Synthesis and Biological Evaluation of (*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acids: A Novel Series of PPARγ Agonists

Satoru AZUKIZAWA,[a] Masayasu KASAI,[a] Kenji TAKAHASHI,[a] Tomohiro MIIKE,[a] Kazuyoshi KUNISHIRO,[a] Mamoru KANDA,[a] Chisato MUKAI,[b] and Hiroaki SHIRAHASE*,[a]

[a] *Research Laboratories, Kyoto Pharmaceutical Industries, Ltd.; 38, Nishinokyo Tsukinowa-cho, Nakagyo-ku, Kyoto 604–8444, Japan: and* [b] *Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University; Kakuma-machi, Kanazawa, Ishikawa 920–1192, Japan.*
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A novel series of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives were synthesized and biologically evaluated. (*S*)-2-Benzyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (10, KY-021) was identified as a novel peroxisome proliferators-activated receptor (PPAR)γ agonist, which showed potent activity in human PPARγ (EC_{50}=11.8 nM). KY-021 reduced plasma glucose and triglyceride levels at 3 mg/kg/d for 7 d in male KK-A^y mice. KY-021 also decreased plasma triglyceride levels at 0.3—3 mg/kg/d for 6 d, and improved oral glucose tolerance at 1 and 3 mg/kg/d for 7 d in male Zucker fatty rats. Maximal plasma concentration of KY-021 after oral administration at 10 mg/kg was 6.6 μg/ml and 2.1 μg/ml in male ICR mice and male SD rats, respectively. Repeated oral administration of KY-021 at 30 mg/kg/d for 10 weeks had little toxicity in male SD rats. These results demonstrated that KY-021 has great potential as an efficacious and safe drug for diabetes.

Key words tetrahydroisoquinoline derivative; diabetes; KK-A^y mouse; peroxisome proliferators-activated receptor (PPAR)γ agonist; hypoglycemic effect; hypolipidemic effect

Peroxisome proliferators-activated receptors (PPARs) are a subfamily of nuclear hormone receptors, which are ligand-activated transcription factors. There are three subtypes of PPAR: PPARα expressed in the liver and related to fatty acid metabolism, PPARγ expressed in adipocytes and playing a role in its differentiation, and PPARδ expressed in most cell types and involved in dyslipidemia, cancer and the central nervous system; therefore, PPARs have been focused on as a potential target for metabolic diseases such as diabetes, dyslipidemia and atherosclerosis.[1—3] Fibrates such as clofibrate, bezafibrate and fenofibrate, which have been long and widely used as anti-hyperlipidemic drugs, are known to exert their effect *via* activation of PPARα. Thiazolidinedione derivatives (glitazones), such as pioglitazone and rosiglitazone, known as anti-diabetic drugs, activate PPARγ and enhance insulin sensitivity.[4,5]

Thiazolidinedione derivatives cause edema, increase the risk of weight gain and congestive heart failure, and rarely show hepatotoxicity.[6,7] There have been a great number of attempts to find a novel PPARγ agonist that is structurally different from thiazolidinedione derivatives and has higher efficacy and safety. Thiazolidinedione moiety was replaced by oxadiazolidinedione and isoxazolidinedione in YM-440 and JTT-501, respectively (Fig. 1).[8,9] Endogenous ligands for PPARγ have been reported to be fatty acids and eicosanoids, such as 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2.[2,10] Thus, a number of carboxylic acid derivatives have been designed and synthesized to enhance drug-protein interaction and to modify PPAR subtype selectivity (Fig. 1)[2,11—13]; however, no non-thiazolidinedione derivatives have been developed successfully as new anti-diabetic drugs; therefore, further efforts are necessary to identify a structurally new PPARγ agonist.

As shown in Fig. 1, some recent PPARγ agonists are benzene derivatives with carboxylic acid moiety and two lipophilic moieties, which are postulated to have lipophilic interaction with two regions of a PPARγ protein.[14] However, in these compounds, a carboxylic acid moiety, lipophilic moiety and benzyl moiety with a lipophilic chain are attached to a central atom (C or N) *via* a single bond, thus, each moiety can bend and/or rotate freely (Fig. 1). We hypothesized that in these carboxylic acid-type derivatives, the limitation of movement of the three moieties and fixation of their direction may enhance their PPARγ agonist activity and reduce their side effects. In the present study, a tyrosine derivative was cyclized to a 1,2,3,4-tetrahydroisoquinoline derivative and then various side chains were introduced into the 2nd and 7th positions of the 1,2,3,4-tetrahydroisoquinoline ring (Fig. 2). Biological activities were evaluated in a series of 1,2,3,4-tetrahydroisoquinoline derivatives and their structure–activity relationships are discussed.

Chemistry The general approach to the synthesis of (*S*)-2-substituted-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives **19** is outlined in Chart 1. The tetrahydroisoquinoline carboxylate **13** was prepared by Pictet–Spengler reaction of 3,5-diiodotyrosine (**12**)[15] followed by esterification. Catalytic dehalogenation of **13** and following protection of the amine with the Boc group afforded ethyl (*S*)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**14**). Etherification of **14** with methanesulfonate **15**[9,16] in the presence of K_2CO_3 afforded **16**. The Boc group of **16** was removed with HCl/HCO_2H, affording **17**. Acylation or alkylation of **17** afforded 2-Acyl or 2-Alkyl tetrahydroisoquinoline derivatives **18**. Hydrolysis of the esters provided carboxylic acid derivatives **19**.

Results and Discussion

Among benzene-based PPARγ agonists with carboxylic acid moiety and two lipophilic moieties (Fig. 1), compound **5** (farglitazar), a tyrosine derivative, has potent and selective PPARγ agonist activity but inevitably causes edema.[17] It has

* To whom correspondence should be addressed. e-mail: shirahase@kyoto-pharm.co.jp

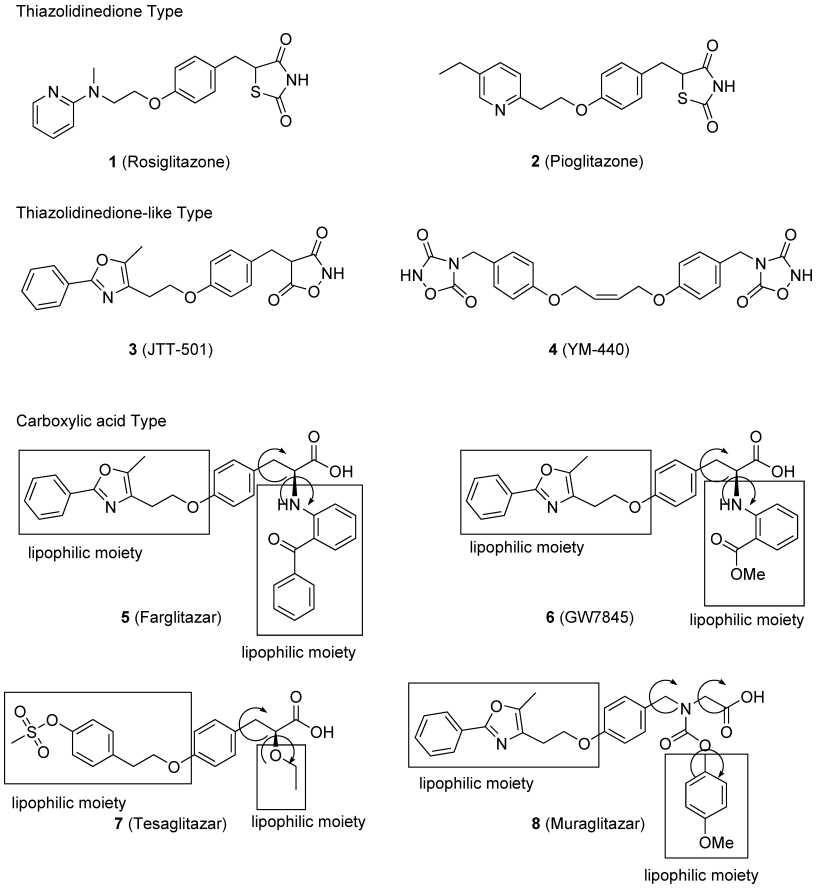
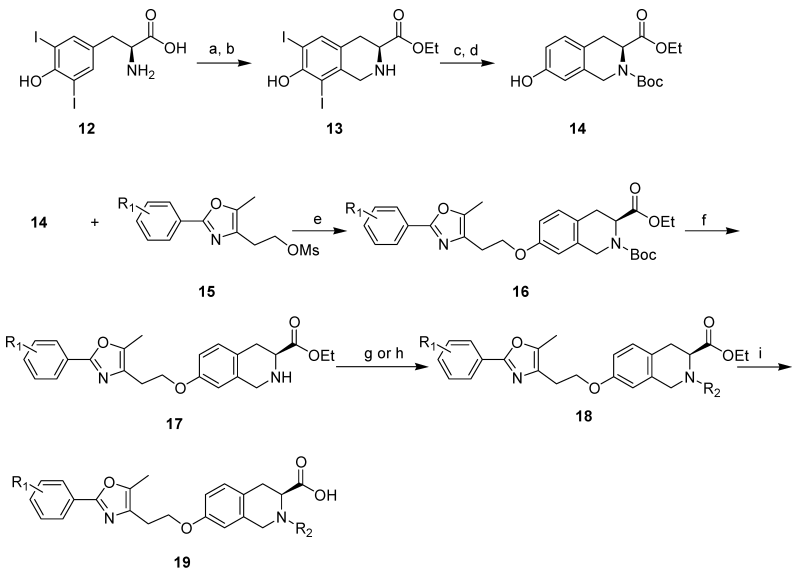


Fig. 1. Chemical Structure of PPARγ Agonists



Reagents: (a) formalin,c-HCl, 1,2-dimethoxyethane; (b) c-HCl, EtOH; (c) H_2, Pd-C, Et_3N, MeOH; (d) Boc_2O, THF; (e) K_2CO_3, DMF; (f) HCl, HCO_2H; (g) acyl chloride, Et_3N, CH_2Cl_2 ; (h) alkyl halide, base, DMF; (i) LiOH, MeOH, THF.

