Regular Article

Novel 2,7-Substituted (*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acids: Peroxisome Proliferator-Activated Receptor γ Partial Agonists with Protein–Tyrosine Phosphatase 1B Inhibition

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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*-butylamine salt (13jE) was identified as a potent human peroxisome proliferator-activated receptor γ (PPARγ)-selective agonist (EC_{50}=85 nM) and human protein–tyrosine phosphatase 1B (PTP-1B) inhibitor (IC_{50}=1.0 μM). Compound 13jE partially activated PPARγ, but not PPARα or PPARδ, and antagonized farglitazar, a full PPARγ agonist. C_{max} after the oral administration of 13jE at 10 mg/kg was 28.6 μg/mL (53 μM) 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 PPARγ agonism 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 γ (PPARγ), 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 PPARα/γ dual agonist and a partial PPARγ agonist. PPARα is expressed in the liver and related to fatty acid metabolism[8]; fibrates, PPARα 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] PPARα agonists have a body-weight-reducing effect, and show no hemodilution effects.[12] The combination of PPARα and PPARγ agonists has been expected to show synergistic anti-diabetic effects with high safety.[13,14] However, the development of PPARα/γ 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 PPARα and PPARγ agonist activity may lead to carcinogenesis and to adverse effects in the liver, heart and kidney.[14,18–21] Thus, PPARγ 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 PPARγ agonist and PPARα/γ dual agonist with protein–tyrosine phosphatase 1B (PTP-1B) inhibitory activity.[23–26] 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 PPARα/γ agonists with PTP-1B inhibitory activity has been reported to show effective anti-diabetic activities with high safety,[30] probably due to its partial PPARγ activation and PTP-1B inhibition. However, it may not be a true partial PPARγ agonist, since it does not antagonize a full PPARγ agonist. Furthermore, its risk of carcinogenesis by both PPARα and PPARγ 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 PPARγ 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*-butoxycarbonyl-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_2CO_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_2H to give **6a–c** and **7c–j**, respectively. Acylation of **6a–c** and **7c–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_3N), to give corresponding amides **10aA–cA**, **11cA–jA**, **gB–gE** and **jE–jG**. Hydrolysis of the ester group with aqueous LiOH afforded **12aA–cA**, **13cA–jA**, **gB–gF** and

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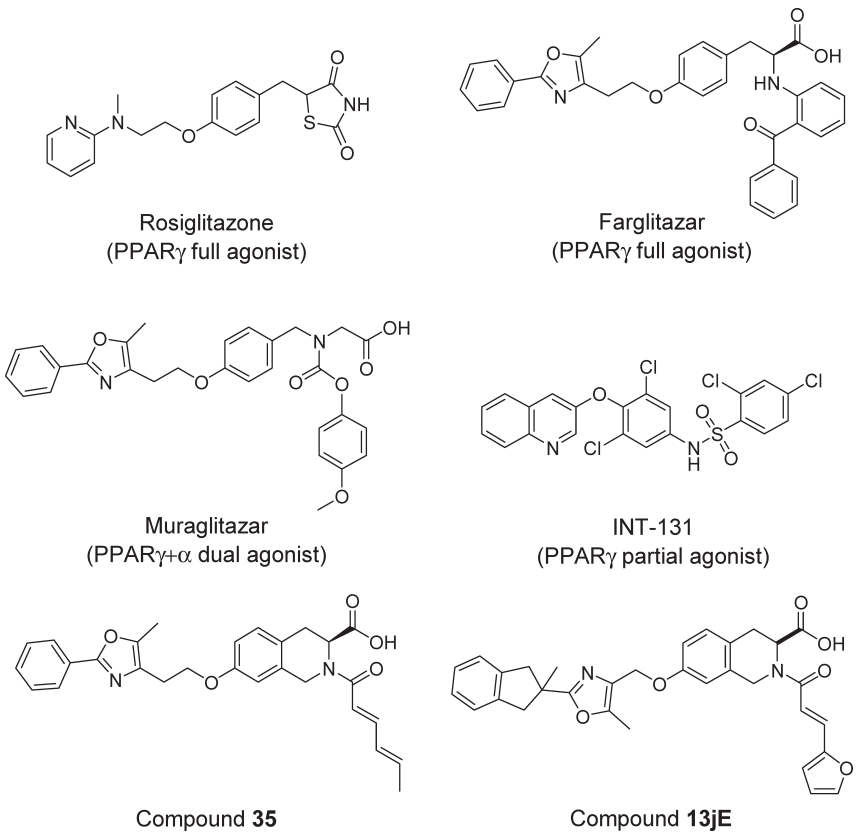


Fig. 1. Chemical Structures of PPARγ Agonists

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,[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 $LiAlH_4$ or $NaBH_4$ to give alcohols **17a**–**c**, and then methanesulfonylated to afford **2a**–**c**.

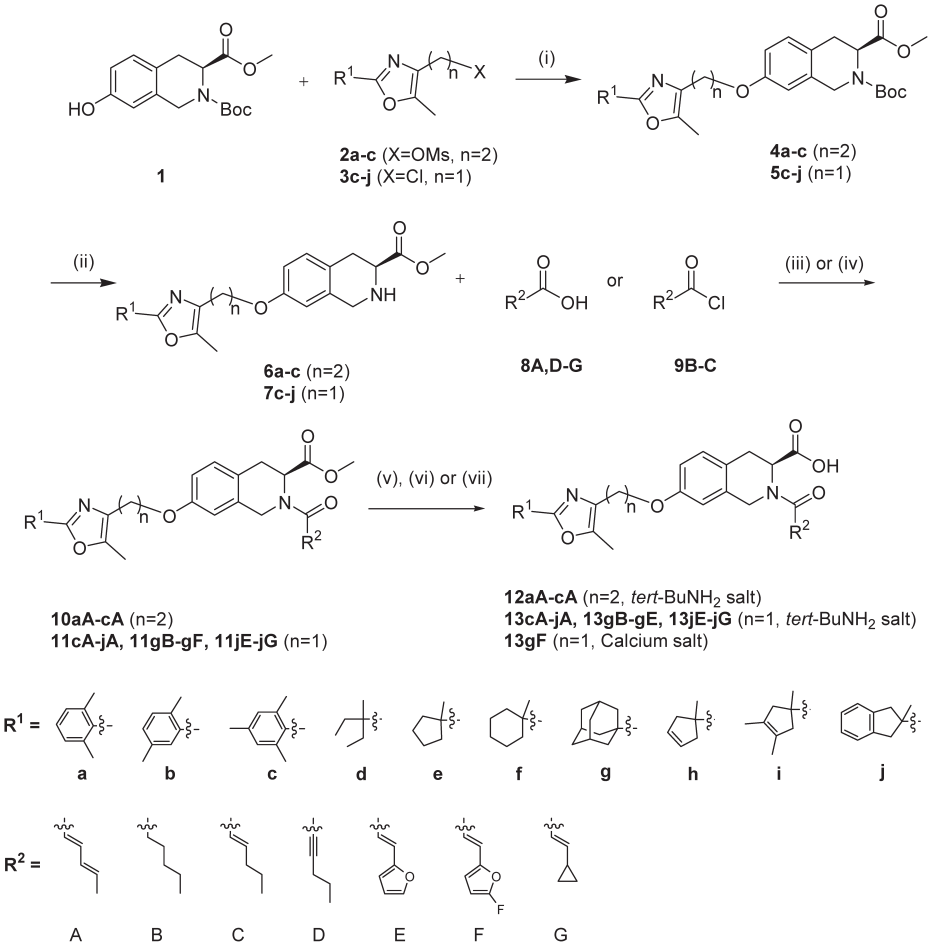
2-Substituted-4-chloromethyl-5-methyloxazoles **3c**–**j** were synthesized *via* Routes B and C in Chart 2. In Route B, aldehydes **18c**, **d**,[31] **e**, **f**[32] and **g**,[33] which were purchased or prepared according to the literature, were treated with HCl gas and diacetyl monoxime (**19**) to give oxazole *N*-oxides **20c**–**g**, followed by treatment with phosphorous oxychloride to afford 4-chloromethyloxazole derivatives (**3c**–**g**).[34] In Route C, carboxylic acids **24h**[35] and **j**[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**).[36] Diethyl malonate was alkylated with **21** and formed a cyclopentene ring **22**. The diester group was hydrolyzed and decarboxlated 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**[37] *via* acyl chloride, followed by cyclization with I_2, triphenylphosphine (PPh_3) and Et_3N to give oxazole derivatives **26h**–**j**. The ester group was transformed to a chloromethyl group by reduction with $LiAlH_4$ and then chlorinated with $SOCl_2$ to give **3h**–**j**.

