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Discovery of a highly orally bioavailable *c*-5-[6-(4-Methanesulfonyloxyphenyl)-hexyl]-2-methyl-1,3-dioxane-*r*-2-carboxylic acid as a potent hypoglycemic and hypolipidemic agent ☆

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ABSTRACT

A series of novel 1,3-dioxane-2-carboxylic acid derivatives containing alkyl chain tether and substituted phenyl group as a lipophilic tail have been prepared as agonists of PPARα and γ. *c*-5-[6-(4-Methanesulfonyloxyphenyl)hexyl]-2-methyl-1,3-dioxane-*r*-2-carboxylic acid **13c** exhibited potent hypoglycemic and lipid lowering activity with high oral bioavailability in animal models.

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Prevalence of Type 2 diabetes and adverse cardiovascular conditions associated with this disease are increasing world wide and are considered as a major threat to human health in the 21st century.[1] The defects in lipid and carbohydrate metabolism are the main causes of this disease and the nuclear hormone receptors PPARα and PPARγ agonists have shown therapeutic benefits in the treatment of diabetes and dyslipidemia.[2] PPARγ has been identified as a key regulator for insulin sensitivity, and two PPARγ agonists, **Rosiglitazone** and **Pioglitazone** have demonstrated clinical success in the treatment of Type 2 diabetes. Unfortunately, these agents are found to cause adverse effects including weight gain, edema and anemia in both animal models and humans. Fibrate class of compounds have been shown to lower plasma lipid, triglyceride (TG), levels and have been in clinical use for the treatment of dyslipidemia. However these are poor activators of PPARα and need high doses to exert therapeutic effect. Treatment with PPARγ and PPARα dual agonists found to be useful in the treatment of hyperglycemia and hyperlipidemia in animal models and a number of PPARα/γ dual agonists have been discovered and evaluated by different research groups.[3] Till date none of these dual agonists are marketed including **Farglitazar**,[4] **Ragaglitazar**,[5] **Tesaglitazar**[6] and **Muraglitazar**[7] which were dropped from late clinical development due to adverse effects like edema, carcinogencity in rodent toxicity models, heart failure or cardiovascular deaths and elevated serum creatinine. The unsuccessful efforts to develop dual agonist and recent research findings that activation of PPARα lower triglycerides, elevate HDL and exert insulin-sensitizing effects[8] led to the discovery of potent and selective activators of PPARα as remedy for disorders mediated by lipid and carbohydrate metabolism. A potent and selective PPARα agonist **NS-220**[9] is reported to exert hypoglycemic and lipid modulating effects in animal models but the further development of this compound is discontinued for unknown reasons. Another compound **K-111**,[10] a relatively weak PPARα agonist is presently undergoing clinical trials for the treatment of Type 2 diabetes. As a part of our research in the field of PPAR,[11] we have recently reported a series of oxazole containing 1,3-dioxane-2-carboxylic acid derivatives as PPARα/γ dual agonist.[12] In this communication we report a series of novel 1,3-dioxane carboxylic acid derivatives designed by the hybridization of the compounds **NS-220** and **K-111** and mimicking **Tesaglitazar** (Fig. 1) in order to optimize the lead candidate.

The synthesis of compounds **7a–e** is outlined in Scheme 1. Starting materials **1a–e**, procured from commercial sources were reduced initially with Zn/Hg to compounds **2a–e** which were further reduced with $LiAlH_4$ to yield the hydroxy compounds