Chart 1

relatively high molecular weight (MW: 546.61) and thus is highly lipophilic (log *P*: 4.2). We synthesized a series of 1,2,3,4-tetrahydroisoquinoline derivatives by cyclization of a tyrosine derivative to find a novel class of PPARγ agonist with a more rigid structure, lower molecular weight and lipophilicity (Fig. 2). In compound **9** lacking a lipophilic moiety at the 2nd position of 1,2,3,4-tetrahydroisoquinoline, lipophilicity as well as PPARγ agonist activity was drasti-

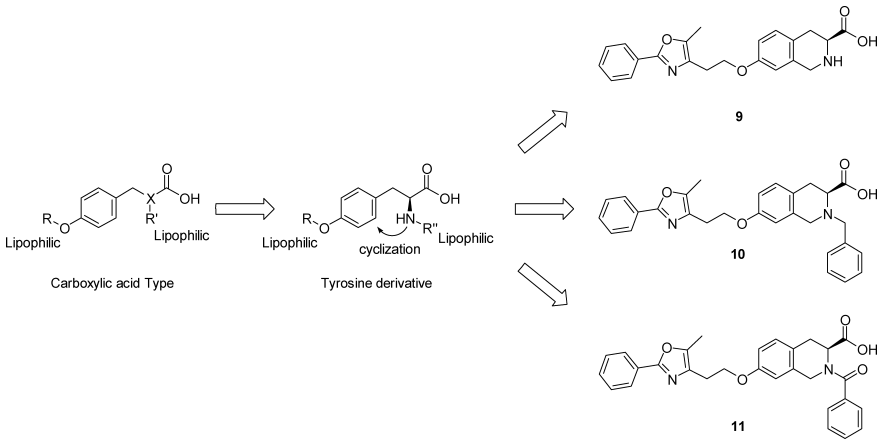


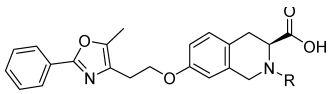
Fig. 2. Structural Concept of a 1,2,3,4-Tetrahydroisoquinoline-Based PPARγ Agonist

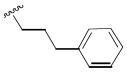
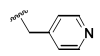
cally reduced (log *P*: 1.4, EC_{50}: $>10\,\mu$M). Then, two types of aromatic moieties (benzyl and benzoyl) were introduced into the 2nd position. Compound **10** with a benzyl moiety showed potent PPARγ agonist activity (EC_{50}: 11.8 ± 1.8 nM, $n=4$) comparable to that of farglitazar (EC_{50}: 8.7 ± 2.1 nM, $n=4$), while it had lower molecular weight and was less lipophilic than farglitazar (MW: 468.54 *vs.* 546.61; log *P*: 3.2 *vs.* 4.2). Compound **10** and farglitazar showed similar insulin-sensitizing activities determined as an increasing effect on cellular triglyceride (TG) levels during insulin-stimulated adipocyte differentiation in 3T3-L1 cells (EC_{50}: 3.1 ± 0.9 nM and 2.6 ± 0.8 nM, respectively, $n=4$). Compound **11** with a benzoyl moiety showed very weak PPARγ agonist activity (EC_{50}: $1.4\pm0.4\,\mu$M, $n=4$). Thus, in the following experiments, a series of derivatives were synthesized by modification at the 2nd and 7th positions based on compound **10**, and structure–activity relationships were explored. Insulin-sensitizing activities of the derivatives were determined in comparison with compound **10**, as described above, in adipocyte differentiation using 3T3-L1 cells, and expressed as relative activity to compound **10** (a reciprocal of equipotent concentration ratio). Glucose- and TG-lowering effects of the derivatives and **10** were also examined in KK-A^y mice, a type 2 diabetic model animal, and expressed as a %decrease in glucose and TG in comparison with control mice administered vehicle.

In Table 1, elongation of a benzyl moiety by insertion of an ethyl chain in compound **20** markedly reduced *in vitro* activity in 3T3-L1 cells. Reduction of benzene to cyclohexane (compound **21**) enhanced *in vitro* activity but markedly decreased glucose-lowering activity: cyclohexyl moiety may have been easily metabolized, resulting in a low plasma concentration. Replacement of the benzyl group with pyridinyl (compounds **22**, **23**) also reduced *in vitro* activity, suggesting that a basic nitrogen atom may have disturbed the interaction between the compound and lipophilic region of the protein.

In Table 2, moving the phenyl oxazole ethoxy moiety from the 7th to 6th position (compound **24**) and shortening the chain at the 7th position (compound **25**) remarkably reduced *in vitro* and *in vivo* activity. Compound **26**, an *R* isomer, showed much less activity than compound **10**, an *S* isomer. Interestingly, it was reported that the *S* isomer is more potent than the *R* isomer in tyrosine derivatives and α-alkoxy propionic acid derivatives.[18,19] The desirable direction of carboxylic acid and two lipophilic moieties was considered to be achieved in the *S* conformation in cyclic as well as branched molecules. In compounds **27** and **28**, the pyridinyl moiety used in **1** (rosiglitazone) and **2** (pioglitazone) was introduced into the 7th position: *in vitro* and *in vivo* activity were markedly reduced. These pyridinyl moieties maintained the activity in farglitazar-related derivatives.[11] In the present type of compounds, movement of the carboxyl moiety and two lipophilic moieties was limited and their direction was fixed; thus, the above pyridinyl chains may not have suitably

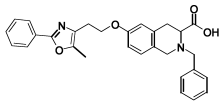
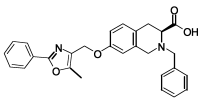
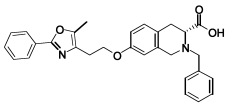
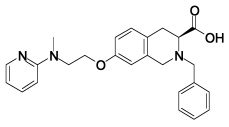
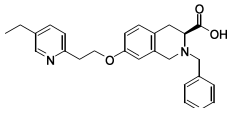
Table 1. Insulin-Sensitizing Effects on 3T3-L1 Cells, and Hypoglycemic and Hypolipidemic Effects in KK-A^y Mice of 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acids with Various Substituents at 2-Position



Compound	R	3T3-L1[a] Activity ratio	KK-A^y mouse[b] Glucose % decrease	KK-A^y mouse[b] TG % decrease
10		1	45**	29*
11		0.01	6	3
20		<0.01	10 (47**)	0 (49**)
21		5.0	6 (47**)	9 (49**)
22		0.02	16 (61**)	8 (54**)
23		0.01	7 (61**)	14 (54**)

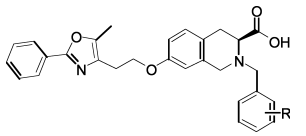
a) Duplicate assay, relative activity against compound **10** for TG-increasing effect during insulin-stimulated adipocyte differentiation, expressed as a reciprocal of equipotent concentration ratio of test compound/compound **10**. *b*) $n=5$, % decrease values of compound **10** in the same experiment are shown in parentheses. $*p<0.05$, $**p<0.01$, *vs.* corresponding Control, Student's *t*-test.

Table 2. Insulin-Sensitizing Effects on 3T3-L1 Cells, and Hypoglycemic and Hypolipidemic Effects in KK-A^y Mice of 2-Benzyl-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acids with Various Substituents at 6- or 7-Position

Compound	R	3T3-L1[a] Activity ratio	KK-A^y mouse[b] Glucose % decrease	KK-A^y mouse[b] TG % decrease
24		<0.01	16 (51**)	19 (24)
25		<0.01	13 (45**)	−12 (24)
26		0.02	8 (42**)	−2 (40*)
27		<0.01	−13 (38*)	11 (59**)
28		<0.01	2 (45**)	−13 (29*)

a) Duplicate assay, relative activity against compound **10** for TG-increasing effect during insulin-stimulated adipocyte differentiation, expressed as a reciprocal of equipotent concentration ratio of test compound/compound **10**. *b*) $n=5$, % decrease values of compound **10** in the same experiment are shown in parentheses. $*p<0.05$, $**p<0.01$, *vs.* corresponding Control, Student's *t*-test.

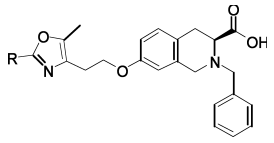
Table 3. Insulin-Sensitizing Effects on 3T3-L1 Cells, and Hypoglycemic and Hypolipidemic Effects in KK-A^y Mice of 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acids with Various Benzyl Analogues at 2-Position



Compound	R	3T3-L1[a] Activity ratio	KK-A^y mouse[b] Glucose % decrease	KK-A^y mouse[b] TG % decrease
29	4-OMe	20	35** (61**)	20 (54**)
30	4-Me	0.12	40** (61**)	46** (54**)
31	4-vinyl	1.28	41** (45**)	18 (24)
32	4-F	4	43** (61**)	24* (54**)
33	3-F	0.46	31* (35*)	29 (29)
34	4-CF_3	0.3	19 (33*)	0 (33*)
35	3-CF_3	0.1	26 (33*)	25 (33*)
36	3-acetyl	0.01	15 (51**)	15 (34)
37	2-acetyl	0.04	−2 (41**)	−1 (43**)

a) Duplicate assay, relative activity against compound **10** for TG-increasing effect during insulin-stimulated adipocyte differentiation, expressed as a reciprocal of equipotent concentration ratio of test compound/compound **10**. *b*) $n=5$, % decrease values of compound **10** in the same experiment are shown in parentheses. $*p<0.05$, $**p<0.01$, *vs.* corresponding Control, Student's *t*-test.

Table 4. Insulin-Sensitizing Effects on 3T3-L1 Cells, and Hypoglycemic and Hypolipidemic Effects in KK-A^y Mice of 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acids with Various Substituted Oxazole Rings at 7-Position



Compound	R	3T3-L1[a] Activity ratio	KK-A^y mouse[b] Glucose % decrease	KK-A^y mouse[b] TG % decrease
38		0.35	39** (38**)	42** (56**)
39		0.1	36** (30*)	32 (37)
40		0.16	24* (38**)	17 (36*)
41		0.03	0.1 (38**)	14 (56**)
42		0.32	0 (33**)	3 (35*)
43		0.06	23* (45**)	14 (32*)
44		2.3	6 (33*)	−4 (35*)
45		10	11 (33*)	−35 (35*)

a) Duplicate assay, relative activity against compound **10** for TG-increasing effect during insulin-stimulated adipocyte differentiation, expressed as a reciprocal of equipotent concentration ratio of test compound/compound **10**. *b*) $n=5$, % decrease values of compound **10** in the same experiment are shown in parentheses. $*p<0.05$, $**p<0.01$, *vs.* corresponding Control, Student's *t*-test.

interacted with PPARγ protein.

