A Novel Series of (*S*)-2,7-Substituted-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acids: Peroxisome Proliferator-Activated Receptor α/γ Dual Agonists with Protein-Tyrosine Phosphatase 1B Inhibitory Activity

Kazuya Otake, Satoru Azukizawa, Masaki Fukui, Michiko Shibabayashi, Hikaru Kamemoto, Tomohiro Miike, Kazuyoshi Kunishiro, Masayasu Kasai, and Hiroaki Shirahase*

Research Laboratories, Kyoto Pharmaceutical Industries, Ltd.; 38, Nishinokyo Tsukinowa-cho, Nakagyo-ku, Kyoto 604–8444, Japan. Received May 30, 2011; accepted July 22, 2011

Novel 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives were synthesized and (*S*)-7-(2-{2-[(*E*)-2-cyclopentylvinyl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (14c) was identified as a peroxisome proliferator-activated receptor (PPAR) α/γ dual agonist. The transactivation activity of 14c was comparable to that of rosiglitazone in human PPARγ (EC_{50}=0.14 μM) and was much higher than in human PPARα (EC_{50}=0.20 μM). In addition, 14c, but not rosiglitazone, showed human protein-tyrosine phosphatase 1B (PTP-1B) inhibitory activity (IC_{50}=1.85 μM). 14c showed about 10-fold stronger hypoglycemic and hypotriglyceridemic effects than rosiglitazone by repeated application for 14 d in male KK-A^y mice. Furthermore, 14c, but not rosiglitazone, increased hepatic peroxisome acyl CoA oxidase activity at 30 mg/kg/d for 7 d in male Syrian hamsters, probably due to its PPARα agonist activity. 14c did not affect plasma volume at 100 mg/kg/d for 14 d in male ICR mice, while rosiglitazone significantly increased it. In conclusion, 14c is a promising candidate for an efficacious and safe anti-diabetic drug with triple actions as a PPARα/γ dual agonist with PTP-1B inhibitory activity.

Key words peroxisome proliferator-activated receptor; diabetes; hypoglycemic effect; tetrahydroisoquinoline derivative; protein-tyrosine phosphatase 1B; KK-A^y mouse

Thiazolidinedione (TZD) derivatives, such as rosiglitazone, have been used as anti-diabetic drugs and are known to enhance insulin sensitivity by activating peroxisome proliferator-activated receptor γ (PPARγ) mainly expressed in adipocytes, resulting in the reduction of blood glucose levels in type 2 diabetic patients[1—3]; however, TZD derivatives cause edema, increase the risk of weight gain and congestive heart failure, and cause hepatotoxicity.[4—7] Thus, to find a new PPARγ agonist without such adverse effects, many non-TZD derivatives have been synthesized but none have been developed successfully. Farglitazar, a tyrosine derivative, is a potent PPARγ agonist showing efficacious anti-diabetic effects, but its development was discontinued due to adverse effects such as edema[8] (Fig. 1). We synthesized a novel se-

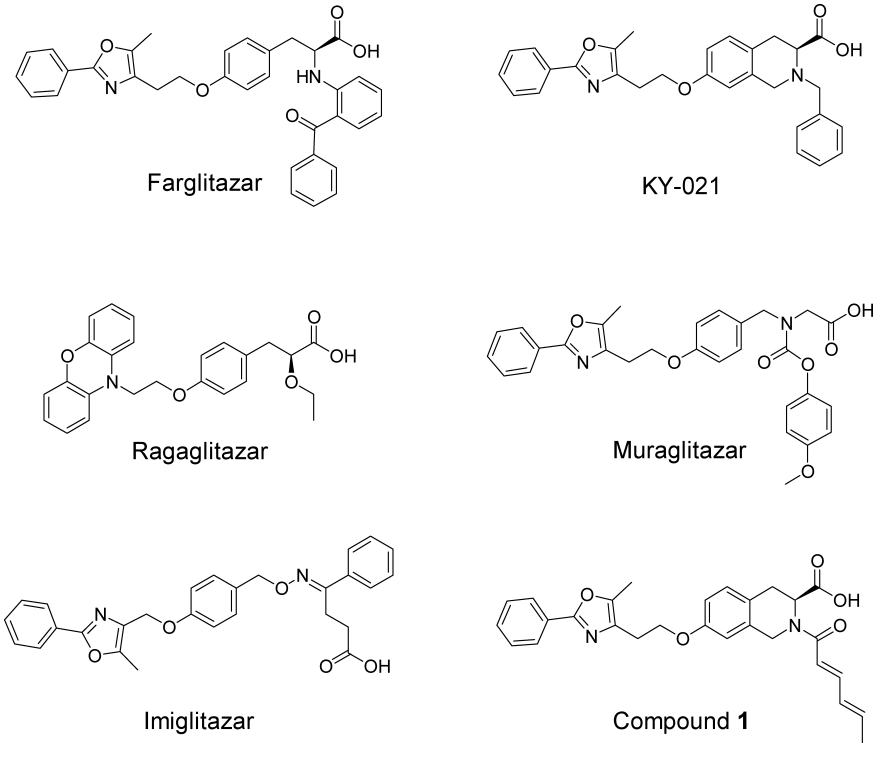


Fig. 1. Chemical Structures of PPAR Agonists

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

ries of tetrahydroisoquinoline derivatives, in which KY-021 has been identified as a PPARγ agonist with high anti-diabetic efficacy and safety in experimental animals[9]; however, its clinical efficacy and safety remain to be determined (Fig. 1).

In recent years, many efforts have been made to develop a PPARα/γ dual agonist. PPARα is expressed in the liver and is related to fatty acid metabolism[10]; fibrates, including clofibrate, bezafibrate and fenofibrate, have been used as anti-hyperlipidemic drugs and are known to exert their effects *via* hepatic PPARα activation. PPARα agonists improved insulin resistance by reducing plasma lipids in experimental animals, and showed hypoglycemic and insulin-resistance-improving effects in patients.[11—13] Their hypocholesterolemic effects are expected to protect against cardiovascular diseases in diabetic patients with hyperlipidemic complications. Furthermore, PPARα agonists have a body weight-reducing effect, while PPARγ agonists have a risk of body weight gain.[14] Thus, the combination of PPARα and PPARγ agonistic activities would result in synergenistic anti-diabetic efficacy and safety.[15,16] A number of carboxylic acid derivatives have been reported as PPARα/γ dual agonists;[17—21] however, clinical development of most compounds has been discontinued: *e.g.*, ragaglitazar due to carcinogenicity; muraglitazar due to the risk of cardiovascular events; imiglitazar due to the potential risk of liver injury (Fig. 1). Excess activation of PPARα as well as PPARγ may lead to carcinogenesis and to adverse effects on the kidneys, heart and liver.[16,22—26] Furthermore, many PPARα/γ dual agonists have a relatively high molecular weight and 3—4 aromatic rings, and show high lipophilicity; these structural and physicochemical properties may also be related to their adverse effects.[27] On the other hand, we have found a new tetrahydroisoquinoline derivative (compound **1**, Fig. 1), which has a relatively low molecular weight and smaller number of aromatic rings, as a lead compound for a PPARα/γ dual agonist (EC_{50}: 0.38, 0.16 μM, respectively) with weak protein-tyrosine phosphatase 1B (PTP-1B) inhibitory activity (9.4 μM).[28] PTP-1B is known to play a role as a negative regulator of insulin signaling, and PTP-1B inhibition has been reported to enhance insulin sensitivity.[29] Therefore, PTP-1B inhibitory activity is expected to potentiate the insulin sensitivity-enhancing effect but not the adverse effects of PPARα/γ dual agonist. In the present study, to find a novel PPARα/γ dual agonist with potent PTP-1B inhibitory activity, a new series of 2,7-substituted-tetrahydroisoquinoline derivatives were synthesized by replacing of a phenyl group with a side chain having a non-aromatic ring on the oxazole ring in compound **1**.

Chemistry (*S*)-7-Substituted-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives (**14a**—**i**) were synthesized by alkylation with 2-(2-substituted-5-methyloxazol-4-yl)ethyl methanesulfonate (**9a**—**i**) at the 7-position of methyl (*S*)-2-*tert*-butoxycarbonyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**10**),[9] followed by conversion of the *tert*-butoxycarbonyl (Boc) group to hexadienoyl group at the 2-position, and hydrolysis of the methyl ester.

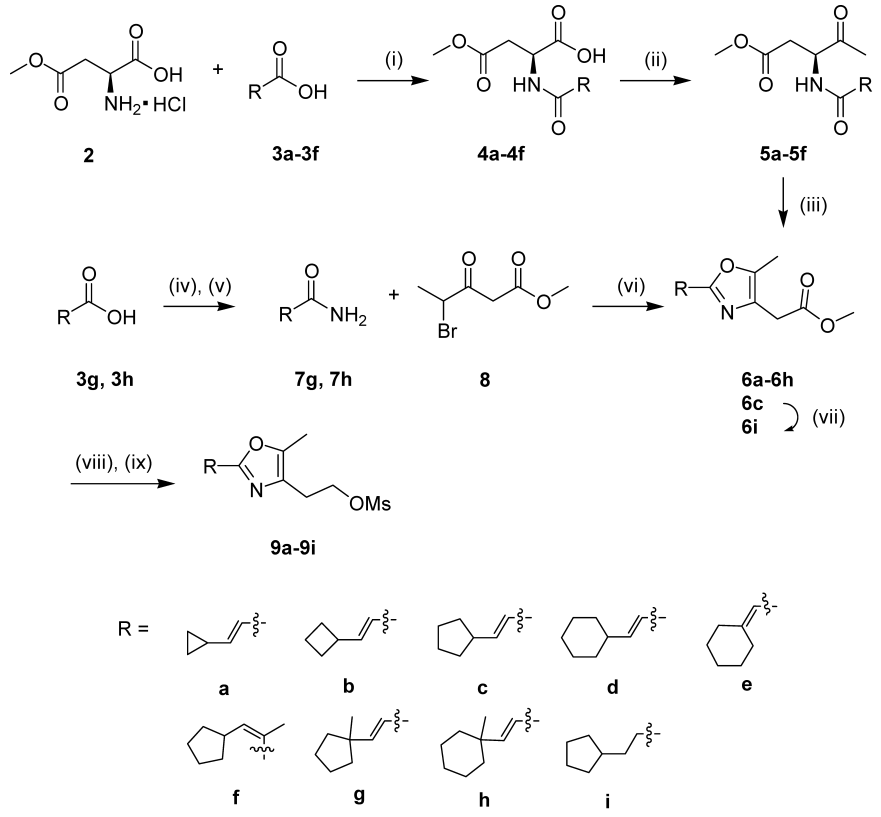
The general approach to the synthesis of **9a**—**i** is outlined in Chart 1. Acylation of L-aspartic acid β-methyl ester (**2**) with **3a**—**f** afforded **4a**—**f**. The carboxylic acid of **4a**—**f** was transformed to methylketone by the Dakin–West reaction with acetic anhydride and bases to give **5a**—**f**, which were treated with phosphorous oxychloride to afford oxazole derivatives (**6a**—**f**).[30] Amidation of **3g** and **h** afforded **7g** and **h**, which were treated with methyl 4-bromo-3-oxopentanoate (**8**) to give oxazole derivatives (**6g**, **h**). Hydrogenation of **6c** afforded **6i**. Reduction of **6a**—**i** was performed with diisobutyl aluminum hydride (DIBAH), and the products were methanesulfonylated to afford **9a**—**i**.