Carboxylic acids **8A**, **D** and **E** were purchased, **8G** was prepared according to the literature[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 fluorine with Selectfluor and $NaHCO_3$, 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 hydroxyethyl 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 PPARγ full agonist with a weak PTP-1B inhibitory activity, was chemically modified



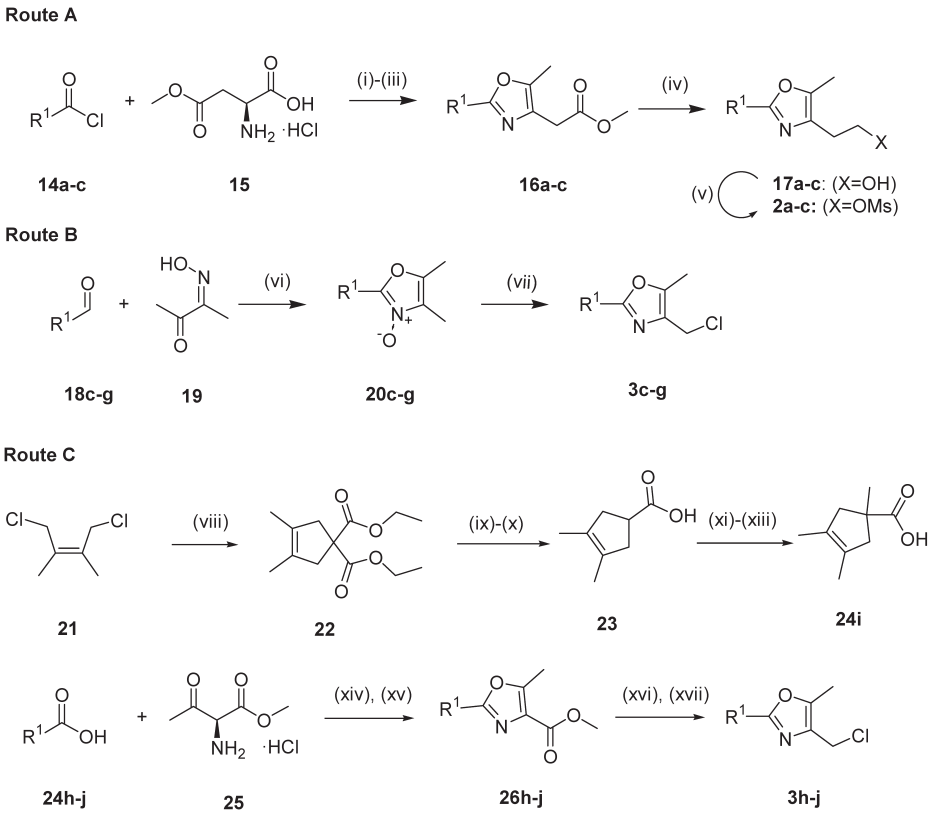
(i) K_2CO_3, tetraethylammonium fluoride hydrate, toluene, (ii) HCl, HCO_2H, (iii) **8A**, **D**–**G**, EDC·HCl, CH_2Cl_2, (iv) **9B**, **C**, Et_3N, CH_2Cl_2, (v) LiOHaq., THF–MeOH, (vi) *tert*-$BuNH_2$, MeOH, *i*-Pr_2O, (vii) $KHCO_3$, $CaCl_2$, THF, H_2O.

Chart 1. Synthesis of 2,7-Substituted-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acids

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 PPARγl plasmid, and human retinoid X receptor alpha (RXRα) plasmid with reporter plasmid pGL3-PPREx4-tk-luc, EC_{50} 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-A^y 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.

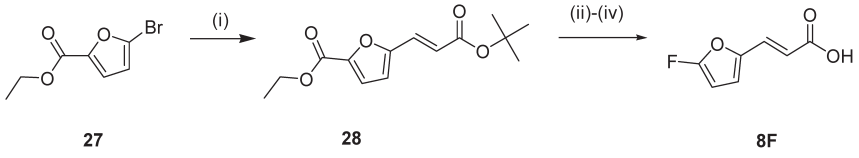
In the first experiments, methyl groups were introduced on the phenyl ring of compound **35** (**12aA**–**cA** and **13cA**) (Table 1). Interestingly, the introduction of two methyl groups at the 2- and 5-positions (**12bA**) markedly increased the affinity, and slightly decreased the maximal level of 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 (EC_{50}: 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** (C_{max}: 11.0 and 1.2 μg/mL, respectively). An adamantyl ring may be easily metabolized after oral adminis-



(i) Et_3N, CH_2Cl_2, (ii) Ac_2O, *N*-methylmorpholine, DMAP, toluene, (iii) $POCl_3$, toluene, (iv) $NaBH_4$, MeOH, THF or $LiAlH_4$, THF, (v) MsCl, Et_3N, CH_2Cl_2, (vi) HCl (g), AcOEt, (vii) $POCl_3$, toluene, (viii) diethyl malonate, LiH, THF, (ix) KOH aq., MeOH, (x) pyridine, (xi) K_2CO_3, MeI, DMF, THF, (xii) *i*-Pr_2NH, *n*-BuLi in hexane, MeI, THF, (xiii) LiOH aq., MeOH, THF, (xiv) $(COCl)_2$, DMF, **25**, *i*-Pr_2NEt, CH_2Cl_2, (xv) I_2, PPh_3, Et_3N, CH_2Cl_2, (xvi) $LiAlH_4$, THF, (xvii) $SOCl_2$, CH_2Cl_2.

Chart 2. Synthesis of 2-(2-Substituted-5-methyloxazol-4-yl)ethyl Methanesulfonates and 2-Substituted-4-chloromethyl-5-methyloxazole Derivatives



(i) *tert*-Butyl acrylate, $Pd(OAc)_2$, P(*o*-tol)$_3$, *i*-Pr_2NEt, LiCl, DMF, (ii) LiOHaq., THF–MeOH, (iii) Selectfluor, $NaHCO_3$, Et_2O, H_2O, (iv) TFA, CH_2Cl_2.

Chart 3. Synthesis of 3-(5-Fluorofuryl)acrylic Acid

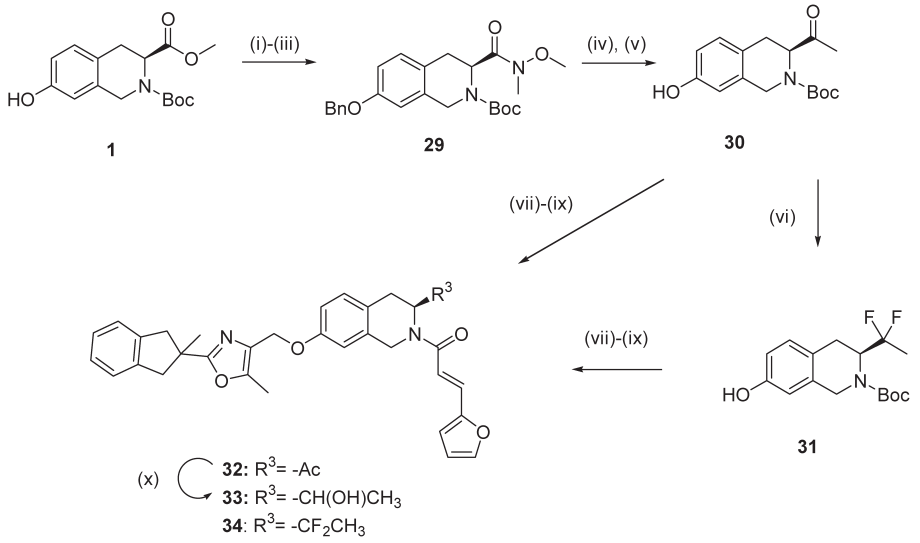
tration of **13gA**.

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 carboxyl group, un-ionized polar groups may not interact fully with PPARγ 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 PPARγ antagonist.

Compound **13jE** with potent PPARγ partial agonist activity and good oral absorption was chosen for further biological evaluation (Table 4). Compound **13jE** did not activate PPARα and PPARδ, even at 10^{-5} M. Compound **13jE** inhibited PTP-1B activity (IC_{50}=1.0 μM). In KK-A^y mice, **13jE** more potently reduced the plasma glucose and triglyceride levels than rosiglitazone, while rosiglitazone but not **13jE** showed hemodilution and hepatomegalysis (Table 5). The PPARγ agonist activity of **13jE** was lower than that of rosiglitazone. Its hypoglycemic effect is likely mediated by partial PPARγ activation and PTP-1B inhibition, resulting in high efficacy with no PPARγ-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 PPARγ selective partial agonist with PTP-1B inhibitory activity, and a furylacryloyl moiety and an indan ring are suitable for partial agonist activity and oral



(i) K_2CO_3, BnBr, DMF, (ii) LiOHaq., THF–MeOH, (iii) *N*,*O*-dimethylhydroxyamine, Et_3N, EDC·HCl, CH_2Cl_2, (iv) MeMgI in THF, THF, (v) Pd–C, H_2, MeOH, (vi) DAST, CH_2Cl_2, (vii) **3j**, K_2CO_3, tetraethylammonium fluoride hydrate, toluene, (viii) HCl, HCO_2H, (ix) 2-furylacrylic acid, $(COCl)_2$, DMF, CH_2Cl_2, then Et_3N, (x) $NaBH_4$, MeOH, THF.

Chart 4. Synthesis of Non-carboxylic Acid-Type Derivatives

absorption. Compound **13jE** is a potential candidate of a safe and efficacious anti-diabetic drug, and its clinical development is desirable.

