A novel series of 2,7-substituted 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives were synthesized and biologically evaluated. (S)-2-(2-Furylacryloyl)-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid tert-butyramine salt (13jE) was identified as a potent human peroxisome proliferator-activated receptor \( \gamma \) (PPAR\( \gamma \))-selective agonist (EC\( _{50} \)=85 nM) and human protein–tyrosine phosphatase 1B (PTP-1B) inhibitor (IC\( _{50} \)=1.0 \( \mu \)M). Compound 13jE partially activated PPAR\( \gamma \), but not PPAR\( \alpha \) or PPAR\( \alpha \), and antagonized farglitazar, a full PPAR\( \gamma \) agonist. \( C_{\text{max}} \) after the oral administration of 13jE at 10 mg/kg was 28.6 \( \mu \)g/mL (53 \( \mu \)M) in male Sprague-Dawley (SD) rats. Repeated administration of 13jE and rosiglitazone for 14 d at 10 mg/kg/d decreased plasma glucose and triglyceride levels significantly in male KK-A\(^y\) mice. Rosiglitazone, but not 13jE, significantly increased the plasma volume and liver weight. In conclusion, 13jE showed stronger hypoglycemic and hypolipidemic effects and weaker hemodilution and hepatotoxic effects than rosiglitazone, suggesting that its safer efficacy may be due to its partial PPAR\( \gamma \) agonist and PTP-1B inhibition.

Key words peroxisome proliferator-activated receptor gamma; partial agonist; diabetes; adverse effect; protein–tyrosine phosphatase 1B inhibitor; insulin resistance

Thiazolidinedione (TZD) derivatives such as rosiglitazone (Fig. 1) have been used clinically as anti-diabetic drugs. Rosiglitazone is known to enhance insulin sensitivity by the activation of peroxisome proliferator-activated receptor \( \gamma \) (PPAR\( \gamma \)), causing the reduction of blood glucose levels in type 2 diabetic patients\(^{1–3}\), however, it induces edema and increases the risks of weight gain and congestive heart failure.\(^{4–7}\)

Thus, many efforts have been made to develop a PPAR\( \alpha \)/PPAR\( \gamma \) dual agonist and a partial PPAR\( \gamma \) agonist. PPAR\( \alpha \) is expressed in the liver and related to fatty acid metabolism\(^{8}\); fibrates, PPAR\( \alpha \) agonists, have been used as anti-hyperlipidemic drugs, and reported to improve insulin resistance and show hypoglycemic effects in diabetic animals and patients.\(^{9–11}\) PPAR\( \alpha \) agonists have a body-weight-reducing effect, and show no hemodilution effects.\(^{12}\) The combination of PPAR\( \alpha \) and PPAR\( \gamma \) agonists has been expected to show synergistic anti-diabetic effects with high safety.\(^{13,14}\) However, the development of PPAR\( \alpha \)/PPAR\( \gamma \) dual agonists including muraglitazar, were suspended due to the risk of cardiovascular events, carcinogenicity and the potential risks of liver injury and/or renal dysfunction\(^{15–17}\). Overactivation of PPAR with both PPAR\( \alpha \) and PPAR\( \gamma \) agonist activity may lead to carcinogenesis and to adverse effects in the liver, heart and kidney.\(^{12,18–21}\) Thus, PPAR\( \gamma \) partial agonists, such as INT-131, have been researched and studied clinically.\(^{22}\) They showed higher efficacy with lower toxicity in experimental diabetic animals; however, none of them has been successfully developed.

We have reported a PPAR\( \alpha \) agonist and PPAR\( \alpha \)/PPAR\( \gamma \) dual agonist with protein–tyrosine phosphatase 1B (PTP-1B) inhibitory activity.\(^{22,29}\) PTP-1B is known to regulate the insulin signal negatively and its overexpression is involved in insulin resistance; thus, PTP-1B inhibitors have been focused on as insulin sensitizers.\(^{27–29}\) Indeed, one of the PPAR\( \alpha \)/PPAR\( \gamma \) agonists with PTP-1B inhibitory activity has been reported to show effective anti-diabetic activities with high safety,\(^{30}\) probably due to its partial PPAR\( \gamma \) activation and PTP-1B inhibition. However, it may not be a true partial PPAR\( \gamma \) agonist, since it does not antagonize a full PPAR\( \gamma \) agonist. Furthermore, its risk of carcinogenesis by both PPAR\( \alpha \) and PPAR\( \gamma \) activation has not been examined. In the present study, we found that (S)-2-(2-furylacryloyl)-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid tert-butylamine salt (13jE, Fig. 1) is a true partial PPAR\( \gamma \) agonist with PTP-1B inhibitory activity, and shows safer anti-diabetic effects than rosiglitazone in KK-A\(^y\) mice.

**Chemistry**

The synthesis of 2,7-substituted-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives from methyl 2- tert-butoxy-carbonyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1)\(^{23}\) is outlined in Chart 1. The hydroxyl group at the 7-position of 1 was alkylated with oxazole derivatives 2a–c and 3c–j in the presence of K\(_2\)CO\(_3\) and tetraethylammonium fluoride hydrate to give 4a–c and 5c–j, and then the tert-butoxycarbonyl (Boc) group at the 2-position was removed with HCl/HCO\(_2\)H to give 6a–c and 7e–j, respectively. Acylation of 6a–c and 7e–j was performed with carboxylic acids 8A, D–G and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC-HCl), or acyl chlorides 9B, C and triethylamine (Et\(_3\)N), to give corresponding amides 10A–cA, 11cA–jA, gB–gE and JE–fG. Hydrolysis of the ester group with aqueous LiOH afforded 12Aa–cA, 13cA–jA, gB–gF and...
jE–jG, which were isolated as tert-butylamine salt or calcium salt.

2-(2-Substituted-5-methyloxazol-4-yl)ethyl methanesulfonates 2a–c were prepared according to the previously reported procedure,\textsuperscript{25} as shown in Route A in Chart 2. Acylation of L-aspartic acid β-methyl ester 15 with acyl chlorides 14a–c afforded 2-acyl L-aspartic acid β-methyl esters. The carboxylic acid group was transformed to an acetyl group by the Dakin–West reaction with acetic anhydride and bases, which was treated with phosphorous oxychloride to give oxazole derivatives 16a–c. The ester group of 16a–c was reduced by LiAlH\textsubscript{4} or NaBH\textsubscript{4} to give alcohols 17a–c, and then methanesulfonated to afford 2a–c.

2-Substituted-4-chloromethyl-5-methyloxazoles 3c–j were synthesized via Routes B and C in Chart 2. In Route B, aldehydes 18c, d,\textsuperscript{31} e, f,\textsuperscript{32} and g,\textsuperscript{33} which were purchased or prepared according to the literature, were treated with HCl gas and diacetyl monoxime (19) to give oxazole N-oxides 20c–g, followed by treatment with phosphorous oxychloride to afford 4-chloromethyloxazole derivatives (3c–g).\textsuperscript{34} In Route C, carboxylic acids 24h,\textsuperscript{35} and j\textsuperscript{32} were prepared according to the literature, and 1,3,4-trimethyl-3-cyclopentenecarboxylate (24i) was synthesized from 1,4-dichloro-2,3-dimethyl-but-2-ene (21).\textsuperscript{36} Diethyl malonate was alkylated with 21 and formed a cyclopentene ring 22. The diester group was hydrolyzed and decarboxylated to give monocarboxylic acid 23. Carboxylic acid was esterified and then methylated with lithium diisopropylamide (LDA) and methyl iodide (MeI), followed by hydrolysis, affording 24i. Compounds 24h–j were amidated with 25\textsuperscript{37} via acyl chloride, followed by cyclization with I\textsubscript{2}, triphenylphosphine (PPh\textsubscript{3}) and Et\textsubscript{3}N to give oxazole derivatives 26h–j. The ester group was transformed to a chloromethyl group by reduction with LiAlH\textsubscript{4} and then chlorinated with SOCl\textsubscript{2} to give 3h–j.

Carboxylic acids 8A, D and E were purchased, 8G was prepared according to the literature\textsuperscript{35} and 3-(5-fluorofuryl)-acrylic acid (8F) was synthesized from ethyl 5-bromofuran-2-carboxylate (27), as shown in Chart 3. Compound 28 was prepared by the Heck reaction from 27 and ethyl ester was hydrolyzed. The carboxylic acid group was converted to fluorene with Selectfluor and NaHCO\textsubscript{3} followed by deprotection of the tert-butoxycarbonyl group with trifluoroacetic acid (TFA) to give 8F.