The general approach to the synthesis of **14a**—**i** is outlined in Chart 2. Alkylation of **10** with **9a**—**i** in the presence of K_2CO_3 and tetrabutylammonium fluoride afforded **11a**—**i** in good yield. The Boc group of **11a**—**i** was removed with HCl/HCO_2H, affording **12a**—**i**, which were treated with sorbic acid and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), or (2*E*,4*E*)-hexadienoyl chloride and triethylamine, to give **13a**—**i**, which were treated with aqueous LiOH to give carboxylic acid derivatives, and then **14a**—**i** were isolated as *tert*-butylamine salts.[28]

Results and Discussion

In the previous study, we synthesized a series of tetrahydroisoquinoline derivatives and found a novel PPARγ agonist, KY-021, which has a more rigid structure, lower molecular weight and lipophilicity, and higher efficacy and safety than farglitazar.[9] Then, we found a new tetrahydroisoquinoline derivative as a lead compound for a PPARα/γ agonist with weak PTP-1B inhibitory activity.[28] In the present study, another series of tetrahydroisoquinoline derivatives with various aliphatic ring moieties instead of phenyl moiety at the 2-position of oxazole were synthesized to find a novel PPARα/γ dual agonist with potent PTP-1B inhibitory activity. PPARγ and PPARα agonist activity was determined as transactivation activity in COS-1 cells transfected with full-length human PPARγ1 plasmid or PPARα plasmid, and human RXRα plasmid with reporter plasmid pGL3-PPREx4-tk-luc; EC_{50} and the maximal activation level relative to the level activated by farglitazar, a PPARγ agonist (10^{-7} M) or Wy-14643, a PPARα agonist (10^{-5} M) were determined. Glucose-lowering effects of derivatives were examined in KK-A^y mice, a type 2 diabetic model animal, and expressed as a % decrease in glucose in comparison with control mice administered the vehicle. All animal experiments in the present study were conducted according to the guidelines for animal experiments of our institute and the guidelines for animal experimentation approved by the Japanese Association of Laboratory Animal Science. PTP-1B inhibitory activity was determined using human PTP-1B as an enzyme and *p*-nitrophenylphosphonic acid (*p*NPP) as a substrate, and IC_{50} values were calculated.[28]

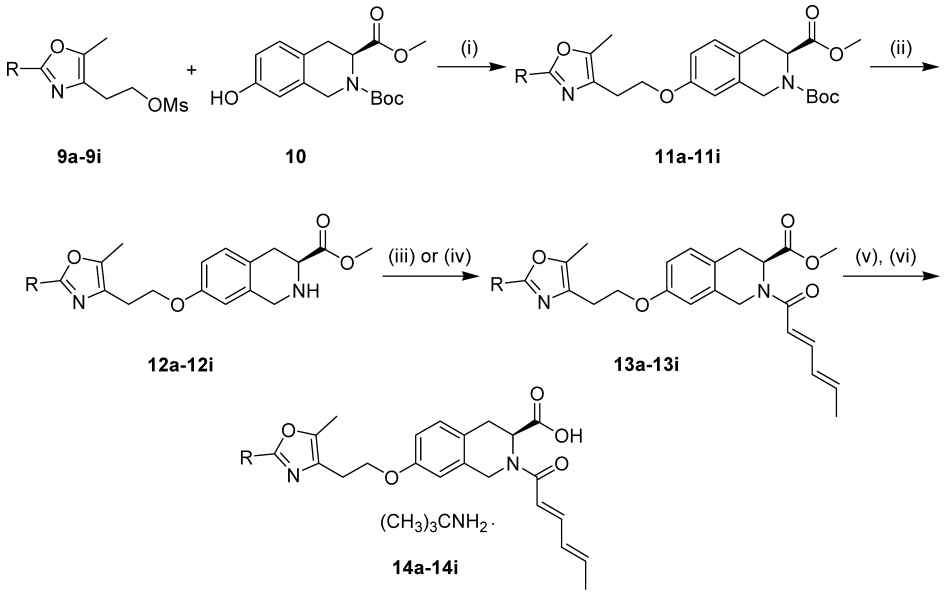
Compounds **14a**—**i** showed moderate to potent PPARγ agonist activities (Table 1). In the compounds with cycloalkylvinyl moieties (**14a**—**d**), activity increased dependent on the aliphatic ring size (cyclopropyl to cyclohexyl). Insertion of a methyl group at the 1-position of the cycloalkyl group (**14c** *vs.* **14g**, **14d** *vs.* **14h**) and at the 1-position of the vinyl group (**14c** *vs.* **14f**) decreased the activity. The cycloalkylidene structure (**14e**) and reduction of the vinyl group (**14i**) markedly reduced the activity. All the compounds showed almost full activation of PPARγ (Max: 83—113%). The PPARγ agonist activity of compound **14c** and **d** was comparable to that of rosiglitazone and stronger than



(i) *i*-BuOCOCl, Et_3N, CH_2Cl_2; (ii) Ac_2O, *N*-methylmorpholine, DMAP, toluene; (iii) $POCl_3$, toluene;

(iv) $SOCl_2$; (v) NH_3 aq.; (vi) toluene; (vii) Pd-C, H_2, MeOH; (viii) DIBAH, toluene; (ix) MsCl, Et_3N, CH_2Cl_2.

Chart 1. Synthesis of 2-(2-Substituted-5-methyloxazol-4-yl)ethyl Methanesulfonates

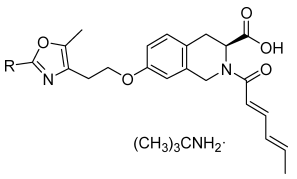


(i) K_2CO_3, tetraethylammonium fluoride, toluene; (ii) HCl, HCO_2H; (iii) sorbic acid, EDC, CH_2Cl_2;

(iv) (2*E*,4*E*)-hexadienoyl chloride, Et_3N, CH_2Cl_2; (v) LiOH aq., THF-MeOH, (vi) *tert*-$BuNH_2$, MeOH-*i*-Pr_2O.

Chart 2. Synthesis of 2,7-Substituted-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acids

Table 1. Molecular Weight, Log $D_{7.0}$, PPARγ and PPARα Transactivation Effects, PTP-1B Inhibition, and Hypoglycemic Effects in KK-A^y Mice of 2,7-Substituted-tetrahydroisoquinoline-3-carboxylic Acids



Compound	R	M.W.[a]	log $D_{7.0}$	PPARγ[b]		PPARα[b]		PTP-1B[b]	KK-A^y mice (10 mg/kg, 4 d)[e]
				EC_{50} (μM)	Max[c] (%)	EC_{50} (μM)	Max[d] (%)	IC_{50} (μM)	Glucose % decrease
14a		462.54	2.42	1.08	113	1.01	81	8.20	50**
14b		476.56	3.15	0.27	110	0.23	81	4.90	43*
14c		490.59	3.54	0.14	84	0.20	76	1.85	45**
14d		504.62	4.01	0.10	98	0.13	47	1.80	54**
14e		490.59	3.38	0.43	84	0.15	35	3.40	5
14f		504.62	3.95	0.25	85	0.18	53	1.38	13
14g		504.62	3.81	0.24	94	—	—	1.28	27
14h		518.64	4.22	0.41	90	—	—	6.35	21
14i		492.61	3.41	0.23	83	—	—	1.28	45**
Rosiglitazone		357.43	NT	0.14	128	(125% at 10 μM)		>30	48**
Ertiprotafib		559.51	NT	NT	NT	NT	NT	1.59	NT

NT: not tested. *a*) Molecular weight as free form. *b*) $n=2$. *c*) The activation level induced by farglitazar (10^{-7} M) was taken as 100%. *d*) The activation level induced by Wy-14643 (10^{-5} M) was taken as 100%. *e*) $n=5$, $*p<0.05$, $**p<0.01$, *vs.* control, Student's *t*-test.

that of compound **1**, indicating that a medium-sized cycloalkylvinyl structure is more preferable than a phenyl structure for interaction with PPARγ protein.

On the other hand, compounds **14a**—**f** showed moderate to potent PPARα agonist activities, which increased dependent on the aliphatic ring size; however, the maximal activation level decreased dependent on the aliphatic ring size: the maximal response of **14d** was lower than 50% at 10 μM. The cycloalkylidene structure (**14e**) and insertion of a methyl group at the 1-position of vinyl group (**14f**) also markedly reduced the maximal response. Insertion of a methyl group at the 1-position of the cycloalkyl group (**14g**, **h**) and reduction of the vinyl group (**14i**) abolished PPARα agonist activity. From these results, a relatively small cycloalkylvinyl structure is preferable for interaction with PPARα protein; however, the structural requirement was different from the interaction with PPARγ. Among the compounds, **14b** and **c** showed higher activity than compound **1**.

All the compounds showed moderate to potent PTP-1B inhibitory activities, which increased dependent on the ring size. Insertion of a methyl group at the 1-position of cycloalkyl and vinyl groups in a cyclopentylvinyl derivative increased activity (**14f**, **g**), while addition of a methyl group at the 1-position of cycloalkyl in a cyclohexylvinyl derivative markedly decreased activity (**14h**). Reduction of the vinyl group increased activity (**14i**). The activity of compounds **14c**, **d**, **f**, **g** and **i** was approximately 5-fold stronger than that of compound **1** and comparable to that of Ertiprotafib.

Among the compounds, **14a**—**d** and **i** showed similar hypoglycemic effects in KK-A^y mice, which are considered to be due to PPARγ activation because the compounds failed to activate mouse PPARα (unpublished data); however, PPARγ agonist activity was not related to hypoglycemic effects, suggesting that the activity may inversely relate to oral bioavailability. Furthermore, the potent PTP-1B inhibitory activity of **14c**, **d** and **i** may have contributed to their hypoglycemic effects. From the results, **14c** was chosen for further evaluation as a potent and well-balanced PPARα/γ dual agonist with

Table 2. Effects of Repeated Administration of **14c** and Rosiglitazone for 14 d on Plasma Glucose and Triglyceride Levels in Male KK-A^y Mice

Compound	Dose (mg/kg/d)	Glucose (mg/dl)	Triglyceride (mg/dl)
Control	—	623.2±49.8	790.2±123.6
14c	1	450.2±48.1*	832.2±71.8
	3	338.0±32.3**	464.7±42.4*
Control	—	676.9±53.5	788.5±152.1
Rosiglitazone	10	430.1±49.0*	603.1±72.0
	30	320.4±42.3**	481.4±97.6

Mean±S.E. $n=4$. * $p<0.05$, ** $p<0.01$, *vs.* control, Student's *t*-test.

