Bioorganic & Medicinal Chemistry 20 (2012) 1060–1075

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Novel (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids: Peroxisome proliferator-activated receptor γ selective agonists with protein-tyrosine phosphatase 1B inhibition

Kazuya Otake, Satoru Azukizawa, Masaki Fukui, Kazuyoshi Kunishiro, Hikaru Kamemoto, Mamoru Kanda, Tomohiro Miike, Masayasu Kasai, Hiroaki Shirahase *

Research Laboratories, Kyoto Pharmaceutical Industries, Ltd, 38, Nishinokyo Tsukinowa-cho, Nakagyo-ku, Kyoto 604-8444, Japan

ARTICLE INFO

Article history:
Received 20 September 2011
Revised 15 November 2011
Accepted 17 November 2011
Available online 1 December 2011

Keywords:
Tetrahydroisoquinoline derivative
Peroxisome proliferators-activated receptor γ agonist
Protein-tyrosine phosphatase 1B inhibitor
Diabetes
Hemodilution
KK-A^{y} mouse
SD rat

ABSTRACT

A novel series of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives were synthesized and (*S*)-2-[(2*E*,4*E*)-hexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**14i**) was identified as a potent human peroxisome proliferator-activated receptor γ (PPARγ) selective agonist (EC_{50} = 0.03 μM) and human protein-tyrosine phosphatase 1B (PTP-1B) inhibitor (IC_{50} = 1.18 μM). C_{max} after oral administration of **14i** at 10 mg/kg was 2.2 μg/ml (4.5 μM) in male SD rats. Repeated administration of **14i** and rosiglitazone for 14 days dose-dependently decreased plasma glucose levels, ED_{50} = 4.3 and 23 mg/kg/day, respectively, in male KK-A^{y} mice. In female SD rats, repeated administration of **14i** at 12.5–100 mg/kg/day for 28 days had no effect on the hematocrit value (Ht) and red blood cell count (RBC), while rosiglitazone significantly decreased them from 25 mg/kg/day. In conclusion, **14i** showed about a fivefold stronger hypoglycemic effect and fourfold or more weaker hemodilution effect than rosiglitazone, indicating that **14i** is 20-fold or more safer than rosiglitazone. Compound **14i** is a promising candidate for an efficacious and safe anti-diabetic drug targeting PPARγ and PTP-1B.

1. Introduction

Thiazolidinedione (TZD) derivatives such as rosiglitazone (Fig. 1) are known to enhance insulin sensitivity by the activation of peroxisome proliferator-activated receptor γ (PPARγ) in adipocytes, resulting in the reduction of blood glucose levels in type 2 diabetic patients[1–3]; however, TZD derivatives cause edema, increase the risk of weight gain and congestive heart failure, and rarely cause hepatotoxicity.[4–7]

In recent years, many efforts have been made to develop a PPARα/γ dual agonist. PPARα is expressed in the liver and related to fatty acid metabolism[8]; fibrates have been used as anti-hyperlipidemic drugs, and are known to exert their effects via PPARα activation. PPARα agonists also improved insulin resistance in experimental animals, and showed hypoglycemic and insulin-resistance-improving effects in diabetic patients.[9–11] PPARα agonists have a body weight-reducing effect, while PPARγ agonists have a body weight-increasing risk.[12] Thus, the combination of PPARα and PPARγ agonistic activities has been expected to show synergenistic anti-diabetic effects with high safety.[13,14] Many carboxylic acid derivatives have been reported as PPARα/γ dual agonists; however, none have been developed successfully due to carcinogenicity, the risk for cardiovascular events, the potential risk of liver injury and/or renal dysfunction.[15–19] PPARα is expressed in the liver, heart and kidney[20]; excess activation of PPARα as well as PPARγ may lead to carcinogenesis and to adverse effects on the liver, heart and kidney.[14,21–24] We have reported that (*S*)-2-[(2*E*,4*E*)-hexadienoyl]-7-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (compound **1**, Fig. 1) is a PPARα/γ agonist (PPARγ EC_{50}: 0.16 μM, PPARα: 0.38 μM, respectively) with weak PTP-1B inhibitory activity (IC_{50}: 9.4 μM).[25] PTP-1B is known to play a role in cancellation of the insulin signal and its overexpression has been reported to be involved in insulin resistance; thus, PTP-1B inhibitors have been focused on as insulin-sensitivity enhancers. A PPARα/γ agonist with PTP-1B inhibitory activity is considered to show effective anti-diabetic activities with high safety, since PTP-1B inhibition may exert synergestic insulin-sensitizing effects with PPARγ activation without causing PPARγ-dependent adverse effects.[26] However, activation of both PPARγ and PPARα may have risks for carcinogenesis and/or cardiovascular adverse effects to some extent. Thus, a selective PPARγ agonist, rather than a PPARα/γ dual agonist, with PTP-1B inhibitory activity is an alternative candidate for a new

* Corresponding author. Tel.: +81 075 812 2247.
E-mail address: shirahase@kyoto-pharm.co.jp (H. Shirahase).

0968-0896/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2011.11.035

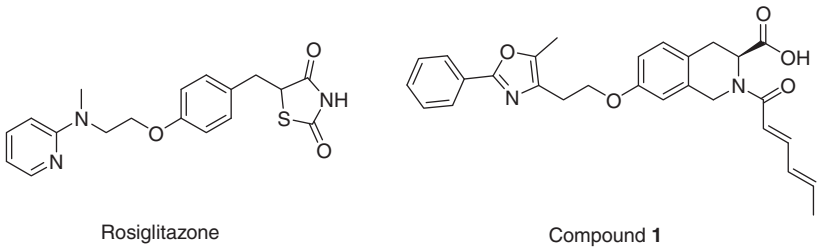


Figure 1. Chemical structures of rosiglitazone and compound **1**.

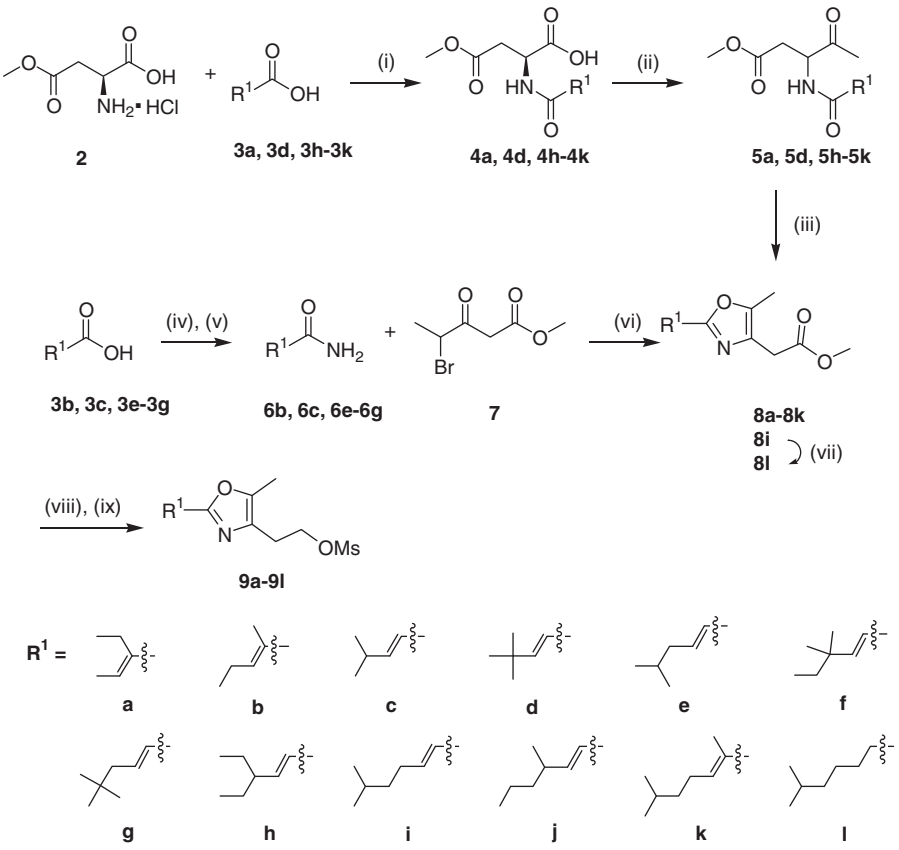
efficacious and safe insulin-sensitivity enhancer. We have synthesized a new series of tetrahydroisoquinoline derivatives with a 2-alkylvinyloxazole group at the 7-position and an acyl group at the 2-position, and found that (*S*)-2-[(2*E*,4*E*)-hexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2, 3,4-tetrahydroisoquinoline-3-carboxylic acid (**14i**) showed potent human PPARγ selective agonist activity and human PTP-1B inhibitory activity, which were both much stronger than compound **1**.

2. Chemistry

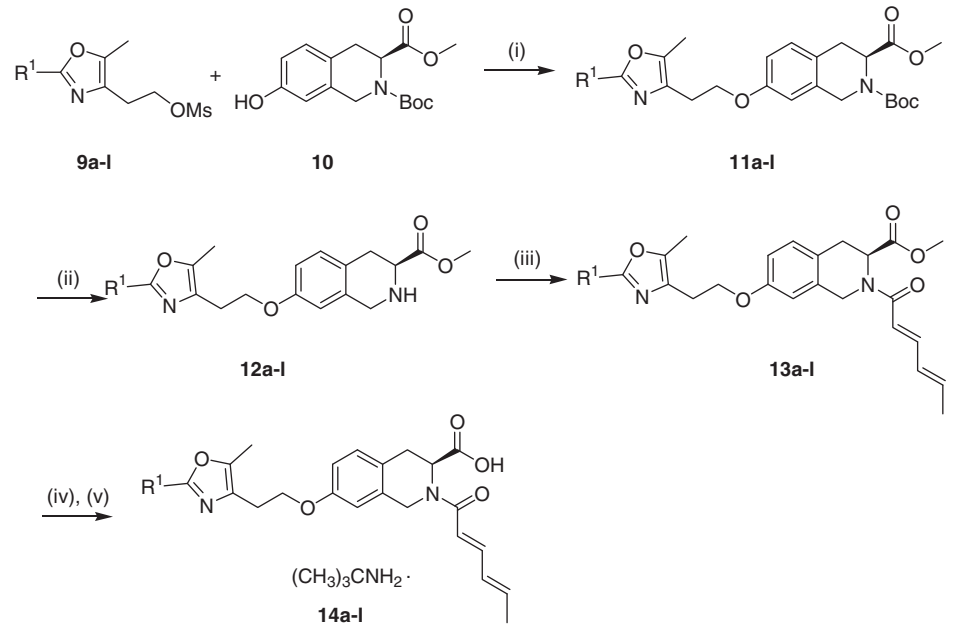
(*S*)-2,7-Substituted-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives (**14a**–**14l**, **16a**–**16n**) were synthesized by alkylation of methyl (*S*)-2-*tert*-butoxycarbonyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**10**)[27] at the 7-position with 2-(2-substituted-5-methyloxazol-4-yl)ethyl methanesulfonate (**9a**–**9l**), followed by conversion of the *tert*-butoxycarbonyl (Boc) group to various acyl groups at the 2-position, and hydrolysis of the methyl ester.

The general approach to the synthesis of **9a**–**9l** is outlined in Scheme 1. Acylation of L-aspartic acid β-methyl ester (**2**) with **3a**, **3d** and **3h**–**3k** afforded **4a**, **4d** and **4h**–**4k**, respectively**.** The carboxylic acid was transformed to methylketone by the Dakin–West reaction; **4a**, **4d** and **4h**–**k** were treated with acetic anhydride and bases to give **5a**, **5d** and **5h**–**5k**, respectively. Treatment of **5a**, **5d** and **5h**–**5k** with phosphorous oxychloride afforded oxazole derivatives (**8a**, **8d**, **8h**–**8k**). Amidation of **3b**, **3c** and **3e**–**3g** afforded **6b**, **6c**, **6e**–**6g**, which were treated with methyl 4-bromo-3-oxo-pentanoate (**7**) to give oxazole derivatives (**8b**, **8c**, **8e**–**8g**). Hydrogenation of **8i** afforded **8l**. Reduction of **8a**–**8l** with diisobutyl aluminum hydride (DIBAH) and methanesulfonylation afforded methanesulfonates (**9a**–**9l**).

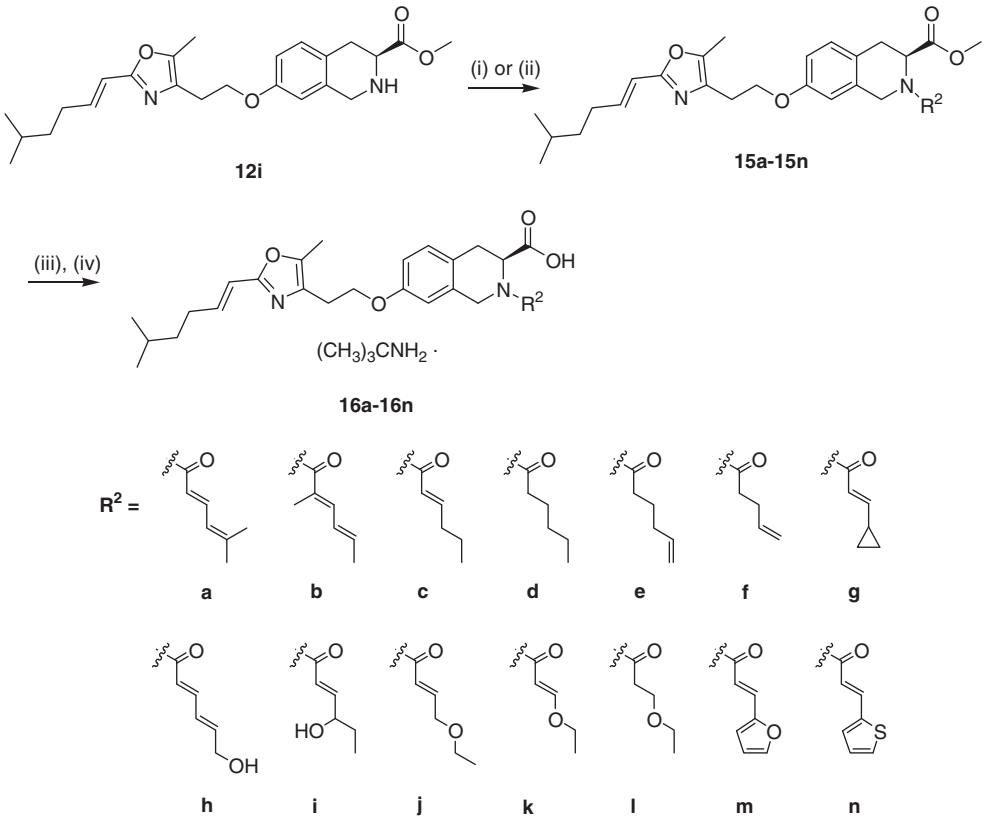
The general approach to the synthesis of **14a**–**14l** and **16a**–**16n** is outlined in Scheme 2 and Scheme 3, respectively. Alkylation of **10** with **9a**–**9l** in the presence of K_2CO_3 and



Scheme 1. Synthesis of 2-(2-substituted-5-methyloxazol-4-yl)ethyl methanesulfonates. Reagents and conditions: (i) *i*-BuOCOCl, Et_3N, CH_2Cl_2; (ii) Ac_2O, *N*-methylmorpholine, DMAP, toluene; (iii) $POCl_3$, toluene; (iv) $SOCl_2$; (v) NH_3 aq.; (vi) toluene; (vii) Pd–C, H_2, MeOH; (viii) DIBAH, toluene; (ix) MsCl, Et_3N, CH_2Cl_2.



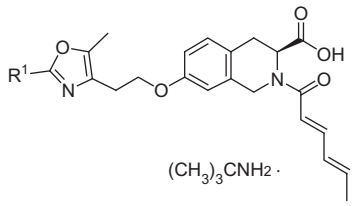
Scheme 2. Synthesis of 7-substituted-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids. R^1 is shown in Chart 1. Reagents and conditions: (i) K_2CO_3, tetraethylammonium fluoride, toluene; (ii) HCl, HCO_2H; (iii) hexadienoyl chloride, Et_3N, CH_2Cl_2; (iv) LiOH aq., THF–MeOH; (v) *tert*-$BuNH_2$, MeOH–*i*-Pr_2O.