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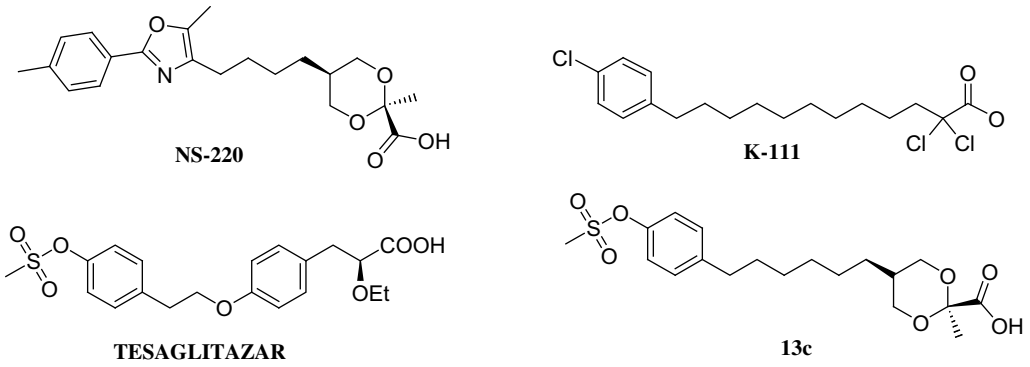
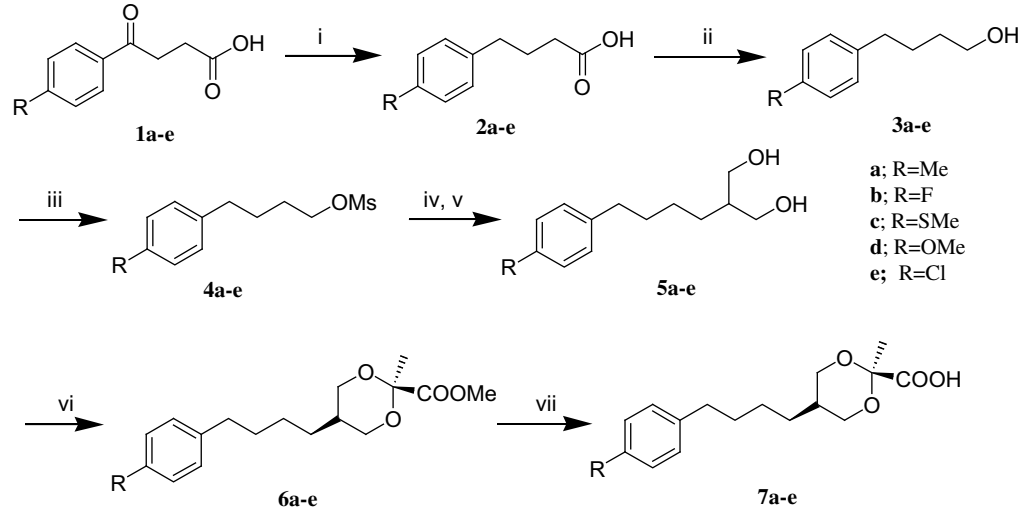
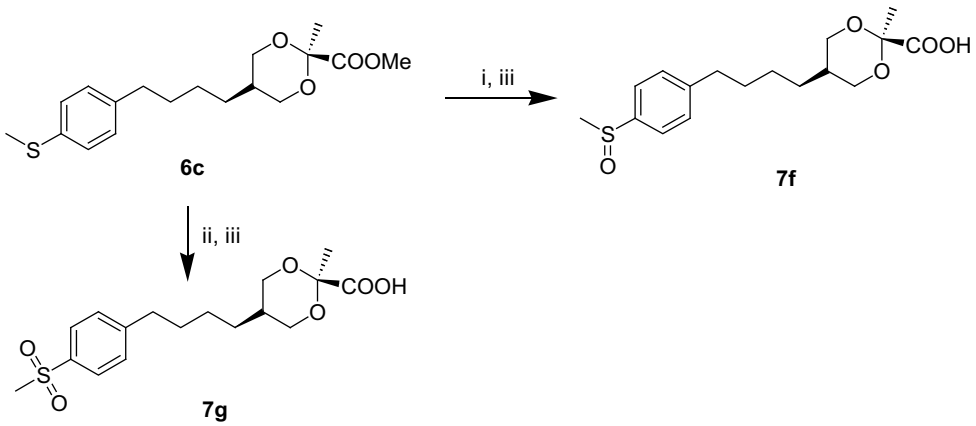


Figure 1. Structures of PPAR agonists.



