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Discovery of novel tricyclic compounds as squalene synthase inhibitors

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ABSTRACT

In the present article, we have reported the design, synthesis, and identification of highly potent benzhydrol derivatives as squalene synthase inhibitors (compound **1**). Unfortunately, the in vivo efficacies of the compounds were not enough for acquiring the clinical candidate. We continued our investigation to obtain a more in vivo efficacious template than the benzhydrol template.

In our effort, we focused on a benzoxazepine ring and designed a new tricyclic scaffold by the incorporation of heterocycle into it. Prepared pyrrolobenzoxazepine derivatives showed further efficient in vitro and in vivo activities.

1. Introduction

The western dietary pattern has increased hyperlipidemia around the world. The high level serum low density lipoprotein (LDL) cholesterol is one of the risk factors associated with coronary heart disease (CHD). 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, statins, were regarded as the first line medicine for the patients who have higher serum level of LDL cholesterol.

Statins' CHD risk reducing abilities, owing to their LDL cholesterol lowering effects, were proofed by many clinical trials.[1] However, statins have potential adverse effects, such as myotoxicity, muscle pain and, in very rare case, rhabdomyolysis.[2] Because of the inhibition of HMG-CoA reductase also interferes with the synthesis of many biologically essential non-steroidal isoprenoid molecules. Cerivastatin, one of the strongest statin, was withdrawn from the world market in 2001, due to its adverse effect.[3]

In the cholesterol biosynthesis cascade, squalene synthase is located in the downstream of HMG-CoA reductase and the first step of the steroids synthesis.[4] This means the inhibitor of the enzyme prevents cholesterol biosynthesis without interrupting isoprenoids production.[5] In other words, the squalene synthase inhibitor has a chance of avoiding the statin's adverse effects.

Medicinal chemistry efforts to identify small and efficient squalene synthase inhibitors have been reported by some research groups.[6]

We have already reported an original 2-aminobenzhydrol template for highly potent squalene synthase inhibitors.[7] Interestingly, these compounds formed 11-membered ring active conformations with intramolecular hydrogen bonds between its benzhydrol hydroxyl part and side chain amide carbonyl oxygen in the squalene synthase catalytic domain. Moreover, we have recently disclosed the fixation of active conformation without loss of the activities by using alkoxy-aminobenzhydrol template.[8] These compounds showed in vitro strong inhibitory activities, their IC_{50} values reaching nanomolar order and the derivatives demonstrated plasma lipid-lowering effects in repeated dose studies in animal models.

Unfortunately, the in vivo efficacies of these compounds were not enough for acquiring the clinical candidate in spite of their strong in vitro activities. We needed to obtain a more in vivo efficacious template than the benzhydrol derivatives.

We anticipated the reasons why these compounds were insufficient in vivo. One, the intramolecular hydrogen bond was probably inadequate to keep the active conformation. Another, their metabolic and chemical instabilities were likely to cause their insufficient concentrations of compounds in target organ (liver).

To obtain a more effective template in the biological condition, we focused on the benzoxazepine ring structure, because ether bond was more stable than the intramolecular hydrogen bond of the benzhydrol part.[9] Furthermore, we designed a new tricyclic

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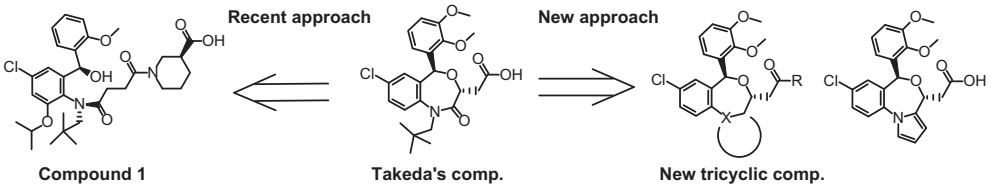


Figure 1.

scaffold which incorporated one more heteroaryl ring within the benzoxazepine bicyclic template, instead of the bulky neopentyl amide part, to aim at fixing the template more rigid and improving the in vivo stability. Initially, we synthesized five membered pyrrole ring incorporated tricyclic compounds, as shown in Figure 1.

In this article, we will describe our investigation of the discovery of further in vivo efficacious novel tricyclic compounds, as well as their structure–activity relationship (SAR) as squalene synthase inhibitors, and in vivo lipid lowering effects in animal models.

2. Result

2.1. Chemistry

A series of the novel pyrrolobenzoxazepine derivatives were prepared from 2-aminobenzophenone via Michael reaction of α,β-unsaturated ester as shown in Scheme 1. Commercially available 2-aminobenzophenone **2** was treated by 2,4-dimethoxytetrahydrofuran and acetic acid to have a pyrrole compound **3**, followed by the Vilsmeier reaction to obtain aldehyde **4** in good yield. α,β-Unsaturated ester **5** was prepared by Wittig reagent from the aldehyde.

In our synthetic strategy to prepare the pyrrolobenzoxazepine template, seven membered oxazepine ring cyclization was the key step. First, we tried the basic condition to cyclize α,β-unsaturated ester attached benzhydrol intermediate **6**. However, the cyclization did not proceed. Second, we chose acidic conditions, by using excess amounts of formic acid or trifluoroacetic acid, and only a trace amount of cyclized compound was detected. Finally, we optimized the reaction condition by reducing the volume of trifluoroacetic acid, and obtained a cyclized pyrrolobenzoxazepine template **7**, containing small amount of cis isomer, from α,β-unsaturated methyl ester intermediate **6**. The following side chain conversion gave the ester and acid compounds **8**–**10**.

Then, we prepared 2-substituted pyrrole derivatives **11**–**13** from the tricyclic template, using *N*-chloro succinamide or the Mannich reaction with amines and formalin.

The upper aryl ring changed compounds were prepared from 2-bromoaniline **16** or *N*-Boc aniline **20** as outlined in Scheme 1. Pyrrole ring cyclization and coupling with aldehydes gave benzhydrols **17A**,**B**. Subsequent manganese oxidation of **17A**,**B** afforded benzophenones **18A**,**B**. From *N*-Boc aniline **20**, rtho lithiation and aldehyde coupling gave benzhydrol **21**, following manganese oxidation, acidic deprotection, and pyrrole cyclization afforded **18C**. Subsequent sequential steps, formilation, Wittig reaction, $NaBH_4$ reduction, and optimized acidic condition cyclization gave tricyclic ester intermediates. A series of acid derivatives **19A**–**C** were also prepared from these esters in a similar manner.

Chiral pyrrolobenzoxazepine ester compounds, (**4*R*,6*S*)-14a** and (**4*S*,6*R*)-14a**, were separated and purified by HPLC with the chiral column.

Side chain extended compounds were prepared from compound **7**. $LiAlH_4$ reduction of separated chiral ester **24**, following methanesulfonylation, cyano conversion, and hydrolysis gave extended acid. Amide derivatives were prepared same as the shorter amides (Scheme 2).

Heteroaryl substituted compounds were prepared from methansulfonate **26** as shown in Scheme 3. Azide intermediate **31** was obtained from **26** using sodium azide, and the following cyclization with various alkynes obtained 1,2,3-triazole derivatives **32a**–**f**. Other heteroaryl derivatives **34a**–**k** were prepared by direct substitutions of **26** with pyrazole or tetrazole rings. Hydrolysis of the esters gave final acids **33a**–**f** and **35a**–**k**, successively.

2.2. Evaluation and discussion

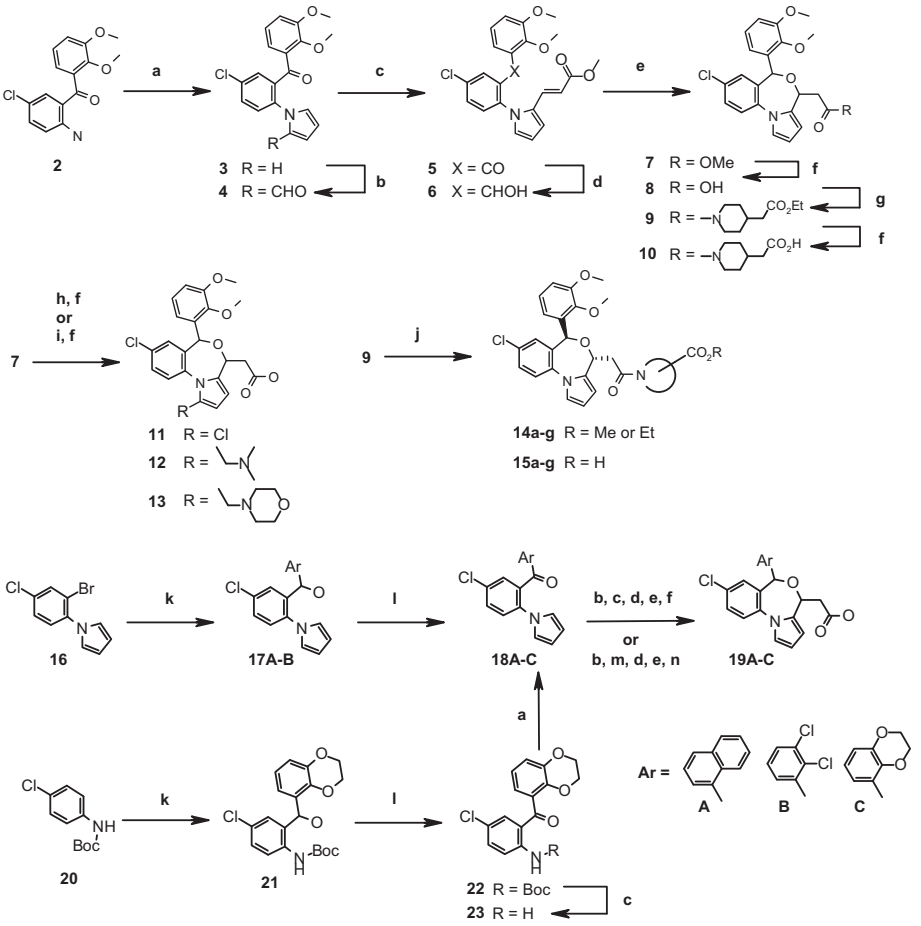
In order to obtain the structure–activity relationship (SAR), prepared derivatives were evaluated in terms of their squalene synthase inhibitory (SSI) activities and cholesterol synthesis inhibitory (CSI) activities in rat hepatic cells.[10] Cell-base CSI activity was used as a potential parameter to predict in vivo CSI activity, and was considered more important than SSI activity as a guide to afford effective cholesterol lowering medicine. Because CSI activity is including cell permeability and cell surface transporter recognition of evaluated compound. At the next stage, compounds were evaluated in an acute in vivo model; hepatic cholesterol synthesis inhibitory (in vivo CSI) activities were measured in rat 3 mg/kg single oral administration. The reduction of cholesterol in hepatic cell causes an expression of LDL receptor on the surface of the hepatic cell, via SREBP1 activation. As a consequence of an influx of LDL lipoprotein to hepatic cell, serum lipid levels are decreased.[11] Therefore, selected effective compounds were going to evaluate in final chronic model, serum lipid lowering test in marmoset 100 mg/kg/day orally repeated dose for 7 days.

As summarized in Table 1, firstly prepared pyrrolobenzoxazepine racemic compounds showed highly potent SSI activities. The acetic acid **8** and 4-piperidinyl acetic acid **10** showed low nanomolar order IC_{50} value (3.3 nM for **8**, 2.7 nM for **10**, respectively). The validity of our new designed template was proved by these data. The new tricyclic template would fix the direction of the upper ring part to appropriate positions in squalene synthase, like intramolecular hydrogen bonded 2-aminobenzhydrol derivatives, as expected.

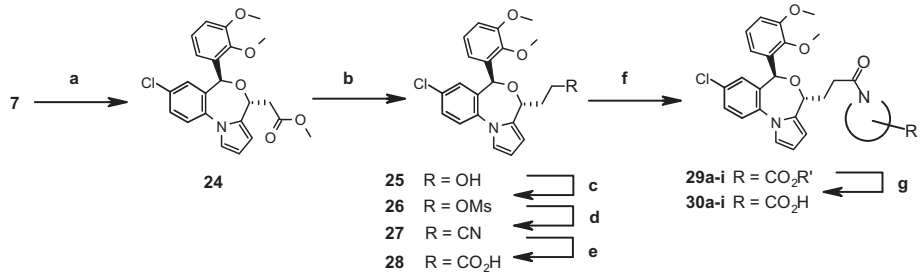
Moreover, two 1-substituted pyrrolobenzoxazepine derivatives, one being 1-chloro compound **11**, another being 1-morpholinylmethyl compound **12**, also showed high SSI potentials. It could be said that we had found a way to adjust physiological properties of the new template without loss of the potency. Furthermore, Table 1 suggested that the amide type side chain probably be superior to acetic acid side chain in terms of CSI activity. After that we focused on the amide side chain optimization.

To have SAR about the upper aryl ring part, we then tried to prepare and evaluate 2,3-dimethoxyphenyl ring replaced compounds, such as 1-naphtyl, 2,3-dichlorophenyl, and 1,4-benzdioxane-8-yl derivatives (**19A**–**C**). As a result, these compounds showed weaker SSI activities compared with **8** (Table 2), despite 1,4-benzdioxane-8-yl part showed one of the highest potency on the 2-aminobenzhydrol template.[7] Obviously, another SAR was obtained from our new template. We hypothesized that more rigid tricyclic template was recognized more strictly by the squalene synthase active cite.

At the next stage, we prepared chiral tricyclic compounds using the HPLC with chiral column, and prepared varied amide side chain compounds. The compounds and data were listed in Table 3. Only



Scheme 1. General synthetic procedure. Reagents and conditions: (a) 2,5-dimethoxytetrahydrofuran, AcOH, reflux, 1 h; (b) $POCl_3$, DMF, DCE, 50 °C, 3 h; (c) methyl (triphenylphosphoranylidene)acetate, toluene, 100 °C, 7 h; (d) $NaBH_4$, MeOH, rt, 1 h; (e) 1.5 equiv TFA, DCM, rt, 8 h; (f) K_2CO_3, MeOH–H_2O, rt; (g) amine, EDC, HOBt, DCM, rt; (h) NCS, THF, rt; (i) HCHO, amine, AcOH, rt; (j) HPLC separation by using CHIRALCEL OD (2-PrOH–Hexane); (k) *n*BuLi, THF, −78 °C then aldehyde; (l) MnO_2, DCM, 50 °C; (m) benzyl (triphenylphosphoranylidene)acetate; (n) H_2, Pd-C, MeOH.

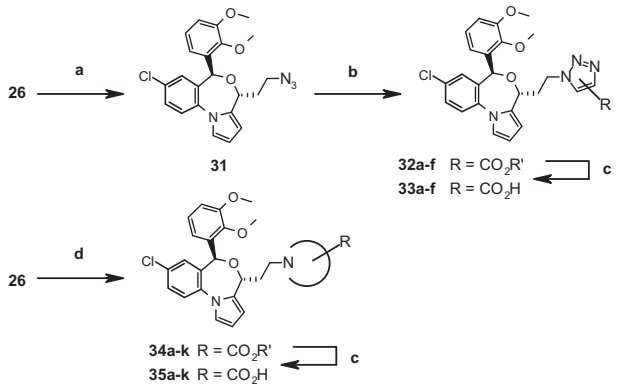


Scheme 2. Side chain extension. Reagents and conditions: (a) HPLC separation by using CHIRALCEL OD (2-PrOH–Hexane); (b) $LiAlH_4$, THF, 0 °C, 3 h; (c) MsCl, EtN_3, 0 °C, 3 h; (d) NaCN, DMSO, 50 °C, 13 h; (e) NaOH, 2-PrOH–H_2O, reflux; (f) amine, EDC, HOBt, DCM, rt; (g) K_2CO_3, MeOH–H_2O, rt.

(4*R*,6*S*)-isomers showed SSI activities, and many highly potent compounds were obtained, even though their CSI activities were insufficient.

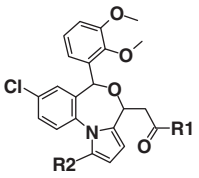
To elucidate the binding mode of our tricyclic template, we investigated the X-ray structure analysis of squalene synthase co-crystallized with compound (**4*R*,6*S*)-15a** (Fig. 2).[12] The tricyclic template with the upper ring part was deeply buried in the lipophilic pocket of the squalene synthase active site. There was no hydrogen bond interaction around the pyrrolobenzoxazepine template. Independently, Bayer's research team has reported a tricyclic template for squalene synthase inhibitors.[13] In the report, they focused on the water mediated hydrogen bond between the amide carbonyl group of the squalene synthase inhibitor (**CP-320473**) and Asn 215 observed in the published X-ray crystal structure (PDB ID: 1EZF)[14] and they designed an oxazolobenzoxazepine template to retain this hydrogen bond by replacing the amide carbonyl group to the oxazole ring. However, our original pyrrolobenzoxazepine template revealed that the hydrogen bond poorly contributed to the inhibitory activity, because our compounds demonstrated highly potent inhibitory activities without such a hydrogen bond. In other words, lipophilic interaction between the rigid scaffold and the lipophilic pocket of the enzyme caused such strong SSI activities.

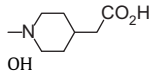
According to our X-ray structure analysis, the piperidine amide side chain is bending along with the slit to the active site of squalene synthase, and forming two hydrogen bonds with squalene



Scheme 3. Synthesis of heteroaryl substituted compounds. Reagents and conditions: (a) NaN_3, DMF, 40 °C, 6 h; (b) alkyn, toluene, reflux; (c) K_2CO_3, MeOH–H_2O, rt; (d) heteroaryl ester, NaH, DMF, then **28**, 0 °C.

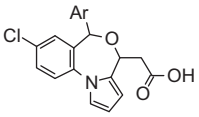
Table 1
Evaluation of squalene synthase inhibitory (SSI) activities and cholesterol synthesis inhibitory (CSI) activities of racemic compounds



	R_1	R_2	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)
7	OMe	H	220	—
8	OH	H	3.3	250
10		H	2.7	63
11	OH	Cl	1.6	560
12	OH		540	—
13	OH		7.6	160

SSI: Squalene Synthase Inhibitory activity. CSI: Cholestrol Synthesis Inhibitory activity in rat hepatic cell. '—, not tested'.

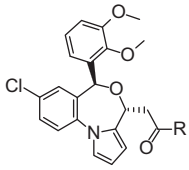
Table 2
Evaluation of SSI and CSI activities of various upper aryl ring compounds

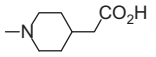
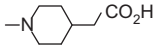
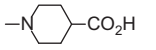
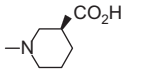
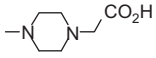
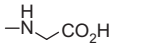
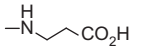
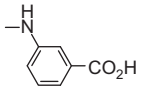


	Ar	SSI (IC_{50}, nM)
8		3.3
19A		>600
19B		52
19C		440

SSI: Squalene Synthase Inhibitory activity.

Table 3
Evaluation of SSI and CSI activities of various chiral compounds



	R	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)
(**4*S*,6*R***)-**15a**		>600	—
(**4*R*,6*S***)-**15a**		1.3	49
15b		3.4	170
15c		2.3	60
15d		4.3	150
15e		2.3	94
15f		2.9	160
15g		4.0	150

SSI: Squalene Synthase Inhibitory activity. CSI: Cholestrol Synthesis Inhibitory activity in rat hepatic cell. '—, not tested'.

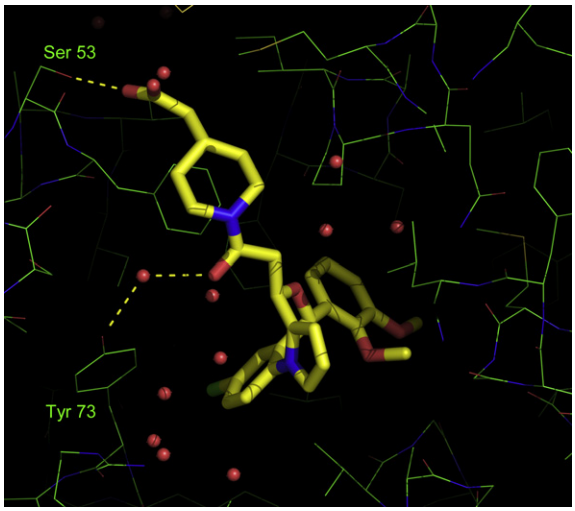


Figure 2. Crystal structure of compound (**4*R*,6*S*)-15a** bound in squalene synthase active site (PDB code: **3V66**).[12]

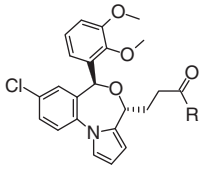
synthase, one is between the amide carbonyl group and Tyr73 via water, and another is between the carboxylic acid group and Ser53.

