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Structure–activity studies on 1,3-dioxane-2-carboxylic acid derivatives, a novel class of subtype-selective peroxisome proliferator-activated receptor α (PPARα) agonists

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Abstract—A series of 1,3-dioxane carboxylic acid derivatives was synthesized and evaluated for human PPAR transactivation activity. Structure–activity relationships on the phenyloxazole moiety of the lead compound **3** revealed that the introduction of small hydrophobic substituents at the 4-position of the terminal phenyl ring increased the PPARα agonist activity, and that the oxazole heterocycle was essential to the maintenance of both potency and PPARα subtype-selectivity. This investigation led to the identification of **14d** (NS-220) and **14i** as highly potent and selective human PPARα agonists. In KK-A^y type 2 diabetic mice, these compounds significantly lowered plasma triglyceride and very-low-density plus low-density lipoprotein cholesterol levels while simultaneously raising HDL cholesterol levels. Our results suggest that highly potent and subtype-selective PPARα agonists will be promising drugs for the treatment of metabolic disorders in type 2 diabetes.

1. Introduction

Hypolipidemic fibrate drugs (fibrates), such as bezafibrate **1** and fenofibrate **2** (Fig. 1), lower serum triglyceride levels and moderately raise high-density lipoprotein (HDL) cholesterol levels in patients with hyperlipidemia or type 2 diabetes[1] and prevent coronary heart disease and stroke.[2] Fibrates were originally developed without knowledge of their molecular target, and in 1990 they were identified as agonists of peroxisome proliferator-activated receptor α (PPARα).[3] Peroxisome proliferator-activated receptors (PPARs) are members of the thyroid/steroid hormone nuclear receptor superfamily and ligand-activated transcription factors that form functionally active heterodimers with another nuclear receptor, the 9-*cis*-retinoic acid receptor (RXR).[4] To date, three distinct PPAR subtypes, α, γ, and δ, have been identified in various species, including humans.[4,5] PPARα is expressed at high levels in metabolically active tissues, such as liver, heart, kidney, and skeletal muscle, and it plays a central role in the oxidation of fatty acids and in lipoprotein metabolism.[6] Although fibrates constitute an important class of PPARα ligands, a recent molecular-pharmacological study reveals that they have relatively weak affinity for PPARα and poor subtype-selectivity,[4b] so that fibrates must be used at high doses to achieve useful clinical effects in humans. More-potent and subtype-selective PPARα agonists are expected to be promising drugs for the treatment of metabolic syndrome and atherosclerosis.

Although some groups have already disclosed potent and subtype-selective PPARα agonists,[7–10] these compounds are not on the market. In another paper,[11] we describe the discovery of 2-methyl-*c*-5-{4-[5-methyl-2-phenyl-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid **3** (Fig. 1) as a potent and subtype-selective human PPARα agonist. This representative compound exhibits superior hypolipidemic activity in type 2 diabetic KK-A^y mice. (KK-A^y mice display severe hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and obesity, the typical symptoms of type 2 diabetes, and are widely used as animal models of type 2 diabetes.[12]) Structure–activity studies on the linker and the dioxane moiety

Keywords: Selective PPARα agonist; 1,3-Dioxane carboxylic acid; Metabolic disorder.
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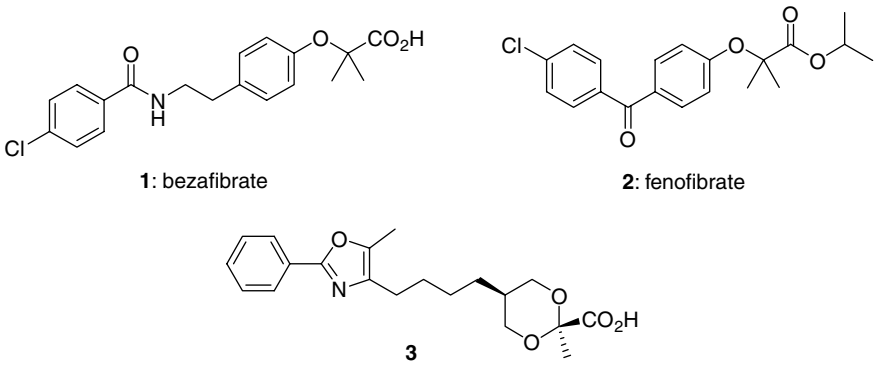
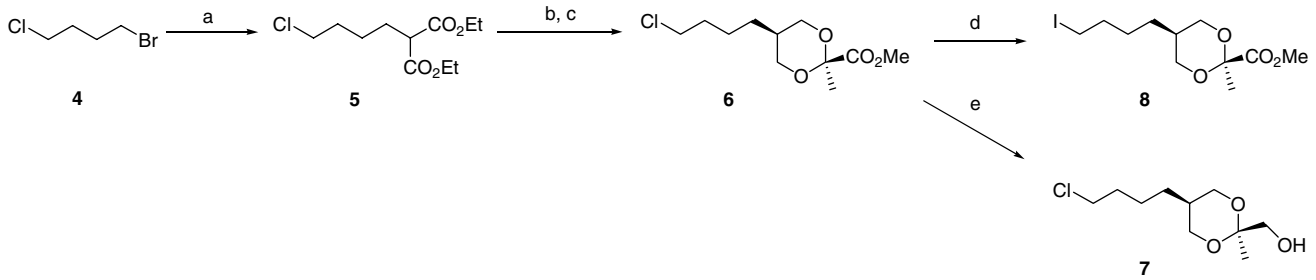


Figure 1. Chemical structures of fibrates **1**, **2**, and **3**.

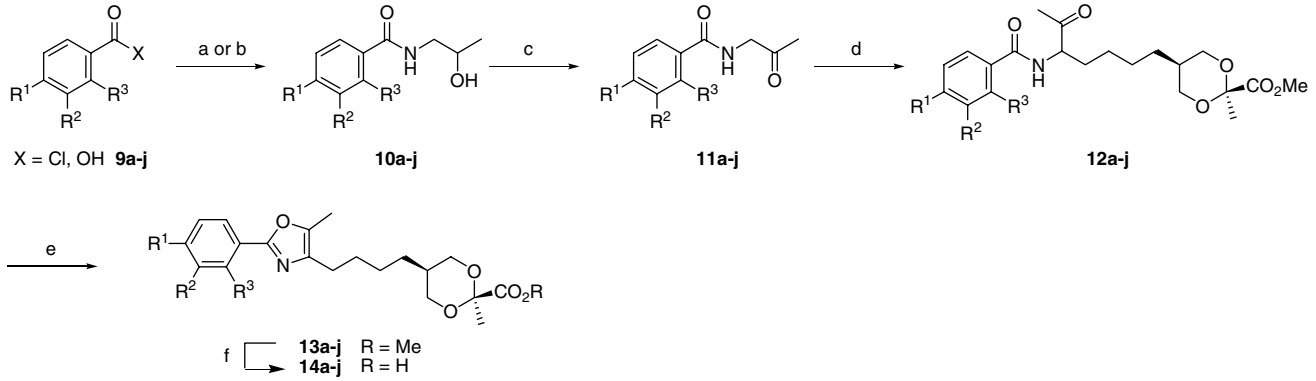
of 1,3-dioxane-2-carboxylic acid derivatives reveal that both the biological activity and the PPARα subtype-selectivity are sensitive to linker length and the geometrical configuration of the 1,3-dioxane ring.[11] These observations encouraged us to further optimize the human PPARα agonist activity by investigating various 1,3-dioxane-2-carboxylic acid derivatives. In the present report, we highlight the effects of structural variations associated with the phenyloxazole moiety of **3**. The objectives of this study were to explore the role of the phenyl ring and the oxazole heterocycle in the expression of PPARα agonism and to develop a more potent and subtype-selective PPARα agonist. Compounds of this series which were identified by their PPARα agonist activity were evaluated for their in vivo hypolipidemic and hypoglycemic effects to establish their potential benefit in the treatment of hyperlipidemia and metabolic disorders in type 2 diabetes.

2. Chemistry

Compounds **14a**–**j** were prepared according to Schemes 1 and 2. For this purpose, we designed a convergent synthesis which was more efficient than the linear one described previously.[11] The 1,3-dioxane derivative **8** was chosen as a common intermediate in this method, and it was synthesized by the following simple method (Scheme 1). Alkylation of diethyl malonate with 1-bromo-4-chlorobutane **4** provided the diester **5**. Reduction



Scheme 1. Reagents: (a) $CH_2(CO_2Et)_2$, NaH, 1,3-dimethyl-2-imidazolidinone; (b) $LiAlH_4$, Et_2O; (c) $MeCOCO_2Me$, $BF_3{\cdot}OEt_2$, CH_3CN; (d) NaI, acetone; (e) $LiAlH_4$, THF.



Scheme 2. Reagents: (a) 1-amino-2-propanol, Et_3N, toluene; (b) 1-amino-2-propanol, EDC hydrochloride, HOBt, Et_3N, DMF; (c) PCC, CH_2Cl_2; (d) i—NaH, DMF; ii—**8**; (e) $POCl_3$, toluene; (f) aq NaOH, MeOH.

of **5** with lithium aluminum hydride followed by dioxane ring formation brought about by methyl pyruvate gave the 1,3-dioxane derivative **6**. Formation of the dioxane ring from the diol intermediate on refluxing with boron trifluoride in CH_3CN yielded a mixture of geometrical isomers. This mixture was resolved by chromatography on a column of silica gel to give the pure *cis*-isomer **6**, which has a chemical-shift pattern identical to that of other *cis*-derivatives.[11] The *cis*-configuration of **6** was also confirmed by an NOE experiment on the corresponding alcohol **7**, which has protons that allow determination of the configuration of the dioxane ring moiety. Compound **7** was synthesized by $LiAlH_4$ reduction of **6** free of *trans*-isomer. α-Protons at the 4- and 6-positions were clearly distinguished from the β-protons by the observed NOE correlation between the 5-α- and 4-α(6-α)-protons. The strong NOE from the 4,6-β-protons assigned above to the 2-hydroxymethyl protons shows conclusively that the configuration is *cis* (Fig. 2). Sequential iodination of **6** with sodium iodide in acetone was accomplished quantitatively to give the key intermediate **8**. Condensation of the various acid chlorides or carboxylic acids **9a**–**j** with 1-amino-2-propanol and subsequent oxidation with pyridinium chlorochromate gave the benzamides **11a**–**j**. Coupling[13] of **11a**–**j** with **8** by using sodium hydride as a base gave **12a**–**j**, which were converted to the oxazoles **13a**–**j** by treatment with phosphorus oxychloride. Hydrolysis of **13a**–**j** with aqueous sodium hydroxide in methanol then yielded the target products **14a**–**j**.

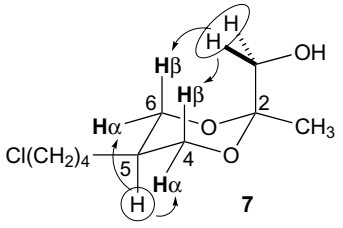
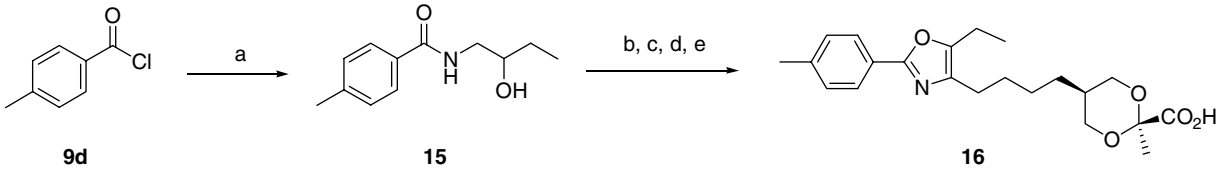


Figure 2. Interpretation of NOE experiment on **7**, which has a 1,3-dioxane ring system.