Table 3. Effects of Repeated Administration of **14c** and Rosiglitazone for 7 d on Hepatic Acyl CoA Oxidase (ACO) Activity in Male Syrian Hamsters

Compound	Dose (mg/kg/d)	ACO activity (ΔOD_{502}/min/mg)
Control	—	0.107±0.009
14c	10	0.156±0.016
	30	0.244±0.023**
Rosiglitazone	10	0.152±0.021
	30	0.160±0.017

Mean±S.E. $n=4$. ** $p<0.01$, *vs.* control, Student's *t*-test.

Table 4. Effects of Repeated Administration of **14c** and Rosiglitazone for 14 d in Male ICR Mice

	Control	**14c** (mg/kg/d)		Control	Rosiglitazone (mg/kg/d)	
		30	100		30	100
Plasma (ml)	1.53±0.06	1.64±0.07	1.71±0.16	1.73±0.26	2.02±0.20	2.10±0.16*
Heart (g)	0.18±0.01	0.19±0.01	0.18±0.00	0.18±0.01	0.19±0.02	0.19±0.01
Liver (g)	2.41±0.07	2.32±0.13	2.12±0.11	2.53±0.17	2.76±0.27	2.78±0.20*

Mean±S.E. $n=5$—6. * $p<0.05$, *vs.* control, Student's *t*-test.

potent PTP-1B inhibitory activity.

The effects of **14c** were pharmacologically and toxicologically evaluated in comparison with rosiglitazone. Compound **14c** (1, 3 mg/kg/d) and rosiglitazone (10, 30 mg/kg/d) showed similar hypoglycemic and hypotriglyceridemic effects in KK-A^y mice, indicating that **14c** was about 10-fold stronger than rosiglitazone (Table 2); however, PPARγ agonist activity of **14c** was comparable to that of rosiglitazone, and its insulin-enhancing activity in adipocyte differentiation was about 1/5-fold weaker than that of rosiglitazone (unpublished data). In separate experiments, the C_{max} of **14c** (3 mg/kg) and rosiglitazone (30 mg/kg) after oral administration in KK-A^y mice was 1.7 and 34.6 μg/ml, respectively. It remains to be determined why **14c** had greater hypoglycemic and hypotriglyceridemic effects despite comparable PPARγ agonist activity and lower plasma concentrations than rosiglitazone. It is likely that PTP-1B inhibitory activity is involved in the hypoglycemic and hypotriglyceridemic effects since C_{max} of **14c** exceeded the IC_{50} value for PTP-1B inhibition. Involvement of PPARα agonist activity can be eliminated in KK-A^y mice since it failed to activate mouse PPARα. However, in male Syrian hamsters, compound **14c**, but not rosiglitazone, at 30 mg/kg/d for 7 d significantly increased hepatic peroxisome acyl CoA oxidase (ACO) activity, probably due to its PPARα agonist activity (Table 3). It has been reported that TZD18, a human but not mouse PPARα/γ dual agonist, increased hamster ACO activities.[31] In male ICR mice, repeated administration of **14c** at 30 and 100 mg/kg/d for 14 d had little toxicity, while rosiglitazone at 100 mg/kg/d significantly increased plasma volume and liver weight (Table 4). From the results in KK-A^y mice and ICR mice, the safety margin of **14c** and rosiglitazone was estimated to be >100-fold and 10-fold, respectively.

In conclusion, new tetrahydroisoquinoline derivatives were identified as a PPARα/γ dual agonist with PTP-1B inhibitory activity stronger than compound **1**. Cycloalkylvinyl moiety was demonstrated to be more suitable than a phenyl group for interaction with PPARγ, PPARα and PTP-1B protein. Compound **14c** was proven to be more efficacious and safer as an anti-diabetic drug than rosiglitazone in mice, which may be due to, at least in part, its PTP-1B inhibitory activity. In patients, its human PPARα agonist activity is also expected to potentiate PPARγ-mediated anti-diabetic effects and reduce adverse effects.

Experimental

General Melting points were measured on a melting point apparatus (Yamato MP-21; Yamato Scientific Co., Ltd., Tokyo, Japan) and are uncorrected. ^{1}H-NMR spectra were obtained on a nuclear magnetic resonance spectrometer at 90 MHz (R-1900; Hitachi High-Technologies Corporation, Tokyo, Japan) or 400 MHz (JNM-AL-400; JEOL Ltd., Tokyo, Japan) using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded with an infrared spectrometer (FT-IR8200PC; Shimadzu Corporation, Kyoto, Japan). MS spectra were obtained on a QTRAP LC/MS/MS system (API2000; Applied Biosystems, Foster, U.S.A.). Column chromatography was performed on silica gel (Daisogel No.1001W; Daiso Co., Ltd., Osaka, Japan). Reactions were monitored by TLC (TLC silica gel 60 F_{254}, Merck, Darmstadt, Germany).

Methyl {2-[(*E*)-2-Cyclopropylvinyl]-5-methyloxazol-4-yl}acetate (6a) Triethylamine (52.0 ml, 373 mmol) was added dropwise to a suspension of **2** (22.7 g, 124 mmol) in CH_2Cl_2 (320 ml) and the suspension was stirred at room temperature for 30 min. Separately, to a solution of **3a** (9.40 g, 83.8 mmol) and triethylamine (13.0 ml, 93.3 mmol) in CH_2Cl_2 (130 ml) was added isobutyl chloroformate (12.0 ml, 92.5 mmol) below 10 °C. After stirring at the same temperature for 20 min, the mixture was added to the above suspension below 10 °C, and stirred at the same temperature for 1 h. The reaction mixture was washed with water, 1 M HCl and saturated brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give crude **4a** (24.1 g) as an oil. Crude **4a** (24.1 g), acetic anhydride (39.0 ml, 413 mmol), *N*-methylmorpholine (36.0 ml, 327 mmol) and 4-dimethylaminopyridine (DMAP) (2.00 g, 16.3 mmol) were dissolved in toluene (240 ml) and stirred at 60—70 °C for 1.5 h. After cooling to room temperature, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution and separated into two layers. The organic layer was washed with water and saturated brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give crude **5a** (7.68 g) as a solid. To a solution of crude **5a** (7.68 g) in toluene (150 ml) was added $POCl_3$ (4.0 ml. 43 mmol), and the mixture was stirred at 100 °C for 45 min. After cooling, the mixture was poured into cold water, neutralized with $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with water and saturated brine, dried over Na_2SO_4, and then evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give **6a** (2.17 g, 12% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.45—0.70 (2H, m), 0.75—1.05 (2H, m), 1.40—1.80 (1H, m), 2.25 (3H, s), 3.46 (2H, s), 3.70 (3H, s), 5.95—6.45 (2H, m). IR (neat) cm^{-1}: 1744, 1655, 1537.

Compounds **6b**—**f** were prepared according to the procedure for the synthesis of **6a**.

Methyl {2-[(*E*)-2-Cyclobutylvinyl]-5-methyloxazol-4-yl}acetate (6b) Yield 32%. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.01 (4H, m), 2.12—2.24 (2H, m), 2.27 (3H, s), 3.04—3.16 (1H, m), 3.47 (2H, s), 3.70 (3H, s), 6.13 (1H, dd, J=15.9, 1.5 Hz), 6.72 (1H, dd, J=15.9, 7.1 Hz). IR (neat) cm^{-1}: 1746, 1644, 1610, 1534.

Methyl {2-[(*E*)-2-Cyclopentylvinyl]-5-methyloxazol-4-yl}acetate (6c) Yield 30%. ^{1}H-NMR ($CDCl_3$) δ: 1.10—2.00 (8H, m), 2.27 (3H, s), 2.35—2.78 (1H, m), 3.47 (2H, s), 3.70 (3H, s), 6.16 (1H, d, J=16.0 Hz), 6.62 (1H, dd, J=16.0, 7.5 Hz). IR (neat) cm^{-1}: 2953, 2870, 1746, 1659, 1643, 1551, 1535.

Methyl {2-[(*E*)-2-Cyclohexylvinyl]-5-methyloxazol-4-yl}acetate (6d) Yield 38%. ^{1}H-NMR ($CDCl_3$) δ: 0.80—2.40 (11H, m), 2.27 (3H, s), 3.47 (2H, s), 3.70 (3H, s), 6.14 (1H, d, J=16.0 Hz), 6.60 (1H, dd, J=16.0, 6.3 Hz). IR (neat) cm^{-1}: 1746, 1643, 1533.

Methyl (2-Cyclohexylidenemethyl-5-methyloxazol-4-yl)acetate (6e) Yield 23%. ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.90 (6H, m), 2.00—2.35 (2H, m), 2.60—3.00 (2H, m), 2.27 (3H, s), 3.49 (2H, s), 3.70 (3H, s), 5.95 (1H, s). IR (neat) cm^{-1}: 2930, 2855, 1778, 1743, 1655, 1546, 1520.

Methyl {2-[(*Z*)-2-Cyclopentyl-1-methylvinyl]-5-methyloxazol-4-yl}acetate (6f) Yield 40%. ^{1}H-NMR ($CDCl_3$) δ: 1.05—2.15 (8H, m), 2.05 (3H, s), 2.29 (3H, s), 3.16—3.60 (1H, m), 3.52 (2H, s), 3.71 (3H, s), 5.66 (1H, dd, J=9.5, 0.9 Hz). IR (neat) cm^{-1}: 2953, 2866, 1747, 1645, 1541, 1522.

(*E*)-3-(1-Methylcyclopentyl)acrylamide (7g) Thionyl chloride (18 ml, 0.25 mol) was added to (*E*)-3-(1-methylcyclopentyl)acrylic acid (12.5 g, 81.0 mmol) and the mixture was stirred at room temperature for 2 h. Thionyl chloride was evaporated under reduced pressure, and the obtained residue was added dropwise to 28% aqueous NH_3 (50 ml, 0.74 mol) below 0 °C and the mixture was stirred at the same temperature for 1 h. AcOEt was added to the reaction mixture and the organic layer was washed with saturated brine, dried over Na_2SO_4, and then evaporated under reduced pressure. The obtained residue was rinsed with *n*-hexane to give **7g** (9.77 g, 79% yield) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, s), 1.30—2.00 (8H, m), 5.20—6.40 (2H, br), 5.75 (1H, d, J=15.8 Hz), 6.92 (1H, d, J=15.8 Hz). IR (Nujol) cm^{-1}: 3350, 3161, 1668, 1601.