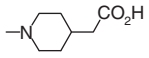
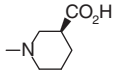
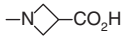
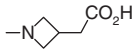
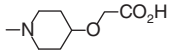
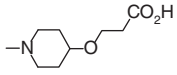
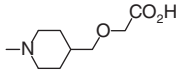
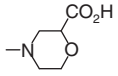
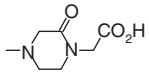
We considered that the amide side chain was the most permissive part for structure conversion, due to its location; it was in the edge of the active site and facing to the solvent side, and the water mediated hydrogen bond of the amide group could be optimized.

To find a more efficacious inhibitor, we focused our SAR studies on this side chain part.

In consequence, we found that some side chain extended compounds were successively improved on their CSI activities. These extended compounds showed stronger SSI and CSI activities than the shorter side chain compounds (Table 4). 4-(Piperidinyloxy)acetic acid **30e** and 2-morpholine carboxylic acid **30h** showed very

Table 4
Evaluation of SSI, CSI and in vivo hepatic cholesterol synthesis inhibitory activities of side chain extended compounds



	R	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)	Rat in vivo CSI (3 mg/kg, po, %)
28	OH	3.1	>1000	—
30a		2.4	93	35
30b		1.4	70	53
30c		2.2	23	31
30d		7.0	36	41
30e		0.8	7.2	18
30f		1.4	35	23
30g		0.9	10	7
30h		1.6	9.7	13
30i		2.2	11	1

SSI: Squalene Synthase Inhibitory activity. CSI: Cholestrol Synthesis Inhibitory activity in rat hepatic cell. Rat in vivo CSI: hepatic cholestrol synthesis inhibition (%) in rat at 1 h after 3 mg/kg single dose oral administration (n = 4–6). '—, not tested'.

strong CSI activities, the IC_{50} values were 7.2 and 9.7 nM, respectively.

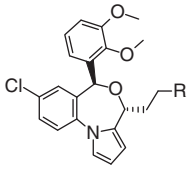
Some of these extended amide compounds showed efficacious in vivo hepatic cholesterol synthesis inhibitory (in vivo CSI) activities. Especially, compound **30b** showed 53% inhibition. Nevertheless, we estimated that more efficacious in vivo CSI activity was required for serum lipid reduction in a repeated dose test.

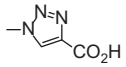
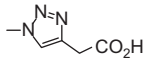
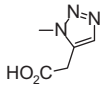
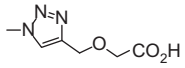
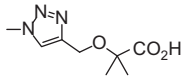
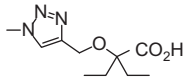
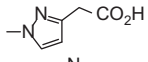
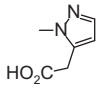
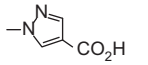
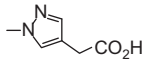
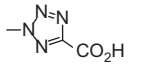
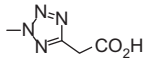
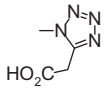
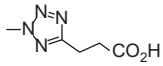
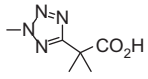
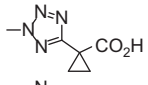
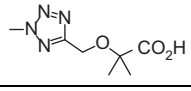
We supposed that the inhibitor's hepatic concentration was important for in vivo CSI activity. There were a few reasons for this. First, squalene synthase is expressed in the liver, main metabolic organ in animal. Second, our inhibitors with amide bond are metabolized to acid derivatives. Third, CSI activities of the acid metabolites may drop, as shown in Table 1. We next turned our attention to replace amide part to more metabolic stable heteroaryl ring, such as 1,2,3-triazole, pyrazole, and tetrazole rings.

Surprisingly, prepared amide changed heteroaryl compounds showed improved SSI and CSI potencies than amide compounds. The results appear in Table 5. In our speculation, these incorporated heteroaryl rings would directly interact with Tyr 73. As a result, in vitro activities were improved. Especially, compound **33b** and **35a**, **f**, **h** further progressed in in vivo CSI activities (the values of % reduction were 66%, 64%, 86%, and 64%, respectively).

Finally, we investigated in marmoset serum lipid lowering test with selected compounds (**4*R*,6*S*)-15a**, **30b**, **33b**, **35a**, **f** and Takeda's phase III entered **TAK-475**,[15] as positive control, at 100 mg/kg/day repeated oral administrations for 7 days (Table 6). In this study, non-HDL cholesterol reduction was more important than total cholesterol (TC) reduction, which including HDL cholesterol reduction. Triglyceride (TG) reduction was also significant for an anti-hyperlipidemic reagent.

Table 5
Evaluation of SSI, CSI and in vivo hepatic cholesterol synthesis inhibitory activities of heteroaryl substituted compounds

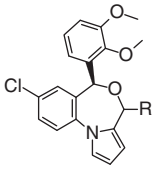


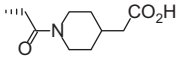
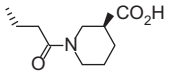
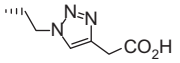
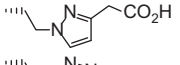
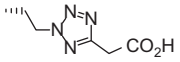
	R	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)	Rat in vivo CSI (3 mg/kg, po, %)
33a		0.59	25	44
33b		0.51	24	66
33c		0.81	41	50
33d		0.68	19	18
33e		0.69	7.3	36
33f		1.7	14	45
35a		1.3	58	64
35b		1.6	210	5
35c		2.1	54	56
35d		3.1	62	34
35e		0.89	18	38
35f		1.1	36	86
35g		1.1	130	—
35h		0.85	70	64
35i		1.1	58	44
35j		1.7	52	53
35k		2.5	10	51

SSI: Squalene Synthase Inhibitory activity. CSI: Cholestrol Synthesis Inhibitory activity in rat hepatic cell. Rat in vivo CSI: hepatic cholestrol synthesis inhibition (%) in rat at 1 h after 3 mg/kg single dose oral administration (n = 4–6). '—, not tested'.

Consequently, compound **30b**, **33b**, **35a** demonstrated statistically significant reduction of serum non-HDL cholesterol levels, from 21% to 52% reduction compared with pre-values, especially

Table 6
Evaluation of serum lipid lowering effects of selected compounds in marmoset 100 mg/kg/day orally repeated doses for 7 days



R		TC (%)	HDL-Cho (%)	non-HDL-Cho (%)	TG (%)
TAK-475		23	14	29	25
(**4*R*,6*S***)-**15a**		4	−11	9	28**
30b		9*	−21	23**	21
33b		10*	−8	21**	24
35a		27**	−10	52**	16
35f		14	6	21	12

TC: Total Cholestrol (% reduction compared with pre-value). HDL-Cho: HDL Cholestrol. non-HDL-Cho: non-HDL Cholestrol. TG: Triglyceride. $n = 6–8$ (TAK-475, $n = 41$).
* $P < 0.05$.
** $P < 0.05$ versus vehicle.

35a showed highest 52% reduction. Moreover, compound (**4*R*,6*S***)-**15a**, **30b**, **33b** showed highly triglyceride reducing potencies (28%, 21%, and 41%, respectively). Furthermore, all our compounds except for **35f** slightly increased HDL cholesterol levels, up to 21% increase. Those data indicated that we have found quite efficacious anti-hyperlipidemic reagents, superior to the original aminobenzhydrol derivatives.[16]

3. Conclusion

In order to obtain more in vivo efficient inhibitors, we focused on a benzoxazepin ring and designed a new tricyclic scaffold by the incorporation of heterocycle within. A new series of squalene synthase inhibitors based on the pyrrolobenzoxazepine template has been identified. Many of the derivatives of this series exhibited good squalene synthase inhibitory (SSI) potencies. Through side chain optimization, some extended amide derivatives showed improved cholesterol synthesis inhibitory (CSI) potency in rat hepatic cell.

Additionally, we succeeded in improving in vivo efficacy in rat single dose hepatic cholesterol synthesis inhibitory studies by replacing the side chain amide groups to the heteroaryl rings. Consequently, highly potent squalene synthase inhibitors were obtained. Furthermore, our novel compounds, especially **35a**, have demonstrated excellent serum lipid ameliorating efficacies in the marmoset oral repeated doses study.

4. Experimental

4.1. Chemistry

4.1.1. General

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded on JEOL JNM-EX400 spectrometers, and chemical shifts are given in ppm from tetramethylsilane as an internal standard. Parenthetical peak derives from minor atropisomer. FAB mass spectra were recorded on a JEOL JMS-HX110 spectrometer. HR-FAB mass spectra were recorded on a JEOL JMS-700. ESI mass spectra were recorded on SCIEX API-150EX and Agilent Technologies Agilent 1100 series LC/MS. Column chromatography was performed with Merck silica gel 60 (particle size 0.060–0.200 or 0.040–0.063). Flash column chromatography was performed with YAMAZEN cartridge series or ultra pack series. Thin-layer chromatography (TLC) was performed on Merck precoated TLC glass sheets with silica gel 60F254 or Whatman Partisil PLK5F with Silica gel 150 Å.

4.1.1.1. [5-Chloro-2-(1*H*-pyrrol-1-yl)phenyl](2,3-dimethoxyphenyl)methanone (3). (2-Amino-5-chlorophenyl)(2,3-dimethoxyphenyl)methanone **2** (2.91 g, 9.97 mmol) was dissolved in acetic acid (60 ml). To the resulting solution was added 2,5-dimethoxytetrahydrofuran (2.07 ml, 15.96 mmol) and the resulting mixture was heated under reflux for 30 min. After cooling the reaction mixture to room temperature, it was concentrated. The concentrate was diluted with ethyl acetate, and washed with satd $NaHCO_3$ aq and brine. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate–hexane = 1:20) to give the title compound **3** (1.80 g, 5.27 mmol, 55%). MS(ESI) *m/z* 342 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 3.52 (3H, s), 3.83 (3H, s), 6.06 (2H, t, $J = 2.2$ Hz), 6.73 (2H, t, $J = 2.2$ Hz), 6.97 (2H, d, $J = 5.1$ Hz), 7.02–7.03 (1H, m), 7.30–7.32 (1H, m), 7.48–7.51 (2H, m).

4.1.1.2. 1-[4-Chloro-2-(2,3-dimethoxybenzoyl)phenyl]-1*H*-pyrrole-2-carbaldehyde (4). To *N*,*N*-dimethylformamide (1.71 ml, 22.12 mmol) was added phosphorus oxychloride (1.62 ml, 17.38 mmol) under ice-cooling, and the resulting mixture was stirred at room temperature for 10 min. A solution of compound **3** (1.80 g, 5.27 mmol) in dichloroethane (40 ml) was added dropwise to the reaction mixture. After warming to 50 °C, the reaction mixture was stirred under heat for 2 h. An aqueous solution (40 ml) of sodium acetate trihydrate (3.94 g, 29.0 mmol) was added to the reaction mixture, followed by heating under reflux for 30 min. After cooling to room temperature, the reaction mixture was diluted with chloroform and washed with brine. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate–hexane = 1:8) to give the title compound **4** (1.19 g, 3.22 mmol, 61%) and 3-aldehyde isomer (0.52 g, 1.41 mmol, 27%). MS (ESI) *m/z* 370 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 3.62 (3H, s), 3.83 (3H, s), 6.19 (1H, dd, $J = 3.9$, 2.4 Hz), 6.84–6.91 (2H, m), 6.92–6.97 (3H, m), 7.29 (1H, d, $J = 8.3$ Hz), 7.53 (1H, dd, $J = 8.3$, 2.4 Hz), 7.59 (1H, d, $J = 2.4$ Hz), 9.39 (1H, s).

4.1.1.3. Methyl (*E*)-3-{1-[4-chloro-2-(2,3-dimethoxybenzoyl)phenyl]-1*H*-pyrrol-2-yl}-2- propenoate (5). Compound **4** (1.19 g, 3.22 mmol) was dissolved in toluene (20 ml). To the resulting solution, methoxycarbonylmethylene triphenylphosphorane (2.15 g, 6.44 mmol) was added and the mixture was heated and stirred overnight at 100 °C. The reaction mixture was cooled to room temperature and then concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate–hexane = 1:9) to give the title compound **5** (1.20 g, 2.82 mmol, 88%). ^{1}H NMR ($CDCl_3$) δ 3.55 (3H, s), 3.72 (3H, s), 3.80 (3H, s), 5.92 (1H, d, $J = 15.9$ Hz), 6.07–6.10 (1H, m), 6.49–6.52 (1H, m), 6.78–6.80 (1H, m), 6.89–6.85 (1H, m), 6.92–6.94 (2H, m), 7.19 (1H, d, $J = 15.9$ Hz), 7.24 (1H, d, $J = 8.3$ Hz), 7.55 (1H, dd, $J = 8.3$, 2.4 Hz), 7.60 (1H, d, $J = 2.4$ Hz).

4.1.1.4. Methyl (*E*)-3-(1-{4-chloro-2-[(2,3-dimethoxyphenyl)(hydroxy)methyl]phenyl}-1*H*-pyrrol-2-yl)-2-propenoate (6). Compound **5** (1.20 g, 2.82 mmol) was dissolved in methanol (30 ml). To the resulting solution was added sodium borohydride (160 mg, 4.23 mmol), followed by stirring at room temperature for 1 h. Water was added to the reaction mixture, and then the organic materials were extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo to give the title compound **6** (1.25 g, 2.82 mmol, 100%). MS (ESI) *m/z* 428 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 3.50 (1.5H, s), 3.53 (1.5H, s), 3.64 (1.5H, s), 3.70 (1.5H, s), 3.78 (1.5H, s), 3.83 (1.5H, s), 5.65–5.71 (1.0H, m), 5.72 (0.5H, d, *J* = 6.1 Hz), 5.92 (0.5H, d, *J* = 15.9 Hz), 6.18 (0.5H, t, *J* = 3.3 Hz), 6.36 (0.5H, t, *J* = 3.3 Hz), 6.42–6.45 (0.5H, m), 6.46–6.48 (0.5H, m), 6.62–6.66 (1.0H, m), 6.70–6.77 (1.5H, m), 6.84–6.84 (0.5H, m), 6.86–6.86 (0.5H, m), 6.93–6.95 (0.5H, m), 6.96–7.01 (0.5H, m), 7.11 (0.5H, d, *J* = 8.3 Hz), 7.15 (0.5H, d, *J* = 8.3 Hz), 7.23 (0.5H, d, *J* = 15.9 Hz), 7.36–7.39 (1.0H, m), 7.67 (0.5H, d, *J* = 2.4 Hz), 7.71 (0.5H, d, *J* = 2.4 Hz).

4.1.1.5. Methyl 2-[8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetate (7). Compound **6** (1.25 g, 2.82 mmol) was dissolved in dichloromethane (30 ml). To the resulting solution, trifluoroacetic acid (0.270 ml, 3.51 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with chloroform and then washed with satd $NaHCO_3$ aq and brine. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate–hexane = 1:15) to give the title compound **7** (627 mg, 1.46 mmol, 52%). MS (ESI) *m/z* 462 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 3.02 (1H, dd, *J* = 15.0, 6.0 Hz), 3.10 (1H, dd, *J* = 15.0, 8.2 Hz), 3.44 (3H, s), 3.71 (3H, s), 3.85 (3H, s), 4.90 (1H, dd, *J* = 8.2, 6.0 Hz), 5.71 (1H, s), 6.28–6.29 (1H, m), 6.37 (1H, t, *J* = 3.2 Hz), 6.72 (1H, d, *J* = 2.0 Hz), 6.94 (1H, dd, *J* = 8.0, 1.5 Hz), 7.09–7.12 (1H, m), 7.16 (1H, t, *J* = 8.0 Hz), 7.23–7.27 (1H, m), 7.35–7.37 (2H, m). Anal. Calcd for $C_{23}H_{22}NO_5Cl{\cdot}0.25$ 1,4-dioxane: C, 64.07; H, 5.38; N, 3.11. Found: C, 63.89; H, 5.41; N, 3.00.

4.1.1.6. 2-[8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetic acid (8). Compound **7** (142 mg, 0.33 mmol) was dissolved in methanol–water–tetrahydrofuran (2:1:0.5, 3.5 ml). To the resulting mixture, potassium carbonate (206 mg, 1.50 mmol) was added, followed by stirring overnight at room temperature. After addition of acetic acid (0.086 ml, 1.50 mmol), the resulting mixture was diluted with chloroform and washed with water. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by preparative TLC (methanol–chloroform = 1:10) to give the title compound **8** (81 mg, 0.19 mmol, 57%, *trans*–*cis* = 10:1). MS (ESI) *m/z* 414 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.98–3.12 (2H, m), 3.44 (3H, s), 3.84 (3H, s), 4.82–4.90 (1H, m), 5.72 (1H, s), 6.24–6.37 (2H, m), 6.71–6.75 (1H, m), 6.92 (1H, d, *J* = 8.1 Hz), 7.08–7.10 (1H, m), 7.14 (1H, t, *J* = 8.1 Hz), 7.25–7.28 (1H, m), 7.33–7.36 (2H, m). Anal. Calcd for $C_{22}H_{20}NO_5Cl{\cdot}0.75$ 1,4-dioxane: C, 62.57; H, 5.46; N, 2.92. Found: C, 62.41; H, 5.51; N, 2.66.

4.1.1.7. Ethyl 2-(1-{2-[8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1] benzoxazepin-4-yl]acetyl}-4-piperidinyl)acetate (9). Compound **8** (81 mg, 0.19 mmol) and ethyl 2-(4-piperidinyl)acetate (36 mg, 0.21 mmol) were dissolved in dichloromethane (3 ml). To the solution, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (44 mg, 0.23 mmol) and 1-hydroxybenzotriazole (9 mg, 0.06 mmol) were added, followed by stirring at room temperature for 3 h. The reaction mixture was diluted with chloroform and washed with satd $NaHCO_3$ aq and brine. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by preparative TLC (methanol–chloroform = 1:100) to give the title compound **9** (83 mg, 0.15 mmol, 77%). MS (ESI) *m/z* 567 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.06–1.23 (2H, m), 1.26 (3H, t, *J* = 7.1 Hz), 1.72–1.80 (2H, m), 1.95–2.06 (1H, m), 2.11–2.17 (1H, m), 2.22–2.27 (1H, m), 2.54–2.70 (1H, m), 2.79–2.91 (1H, m), 2.95–3.13 (1H, m), 3.22–3.30 (1H, m), 3.42 (3H, s), 3.85 (3H, s), 4.01–4.07 (1H, m), 4.09–4.17 (2H, m), 4.61–4.73 (1H, m), 4.91–5.01 (1H, m), 5.72–5.75 (1H, m), 6.23–6.25 (1H, m), 6.35–6.37 (1H, m), 6.67–6.71 (1H, m), 6.92–6.96 (1H, m), 7.08–7.10 (1H, m), 7.13–7.19 (1H, m), 7.23–7.31 (1H, m), 7.33–7.37 (2H, m).