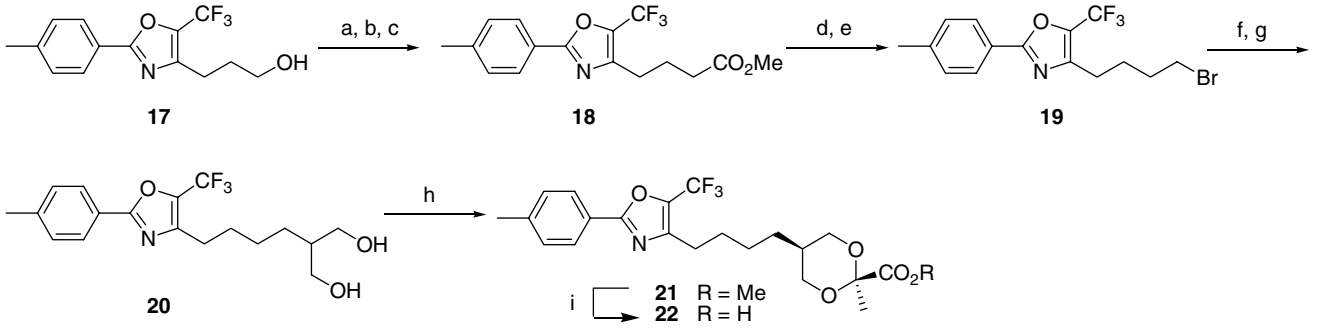
The synthesis of the 5-ethyloxazole derivative **16** is shown in Scheme 3. This compound was prepared from **9d** and 1-amino-2-butanol in a manner similar to that shown in Scheme 2.

The synthesis of the 5-trifluoromethyloxazole derivative **22** is shown in Scheme 4. The alcohol **17** was readily prepared from *N*-(4-methylbenzoyl)proline by a known method.[14] Tosylation of **17** followed by cyanation gave the corresponding nitrile, which was converted to the methyl ester **18** by treatment with methanol–hydrogen chloride and then with water. Reduction of **18** with $LiAlH_4$ and subsequent bromination with carbon tetrabromide/triphenylphosphine gave the bromide **19**. Conversion of **19** into the 1,3-dioxane derivative **21** was accomplished in a manner similar to that shown in Scheme 1, after which alkaline hydrolysis of **21** gave the desired product **22**.

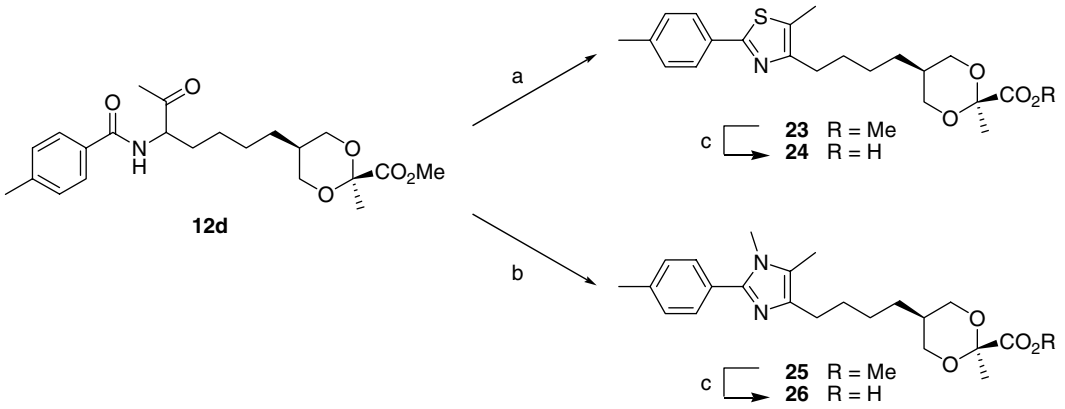
The preparation of the thiazole derivative **24** and the imidazole derivative **26** is shown in Scheme 5. The thiazole skeleton of **24** was constructed by a previously reported procedure.[13] Compound **12d** mentioned above was cyclized by treatment with Davy Reagent Methyl[15] (2,4-bis(methylthio)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) to provide the thiazole **23**, which was hydrolyzed in the usual manner to give the desired thiazole **24**. The construction of the imidazole skeleton was accomplished by cyclization of **12d** with methylamine in a mixture of acetic acid and xylene at reflux to give the imidazole **25**, which was then converted to the target product **26** by alkaline hydrolysis.



Scheme 3. Reagents: (a) 1-amino-2-butanol, Et_3N, THF; (b) PCC, CH_2Cl_2; (c) i—NaH, DMF; ii—**8**; (d) $POCl_3$, toluene; (e) aq NaOH, MeOH.



Scheme 4. Reagents: (a) TsCl, Et_3N, DMAP, THF; (b) NaCN, DMSO; (c) i—HCl, MeOH; ii—H_2O; (d) $LiAlH_4$, THF; (e) PPh_3, CBr_4, CH_2Cl_2; (f) $CH_2(CO_2Et)_2$, NaH, THF, DMF; (g) $LiAlH_4$, THF; (h) $MeCOCO_2Me$, $BF_3{\cdot}OEt_2$, MeCN; (i) aq NaOH, MeOH.

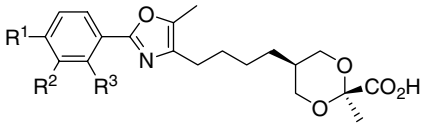


Scheme 5. Reagents: (a) Davy Reagent Methyl, THF; (b) 2 M $MeNH_2$ in THF, AcOH, xylene; (c) aq NaOH, MeOH.

3. In vitro structure–activity relationship (SAR) studies

The newly synthesized compounds were screened for activity at each of the human PPAR subtypes by using an established cell-based transactivation assay in CV-1 cells.[16] We investigated the effect of substitution at the phenyl ring of **3** on the agonist activity at the human PPARα subtype. PPARα agonist activity was remarkably sensitive to modification of the terminal phenyl ring (Table 1). First, we tested the effect of substitution at the 4-position in compounds **14a**–**e**. The introduction of a chloro, trifluoromethyl or methoxy substituent at this position (**14a**–**c**) resulted in a 10-fold improvement (EC_{50} = 0.03 μM) in PPARα agonist activity compared to **3** (EC_{50} = 0.3 μM). Unexpectedly, the 4-methyl analogue **14d** (EC_{50} = 0.01 μM) and the 4-ethyl analogue **14e** (EC_{50} = 0.01 μM) were 30-fold more effective than **3**. Strikingly, the 4-methylated compound **14d** activated human PPARα with more than 1000-fold selectivity over the human γ and δ subtypes, while the 4-ethyl analogue **14e** exhibited less subtype-selectivity than **14d** (300-fold selectivity over human PPARγ). These observations suggest that the hydrophobic character and steric bulk of the substituent at the 4-position have important effects on PPARα agonist activity and subtype-selectivity. Further modification was focused on methyl substitution at other positions on the phenyl ring. Though the activity of the 2-methyl analogue **14h** (EC_{50} = 0.3 μM) was not markedly different from that of **3**, the 3-methyl analogue **14g** (EC_{50} = 0.03 μM) showed 10-fold-enhanced potency compared to **3**. Based on these investigations, we synthesized the two dimethyl-

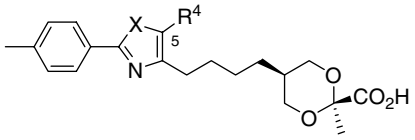
Table 1. Effect of phenyl-ring substituents on the agonist activity of human PPAR subtypes



Compound	R^1	R^2	R^3	Human PPARs (EC_{50}, μM)[a,b]		
				α	γ	δ
3	H	H	H	0.3	100	(0%)[c]
14a	Cl	H	H	0.03	(21%)	(9%)
14b	CF_3	H	H	0.03	(41%)	(34%)
14c	OMe	H	H	0.03	(18%)	(20%)
14d	Me	H	H	0.01[d]	(31%)[d]	(7%)[d]
14e	Et	H	H	0.01	3	(0%)
14f	Me	F	H	0.01	(45%)	(25%)
14g	H	Me	H	0.03	(34%)	(16%)
14h	H	H	Me	0.3	(23%)	(5%)
14i	Me	Me	H	0.003	(42%)	(0%)
14j	Me	H	Me	0.03	(35%)	(16%)
	Fenofibric acid			30	>100	>100
	Bezafibrate			30	100	30

[a] The agonist activity of each PPAR subtype was measured by the corresponding transactivation assay in transiently transfected CV-1 cells (n = 2).
[b] EC_{50} is the concentration of test compounds that gave 50% of the maximum transactivation activity of each positive control.
[c] Less than 50% of maximum activity at 10 μM. The percentage of maximum activation observed at 10 μM is shown in parentheses.
[d] The EC_{50} values of compound **14d** for PPARα, PPARγ, and PPARδ were reported as 0.019 μM, 9.6 μM as a partial agonist for PPARγ, and >100 μM, respectively, in a previous article[16] from different assay data.

Table 2. Effects of substituents at the 5-position of the oxazole ring and replacement of the oxazole ring on the agonist activity of human PPAR subtypes



Compound	X	R^4	Human PPARs (EC_{50}, μM)[a,b]		
			α	γ	δ
14d	O	Me	0.01[d]	(31%)[c,d]	(7%)[d]
16	O	Et	0.03	10	(3%)
22	O	CF_3	0.3	3	(24%)
24	S	Me	0.3	(25%)	(0%)
26	NMe	Me	(6%)	(0%)	(0%)

See corresponding footnotes to Table 1.

ated compounds **14i** and **14j**. The 3,4-dimethyl derivative **14i** (EC_{50} = 0.003 μM) exhibited the most potent human PPARα agonist activity of all the compounds listed in Table 3, and it also exhibited high subtype-selectivity.

Having optimized the structural features for the distal phenyl ring, we then turned our attention to the oxazole moiety. We investigated the effect of both the substituent at the 5-position of the oxazole ring and structural variations in the oxazole ring itself (Table 2). We synthesized the **14d**-related 5-ethyl and 5-trifluoromethyl derivatives **16** and **22**. Replacement of the methyl group at the 5-position reduced both the potency and the subtype-selectivity compared to **14d**. This study revealed that the methyl substituent at the 5-position of the oxazole ring contributes to a potent PPARα agonist activity and a high PPARα selectivity. We also explored replacement of the oxazole ring in **14d** by other heterocycles. The thiazole derivative **24** (EC_{50} = 0.3 μM) was 30-fold less potent than the prototype **14d**. The basic imidazole derivative **26** showed no activity at any of the three PPAR subtypes. These structure–activity correlations suggest that the role of the oxazole heterocycle is more than that of a simple scaffold and that in fact the oxazole heteroatoms play a role in the binding interaction with PPARα.

4. Animal experiments

To assess the potential utility of the optimized compounds as PPARα agonists, we selected **14d**, **14f**, and **14i** for further testing because of their superior PPARα agonist activity and subtype-selectivity. These compounds activated mouse PPARα 3- to 10-fold less potently than human PPARα (Table 3). Nevertheless, they had sufficient in vitro activity with high selectivity for mouse PPARα over mouse PPARγ to allow in vivo evaluation of their potential benefit. We then examined the pharmacological effects of **3**, **14d**, **14f**, and **14i** in type 2 diabetic KK-A^y mice[12] (Table 4). Each

Table 3. In vitro activity of **3**, **14d**, **14f**, and **14i** at mouse PPAR subtypes α and γ

Compound	Mouse PPARs (EC_{50}, μM)[a,b]	
	α	γ
3	1	(11%)[c]
14d	0.03	(45%)
14f	0.1	10
14i	0.03	(42%)

See corresponding footnotes to Table 1.