The synthesis of non-carboxylic acid-type derivatives 32–34 is outlined in Chart 4. The hydroxyl group of 1 was protected with a benzyl group, and then the ester group was converted to Weinreb’s amide 29 via carboxylic acid, and then transformed to an acetyl group with MeMgI, followed by deprotection of the benzyl group to give 30. Compound 30 was alkylated with 3j at the 7-position, subjected to removal of the Boc group, and acylated with 3-furylacrylic acid via acid chloride to give 32. Reduction of the acetyl group of 32 afforded hydroxethyl derivative 33 as a diastereomixture (d.r.=71:29). Separately, 30 was treated with diethylaminosulfur trifluoride (DAST) to give 31. Difluoroethyl derivative 34 was synthesized from 31 in a similar manner as for the synthesis of 32.

Results and Discussion
In the present study, (S)-2-(2,4-hexadienoyl)-7-[(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (35, Fig. 1), a PPAR\textsubscript{γ} full agonist with a weak PTP-1B inhibitory activity, was chemically modified.
at the 2-, 3- and 7-positions. Then, PPARγ agonist activity was determined as the transactivation activity in COS-1 cells transfected with full-length human PPARγ1 plasmid, and human retinoid X receptor alpha (RXRα) plasmid with reporter plasmid pGL3-PPREx4-tk-luc, EC50 and the maximal activation level relative to the maximal level induced by farglitazar, a PPARγ full agonist (10−7 M) (Fig. 1). The antagonist activity against farglitazar (10−7 M) was also determined. The effects of the compounds on PTP-1B activities were examined using a human PTP-1B enzyme. For some compounds, plasma concentrations after oral administration at 10 mg/kg were determined in male Sprague-Dawley (SD) rats, and anti-diabetic effects were investigated in KK-Ay mice, a type 2 diabetic animal. 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.

In the first experiments, methyl groups were introduced on the phenyl ring of compound 35 (12aA–cA and 13cA) (Table 1). Interestingly, the introduction of two methyl groups at the 2- and 5-positions (12bA) markedly increased the affinity, and slightly decreased the maximal level of PPARγ activation. However, its antagonistic activity against farglitazar was not observed. The introduction at the 2- and 6-positions (12aA) brought typical partial agonist activity: 66% maximal activation and 14% maximal inhibition. The introduction of three methyl groups at the 2-, 4- and 6-positions (12cA) slightly enhanced the partial agonist activity of 12aA. Furthermore, the shortening of the alkoxy chain (13cA) increased the affinity. These results suggest that appropriate bulkiness and steric hindrance near the 2-position of the oxazole ring in a side chain at the 7-position of a tetrahydroisoquinoline ring are needed to exhibit the partial agonist property. The shortening of the alkoxy chain was shown to increase the affinity to PPARγ protein. In the structural study, other partial PPARγ agonists with a carboxyl group interacted with PPARγ protein differently from a full PPARγ agonist, leading to insufficient PPARγ activation. 38) Conformational change of the phenyloxazole moiety by the introduction of 2 or 3 methyl groups may lead to conformational change of the whole molecule, thereby changing the interaction with PPARγ protein.

In the second experiments, the phenyl ring at the 2-position of oxazole in 13cA was replaced by bulky aliphatic moieties, which bind to the oxazole ring via quaternary carbon (Table 1). The seven synthesized compounds all showed partial agonist activity (EC50: 117–237 nM, max: 52–71%). Among the compounds, 13gA with an adamantyl group and 13jA with an indanyl group showed higher affinity than the other compounds. The oral absorption of 13jA was much higher than that of 13gA (Cmax: 11.0 and 1.2 µg/mL, respectively). An adamantyl ring may be easily metabolized after oral adminis-

(i) K2CO3, tetraethylammonium fluoride hydrate, toluene, (ii) HCl, HCO2H, (iii) D–G, EDC·HCl, CH2Cl2, (iv) 9B, C, Et3N, CH2Cl2, (v) LiOHq., THF–MeOH, (vi) tert-BuNH2, MeOH, i-Pr2O, (vii) KHCO3, CaCl2, THF, H2O.

Chart 1. Synthesis of 2,7-Substituted-2-[2(E,4E)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acids
The substituent at the 2-position of \( 13gA \) and \( jA \) was replaced by various chains (Table 2). Hexanoyl, hexenoyl and hexynoyl chains did not affect the partial agonist activity of \( 13gA \). A furylacryloyl chain enhanced the affinity by about 2-fold and showed the lowest maximal levels (\( 13gE \), \( gF \)). The oral absorptions of these adamantyl derivatives were all lower than that of \( 13gA \). Among the indan derivatives, a furylacryloyl group moderately enhanced the partial agonist activity and markedly increased the oral absorption (\( 13jE \)). A (5-fluorofuryl) acryloyl group reduced the affinity (\( 13jF \)) and a cyclopropylacryloyl group enhanced the affinity and slightly reduced the oral absorption (\( 13jG \)).

Finally, the carboxyl group of \( 13jE \) was replaced by an un-ionized polar group: acetyl (32), hydroxyethyl (33) and difluoroethyl (34) groups markedly decreased the maximal levels and enhanced the inhibitory activity (Table 3). Unlike a carboxy group, un-ionized polar groups may not interact fully with PPAR<sub>γ</sub> protein, resulting in insufficient recruitment of coactivators. These compounds were not orally absorbed in SD rats. The tetrahydroisoquinoline with an un-ionized moiety at the 3-position may be a useful scaffold for PPAR<sub>γ</sub> antagonist.

Compound \( 13jE \) with potent PPAR<sub>γ</sub> partial agonist activity and good oral absorption was chosen for further biological evaluation (Table 4). Compound \( 13jE \) did not activate PPAR<sub>α</sub> and PPAR<sub>δ</sub>, even at \( 10^{-5} \) M. Compound \( 13jE \) inhibited PTP-1B activity (IC<sub>50</sub>=1.0 µM). In KK-A<sup>−</sup> mice, \( 13jE \) more potently reduced the plasma glucose and triglyceride levels than rosiglitazone, while rosiglitazone but not \( 13jE \) showed hemodilution and hepatomegaly (Table 5). The PPAR<sub>γ</sub> agonist activity of \( 13jE \) was lower than that of rosiglitazone. Its hypoglycemic effect is likely mediated by partial PPAR<sub>γ</sub> activation and PTP-1B inhibition, resulting in high efficacy with no PPAR<sub>γ</sub>-related adverse effects.

In conclusion, 2,7-substituted 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives were demonstrated to be good scaffolds for a PPAR<sub>γ</sub> selective partial agonist with PTP-1B inhibitory activity, and a furylacryloyl moiety and an indan ring are suitable for partial agonist activity and oral.
the procedure for the synthesis of 7.20 (1H, t, \( J = 300 \) mg) and K\(_2\)CO\(_3\) (1.91 g, 13.8 mmol) in toluene (50 mL) was crude. A mixture of oxime-3-carboxylate (4\(a\)) DAST, CH\(_2\)Cl\(_2\), (vii) silica gel 60 F\(_{254}\); Merck, Darmstadt, Germany). Reactions were monitored by TLC (TLC was performed on silica gel (Daisogel No.1001W; Daiso Co., Ltd., Osaka, Japan). Reactions were monitored by TLC (TLC 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 were obtained on a nuclear magnetic resonance spectrometer (IR, 400 MHz (JNM-AL-400; JEOL Ltd., Tokyo, Japan) or 400 MHz (R-1900; Hitachi High-Technologies Corporation, Tokyo, Japan) and are uncorrected. 1H-NMR spectra were obtained on a melting point apparatus (Yamato MP-21; Yamato Scientific Co., Ltd., Tokyo, Japan). 1H-NMR (CDCl\(_3\)) as an oil. 1H-NMR (CDCl\(_3\)) fied by silica gel column chromatography to give 4\(a\) quant.) as an oil. 1H-NMR (CDCl\(_3\)) \( \delta \): 1.45, 1.52 (total 9H, s, s), 2.23 (6H, s), 2.35 (3H, s), 2.97 (2H, t, \( J = 6.6 \) Hz), 3.05–3.20 (2H, m), 3.60, 3.63 (total 3H, s, s), 4.23 (2H, t, \( J = 6.6 \) Hz), 4.38–4.50 (1H, m), 4.60–4.75 (1.5H, m), 5.06–5.13 (0.5H, m), 6.60–6.75 (2H, m), 6.98–7.03 (1H, m), 7.06 (2H, d, \( J = 7.6 \) Hz), 7.20 (1H, t, \( J = 7.6 \) Hz).

Compounds 4\(b\) and 4\(c\)–j were prepared according to the procedure for the synthesis of 4\(a\). Methyl (S)-2-tert-Butoxycarbonyl-7-[2-(2,6-dimethylphenyl)-5-methoxyazol-4-ylethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (4\(b\)) Yield 99%. 1H-NMR (CDCl\(_3\)) \( \delta \): 1.35–1.70 (9H, m), 2.20 (6H, s), 2.29 (3H, t, \( J = 6.8 \) Hz), 3.00–3.25 (2H, m), 3.61 (3H, s, s), 4.22 (2H, t, \( J = 6.6 \) Hz), 4.30–5.20 (3H, m), 6.60–6.80 (2H, m), 6.90 (2H, s), 7.02 (1H, d, \( J = 8.4 \) Hz).