4.1.1.8. 2-(1-{2-[8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}-4-piperidinyl)acetic acid (10). Compound **9** (83 mg, 0.15 mmol) was dissolved in methanol–water–tetrahydrofuran (2:1:0.5, 3.5 ml). To the resulting solution, potassium carbonate (91 mg, 0.66 mmol) was added, followed by stirring overnight at room temperature. The temperature was raised to 45 °C and stirring was continued for a further 7 h. To the reaction mixture, acetic acid (0.038 ml, 0.66 mmol) was added and the mixture was diluted with chloroform and washed with brine. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by preparative TLC (methanol–chloroform = 1:10) to give the title compound **10** (64 mg, 0.12 mmol, 81%). MS (ESI) *m/z* 539 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.01–1.24 (2H, m), 1.59–1.82 (2H, m), 1.93–2.02 (1H, m), 2.13–2.15 (1H, m), 2.24–2.28 (1H, m), 2.53–2.69 (1H, m), 2.79–2.91 (1H, m), 2.95–3.12 (1H, m), 3.23–3.32 (1H, m), 3.41 (3H, s), 3.85 (3H, s), 4.02–4.06 (1H, m), 4.62–4.73 (1H, m), 4.90–4.99 (1H, m), 5.72–5.76 (1H, m), 6.24 (1H, br s), 6.36 (1H, t, *J* = 3.2 Hz), 6.68–6.70 (1H, m), 6.92–6.95 (1H, m), 7.08–7.10 (1H, m), 7.15 (1H, t, *J* = 7.9 Hz), 7.21–7.36 (3H, m). Anal. Calcd for $C_{29}H_{31}N_2O_6Cl{\cdot}0.75$ 1,4-dioxane: C, 63.52; H, 6.16; N, 4.63. Found: C, 63.12; H, 5.91; N, 4.64.

4.1.1.9. Methyl 2-[1,8-dichloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1] benzoxazepin-4-yl]acetate. Compound **7** (52 mg, 0.12 mmol) was dissolved in tetrahydrofuran (3 ml). *N*-chlorosuccinimide (16.2 mg, 0.12 mmol) was added and the resulting mixture was stirred overnight at room temperature. Water was added to the reaction mixture, followed by extraction with chloroform. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by preparative TLC (ethyl acetate–*n*-hexane = 1:6) to give the title compound (52 mg, 0.11 mmol, 93%). MS (ESI) *m/z* 462 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.99 (1H, dd, *J* = 15.3, 6.5 Hz), 3.06 (1H, dd, *J* = 15.3, 7.8 Hz), 3.42 (3H, s), 3.71 (3H, s), 3.85 (3H, s), 4.72–4.74 (1H, m), 5.62 (1H, s), 6.23 (1H, d, *J* = 3.9 Hz), 6.29 (1H, d, *J* = 3.9 Hz), 6.76 (1H, d, *J* = 2.4 Hz), 6.94 (1H, dd, *J* = 7.9, 1.3 Hz), 7.16 (1H, t, *J* = 7.9 Hz), 7.21–7.22 (1H, m), 7.41 (1H, dd, *J* = 8.5, 2.4 Hz), 7.51 (1H, d, *J* = 8.5 Hz).

4.1.1.10. 2-[1,8-Dichloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetic acid (11). Methyl 2-(1,8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)acetate (73 mg, 0.16 mmol) was treated by using potassium carbonate (66 mg, 0.47 mmol) to give the title compound **11** (28 mg, 0.06 mmol, 40%), in a similar manner described for **8**. MS (ESI) *m/z* 449 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.94–3.06 (2H, m), 3.42 (3H, s), 3.84 (3H, s), 4.69 (1H, t, *J* = 6.3 Hz), 5.63 (1H, s), 6.24 (1H, d, *J* = 3.7 Hz), 6.27 (1H, d, *J* = 3.7 Hz), 6.75–6.78 (1H, m), 6.92 (1H, d, *J* = 7.9 Hz), 7.13 (1H, t, *J* = 7.9 Hz), 7.22 (1H, d, *J* = 7.9 Hz), 7.39 (1H, dd, *J* = 8.5, 2.2 Hz), 7.49 (1H, d, *J* = 8.5 Hz). Anal. Calcd for $C_{22}H_{19}NO_5Cl_2{\cdot}0.5H_2O{\cdot}0.1$ 1,4-dioxane: C, 57.72; H, 4.50; N, 3.00. Found: C, 57.28; H, 4.80; N, 2.66.

4.1.1.11. Methyl 2-{8-chloro-6-(2,3-dimethoxyphenyl)-1-[(dimethylamino)methyl]-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl}acetate. Thirty-eight percentage of formaldehyde (0.055 ml) and 50% dimethylamine in water (0.11 ml) were dissolved in acetic acid (1 ml). The mixture was added to the acetic acid solution (2 ml) of compound **7** (60 mg, 0.14 mmol). Then, the reaction mixture was stirred at room temperature for 15 h and concentrated in reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated $NaHCO_3$ solution. The combined organic layer was washed with brine. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by preparative TLC (methanol–chloroform = 1:10) to give the title compound (70 mg, 0.14 mmol, 100%). MS (ESI) *m/z* 485 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.19 (6H, s), 3.00 (1H, dd, *J* = 15.0, 6.0 Hz), 3.08 (1H, dd, *J* = 15.0, 8.2 Hz), 3.39 (3H, s), 3.43 (1H, d, *J* = 13.9 Hz), 3.50 (1H, d, *J* = 13.9 Hz), 3.71 (3H, s), 3.84 (3H, s), 4.77 (1H, dd, *J* = 8.2, 6.0 Hz), 5.58 (1H, s), 6.21 (1H, d, *J* = 3.4 Hz), 6.27 (1H, d, *J* = 3.4 Hz), 6.71 (1H, d, *J* = 2.4 Hz), 6.93 (1H, dd, *J* = 8.1, 1.5 Hz), 7.16 (1H, t, *J* = 8.1 Hz), 7.24 (1H, dd, *J* = 8.1, 1.5 Hz), 7.37 (1H, dd, *J* = 8.5, 2.4 Hz), 7.74 (1H, d, *J* = 8.5 Hz).

4.1.1.12. 2-{8-Chloro-6-(2,3-dimethoxyphenyl)-1-[(dimethylamino)methyl]-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl} acetic acid (12). Methyl 2-{8-chloro-6-(2,3-dimethoxyphenyl)-1-[(dimethylamino)methyl]-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl}acetate (70 mg, 0.14 mmol) was treated by using potassium carbonate (80 mg, 0.58 mmol) to give the title compound **12** (34 mg, 0.07 mmol, 49%), in a similar manner described for **8**. MS (ESI) *m/z* 471 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.21 (6H, s), 2.97 (2H, d, *J* = 6.8 Hz), 3.37 (3H, s), 3.68 (1H, d, *J* = 13.9 Hz), 3.83 (3H, s), 3.88 (1H, d, *J* = 13.9 Hz), 4.72 (1H, t, *J* = 6.8 Hz), 5.54 (1H, s), 6.30 (2H, s), 6.71–6.71 (1H, m), 6.91 (1H, d, *J* = 8.3 Hz), 7.12 (1H, t, *J* = 8.3 Hz), 7.29–7.31 (2H, m), 7.38 (1H, d, *J* = 8.3 Hz). Anal. Calcd for $C_{25}H_{27}N_2O_5Cl{\cdot}1H_2O{\cdot}1.75$ 1,4-dioxane: C, 59.76; H, 6.74; N, 4.36. Found: C, 59.28; H, 6.43; N, 4.85.

4.1.1.13. Methyl 2-[8-chloro-6-(2,3-dimethoxyphenyl)-1-(4-morpholinylmethyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl] acetate. Compound **7** (56 mg, 0.13 mmol) was treated by using 38% formaldehyde (0.050 ml) and morphorine (0.034 ml, 0.39 mmol) to give the title compound (69 mg, 0.13 mmol, 100%), in a similar manner described for **8**. MS (ESI) *m/z* 527 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.33–2.41 (2H, m), 2.53–2.61 (2H, m), 3.00 (1H, dd, *J* = 15.0, 6.0 Hz), 3.08 (1H, dd, *J* = 15.0, 8.1 Hz), 3.41 (3H, s), 3.43–3.52 (2H, m), 3.66–3.71 (4H, m), 3.71 (3H, s), 3.84 (3H, s), 4.76–4.81 (1H, m), 5.53 (1H, s), 6.21 (1H, d, *J* = 3.4 Hz), 6.26 (1H, d, *J* = 3.4 Hz), 6.92–6.96 (1H, m), 7.16 (1H, t, *J* = 7.9 Hz), 7.23 (1H, d, *J* = 7.9 Hz), 7.36 (1H, dd, *J* = 8.5, 2.2 Hz), 7.94 (1H, d, *J* = 8.5 Hz).

4.1.1.14. 2-[8-Chloro-6-(2,3-dimethoxyphenyl)-1-(4-morpholinylmethyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetic acid (13). Methyl 2-[8-chloro-6-(2,3-dimethoxyphenyl)-1-(4-morpholinylmethyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetate (69 mg, 0.13 mmol) was treated by using potassium carbonate (110 mg, 0.78 mmol) to give the title compound **13** (25 mg, 0.05 mmol, 37%), in a similar manner described for **8**. MS (ESI) *m/z* 513 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.33–2.41 (2H, m), 2.50–2.57 (2H, m), 2.97–3.04 (2H, m), 3.41 (3H, s), 3.51 (1H, d, *J* = 13.9 Hz), 3.59 (1H, d, J = 13.9 Hz), 3.64–3.69 (4H, m), 3.83 (3H, s), 4.71–4.77 (1H, m), 5.54 (1H, s), 6.21–6.27 (2H, m), 6.73 (1H, d, *J* = 2.4 Hz), 6.90 (1H, d, *J* = 8.0 Hz), 7.12 (1H, t, *J* = 8.0 Hz), 7.23–7.26 (1H, m), 7.34 (1H, dd, *J* = 8.5, 2.4 Hz), 7.79 (1H, d, *J* = 8.5 Hz). Anal. Calcd for $C_{25}H_{27}N_2O_5Cl{\cdot}1H_2O{\cdot}1.75$ 1,4-dioxane: C, 59.76; H, 6.74; N, 4.36. Found: C, 59.28; H, 6.43; N, 4.85.

4.1.1.15. Ethyl 2-(1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}-4-piperidinyl)acetate ((4*R*,6*S*)-14a) and ethyl 2-(1-{2-[(4*S*,6*R*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}-4-piperidinyl)acetate ((4*S*,6*R*)-14a). Compound **9** (89.0 mg, 0.157 mmol) was isolated and purified by HPL [CHIRALCEL OD (Daicel, 50φ × 500 mm), eluting solvent 20% 2-propanol–*n*-hexane, dissolution rate: 10 ml/min], whereby the (4*R*,6*S*)-**14a** (30.2 mg) was obtained from the fraction with a retention time of 19 min and the (4*S*,6*R*)-**14a** (33.3 mg) was obtained from the fraction with a retention time of 35 min, respectively.

4.1.1.16. 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}-4-piperidinyl)acetic acid ((4*R*,6*S*)-15a). Compound (4*R*,6*S*)-**14a** (30.2 mg, 0.053 mmol) was dissolved in methanol–water–tetrahydrofuran (2:1:0.5, 3.5 ml). To the solution, potassium carbonate (22.1 mg, 0.160 mmol) was added and the resulting mixture was stirred overnight at room temperature. After the temperature was raised to 45 °C, stirring was continued for a further 7 h. After addition of acetic acid (0.0091 ml, 0.128 mmol), the resulting mixture was diluted with chloroform and washed with brine. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by preparative TLC (methanol–chloroform = 1:10) to give the title compound (**4*R*,6*S*)-15a** (24.1 mg, 0.045 mmol, 84%). The acid was dissolved in ethanol. To the solution, equivalent 1 N sodium hydroxide was added at room temparature and concentrated in vacuo. The residue was solidified by diisopropyl ether–*n*-hexane. Then the solid was filtrated out and dried in vacuo to obtain sodium salt of (**4*R*,6*S*)-15a**. MS (ESI) *m/z* 539 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.01–1.24 (2H, m), 1.59–1.82 (2H, m), 1.93–2.02 (1H, m), 2.13–2.15 (1H, m), 2.24–2.28 (1H, m), 2.53–2.69 (1H, m), 2.79–2.91 (1H, m), 2.95–3.12 (1H, m), 3.23–3.32 (1H, m), 3.41 (3H, s), 3.85 (3H, s), 4.02–4.06 (1H, m), 4.62–4.73 (1H, m), 4.90–4.99 (1H, m), 5.72–5.76 (1H, m), 6.24 (1H, brs), 6.36 (1H, t, *J* = 3.2 Hz), 6.68–6.70 (1H, m), 6.92–6.95 (1H, m), 7.08–7.10 (1H, m), 7.15 (1H, t, *J* = 7.9 Hz), 7.21–7.36 (3H, m). Anal. Calcd for $C_{29}H_{30}N_2O_6ClNa{\cdot}1H_2O$: C, 60.16; H, 5.57; N, 4.84. Found: C, 60.11; H, 5.83; N, 4.51.

4.1.1.17. 2-(1-{2-[(4*S*,6*R*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}-4-piperidinyl)acetic acid (4*S*,6*R*)-15a). Compound (4*S*,6*R*)-**14a** (33.3 mg, 0.059 mmol) was treated by using potassium carbonate (24.3 mg, 0.176 mmol) to give the title compound (**4*S*,6*R*)-15a** (20.4 mg, 0.038 mmol, 64%), in a similar manner described for (**4*R*,6*S*)-15a**. MS (ESI) *m/z* 539 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.01–1.24 (2H, m), 1.59–1.82 (2H, m), 1.93–2.02 (1H, m), 2.13–2.15 (1H, m), 2.24–2.28 (1H, m), 2.53–2.69 (1H, m), 2.79–2.91 (1H, m), 2.95–3.12 (1H, m), 3.23–3.32 (1H, m), 3.41 (3H, s), 3.85 (3H, s), 4.02–4.06 (1H, m), 4.62–4.73 (1H, m), 4.90–4.99 (1H, m), 5.72–5.76 (1H, m), 6.24 (1H, brs), 6.36 (1H, t, *J* = 3.2 Hz), 6.68–6.70 (1H, m), 6.92–6.95 (1H, m), 7.08–7.10 (1H, m), 7.15 (1H, t, *J* = 7.9 Hz), 7.21–7.36 (3H, m). Anal. Calcd for $C_{29}H_{31}N_2O_6Cl{\cdot}1.5H_2O{\cdot}0.5\ CHCl_3{\cdot}0.5$ 1,4-dioxane: C, 56.83; H, 5.81; N, 4.14. Found: C, 57.01; H, 5.60; N, 3.85.

4.1.1.18. [5-Chloro-2-(1*H*-pyrrol-1-yl)phenyl](1-naphthyl)methanol (17A). 1-(2-Bromo-4-chlorophenyl)-1*H*-pyrrole[17] (**16**, 6.00 g, 23.4 mmol) was dissolved in diethyl ether (200 ml). *n*-Butyl lithium (1.6 M in *n*-hexane, 18.00 ml, 28.1 mmmol) was dropwised to the resulting solution at −78 °C. The reaction mixture was stirred for 1 h and gradually warmed to ice-cooling temperature. To the solution, 1-naphthaldehyde (3.81 ml, 28.1 mmol) was added under ice-cooling, followed by stirring for 30 min. Satd NH_4Cl aq

was added to the reaction mixture, and then organic materials were extracted with ethyl acetate. After the organic layer was dried over Na_2SO_4, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate–*n*-hexane = 1:20) to give the title compound **17A** (5.78 g, 17.3 mmol, 74%). MS (EI) *m/z* 333 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 6.25–6.28 (2H, m), 6.48 (1H, s), 6.80–6.84 (2H, m), 7.24–7.52 (5H, m), 7.56–7.63 (2H, m), 7.79–7.86 (2H, m).

4.1.1.19. 1-[4-Chloro-2-(1-naphthoyl)phenyl]-1*H*-pyrrol-2-carbaldehyde. Compound **17A** (5.78 g, 17.3 mmol) was dissolved in dichloromethane (200 ml). To the resulting mixture, manganese dioxide (15.1 g, 170 mmol) was added and stirred overnight at 50 °C. The reaction mixture was filtered through a Kiriyama funnel. The filtrate was concentrated under reduced pressure. Then, phosphorus oxychloride (4.84 ml, 51.9 mmol) was dissolved in dichloromethane (200 ml). To the solution, *N*,*N*-dimethylformamide (5.36 ml, 69.2 mmol) was added dropwise under ice-cooling, followed by stirring for 20 min. A dichloromethane solution (50 ml) of the previously-obtained residue was added dropwise to the ice-cooling reaction mixture, followed by stirring at room temperature for 3 h. An aqueous solution (200 ml) of sodium acetate (21.3 g, 260 mmol) was added to the reaction mixture and the organic materials were extracted with dichloromethane. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate–*n*-hexane = 1:10) to give the title compound (2.95 g, 8.15 mmol, 47%). MS (EI) *m/z* 359 M^+. ^1H NMR ($CDCl_3$) δ 5.96 (1H, dd, *J* = 4.0, 2.6 Hz), 6.60 (1H, dd, *J* = 4.0, 1.6 Hz), 6.88 (1H, s), 7.25–7.35 (2H, m), 7.47–7.62 (4H, m), 7.69 (1H, d, *J* = 2.4 Hz), 7.79–7.83 (1H, m), 7.88 (1H, d, *J* = 8.3 Hz), 8.54 (1H, d, *J* = 8.3 Hz), 9.29 (1H, s).

4.1.1.20. Methyl (*E*)-3-{1-[4-chloro-2-(1-naphthoyl)phenyl]-1*H*-pyrrol-2-yl}-2-propenoate. Compound **18A** (2.95 g, 8.20 mmol) was treated by using methyl (trimethylphosphoranylidene)acetate (7.13, 21.3 mmol) to give the title compound (3.18 g, 7.61 mmol, 93%), in a similar manner described for **5**. MS (FAB) *m/z* 415 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 3.75 (3H, s), 5.76–5.84 (2H, m), 6.18–6.21 (1H, m), 6.65–6.68 (1H, m), 7.16 (1H, d, *J* = 15.6 Hz), 7.20–7.27 (2H, m), 7.30 (1H, d, *J* = 8.5 Hz), 7.34 (1H, d, *J* = 7.1 Hz), 7.46–7.56 (2H, m), 7.64 (1H, dd, *J* = 8.5, 2.4 Hz), 7.75–7.81 (2H, m), 7.84 (1H, d, *J* = 8.1 Hz), 8.48 (1H, d, *J* = 8.1 Hz).

4.1.1.21. Methyl 2-[8-chloro-6-(1-naphthyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetate. Methyl (*E*)-3-{1-[4-chloro-2-(1-naphthoyl)phenyl]-1*H*-pyrrol-2-yl}-2-propenoate (100 mg, 0.24 mmol) was dissolved in methanol (3 ml). Sodium borohydride (18 mg, 0.48 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 1 h, and then concentrated in vacuo. Water and ethyl acetate were added to the residue, and the organic layer was separated and dried over Na_2SO_4, and then concentrated in vacuo. The residue was dissolved in dichloromethane (5 ml). To the solution, trifluoroacetic acid (0.028 ml, 0.36 mmol) was added and stirred overnight at room temperature. To the reaction mixture, satd $NaHCO_3$ aq was added, and the layers were separated. The organic layer was dried over Na_2SO_4. The solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate–*n*-hexane = 1:9) to give the title compound (63 mg, 0.15 mmol, 63%). MS (FAB) *m/z* 418 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 3.07 (1H, dd, *J* = 15.1, 5.6 Hz), 3.16 (1H, dd, *J* = 15.1, 8.3 Hz), 3.74 (3H, s), 5.04 (1H, dd, *J* = 8.3, 5.6 Hz), 6.07 (1H, s), 6.30–6.37 (1H, m), 6.40–6.44 (1H, m), 6.59 (1H, d, *J* = 2.2 Hz), 7.18–7.22 (1H, m), 7.26–7.33 (2H, m), 7.34–7.46 (3H, m), 7.49–7.61 (1H, m), 7.80–7.92 (3H, m).