Compound **7h** was prepared according to the procedure for the synthesis of **7g**.

(*E*)-3-(1-Methylcyclohexyl)acrylamide (7h) Yield 96%. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, s), 1.10—1.75 (10H, m), 5.20—6.20 (2H, br), 5.75 (1H, d, J=16.0 Hz), 6.84 (1H, d, J=16.0 Hz). IR (Nujol) cm^{-1}: 3339, 3186, 2928, 2853, 1672, 1638, 1609.

Methyl {5-Methyl-2-[(*E*)-2-(1-methylcyclopentyl)vinyl]oxazol-4-yl}acetate (6g) Compound **8** (17.5 g, 83.7 mmol) was added to a suspension of **7g** (9.75 g, 63.6 mmol) in toluene (50 ml) and the suspension was refluxed for 14 h. AcOEt (100 ml) was added to the reaction mixture, and the mixture was washed with water and saturated brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give **6g** (5.40 g, 32% yield) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, s), 1.30—2.00 (8H, m), 2.27 (3H, s), 3.48 (2H, s), 3.71 (3H, s), 6.15 (1H, d, J=16.5 Hz), 6.71 (1H, d, J=16.5 Hz). IR (neat) cm^{-1}: 2955, 2872, 1746, 1653, 1551.

Compound **6h** was prepared according to the procedure for the synthesis of **6g**.

Methyl {5-Methyl-2-[(*E*)-2-(1-methylcyclohexyl)vinyl]oxazol-4-yl}acetate (6h) Yield 29%. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, s), 1.20—1.80 (10H, m), 2.28 (3H, s), 3.48 (2H, s), 3.71 (3H, s), 6.15 (1H, d, J=16.5 Hz), 6.63 (1H, d, J=16.5 Hz). IR (neat) cm^{-1}: 2928, 2853, 1746, 1647.

Methyl [2-(2-Cyclopentylethyl)-5-methyloxazol-4-yl]acetate (6i) Compound **6c** (2.00 g, 8.02 mmol) in MeOH (40 ml) was hydrogenated at 0.4 MPa in the presence of 10% Pd–C (300 mg) at room temperature for 15 h. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure to give crude **6i** (1.86 g) as an oil. Crude **6i** was used for subsequent reaction without further purification.

2-{2-[(*E*)-2-Cyclopropylvinyl]-5-methyloxazol-4-yl}ethyl Methanesulfonate (9a) To a solution of **6a** (2.15 g, 9.72 mmol) in toluene (30 ml) was added 1.5 M diisobutylaluminum hydride in toluene (20.0 ml, 30.0 mmol) at −40 °C, and the mixture was stirred at the same temperature for 1 h. The mixture was poured into cold water (50 ml) and stirred at room temperature for 30 min. The precipitate was removed by filtration, and the filtrate was separated into two layers. The organic layer was washed with saturated brine, dried over Na_2SO_4, and then evaporated under reduced pressure. To a solution of the obtained residue (1.81 g) and triethylamine (1.76 ml, 12.6 mmol) in CH_2Cl_2 (20 ml) was added methanesulfonyl chloride (0.90 ml, 12 mmol) at 0 °C, and the mixture was stirred for 20 min. The reaction mixture was washed with 10% aqueous citric acid solution and saturated brine, and dried over Na_2SO_4, The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give **9a** (1.67 g, 63% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.50—0.70 (2H, m), 0.75—1.10 (2H, m), 1.40—1.80 (1H, m), 2.25 (3H, s), 2.85 (2H, t, J=6.6 Hz), 2.93 (3H, s), 4.44 (2H, t, J=6.6 Hz), 5.95—6.40 (2H, m). IR (neat) cm^{-1}: 1655, 1538.

Compounds **9b**—**i** were prepared according to the procedure for the synthesis of **9a**.

2-{2-[(*E*)-2-Cyclobutylvinyl]-5-methyloxazol-4-yl}ethyl Methanesulfonate (9b) Yield 63%. ^{1}H-NMR ($CDCl_3$) δ: 1.77—2.01 (4H, m), 2.12—2.23 (2H, m), 2.27 (3H, s), 2.86 (2H, t, J=6.6 Hz), 2.94 (3H, s), 3.04—3.16 (1H, m), 4.45 (2H, t, J=6.6 Hz), 6.10 (1H, dt, J=16.1, 1.4 Hz), 6.71 (1H, dt, J=16.1, 7.1 Hz). IR (neat) cm^{-1}: 1645, 1533.

2-{2-[(*E*)-2-Cyclopentylvinyl]-5-methyloxazol-4-yl}ethyl Methanesulfonate (9c) Yield 68%. ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.00 (8H, m), 2.26 (3H, s), 2.36—2.78 (1H, m), 2.86 (2H, t, J=6.6 Hz), 2.94 (3H, s), 4.44 (2H, t, J=6.6 Hz), 6.14 (1H, d, J=15.8 Hz), 6.62 (1H, dd, J=15.8, 7.5 Hz). IR (neat) cm^{-1}: 2955, 2870, 1736, 1645, 1533.

2-{2-[(*E*)-2-Cyclohexylvinyl]-5-methyloxazol-4-yl}ethyl Methanesulfonate (9d) Yield 33%. ^{1}H-NMR ($CDCl_3$) δ: 0.85—2.50 (11H, m), 2.26 (3H, s), 2.86 (2H, t, J=6.6 Hz), 2.94 (3H, s), 4.44 (2H, t, J=6.6 Hz), 6.11 (1H, d, J=16.1 Hz), 6.46 (1H, dd, J=16.1, 6.6 Hz). IR (neat) cm^{-1}: 1643, 1533.

2-(2-Cyclohexylidenemethyl-5-methyloxazol-4-yl)ethyl Methanesulfonate (9e) Yield 69%. ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.90 (6H, m), 2.00—2.35 (2H, m), 2.60—3.00 (2H, m), 2.26 (3H, s), 2.86 (2H, t, J=6.6 Hz), 2.93 (3H, s), 4.46 (2H, t, J=6.6 Hz), 5.95 (1H, s). IR (neat) cm^{-1}: 1651, 1545.

2-{2-[(*Z*)-2-Cyclopentyl-1-methylvinyl]-5-methyloxazol-4-yl}ethyl Methanesulfonate (9f) Yield 88%. ^{1}H-NMR ($CDCl_3$) δ: 1.08—2.06 (8H, m), 2.04, (3H, s), 2.29 (3H, s), 2.89 (2H, t, J=6.6 Hz), 2.94 (3H, s), 3.12—3.61 (1H, m), 4.47 (2H, t, J=6.6 Hz), 5.67 (1H, dd, J=9.5, 1.2 Hz). IR (neat) cm^{-1}: 3630, 3416, 3020, 2953, 2866, 1645, 1522.

2-{5-Methyl-2-[(*E*)-2-(1-methylcyclopentyl)vinyl]oxazol-4-yl}ethyl Methanesulfonate (9g) Yield 96%. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, s), 1.20—1.80 (8H, m), 2.28 (3H, s), 2.87 (2H, t, J=6.7 Hz), 2.95 (3H, s), 4.45 (2H, t, J=6.7 Hz), 6.12 (1H, d, J=16.5 Hz), 6.63 (1H, d, J=16.5 Hz). IR (neat) cm^{-1}: 2928, 2852, 1645, 1531.

2-{5-Methyl-2-[(*E*)-2-(1-methylcyclohexyl)vinyl]oxazol-4-yl}ethyl Methanesulfonate (9h) Yield 81%. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, s), 1.35—1.90 (10H, m), 2.27 (3H, s), 2.86 (2H, t, J=6.6 Hz), 2.94 (3H, s), 4.45 (2H, t, J=6.6 Hz), 6.13 (1H, d, J=16.3 Hz), 6.71 (1H, d, J=16.3 Hz). IR (neat) cm^{-1}: 2957, 2871, 1645, 1551, 1533.

2-[2-(2-Cyclopentylethyl)-5-methyloxazol-4-yl]ethyl Methanesulfonate (9i) Yield 63%. ^{1}H-NMR ($CDCl_3$) δ: 1.06—1.18 (2H, m), 1.46—1.65 (4H, m), 1.68—1.83 (5H, m), 2.23 (3H, s), 2.67 (2H, t, J=7.8 Hz), 2.84 (2H, t, J=6.8 Hz), 2.94 (3H, s), 4.42 (2H, t, J=6.8 Hz). IR (neat) cm^{-1}: 1738, 1653, 1578.

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-(2-{2-[(*E*)-2-cyclopropylvinyl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11a) A mixture of **10** (1.25 g, 4.07 mmol), **9a** (1.65 g, 6.08 mmol), tetraethylammonium fluoride (250 mg) and K_2CO_3 (1.70 g, 12.3 mmol) in toluene (40 ml) was stirred at 90 °C for 12 h. AcOEt was added to the reaction mixture, which was washed with water and saturated brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give **11a** (1.95 g, 80% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.50—0.70 (2H, m), 0.75—1.10 (2H, m), 1.40—1.80 (10H, m), 2.26 (3H, s), 2.86 (2H, t, J=6.6 Hz), 2.95—3.25 (2H, m), 3.61 (3H, s), 4.16 (2H, t, J=6.6 Hz), 4.25—5.20 (3H, m), 5.95—6.40 (2H, m), 6.55—6.80 (2H, m), 7.01 (1H, d, J=8.6 Hz). IR (neat) cm^{-1}: 1742, 1699, 1655, 1614, 1587, 1535, 1506.

Compounds **11b**—**i** were prepared according to the procedure for the synthesis of **11a**.

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-(2-{2-[(*E*)-2-cyclobutylvinyl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11b) Yield 87%. ^{1}H-NMR ($CDCl_3$) δ: 1.45, 1.52 (total 9H, s, s), 1.77—2.01 (4H, m), 2.12—2.23 (2H, m), 2.28 (3H, s), 2.87 (2H, t, J=6.6 Hz), 3.02—3.21 (3H, m), 3.60, 3.62 (total 3H, s, s), 4.14 (2H, t, J=6.6 Hz), 4.41, 4.64 (1H, AB-q, J=16.4 Hz), 4.46, 4.67 (1H, AB-q, J=16.4 Hz), 4.74 (0.5H, t, J=5.6 Hz), 5.10 (0.5H, dd, J=5.6, 2.7 Hz), 6.11 (1H, d, J=16.1 Hz), 6.58—6.75 (3H, m), 7.01 (1H, d, J=8.3 Hz). IR (neat) cm^{-1}: 1743, 1699, 1615, 1533, 1506.