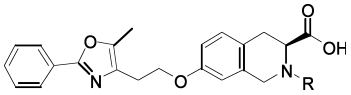
In Table 3, various substituents were introduced to the benzene ring of the benzyl moiety. At the 4th position, methyl and trifluoromethyl groups reduced (**30**, **34**), methoxy and fluoro groups enhanced (**29**, **32**), and the vinyl group did not alter *in vitro* activity (**31**). Methoxy and fluoro groups may have been involved in hydrogen bond interaction between compounds and protein. At the 3rd position, fluoro, trifluoromethyl and acetyl moiety reduced *in vitro* activity (**33**, **35**, **36**). Acetyl moiety at the 2nd position also reduced the activity (**37**). Trifluoromethyl and acetyl moiety may have reduced the activity by reducing the electron density of the benzene ring. Compounds **29**—**33** showed relatively potent *in vivo* activities. In Table 4, the effects of substituents at the 2nd position of the oxazole ring were examined. Thiophenyl, *tert*-butyl, isopropyl, cyclopropyl, neopentyl and 2-methylpropenyl moieties markedly decreased *in vitro* activity (**38**—**43**). However, **38**, **39**, **40** and **43** showed hypoglycemic activity similar to or weaker than that of **10**. Butenyl moieties enhanced *in vitro* activity but not *in vivo* activity (**44**, **45**). *In vitro* activity appears dependent on the bulkiness of sub-

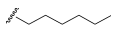
stituents on the oxazole ring, except for alkenyl groups.

In Table 5, aliphatic groups (carbon numbers 3—6) were introduced into the 2nd position. Isobutyl, *n*-butyl, neopentyl, *n*-hexyl, allyl, 3-butenyl and 3-methyl-2-butenyl markedly reduced (**46**—**50**, **53**, **54**), and propynyl and 2-butenyl maintained *in vitro* activity (**51**, **52**). These findings are interesting, since these compounds with small alkyl chains at the 2nd position can be regarded as a model of cyclization of α-alkoxy propionic acid-type PPARγ agonists. Among them, compounds with isobutyl, *n*-butyl, neopentyl, allyl, propynyl, 2-butenyl and 3-butenyl (**46**—**48**, **50**—**53**) showed hypoglycemic activity similar to or weaker than that of **10**. In Tables 3 and 4, compounds **29**, **32**, **44** and **45** showed stronger *in vitro* activity and weaker hypoglycemic activity than that of **10**; their intestinal absorption or distribution to a target organ may have been lower than that of **10**. In Tables 3—5, compounds **30**, **33**, **38**, **39**, **48** and **53** showed hypoglycemic effects similar to that of **10** in spite of weaker *in vitro* activity; they may have been highly absorbed, resistant to metabolism or efficiently distributed to a target organ.

Finally, compound **10** (KY-021) with relatively low molecular weight and lipophilicity, and showing high *in vitro* activity and *in vivo* hypoglycemic effects comparable to those of farglitazar, was selected and further compared with farglitazar. Oral administration of KY-021 and farglitazar as a dietary admixture for 7 d reduced plasma glucose and TG levels at 1 and 3 mg/kg/d in KK-A^y mice (Table 6). KY-021 and farglitazar dose-dependently lowered plasma TG levels at 0.3—3 mg/kg/d for 6 d in Zucker fatty rats; the effects of KY-021 were greater than those of farglitazar (Table 7). KY-021 but not farglitazar at 1 and 3 mg/kg/d for 7 d significantly inhibited the increase of plasma glucose levels after oral glucose load in male Zucker fatty rats, indicating that KY-021 improved glucose tolerance. After oral administration at 10 mg/kg, the maximal plasma concentration (C_{max}) of KY-021 reached about 7 μg/ml in male ICR mice and 2 μg/ml in male SD rats, while C_{max} of farglitazar was 0.7 μg/ml in mice and 0.4 μg/ml in rats (Table 8). KY-021 may have been more efficiently dissolved and absorbed in the intestines than farglitazar due to its lower lipophilicity. Repeated administration of KY-021 and farglitazar at 30 mg/kg/d for 10 weeks had no severe toxic effects on the general condition, body weight changes and hematological analyses. However, farglitazar, but not KY-021, significantly increased heart weight (Control: 0.30±0.008, farglitazar: 0.34±0.004**, KY-021: 0.32±0.008 g/100 g body weight, n=7, mean±S.E., ** p<

Table 5. Insulin-Sensitizing Effects on 3T3-L1 Cells, and Hypoglycemic and Hypolipidemic Effects in KK-A^y Mice of 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acids with Various Aliphatic Chains at 2-Position



Compound	R	3T3-L1[a] Activity ratio	KK-A^y mouse[b] Glucose % decrease	KK-A^y mouse[b] TG % decrease
46		0.09	17* (45**)	1 (29**)
47		0.09	22** (33*)	12 (35**)
48		0.29	43** (38**)	50** (36**)
49		0.21	12 (47**)	10 (49**)
50		0.09	28** (38**)	30 (36*)
51		0.92	31** (38**)	16 (36*)
52		1.3	46** (45**)	36* (32*)
53		0.46	44** (45**)	32 (32*)
54		0.06	9 (45**)	0 (32*)

a) Duplicate assay, relative activity against compound **10** for TG-increasing effect during insulin-stimulated adipocyte differentiation, expressed as a reciprocal of equipotent concentration ratio of test compound/compound **10**. *b*) n=5, % decrease values of compound **10** in the same experiment are shown in parentheses. * p<0.05, ** p<0.01, *vs.* corresponding Control, Student's *t*-test.

Table 6. Effects of KY-021 and Farglitazar Administered as Dietary Admixtures for 7 d on Plasma Glucose and Triglyceride Levels in Male KK-A^y Mice

	Control	KY-021 (mg/kg)			Farglitazar (mg/kg)		
		0.3	1	3	0.3	1	3
Glu (mg/dl)	514±29	503±34	424±34	263±40**	476±47	360±59*	253±25**
TG (mg/dl)	510±57	541±29	481±49	274±15**	507±42	430±49	317±24*

Glu: glucose, TG: triglyceride, Mean±S.E. (n=6) * p<0.05, ** p<0.01 *vs.* Control.

Table 7. Effects of KY-021 and Farglitazar Administered for 6 d on Plasma TG Levels and for 7 d on Oral Glucose Tolerance in Male Zucker Fatty Rats

	KY-021 (mg/kg)			Farglitazar (mg/kg)		
	0.3	1	3	0.3	1	3
TG (Δ%)	24.7±3.2**	45.3±3.5**	66.2±2.1**	16.1±4.0*	12.1±7.2	30.5±3.2**
OGTT-AUC (Δ%)	5.9±10.5	43.1±8.4*	39.6±6.4**	4.2±15.7	15.9±9.1	15.9±10.6

TG (Δ%): percent decrease in plasma TG levels 24 h after administration on the 6th day in comparison with the mean value of the control group. OGTT-AUC (Δ%): percent decrease in the area under the curve in oral glucose tolerance test performed 24 h after administration on the 7th day in comparison with the mean value of the control group. Mean±S.E. (n=7), * p<0.05, ** p<0.01 *vs.* Control.

Table 8. Plasma Concentrations of KY-021 and Farglitazar after Oral Administration at 10 mg/kg in Non-Fasted Male ICR Mice and Male SD Rats

	Mouse		Rat	
	C_{max}	*AUC*	C_{max}	*AUC*
KY-021	6.61±0.45	29.9	2.13±0.25	12.6±1.2
Farglitazar	0.74±0.08	5.28	0.38±0.02	5.04±0.87

Mean±S.E. (n=4), C_{max}: μg/ml, *AUC*: μg·h/ml.

0.01 *vs.* Control, Student's *t*-test) and white adipose tissue weight (Control: 1.84±0.15, farglitazar: 3.48±0.43**, KY-021: 2.60±0.36 g/100 g body weight, ** $p<0.01$ *vs.* Control), suggesting that farglitazar may have a risk for volume expansion and increase in weight gain. KY-021 is smaller and less lipophilic than farglitazar, and has a more rigid structure with carboxylic acid and lipophilic moieties. Therefore, KY-021 may interact with PPARγ protein more specifically and efficiently than farglitazar; however, further study is needed to clarify the mode of interaction of KY-021 and protein.

Conclusion

A series of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives were synthesized to find a useful PPARγ agonist based on a more rigid structure than benzene derivatives, and (*S*)-2-benzyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (KY-021) has been identified as a novel PPARγ agonist. KY-021 showed potent antihyperglycemic and hypolipidemic effects in male KK-A^y mice, and improved oral glucose tolerance in male Zucker fatty rats. KY-021 had excellent oral absorption in male ICR mice and male SD rats. Repeated oral administration of KY-021 at 30 mg/kg/d for 10 weeks showed little toxicity in male SD rats. From these results, KY-021 is concluded to be a novel 1,2,3,4-tetrahydroisoquinoline-based PPARγ agonist and a promising candidate for an anti-diabetic drug.

Experimental

General Melting points were measured on a Yamato MP-21 melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained on a Hitachi FT-NMR R-1900 NMR spectrometer, using tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were recorded with a Shimadzu FT-IR8200PC spectrometer. Mass spectra were obtained on an Applied Biosystems API2000 QTRAP LC/MS/MS system. Daisogel No. 1001W (70—230 mesh, Daiso) was used for column chromatography. TLC was performed on pre-coated TLC plates with 60F254 (Merck).

(*S*)-7-Hydroxy-6,8-diiodo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Hydrochloride To a suspension of 3,5-diiodo-L-tyrosine dihydrate (**12**, 25.0 g, 53.3 mmol) in concentrated hydrochloric acid (250 ml) was successively added 1,2-dimethoxyethane (18 ml) and 37% formalin (20 ml, 242 mmol), and the mixture was warmed to 75 °C over 30 min. To the reaction mixture was further added concentrated hydrochloric acid (120 ml), 1,2-dimethoxyethane (9 ml) and 37% formalin (10 ml, 121 mmol), and the mixture was stirred at 75 °C for 18 h. The precipitated crystals were collected by filtration and washed with 1,2-dimethoxyethane (20 ml) to give 7-hydroxy-6,8-diiodo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride (12.8 g, 50%). ^{1}H-NMR ($CDCl_3$) δ: 3.00—3.30 (2H, m), 4.05 (2H, s), 4.30 (1H, dd, J=5.9, 9.5 Hz), 7.71 (1H, s). IR (nujol) cm^{-1}: 1751, 1599, 1578.

Ethyl (*S*)-7-Hydroxy-6,8-diiodo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13) To a suspension of 7-hydroxy-6,8-diiodo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride (12.8 g, 127.1 mmol) in ethanol (500 ml) was added concentrated hydrochloric acid (10 ml) and the mixture was refluxed for 15 h. After evaporation of the solvent under reduced pressure, ethyl acetate (300 ml) was added to the obtained residue, and the organic layer was washed with saturated aqueous sodium hydrogencarbonate solution (100 ml) and saturated brine (100 ml) and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure to give ethyl 7-hydroxy-6,8-diiodo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11.1 g, 89%) as a solid. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.0 Hz), 2.80—3.00 (2H, m), 3.30—4.10 (5H, m), 4.23 (2H, q, J=7.0 Hz), 7.46 (1H, s).