Experimental

General Procedures 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 (*S*)-2-*tert*-Butoxycarbonyl-7-[2-(2,6-dimethylphenyl)-5-methyloxazol-4-ylethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (4a) A mixture of **1** (1.42 g, 4.62 mmol), crude **2a** (2.13 g), tetraethylammonium fluoride hydrate (300 mg) and K_2CO_3 (1.91 g 13.8 mmol) in toluene (50 mL) was stirred at 85°C 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 **4a** (2.47 g, quant.) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 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 **4b** and **c** and **5c**–**j** were prepared according to the procedure for the synthesis of **4a**.

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-[2-(2,5-dimethylphenyl)-5-methyloxazol-4-ylethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (4b) Yield 99%. ^{1}H-NMR ($CDCl_3$) δ: 1.45, 1.51 (total 9H, s, s), 2.35 (3H, s), 2.37 (3H, s), 2.59 (3H, s), 2.96 (2H, t, J=6.6 Hz), 3.04–3.21 (2H, m), 3.60, 3.62 (total 3H, s, s), 4.21 (2H, t, J=6.6 Hz), 4.37–4.50 (1H, m), 4.60–4.76 (1.5H, m), 5.07–5.13 (0.5H, m), 6.61–6.75 (2H, m), 6.98–7.15 (3H, m), 7.69–7.74 (1H, m).

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-[2-(2,4,6-dimethylphenyl)-5-methyloxazol-4-ylethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (4c) Quant. ^{1}H-NMR ($CDCl_3$) δ: 1.35–1.70 (9H, m), 2.20 (6H, s), 2.29 (3H, s), 2.33 (3H, s), 2.96 (2H, t, J=6.8 Hz), 3.00–3.25 (2H, m), 3.61 (3H, 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).

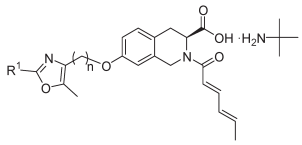
Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-[2-(2,4,6-dimethylphenyl)-5-methyloxazol-4-ylmethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5c) Yield 94%. ^{1}H-NMR ($CDCl_3$) δ: 1.45, 1.52 (total 9H, s, s), 2.23 (6H, s), 2.31 (3H, s), 2.39 (3H, s), 3.05–3.25 (2H, m), 3.60, 3.63 (total 3H, s, s), 4.40–4.53 (1H, m), 4.62–4.79 (1.5H, m), 4.99 (2H, s), 5.10–5.15 (0.5H, m), 6.76–6.88 (2H, m), 6.90 (2H, s), 7.01–7.07 (1H, m).

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-[2-(1-ethyl-1-methylpropan-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5d) Quant. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (6H, J=7.6 Hz), 0.98 (9H, s), 1.29, 1.52 (total 9H, s, s), 1.45 (3H, s), 1.56–1.69 (2H, m), 1.72–1.84 (2H, m), 2.29 (3H, s), 3.02–3.21 (2H, m), 3.61, 3.63 (total 3H, s, s), 4.38–4.76 (2.5H, m), 4.86, 4.87 (total 2H, s, s), 5.05–5.14 (0.5H, m), 6.68–6.83 (2H, m), 6.98–7.05 (1H, m).

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-[2-(1-methylcyclopentan-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5e) Yield 92%. ^{1}H-NMR ($CDCl_3$) δ: 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-

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



Compound	R^1	*n*	M.W.[a]	PPARγ[b]				Plasma levels[e]	
				EC_{50} (nM)	Max[c] (%)	IC_{50} (nM)	Max[d] (%)	C_{max} (μg/mL)	*AUC* (μg·h/mL)
35		2	472.53	1062	105	>1000	—	39	177
12aA		2	500.59	972	66	—	14	—	—
12bA		2	500.59	156	87	>1000	<10	—	—
12cA		2	514.61	518	62	94	22	—	—
13cA		1	500.59	301	51	62	21	0.32	3.4
13dA		1	466.57	237	52	124	30	2.9	6.0
13eA		1	454.55	131	55	227	25	3.4	14.2
13fA		1	478.58	230	68	177	15	2.8	9.0
13gA		1	516.63	117	63	314	35	1.2	5.5
13hA		1	462.54	184	62	45	30	9.4	52.9
13iA		1	490.59	142	71	476	17	11.9	114.5
13jA		1	512.60	122	69	622	26	11.0	74.9
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, $n=3$.

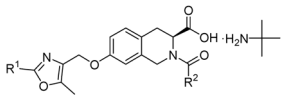
hexyl-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5f) Yield 98%. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, s), 1.32–1.60 (17H, m), 2.08–2.21 (2H, m), 2.30 (3H, s), 3.05–3.23 (2H, m), 3.61, 3.63 (total 3H, s, s), 4.38–4.52 (1H, m), 4.60–4.80 (1.5H, m), 4.86 (2H, s), 5.06–5.18 (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%. ^{1}H-NMR ($CDCl_3$) 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%. ^{1}H-NMR ($CDCl_3$) 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).

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-[2-(1,4,5-trimethyl-

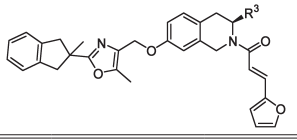
Table 2. Chemical Structure, Molecular Weight, PPARγ Agonist and Antagonist Activity and Plasma Concentration in Male SD Rats of 2,7-Disubstituted-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Derivatives



Compound	R^1	R^2	M.W.[a]	PPARγ[b]				Plasma levels[e]	
				EC_{50} (nM)	Max[c] (%)	IC_{50} (nM)	Max[d] (%)	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
13gF[f]			560.61	70	52	82	32	—	—
13jA			512.60	122	69	622	26	11.0	74.9
13jE			538.59	85	65	202	20	28.6	367.9
13jF			556.58	193	62	120	20	20.4	229.5
13jG			512.60	87	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.

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	R^3	M.W.[a]	PPARγ[b]				Plasma levels[e]	
			EC_{50} (nM)	Max[c] (%)	IC_{50} (nM)	Max[d] (%)	C_{max} (μg/mL)	*AUC* (μg·h/mL)
13jE[f]		538.59	85	65	202	20	28.6	367.9
32		536.62	30	21	169	63	0.07	0.04
33		538.63	120	38	1597	54	—	—
34		558.62	62	24	2221	62	—	—

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*) *t*-$BuNH_2$ salt.

cyclopent-3-en-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5i) Yield 97%. ^{1}H-NMR ($CDCl_3$) 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).

Methyl (*S*)-2-*tert*-Butoxycarbonyl-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5j) Yield 93%. ^{1}H-NMR ($CDCl_3$) 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).

Table 4. PPARγ, PPARα and PPARδ Transactivation Effects and PPARγ Inhibition and PTP-1B Inhibition of Compound **13jE** and Rosiglitazone

Compound	PPAR$\gamma^{a)}$				PPAR$\alpha^{a)}$	PPAR$\delta^{a)}$	PTP-1B$^{a)}$
	EC_{50} (nM)	Max$^{b)}$ (%)	IC_{50} (nM)	Max$^{c)}$ (%)	EC_{50} (nM)	EC_{50} (nM)	IC_{50} (μM)
13jE	85	65	202	20	>1000	>1000	1.0
Rosiglitazone	70	119	>1000	—	>1000	>1000	>30

a) $n=3$. *b*) The activation level induced by farglitazar (10^{-7}M) was taken as 100%. *c*) The maximal inhibitory effects against the response induced by farglitazar (10^{-7}M).

Table 5. Effects of Repeated Administration of Compound **13jE** and Rosiglitazone in Male KK-A^y Mice

Compound	KK-A^y mice (10 mg/kg, 14 d)			
	Glucose % decrease$^{a)}$	TG % decrease$^{a)}$	Plasma volume % increase$^{b)}$	Liver weight % increase$^{b)}$
13jE	45.0±7.2**	41.0±3.7**	0.7±7.5	29.1±9.0
Rosiglitazone	31.8±4.5**	35.4±8.6*	13.1±3.9*	60.8±15.6**

Mean±S.E. *$p<0.05$, **$p<0.01$. The mean value in control mice were taken as 100%. *a*) **13jE**; $n=6$, rosiglitazone; $n=11$. *b*) **13jE**; $n=6$, rosiglitazone; $n=5$.

Methyl (*S*)-7-[2-(2,6-Dimethylphenyl)-5-methyloxazol-4-ylethoxy]-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 $NaHCO_3$ solution and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give **6a** (1.90 g, 92% yield) as an oil. ^{1}H-NMR ($CDCl_3$) 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 **c** and **7c–j** were prepared according to the procedure for the synthesis of **6a**.