Table 4. Hypolipidemic and hypoglycemic effects of **3**, **14d**, **14f**, and **14i** in diabetic KK-A^y mice

Compound	Dose (mg/kg)	% Change			
		TG	PG	(V)LDL-C	HDL-C
3	1	−46	−12	−29	36
14d	1	−71	−21	−50	34
14f	1	−53	−12	−63	21
14i	1	−89	−32	−92	21
Fenofibrate	300	−40	−25	−31	17

Compounds were orally administered to male KK-A^y mice (aged 10 weeks, n = 5) once a day for 4 days at the indicated dose. Each value represents the percentage change of the mean value from the control group; TG = plasma triglyceride; PG = plasma glucose; (V)LDL-C = very-low-density plus low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

compound was orally administered at 1 mg/kg to 10-week-old male KK-A^y mice once a day for 4 days. All compounds markedly lowered plasma triglyceride levels (TG) and very-low-density plus low-density lipoprotein cholesterol levels ((V)LDL-C), while they raised HDL cholesterol levels (HDL-C). These compounds also decreased glucose levels. For purposes of comparison, in this study fenofibrate **2** was orally administered at 300 mg/kg. Although **2** showed similar effects at 300 mg/kg, it was significantly less potent than our compounds. The hypolipidemic effects of our compounds were correlated with their PPARα agonist activities. This result provides clear evidence that PPARα agonists have superior efficacy in the treatment of hyperlipidemia and hyperglycemia. The detailed pharmacological properties of **14d** have been investigated and published elsewhere.[16]

5. Conclusion

To identify more-potent PPARα agonists, we investigated the structure–activity relationships (SAR) for the phenyloxazole moiety of 1,3-dioxane derivative **3**. We found that key roles are played by the methyl group at the 4-position of the terminal phenyl ring, and by the oxazole heterocycle itself, in determining the potency and subtype-selectivity of the compound as a PPARα agonist. Our investigation led to the identification of **14d** (NS-220) and **14i** as highly potent and selective human PPARα agonists. In addition, as we had predicted, these compounds exhibited excellent hypolipidemic activity in diabetic KK-A^y mice. Our results suggest that the development of potent and selective PPARα agonists

will be useful in the treatment of hyperlipidemia and metabolic disorders in type 2 diabetes.

6. Experimental

Reagents and solvents were used as obtained from the supplier without further purification. Melting points were determined on a Shibata melting point apparatus and are uncorrected. Column chromatography was carried out on a silica gel column (Wako Wakogel® C-200 or Fuji Silysia PSQ-100B). TLC was carried out on Merck TLC aluminum sheets silica gel 60 F_{254}, and spots were visualized under 254-nm UV light or spraying with phosphomolybdic acid. Yields were not optimized. ^{1}H NMR spectra were recorded on a Varian Gemini 2000 (200 MHz) or a Varian UnityPlus 300 (300 MHz) spectrometer. Chemical shifts (δ) are given in ppm relative to the internal standard, tetramethylsilane, and coupling constants are given in Hertz (Hz). Mass spectra were recorded on a JEOL JMS-700 mass spectrometer and IR spectra were recorded on a Shimadzu FT IR-8100 spectrometer.

6.1. Preparation of 8

6.1.1. Diethyl 2-(4-chlorobutyl)malonate (5). To a precooled (7 °C) suspension of NaH (60% dispersion in oil; 140 g, 3.5 mol) in 1,3-dimethyl-2-imidazolidinone (600 mL) was added dropwise diethyl malonate (1121 g, 7.0 mol) below 20 °C. After having been stirred at room temperature for 1 h, the mixture was cooled on an ice-bath and a solution of **4** (600 g, 0.87 mmol) was added dropwise over 1 h. The resulting mixture was stirred below 20 °C for 3 h and then recooled on the ice-bath. The reaction was quenched with a mixture of concd HCl (53.2 g) and water (1.5 L). The organic layer was washed with water (1 L) and purified by distillation to afford **5** (477.3 g, 54%) as a colorless oil. Bp 120–132 °C (4 mm Hg). FAB-MS *m*/*z* 251 $[MH]^+$. ^{1}H NMR ($CDCl_3$) δ: 1.27 (6H, t, J = 7.2 Hz), 1.41–1.59 (2H, m), 1.74–1.98 (4H, m), 3.33 (1H, t, J = 7.5 Hz), 3.54 (2H, t, J = 6.6 Hz), 4.20 (4H, q, J = 7.2 Hz). Anal. Calcd for $C_{11}H_{19}ClO_4{\cdot}0.2H_2O$: C, 51.95; H, 7.69. Found: C, 51.85; H, 7.38.

6.1.2. Methyl *c*-5-(4-chlorobutyl)-2-methyl-1,3-dioxane-*r*-2-carboxylate (6). To an ice-cooled suspension of $LiAlH_4$ (3.84 g, 101 mmol) in Et_2O (100 mL) was added dropwise a solution of **5** (12.69 g, 51 mmol) in Et_2O (25 mL) over a period of 1 h at 4–15 °C. The mixture was stirred with ice-cooling for 2 h and the reaction was quenched with water (3.8 mL), aqueous 15% NaOH (3.8 mL), and water (11.4 mL), in that order. The mixture was stirred at room temperature for 1 h. The insoluble precipitate was filtered off and the filtrate was evaporated in vacuo. The residue was purified by chromatography on silica gel with hexane–EtOAc (1:3) as the eluent to give 6-chloro-2-hydroxymethyl-1-hexanol (4.07 g, 48%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.23–1.40 (2H, m), 1.40–1.58 (2H, m), 1.64–1.90 (3H, m), 2.34 (2H, br), 3.55 (2H, t, J = 6.4 Hz), 3.68 (2H, dd, J = 10.6, 6.8 Hz), 3.84 (2H, dd, J = 10.6, 3.6 Hz).

A mixture of 6-chloro-2-hydroxymethyl-1-hexanol (3.92 g, 24 mmol), methyl pyruvate (9.61 g, 94 mmol), and boron trifluoride diethyl ether complex (13.36 g, 94 mmol) in CH_3CN (60 mL) was heated at 60 °C for 1.5 h. After cooling to room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by chromatography on silica gel with hexane–EtOAc (7:1) as the eluent to give *cis*-isomer **6** (1.72 g, 29%) as a pale yellow oil and a mixture of **6** and its *trans*-isomer (2.70 g, *cis*:*trans* = ca. 1:1 by ^{1}H NMR analysis) as a pale yellow oil. Compound **6**: TLC R_f = 0.40 (hexane–EtOAc, 1:4) (*trans*-isomer: R_f = 0.35). FAB-MS *m*/*z* 251 $[MH]^+$. ^{1}H NMR ($CDCl_3$) δ: 0.96–1.13 (2H, m), 1.34–1.60 (2H, m), 1.51 (3H, s), 1.65–1.85 (2H, m), 1.90–2.15 (1H, m), 3.40 (2H, t, J = 11.4 Hz), 3.52 (2H, t, J = 6.4 Hz), 3.83 (3H, s), 3.96 (2H, dd, J = 11.4, 4.8 Hz). Anal. Calcd for $C_{11}H_{19}ClO_4{\cdot}0.1H_2O$: C, 52.32; H, 7.66. Found: C, 52.20; H, 7.61.

6.1.3. *c*-5-(4-Chlorobutyl)-*r*-2-hydroxymethyl-2-methyl-1,3-dioxane (7). To an ice-cooled suspension of $LiAlH_4$ (91 mg, 2.4 mmol) in THF (5 mL) was added dropwise a solution of **6** (500 mg, 2.0 mmol) in THF (2 mL) over 5 min. The mixture was stirred with ice-cooling for 1 h. After the reaction had been quenched with water (1 mL), the insoluble precipitate was filtered off. The filtrate was diluted with EtOAc, washed with water, and dried over $MgSO_4$. Removal of the solvent by evaporation gave **7** (400 mg, 90%) as a colorless oil. FAB-MS *m*/*z* 223 $[MH]^+$. ^{1}H NMR (300 MHz) (C_5D_5N) δ: 1.13–1.32 (4H, m), 1.58 (2H, m), 1.66 (1H, m, H-5α), 1.70 (3H, s), 3.47 (2H, t, J = 6.6 Hz), 3.68 (2H, dd, J = 11.7, 7.5 Hz, H-4,6β), 3.96 (2H, dd, J = 11.7, 4.5 Hz, H-4,6α), 4.06 (2H, d, J = 3.3 Hz, 2β-CH_2OH), 6.29 (1H, br). Anal. Calcd for $C_{10}H_{19}ClO_3$: C, 53.93; H, 8.60. Found: C, 53.57; H, 8.75.

6.1.4. Methyl *c*-5-(4-iodobutyl)-2-methyl-1,3-dioxane-*r*-2-carboxylate (8). A mixture of **6** (1.65 g, 6.6 mmol) and sodium iodide (2.97 g, 19.8 mmol) in acetone (12 mL) was heated at reflux for 13 h. The mixture was then diluted with water and extracted with EtOAc. The organic layer was washed successively with water and brine, and dried over $MgSO_4$. Removal of the solvent by evaporation gave **8** (2.00 g, 89%) as a pale yellow oil. The product was used for the next step without further purification. FAB-MS *m*/*z* 343 $[MH]^+$. ^{1}H NMR ($CDCl_3$) δ: 0.97–1.16 (2H, m), 1.30–1.45 (2H, m), 1.51 (3H, s), 1.69–1.89 (2H, m), 1.91–2.14 (1H, m), 3.16 (2H, t, J = 6.9 Hz), 3.40 (2H, t, J = 12.0 Hz), 3.83 (3H, s), 3.96 (2H, dd, J = 12.0, 4.8 Hz). Anal. Calcd for $C_{11}H_{19}IO_4$: C, 38.61; H, 5.60. Found: C, 38.94; H, 5.47.

6.2. Preparation of 10a–j

6.2.1. General procedure for the synthesis of 10d, 10g, 10h: *N*-(2-hydroxypropyl)-4-methylbenzamide (10d). A solution of *p*-toluoyl chloride (20.01 g, 0.129 mol) in toluene (10 mL) was added dropwise over 10 min to an ice-cooled solution of 1-amino-2-propanol (10.58 g,

0.141 mol) and triethylamine (14.49 g, 0.143 mol) in toluene (70 mL). The reaction mixture was stirred at room temperature for 2.5 h and diluted with water. The resulting precipitate was collected by filtration, washed successively with water and toluene, and dried under reduced pressure, to give **10d** (17.64 g, 71%) as colorless crystals. Mp 121–124 °C. FAB-MS *m*/*z* 194 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.24 (3H, d, J = 6.2 Hz), 2.34 (3H, s), 2.93 (1H, br), 3.29 (1H, ddd, J = 13.8, 7.8, 5.2 Hz), 3.64 (1H, ddd, J = 13.8, 6.6, 3.0 Hz), 3.97–4.07 (1H, m), 6.69 (1H, br), 7.22 (2H, d, J = 8.2 Hz), 7.68 (2H, d, J = 8.2 Hz). Anal. Calcd for $C_{11}H_{15}NO_2 \cdot 0.1H_2O$: C, 67.74; H, 7.85; N, 7.18. Found: C, 67.83; H, 7.78; N, 7.35.

6.2.2. *N*-(2-Hydroxypropyl)-3-methylbenzamide (10g). Compound **10g** was prepared from 3-methylbenzoyl chloride in a manner similar to that described for **10d**. Yield 35%, colorless crystals. Mp 92–93 °C. FAB-MS *m*/*z* 194 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.24 (3H, d, J = 6.2 Hz), 2.38 (3H, s), 2.88 (1H, d, J = 4.8 Hz), 3.30 (1H, ddd, J = 14.0, 7.7, 5.0 Hz), 3.65 (1H, ddd, J = 14.0, 6.6, 2.8 Hz), 3.97–4.10 (1H, m), 6.71 (1H, br), 7.27–7.40 (2H, m), 7.50–7.60 (2H, m). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.19; H, 7.72; N, 7.43.