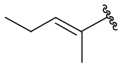
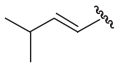
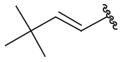
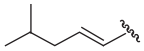
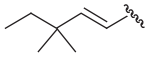
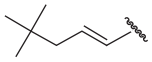
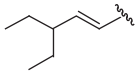
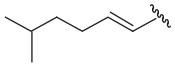
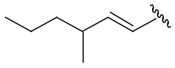
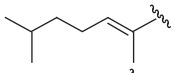
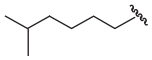


Scheme 3. Synthesis of 2-substituted-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids. Reagents and conditions: (i) various carboxylic acids, EDC·HCl, CH_2Cl_2; (ii) acyl chloride, Et_3N, CH_2Cl_2; (iii) LiOH aq., THF–MeOH; (iv) *tert*-$BuNH_2$, MeOH–*i*-Pr_2O.

tetraethylammonium fluoride afforded **11a–11l** in good yield. The Boc group of **11a–11l** was removed with HCl/HCO_2H, affording **12a–12l**, which were treated with acyl chloride and triethylamine, or carboxylic acid and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), to give **13a–13l** and **15a–15n**, which were treated with aqueous LiOH to give carboxylic acid derivatives, and then **14a–14l** and **16a–16n** were isolated as *tert*-butylamine salts.

Table 1
Molecular weight, log$D_{7.0}$, PPARγ and PPARα transactivation effects and hypoglycemic effects in KK-A^y mice of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids with various side chains containing the branched structure at the 2-position of oxazole moiety



Compound	R[1]	M.W.[a]	Log$D_{7.0}$	PPARγ[b]		PPARα[b]		PTP-1B[b]	KK-A^y mice (10 mg/kg, 4 days)[g]
				EC_{50} (μM)	Max[c] (%)	EC_{50} (μM)	Max[d] (%)	IC_{50} (μM)	Glucose %decrease
14a		464.55	2.75	0.35	91	—[e]	<50[f]	5.60	47**
14b		464.55	2.88	0.12	96	—[e]	<50[f]	4.40	40
14c		464.55	2.77	0.67	104	0.30	62	2.20	38*
14d		478.58	3.10	0.54	97	—[e]	<50[f]	2.25	23
14e		478.58	3.23	0.16	103	0.24	81	2.00	58**
14f		492.61	3.52	0.76	77	—[e]	<50[f]	1.2	16
14g		492.61	3.59	0.16	92	—[e]	<50[f]	1.95	39**
14h		492.61	3.68	0.76	90	—[e]	66[f]	1.30	18
14i		492.61	3.81	0.03	98	—[e]	<50[f]	1.18	55**
14j		492.61	3.84	0.31	82	—[e]	<50[f]	1.41	71**
14k		506.63	4.29	0.02	119	—[e]	<50[f]	1.02	56**
14l		494.62	3.79	0.11	89	—[e]	<50[f]	1.15	17
Rosiglitazone		357.43	NT	0.12	136	—[e]	105[f]	>30	48**
Ertiprotafib		559.51	NT	NT	NT	NT	NT	0.41	NT

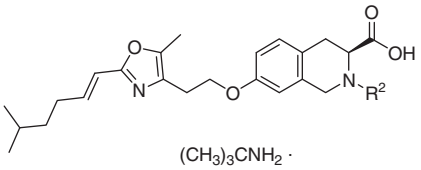
NT: not tested.
[a] Molecular weight as free form.
[b] $n = 2$.
[c] The activation level induced by farglitazar (10^{-7} M) was taken as 100%.
[d] The activation level induced by Wy-14643 (10^{-5} M) was taken as 100%.
[e] The EC_{50} value was not determined, since the response did not reach the plateau level at 10^{-5} M.
[f] Response induced at 10^{-5} M.
[g] $n = 5$.
* $p < 0.05$.
** $p < 0.01$, versus control, Student's *t*-test.

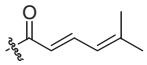
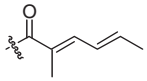
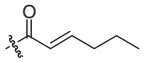
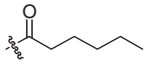
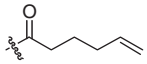
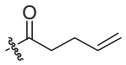
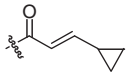
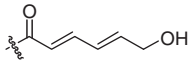
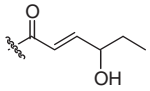
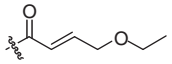
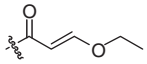
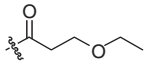
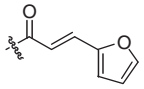
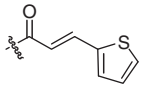
3. Results and discussion

In the present study, a novel series of tetrahydroisoquinoline derivatives with a branched alkyl or alkenyl group were synthesized and evaluated to find novel PPARγ agonists with PTP-1B inhibitory activity. PPARγ agonist activity was determined as transactivation activity in COS-1 cells transfected with full-length human PPARγ1 plasmid or human PPARα plasmid, and human RXRα plasmid with reporter plasmid pGL3-PPREx4-tk-luc; EC_{50} and the maximal activation level relative to the level activated by farglitazar, a PPARγ agonist (10^{-7} M), or Wy-14643, a PPARα agonist (10^{-5} M) were determined. The inhibitory effects of the compounds on PTP-1B activities were also examined: PTP-1B inhibition is expected to enhance insulin sensitivity. Glucose-lowering effects of derivatives were examined in KK-A^y mice, a type 2 diabetic model animal, and expressed as a % decrease in glucose in comparison with control mice administered a vehicle. All animal experiments in the present study were conducted according to the guidelines for animal experiments of our institute and the guidelines for animal experimentation approved by the Japanese Association of Laboratory Animal Science.

Branched aliphatic chains consisting of 5–8 carbon atoms were introduced at the 2-position of the oxazole ring (Table 1). Compound **14a** with a 1-ethylpropenyl group showed about threefold weaker PPARγ agonist activity than rosiglitazone. 1-Methylbutenyl group (**14b**) markedly increased the activity, which was

Table 2
Molecular weight, log $D_{7.0}$, PPARγ and PPARα transactivation effects and hypoglycemic effects in KK-A^y mice of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids with various side chains at the 2-position of 1,2,3,4-tetrahydroisoquinoline moiety



Compound	R^2	M.W.[a]	Log $D_{7.0}$	PPARγ[b]		PPARα[b]		PTP-1B[b]	KK-A^y mice (10 mg/kg, 4 days)[g]
				EC_{50} (μM)	Max[c] (%)	EC_{50} (μM)	Max[d] (%)	IC_{50} (μM)	Glucose %decrease
16a		506.63	4.09	0.03	85	0.10	64	0.95	44**
16b		506.63	4.10	0.05	98	—[e]	<50[f]	2.03	21
16c		494.42	4.04	0.03	96	—[e]	<50[f]	1.18	50**
16d		496.64	4.34	0.02	94	—[e]	<50[f]	0.94	30
16e		494.42	4.03	0.05	106	—[e]	<50[f]	1.43	22
16f		480.60	3.76	0.04	105	—[e]	<50[f]	1.69	45**
16g		492.61	3.69	0.07	84	—[e]	<50[f]	1.05	27
16h		508.61	3.09	—[e]	61[f]	—[e]	<50[f]	3.20	14
16i		510.62	3.33	0.24	104	—[e]	<50[f]	6.20	19
16j		510.62	3.52	0.09	108	—[e]	<50[f]	3.80	3
16k		496.60	3.56	0.02	101	—[e]	<50[f]	2.55	33
16l		498.61	3.48	0.07	86	—[e]	<50[f]	3.35	−13
16m		518.60	3.76	0.07	102	—[e]	<50[f]	0.57	29
16n		534.67	3.95	0.04	99	—[e]	<50[f]	1.05	45**

[a] Molecular weight as free form.
[b] $n = 2$.
[c] The activation level induced by farglitazar (10^{-7} M) was taken as 100%.
[d] The activation level induced by Wy-14643 (10^{-5} M) was taken as 100%.
[e] The EC_{50} value was not determined, since the response did not reach the plateau level at 10^{-5} M.
[f] Response induced at 10^{-5} M.
[g] $n = 5$.
* $p < 0.05$.
** $p < 0.01$, versus control, Student's *t*-test.

comparable to that of rosiglitazone, suggesting that a longer alkenyl chain and shorter 1-alkyl chain were favorable for PPARγ agonist activity. However, 3-methyl and 3,3-dimethylbutenyl groups (**14c** and **14d**), and 3,3-dimethyl and 3-ethylpentenyl groups (**14f** and **14h**) decreased the activity, indicating that 3-alkyl groups disturbed the interaction of compounds with PPARγ protein. Alkenyl chains increased the activity dependent on chain length (**14c**, **14e** and **14i**). 4-Methyl and 4,4-dimethylpentenyl groups (**14e** and **14g**) showed similar activity. Among the compounds, **14i** with 5-methylhexenyl and **14k** with 1,5-dimethylhexenyl showed the most potent PPARγ agonist activity, which was 4- to 8-fold stronger than that of rosiglitazone and compound **1**, and 5-methyhexyl (reduction of vinyl moiety) (**14l** vs **14i**) and 3-methylhexenyl (**14j** vs **14i**) reduced the activity. Compounds **14c**, **14e** and **14h**

activated PPARα to levels higher than 50%, indicating that these are weak PPARα/γ dual agonists; however, the maximal PPARα activation levels by other compounds remained less than 50% even at 10 μM, indicating that these are selective PPARγ agonists. Among compounds with an isopropyl group at the end of the chain, **14i** with 5-methylhexenyl and **14k** with 1,5-dimethylhexenyl moieties appear to be suitable for interaction with PPARγ protein, while **14c** and **14e** with shorter chains may be preferable for interaction with PPARα protein. In PPARγ agonists with phenyl oxazole moiety, a phenyl ring interacts with the hydrophobic region of PPARγ protein consisting of hydrophobic amino acids such as Ile281, Ile341 and Met348 residues.[28] From the present results, the 5-methylhexenyl chain, a relatively long flexible chain structure, was considered to be more preferable for interaction with PPARγ protein than a phenyl ring, which is a plane structure. Compounds **14f**, **14i**, **14k** and **14l** had stronger PTP-1B inhibitory activity (IC_{50} = about 1 μM) than other compounds and compound **1**. Although the structure–activity relationships were not clear, the number of carbons in the chain (bulkiness or lipophilicity) are probably related to the activity. PTP-1B catalyzes the hydrolyzation of a protein-tyrosine phsophate, thus most PTP-1B inhibitors have a phosphonate or phosphonate-like moiety such as carboxylate or isothiazolidinone, and lipophilic moiety, which bind to Arg221 at a catalytic site and hydrophobic region, respectively.[29,30] The present compounds also have a carboxylic acid group and two lipophilic side chains, which are considered to interact at the catalytic site and hydrophobic region of PTP-1B, respectively.

Among these compounds, **14a**–**14c**, **14e**, **14g** and **14i**–**14k** at 10 mg/kg markedly reduced the plasma glucose level in KK-A^y mice. These hypoglycemic effects are mediated mainly by PPARγ activation and possibly by PTP-1B inhibition. However, hypoglycemic effects were not necessarily dependent on PPARγ agonist activities and PTP-1B inhibitory activities; oral absorbability may greatly differ among the compounds. In compounds **14c** and **14e** with PPARγ and PPARα activation, PPARα activation was unlikely to be involved in their hypoglycemic effects, since neither activated mouse PPARα (data not shown). Compound **14i** was considered to be the best candidate for a selective PPARγ agonist with PTP-1B inhibitory activity; its PPARγ agonist activity was 4- and 5-fold stronger than rosiglitazone and compound **1**, and its PTP-1B inhibitory activity was eightfold stronger than compound **1** and threefold weaker than ertiprotafib.

In the next set of experiments, the hexadienoyl group at the 2-position of **14i** was replaced by various acyl moieties (Table 2). Addition of a methyl group (**16a**, **16b**), reduction of double bonds (**16c**, **16d**), change of double bond position (**16e**, **16f**), change of propenyl to cyclopropyl (**16g**), insertion of an ether structure (**16j**, **16k**, **16l**) and addition of furan and thiophene (**16m**, **16n**) had little effect on the PPARγ agonist activity of **14i**. Addition of a hydroxyl group (**16h**, **16i**) markedly reduced the activity. On the other hand, only **16a** showed PPARα agonist activity, and was therefore considered to be a PPARα/γ dual agonist. Among the compounds, **16a**, **16c**, **16d**, **16g**, **16m**, and **16n** had strong PTP-1B inhibitory activity (IC_{50}: about 1 μM) comparable to that of compound **14i**. In compounds containing a hydroxyl group or ether structure (**16h**–**16l**), PTP-1B inhibitory activity was greatly reduced in comparison with **14i**, probably due to the reduction of lipophilicity. Compounds **16a**, **16c**, **16f** and **16n** showed significant hypoglycemic effects, slightly weaker than **14i** in KK-A^y mice. The other compounds with high PPARγ agonist and PTP-1B inhibitory activities failed to reduce plasma glucose probably due to low oral absorption. Finally, **14i** was chosen for further evaluation as a selective PPARγ agonist with PTP-1B inhibitory activity.

Compound **14i** and rosiglitazone (3–30 mg/kg for 14 days) dose-dependently reduced plasma glucose and triglyceride (TG) in male KK-A^y mice, and the effects of **14i** were about fivefold stronger than rosiglitazone (Table 3). Repeated administration of **14i** at 12.5–100 mg/kg/day for 28 days had no effects on hematocrit values (Ht) and red blood cell counts (RBC) in female SD rats, while rosiglitazone significantly reduced them from 25 mg/kg/day (Table 4). These results demonstrated that the hemodilution effects of **14i** were fourfold or more weaker than rosiglitazone. Based on data of hypoglycemic and hemodilution effects, **14i** was concluded to be 20-fold or more safer than rosiglitazone, although the reason why **14i** was more potent and safer than rosiglitazone remains to be determined. The PPARγ agonist activity of **14i** was about fourfold stronger than rosiglitazone, and adipocyte differentiation activity was comparable to rosiglitazone (data not shown); however, C_{max} after oral administration of **14i** at 10 mg/kg was much lower than that of rosiglitazone in male SD rats: 2.2 μg/ml (4.5 μM) and 12.4 μg/ml (34.7 μM), respectively. The C_{max} of **14i** exceeded its IC_{50} values for PTP-1B inhibition, suggesting that PTP-1B inhibitory activity may potentiate hypoglycemic effects without causing side effects. Further study is needed to clarify the involvement of PTP-1B inhibitory activity in the anti-diabetic effects of **14i**.

In conclusion, a new series of tetrahydroisoquinoline derivatives were synthesized and **14i** was found to be a selective PPARγ agonist with potent PTP-1B inhibitory effects. Structurally, a branched alkenyl moiety was demonstrated to be more suitable than a phenyl group for interaction with PPARγ receptor and PTP-1B protein. Compound **14i** showed greater hypoglycemic and hypolipidemic effects in KK-A^y mice, and weaker hemodilution effects in SD rats than rosiglitazone: **14i** was 20-fold or more safer as an anti-diabetic PPARγ agonist than rosiglitazone, probably due to

Table 3
Effects of repeated administration of **14i** and Rosiglitazone for 14 days on plasma glucose and triglyceride levels in male KK-A^y mice

	Dose (mg/kg)	Glucose (mg/dl)	Triglyceride (mg/dl)
Control		648.4 ± 77.1	819.9 ± 135.5
14i	3	385.2 ± 46.3**	625.6 ± 136.3
	10	273.7 ± 64.8**	243.8 ± 55.6**
	30	252.5 ± 49.2**	318.4 ± 53.7*
	ED_{50} (mg/kg)	4.3	6.2
Rosiglitazone	3	413.5 ± 25.7**	593.3 ± 132.4
	10	392.9 ± 47.5**	672.3 ± 60.5
	30	320.6 ± 32.8**	504.9 ± 83.2
	ED_{50} (mg/kg)	23	>30

Mean ± SE (n = 4).
* p <0.05.
** p <0.01, versus control, Student's t-test.

Table 4
Effects of repeated administration of **14i** and Rosiglitazone administered for 28 days in female SD rats

	Dose (mg/kg)	Ht (%)	RBC ($\times 10^4$/μl)
14i	0	49.4 ± 0.4	862 ± 21.5
	12.5	49.7 ± 0.9	868 ± 23.7
	25	47.1 ± 1.3	807 ± 33.2
	50	48.2 ± 1.0	835 ± 15.7
	100	47.8 ± 1.2	817 ± 26.0
Rosiglitazone	0	47.5 ± 0.6	832 ± 25.2
	12.5	46.3 ± 0.7	791 ± 6.8
	25	43.9 ± 1.1*	727 ± 13.8**
	50	43.1 ± 1.6*	724 ± 28.4*
	100	42.3 ± 0.9**	679 ± 27.8**

Mean ± SE (n = 5).
* p <0.05.
** p <0.01, versus control, Student's t-test.

the synergestic effects of PPARγ agonist and PTP-1B inhibitory activity, and is thus expected to be a new efficacious and safe anti-diabetic insulin-sensitivity enhancer.