4.1.1.22. 2-[8-Chloro-6-(1-naphthyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetic acid (19A). Methyl 2-[8-chloro-6-(1-naphthyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetate (300 mg, 0.73 mmol) was dissolved in the mixture of tetrahydrofuran (5 ml), methanol (3 ml) and 1 N sodium hydroxide aqueous solution (1.16 ml). The resulting mixture was stirred overnight at room temperature, and then concentrated in vacuo. Chloroform and a 10% aqueous citric acid solution were added to the residue, and the layers were separated. The organic layer was dried over Na_2SO_4, the solvent was distilled off under reduced pressure to give the title compound **19A** (153 mg, 0.38 mmol, 48%). MS (EI) *m/z* 403 M^+. ^1H NMR ($CDCl_3$) δ 3.11–3.18 (1H, m), 3.18–3.25 (1H, m), 5.01–5.07 (1H, m), 6.11 (1H, s), 6.37–6.41 (1H, m), 6.43–6.47 (1H, m), 6.62 (1H, s), 7.20–7.23 (1H, m), 7.25–7.33 (2H, m), 7.37–7.49 (3H, m), 7.56 (1H, t, *J* = 7.8 Hz), 7.80–7.91 (3H, m). Anal. Calcd for $C_{29}H_{28}ClN_3O_8{\cdot}0.5H_2O{\cdot}0.2CHCl_3$: C, 66.74; H, 4.41; N, 3.19. Found: C, 66.87; H, 4.24; N, 3.22.

4.1.1.23. [5-Chloro-2-(1*H*-pyrrol-1-yl)phenyl](2,3-dichlorophenyl)methanol (17B). Compound **16** (6.00 g, 23.4 mmo) was treated by using *n*-butyl lithium hexane solution (18.00 ml, 28.1 mmol) and 2,3-dichlorobenzaldehyde (4.91 g, 28.1 mmol) to give the title compound **17B** (6.10 g, 17.3 mmol, 74%), in a similar manner described for **17A**. MS (EI) *m/z* 352 M^+. ^1H NMR ($CDCl_3$) δ 6.05 (1H, s), 6.29–6.33 (2H, m), 6.78–6.81 (2H, m), 7.17–7.20 (1H, m), 7.25–7.31 (2H, m), 7.33–7.38 (1H, m), 7.43 (1H, d, *J* = 7.8 Hz), 7.52 (1H, d, *J* = 7.8 Hz).

4.1.1.24. 1-[4-Chloro-2-(2,3-dichlorobenzoyl)phenyl]-1*H*-pyrrol-2-carbaldehyde. Compound **17B** (6.10 g, 17.3 mmol) was treated by using manganese dioxide (15.0 g, 170 mmol), phosphorus oxychloride (4.84 ml, 51.9 mmol) and *N*,*N*-dimethylformamide (5.36 ml, 69.2 mmol) to give the title compound (3.43 g, 9.1 mmol, 55%), in a similar manner described for 1-[4-chloro-2-(1-naphthoyl)phenyl]-1*H*-pyrrol-2-carbaldehyde, via **18B**. MS (EI) *m/z* 378 M^+. ^1H NMR ($CDCl_3$) δ 6.21–6.24 (1H, m), 6.79–6.82 (1H, m), 6.90 (1H, s), 7.06–7.19 (2H, m), 7.29 (1H, d, *J* = 8.5 Hz), 7.42–7.45 (1H, m), 7.60 (1H, dd, *J* = 8.5, 2.0 Hz), 7.71 (1H, d, *J* = 2.0 Hz), 9.35 (1H, s).

4.1.1.25. Methyl (*E*)-3-{1-[4-chloro-2-(2,3-dichlorobenzoyl) phenyl]-1*H*-pyrrol-2-yl}-2-propenoate. 1-[4-Chloro-2-(2,3-dichlorobenzoyl)phenyl]-1*H*-pyrrol-2-carbaldehyde (3.42 g, 9.03 mmol) was treated by using methyl (trimethylphosphoranylidene)acetate (7.85 g, 23.5 mmol) to give the title compound (4.05 g, 9.03 mmol, quant.), in a similar manner described for **5**. MS (EI) *m/z* 433 M^+. ^1H NMR ($CDCl_3$) δ 3.73(3H, s), 5.88 (1H, d, *J* = 15.9 Hz), 6.03–6.07 (1H, m), 6.37–6.42 (1H, m), 6.66–6.70 (1H, m), 6.99–7.05 (2H, m), 7.12 (1H, d, *J* = 15.9 Hz), 7.23–7.28 (2H, m), 7.35–7.41 (1H, m), 7.65 (1H, dd, *J* = 8.3, 2.4 Hz), 7.81 (1H, d, *J* = 2.4 Hz).

4.1.1.26. Methyl 2-[8-chloro-6-(2,3-dichlorobenzoyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetate. Methyl (*E*)-3-{1-[4-chloro-2-(2,3-dichlorobenzoyl)phenyl]-1*H*-pyrrol-2-yl}-2-propenoate (100 mg, 0.23 mmol) was treated by using sodium boro hydride (17 mg, 0.46 mmol) and trifluoroacetic acid (0.027 ml, 0.34 mmol) to give the title compound (73 mg, 0.17 mmol, 73%), in a similar manner described for **6** and **7**. MS (FAB) *m/z* 436 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 3.03 (1H, dd, *J* = 15.1, 5.7 Hz), 3.11 (1H, dd, *J* = 15.1, 8.3 Hz), 3.73 (3H, s), 4.91 (1H, dd, *J* = 8.3, 5.7 Hz), 5.68 (1H, s), 6.29–6.32 (1H, m), 6.39 (1H, t, *J* = 3.3 Hz), 6.56 (1H, d, *J* = 2.2 Hz), 7.11–7.14 (1H, m), 7.33–7.45 (3H, m), 7.50 (1H, dd, *J* = 7.8, 1.5 Hz), 7.71 (1H, d, *J* = 7.8 Hz).

4.1.1.27. 2-[8-Chloro-6-(2,3-dichlorobenzoyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetic acid (19B). Methyl 2-[8-chloro-6-(2,3-dichlorobenzoyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]-benzoxazepin-4-yl]acetate (200 mg, 0.46 mmol) was treated by using 1 N aqueous sodium hydroxide solution (0.733 ml, 0.73 mmol) to give the title compound **19B** (61 mg, 0.14 mmol, 32%), in a similar manner described for **19A**. MS (EI) *m/z* 421 M^+. ^{1}H NMR ($CDCl_3$) δ 3.04–3.19 (2H, m), 4.88–4.95 (1H, m), 5.70 (1H, s), 6.32–6.37 (1H, m), 6.38–6.42 (1H, m), 6.57 (1H, d, *J* = 2.2 Hz), 7.13–7.15 (1H, m), 7.31–7.45 (3H, m), 7.50 (1H, d, *J* = 8.1 Hz), 7.73 (1H, d, *J* = 8.1 Hz). Anal. Calcd for $C_{20}H_{14}Cl_3NO_3$: C, 56.83; H, 3.34; N, 3.31. Found: C, 56.44; H, 3.54; N, 3.14.

4.1.1.28. 2,3-Dihydro-1,4-benzodioxin-5-carbaldehyde. To an *N*,*N*-dimethylformamide solution (360 ml) of 2,3-dihydroxybenzaldehyde (5.16 g, 37.4 mmol) were added 1,2-dibromoethane (3.86 ml, 44.6 mmol) and potassium carbonate (13.94 g, 100.9 mmol). The resulting mixture was stirred at 70 °C for 3 h. After the reaction mixture was cooled to room temperature, the solid component was filtered out. The filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (ethyl acetate–*n*-hexane = 1:5) to give the title compound (3.90 g, 23.8 mmol, 64%). MS (ESI) *m/z* 165 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 4.31–4.35 (2H, m), 4.38–4.41 (2H, m), 6.91 (1H, t, *J* = 7.8 Hz), 7.10 (1H, dd, *J* = 8.1, 1.7 Hz), 7.38–7.41 (1H, m), 10.37 (1H, s). IR (ATR) cm^{-1}: 2879, 1680, 1597, 1477, 1282, 1248, 1203, 1082, 887, 781, 723.

4.1.1.29. *tert*-Butyl 4-chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenylcarbamate (21). *sec*-Butyl lithium (0.99 mol/l, 44.3 ml, 43.8 mmol) was added dropwise to a tetrahydrofuran solution (140 ml) of *tert*-butyl 4-chlorophenylcarbamate (**20**, 4.16 g, 18.3 mmol) at −78 °C. While warming to -20 °C, the reaction mixture was stirred for 1.5 h. Under ice-cooling, the mixture was stirred for a further 0.5 h, cooled to −78 °C again, and 2,3-dihydro-1,4-benzodioxin-5-carbaldehyde (3.90 g, 23.8 mmol) was added thereto. The reaction mixture was stirred for 2 h while warming to room temperature. Then, satd NH_4Cl aq was added to the reaction mixture and the layers were separated. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate–*n*-hexane = 1:9) to give the title compound **21** (3.54 g, 9.0 mmol, 49%). MS (ESI) *m/z* 318 $(M-t\text{BuO})^+$. ^{1}H NMR ($CDCl_3$) δ 1.50 (9H, s), 3.14 (1H, d, *J* = 4.9 Hz), 4.22–4.37 (4H, m), 6.04 (1H, d, *J* = 5.4 Hz), 6.77–6.82 (1H, m), 6.85–6.89 (2H, m), 7.08 (1H, d, *J* = 2.5 Hz), 7.23 (1H, dd, *J* = 8.8, 2.5 Hz), 7.91 (2H, d, *J* = 8.3 Hz), 7.95 (1H, br s).

4.1.1.30. *tert*-Butyl 4-chloro-2-(2,3-dihydro-1,4-benzodioxin-5-ylcarbonyl)phenylcarbamate (22). The title compound **22** (3.16 g, 8.11 mmol, 90%) was prepared from compound **21** (3.53 g, 9.01 mmol) by using manganese dioxide (7.83 g), in a similar manner described for compound **18A**.

MS (ESI) *m/z* 290 $(M-t\text{BuO})^+$. ^{1}H NMR ($CDCl_3$) δ 1.53 (9H, s), 4.20–4.25 (2H, m), 4.27–4.31 (2H, m), 6.86 (1H, dd, *J* = 7.6, 1.7 Hz), 6.93 (1H, t, *J* = 7.6 Hz), 7.04 (1H, dd, *J* = 7.8, 1.5 Hz), 7.44–7.48 (2H, m), 8.47 (1H, dd, *J* = 7.4, 2.5 Hz), 10.65 (1H,s). IR (ATR) cm^{-1} 3276, 2979, 1728, 1641, 1574, 1506, 1248, 1147, 1086, 829.

4.1.1.31. (2-Amino-5-chlorophenyl)(2,3-dihydro-1,4-benzodioxin-5-yl)methanone (23). In accordance with the reported process,[18] the title compound **23** (2.15 g, 7.41 mmol, 92%) was prepared from compound **22** (3.16 g, 8.11 mmol) by using trifluoroacetic acid (8.2 ml). MS (ESI) *m/z* 290 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.55 (9H, s), 4.22–4.25 (2H, m), 4.28–4.32 (2H, m), 6.38 (2H, br s), 6.65 (1H, d, *J* = 8.8 Hz), 6.83 (1H, dd, *J* = 7.6, 1.7 Hz), 6.91 (1H, t, *J* = 7.8 Hz), 6.99 (1H, dd, *J* = 8.1, 1.5 Hz), 7.22 (1H, dd, *J* = 8.8, 2.4 Hz), 7.31 (1H, d, *J* = 2.4 Hz). IR (ATR) cm^{-1} 3452, 3336, 1624, 1468, 1281, 1088, 926, 804, 733.

4.1.1.32. [5-Chloro-2-(1*H*-pyrrol-1-yl)phenyl](2,3-dihydro-1,4-benzodioxin-5-yl)methanone (18C). The title compound **18C** (2.07 g, 6.09 mmol, 82%) was obtained from compound **23** (2.14 g, 7.39 mmol) by using 2,5-dimethoxytetrahydrofuran (0.977 ml, 7.55 mmol), in a similar manner described for compound **3**. MS (ESI) *m/z* 340 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 4.11–4.16 (2H, m), 4.19–4.22 (2H, m), 6.05 (2H, t, *J* = 2.2 Hz), 6.66 (2H, t, *J* = 2.2 Hz), 6.69 (1H, d, *J* = 7.8 Hz), 6.84–6.90 (2H, m), 7.29 (1H, d, *J* = 8.6 Hz), 7.50 (1H, dd, *J* = 8.3, 2.5 Hz), 7.57 (1H, d, *J* = 2.5 Hz). IR (ATR) cm^{-1} 1664, 1595, 1495, 1469, 1282, 1254, 1090, 924, 806, 754, 725.

4.1.1.33. 1-[4-Chloro-2-(2,3-dihydro-1,4-benzodioxin-5-ylcarbonyl)phenyl]-1*H*-pyrrol-2-carbaldehyde. The title compound (0.75 g, 2.04 mmol, 52%) was obtained from compound **18C** (1.34 g, 3.94 mmol) by using phosphorus oxychloride (0.441 ml, 4.73 mmol) and *N*,*N*-dimethylformamide (0.610 ml, 7.88 mmol), in a similar manner described for **4**. MS (ESI) *m/z* 368 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 4.09–4.21 (4H, m), 6.20 (1H, dd, *J* = 3.9, 2.7 Hz), 6.68 (1H, t, *J* = 8.0 Hz), 6.81–6.85 (2H, m), 6.86–6.90 (2H, m), 7.29 (2H, d, *J* = 8.3 Hz), 7.53 (1H, dd, *J* = 8.6, 2.5 Hz), 7.61 (1H, d, *J* = 2.5 Hz), 9.36 (1H, s). IR (ATR) cm^{-1} 1662, 1589, 1468, 1281, 1252, 1086, 1036, 897, 806, 756, 731.

4.1.1.34. Benzyl (*E*)-3-{1-[4-chloro-2-(2,3-dihydro-1,4-benzodioxin-5-ylcarbonyl)phenyl]-1*H*-pyrrol-2-yl}-2-propenoate. The title compound (410 mg, 0.82 mmol, 85%) was obtained from 1-[4-chloro-2-(2,3-dihydro-1,4-benzodioxin-5-ylcarbonyl)phenyl]-1*H*-pyrrol-2-carbaldehyde (355 mg, 0.98 mmol) by using benzyl(triphenylphosphoranylidene)acetate (429 mg, 1.05 mmol), in a similar manner described for **5**. MS (ESI) *m/z* 500 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 3.94–4.06 (4H, m), 5.16 (2H, d, *J* = 5.6 Hz), 6.03 (1H, d, *J* = 15.7 Hz), 6.10–6.12 (1H, m), 6.54 (1H, dd, *J* = 4.0, 1.3 Hz), 6.64–6.69 (1H, m), 6.76 (1H, q, *J* = 1.4 Hz), 6.84 (1H, dd, *J* = 8.1, 1.5 Hz), 6.88 (1H, dd, *J* = 7.8, 1.7 Hz), 7.20 (1H, d, *J* = 8.3 Hz), 7.29–7.40 (6H, m), 7.55 (1H, dd, *J* = 8.3, 2.5 Hz), 7.61 (1H, d, *J* = 2.5 Hz). IR (ATR) cm^{-1} 1699, 1620, 1450, 1282, 1244, 1142, 1088, 727.

4.1.1.35. Benzyl (*E*)-3-(1-{4-chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl}-1*H*-pyrrol-2-yl)-2-propenoate. The title compound (430 mg, 0.81 mmol, 100%) was obtained from benzyl (*E*)-3-{1-[4-chloro-2-(2,3-dihydro-1,4-benzodioxin-5-ylcarbonyl)phenyl]-1*H*-pyrrol-2-yl}-2-propenoic acid (406 mg, 0.81 mmol) by using sodium borohydride (50 mg, 1.32 mmol), in a similar manner described for **6**. MS (ESI) *m/z* 484 $(M-OH)^+$. ^{1}H NMR ($CDCl_3$) δ 3.68 (1H, d, *J* = 17.2 Hz), 3.86–4.15 (4H, m), 4.70 (1H, d, *J* = 5.9 Hz), 5.13 (1H, d, *J* = 17.4 Hz), 5.74–6.01 (2H, m), 6.14–6.17 and 6.52–6.57 (1H, m), 6.29–6.37 (1H, m), 6.65–6.78 (4H, m), 6.86–7.00 (1H, m), 7.08–7.12 (1H, m), 7.28–7.40 (5H, m), 7.54 and 7.79 (1H, d, *J* = 2.5 Hz). IR (ATR) cm^{-1} 1685, 1618, 1473, 1450, 1279, 1244, 1165, 1088, 1036, 957, 731.

4.1.1.36. Benzyl 2-[8-chloro-6-(2,3-dihydro-1,4-benzodioxin-5-yl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetate. The title compound (177 mg, 0.35 mmol, 42%) was obtained from benzyl (*E*)-3-(1-{4-chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl}-1*H*-pyrrol-2-yl)-2-propenoate (418 mg, 0.83 mmol) by using trifluoroacetic acid (0.077 ml), in a similar manner described for **7**. MS (ESI) *m/z* 502 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 2.46–2.76 and 2.98–3.19 (2H, m), 3.66 and 3.71 (1H, s), 3.96–4.01 and 4.03–4.08 (2H, m), 4.10–4.16 (2H, m), 4.87–4.95 (1H, m), 5.10

and 5.17 (1H, s), 5.65 and 5.66 (1H, s), 6.26–6.33 (1H, m), 6.35–6.38 (1H, m), 6.76–6.82 (1H, m), 6.85–7.02 (2H, m), 7.09–7.15 and 7.20–7.24 (2H, m), 7.30–7.41 (7H, m). IR (ATR) cm^{-1} 1736, 1604, 1473, 1281, 1171, 1099, 1051, 889, 823, 717.

4.1.1.37. 2-[8-Chloro-6-(2,3-dihydro-1,4-benzodioxin-5-yl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetic acid (19C). To an ethyl acetate solution (8 ml) of benzyl 2-[8-chloro-6-(2,3-dihydro-1,4-benzodioxin-5-yl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetate (173 mg, 0.35 mmol), 10% palladium-carbon (wet, 102 mg) was added. The resulting mixture was stirred for 29 h in a hydrogen atmosphere. The catalyst was filtered off, followed by washing with ethyl acetate sufficiently. The filtrate was concentrated under reduced pressure to give the title compound **19C** (173 mg, 0.35 mmol, 100%). MS (ESI) *m/z* 410 $(M-H)^+$. ^1H NMR ($CDCl_3$) δ 2.98–3.20 (2H, m), 3.97–4.19 (4H, m), 4.85–4.93 (1H, m), 5.63–5.72 (1H, m), 6.25–6.44 (2H, m), 6.70–7.03 (3H, m), 7.06–7.24 (2H, m), 7.33–7.45 (2H, m). Anal. Calcd for $C_{32}H_{43}ClN_2O_7 \cdot 0.2\ H_2O \cdot 0.2$ *n*-hexane: C, 64.40; H, 4.94; N, 3.24. Found: C, 64.58; H, 4.62; N, 3.06.

4.1.1.38. 1-{2-[(4R,6S)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}-4-piperidine carboxylic acid (15b). Ethyl 1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}-4-piperidine carboxylate (66.1 mg, 0.120 mmol, prepared from **8**) was treated by using potassium carbonate (66.3 mg, 0.480 mmol) to give the title compound **15b** (58.7 mg, 0.112 mmol, 93%), in a similar manner described for **10**. MS (ESI) *m/z* 525 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.6–1.8 (2H, m), 1.8–2.0 (2H, m), 2.5–2.6 (1H, m), 2.9 (1H, dd, *J* = 14.2, 4.6 Hz), 2.9–3.3 (2H, m), 3.4 (3H, s), 3.9 (3H, s), 3.9–4.1 (1H, m), 4.3–4.6 (1H, m), 4.9–5.0 (1H, m), 5.7 (1H, s), 6.2–6.3 (1H, m), 6.3–6.4 (1H, m), 6.7 (1H, d, *J* = 8.5 Hz), 6.9 (1H, dd, *J* = 13.7, 7.6 Hz), 7.1 (1H, dd, *J* = 2.7, 1.5 Hz), 7.1 (1H, td, *J* = 7.9, 3.3 Hz), 7.2–7.3 (2H, m), 7.3–7.4 (2H, m). Anal. Calcd for $C_{28}H_{29}ClN_2O_6$: C, 64.06; H, 5.57; N, 5.34. Found: C, 63.78; H, 5.69; N, 5.21.