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-(2-{2-[(*E*)-2-cyclopentylvinyl]-5-

methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11c) Yield 80%. ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.00 (17H, m), 2.27 (3H, s), 2.34—2.74 (1H, m), 2.86 (2H, t, J=6.6 Hz), 2.99—3.20 (2H, m), 3.61 (3H, s), 4.12 (2H, t, J=6.6 Hz), 4.24—5.20 (3H, m), 6.15 (1H, d, J=16.1 Hz), 6.61 (1H, dd, J=16.1, 7.5 Hz), 6.53—6.80 (2H, m), 7.01 (1H, d, J=8.3 Hz). IR (neat) cm^{-1}: 2955, 2970, 1742, 1699, 1614, 1533, 1506.

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-(2-{2-[(*E*)-2-cyclohexylvinyl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11d) Yield 91%. ^{1}H-NMR ($CDCl_3$) δ: 0.70—2.50 (11H, m), 1.46, 1.51 (total 9H, s, s), 2.27 (3H, s), 2.86 (2H, t, J=6.7 Hz), 2.95—3.25 (2H, m), 3.61 (3H, s), 4.14 (2H, t, J=6.6 Hz), 4.25—5.20 (3H, m), 6.13 (1H, d, J=16.0 Hz), 6.35—6.80 (3H, m), 7.01 (1H, d, J=8.3 Hz). IR (neat) cm^{-1}: 1742, 1703, 1614, 1506.

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-[2-(2-cyclohexylidenemethyl-5-methyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11e) Yield quant. ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.95 (15H, m), 2.00—2.35 (2H, m), 2.60—3.00 (2H, m), 2.27 (3H, s), 2.87 (2H, t, J=6.6 Hz), 3.00—3.25 (2H, m), 3.61 (3H, s), 4.15 (2H, t, J=6.6 Hz), 4.25—5.25 (3H, m), 5.94 (1H, s), 6.55—6.80 (2H, m), 7.01 (1H, d, J=8.4 Hz). IR (neat) cm^{-1}: 2977, 2930, 2855, 1741, 1701, 1654, 1643, 1613, 1546, 1507.

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-(2-{2-[(*Z*)-2-cyclopentyl-1-methylvinyl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11f) Yield quant. ^{1}H-NMR ($CDCl_3$) δ: 1.10—2.10 (17H, m), 2.05 (3H, s), 2.30 (3H, s), 2.90 (2H, t, J=6.8 Hz), 3.00—3.20 (2H, m), 3.20—3.60 (1H, m), 3.62 (3H, s), 4.16 (2H, t, J=6.6 Hz), 4.28—5.25 (3H, m), 5.65 (1H, d, J=9.6 Hz), 6.58—6.83 (2H, m), 7.02 (1H, d, J=8.4 Hz). IR (neat) cm^{-1}: 3464, 2928, 2870, 1742, 1699, 1645, 1614, 1587, 1506.

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-(2-{5-methyl-2-[(*E*)-2-(1-methylcyclopentyl)vinyl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11g) Yield 99%. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, s), 1.25—2.00 (17H, m), 2.28 (3H, s), 2.87 (2H, t, J=6.8 Hz), 3.00—3.25 (2H, m), 3.61 (3H, s), 4.15 (2H, t, J=6.8 Hz), 4.45—5.30 (3H, m), 6.14 (1H, d, J=16.3 Hz), 6.60—6.90 (3H, m), 7.01 (1H, d, J=8.6 Hz). IR (neat) cm^{-1}: 2934, 2872, 1740, 1699, 1647, 1616, 1533, 1506.

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-(2-{5-methyl-2-[(*E*)-2-(1-methylcyclohexyl)vinyl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11h) Yield quant. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, s), 1.10—1.80 (19H, m), 2.28 (3H, s), 2.87 (2H, t, J=6.6 Hz), 2.95—3.20 (2H, m), 3.61 (3H, s), 4.15 (2H, t, J=6.6 Hz), 4.25—5.25 (3H, m), 6.14 (1H, d, J=16.5 Hz), 6.60—6.85 (3H, m), 7.01 (1H, d, J=8.6 Hz). IR (neat) cm^{-1}: 2928, 2853, 1742, 1701, 1616, 1506.

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-{2-[2-(2-cyclopentylethyl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11i) Yield quant. ^{1}H-NMR ($CDCl_3$) δ: 1.06—1.16 (2H, m), 1.44, 1.52 (total 9H, s, s), 1.46—1.64 (4H, m), 1.70—1.83 (5H, m), 2.23 (3H, s), 2.67 (2H, t, J=7.8 Hz), 2.84 (2H, t, J=6.8 Hz), 3.02—3.21 (2H, m), 3.60, 3.63 (total 3H, s, s), 4.07—4.17 (2H, m), 4.36—4.50 (1H, m), 4.58—4.77 (1.5H, m), 5.07—5.14 (0.5H, m), 6.58—6.75 (2H, m), 7.01 (1H, d, J=8.3 Hz). IR (neat) cm^{-1}: 1741, 1703, 1653, 1614, 1578, 1506.

Methyl (*S*)-7-(2-{2-[(*E*)-2-Cyclopropylvinyl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12a) To a solution of **11a** (1.93 g, 4.00 mmol) in formic acid (10 ml) was added saturated hydrogen chloride solution in 2-propanol (1.20 ml) under ice-cooling, which was stirred at room temperature for 30 min. AcOEt (100 ml) was added to the reaction mixture, and the mixture was neutralized with saturated aqueous $NaHCO_3$ solution and separated into two layers. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give **12a** (1.41 g, 92% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.50—0.70 (2H, m), 0.75—1.10 (2H, m), 1.40—1.80 (1H, m), 2.25 (3H, s), 2.85 (2H, t, J=6.6 Hz), 2.90—3.10 (2H, m), 3.60—3.80 (1H, m), 3.76 (3H, s), 4.04 (2H, s), 4.16 (2H, t, J=6.6 Hz), 5.95—6.40 (2H, m), 6.54 (1H, d, J=2.4 Hz), 6.69 (1H, dd, J=8.3, 2.4 Hz), 6.99 (1H, d, J=8.3 Hz). IR (neat) cm^{-1}: 1738, 1651, 1614, 1583, 1537, 1504.

Compounds **12b**—**i** were prepared according to the procedure for the synthesis of **12a**.

Methyl (*S*)-7-(2-{2-[(*E*)-2-Cyclobutylvinyl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12b) Yield 94%. ^{1}H-NMR ($CDCl_3$) δ: 1.76 (1H, br s), 1.77—2.01 (4H, m), 2.12—2.23 (2H, m), 2.28 (3H, s), 2.86 (1H, dd, J=15.9, 10.2 Hz), 2.87 (2H, t, J=6.8 Hz), 3.01 (1H, dd, J=15.9, 4.4 Hz), 3.04—3.15 (1H, m), 3.71 (1H, dd, J=10.2, 4.4 Hz), 3.77 (3H, s), 4.02 (1H, d, J=16.1 Hz), 4.07 (1H, d, J=16.1 Hz), 4.14 (2H, t, J=6.8 Hz), 6.11 (1H, dd, J=16.1, 1.2 Hz), 6.54 (1H, d, J=2.4 Hz), 6.64—6.76 (2H, m), 6.99 (1H, d, J=8.3 Hz). IR (neat) cm^{-1}: 1739, 1644, 1615, 1583, 1505.

Methyl (*S*)-7-(2-{2-[(*E*)-2-Cyclopentylvinyl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12c) Yield 98%. ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.97 (8H, m), 1.99 (1H, s), 2.27 (3H, s), 2.30—2.77 (1H, m), 2.86 (2H, t, J=6.7 Hz), 2.80—3.10 (2H, m), 3.60—3.83 (1H, m), 3.76 (3H, s), 3.95—4.34 (4H, m), 6.15 (1H, d, J=16.0 Hz), 6.41—6.80 (3H, m), 6.99 (1H, d, J=8.4 Hz). IR (neat) cm^{-1}: 3344, 2951, 2870, 2777, 2740, 1659, 1643, 1612, 1504.

Methyl (*S*)-7-(2-{2-[(*E*)-2-Cyclohexylvinyl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12d) Yield 92%. ^{1}H-NMR ($CDCl_3$) δ: 0.80—2.45 (12H, m), 2.27 (3H, s), 2.70—3.20 (2H, m), 2.86 (2H, t, J=6.8 Hz), 3.55—3.85 (1H, m), 3.76 (3H, s), 4.04 (2H, s), 4.14 (2H, t, J=6.8 Hz), 6.12 (1H, d, J=16.0 Hz), 6.40—6.80 (3H, m), 6.99 (1H, d, J=8.4 Hz). IR (neat) cm^{-1}: 1740, 1612, 1504.

Methyl (*S*)-7-[2-(2-Cyclohexylidenemethyl-5-methyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12e) Yield 94%. ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.95 (6H, m), 2.00—2.35 (2H, m), 2.60—3.00 (2H, m), 2.16 (1H, s), 2.27 (3H, s), 2.70—3.10 (4H, m), 3.50—3.70 (1H, m), 3.76 (3H, s), 4.05 (2H, s), 4.15 (2H, t, J=6.8 Hz), 5.94 (1H, s), 6.55 (1H, d, J=1.5 Hz), 6.70 (1H, dd, J=8.3, 1.5 Hz), 6.99 (1H, d, J=8.3 Hz). IR (neat) cm^{-1}: 3344, 2929, 2854, 1740, 1653, 1645, 1612, 1545, 1505.

Methyl (*S*)-7-(2-{2-[(*Z*)-2-Cyclopentyl-1-methylvinyl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12f) Yield quant. ^{1}H-NMR ($CDCl_3$) δ: 1.09—2.09 (9H, m), 2.04 (3H, s), 2.29 (3H, s), 2.85—3.04 (4H, m), 3.16—3.60 (1H, m), 3.60—3.75 (1H, m), 3.76 (3H, s), 4.05 (2H, s), 4.16 (2H, t, J=6.5 Hz), 5.64 (1H, d, J=9.5 Hz), 6.46—6.80 (2H, m), 7.00 (1H, d, J=8.2 Hz). IR (neat) cm^{-1}: 3346, 2951, 2868, 1740, 1643, 1612, 1504.

Methyl (*S*)-7-(2-{5-Methyl-2-[(*E*)-2-(1-methylcyclopentyl)vinyl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12g) Yield 93%. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, s), 1.30—1.94 (8H, m), 2.28 (3H, s), 2.31 (1H, s), 2.65—3.25 (4H, m), 3.60—3.80 (1H, m), 3.76 (3H, s), 4.08 (2H, s), 4.14 (2H, t, J=6.8 Hz), 6.14 (1H, d, J=16.3 Hz), 6.50—6.80 (3H, m), 6.99 (1H, d, J=8.1 Hz). IR (neat) cm^{-1}: 3323, 2955, 2872, 1736, 1618, 1531, 1506.

