLC: 96%; IR (KBr): 1739, 1610, 1585, 1269, 1234, 1218, 1147, and 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.58 (s, 3H), 2.42 (s, 3H), 3.16–3.25 (m, 1H), 3.83 (d, J = 11.8 Hz, 2H), 3.88 (s, 3H), 4.03–4.12 (dd, J = 11.8 and 4.6 Hz, 2H), 4.96 (s, 2H), 6.96 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 7.42–7.44 (m, 3H), 7.99–8.02 (m, 2H); ESI-MS m/z: 424.2 $(M+H)^+$.

6.3.8. Methyl {2-Methyl-*c*-5-[4-(5-methyl-2-(4-methylphenyl) oxazol-4-ylmethoxy)phenyl]}-1,3-dioxane-*r*-2-carboxylate (6b)

This compound was prepared from **4c** and **5b** by means of a procedure similar to that reported for **6a**. White solid; yield: 90%; mp: 145–147 °C; purity by HPLC: 96%; IR (KBr): 1741, 1515, 1267, 1242, 1215, 1141, 1045, 1012, and 732 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.58 (s, 3H), 2.40 (s, 3H), 2.42 (s, 3H), 3.18–3.21 (m, 1H), 3.82 (d, J = 11.6 Hz, 2H), 3.88 (s, 3H, s), 4.03–4.08 (dd, J = 11.8 and 4.6 Hz, 2H), 5.00 (s, 2H), 6.96 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 7.65 Hz, 2H), 7.95 (d, J = 8.0 Hz, 2H); ESI-MS m/z: 438.2 $(M+H)^+$.

6.3.9. Methyl {2-Methyl-*c*-5-[4-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)phenyl]}-1,3-dioxane-*r*-2-carboxylate (6c)

This compound was prepared from **4c** and **5c** by means of a procedure similar to that reported for **6a**. Thick oil; yield: 57%; purity by HPLC: 91%; IR (Nujol): 1745, 1514, 1218, 1260, 1143, 1049, and 756 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.57 (s, 3H), 2.36 (s, 3H), 2.95 (d, J = 6.6 Hz, 2H), 3.13–3.21 (m, 1H), 3.81 (d, J = 11.8 Hz, 2H), 3.87 (s, 3H, s), 4.01–4.11 (dd, J = 11.8 and 4.7 Hz, 2H), 4.20 (t, J = 6.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 7.40–7.42 (m, 3H), 7.94–7.98 (m, 2H); ESI-MS m/z: 438.2 $(M+H)^+$.

6.3.10. Methyl 2-Methyl-*c*-5-{4-[2-(5-methyl-2-(4-methylphenyl) oxazol-4-yl)ethoxy]-phenyl}-1,3-dioxane-*r*-2-carboxylate (6d)

This compound was prepared from **4c** and **5d** by means of a procedure similar to that used for **6a**. White solid; yield: 42%; mp: 121–123 °C; purity by HPLC: 98%; IR (KBr): 1718, 1515, 1269, 1244, 1045, and 823 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.58 (s, 3H), 2.35 (s, 3H), 2.38 (s, 3H), 2.95 (t, J = 6.6 Hz, 2H), 3.16–3.21 (m, 1H), 3.80 (t, J = 11.9 Hz, 2H), 3.88 (s, 3H), 4.01–4.07 (dd, J = 12.0 and 4.7 Hz, 2H), 4.20 (t, J = 6.7 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.16 Hz, 2H); ESI-MS m/z: 452.2 $(M+H)^+$.