6.2.3. *N*-(2-Hydroxypropyl)-2-methylbenzamide (10h). A solution of *o*-toluoyl chloride (2.00 g, 12.9 mmol) in toluene (2 mL) was added dropwise over 10 min to an ice-cooled solution of 1-amino-2-propanol (1.07 g, 14.2 mmol) and triethylamine (2.0 mL, 14.3 mmol) in toluene (7 mL). The reaction mixture was stirred at room temperature for 2 h, then it was diluted with water and extracted twice with EtOAc. The organic layers were combined and washed successively with 10% aqueous HCl and water, and dried over $MgSO_4$. After evaporation of the solvent, the resulting solid was washed with Et_2O, collected by filtration, and dried in vacuo to give **10h** (1.21 g, 48%) as colorless crystals. Mp 83–84 °C. FAB-MS *m*/*z* 194 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.24 (3H, d, J = 6.2 Hz), 2.44 (3H, s), 2.66 (1H, br), 3.27 (1H, ddd, J = 14.0, 7.6, 5.9 Hz), 3.62 (1H, ddd, J = 14.0, 6.4, 3.2 Hz), 3.90–4.10 (1H, m), 6.30 (1H, br), 7.10–7.40 (4H, m). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.27; H, 7.93; N, 7.24.

6.2.4. General procedure for the synthesis of 10a–c, 10e, 10f, 10i, 10j: 3-fluoro-*N*-(2-hydroxypropyl)-4-methylbenzamide (10f). To a mixture of 3-fluoro-4-methylbenzoic acid (5.00 g, 32 mmol), 1-amino-2-propanol (2.68 g, 36 mmol), and 1-hydroxybenzotriazole (4.81 g, 36 mmol) in DMF (30 mL) were added triethylamine (6.8 mL, 49 mmol) and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC hydrochloride) (4.81 g, 36 mmol). The mixture was stirred at room temperature for 6 h, then diluted with water and extracted twice with EtOAc. The organic layers were combined and washed successively with 10% aqueous HCl, water and saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. After evaporation of the solvent, the resulting solid was washed with Et_2O, collected by filtration, and dried in vacuo to give **10f** (6.06 g, 88%) as colorless crystals. Mp 140–141 °C. FAB-MS *m*/*z* 212 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.25 (3H, d, J = 6.4 Hz), 2.31 (3H, d, J = 2.2 Hz), 2.72 (1H, br), 3.28 (1H, ddd, J = 13.8, 8.0, 5.2 Hz), 3.65 (1H, ddd, J = 13.8, 6.6, 3.0 Hz), 3.92–4.11 (1H, m), 6.68 (1H, br), 7.20 (1H, t, J = 8.0 Hz), 7.44 (1H, d, J = 8.0 Hz), 7.45 (1H, d, J = 10.2 Hz). Anal. Calcd for $C_{11}H_{14}FNO_2$: C, 62.55; H, 6.68; N, 6.63. Found: C, 62.55; H, 6.48; N, 6.70.

6.2.5. 4-Chloro-*N*-(2-hydroxypropyl)benzamide (10a). Compound **10a** was prepared from 4-chlorobenzoic acid in a manner similar to that described for **10f**. Yield 85%, colorless crystals. Mp 146–147 °C. FAB-MS *m*/*z* 214 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.26 (3H, d, J = 6.2 Hz), 2.58 (1H, br), 3.28 (1H, ddd, J = 13.8, 7.6, 5.2 Hz), 3.67 (1H, ddd, J = 13.8, 6.6, 2.9 Hz), 3.90–4.10 (1H, m), 6.67 (1H, br), 7.40 (2H, d, J = 8.4 Hz), 7.72 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.13; H, 5.69; N, 6.57.

6.2.6. *N*-(2-Hydroxypropyl)-4-trifluoromethylbenzamide (10b). Compound **10b** was prepared from 4-trifluoromethylbenzoic acid in a manner similar to that described for **10f**. Yield 91%, colorless crystals. Mp 163–166 °C. FAB-MS *m*/*z* 248 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.27 (3H, d, J = 6.2 Hz), 2.40 (1H, br), 3.30 (1H, ddd, J = 14.0, 8.0, 5.2 Hz), 3.71 (1H, ddd, J = 14.0, 6.4, 3.2 Hz), 3.98–4.15 (1H, m), 6.71 (1H, br), 7.69 (2H, d, J = 8.6 Hz), 7.90 (2H, d, J = 8.6 Hz). Anal. Calcd for $C_{11}H_{12}F_3NO_2$: C, 53.44; H, 4.89; N, 5.67. Found: C, 53.30; H, 4.88; N, 5.65.

6.2.7. *N*-(2-Hydroxypropyl)-4-methoxybenzamide (10c). Compound **10c** was prepared from 4-methoxybenzoic acid in a manner similar to that described for **10f**. Yield 53%, colorless crystals. Mp 100–101 °C. FAB-MS *m*/*z* 210 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.23 (3H, d, J = 6.2 Hz), 3.04 (1H, br), 3.29 (1H, ddd, J = 14.0, 7.7, 5.1 Hz), 3.63 (1H, ddd, J = 14.0, 6.2, 3.0 Hz), 3.84 (3H, s), 3.90–4.10 (1H, m), 6.68 (1H, br), 6.90 (2H, d, J = 9.0 Hz), 7.75 (2H, d, J = 9.0 Hz). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.05; H, 7.22; N, 6.73.

6.2.8. 4-Ethyl-*N*-(2-hydroxypropyl)benzamide (10e). Compound **10e** was prepared from 4-ethylbenzoic acid in a manner similar to that described for **10f**. Yield 81%, colorless crystals. Mp 83–85 °C. FAB-MS *m*/*z* 208 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.24 (3H, d, J = 6.2 Hz), 1.24 (3H, t, J = 7.6 Hz), 2.68 (2H, q, J = 7.6 Hz), 2.94 (1H, d, J = 4.4 Hz), 3.30 (1H, ddd, J = 13.9, 7.9, 5.3 Hz), 3.65 (1H, ddd, J = 13.9, 6.6, 2.8 Hz), 3.90–4.12 (1H, m), 6.71 (1H, br), 7.24 (2H, d, J = 8.4 Hz), 7.71 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.31; H, 8.33; N, 6.69.

6.2.9. 3,4-Dimethyl-*N*-(2-hydroxypropyl)benzamide (10i). Compound **10i** was prepared from 3,4-dimethylbenzoic acid in a manner similar to that described for **10f**. Yield 53%, colorless crystals. Mp 80–82 °C. FAB-MS *m*/*z* 208 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.24 (3H, d, J = 6.2 Hz),

2.29 (6H, s), 2.90 (1H, br), 3.30 (1H, ddd, J = 14.0, 7.3, 5.1 Hz), 3.64 (1H, ddd, J = 14.0, 6.5, 2.9 Hz), 3.90–4.10 (1H, m), 6.66 (1H, br), 7.16 (1H, d, J = 7.8 Hz), 7.49 (1H, dd, J = 7.8, 1.7 Hz), 7.57 (1H, d, J = 1.7 Hz). Anal. Calcd for $C_{12}H_{17}NO_2 \cdot 0.1H_2O$: C, 68.94; H, 8.29; N, 6.70. Found: C, 68.76; H, 8.14; N, 6.77.

6.2.10. 2,4-Dimethyl-*N*-(2-hydroxypropyl)benzamide (10j). Compound **10j** was prepared from 2,4-dimethylbenzoic acid in a manner similar to that described for **10f**. Yield 32%, colorless crystals. Mp 89–90 °C. FAB-MS m/z 208 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.23 (3H, d, J = 6.2 Hz), 2.32 (3H, s), 2.41 (3H, s), 2.77 (1H, br), 3.26 (1H, ddd, J = 13.8, 7.4, 5.2 Hz), 3.60 (1H, ddd, J = 13.8, 6.6, 3.2 Hz), 3.90–4.07 (1H, m), 6.30 (1H, br), 6.98 (1H, d, J = 8.2 Hz), 7.02 (1H, s), 7.27 (1H, d, J = 8.2 Hz). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.27; H, 8.27; N, 6.78.

6.3. Preparation of 11a–j

6.3.1. General procedure for the synthesis of 11a–j: *N*-acetonyl-4-methylbenzamide (11d). Celite (11.15 g) and finely powdered pyridinium chlorochromate (11.15 g, 52 mmol) were added to a solution of **10d** (5.00 g, 26 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was stirred at room temperature for 6 h and then diluted with Et_2O (200 mL). The mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was subjected to silica gel column chromatography with hexane–EtOAc (1:3) as the eluent to give **11d** (3.53 g, 71%) as colorless crystals. Mp 90–92 °C. FAB-MS m/z 192 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 2.27 (3H, s), 2.40 (3H, s), 4.36 (2H, d, J = 4.4 Hz), 6.91 (1H, br), 7.25 (2H, d, J = 8.2 Hz), 7.72 (2H, d, J = 8.2 Hz). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.02; H, 6.76; N, 7.42.

6.3.2. *N*-Acetonyl-4-chlorobenzamide (11a). Compound **11a** was prepared from **10a** in a manner similar to that described for **11d**. Yield 70%, colorless crystals. Mp 133–135 °C. FAB-MS m/z 212 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 2.29 (3H, s), 4.36 (2H, d, J = 4.2 Hz), 6.91 (1H, br), 7.43 (2H, d, J = 8.6 Hz), 7.77 (2H, d, J = 8.6 Hz). Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.74; H, 4.57; N, 6.68.

6.3.3. *N*-Acetonyl-4-trifluoromethylbenzamide (11b). Compound **11b** was prepared from **10b** in a manner similar to that described for **11d**. Yield 50%, colorless crystals. Mp 139–141 °C. FAB-MS m/z 246 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 2.30 (3H, s), 4.39 (2H, d, J = 4.4 Hz), 6.98 (1H, br), 7.72 (2H, d, J = 8.4 Hz), 7.94 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{11}H_{10}F_3NO_2$: C, 53.88; H, 4.11; N, 5.71. Found: C, 53.72; H, 4.10; N, 5.71.

6.3.4. *N*-Acetonyl-4-methoxybenzamide (11c). Compound **11c** was prepared from **10c** in a manner similar to that described for **11d**. Yield 47%, colorless crystals. Mp 80–82 °C. FAB-MS m/z 208 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 2.27 (3H, s), 3.86 (3H, s), 4.35 (2H, d, J = 4.4 Hz), 6.85 (1H, br), 6.94 (2H, d, J = 8.8 Hz), 7.79 (2H, d, J = 8.8 Hz). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.80; H, 6.21; N, 6.80.

6.3.5. *N*-Acetonyl-4-ethylbenzamide (11e). Compound **11e** was prepared from **10e** in a manner similar to that described for **11d**. Yield 72%, colorless crystals. Mp 57–59 °C. FAB-MS m/z 206 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.25 (3H, t, J = 7.7 Hz), 2.27 (3H, s), 2.70 (2H, q, J = 7.7 Hz), 4.36 (2H, d, J = 4.4 Hz), 6.92 (1H, br), 7.27 (2H, d, J = 8.2 Hz), 7.75 (2H, d, J = 8.2 Hz). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.22; H, 7.38; N, 6.85.