Methyl (S)-2-tert-Butoxycarbonyl-7-[2-(2,4,6-dimethylphenyl)-5-methoxyazol-4-ylmethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (4\(c\)) Yield 92%. 1H-NMR (CDCl\(_3\)) \( \delta \): 1.39 (3H, s), 1.45, 1.52 (total 9H, s, s), 1.61–1.79 (6H, m), 2.15–2.24 (2H, m), 2.30 (3H, s), 3.05–3.20 (2H, m), 3.61, 3.63 (total 3H, s, s), 4.40–4.52 (1H, m), 4.62–4.78 (1.5H, m), 4.84 (2H, s), 5.08–5.15 (0.5H, m), 6.72–6.82 (2H, m), 7.00–7.06 (1H, m).

Methyl (S)-2-tert-Butoxycarbonyl-7-[2-(1-methylcyclo-pentan-1-yl)-5-methoxyazol-4-ylmethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5\(e\)) Yield 92%. 1H-NMR (CDCl\(_3\)) \( \delta \): 1.39 (3H, s), 1.45, 1.52 (total 9H, s, s), 1.61–1.79 (6H, m), 2.15–2.24 (2H, m), 2.30 (3H, s), 3.05–3.20 (2H, m), 3.61, 3.63 (total 3H, s, s), 4.40–4.52 (1H, m), 4.62–4.78 (1.5H, m), 4.84 (2H, s), 5.08–5.15 (0.5H, m), 6.72–6.82 (2H, m), 7.00–7.06 (1H, m).
hexyl-1-yl)-5-methyloxazol-4-yl)methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5f) Yield 98%. 1H-NMR (CDCl3) δ: 1.27 (3H, s), 1.32–1.60 (17H, m), 2.08–2.21 (2H, m), 2.30 (3H, s), 3.05–3.23 (2H, m), 3.61, 3.63 (total 3H, s, s), 4.38–4.52 (1H, m), 4.60–4.80 (1.5H, m), 4.86 (2H, s), 5.06–5.18 (0.5H, m), 6.72–6.86 (2H, m), 6.98–7.06 (1H, m).

Methyl (S)-2-tert-Butoxycarbonyl-7-[2-(adamantan-1-yl)-5-methyloxazol-4-yl)methoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5g) Yield 98%. 1H-NMR (CDCl3) δ: 1.45, 1.52 (total 9H, s, s), 1.70–1.81 (6H, m), 1.98–2.10 (9H, br), 2.30 (3H, s), 3.03–3.22 (2H, m), 3.61, 3.63 (total 3H, s, s), 4.40–4.52 (1H, m), 4.64–4.77 (1.5H, m), 4.84 (2H, s), 5.08–5.15 (0.5H, m), 6.70–6.84 (2H, m), 7.00–7.07 (1H, m).

Methyl (S)-2-tert-Butoxycarbonyl-7-[2-(1-methylcyclopent-3-en-1-yl)-5-methyloxazol-4-yl)methoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5h) Yield 99%. 1H-NMR (CDCl3) δ: 1.45, 1.46, 1.52 (total 12H, s, s, s), 2.31 (3H, s), 2.34–2.44 (2H, m), 2.95–3.22 (4H, m), 3.61, 3.63 (total 3H, s, s), 4.40–4.52 (1H, m), 4.64–4.78 (1.5H, m), 4.84 (2H, s), 5.07–5.15 (0.5H, m), 5.66 (2H, s), 6.70–6.84 (2H, m), 7.00–7.06 (1H, m).

| Compound | R1 | n | M.W. | EC50 (nM) | Maxa (%) | IC50 (nM) | Maxb (%) | Cmax (µg/mL) | AUC (µg·h/mL) |
|----------|----|---|------|-----------|----------|-----------|----------|-------------|---------------|
| 35 | | | 472.53 | 1062 | 105 | >1000 | — | 39 | 177 |
| 12a | | | 500.59 | 972 | 66 | — | 14 | — | — |
| 12b | | | 500.59 | 156 | 87 | >1000 | <10 | — | — |
| 12c | | | 514.61 | 518 | 62 | 94 | 22 | — | — |
| 13a | | | 500.59 | 301 | 51 | 62 | 21 | 0.32 | 3.4 |
| 13d | | | 466.57 | 237 | 52 | 124 | 30 | 2.9 | 6.0 |
| 13e | | | 454.55 | 131 | 55 | 227 | 25 | 3.4 | 14.2 |
| 13f | | | | | | | | | |
| 13g | | | | | | | | | |
| 13h | | | | | | | | | |
| 13i | | | | | | | | | |
| 13j | | | | | | | | | |
| Rosiglitazone | | | 357.43 | 70 | 119 | >1000 | — | — | — |

a) Molecular weight as the free form. b) n=3. c) The activation level induced by farglitazar (10−7 M) was taken as 100%. d) The maximal inhibitory effects against the response induced by farglitazar (10−7 M). e) Plasma levels after oral administration at 10 mg/kg in male SD rats, n=3.
cyclopent-3-en-1-yl)-5-methyloxazol-4-yl)methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5i) Yield 97%. 1H-NMR (CDCl₃) δ: 1.44, 1.52 (total 9H, s, s), 1.45 (3H, s), 1.61 (6H, s), 2.25–2.33 (5H, m), 2.95–3.22 (4H, m), 3.61, 3.63 (total 3H, s, s), 4.40–4.51 (1H, m), 4.64–4.79 (1.5H, m), 4.84 (2H, s), 5.07–5.14 (0.5H, m), 6.70–6.85 (2H, m), 6.97–7.05 (1H, m).

Table 2. Chemical Structure, Molecular Weight, PPARγ Agonist and Antagonist Activity and Plasma Concentration in Male SD Rats of 2,7-Disubstituted-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Derivatives

| Compound | R¹ | R² | M.W. | EC₅₀ (nM) | Max¹ (%) | IC₅₀ (nM) | Max² (%) | C_max (µg/mL) | AUC (µg·h/mL) |
|----------|----|----|------|-----------|---------|---------|---------|-------------|-------------|
| 13gA     |    |    | 516.63 | 117       | 63      | 314     | 35      | 1.2         | 5.5         |
| 13gB     |    |    | 520.66 | 117       | 60      | 108     | 27      | 0.22        | 0.92        |
| 13gC     |    |    | 518.64 | 139       | 61      | 170     | 30      | 0.12        | 0.69        |
| 13gD     |    |    | 516.63 | 154       | 59      | 27      | 32      | 0.23        | 0.81        |
| 13gE     |    |    | 542.62 | 48        | 48      | 14      | 29      | 0.13        | 0.81        |
| 13gF⁹    |    |    | 560.61 | 70        | 52      | 82      | 32      | —           | —           |

Table 3. Chemical Structure, Molecular Weight, PPARγ Agonist and Antagonist Activity and Plasma Concentration in Male SD Rats of 3,7-Substituted-2-furylacryloyl-1,2,3,4-tetrahydroisoquinoline Derivatives

| Compound | R³ | M.W. | EC₅₀ (nM) | Max¹ (%) | IC₅₀ (nM) | Max² (%) | C_max (µg/mL) | AUC (µg·h/mL) |
|----------|----|------|-----------|---------|---------|---------|-------------|-------------|
| 13jA     |    | 512.60 | 122       | 69      | 622     | 26      | 11.0        | 74.9        |
| 13jB     |    | 538.59 | 65        | 202     | 20      | 20.6    | 367.9       |             |
| 13jC     |    | 556.58 | 62        | 120     | 20      | 20.4    | 229.5       |             |
| 13jD     |    | 560.61 | 55        | 214     | 30      | 8.5     | 97.4        |             |

a) Molecular weight as the free form. b) n=3. c) The activation level induced by farglitazar (10⁻⁷ M) was taken as 100%. d) The maximal inhibitory effects against the response induced by farglitazar (10⁻⁷ M). e) Plasma levels after oral administration at 10 mg/kg in male SD rats, n=3. f) Calcium salt.