6.3.11. 2-Methyl-*c*-5-[4-(5-methyl-2-phenyloxazol-4-ylmethoxy) phenyl]-1,3-dioxane-*r*-2 carboxylic acid (7a)

To a solution of **6a** (850 mg, 2.0 mmol) in THF (9 mL), MeOH (3 mL) and H_2O (3 mL), $LiOH{\cdot}H_2O$ (168 mg, 4.0 mmol) was added and stirred at 25 °C for 18 h. The reaction mixture was concentrated in vacuo. Twenty millilitres of water were added to the reaction mixture, acidified by HCl and extracted with ethyl acetate (3× 20 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure to give title compound **7a** as white solid. (425 mg) Yield: 51%; mp: 172–174 °C; purity by HPLC: 99%; IR (KBr): 3448, 1710, 1271, 1240, 1215, and 1151 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.61 (s, 3H), 2.46 (s, 3H), 3.02–3.10 (m, 1H), 3.65 (t, J = 11.5 Hz, 2H), 3.71–3.77 (dd, J = 11.7 and 4.8 Hz, 2H), 5.05 (s, 2H, s), 6.88–6.96 (m, 4H), 7.46–7.48 (m, 3H), 8.04–8.07 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 10.46, 26.13, 39.74, 60.75, 68.15, 98.04, 114.83, 126.44, 126.66, 129.11, 129.94, 131.05, 131.26, 147.74, 157.80, 160.89, 172.9; ESI-MS m/z: 410.1 $(M+H)^+$.

6.3.12. {2-Methyl-*c*-5-[4-(5-methyl-2-(4-methylphenyl)oxazol-4-ylmethoxy)phenyl]}-1,3-dioxane-*r*-2-carboxylic acid (7b)

This compound was prepared from **6b** by means of a procedure similar to that used for **7a**. White solid; yield: 90%; mp: 193–195 °C; purity by HPLC: 98%; IR (KBr): 2922, 1735, 1514, 1244,

122, 1145, and 1049 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.61 (s, 3H), 2.40 (s, 3H), 2.45 (s, 3H), 3.03–3.08 (m, 1H), 3.60 (t, J = 11.5 Hz, 2H), 3.69–3.74 (dd, J = 11.6 and 4.0 Hz, 2H), 5.05 (s, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 10.40, 21.14, 26.11, 39.74, 60.67, 68.11, 98.02, 114.79, 123.67, 126.63, 129.10, 129.49, 129.80, 130.37, 141.49, 147.36, 157.79, 161.14, 172.89; ESI-MS m/z: 424.2 $(M+H)^+$.

6.3.13. {2-Methyl-*c*-5-[4-(2-(5-methyl-2-phenyloxazol-4-yl) ethoxy)phenyl]}-1,3-dioxane-*r*-2-carboxylic acid (7c)

This compound was prepared from **6c** by means of a procedure similar to that used for **7a**. Off white solid; yield: 81%; mp: 145–147 °C; purity by HPLC: 98%; IR (KBr): 2964, 2927, 1720, 1550, 1269, 144, 1218, 1110, 1024, and 759 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.63 (s, 3H), 2.40 (s, 3H), 3.06 (t, J = 6.5 Hz, 2H), 3.12–3.21 (m, 1H), 3.88 (t, J = 11.5 Hz, 2H), 3.94–4.01 (dd, J = 11.6 and 4.8 Hz, 2H), 4.17 (t, J = 6.6 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 7.42–7.44 (m, 3H), 7.97–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 10.26, 21.58, 26.03, 39.37, 66.72, 68.36, 98.13, 114.85, 124.12, 126.34, 128.64, 129.59, 131.81, 140.92, 145.25, 158.05, 160.33, 173.13; ESI-MS m/z: 424.2 $(M+H)^+$.

6.3.14. 2-Methyl-*c*-5-{4-[2-(5-methyl-2-(4-methylphenyl) oxazol-4-yl)ethoxy]phenyl}-1,3-dioxane-*r*-2-carboxylic acid (7d)

This compound was prepared from **6d** by means of a procedure similar to that used for **7a**. White solid; yield: 94%; mp: 184–186 °C; purity by HPLC: 99%; IR (KBr): 2925, 1724, 1651, 1515, 1269, 1244, 1218, and 759 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.64 (s, 3H), 2.38 (s, 3H), 2.39 (s, 3H), 3.07 (t, J = 6.5 Hz, 2H), 3.15–3.18 (m, 1H), 3.88 (t, J = 11.5 Hz, 2H), 3.96–4.01 (dd, J = 11.7 and 4.8 Hz, 2H), 4.19 (t, J = 6.6 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 9.96 Hz, 2H), 7.87 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 10.26, 21.58, 25.87, 26.03, 39.37, 66.72, 68.36, 98.13, 114.85, 124.12, 126.34, 128.64, 129.59, 131.81, 140.92, 145.25, 158.05, 160.33, 173.13; ESI-MS m/z: 437.9 $(M+H)^+$.