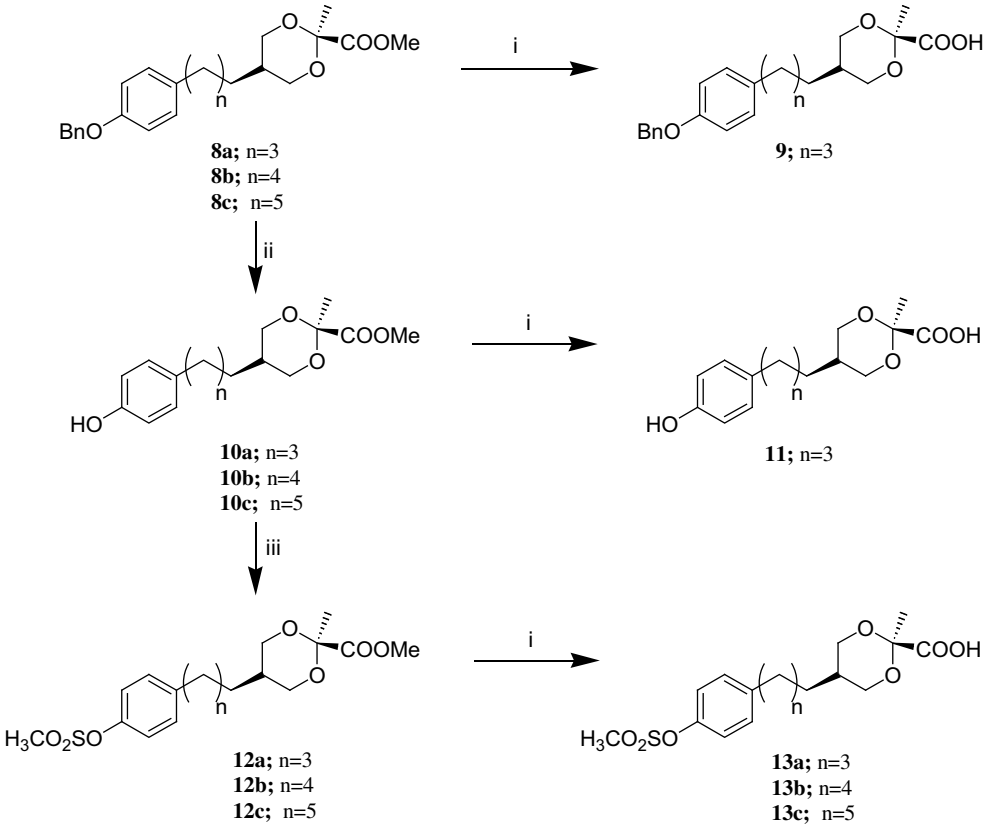
Scheme 1. Reagents and conditions: (i) Zn/Hg, Toluene, AcOH, H_2O, reflux, 4 h; (ii) $LiAlH_4$, THF, 0–10 °C, 1 h; (iii) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0–10 °C, 30 min; (iv) diethyl malonate, NaH, THF, 60 °C, 48 h; (v) $LiAlH_4$, THF, 0-10 °C, 2 h; (vi) BF_3·etherate, methyl pyruvate, CH_3CN, 25 °C, 2 h; (vii) $LiOH.H_2O$, H_2O, THF, MeOH, 25 °C, 18 h.

3a–**e**. These compounds (**3a**–**e)** were converted to their corresponding mesylate derivatives (**4a**–**e)** and treated with diethylmalonate in the presence of sodium hydride. The diesters so obtained were reduced with $LiAlH_4$ to diols **5a**–**e**. These diols when reacted with methylpyruvate in the presence of borontrifluoride etherate in acetonitrile yielded the esters as a mixture of diastereomeric isomers. The mixture was separated by chromatography to get the *cis*-isomers **6a**–**e** which showed a chemical shift pattern in ^1H NMR identical to that of the other *cis* derivatives reported.[13] These esters **6a**–**e** were hydrolyzed using aqueous NaOH to obtain the acids **7a**–**e**. Compounds **7f** and **7g** were synthesized as illustrated in Scheme 2. Sulfanyl derivative **6c** when treated with 1.2 molar equivalent of *m*-CPBA gave corresponding sulfinyl derivative which on hydrolysis gave the acid



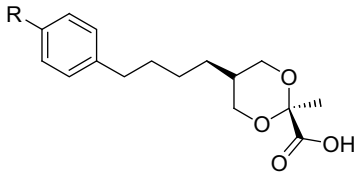
Scheme 2. Reagents and conditions: (i) *m*-CPBA (1.2 equiv), $CHCl_3$, 0–10 °C, 30 min; (ii) *m*-CPBA (3 equiv), $CHCl_3$, 25 °C, 1 h; (iii) LiOH, H_2O, THF, MeOH, 25 °C, 18 h.