4.1.1.39. (3*S*)-1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}-3-piperidine carboxylic acid (15c). Ethyl (3*S*)-1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}-3-piperidine carboxylate (127 mg, 0.23 mmol, prepared from **8**) was treated by using potassium carbonate (127 mg, 0.92 mmol) to give the title compound **15c** (78.7 mg, 0.150 mmol, 65%), in a similar manner described for **10**. MS (ESI) *m/z* 525 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.4–1.6 (1H, m), 1.6–1.8 (2H, m), 1.9–2.1 (1H, m), 2.5–2.6 (1H, m), 2.8–3.1 (2H, m), 3.1–3.4 (2H, m), 3.4 (3H, s), 3.8 (3H, s), 4.0–4.3 (1H, m), 4.6–4.6 (1H, m), 4.9–5.0 (1H, m), 5.8 (1H, s), 6.2 (1H, br s), 6.4 (1H, t, *J* = 3.2 Hz), 6.7–6.7 (1H, m), 6.9–7.0 (1H, m), 7.1 (1H, br s), 7.1–7.2 (1H, m), 7.2–7.4 (3H, m). Anal. Calcd for $C_{28}H_{29}ClN_2O_6 \cdot 0.25H_2O$: C, 63.51; H, 5.62; N, 5.29. Found: C, 63.62; H, 5.43; N, 5.30.

4.1.1.40. 2-(4-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}-1-piperazinyl)acetic acid (15d). Ethyl 2-(4-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}-1-piperazinyl)acetate (79 mg, 0.139 mmol, prepared from **8**) was treated by using potassium carbonate (77 mg, 0.56 mmol) to give the title compound **15d** (49 mg, 0.09 mmol, 65%), in a similar manner described for **10**. MS (ESI) *m/z* 541 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.6–2.9 (2H, m), 3.0–3.4 (3H, m), 3.4 (3H, s), 3.6–3.8 (2H, m), 3.8 (3H, s), 4.1–4.4 (3H, m), 4.9–5.0 (1H, m), 5.8 (1H, s), 6.3 (1H, br s), 6.4–6.4 (1H, m), 6.7–6.8 (2H, m), 6.9–7.0 (1H, m), 7.1–7.1 (1H, m), 7.1–7.2 (2H, m), 7.3–7.4 (3H, m). Anal. Calcd for $C_{28}H_{30}ClN_3O_6 \cdot 1.0H_2O$: C, 60.27; H, 5.78; N, 7.53. Found: C, 59.90; H, 5.76; N, 7.12.

4.1.1.41. 2-({2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}amino)acetic acid (15e). Methyl 2-({2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}-amino)acetate (63 mg, 0.13 mmol, prepared from **8**) was treated by using potassium carbonate (72 mg, 0.52 mmol) to give the title compound **15e** (51.7 mg, 0.11 mmol, 84%), in a similar manner described for **10**. MS (ESI) *m/z* 471 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 3.0–3.0 (2H, m), 3.5 (3H, s), 3.9 (3H, s), 4.1–4.1 (2H, m), 4.8–4.9 (1H, m), 5.8 (1H, s), 6.3–6.3 (1H, m), 6.4–6.4 (1H, m), 6.8–6.8 (1H, m), 7.0 (1H, dd, *J* = 8.1, 1.5 Hz), 7.1–7.1 (1H, m), 7.2 (1H, t, *J* = 7.9 Hz), 7.2 (2H, br s), 7.3–7.4 (2H, m). Anal. Calcd for $C_{24}H_{23}ClN_2O_6$: C, 61.21; H, 4.92; N, 5.95. Found: C, 61.15; H, 4.86; N, 5.71.

4.1.1.42. 3-({2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}amino)propionic acid (15f). Ethyl 3-({2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}-amino)propionate (98 mg, 0.19 mmol, prepared from **8**) was treated by using potassium carbonate (106 mg, 0.76 mmol) to give the title compound **15f** (67.8 mg, 0.14 mmol, 73%), in a similar manner described for **10**. MS (ESI) *m/z* 485 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.6–2.6 (2H, m), 2.9–2.9 (2H, m), 3.4 (3H, s), 3.4–3.5 (1H, m), 3.5–3.7 (2H, m), 3.8–3.8 (1H, m), 3.9 (3H, s), 4.8 (1H, dd, *J* = 5.1, 6.6 Hz), 5.8 (1H, s), 6.3–6.4 (2H, m), 6.7–6.8 (1H, m), 7.0 (1H, dd, *J* = 7.9, 1.6 Hz), 7.1–7.1 (1H, m), 7.2–7.3 (2H, m), 7.3–7.4 (2H, m). Anal. Calcd for $C_{25}H_{25}ClN_2O_6$: C, 61.92; H, 5.20; N, 5.78. Found: C, 61.94; H, 5.23; N, 5.47.

4.1.1.43. 3-({2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}amino)benzoic acid (15g). Methyl 3-({2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxy phenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetyl}amino) benzoate (109 mg, 0.20 mmol, prepared from **8**) was treated by using potassium carbonate (111 mg, 0.80 mmol) to give the title compound **15g** (71.8 mg, 0.13 mmol, 67%), in a similar manner described for **10**. MS (ESI) *m/z* 533 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 3.1 (1H, m), 3.5 (3H, s), 3.9 (3H, s), 4.9–5.0 (1H, m), 5.9 (1H, s), 6.4 (2H, m), 6.6–7.4 (6H, m), 7.6–8.1 (6H, m), 8.6 (1H, br s). Anal. Calcd for $C_{29}H_{25}ClN_2O_6$: C, 65.35; H, 4.73; N, 5.26. Found: C, 65.11; H, 4.93; N, 5.06.

4.1.1.44. Methyl [(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]acetate (24). Compound **7** (12.0 g) was isolated and purified by HPL [CHIRALCEL OD (Daicel, 50φ × 500 mm), eluting solvent *n*-hexane–isopropanol = 50:50, dissolution rate: 50 ml/min], whereby the (4*R*,6*S*)-isomer (**24**, 5.9 g) was obtained from the fraction with a retention time of 23 min and the (4*S*,6*R*)-isomer (5.9 g) was obtained from the fraction with a retention time of 36 min, respectively.

4.1.1.45. 2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethanol (25). Compound **24** (5.92 g, 13.8 mmol) was dissolved in tetrahydrofuran (100 ml). Under ice-cooling, lithium aluminum hydride (856 mg, 20.8 mmol) was added to the resulting mixture and stirred for 3 h. To the solution, water (1 ml), a 15% aqueous sodium hydroxide solution (1 ml), and water (3 ml) were added successively. The mixture was stirred for 3 h. $MgSO_4$ was added to dry the mixture. After filtration through celite, the solvent was distilled off under reduced pressure to give the title compound **25** (4.80 g, 12.0 mmol, 87%). ^1H NMR ($CDCl_3$) δ 2.16–2.50 (3H, m), 3.45 (3H, s), 3.86 (3H, s),

3.93–3.99 (2H, m), 4.61–4.66 (1H, m), 5.76 (1H, s), 6.31–6.35 (1H, m), 6.39 (1H, t, *J* = 3.1 Hz), 6.72–6.75 (1H, m), 6.95 (1H, d, *J* = 8.3 Hz), 7.09–7.11 (1H, m), 7.19 (1H, t, *J* = 7.8 Hz), 7.25–7.28 (1H, m), 7.33–7.39 (2H, m).

4.1.1.46. 2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethylmethanesulfonate (26). Compound **25** (4.79 g, 12.0 mmol) was dissolved in dichloromethane (60 ml). Under ice-cooling, triethylamine (2.51 ml, 18.0 mmol) and methanesulfonic acid chloride (1.11 ml, 14.4 mmol) were added. The resulting mixture was stirred for 3 h and diluted with dichloromethane and washed with water and satd $NaHCO_3$ aq. The organic layer was dried over Na_2SO_4. The solvent was distilled off under reduced pressure to give the title compound **26** (5.77 g, 12.0 mmol, quant.). ^{1}H NMR ($CDCl_3$) δ 2.41–2.57 (2H, m), 2.98 (3H, s), 3.43 (3H, s), 3.85 (3H, s), 4.48–4.62 (3H, m), 5.73 (1H, s), 6.32–6.29 (1H, m), 6.39 (1H, t, *J* = 3.2 Hz), 6.72 (1H, d, *J* = 2.2 Hz), 6.96 (1H, dd, *J* = 8.1, 1.46 Hz), 7.11 (1H, q, *J* = 1.5 Hz), 7.20 (1H, t, *J* = 8.1 Hz), 7.25–7.31 (1H, m), 7.33–7.41 (2H, m).

4.1.1.47. 3-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propionitrile (27). Compound **26** (5.77 g, 12.0 mmol) was dissolved in dimethylsulfoxide (60 ml). To the solution, sodium cyanide (1.21 g, 24.0 mmol) was added. The resulting mixture was stirred at 50 °C for 13 h. After the reaction mixture was allowed to warm to room temparature, water and ethyl acetate were added. The organic layer was separated and washed with brine, and dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane–ethyl acetate) to give the title compound **27** (4.51 g, 11.0 mmol, 92%). ^{1}H NMR ($CDCl_3$) δ 2.48–2.30 (2H, m), 2.68 (2H, t, *J* = 7.3 Hz), 3.43 (3H, s), 3.86 (3H, s), 4.49 (1H, dd, *J* = 9.3, 3.9 Hz), 5.73 (1H, s), 6.27–6.30 (1H, m), 6.39 (1H, t, *J* = 3.2 Hz), 6.72–6.74 (1H, m), 6.96 (1H, d, *J* = 8.1 Hz), 7.10–7.13 (1H, m), 7.17–7.23 (1H, m), 7.25–7.29 (1H, m), 7.33–7.41 (2H, m).

4.1.1.48. 3-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propionic acid (28). Compound **27** (4.51 g, 11.0 mmol) was dissolved in 2-propanol (50 ml). A 5 N aqueous sodium hydroxide solution (50 ml) was added and the resulting mixture was heated under reflux for 4 days. The reaction mixture was concentrated in vacuo. Under ice-cooling, 1 N hydrochloric acid was added to make the residue acidic, followed by extraction with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (chloroform–methanol) to give the title compound **28** (4.56 g, 10.7 mmol, 97%). ^{1}H NMR ($CDCl_3$) δ 1.55 (1H, br s), 2.80–2.30 (4H, m), 3.43 (3H, s), 3.85 (3H, s), 4.41 (1H, q, *J* = 4.5 Hz), 5.72 (1H, s), 6.35–6.32 (1H, m), 6.38 (1H, t, *J* = 3.2 Hz), 6.71 (1H, d, *J* = 2.2 Hz), 6.94 (1H, dd, *J* = 8.3, 1.5 Hz), 7.09–7.10 (1H, m), 7.18 (1H, t, *J* = 7.9 Hz), 7.25–7.39 (3H, m). Anal. Calcd for $C_{23}H_{22}ClNO_5 \cdot 0.5$ 2-propanol: C, 64.26; H, 5.72; N, 3.06. Found: C, 64.30; H, 5.70; N, 3.02.

4.1.1.49. 2-(1-{3-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propanoyl}-4-piperidinyl)acetate (29a). Compound **28** (1.04 g, 2.43 mmol) was treated by using ethyl piperidine-4-acetate (500 mg, 2.92 mmol) to give the title compound **29a** (1.32 g, 2.27 mmol, 93%), in a similar manner described for **9**. ^{1}H NMR ($CDCl_3$) δ 1.11 (2H, br s), 1.26 (3H, t, *J* = 7.1 Hz), 1.50–1.53 (1H, m), 1.69–1.80 (2H, m), 2.00 (1H, br s), 2.19–2.26 (2H, m), 2.36–2.43 (2H, m), 2.55–2.61 (2H, m), 3.01 (1H, s), 3.43 (3H, s), 3.85 (3H, s), 4.13 (2H, q, *J* = 7.2 Hz), 4.42–4.37 (1H, m), 4.64–4.56 (1H, m), 5.70 (1H, s), 6.40–6.34 (2H, m), 6.70 (1H, d, *J* = 2.0 Hz), 6.95 (1H, dd, *J* = 8.2, 1.6 Hz), 7.10–7.07 (1H, m), 7.21–7.15 (1H, m), 7.28–7.31 (2H, m), 7.36–7.34 (2H, m).

4.1.1.50. 2-(1-{3-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propanoyl}-4-piperidinyl)acetic acid (30a). Compound **29a** (86 mg, 0.15 mmol) was treated by using potassium carbonate (82 mg, 0.59 mmol) to give the title compound **30a** (61.2 mg, 0.11 mmol, 73%), in a similar manner described for **10**. ^{1}H NMR ($CDCl_3$) δ 1.89–1.04 (4H, m), 2.00 (1H, br), 2.46–2.20 (4H, m), 2.75–2.47 (3H, m), 3.07–2.96 (1H, m), 3.43 (3H, s), 3.98–3.80 (4H, m), 4.44–4.36 (1H, m), 4.66–4.57 (1H, m), 5.70 (1H, s), 6.40–6.33 (2H, m), 6.72–6.69 (1H, m), 6.98–6.93 (1H, m), 7.11–7.07 (1H, m), 7.21–7.15 (1H, m), 7.39–7.25 (3H, m). Anal. Calcd for $C_{30}H_{33}ClN_2O$: C, 65.15; H, 6.01; N, 5.07. Found: C, 65.36; H, 6.20; N, 4.80.

4.1.1.51. Ethyl (3*S*)-1-(3-((4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)propanoyl)-3-piperidine carboxylate (29b). Compound **29a** (1.00 g, 2.34 mmol) was treated by using (*S*)-(+)-ethylnipecotate (440 mg, 2.80 mmol) to give the title compound **29b** (1.21 g, 2.13 mmol, 91%), in a similar manner described for **9**. MS (ESI) *m*/*z* 567 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.21–1.28 (3H, m), 1.38–1.49 (1H, m), 1.63–1.81 (2H, m), 1.99–2.09 (1H, m), 2.36–2.46 (3H, m), 2.52–2.84 (2H, m), 2.98–3.06 (1H, m), 3.43 (3H, s), 3.80–3.87 (4H, m), 4.09–4.18 (2H, m), 4.38–4.42 (1H, m), 5.70 (1H, s), 6.34–6.39 (2H, m), 6.70–6.72 (1H, m), 6.94 (1H, d, *J* = 8.1 Hz), 7.08 (1H, dd, *J* = 2.7, 1.5 Hz), 7.17 (1H, t, *J* = 8.0 Hz), 7.26–7.36 (3H, m).

4.1.1.52. (3*S*)-1-(3-((4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)propanoyl)-3-piperidine carboxylic acid (30b). Compound **29b** (100 mg, 0.18 mmol) was treated by using potassium carbonate (49 mg, 0.35 mmol) to give the title compound **30b** (85 mg, 0.16 mmol, 89%), in a similar manner described for **10**.

MS (ESI) *m*/*z* 539 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.25–1.32 (1H, m), 1.41–1.53 (1H, m), 1.65–1.87 (2H, m), 1.99–2.13 (1H, m), 2.37–2.78 (4H, m), 2.91–3.15 (2H, m), 3.43 (3H, s), 3.76–4.03 (5H, m), 4.37–4.42 (1H, m), 5.71 (1H, s), 6.34–6.39 (2H, m), 6.70–6.72 (1H, m), 6.94 (1H, d, *J* = 7.8 Hz), 7.07–7.10 (1H, m), 7.17 (1H, t, *J* = 8.0 Hz), 7.27–7.36 (6H, m). Anal. Calcd for $C_{29}H_{31}ClN_2O_6 \cdot 0.25H_2O$: C, 64.08; H, 5.84; N, 5.15. Found: C, 64.22; H, 5.98; N, 4.82.

4.1.1.53. Methyl 1-(3-((4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)propanoyl)-3-azetidine carboxylate (29c). Compound **28** (58 mg, 0.14 mmol) was treated by using 3-methylazetidine hydrochloride (27 mg, 0.16 mmol) to give the title compound **29c** (51 mg, 0.10 mmol, 72%), in a similar manner described for **9**. MS (ESI) *m*/*z* 525 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 2.28–2.48 (4H, m), 3.24–3.47 (4H, m), 3.75 (3H, s), 3.85 (3H, s), 4.06–4.34 (4H, m), 4.36–4.40 (1H, m), 5.70 (1H, s), 6.32–6.34 (1H, m), 6.37 (1H, t, *J* = 3.2 Hz), 6.71 (1H, d, *J* = 2.0 Hz), 6.95 (1H, d, *J* = 8.1 Hz), 7.08 (1H, dd, *J* = 2.7, 1.5 Hz), 7.19 (1H, t, *J* = 8.1 Hz), 7.26–7.41 (3H, m).

4.1.1.54. 1-(3-((4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)propanoyl)-3-azetidine carboxylic acid (30c). Compound **29c** (51 mg, 0.10 mmol) was treated by using potassium carbonate (40 mg, 0.29 mmol) to give the title compound **30c** (47 mg, 0.09 mmol, 95%), in a similar manner described for **10**. MS (ESI) *m*/*z* 512 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 2.09–2.34 (4H, m), 3.02–3.13 (1H, m), 3.29–3.44 (4H, m), 3.78 (3H, s), 3.87–4.05 (2H, m), 4.10–4.19 (1H, m), 4.26–4.33 (1H, m), 5.64 (1H, s), 6.24–6.30 (1H, m), 6.65–6.70 (1H, m), 6.83–6.90 (1H, m), 6.96–7.02 (1H, m), 7.09–7.15

(1H, m), 7.22–7.30 (3H, m). Anal. Calcd for $C_{27}H_{28}ClN_2O_6 \cdot 0.25H_2O \cdot 0.75CHCl_3$: C, 54.93; H, 4.98; N, 4.62. Found: C, 54.89; H, 5.06; N, 4.59.

4.1.1.55. Ethyl 2-(3-azetidinyl)acetate hydrochloride. To a solution of ethyl 2-(1-benzhydryl-3-azetidinylidene)acetate (1.41 g, 3.00 mmol) in ethanol (15.0 ml), 1 N hydrochloric acid (3.6 ml) and 10% palladium-carbon (1.5 g) were added, followed by catalytic hydrogenation at 5 atm for 14 h. The catalyst was filtered out and the filtrate was concentrated in vacuo. The residue was dissolved in ethanol (10 ml) to obtain the title compound as a 0.3 M ethanol solution.

4.1.1.56. Ethyl 2-(1-(3-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propano yl)-3-azetidinyl)acetate (29d). Compound **28** (86 mg, 0.20 mmol) was treated by using the 0.3 M ethanol solution (1.30 ml, 0.40 mmol) of ethyl 2-(3-azetidinyl)acetate hydrochloride to give the title compound **29d** (109 mg, 0.20 mmol, 96%), in a similar manner described for **9**.

MS (ESI) *m/z* 553 $(M+H)^+$.

^1H NMR ($CDCl_3$) δ 1.22–1.27 (3H, m), 2.29–2.44 (4H, m), 2.51–2.54 (1H, m), 2.60 (1H, dd, *J* = 7.8, 3.4 Hz), 2.82–2.97 (1H, m), 3.42 (3H, s), 3.60–3.66 (1H, m), 3.73–3.81 (1H, m), 3.84 (3H, s), 4.08–4.16 (3H, m), 4.26 (1H, t, *J* = 8.5 Hz), 4.36–4.40 (1H, m), 5.69–5.71 (1H, m), 6.32–6.34 (1H, m), 6.37 (1H, t, *J* = 3.2 Hz), 6.70–6.72 (1H, m), 6.94 (1H, dd, *J* = 8.3, 1.5 Hz), 7.06–7.09 (1H, m), 7.16–7.20 (2H, m), 7.26–7.35 (2H, m)

4.1.1.57. 2-(1-(3-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propanoyl)-3-azetidinyl)acetic acid (30d). Compound **29d** (109 mg, 0.20 mmol) was treated by using potassium carbonate (82 mg, 0.59 mmol) to give the title compound **30d** (88 mg, 0.17 mmol, 85%), in a similar manner described for **10**. MS (ESI) *m/z* 525 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.28–2.42 (4H, m), 2.53 (1H, d, *J* = 7.4 Hz), 2.61 (1H, d, *J* = 7.4 Hz), 2.80–2.94 (1H, m), 3.42 (3H, s), 3.59–3.68 (1H, m), 3.73–3.79 (1H, m), 3.84 (3H, s), 4.07–4.14 (1H, m), 4.25 (1H, t, *J* = 8.6 Hz), 4.34–4.39 (1H, m), 5.69 (1H, s), 6.31–6.34 (1H, m), 6.37 (1H, t, *J* = 3.2 Hz), 6.69–6.72 (1H, m), 6.92–6.96 (1H, m), 7.06–7.09 (1H, m), 7.18 (1H, t, *J* = 7.8 Hz), 7.27–7.30 (1H, m), 7.34–7.36 (2H, m). Anal. Calcd for $C_{28}H_{29}ClN_2O_6 \cdot 0.75H_2O \cdot 0.25CHCl_3$: C, 59.67; H, 5.50; N, 4.93.Found: C, 59.69; H, 5.57; N, 4.74.