Methyl (*S*)-7-[2-(2,5-Dimethylphenyl)-5-methyloxazol-4-ylethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (6b) Yield 98%. ^{1}H-NMR ($CDCl_3$) 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, 2.7 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-ylethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (6c) Yield 91%. ^{1}H-NMR ($CDCl_3$) 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-(2,4,6-Dimethylphenyl)-5-methyloxazol-4-ylmethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7c) Quant. ^{1}H-NMR ($CDCl_3$) δ: 1.60–1.85 (1H, br), 2.22 (6H, s), 2.30 (3H, s), 2.39 (3H, s), 2.88 (1H, dd, J=15.6, 10.5 Hz), 3.03 (1H, dd, J=15.6, 4.6 Hz), 3.72 (1H, dd, J=10.5, 4.6 Hz), 3.77 (3H, s), 4.02–4.10 (2H, m), 4.99 (2H, s), 6.71 (1H, d, J=2.4 Hz), 6.85 (1H, dd, J=8.3, 2.4 Hz), 6.90 (2H, s), 7.02 (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 (7d) Yield 92%. ^{1}H-NMR ($CDCl_3$) 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), 2.29 (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-Methylcyclopentan-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7e) Yield 89%. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, s), 1.61–1.78 (6H, m), 2.10–2.24 (2H, m), 2.30 (3H, s), 2.89 (1H, dd, J=15.9, 10.2 Hz), 3.04 (1H, dd, J=15.9, 4.4 Hz), 3.72–3.77 (1H, m), 3.78 (3H, s), 4.05 (1H, d, J=16.1), 4.11 (1H, d, J=16.1 Hz), 4.84 (2H, s), 6.67 (1H, d, J=2.4 Hz), 6.80 (1H, dd, J=8.6, 2.4 Hz), 7.01 (1H, d, J=8.6 Hz).

Methyl (*S*)-7-[2-(1-Methylcyclohexyl-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7f) Yield 95%. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, s), 1.32–1.63 (8H, m), 2.08–2.18 (2H, m), 2.30 (3H, s), 2.87 (1H, dd, J=15.9, 10.5 Hz), 3.02 (1H, dd, J=15.9, 4.4 Hz), 3.67–3.77 (1H, m), 3.77 (3H, s), 4.00–4.10 (2H, m), 4.86 (2H, s), 6.67 (1H, d, J=2.4 Hz), 6.80 (1H, dd, J=8.3, 2.4 Hz), 7.01 (1H, d, J=8.3 Hz).

Methyl (*S*)-7-{[2-(Adamantan-1-yl)-5-methyloxazol-4-yl]-methoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7g) Yield 92%. ^{1}H-NMR ($CDCl_3$) 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, d, J=8.5 Hz).

Methyl (*S*)-7-[2-(1-Methylcyclopent-3-en-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7h) Yield 94%. ^{1}H-NMR ($CDCl_3$) 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), 3.78 (3H, s), 4.03–4.12 (2H, m), 4.84 (2H, s), 5.67 (2H, s), 6.66 (1H, d, J=2.4 Hz), 6.80 (1H, dd, J=8.3, 2.4 Hz), 7.01 (1H, d, J=8.3 Hz).

Methyl (*S*)-7-[2-(1,4,5-Trimethylcyclopent-3-en-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7i) Yield 94%. ^{1}H-NMR ($CDCl_3$) 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,

d, J=16.1 Hz), 4.55 (1H, d, J=16.1 Hz), 4.84 (2H, s), 6.72 (1H, d, J=2.0 Hz), 6.87 (1H, dd, J=8.5, 2.0 Hz), 7.05 (1H, d, J=8.5 Hz).

Methyl (*S*)-7-[2-(2-Methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7j) Yield 79%. ^{1}H-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, d, 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-(2,6-Dimethylphenyl)-5-methyloxazol-4-ylethoxy]-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (10aA) To a solution of **6a** (1.88 g, 4.47 mmol) in CH_2Cl_2 (40 mL) was added (2*E*,4*E*)-5-methylhexadienoic acid (601 mg, 5.36 mmol) and EDC·HCl (1.03 g, 5.37 mmol) at room temperature and the mixture was stirred 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 **10a** (1.88 g, 82% yield) as an oil. ^{1}H-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).

Compounds **10bA** and **cA** and **11cA**–**jA** were prepared according to the procedure for the synthesis of **10aA**.

Methyl (*S*)-7-[2-(2,5-Dimethylphenyl)-5-methyloxazol-4-ylethoxy]-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (10bA) Yield 81%. ^{1}H-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), 4.77 (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), 6.99–7.15 (3H, m), 7.27–7.36 (1H, m), 7.73 (1H, s).

Methyl (*S*)-7-[2-(2,4,6-Dimethylphenyl)-5-methyloxazol-4-ylethoxy]-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (10cA) Quant. ^{1}H-NMR ($CDCl_3$) δ: 1.85 (3H, d, J=4.8 Hz), 2.20 (6H, s), 2.29 (3H, s), 2.34 (3H, s), 2.97 (2H, t, J=6.8 Hz), 3.00–3.25 (2H, m), 3.60 (3H, s), 4.24 (2H, t, J=6.8 Hz), 4.50–5.10 (2H, m), 5.40–5.65 (1H, m), 6.00–6.55 (3H, m), 6.60–6.85 (2H, m), 6.89 (2H, s), 7.04 (1H, d, J=8.4 Hz), 7.15–7.55 (1H, m).

Methyl (*S*)-7-[2-(2,4,6-Dimethylphenyl)-5-methyloxazol-4-ylmethoxy]-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11cA) Yield 95%. ^{1}H-NMR ($CDCl_3$) δ: 1.83–1.90 (3H, m), 2.22 (6H, s), 2.31 (3H, s), 2.40 (3H, s), 3.03–3.32 (2H, m), 3.60 (3H, s) 4.55 (0.3H, d, J=17.6 Hz), 4.68–5.03 (4H, m), 5.51–5.57 (0.7H, m), 6.07–6.36 (3H, m), 6.80–6.93 (4H, m), 7.03–7.10 (1H, m), 7.27–7.39 (1H, m).

Methyl (*S*)-7-[2-(1-Ethyl-1-methylpropan-1-yl)-5-methyloxazol-4-yl]methoxy-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11dA) Yield 87%. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (6H, J=7.6 Hz), 1.29 (3H, s), 1.56–1.68 (2H, m), 1.73–1.90 (5H, m), 2.30 (3H, s), 3.00–3.30 (2H, m), 3.59 (3H, s), 4.54 (0.3H, d, J=17.6 Hz), 4.66–4.96 (4H, m), 5.50–5.58 (0.7H, m), 6.05–6.37 (3H, m), 6.70–6.84 (2H, m), 7.00–7.07 (1H, m), 7.27–7.39 (1H, m).

Methyl (*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-[2-(1-methylcyclopentan-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11eA) Yield 99%. ^{1}H-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=15.0 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).

Methyl (*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-[2-(1-methylcyclohexyl-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11fA) Yield 89%. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, s), 1.32–1.63 (8H, m), 1.82–1.91 (3H, m), 2.08–2.20 (2H, m), 2.31 (3H, s), 3.00–3.30 (2H, m), 3.60 (3H, s), 4.55 (0.3H, d, J=17.3 Hz), 4.67–4.98 (4H, m), 5.50–5.59 (0.7H, m), 6.05–6.40 (3H, m), 6.72–6.86 (2H, m), 7.04–7.09 (1H, m), 7.27–7.38 (1H, m).

Methyl (*S*)-7-{[2-(Adamantan-1-yl)-5-methyloxazol-4-yl]-methoxy}-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11gA) Yield 86%. ^{1}H-NMR ($CDCl_3$) δ: 1.72–1.82 (6H, m), 1.83–1.89 (3H, m), 1.97–2.10 (9H, m), 2.30 (3H, s), 3.00–3.30 (2H, m), 3.60 (3H, s), 4.55 (0.3H, d, J=17.3 Hz), 4.67–4.98 (4H, m), 5.51–5.58 (0.7H, m), 6.05–6.38 (3H, m), 6.71–6.86 (2H, m), 7.02–7.09 (1H, m), 7.27–7.37 (1H, m).

Methyl (*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-[2-(1-methylcyclopent-3-en-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11hA) Yield 93%. ^{1}H-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), 5.67 (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).

Methyl (*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-[2-(1,4,5-trimethylcyclopent-3-en-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11iA) Yield 96%. ^{1}H-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), 7.29–7.40 (1H, m).

Methyl (*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11jA) Yield 91%. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, s), 1.80–1.90 (3H, m), 2.32 (3H, m), 2.94–3.30 (4H, m), 3.55–3.64 (5H, m), 4.55 (0.3H, d, J=16.8 Hz), 4.67–4.98 (4H, m), 5.50–5.58 (0.7H, m), 6.05–6.40 (3H, m), 6.72–6.86 (2H, m), 7.02–7.10 (1H, m), 7.13–7.24 (4H, m), 7.27–7.40 (1H, m).

Compounds **11gE** and **F** and **11jE**–**G** were prepared according to the procedure for the synthesis of **10aA** using corresponding carboxylic acid.

Methyl (*S*)-7-{[2-(Adamantann-1-yl)-5-methyloxazol-4-yl]methoxy}-2-(2-hexynoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11gD) Quant. ^{1}H-NMR ($CDCl_3$) δ (ppm): 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), 2.30, 2.31 (total 3H, s, s), 2.35 (1H, t, J=7.1 Hz), 2.41 (1H, t, J=7.1 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,

d, J=17.6 Hz), 5.08 (0.5H, d, J=16.3 Hz), 5.35–5.42 (1H, m), 6.74–6.86 (2H, m), 7.03–7.09 (1H, m).