4. Experimental section

4.1. General procedures

Melting points were measured on a melting point apparatus (Yamato MP-21; Yamato Scientific Co. Ltd, Tokyo, Japan) and are uncorrected. Optical rotations were measured on polarimeter (DIP-1000; JASCO Corporation, Tokyo, Japan). ^{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, USA). 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).

4.2. Procedure for preparation of 6

4.2.1. 2-Methyl-(2*E*)-pentenamide (6b)

Thionyl chloride (14.5 ml, 199 mmol) was added to 2-methyl (2*E*)-pentenoic acid (15.0 g, 131 mmol) and the mixture was stirred at room temperature for 20 h. Thionyl chloride was evaporated under reduced pressure, and the obtained residue was added dropwise to 28% aqueous NH_3 below 0 °C and stirred at the same temperature for 2 h. The reaction mixture was 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 rinsed with *n*-hexane to give **6b** (9.53 g, 64% yield) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 1.04 (3H, t, J = 7.5 Hz), 1.84 (3H, s), 2.17 (2H, quintet, J = 7.5 Hz), 5.40–6.60 (2H, br), 6.40 (1H, t, J = 7.5 Hz). IR (Nujol) cm^{-1}: 3346, 3177, 1666, 1605.

Compounds **6c** and **6e**–**6g** were prepared according to the procedure for the synthesis of **6b**.

4.2.2. 5-Methyl-(2*E*)-hexenamide (6e)

Yield 90%. ^{1}H NMR ($CDCl_3$) δ: 0.92 (6H, d, J = 6.4 Hz), 1.60–2.10 (1H, m), 2.08 (2H, t, J = 7.0 Hz), 5.60–7.20 (2H, br), 5.87 (1H, d, J = 15.3 Hz), 6.81 (1H, dt, J = 15.3, 7.3 Hz). IR (Nujol) cm^{-1}: 3325, 3171, 1674, 1616.

4.2.3. 4,4-Dimethyl-(2*E*)-hexenamide (6f)

Yield 79%. ^{1}H NMR ($CDCl_3$) δ: 0.81 (3H, t, J = 7.3 Hz), 1.03 (6H, s), 1.40 (2H, q, J = 7.3 Hz), 5.10–6.30 (2H, br), 5.72 (1H, d, J = 15.8 Hz), 6.80 (1H, d, J = 15.8 Hz). IR (Nujol) cm^{-1}: 3391, 3333, 3196, 1668, 1634, 1607.

4.2.4. 5,5-Dimethyl-(2*E*)-hexenamide (6g)

Yield 79%. ^{1}H NMR ($CDCl_3$) δ: 0.93 (9H, s), 2.07 (2H, d, J = 7.7 Hz), 5.00–6.60 (2H, br), 5.82 (1H, d, J = 15.4 Hz), 6.88 (1H, dt, J = 15.4, 7.7 Hz). IR (Nujol) cm^{-1}: 3352, 3173, 1678, 1622, 1464.

4.3. Procedure for preparation of 8

4.3.1. Methyl {5-methyl-2-[(1*E*)-1-methylbuten-1-yl]oxazol-4-yl}acetate (8b)

Compound **7** (22.8 g, 109 mmol) was added to a suspension of **6b** (9.53 g, 84.2 mmol) in toluene (50 ml) and the suspension was refluxed for 16 h. AcOEt (50 ml) was added to the reaction mixture, which was washed with water and saturated brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give **8b** (5.43 g, 29% yield) as a white solid. ^{1}H NMR ($CDCl_3$) δ: 1.06 (3H, t, J = 7.2 Hz), 2.00 (3H, s), 2.10–2.45 (2H, m), 2.26 (3H, s), 3.50 (2H, s), 3.70 (3H, s), 6.45 (1H, dt, J = 7.2, 1.3 Hz).

Compounds **8c** and **8e**–**8g** were prepared according to the procedure for the synthesis of **8b**.

4.3.2. Methyl {5-methyl-2-[(1*E*)-4-methylpenten-1-yl]oxazol-4-yl}acetate (8e)

Yield 32%. ^{1}H NMR ($CDCl_3$) δ: 0.94 (6H, d, J = 6.4 Hz), 1.50–2.10 (1H, m), 2.11 (2H, t, J = 6.9 Hz), 2.27 (3H, s), 3.50 (2H, s), 3.71 (3H, s), 6.17 (1H, d, J = 16.0 Hz), 6.61 (1H, dt, J = 16.0, 6.9 Hz). IR (Nujol) cm^{-1}: 1746, 1643, 1551.

4.3.3. Methyl {2-[(1*E*)-3,3-dimethylpenten-1-yl]-5-methyloxazol-4-yl}acetate (8f)

Yield 39%. ^{1}H NMR ($CDCl_3$) δ: 0.83 (3H, t, J = 7.3 Hz), 1.06 (6H, s), 1.42 (2H, q, J = 7.3 Hz), 2.28 (3H, s), 3.48 (2H, s), 3.71 (3H, s), 6.12 (1H, d, J = 16.5 Hz), 6.59 (1H, d, J = 16.5 Hz). IR (neat) cm^{-1}: 3468, 3059, 2964, 2926, 2878, 2855, 1746, 1647, 1551, 1533.

4.3.4. Methyl {2-[(1*E*)-4,4-dimethylpenten-1-yl]-5-methyloxazol-4-yl}acetate (8g)

Yield 23%. ^{1}H NMR ($CDCl_3$) δ: 0.94 (9H, s), 2.10 (2H, d, J = 7.7 Hz), 2.28 (3H, s), 3.48 (2H, s), 3.71 (3H, s), 6.17 (1H, d, J = 15.8 Hz), 6.64 (1H, dt, J = 15.8, 7.5 Hz). IR (neat) cm^{-1}: 1746, 1643, 1535.

4.3.5. Methyl {2-[(1*E*)-1-ethylpropen-1-yl]-5-methyloxazol-4-yl}acetate (8a)

Triethylamine (76.5 ml, 549 mmol) was added dropwise to a suspension of **2** (33.5 g, 182 mmol) in CH_2Cl_2 (470 ml) and the suspension was stirred at room temperature for 30 min. Separately, to a solution of **3a** (13.9 g, 122 mmol) and triethylamine (19.0 ml, 136 mmol) in CH_2Cl_2 (250 ml) was added isobutyl chloroformate (17.7 ml, 136 mmol) below 10 °C. After stirring at the same temperature for 20 min, the mixture was added to the above mentioned suspension below 10 °C, and stirred at the same temperature for 1 h. The reaction mixture was washed with water, 1 M HCl and saturated brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give crude **4a** (35.2 g) as an oil. Crude **4a** (35.2 g), acetic anhydride (57.0 ml, 600 mmol), *N*-methylmorpholine (53.0 ml, 480 mmol) and 4-dimethylaminopyridine (3.00 g, 24.6 mmol) were dissolved in toluene (350 ml), and stirred 60–70 °C for 3.5 h. After cooling to room temperature, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution and separated into two layers. The organic layer was washed with water and saturated brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give crude **5a** (8.67 g) as a solid. To a solution of crude **5a** (8.67 g) in toluene (175 ml) was added $POCl_3$ (5.0 ml, 54 mmol) and stirred at 100 °C for 1 h. After cooling, the mixture was poured into cold water, neutralized with $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with water and saturated brine, dried over Na_2SO_4, and then evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give **8a** (5.10 g, 19% yield) as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.08 (3H, t, J = 7.5 Hz), 1.81 (3H, d, J = 7.3 Hz), 2.26 (3H, s), 2.51 (2H, q, J = 7.5 Hz), 3.49 (2H, s), 3.70 (3H, s), 6.49 (1H, q, J = 7.3 Hz). IR (neat) cm^{-1}: 1746, 1647, 1535.

Compounds **8d** and **8h**–**8k** were prepared according to the procedure for the synthesis of **8a**.

4.3.6. Methyl {2-[(1*E*)-3-ethylpenten-1-yl]-5-methyloxazol-4-yl}acetate (8h)

Yield 18%. ^{1}H NMR ($CDCl_3$) δ: 0.87 (6H, t, J = 7.3 Hz), 1.10–2.15 (5H, m), 2.28 (3H, s), 3.48 (2H, s), 3.71 (3H, s), 6.14 (1H, d, J = 15.8 Hz), 6.41 (1H, dd, J = 15.8, 7.7 Hz). IR (neat) cm^{-1}: 1771, 1746, 1643, 1533.

4.3.7. Methyl {5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}acetate (8i)

Yield 20%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.1 Hz), 1.14–1.80 (3H, m), 2.22 (2H, q, J = 7.2 Hz), 2.27 (3H, s), 3.47 (2H, s), 3.70 (3H, s), 6.18 (1H, d, J = 15.7 Hz), 6.62 (1H, dt, J = 15.7, 7.7 Hz). IR (neat) cm^{-1}: 3445, 2955, 2928, 2870, 2851, 1747, 1645, 1537.

4.3.8. Methyl {5-methyl-2-[(1*E*)-3-methylhexen-1-yl]oxazol-4-yl}acetate (8j)

Yield 46%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 7.6 Hz), 1.06 (3H, d, J = 6.8 Hz), 1.30–1.38 (4H, m), 2.27 (3H, s), 2.28–2.35 (1H, m), 3.48 (2H, s), 3.71 (3H, s), 6.16 (1H, dd, J = 15.9, 1.2 Hz), 6.51 (1H, dd, J = 15.9, 7.8 Hz). IR (neat) cm^{-1}: 2957, 2928, 1747.

4.3.9. Methyl {2-[(1*E*)-1,5-dimethylhexen-1-yl]-5-methyloxazol-4-yl}acetate (8k)

Yield 34%. ^{1}H NMR ($CDCl_3$) δ: 0.91 (6H, d, J = 6.6 Hz), 1.33 (2H, dt, J = 7.8, 7.0 Hz), 1.55–1.64 (1H, m), 2.01 (3H, d, J = 1.2 Hz), 2.21 (2H, dt, J = 7.8, 7.3 Hz), 2.27 (3H, s), 3.50 (2H, s), 3.70 (3H, s), 6.44 (1H, dt, J = 7.3, 1.2 Hz). IR (neat) cm^{-1}: 1747, 1647, 1537.

4.3.10. Methyl [5-methyl-2-(5-methylhexyl)oxazol-4-yl]acetate (8l)

Compound **8i** (3.00 g, 11.9 mmol) in MeOH (60 ml) was hydrogenated at 0.4 MPa in the presence of 10% Pd–C (600 mg) at room temperature for 15 h. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure to give crude **8l** (3.02 g) as an oil. Crude **8l** was used in subsequent reactions without further purification.

4.4. Procedure for preparation of 9

4.4.1. 2-{2-[(1*E*)-1-Ethylpropen-1-yl]-5-methyloxazol-4-yl}ethyl methanesulfonate (9a)

To a solution of **8a** (5.00 g, 22.4 mmol) in toluene (100 ml) was added 1.5 M diisobutyl aluminum hydride in toluene (60 ml, 90 mmol) at −30 °C and stirred at the same temperature for 1 h. The mixture was poured into cold water (200 ml) and stirred at room temperature for 30 min. The precipitate was removed by filtration, and the filtrate was separated into two layers. The organic layer was washed with saturated brine, dried over Na_2SO_4, and then evaporated under reduced pressure. To a solution of the obtained residue (4.17 g) and triethylamine (3.60 ml, 25.8 mmol) in CH_2Cl_2 (42 ml) was added methanesulfonyl chloride (1.80 ml, 23.3 mmol) at 0 °C and stirred for 20 min. The reaction mixture was washed with 10% aqueous citric acid solution and saturated brine and dried over Na_2SO_4, The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give **9a** (5.18 g, 85% yield) as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.07 (3H, t, J = 7.5 Hz), 1.82 (3H, d, J = 7.0 Hz), 2.26 (3H, s), 2.50 (2H, q, J = 7.5 Hz), 2.87 (2H, t, J = 6.6 Hz), 2.93 (3H, s), 4.45 (2H, t, J = 6.6 Hz), 6.48 (1H, q, J = 7.0 Hz). IR (neat) cm^{-1}: 1701, 1647, 1535.

Compounds **9b**–**9l** were prepared according to the procedure for the synthesis of **9a**.

4.4.2. 2-{5-Methyl-2-[(1*E*)-1-methylbuten-1-yl]oxazol-4-yl}ethyl methanesulfonate (9b)

Yield 50%. ^{1}H NMR ($CDCl_3$) δ: 1.06 (3H, t, J = 7.3 Hz), 2.04 (3H, s), 2.10–2.45 (2H, m), 2.27 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 2.90 (3H, s), 3.70 (3H, s), 4.45 (2H, t, J = 6.6 Hz), 6.44 (1H, dt, J = 7.3, 1.3 Hz). IR (neat) cm^{-1}: 2966, 2934, 2876, 1647, 1572, 1535.

4.4.3. 2-{2-[(1*E*)-3,3-Dimethylbuten-1-yl]-5-methyloxazol-4-yl}ethyl methanesulfonate (9d)

Yield 75%. ^{1}H NMR ($CDCl_3$) δ: 1.11 (9H, s), 2.27 (3H, s), 2.86 (2H, t, J = 6.7 Hz), 2.94 (3H, s), 4.45 (2H, t, J = 6.7 Hz), 6.11 (1H, d, J = 16.2 Hz), 6.67 (1H, d, J = 16.2 Hz).

4.4.4. 2-{5-Methyl-2-[(1*E*)-4-methylpenten-1-yl]oxazol-4-yl}ethyl methanesulfonate (9e)

Yield 53%. ^{1}H NMR ($CDCl_3$) δ: 0.94 (6H, d, J = 6.4 Hz), 1.50–2.10 (1H, m), 2.12 (2H, t, J = 7.0 Hz), 2.27 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 2.94 (3H, s), 4.45 (2H, t, J = 6.6 Hz), 6.15 (1H, d, J = 15.8 Hz), 6.62 (1H, dt, J = 15.8, 7.0 Hz). IR (neat) cm^{-1}: 1643, 1535.

4.4.5. 2-{2-[(1*E*)-3,3-Dimethylpenten-1-yl]-5-methyloxazol-4-yl}ethyl methanesulfonate (9f)

Yield 69%. ^{1}H NMR ($CDCl_3$) δ: 0.83 (3H, t, J = 7.4 Hz), 1.06 (6H, s), 1.43 (2H, q, J = 7.4 Hz), 2.27 (3H, s), 2.87 (2H, t, J = 6.7 Hz), 2.94 (3H, s), 4.45 (2H, t, J = 6.7 Hz), 6.09 (1H, d, J = 16.5 Hz), 6.59 (1H, d, J = 16.5 Hz). IR (neat) cm^{-1}: 3034, 3005, 1643, 1545.

4.4.6. 2-{2-[(1*E*)-4,4-Dimethylpenten-1-yl]-5-methyloxazol-4-yl}ethyl methanesulfonate (9g)

Yield 73%. ^{1}H NMR ($CDCl_3$) δ: 0.95 (9H, s), 2.10 (2H, d, J = 7.5 Hz), 2.28 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 2.94 (3H, s), 4.45 (2H, t, J = 6.6 Hz), 6.15 (1H, d, J = 16.0 Hz), 6.65 (1H, dt, J = 16.0, 7.5 Hz). IR (neat) cm^{-1}: 1661, 1643, 1533.

4.4.7. 2-{2-[(1*E*)-3-Ethylpenten-1-yl]-5-methyloxazol-4-yl}ethyl methanesulfonate (9h)

Yield 50%. ^{1}H NMR ($CDCl_3$) δ: 0.86 (6H, t, J = 6.8 Hz), 1.20–1.70 (4H, m), 1.70–2.20 (1H, m), 2.27 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 2.94 (1H, s), 4.45 (2H, t, J = 6.6 Hz), 6.12 (1H, d, J = 15.8 Hz), 6.41 (1H, dd, J = 15.8, 7.9 Hz). IR (neat) cm^{-1}: 2963, 2928, 2876, 1643, 1578, 1551, 1533.

4.4.8. 2-{5-Methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethyl methanesulfonate (9i)

Yield 66%. ^{1}H NMR ($CDCl_3$) δ: 0.91 (6H, d, J = 6.2 Hz), 1.13–1.90 (3H, m), 2.00–2.22 (2H, m), 2.26 (3H, s), 2.86 (2H, t, J = 6.7 Hz), 2.94 (3H, s), 4.45 (2H, t, J = 6.7 Hz), 6.20 (1H, d, J = 15.7 Hz), 6.62 (1H, dt, J = 15.7, 6.2 Hz). IR (neat) cm^{-1}: 3632, 3410, 2957, 2928, 2870, 1661, 1643, 1535.