6.3.6. *N*-Acetonyl-3-fluoro-4-methylbenzamide (11f). Compound **11f** was prepared from **10f** in a manner similar to that described for **11d**. Yield 63%, colorless crystals. Mp 103–105 °C. FAB-MS m/z 210 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 2.28 (3H, s), 2.32 (3H, d, J = 1.8 Hz), 4.35 (2H, d, J = 4.4 Hz), 6.89 (1H, br), 7.25 (1H, t, J = 7.8 Hz), 7.48 (1H, d, J = 7.8 Hz), 7.49 (1H, d, J = 10.6 Hz). Anal. Calcd for $C_{11}H_{12}FNO_2$: C, 63.15; H, 5.78; N, 6.69. Found: C, 63.04; H, 5.73; N, 6.67.

6.3.7. *N*-Acetonyl-3-methylbenzamide (11g). Compound **11g** was prepared from **10g** in a manner similar to that described for **11d**. Yield 76%, colorless oil. FAB-MS m/z 192 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 2.28 (3H, s), 2.41 (3H, s), 4.36 (2H, d, J = 4.4 Hz), 6.93 (1H, br), 7.20–7.40 (2H, m), 7.55–7.70 (2H, m). Anal. Calcd for $C_{11}H_{13}NO_2 \cdot 0.35H_2O$: C, 66.88; H, 6.99; N, 7.09. Found: C, 66.48; H, 6.60; N, 7.13.

6.3.8. *N*-Acetonyl-2-methylbenzamide (11h). Compound **11h** was prepared from **10h** in a manner similar to that described for **11d**. Yield 66%, colorless crystals. Mp 65.5–66 °C. FAB-MS m/z 192 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 2.27 (3H, s), 2.46 (3H, s), 4.35 (2H, d, J = 4.8 Hz), 6.54 (1H, br), 7.18–7.45 (4H, m). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.99; H, 6.81; N, 7.41.

6.3.9. *N*-Acetonyl-3,4-dimethylbenzamide (11i). Compound **11i** was prepared from **10i** in a manner similar to that described for **11d**. Yield 63%, colorless crystals. Mp 99–100 °C. FAB-MS m/z 206 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 2.27 (3H, s), 2.31 (6H, s), 4.36 (2H, d, J = 4.4 Hz), 6.91 (1H, br), 7.19 (1H, d, J = 7.7 Hz), 7.54 (1H, d, J = 7.7 Hz), 7.60 (1H, s). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.09; H, 7.30; N, 6.83.

6.3.10. *N*-Acetonyl-2,4-dimethylbenzamide (11j). Compound **11j** was prepared from **10j** in a manner similar to that described for **11d**. Yield 66%, colorless crystals. Mp 73–75 °C. FAB-MS m/z 206 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 2.25 (3H, s), 2.33 (3H, s), 2.43 (3H, s), 4.32 (2H, d, J = 4.4 Hz), 6.56 (1H, br), 7.01 (1H, d, J = 7.6 Hz), 7.04 (1H, s), 7.33 (1H, d, J = 7.6 Hz). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.13; H, 7.34; N, 6.84.

6.4. Preparation of 12a–j

6.4.1. General procedure for the synthesis of 12a–j: methyl *c*-5-[5-(4-methylbenzoylamino)-6-oxoheptyl]-2-methyl-1,3-dioxane-*r*-2-carboxylate (12d). Compound **12d** was prepared from **11d** and **8** in a manner similar to that described previously.[13] To a stirred suspension of NaH (60% dispersion in oil, 0.31 g, 7.8 mmol) in DMF (10 mL) was added dropwise a solution of **11d** (1.50 g, 7.8 mmol) in DMF (4 mL) at −25 to −20 °C under argon. The mixture was stirred for 1 h, and then a solution of **8** (2.68 g, 7.8 mmol) in DMF (4 mL) was added dropwise at the same temperature and the mixture was stirred for 0.5 h. The temperature was allowed to rise to 0 °C within 0.5 h, and then the reaction mixture was poured into water and extracted twice with Et_2O. The combined extracts were washed successively with water and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was subjected to silica gel column chromatography with hexane–EtOAc (1:1) as the eluent to give **12d** (2.35 g, 74%) as a colorless oil. FAB-MS *m*/*z* 406 $[MH]^+$. ^{1}H NMR ($CDCl_3$) δ: 0.82–1.05 (2H, m), 1.10–1.45 (4H, m), 1.50 (3H, s), 1.52–1.80 (1H, m), 1.84–2.20 (2H, m), 2.27 (3H, s), 2.40 (3H, s), 3.37 (2H, t, J = 11.9 Hz), 3.82 (3H, s), 3.92 (2H, dd, J = 11.9, 4.7 Hz), 4.84 (1H, td, J = 7.0, 4.8 Hz), 6.90 (1H, d, J = 7.0 Hz), 7.25 (2H, d, J = 8.4 Hz), 7.71 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{22}H_{31}NO_6$·0.5EtOAc·0.3H_2O: C, 63.36; H, 7.89; N, 3.08. Found: C, 63.03; H, 7.72; N, 3.29.

6.4.2. Methyl *c*-5-[5-(4-chlorobenzoylamino)-6-oxoheptyl]-2-methyl-1,3-dioxane-*r*-2-carboxylate (12a). Compound **12a** was prepared from **11a** in a manner similar to that described for **12d**. Yield 62%, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 0.90–1.10 (2H, m), 1.10–1.45 (4H, m), 1.50 (3H, s), 1.55–1.80 (1H, m), 1.84–2.20 (2H, m), 2.27 (3H, s), 3.37 (2H, t, J = 11.9 Hz), 3.82 (3H, s), 3.92 (2H, dd, J = 11.9, 4.7 Hz), 4.85 (1H, td, J = 6.7, 4.8 Hz), 6.91 (1H, d, J = 6.7 Hz), 7.42 (2H, d, J = 8.7 Hz), 7.75 (2H, d, J = 8.7 Hz).

6.4.3. Methyl *c*-5-[5-(4-trifluoromethylbenzoylamino)-6-oxoheptyl]-2-methyl-1,3-dioxane-*r*-2-carboxylate (12b). Compound **12b** was prepared from **11b** in a manner similar to that described for **12d**. Yield 60%, pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 0.75–1.10 (2H, m), 1.10–1.45 (4H, m), 1.50 (3H, s), 1.52–1.82 (1H, m), 1.82–2.20 (2H, m), 2.29 (3H, s), 3.37 (2H, t, J = 11.8 Hz), 3.82 (3H, s), 3.92 (2H, dd, J = 11.8, 4.8 Hz), 4.86 (1H, td, J = 6.8, 5.2 Hz), 7.00 (1H, d, J = 6.8 Hz), 7.72 (2H, d, J = 8.4 Hz), 7.92 (2H, d, J = 8.4 Hz).

6.4.4. Methyl *c*-5-[5-(4-methoxybenzoylamino)-6-oxoheptyl]-2-methyl-1,3-dioxane-*r*-2-carboxylate (12c). Compound **12c** was prepared from **11c** in a manner similar to that described for **12d**. Yield 37%, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 0.90–1.08 (2H, m), 1.10–1.45 (4H, m), 1.50 (3H, s), 1.56–1.80 (1H, m), 1.85–2.20 (2H, m), 2.27 (3H, s), 3.37 (2H, t, J = 11.8 Hz), 3.82 (3H, s), 3.86 (3H, s), 3.92 (2H, dd, J = 11.8, 4.8 Hz), 4.84 (1H, td, J = 7.0, 4.6 Hz), 6.84 (1H, d, J = 7.0 Hz), 6.94 (2H, d, J = 8.7 Hz), 7.78 (2H, d, J = 8.7 Hz).

6.4.5. Methyl *c*-5-[5-(4-ethylbenzoylamino)-6-oxoheptyl]-2-methyl-1,3-dioxane-*r*-2-carboxylate (12e). Compound **12e** was prepared from **11e** in a manner similar to that described for **12d**. Yield 81%, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 0.85–1.10 (2H, m), 1.10–1.43 (4H, m), 1.25 (3H, t, J = 7.4 Hz), 1.50 (3H, s), 1.52–1.80 (1H, m), 1.85–2.20 (2H, m), 2.27 (3H, s), 2.70 (2H, q, J = 7.4 Hz), 3.36 (2H, t, J = 11.9 Hz), 3.82 (3H, s), 3.92 (2H, dd, J = 11.9, 4.8 Hz), 4.85 (1H, td, J = 6.6, 4.8 Hz), 6.89 (1H, d, J = 6.6 Hz), 7.27 (2H, d, J = 8.3 Hz), 7.73 (2H, d, J = 8.3 Hz).

6.4.6. Methyl *c*-5-[5-(3-fluoro-4-methylbenzoylamino)-6-oxoheptyl]-2-methyl-1,3-dioxane-*r*-2-carboxylate (12f). Compound **12f** was prepared from **11f** in a manner similar to that described for **12d**. Yield 45%, pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 0.90–1.07 (2H, m), 1.10–1.42 (4H, m), 1.50 (3H, s), 1.55–1.80 (1H, m), 1.85–2.20 (2H, m), 2.27 (3H, s), 2.32 (3H, s), 3.37 (2H, t, J = 11.9 Hz), 3.82 (3H, s), 3.92 (2H, dd, J = 11.9, 4.7 Hz), 4.83 (1H, td, J = 6.8, 4.4 Hz), 6.92 (1H, d, J = 6.8 Hz), 7.25 (1H, t, J = 8.0 Hz), 7.47 (2H, d, J = 9.6 Hz).

6.4.7. Methyl *c*-5-[5-(3-methylbenzoylamino)-6-oxoheptyl]-2-methyl-1,3-dioxane-*r*-2-carboxylate (12g). Compound **12g** was prepared from **11g** in a manner similar to that described for **12d**. Yield 51%, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 0.90–1.10 (2H, m), 1.10–1.45 (4H, m), 1.50 (3H, s), 1.53–1.85 (1H, m), 1.85–2.20 (2H, m), 2.27 (3H, s), 2.41 (3H, s), 3.37 (2H, t, J = 11.8 Hz), 3.82 (3H, s), 3.92 (2H, dd, J = 11.8, 4.8 Hz), 4.85 (1H, td, J = 6.7, 4.8 Hz), 6.91 (1H, d, J = 6.7 Hz), 7.32–7.40 (2H, m), 7.56–7.61 (2H, m).

6.4.8. Methyl *c*-5-[5-(2-methylbenzoylamino)-6-oxoheptyl]-2-methyl-1,3-dioxane-*r*-2-carboxylate (12h). Compound **12h** was prepared from **11h** in a manner similar to that described for **12d**. Yield 53%, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 0.93–1.15 (2H, m), 1.17–1.46 (4H, m), 1.51 (3H, s), 1.53–1.80 (1H, m), 1.89–2.20 (2H, m), 2.29 (3H, s), 2.44 (3H, s), 3.39 (2H, t, J = 11.9 Hz), 3.83 (3H, s), 3.94 (2H, dd, J = 11.9, 4.8 Hz), 4.84 (1H, td, J = 7.2, 4.8 Hz), 6.49 (1H, d, J = 7.2 Hz), 7.15–7.45 (4H, m).

6.4.9. Methyl *c*-5-[5-(3,4-dimethylbenzoylamino)-6-oxoheptyl]-2-methyl-1,3-dioxane-*r*-2-carboxylate (12i). Compound **12i** was prepared from **11i** in a manner similar to that described for **12d**. Yield 29%, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 0.90–1.10 (2H, m), 1.10–1.46 (4H, m), 1.50 (3H, s), 1.55–1.80 (1H, m), 1.85–2.20 (2H, m), 2.27 (3H, s), 2.31 (6H, s), 3.36 (2H, t, J = 11.9 Hz), 3.82 (3H, s), 3.92 (2H, dd, J = 11.9, 4.8 Hz), 4.84 (1H, td, J = 7.0, 4.8 Hz), 6.88 (1H, d, J = 7.0 Hz), 7.20 (1H, d, J = 8.3 Hz), 7.53 (1H, d, J = 8.3 Hz), 7.58 (1H, s).