6.3.15. Diethyl-2-(4-benzyloxybenzyl)malonate (9)

To an ice-cold suspension of NaH (60%, 178 g, 3.7 mol) in THF (1000 mL), diethyl malonate (704 mL, 4.66 mol) was added dropwise over a period of 30 min at 0–10 °C and stirred at the same temperature for 30 min. A solution of 4-benzyloxybenzyl chloride **8** (434 g, 1.864 mol) in THF (500 mL) was added to the reaction mixture at 0–10 °C and stirred at 25 °C for 14 h. The reaction mixture was poured into ice-cold water (2 L) and extracted with ethyl acetate (3× 1000 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure. Excess diethyl malonate was distilled out under vacuum to give tittle compound **9** as thick oil. (525 g) Yield: 79%; purity by HPLC: 90%; IR (Nujol): 1728, 1512, 1217, and 756 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.20 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 6.9 Hz, 3H), 3.15 (d, J = 7.7 Hz, 2H), 3.59 (t, J = 7.9 Hz, 1H), 4.08–4.24 (m, 4H), 5.03 (s, 2H), 6.88 (d, J = 8.55 Hz, 2H), 7.12 (d, J = 8.49 Hz, 2H), 7.31–7.43 (m, 5H); ESI-MS m/z: 357.2 $(M+H)^+$.

6.3.16. 2-(4-Benzyloxybenzyl)propane-1,3-diol (10)

This compound was prepared from **9** by means of a procedure similar to that reported for **3**. White solid (4.0 g). Yield: 47%; mp: 81–82 °C; purity by HPLC: 98%; IR (KBr): 3064, 2922, 1635, 1514, 1245, and 748 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.99–2.06 (m, 3H), 2.57 (d, J = 7.5 Hz, 2H), 3.64–3.70 (dd, J = 10.4 and 7.0 Hz, 2H), 3.78–3.70 (dd, J = 10.5 and 3.9 Hz, 2H), 5.04 (s, 2H), 6.90 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 7.29–7.44 (m, 5H); ESI-MS m/z: 273.2 $(M+H)^+$.

6.3.17. Methyl 5-(4-benzyloxybenzyl)-2-methyl-1,3-dioxane-2-carboxylate (11a)

This compound was prepared from **10** by means of a procedure similar to that described in section **6.4.3** and obtained as a thick oil containing mixture of *cis*- and *trans*-isomers. Separation of these isomers by column chromatography was unsuccessful and the mixture was subjected to debenzylation as described in the following experiment. Yield: 76%; ESI-MS m/z: 357.2 $(M+H)^+$.

6.3.18. Methyl *c*-5-(4-hydroxybenzyl)-2-methyl-1,3-dioxane-*r*-2-carboxylate (11b)

The mixture of isomers **11a** obtained in the previous experiment was subjected to debenzylation by method similar to that used for **4c**. The crude product was recrystallized from a mixture of ethylacetate and hexane (1:2). The first crop yielded pure *cis*-isomer as white solid. Yield: 46%; mp: 119–120 °C; purity: 99% by HPLC; IR (KBr): 1724, 1610, 1267, 1184, and 1099 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50 (s, 3H), 2.27 (s, 3H), 3.46 (t, J = 10.9 Hz, 2H), 3.84 (s, 3H), 3.86–3.91 (dd, J = 11.8 and 3.3 Hz, 2H), 5.02 (s, 1H), 6.74 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 2.3 Hz, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 25.64, 32.81, 35.27, 52.23, 67.08, 97.40, 115.15, 127.90, 129.17, 155.64, and 170.43; ESI-MS m/z: 288.9 $(M+Na)^+$.