4.4.9. 2-{5-Methyl-2-[(1*E*)-3-methylhexen-1-yl]oxazol-4-yl}ethyl methanesulfonate (9j)

Yield 67%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 6.8 Hz), 1.07 (3H, d, J = 6.6 Hz), 1.30–1.41 (4H, m), 2.27 (3H, s), 2.29–2.36 (1H, m), 2.87 (2H, t, J = 6.6 Hz), 2.94 (3H, s), 4.45 (2H, t, J = 6.6 Hz), 6.14 (1H, dd, J = 16.1, 1.0 Hz), 6.51 (1H, dd, J = 16.1, 7.8 Hz). IR (neat) cm^{-1}: 2959, 2928, 1738, 1643.

4.4.10. 2-{2-[(1*E*)-1,5-Dimethylhexen-1-yl]-5-methyloxazol-4-yl}ethyl methanesulfonate (9k)

Yield 86%. ^{1}H NMR ($CDCl_3$) δ: 0.91 (6H, d, J = 6.6 Hz), 1.34 (2H, dt, J = 7.8, 7.6 Hz), 1.55–1.64 (1H, m), 2.01 (3H, d, J = 1.2 Hz), 2.22 (2H, dt, J = 7.8, 7.6 Hz), 2.27 (3H, s), 2.88 (2H, t, J = 6.6 Hz), 2.94 (3H, s), 4.45 (2H, t, J = 6.6 Hz), 6.44 (1H, t, J = 7.8 Hz). IR (neat) cm^{-1}: 1647, 1535.

4.4.11. 2-[5-Methyl-2-(5-methylhexyl)oxazol-4-yl]ethyl methanesulfonate (9l)

Yield 56%. ^{1}H NMR ($CDCl_3$) δ: 0.86 (6H, t, J = 6.6 Hz), 1.16–1.24 (2H, m), 1.30–1.38 (2H, m), 1.53 (1H, heptet, J = 6.6 Hz), 1.69 (2H,

quintet, J = 7.8 Hz), 2.23 (3H, s), 2.66 (2H, t, J = 7.8 Hz), 2.84 (2H, t, J = 6.1 Hz), 2.94 (3H, s), 4.43 (2H, t, J = 6.1 Hz).

4.5. Procedure for preparation of 11

4.5.1. Methyl (*S*)-2-*tert*-butoxycarbonyl-7-{2-[(1*E*)-1-ethylpropen-1-yl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11a)

A mixture of **10** (3.00 g, 9.76 mmol), **9a** (3.90 g, 14.3 mmol), tetraethylammonium fluoride (600 mg) and K_2CO_3 (4.05 g 29.3 mmol) in toluene (120 ml) was stirred at 90 °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 **11a** (4.84 g, 91% yield) as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.08 (3H, t, J = 7.5 Hz), 1.30–1.70 (9H, m), 1.82 (3H, d, J = 7.0 Hz), 2.27 (3H, s), 2.52 (2H, q, J = 7.5 Hz), 2.88 (2H, t, J = 6.8 Hz), 2.90–3.20 (2H, m), 3.61 (3H, s), 4.14 (2H, t, J = 6.8 Hz), 4.20–5.25 (3H, m), 6.47 (1H, q, J = 7.0 Hz), 6.55–6.90 (2H, m), 7.01 (1H, d, J = 8.6 Hz). IR (neat) cm^{-1}: 1744, 1699, 1647, 1614, 1587, 1533, 1506.

Compounds **11b**–**11l** were prepared according to the procedure for the synthesis of **11a**.

4.5.2. Methyl (*S*)-2-*tert*-butoxycarbonyl-7-(2-{5-methyl-2-[(1*E*)-1-methylbuten-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11b)

Yield 74%. ^{1}H NMR ($CDCl_3$) δ: 1.06 (3H, t, J = 7.3 Hz), 1.35–1.65 (9H, m), 2.03 (3H, s), 2.10–2.45 (2H, m), 2.27 (3H, s), 2.88 (2H, t, J = 6.6 Hz), 3.00–3.25 (2H, m), 3.61 (3H, s), 4.14 (2H, t, J = 6.6 Hz), 4.25–5.25 (3H, m), 6.44 (1H, dt, J = 7.3, 1.3 Hz), 6.60–6.85 (3H, m), 7.01 (1H, d, J = 8.4 Hz). IR (neat) cm^{-1}: 2967, 2932, 1742, 1703, 1648, 1614, 1587, 1534, 1507.

4.5.3. Methyl (*S*)-2-*tert*-butoxycarbonyl-7-(2-{5-methyl-2-[(1*E*)-3-methylbuten-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11c)

Yield 45%. ^{1}H NMR ($CDCl_3$) δ: 1.08 (6H, d, J = 6.8 Hz), 1.35–1.60 (9H, m), 2.20–2.80 (1H, m), 2.27 (3H, s), 2.86 (2H, t, J = 6.6 Hz), 3.00–3.20 (2H, m), 3.61 (3H, s), 4.14 (2H, t, J = 6.6 Hz), 4.25–5.25 (3H, m), 6.14 (1H, d, J = 15.8 Hz), 6.45–6.80 (3H, m), 7.01 (1H, d, J = 8.6 Hz). IR (neat) cm^{-1}: 2961, 2930, 1746, 1699, 1643, 1614, 1585, 1533, 1506.

4.5.4. Methyl (*S*)-2-*tert*-butoxycarbonyl-7-(2-{5-methyl-2-[(1*E*)-4-methylpenten-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11e)

Yield 99%. ^{1}H NMR ($CDCl_3$) δ: 0.94 (6H, d, J = 6.3 Hz), 1.35–1.95 (10H, m), 2.11 (2H, t, J = 6.8 Hz), 2.28 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 3.00–3.25 (2H, m), 3.61 (3H, s), 4.15 (2H, t, J = 6.6 Hz), 4.45–5.25 (3H, m), 6.15 (1H, d, J = 15.8 Hz), 6.45–6.80 (3H, m), 7.01 (1H, d, J = 8.8 Hz). IR (neat) cm^{-1}: 1744, 1701, 1663, 1638, 1614, 1587, 1533, 1506.

4.5.5. Methyl (*S*)-2-*tert*-butoxycarbonyl-7-(2-{2-[(1*E*)-3,3-dimethylpenten-1-yl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11f)

Yield 89%. ^{1}H NMR ($CDCl_3$) δ: 0.83 (3H, t, J = 7.2 Hz), 1.05 (6H, s), 1.22–1.76 (11H, m), 2.28 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 2.98–3.20 (2H, m), 3.61 (3H, s), 4.15 (2H, t, J = 6.6 Hz), 4.40–5.20 (3H, m), 6.10 (1H, d, J = 16.5 Hz), 6.43–6.86 (3H, m), 7.01 (1H, d, J = 8.5 Hz). IR (neat) cm^{-1}: 3464, 2964, 2928, 2876, 1742, 1699, 1643, 1614, 1531, 1506.

4.5.6. Methyl (*S*)-2-*tert*-butoxycarbonyl-7-(2-{2-[(1*E*)-4,4-dimethylpenten-1-yl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11g)

Yield 98%. ^{1}H NMR ($CDCl_3$) δ: 0.94 (9H, s), 1.46, 1.51 (total 9H, s, s), 2.10 (2H, d, J = 7.7 Hz), 2.28 (3H, s), 2.87 (2H, t, J = 6.7 Hz), 3.00–3.25 (2H, m), 3.61 (3H, s), 4.15 (2H, t, J = 6.7 Hz), 4.25–5.25 (3H, m), 6.16 (1H, d, J = 16.0 Hz), 6.40–6.80 (3H, m), 7.01 (1H, d, J = 8.4 Hz). IR (neat) cm^{-1}: 1744, 1703, 1614, 1533, 1506.

4.5.7. Methyl (*S*)-2-*tert*-butoxycarbonyl-7-(2-{2-[(1*E*)-3-ethylpenten-1-yl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11h)

Yield 89%. ^{1}H NMR ($CDCl_3$) δ: 0.87 (6H, t, J = 7.1 Hz), 1.10–1.70 (4H, m), 1.46, 1.51 (total 9H, s, s), 1.70–2.30 (1H, m), 2.28 (3H, s), 2.87 (2H, t, J = 6.8 Hz), 2.95–3.20 (2H, m), 3.61 (3H, s), 4.15 (2H, t, J = 6.8 Hz), 4.20–5.20 (3H, m), 6.13 (1H, d, J = 16.0 Hz), 6.40 (1H, dd, J = 16.0, 7.5 Hz), 6.50–6.80 (2H, m), 7.01 (1H, d, J = 8.4 Hz). IR (neat) cm^{-1}: 1742, 1701, 1614, 1506.

4.5.8. Methyl (*S*)-2-*tert*-butoxycarbonyl-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11i)

Yield 71%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.2 Hz), 1.16–1.72 (12H, m), 2.06–2.40 (2H, m), 2.27 (3H, s), 2.86 (2H, t, J = 6.6 Hz), 2.98–3.20 (2H, m), 3.61 (3H, s), 4.14 (2H, t, J = 6.6 Hz), 4.24–5.20 (3H, m), 6.17 (1H, d, J = 16.0 Hz), 6.48 (1H, d, J = 8.1 Hz), 6.55–6.80 (2H, m), 7.01 (1H, d, J = 8.1 Hz). IR (neat) cm^{-1}: 3389, 2955, 2930, 2870, 1746, 1699, 1614, 1533, 1506.

4.5.9. Methyl (*S*)-2-*tert*-butoxycarbonyl-7-(2-{5-methyl-2-[(1*E*)-3-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11j)

Yield 95%. ^{1}H NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7.1 Hz), 1.06 (3H, d, J = 6.6 Hz), 1.30–1.39 (4H, m), 1.45, 1.52 (total 9H, s, s), 2.28 (3H, s), 2.28–2.35 (1H, m), 2.87 (2H, t, J = 6.6 Hz), 3.02–3.20 (2H, m), 3.60, 3.63 (total 3H, s, s), 4.14 (2H, t, J = 6.6 Hz), 4.20–5.25 (3H, m), 6.15 (1H, dd, J = 16.1, 1.0 Hz), 6.40–6.90 (3H, m), 7.01 (1H, d, J = 8.4 Hz). IR (neat) cm^{-1}: 2959, 2928, 2872, 1742, 1703, 1506.

4.5.10. Methyl (*S*)-2-*tert*-butoxycarbonyl-7-(2-{2-[(1*E*)-1,5-dimethylhexen-1-yl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (11k)

Yield 86%. ^{1}H NMR ($CDCl_3$) δ: 0.91 (6H, d, J = 6.6 Hz), 1.34 (2H, dt, J = 7.8, 7.6 Hz), 1.30–1.70 (10H, m), 2.02 (3H, s), 2.21 (2H, dt, J = 7.8, 7.6 Hz), 2.28 (3H, s), 2.88 (2H, t, J = 6.6 Hz), 3.02–3.21 (2H, m), 3.61 (3H, s), 4.14 (2H, t, J = 6.8 Hz), 4.20–5.25 (3H, m), 6.43 (1H, t, J = 7.6 Hz), 6.55–6.90 (2H, m), 7.01 (1H, d, J = 8.5 Hz). IR (neat) cm^{-1}: 1742, 1703, 1648, 1614, 1534, 1507.

4.6. Procedure for preparation of 12

4.6.1. Methyl (*S*)-7-{2-[(1*E*)-1-ethylpropen-1-yl]-5-methyloxazol-4-yl)ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12a)

To a solution of **11a** (4.80 g, 9.91 mmol) in formic acid (10 ml) was added saturated hydrogen chloride solution in 2-propanol (3.00 ml) under ice-cooling, and the mixture was stirred at room temperature for 15 min. AcOEt (100 ml) was added to the reaction mixture, and the mixture was neutralized with saturated aqueous $NaHCO_3$ solution and separated into two layers. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give **12a** (3.52 g, 92% yield) as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.08 (3H, t, J = 7.5 Hz), 1.82 (3H, d, J = 7.3 Hz), 2.26 (3H, s), 2.51 (2H, q, J = 7.5 Hz), 2.88 (2H, t, J = 6.8 Hz), 2.90–3.20 (2H, m), 3.60–3.83 (1H, m), 3.76 (3H, s),

4.05 (1H, s), 4.14 (2H, t, J = 6.8 Hz), 4.20–5.25 (3H, m), 6.47 (1H, q, J = 7.3 Hz), 6.50–6.85 (2H, m), 6.99 (1H, d, J = 8.3 Hz).

Compounds **12b**–**12l** were prepared according to the procedure for the synthesis of **12a**.

4.6.2. Methyl (*S*)-7-(2-{5-methyl-2-[(1*E*)-1-methylbuten-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12b)

Yield 95%. ^{1}H NMR ($CDCl_3$) δ: 1.06 (3H, t, J = 7.3 Hz), 2.01 (3H, s), 2.10–2.45 (3H, m), 2.27 (3H, s), 2.70–3.10 (4H, m), 3.50–3.70 (1H, m), 3.76 (3H, s), 4.05 (2H, s), 4.14 (2H, t, J = 6.8 Hz), 6.30–6.85 (3H, m), 6.99 (1H, d, J = 8.4 Hz). IR (neat) cm^{-1}: 3342, 2956, 2932, 2875, 1738, 1646, 1611, 1533, 1505.

4.6.3. Methyl (*S*)-7-(2-{5-methyl-2-[(1*E*)-3-methylbuten-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12c)

Yield 85%. ^{1}H NMR ($CDCl_3$) δ: 1.08 (6H, d, J = 6.6 Hz), 2.20–2.80 (1H, m), 2.27 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 2.95–3.10 (2H, m), 3.77 (3H, s), 3.90–4.10 (2H, m), 4.14 (2H, t, J = 6.6 Hz), 6.17 (1H, d, J = 16.0 Hz), 6.40–6.80 (3H, m), 6.99 (1H, d, J = 8.3 Hz). IR (neat) cm^{-1}: 3342, 2957, 2928, 2870, 1742, 1686, 1643, 1580, 1533, 1504.

4.6.4. Methyl (*S*)-7-(2-{5-methyl-2-[(1*E*)-4-methylpenten-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12e)

Yield 91%. ^{1}H NMR ($CDCl_3$) δ: 0.94 (6H, d, J = 6.3 Hz), 1.50–1.95 (1H, m), 2.11 (2H, t, J = 6.6 Hz), 2.12 (1H, s), 2.28 (3H, s), 2.87 (2H, t, J = 6.8 Hz), 2.90–3.10 (2H, m), 3.67 (1H, d, J = 5.5 Hz), 3.77 (3H, s), 4.06 (2H, s), 4.14 (2H, t, J = 6.8 Hz), 6.16 (1H, d, J = 15.8 Hz), 6.40–6.80 (3H, m), 7.00 (1H, d, J = 8.8 Hz). IR (neat) cm^{-1}: 3344, 1738, 1661, 1641, 1612, 1583, 1533, 1504.

4.6.5. Methyl (*S*)-7-(2-{2-[(1*E*)-3,3-dimethylpenten-1-yl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12f)

Yield 99%. ^{1}H NMR ($CDCl_3$) δ: 0.83 (3H, t, J = 7.2 Hz), 1.05 (6H, s), 1.42 (2H, q, J = 7.2 Hz), 2.12 (1H, s), 2.28 (3H, s), 2.86 (2H, t, J = 6.5 Hz), 2.90–3.08 (2H, m), 3.60–3.85 (1H, m), 3.76 (3H, s), 4.05 (2H, s), 4.14 (2H, t, J = 6.5 Hz), 6.10 (1H, d, J = 16.2 Hz), 6.42–6.80 (3H, m), 6.99 (1H, d, J = 8.4 Hz). IR (neat) cm^{-1}: 3348, 2963, 2924, 2878, 1744, 1643, 1612, 1504.

4.6.6. Methyl (*S*)-7-(2-{2-[(1*E*)-4,4-dimethylpenten-1-yl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12g)

Yield 99%. ^{1}H NMR ($CDCl_3$) δ: 0.95 (9H, s), 2.06 (1H, s), 2.10 (2H, d, J = 6.8 Hz), 2.28 (3H, s), 2.87 (2H, t, J = 6.8 Hz), 2.90–3.10 (2H, m), 3.60–3.85 (1H, m), 3.76 (3H, s), 4.04 (2H, s), 4.14 (2H, t, J = 6.8 Hz), 6.16 (1H, d, J = 15.8 Hz), 6.40–6.80 (3H, m), 6.99 (1H, d, J = 8.3 Hz). IR (neat) cm^{-1}: 3346, 1742, 1641, 1612, 1533, 1506.