Methyl (*S*)-7-(2-{5-Methyl-2-[(*E*)-2-(1-methylcyclohexyl)vinyl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12h) Yield 97%. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, s), 1.20—1.80 (10H, m), 1.97 (1H, s), 2.28 (3H, s), 2.87 (2H, t, J=6.8 Hz), 2.90—3.05 (2H, m), 3.60—3.80 (1H, m), 3.76 (3H, s), 4.04 (2H, s), 4.15 (2H, t, J=6.8 Hz), 6.14 (1H, d, J=16.5 Hz), 6.55—6.85 (3H, m), 6.99 (1H, d, J=8.6 Hz). IR (neat) cm^{-1}: 3346, 2926, 2851, 1740, 1645, 1612, 1531, 1504.

Methyl (*S*)-7-{2-[2-(2-Cyclopentylethyl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12i) Yield 90%. ^{1}H-NMR ($CDCl_3$) δ: 1.03—1.19 (2H, m), 1.45—1.64 (4H, m), 1.68—1.83 (5H, m), 2.20—2.27 (4H, m), 2.67 (2H, t, J=7.8 Hz), 2.82—2.91 (3H, m), 3.01 (1H, dd, J=15.8, 4.6 Hz), 3.72 (1H, dd, J=10.2, 4.6 Hz), 3.77 (3H, s), 4.00—4.16 (4H, m), 6.55 (1H, d, J=2.2 Hz), 6.70 (1H, dd, J=8.3, 2.2 Hz), 6.99 (1H, d, J=8.3 Hz). IR (neat) cm^{-1}: 1742, 1653, 1612, 1578, 1504.

Methyl (*S*)-7-(2-{2-[(*E*)-2-Cyclopropylvinyl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13a) To a solution of **12a** (1.39 g, 3.63 mmol) in CH_2Cl_2 (15 ml) was added triethylamine (0.76 ml, 5.5 mmol) and (2*E*,4*E*)-hexadienoyl chloride (570 mg, 4.37 mmol) under ice-cooling, and the mixture was stirred at the same temperature for 30 min. The reaction mixture was washed with water and saturated brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to give **13a** (1.42 g, 82% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.50—0.70 (2H, m), 0.75—1.10 (2H, m), 1.40—1.80 (1H, m), 1.80—2.00 (3H, m), 2.26 (3H, s), 2.86 (2H, t, J=6.6 Hz), 3.00—3.25 (2H, m), 3.60 (3H, s), 4.16 (2H, t, J=6.6 Hz), 4.40—5.20 (2H, m), 5.40—5.65 (1H, m), 5.80—6.50 (5H, m), 6.60—6.85 (2H, m), 7.03 (1H, d, J=8.4 Hz), 7.20—7.55 (1H, m). IR (neat) cm^{-1}: 1738, 1653, 1628, 1614, 1535, 1506.

Compounds **13b**, **13f**—**h** were prepared according to the procedure for the synthesis of **13a**.

Methyl (*S*)-7-(2-{2-[(*E*)-2-Cyclobutylvinyl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13b) Yield 88%. ^{1}H-NMR ($CDCl_3$) δ: 1.79—1.99 (7H, m), 2.13—2.23 (2H, m), 2.28 (3H, s), 2.87 (2H, t, J=6.6 Hz), 3.04 (0.66H, dd, J=14.9, 5.8 Hz), 3.07—3.28 (1.68H, m), 3.15 (0.66H, dd, J=14.9, 3.4 Hz), 3.60 (3H, s), 4.14 (2H, t, J=6.6 Hz), 4.52, 4.93 (0.68H, AB-q, J=17.6 Hz), 4.70, 4.77 (1.32H, AB-q, J=15.4 Hz), 4.87—4.93 (0.34H, m), 5.53 (0.66H,

dd, J=5.8, 3.4 Hz), 6.06—6.36 (3H, m), 6.11 (1H, d, J=16.1 Hz), 6.63 (1H, br s), 6.67—6.75 (2H, m), 7.03 (1H, d, J=8.3 Hz), 7.34 (1H, dd, J=14.7, 10.8 Hz). IR (neat) cm^{-1}: 1739, 1652, 1627, 1606, 1532, 1505.

Methyl (*S*)-7-(2-{2-[(*Z*)-2-Cyclopentyl-1-methylvinyl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13f) Yield 85%. ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.15 (11H, m), 2.04 (3H, s), 2.29 (3H, s), 2.90 (2H, t, J=6.9 Hz), 3.00—3.22 (2H, m), 3.22—3.70 (1H, m), 3.60 (3H, s), 4.16 (2H, t, J=6.6 Hz), 4.33—5.65 (3H, m), 5.65 (1H, d, J=9.6 Hz), 6.00—6.86 (5H, m), 7.04 (1H, d, J=8.3 Hz), 7.16—7.62 (1H, m). IR (neat) cm^{-1}: 3464, 2953, 2868, 1740, 1653, 1628, 1614, 1506.

Methyl (*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-(2-{5-methyl-2-[(*E*)-2-(1-methylcyclopentyl)vinyl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13g) Yield 87%. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, s), 1.40—2.00 (11H, m), 2.28 (3H, s), 2.88 (2H, t, J=6.8 Hz), 3.00—3.30 (2H, m), 3.60 (3H, s), 4.16 (2H, t, J=6.8 Hz), 4.50—5.20 (2H, m), 5.40—5.60 (1H, m), 6.00—6.50 (4H, m), 6.60—6.90 (3H, m), 6.99 (1H, d, J=8.1 Hz), 7.15—7.55 (1H, m). IR (neat) cm^{-1}: 1740, 1653, 1616, 1531, 1506.

Methyl (*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-(2-{5-methyl-2-[(*E*)-2-(1-methylcyclohexyl)vinyl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13h) Yield 99%. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, s), 1.40—1.80 (10H, m), 1.86 (3H, d, J=4.9 Hz), 2.29 (3H, s), 2.88 (2H, t, J=6.8 Hz), 3.00—3.25 (2H, m), 3.60 (3H, s), 4.16 (2H, t, J=6.8 Hz), 4.55—5.20 (2H, m), 5.45—5.65 (1H, m), 6.00—6.50 (4H, m), 6.60—6.90 (3H, m), 7.04 (1H, d, J=8.6 Hz), 7.20—7.55 (1H, m). IR (neat) cm^{-1}: 2928, 2853, 1740, 1653, 1628, 1616, 1531, 1506.

Methyl (*S*)-7-(2-{2-[(*E*)-2-Cyclopentylvinyl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13c) To a solution of **12c** (9.46 g, 23.0 mmol) in CH_2Cl_2 (100 ml) was added sorbic acid (2.70 g, 24.1 mmol) and EDC (5.20 g, 27.1 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was washed with water and saturated brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to give **13c** (7.54 g, 64% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.97 (8H, m), 1.85 (3H, d, J=4.8 Hz), 2.27 (3H, s), 2.40—2.75 (1H, m), 2.86 (2H, t, J=6.5 Hz), 3.00—3.22 (2H, m), 3.59 (3H, s), 4.14 (2H, t, J=6.5 Hz), 4.36—5.00 (2H, m), 5.40—5.60 (1H, m), 6.07—6.80 (5H, m), 6.15 (1H, d, J=16.1 Hz), 6.61 (1H, dd, J=16.1, 7.2 Hz), 7.03 (1H, d, J=8.4 Hz), 7.13—7.50 (1H, m). IR (neat) cm^{-1}: 3464, 2953, 2870, 1740, 1657, 1628, 1605, 1506.

Compounds **13d**, **e**, **i** were prepared according to the procedure for the synthesis of **13c**.

Methyl (*S*)-7-(2-{2-[(*E*)-2-Cyclohexylvinyl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13d) Yield 77%. ^{1}H-NMR ($CDCl_3$) δ: 0.85—2.45 (14H, m), 2.27 (3H, s), 2.87 (2H, t, J=6.8 Hz), 3.00—3.35 (2H, m), 3.59 (3H, s), 4.15 (2H, t, J=6.8 Hz), 4.30—5.65 (3H, m), 6.00—7.55 (8H, m), 7.03 (1H, d, J=8.4 Hz). IR (neat) cm^{-1}: 1745, 1614, 1531, 1506.

Methyl (*S*)-7-[2-(2-Cyclohexylidenemethyl-5-methyloxazol-4-yl)ethoxy]-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13e) Yield 92%. ^{1}H-NMR ($CDCl_3$) δ: 1.45—1.80 (6H, m), 1.80—2.00 (3H, m), 2.00—2.35 (2H, m), 2.60—3.00 (2H, m), 2.27 (3H, s), 2.87 (2H, t, J=6.8 Hz), 3.00—3.25 (2H, m), 3.59 (3H, s), 4.15 (2H, t, J=6.8 Hz), 4.45—5.20 (2H, m), 5.40—5.70 (1H, m), 5.94 (1H, s), 5.95—6.50 (3H, m), 6.60—6.90 (2H, m), 7.04 (1H, d, J=8.2 Hz), 7.15—7.55 (1H, m). IR (neat) cm^{-1}: 2930, 2855, 1740, 1657, 1628, 1614, 1545, 1506.

Methyl (*S*)-7-{2-[2-(2-Cyclopentylethyl)-5-methyloxazol-4-yl]ethoxy}-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13i) Yield 87%. ^{1}H-NMR ($CDCl_3$) δ: 1.04—1.17 (2H, m), 1.45—1.66 (4H, m), 1.69—1.82 (5H, m), 1.83—1.92 (3H, m), 2.24 (3H, s), 2.67 (2H, t, J=7.8 Hz), 2.85 (2H, t, J=6.6 Hz), 3.01—3.29 (2H, m), 3.60 (3H, s), 4.14 (2H, t, J=6.6 Hz), 4.52 (0.2H, d, J=17.3 Hz), 4.70 (0.8H, d, J=15.4 Hz), 4.77 (0.8H, d, J=15.4 Hz), 4.88—4.93 (0.8H, m), 4.93 (0.2H, d, J=17.3 Hz), 6.08—6.37 (3H, m), 6.63 (0.8H, s), 6.66—6.78 (1.2H, m), 7.03 (1H, d, J=8.5 Hz), 7.33 (1H, dd, J=14.6, 10.7 Hz). IR (neat) cm^{-1}: 1740, 1655, 1628, 1578, 1506.