6.3.19. Methyl *t*-5-(4-hydroxybenzyl)-2-methyl-1,3-dioxane-*r*-2-carboxylate (11c)

The filtrate from the previous experiment on subjecting to repeated crystallizations from a mixture of ethylacetate and hexane (1:1) for 2 times gave the *trans*-isomer as white solid. Yield: 30%; mp: 62–64 °C; purity by HPLC: 98%; IR (KBr): 3373, 2972, 1710, 1517, 1442, 1265, 1211, 1145, 1055, and 956 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.51–1.57 (m, 1H), 1.59 (s, 3H), 2.93 (d, J = 8.0 Hz, 2H), 3.76 (d, J = 12.0 Hz, 2H), 3.92–3.95 (dd, J = 10.8 and 1.6 Hz, 2H), 5.02 (s, 1H), 6.77 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.64, 33.85, 34.39, 52.23, 65.06, 97.97, 115.15, 129.89, 30.16, 155.56, 170.59; ESI-MS m/z: 288.9 $(M+Na)^+$.

6.3.20. Methyl 2-methyl-*c*-5-[4-(5-methyl-2-phenyloxazol-4-ylmethoxy)benzyl]-1,3-dioxane-*r*-2-carboxylate (12a)

This compound was prepared from **11b** and **5a** by means of a procedure similar to that used for **6a**. Thick oil; yield: 62%; purity by HPLC: 95%; IR (Nujol): 1741, 1508, 1262,116, and 754 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.51 (s, 3H), 2.26–2.28 (m, 3H), 2.42 (s, 3H), 3.46 (t, J = 10.8 Hz, 2H), 3.74–76 (dd, J = 11.8 and 3.6 Hz, 2H), 3.82 (s, 3H), 4.96 (s, 2H), 6.93 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 7.43–7.45 (m, 3H), 8.00–8.03 (m, 2H); ESI-MS m/z: 438.2 $(M+H)^+$.

6.3.21. Methyl 2-methyl-*c*-5-[4-(5-methyl-2-(4-methylphenyl) oxazol-4-ylmethoxy)benzyl]-1,3-dioxane-*r*-2-carboxylate (12b)

This compound was prepared from **11b** and **5b** by means of a procedure similar to that used for **6a**. Thick oil; yield: 97%; purity by HPLC: 97%; IR (Nujol): 1745, 1500, 1244, 1141, 1116, and 1022 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.58 (s, 3H), 2.20–2.2 (m, 3H), 2.39 (s, 3H), 2.41 (s, 3H), 3.46 (t, J = 10.9 Hz, 2H), 3.84 (s, 3H), 3.86–3.90 (m, 2H), 4.95 (s, 2H), 6.92 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 7.90 (d, J = 8.1 Hz, 2H); ESI-MS m/z: 452.4 $(M+H)^+$.

6.3.22. Methyl 2-methyl-*c*-5-[4-{2-(5-methyl-2-phenyloxazol-4-yl)ethoxy}benzyl]-1,3-dioxane-*r*-2-carboxylate (12c)

This compound was prepared from **11b** and **5c** by means of a procedure similar to that reported for **6a**. Thick oil; yield: 76%; pur-

ity by HPLC: 96%; IR (Nujol): 1732, 1537, 1217, 1188, 1143, and 785 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.49 (s, 3H), 2.27 (s, 3H), 2.32 (s, 3H), 2.96 (t, J = 6.7 Hz, 2H), 3.45 (t, J = 10.4 Hz, 2H), 3.83–3.90 (m, 5H), 4.21 (t, J = 6.7 Hz, 2H), 6.73–6.75 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 7.39–7.44 (m, 3H), 7.97 (m, 1H); ESI-MS m/z: 452.0 $(M+H)^+$.