4.6.7. Methyl (*S*)-7-(2-{2-[(1*E*)-3-ethylpenten-1-yl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12h)

Yield 89%. ^{1}H NMR ($CDCl_3$) δ: 0.87 (6H, t, J = 7.1 Hz), 1.10–1.70 (4H, m), 1.70–2.55 (2H, m), 2.28 (3H, s), 2.70–3.20 (3H, m), 3.55–3.95 (1H, m), 3.76 (3H, s), 4.05 (2H, s), 4.15 (2H, t, J = 6.6 Hz), 6.12 (1H, d, J = 15.8 Hz), 6.40 (1H, dd, J = 15.8, 7.5 Hz), 6.55 (1H, d, J = 2.0 Hz), 6.70 (1H, dd, J = 8.3, 2.0 Hz), 6.99 (1H, d, J = 8.3 Hz). IR (neat) cm^{-1}: 1740, 1612, 1504.

4.6.8. Methyl (*S*)-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12i)

Yield quant., ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.1 Hz), 1.15–1.73 (3H, m), 1.86 (1H, br s), 2.04–2.40 (2H, m), 2.27 (3H, s), 2.86 (2H, t, J = 6.6 Hz), 2.90–3.06 (2H, m), 3.55–3.75 (1H, m), 3.77 (3H, s), 4.04 (2H, s), 4.22 (2H, t, J = 6.6 Hz), 6.17 (1H, d, J = 16.0 Hz), 6.39–6.81 (3H, m), 6.99 (1H, d, J = 8.3 Hz). IR (neat) cm^{-1}: 3346, 2953, 2926, 2870, 2849, 1742, 1641, 1612, 1533, 1504.

4.6.9. Methyl (*S*)-7-(2-{5-methyl-2-[(1*E*)-3-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12j)

Yield 95%. ^{1}H NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7.1 Hz), 1.06 (3H, d, J = 6.6 Hz), 1.30–1.39 (4H, m), 2.28 (3H, s), 2.28–2.35 (1H, m), 2.82–2.91 (4H, m), 3.71 (1H, dd, J = 11.1, 5.4 Hz), 3.77 (3H, s), 4.02 (1H, d, J = 16.1 Hz), 4.08 (1H, d, J = 16.1 Hz), 4.14 (2H, t, J = 6.6 Hz), 6.15 (1H, dd, J = 16.0, 1.0 Hz), 6.49 (1H, dd, J = 16.0, 8.0 Hz), 6.55 (1H, d, J = 2.7 Hz), 6.70 (1H, dd, J = 8.6, 2.7 Hz), 6.99 (1H, d, J = 8.6 Hz). IR (neat) cm^{-1}: 2957, 2928, 2872, 1742, 1612.

4.6.10. Methyl (*S*)-7-(2-{2-[(1*E*)-1,5-dimethylhexen-1-yl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12k)

Yield 95%. ^{1}H NMR ($CDCl_3$) δ: 0.91 (6H, d, J = 6.6 Hz), 1.34 (2H, dt, J = 7.8, 7.3 Hz), 1.55–1.64 (1H, m), 1.87 (1H, s), 2.02 (3H, s), 2.21 (2H, dt, J = 7.8, 7.3 Hz), 2.27 (3H, s), 2.86 (1H, dd, J = 15.9, 10.5 Hz), 2.88 (2H, t, J = 6.8 Hz), 3.01 (1H, dd, J = 15.9, 4.6 Hz), 3.71 (1H, dd, J = 10.5, 4.6 Hz), 3.76 (3H, s), 4.02 (1H, d, J = 16.1 Hz), 4.07 (1H, d, J = 16.1 Hz), 4.13 (2H, t, J = 6.8 Hz), 6.42 (1H, t, J = 7.6 Hz), 6.54 (1H, d, J = 2.4 Hz), 6.68 (1H, dd, J = 8.3, 2.4 Hz), 6.99 (1H, d, J = 8.3 Hz). IR (neat) cm^{-1}: 1739, 1644, 1615, 1583, 1505.

4.7. Procedure for preparation of 13 and 15

4.7.1. Methyl (*S*)-7-(2-{2-[(1*E*)-1-ethylpropen-1-yl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13a)

To a solution of **12a** (1.50 g, 3.90 mmol) in CH_2Cl_2 (15 ml) was added triethylamine (0.82 ml, 5.9 mmol) and (2*E*,4*E*)-hexadienoyl chloride (610 mg, 4.67 mmol) under ice-cooling, and the mixture was stirred at the same temperature 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, and the obtained residue was purified by silica gel column chromatography to give **13a** (1.40 g, 75% yield) as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.08 (3H, t, J = 7.5 Hz), 1.70–2.00 (3H, m), 1.81 (3H, d, J = 7.0 Hz), 2.27 (3H, s), 2.52 (2H, q, J = 7.5 Hz), 2.88 (2H, t, J = 6.6 Hz), 3.00–3.25 (2H, m), 3.59 (3H, s), 4.14 (2H, t, J = 6.6 Hz), 4.50–5.20 (3H, m), 5.40–5.65 (1H, m), 5.80–6.80 (6H, m), 7.03 (1H, d, J = 8.4 Hz), 7.15–7.55 (1H, m). IR (neat) cm^{-1}: 1740, 1655, 1628, 1605, 1533, 1506.

Compounds **13b**–**13l**, **15d** and **15e** were prepared according to the procedure for the synthesis of **13a**.

4.7.2. Methyl (*S*)-2-[(2*E*,4*E*)-hexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-1-methylbuten-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13b)

Yield 76%. ^{1}H NMR ($CDCl_3$) δ: 1.06 (3H, t, J = 7.5 Hz), 1.85 (3H, d, J = 5.0 Hz), 2.01 (3H, s), 2.10–2.45 (2H, m), 2.28 (3H, s), 2.89 (2H, t, J = 6.5 Hz), 3.00–3.30 (2H, m), 3.60 (3H, s), 4.15 (2H, t, J = 6.6 Hz), 4.35–5.20 (2H, m), 5.40–5.70 (1H, m), 5.95–6.90 (6H, m), 7.04 (1H, d, J = 8.4 Hz), 7.15–7.55 (1H, m). IR (neat) cm^{-1}: 2961, 2933, 2875, 1739, 1652, 1627, 1605, 1534, 1506.

4.7.3. Methyl (*S*)-2-[(2*E*,4*E*)-hexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-3-methylbuten-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13c)

Yield 54%. ^{1}H NMR ($CDCl_3$) δ: 1.08 (6H, d, J = 6.6 Hz), 1.80–1.95 (3H, m), 2.20–2.80 (1H, m), 2.27 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 3.00–3.30 (2H, m), 3.60 (3H, s), 4.15 (2H, t, J = 6.6 Hz), 4.50–5.15 (2H, m), 5.40–5.70 (1H, m), 6.00–6.90 (7H, m), 7.04 (1H, d, J = 8.2 Hz), 7.15–7.55 (1H, m). IR (neat) cm^{-1}: 2957, 2928, 2872, 1739, 1651, 1614, 1533, 1506.

4.7.4. Methyl (*S*)-7-(2-{2-[(1*E*)-3,3-dimethylbuten-1-yl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13d)

Yield 78%. ^{1}H NMR ($CDCl_3$) δ: 1.11 (9H, s), 1.85 (3H, d, J = 5.0 Hz), 2.28 (3H, s), 2.87 (2H, t, J = 6.8 Hz), 3.01–3.35 (2H, m), 3.60 (3H, s), 4.15 (2H, t, J = 6.8 Hz), 4.39–5.08 (2H, m), 5.38–5.65 (1H, m), 6.00–7.50 (9H, m). IR (neat) cm^{-1}: 3464, 3020, 2959, 2868, 1740, 1657, 1628, 1531.

4.7.5. Methyl (*S*)-2-[(2*E*,4*E*)-hexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-4-methylpenten-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13e)

Yield 96%. ^{1}H NMR ($CDCl_3$) δ: 0.94 (6H, d, J = 6.4 Hz), 1.50–1.95 (4H, m), 2.11 (2H, t, J = 7.0 Hz), 2.28 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 3.00–3.30 (2H, m), 3.60 (3H, s), 4.15 (2H, t, J = 6.6 Hz), 4.50–5.15 (2H, m), 5.40–5.70 (1H, m), 6.00–6.90 (7H, m), 7.04 (1H, d, J = 8.2 Hz), 7.15–7.55 (1H, m). IR (neat) cm^{-1}: 1740, 1655, 1628, 1533, 1508.

4.7.6. Methyl (*S*)-7-(2-{2-[(1*E*)-3,3-dimethylpenten-1-yl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13f)

Yield 79%. ^{1}H NMR ($CDCl_3$) δ: 0.83 (3H, t, J = 7.0 Hz), 1.06 (6H, s), 1.42 (2H, q, J = 7.0 Hz), 1.75–1.95 (3H, m), 2.28 (3H, s), 2.87 (2H, t, J = 6.8 Hz), 3.01–3.24 (2H, m), 3.59 (3H, s), 4.15 (2H, t, J = 6.8 Hz), 4.33–5.02 (2H, m), 5.40–5.66 (1H, m), 6.06–6.80 (7H, m), 7.04 (1H, d, J = 8.1 Hz), 7.16–7.53 (1H, m). IR (neat) cm^{-1}: 3466, 2963, 2924, 2878, 1740, 1653, 1628, 1614, 1531, 1506.

4.7.7. Methyl (*S*)-7-(2-{2-[(1*E*)-4,4-dimethylpenten-1-yl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13g)

Yield 79%. ^{1}H NMR ($CDCl_3$) δ: 0.94 (9H, s), 1.75–1.95 (3H, m), 2.10 (2H, d, J = 7.7 Hz), 2.28 (3H, s), 2.87 (2H, t, J = 6.7 Hz), 3.00–3.30 (2H, m), 3.61 (3H, s), 4.15 (2H, t, J = 6.7 Hz), 4.50–5.15 (2H, m), 5.40–5.70 (1H, m), 6.00–6.90 (7H, m), 7.03 (1H, d, J = 8.3 Hz), 7.15–7.55 (1H, m).

4.7.8. Methyl (*S*)-7-(2-{2-[(1*E*)-3-ethylpenten-1-yl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13h)

Yield 79%. ^{1}H NMR ($CDCl_3$) δ: 0.87 (6H, t, J = 7.5 Hz), 1.10–1.70 (4H, m), 1.70–2.20 (1H, m), 1.85 (3H, d, J = 4.8 Hz), 2.28 (3H, s), 2.87 (2H, t, J = 6.8 Hz), 3.00–3.30 (2H, m), 3.59 (3H, s), 4.15 (2H, t, J = 6.8 Hz), 4.50–5.65 (3H, m), 5.80–6.50 (5H, m), 6.55–6.80 (2H, m), 7.03 (1H, d, J = 8.4 Hz), 7.15–7.50 (1H, m). IR (neat) cm^{-1}: 1740, 1655, 1628, 1605, 1533, 1506.

4.7.9. Methyl (*S*)-2-[(2*E*,4*E*)-hexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13i)

Yield 67%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.2 Hz), 1.14–1.72 (3H, m), 1.86 (3H, d, J = 5.0 Hz), 2.05–2.40 (2H, m), 2.27 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 3.00–3.25 (2H, m), 3.60 (3H, s), 4.15 (2H, t, J = 6.6 Hz), 4.39–5.20 (2H, m), 5.42–5.65 (1H, m), 6.00–6.87 (7H, m), 7.04 (1H, d, J = 8.1 Hz), 7.18–7.51 (1H, m). IR (neat) cm^{-1}: 3462, 2955, 2928, 2870, 1740, 1653, 1630, 1533, 1506.

4.7.10. Methyl (*S*)-2-[(2*E*,4*E*)-hexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-3-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13j)

Yield 81%. ^{1}H NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7.1 Hz), 1.06 (3H, d, J = 6.6 Hz), 1.29–1.40 (4H, m), 1.87 (3H, d, J = 6.6 Hz), 2.28 (3H, s), 2.29–2.35 (1H, m), 2.88 (2H, t, J = 6.6 Hz), 3.00–3.25 (2H, m), 3.60 (3H, s), 4.14 (2H, t, J = 6.6 Hz), 4.52, 4.94 (0.6H, AB-q, J = 17.2 Hz), 4.70, 4.77 (1.4H, AB-q, J = 15.4 Hz), 4.85–5.53 (1H, m), 6.07–6.75 (7H, m), 7.00–7.10 (1H, m), 7.34 (1H, dd, J = 14.9, 11.0 Hz). IR (neat) cm^{-1}: 2957, 2928, 1740, 1655, 1628, 1612, 1506.

4.7.11. Methyl (*S*)-7-(2-{2-[(1*E*)-1,5-dimethylhexen-1-yl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13k)

Yield 78%. ^{1}H NMR ($CDCl_3$) δ: 0.91 (6H, d, J = 6.6 Hz), 1.34 (2H, dt, J = 7.8, 7.6 Hz), 1.55–1.64 (1H, m), 1.82–1.88 (3H, m), 2.02 (3H, s), 2.21 (2H, dt, J = 7.8, 7.3 Hz), 2.28 (3H, s), 2.89 (2H, t, J = 6.8 Hz), 3.00–3.25 (2H, m), 3.60 (3H, s), 4.14 (2H, t, J = 6.6 Hz), 4.52, 4.93 (0.4H, AB-q, J = 17.3 Hz), 4.70, 4.77 (1.6H, AB-q, J = 15.4 Hz), 4.85–5.20 (1H, m), 6.06–6.36 (3H, m), 6.43 (1H, t, J = 7.6 Hz), 6.60–6.75 (1H, m), 6.72 (1H, m), 7.01 (1H, d, J = 8.3 Hz), 7.33 (1H, dd, J = 14.7, 10.8 Hz). IR (neat) cm^{-1}: 1740, 1657, 1628, 1614, 1535, 1506.

4.7.12. Methyl (*S*)-2-[(2*E*,4*E*)-hexadienoyl]-7-{2-[5-methyl-2-(5-methylhexyl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13l)

Yield 88%. ^{1}H NMR ($CDCl_3$) δ: 0.85 (6H, d, J = 6.8 Hz), 1.13–1.23 (2H, m), 1.29–1.39 (2H, m), 1.53 (1H, heptet, J = 6.8 Hz), 1.70 (2H, quintet, J = 7.6 Hz), 1.79–1.91 (3H, m), 2.23 (3H, s), 2.65 (2H, t, J = 7.6 Hz), 2.85 (2H, t, J = 7.6 Hz), 3.00–3.09 (1H, m), 3.14–3.26 (1H, m), 3.60 (3H, s), 4.53 (0.3H, d, J = 17.3 Hz), 4.70 (0.7H, d, J = 15.6 Hz), 4.77 (0.7H, d, J = 15.6 Hz), 4.87–4.93 (0.3H, m), 4.94 (0.3H, d, J = 17.3 Hz), 5.48–5.56 (0.7H, m), 6.04–6.35 (3H, m), 6.55–6.76 (2H, m), 6.98–7.07 (1H, m), 7.27–7.39 (1H, m). IR (neat) cm^{-1}: 1740, 1655, 1629, 1614, 1578, 1506.

4.7.13. Methyl (*S*)-2-hexanoyl-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15d)

Yield 89%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 0.91 (3H, t, J = 6.9 Hz), 1.30–1.43 (6H, m), 1.45–1.77 (3H, m), 2.18–2.27 (2H, m), 2.28 (3H, s), 2.42–2.50 (2H, m), 2.88 (2H, t, J = 6.6 Hz), 3.00–3.30 (2H, m), 3.60 (3H, s), 4.15 (2H, t, J = 6.6 Hz), 4.30–5.60 (3H, m), 6.18 (1H, dt, J = 15.9, 1.4 Hz), 6.18 (1H, dt, J = 15.9, 7.1 Hz), 6.60–6.80 (2H, m), 6.99–7.05 (1H, m). IR (neat) cm^{-1}: 1743, 1657, 1614, 1587, 1533, 1506.

4.7.14. Methyl (*S*)-2-(5-hexenoyl)-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15e)

Yield 93%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 1.35 (2H, dt, J = 7.8, 6.8 Hz), 1.54–1.68 (1H, m), 1.74–1.87 (2H, m), 2.09–2.27 (4H, m), 2.28 (3H, s), 2.47 (2H, dd, J = 8.3, 6.6 Hz), 2.87 (2H, t, J = 6.8 Hz), 3.00–3.30 (2H, m), 3.60 (3H, s), 4.14 (2H, t, J = 6.8 Hz), 4.30–5.90 (6H, m), 6.19 (1H, dt, J = 15.9, 1.4 Hz), 6.59 (1H, dt, J = 15.9, 7.1 Hz), 6.60–7.05 (3H, m). IR (neat) cm^{-1}: 1744, 1651, 1614, 1589, 1533, 1506.