(*S*)-7-(2-{2-[(*E*)-2-Cyclopropylvinyl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (14a) To a solution of **13a** (1.40 g, 2.03 mmol) in tetrahydrofuran (THF)–MeOH (3 : 1, 20 ml) was added 1.0 M aqueous lithium hydroxide solution (9.0 ml, 9.0 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was acidified with 6 M HCl and the solvent was evaporated under reduced pressure. The obtained residue was extracted with AcOEt, and the organic layer was washed with water and saturated brine, and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in MeOH (2.0 ml). After dropwise addition of *tert*-butylamine (0.60 ml, 5.7 mmol), diisopropyl ether (100 ml) was added and the mixture was stirred under ice-cooling for 0.5 h. The precipitate was collected by filtration to give **14a** (1.20 g, 76% yield) as a pale yellow solid, mp 169—171 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.50—0.70 (2H, m), 0.75—1.10 (2H, m), 0.98 (9H, s), 1.40—1.80 (1H, m), 1.80—2.00 (3H, m), 2.25 (3H, s), 2.84 (2H, t, J=6.6 Hz), 2.90—3.40 (2H, m), 4.16 (2H, t, J=6.6 Hz), 4.25—5.45 (3H, m), 5.60—6.75 (8H, m), 6.60—6.85 (2H, m), 6.96 (1H, d, J=7.9 Hz), 7.05—7.35 (1H, m). IR (Nujol) cm^{-1}: 1652, 1624, 1601, 1587, 1504. MS *m/z*: 463 $[M+H]^+$. *Anal.* Calcd for $C_{27}H_{30}N_2O_5 \cdot C_4H_{11}N \cdot 0.6H_2O$: C, 68.13; H, 7.78; N, 7.69. Found: C, 67.88; H, 7.54; N,7.62.

Compounds **14b**—**i** were prepared according to the procedure for the synthesis of **14a**.

(*S*)-7-(2-{2-[(*E*)-2-Cyclobutylvinyl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (14b) Yield 75%. A white solid, mp 167—169.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (9H, s), 1.77—2.01 (4H, m), 1.79 (1.5H, d, J=6.4 Hz), 1.85 (1.5H, d, J=6.8 Hz), 2.13—2.23 (2H, m), 2.27, 2.28 (total 3H, s, s), 2.85—3.21 (5H, m), 4.09 (1H, t, J=6.4 Hz), 4.10 (1H, t, J=6.4 Hz), 4.45, 4.92 (1H, AB-q, J=17.6 Hz), 4.65, 4.70 (1H, AB-q, J=16.4 Hz), 4.61—4.65 (0.5H, m), 5.00—5.05 (0.5H, m), 5.10—5.80 (3H, br), 5.97—6.36 (4H, m), 6.56—6.74 (3H, m), 6.93 (0.5H, d, J=8.3 Hz), 6.97 (0.5H, d, J=8.3 Hz), 7.17 (0.5H, dd, J=14.4, 10.7 Hz), 7.20 (0.5H, dd, J=14.4, 10.7 Hz). IR (Nujol) cm^{-1}: 1653, 1626, 1587, 1553, 1506. MS *m/z*: 477 $[M+H]^+$. *Anal.* Calcd for $C_{28}H_{32}N_2O_5 \cdot C_4H_{11}N \cdot 0.5H_2O$: C, 68.79; H, 7.94; N, 7.52. Found: C, 68.76; H, 7.79; N,7.45.

(*S*)-7-(2-{2-[(*E*)-2-Cyclopentylvinyl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (14c) Yield 64%. A white solid. mp 115—118 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (9H, s), 1.20—2.05 (11H, m), 2.27 (3H, s), 2.38—2.73 (1H, m), 2.85 (2H, t, J=6.5 Hz), 2.90—3.40 (2H, m), 4.10 (2H, t, J=6.5 Hz), 4.26—5.20 (3H, m), 5.86—7.38 (12H, m). IR (Nujol) cm^{-1}: 3464, 2731, 2631, 2544, 1653, 1626, 1553, 1506. MS *m/z*: 491 $[M+H]^+$. *Anal.* Calcd for $C_{29}H_{34}N_2O_5 \cdot C_4H_{11}N$: C, 70.31; H, 8.05; N, 7.45. Found: C, 70.29; H, 7.92; N, 7.45.

(*S*)-7-(2-{2-[(*E*)-2-Cyclohexylvinyl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (14d) Yield 82%. A white solid, mp 170.5—173 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (9H, s), 1.00—2.40 (14H, m), 2.27 (3H, s), 2.85 (2H, t, J=6.8 Hz), 2.90—3.30 (2H, m), 4.10 (2H, t, J=6.8 Hz), 4.20—5.20 (3H, m), 5.80—7.45 (12H, m). IR (Nujol) cm^{-1}: 2739, 2635, 2548, 1655, 1630, 1560, 1506. MS *m/z*: 505 $[M+H]^+$. *Anal.* Calcd for $C_{30}H_{36}N_2O_5 \cdot C_4H_{11}N \cdot 0.6H_2O$: C, 69.38; H, 8.25; N, 7.14. Found: C, 69.19; H, 8.10; N,7.18.

(*S*)-7-[2-(2-Cyclohexylidenemethyl-5-methyloxazol-4-yl)ethoxy]-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (14e) Yield 72%. A pale yellow solid, mp 161.5—163.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (9H, s), 1.45—1.75 (6H, m), 1.75—2.00 (3H, m), 2.00—2.40 (2H, m), 2.65—3.00 (2H, m), 2.27 (3H, s), 2.86 (2H, t, J=6.6 Hz), 2.90—3.30 (2H, m), 4.12 (2H, t, J=6.6 Hz), 4.25—5.20 (3H, m), 5.94 (1H, s), 5.95—7.40 (10H, m). IR (Nujol) cm^{-1}: 2631, 1542, 1652, 1624, 1549, 1506. MS *m/z*: 491 $[M+H]^+$. *Anal.* Calcd for $C_{29}H_{34}N_2O_5 \cdot C_4H_{11}N \cdot 1.0H_2O$: C, 68.13; H, 8.14; N, 7.22. Found: C, 68.31; H, 7.99; N,7.35.

(*S*)-7-(2-{2-[(*Z*)-2-Cyclopentyl-1-methylvinyl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (14f) Yield 65%. A white solid, mp 131.5—133.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (9H, s), 1.10—2.10 (11H, d, J=6.6 Hz), 2.05 (3H, s), 2.29 (3H, s), 2.89 (2H, t, J=6.7 Hz), 2.90—3.20 (2H, m), 3.10—3.70 (1H, m), 4.12 (2H, t, J=6.7 Hz), 4.25—5.20 (3H, m), 5.64 (1H, d, J=9.5 Hz), 5.90—7.53 (10H, m). IR (Nujol) cm^{-1}: 3017, 2735, 2623, 2523, 1653, 1626, 1593, 1537. MS *m/z*: 505 $[M+H]^+$. *Anal.* Calcd for $C_{30}H_{36}N_2O_5 \cdot C_4H_{11}N \cdot 0.5H_2O$: C, 69.60; H, 8.25; N, 7.16. Found: C, 68.69; H, 8.26; N, 7.14.

(*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-(2-{5-methyl-2-[(*E*)-2-(1-methylcyclopentyl)vinyl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (14g) Yield 81%. A white solid. mp 145—147.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (9H, s), 1.14 (3H, s), 1.30—2.05 (11H, m), 2.28 (3H, s), 2.86 (2H, t, J=6.8 Hz), 2.90—3.40 (2H, m), 4.11 (2H, t, J=6.8 Hz), 4.25—5.30 (3H, m), 5.80—7.40 (12H, m). IR (Nujol) cm^{-1}: 2632, 2543, 2212, 1634, 1549, 1504. MS *m/z*: 505 $[M+H]^+$.

Anal. Calcd for $C_{30}H_{36}N_2O_5 \cdot C_4H_{11}N \cdot 0.5H_2O$: C, 69.60; H, 8.25; N, 7.16. Found: C, 69.48; H, 8.07; N, 7.16.

(*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-(2-{5-methyl-2-[(*E*)-2-(1-methylcyclohexyl)vinyl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (14h) Yield 62%. A white solid. mp 137.5—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (9H, s), 1.05 (3H, s), 1.20—2.00 (13H, m), 2.28 (3H, s), 2.86 (2H, t, J=6.6 Hz), 2.90—3.40 (2H, m), 4.11 (2H, t, J=6.6 Hz), 4.25—5.20 (3H, m), 5.80—7.50 (12H, m). IR (Nujol) cm^{-1}: 1651, 1622, 1599, 1585, 1547, 1508. MS *m/z*: 519 $[M+H]^+$. *Anal.* Calcd for $C_{31}H_{38}N_2O_5 \cdot C_4H_{11}N \cdot 0.2H_2O$: C, 70.61; H, 8.36; N, 7.06. Found: C, 70.45; H, 8.17; N, 6.96.

(*S*)-7-{2-[2-(2-Cyclopentylethyl)-5-methyloxazol-4-yl]ethoxy}-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (14i) Yield 78%. A white solid, mp 151—153.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (9H, s), 1.02—1.18 (2H, m), 1.42—1.66 (4H, m), 1.68—1.88 (8H, m), 2.24 (3H, s), 2.66 (2H, t, J=6.3 Hz), 2.78—2.88 (2H, m), 2.90—3.30 (2H, m), 4.02—4.15 (2H, m), 4.43 (0.4H, d, J=17.6 Hz), 4.57—4.74 (1.6H, m), 4.96—5.09 (1H, m), 5.95—6.34 (3H, m), 6.40—7.20 (3H, br), 6.52—6.78 (2H, m), 6.89—7.01 (1H, m), 7.13—7.25 (1H, m). IR (Nujol) cm^{-1}: 1654, 1626, 1595, 1576, 1539, 1506. MS *m/z*: 493 $[M+H]^+$. *Anal.* Calcd for $C_{29}H_{36}N_2O_5 \cdot C_4H_{11}N \cdot 0.5H_2O$: C, 68.96; H, 8.42; N, 7.31. Found: C, 69.12; H, 8.40; N,7.30.

Partition Coefficient at pH 7.0 Log $D_{7.0}$ values (logarithm of *n*-octanol–water partition coefficients at pH 7.0) were determined by HPLC methods.[32] Acetanilide, benzonitrile, benzene, bromobenzene, biphenyl and hexachlorobenzene, the log $D_{7.0}$ values of which are known, were used as reference substances. Test compounds and reference substances were dissolved in acetonitrile containing 1% dimethylsulfoxide (DMSO) at 10 μg/ml, and then 10 μl of the solution was injected into the HPLC system. The HPLC equipment consisted of a pump (PU-980; JASCO Corporation, Tokyo, Japan), a UV detector (UV-970; JASCO Corporation), an autoinjector (AS-950; JASCO Corporation), and a Cosmosil 5C18-AR-II column (5 μm, 4.6 mm×150 mm; Nacalai Tesque, Inc., Kyoto, Japan). Phosphate buffer (pH 7.0)–MeOH (8 : 2) was used as the eluent. The capacity factors of test substances and reference substances were calculated from their retention time. The log $D_{7.0}$ values of test compounds were calculated using these capacity factors and the reported log $D_{7.0}$ values of reference substances.