7f where as the same compound **6c** on treatment with 3 molar equivalents of *m*-CPBA gave the sulfonyl derivative which upon hydrolysis yielded the acid **7g**. The synthesis of compounds **9**, **11**, and **13a–c** was as illustrated in Scheme 3. Compounds **8a–**



Scheme 3. Reagents and conditions: (i) LiOH, H_2O, THF, MeOH, 25 °C, 18 h; (ii) $HCOONH_4$, Pd/C (10%), MeOH, reflux, 2 h; (iii) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0–10 °C, 30 min.

Table 1
In vitro hPPAR transactivation and TG reducing activity of compounds **7a–g**, **9**, **11**, and **13a**



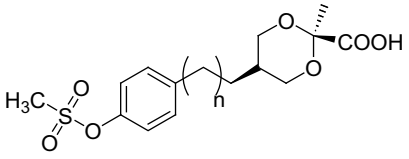
Compound	R	hPPAR transactivation[a,b]			% Change in TG in SAM[c]
		α (10 μM)	γ (0.2 μM)	δ (0.2 μM)	
7a	Me	3.2	1.5	1.1	−22
7b	F	2.3	2.1	1.2	−9
7c	SMe	4	1.9	1.9	−14
7d	OMe	2.5	1.2	1.2	−11
7e	Cl	2.6	2.2	2.2	−10
7f	SOMe	2	1.8	1.8	−12
7g	SO_2Me	1	2.2	2.2	−7
9	OBn	2.3	1.0	1.0	−25
11	OH	1.2	1.4	1.4	−15
13a	OSO_2Me	3.0	1.0	1.0	−32
Vehicle		1.0	1.0	1.0	0.0
WY-14643		3.3	ND	ND	ND
Rosiglitazone		ND	10.2	ND	ND
GW-501516		ND	ND	5.6	

[a] HepG2 cells were transfected with pSG5 expression vector containing the cDNA of hPPARα or hPPARγ or hPPARδ and cotransfected with PPRE3-TK-luc. The Luciferase activity was determined using commercial fire-fly luciferase assay and β-galactosidase activity was determined in ELISA reader. Activities are presented by fold induction of PPARα and γ activation. IA denotes inactive.

[b] In hPPARδ transactivation assay, any of these compounds did not show any activation above basal level.

[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.

Table 2
In vitro hPPAR transactivation and TG reducing activity of compounds **13a–c**



Compound	*n*	hPPAR transactivation EC_{50} (μM)		% Change in TG in SAM
		α	γ	
13a	3	20	IA	−32
13b	4	2.5	IA	−28
13c	5	2	15	−71
NS-220		0.05	7	−67
Tesaglitazar		0.82	0.013	−79

Table 3
Hypoglycemic and hypolipidemic activities of compound **13c** in *db/db* mice[a]

Compound	Dose (mg/kg/day)	% Change	
		TG	PG
13c	3	−50	−53
NS-220	3	−54	−44
Tesaglitazar	3	−60	−54

[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.

Table 4
Hypolipidemic activity of compound **13c** in HC fed SD rats[a]

Compound	Dose (mg/kg/day)	% Change			
		TG	TC	LDL-C	HDL-C
13c	3	−63	−56	−46	51
NS-220	3	−54	−49	−68	88
Tesaglitazar	3	−51	−59	−31	18

[a] Male Sprague–Dawley (SD) rats were fed with diet containing high cholesterol for 15 days then dosed with vehicle or the indicated doses of test compound daily for 4 days by oral gavage. Serum triglycerides (TG), total cholesterol (TC), LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C) were measured. Values reported are % change versus control group.