6.3.23. Methyl 2-methyl-*c*-5-{4-[2-(5-methyl-2-(4-methyl-phenyl)oxazol-4-yl)ethoxy]benzyl}-1,3-dioxane-*r*-2-carboxylate (12d)

This compound was prepared from **11b** and **5d** by means of a procedure similar to that reported for **6a**. Thick oil; yield: 79%; purity by HPLC: 95%; IR (Nujol): 1747, 1514, 1245, 1217, 1190, 1167, and 785 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.49 (s, 3H), 2.04 (s, 3H), 2.35 (s, 3H), 2.38 (s, 3H), 2.95 (t, J = 6.7 Hz, 2H), 3.45 (t, J = 9.0 Hz, 2H), 3.84–3.90 (m, 5H), 4.20 (t, J = 13.5 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.2 Hz, 2H); ESI-MS m/z: 466.1 $(M+H)^+$.

6.3.24. Methyl 2-methyl-*c*-5-{4-[3-(5-methyl-2-(4-methylphenyl)oxazol-4-yl)propoxy]benzyl}-1,3-dioxane-*r*-2-carboxylate (12e)

This compound was prepared from **11b** and **5e** by means of a procedure similar to that reported for **6a**. Thick oil; yield: 83%; purity by HPLC: 92%; IR (Nujol): 1747, 1512, 1245, 1217, 1143, 1116, and 786 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50 (s, 3H), 2.09–2.18 (m, 2H), 2.25 (s, 3H), 2.27 (s, 3H), 2.38 (s, 3H), 2.68 (t, J = 7.2 Hz, 2H), 3.46 (t, J = 11.3 Hz, 2H), 3.84 (s, 3H), 3.86–3.96 (m, 4H), 6.81 (d, J = 8.5 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H); ESI-MS m/z: 480.2 $(M+H)^+$.

6.3.25. Methyl 2-methyl-*c*-5-{4-[5-methyl-2-(5-methylthiophen-2-yl)oxazol-4-ylmethoxy]benzyl}-1,3-dioxane-*r*-2-carboxylate (12f)

This compound was prepared from **11b** and **5f** by means of a procedure similar to that reported for **6a**. Thick oil; yield: 80%; purity by HPLC: 95%; IR (Nujol): 1747, 1591, 1234, 1213, and 1087 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.62 (s, 3H), 2.22–2.28 (m, 3H), 2.38 (s, 3H), 2.52 (s, 3H), 3.46 (t, J = 11.0 Hz, 2H), 3.84 (s, 3H), 3.86–3.91 (dd, J = 12.0 and 3.6 Hz, 2H), 4.92 (s, 2H), 6.74 (d, J = 2.8 Hz, 1H), 6.90 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 3.5 Hz, 1H); ESI-MS m/zs: 458.3 $(M+H)^+$.

6.3.26. Methyl 2-methyl-*c*-5-{4-[2-(5-methyl-2-(5-methylthiophen-2-yl)oxazol-4-yl)ethoxy]benzyl}-1,3-dioxane-*r*-2-carboxylate (12g)

This compound was prepared from **11b** and **5g** by means of a procedure similar to that reported for **6a**. Thick oil; yield: 55%; purity by HPLC: 94%; IR (Nujol): 1747, 1512, 1245, 1218, 1116, and 758 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.49 (3H, s), 2.21–2.26 (3H, m), 2.32 (s, 3H), 2.51 (s, 3H), 2.92 (t, J = 6.5 Hz, 2H), 3.42–3.48 (m, 2H), 3.82–3.90 (m, 5H), 4.17 (t, J = 6.6 Hz, 2H), 6.74 (d, J = 2.8 Hz, 1H), 6.90 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 3.5 Hz, 1H); ESI-MS m/z: 472.1 $(M+H)^+$.

6.3.27. Methyl *c*-5-[4-(2-*tert*-Butyl-5-methyloxazol-4-ylmethoxy)benzyl]-2-methyl-1,3-dioxane-*r*-2-carboxylate (12h)

This compound was prepared from **11b** and **5h** by means of a procedure similar to that reported for **6a**. Thick oil; yield: 95%; purity by HPLC: 95%; IR (Nujol): 1743, 1612, 1566, 1238, 1217, 1118, and 756 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38 (s, 9H), 1.51 (s, 3H), 2.12 (d, J = 7.2 Hz, 2H), 2.22–2.26 (m, 1H), 2.33 (s, 3H), 3.43 (t, J = 11.3 Hz, 2H), 3.72–3.80 (dd, J = 11.8 and 4.1 Hz, 2H), 3.84 (s, 3H), 4.90 (s, 2H), 6.82 (d, J = 8.3 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H); ESI-MS m/z: 418.1 $(M+H)^+$.