Ethyl (*S*)-7-Hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate To a suspension of 10% Pd–C (350 mg) in MeOH (60 ml) was added **13** (2.80 g, 5.92 mmol) and triethylamine (2.0 ml, 14.3 mmol), and the compound was catalytically hydrogenated under H_2 (0.3 MPa) at room temperature for 3 h. Pd–C was removed by filtration, and MeOH was evaporated under reduced pressure. Ethyl acetate (10 ml) was added to the obtained residue. The mixture was washed with saturated brine (100 ml) and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure to give ethyl 7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.14 g, 89%) as a solid. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.0 Hz), 2.80—3.10 (3H, m), 3.60—3.80 (1H, m), 3.97 (2H, s), 4.05—4.20 (4H, m), 6.43 (1H, s), 6.50—6.80 (1H, m), 6.92 (1H, d, J=8.4 Hz). IR (nujol) cm^{-1}: 1732, 1607, 1516.

Ethyl (*S*)-2-*tert*-Butoxycarbonyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (14) To a solution of ethyl 7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.13 g, 5.11 mmol) in THF (20 ml) was added di-*tert*-butyl dicarbonate (1.50 g, 6.87 mmol), and the mixture was stirred at room temperature for 1 h. Ethyl acetate (30 ml) was added to the reaction mixture, and the mixture was washed with saturated brine (20 ml) and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure. The obtained residue was purified by column chromatography to give **14** (1.51 g, 92%) as a solid. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.0 Hz), 1.47 (9H, s), 3.08 (2H, d, J=5.2 Hz), 4.21 (2H, q, J=7.0 Hz), 4.41 (1H, d, J=15.5 Hz), 4.60—5.25 (1H, m), 4.65 (1H, d, J=15.5 Hz), 5.00—6.00 (1H, br), 6.50—6.80 (2H, m), 6.98 (1H, d, J=8.1 Hz). IR (nujol) cm^{-1}: 3260, 1756, 1671, 1615, 1506.

Ethyl (*S*)-2-*tert*-Butoxycarbonyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)-ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (16) A mixture of **14** (1.50 g, 4.67 mmol), 2-(5-methyl-2-phenyloxazol-4-yl)ethyl methanesulfonate (**15**, 2.50 g, 9.28 mmol) and K_2CO_3 (2.0 g 14.5 mmol) in *N*,*N*-dimethylformamide (DMF) (20 ml) was stirred at 80 °C for 5 h. Ethyl acetate (100 ml) was added to the reaction mixture, and the mixture was washed with water and saturated brine and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give **16** (1.62 g, 68%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, t, J=7.0 Hz), 1.46, 1.50 (9H, s, s), 2.36 (3H, s), 2.95 (2H, t, J=6.8 Hz), 2.90—3.30 (2H, m), 4.00—4.40 (4H, m), 4.51, 4.61 (2H, s, s), 4.70—4.90, 5.00—5.20 (1H, m, m), 6.60—6.90 (2H, m), 7.12 (1H, d, J=8.4 Hz), 7.30—7.55 (3H, m), 7.90—8.15 (2H, m). IR (neat) cm^{-1}: 2978, 2930, 1738, 1699, 1614, 1587.

Ethyl (*S*)-7-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (17) To a solution of **16** (5.20 g, 10.3 mmol) in formic acid (20 ml) was added saturated hydrogen chloride solution in 2-propanol (6.0 ml) under ice-cooling, and the mixture was stirred at room temperature for 10 min. Ethyl acetate (100 ml) was added to the reaction mixture, and the mixture was neutralized with saturated aqueous solution of $NaHCO_3$ and separated into two layers. The obtained ethyl acetate layer was washed with brine and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure to give **17** (3.6 g, 86%) as a solid. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.0 Hz), 2.02 (1H, s), 2.36 (3H, s), 2.80—3.10 (4H, m), 3.50—3.80 (1H, m), 4.00—4.40 (6H, m), 6.50—6.80 (2H, m), 7.00 (1H, d, J=8.4 Hz), 7.30—7.50 (3H, m), 7.90—8.10 (2H, m). IR (nujol) cm^{-1}: 3476, 1742, 1639, 1611, 1553.

Ethyl (*S*)-2-Benzyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate To a solution of **17** (1.40 g, 3.44 mmol) in DMF (20 ml) was added sodium hydride (60% oil dispersion, 160 mg, 4.0 mmol) under ice-cooling, and the mixture was stirred at room temperature for 20 min. Then benzyl bromide (0.40 ml, 3.36 mmol) was added to the mixture, and stirred 1 h at the same temperature. Ethyl acetate (50 ml) was added to the reaction mixture, and the mixture was washed with water (50 ml) and saturated brine (30 ml) and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to give ethyl 2-benzyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.38 g, 81%) as a solid. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7.0 Hz), 2.34 (3H, s), 2.92 (2H, t, J=7.0 Hz), 3.05—3.20 (2H, m), 3.60—4.00 (5H, m), 4.12 (2H, q, J=7.0 Hz), 4.16 (2H, t, J=7.0 Hz), 6.51 (1H, d, J=2.0 Hz), 6.68 (1H, dd, J=2.0, 8.4 Hz), 6.99 (1H, d, J=8.4 Hz), 7.30—7.50 (8H, m), 7.80—8.10 (2H, m). IR (nujol) cm^{-1}: 1728, 1639, 1614, 1551.

(*S*)-2-Benzyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (10) To a solution of ethyl 2-benzyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5.20 g, 10.5 mmol) in THF–MeOH (3 : 1, 50 ml) was added 1 M aqueous lithium hydroxide solution (30 ml), and the mixture was stirred at 50 °C for 2 h. After evaporation of the solvent, the obtained residue was acidified with citric acid. The precipitated crystals were collected by filtration. The obtained crude crystals (4.80 g) were recrystallized from MeOH to give **10** (2.56 g, 52%) as colorless crystals. mp 154—156 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s), 2.65—3.30 (4H, m), 3.50—4.00 (5H, m), 4.00—6.20 (1H, br), 4.13 (2H, t, J=7.0 Hz), 6.59 (1H, br s), 6.68 (1H, br d, J=8.4 Hz), 7.01 (1H, d, J=8.4 Hz), 7.32 (5H, s), 7.35—7.70 (3H, m), 7.85—8.10 (2H, m). IR (nujol) cm^{-1}: 1638, 1501. MS *m/z*: 469 [M+H]$^+$. *Anal*. Calcd for $C_{29}H_{28}N_2O_4$: C, 74.34; H, 6.02; N, 5.98. Found: C, 74.09; H, 6.07; N, 5.96.

(*R*)-2-Benzyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (26) This compound was prepared by a similar procedure to that described in the synthesis of **10**. A colorless solid, mp 155—157 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s), 2.95 (1H, t, J=6.6 Hz), 2.90—3.10 (2H, m), 3.50—4.00 (5H, m), 4.00—6.20 (1H, br), 4.13 (2H, t, J=6.6 Hz), 6.57 (1H, br s), 6.67 (1H, br d, J=8.4 Hz), 7.01 (1H, d, J=8.4 Hz), 7.31 (5H, s), 7.40—7.60 (3H, m), 7.85—8.05 (2H, m). IR (nujol) cm^{-1}: 1636, 1501. MS *m/z*: 469 [M+H]$^+$.

Ethyl (*S*)-2-Benzoyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate To a solution of **17** (1.4 g 3.44 mmol) in CH_2Cl_2 (14 ml) was added benzoyl chloride (0.48 ml, 4.14 mmol) and triethylamine (0.72 ml, 5.17 mmol) under ice-cooling, and the mixture was stirred at the same temperature for 15 min. Ethyl acetate (100 ml) was added to the reaction mixture, and the mixture was washed successively with 10% aqueous citric acid solution (50 ml), saturated aqueous $NaHCO_3$ solution (50 ml) and then saturated brine (50 ml) and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give ethyl 2-benzoyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.16 g, 66%) as a solid. ^{1}H-NMR ($CDCl_3$) δ: 0.75—1.15 (3H, m), 2.35 (3H, s), 2.93 (2H, t, J=6.6 Hz), 3.05—3.25 (2H, m), 3.85—4.40 (4H, m), 4.20—4.80 (2H, m), 5.00—5.60 (1H, m), 6.47 (1H, br s), 6.72 (1H, br d, J=8.4 Hz), 7.05 (1H, br d, J=8.4 Hz), 7.30—7.60 (8H, m), 7.80—8.10 (2H, m). IR (nujol) cm^{-1}: 1734, 1638, 1612, 1591.

(*S*)-2-Benzoyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (11) To a solution of ethyl 2-benzoyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.0 g, 2.01 mmol) in THF–MeOH (3 : 1, 10 ml) was added 1 M aqueous lithium hydroxide solution (6.0 ml), and the mixture was stirred at room temperature for 1.5 h. The solvent was evaporated under reduced pressure. To the obtained residue was added water (20 ml), and the mixture was washed with ethyl acetate (10 ml). The obtained aqueous layer was acidified with hydrochloric acid, and the mixture was extracted twice with diethyl ether (20 ml). The diethyl ether layer was washed with saturated brine (30 ml) and dried over Na_2SO_4. Diethyl ether was evaporated under reduced pressure. The obtained residue was recrystallized from MeOH to give **11** (0.75 g, 79%) as colorless crystals. mp 96—98 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s), 2.87 (2H, t, J=6.4 Hz), 3.00—3.35 (2H, m), 4.02 (2H, t, J=6.4 Hz), 4.40—4.90 (2H, m), 4.90—5.30 (1H, br), 5.00—5.65 (1H, m), 6.40 (1H, br s), 6.50—6.80 (1H, m), 7.03 (1H, d, J=8.4 Hz), 7.20—7.60 (8H, m), 7.75—8.05 (2H, m). IR (nujol) cm^{-1}: 1730, 1636, 1551. MS *m/z*: 483 [M+H]$^+$.

Ethyl (*S*)-7-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-(3-phenylpropyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate To a solution of **17** (1.40 g, 3.44 mmol) in DMF (14 ml) was added 3-phenylpropyl bromide (0.78 ml, 5.17 mmol) and potassium carbonate (0.95 g, 6.87 mmol), and the mixture was stirred at 50 °C for 22 h. Water (100 ml) was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate (50 ml). The organic layer was washed with saturated brine (100 ml) and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give ethyl 7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-2-(3-phenylpropyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.05 g, 58%) as a powder. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, t, J=7.0 Hz), 1.60—2.05 (2H, m), 2.35 (3H, s), 2.50—2.80 (4H, m), 2.94 (2H, t, J=7.1 Hz), 3.04 (2H, d, J=5.7 Hz), 3.67 (1H, t, J=5.7 Hz), 3.84 (1H, s), 3.94 (1H, s), 4.04 (2H, t, J=7.1 Hz), 4.16 (2H, q, J=7.0 Hz), 6.50—6.80 (2H, m), 7.07 (1H, d, J=9.0 Hz), 7.20 (5H, s), 7.10—7.50 (3H, m), 7.80—8.10 (2H, m). IR (nujol) cm^{-1}: 1720, 1647, 1612, 1504.