4.7.15. Methyl (*S*)-2-[(2*E*,4*E*)-5-methylhexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15a)

To a solution of **12i** (700 mg, 1.70 mmol) in CH_2Cl_2 (7 ml) was added (2*E*,4*E*)-5-methylhexadienoic acid (180 mg, 2.22 mmol) and EDC (490 mg, 2.56 mmol) under ice-cooling, and the mixture was stirred at room temperature for 15 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 **15a** (700 mg, 79% yield) as an oil. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.1 Hz), 1.10–1.30 (3H, m), 1.88 (6H, s), 2.00–2.40 (2H, m), 2.27 (3H, s), 2.87 (2H, t, J = 6.8 Hz), 3.00–3.30 (2H, m), 3.60 (3H, s), 4.15 (2H, t, J = 6.8 Hz), 4.30–5.70 (3H, m), 5.85–6.85 (4H, m), 6.17 (1H, d, J = 16.1 Hz), 6.65 (1H, s), 7.03 (1H, d, J = 8.4 Hz), 7.30–7.80 (1H, m). IR (neat) cm^{-1}: 2743, 2637, 2552, 1655, 1626, 1603, 1556, 1506.

Compounds **15b**, **15c** and **15f**–**15n** were prepared according to the procedure for the synthesis of **15a**.

4.7.16. Methyl (*S*)-2-[(2*E*,4*E*)-2-methylhexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15b)

Yield 69%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.1 Hz), 1.20–1.50 (2H, m), 1.50–1.90 (4H, m), 1.96 (3H, s), 2.00–2.40 (2H, m), 2.27 (3H, s), 2.86 (2H, t, J = 6.8 Hz), 3.00–3.20 (2H, m), 3.64 (3H, s), 4.13 (2H, t, J = 6.8 Hz), 4.30–5.40 (3H, m), 5.60–6.75 (7H, m), 7.03 (1H, d, J = 8.4 Hz). IR (neat) cm^{-1}: 2955, 2928, 2853, 1740, 1641, 1612, 1506.

4.7.17. Methyl (*S*)-2-[(2*E*)-hexenoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15c)

Yield 79%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 0.96 (3H, t, J = 6.9 Hz), 1.35 (2H, dt, J = 8.3, 7.1 Hz), 1.45–1.67 (3H, m), 2.18–2.27 (4H, m), 2.28 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 3.00–3.30 (2H, m), 3.60 (3H, s), 4.14 (2H, t, J = 6.6 Hz), 4.30–5.70 (3H, m), 6.00–7.05 (7H, m). IR (neat) cm^{-1}: 1742, 1661, 1622, 1533, 1506.

4.7.18. Methyl (*S*)-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-2-(4-pentenoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15f)

Yield 81%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 1.31–1.39 (2H, m), 1.55–1.65 (1H, m), 2.18–2.26 (2H, m), 2.28 (3H, s), 2.36–2.53 (2H, m), 2.54–2.60 (2H, m), 2.87 (2H, t, J = 6.6 Hz), 3.00–3.30 (2H, m), 3.60, 3.61 (total 3H, s, s), 4.15 (2H, t, J = 6.6 Hz), 4.30–5.55 (5H, m), 6.19 (1H, dt, J = 16.1, 1.5 Hz), 6.56–6.76 (3H, m), 7.00–7.05 (1H, m). IR (neat) cm^{-1}: 2955, 2928, 2851, 1740, 1659, 1614, 1506.

4.7.19. Methyl (*S*)-2-(3-cyclopropylacryloyl)-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15g)

Yield 75%. ^{1}H NMR ($CDCl_3$) δ: 0.50–1.90 (14H, m), 2.00–2.45 (2H, m), 2.27 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 3.00–3.26 (2H, m), 3.60 (3H, s), 4.15 (2H, t, J = 6.6 Hz), 4.50–5.70 (3H, m), 6.17 (1H, d, J = 16.1 Hz), 6.21–6.87 (5H, m), 7.04 (1H, d, J = 8.8 Hz). IR (neat) cm^{-1}: 3462, 2955, 2928, 2870, 1738, 1659, 1614.

4.7.20. Methyl (*S*)-2-[(2*E*,4*E*)-6-hydroxyhexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15h)

Yield 77%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 1.35 (2H, dt, J = 8.3, 7.1 Hz), 1.54–1.67 (1H, m), 1.88–2.03 (1H, br), 2.18–2.27 (2H, m), 2.28 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 3.00–3.30 (2H, m), 3.60 (3H, s), 4.14 (2H, t, J = 6.6 Hz), 4.25–4.34 (2H, m), 4.45–5.70 (3H, m), 6.00–6.26 (2H, m), 6.37–6.50 (2H, m), 6.59 (1H, dt, J = 15.9, 7.1 Hz), 6.60–6.75 (2H, m), 7.00–7.04 (1H, m), 7.34 (1H, dd, J = 14.9, 11.2 Hz). IR (neat) cm^{-1}: 3402, 1740, 1653, 1622, 1553, 1506.

4.7.21. Methyl (*S*)-2-[(2*E*)-4-hydroxyhexenoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]-oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15i)

Yield 79%. ^{1}H NMR ($CDCl_3$) δ: 0.91 (6H, d, J = 6.3 Hz), 1.00, 1.01 (total 3H, t, t, J = 7.4 Hz), 1.35 (2H, dt, J = 8.1, 7.1 Hz), 1.56–1.73 (4H, m), 2.18–2.27 (2H, m), 2.28 (3H, s), 2.87 (2H, t, J = 6.8 Hz), 3.00–3.25 (2H, m), 3.60 (3H, s), 4.14 (2H, t, J = 6.8 Hz), 4.21–4.38 (2H, m), 4.45–5.70 (3H, m), 6.16 (1H, d, J = 15.9 Hz), 6.55–6.76 (4H, m), 6.95–7.08 (2H, m). IR (neat) cm^{-1}: 3389, 1744, 1661, 1614, 1506.

4.7.22. Methyl (*S*)-2-[(2*E*)-4-ethoxybutenoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15j)

Yield 34%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.8 Hz), 1.24, 1.28 (total 3H, t, t, J = 7.1 Hz), 1.31–1.39 (2H, m), 1.54–1.66 (1H, m), 2.19–2.26 (2H, m), 2.28 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 3.00–3.30 (2H, m), 3.56, 3.58 (total 2H, q, q, J = 7.1 Hz), 3.59 (3H, s), 4.11–4.22 (4H, m), 4.45–5.60 (3H, m), 6.19 (1H, dt, J = 15.8, 1.5 Hz), 6.40–7.08 (6H, m). IR (neat) cm^{-1}: 2955, 2928, 2870, 1742, 1666, 1626, 1533, 1506.

4.7.23. Methyl (*S*)-2-[(2*E*)-3-ethoxyacryloyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]-oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15k)

Yield 78%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 1.32–1.41 (5H, m), 1.54–1.67 (1H, m), 2.18–2.27 (2H, m), 2.28 (3H, s), 2.87 (2H, t, J = 6.8 Hz), 3.00–3.30 (2H, m), 3.59 (3H, s), 3.99 (2H, q, J = 6.8 Hz), 4.14 (2H, t, J = 6.8 Hz), 4.67 (2H, s), 5.48–5.57 (1H, m), 5.74 (1H, d, J = 11.7 Hz), 6.19 (1H, dt, J = 16.1, 1.5 Hz), 6.59 (1H, dt, J = 16.1, 7.1 Hz), 6.61–6.73 (2H, m), 7.03 (1H, d, J = 8.3 Hz), 7.64 (1H, d, J = 11.7 Hz). IR (neat) cm^{-1}: 3458, 1740, 1651, 1597, 1551, 1533, 1506.

4.7.24. Methyl (*S*)-2-(3-ethoxypropionyl)-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15l)

Yield 93%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 1.26 (3H, t, J = 7.3 Hz), 1.35 (2H, dt, J = 7.8, 7.1 Hz), 1.54–1.67 (1H, m), 2.18–2.27 (2H, m), 2.28 (3H, s), 2.74–2.81 (2H, m), 2.83–2.93 (2H, m), 3.00–3.30 (2H, m), 3.60 (3H, s), 3.73–3.85 (2H, m), 4.10–4.17 (2H, m), 4.40–5.50 (3H, m), 6.19 (1H, dt, J = 15.9, 1.2 Hz), 6.54–6.66 (2H, m), 6.68–6.76 (1H, m), 7.00–7.04 (1H, m). IR (neat) cm^{-1}: 1744, 1653, 1616, 1506.

4.7.25. Methyl (*S*)-2-[(2*E*)-3-(furan-2-yl)acryloyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15m)

Yield 93%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 1.31–1.39 (2H, m), 1.54–1.65 (1H, m), 2.18–2.26 (2H, m), 2.28 (3H, s), 2.88 (2H, t, J = 6.8 Hz), 3.05–3.35 (2H, m), 3.61 (3H, s), 4.15 (2H, t, J = 6.6 Hz), 4.50–5.60 (3H, m), 6.19 (1H, dt, J = 15.9, 1.5 Hz), 6.43–6.50 (1H, m), 6.54–6.64 (2H, m), 6.65–7.07 (4H, m), 7.42–7.56 (2H, m). IR (neat) cm^{-1}: 2978, 2955, 1740, 1655, 1614, 1506.

4.7.26. Methyl (*S*)-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-2-[(2*E*)-3-(thiophen-2-yl)acryloyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15n)

Yield 89%. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 1.31–1.39 (2H, m), 1.54–1.64 (1H, m), 2.19–2.26 (2H, m), 2.28 (3H, s), 2.88 (2H, t, J = 6.8 Hz), 3.03–3.33 (2H, m), 3.61 (3H, s), 4.16 (2H, t,

J = 6.6 Hz), 4.50–5.60 (3H, m), 6.19 (1H, dt, *J* = 16.1, 1.5 Hz), 6.59 (1H, dt, *J* = 16.1, 7.1 Hz), 6.67–6.72 (1H, m), 6.74 (1H, dd, *J* = 8.3, 2.4 Hz), 6.78 (1H, d, *J* = 15.1 Hz), 7.01–7.08 (1H, m), 7.30–7.38 (1H, m), 7.83–7.91 (1H, m). IR (neat) cm^{-1}: 2955, 2928, 2870, 1740, 1645, 1605, 1506.

4.8. Procedure for preparation of 14 and 16

4.8.1. (*S*)-7-(2-{2-[(1*E*)-1-Ethylpropen-1-yl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (14a)

To a solution of **13a** (1.38 g, 2.88 mmol) in THF–MeOH (3:1, 28 ml) was added 1 M aqueous lithium hydroxide solution (9.0 ml, 9.0 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was acidified with 6 M HCl and the solvent was evaporated under reduced pressure. The obtained residue was extracted with AcOEt, and the organic layer was washed with water and saturated brine, and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the obtained residue was dissolved in MeOH (5 ml). After dropwise addition of *tert*-butylamine (0.5 ml), diisopropyl ether (200 ml) was added, and the mixture was stirred under ice-cooling for 1 h. The precipitated crystals were collected by filtration to give **14a** (1.40 g, 90% yield) as a white solid, mp 149.5–151.5 °C. $[\alpha]_D^{20}$ −20.4 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.97 (9H, s), 1.08 (3H, t, *J* = 7.5 Hz), 1.65–1.95 (3H, m), 1.81 (3H, d, *J* = 7.0 Hz), 2.27 (3H, s), 2.51 (2H, q, *J* = 7.5 Hz), 2.87 (2H, t, *J* = 6.6 Hz), 2.90–3.35 (2H, m), 4.10 (2H, t, *J* = 6.6 Hz), 4.20–5.30 (3H, m), 5.90–6.80 (9H, m), 6.85–7.50 (2H, m). IR (Nujol) cm^{-1}: 1653, 1626, 1605, 1585, 1556, 1506. MS *m*/*z*: 465 $[M+H]^+$. Anal. Calcd for $C_{27}H_{32}N_2O_5{\cdot}C_4H_{11}N{\cdot}0.4H_2O$: C, 68.33; H, 8.10; N, 7.71. Found: C, 68.44; H, 7.78; N, 7.98.

Compounds **14b**–**14l** and **16a**–**16n** were prepared according to the procedure for the synthesis of **14a**.

4.8.2. (*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-1-methylbuten-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (14b)

Yield 86%. A white solid. Mp 160–163 °C. $[\alpha]_D^{20}$ −13.3 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.99 (9H, s), 1.05 (3H, t, *J* = 7.5 Hz), 1.60–1.95 (3H, m), 2.01 (3H, s), 2.10–2.45 (2H, m), 2.28 (3H, s), 2.87 (2H, t, *J* = 6.8 Hz), 2.90–3.30 (2H, m), 4.11 (2H, t, *J* = 6.8 Hz), 4.25–5.25 (3H, m), 5.95–8.20 (11H, m). IR (Nujol) cm^{-1}: 2638, 1652, 1623, 1600, 1554, 1506. MS *m*/*z*: 465 $[M+H]^+$. Anal. Calcd for $C_{27}H_{32}N_2O_5{\cdot}C_4H_{11}N{\cdot}0.5H_2O$: C, 68.11; H, 8.11; N, 7.69. Found: C, 68.26; H, 7.91; N, 7.83.

4.8.3. (*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-(5-methyl-2-{2-[(1*E*)-3-methylbuten-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoqunoline-3-carboxylic acid *tert*-butylamine salt (14c)

Yield 79%. A pale brown solid. Mp 166–168 °C. ^1H NMR ($CDCl_3$) δ: 1.01 (9H, s), 1.08 (6H, d, *J* = 6.8 Hz), 1.60–2.00 (3H, m), 2.20–2.80 (1H, m), 2.28 (3H, s), 2.86 (2H, t, *J* = 6.8 Hz), 2.80–3.40 (2H, m), 4.11 (2H, t, *J* = 6.8 Hz), 4.25–5.20 (3H, m), 5.95–8.00 (12H, m). IR (Nujol) cm^{-1}: 2741, 2633, 2544, 2432, 2363, 1651, 1622, 1553, 1506. MS *m*/*z*: 465 $[M+H]^+$.

4.8.4. (*S*)-2-[(2*E*,4*E*)]-Hexadienoyl]-7-(2-{2-[(1*E*)-3,3-dimethylbuten-1-yl]-5-methyloxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (14d)

Yield 85%. A pale yellow solid, mp 177–179.5 °C. $[\alpha]_D^{20}$ −9.8 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.97 (18H, s), 1.60–2.00 (3H, m), 2.28 (3H, s), 2.86 (2H, t, *J* = 6.5 Hz), 2.90–3.35 (2H, m), 4.11 (2H, t, *J* = 6.5 Hz), 4.28–5.20 (3H, m), 5.90–7.48 (12H, m). IR (Nujol) cm^{-1}: 3568, 2745, 2637, 2216, 1653, 1553. MS *m*/*z*: 479 $[M+H]^+$. Anal. Calcd for $C_{28}H_{34}N_2O_5{\cdot}C_4H_{11}N{\cdot}0.4H_2O$: C, 68.76; H, 8.26; N, 7.52. Found: C, 68.85; H, 8.06; N, 7.53.

4.8.5. (*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-(2-{5-methyl-2-{[(1*E*)-4-methylpenten-1-yl]oxazol-4-yl}ethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (14e)

Yield 75%. A white solid. Mp 122.5–125 °C. $[\alpha]_D^{20}$ −11.2 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.75–1.30 (15H, m), 1.60–2.00 (4H, m), 2.10 (2H, t, *J* = 6.8 Hz), 2.28 (3H, s), 2.86 (2H, t, *J* = 6.8 Hz), 2.90–3.40 (2H, m), 4.11 (2H, t, *J* = 6.8 Hz), 4.30–5.25 (3H, m), 6.00–7.50 (7H, m). IR (Nujol) cm^{-1}: 1653, 1630, 1551, 1504. MS *m*/*z*: 479 $[M+H]^+$. Anal. Calcd for $C_{28}H_{34}N_2O_5{\cdot}C_4H_{11}N{\cdot}0.5H_2O$: C, 68.54; H, 8.27; N, 7.49. Found: C, 68.42; H, 8.14; N, 7.48.

4.8.6. (*S*)-7-(2-{2-[(1*E*)-3,3-Dimethylpenten-1-yl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (14f)

Yield 82%. A white solid. Mp 138–140.5 °C. $[\alpha]_D^{20}$ −10.3 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.82 (3H, t, *J* = 7.3 Hz), 0.98 (9H, s), 1.05 (6H, s), 1.41 (2H, q, *J* = 7.3 Hz), 1.63–1.94 (3H, m), 2.28 (3H, s), 2.86 (2H, t, *J* = 6.8 Hz), 2.90–3.37 (2H, m), 4.11 (2H, t, *J* = 6.8 Hz), 4.23–5.20 (3H, m), 6.00–7.39 (12H, m). IR (Nujol) cm^{-1}: 3400, 2745, 2635, 2544, 2220, 1651, 1622, 1553. MS *m*/*z*: 493 $[M+H]^+$. Anal. Calcd for $C_{29}H_{36}N_2O_5{\cdot}C_4H_{11}N{\cdot}0.5H_2O$: C, 68.96; H, 8.42; N, 7.31. Found: C, 69.05; H, 8.34; N, 7.32.