4.1.1.58. Methyl 2-[(1-{3-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propanoyl}-4-piperidinyl)oxy]acetate (29e). Compound **28** (86 mg, 0.20 mmol) was treated by using methyl 2-(4-piperidinyloxy)acetate[19] (52 mg, 0.30 mmol) to give the title compound **29e** (116 mg, 0.20 mmol, 99%), in a similar manner described for **9**. MS (ESI) *m/z* 583 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.53–1.90 (4H, m), 2.35–2.43 (2H, m), 2.52–2.60 (1H, m), 2.65–2.74 (1H, m), 3.20–3.35 (2H, m), 3.43 (3H, s), 3.59–3.65 (1H, m), 3.68–3.78 (4H, m), 3.84–4.03 (4H, m), 4.10–4.15 (3H, m), 4.37–4.43 (1H, m), 5.69–5.72 (1H, m), 6.34–6.39 (2H, m), 6.70 (1H, s), 6.95 (1H, dd, *J* = 8.3, 1.5 Hz), 7.08 (1H, dd, *J* = 2.7, 1.5 Hz), 7.18 (1H, td, *J* = 8.0, 2.1 Hz), 7.26–7.32 (1H, m), 7.33–7.37 (2H, m).

4.1.1.59. 2-[(1-{3-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propanoyl}-4-piperidinyl)oxy]acetic acid (30e). Compound **29e** (116 mg, 0.20 mmol) was treated by using potassium carbonate (90 mg, 0.65 mmol) to give the title compound **30e** (110 mg, 0.19 mmol, 97%), in a similar manner described for **10**. MS (ESI) *m/z* 569 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.42–1.56 (2H, m), 1.78–1.91 (2H, m), 2.65–2.32 (5H, m), 2.94–3.18 (2H, m), 3.49–3.59 (1H, m), 3.71 (3H, s), 3.83 (3H, s), 3.97–4.14 (3H, m), 4.36–4.40 (1H, m), 5.69 (1H, s), 6.32–6.36 (2H, m), 6.69 (1H, s), 6.91–6.95 (1H, m), 7.05–7.08 (1H, m), 7.16 (1H, t, *J* = 8.1 Hz), 7.27–7.30 (1H, m), 7.32–7.35 (2H, m). Anal. Calcd for $C_{30}H_{33}ClN_2O_7 \cdot 1.0H_2O \cdot 0.25CHCl_3$: C, 58.87; H, 5.80; N, 4.54. Found: C, 58.73; H, 5.65; N, 4.48.

4.1.1.60. Methyl 3-[(1-{3-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propanoyl}-4-piperidinyl)oxy]propanoate (29f). Compound **29e** (116 mg, 0.20 mmol) was treated by using methyl 3-(4-piperidinyloxy)propanoate[20] (41 mg, 0.22 mmol) to give the title compound **29f** (110 mg, 0.18 mmol, 92%), in a similar manner described for **9**. MS (ESI) *m/z* 597 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.05–1.21 (1H, m), 1.49–1.60 (1H, m), 1.70–1.90 (2H, m), 2.35–2.43 (2H, m), 2.51–2.72 (4H, m), 3.21–3.41 (2H, m), 3.43 (3H, s), 3.50–3.57 (1H, m), 3.60–4.08 (11H, m), 4.37–4.42 (1H, m), 5.70 (1H, s), 6.34–6.39 (2H, m), 6.70 (1H, d, *J* = 1.7 Hz), 6.95 (1H, dd, *J* = 8.2, 1.5 Hz), 7.08 (1H, dd, *J* = 2.9, 1.7 Hz), 7.18 (1H, t, *J* = 8.2 Hz), 7.27–7.32 (1H, m), 7.34–7.35 (2H, m).

4.1.1.61. 3-[(1-{3-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propanoyl}-4-piperidinyl)oxy]propanoic acid (30f). Compound **29f** (110 mg, 0.18 mmol) was treated by using potassium carbonate (76 mg, 0.55 mmol) to give the title compound **30f** (66 mg, 0.11 mmol, 61%), in a similar manner described for **10**. MS (ESI) *m/z* 583 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.51–1.59 (2H, m), 1.75–1.84 (2H, m), 2.35–2.42 (2H, m), 2.51–2.72 (4H, m), 3.21–3.38 (2H, m), 3.43 (3H, s), 3.53–3.58 (1H, m), 3.64–3.75 (3H, m), 3.83–3.89 (4H, m), 4.36–4.42 (1H, m), 5.70–5.71 (1H, m), 6.34–6.38 (2H, m), 6.70–6.71 (1H, m), 6.95 (1H, dd, *J* = 8.2, 1.3 Hz), 7.07–7.09 (1H, m), 7.18 (1H, t, *J* = 8.0 Hz), 7.28–7.35 (3H, m). Anal. Calcd for $C_{31}H_{35}ClN_2O_7 \cdot 1.25H_2O$: C, 61.48; H, 6.24; N, 4.63. Found: C, 61.44; H, 5.93; N, 4.48.

4.1.1.62. Methyl 2-[(1-{3-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propanoyl}-4-piperidinyl)methoxy]acetate (29g). Compound **28** (86 mg, 0.20 mmol) was treated by using methyl 2-(4-piperidinylmethoxy)acetate[21] (56 mg, 0.30 mmol) to give the title compound **29g** (117 mg, 0.196 mmol, 97%), in a similar manner described for **9**. MS (ESI) *m/z* 597 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.05–1.20 (2H, m), 1.70–1.91 (3H, m), 2.35–2.43 (2H, m), 2.50–2.73 (3H, m), 2.95–3.04 (1H, m), 3.32–3.40 (2H, m), 3.43 (3H, s), 3.75 (3H, s), 3.84–3.97 (4H, m), 4.07 (2H, s), 4.37–4.42 (1H, m), 4.57–4.65 (1H, m), 5.70 (1H, s), 6.34–6.39 (2H, m), 6.69–6.71 (1H, m), 6.95 (1H, dd, *J* = 8.3, 1.5 Hz), 7.08 (1H, dd, *J* = 2.7, 1.5 Hz), 7.18 (1H, t, *J* = 7.9 Hz), 7.29 (1H, dd, *J* = 7.9, 1.0 Hz), 7.33–7.36 (2H, m).

4.1.1.63. 2-[(1-{3-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propanoyl}-4-piperidinyl)methoxy]acetic acid (30g). Compound **29g** (117 mg, 0.20 mmol) was treated by using potassium carbonate (81 mg, 0.59 mmol) to give the title compound **30g** (110 mg, 0.19 mmol, 96%), in a similar manner described for **10**. MS (ESI) *m/z* 583 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.18–1.01 (2H, m), 1.70–1.91 (3H, m), 2.35–2.43 (2H, m), 2.50–2.73 (3H, m), 3.04–2.93 (1H, m), 3.38–3.30 (2H, m), 3.42 (3H, s), 3.82–4.03 (6H, m), 4.35–4.42 (1H, m), 4.54–4.63 (1H, m), 5.69 (1H, s), 6.33–6.39 (2H, m), 6.69–6.71 (1H, m), 6.92–6.96 (1H, m), 7.06–7.09 (1H, m), 7.16 (1H, t, *J* = 7.8 Hz), 7.28–7.30 (1H, m), 7.33–7.36 (2H, m). Anal. Calcd for $C_{31}H_{35}ClN_2O_7 \cdot 0.75H_2O \cdot 0.25CHCl_3$: C, 59.89; H, 5.95; N, 4.47. Found: C, 59.78; H, 5.84; N, 4.40.

4.1.1.64. 4-(*tert*-Butyl) 2-methyl 2,4-morpholine dicarboxylate. To a solution of 4-(*tert*-butoxycarbonyl)-2-morpholine dicarboxylic acid (231 mg, 1.00 mmol) in dimethylformamide (2.0 ml), methyl iodide (0.125 ml, 1.33 mmol) and potassium carbonate (152 mg, 1.10 mmol) were added. The resulting mixture was stirred at room temperature for 24 h. To the reaction mixture, a 10% aqueous citric acid solution was added. The resulting mixture was diluted with ethyl acetate. After the organic layer was dried over Na_2SO_4, the solvent was distilled off to give the title compound (232 mg, 0.95 mmol, 95%). MS (ESI) *m/z* 246 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.47 (9H, s), 3.02–3.18 (2H, m), 3.58 (1H, td, *J* = 11.1, 2.6 Hz), 3.74–3.80 (4H, m), 3.98–4.14 (3H, m).

4.1.1.65. Methyl 2-morpholine carboxylate hydrochloride. To a solution of 4-(*tert*-butyl) 2-methyl 2,4-morpholine dicarboxylate (232 mg, 0.95 mmol) in dioxane (1.0 ml), 4 N hydrochloric acid in dioxane (1.18 ml) was added. The resulting mixture was stirred at room temperature for 15 h. The solvent was distilled off under reduced pressure to give the title compound (232 mg, 0.95 mmol, quant.). ^1H NMR ($CDCl_3$) δ 3.03–3.19 (2H, m), 3.26–3.45 (2H, m), 3.55–3.69 (1H, m), 3.82 (3H, s), 4.03–4.22 (2H, m), 4.58–4.69 (1H, m).

4.1.1.66. Methyl 4-{3-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propanoyl}-2-morpholine carboxylate (29h). Compound **28** (86 mg, 0.20 mmol) was treated by using methyl 2-morpholine carboxylate hydrochloride (44 mg, 0.24 mmol) to give the title compound **29h** (119 mg, 0.20 mmol, quant.), in a similar manner described for **9**. MS (ESI) *m/z* 555 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.31–4.64 (21H, m), 5.70–5.74 (1H, m), 6.33–6.42 (2H, m), 6.70–6.75 (1H, m), 6.94–7.41 (6H, m).

4.1.1.67. 4-{3-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propanoyl}-2-morpholine carboxylic acid (30h). Compound **29h** (154 mg, 0.28 mmol) was treated by using potassium carbonate (115 mg, 0.83 mmol) to give the title compound **30h** (70 mg, 0.13 mmol, 47%), in a similar manner described for **10**. MS (ESI) *m/z* 541 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.37–2.46 (2H, m), 2.55–2.79 (2H, m), 3.43 (3H, s), 3.56–3.72 (1H, m), 3.81–3.88 (4H, m), 3.99–4.22 (4H, m), 4.39–4.44 (1H, m), 5.71 (1H, s), 6.34–6.40 (2H, m), 6.69–6.74 (1H, m), 6.93–6.97 (1H, m), 7.08–7.11 (1H, m), 7.13–7.22 (1H, m), 7.27–7.32 (1H, m), 7.34–7.41 (2H, m). Anal. Calcd for $C_{28}H_{29}ClN_2O_7 \cdot 1.25H_2O \cdot 0.25$ diisopropyl ether: C, 60.15; H, 5.99; N, 4.76. Found: C, 60.14; H, 5.75; N, 4.57.

4.1.1.68. Ethyl 2-(4-{3-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propanoyl}-2-oxo-1-piperazinyl)acetate (29i). Compound **28** (100 mg, 0.23 mmol) was treated by using ethyl 2-oxopiperazineacetate[22] hydrochloride (62 mg, 0.28 mmol) to give the title compound **29i** (100 mg, 0.17 mmol, 72%), in a similar manner described for **9**. MS (EI) *m/z* 595 M^+. ^1H NMR ($CDCl_3$) δ 1.28 (3H, t, *J* = 7.2 Hz), 2.37–2.47 (2H, m), 2.52–2.73 (2H, m), 3.39–3.44 (5H, m), 3.75–3.92 (5H, m), 4.11–4.30 (6H, m), 4.41 (1H, t, *J* = 6.3 Hz), 5.71 (1H, s), 6.33–6.40 (2H, m), 6.71 (1H, s), 6.95 (1H, d, *J* = 7.1 Hz), 7.09 (1H, s), 7.15–7.39 (4H, m).

4.1.1.69. 2-(4-{3-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]propanoyl}-2-oxo-1-piperazinyl)acetic acid (30i). Compound **29i** (94 mg, 0.16 mmol) was treated by using potassium carbonate (65 mg, 0.47 mmol) to give the title compound **30i** (80 mg, 0.14 mmol, 78%), in a similar manner described for **10**. MS (FAB) *m/z* 568 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.35–2.46 (2H, m), 2.51–2.76 (2H, m), 3.36–3.46 (5H, m), 3.80–3.89 (5H, m), 4.10–4.30 (4H, m), 4.35–4.44 (1H, m), 5.70 (1H, s), 6.31–6.40 (2H, m), 6.71 (1H, s), 6.91–6.98 (1H, m), 7.08 (1H, s), 7.19–7.38 (4H, m). Anal. Calcd for $C_{29}H_{30}ClN_3O_7 \cdot 0.1H_2O \cdot 0.6CHCl_3$: C, 55.92; H, 4.79; N, 6.48. Found: C, 56.17; H, 5.03; N, 6.12.

4.1.1.70. (4*R*,6*S*)-4-(2-Azidoethyl)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine (31). To a *N*,*N*-dimethylformamide–H_2O (10:1, 22 ml) mixed solution of compound **26** (891 mg, 1.86 mmol), sodium azide (727 mg, 11.2 mmol) was added. The resulting mixture was stirred at 80 °C overnight. The reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate–*n*-hexane = 1:4) to give the title compound **31** (780 mg, 1.84 mmol, 99%). ^1H NMR ($CDCl_3$) δ 2.20–2.29 (1H, m), 2.33–2.43 (1H, m), 3.43 (3H, s), 3.52–3.68 (2H, m), 3.85 (3H, s), 4.48–4.53 (1H, m), 5.72 (1H, s), 6.29–6.31 (1H, m), 6.37–6.40 (1H, m), 6.72–6.74 (1H, m), 6.93–6.97 (1H, m), 7.10–7.12 (1H, m), 7.17–7.23 (1H, m), 7.27–7.31 (2H, m), 7.40–7.33 (2H, m).

4.1.1.71. Ethyl 1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-4-carboxylate (32a) and ethyl 1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-5-carboxylate. To a solution of compound **31** (180 mg, 0.42 mmol) in toluene (5 ml), ethyl propiolate (0.094 ml, 0.93 mmol) was added. Then, the mixture was heated under reflux overnight. After the reaction mixture was concentrated in vacuo, the residue was purified by preparative TLC (methanol–chloroform = 1:100) to give the title compounds, 4-isomer **32a** (140 mg, 0.27 mmol, 64%) and 5-isomer (61.4 mg, 0.12 mmol, 30%). 4-isomer **32a** (high polarity fraction): MS (ESI) *m/z* 523 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.39 (3H, t, *J* = 7.2 Hz), 2.62–2.74 (2H, m), 3.44 (3H, s), 3.86 (3H, s), 4.38–4.43 (3H, m), 4.70–4.76 (2H, m), 5.76 (1H, s), 6.30–6.31 (1H, m), 6.38 (1H, t, *J* = 3.3 Hz), 6.74 (1H, d, *J* = 2.2 Hz), 6.96–6.99 (1H, m), 7.10–7.11 (1H, m), 7.21 (1H, t, *J* = 7.9 Hz), 7.27–7.29 (1H, m), 7.33–7.39 (2H, m), 8.10 (1H, s). 5-Isomer (low polarity fraction): MS (ESI) *m/z* 523 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.36 (3H, t, *J* = 7.1 Hz), 2.57–2.74 (2H, m), 3.44 (3H, s), 3.86 (3H, s), 4.35 (2H, q, *J* = 7.1 Hz), 4.44–4.47 (1H, m), 5.03 (2H, t, *J* = 7.4 Hz), 5.74 (1H, s), 6.35–6.39 (2H, m), 6.73 (1H, d, *J* = 2.2 Hz), 6.96 (1H, dd, *J* = 7.9, 1.5 Hz), 7.09–7.10 (1H, m), 7.21 (1H, t, *J* = 7.9 Hz), 7.32–7.41 (3H, m), 8.10 (1H, s).

4.1.1.72. 1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazole-4-carboxylic acid (33a). Compound **32a** (48.7 mg, 0.093 mmol) was treated by using potassium carbonate (38.6 mg, 0.279 mmol) to give the title compound **33a** (41.5 mg, 0.084 mmol, 90%), in a similar manner described for **10**. MS (ESI) *m/z* 495 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.30–2.42 (2H, m), 3.32 (3H, s), 3.77 (3H, s), 4.16–4.40 (3H, m), 5.61 (1H, s), 6.18–6.20 (2H, m), 6.64–6.66 (1H, m), 6.82–6.84 (1H, m), 6.92–6.95 (1H, m), 7.05–7.09 (1H, m), 7.18–7.24 (3H, m), 7.91–7.94 (1H, m). Anal. Calcd for $C_{25}H_{23}N_4O_5Cl \cdot 2H_2O \cdot 0.5CHCl_3$: C, 51.81; H, 4.77; N, 9.48. Found: C, 51.46; H, 4.38; N, 9.26.

4.1.1.73. (1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-4-yl)methanol. Compound **33a** (91.3 mg, 0.175 mmol) was treated by using lithium aluminum hydride (19.9 mg, 0.524 mmol) to give the title compound (86.8 mg, 0.175 mmol, quant.), in a similar manner described for **25**. MS (ESI) *m/z* 481

(M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 2.57–2.74 (2H, m), 3.44 (3H, s), 3.87 (3H, s), 4.39–4.41 (1H, m), 4.62–4.73 (2H, m), 4.76 (2H, d, J = 6.1 Hz), 5.76 (1H, s), 6.29–6.31 (1H, m), 6.38 (1H, t, J = 3.2 Hz), 6.73 (1H, d, J = 2.2 Hz), 6.97 (1H, dd, J = 8.1, 1.5 Hz), 7.10–7.11 (1H, m), 7.21 (1H, t, J = 8.1 Hz), 7.29–7.31 (1H, m), 7.33–7.35 (1H, m), 7.35–7.39 (1H, m), 7.55 (1H, s).

4.1.1.74. 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-4-yl)acetonitrile. (1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-4-yl)methanol (86.8 mg, 0.180 mmol) was treated by using methanesulfonyl chloride (0.021 ml, 0.271 mmol) to give the methanesulfonate (123.0 mg, 0.180 mmol, quant.). Then the methanesulfonate was treated by sodium cyanide (21.6 mg, 0.440 mmol) to give the title compound (67.0 mg, 0.137 mmol, 76%), in a similar manner described for **26** and **27**. MS (ESI) *m/z* 491 (M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 2.58–2.75 (2H, m), 3.44 (3H, s), 3.83 (2H, s), 3.87 (3H, s), 4.40 (1H, dd, J = 9.3, 3.9 Hz), 4.63–4.76 (2H, m), 5.76 (1H, s), 6.30–6.31 (1H, m), 6.39 (1H, t, J = 3.3 Hz), 6.74 (1H, d, J = 2.2 Hz), 6.98 (1H, dd, J = 7.9, 1.5 Hz), 7.11–7.12 (1H, m), 7.22 (1H, t, J = 7.9 Hz), 7.28 (1H, dd, J = 7.9, 1.5 Hz), 7.33–7.40 (2H, m), 7.62 (1H, s).