(*S*)-7-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-(3-phenylpropyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (20) To a solution of ethyl 7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-2-(3-phenylpropyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.0 g, 1.91 mmol) in THF–MeOH (3 : 1, 10 ml) was added 2 M aqueous lithium hydroxide solution (4.77 ml), and the mixture was stirred at room temperature for 10 h. The solvent was evaporated under reduced pressure, and the obtained residue was acidified with citric acid. The precipitated solid was collected by filtration to give **20** (0.66 g, 70%) as a colorless solid. mp 104—105 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.70—2.20 (3H, m), 2.35 (3H, s), 2.40—2.70 (4H, m), 2.70—3.30 (2H, m), 2.92 (2H, t, J=6.3 Hz), 3.10 (2H, d, J=7.0 Hz), 3.65 (1H, t, J=7.0 Hz), 3.90—4.30 (4H, m), 5.12 (1H, br s), 6.55—6.80 (2H, m), 6.90—7.25 (6H, m), 7.25—7.55 (3H, m) , 7.80—8.10 (2H, m). IR (nujol) cm^{-1}: 3346, 1616, 1556, 1506. MS *m/z*: 497 [M+H]$^+$. *Anal.* Calcd for $C_{31}H_{34}N_2O_5 \cdot H_2O$: C, 72.35; H, 6.66; N, 5.44. Found: C, 72.11; H, 6.68; N, 5.41.

(*S*)-2-Cyclohexylmethyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (21) This compound was prepared by a similar procedure to that described in the synthesis of **20**. A pale yellow solid, mp 112—114 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.70—2.10 (11H, m), 2.36 (3H, s), 2.40—2.55 (2H, m), 2.93 (2H, t, J=6.4 Hz), 3.16 (2H, d, J=7.2 Hz), 3.70 (1H, t, J=7.2 Hz), 4.00—4.30 (4H, m), 5.30 (1H, br s), 6.60—6.90 (2H, m), 7.08 (1H, d, J=8.4 Hz), 7.30—7.50 (3H, m), 7.80—8.10 (2H, m). IR (nujol) cm^{-1}: 3319, 1624, 1506. MS *m/z*: 475 [M+H]$^+$. *Anal*. Calcd for $C_{29}H_{34}N_2O_4 \cdot H_2O$: C, 70.71; H, 7.37; N, 5.69. Found: C, 70.83; H, 7.51; N, 5.66.

Compounds **22**—**25** were prepared by a similar procedure to that described in the synthesis of **10**.

Sodium (*S*)-7-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (22) A pale yellow solid, mp 91—93 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s), 2.60—3.20 (4H, m), 3.20—3.90 (5H, m), 4.08 (2H, br t, J=6.5 Hz), 6.15—6.40 (1H, m), 6.40—6.70 (1H, m), 7.75—8.20 (3H, m), 7.20—7.65 (4H, m), 7.75—8.10 (2H, m), 8.25—8.60 (1H, m). IR (nujol) cm^{-1}: 1609, 1575, 1554, 1502. MS *m/z*: 492 [M+H]$^+$.

Sodium (*S*)-7-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (23) A pale yellow solid, mp 76—78 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.34 (3H, s), 2.70—3.05 (4H, m), 3.10—3.60 (3H, m), 3.98 (2H, br t, J=5.7 Hz), 4.10—4.25 (2H, m), 6.51 (1H, br s), 6.61 (1H, br d, J=8.7 Hz), 6.94 (1H, br d, J=8.7 Hz), 7.25—7.65 (5H, m), 7.75—8.00 (2H, m), 8.46 (2H, d, J=5.2 Hz). IR (nujol) cm^{-1}: 3420, 3177, 1639, 1558, 1504. MS *m/z*: 492 [M+H]$^+$.

(*RS*)-2-Benzyl-6-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (24) A colorless solid, mp 151—153 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.35 (3H, s), 2.65—3.25 (4H, m), 3.40—4.00 (3H, m), 3.90 (2H, s), 4.17 (2H, br t, J=6.4 Hz), 6.20—10.00 (1H, br), 6.50—7.00 (2H, m), 6.71 (1H, s), 7.30—7.70 (3H, m), 7.32 (5H, s), 7.75—8.15 (2H, m). IR (nujol) cm^{-1}: 1634, 1614, 1499. MS *m/z*: 469 [M+H]$^+$. *Anal*. Calcd for $C_{29}H_{28}N_2O_4$: C, 74.34; H, 6.13; N, 5.98. Found: C, 74.26; H, 6.13; N, 5.93.

(*S*)-2-Benzyl-7-[(5-methyl-2-phenyloxazol-4-yl)methoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (25) A pale brown solid, mp 92—95 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.41 (3H, s), 2.83—3.20 (2H, m), 3.44—4.20 (5H, m), 4.91 (2H, s), 6.73 (1H, br s), 6.77 (1H, d, J=8.1 Hz), 7.34 (1H, d, J=8.1 Hz), 7.34 (5H, s), 7.40—7.68 (3H, m), 7.75—8.10 (2H, m). IR (nujol) cm^{-1}: 3462, 1680, 1614, 1556, 1508. MS *m/z*: 455 [M+H]$^+$. *Anal*. Calcd for $C_{28}H_{26}N_2O_4$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.61; H, 5.70; N, 6.16.

Ethyl (*S*)-2-Benzyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate To a solution of ethyl (*S*)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (8.1 g, 36.6 mmol) and triethylamine (5.6 ml, 40.2 mmol) in DMF (80 ml) was added benzyl bromide (4.57 ml, 38.4 mmol), and the mixture was stirred at room temperature for 3 h. Water (500 ml) was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate (200 ml). The combined ethyl acetate layer was washed with saturated brine (500 ml) and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure. The obtained residue was purified by column chromatography to give ethyl (*S*)-2-benzyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (10.5 g, 92%) as a solid. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.0 Hz), 3.06 (2H, d, J=5.0 Hz), 3.66 (1H, t, J=5.0 Hz), 3.78 (2H, s), 3.90 (2H, s), 4.13 (2H, q, J=7.0 Hz), 6.37 (1H, d, J=2.0 Hz), 6.56 (1H, dd, J=2.0, 8.4 Hz), 6.92 (1H, d, J=8.4 Hz), 7.20—7.50 (5H, m). IR (nujol) cm^{-1}: 3410, 1717, 1624, 1506.

Ethyl (*S*)-2-Benzyl-7-[2-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate To a solution of ethyl (*S*)-2-benzyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.38 g, 4.43 mmol) in DMF (10 ml) was added sodium hydride (60% oil dispersion, 210 mg, 5.25 mmol) under ice-cooling and the mixture was stirred at room temperature for 30 min. To the obtained mixture was added 2-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)ethyl methanesulfonate (1.30 g, 5.13 mmol) and the mixture was stirred further at the same temperature for 1 h. Ethyl acetate (50 ml) was added to the reaction mixture, and the mixture was washed with water (50 ml) and saturated brine (30 ml) and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give ethyl (*S*)-2-benzyl-7-[2-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.44 g, 69%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz), 1.44 (9H, s), 2.95 (3H, s), 3.08 (2H, d, J=4.9 Hz), 3.54 (2H, t, J=5.5 Hz), 3.60—4.30 (7H, m), 6.50 (1H, d, J=2.0 Hz), 6.68 (1H, dd, J=2.0, 8.1 Hz), 7.01 (1H, d, J=8.1 Hz), 7.20—7.50 (5H, m). IR (neat) cm^{-1}: 2978, 2932, 1732, 1695, 1614.

Ethyl (*S*)-2-Benzyl-7-(2-methylaminoethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate To a solution of ethyl (*S*)-2-benzyl-7-[2-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.44 g, 3.07 mmol) in formic acid (7.0 ml) was added saturated hydrogen chloride solution in 2-propanol (2.0 ml), and the mixture was stirred at room temperature for 15 min. Ethyl acetate (100 ml) was added to the reaction mixture, and the mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution, and then the two layers were separated. The obtained ethyl acetate layer was washed with saturated brine (50 ml) and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure to give ethyl (*S*)-2-benzyl-7-(2-methylaminoethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.08 g, 95%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.0 Hz), 2.41 (1H, br s), 2.49 (3H, s), 2.95 (2H, t, J=5.5 Hz), 3.08 (2H, d, J=4.9 Hz), 3.60—4.25 (7H, m), 6.52 (1H, d, J=2.0 Hz), 6.70 (1H, dd, J=2.0, 8.4 Hz), 7.00 (1H, d, J=8.4 Hz), 7.20—7.50 (5H, m). IR (neat) cm^{-1}: 3332, 1732, 1612, 1504.

Ethyl (*S*)-2-Benzyl-7-{2-[*N*-methyl-*N*-(pyridin-2-yl)amino]ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate Ethyl (*S*)-2-benzyl-7-(2-methylaminoethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.05 g, 2.85 mmol) was dissolved in 2-chloropyridine (2.0 ml), and the mixture was stirred at 140 °C for 16 h. The reaction mixture was purified by silica gel column chromatography to give ethyl (*S*)-2-benzyl-7-{2-[*N*-methyl-*N*-(pyridin-2-yl)amino]ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (0.50 g, 39%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.0 Hz), 3.06 (2H, d, J=6.2 Hz), 3.11 (3H, s), 3.60—4.30 (11H, m), 6.40—6.80 (4H, m), 6.97 (1H, d, J=8.4 Hz), 7.20—7.50 (6H, m), 8.00—8.20 (1H, m). IR (neat) cm^{-1}: 2932, 2905, 1732, 1597, 1560, 1504.

Sodium (*S*)-2-Benzyl-7-{2-[*N*-methyl-*N*-(pyridin-2-yl)amino]ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (27) To a solution of ethyl (*S*)-2-benzyl-7-{2-[*N*-methyl-*N*-(pyridin-2-yl)amino]ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (488 mg, 1.10 mmol) in THF–MeOH (3 : 1, 5.0 ml) was added 1 M aqueous sodium hydroxide solution (2.2 ml), and the mixture was stirred at room temperature for 6 h. The solvent was evaporated under reduced pressure, and the mixture was extracted three times with ethyl acetate (30 ml). The ethyl acetate layer was washed with saturated brine (10 ml) and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure. Diethyl ether was added to the obtained residue. The solid was collected by filtration to give **27** (356 mg, 74%) as a pale yellow solid. mp 115—118 °C (dec.). ^{1}H-NMR (MeOH-d_4) δ: 2.95—3.20 (2H, m), 3.07 (3H, s), 3.40—4.20 (9H, m), 6.40—6.70 (4H, m), 6.92 (1H, d, J=8.4 Hz), 7.20—7.50 (3H, m), 7.90—8.15 (1H, m). IR (nujol) cm^{-1}: 1597, 1497. MS *m*/*z*: 440 $[M+H]^+$.