Methyl (S)-2-tert-Butyloxycarbonyl-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl)methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5j) Yield 93%. 1H-NMR (CDCl₃) δ: 1.45, 1.52 (total 9H, s, s), 1.50 (3H, s), 2.32 (3H, s), 2.93–3.22 (4H, m), 3.55–3.66 (5H, m), 4.41–4.51 (1H, m), 4.64–4.79 (1.5H, m), 4.85 (2H, s), 5.07–5.15 (0.5H, m), 6.70–6.85 (2H, m), 6.98–7.06 (1H, m), 7.11–7.23 (4H, m).
Methyl (S)-7-[2-(2,6-Dimethylphenyl)-5-methyloxazol-4-yl]ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (6a) To a solution of 4a (2.45 g, 4.70 mmol) in formic acid (5 mL) was added 8.6 m hydrogen chloride solution in 2-propanol (1.64 mL, 14.1 mmol) under ice-cooling, and the mixture was stirred at room temperature for 15 min. The reaction mixture was neutralized with saturated aqueous NaHCO₃ solution and extracted with AcOEt. The organic layer was washed with brine and dried over Na₂SO₄. The solvent was evaporated under reduced pressure to give 6a (1.90 g, 92% yield) as an oil. ¹H-NMR (CDCl₃): δ: 2.22 (6H, s), 2.35 (3H, s), 2.86 (1H, dd, J = 15.6, 10.2 Hz), 2.95–3.04 (3H, m), 3.71 (1H, dd, J = 10.2, 4.6 Hz), 3.77 (3H, s), 4.03 (1H, d, J = 15.6 Hz), 4.07 (1H, d, J = 15.6 Hz), 4.23 (2H, t, J = 6.6 Hz), 6.58 (1H, d, J = 2.4 Hz), 6.73 (1H, dd, J = 8.6, 2.4 Hz), 6.99 (1H, d, J = 8.6 Hz), 7.06 (2H, d, J = 7.3 Hz), 7.20 (1H, t, J = 7.3 Hz).

Compounds 6b and 6c and 7e–j were prepared according to the procedure for the synthesis of 6a.

Methyl (S)-7-[2-(2,5-Dimethylphenyl)-5-methyloxazol-4-yl]ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (6b) Yield 98%. ¹H-NMR (CDCl₃): δ: 2.34 (3H, s), 2.36 (3H, s), 2.59 (3H, s), 2.86 (1H, dd, J = 16.1, 10.5 Hz), 2.92–3.04 (3H, m), 3.70 (1H, dd, J = 10.5, 4.6 Hz), 3.76 (3H, s), 4.03 (1H, d, J = 16.4 Hz), 4.07 (1H, d, J = 16.4 Hz), 4.21 (2H, t, J = 6.6 Hz), 6.57 (1H, d, J = 2.7 Hz), 6.72 (1H, dd, J = 8.5, 7.1 Hz), 6.99 (1H, d, J = 8.5 Hz), 7.06–7.14 (2H, m), 7.69–7.73 (1H, m).

Methyl (S)-7-[2-(2,4,6-Dimethylphenyl)-5-methyloxazol-4-yl]ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (6c) Yield 91%. ¹H-NMR (CDCl₃): δ: 2.19 (6H, s), 2.29 (3H, s), 2.33 (3H, s), 2.90–3.10 (4H, m), 3.68 (1H, d, J = 5.5 Hz), 3.77 (3H, s), 4.06 (2H, s), 4.22 (2H, t, J = 7.3 Hz), 6.59 (1H, d, J = 2.4 Hz), 6.60–6.85 (1H, m), 6.88 (2H, s), 7.00 (1H, d, J = 8.1 Hz).

Methyl (S)-7-[2-(2,4-Dimethylphenyl)-5-methyloxazol-4-yl]methoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7a) Yield 92%. ¹H-NMR (CDCl₃): δ: 0.77 (6H, J = 7.3 Hz), 1.29 (3H, s), 1.56–1.69 (2H, m), 1.72–1.85 (2H, m), 1.97–2.07 (1H, br), 2.39 (3H, s), 2.87 (1H, dd, J = 15.9, 10.2 Hz), 3.02 (1H, dd, J = 15.9, 4.6 Hz), 3.71 (1H, dd, J = 10.2, 4.6 Hz), 3.77 (3H, s), 3.99–4.10 (2H, m), 4.87 (2H, s), 6.65 (1H, d, J = 2.4 Hz), 6.79 (1H, dd, J = 8.3, 2.4 Hz), 7.00 (1H, d, J = 8.3 Hz).

Methyl (S)-7-[2-(1-Methylcyclopent-3-en-1-yl)-5-methyloxazol-4-yl]methoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7b) Yield 94%. ¹H-NMR (CDCl₃): δ: 1.46 (3H, s), 1.86–2.03 (1H, br), 2.31 (3H, s), 2.35–2.44 (2H, m), 2.87 (1H, dd, J = 15.9, 10.5 Hz), 2.95–3.08 (3H, m), 3.72 (1H, dd, J = 10.2, 4.6 Hz), 3.74 (3H, s), 4.03–4.12 (2H, m), 4.84 (2H, s), 6.66 (1H, d, J = 2.7 Hz), 6.79 (1H, dd, J = 8.5, 2.7 Hz), 7.01 (1H, dd, J = 8.5 Hz).

Methyl (S)-7-[2-(Adamanantan-1-yl)-5-methyloxazol-4-yl]methoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7c) Yield 92%. ¹H-NMR (CDCl₃): δ: 1.71–1.83 (6H, m), 1.95–2.10 (10H, br), 2.30 (3H, s), 2.87 (1H, dd, J = 15.9, 10.2 Hz), 3.02 (1H, dd, J = 15.9, 4.6 Hz), 3.72 (1H, dd, J = 10.2, 4.6 Hz), 3.74 (3H, s), 4.00–4.12 (2H, m), 4.84 (2H, s), 6.66 (1H, d, J = 2.7 Hz), 6.79 (1H, dd, J = 8.5, 2.7 Hz), 7.01 (1H, dd, J = 8.5 Hz).

Methyl (S)-7-[2-(1-Methylcyclohexyl-1-yl)-5-methyloxazol-4-yl]methoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7d) Yield 92%. ¹H-NMR (CDCl₃): δ: 2.77 (6H, J = 7.3 Hz), 1.29 (3H, s), 1.56–1.69 (2H, m), 1.72–1.85 (2H, m), 1.97–2.07 (1H, br), 2.39 (3H, s), 2.87 (1H, dd, J = 15.9, 10.2 Hz), 3.02 (1H, dd, J = 15.9, 4.6 Hz), 3.71 (1H, dd, J = 10.2, 4.6 Hz), 3.77 (3H, s), 3.99–4.10 (2H, m), 4.87 (2H, s), 6.65 (1H, d, J = 2.4 Hz), 6.79 (1H, dd, J = 8.3, 2.4 Hz), 7.00 (1H, d, J = 8.3 Hz).

Methyl (S)-7-[2-(1-Ethyl-1-methylpropan-1-yl)-5-methyloxazol-4-yl]methoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7e) Yield 92%. ¹H-NMR (CDCl₃): δ: 1.44 (3H, s), 1.61 (6H, s), 2.25–2.34 (5H, m), 2.95–3.03 (2H, m), 3.20–3.35 (2H, m), 3.83 (3H, s), 4.17–4.25 (1H, m), 4.36 (1H, J = 4.6 Hz, 7.3 Hz).
isoquinoline-3-carboxylate (11cA)

Yield 79%. 1H-NMR (CDCl 3) δ: 1.50 (3H, s), 1.51–1.70 (1H, br), 2.32 (3H, s), 2.83–3.05 (4H, m), 3.55–3.65 (2H, m), 3.69–3.75 (1H, m), 3.78 (3H, s), 4.01–4.12 (2H, m), 4.85 (2H, s), 6.66 (1H, J = 2.4 Hz), 6.80 (1H, dd, J = 8.3, 2.4 Hz), 7.01 (1H, d, J = 8.3 Hz), 7.14–7.24 (4H, m).

Methyl (S)-7-[2-(2-Methylindane-2-yl)-5-methoxylazol-4-ylmethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (10Aa) To a solution of 6a (1.88 g, 4.47 mmol) in CH 2 Cl 2 (40 mL) was added (2E,4E)-5-methylhexylidenic acid (60 mg, 0.53 mmol) and EDC-HCl (1.03 g, 5.37 mmol) at room temperature and the mixture was stirred for 1 h. The reaction mixture was washed with water and saturated brine and dried over Na 2 SO 4 . The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to give 10a (1.88 g, 82% yield) as an oil. 1H-NMR (CDCl 3 ) δ: 1.81–1.89 (3H, m), 2.23 (6H, s), 2.35 (3H, s), 2.98 (2H, t, J = 6.6 Hz), 3.03–3.27 (2H, m), 3.60 (3H, s), 4.24 (2H, t, J = 6.6 Hz), 4.53 (0.25H, d, J = 17.3 Hz), 4.71 (0.75H, d, J = 15.6 Hz), 4.77 (0.75H, d, J = 15.6 Hz), 4.87–4.98 (0.5H, m), 5.53 (0.75H, dd, J = 5.8, 3.4 Hz), 6.05–6.35 (3H, m), 6.64–6.78 (2H, m), 7.00–7.09 (3H, m), 7.21 (1H, t, J = 7.6 Hz), 7.27–7.36 (1H, m).