Table 5
Mean pharmacokinetic parameters[a] of **13c** in fasted male wistar rat

Compound	Route	Dose (mg/kg)	T_{max} (h)	C_{max} (μg/mL)	$T_{1/2}$ (h)	AUC(0-∞) (h μg/mL)
13c	Oral	30	4(±0.0)	127(±4.6)	12(±0.9)	1491(±78)
NS-220	Oral	30	0.67(±0.0)	41(±3.8)	1.5(±0.3)	99(±5.2)

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

c are prepared following the procedures similar to those described in Scheme 1. Compound **8a** was hydrolyzed to obtain the compound **9** where as the compounds **8a–c** were debenzylated under hydrogen transfer reaction condition to yield the compounds **10a–c**. Compound **10a** was hydrolyzed to compound **11** while **10a–c** were treated with mathanesulfonyl chloride to obtain the compounds **12a–c** which were subsequently hydrolyzed to compounds **13a–c**.

The newly synthesized compounds[14] have been screened for hPPARα, γ and δ agonistic activity by using PPAR receptor transfected HepG2 cells. **WY-14643**, **Rosiglitazone** and **GW501516** were used as PPARα, γ and δ controls, respectively. Initial compounds **7a–g**, **9**, **11**, and **13a** are designed by hybridizing the structures of **NS-220** and **K-111** wherein the phenyl ring is connected with 1,3-dioxane acidic head with an alkyl tether. Phenyl ring has been substituted at para-position as the activity of these compounds is sensitive to substituent at this position. In vitro hPPAR transactivation is reported as fold induction and their ability to reduce plasma triglycerides (TG) in male *swiss albino mice* (SAM) which is a moderately hyperlipidemic model and the results are shown in Table 1. These results reveal that the substitution at para-position on the phenyl ring contributes significantly to the in vitro as well as in vivo triglyceride lowering activity of these compounds. Based on these results **13a** was selected for further modifications. We fixed the tail group as *para*-methanesulfonyloxy phenyl group and opted to optimize the tether length. Compounds **13b** and **13c** were synthesized by elongating the tether length to pentamethylene and hexamethylene, respectively. PPAR in vitro activities of these compounds (**13b–c**) and their TG lowering activity in SAM model are summarized in Table 2. Compound **13b** containing pentamethylene chain as tether found inferior to **13a** but surprisingly compound **13c** containing hexamethylene chain as tether reduced plasma TG significantly (71%). The transient transactivation results of these compounds are reported as EC_{50} (Table 2) which shows that the compound **13c** is a moderate activator of PPAR. Having surprised and encouraged with the initial results of compound **13c**, we evaluated it in *db/db* mice and high cholesterol fed Sprague–Dawley rats (HC fed SD rats). In *db/db* mice model the compound **13c** showed excellent plasma glucose and TG reductions which are comparable to **NS-220** (Table 3). In HC fed SD rat model the same compound exhibited excellent reduction in TG and cholesterol superior to **NS-220** (Table 4). To further understand and to draw correlation between moderate in vitro potency and high in vivo efficacy of compound **13c** we evaluated its pharmacokinetic parameters which are presented in Table 5. Compound **13c** showed C_{max} of 127 μg/mL and an AUC of 1491 h μg/mL when administered orally to male wistar rat at a dose of 30 mg/kg body weight. These results clearly established the compound **13c** as highly efficacious and bioavailable hypoglycemic and hypolipidemic agent with moderate in vitro potency and this compound is currently undergoing pre-clinical toxicity studies in order to evaluate the other effects of this compound in animal models.

In summary *c*-5-[(phenyl)-alkyl]-2-methyl-1,3-dioxane-*r*-2-carboxylic acid derivatives have been prepared with substitutions on phenyl ring and are evaluated in vitro for their PPAR agonistic potential followed by in vivo hypoglycemic and hypolipidemic activities. Lead compound *c*-5-[6-(4-Methanesulfonyloxyphenyl)hexyl]-2-methyl-1,3-dioxane-*r*-2-carboxylic acid **13c** showed excellent hypoglycemic and hypolipidemic activities with very modest in vitro potency and has exhibited high oral bioavailability.