Ethyl (*S*)-2-Benzyl-7-[2-(5-ethylpyridin-2-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate To a solution of 5-ethyl-2-pyridineethanol (1.5 g, 9.92 mmol) and triethylamine (1.68 ml, 12.1 mmol) in CH_2Cl_2 (40 ml) was added trifluoromethanesulfonic anhydride (2.0 ml, 11.9 mmol) under ice-cooling, and the mixture was stirred at room temperature for 30 min. The reaction mixture was washed with water (30 ml), dried over Na_2SO_4, and then CH_2Cl_2 was evaporated under reduced pressure to give crude 5-ethyl-2-pyridineethyl trifluoromethanesulfonate (2.81 g). Separately, to a solution of ethyl (*S*)-2-benzyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.0 g, 3.21 mmol) in DMF (10 ml) was added sodium hydride (60% oil dispersion, 200 mg, 5.0 mmol) under ice-cooling and the mixture was stirred at room temperature for 30 min to give a solution. Crude trifluoromethanesulfonate was added to the above solution, and the mixture was stirred at room temperature for 30 min. Ethyl acetate (100 ml) was added to the reaction mixture, and the mixture was washed with water (50 ml) and saturated brine (50 ml) and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give ethyl (*S*)-2-benzyl-7-[2-(5-ethylpyridin-2-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (0.58 g, 41%) as a powder. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (6H, t, J=7.2 Hz), 2.61 (2H, q, J=7.2 Hz), 3.07 (2H, d, J=5.5 Hz), 3.18 (2H, t, J=6.6 Hz), 3.72 (1H, t, J=5.5 Hz), 3.81 (1H, s), 3.90 (4H, s), 4.13 (2H, q, J=7.2 Hz), 4.27 (2H, t, J=6.6 Hz), 6.51 (1H, d, J=2.0 Hz), 6.69 (1H, dd, J=2.0, 8.4 Hz), 6.98 (1H, d, J=8.4 Hz), 7.10—7.50 (7H, m), 8.00—8.20 (1H, m). IR (nujol) cm^{-1}: 1732, 1612, 1504.

Sodium (*S*)-2-Benzyl-7-[2-(5-ethylpyridin-2-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (28) To a solution of ethyl (*S*)-2-benzyl-7-[2-(5-ethylpyridin-2-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (0.94 g, 2.11 mmol) in THF–MeOH (3 : 1, 40 ml) was added 2 M aqueous sodium hydroxide solution (6.0 ml), and the mixture was stirred at 40 °C for 2 h. The solvent was evaporated under reduced pressure. Water (10 ml) and then NaCl was added to saturation, and the mixture was extracted three times with ethyl acetate (30 ml). The ethyl acetate layer was washed with saturated brine (10 ml) and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure. Diisopropyl ether was added to the obtained residue. The solid was collected by filtration to give **28** (0.58 g, 65%) as a pale yellow solid. mp 67—68 °C. ^{1}H-NMR (MeOH-d_4) δ: 1.22 (6H, t, J=7.5 Hz), 2.63 (2H, q, J=7.5 Hz), 2.90—3.20 (4H, m), 3.72 (1H, s), 3.85 (1H, s), 3.95—4.35 (5H, m), 4.27 (2H, t, J=6.6 Hz), 6.40—6.75 (2H, m), 6.91 (1H, d, J=8.4 Hz), 7.20—7.65 (7H, m), 8.20—8.35 (1H, m). IR (nujol) cm^{-1}: 1576, 1504. MS *m*/*z*: 439 $[M+H]^+$.

Compounds **29**—**45** were prepared by a similar procedure to that described in the synthesis of **10**.

(*S*)-2-(4-Methoxybenzyl)-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (29) A colorless solid, mp 146—148 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 2.93 (2H, t, J=6.4 Hz), 3.18 (2H, d, J=6.8 Hz), 3.70—4.10 (5H, m), 3.77 (3H, s), 4.17 (2H, t, J=6.4 Hz), 4.50 (1H, br s), 6.60 (1H, d, J=2.0 Hz), 6.65—6.95 (3H, m), 7.08 (2H, d, J=8.4 Hz), 7.20—7.60 (5H, m), 7.80—8.10 (2H, m). IR (nujol) cm^{-1}: 3288, 1612, 1555, 1514. MS *m*/*z*: 499 $[M+H]^+$. *Anal*. Calcd for $C_{30}H_{30}N_2O_5\cdot H_2O$: C, 69.75; H, 6.24; N, 5.39. Found: C, 69.65; H, 6.25; N, 5.39.

(*S*)-2-(4-Methylbenzyl)-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (30) A colorless solid, mp 136—137 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s), 2.35 (3H, s), 2.93 (2H, t, J=7.0 Hz), 3.17 (2H, d, J=6.6 Hz), 3.65—4.05 (5H, m), 4.17 (2H, t, J=7.0 Hz), 4.73 (1H, br s), 6.60 (1H, d, J=2.0 Hz), 6.77 (1H, dd, J=2.0, 8.8 Hz), 6.95—7.60 (8H, m), 7.85—8.10 (2H, m). IR (nujol) cm^{-1}: 1620, 1555, 1506. MS *m*/*z*: 483 $[M+H]^+$. *Anal*. Calcd for $C_{30}H_{30}N_2O_4\cdot H_2O$: C, 71.98; H, 6.44; N, 5.60. Found: C, 71.86; H, 6.44; N, 5.56.

(*S*)-7-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-(4-vinylbenzyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (31) A colorless solid, mp 126—128 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.70—3.10 (4H, m), 3.50—4.00 (3H, m), 3.88 (2H, s), 4.13 (2H, t, J=6.5 Hz), 5.22 (1H, d, J=11.0 Hz), 5.77 (1H, d, J=17.4 Hz), 6.50—7.20 (4H, m), 7.20—7.70 (7H, m), 7.80—8.10 (2H, m). IR (nujol) cm^{-1}: 1693, 1622. MS *m*/*z*: 495 $[M+H]^+$. *Anal*. Calcd for $C_{31}H_{30}N_2O_4\cdot H_2O$: C, 72.64; H, 6.29; N, 5.47. Found: C, 72.29; H, 6.24; N, 5.48.

(*S*)-2-(4-Fluorobenzyl)-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (32) A colorless solid, mp 132—134 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 2.94 (2H, t, J=6.4 Hz), 3.15 (2H, d, J=6.4 Hz), 3.45—4.00 (5H, m), 4.19 (2H, t, J=6.4 Hz), 6.60 (1H, d, J=2.0 Hz), 6.75 (1H, dd, J=2.0, 8.6 Hz), 6.90—7.55 (8H, m), 7.90—8.10 (2H, m). IR (nujol) cm^{-1}: 3398, 1614, 1555, 1510. MS *m*/*z*: 487 $[M+H]^+$. *Anal*. Calcd for $C_{29}H_{27}FN_2O_4\cdot H_2O$: C, 69.03; H, 5.79; N, 5.55. Found: C, 68.84; H, 5.75; N, 5.45.

(*S*)-2-(3-Fluorobenzyl)-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (33) A colorless solid, mp 155—157 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.34 (3H, s), 2.70—3.10 (4H, m), 3.45—4.00 (5H, m), 4.14 (2H, t, J=6.4 Hz), 6.50—6.80 (2H, m), 6.90—7.70 (8H, m), 7.90—8.10 (2H, m). IR (nujol) cm^{-1}: 1624, 1508. MS *m*/*z*: 487 $[M+H]^+$. *Anal*. Calcd for $C_{29}H_{27}FN_2O_4$: C, 71.59; H, 5.59; N, 5.76. Found: C, 71.20; H, 5.70; N, 5.75.

(*S*)-7-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-(4-trifluoromethylbenzyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (34) A colorless solid, mp 106—110 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s), 2.88 (2H, d, J=6.4 Hz), 2.90—3.20 (2H, m), 3.50—4.10 (5H, m), 4.13 (2H, t, J=6.4 Hz), 6.59 (1H, s), 6.69 (1H, d, J=8.1 Hz), 7.03 (1H, d, J=8.1 Hz), 6.55—7.80 (7H, m), 7.80—8.05 (2H, m). IR (nujol) cm^{-1}: 1692, 1620,

1506. MS *m/z*: 537 $[M+H]^+$. *Anal*. Calcd for $C_{30}H_{27}F_3N_2O_4 \cdot H_2O$: C, 64.97; H, 5.27; N, 5.05. Found: C, 64.98; H, 5.30; N, 5.02.

(*S*)-7-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-(3-trifluoromethylbenzyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (35) A colorless solid, mp 138—140 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s), 2.70—3.20 (4H, m), 3.50—4.30 (7H, m), 6.60 (1H, s), 6.69 (1H, d, J=8.1 Hz), 7.03 (1H, d, J=8.1 Hz), 6.30—7.80 (7H, m), 7.80—8.05 (2H, m). IR (nujol) cm^{-1}: 1692, 1610, 1506. MS *m/z*: 537 $[M+H]^+$. *Anal*. Calcd for $C_{30}H_{27}F_3N_2O_4 \cdot 1.5H_2O$: C, 63.94; H, 5.37; N, 4.97. Found: C, 64.20; H, 5.15; N, 4.94.

(*S*)-2-(3-Acetylbenzyl)-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (36) A colorless solid, mp 147—150 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s), 2.56 (3H, s), 2.70—3.20 (4H, m), 3.50—4.30 (5H, m), 3.97 (2H, s), 6.50—6.90 (2H, m), 7.02 (1H, d, J=8.4 Hz), 7.30—8.00 (9H, m). IR (nujol) cm^{-1}: 1682, 1620, 1508. MS *m/z*: 511 $[M+H]^+$. *Anal*. Calcd for $C_{31}H_{30}N_2O_5 \cdot H_2O$: C, 70.44; H, 6.10; N, 5.30. Found: C, 70.13; H, 6.18; N, 5.22.

(*S*)-2-(2-Acetylbenzyl)-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (37) A blue solid, mp 81—83 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s), 2.36 (3H, s), 2.70—3.20 (4H, m), 3.30—4.30 (5H, m), 6.57 (1H, d, J=2.0 Hz), 6.66 (1H, dd, J=2.0, 8.4 Hz), 7.00 (1H, d, J=8.4 Hz), 7.20—7.75 (7H, m), 7.75—8.10 (2H, m). IR (nujol) cm^{-1}: 1668, 1643, 1614, 1504. MS *m/z*: 511 $[M+H]^+$.