Methyl (*S*)-7-{[2-(Adamantann-1-yl)-5-methyloxazol-4-yl]methoxy}-2-(2-furylacryloyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11gE) Yield 98%. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.73–1.82 (6H, m), 2.00–2.10 (9H, m), 2.31 (3H, s), 3.05–3.35 (2H, m), 3.61 (3H, s), 4.59 (0.3H, d, J=17.1 Hz), 4.78–5.07 (4H, m), 5.55–5.63 (0.7H, m), 6.45–6.51 (1H, m), 6.56–6.62 (1H, m), 6.45–6.51 (1H, m), 6.74–6.94 (3H, m), 7.03–7.12 (1H, m), 7.44–7.55 (1H, m).

Methyl (*S*)-7-{[2-(Adamantann-1-yl)-5-methyloxazol-4-yl]methoxy}-2-[2-(5-fluorofuryl)acryloyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11gF) Yield 92%. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.70–1.80 (6H, m), 1.97–2.09 (9H, m), 2.31 (3H, s), 3.05–3.35 (2H, m), 3.62 (3H, s), 4.59 (0.3H, d, J=17.3 Hz), 4.77–5.07 (4H, m), 5.51–5.61 (1.7H, m), 6.45–6.58 (1.3H, m), 6.72–6.88 (2.7H, m), 7.03–7.12 (1H, m), 7.34–7.43 (1H, m).

Methyl (*S*)-2-(2-Furylacryloyl)-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11jE) Quant. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, s), 2.32 (3H, s), 2.94–3.35 (4H, m), 3.56–3.66 (5H, m), 4.59 (0.3H, d, J=17.4 Hz), 4.77–4.93 (3.5H, m), 4.95–5.09 (0.5H, m), 5.55–5.62 (0.7H, m), 6.42–6.50 (1H, m), 6.55–6.61 (1H, m), 6.69 (0.3H, d, J=15.1 Hz), 6.75–6.87 (2H, m), 6.91 (0.7H, d, J=15.1 Hz), 7.05–7.10 (1H, m), 7.14–7.23 (4H, m), 7.42–7.56 (2H, m).

Methyl (*S*)-2-[2-(5-Fluorofuryl)acryloyl-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11jF) Yield 72%. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (3H, s), 2.33 (3H, s), 2.95–3.35 (4H, m), 3.56–3.65 (5H, m), 4.58 (0.3H, d, J=18.1 Hz), 4.75–4.89 (3.5H, m), 4.94–5.06 (0.5H, m), 5.54–5.60 (1.7H, m), 6.45–6.55 (1.3H, m), 6.74–6.86 (2.7H, m), 7.02–7.09 (1H, m), 7.13–7.23 (4H, m), 7.34–743 (1H, m).

Methyl (*S*)-2-(2-Cyclopropylacryloyl)-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11jG) Quant. ^{1}H-NMR ($CDCl_3$) δ: 0.57–0.72 (2H, m), 0.83–1.00 (2H, m), 1.50 (3H, s), 2.32 (3H, s), 2.93–3.30 (4H, m), 3.56–3.65 (5H, m), 4.53 (0.3H, d, J=17.6 Hz), 4.66–5.00 (4H, m), 5.45–5.58 (0.7H, m), 6.24 (0.3H, d, J=14.9 Hz), 6.35–6.53 (1.7H, m), 6.70–6.88 (2H, m), 7.00–7.10 (1H, m), 7.13–7.27 (5H, m), 7.34–743 (1H, m).

Methyl (*S*)-7-{[2-(Adamantann-1-yl)-5-methyloxazol-4-yl]methoxy}-2-hexanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11gB) To a solution of **7g** (500 mg, 1.15 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (0.24 mL, 1.72 mmol) and hexanoyl chloride (0.17 mL, 1.27 mmol) under ice-cooling, and the mixture was stirred for 15 min under ice-cooling. To the reaction mixture was added water and extracted with $CHCl_3$. The organic layer was washed with water 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 **11gB** (0.62 g, quant.) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.86–0.96 (3H, m), 1.29–1.40 (4H, m), 1.55–1.62 (0.6H, m), 1.65–1.81 (8H, m), 2.01–2.10 (9H, m), 2.30, 2.30 (total 3H, s, s), 2.44–2.52 (1.4H, m), 3.00–3.31 (2H, m), 3.61 (3H, s), 4.45 (0.3H, d, J=17.1 Hz), 4.65 (1.4H, s), 4.80–4.86 (2.3H, m), 5.46–5.51 (0.7H, m), 6.73–6.85 (2H, m), 7.03–7.10 (1H, m).

Compound **11gC** was prepared according to the procedure for the synthesis of **11gB**.

Methyl (*S*)-7-{[2-(Adamantann-1-yl)-5-methyloxazol-4-yl]methoxy}-2-(2-hexenoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11gC) Quant. ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.91–1.00 (3H, m), 1.45–1.57 (2H, m), 1.72–1.82 (6H, m), 2.01–2.10 (9H, m), 2.13–2.27 (2H, m), 2.31 (3H, s), 3.02–3.30 (2H, m), 3.61 (3H, s), 4.53 (0.3H, d, J=17.6 Hz), 4.68–4.96 (4H, m), 5.50–5.56 (0.7H, m), 6.14 (0.3H, d, J=15.2 Hz), 6.37 (0.7H, d, J=15.2 Hz), 6.75–7.08 (4H, m).

(*S*)-7-[2-(2,6-Dimethylphenyl)-5-methyloxazol-4-ylethoxy]-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (12aA) To a solution of **10aA** (1.88 g, 3.65 mmol) in tetrahydrofuran (THF)–MeOH (3 : 1, 20 mL) was added 1 M aqueous lithium hydroxide solution (11.0 mL, 11.0 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 Na_2SO_4. 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), diisopropyl ether (100 mL) was added, and the mixture was stirred at room temperature for 1 h. The precipitated crystals were collected by filtration to give **12aA** (2.14 g, quant) as a white solid, mp 135–137°C. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (9H, s), 1.78, 1.84 (total 3H, d, d, J=6.6, 5.8 Hz), 2.22 (6H, s), 2.35 (3H, s), 2.87–3.05 (3H, m), 3.12–3.30 (1H, m), 4.10–4.25 (2H, m), 4.45 (0.5H, d, J=17.8 Hz), 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=7.3 Hz), 7.12–7.25 (2H, m). IR attenuated total reflectance (ATR) cm^{-1}: 1652, 1623, 1589, 1538, 1392. MS m/z: 501 $[M+H]^+$.

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

(*S*)-7-[2-(2,5-Dimethylphenyl)-5-methyloxazol-4-ylethoxy]-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (12bA) Quant. A white solid. mp 134–135°C. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (9H, s), 1.78, 1.84 (total 3H, d, d, J=6.8, 6.6 Hz), 2.34 (3H, s), 2.36 (3H, s), 2.59 (3H, s), 2.88–3.05 (3H, m), 3.12–3.26 (1H, m), 4.13–4.21 (2H, m), 4.45 (0.5H, d, J=17.3 Hz), 4.59–4.72 (1.5H, m), 4.96–5.04 (1H, m), 5.95–6.35 (3H, m), 6.57–6.71 (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, 1506, 1378. MS m/z: 501 $[M+H]^+$.

(*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-[2-(2,4,6-trimethylphenyl)-5-methyloxazol-4-ylethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (12cA) Yield 72%. A white solid. mp 130–132°C. ^{1}H-NMR ($CDCl_3$) δ: 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=6.8 Hz), 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*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-[2-(2,4,6-trimethylphenyl)-5-methyloxazol-4-ylmethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (13cA) Yield 63%. A white solid. mp 135–138°C. ^{1}H-NMR ($CDCl_3$) δ: 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, s), 2.90–3.07 (1H, m), 3.15–3.32 (1H, m), 4.49 (0.5H, d, J=17.1 Hz), 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-[2-(1-Ethyl-1-methylpropan-1-yl)-5-methyloxazol-4-yl]methoxy-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (13dA) Yield 70%. A white solid. mp 120–123°C. ^{1}H-NMR ($CDCl_3$) *δ*: 0.78 (6H,, *J*=7.6 Hz), 0.98 (9H, s), 1.29, 1.28 (total 3H, s), 1.56–1.69 (2H, m), 1.75–1.88 (5H, 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), 7.16–7.25 (1H, m). IR (ATR) cm^{-1}: 1652, 1627, 1560, 1504, 1384. MS *m/z*: 467 $[M+H]^+$.

(*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-[2-(1-methylcyclopentan-1-yl)-5-methyloxazol-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 ($CDCl_3$) *δ*: 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-[(2*E*,4*E*)-Hexadienoyl]-7-[2-(1-methylcyclohexyl-1-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (13fA) Yield 70%. A white solid. ^{1}H-NMR ($CDCl_3$) *δ* (ppm): 1.01 (9H, s), 1.28 (3H, s), 1.32–1.65 (8H, m), 1.79, 1.85 (total 3H, d, d, *J*=6.3, 6.6 Hz), 2.06–2.18 (2H, m), 2.30 (3H, s), 2.90–3.08 (1H, m), 3.11–3.29 (1H, m), 4.48 (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-methyloxazol-4-yl]-methoxy}-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (13gA) Yield 82%. A white solid. mp 154–156°C. ^{1}H-NMR ($CDCl_3$) *δ*: 0.99 (9H, s), 1.72–1.89 (9H, m), 2.03 (6H, s), 2.03–2.10 (3H, br), 2.29 (3H, s), 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-[(2*E*,4*E*)-Hexadienoyl]-7-[2-(1-methylcyclopent-3-en-1-yl)-5-methyloxazol-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 ($CDCl_3$) *δ*: 1.01 (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, 1504, 1382. MS *m/z*: 463 $[M+H]^+$.