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14. Spectroscopic analysis of the compounds **7a**–**7g**, **9**, **11**, **13a**–**13c**:**7a**: *2-Methyl-c-5-(4-(4-methylphenyl)-butyl)-1,3-dioxane-r-2-carboxylic acid*; White solid; mp: 111–113 °C; Yield: 86%; Purity: 99% by HPLC; IR (KBr): 3003, 2923, 1716, 1284, 1207, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.02–1.09 (m, 2H), 1.23–1.31 (m, 2H), 1.51–1.64 (m, 5H), 1.95–2.05 (m, 1H), 2.31 (s, 3H), 2.54 (t, *J* = 7.5 Hz, 2H), 3.44 (t, *J* = 11.6 Hz, 2H), 3.94–3.99 (dd, *J* = 11.8 and 4.6 Hz, 2H), 7.01–7.09 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.63, 25.34, 25.63, 27.38, 31.24, 32.92, 34.54, 67.32, 97.76, 128.11, 128.61, 134.44, 139.04, 171.46; ESI-MS *m*/*z*: 310.2 $(M+NH_4)^+$.**7b**: *c-5-[4-(4-Fluoro-phenyl)-butyl]-2-methyl-1,3-dioxane-r-2-carboxylic acid*: White solid; mp: 90–92 °C; Yield: 88%; Purity: 98% by HPLC; IR (KBr): 3020, 2923, 2852, 1716, 1284, 1209, 806 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.02–1.10 (m, 2H), 1.23–1.31 (m, 2H), 1.51–1.64 (m, 5H), 1.95–2.05 (m, 1H), 2.55 (t, *J* = 7.5 Hz, 2H), 3.44 (t, *J* = 11.5 Hz, 2H), 3.94–3.99 (dd, *J* = 11.8 and 4.6 Hz, 2H), 6.94 (t, *J* = 8.6 Hz, 2H), 7.06–7.14 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.33, 25.65, 27.47, 31.41, 33.05, 33.93, 67.07, 98.07, 115.01, 128.64, 132.14, 155.25, 171.60; ESI-MS *m*/*z*: 313.6 $(M+NH_4)^+$.**7c**: *2-Methyl-c-5-[4-(4-methylsulfanyl-phenyl)-butyl]-1,3-dioxane-r-2-carboxylic acid*: White solid; mp: 103–105 °C; Yield: 90%; Purity: 98% by HPLC; IR (KBr): 3040, 2931, 1720, 1492, 1284, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.02–1.09 (m, 2H), 1.25–1.33 (m, 2H), 1.51–1.61 (m, 5H), 1.98–2.02 (m, 1H), 2.46 (s, 3H), 2.51 (t, *J* = 7.6 Hz, 2H), 3.40 (t, *J* = 11.8 Hz, 2H), 3.94–3.99 (dd, *J* = 11.8 and 4.4 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.09, 25.14, 25.57, 27.27, 31.03, 32.82, 34.27, 67.26, 97.50, 126.30, 128.87, 134.72, 139.07, 171.35; ESI-MS *m*/*z*: 342.2 $(M+NH_4)^+$.**7d**: *c-5-[4-(4-Methoxy-phenyl)-butyl]-r-2-methyl-1,3-dioxane-2-carboxylic acid*: White solid; mp: 84–86 °C; Yield: 80%; Purity: 98% by HPLC; IR (KBr): 3020, 2938, 1727, 1556, 1228, 1136, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.02–1.09 (m, 2H), 1.23–1.30 (m, 2H), 1.50–1.52 (m, 2H), 1.60 (s, 3H), 1.98–2.0 (m, 1H), 2.52 (t, *J* = 7.5 Hz, 2H), 3.44 (t, *J* = 11.5 Hz, 2H), 3.78 (s, 3H), 3.94–3.99 (dd, *J* = 11.9 and 4.4 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.09, 25.54, 27.26, 31.29, 32.80, 33.93, 54.90, 67.24, 97.48, 113.90, 129.07, 133.98, 157.27, 171.32; ESI-MS *m*/*z*: 309.3 $(M+H)^+$.