PPARγ and PPARα Agonist Activity Full-length human PPARγ1 plasmid (Open Biosystems, Huntsville, U.S.A.) or PPARα plasmid (GeneCopoeia Inc., Rockville, U.S.A.), and human RXRα plasmid (GeneCopoeia Inc.) with reporter plasmid pGL3-PPREx4-tk-luc were electroporated into COS-1 cells (Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan) using Nucleofator II (AAD-1001S, Lonza Group Ltd., Basel, Switzerland). The cells were incubated for 24 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 10% fetal bovine serum (FBS) under 5% CO_2 at 37 °C. The medium was removed and then luciferase activities were determined using a commercial kit (PicaGene LT7.5, TOYO B-Net Co., Ltd., Tokyo, Japan) and a microplate luminescence reader (Dainippon Sumitomo Pharma Co., Ltd.). EC_{50} values and the maximal activation level relative to the level activated by farglitazar, a PPARγ agonist (10^{-7} M) or Wy-14643, a PPARα agonist (10^{-5} M) were determined.

PTP-1B Inhibitory Activity PTP-1B inhibitory activities were determined in the absence or presence of the test compound in 50 mM sodium acetate buffer (pH 5.5) containing the enzyme, 3 mM *p*NPP, 1 mM dithiothreitol and 1 mM ethylenediaminetetraacetic acid (EDTA). The reaction was started by addition of *p*NPP and stopped by the addition of 50 μl of 1 M NaOH after 30 min of incubation at 37 °C, and the absorbance was determined at 405 nm.

Hypohyperglycemic and Hypotriglyceridemic Effects in Male KK-A^y Mice Male KK-A^y mice (11 weeks old; Clea Japan, Inc., Tokyo, Japan) were allocated to control and treated groups (n=4). Test compounds were suspended in 0.5% methylcellulose solution and orally administered once a day for 4 or 14 d. Blood samples were taken from the tail vein of non-fasted mice 24 h after the final administration. Plasma glucose and triglyceride levels in mice administered the vehicle or test compounds were determined using commercial kits (Wako Pure Chemical Industries, Ltd., Osaka, Japan).

Effects of 14c and Rosiglitazone in Male Syrian Hamsters Male Syrian hamsters (10 weeks old; Japan SLC, Inc., Hamamatsu, Japan) were allocated to control and treated groups (n=4). **14c** and rosiglitazone were suspended in 0.5% methylcellulose solution and orally administered once a day for 7 d. Animals were anesthetized with sodium pentobarbital (50 mg/kg, intraperitoneally (i.p.)) 24 h after the final administration and blood samples were collected from the abdominal aorta. They were then bled to death under deep anesthesia. After euthanasia, livers were isolated and weighed. Livers were homogenized and peroxisome fractions were isolated. Acyl CoA oxidase activities were determined according to the methods previously reported.[33] Enzyme activity was expressed as a change in absorbance at 502 nm (Δabsorbance/min).

Effects of 14c and Rosiglitazone in Male ICR Mice Male ICR mice (7 weeks old, Japan SLC, Inc.) were allocated to control and treated groups (n=5—6). **14c** and rosiglitazone were suspended in 0.5% methylcellulose solution and administered once a day for 14 d. Plasma volume was determined by the dye dilution method using Evans blue.[34] Briefly, mice were injected intravenously with Evans blue solution (100 μg/animal) 24 h after the last administration, and anesthetized with diethyl ether, and then blood samples were collected by orbital sinus puncture. Plasma concentrations of dye were determined and plasma volume was calculated. The mice were bled to death under deep anesthesia, after which the hearts and livers were isolated and weighed.

Plasma Concentration after Oral Administration of 14c and Rosiglitazone in KK-A^y Mice Male KK-A^y mice (11 weeks old; Japan SLC, Inc.) were used. **14c** (3 mg/kg) and rosiglitazone (30 mg/kg) suspended in 0.5% methylcellulose solution were orally administered and then a blood sample was taken by heart puncture under ether anesthesia at 1, 4, 12 or 24 h after administration in KK-A^y mice. Plasma concentrations of compounds were determined using an HPLC system consisting of a pump (PU-980; JASCO), UV detector (UV-970; JASCO), autoinjector (AS-950; JASCO), and STR-ODS-II column (5 μm, 4.6 mm×150 mm; Shimadzu Techno Research, Inc., Kyoto, Japan). The C_{max} and *AUC* were calculated.

References

1) Bloomgarden Z. T., *Diabetes Care*, **28**, 488—493 (2005).
2) Lebovitz H. E., Banerji M. A., *Recent Prog. Horm. Res.*, **56**, 265—294 (2001).
3) Tack C. J., Smits P., *Neth. J. Med.*, **64**, 166—174 (2006).
4) Staels B., *Cell Metab.*, **2**, 77—78 (2005).
5) Lehrke M., Lazar M. A., *Cell*, **123**, 993—999 (2005).
6) Krische D., *West. J. Med.*, **173**, 54—57 (2000).
7) Hussein Z., Wentworth J. M., Nankervis A. J., Proietto J., Colman P. G., *Med. J. Aust.*, **181**, 536—539 (2004).
8) Henke B. R., Blanchard S. G., Brackeen M. F., Brown K. K., Cobb J. E., Collins J. L., Harrington W. W. Jr., Hashim M. A., Hull-Ryde E. A., Kaldor I., Kliewer S. A., Lake D. H., Leesnitzer L. M., Lehmann J. M., Lenhard J. M., Orband-Miller L. A., Miller J. F., Mook R. A. Jr., Noble S. A., Oliver W. Jr., Parks D. J., Plunket K. D., Szewczyk J. R., Willson T. M., *J. Med. Chem.*, **41**, 5020—5036 (1998).
9) Azukizawa S., Kasai M., Takahashi K., Miike T., Kunishiro K., Kanda M., Mukai C., Shirahase H., *Chem. Pharm. Bull.*, **56**, 335—345 (2008).
10) Everett L., Galli A., Crabb D., *Liver*, **20**, 191—199 (2000).
11) Chou C. J., Haluzik M., Gregory C., Dietz K. R., Vinson C., Gavrilova O., Reitman M. L., *J. Biol. Chem.*, **277**, 24484—24489 (2002).
12) Kuwabara K., Murakami K., Todo M., Aoki T., Asaki T., Murai M., Yano J., *J. Pharmacol. Exp. Ther.*, **309**, 970—977 (2004).
13) Koh K. K., Han S. H., Quon M. J., Yeal Ahn J., Shin E. K., *Diabetes Care*, **28**, 1419—1424 (2005).
14) Chaput E., Saladin R., Silvestre M., Edgar A. D., *Biochem. Biophys. Res. Commun.*, **271**, 445—450 (2000).
15) Yajima K., Hirose H., Fujita H., Seto Y., Fujita H., Ukeda K., Miyashita K., Kawai T., Yamamoto Y., Ogawa T., Yamada T., Saruta T., *Am. J. Physiol. Endocrinol. Metab.*, **284**, E966—E971 (2003).
16) Fiévet C., Fruchart J. C., Staels B., *Curr. Opin. Pharmacol.*, **6**, 606—614 (2006).
17) Henke B. R., *J. Med. Chem.*, **47**, 4118—4127 (2004).
18) Ebdrup S., Pettersson I., Rasmussen H. B., Deussen H. J., Frost Jensen A., Mortensen S. B., Fleckner J., Pridal L., Nygaard L., Sauerberg P., *J. Med. Chem.*, **46**, 1306—1317 (2003).
19) Devasthale P. V., Chen S., Jeon Y., Qu F., Shao C., Wang W., Zhang H., Cap M., Farrelly D., Golla R., Grover G., Harrity T., Ma Z., Moore L., Ren J., Seethala R., Cheng L., Sleph P., Sun W., Tieman A., Wetterau J. R., Doweyko A., Chandrasena G., Chang S. Y., Humphreys W. G., Sasseville V. G., Biller S. A., Ryono D. E., Selan F., Hariharan N., Cheng P. T., *J. Med. Chem.*, **48**, 2248—2250 (2005).
20) Cronet P., Petersen J. F., Folmer R., Blomberg N., Sjöblom K., Karlsson U., Lindstedt E. L., Bamberg K., *Structure*, **9**, 699—706 (2001).
21) Imoto H., Matsumoto M., Odaka H., Sakamoto J., Kimura H., Nonaka M., Kiyota Y., Momose Y., *Chem. Pharm. Bull.*, **52**, 120—124 (2004).

22) Michalik L., Auwerx J., Berger J. P., Chatterjee V. K., Glass C. K., Gonzalez F. J., Grimaldi P. A., Kadowaki T., Lazar M. A., O'Rahilly S., Palmer C. N. A., Plutzky J., Reddy J. K., Spiegelman B. M., Staels B., Wahli W., *Pharmacol. Rev.*, **58**, 726—741 (2006).
23) Lai D. Y., *J. Environ. Sci. Health C. Environ. Carcinog. Ecotoxicol. Rev.*, **22**, 37—55 (2004).
24) Cornwell P. D., De Souza A. T., Ulrich R. G., *Mutat. Res.*, **549**, 131—145 (2004).
25) Zungu M., Felix R., Essop M. F., *Mitochondrion*, **6**, 315—322 (2006).
26) Rubenstrunk A., Hanf R., Hum D. W., Fruchart J. C., Staels B., *Biochim. Biophys. Acta*, **1771**, 1065—1081 (2007).
27) Ritchie T. J., Macdonald S. J., *Drug Discov. Today*, **14**, 1011—1020 (2009).
28) Otake K., Azukizawa S., Takahashi K., Fukui M., Shibabayashi M., Kamemoto H., Kasai M., Shirahase H., *Chem. Pharm. Bull.*, **59**, 876—879 (2011).
29) Thareja S., Aggarwal S., Bhardwaj T. R., Kumar M., *Med. Res. Rev.*, 2010 Sep. 2 [Epub ahead of print].
30) Sohda T., Mizuno K., Momose Y., Ikeda H., Fujita T., Meguro K., *J. Med. Chem.*, **35**, 2617—2626 (1992).
31) Guo Q., Sahoo S. P., Wang P. R., Milot D. P., Ippolito M. C., Wu M. S., Baffic J., Biswas C., Hernandez M., Lam M. H., Sharma N., Han W., Kelly L. J., MacNaul K. L., Zhou G., Desai R., Heck J. V., Doebber T. W., Berger J. P., Moller D. E., Sparrow C. P., Chao Y. S., Wright S. D., *Endocrinology*, **145**, 1640—1648 (2004).
32) Masumoto K., Takeyasu A., Oizumi K., Kobayashi T., *Yakugaku Zasshi*, **115**, 213—220 (1995).
33) Small G. M., Burdett K., Connock M. J., *Biochem. J.*, **227**, 205—210 (1985).
34) Wilson R. J., Mills I. H., *J. Clin. Pathol.*, **23**, 286—290 (1970).