Yield 81%. 1H-NMR (CDCl 3 ) δ: 1.80–1.89 (3H, m), 2.35 (3H, s), 2.36 (3H, s), 2.59 (3H, s), 2.97 (2H, t, J = 6.6 Hz), 3.02–3.28 (2H, m), 3.59 (3H, s), 4.22 (2H, t, J = 6.6 Hz), 4.53 (0.25H, d, J = 17.6 Hz), 4.70 (0.75H, d, J = 15.4 Hz), 4.88–4.97 (0.5H, m), 5.53 (0.75H, dd, J = 5.8, 3.4 Hz), 6.06–6.34 (3H, m), 6.64–6.78 (2H, m), 7.00–7.09 (3H, m), 7.21 (1H, t, J = 7.6 Hz), 7.27–7.36 (1H, m).

Yield 93%. 1H-NMR (CDCl 3 ) δ: 1.47 (3H, s), 1.80–1.90 (3H, m), 2.25–2.45 (5H, m), 2.95–3.30 (4H, m), 3.60 (3H, s), 4.55 (0.3H, d, J = 17.3 Hz), 4.68–4.98 (4H, m), 5.51–5.58 (0.7H, m), 6.27 (2H, s), 6.07–6.40 (3H, m), 6.72–6.86 (2H, m), 7.02–7.10 (1H, m), 7.27–7.38 (1H, m).

Yield 96%. 1H-NMR (CDCl 3 ) δ: 1.44 (3H, s), 1.61 (6H, s), 1.85–1.90 (3H, m), 2.27–2.32 (5H, m), 2.95–3.31 (4H, m), 3.60 (3H, s), 4.55 (0.3H, d, J = 17.6 Hz), 4.69–4.98 (4H, m), 5.51–5.58 (0.7H, m), 6.07–6.38 (3H, m), 6.74–6.86 (2H, m), 7.02–7.10 (1H, m), 7.27–7.38 (1H, m).

Yield 99%. 1H-NMR (CDCl 3 ) δ: 1.39 (3H, s), 1.60–1.78 (6H, m), 1.82–1.89 (3H, m), 2.15–2.24 (2H, m), 2.31 (3H, s), 3.06–3.30 (2H, m), 3.60 (3H, s), 4.55 (0.3H, d, J = 15.01 Hz), 4.68–5.00 (4H, m), 5.55 (0.7H, dd, J = 5.9, 3.4 Hz), 6.06–6.38 (3H, m), 6.73–6.86 (2H, m), 7.04–7.09 (1H, m), 7.27–7.38 (1H, m).

Yield 99%. 1H-NMR (CDCl 3 ) δ: 1.01 (1.5H, t, J = 7.5 Hz), 1.07 (1.5H, t, J = 7.5 Hz), 1.56–1.70 (2H, m), 1.72–1.81 (6H, m), 2.00–2.11 (9H, m), 2.50, 2.31 (total 3H, s, s), 2.35 (1H, t, J = 7.11 Hz), 2.41 (1H, t, J = 7.11 Hz), 3.05–3.32 (2H, m), 3.63, 3.64 (total 3H, s, s), 4.49 (0.5H, d, J = 17.8 Hz), 4.49 (0.5H, d, J = 17.6 Hz), 4.64 (0.5H, d, J = 16.3 Hz), 4.83, 4.86 (total 2H, s, s), 4.94 (0.5H, m), 7.00–7.07 (1H, m), 7.27–7.39 (1H, m).
Methyl (5)-7-[2-(Adamantann-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11gB) 

Yield 92%. 1H-NMR (CDCl 3):  δ (ppm): 0.57–0.72 (2H, m), 0.83–0.99 (2H, m), 1.02 (9H, s), 1.78, 1.84 (total 3H, d, d, J = 6.6 Hz), 165.7–7.01 (2H, m), 6.92–7.00 (1H m), 7.05–7.26 (3H, m), 7.67–7.61 (2H, m), 1050, 1380. MS m/z: 501 [M+H] +

Compounds 12bA and 13aA–JA were prepared according to the procedure for the synthesis of 12aA.

Methyl (5)-7-[2-(2,5-Dimethylphenyl)-5-methyloxazol-4-yloxy]-2-[(2E,4E)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid tert-Butylamine Salt (12bA) 

To a solution of 12aA (1.88 g, 3.65 mmol) in tetrahydrofuran (THF)–MeOH (3:1, 20 mL) was added 1 M aqueous lithium hydroxide solution (110 mL, 11.0 mmol), and the mixture was stirred at room temperature for 1h. The mixture was acidified with 10% citric acid in water and extracted with AcOEt. The organic layer was washed with saturated brine and then dried over Na2SO4. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in MeOH (5 mL). After dropwise addition of tert-butylamine (0.77 mL, 7.33), disopropyl ether (100 mL) was added, and the mixture was stirred at room temperature for 1h. The precipitated crystals were collected by filtration to give 12aA (2.14g, quant) as a white solid, mp 135–137°C. 1H-NMR (CDCl 3):  δ (ppm): 1.02 (9H, s), 1.78, 1.84 (total 3H, d, d, J = 6.6, 8.1 Hz), 2.22 (6H, s), 2.35 (3H, s), 2.87–3.05 (3H, m), 3.12–3.00 (1H, m), 4.10–4.25 (2H, m), 4.45 (0.5H, d, J = 17.8Hz), 4.55–4.77 (1.5H, m), 4.95–5.09 (1H, m), 5.95–6.40 (3H, m), 6.56–6.72 (2H, m), 6.90–7.00 (1H m), 7.06 (2H, d, J = 7.3Hz), 7.12–7.25 (2H, m). IR attenuated total reflectance (ATR) cm⁻¹: 1652, 1623, 1583, 1539, 1392. MS m/z: 501 [M+H] +

(S)-7-[2-(2,4,6-Trimethylphenyl)-5-methyloxazol-4-yloxy]-2-[(2E,4E)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid tert-Butylamine Salt (12cA) 

A white solid. mp 134–135°C. 1H-NMR (CDCl 3):  δ (ppm): 0.99 (9H, s), 1.78, 1.84 (total 3H, d, d, J = 6.8, 6.6 Hz), 2.34 (3H, s), 2.49 (3H, s), 2.87–3.05 (3H, m), 3.12–3.26 (1H, m), 4.13–4.21 (2H, m), 4.45 (0.5H, d, J = 17.3Hz), 4.59–4.72 (1.5H, m), 4.96–5.04 (1H, m), 5.95–6.35 (3H, m), 6.67–6.71 (2H, m), 6.92–7.00 (1H m), 7.05–7.26 (3H, m), 7.72 (1H, s), IR (ATR) cm⁻¹: 1650, 1621, 1585, 1508, 1378. MS m/z: 501 [M+H] +

(S)-7-[2-(2,4,6-Trimethylphenyl)-5-methyloxazol-4-yloxy]-2-[(2E,4E)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid tert-Butylamine Salt (13aA) 

Yield 72%. A white solid. mp 130–132°C. 1H-NMR (CDCl 3):  δ (ppm): 0.98 (9H, s), 1.60–2.05 (3H, m), 2.20 (6H, s), 2.29 (3H, s), 2.34 (3H, s), 2.75–3.40 (4H, m), 4.19 (2H, t, J = 6.8Hz), 4.45–5.25 (3H, m), 5.80–7.40 (12H, m). IR (ATR) cm⁻¹: 1652, 1623, 1592, 1540, 1504, 1394. MS m/z: 515 [M+H] +

(S)-7-[2-(2,4,6-Trimethylphenyl)-5-methyloxazol-4-yloxy]-2-[(2E,4E)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid tert-Butylamine Salt (13bA) 

Yield 63%. A white solid. mp 135–138°C. 1H-NMR (CDCl 3):  δ (ppm): 1.01 (9H, s), 1.78, 1.84 (total 3H, d, d, J = 6.6, 6.3 Hz), 2.22 (6H, s), 2.30 (3H, s), 2.38, 2.39 (total 3H, s), 2.90–3.07 (1H, m), 3.15–3.32 (1H, m), 4.49 (0.5H, d, J = 17.1Hz), 4.55–4.75 (1.5H, m), 4.91–5.08 (3H, m), 5.95–6.35 (3H, m), 6.72–6.84
(2H, m), 6.89 (2H, s), 6.95–7.04 (1H, m), 7.16–7.25 (1H, m). IR (ATR) cm$^{-1}$: 1652, 1623, 1592, 1536, 1504, 1392. MS m/z: 501 [M$^+$H$^+$].