**7e**: *c-5-[4-(4-Chloro-phenyl)-butyl]-r-2-methyl-1,3-dioxane-2-carboxylic acid*: White solid; mp: 94–96 °C; Yield: 86%; Purity: 99%; IR (KBr): 3030, 2936, 1723, 1516, 1228, 1136, 813 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.92–1.00 (m, 2H), 1.13–1.21 (m, 2H), 1.31 (s, 3H), 1.38–1.49 (m, 2H), 1.75–1.83 (m, 1H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.22 (t, *J* = 11.5 Hz, 2H), 3.76–3.82 (dd, *J* = 11.7 and 4.4 Hz, 2H), 6.61 (d, *J* = 8.3 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 9.06 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.33, 25.66, 27.47, 31.39, 32.99, 34.03, 67.07, 98.07, 114.97, 128.60, 132.10, 155.24, 171.60; ESI-MS *m*/*z*: 335.1 $(M+Na)^+$.**7f**: *2-Methyl-c-5-[4-(4-methylsulfinyl-phenyl)-butyl]-1,3-dioxane-r-2-carboxylic acid*: White solid; mp: 147–149 °C; Yield: 63%, Purity: 99% by HPLC; IR (KBr): 3040, 2939, 1730, 1265, 1197, 1147, 1001 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.98–1.06 (m, 2H), 1.21–1.32 (m, 2H), 1.53 (s, 3H), 1.57–1.65 (m, 2H), 1.98–2.04 (m, 1H), 2.65 (t, *J* = 7.48 Hz, 2H), 2.72 (s, 3H), 3.39 (t, *J* = 11.5 Hz, 2H), 3.88–3.93 (dd, *J* = 11.6 and 4.2 Hz, 2H,), 7.52 (d, *J* = 8.07 Hz, 2H), 7.6 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.18, 25.55, 27.22, 30.86, 32.77, 34.59, 43.20, 67.24, 97.48, 123.60, 129.10, 143.46, 145.26, 171.33; ESI-MS *m*/*z*: 341.1 $(M+H)^+$.**7g**: *2-Methyl-c-5-[4-(4-methylsulfonyl-phenyl)-butyl]-1,3-dioxane-r-2-carboxylic acid*: White solid; mp: 152-154 °C; Yield: 88%; Purity: 97% by HPLC; IR (KBr): 3020, 2933, 1743, 1299, 1134, 1118, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.04–1.11 (m, 2H), 1.26–1.36 (m, 2H), 1.56 (s, 3H), 1.59–1.67 (m, 2H), 2.01–2.06 (m, 1H), 2.68 (t, *J* = 7.6 Hz, 2H), 3.05 (s, 3H), 3.45 (t, *J* = 11.5 Hz, 2H), 3.93–3.99 (dd, *J* = 11.9 and 4.4 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.22, 25.60, 27.25, 30.72, 32.81, 34.72, 67.28, 97.58, 127.01, 129.21, 138.31, 148.59, 171.43; ESI-MS *m*/*z*: 379.2 $(M+Na)^+$.**9**: *c-5-[4-(4-Benzyloxy-phenyl)-butyl]-r-2-methyl-1,3-dioxane-r-2-carboxylic acid*: White solid; mp: 102–104 °C; Yield: 84%; Purity: 99% by HPLC; IR (KBr): 3020, 2929, 1728, 1510, 1236, 1047, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.04-1.09 (m, 2H), 1.23–1.33 (m, 2H), 1.50–1.62 (m, 5H), 1.97–2.03 (m, 1H), 2.50 (t, *J* = 7.5 Hz, 2H), 3.40 (t, *J* = 11.5 Hz, 2 H), 3.94-3.99 (dd, *J* = 11.8 and 4.4 Hz, 2H), 5.03 (s, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.29–7.44 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.17, 25.61, 27.32, 31.36, 32.85, 34.02, 67.31, 69.13, 97.56, 114.56, 127.66, 128.42, 129.18, 134.34, 137.30, 156.43, 171.42, 185.15; ESI-MS *m*/*z*: 402.3 $(M+NH_4)^+$.