6.4.10. Methyl *c*-5-[5-(2,4-dimethylbenzoylamino)-6-oxoheptyl]-2-methyl-1,3-dioxane-*r*-2-carboxylate (12j). Compound **12j** was prepared from **11j** in a manner similar to that described for **12d**. Yield 91%, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 0.80–1.10 (2H, m), 1.10–1.46 (4H, m), 1.51 (3H, s), 1.53–1.80 (1H, m), 1.89–2.20 (2H, m), 2.27 (3H, s), 2.33 (3H, s), 2.42 (3H, s), 3.38 (2H, t, J = 12.0 Hz), 3.83 (3H, s), 3.93 (2H, dd, J = 12.0,

4.6 Hz), 4.83 (1H, td, J = 7.2, 4.4 Hz), 6.46 (1H, d, J = 7.2 Hz), 7.02 (1H, d, J = 7.8 Hz), 7.04 (1H, s), 7.31 (1H, d, J = 7.8 Hz).

6.5. Preparation of 14a–j

6.5.1. General procedure for the synthesis of 14a–j: 2-methyl-*c*-5-{4-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (14d)

6.5.1.1. Step 1: methyl 2-methyl-*c*-5-{4-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylate (13d). A mixture of **12d** (1.85 g, 4.6 mmol) and phosphorus oxychloride (1.40 g, 9.1 mmol) in toluene (37 mL) was heated at reflux for 2 h. The resulting mixture was poured into ice water and extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by chromatography on silica gel with hexane–EtOAc (5:1) as the eluent to give **13d** (1.23 g, 69%) as colorless crystals. Mp 93.5–94.5 °C. FAB-MS m/z 388 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.00–1.15 (2H, m), 1.20–1.42 (2H, m), 1.51 (3H, s), 1.51–1.70 (2H, m), 1.89–2.15 (1H, m), 2.29 (3H, s), 2.38 (3H, s), 2.44 (2H, t, J = 7.5 Hz), 3.39 (2H, t, J = 11.9 Hz), 3.83 (3H, s), 3.95 (2H, dd, J = 11.9, 4.4 Hz), 7.22 (2H, d, J = 8.5 Hz), 7.86 (2H, d, J = 8.5 Hz). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 68.15; H, 7.47; N, 3.91.

6.5.1.2. Step 2: 2-methyl-*c*-5-{4-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (14d). To a stirred suspension of **13d** (1.01 g, 2.6 mmol) in MeOH (10 mL) was added 1 N NaOH (5.2 mL), and the mixture was heated at reflux for 1 h. After the reaction mixture was evaporated in vacuo, the residue was diluted with water, neutralized with 1 N HCl, and extracted with EtOAc. The extract was dried over $MgSO_4$ and evaporated in vacuo. The residual solid was recrystallized from EtOAc–hexane to give **14d** (0.90 g, 93%) as colorless crystals. Mp 150–152 °C. FAB-MS m/z 374 $[MH]^+$. IR (KBr): 2998, 1729, 1503, 1152, 828, 754 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.99–1.15 (2H, m), 1.27–1.46 (2H, m), 1.50–1.75 (2H, m), 1.58 (3H, s), 1.90–2.16 (1H, m), 2.31 (3H, s), 2.38 (3H, s), 2.53 (2H, t, J = 7.7 Hz), 3.50 (2H, t, J = 11.7 Hz), 3.99 (2H, dd, J = 11.7, 4.4 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.86 (2H, d, J = 8.0 Hz), 11.40 (1H, br). Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.48; H, 7.20; N, 3.78.

6.5.2. 2-Methyl-*c*-5-{4-[2-(4-chlorophenyl)-5-methyl-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (14a). Compound **14a** was prepared from **12a** in a manner similar to that described for **14d**. Yield 39% (in two steps), colorless crystals. Mp 145–146 °C. FAB-MS m/z 393 $[MH]^+$. IR (KBr): 2940, 1721, 1213, 1171, 758 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00–1.15 (2H, m), 1.26–1.43 (2H, m), 1.50–1.73 (2H, m), 1.57 (3H, s), 1.90–2.12 (1H, m), 2.31 (3H, s), 2.50 (2H, t, J = 7.7 Hz), 3.48 (2H, t, J = 11.8 Hz), 3.99 (2H, dd, J = 11.8, 4.6 Hz), 5.10 (1H, br), 7.40 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz). Anal. Calcd for $C_{20}H_{24}NO_5Cl$: C, 60.99; H, 6.14; N, 3.56. Found: C, 60.75; H, 6.25; N, 3.36.

6.5.3. 2-Methyl-*c*-5-{4-[5-methyl-2-(4-trifluoromethylphenyl)-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (14b). Compound **14b** was prepared from **12b** in a manner similar to that described for **14d**. Yield 34% (in two steps), colorless crystals. Mp 132–134 °C. FAB-MS m/z 428 $[MH]^+$. IR (KBr): 2924, 1725, 1321, 1258, 1067, 847, 760 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00–1.15 (2H, m), 1.20–1.45 (2H, m), 1.50–1.75 (2H, m), 1.57 (3H, s), 1.90–2.20 (1H, m), 2.34 (3H, s), 2.52 (2H, t, J = 7.5 Hz), 3.48 (2H, t, J = 11.8 Hz), 3.99 (2H, dd, J = 11.8, 4.8 Hz), 6.30 (1H, br), 7.69 (2H, d, J = 8.0 Hz), 8.10 (2H, d, J = 8.0 Hz). Anal. Calcd for $C_{21}H_{24}F_3NO_5$: C, 59.01; H, 5.66; N, 3.28. Found: C, 59.14; H, 5.83; N, 3.29.

6.5.4. 2-Methyl-*c*-5-{4-[2-(4-methoxyphenyl)-5-methyl-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (14c). Compound **14c** was prepared from **12c** in a manner similar to that described for **14d**. Yield 64% (in two steps), colorless crystals. Mp 157–158 °C. FAB-MS m/z 390 $[MH]^+$. IR (KBr): 2926, 1717, 1615, 1505, 1260, 1169, 1034, 835, 762 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00–1.15 (2H, m), 1.26–1.47 (2H, m), 1.50–1.75 (2H, m), 1.57 (3H, s), 1.90–2.15 (1H, m), 2.30 (3H, s), 2.52 (2H, t, J = 7.7 Hz), 3.51 (2H, t, J = 11.9 Hz), 3.84 (3H, s), 3.99 (2H, dd, J = 11.9, 4.4 Hz), 6.94 (2H, d, J = 8.8 Hz), 7.92 (2H, d, J = 8.8 Hz), 8.90 (1H, br). Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.80; H, 7.13; N, 3.57.

6.5.5. 2-Methyl-*c*-5-{4-[2-(4-ethylphenyl)-5-methyl-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (14e). Compound **14e** was prepared from **12e** in a manner similar to that described for **14d**. Yield 20% (in two steps), colorless crystals. Mp 147 °C. FAB-MS m/z 387 $[MH]^+$. IR (KBr): 2969, 1732, 1499, 1165, 839, 752 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00–1.15 (2H, m), 1.25 (3H, t, J = 7.6 Hz), 1.25–1.45 (2H, m), 1.50–1.72 (2H, m), 1.57 (3H, s), 1.90–2.20 (1H, m), 2.31 (3H, s), 2.52 (2H, t, J = 7.9 Hz), 2.68 (2H, q, J = 7.6 Hz), 3.50 (2H, t, J = 11.9 Hz), 3.99 (2H, dd, J = 11.9, 4.4 Hz), 6.32 (1H, br), 7.25 (2H, d, J = 8.4 Hz), 7.89 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 67.99; H, 7.50; N, 3.76.

6.5.6. 2-Methyl-*c*-5-{4-[2-(3-fluoro-4-methylphenyl)-5-methyl-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (14f). Compound **14f** was prepared from **12f** in a manner similar to that described for **14d**. Yield 32% (in two steps), colorless crystals. Mp 139–140 °C. FAB-MS m/z 391 $[MH]^+$. IR (KBr): 2924, 1730, 1646, 1505, 1169, 1144, 889, 760 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00–1.15 (2H, m), 1.25–1.47 (2H, m), 1.50–1.70 (2H, m), 1.58 (3H, s), 1.90–2.20 (1H, m), 2.30 (3H,s), 2.31 (3H, s), 2.51 (2H, t, J = 7.7 Hz), 3.49 (2H, t, J = 11.6 Hz), 3.99 (2H, dd, J = 12.2, 4.8 Hz), 5.80 (1H, br), 7.21 (1H, t, J = 7.8 Hz), 7.60 (1H, dd, J = 13.2, 1.8 Hz), 7.66 (1H, dd, J = 7.8, 1.8 Hz). Anal. Calcd for $C_{21}H_{26}FNO_5$: C, 64.44; H, 6.69; N, 3.58. Found: C, 64.49; H, 6.68; N, 3.90.

6.5.7. 2-Methyl-*c*-5-{4-[5-methyl-2-(3-methylphenyl)-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (14g). Compound **14g** was prepared from **12g** in a manner similar to that described for **14d**. Yield 55% (in two steps),

colorless crystals. Mp 168–168.5 °C. FAB-MS *m/z* 373 $[MH]^+$. IR (KBr): 2990, 2822, 1717, 1649, 1551, 1213, 887, 760, 725 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00–1.15 (2H, m), 1.25–1.45 (2H, m), 1.53–1.75 (2H, m), 1.57 (3H, s), 1.90–2.20 (1H, m), 2.32 (3H, s), 2.39 (3H, s), 2.52 (2H, t, J = 7.7 Hz), 3.50 (2H, t, J = 11.9 Hz), 3.99 (2H, dd, J = 11.9, 4.4 Hz), 7.23 (1H, d, J = 7.6 Hz), 7.32 (1H, t, J = 7.6 Hz), 7.77 (1H, d, J = 7.6 Hz), 7.81 (1H, s). Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.57; H, 7.22; N, 3.80.

6.5.8. 2-Methyl-*c*-5-{4-[5-methyl-2-(2-methylphenyl)-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (14h). Compound **14h** was prepared from **12h** in a manner similar to that described for **14d**. Yield 32% (in two steps), colorless crystals. Mp 121–122 °C. FAB-MS *m/z* 373 $[MH]^+$. IR (KBr): 2971, 1734, 1647, 1215, 1142, 752, 729 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00–1.15 (2H, m), 1.25–1.45 (2H, m), 1.51 (3H, s), 1.55–1.75 (2H, m), 1.90–2.20 (1H, m), 2.32 (3H, s), 2.52 (2H, t, J = 7.6 Hz), 2.59 (3H, s), 3.46 (2H, t, J = 11.8 Hz), 3.97 (2H, dd, J = 11.8, 4.8 Hz), 7.19–7.35 (3H, m), 7.85 (1H, dd, J = 7.8, 1.8 Hz). Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.47; H, 7.29; N, 3.71.

6.5.9. 2-Methyl-*c*-5-{4-[2-(3,4-dimethylphenyl)-5-methyl-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (14i). Compound **14i** was prepared from **12i** in a manner similar to that described for **14d**. Yield 65% (in two steps), colorless crystals. Mp 169.5–170 °C. FAB-MS *m/z* 387 $[MH]^+$. IR (KBr): 2950, 1730, 1651, 1489, 1169, 1047, 887, 760, 733 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00–1.15 (2H, m), 1.25–1.45 (2H, m), 1.50–1.72 (2H, m), 1.58 (3H, s), 1.90–2.15 (1H, m), 2.29 (6H, s), 2.30 (3H, s), 2.51 (2H, t, J = 7.7 Hz), 3.50 (2H, t, J = 11.9 Hz), 3.99 (2H, dd, J = 11.9, 4.8 Hz), 7.18 (1H, d, J = 8.0 Hz), 7.69 (1H, dd, J = 8.0, 1.4 Hz), 7.76 (1H, d, J = 1.4 Hz). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 68.31; H, 7.53; N, 3.65.