6.3.28. Methyl *c*-5-[4-{2-(2-*tert*-Butyl-5-methyloxazol-4-yl)ethoxy}benzyl]-2-methyl-1, 3-dioxane-*r*-2-carboxylate (12I)

This compound was prepared from **11b** and **5i** by means of a procedure similar to that reported for **6a**. Thick oil; yield: 97%; purity by HPLC: 94%; IR (Nujol): 1735, 1512, 1251, 1143, 1109, and 756 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35 (s, 9H), 1.54 (s, 3H), 2.24 (s, 3H), 2.27 (s, 3H), 2.89–2.96 (dd, J = 15.0 and 8.1 Hz, 2H), 3.50 (t, J = 9.5 Hz, 2H), 3.84–3.89 (m, 5H), 4.12 (t, J = 6.7 Hz, 2H), 6.78 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 8.1 Hz, 2H); ESI-MS m/z: 432.2 $(M+H)^+$.

6.3.29. 2-Methyl-*c*-5-[4-(5-methyl-2-phenyloxazol-4-ylmethoxy)benzyl]-1,3-dioxane-*r*-2-carboxylic acid (13a)

To a solution of **12a** (1.0 g, 2.2 mmol.) in EtOH (10 mL), a solution of NaOH (176 mg, 4.4 mmol) in H_2O (5 mL) was added and stirred at 25 °C for 18 h. The reaction mixture was concentrated in vacuo. Twenty millilitres water were added to the residue, acidified by HCl and extracted with ethyl acetate (3× 20 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure to give title compound **13a** as off-white solid. (0.78 g) Yield: 85%; mp: 170–171 °C; purity by HPLC: 98%; IR (KBr): 2930, 1720, 1512, 1271, 1236, 1124, and 1056 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.52 (s, 3H), 2.21–2.24 (m, 3H), 2.43 (s, 3H), 3.60 (t, J = 10.8 Hz, 2H), 3.83–86 (dd, J = 11.8 and 3.6 Hz, 2H), 4.96 (s, 2H), 6.93 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 7.43–7.45 (m, 3H), 8.00–8.03 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 9.96, 25.54, 32.89, 34.38, 61.38, 67.09, 97.78, 114.98, 125.59, 126.87, 129.05, 129.63, 129.99, 130.30, 132.04, 147.36, 156.56, 158.82, 171.32; ESI-MS m/z: 424.3 $(M+H)^+$.

6.3.30. 2-Methyl-*c*-5-[4-(5-methyl-2-(4-methylphenyl)oxazol-4-ylmethoxy)benzyl]-1,3-dioxane-*r*-2-carboxylic acid (13b)

This compound was prepared from **12b** by means of a procedure similar to that reported for **13a**. White solid; yield: 95%; mp: 197–198 °C; purity by HPLC: 99%; IR (KBr): 2929, 1759, 1610, 1502,1286, 1226, 1182, and 827 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.32 (s, 3H), 2.09–2.13 (m, 1H), 2.27 (d, J = 6.9 Hz, 2H), 2.36 (s, 3H), 2.42 (s, 3H), 3.42 (t, J = 11.4 Hz, 2H), 3.69-3.74 (dd, J = 11.6 and 4.1 Hz, 2H), 4.94 (s, 2H), 6.94 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.1 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 9.93, 20.96, 25.52, 32.87, 34.86, 61.38, 67.07, 97.56, 114.64, 124.24, 125.57, 129.62, 130.58, 131.85, 140.15, 146.95, 156.65, 158.98, 171.31; SI-MS m/z: 438.4 $(M+H)^+$.