4.1.1.75. 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-4-yl)acetic acid (33b). 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-4-yl)acetonitrile (67.0 mg, 0.137 mmol) was treated by using 5 M aqueous sodium hydroxide solution (1 ml) to give the title compound **33b** (61.1 mg, 0.120 mmol, 88%), in a similar manner described for **28**. MS (ESI) *m/z* 509 (M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 2.45–2.63 (2H, m), 3.40 (3H, s), 3.56–3.59 (2H, m), 3.83 (3H, s), 4.35–4.38 (1H, m), 4.45–4.61 (2H, m), 5.71 (1H, s), 6.24–6.26 (1H, m), 6.31 (1H, t, J = 3.2 Hz), 6.70 (1H, d, J = 2.0 Hz), 6.91–6.93 (1H, m), 7.03–7.04 (1H, m), 7.16 (1H, t, J = 8.1 Hz), 7.26–7.32 (3H, m), 7.49 (1H, s). Anal. Calcd for $C_{26}H_{25}N_4O_5Cl{\cdot}2.75H_2O{\cdot}0.1CHCl_3$: C, 54.95; H, 5.42; N, 9.82. Found: C, 54.81; H, 4.95; N, 9.52.

4.1.1.76. (1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-5-yl)methanol. Ethyl 1-{2-[(4*R*,6*S*)-8-chloro- 6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazole-5-carboxylate (61.6 mg, 0.118 mmol) was treated by using lithium aluminum hydride (13.4 mg, 0.353 mmol) to give the title compound (53.3 mg, 0.111 mmol, 94%), in a similar manner described for **25**. MS (ESI) *m/z* 481 (M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 2.37 (1H, br s), 2.67–2.73 (2H, m), 3.43 (3H, s), 3.86 (3H, s), 4.43–4.47 (1H, m), 4.63–4.76 (4H, m), 5.75 (1H, s), 6.31–6.33 (1H, m), 6.37 (1H, t, J = 3.2 Hz), 6.74 (1H, d, J = 2.0 Hz), 6.96 (1H, dd, J = 7.9, 1.3 Hz), 7.09–7.10 (1H, m), 7.20 (1H, t, J = 7.9 Hz), 7.32–7.38 (3H, m), 7.53 (1H, s).

4.1.1.77. 2-(1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-5-yl)acetonitrile. (1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-5-yl)methanol (53.3 mg, 0.111 mmol) was treated by using methanesulfonyl chloride (0.013 ml, 0.166 mmol) to give methanesulfonate (83.0 mg, 0.111 mmol, quant.). The methanesulfonate was treated by sodium cyanide (14.6 mg, 0.297 mmol) to give the title compound (20.2 mg, 0.041 mmol, 37%), in a similar manner described for **26** and **27**. MS (ESI) *m/z* 491 (M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 2.66–2.71 (2H, m), 3.44 (3H, s), 3.77 (2H, s), 3.87 (3H, s), 4.42 (1H, t, J = 6.6 Hz), 4.58–4.72 (2H, m), 5.77 (1H, s), 6.30–6.31 (1H, m), 6.39 (1H, t, J = 3.3 Hz), 6.75 (1H, d, J = 2.2 Hz), 6.98 (1H, dd, J = 7.9, 1.6 Hz), 7.11–7.12 (1H, m), 7.22 (1H, t, J = 7.9 Hz), 7.27 (1H, dd, J = 7.9, 1.3 Hz), 7.34–7.40 (2H, m), 7.66 (1H, s).

4.1.1.78. 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-5-yl)acetic acid (33c). 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-5-yl)acetonitrile (20.2 mg, 0.041 mmol) was treated by using 5 M aqueous sodium hydroxide solution (1 ml) to give the title compound **33c** (15.1 mg, 0.030 mmol, 73%), in a similar manner described for **28**. MS (ESI) *m/z* 509 (M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 2.41–2.54 (2H, m), 3.33 (3H, s), 3.40–3.43 (2H, m), 3.75 (3H, s), 4.32–4.45 (3H, m), 5.66 (1H, s), 6.22–6.24 (2H, m), 6.65–6.67 (1H, m), 6.83–6.84 (1H, m), 6.95–6.98 (1H, m), 7.08–7.11 (1H, m), 7.20–7.23 (2H, m), 7.27–7.29 (1H, m), 7.36–7.38 (1H, m). Anal. Calcd for $C_{26}H_{25}N_4O_5Cl{\cdot}3H_2O{\cdot}0.4CHCl_3$: C, 51.88; H, 5.24; N, 9.17. Found: C, 51.60; H, 5.23; N, 8.77.

4.1.1.79. Ethyl 2-[(1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-4-yl)methoxy]acetate (32d) and ethyl 2-[(1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-5-yl)methoxy]-acetate. Compound **31** (151 mg, 0.355 mmol) was treated by using ethyl 2-(2-propynyloxy)acetate (151 mg, 1.06 mmol) to give the title compounds, 4-isomer **32d** (69.7 mg, 0.123 mmol, 35%) and 5-isomer (50.0 mg, 0.088 mmol, 24%), in a similar manner described for **32a**. 4-Isomer (low polarity fraction): MS (ESI) *m/z* 567 (M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, t, J = 7.2 Hz), 2.63–2.68 (2H, m), 3.44 (3H, s), 3.86 (3H, s), 4.12 (2H, s), 4.21 (2H, q, J = 7.2 Hz), 4.38–4.42 (1H, m), 4.64–4.70 (2H, m), 4.72 (2H, s), 5.76 (1H, s), 6.30–6.31 (1H, m), 6.37–6.39 (1H, m), 6.74 (1H, d, J = 2.2 Hz), 6.97 (1H, dd, J = 8.1, 1.5 Hz), 7.10–7.11 (1H, m), 7.22 (1H, t, J = 8.1 Hz), 7.29–7.39 (3H, m), 7.65 (1H, s). 5-Isomer (high polarity fraction): MS (ESI) *m/z* 567 (M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.2 Hz), 2.63–2.78 (2H, m), 3.43 (3H, s), 3.86 (3H, s), 4.01 (2H, s), 4.17 (2H, q, J = 7.2 Hz), 4.46–4.49 (1H, m), 4.64–4.79 (4H, m), 5.74 (1H, s), 6.32–6.34 (1H, m), 6.37–6.38 (1H, m), 6.73 (1H, d, J = 2.0 Hz), 6.96 (1H, dd, J = 8.2, 1.3 Hz), 7.09–7.10 (1H, m), 7.19 (1H, t, J = 8.2 Hz), 7.32–7.38 (3H, m), 7.61 (1H,s).

4.1.1.80. 2-[(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-4-yl)methoxy]acetic acid (33d). Compound **32d** (69.7 mg, 0.123 mmol) was treated by using potassium carbonate (51.0 mg, 0.37 mmol) to give the title compound **33d** (63.3 mg, 0.117 mmol, 96%), in a similar manner described for **10**. MS (ESI) *m/z* 539 (M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 2.47–2.60 (2H, m), 3.38 (3H, s), 3.81 (5H, s), 4.35–4.37 (1H, m), 4.45–4.61 (4H, m), 5.69 (1H, s), 6.23–6.26 (1H, m), 6.27–6.29 (1H, m), 6.68 (1H, s), 6.89–6.92 (1H, m), 7.01–7.02 (1H, m), 7.12–7.17 (1H, m), 7.25–7.30 (5H, m), 7.63 (1H, s). Anal. Calcd for $C_{27}H_{27}N_4O_6Cl{\cdot}1.75H_2O{\cdot}0.4CHCl_3$: C, 53.20; H, 5.10; N, 9.06. Found: C, 53.41; H, 5.22; N, 8.39.

4.1.1.81. Methyl 2,2-dimethyl-3-(prop-2-yn-1-yloxy)propanoate. To an ice-cooling *N*,*N*-dimethylformamide solution (40 ml) of methyl 2,2-dimethyl-3-hydroxypropionate (611 mg, 4.62 mmol), sodium hydride (60% in oil, 220 mg, 5.50 mmol) was added. The resulting mixture was stirred for 5 min. While still ice-cooling, propargyl bromide (500 mg, 4.20 mmol) was added to the reaction mixture. The solution was gradually warmed to room temperature and stirred overnight. Distilled water was added to the reaction mixture, and the organic materials were extracted with diethyl ether. The organic layer was washed with brine and

dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate–*n*-hexane = 1:10) to give the title compound (554 mg, 3.25 mmol, 70%). ^{1}H NMR ($CDCl_3$) δ 1.21 (6H, s), 2.40–2.42 (1H, m), 3.53 (2H, s), 3.69 (3H, s), 4.16–4.13 (2H, m).

4.1.1.82. Methyl 2-[(1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-4-yl)methoxy]-2-methylpropanoate (32e) and methyl 2-[(1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-5-yl)methoxy]-2-methylpropanoate. Compound **31** (145 mg, 0.341 mmol) was treated by using methyl 2-methyl-2-(2-propynyloxy)propanoate (160 mg, 1.02 mmol) to give the title compounds, 4-isomer **32e** (69.2 mg, 0.119 mmol, 47%) and 5-isomer (50.1 mg, 34%), in a similar manner described for **32a**. 4-Isomer **32e** (low polarity fraction): MS (ESI) *m/z* 581 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.47–1.48 (6H, m), 2.56–2.73 (2H, m), 3.43–3.44 (3H, m), 3.73–3.73 (3H, m), 3.86–3.86 (3H, m), 4.40–4.42 (1H, m), 4.58–4.59 (2H, m), 4.62–4.69 (2H, m), 5.76 (1H, s), 6.30–6.31 (1H, m), 6.37–6.39 (1H, m), 6.72–6.73 (1H, m), 6.97 (1H, d, *J* = 8.3 Hz), 7.09–7.11 (1H, m), 7.31–7.38 (1H, m), 7.33–7.36 (3H, m), 7.63 (1H, s). 5-Isomer (high polarity fraction): MS (ESI) *m/z* 581 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.42–1.43 (6H, m), 2.62–2.78 (2H, m), 3.43–3.43 (3H, m), 3.64–3.65 (3H, m), 3.86–3.86 (3H, m), 4.49–4.52 (1H, m), 4.55–4.57 (2H, m), 4.65–4.80 (2H, m), 5.75 (1H, s), 6.32–6.33 (1H, m), 6.36–6.38 (1H, m), 6.73 (1H, s), 6.95 (1H, d, *J* = 8.1 Hz), 7.09–7.10 (1H, m), 7.18 (1H, t, *J* = 8.1 Hz), 7.33–7.38 (3H, m), 7.57 (1H, s).

4.1.1.83. 2-[(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-4-yl)methoxy]-2-methylpropanoic acid (33e). Compound **32e** (69.2 mg, 0.12 mmol) was treated by using potassium carbonate (49.4 mg, 0.36 mmol) to give the title compound **33e** (50.5 mg, 0.089 mmol, 75%), in a similar manner described for **10**. MS (ESI) *m/z* 567 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.47 (6H, s), 2.52–2.67 (2H, m), 3.43 (3H, s), 3.86 (3H, s), 4.38–4.40 (1H, m), 4.56–4.65 (4H, m), 5.74 (1H, s), 6.27–6.29 (1H, m), 6.35–6.37 (1H, m), 6.72–6.73 (1H, m), 6.96 (1H, d, *J* = 8.3 Hz), 7.08–7.10 (1H, m), 7.20 (1H, t, *J* = 7.9 Hz), 7.26–7.37 (4H, m), 7.56 (1H, s). Anal. Calcd for $C_{29}H_{31}N_4O_6Cl{\cdot}0.5H_2O$: C, 60.47; H, 5.60; N, 9.73. Found: C, 60.56; H, 5.94; N, 9.88.

4.1.1.84. Methyl 2-ethyl-2-(2-propynyloxy)butanoate. Methyl 2-ethyl-2-hydroxybutanoate (1.10 g, 7.52 mmol) was treated by sodium hydride (55% in oil, 0.36 g, 8.28 mmol) and propargyl bromide (0.85 ml, 11.3 mmol) to give the title compound (0.38 g, 2.06 mmol, 27%), in a similar manner described for methyl 2,2-dimethyl-3-(prop-2-yn-1-yloxy)propanoate. ^{1}H NMR ($CDCl_3$) δ 0.85–0.90 (6H, m), 1.80–1.84 (4H, m), 2.42 (1H, t, *J* = 2.4 Hz), 3.74 (3H, s), 4.13 (2H, d, *J* = 2.4 Hz).

4.1.1.85. Methyl 2-[(1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-4-yl)methoxy]-2-ethylbutanoate (32f) and methyl 2-[(1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-5-yl)methoxy]-2-ethylbutanoate. Compound **31** (140 mg, 0.33 m mol) was treated by using methyl 2-ethyl-2-(2-propynyloxy)butanoate (182 mg, 0.99 mmol) to give the title compounds, 4-isomer **32f** (117 mg, 0.19 mmol, 58%) and 5-isomer (23 mg, 0.04 mmol, 12%), in a similar manner described for **32a**. 4-Isomer **32f** (low polarity fraction): MS (ESI) *m/z* 609 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 0.83–0.87 (6H, m), 1.85 (4H, q, *J* = 7.5 Hz), 2.58–2.74 (2H, m), 3.44 (3H, s), 3.73 (3H, s), 3.86 (3H, s), 4.40–4.44 (1H, m), 4.52–4.59 (2H, m), 4.62–4.72 (2H, m), 5.76 (1H, s), 6.31–6.32 (1H, m), 6.37–6.39 (1H, m), 6.73 (1H, d, *J* = 2.0 Hz), 6.96–6.98 (1H, m), 7.10–7.11 (1H, m), 7.22 (1H, t, *J* = 7.9 Hz), 7.31–7.38 (4H, m), 7.64 (1H, s). 5-Isomer (high polarity fraction): MS (ESI) *m/z* 609 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 0.77–0.83 (6H, m), 1.76–1.83 (4H, m), 2.62–2.80 (2H, m), 3.43 (3H, s), 3.63 (3H, s), 3.86 (3H, s), 4.50–4.56 (2H, m), 4.65–4.81 (2H, m), 5.75 (1H, s), 6.32–6.34 (1H, m), 6.36–6.38 (1H, m), 6.73 (1H, d, *J* = 2.2 Hz), 6.95 (1H, dd, *J* = 8.1, 1.5 Hz), 7.09–7.10 (1H, m), 7.17 (1H, t, *J* = 8.1 Hz), 7.32–7.38 (3H, m), 7.57 (1H, s).

4.1.1.86. 2-[(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3-triazol-4-yl)methoxy]-2-ethylbutanoic acid (33f). Compound **32f** (140 mg, 0.23 mmol) was dissolved in methanol–water–tetrahydrofuran (2:1:2, 2.5 ml). To the resulting solution, 5 N aqueous sodium hydroxide solution (0.23 ml, 1.15 mmol) was added and stirred overnight at 80 °C. After the reaction mixture was neutralized with an ion exchange resin (Amberlite IR-120B), the resin was filtered out and the filtrate was concentrated in vacuo. The residue was purified by preparative thin layer chromatography on silica gel (methanol–chloroform = 1:10) to give the title compound **33f** (92 mg, 0.15 mmol, 67%). MS (ESI) *m/z* 595 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 0.77–0.86 (6H, m), 1.75–1.90 (4H, m), 2.53–2.70 (2H, m), 3.43 (3H, s), 3.86 (3H, s), 4.37–4.41 (1H, m), 4.47–4.51 (2H, m), 4.59–4.68 (2H, m), 5.75 (1H, s), 6.28–6.29 (1H, m), 6.35–6.37 (1H, m), 6.72 (1H, d, *J* = 2.0 Hz), 6.95–6.97 (1H, m), 7.08–7.10 (1H, m), 7.20 (1H, t, *J* = 7.9 Hz), 7.27–7.37 (3H, m), 7.59 (1H, s). Anal. Calcd for $C_{31}H_{35}N_4O_6Cl{\cdot}2H_2O{\cdot}0.25$ 1,4-dioxane: C, 58.85; H, 6.33; N, 8.58. Found: C, 59.35; H, 6.00; N, 8.10.

4.1.1.87. Ethyl 1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazole-5-carboxylate and ethyl 1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethy l}-1*H*-pyrazole-3-carboxylate. To an *N*,*N*-dimethylformamide solution (2.0 ml) of ethyl 1H-pyrazole-3-carboxylate (111 mg, 0.79 mmol), sodium hydride (60% in oil, 70 mg, 1.75 mmol) was added under ice-cooling. The resulting mixture was stirred for 5 min. To the reaction mixture, an *N*,*N*-dimethylformamide solution (5.0 ml) of compound **26** (815 mg, 1.71 mmol) and tetrabutylammonium iodide (209 mg, 0.56 mmol) were added. While warming to room temperature, the resulting mixture was stirred for 14 h. The reaction mixture was concentrated in vacuo. To the residue, diethyl ether and distilled water were added. The organic layer was separated and dried over Na_2SO_4. The solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (methanol–dichloromethane = 1:100) to give the title compounds, 3-isomer (92 mg, 0.18 mmol, 10%) and 5-isomer (78 mg, 0.15 mmol, 9%), respectively. 3-isomer: MS (ESI) *m/z* 522 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, *J* = 7.1 Hz), 2.56–2.69 (2H, m), 3.43 (3H, s), 3.86 (3H, s), 4.28–4.34 (1H, m), 4.38 (2H, q, *J* = 7.1 Hz), 4.43–4.63 (2H, m), 5.74 (1H, s), 6.27–6.32 (1H, m), 6.35–6.38 (1H, m), 6.71–6.77 (2H, m), 6.97 (1H, dd, *J* = 8.1, 1.5 Hz), 7.07–7.10 (1H, m), 7.21 (1H, t, *J* = 8.0 Hz), 7.29–7.39 (3H, m), 7.44 (1H, d, *J* = 2.2 Hz). 5-isomer: MS (ESI) *m/z* 522 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, t, *J* = 7.1 Hz), 2.48–2.67 (2H, m), 3.43 (3H, s), 3.85 (3H, s), 4.30 (2H, q, *J* = 7.1 Hz), 4.38–4.46 (1H, m), 4.81–4.90 (2H, m), 5.72 (1H, s), 6.31–6.40 (2H, m), 6.73 (1H, d, *J* = 2.2 Hz), 6.81 (1H, d, *J* = 2.0 Hz), 6.95 (1H, dd, *J* = 8.1, 1.2 Hz), 7.08 (1H, t, *J* = 2.1 Hz), 7.19 (1H, t, *J* = 8.1 Hz), 7.28–7.38 (2H, m), 7.40–7.46 (2H, m).

4.1.1.88. (1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1 *H*-pyra zol -3-yl)methanol. 1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dime-

thoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl] ethyl}-1*H*-pyrazole-3-carboxylate (91 mg, 0.17 mmol) was treated by using lithium aluminum hydride (11 mg, 0.29 mmol) to give the title compound (93 mg, 0.17 mmol, quant.), in a similar manner described for **25**. MS (ESI) *m/z* 480 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 2.53–2.64 (2H, m), 3.44 (3H, s), 3.86 (3H, s), 4.27–4.53 (3H, m), 4.64 (2H, s), 5.74 (1H, s), 6.17 (1H, d, J = 2.2 Hz), 6.28–6.32 (1H, m), 6.35–6.39 (1H, m), 6.70–6.77 (1H, m), 6.97 (1H, dd, J = 8.3, 1.5 Hz), 7.08–7.11 (1H, m), 7.21 (1H, t, J = 8.1 Hz), 7.29–7.40 (4H, m). IR (ATR) cm^{-1} 2937, 1720, 1587, 1277, 1223, 1101, 1032, 750, 715.