(*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-[2-(1,4,5-trimethylcyclopent-3-en-1-yl)-5-methyloxazol-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 ($CDCl_3$) *δ*: 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 (5H, 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*E*,4*E*)-Hexadienoyl]-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (13jA) Yield 65%. A white solid. mp 150–155°C (dec.). ^{1}H-NMR ($CDCl_3$) *δ*: 1.02 (9H, s), 1.49, 1.50 (total 3H, s, s), 1.78, 1.84 (total 3H, d, d, *J*=6.6, 6.4 Hz), 2.30, 2.31 (total 3H, s, s), 2.90–3.06 (3H, m), 3.15–3.31 (1H, m), 3.60 (2H, d, *J*=15.9 Hz), 4.47 (0.5H, d, *J*=17.4 Hz), 4.64–4.76 (1.5H, m), 4.80, 4.81 (total 2H, s, s), 5.00–5.10 (1H, m), 5.95–6.37 (3H, m), 6.66–6.79 (2H, m), 6.94–7.03 (1H, m), 7.12–7.26 (5H, m). IR (ATR) cm^{-1}: 1652, 1625, 1554, 1504, 1380. MS *m/z*: 513 $[M+H]^+$.

Compounds **13gB**–**E** and **13jE** and **F** were prepared according to the procedure for the synthesis of **12aA**.

(*S*)-7-{[2-(Adamantann-1-yl)-5-methyloxazol-4-yl]-methoxy}-2-hexanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (13gB) Yield 76%. A white solid. mp 124–126°C. ^{1}H-NMR ($CDCl_3$) *δ*: 0.86–0.95 (3H, m), 1.03 (9H, s), 1.25–1.39 (4H, m), 1.58–1.69 (2H, m), 1.25–1.39 (4H, m), 1.72–1.81 (6H, br), 2.03 (6H, s), 2.03–2.10 (3H, br), 2.29, 2.30 (total 3H, s, s), 2.31–2.48 (2H, m), 2.92–3.06 (1H, m), 3.13–3.33 (1H, m), 4.45–4.70 (2H, m), 4.80, 4.82 (total 2H, s, s), 4.94–5.05 (1H, m), 6.66–6.80 (2H, m), 6.95–7.04 (1H, m). IR (ATR) cm^{-1}: 1635, 1548, 1504, 1382. MS *m/z*: 521 $[M+H]^+$.

(*S*)-7-{[2-(Adamantann-1-yl)-5-methyloxazol-4-yl]-methoxy}-2-(2-hexenoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (13gC) Yield 79%. A white solid. mp 141–143°C. ^{1}H-NMR ($CDCl_3$) *δ* (ppm): 0.86–0.98 (3H, m), 1.03 (9H, s), 1.38–1.55 (2H, m), 1.72–1.81 (6H, br), 2.02–2.25 (11H, m), 2.29, 2.29 (total 3H, s, s), 2.95–3.07 (1H, m), 3.15–3.33 (1H, m), 4.47 (0.5H, d, *J*=17.3 Hz), 4.62–4.76 (1.5H, m), 4.80, 4.82 (total 2H, s, s), 4.96–5.09 (1H, m), 6.25, 6.35 (total 1H, d, d, *J*=15.1, 15.2 Hz), 6.67–6.85 (3H, m), 6.95–7.04 (1H, m). IR (ATR) cm^{-1}: 1658, 1621, 1548, 1504, 1384. MS *m/z*: 519 $[M+H]^+$.

(*S*)-7-{[2-(Adamantann-1-yl)-5-methyloxazol-4-yl]-methoxy}-2-(2-hexynoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (13gD) Yield 67%. A white solid. mp 133–135°C. ^{1}H-NMR ($CDCl_3$) *δ* (ppm): 0.89–1.05 (12H, m), 1.54–1.69 (2H, m), 1.72–1.81 (6H, br), 2.02 (6H, s), 2.03–2.10 (3H, br), 2.25–2.35 (4H, m), 2.37 (1H, t, *J*=7.1 Hz), 2.95–3.10 (1H, m), 3.13–3.35 (1H, m), 4.46 (0.5H, d, *J*=17.6 Hz), 4.69–4.84 (2.5H, m), 4.89–4.95 (0.5H, m), 4.97–5.12 (1H, m), 6.65–6.80 (2H, m), 6.94–7.04 (1H, m). IR (ATR) cm^{-1}: 1627, 1554, 1506, 1378. MS *m/z*: 517 $[M+H]^+$.

(*S*)-7-{[2-(Adamantann-1-yl)-5-methyloxazol-4-yl]-methoxy}-2-(2-furylacryloyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (13gE) Yield 60%. A white solid. mp 140–142°C. *δ* (ppm): 1.01 (9H, s), 1.72–1.81 (6H, br), 1.97–2.10 (9H, br), 2.29 (3H, s), 2.94–3.10 (1H, m), 3.13–3.35 (1H, m), 4.52 (0.5H, d, *J*=17.3 Hz), 4.69–4.85 (3.5H, m), 5.00–5.13 (1H, m), 6.37–6.58 (2H, m), 6.67–7.03 (1H, m), 7.35–7.50 (2H, m). IR (ATR) cm^{-1}: 1648, 1608, 1554, 1504, 1382. MS *m/z*: 543 $[M+H]^+$.

(*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) Yield 63%. A white solid. mp 165–170°C (dec.). ^{1}H-NMR ($CDCl_3$) 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 $[M+H]^+$. *Anal.* Calcd for $C_{29}H_{38}N_2O_5 \cdot C_4H_{11}N \cdot 0.5H_2O$: C, 69.66; H, 6.82; N, 6.77. Found: C, 69.54; H, 7.00; N, 6.58.

(*S*)-2-[2-(5-Fluorofuryl)acryloyl-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (13jF) Yield 64%. A white solid. mp 168–171°C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.00 (9H, s), 1.49, 1.50 (total 3H, s, s), 2.30, 2.30 (total 3H, s, s), 2.90–3.08 (3H, m), 3.14–3.32 (1H, m), 3.53–3.65 (2H, m), 4.49 (0.5H, d, J=17.7 Hz), 4.70–4.84 (3.5H, m), 5.01–5.12 (1H, m), 5.45–5.55 (1H, m), 6.36–6.48 (1H, m), 6.60–6.79 (2H, m), 6.96–7.02 (1H, m), 7.12–7.30 (5H, m). IR (ATR) cm^{-1}: 1652, 1569, 1542, 1506, 1376. MS *m/z*: 557 $[M+H]^+$.

(*S*)-2-(2-Cyclopropylacryloyl)-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid *tert*-Butylamine Salt (13jG) Yield 65%. A white solid. mp 148–156°C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.50–0.65 (2H, m), 0.77–0.95 (2H, m), 1.04 (9H, s), 1.49, 1.50 (total 3H, s, s), 2.30, 2.31 (total 3H, s, s), 2.92–3.07 (3H, m), 3.05–3.32 (1H, m), 3.54–3.65 (2H, m), 4.46 (0.5H, d, J=17.6 Hz), 4.64–4.87 (3.5H, m), 4.94–5.08 (1H, m), 6.45–6.53 (2H, m), 6.67–6.80 (2H, m), 6.95–7.05 (1H, m), 7.12–7.27 (4H, m). IR (ATR) cm^{-1}: 1654, 1610, 1550, 1504, 1382. MS *m/z*: 513 $[M+H]^+$.

(*S*)-7-{[2-(Adamantann-1-yl)-5-methyloxazol-4-yl]-methoxy}-2-[2-(5-fluorofuryl)acryloyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Calcium Salt (13gF) To a solution of **11gE** (1.82 g, 3.17 mmol) in 1,4-dioxane (38 mL) was added 1 M aqueous lithium hydroxide solution (9.5 mL, 9.5 mmol) dropwise, and the mixture was stirred at room temperature for 2 h. The mixture was acidified with 2 M HCl and extracted with AcOEt. 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 purified by silica gel column chromatography to give the free form of **11gF** (1.65 g) as a crude oil. To a solution of the free form of **11gF** (500 mg, 0.89 mmol) in THF (25 mL) was added 0.1 M aqueous $KHCO_3$ (9.0 mL, 0.9 mmol), and the mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure, and the obtained residue was dissolved in 10% MeCN in water and passed through an ODS silica gel (Fuji Silysia, Kasugai, Japan) column chromatograph. Fractions containing the compound were collected and MeCN was evaporated under reduced pressure. To the obtained residue was added 1 M aqueous $CaCl_2$ solution (1.0 mL, 1.0 mmol) dropwise, and the mixture was stirred at room temperature for 3 h. The precipitated crystals were collected by filtration to give **11gF** (390 mg, 76% yield) as a white solid. mp 160–166°C. ^{1}H-NMR (DMSO-d_6) δ: 1.65–1.75 (6H, br), 1.86–2.05 (9H, br), 2.27 (3H, s), 2.73–2.95 (1H, m), 3.25–3.40 (1H, m), 4.52 (0.7H, d, J=18.3 Hz), 4.56–4.69 (0.7H, br), 4.70–4.95 (3.3H, m), 5.12–5.21 (0.3H, m), 5.86–5.60 (1H, m), 6.67–6.92 (4H, m), 6.96–7.06 (1H, m), 7.15–7.27 (1H, m). IR (ATR) cm^{-1}: 1648, 1608, 1569, 1544, 1502, 1427, 1384. MS *m/z*: 561 $[M+H]^+$.