6.3.31. 2-Methyl-*c*-5-[4-{2-(5-methyl-2-phenyloxazol-4-yl)ethoxy}benzyl]-1,3-dioxane-*r*-2-carboxylic acid (13c)

This compound was prepared from **12c** by means of a procedure similar to that reported for **13a**. Thick oil; yield: 32%; purity by HPLC: 97%; IR (Nujol): 2925, 1732, 1512, 1245, 1217, and 1145 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.54 (s, 3H), 2.29 (s, 3H), 2.37 (s, 3H), 2.97 (t, J = 6.7 Hz, 2H), 3.51–3.55 (m, 2H), 3.89–3.93 (dd, J = 12.6 and 4.2 Hz, 2H), 4.21 (t, J = 6.7 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 7.40–7.43 (m, 3H), 7.95–7.99 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 9.78, 25.54, 32.88, 34.88, 66.07, 67.09, 97.79, 114.33, 125.43, 126.92, 128.69, 129.60, 129.96, 130.27, 132.95, 145.01, 156.72, 158.38, 171.49; ESI-MS m/z: 438.2 $(M+H)^+$.

6.3.32. 2-Methyl-*c*-5-{4-[2-(5-methyl-2-(4-methylphenyl)oxazol-4-yl)ethoxy]benzyl}-1,3-dioxane-*r*-2-carboxylic acid (13d)

This compound was prepared from **12d** by means of a procedure similar to that reported for **13a**. Off-white solid; yield: 31%; mp: 129–131 °C; purity by HPLC: 99%; IR (KBr): 2923, 1718, 1500, 1247, 1217, and 1143 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.54 (s, 3H), 2.27 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.98 (t, J = 6.7 Hz, 2H),

3.52 (t, J = 10.7 Hz, 2H), 3.89–3.93 (dd, J = 12.6 and 4.2 Hz, 2H), 4.20 (t, J = 6.7 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 8.1 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 9.78, 20.94, 25.51, 32.84, 34.88, 66.08, 67.01, 97.56, 114.33, 124.56, 125.41, 129.60, 129.97, 130.26, 132.50, 139.76, 144.59, 156.65, 158.54, 171.32; ESI-MS m/z: 452.2 $(M+H)^+$.

6.3.33. 2-Methyl-*c*-5-{4-[3-(5-methyl-2-(4-methylphenyl) oxazol-4-yl)propoxy]benzyl}-1,3-dioxane-*r*-2-carboxylic acid (13e)

This compound was prepared from **12e** by means of a procedure similar to that reported for **13a**. White solid; yield: 73%; mp: 126–128 °C; purity by HPLC: 97%; IR (KBr): 2922, 1716, 1556, 1469, 1244, 1215, 1120, and 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.56 (s, 3H), 2.05–2.15 (m, 2H), 2.27–2.29 (m, 6H), 2.38 (s, 3H), 2.72 (t, J = 7.2 Hz, 2H), 3.55 (t, J = 10.8 Hz, 2H), 3.89-3.97 (m, 4H), 6.80 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 7.22–7.26 (m, 2H), 7.84 (d, J = 8.2 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 9.62, 20.93, 21.42, 25.53, 27.98, 32.87, 34.89, 66.33, 67.09, 97.56, 114.29, 124.65, 125.38, 129.52, 130.12, 134.89, 139.66, 143.39, 157.02, 158.50, 171.31; ESI-MS m/z: 466.2 $(M+H)^+$.

6.3.34. 2-Methyl-*c*-5-{4-[5-methyl-2-(5-methylthiophen-2-yl) oxazol-4-ylmethoxy]benzyl}-1,3-dioxane-*r*-2-carboxylic acid (13f)

This compound was prepared from **12f** by means of a procedure similar to that reported for **13a**. Pale yellow solid; yield: 64%; mp: 172–173 °C; purity by HPLC: 99%; IR (KBr): 2923, 1718, 1508, 1259, 1224, and 1122 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.54 (s, 3H), 2.21–2.28 (m, 3H), 2.39 (s, 3H), 2.52 (s, 3H), 3.49 (t, J = 11.1 Hz, 2H), 3.89–3.93 (dd, J = 12.6 and 4.2 Hz, 2H), 4.96 (s, 2H), 6.75 (d, J = 2.8 Hz, 1H), 6.91 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 3.6 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 9.86, 14.95, 25.53, 32.89, 34.86, 61.23, 67.08, 97.56, 114.64, 126.74, 127.54, 129.62, 130.61, 131.68, 142.95, 146.49, 155.13, 156.61, 171.31; ESI-MS m/z: 444.2 $(M+H)^+$.