(S)-7-[(1-ethyl-1-methylpropan-1-yl)-5-methoxy-4-yl]methoxy-2-[(2E,4E)-hexadienyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid tert-Butylamine Salt (13dA)

Yield 70%. A white solid. mp 120–123°C. $^1$H-NMR (CDCl$_3$) $\delta$: 0.78 (6H, $E$, $J=7.6$ Hz), 0.98 (9H, s), 1.29, 1.28 (total 3H, s), 1.56–1.69 (2H, m), 1.75–1.85 (8H, m), 2.29 (3H, s), 2.92–3.07 (1H, m), 3.15–3.30 (1H, m), 4.47 (0.5H, d, $J=17.8$ Hz), 4.65–4.75 (1.5H, m), 4.82, 4.83 (total 2H, s, s), 4.99–5.12 (1H, m), 5.96–6.37 (3H, m), 6.65–6.78 (2H, m), 6.93–7.00 (1H, m). IR (ATR) cm$^{-1}$: 1652, 1627, 1560, 1504, 1384. MS m/z: 467 [M$^+$H$^+$].

(S)-2-[(2E,4E)-Hexadienyl]-7-[(2-methylcyclopent-1-yl)-5-methoxy-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid tert-Butylamine Salt (13eA)

Yield 74%. A white solid. mp 130–133°C. $^1$H-NMR (CDCl$_3$) $\delta$: 0.99 (9H, s), 1.38, 1.39 (total 3H, s), 1.60–1.88 (9H, m), 2.13–2.24 (2H, m), 2.29, 2.30 (total 3H, s, s), 2.91–3.07 (1H, m), 3.15–3.30 (1H, m), 4.47 (0.5H, d, $J=17.3$ Hz), 4.63–4.77 (1.5H, m), 4.80, 4.81 (total 2H, s, s), 5.04 (0.5H, d, $J=17.3$ Hz), 5.08–5.13 (0.5H, m), 5.96–6.37 (3H, m), 6.64–6.78 (2H, m), 6.93–7.02 (1H, m), 7.15–7.26 (1H, m). IR (ATR) cm$^{-1}$: 1652, 1623, 1592, 1538, 1506, 1394. MS m/z: 465 [M$^+$H$^+$].

(S)-2-[(2E,4E)-Hexadienyl]-7-[(2-methylcyclohexyl-1-yl)-5-methoxy-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid tert-Butylamine Salt (13fA)

Yield 70%. A white solid. $^1$H-NMR (CDCl$_3$) $\delta$: 0.78 (6H, $E$, $J=6.3$, 6.6 Hz), 0.95, 0.97 (total 3H, s, s), 2.61–2.78 (3H, m), 2.81, 2.81 (total 3H, s, s), 3.04 (1H, m), 3.50–3.59 (1H, m), 3.96–4.01 (1H, m), 4.47 (0.5H, d, $J=17.1$ Hz), 4.62–4.71 (1.5H, m), 4.81, 4.83 (total 2H, s, s), 4.96–5.12 (1H, m), 5.96–6.37 (3H, m), 6.66–6.81 (2H, m), 6.93–7.05 (1H, m), 7.15–7.26 (1H, m). IR (ATR) cm$^{-1}$: 1652, 1625, 1554, 1502, 1378. MS m/z: 479 [M$^+$H$^+$].

(S)-7-[(2-Adamantan-1-yl)-5-methoxy-4-yl]methoxy-2-[(2E,4E)-hexadienyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid tert-Butylamine Salt (13gA)

Yield 82%. A white solid. mp 154–156°C. $^1$H-NMR (CDCl$_3$) $\delta$: 0.99 (9H, s), 1.72–1.89 (9H, m), 2.03 (6H, s), 2.03–2.10 (3H, br, br), 2.89 (3H, 2.90–3.07 (1H, m), 3.13–3.31 (1H, m), 4.47 (0.5H, d, $J=17.4$ Hz), 4.58–4.78 (1.5H, m), 4.80, 4.81 (total 2H, s, s), 4.99–5.13 (1H, m), 5.96–6.38 (3H, m), 6.66–6.78 (2H, m), 6.95–7.04 (1H, m), 7.15–7.26 (1H, m). IR (ATR) cm$^{-1}$: 1652, 1623, 1592, 1540, 1506, 1392. MS m/z: 517 [M$^+$H$^+$].

(S)-2-[(2E,4E)-Hexadienyl]-7-[(2-methylcyclopent-3-en-1-yl)-5-methoxy-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid tert-Butylamine Salt (13hA)

Yield 59%. A white solid. mp 134–137°C. $^1$H-NMR (CDCl$_3$) $\delta$: 0.10 (9H, s), 1.46, 1.46 (total 3H, s), 1.78, 1.85 (total 3H, d, d, $J=6.8$, 6.8 Hz), 2.30, 2.31 (total 3H, s, s), 2.35–2.44 (2H, m), 2.93–3.08 (3H, m), 3.15–3.31 (1H, m), 4.47 (0.5H, d, $J=17.6$ Hz), 4.59–4.85 (3.5H, m), 4.99–5.12 (1H, m), 5.66 (1H, s), 5.96–6.37 (3H, m), 6.66–6.79 (2H, m), 6.93–7.02 (1H, m), 7.15–7.26 (1H, m). IR (ATR) cm$^{-1}$: 1652, 1625, 1592, 1560, 1540, 1382. MS m/z: 463 [M$^+$H$^+$].

(S)-2-[(2E,4E)-Hexadienyl]-7-[(2-(1,4,5-trimethylcyclopent-3-en-1-yl)-5-methoxy-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid tert-Butylamine Salt (13iA)

Yield 63%. A white solid. mp 114–116°C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.03 (9H, s), 1.43 (3H, s), 1.61 (6H, s), 1.78, 1.85 (total 3H, d, d, $J=6.6$, 6.6 Hz), 2.23–2.33 (3H, m), 2.92–3.04 (3H, m), 3.15–3.31 (1H, m), 4.49 (0.5H, d, $J=17.6$ Hz), 4.65–4.85 (3.5H, m), 4.97–5.08 (1H, m), 5.96–6.37 (3H, m), 6.66–6.79 (2H, m), 6.95–7.05 (1H, m), 7.15–7.26 (1H, m). IR (ATR) cm$^{-1}$: 1652, 1625, 1554, 1504, 1378. MS m/z: 491 [M$^+$H$^+$].
(S)-2-(2-Furylacryloyl)-7-[2-(2-methylindane-2-yl)-5-methoxyazo-4-yld]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid tert-Butylamine Salt (13jE) Yield 63%. A white solid. mp 165–171°C (dec.). 1H-NMR: (CDCl₃) δ: 0.97 (9H, s), 1.50 (3H, s), 2.30 (3H, s), 2.90–3.08 (3H, m), 3.15–3.31 (1H, m), 3.60 (2H, d, J = 15.9 Hz), 4.49 (0.5H, d, J = 17.4 Hz), 4.66–4.84 (3.5H, m), 5.02–5.20 (1H, m), 6.35–6.57 (2H, m), 6.67–7.02 (4H, m), 7.12–7.24 (4H, m), 7.30–7.46 (3H, m). IR (ATR) cm⁻¹: 1650, 1616, 1556, 1504, 1376. MS m/z: 539 [M+H⁺].

Methyl [5-Methyl-2-(2,6-dimethylphenyl)oxazol-4-yl]acetate (16a) To a suspension of the free form of 16a (11.8 g, 70 mmol) and 15 (18.4 g, 100 mmol) in CH₂Cl₂ (450 mL) was added triethylamine (27.8 mL, 200 mmol) dropwise at −10°C, and stirred at the same temperature for 2 h. The reaction mixture was washed with water, 6% HCl and saturated brine, and dried over Na₂SO₄. The solvent was evaporated under reduced pressure to give a crude oil (16.8 g).

The crude oil (16.8 g), acetic anhydride (18.4 mL, 195 mmol), N-methylmorpholine (21.1 mL, 192 mmol) and 4-dimethylaminopyridine (1.21 g, 9.9 mmol) were dissolved in toluene (250 mL) and stirred at 70–80°C for 1.5 h. After cooling to room temperature, the reaction mixture was neutralized with saturated aqueous NaHCO₃ solution and separated into two layers. The organic layer was washed with water and saturated brine, and dried over Na₂SO₄. The solvent was evaporated under reduced pressure to give a crude solid (16.9 g).

To a solution of the crude solid (16.6 g) in toluene (200 mL) was added POCI₃ (10.0 mL, 107 mmol), which was refluxed for 1.5 h. After cooling, the mixture was poured into cold water, neutralized with K₂CO₃ and extracted with AcOEt. The organic layer was washed with water and saturated brine, dried over Na₂SO₄ and then evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give 16b (2.25 g, 12.3% yield) as an oil. ¹H-NMR (CDCl₃) δ: 2.24 (6H, s), 2.35 (3H, s), 3.60 (2H, s), 3.73 (3H, s), 7.07 (2H, d, J = 7.6 Hz), 7.21 (1H, t, J = 7.6 Hz).

Compounds 16b, c were prepared according to the procedure for the synthesis of 16a.