**11**: *c-5-[4-(4-Hydroxy-phenyl)-butyl]-2-methyl-1,3-dioxane-r-2-carboxylic acid*: White solid; mp: 157–159 °C; Yield: 86%; Purity: 99% by HPLC; IR (KBr): 3073, 2933, 1720, 1514, 1228, 1136, 813 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.92–1.00 (m, 2H), 1.13–1.22 (m, 2H), 1.31 (s, 3H), 1.38–1.52 (m, 2H), 1.75–1.83 (m, 1H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.22 (t, *J* = 11.5 Hz, 2H), 3.76–3.82 (dd, *J* = 11.7 and 4.4 Hz, 2H), 6.61 (d, *J* = 8.3 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 9.06 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.32, 25.63, 27.42, 31.39, 32.99, 34.03, 67.07, 98.07, 114.97, 128.60, 132.10, 155.24, 171.60; ESI-MS *m*/*z*: 317.1 $(M+Na)^+$.**13a**: *c-5-[5-(4-Methanesulfonyloxy-phenyl)-butyl]-2-methyl-1,3-dioxane-r-2-carboxylic acid*: White solid; mp: 140–142 °C; Yield: 84%; Purity: 98% by HPLC; IR (KBr): 3020, 2927, 1753, 1506, 1346, 1261, 1170, 987 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 1.03–1.10 (q, *J* = 7.5 Hz, 2H), 1.28–1.34 (m, 2H), 1.53 (s, 3H), 1.98–2.04 (m, 1H), 2.59 (t, *J* = 7.5 Hz, 2H), 3.13 (s, 3 H), 3.44 (t, *J* = 11.6 Hz, 2H), 3.93–3.99 (dd, *J* = 4.7 and 11.9 Hz, 2H), 7.18 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.20, 25.56, 27.25, 30.94, 32.80, 34.19, 37.23, 67.26, 97.50, 121.91, 129.72, 141.51, 147.15, 171.34; ESI-MS *m*/*z*: 395.0 $(M+Na)^+$.**13b**: *c-5-[5-(4-Methanesulfonyloxy-phenyl)-pentyl]-2-methyl-1,3-dioxane-r-2-carboxylic acid*: White solid; mp: 102–104 °C; Yield: 94%; Purity: 98% by HPLC; IR (KBr): 3036, 2930, 1720, 1498, 1363, 1290, 1211, 1168, 1145, 974, 867, 775, 538, 526 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.0 (m, 2H), 1.2 (m, 4H), 1.5 (m, 5H), 2.0 (m, 1H), 2.6 (t, *J* = 7.4 Hz, 2H), 3.1 (s, 3H), 3.4 (t, *J* = 11.6 Hz, 2H), 3.9 (dd, *J* = 12.0 and 4.5 Hz, 2H), 7.2 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.34, 25.54, 27.41, 28.71, 30.54, 32.86, 34.33, 37.22, 67.27, 97.49, 121.86, 129.70, 141.54, 147.12, 171.32; ESI-MS *m*/*z*: 409.0 $(M+Na)^+$.**13c**: *c-5-[6-(4-Methanesulfonyloxy-phenyl)-hexyl]-2-methyl-1,3-dioxane-r-2-carboxylic acid*: White solid; mp: 104–106 °C; Yield: 93%; Purity: 97.5% by HPLC; IR (KBr): 3026, 2922, 1755, 1467, 1259, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.02-1.05 (m, 2H), 1.27 (bm, 6H), 1.57 (bm, 5H), 1.98–2.06 (m, 1H), 2.59 (t, *J* = 7.6 Hz, 2H), 3.12 (s, 3H), 3.46 (t, *J* = 11.6 Hz, 2H), 3.96–4.00 (dd, *J* = 12.0 and 4.4 Hz, 2H), 7.16–7.28 (m, 4H); ^{13}C NMR: (100 MHz, DMSO-d_6): δ 25.60, 26.72, 28.46, 29.02, 32.47, 33.06, 34.46, 37.23, 67.35, 97.13, 121.64, 129.47, 141.35, 147.50, 171.40; ESI-MS *m*/*z*: 423.0 $(M+Na)^+$.