6.3.35. 2-Methyl-*c*-5-{4-[2-(5-methyl-2-(5-methylthiophen-2-yl) oxazol-4- yl)ethoxy]benzyl}-1,3-dioxane-*r*-2-carboxylic acid (13g)

This compound was prepared from **12g** by means of a procedure similar to that reported for **13a**. Off-white solid; yield: 46%; mp: 122–124 °C; purity by HPLC: 96%; IR (KBr): 2922, 1718, 1514, 1249, and 1118 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.55 (s, 3H), 2.20–2.26 (m, 3H), 2.34 (s, 3H), 2.51 (s, 3H), 2.95–2.97 (t, J = 6.7 Hz, 2H), 3.5 (t, J = 10.7 Hz, 2H), 3.90 (d, J = 9.9 Hz, 2H), 4.18 (t, J = 6.3 Hz, 2H), 6.73 (d, J = 2.8 Hz, 1H), 6.80 (d, J = 8.2 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 3.6 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 9.71, 14.93, 25.55, 32.90, 34.89, 66.01, 67.10, 97.58, 114.33, 126.72, 127.01, 127.20, 129.60, 130.27, 132.40, 142.41, 144.17, 154.73, 156.71, 171.35; ESI-MS m/z: 458.2 $(M+H)^+$.

6.3.36. *c*-5-[4-(2-*tert*-Butyl-5-methyloxazol-4-ylmethoxy) benzyl]-2-methyl-1,3-dioxane-*r*-2-carboxylic acid (13h)

This compound was prepared from **12h** by means of a procedure similar to that reported for **13a**. White solid; yield: 49%; mp: 117–118 °C; purity by HPLC: 99%; IR (KBr): 2968, 1735, 1514, 1217, 1120, and 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 9H), 1.51 (s, 3H), 2.12 (d, J = 7.2 Hz, 2H), 2.22–2.26 (m, 1H), 2.33 (s, 3H), 3.43 (t, J = 11.3 Hz, 2H), 3.72–3.80 (dd, J = 11.8 and 4.1 Hz, 2H), 4.90 (s, 2H), 6.82 (d, J = 8.3 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 10.35, 25.84, 28.53, 33.69, 33.86, 34.77, 61.63, 68.10, 98.24, 114.97, 129.39, 129.64, 130.66, 146.63, 157.28, 170.17, 173.09; ESI-MS m/z: 404.1 $(M+H)^+$.

6.3.37. *c*-5-[4-{2-(2-*tert*-Butyl-5-methyloxazol-4-yl)ethoxy} benzyl]-2-methyl-1, 3-dioxane-*r*-2-carboxylic acid (13i)

This compound was prepared from **12i** by means of a procedure similar to that reported for **13a**. Off-white solid; yield: 60%; mp: 140–141 °C; purity by HPLC: 98%; IR (KBr): 2960, 2923, 1718, 1514, 1249, 1120, and 767 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9H), 1.54 (s, 3H), 2.24 (s, 3H), 2.27 (s, 3H), 2.89–2.96 (dd, J = 15.0 and 8.1 Hz, 2H), 3.50 (t, J = 9.5 Hz, 2H), 3.84–3.89 (m, 2H), 4.12 (t, J = 6.7 Hz, 2H), 6.78 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.45, 25.84, 28.83, 33.69, 33.86, 34.87, 61.43, 68.10, 98.24, 114.97, 129.39, 129.64, 130.66, 146.63, 157.28, 170.17, 173.09; ESI-MS m/z: 418.1 $(M+H)^+$.

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