6.5.10. 2-Methyl-*c*-5-{4-[2-(2,4-dimethylphenyl)-5-methyl-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (14j). Compound **14j** was prepared from **12j** in a manner similar to that described for **14d**. Yield 20% (in two steps), colorless crystals. Mp 130–131 °C. FAB-MS *m/z* 387 $[MH]^+$. IR (KBr): 2910, 1732, 1485, 1150, 1061, 758 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00–1.15 (2H, m), 1.25–1.45 (2H, m), 1.51 (3H, s), 1.52–1.75 (2H, m), 1.90–2.15 (1H, m), 2.31 (3H, s), 2.33 (3H, s), 2.51 (2H, t, J = 8.0 Hz), 2.54 (3H, s), 3.46 (2H, t, J = 11.9 Hz), 3.97 (2H, dd, J = 11.9, 4.8 Hz), 7.04 (1H, d, J = 7.9 Hz), 7.06 (1H, s), 7.73 (1H, d, J = 7.9 Hz), 8.65 (1H, br). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 68.25; H, 7.53; N, 3.65.

6.6. Preparation of 16

6.6.1. *N*-(2-Hydroxybutyl)-4-methylbenzamide (15). Compound **15** was prepared from 3-methylbenzoyl chloride and 1-amino-2-butanol in a manner similar to that described for **10d**. Yield 93%, colorless crystals. Mp 80–83 °C. FAB-MS *m/z* 208 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 0.99 (3H, t, J = 7.5 Hz), 1.55 (2H, qn, J = 7.5 Hz), 2.39 (3H, s), 2.90 (1H, br), 3.31 (1H, ddd, J = 14.1, 8.2, 5.4 Hz), 3.63–3.80 (2H, m), 6.69 (1H, br), 7.22 (2H, d, J = 8.2 Hz), 7.68 (2H, d, J = 8.2 Hz). Anal. Calcd for $C_{12}H_{17}NO_2{\cdot}0.5H_2O$: C, 66.64; H, 8.39; N, 6.48. Found: C, 66.44; H, 8.23; N, 6.88.

6.6.2. 2-Methyl-*c*-5-{4-[5-ethyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (16). *N*-(2-Oxobutyl)-4-methylbenzamide was prepared from **15** in a manner similar to that described for **11d**. Yield 66%, colorless crystals. Mp 80–81 °C. FAB-MS *m/z* 206 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.16 (3H, t, J = 7.5 Hz), 2.40 (3H, s), 2.55 (2H, q, J = 7.5 Hz), 4.35 (2H, d, J = 4.4 Hz), 6.95 (1H, br), 7.25 (2H, d, J = 8.0 Hz), 7.72 (2H, d, J = 8.0 Hz). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.09; H, 7.17; N, 6.88.

Methyl *c*-5-[5-(4-methylbenzoylamino)-6-oxooctyl]-2-methyl-1,3-dioxane-*r*-2-carboxylate was prepared from *N*-(2-oxobutyl)-4-methylbenzamide and **8** in a manner similar to that described for **12d**. Yield 73%, colorless crystals. Mp 87–89 °C. FAB-MS *m/z* 420 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 0.90–1.42 (6H, m), 1.12 (3H, t, J = 7.3 Hz), 1.50 (3H, s), 1.51–1.75 (1H, m), 1.80–2.13 (2H, m), 2.40 (3H, s), 2.46–2.70 (2H, m), 3.36 (2H, t, J = 12.0 Hz), 3.82 (3H, s), 3.92 (2H, dd, J = 12.0, 4.8 Hz), 4.85 (1H, td, J = 7.4, 4.8 Hz), 6.90 (1H, d, J = 7.4 Hz), 7.25 (2H, d, J = 8.4 Hz), 7.70 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93; N, 3.34. Found: C, 65.75; H, 7.87; N, 3.34.

Compound **16** was prepared from methyl *c*-5-[5-(4-methylbenzoylamino)-6-oxooctyl]-2-methyl-1,3-dioxane-*r*-2-carboxylate in a manner similar to that described for **14d**. Yield 63% (in two steps), colorless crystals. Mp 160–161 °C. FAB-MS *m/z* 388 $[MH]^+$. IR (KBr): 2939, 1717, 1501, 1156, 766 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00–1.15 (2H, m), 1.20–1.47 (2H, m), 1.27 (3H, t, J = 7.5 Hz), 1.50–1.80 (2H, m), 1.57 (3H, s), 1.90–2.20 (1H, m), 2.38 (3H, s), 2.53 (2H, t, J = 7.7 Hz), 2.67 (2H, q, J = 7.5 Hz), 3.50 (2H, t, J = 11.9 Hz), 3.99 (2H, dd, J = 11.9, 4.6 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.40 (1H, br), 7.87 (2H, d, J = 8.0 Hz). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 68.25; H, 7.53; N, 3.65.

6.7. Preparation of 22

6.7.1. 3-[2-(4-Methylphenyl)-5-trifluoromethyloxazol-4-yl]-1-propanol (17). Compound **17** was prepared in 67% yield from *N*-(4-methylbenzoyl)proline according to a known method.[14] Mp 87–89 °C. FAB-MS *m/z* 286 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.98 (2H, qn, J = 6.4 Hz), 2.30 (1H, br), 2.42 (3H, s), 2.82 (2H, td, J = 6.4, 1.6 Hz), 3.74 (2H, t, J = 6.4 Hz), 7.28 (2H, d, J = 8.0 Hz), 7.93 (2H, d, J = 8.0 Hz). Anal. Calcd for $C_{14}H_{14}F_3NO_2$: C, 58.95; H, 4.95; N, 4.91. Found: C, 58.96; H, 4.87; N, 4.89.

6.7.2. Methyl 4-[2-(4-methylphenyl)-5-trifluoromethyloxazol-4-yl]butyrate (18). To a stirred solution of **17** (6.40 g, 22 mmol), triethylamine (4.7 mL, 34 mmol), and 4-dimethylaminopyridine (0.29 g, 2.4 mmol) in CH_2Cl_2

(35 mL) was added *p*-toluenesulfonyl chloride (5.13 g, 27 mmol) and stirring was continued for 3 h at room temperature. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed successively with 10% aqueous HCl, water, and saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent by evaporation gave 3-[2-(4-methylphenyl)-5-trifluoromethyloxazol-4-yl]propyl *p*-toluenesulfonate (10.08 g, quant) as pale brown crystals. Mp 57–58 °C. FAB-MS *m*/*z* 440 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.98 (2H, qn, J = 6.4 Hz), 2.42 (6H, s), 2.82 (2H, td, J = 6.4, 1.4 Hz), 4.14 (2H, t, J = 6.4 Hz), 7.28 (2H, d, J = 6.8 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.79 (2H, d, J = 8.4 Hz), 7.89 (2H, d, J = 6.8 Hz). Anal. Calcd for $C_{21}H_{20}F_3NO_4S{\cdot}0.6H_2O$: C, 56.02; H, 4.75; N, 3.11. Found: C, 56.04; H, 4.75; N, 3.21.

A mixture of this compound and sodium cyanide (1.16 g, 24 mmol) in DMSO (40 mL) was heated at 90 °C for 2 h. The mixture was diluted with water and extracted with Et_2O, and the extract was washed with water and dried over $MgSO_4$. Removal of the solvent by evaporation gave 4-[2-(4-methylphenyl)-5-trifluoromethyloxazol-4-yl]butyronitrile (6.35 g, 96%) as pale brown crystals. Mp 41–42.5 °C. FAB-MS *m*/*z* 295 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 2.12 (2H, qn, J = 7.0 Hz), 2.42 (3H, s), 2.47 (2H, t, J = 7.0 Hz), 2.86 (2H, td, J = 7.0, 1.4 Hz), 7.29 (2H, d, J = 8.2 Hz), 7.94 (2H, d, J = 8.2 Hz). Anal. Calcd for $C_{15}H_{13}F_3N_2O$: C, 61.22; H, 4.15; N, 9.52. Found: C, 61.12; H, 4.45; N, 9.32.

HCl gas was passed through an ice-cooled solution of 4-[2-(4-methylphenyl)-5-trifluoromethyloxazol-4-yl]butyronitrile (5.28 g, 18 mmol) in dry MeOH (42 mL) until the solution was saturated with HCl gas. The mixture was stirred at room temperature for 30 min, and after water (5.3 mL, 294 mmol) was added, the mixture was allowed to stand at room temperature for 16 h. The reaction mixture was diluted with water and then extracted twice with EtOAc. The organic extracts were combined and washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After evaporation of solvent, the residue was subjected to chromatography on silica gel with hexane–EtOAc (4:1) as the eluent to give **18** (5.63 g, 96%) as colorless crystals. Mp 44.5–45 °C. FAB-MS *m*/*z* 328 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.95–2.14 (2H, m), 2.40 (2H, t, J = 7.4 Hz), 2.42 (3H, s), 2.75 (2H, td, J = 7.4, 1.2 Hz), 3.68 (3H, s), 7.28 (2H, d, J = 8.0 Hz), 7.94 (2H, d, J = 8.0 Hz). Anal. Calcd for $C_{16}H_{16}F_3NO_3$: C, 58.71; H, 4.93; N, 4.28. Found: C, 58.64; H, 4.88; N, 4.30.

6.7.3. 4-(4-Bromobutyl)-2-(4-methylphenyl)-5-trifluoromethyloxazole (19). To an ice-cooled suspension of $LiAlH_4$ (0.76 g, 20 mmol) in THF (40 mL) was added dropwise a solution of **17** (5.47 g, 17 mmol) in THF (20 mL) at 4–13 °C. The mixture was stirred at room temperature for 1 h and then recooled in an ice-bath. The reaction was quenched with water (0.75 mL), aqueous 15% NaOH (0.75 mL), and water (2.2 mL), in that order. The mixture was stirred at room temperature for 1 h. The insoluble precipitate was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in EtOAc and the solution was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel with hexane–EtOAc (2:1) as the eluent to give crude 4-[2-(4-methylphenyl)-5-trifluoromethyloxazol-4-yl]-1-butanol (5.17 g) as a wet, colorless solid. To a solution of this crude product in CH_2Cl_2 (90 mL) were added triphenylphosphine (4.98 g, 19 mmol) and carbon tetrabromide (6.30 g, 19 mmol). The mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was purified by chromatography on silica gel with hexane–EtOAc (10:1) as the eluent to give **19** (0.97 g, 16% in two steps) as a colorless oil. ^1H NMR ($CDCl_3$) δ: 1.80–2.05 (4H, m), 2.42 (3H, s), 2.72 (2H, t, J = 6.2 Hz), 3.44 (2H, t, J = 6.2 Hz), 7.28 (2H, d, J = 8.6 Hz), 7.94 (2H, d, J = 8.6 Hz).