(*S*)-2-Benzyl-7-{2-[5-methyl-2-(thiophen-2-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (38) A colorless solid, mp 112—115 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.31 (3H, s), 2.70—3.10 (4H, m), 3.39 (2H, s), 3.40—4.00 (4H, m), 4.11 (2H, d, J=6.2 Hz), 6.59 (1H, br s), 6.67 (1H, d, J=8.4 Hz), 7.01 (1H, d, J=8.4 Hz), 7.05—7.80 (3H, m), 7.32 (5H, s). IR (nujol) cm^{-1}: 3423, 1616, 1578, 1510. MS *m/z*: 475 $[M+H]^+$. *Anal*. Calcd for $C_{27}H_{26}N_2O_4S \cdot 0.2H_2O$: C, 67.90; H, 5.56; N, 5.87. Found: C, 67.87; H, 5.40; N, 5.93.

(*S*)-2-Benzyl-7-[2-(2-*tert*-butyl-5-methyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (39) A colorless solid, mp 137—140 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 1.32 (9H, s), 2.23 (3H, s), 2.83 (2H, t, J=6.6 Hz), 3.18 (2H, d, J=5.9 Hz), 3.65—4.40 (7H, m), 5.60 (1H, br s), 6.56 (1H, br s), 6.73 (1H, br d, J=8.4 Hz), 7.06 (1H, d, J=8.4 Hz), 7.20—7.55 (5H, m). IR (nujol) cm^{-1}: 3458, 1682, 1618, 1587, 1510. MS *m/z*: 449 $[M+H]^+$. *Anal*. Calcd for $C_{27}H_{32}N_2O_4 \cdot H_2O$: C, 69.50; H, 7.35; N, 6.00. Found: C, 69.59; H, 7.18; N, 6.04.

(*S*)-2-Benzyl-7-[2-(2-isopropyl-5-methyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (40) A colorless solid, mp 95—99 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (6H, m), 2.19 (3H, s), 2.70—3.10 (5H, m), 3.50—4.20 (5H, m), 6.40—6.85 (2H, m), 7.01 (1H, d, J=8.1 Hz), 7.34 (5H, br s). IR (nujol) cm^{-1}: 3456, 1684, 1614, 1576, 1510. MS *m/z*: 435 $[M+H]^+$.

(*S*)-2-Benzyl-7-[2-(2-cyclopropyl-5-methyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (41) A colorless solid, mp 109—112 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.70—1.10 (4H, m), 1.80—2.20 (1H, m), 2.16 (3H, s), 2.60—2.85 (2H, m), 2.90—3.15 (2H, m), 3.50—4.20 (5H, m), 6.50—6.80 (2H, m), 7.03 (1H, d, J=8.1 Hz), 7.34 (5H, s). IR (nujol) cm^{-1}: 3470, 1684, 1618, 1583, 1510. MS *m/z*: 433 $[M+H]^+$. *Anal*. Calcd for $C_{26}H_{28}N_2O_4 \cdot 0.2H_2O$: C, 71.60; H, 6.56; N, 6.42. Found: C, 71.43; H, 6.58; N, 6.31.

(*S*)-2-Benzyl-7-{2-[2-(2,2-dimethylpropyl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (42) A colorless powder, mp 75—78 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (9H, s), 2.34 (3H, s), 2.55 (2H, s), 2.60—3.00 (2H, m), 3.00—3.30 (2H, m), 3.80—4.40 (7H, m), 6.64 (1H, br s), 6.70 (1H, d, J=8.8 Hz), 7.02 (1H, d, J=8.8 Hz), 7.32 (5H, s), 7.80 (1H, br s). IR (nujol) cm^{-1}: 1722, 1614, 1568, 1506. MS *m/z*: 463 $[M+H]^+$. *Anal*. Calcd for $C_{28}H_{34}N_2O_4$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.45; H, 7.60; N, 5.92.

(*S*)-2-Benzyl-7-{2-[5-methyl-2-(2-methylpropenyl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (43) A colorless solid, mp 109—111 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.89 (3H, s), 2.11 (3H, s), 2.27 (3H, s), 2.79 (2H, t, J=6.1 Hz), 2.90—3.20 (2H, m), 3.50—4.00 (4H, m), 3.93 (2H, s), 4.07 (2H, t, J=6.1 Hz), 5.99 (1H, s), 6.58 (1H, s), 6.67 (1H, d, J=8.2 Hz), 6.72 (1H, d, J=8.2 Hz), 7.33 (5H, s). IR (nujol) cm^{-1}: 3443, 3300, 1695, 1655, 1622, 1543, 1508. MS *m/z*: 447 $[M+H]^+$. *Anal*. Calcd for $C_{27}H_{30}N_2O_4 \cdot H_2O$: C, 69.81; H, 6.94; N,6.05. Found: C, 69.54; H, 6.91; N, 6.03.

(*S*)-2-Benzyl-7-{2-[2-(1-butenyl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (44) A pale yellow solid, mp 98—100 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, t, J=7.5 Hz), 2.05—2.20 (1H, m), 2.26 (3H, s), 2.50—3.00 (3H, m), 3.65—4.45 (7H, m), 5.92 (1H, br s), 6.17 (1H, d, J=16.3 Hz), 6.45—6.85 (3H, m), 7.05 (1H, d, J=8.4 Hz), 7.34 (5H, s). IR (nujol) cm^{-1}: 3470, 1682, 1614, 1585, 1512. MS *m/z*: 447 $[M+H]^+$. *Anal*. Calcd for $C_{27}H_{30}N_2O_4 \cdot 1.2H_2O$: C, 69.27; H, 6.98; N, 5.98. Found: C, 69.24; H, 6.97; N, 6.03.

(*S*)-2-Benzyl-7-{2-[2-(3-butenyl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (45) A colorless solid, mp 87—89 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 2.49 (2H, t, J=6.2 Hz), 2.65—2.90 (4H, m), 3.05—3.30 (2H, m), 3.75—4.50 (8H, m), 4.90—5.20 (2H, m), 5.65—6.10 (1H, m), 6.58 (1H, d, J=1.7 Hz), 6.75 (1H, dd, J=1.7, 8.2 Hz), 7.07 (1H, d, J=8.2 Hz), 7.35 (5H, s). IR (nujol) cm^{-1}: 3442, 1688, 1614, 1578, 1508. MS *m/z*: 447 $[M+H]^+$.

Compounds **46**—**54** were prepared by a similar procedure to that described in the synthesis of **20**.

(*S*)-2-Isobutyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (46) A colorless solid, mp 148—150 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, d, J=6.7 Hz), 1.01 (3H, d, J=7.0 Hz), 1.95—2.15 (1H, m), 2.36 (3H, s), 2.60—2.80 (2H, m), 2.94 (2H, t, J=6.7 Hz), 3.16 (2H, d, J=6.6 Hz), 3.70 (1H, t, J=6.6 Hz), 4.11 (2H, t, J=6.1 Hz), 6.60—6.90 (2H, m), 7.25—7.50 (3H, m), 7.49 (1H, d, J=6.6 Hz), 7.85—8.10 (2H, m). IR (nujol) cm^{-1}: 1620. MS *m/z*: 435 $[M+H]^+$.

(*S*)-2-Butyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (47) A pale yellow solid, mp 154—157 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.10—1.95 (4H, m), 2.36 (3H, s), 2.75—3.40 (6H, m), 3.71 (2H, br t J=6.1 Hz), 3.95—4.25 (4H, m), 6.57—7.57 (6H, m), 7.80—8.10 (3H, m). IR (nujol) cm^{-1}: 3382, 1722, 1614, 1554, 1506. MS *m/z*: 435 $[M+H]^+$. *Anal*. Calcd for $C_{26}H_{30}N_2O_4 \cdot 0.4H_2O$: C, 70.69; H, 7.03; N, 6.34. Found: C, 70.77; H, 7.02; N, 6.28.

(*S*)-2-(2,2-Dimethylpropyl)-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (48) A pale yellow powder, mp 85—88 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.96 (9H, s), 2.35 (3H, s), 2.46, 2.73 (2H, ABq, J=13.9 Hz), 2.93 (2H, t, J=6.7 Hz), 3.03—3.23 (2H, m), 3.57—3.78 (1H, m), 3.91, 4.18 (1H, ABq, J=15.4 Hz), 4.17 (2H, t, J=6.7 Hz), 5.60—6.05 (1H, br), 6.60 (1H, d, J=2.0 Hz), 6.73 (1H, dd, J=2.0, 8.4 Hz), 7.04 (1H, d, J=8.4 Hz), 7.30—7.55 (3H, m), 7.80—8.10 (2H, m). IR (nujol) cm^{-1}: 3391, 3279, 1668, 1645, 1616, 1597, 1497. MS *m/z*: 449 $[M+H]^+$. *Anal*. Calcd for $C_{27}H_{32}N_2O_4 \cdot 0.6H_2O$: C, 70.60; H, 7.28; N, 6.25. Found: C, 70.31; H, 7.32; N, 6.05.

(*S*)-2-Hexyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (49) A colorless solid, mp 149—152 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.70—0.95 (3H, m), 1.05—1.40 (6H, m), 1.50—1.90 (2H, m), 2.36 (3H, s), 2.70—3.30 (2H, m), 2.93 (2H, t, J=6.2 Hz), 3.15 (2H, d, J=6.4 Hz), 3.75 (1H, t, J=6.4 Hz), 4.00—4.40 (4H, m), 6.10—6.35 (1H, br), 6.60—6.85 (2H, m), 7.06 (1H, d, J=8.4 Hz), 7.30—7.60 (3H, m), 7.80—8.10 (2H, m). IR (nujol) cm^{-1}: 1620. MS *m/z*: 463 $[M+H]^+$. *Anal*. Calcd for $C_{28}H_{34}N_2O_4 \cdot 0.5H_2O$: C, 71.31; H, 7.48; N, 5.94. Found: C, 71.14; H, 7.38; N, 5.86.

(*S*)-2-Allyl-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (50) A colorless solid, mp 133—136 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.35 (3H, s), 2.70—3.15 (4H, m), 3.38 (2H, d, J=6.2 Hz), 3.55—4.00 (3H, m), 4.16 (2H, t, J=6.6 Hz), 4.40—5.50 (1H, br) 5.00—5.40 (2H, m), 5.60—6.10 (1H, m), 6.65 (1H, s), 6.69 (1H, d, J=8.1 Hz) 7.01 (1H, d, J=8.1 Hz), 7.35—7.65 (3H, m), 7.75—8.10 (2H, m). IR (nujol) cm^{-1}: 3335, 1690, 1618, 1553, 1506. MS *m/z*: 419 $[M+H]^+$. *Anal*. Calcd for $C_{25}H_{26}N_2O_4 \cdot 1.2H_2O$: C, 68.23; H, 6.50; N, 6.37. Found: C, 68.23; H, 6.50; N, 6.37.