Methyl [5-Methyl-2-(2,6-dimethylphenyl)oxazol-4-yl]acetate (16a) To a suspension of the 2,6-dimethylbenzoyl chloride **14a** (11.8 g, 70 mmol) and **15** (18.4 g, 100 mmol) in CH_2Cl_2 (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 M HCl and saturated brine, and dried over Na_2SO_4. 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, 9.90 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 $NaHCO_3$ 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 a crude solid (16.6 g).

To a solution of the crude solid (16.6 g) in toluene (200 mL) was added $POCl_3$ (10.0 mL, 107 mmol), which was refluxed for 1.5 h. After cooling, the mixture was poured into cold water, neutralized with K_2CO_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 **16a** (2.25 g, 12.3% yield) as an oil. ^{1}H-NMR ($CDCl_3$) 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%. ^{1}H-NMR ($CDCl_3$) 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%. ^{1}H-NMR ($CDCl_3$) 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 $NaBH_4$ (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 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 **17a** (1.60 g, 80 yield) as an oil. ^{1}H-NMR ($CDCl_3$) 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%. ^{1}H-NMR ($CDCl_3$) 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 Na_2SO_4 and then evaporated under reduced pressure to give **17c** (3.07 g, 95% yield) as an oil. ^{1}H-NMR ($CDCl_3$) 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 CH_2Cl_2 (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 Na_2SO_4. 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 (15.8 g, 416 mmol) in AcOEt (40 mL) was added **19** (10 g, 98.9 mmol) and HCl gas was bubbled through the solution at 0°C for 0.5 h. The mixture was stirred at the same temperature for 1.5 h. To the reaction mixture was added i-Pr_2O and precipitated crystals were collected by filtration to give a crude **20c** (13.8 g).

To a solution of the crude **20c** (13.8 g) in $CHCl_3$ (140 mL) was added $POCl_3$ (6.9 mL, 74.8 mmol), which was refluxed for 3 h. After cooling, the mixture was poured into cold water and extracted with AcOEt. The organic layer was washed with 1 M NaOH 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 **3c** (4.39 g, 29% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (6H, s), 2.30 (3H, s), 2.41 (3H, s), 4.57 (2H, s), 6.90 (2H, s).

Compounds **3d**–**g** were prepared according to the procedure for the synthesis of **3c**.

4-Chloromethyl-2-(1-ethyl-1-methylpropyl)-5-methyloxazole (3d) 21% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.77 (6H, t, J=7.3 Hz), 1.21 (3H, s), 1.56–1.66 (2H, m), 1.72–1.83 (2H, m), 2.30 (3H, s), 4.47 (2H, s).

4-Chloromethyl-2-(1-methyl-cyclopentan-1-yl)-5-methyloxazole (3e) 24% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, s), 1.59–1.79 (6H, m), 1.71–1.78 (2H, m), 2.30 (2H, s), 4.47 (2H, s).

4-Chloromethyl-2-(1-methyl-cyclohexan-1-yl)-5-methyloxazole (3f) 8.7% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, s), 1.35–1.62 (8H, m), 2.07–2.18 (2H, m), 2.31 (2H, s), 4.48 (2H, s).

4-Chloromethyl-2-(Adamantan-1-yl)-5-methyloxazole (3g) 11% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.70–1.80 (6H, m), 2.01 (6H, s), 2.03–2.09 (3H, br), 2.29 (3H, s), 4.47 (2H, s).

Diethyl 3,4-Dimethylcyclopent-3-ene-1,1-dicarboxylate (22) To a solution of diethyl malonate (4.57 g 28.5 mmol) in *N*,*N*-dimethylformamide (DMF) (100 mL) was added LiH (567 mg, 71.3 mmol) portionwise at room temperature, the mixture was stirred for 1 h and then **21** in DMF (10 mL) was added dropwise at the same temperature for 5 d. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with 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 **22** (3.55 g, 51% yield) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (6H, t, J=7.1), 1.59 (6H, s), 2.92 (4H, s), 4.18 (4H, q, J=7.1 Hz).

3,4-Dimethylcyclopent-3-enecarboxylic Acid (23) To a solution of **22** (3.55 g, 14.8 mmol) in MeOH (70 mL) was added potassium hydroxide (KOH) (5.85 g, 88.6 mmol) in water (25 mL) at room temperature and the mixture was stirred at 50°C for 5 h. The reaction mixture was evaporated under reduced pressure. The obtained residue was acidified with conc. HCl and extracted with AcOEt. The organic layer was washed with saturated brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure.

The obtained residue was dissolved in pyridine (25 mL) and stirred at 110°C for 3 h. After cooling to room temperature, the reaction mixture was acidified with 6 M HCl and extracted with AcOEt. The organic layer was washed with 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 **23** (1.62 g, 78% yield) as an oil. ^{1}H-NMR ($CDCl_3$) 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 K_2CO_3 (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 Et_2O. The organic layer was washed with saturated brine and dried over Na_2SO_4. 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 Et_2O. The organic layer was washed with saturated brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a crude oil (2.12 g).

To a solution of the crude oil (2.12 mmol) in THF (45 mL) and MeOH (15 mL) was added 1 M aqueous LiOH solution (20.0 mL, 20.0 mmol) at room temperature for 2 h and the mixture was stirred at 40°C for 2 h. The reaction mixture was evaporated under reduced pressure. The obtained residue was acidified with citric acid and extracted with AcOEt. The organic layer was washed with water and saturated brine, and then dried over Na_2SO_4. The obtained residue was purified by silica gel column chromatography to give **24i** (1.27 g, 82% yield, 3 steps) as an oil.

Methyl 5-Methyl-2-(Cyclopent-3-enyl)oxazole-4-carboxylate (26h) To a solution of **24h** (34.0 g, 0.27 mmol) in CH_2Cl_2 (370 mL) was added $(COCl)_2$ (23.2 mL, 270 mmol) and DMF (3 mL) at room temperature, which was stirred for 1 h. To the reaction mixture was added **25** (37.7 g, 230 mmol) and i-Pr_2NEt (99 mL, 580 mmol) at 0°C and stirred for 1 h. The reaction mixture was washed with 10% citric acid in water, dried over Na_2SO_4 and then evaporated under reduced pressure. The solution of the obtained residue in CH_2Cl_2 (140 mL) was added dropwise to a solution of I_2 (164 g, 650 mmol), PPh_3 (171 g,

650 mmol) and Et_3N (183 mL, 1.31 mol) in CH_2Cl_2 (1.0 L) at 0°C and stirred for 0.5 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and then evaporated under reduced pressure. To the obtained residue was added *i*-Pr_2O, precipitated crystals were filtered out and the filtrate was purified by silica gel column chromatography to give **26h** (29.9 g, 61% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, s), 2.38–2.47 (2H, m), 2.60 (3H, s), 2.99–3.06 (2H, m), 3.89 (3H, s), 5.66 (2H, s).

Compounds **26i** and **j** were prepared according to the procedure for the synthesis of **26h**.

Methyl 5-Methyl-2-(1,3,4-trimethylcyclopent-3-enyl)-oxazole-4-carboxylate (26i) Fifty percent yield. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, s), 1.61 (6H, s), 2.30 (2H, d, *J*=14.9 Hz), 2.60 (3H, s), 3.01 (2H, d, *J*=14.9 Hz), 3.89 (3H, s).

Methyl 5-Methyl-2-(1-methylindan-2-yl)oxazole-4-carboxylate (26j) 46% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (3H, s), 2.61 (3H, s), 2.99 (2H, d, *J*=16.0 Hz), 3.62 (2H, d, *J*=16.0 Hz), 3.89 (3H, s), 7.12–7.26 (4H, m).

4-Chloromethyl-5-methyl-2-(cyclopent-3-en-1-yl)oxazole (3h) To a suspension of lithium aluminum hydride (5.84 g, 150 mmol) in THF (500 mL) was added a solution of **16h** (29.9 g, 140 mmol) in THF (100 mL) below 25°C, and stirred at the same temperature for 1 h. To the reaction mixture was added cold water and AcOEt. 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 give a crude **17h** (25.3 g).

To a solution of the crude **17h** (25.3 g) in CH_2Cl_2 (250 mL) was added SO_2Cl_2 (11.4 g, 160 mmol) dropwise below 30°C. The mixture was poured into water, neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and then evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give **3h** (22.9 g, 79% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, s), 2.31 (3H, s), 2.36–2.46 (2H, m), 2.94–3.04 (2H, m), 4.47 (2H, s), 5.66 (2H, s).