6.7.4. 2-Hydroxymethyl-6-[2-(4-methylphenyl)-5-trifluoromethyloxazol-4-yl]-1-hexanol (20). To an ice-cooled suspension of NaH (60% dispersion in oil, 0.22 g, 5.5 mmol) in THF (10 mL) and DMF (5 mL) was added dropwise diethyl malonate (1.06 g, 6.6 mmol). The mixture was stirred with ice-cooling for 15 min, after which a solution of **19** (0.96 g, 2.7 mmol) was added dropwise. The resulting mixture was stirred at 100 °C for 15 h and then diluted with ice water and extracted with Et_2O. The extract was washed with water and dried over $MgSO_4$. After the solvent was evaporated, the crude product was purified by silica gel column chromatography with hexane–EtOAc (10:1) as the eluent to give crude diethyl 2-{4-[2-(4-methylphenyl)-5-trifluoromethyloxazol-4-yl]butyl}malonate (1.21 g), including diethyl malonate, as a pale yellow oil. Compound **20** was prepared by reduction of crude diethyl 2-{4-[2-(4-methylphenyl)-5-trifluoromethyloxazol-4-yl]butyl}malonate with $LiAlH_4$ in a manner similar to that described for **6**. Yield 54% (in two steps), colorless crystals. Mp 95–97 °C. FAB-MS *m*/*z* 358 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.20–1.50 (4H, m), 1.61–1.82 (3H, m), 2.35 (2H, br), 2.42 (3H, s), 2.71 (2H, td, J = 7.4, 1.2 Hz), 3.67 (2H, dd, J = 10.6, 7.4 Hz), 3.82 (2H, dd, J = 10.6, 3.6 Hz), 7.29 (2H, d, J = 8.4 Hz), 7.95 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{18}H_{22}F_3NO_3{\cdot}1H_2O$: C, 57.59; H, 6.44; N, 3.73. Found: C, 57.65; H, 6.33; N, 3.66.

6.7.5. Methyl 2-methyl-*c*-5-{4-[2-(4-methylphenyl)-5-trifluoromethyl-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylate (21). Compound **21** was prepared from **20** in a manner similar to that described for **6**. Yield 38%, colorless crystals. Mp 58.5–60 °C. FAB-MS *m*/*z* 442 $[MH]^+$. ^1H NMR ($CDCl_3$) δ: 1.04–1.15 (2H, m), 1.20–1.42 (2H, m), 1.51 (3H, s), 1.60–1.75 (2H, m), 1.90–2.20 (1H, m), 2.42 (3H, s), 2.66 (2H, t, J = 6.5 Hz), 3.40 (2H, t, J = 11.8 Hz), 3.83 (3H, s), 3.95 (2H, dd, J = 11.8, 4.4 Hz), 7.28 (2H, d, J = 7.4 Hz), 7.94 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{22}H_{26}F_3NO_5$: C, 59.86; H, 5.94; N, 3.17. Found: C, 60.05; H, 5.92; N, 3.19.

6.7.6. 2-Methyl-*c*-5-{4-[2-(4-methylphenyl)-5-trifluoromethyl-1,3-oxazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (22). Compound **22** was prepared from **21** by alkaline hydrolysis by a method similar to that described for **14d**. Yield 80%, colorless crystals. Mp 130–131 °C. FAB-MS *m*/*z* 428 $[MH]^+$. IR (KBr): 2925, 1738, 1501,

1391, 1130, 1100, 752 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.00–1.15 (2H, m), 1.25–1.45 (2H, m), 1.57 (3H, s), 1.62–1.77 (2H, m), 1.90–2.20 (1H, m), 2.42 (3H, s), 2.68 (2H, t, J = 6.7 Hz), 3.47 (2H, t, J = 11.9 Hz), 3.99 (2H, dd, J = 11.9, 4.4 Hz), 7.28 (2H, d, J = 8.4 Hz), 7.94 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{21}H_{24}F_3NO_5$: C, 59.01; H, 5.66; N, 3.28. Found: C, 59.11; H, 5.67; N, 3.16.

6.8. Preparation of 24

6.8.1. Methyl 2-methyl-*c*-5-{4-[5-methyl-2-(4-methylphenyl)-1,3-thiazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylate (23). A mixture of **12d** (2.02 g, 5 mmol) and Davy Reagent Methyl[15] (2.84 g, 10 mmol) in THF (20 mL) was stirred for 3 h at 55 °C and then for further 3 h at 75 °C. After dilution with EtOAc, the reaction mixture was successively washed with 10% aqueous HCl, water, and saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by chromatography on silica gel with hexane–EtOAc (4:1) as the eluent to give **23** (0.38 g, 19%) as a pale yellow oil. ^1H NMR ($CDCl_3$) δ: 1.00–1.15 (2H, m), 1.23–1.40 (2H, m), 1.51 (3H, s), 1.60–1.77 (2H, m), 1.92–2.14 (1H, m), 2.37 (6H, s), 2.66 (2H, t, J = 7.5 Hz), 3.39 (2H, t, J = 11.9 Hz), 3.83 (3H, s), 3.95 (2H, dd, J = 11.9, 4.8 Hz), 7.20 (2H, d, J = 8.0 Hz), 7.75 (2H, d, J = 8.0 Hz).

6.8.2. 2-Methyl-*c*-5-{4-[5-methyl-2-(4-methylphenyl)-1,3-thiazol-4-yl]butyl}-1,3-dioxane-*r*-2-carboxylic acid (24). Compound **24** was prepared from **23** by alkaline hydrolysis by a method similar to that described for **14d**. Yield 84%, colorless crystals. Mp 172–172.5 °C. FAB-MS *m/z* 390 $[MH]^+$. IR (KBr): 2923, 1728, 1557, 1246, 1210, 1165, 1144, 812 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.02–1.13 (2H, m), 1.26–1.44 (2H, m), 1.54 (3H, s), 1.60–1.72 (2H, m), 1.90–2.15 (1H, m), 2.37 (3H, s), 2.38 (3H, s), 2.70 (2H, t, J = 7.7 Hz), 3.47 (2H, t, J = 11.8 Hz), 3.98 (2H, dd, J = 11.8, 4.6 Hz), 7.20 (2H, d, J = 8.4 Hz), 7.75 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{21}H_{27}NO_4S$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.68; H, 6.97; N, 3.64.

6.9. Preparation of 26

6.9.1. Methyl *c*-5-{4-[1,5-dimethyl-2-(4-methylphenyl)imidazol-4-yl]butyl}-2-methyl-1,3-dioxane-*r*-2-carboxylate (25). Compound **25** was prepared in a manner similar to that previously described.[17] Acetic acid (0.84 mL, 15 mmol) and a solution of 2 M methylamine in THF (1.5 mL, 3 mmol) were added to a solution of **12d** (0.80 g, 2 mmol) in xylene (20 mL). The mixture was refluxed for 2 h with azeotropic removal of water. After cooling, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and the organic layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by chromatography on silica gel with $CHCl_3$–MeOH (100:1) as the eluent to give **25** (0.63 g, 80%) as a pale yellow oil. ^1H NMR ($CDCl_3$) δ: 0.97–1.10 (2H, m), 1.20–1.40 (2H, m), 1.50 (3H, s), 1.54–1.70 (2H, m), 1.90–2.15 (1H, m), 2.18 (3H, s), 2.38 (3H, s), 2.51 (2H, t, J = 7.5 Hz), 3.38 (2H, t, J = 12.0 Hz), 3.53 (3H, s), 3.83 (3H, s), 3.95 (2H, dd, J = 12.0, 4.5 Hz), 7.23 (2H, d, J = 8.2 Hz), 7.45 (2H, d, J = 8.2 Hz).

6.9.2. *c*-5-{4-[1,5-Dimethyl-2-(4-methylphenyl)imidazol-4-yl]butyl}-2-methyl-1,3-dioxane-*r*-2-carboxylic acid (26). To a stirred solution of **25** (572 mg, 1.4 mmol) in MeOH (8 mL) was added 1 N NaOH (2 mL), and the mixture was heated at reflux for 2 h. After evaporation of the solvent, the residue was dissolved in water and washed with Et_2O. The aqueous layer was separated, neutralized with 1 N HCl (2 mL), and extracted with $CHCl_3$ (6 × 30 mL). The organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residual solid was washed with Et_2O and filtered to give **26** (309 mg, 56%) as colorless crystals. Mp 192–194 °C (dec). FAB-MS *m/z* 386 $[MH]^+$. IR (KBr): 2937, 2361, 1169, 1140, 885, 791 cm^{-1}. ^1H NMR (D_2O) δ: 0.80–1.40 (4H, m), 1.28 (3H, s), 1.40–1.60 (2H, m), 1.65–1.95 (1H, m), 2.16 (3H, s), 2.32 (3H, s), 2.55 (2H, t, J = 7.0 Hz), 3.32 (2H, t, J = 11.7 Hz), 3.76 (2H, dd, J = 11.7, 4.6 Hz), 7.35 (2H, d, J = 8.4 Hz), 7.40 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{22}H_{30}N_2O_4 \cdot 1H_2O$: C, 65.32; H, 7.97; N, 6.93. Found: C, 65.36; H, 7.58; N, 6.75.

6.10. Biological procedures

6.10.1. PPAR transactivation assays. Agonist activity at each PPAR subtype was determined by cell-based transactivation assay as described previously.[16] Briefly, CV-1 cells (ATCC, Manassas, VA) were cultured in Dulbecco's modified Eagle's minimal essential medium containing 10% fetal bovine serum, 100 U/mL penicillin G, and 100 μg/mL streptomycin sulfate under humidified 5% CO_2 and 95% air at 37 °C. Three kinds of expression vectors were cotransfected into CV-1 cells using Tfx-20 transfection reagent (Promega, Madison, WI) according to the manufacturer's instructions: (1) pSG5 (Stratagene, La Jolla, CA), containing a full-length cDNA clone of each PPAR subtype (an expression vector); (2) pGL3 (Promega) containing three copies of a peroxisome proliferator response element derived from the promoter region of the rat acyl-CoA oxidase gene and a thymidine kinase promoter sequence (a reporter vector); and (3) phRL-TK (Promega), a *Renilla* luciferase reporter vector for use as an internal standard. All compounds were dissolved in DMSO, and the final concentration of DMSO in the medium was 0.1% (v/v). Cells were treated with DMSO or compound for 48 h, and the luciferase activity of the cell lysate was measured with a Wallac 1420 ARVOsx multilabel counter (Perkin-Elmer Inc., Wellesley, MA) by means of a dual luciferase assay system (Promega). The half-maximum effective concentration (EC_{50}) for each PPAR agonist activity was estimated from the concentration–activity curves as the concentration giving 50% of the maximum activity gained by the relevant positive control. The approximate EC_{50} values were given as the closest concentration in a geometric progression of agonist concentrations with a common ratio of three.

6.10.2. Animal experiments. KK-A^y mice, 8 weeks old, were purchased from Clea Japan, Inc. (Tokyo, Japan). The mice were housed in a room maintained at 23 ± 2 °C under a 12/12 h light/dark cycle. They had free access to laboratory chow (CE-2, Clea Japan) and tap water, and were used for experiments at 10 weeks of

age. They were divided into experimental groups of five animals each based on their plasma TG and glucose levels. The test compounds were administered over a period of four days as suspensions in 0.5% methylcellulose solution. A day after the last administration, blood samples were taken from the tail vein of non fasted mice in the morning for measuring plasma TG and glucose levels. In the afternoon, blood samples were taken from the inferior vena cava of nonfasted animals under sodium pentobarbital anesthesia for measuring plasma lipoprotein cholesterol levels. The plasma TG and glucose levels were determined enzymatically by means of the commercial diagnostic kits Triglyceride E-test Wako and Glucose CII-test Wako (Wako Pure Chemical Industries, Osaka, Japan). Plasma lipoprotein cholesterol levels were determined with an automated Tosoh Lipoprotein Analytical System (Tosoh Co., Tokyo, Japan).[18] Briefly, plasma lipoproteins were resolved by HPLC on a TSKgel Lipopropak column (Tosoh Co., 7.5 mm id × 300 mm) with TSK eluent LP-1 (Tosoh Co.) as the elution buffer. Each 5-μL sample of plasma was applied to the column and the cholesterol was detected by an on-line enzymatic reaction by mixing the effluent from the column with a liquid reagent from a commercial kit, Determiner L TC (Kyowa Medex Co., Tokyo, Japan). All animal procedures were approved by the Committee for the Institutional Care and Use of Animals at Nippon Shinyaku Co.

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