4.8.7. (*S*)-7-(2-{2-[(1*E*)-4,4-Dimethylpenten-1-yl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]- 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (14g)

Yield 59%. A white solid. Mp 147–149.5 °C. $[\alpha]_D^{20}$ −16.8 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.94 (9H, s), 1.01 (9H, s), 1.65–1.95 (4H, m), 2.09 (2H, d, *J* = 7.5 Hz), 2.28 (3H, s), 2.86 (2H, t, *J* = 6.6 Hz), 2.90–3.35 (2H, m), 4.11 (2H, t, *J* = 6.6 Hz), 4.30–5.20 (3H, m), 5.90–7.40 (12H, m). IR (Nujol) cm^{-1}: 1657, 1634, 1611, 1558, 1506. MS *m*/*z*: 493 $[M+H]^+$. Anal. Calcd for $C_{29}H_{36}N_2O_5{\cdot}C_4H_{11}N{\cdot}0.8H_2O$: C, 68.32; H, 8.44; N, 7.44. Found: C, 68.29; H, 8.32; N, 7.29.

4.8.8. (*S*)-7-(2-{2-[(1*E*)-3-Ethylpenten-1-yl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (14h)

Yield 63%. A white solid. Mp 154–156 °C. $[\alpha]_D^{20}$ −15.6 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.87 (6H, t, *J* = 7.2 Hz), 0.96 (9H, s), 1.20–1.63 (4H, m), 1.63–2.10 (4H, m), 2.28 (3H, s), 2.86 (2H, t, *J* = 6.8 Hz), 2.90–3.04 (1H, m), 3.12–3.28 (1H, m), 4.11 (2H, t, *J* = 6.8 Hz), 4.40–5.30 (3H, m), 5.80–7.60 (12H, m). IR (Nujol) cm^{-1}: 2735, 2633, 2544, 1653, 1624, 1599, 1551, 1506. MS *m*/*z*: 493 $[M+H]^+$. Anal. Calcd for $C_{29}H_{36}N_2O_5{\cdot}C_4H_{11}N{\cdot}0.5H_2O$: C, 68.96; H, 8.42; N, 7.31. Found: C, 68.95; H, 8.24; N, 7.34.

4.8.9. (*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-[2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (14i)

Yield 51%. A white solid. Mp 155–158.5 °C. $[\alpha]_D^{20}$ −22.0 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 0.90 (6H, d, *J* = 6.3 Hz), 0.97 (9H, s), 1.20–1.70 (3H, m), 1.70–1.98 (3H, m), 2.06–2.40 (2H, m), 2.27 (3H, s), 2.86 (2H, t, *J* = 6.4 Hz), 2.90–3.25 (2H, m), 4.10 (2H, t, *J* = 6.4 Hz), 4.25–5.20 (3H, m), 5.72–7.38 (12H, m). IR (Nujol)

cm^{-1}: 3400, 2735, 2635, 2550, 1657, 1634, 1558, 1506. MS *m*/*z*: 493 $[M+H]^+$. Anal. Calcd for $C_{29}H_{36}N_2O_5{\cdot}C_4H_{11}N{\cdot}0.1H_2O$: C, 69.84; H, 8.38; N, 7.40. Found: C, 69.61; H, 8.37; N, 7.43.

4.8.10. (*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-3-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (14j)

Yield 76%. A white solid. Mp 102–104.5 °C. $[\alpha]_D^{20}$ −1.1 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.6 Hz), 0.99 (9H, s), 1.08 (3H, d, *J* = 6.6 Hz), 1.25–1.41 (4H, m), 1.75–2.00 (3H, m), 2.26–2.35 (1H, m), 2.27, 2.28 (total 3H, s, s), 2.80–3.28 (4H, m), 4.09, (1H, t, *J* = 6.6 Hz), 4.11 (1H, t, *J* = 6.6 Hz), 4.40–5.10 (3H, m), 5.10–6.60 (8H, m), 6.60–6.70 (1H, m), 6.90–7.30 (2H, m). IR (Nujol) cm^{-1}: 2737, 2633, 2544, 1653, 1634, 1553, 1504. MS *m*/*z*: 493 $[M+H]^+$.

4.8.11. (*S*)-7-(2-{2-[(1*E*)-1,5-Dimethylhexen-1-yl]-5-methyloxazol-4-yl}ethoxy)-2-[(2*E*,4*E*)-hexadienoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (14k)

Yield 42%. A white solid. Mp 119–121 °C. $[\alpha]_D^{20}$ −11.3 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.91 (6H, d, *J* = 6.6 Hz), 0.98 (9H, s), 1.33 (2H, dt, *J* = 7.8, 7.6 Hz), 1.75–2.00 (3H, m), 2.01 (3H, s), 2.21 (2H, dt, *J* = 7.8, 7.6 Hz), 2.27, 2.28 (total 3H, s, s), 2.87 (1H, t, *J* = 6.8 Hz), 2.88 (1H, t, *J* = 6.8 Hz), 2.94 (0.5H, dd, *J* = 15.4, 6.1 Hz), 3.01 (0.5H, dd, *J* = 15.9, 6.1 Hz), 3.00–3.25 (1H, m), 4.09 (1H, t, *J* = 6.8 Hz), 4.10 (1H, t, *J* = 6.8 Hz), 4.40–5.10 (3H, m), 5.10–6.60 (3H, br), 5.90–6.45 (4H, m), 6.56–6.67 (2H, m), 6.93 (0.5H, d, *J* = 8.3 Hz), 6.96 (0.5H, d, *J* = 8.3 Hz), 7.18 (0.5H, dd, *J* = 14.9, 10.7 Hz), 7.20 (0.5H, dd, *J* = 14.9, 10.7 Hz). IR (Nujol) cm^{-1}: 1655, 1632, 1611, 1556, 1504. MS *m*/*z*: 507 $[M+H]^+$. Anal. Calcd for $C_{30}H_{38}N_2O_5{\cdot}C_4H_{11}N{\cdot}0.8H_2O$: C, 68.73; H, 8.58; N, 7.07. Found: C, 68.74; H, 8.41; N, 7.04.

4.8.12. (*S*)-2-[(2*E*,4*E*)-Hexadienoyl]-7-{2-[5-methyl-2-(5-methylhexyl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (14l)

Yield 76%. A white solid. Mp 150.5–153.5 °C. $[\alpha]_D^{20}$ −19.0 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.86 (6H, d, *J* = 6.6 Hz), 0.99 (9H, s), 1.13–1.23 (2H, m), 1.28–1.39 (2H, m), 1.52 (1H, heptet, *J* = 6.6 Hz), 1.70 (2H, quintet, *J* = 7.6 Hz), 1.77 (1.2H, d, *J* = 7.3 Hz), 1.85 (1.8H, d, *J* = 7.3 Hz), 2.23, 2.24 (total 3H, s, s), 2.65 (2H, t, *J* = 7.3 Hz), 2.78–2.88 (2H, m), 2.89–3.05 (1H, m), 3.08–3.26 (1H, m), 4.02–4.13 (2H, m), 4.44, 5.01 (0.8H, AB-q, *J* = 17.6 Hz), 4.60–4.74 (1.6H, m), 5.01–5.08 (0.6H, m), 5.50–6.60 (3H, br), 5.94–6.35 (3H, m), 6.55–6.68 (2H, m), 6.93 (0.4H, d, *J* = 8.8 Hz), 6.97 (0.6H, d, *J* = 8.3 Hz), 7.13–7.24 (1H, m). IR (Nujol) cm^{-1}: 1655, 1628, 1556, 1506. MS *m*/*z*: 495 $[M+H]^+$. Anal. Calcd for $C_{29}H_{38}N_2O_5{\cdot}C_4H_{11}N{\cdot}0.1H_2O$: C, 69.59; H, 8.71; N, 7.38. Found: C, 69.27; H, 8.46; N, 7.34.

4.8.13. (*S*)-2-[(2*E*,4*E*)-5-Methylhexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16a)

Yield 83%. A white solid. Mp 138–140.5 °C. ^1H NMR ($CDCl_3$) δ: 0.90 (6H, d, *J* = 6.6 Hz), 1.01 (9H, s), 1.30–1.39 (2H, m), 1.52–1.66 (1H, m), 1.80, 1.84, 1.86, 1.87 (total 6H, s, s, s, s), 2.17–2.28 (2H, m), 2.27, 2.28 (total 3H, s, s), 2.86 (2H, t, *J* = 6.8 Hz), 2.90–3.30 (2H, m), 4.10 (2H, t, *J* = 6.8 Hz), 4.25–5.20 (6H, m), 5.80–6.45 (3H, s), 6.52–6.68 (3H, m), 6.91–7.01 (1H, m), 7.45–7.55 (1H, m). IR (Nujol) cm^{-1}: 2743, 2637, 2552, 1655, 1626, 1603, 1556, 1506. MS *m*/*z*: 507 $[M+H]^+$. Anal. Calcd for $C_{30}H_{38}N_2O_5{\cdot}C_4H_{11}N$: C, 70.44; H, 8.52; N, 7.25. Found: C, 70.31; H, 8.31; N, 7.19.

4.8.14. (*S*)-2-[(2*E*,4*E*)-2-Methylhexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16b)

Yield 84%. A white solid. Mp 123–127 °C (dec). ^1H NMR ($CDCl_3$) δ: 0.90 (6H, d, *J* = 6.6 Hz), 0.99 (9H, s), 1.30–1.39 (2H, m), 1.52–1.66 (1H, m), 1.77–1.86 (3H, m), 1.88 (3H, s), 2.17–2.26 (2H, m), 2.27 (3H, s), 2.86 (2H, t, *J* = 6.8 Hz), 2.92–3.30 (2H, m), 4.10 (2H, t, *J* = 6.8 Hz), 4.25–5.20 (3H, m), 5.00–6.50 (3H, br), 5.67–5.85 (1H, m), 6.04–6.33 (3H, m), 6.50–6.70 (3H, m), 6.88–7.38 (1H, m). IR (Nujol) cm^{-1}: 2731, 2637, 2552, 1636, 1612, 1558, 1506. MS *m*/*z*: 507 $[M+H]^+$.

4.8.15. (*S*)-2-[(2*E*)-Hexenoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16c)

Yield 73%. A white solid. Mp 124–126.5 °C. ^1H NMR ($CDCl_3$) δ: 0.90 (6H, d, *J* = 6.6 Hz), 0.95 (3H, t, *J* = 7.3 Hz), 0.97 (9H, s), 1.35 (2H, dt, *J* = 8.3, 7.1 Hz), 1.40–1.66 (3H, m), 2.06–2.27 (4H, m), 2.27, 2.28 (total 3H, s, s), 2.80–2.90 (2H, m), 2.90–3.30 (2H, m), 4.05–4.16 (2H, m), 4.30–5.20 (2H, m), 6.00–7.02 (10H, m). IR (Nujol) cm^{-1}: 2745, 2637, 2552, 1665, 1630, 1556, 1506. MS *m*/*z*: 495 $[M+H]^+$. Anal. Calcd for $C_{29}H_{38}N_2O_5{\cdot}C_4H_{11}N$: C, 69.81; H, 8.70; N, 7.40. Found: C, 69.60; H, 8.47; N, 7.39.

4.8.16. (*S*)-2-Hexanoyl-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16d)

Yield 79%. A white solid. Mp 135.5–139 °C. ^1H NMR ($CDCl_3$) δ: 0.88–0.93 (9H, m), 0.96 (9H, s), 1.28–1.41 (6H, m), 1.54–1.68 (3H, m), 2.18–2.27 (4H, m), 2.28 (3H, s), 2.32–2.44 (2H, m), 2.80–3.30 (4H, m), 4.05–4.16 (2H, m), 4.30–5.20 (2H, m), 6.00–7.20 (8H, m). IR (Nujol) cm^{-1}: 2743, 2637, 2552, 1639, 1612, 1589, 1558, 1506. MS *m*/*z*: 497 $[M+H]^+$. Anal. Calcd for $C_{29}H_{40}N_2O_5{\cdot}C_4H_{11}N$: C, 69.56; H, 9.02; N, 7.37. Found: C, 69.26; H, 8.81; N, 7.38.

4.8.17. (*S*)-2-(5-Hexenoyl)-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16e)

Yield 55%. A white solid. Mp 131–133 °C. ^1H NMR ($CDCl_3$) δ: 0.90 (6H, d, *J* = 6.6 Hz), 0.96 (9H, s), 1.30–1.40 (2H, m), 1.53–1.66 (1H, m), 1.67–1.79 (2H, m), 2.04–2.27 (4H, m), 2.27 (3H, s), 2.33–2.44 (2H, m), 2.80–2.90 (2H, m), 2.90–3.30 (2H, m), 4.05–4.16 (2H, m), 4.30–5.10 (5H, m), 6.00–7.20 (8H, m). IR (Nujol) cm^{-1}: 2745, 2637, 2550, 1651, 1612, 1589, 1556. MS *m*/*z*: 495 $[M+H]^+$. Anal. Calcd for $C_{29}H_{38}N_2O_5{\cdot}C_4H_{11}N$: C, 69.81; H, 8.70; N, 7.40. Found: C, 69.54; H, 8.69; N, 7.41.

4.8.18. (*S*)-7-(2-{5-Methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-2-(4-pentenoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16f)

Yield 77%. A white solid. Mp 134.5–136.5 °C. ^1H NMR ($CDCl_3$) δ: 0.90 (6H, d, *J* = 6.6 Hz), 1.01 (9H, s), 1.31–1.39 (2H, m), 1.52–1.65 (1H, m), 2.18–2.26 (2H, m), 2.27, 2.28 (total 3H, s, s), 2.32–2.43 (2H, m), 2.44–2.53 (2H, m), 2.80–3.30 (4H, m), 4.00–5.70 (10H, m), 5.78–5.92 (1H, m), 6.18 (1H, dt, *J* = 16.1, 1.5 Hz), 6.53–6.69 (3H, m), 6.90–7.00 (1H, m). IR (Nujol) cm^{-1}: 2746, 2637, 2548, 1645, 1612, 1556, 1506. MS *m*/*z*: 481 $[M+H]^+$. Anal. Calcd for $C_{28}H_{36}N_2O_5{\cdot}C_4H_{11}N$: C, 69.41; H, 8.56; N, 7.59. Found: C, 69.17; H, 8.42; N, 7.57.

4.8.19. (*S*)-2-(3-Cyclopropylacryloyl)-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16g)

Yield 72%. A white solid. Mp 124–127 °C. ^{1}H NMR ($CDCl_3$) δ: 0.48–0.65 (1H, m), 0.80–0.90 (2H, m), 0.90 (6H, d, J = 6.6 Hz), 1.02 (9H, s), 1.29–1.39 (2H, m), 1.44–1.54 (1H, m), 1.54–1.67 (1H, m), 2.17–2.26 (2H, m), 2.27 (3H, s), 2.81–2.90 (2H, m), 2.90–3.28 (2H, m), 4.04–4.15 (2H, m), 4.39–5.70 (6H, m), 6.13–6.70 (6H, m), 6.92–7.03 (1H, m). IR (Nujol) cm^{-1}: 2741, 2635, 2550, 1661, 1614, 1556. MS m/z: 493 [M+H]$^+$. Anal. Calcd for $C_{29}H_{36}N_2O_5{\cdot}C_4H_{11}N{\cdot}0.5H_2O$: C, 68.96; H, 8.42; N, 7.31. Found: C, 68.96; H, 8.42; N, 7.34.

4.8.20. (*S*)-2-[(2*E*, 4*E*)-6-Hydroxyhexadienoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16h)

Yield 63%. A white solid. Mp 117–120 °C. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 1.00 (9H, s), 1.35 (2H, dt, J = 8.3, 6.8 Hz), 1.52–1.64 (1H, m), 2.18–2.27 (2H, m), 2.27 (3H, s), 2.86 (2H, t, J = 6.8 Hz), 2.92–3.23 (2H, m), 4.05–4.14 (2H, m), 4.17–4.28 (2H, m), 4.40–5.10 (3H, m), 5.20–6.80 (11H, m), 6.92–7.00 (1H, m), 7.09–7.23 (1H, m). IR (Nujol) cm^{-1}: 3337, 1651, 1622, 1558, 1504. MS m/z: 509 [M+H]$^+$. Anal. Calcd for $C_{29}H_{36}N_2O_6{\cdot}C_4H_{11}N{\cdot}0.6H_2O$: C, 66.89; H, 8.20; N, 7.09. Found: C, 66.73; H, 8.14; N, 7.00.