Methyl [5-Methyl-2-(2,5-dimethylphenyl)oxazol-4-yl]acetate (16b) Yield 32%. ¹H-NMR (CDCl₃) δ: 2.34 (3H, s), 2.36 (3H, s), 2.59 (3H, s), 3.58 (2H, s), 3.73 (3H, s), 7.06–7.16 (2H, m), 7.73 (1H, s).

Methyl [5-Methyl-2-(2,4,6-trimethylphenyl)oxazol-4-yl]acetate (16c) Yield 65%. ¹H-NMR (CDCl₃) δ: 2.20 (6H, s), 2.29 (3H, s), 2.31 (3H, s), 3.57 (2H, s), 3.72 (3H, s), 6.82 (2H, s).

2-[5-Methyl-2-(2,6-dimethylphenyl)oxazol-4-yl]ethanol (17a) To a suspension of 16a (2.25 g, 8.68 mmol) and NaBH₄ (1.35 g, 35.7 mmol) in THF (70 mL) was added methanol (10 mL) dropwise at 60°C and stirred for 30 min. After cooling, the mixture was poured into cold water and extracted with AcOEt. The organic layer was washed with water and saturated brine, dried over Na₂SO₄ and then evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give 17a (1.60 g, 80% yield) as a white solid. ¹H-NMR (CDCl₃) δ: 2.26 (6H, s), 2.32 (3H, s), 2.74 (2H, t, J = 4.4 Hz), 3.25–3.40 (1H, br), 3.88–3.95 (2H, m), 7.08 (2H, d, J = 7.6 Hz), 7.22 (1H, t, J = 7.6 Hz).

Compound 17b was prepared according to the procedure for the synthesis of 17a.

2-[5-Methyl-2-(2,5-dimethylphenyl)oxazol-4-yl]ethanol (17b) Yield 42%. ¹H-NMR (CDCl₃) δ: 2.33 (3H, s), 2.36 (3H, s), 2.60 (3H, s), 2.73 (2H, t, J = 5.6 Hz), 3.55–3.70 (1H, br), 3.93 (2H, t, J = 5.6 Hz), 7.07–7.15 (2H, m), 7.74 (1H, s).

2-[5-Methyl-2-(2,4,6-trimethylphenyl)oxazol-4-yl]ethanol (17c) To a solution of 16c (3.60 g, 13.2 mmol) in THF (75 mL) was added lithium aluminum hydride (500 mg, 13.2 mmol)
portionwise below 10°C, and stirred at the same temperature for 1 h. To the reaction mixture was added cold water (100 mL) and AcOEt (100 mL). The precipitate was removed by filtration, and the filtrate was separated into two layers. The organic layer was washed with saturated brine, dried over Na₂SO₄ and then evaporated under reduced pressure to give 17e (3.07 g, 95% yield) as an oil. ¹H-NMR (CDCl₃): δ: 2.22 (6H, s), 2.30 (6H, s), 2.72 (2H, t, J=5.7 Hz), 2.80–3.20 (1H, br), 3.92 (2H, t, J=5.7 Hz), 6.90 (2H, s).

2-[5-Methyl-2-(2,6-dimethylphenyl)oxazol-4-yl]ethyl Methanesulfonate (2a) To a solution of 17a (1.60 g, 6.92 mmol) and triethylamine (1.16 mL, 8.30 mmol) in CH₂Cl₂ (30 mL) was added methanesulfonyl chloride (0.59 mL, 7.61 mmol) at 0°C and stirred for 15 min. The reaction mixture was washed with water and saturated brine, and dried over Na₂SO₄. The solvent was evaporated under reduced pressure to give a crude 2a (2.13 g) as an oil. The crude 2a was used in subsequent reactions without further purification.

Compounds 2b and c were prepared according to the procedure for the synthesis of 2a.

4-Chloromethyl-5-methyl-2-(2,4,6-trimethylphenyl)oxazole (21c) To a solution of mesitylaldehyde (13.8 g) in CHCl₃ (140 mL) was added POCl₃ (6.9 mL, 74.8 mmol), which was refluxed for 3 h. After cooling, the mixture was poured into cold water and extracted with Et₂O. The organic layer was washed with saturated brine and dried over Na₂SO₄. The solvent was evaporated under reduced pressure. The reaction mixture was added i-Pr₂O and precipitated crystals were collected by filtration and dried to give 21c (6.9 mL, 74.8 mmol) as an oil. ¹H-NMR (CDCl₃): δ: 1.60 (6H, s), 2.55–2.71 (4H, m), 3.03–3.14 (1H, m), 9.60–12.40 (1H, br).

1,3,5-Trimethylcyclopent-3-enecarboxylic Acid (24i) To a solution of 23 (1.41 g, 10.1 mmol) in DMF (30 mL) was added K₂CO₃ (4.17 g, 30.2 mmol) and MeI (1.00 mL, 16.1 mmol) at room temperature and the mixture was stirred for 15 h. To the reaction mixture was added water and extracted with Et₂O. The organic layer was washed with saturated brine and dried over Na₂SO₄. The solvent was evaporated under reduced pressure to give a crude oil (2.01 g).

To a solution of diisopropylamine (2.12 mL, 15.1 mmol) in THF (50 mL) was added 2.6 M n-BuLi in hexane (5.83 mL, 15.2 mmol) at −78°C and the mixture was stirred at the same temperature for 15 min, and then the crude oil (2.01 g) in THF (20 mL) was added dropwise at −78°C. The mixture was stirred for 15 min and MeI (0.65 mL, 10.4 mmol) was added to it. The mixture was stirred and slowly warmed to room temperature for 2 h. To the reaction mixture was added water and extracted with Et₂O. The organic layer was washed with saturated brine and dried over Na₂SO₄. The solvent was evaporated under reduced pressure to give a crude oil (2.12 g).
5-(2-tert-Butoxycarbonylvinyl)furan-2-carboxylic Acid

To a solution of 22 (110 g, 414 mmol) in THF (550 mL) and MeOH (550 mL) was added 1 M aqueous LiOH solution (500 mL, 500 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was acidified with 10% citric acid in water and extracted with AcOEt. The organic layer was washed with saturated brine and then dried over \( \text{Na}_2\text{SO}_4 \). The solvent was evaporated under reduced pressure and \( n \)-hexane was added to the obtained residue. The precipitated crystals were collected by filtration to give 5-(2-tert-butoxy carbonylvinyl)furan-2-carboxylic acid (83.3 g, 84% yield) as a white solid. 1H-NMR (CDCl\(_3\)) \( \delta \): 1.52 (9H, s), 6.54 (1H, d, \( J=15.9 \) Hz), 6.68 (1H, d, \( J=3.4 \) Hz), 7.33 (1H, d, \( J=3.4 \) Hz), 7.35 (1H, d, \( J=15.9 \) Hz).

**tert-Butyl 3-(5-Fluorofuryl)acrylate** To a solution of 3-(2-tert-butoxy carbonylvinyl)furan-2-carboxylic acid (83.3 g, 350 mmol) in Et\(_2\)O (420 mL) and water (840 mL) was added NaHCO\(_3\) (70.6 g, 840 mmol), and the mixture was stirred at room temperature for 0.5 h. Then, Selectfluor (149 g, 420 mmol) was added portionwise to the reaction mixture. The mixture was stirred for 1.5 h and separated into two layers. The organic layer was washed with water and saturated brine, and then dried over \( \text{Na}_2\text{SO}_4 \). The solvent was then evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give tert-butyl 3-(5-fluorofuryl)acrylate (43.2 g, 58% yield) as an oil. 1H-NMR (CDCl\(_3\)) \( \delta \): 5.53 (1H, dd, \( J=7.1 \), 3.6 Hz), 6.11 (1H, d, \( J=15.6 \) Hz), 6.41–6.50 (1H, m), 7.16 (1H, dd, \( J=15.6 \), 2.7 Hz).

3-(5-Fluorofuranyl)acrylic Acid (8F) To a solution of tert-butyl 3-(5-fluorofuryl)acrylate (20.4 g, 94.2 mmol) in CH\(_2\)Cl\(_2\) (200 mL) was added TFA (70 mL, 942 mmol) at \( 0^\circ \)C and the mixture was stirred for 1.5 h. The solvent was then evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give a crude \( n \)-Hexane was added to the crude 8F and the precipitated crystals were collected by filtration to give 8F (9.50 g, 65% yield) as a white solid. 1H-NMR (CDCl\(_3\)) \( \delta \): 5.59 (1H, dd, \( J=6.8 \), 3.4 Hz), 6.17 (1H, d, \( J=15.6 \) Hz), 6.56–6.63 (1H, m), 7.16 (1H, dd, \( J=15.6 \), 2.7 Hz).