4-Chloromethyl-5-methyl-2-(1,3,4-trimethylcyclopent-3-enyl)oxazole (3i) 99% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, s), 1.61 (6H, s), 2.28 (2H, d, *J*=14.9 Hz), 2.31 (3H, s), 2.98 (2H, d, *J*=14.9 Hz), 4.48 (2H, s).

4-Chloromethyl-5-methyl-2-(1-methylindan-2-yl)oxazole (3j) Quant. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (3H, s), 2.32 (3H, s), 2.98 (2H, d, *J*=16.0 Hz), 3.59 (2H, d, *J*=16.0 Hz), 4.47 (2H, s), 7.13–7.26 (4H, m)

Ethyl 5-(2-*tert*-Butoxycarbonylvinyl)furan-2-carboxylate (28) Compound **27** (121 g, 556 mmol), *tert*-butyl acrylate (500 mL, 3.43 mol), $Pd(OAc)_2$ (12.5 g, 55.6 mmol), tri(*o*-tolyl)-phosphine (67.7 g, 222 mmol), *i*-Pr_2NEt (284 mL, 1.67 mol) and LiCl (70.8 g, 1.67 mol) were dissolved in DMF (1.1 L) under a nitrogen atmosphere and stirred at 130°C for 0.5 h. After cooling to room temperature, water and Et_2O were added to the reaction mixture, and passed through Celite. The filtrate was separated into two layers, and the organic layer was washed with 10% citric acid in water, 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 **28** (110.2 g, 74% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, *J*=7.6 Hz), 1.52 (9H, s), 4.37 (2H, q, *J*=7.6 Hz), 6.48 (1H, d, *J*=15.8 Hz), 6.62 (1H, d, *J*=3.4 Hz), 7.16 (1H, d, *J*=3.4 Hz), 7.32 (1H, d, *J*=15.8 Hz).

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 Na_2SO_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*-butoxycarbonylvinyl)furan-2-carboxylic acid (83.3 g, 84% yield) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 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 5-(2-*tert*-butoxycarbonylvinyl)furan-2-carboxylic acid (83.3 g, 350 mmol) in Et_2O (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 Na_2SO_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. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (9H, s), 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-Fluorofuryl)acrylic Acid (8F) To a solution of *tert*-butyl 3-(5-fluorofuryl)acrylate (20.0 g, 94.2 mmol) in CH_2Cl_2 (200 mL) was added TFA (70 mL, 942 mmol) at 0°C and the mixture was stirred for 1.5 h. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give a crude **8F**. *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. ^{1}H-NMR ($CDCl_3$) δ: 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_2CO_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 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 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 Na_2SO_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. ^{1}H-NMR ($CDCl_3$) δ: 1.42, 1.51 (9H, s, s), 3.00–3.25 (2H, m), 4.43 (1H, dd, *J*=16.6, 7.8 Hz),

4.64 (1H, dd, J=16.6, 7.8 Hz), 4.70–4.78 (0.5H, m), 5.01 (2H, s), 5.05–5.12 (0.5H, m), 6.70–6.83 (2H, m), 7.05 (1H, d, J=8.3 Hz), 7.27–7.44 (5H, m).

7-Benzyloxy-2-*tert*-butoxycarbonyl-*N*-methoxy-*N*-methyl-tetrahydroisoquinoline-3-carboxamide (29) To a solution of 7-benzyl-2-*tert*-butoxycarbonyl-tetrahydroisoquinoline-3-carboxylic acid (25.0 g, 65.2 mmol) in CH_2Cl_2 (250 mL) was added *N*,*O*-dimethylhydroxylamine (7.63 g, 78.2 mmol), Et_3N (11.8 mL, 84.8 mmol) and EDC·HCl (16.3 g, 84.8 mmol) under ice-cooling, and the mixture was stirred at room temperature for 2 h. The reaction mixture was washed with 10% citric acid in water, and 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 **29** (9.11 g, 33% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.45, 1.50 (total 9H, s, s), 2.85–3.05 (1H, m), 3.07–3.18 (4H, m), 3.76, 3.83 (total 3H, s, s), 4.45–4.90 (2.5H, m), 5.03 (2H, s), 5.18–5.26 (0.5H, m), 6.75–6.85 (2H, m), 7.00–7.06 (1H, m), 7.27–7.44 (5H, m).

3-Acetyl-2-*tert*-butoxycarbonyl-7-benzyloxy-tetrahydroisoquinoline To a solution of **29** (5.0 g, 11.7 mmol) in THF (100 mL) was added 3.0 M MeMgI in Et_2O (19.5 mL, 58.5 mmol) at 0°C and the mixture was stirred at room temperature for 12 h. To the reaction mixture was added 10% citric acid in water at 0°C and extracted with AcOEt. The organic layer was washed with 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 3-acetyl-2-*tert*-butoxycarbonyl-7-benzyloxy-tetrahydroisoquinoline (4.07 g, 91% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.45, 1.52 (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), 7.01–7.07 (1H, m), 7.29–7.44 (5H, m).

3-Acetyl-2-*tert*-butoxycarbonyl-7-hydroxy-tetrahydroisoquinoline (30) 3-Acetyl-2-*tert*-butoxycarbonyl-7-benzyloxy-tetrahydroisoquinoline (4.07 g, 10.7 mmol) in MeOH (80 mL) was hydrogenated at 0.4 MPa in the presence of 10% Pd–C (814 mg) at room temperature for 2 h. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure to give crude **30** (2.93 g) as an oil. Crude **30** was used in subsequent reactions without further purification.

2-*tert*-Butoxycarbonyl-3-(1,1-difluoroethyl)-7-hydroxy-tetrahydroisoquinoline (31) To a solution of **30** (2.0 g, 6.86 mmol) in CH_2Cl_2 (20 mL) was added DAST (2.70 mL, 20.6 mmol) at 0°C. The mixture was stirred at room temperature for 18 h, and then DAST (2.70 mL, 20.6 mmol) was again added to the mixture. The reaction mixture was stirred at room temperature for 18 h, poured into saturated $NaHCO_3$ solution and extracted with AcOEt. The organic layer was washed with 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 **31** (620 mg, 29% yield) as a solid. ^{1}H-NMR ($CDCl_3$) δ: 1.45–1.65 (12H, m), 2.88–3.07 (2H, m), 4.07–4.20 (1H, m), 4.50–5.00 (2H, m), 6.52–6.70 (2H, m), 7.00 (1H, d, J=8.3 Hz).

(*S*)-3-Acetyl-2-*tert*-butoxycarbonyl-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline was prepared according to the procedure for the synthesis of **5j**.

(*S*)-3-Acetyl-2-(2-furylacryloyl)-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline (32) To a solution of (*S*)-3-acetyl-2-*tert*-butoxycarbonyl-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline (955 mg, 1.85 mmol) in formic acid (3 mL) was added 8.6 M hydrogen chloride solution in 2-propanol (0.65 mL, 5.55 mmol) under ice-cooling, and the mixture was stirred at room temperature for 15 min. 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_2SO_4. The solvent was evaporated under reduced pressure, and Et_2O was added to the obtained residue and the mixture was stirred at room temperature for 1 h. The precipitated crystals were collected by filtration to give (*S*)-3-acetyl-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.699 mg, 92% yield) as a white solid.

To a solution of 2-furylacrylic acid (150 mg, 1.09 mmol) in CH_2Cl_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 (*S*)-3-acetyl-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetrahydroiso quinoline hydrochloride (340 mg, 0.720 mmol) and Et_3N (0.51 mL, 3.62 mol) at 0°C and stirred at room temperature for 2 h. To the reaction mixture was added AcOEt, 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 **32** (240 mg, 76% yield) as a white solid. mp 51–52°C. ^{1}H-NMR ($CDCl_3$) δ: 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=15.6 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 (3H, 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 for 0.5 h. To the reaction mixture was added water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_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, Kyoto, Japan), a UV detector (SPD-10Avp; 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_2PO_4 aq.–MeCN (4 : 6) was used. mp 67–69°C. ^{1}H-NMR ($CDCl_3$) δ: 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**.

(*S*)-3-Difluoroethyl-2-(2-furylacryloyl)-7-[2-(2-methylindane-2-yl)-5-methyloxazol-4-yl]methoxy-1,2,3,4-tetra-

hydroisoquinoline (34) Yield 56%. A white solid. mp 50–52°C. ^{1}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=19.2 Hz), 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 $[M+H]^+$.

PPARγ, PPARα and PPARδ Agonist Activity Full-length human PPARγ1 plasmid (Open Biosystems, Huntsville, U.S.A.), human PPARα plasmid (GeneCopoeia Inc., Rockville, U.S.A.) or human PPARδ plasmid (GeneCopoeia Inc.), 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 Nucleofector II (AAD-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 LT7.5; 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 PPARγ agonist (10^{-7} M), Wy-14643, a PPARδ agonist (10^{-5} M), or GW-501516, a PPARδ 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 dithiothreitol 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.[39] 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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