(*S*)-7-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]-2-(2-propynyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (51) A colorless solid, mp 109—111 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.00—6.40 (1H, br), 2.35 (3H, s), 2.70—3.10 (4H, m), 3.10—3.25 (1H, m), 3.50—4.00 (5H, m), 4.17 (2H, t, J=6.4 Hz), 6.66 (1H, s), 6.70 (1H, d, J=8.6 Hz), 7.01 (1H, d, J=8.6 Hz), 7.30—7.70 (3H, m), 7.85—8.05 (2H, m). IR (nujol) cm^{-1}: 3383, 3306, 3221, 1692, 1622, 1508. MS *m/z*: 417 $[M+H]^+$. *Anal*. Calcd for $C_{25}H_{24}N_2O_4 \cdot H_2O$: C, 69.11; H, 6.03; N, 5.45. Found: C, 69.03; H, 6.04; N, 6.43.

(*S*)-2-(2-Butenyl)-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (52) A pale yellow solid, mp 127—131 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.67 (3H, d, J=4.9 Hz), 2.35 (3H, s), 2.70—3.10 (4H, m), 3.20—3.50 (2H, m), 3.50—4.00 (3H, m), 4.16 (2H, t, J=6.4 Hz), 4.35—5.20 (1H, br), 5.25—5.90 (2H, m), 6.55—6.90 (2H, m), 7.01 (2H, d, J=8.1 Hz), 7.35—7.70 (3H, m), 7.75—8.10 (2H, m). IR (nujol) cm^{-1}: 3447, 3342, 1684, 1620, 1556. MS *m/z*: 433 $[M+H]^+$. *Anal*. Calcd for $C_{26}H_{28}N_2O_4 \cdot H_2O$: C, 69.31; H, 6.71; N, 6.22. Found: C, 69.10; H, 6.78;

N, 6.20.

(*S*)-2-(3-Butenyl)-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (53) A pale yellow solid, mp 141—143 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.10—2.40 (2H, m), 2.35 (3H, s), 2.60—3.15 (6H, m), 3.50—4.00 (3H, m), 4.17 (2H, t, J=6.3 Hz), 4.40—5.40 (1H, br), 4.85—5.25 (2H, m), 5.55—6.10 (1H, m), 6.50—6.85 (2H, m), 7.01 (1H, d, J=8.1 Hz), 7.35—7.70 (3H, m), 7.75—8.05 (2H, m). IR (nujol) cm^{-1}: 3425, 1682, 1612, 1555. MS *m/z*: 433 [M+H]$^+$. *Anal*. Calcd for $C_{26}H_{28}N_2O_4 \cdot H_2O$: C, 69.31; H, 6.71; N, 6.22. Found: C, 69.14; H, 6.65; N, 6.10.

(*S*)-2-(3-Methyl-2-butenyl)-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (54) A colorless solid, mp 132—134 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.61 (3H, s), 1.72 (3H, s), 2.35 (3H, s), 2.70—3.20 (4H, m), 3.39 (2H, d, J=7.0 Hz), 3.50—4.01 (3H, m), 4.16 (2H, t, J=7.0 Hz), 4.35—5.60 (1H, br), 5.20—5.30 (1H, m), 6.67 (1H, s), 6.71 (1H, d, J=8.4 Hz), 7.02 (1H, d, J=8.4 Hz), 7.30—7.70 (8H, m), 7.75—8.10 (2H, m). IR (nujol) cm^{-1}: 3447, 3335, 1670, 1668, 1622, 1556, 1506. MS *m/z*: 447 [M+H]$^+$. *Anal*. Calcd for $C_{27}H_{30}N_2O_4 \cdot 1.2H_2O$: C, 69.27; H, 6.98; N, 5.98. Found: C, 69.34; H, 6.95; N, 5.98.

Determination of Octanol–Water Partition Coefficient Compounds were dissolved in 1 ml of octanol and mixed with 1 ml of Britton–Robinson buffer (pH 7.0). The mixed solution was vigorously shaken at room temperature for 30 min and then centrifuged at 3000 r.p.m. for 10 min at room temperature. Concentrations in the octanol fraction and buffer fraction were determined using HPLC or LC-MS/MS. The HPLC equipment consisted of a pump (PU-980, JASCO, Tokyo, Japan), UV detector (UV-970, JASCO), autoinjector (AS-950, JASCO), and Cosmosil-5C18-MS-II column (5 μm, 4.6 mm×150 mm, Nacalai Tesque, Kyoto, Japan). The LC-MS/MS system with a Develosil-ODS-UG-5 column (5 μm, 2.0 mm×100 mm, NOMURA Chemical, Seto, Japan) was used (API2000 QTRAP LC/MS/MS system, Applied Biosystems, Tokyo, Japan). The octanol–water partition coefficient was calculated as a ratio of the concentration in the octanol fraction to that in the buffer fraction. Log *P* was determined as the logarithm of the partition coefficient.

PPARγ Agonist Activity Full-length human PPARγ1 plasmid (GeneCopoeia, Inc., Maryland, U.S.A.), and human RXRα plasmid (GeneCopoeia, Inc.) with reporter plasmid pGL3-PPREx4-tk-luc and pRL-tk (Promega Corporation, Madison, WI, U.S.A.) were transfected to CV-1 cells (Dainippon Pharmaceutical Industries, Co., Ltd., Osaka, Japan) using LipofectAMINE (Invitrogen Corporation, Carlsbad, CA, U.S.A.). The cells were incubated for 24 h under 5% CO_2 at 37 °C. The detached cells were further incubated for 48 h in the presence or absence of the test compound in Dulbecco's modified Eagle's medium (DMEM, Nissui Pharmaceutical, Co., Ltd., Tokyo, Japan) containing 0.1% fatty acid-free bovine serum albumin. The medium was removed and then luciferase activities were determined using a commercial kit (Dual-Luciferase Reporter Assay System, Promega Corporation) and a microplate luminescence reader (Dainippon Pharmaceutical Industries, Co., Ltd.).

Adipocyte Differentiation in 3T3-L1 Cells Confluent 3T3-L1 cells were cultured in DMEM medium containing 5% FBS and 0.5 mM isobutylmethylxanthine (IBMX) for 2 d, and then in DMEM medium containing 5% FBS, insulin (10 ng/ml) in the presence or absence of test compounds for 4 d. The cells were lysed, cellular triglyceride was extracted and determined using a commercial kit (Wako Pure Chemicals, Co., Ltd., Osaka), and protein was determined with Lowry's method. Compound **10** (10^{-10}—10^{-6} M) increased cellular TG produced during insulin-stimulated adipocyte differentiation in a concentration-dependent manner. In each assay, the TG-increasing effect of the test compounds was compared with that of **10**, and the relative activity against **10** was calculated as a reciprocal of the equivalent concentration ratio of test compound/compound **10**.

Anti-hyperglycemic and Hypolipidemic Effects in Male KK-A^y Mice Male KK-A^y mice (14—21 weeks old, Clea Japan, Inc., Tokyo) were allocated to control and treated groups. Each compound was suspended in 5% arabic gum solution and orally administered at 30 mg/kg for 4 d in the treated group, and vehicle in the control group. A blood sample was taken from the tail vein of non-fasted mice 24 h after the final administration. Plasma glucose and TG levels in mice administered the vehicle or test compounds were determined using commercial kits (Wako Pure Chemicals, Co., Ltd.). In each experiment, test compounds and compound **10** were administered. Percent decrease in plasma glucose and TG levels in mice administered the test compounds was calculated in comparison with control mice administered vehicle. In separate experiments, compound **10** (KY-021) and farglitazar at 0.3, 1 and 3 mg/kg were administered as an admixture diet for 7 d in male KK-A^y mice (30 weeks old). On the 7th day, a blood sample was taken from the tail vein and plasma glucose and TG levels were determined. In these experiments, plasma glucose and TG values were statistically compared between the treated group and control group using Student's *t*-test. $p<0.05$ was considered significant.

Hypolipidemic Effects and Glucose Tolerance Improving Effects in Male Zucker Fatty Rats Male Zucker fatty rats (8—12 weeks old, Kiwa Laboratory Animals, Co., Ltd., Wakayama, Japan) were allocated to control and treated groups. KY-021 and farglitazar were suspended in 0.5% methyl cellulose solution and orally administered at 0.3—3 mg/kg for 7 d in male Zucker fatty rats. A blood sample was taken from the external jugular vein of non-fasted rats before the final administration and plasma TG was determined. Glucose (2 g/kg) was orally administered 24 h after the final administration of KY-021 and farglitazar to fasted rats. A blood sample was then taken before and 15, 30, 60, 120 and 180 min after the administration of glucose, and plasma glucose levels were determined. The area under the curve (*AUC*) of plasma glucose was measured. Percent decrease in TG and glucose *AUC* in rats administered KY-021 and farglitazar was calculated by comparison with the mean value in control rats administered vehicle. Plasma TG and glucose *AUC* values were statistically compared between the treated group and control group using Student's *t*-test. $p<0.05$ was considered significant.

Plasma Concentration after Oral Administration of KY-021 and Farglitazar in Male ICR Mice and SD Rats Male ICR mice (6 weeks old, Japan SLC, Inc., Hamamatsu, Japan) and male SD rats (7 weeks old, Japan SLC, Inc.) were used. KY-021 and farglitazar at 10 mg/kg suspended in 0.5% methyl cellulose solution was orally administered and then a blood sample was taken from the external jugular vein 0.5, 1, 3, 5 and 8 h after administration in rats, and by heart puncture under ether-anesthesia 0.25, 0.5, 1, 3, 5 and 8 h after administration in mice. Plasma concentrations of each drug were determined using HPLC system consisting of a pump (PU-980, JASCO, Tokyo, Japan), UV detector (UV-970, JASCO), autoinjector (AS-950, JASCO), and STR-ODS-II column (5 μm, 4.6 mm×150 mm, Shimadzu Techno-research, Kyoto, Japan). The maximal concentration (C_{max}) and *AUC* were calculated.

Toxicity Test of KY-021 Administered at 30 mg/kg for 10 Weeks in Male SD Rats Male SD rats (6 weeks old, Charles River Japan, Inc., Kanagawa, Japan) were allocated to control and treated-groups. KY-021 and farglitazar were suspended in 0.5% methylcellulose solution and administered at 30 mg/kg/d for 10 weeks to the treated group, and vehicle to the control group. The general condition was observed daily and body weight was measured. The rats were anesthetized with pentobarbital (50 mg/kg, i.p.) 24 h after the final administration, and bled to death. After euthanasia, thoracic and abdominal organs, including periepididymal white adipose tissue, were isolated and weighed, and hematological tests were performed.

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