7-Benzyl-2-tert-butoxycarbonyl-tetrahydroisoquinoline-3-carboxylic Acid To a solution of 1 (20.0 g) in DMF (200 mL) was added K\(_2\)CO\(_3\) (13.5 g, 97.6 mmol) and BnBr (7.7 mL, 65.1 mmol) at room temperature, which was stirred for 16 h. To the reaction mixture was added water and extract- ed with AcOEt. The organic layer was washed with water and saturated brine, dried over \( \text{Na}_2\text{SO}_4 \) and then evaporated under reduced pressure.

The obtained residue was dissolved in THF (330 mL) and MeOH (110 mL), and 1 M aqueous lithium hydroxide solution (110 mL, 0.11 mol) was added to the solution at room temperature. The mixture was stirred for 18 h. The reaction mixture was evaporated under reduced pressure, acidified with 10% citric acid in water and extracted with AcOEt. The organic layer was washed with saturated brine and dried over \( \text{Na}_2\text{SO}_4 \). The solvent was evaporated under reduced pressure. \( n \)-Hexane was added to the obtained residue and precipitated crystals were collected by filtration to give 7-benzyl-2-tert-butoxycarbonyl-tetrahydroisoquinoline-3-carboxylic acid (25.7 g, 91% yield) as a white solid. 1H-NMR (CDCl\(_3\)) \( \delta \): 1.42, 1.51 (9H, s), 3.00–3.25 (2H, m), 4.43 (1H, dd, \( J=16.6 \), 7.8 Hz), 7.16 (1H, d, \( J=3.4 \) Hz), 7.32 (1H, d, \( J=15.8 \) Hz).
To a solution of 7-benzyl-2-tetrahydroisoquinoline-3-carboxamide (29) in CH$_2$Cl$_2$ (250 mL) was added 3-carboxylic acid (25.0 g, 65.2 mmol) in CH$_2$Cl$_2$ (20 mL) was added DAST (2.70 mL, 20.6 mmol) and stirred for 2 h. The reaction mixture was added with 10% citric acid in water and stirred at room temperature for 12 h. The reaction mixture was added with 10% Na$_2$SO$_4$ and the mixture was stirred at room temperature for 2 h. To the reaction mixture was added with 10% Na$_2$SO$_4$ and the mixture was stirred at room temperature for 12 h. To the reaction mixture was added with 10% Na$_2$SO$_4$ and the mixture was stirred at room temperature for 2 h. The reaction mixture was neutralized with saturated aqueous NaHCO$_3$ solution and extracted with AcOEt. The organic layer was washed with saturated brine and dried over Na$_2$SO$_4$. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give 29 (91.1 g, 33% yield) as an oil. $^1$H-NMR (CDCl$_3$) $\delta$: 1.45, 1.50 (total 9H, s, s), 1.99, 2.06 (total 3H, s, s), 2.95–3.15 (2H, m), 4.40–4.55 (1.5H, m), 4.60–4.72 (1.0H, m), 4.84–4.90 (0.5H, m), 5.03 (2H, s), 6.70–6.85 (2H, m), 7.00–7.01 (2H, m), 7.29–7.44 (5H, m).

3-Acetyl-2-tert-butoxycarbonyl-7-benzyloxy-tetrahydroisoquinoline (30) To a solution of 2-furylacrylic acid (150 mg, 1.09 mmol) in CH$_2$Cl$_2$ (7 mL) was added (COCl)$_2$ (0.093 mL, 1.09 mmol) and DMF (1 drop) at room temperature, and stirred for 0.5 h. To the reaction mixture was added with 10% Na$_2$SO$_4$ and then evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give 30 (240 mg, 76% yield) as a white solid. mp 51–52°C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.50 (3H, s), 2.00, 2.10 (total 3H, s, s), 2.32 (3H, s), 2.94–3.29 (4H, m), 3.61 (2H, d, J = 5–6 Hz), 4.65–4.97 (4H, m), 5.27–5.35 (1H, m), 6.44–6.51 (1H, m), 6.55–6.62 (1H, m), 6.77–6.95 (1H, m), 7.05–7.24 (5H, m), 7.33–7.57 (2H, m). IR (ATR) cm$^{-1}$: 1718, 1648, 1604, 1558, 1400. MS m/z: 537 [M+H]$^+$. 1-[(S)-2-(2-Furylacryloyl)-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline 3-yl]ethanol (33) To a solution of 32 (120 mg, 0.224 mmol) in THF (1 mL) and MeOH (1 mL) was added NaBH$_4$ (10 mg, 0.268 mmol) under ice-cooling, and the mixture was stirred at room temperature for 0.5 h. To the reaction mixture was added water and extracted with CHCl$_3$. The organic layer was washed with saturated brine and dried over Na$_2$SO$_4$ and then evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give 33 (107 mg, 76% yield) as a white solid. The diastereomeric ratio was 71:29, which was determined using an HPLC equipment consisted of a pump (LC-8A; Shimadzu Corporation), and a Cosmosil 5C18-AR-II column (5 μm, 4.6 mm×150 mm; Nacalai Tesque, Inc., Kyoto, Japan). As the eluent, 0.01 M KH$_2$PO$_4$ aq.–MeCN (4 : 6) was used. mp 67–69°C. $^1$H-NMR (CDCl$_3$) $\delta$: 1.16 (3H, m), 1.51 (3H, s), 2.30 (3H, s), 2.70–2.85 (1H, m), 2.88–3.37 (4H, m), 3.54–3.90 (3H, m), 4.08–4.90 (4.5H, m), 5.25–5.37 (0.5H, m), 6.42–6.62 (2H, m), 6.75–7.12 (4H, m), 7.14–7.24 (4H, m), 7.44–7.54 (2H, m). IR (ATR) cm$^{-1}$: 1644, 1600, 1583, 1558, 1504, 1484, 1419. MS m/z: 539 [M+H]$^+$. Compound 34 was prepared according to the procedure for the synthesis of 32.
hydroisooquinoline (34) Yield 56%. A white solid. mp 50–52°C. H-NMR (CDCl$_3$) δ: 1.40–1.67 (6H, m), 2.32 (3H, s), 2.94–3.15 (4H, m), 3.55–3.67 (2H, m), 4.29 (0.5H, d, J=19.21Hz), 4.50–4.70 (1H, m), 4.84–4.94 (2.5H, m), 5.26–5.45 (1H, m), 6.46–6.60 (2H, m), 6.75–6.94 (3H, m), 7.02–7.27 (5H, m), 7.44–7.54 (2H, m). IR (ATR) cm$^{-1}$: 1648, 1608, 1558, 1506, 1482, 1457, 1400. MS $m/z$: 559 [M+H]$^+$. 

PPAR$\gamma$, PPAR$\alpha$ and PPAR$\delta$ Agonist Activity Full-length human PPAR$\gamma$1 plasmid (Open Biosystems, Huntsville, U.S.A.), human PPAR$\alpha$ plasmid (GeneCopoeia Inc., Rockville, U.S.A.) or human PPAR$\delta$ plasmid (GeneCopoeia Inc.), and human RXR$\alpha$ plasmid (GeneCopoeia Inc.) with reporter plasmid pGL3-PPREEx4-ik-luc were electroplated into COS-1 cells (Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan) using Nucleofector II (AADD-1001S, Lonza Group Ltd., Basel, Switzerland). The cells were incubated for 24 h in the presence or absence of test compounds 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 LT-7.5, TOYO B-Net Co., Ltd., Tokyo, Japan) and a microplate luminescence reader (Dainippon Sumitomo Pharma Co., Ltd.). EC$_{50}$ values were determined from the average dose–response curve using data in three experiments. The maximal activation level relative to the level activated by farglitazar, a PPAR$\gamma$ agonist (10$^{-7}$M), Wy-14643, a PPAR$\alpha$ agonist (10$^{-5}$M), or GW-50156, a PPAR$\delta$ agonist (10$^{-7}$M), were determined.

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

Plasma Concentration after Oral Administration in Male SD Rats Male SD rats (7 weeks old; Japan SLC Inc., Hamamatsu, Japan) were used. The test compound at 10 mg/kg suspended in 0.5% methylcellulose solution was administered orally and then a blood sample was taken from the external jugular vein at 0.5, 1, 3, 5 and 8 h after administration to rats. Plasma concentrations of the compounds were determined using an HPLC equipment consisted 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 GLC Ltd., Tokyo, Japan).

Hypoglycemic 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=5–11). Test compounds were suspended in 0.5% methylcellulose solution and orally administered once a day for 4 d 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 vehicle or test compounds were determined using commercial kits (Wako Pure Chemical Industries, Ltd., Osaka, Japan).

Plasma volume was determined by the dye dilution method using Evans blue. Briefly, mice were injected intravenously with Evans blue solution (100 µg/animal) 48 h after the last administration, 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 livers were isolated and weighed.

**Conflict of Interest** The authors declare no conflict of interest.

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