4.8.21. (*S*)-2-[(2*E*)-4-Hydroxyhexenoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16i)

Yield 31%. A white solid. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 1.05–1.10 (12H, m), 1.34 (2H, dt, J = 7.8, 7.1 Hz), 1.52–1.72 (4H, m), 2.18–2.27 (2H, m), 2.28 (3H, s), 2.82–2.93 (2H, m), 2.95–3.29 (2H, m), 4.05–4.14 (2H, m), 4.11–4.34 (1H, m), 4.42–4.96 (3H, m), 5.10–6.30 (4H, m), 6.54–6.76 (4H, m), 6.96–7.07 (2H, m). IR (Nujol) cm^{-1}: 3377, 1661, 1614, 1553, 1504. MS m/z: 511 [M+H]$^+$.

4.8.22. (*S*)-2-[(2*E*)-4-Ethoxybutenoyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16j)

Yield 60%. A white solid. Mp 101.5–104 °C. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 1.04 (9H, s), 1.19, 1.26 (total 3H, t, t, J = 7.1 Hz), 1.30–1.39 (2H, m), 1.53–1.65 (1H, m), 2.17–2.26 (2H, m), 2.27, 2.28 (total 3H, s, s), 2.85, 2.88 (total 2H, t, t, J = 6.6 Hz), 2.90–3.30 (2H, m), 3.49, 3.56 (total 2H, q, q, J = 7.1 Hz), 3.60–5.10 (9H, m), 6.18 (1H, dt, J = 15.9, 1.5 Hz), 6.40–7.02 (6H, m). IR (Nujol) cm^{-1}: 2743, 2635, 2550, 1665, 1622, 1558, 1506. MS m/z: 511 [M+H]$^+$. Anal. Calcd for $C_{29}H_{38}N_2O_6{\cdot}C_4H_{11}N{\cdot}0.5H_2O$: C, 66.86; H, 8.50; N, 7.09. Found: C, 66.98; H, 8.37; N, 7.10.

4.8.23. (*S*)-2-[(2*E*)-3-Ethoxyacryloyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16k)

Yield 82%. A white solid. Mp 141.5–144 °C. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 1.00 (9H, s), 1.24–1.40 (5H, m), 1.54–1.67 (1H, m), 2.18–2.27 (2H, m), 2.28 (3H, s), 2.80–3.30 (4H, m), 3.80–4.00 (2H, m), 4.05–4.15 (2H, m), 4.40–5.10 (3H, m), 5.60–5.75 (1H, m), 5.80–7.30 (8H, m), 7.50 (1H, d, J = 11.7 Hz). IR (Nujol) cm^{-1}: 2742, 2635, 2550, 1663, 1641, 1601, 1556, 1506. MS m/z: 497 [M+H]$^+$. Anal. Calcd for $C_{28}H_{36}N_2O_6{\cdot}C_4H_{11}N$: C, 67.46; H, 8.31; N, 7.38. Found: C, 67.23; H, 8.25; N, 7.39.

4.8.24. (*S*)-2-(3-Ethoxypropionyl)-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16l)

Yield 67%. A white solid. Mp 121–124 °C. ^{1}H NMR ($CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz), 0.96 (9H, s), 1.15, 1.17 (total 3H, t, t, J = 6.8 Hz), 1.30–1.40 (2H, m), 1.54–1.67 (1H, m), 2.18–2.27 (2H, m), 2.27, 2.28 (total 3H, s, s), 2.44–2.82 (2H, m), 2.83–3.30 (6H, m), 3.48–3.54 (2H, m), 3.66–3.78 (2H, m), 4.09, 4.11 (total 2H, t, t, J = 6.8 Hz), 4.30–5.10 (3H, m), 6.14–6.24 (1H, m), 6.53–6.70 (3H, m), 6.91–6.98 (1H, m). IR (Nujol) cm^{-1}: 2745, 2637, 2550, 1655, 1611, 1558, 1506. MS m/z: 499 [M+H]$^+$. Anal. Calcd for $C_{28}H_{38}N_2O_6{\cdot}C_4H_{11}N$: C, 67.22; H, 8.64; N, 7.35. Found: C, 66.96; H, 8.47; N, 7.38.

4.8.25. (*S*)-2-[(2*E*)-3-(Furan-2-yl)acryloyl]-7-(2-{5-methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16m)

Yield 80%. A white solid. Mp 114.5–117 °C. ^{1}H NMR ($CDCl_3$) δ: 0.89 (6H, d, J = 6.6 Hz), 0.97 (9H, s), 1.30–1.39 (2H, m), 1.53–1.65 (1H, m), 2.17–2.26 (2H, m), 2.27, 2.28 (total 3H, s, s), 2.80–3.30 (4H, m), 4.07–4.13 (2H, m), 4.40–5.10 (3H, m), 5.20–6.86 (9H, m), 6.81–7.00 (2H, m), 7.34–7.50 (2H, m). IR (Nujol) cm^{-1}: 2741, 2635, 2552, 1655, 1614, 1556, 1506. MS m/z: 519 [M+H]$^+$.

4.8.26. (*S*)-7-(2-{5-Methyl-2-[(1*E*)-5-methylhexen-1-yl]oxazol-4-yl}ethoxy)-2-[(2*E*)-3-(thiophen-2-yl)acryloyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butylamine salt (16n)

Yield 84%. A white solid. Mp 119–122 °C. ^{1}H NMR ($CDCl_3$) δ: 0.89 (6H, d, J = 6.8 Hz), 0.98 (9H, s), 1.30–1.39 (2H, m), 1.52–1.65 (1H, m), 2.17–2.26 (2H, m), 2.27, 2.28 (total 3H, s, s), 2.80–3.30 (4H, m), 4.07–4.13 (2H, m), 4.40–5.07 (3H, m), 5.10–6.86 (4H, m), 6.53–6.67 (3H, m), 6.69–6.79 (2H, m), 6.90–7.06 (2H, m), 7.11–7.32 (2H, m), 7.69–7.79 (1H, m). IR (Nujol) cm^{-1}: 2737, 2633, 2550, 1651, 1611, 1553, 1506. MS m/z: 535 [M+H]$^+$. Anal. Calcd for $C_{30}H_{34}N_2O_5S{\cdot}C_4H_{11}N{\cdot}0.3H_2O$: C, 66.64; H, 7.59; N, 6.82. Found: C, 66.59; H, 7.38; N, 6.80.

4.9. Partition coefficient at pH 7.0

Log$D_{7.0}$ values (logarithm of *n*-octanol–water partition coefficients at pH 7.0) were determined by HPLC methods.[31] Acetanilide, benzonitrile, benzene, bromobenzene, biphenyl and hexachlorobenzene, the log$D_{7.0}$ values of which are known, were used as reference substances. Test compounds and reference substances were dissolved in acetonitrile containing 1% dimethylsulfoxide (DMSO) at 10 μg/ml, and then 10 μl of the solution was injected into the HPLC system. The HPLC equipment consisted of a pump (PU-980; JASCO Corporation), a UV detector (UV-970; JASCO Corporation), an autoinjector (AS-950; JASCO Corporation), and a Cosmosil 5C18-AR-II column (5 μm, 4.6 mm × 150 mm; Nacalai Tesque, Inc., Kyoto, Japan). Phosphate buffer (pH 7.0)–MeOH (8:2) was used as the eluent. The capacity factors of test substances and reference substances were calculated from their retention time. The log$D_{7.0}$ values of test compounds were calculated using these capacity factors and the reported log$D_{7.0}$ values of reference substances.

4.10. PPARγ and PPARα agonist activity

Full-length human PPARγ1 plasmid (Open Biosystems, Huntsville, USA) or human PPARα plasmid (GeneCopoeia Inc., Rockville, USA), and human RXRα plasmid (GeneCopoeia Inc.) with reporter plasmid pGL3-PPREx4-tk-luc were electroporated into COS-1 cells

(Dainippon Sumitomo Pharma Co. Ltd, Osaka, Japan) using Nucleofator II (AAD-1001S, Lonza Group Ltd, Basel, Switzerland). The cells were incubated for 24 h in the presence or absence of the test compound in Dulbecco's modified Eagle's medium (DMEM; Nissui Pharmaceutical Co., Ltd, Tokyo, Japan) containing 10% FBS under 5% CO_2 at 37 °C. The medium was removed and then luciferase activities were determined using a commercial kit (PicaGene LT7.5; TOYO B-Net Co., Ltd, Tokyo, Japan) and a microplate luminescence reader (Dainippon Sumitomo Pharma Co. Ltd). EC_{50} values and the maximal activation level relative to the level activated by farglitazar, a PPARγ agonist (10^{-7} M), or Wy-14643, a PPARα agonist (10^{-5} M), were determined.

4.11. PTP-1B inhibitory activity

PTP-1B inhibitory activities were determined in the absence or presence of the test compound in 50 mM sodium acetate buffer (pH 5.5) containing the enzyme, 1 mM *p*-nitrophenylphosphonic acid (*p*NPP), 1 mM dithiothreitol and 1 mM EDTA. The reaction was started by addition of the *p*NPP 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.

4.12. Hypoglycemic and hypotriglyceridemic effects in Male KK-A^y mice

Male KK-A^y mice (11 weeks old; Clea Japan, Inc., Tokyo) were allocated to control and treated groups (n = 4–5). Test compounds were suspended in 0.5% methylcellulose solution and orally administered once a day for 4 or 14 days. 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 Chemicals, Co. Ltd, Osaka, Japan).

4.13. Effects of repeated administration of 14i and rosiglitazone for 28 days in female SD rats

Female SD rats (6 weeks old; Charles River Japan, Yokohama, Japan) were allocated to control and treated groups (n = 5). Compound **14i** and rosiglitazone were suspended in 0.5% methylcellulose solution and administered at 12.5, 25, 50 and 100 mg/kg/day for 28 days to the treated group, and vehicle to the control group. The general condition was observed daily and body weight was measured. The rats were bled to death from the abdominal aorta under deep anesthesia, and Ht and RBC were determined.

4.14. Plasma concentration after oral administration of 14i and rosiglitazone in male SD rats

Male SD rats (7 weeks old; Japan SLC, Inc., Hamamatsu, Japan) were used. Compound **14i** and rosiglitazone 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 each drug were determined using an HPLC system consisting of a pump (PU-980; JASCO, Tokyo, Japan), UV detector (UV-970; JASCO), autoinjector (AS-950; JASCO), and STR-ODS-II column (5 μm, 4.6 mm × 150 mm; Shimadzu Techno-research, Kyoto, Japan).

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.11.035. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Bloomgarden, Z. T. *Diabetes Care* **2005**, *28*, 488.
2. Lebovitz, H. E.; Banerji, M. A. *Recent Prog. Horm. Res.* **2001**, *56*, 265.
3. Tack, C. J.; Smits, P. *Neth. J. Med.* **2006**, *64*, 166.
4. Staels, B. *Cell Metab.* **2005**, *2*, 77.
5. Lehrke, M.; Lazar, M. A. *Cell* **2005**, *123*, 993.
6. Krische, D. *West. J. Med.* **2000**, *173*, 54.
7. Hussein, Z.; Wentworth, J. M.; Nankervis, A. J.; Proietto, J.; Colman, P. G. *Med. J. Aust.* **2004**, *181*, 536.
8. Everett, L.; Galli, A.; Crabb, D. *Liver* **2000**, *20*, 191.
9. Chou, C. J.; Haluzik, M.; Gregory, C.; Dietz, K. R.; Vinson, C.; Gavrilova, O.; Reitman, M. L. *J. Biol. Chem.* **2002**, *277*, 24484.
10. Kuwabara, K.; Murakami, K.; Todo, M.; Aoki, T.; Asaki, T.; Murai, M.; Yano, J. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 970.
11. Koh, K. K.; Han, S. H.; Quon, M. J.; Yeal, A. J.; Shin, E. K. *Diabetes Care* **2005**, *28*, 1419.
12. Chaput, E.; Saladin, R.; Silvestre, M.; Edgar, A. D. *Biochem. Biophys. Res. Commun.* **2000**, *271*, 445.
13. Yajima, K.; Hirose, H.; Fujita, H.; Seto, Y.; Fujita, H.; Ukeda, K.; Miyashita, K.; Kawai, T.; Yamamoto, Y.; Ogawa, T.; Yamada, T.; Saruta, T. *Am. J. Physiol. Endocrinol. Metab.* **2003**, *284*, E966.
14. Fievet, C.; Fruchart, J.; Staels, B. *Curr. Opin. Pharmacol.* **2006**, *6*, 606.
15. Henke, B. R. *J. Med. Chem.* **2004**, *47*, 4118.
16. Ebdrup, S.; Pettersson, I.; Rasmussen, H. B.; Deussen, H. J.; Jensen, A. F.; Mortensen, S. B.; Fleckner, J.; Pridal, L.; Nygaard, L.; Sauerberg, P. *J. Med. Chem.* **2003**, *46*, 1306.
17. Devasthale, P. V.; Chen, S.; Jeon, Y.; Qu, F.; Shao, C.; Wang, W.; Zhang, H.; Cap, M.; Farrelly, D.; Golla, R.; Grover, G.; Harrity, T.; Ma, Z.; Moore, L.; Ren, J.; Seethala, R.; Cheng, L.; Sleph, P.; Sun, W.; Tieman, A.; Wetterau, J. R.; Doweyko, A.; Chandrasena, G.; Chang, S. Y.; Humphreys, W. G.; Sasseville, V. G.; Biller, S. A.; Ryono, D. E.; Selan, F.; Hariharan, N.; Cheng, P. T. *J. Med. Chem.* **2005**, *48*, 2248.
18. Cronet, P.; Petersen, J. F.; Folmer, R.; Blomberg, N.; Sjoblom, K.; Karlsson, U.; Lindstedt, E. L.; Bamberg, K. *Structure* **2001**, *9*, 699.
19. Imoto, H.; Matsumoto, M.; Odaka, H.; Sakamoto, J.; Kimura, H.; Nonaka, M.; Yutaka, K.; Momose, Y. *Chem. Pharm. Bull.* **2004**, *52*, 120.
20. Michalik, L.; Auwerx, J.; Berger, J. P.; Chatterjee, V. K.; Glass, C. K.; Gonzalez, F. J.; Grimaldi, P. A.; Kadowaki, T.; Lazar, M. A.; O'Rahilly, S.; Palmer, C. N. A.; Plutzky, J.; Reddy, J. K.; Spiegelman, B. M.; Staels, B.; Wahli, W. *Pharmacol. Rev.* **2006**, *58*, 726.
21. Lai, D. Y. *J. Environ. Sci. Health C. Environ. Carcinog. Ecotoxicol. Rev.* **2004**, *22*, 37.
22. Cornwell, P. D.; De Souza, A. T.; Ulrich, R. G. *Mutat. Res.* **2004**, *549*, 131.
23. Zungu, M.; Felix, R.; Essop, M. F. *Mitochondrion* **2006**, *6*, 315.
24. Rubenstrunk, A.; Hanf, R.; Hum, D. W.; Fruchart, J. C.; Staels, B. *Biochim. Biophys. Acta* **2007**, *1771*, 1065.
25. Otake, K.; Azukizawa, S.; Takahashi, K.; Fukui, M.; Shibabayashi, M.; Kamemoto, H.; Kasai, M.; Shirahase, H. *Chem. Pharm. Bull.* **2011**, *59*, 876.
26. Thareja, S.; Aggarwal, S.; Bhardwaj, T. R.; Kumar, M. *Med. Res. Rev.* **2010**, Sep. 2 [Epub ahead of print].
27. Azukizawa, S.; Kasai, M.; Takahashi, K.; Miike, T.; Kunishiro, K.; Kanda, M.; Mukai, C.; Shirahase, H. *Chem. Pharm. Bull.* **2008**, *56*, 335.
28. Gampe, R. T.; Montana, V. G.; Lambert, M. H.; Miller, A. B.; Bledsoe, R. K.; Milburn, M. V.; Kliewer, S. A.; Willson, T. M.; Xu, H. E. *Mol. Cell.* **2000**, *5*, 545.
29. Ala, P. J.; Gonneville, L.; Hillman, M.; Becker-Pasha, M.; Yue, E. W.; Douty, B.; Wayland, B.; Polam, P.; Crawley, M. L.; McLaughlin, E.; Sparks, R. B.; Glass, B.; Takvorian, A.; Combs, A. P.; Burn, T. C.; Hollis, G. F.; Wynn, R. *J. Biol. Chem.* **2006**, *281*, 38013.
30. Wrobel, J.; Sredy, J.; Moxham, C.; Dietrich, A.; Li, Z.; Sawicki, D. R.; Seestaller, L.; Wu, L.; Katz, A.; Sullivan, D.; Tio, C.; Zhang, Z. Y. *J. Med. Chem.* **1999**, *42*, 3199.
31. Masumoto, K.; Takeyasu, A.; Oizumi, K.; Kobayashi, T. *Yakugaku Zasshi* **1995**, *115*, 213.