4.1.1.89. 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazol-3-yl)acetonitrile. (1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazol-3-yl)methanol (4.69 g, 9.78 mmol) was dissolved in dichloromethane solution (47 ml). To the solution, triphenylphosphine (3.08 g, 11.73 mmol) and carbon tetrabromide (3.89 g, 11.73 mmol) were added under ice-cooling. The resulting mixture was stirred for 1 h while kept under ice-cooling. At the same temperature, sodium cyanide (2.40 g, 48.88 mmol) and dimethylsulfoxide (47 ml) were added. The reaction mixture was stirred at 40 °C for 2 h (disappearance of a bromine derivative and generation of the intended product were confirmed by TLC). The reaction mixture was cooled to room temperature, and then brine and ethyl acetate were added. The organic layer was separated and washed with water and brine, and then dried over Na_2SO_4. The solvent was distilled off under reduced pressure and the residue was subjected to column chromatography (methanol–chloroform = 1:200) to give the title compound (3.44 g, 7.04 mmol, 72%). MS (ESI) *m/z* 489 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 2.52–2.62 (2H, m), 3.44 (3H, s), 3.70 (2H, s), 3.86 (3H, s), 4.27–4.48 (3H, m), 5.74 (1H, s), 6.21 (1H, dd, J = 2.2, 0.5 Hz), 6.29–6.32 (1H, m), 6.37 (1H, t, J = 3.2 Hz), 6.73 (1H, d, J = 2.0 Hz), 6.97 (1H, dd, J = 8.1, 1.5 Hz), 7.09 (1H, dd, J = 2.9, 1.5 Hz), 7.21 (1H, t, J = 8.0 Hz), 7.30–7.39 (4H, m).

4.1.1.90. 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazol-3-yl)acetic acid (35a). 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-di m ethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl} -1*H*-pyrazol-3-yl)acetonitrile (3.44 g, 7.04 mmol) was treated by using 5 M aqueous sodium hydroxide solution (28 ml) to give the title compound **35a** (3.08 g, 6.06 mmol, 86%), in a similar manner described for **28**. ^{1}H NMR ($CDCl_3$) δ 2.50–2.66 (2H, m), 3.44 (3H, s), 3.73 (2H, s), 3.86 (3H, s), 4.29–4.35 (1H, m), 4.35–4.50 (2H, m), 5.74 (1H, s), 6.10 (1H, d, J = 2.2 Hz), 6.29–6.32 (1H, m), 6.37 (1H, t, J = 3.2 Hz), 6.73 (1H, d, J = 2.2 Hz), 6.97 (1H, dd, J = 8.1, 1.5 Hz), 7.09 (1H, dd, J = 2.9, 1.7 Hz), 7.21 (1H, t, J = 8.1 Hz), 7.29–7.41 (4H, m). IR (ATR) cm^{-1} 2933, 1716, 1481, 1277, 1173, 1099, 1051, 1003, 758, 714. Anal. Calcd for $C_{27}H_{26}ClN_3O_5$: C, 63.84; H, 5.16; N, 8.27. Found: C, 63.66; H, 5.18; N, 8.02.

4.1.1.91. (1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazol-5-yl)methanol. Ethyl 1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimet hoxyp henyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyr azole-5-carboxylate (78 mg, 0.15 mmol) was treated by using lithium aluminum hydride (9.3 mg, 0.25 mmol) to give the title compound (72 mg, 0.15 mmol, quant.), in a similar manner described for **25**. MS (ESI) *m/z* 480 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 2.56–2.71 (2H, m), 3.43 (3H, s), 3.67–3.72 (1H, m), 3.86 (3H, s), 4.37–4.55 (3H, m), 4.60–4.70 (2H, m), 5.74 (1H, s), 6.16 (1H, d, J = 1.7 Hz), 6.31–6.40 (2H, m), 6.74 (1H, d, J = 2.2 Hz), 6.96 (1H, dd, J = 8.3, 1.5 Hz), 7.07–7.10 (1H, m), 7.18–7.23 (1H, m), 7.30–7.44 (3H, m). IR (ATR) cm^{-1} 2935, 1587, 1481, 1277, 1099, 1055, 1005, 748.

4.1.1.92. 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazol-5-yl)acetonitrile. 1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyph enyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyra zol-5-yl)methanol (76 mg, 0.16 mmol) was treated using methanesulfonyl chloride (0.016 ml, 0.15 mmol) and triethylamine (0.024 ml, 0.17 mmol) to give the title compound (97 mg, 0.17 mmol, quant.). This methanesulfonate (88 mg, 0.16 mmol) was treated by using sodium cyanide (16 mg, 0.32 mmol) to give the title compound (34 mg, 0.07 mmol, 43%), in a similar manner described for **26** and **27**. MS (ESI) *m/z* 489 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 2.51–2.67 (2H, m), 3.43 (3H, s), 3.72 (2H, s), 3.87 (3H, s), 4.27–4.49 (3H, m), 5.74 (1H, s), 6.21–6.26 (1H, m), 6.29–6.32 (1H, m), 6.36–6.39 (1H, m), 6.75 (1H, d, J = 2.2 Hz), 6.94–7.00 (1H, m), 7.09–7.15 (1H, m), 7.22 (1H, t, J = 8.0 Hz), 7.29–7.41 (3H, m), 7.43–7.46 (1H, m).

4.1.1.93. 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazol-5-yl)acetic acid (35b). 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dime thoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]et hyl} -1*H*-pyrazol-5-yl)acetonitrile (88 mg, 0.18 mmol) was treated by using 5 M aqueous sodium hydroxide solution to give the title compound **35b** (25 mg, 0.05 mmol, 27%), in a similar manner described for **28**. MS (ESI) *m/z* 508 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 2.47–2.78 (2H, m), 3.40 (3H, d, J = 1.2 Hz), 3.47–3.73 (2H, m), 3.83 (3H, d, J = 1.7 Hz), 4.14–4.47 (3H, m), 5.72 (1H, s), 6.10 (1H, s), 6.27–6.37 (2H, m), 6.69–6.76 (1H, m), 6.87–6.97 (1H, m), 7.04–7.09 (1H, m), 7.10–7.19 (1H, m), 7.29–7.43 (4H, m). IR (ATR) cm^{-1} 2935, 1718, 1587, 1481, 1277, 1173, 1099, 1039, 1003, 760, 714. Anal. Calcd for $C_{27}H_{26}ClN_3O_5 \cdot 1.25H_2O \cdot 0.5CHCl_3$: C, 55.97; H, 4.95; N, 7.12. Found: C, 55.93; H, 4.79; N, 6.93.

4.1.1.94. Ethyl 1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazole-4-carboxylate (34c). Compound **26** (719 mg, 1.50 mmol) was treated by using ethyl 1*H*-pyrazole-4-carboxylate (261 mg, 1.86 mmol) and sodium hydride (55% in oil, 92 mg, 2.11 mmol) to give the title compound **34c** (661 mg, 1.27 mmol, 84%). ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, t, J = 7.1 Hz), 2.57–2.69 (2H, m), 3.44 (3H, s), 3.86 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 4.32–4.55 (3H, m), 5.74 (1H, s), 6.30–6.33 (1H, m), 6.36–6.39 (1H, m), 6.71–6.75 (1H, m), 6.95–6.99 (1H, m), 7.08–7.11 (1H, m), 7.24–7.18 (1H, m), 7.38–7.29 (3H, m), 7.92–7.87 (2H, m).

4.1.1.95. 1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazole-4-carboxylic acid (35c). Compound **34c** (470 mg, 0.90 mmol) was treated by using 5 N aqueous sodium hydroxide solution (9.0 ml) to give the title compound **35c** (280 mg, 0.57 mmol, 63%), in a similar manner described for **10**. MS (ESI) *m/z* 494 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 2.59–2.67 (2H, m), 3.44 (3H, s), 3.86 (3H, s), 4.32–4.55 (3H, m), 5.74 (1H, s), 6.30–6.33 (1H, m), 6.36–6.39 (1H, m), 6.73–6.74 (1H, m), 6.95–6.99 (1H, m), 7.08–7.11 (1H, m), 7.18–7.24 (1H, m), 7.26–7.26 (2H, m), 7.28–7.38 (3H, m), 7.97–7.92 (2H, m). Anal. Calcd for $C_{26}H_{24}ClN_3O_5 \cdot 0.25H_2O \cdot 0.25$ *n*-hexane: C, 63.52; H, 5.43; N, 8.08. Found: C, 63.46; H, 5.28; N, 8.01.

4.1.1.96. (1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazol-4-yl)methanol. Compound **34c** (592 mg, 1.20 mmol) was treated by using lithium aluminum hydride (187 mg, 4.93 mmol) to give the title compound (512 mg, 1.07 mmol, 89%), in a similar manner described for **25**. ^{1}H NMR ($CDCl_3$) δ 2.56–2.63 (2H, m), 3.44 (3H, s), 3.86 (3H, s), 4.29–4.57 (5H, m), 5.73 (1H, s), 6.29–6.32 (1H, m), 6.35–6.39 (1H, m), 6.71–6.79 (1H, m), 6.93–7.00

(1H, m), 7.06–7.12 (1H, m), 7.18–7.24 (1H, m), 7.30–7.40 (3H, m), 7.48–7.41 (2H, m).

4.1.1.97. 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazol-4-yl)acetonitrile. (1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazol-4-yl)methanol (244 mg, 0.51 mmol) was treated by using triphenylphosphine (320 mg, 1.22 mmol), carbon tetrabromide (370 mg, 1.12 mmol) and sodium cyanide (124 mg, 2.53 mmol) to give the title compound (139 mg, 0.28 mmol, 56%). MS (ESI) *m/z* 489 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.55–2.64 (2H, m), 3.44 (3H, s), 3.53 (2H, s), 3.86 (3H, s), 4.29–4.52 (3H, m), 5.73–5.81 (1H, m), 6.28–6.40 (2H, m), 6.72–6.76 (1H, m), 6.94–7.00 (1H, m), 7.07–7.15 (1H, m), 7.19–7.24 (1H, m), 7.29–7.45 (5H, m).

4.1.1.98. 2-(1-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazol-4-yl)acetic acid (35d). 2-(1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-pyrazol-4-yl)acetonitrile (139 mg, 0.28 mmol) was treated by using 5 M aqueous sodium hydroxide solution (2.42 ml) to give the title compound **35d** (80 mg, 0.16 mmol, 56%), in a similar manner described for **28**. MS (ESI) *m/z* 508 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.52–2.61 (2H, m), 3.42 (3H, s), 3.44 (2H, s), 3.85 (3H, s), 4.27–4.48 (3H, m), 5.72 (1H, s), 6.25–6.32 (1H, m), 6.34–6.37 (1H, m), 6.71–6.78 (1H, m), 6.92–7.00 (1H, m), 7.06–7.13 (1H, m), 7.16–7.22 (1H, m), 7.42–7.27 (5H, m).

Anal. Calcd for $C_{27}H_{26}ClN_3O_5 \cdot 1.0\ H_2O$: C, 61.65; H, 5.37; N, 7.99. Found: C, 61.33; H, 5.23; N, 7.64.

4.1.1.99. Ethyl 2-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-2*H*-1,2,3,4-tetrazol-5-carboxylate (34e) and ethyl 2-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3,4-tetrazol-5-carboxylate. Compound **26** (134 mg, 0.280 mmol) was treated using ethyl 1H-tetrazole 5-carboxylate (105 mg, 0.561 mmol), sodium hydride (60% in oil, 70 mg, 1.75 mmol), and tetrabutylammonium iodide (209 mg, 0.56 mmol) to give the title compounds, 2H-isomer **34e** (63.3 mg, 0.121 mmol, 43%) and 1H-isomer (30.3 mg, 0.058 mmol, 21%), which were obtained respectively. 2H-Isomer **34e** (low polarity fraction): MS (ESI) *m/z* 525 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.45 (3H, t, *J* = 7.2 Hz), 2.79–2.85 (2H, m), 3.44 (3H, s), 3.86 (3H, s), 4.39–4.43 (1H, m), 4.51 (2H, q, *J* = 7.2 Hz), 5.01–5.06 (2H, m), 5.75 (1H, s), 6.32–6.33 (1H, m), 6.38–6.39 (1H, m), 6.72 (1H, d, *J* = 2.2 Hz), 6.96–6.98 (1H, m), 7.09–7.12 (1H, m), 7.21 (1H, t, *J* = 7.9 Hz), 7.30–7.36 (3H, m). 1H-Isomer (high polarity fraction): MS (ESI) *m/z* 525 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.42–1.47 (3H, m), 2.60–2.78 (2H, m), 3.43 (3H, s), 3.86 (3H, s), 4.44–4.53 (3H, m), 5.06–5.09 (2H, m), 5.74–5.75 (1H, m), 6.32–6.35 (1H, m), 6.38–6.39 (1H, m), 6.72–6.75 (1H, m), 6.96–6.98 (1H, m), 7.09–7.12 (1H, m), 7.21 (1H, t, *J* = 8.1 Hz), 7.33–7.39 (3H, m).

4.1.1.100. 2-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-2*H*-1,2,3,4-tetrazol-5-carboxylic acid (35e). Compound **34e** (60.3 mg, 0.115 mmol) was treated by using potassium carbonate (47.7 mg, 0.345 mmol) to give the title compound **35e** (42.6 mg, 0.086 mmol, 75%), in a similar manner described for **10**. MS (ESI) *m/z* 496 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.41–2.55 (2H, m), 3.35 (3H, s), 3.79 (3H, s), 4.32–4.35 (1H, m), 4.49–4.51 (1H, m), 4.66–4.68 (1H, m), 5.63–5.66 (1H, m), 6.15–6.22 (2H, m), 6.64–6.67 (1H, m), 6.83–6.94 (2H, m), 7.07–7.10 (1H, m), 7.21–7.25 (3H, m). Anal. Calcd for $C_{24}H_{22}N_5O_5Cl \cdot 1H_2O \cdot 0.4CHCl_3$: C, 52.14; H, 4.45; N, 12.46. Found: C, 51.71; H, 4.04; N, 12.36.

4.1.1.101. Ethyl 2-(2-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-2*H*-1,2,3,4-tetrazol-5-yl)acetate (34f) and Ethyl 2-(2-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3,4-tetrazol-5-yl)acetate (34g). Compound **26** (156 mg, 0.326 mmol) was treated with ethyl 1H-tetrazole 5-acetate (82.3 mg, 0.527 mmol), potassium carbonate (109 mg, 0.791 mmol) and tetrabutylammonium iodide (97.4 mg, 0.264 mmol) to give the title compounds, 2H-isomer **34f** (85.4 mg, 0.159 mmol, 49%) and 1H-isomer **34g** (65.4 mg, 0.122 mmol, 37%). 2H-Isomer **34f** (low polarity fraction): MS (ESI) *m/z* 538 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.24 (3H, t, *J* = 7.2 Hz), 2.75–2.79 (2H, m), 3.44 (3H, s), 3.86 (3H, s), 3.93 (2H, s), 4.18 (2H, q, *J* = 7.2 Hz), 4.41–4.45 (1H, m), 4.91–4.95 (2H, m), 5.75 (1H, s), 6.32–6.34 (1H, m), 6.38–6.39 (1H, m), 6.72 (1H, d, *J* = 2.0 Hz), 6.96 (1H, dd, *J* = 8.1, 1.3 Hz), 7.10–7.11 (1H, m), 7.21 (1H, t, *J* = 8.1 Hz), 7.32–7.38 (3H, m). 1H-Isomer **34g** (high polarity fraction): MS (ESI) *m/z* 538 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.24 (3H, t, *J* = 7.2 Hz), 2.66–2.76 (2H, m), 3.43 (3H, s), 3.86 (3H, s), 3.99–4.00 (2H, m), 4.14–4.20 (2H, m), 4.40–4.43 (1H, m), 4.60–4.67 (2H, m), 5.75 (1H, s), 6.30–6.32 (1H, m), 6.38–6.39 (1H, m), 6.74 (1H, d, *J* = 2.2 Hz), 6.97 (1H, dd, *J* = 8.1, 1.7 Hz), 7.10–7.12 (1H, m), 7.19 (1H, t, *J* = 8.1 Hz), 7.33–7.40 (3H, m).

4.1.1.102. 2-(2-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)ethyl]-2*H*-1,2,3,4-tetrazol-5-yl}acetic acid (35f). Compound **34f** (85.4 mg, 0.159 mmol) was treated by using potassium carbonate (65.8 mg, 0.425 mmol) to give the title compound **35f** (61.2 mg, 0.120 mmol, 76%), in a similar manner described for **10**. MS (ESI) *m/z* 510 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.56–2.67 (2H, m), 3.38 (3H, s), 3.61–3.66 (2H, m), 3.81 (3H, s), 4.35–4.40 (1H, m), 4.66–4.83 (2H, m), 5.68 (1H, s), 6.23–6.28 (2H, m), 6.66–6.68 (1H, m), 6.87–6.89 (1H, m), 7.10–7.15 (1H, m), 7.11–7.13 (1H, m), 7.23–7.30 (3H, m). Anal. Calcd for $C_{25}H_{24}N_5O_5Cl \cdot 2.65H_2O$: C, 53.84; H, 5.30; N, 12.56. Found: C, 53.39; H, 4.50; N, 12.28.

4.1.1.103. 2-(2-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3,4-tetrazol-5-yl)acetic acid (35g). Compound **34g** (65.4 mg, 0.122 mmol) was treated by using potassium carbonate (50.4 mg, 0.365 mmol) to give the title compound **35g** (47.3 mg, 0.093 mmol, 76%), in a similar manner described for **10**. MS (ESI) *m/z* 510 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.45–2.55 (2H, m), 3.34 (3H, s), 3.53–3.55 (2H, m), 3.76 (3H, s), 4.32–4.45 (3H, m), 5.66 (1H, s), 6.19–6.25 (2H, m), 6.64–6.66 (1H, m), 6.81–6.83 (1H, m), 6.92–6.94 (1H, m), 7.08–7.13 (1H, m), 7.16–7.22 (2H, m), 7.30–7.32 (1H, m). Anal. Calcd for $C_{25}H_{24}N_5O_5Cl \cdot 4.7H_2O$: C, 50.50; H, 5.66; N, 11.78. Found: C, 50.17; H, 4.58; N, 11.30.

4.1.1.104. 2-[2-(4-Methoxybenzyl)-2*H*-1,2,3,4-tetrazol-5-yl]-1-ethanol. Ethyl 2-[2-(4-methoxybenzyl)-2*H*-1,2,3,4-tetrazol-5-yl]acetate[23] (5.24 g, 18.9 mmol) was treated using lithium aluminum hydride (1.17 g, 30.8 mmol) to give the title compound (4.44 g, 18.9 mmol, quant.), in a similar manner described for **25**. MS (ESI) *m/z* 235 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.34–2.41 (1H, m), 3.12 (2H, t, *J* = 5.9 Hz), 3.80 (3H, s), 3.99–4.05 (2H, m), 5.63–5.69 (2H, m), 6.87–6.92 (2H, m), 7.27–7.36 (2H, m). IR (ATR) cm^{-1} 2937, 1612, 1514, 1248, 1176, 1026, 779.

4.1.1.105. 2-[2-(4-Methoxybenzyl)-2*H*-1,2,3,4-tetrazol-5-yl]ethyl methanesulfonate. 2-[2-(4-Methoxybenzyl)-2*H*-1,2,3,4-tetrazol-5-yl]-1-ethanol (5.23 g, 22.3 mmol) was treated using methanesulfonyl chloride (2.07 ml, 26.7 mmol) and triethylamine (4.67 ml, 33.5 mmol) to give the title compound (6.20 g, 19.8 mmol, 89%), in a similar manner described for **26**. MS (ESI)

m/z 313 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.91 (3H, s), 3.30–3.36 (2H, m), 3.80 (3H, s), 4.59–4.64 (2H, m), 5.66 (2H, s), 6.86–6.92 (2H, m), 7.28–7.36 (2H, m). IR (ATR) cm^{-1} 1612, 1514, 1350, 1248, 1169, 1028, 960, 906, 779, 526.

4.1.1.106. 3-[2-(4-Methoxybenzyl)-2*H*-1,2,3,4-tetrazol-5-yl]propionitrile. 2-[2-(4-Methoxybenzyl)-2*H*-1,2,3,4-tetrazol-5-yl]ethyl methanesulfonate (6.19 g, 19.8 mmol) was treated using sodium cyanide (1.89 g, 38.6 mmol) to give the title compound (2.77 g, 11.4 mmol, 57%), in a similar manner described for **27**. MS (ESI) *m/z* 266 $(M+Na)^+$. ^1H NMR ($CDCl_3$) δ 2.82–2.89 (2H, m), 3.22–3.28 (2H, m), 3.80 (3H, s), 5.66 (2H, s), 6.87–6.93 (2H, m), 7.31–7.37 (2H, m).

4.1.1.107. 3-[2-(4-Methoxybenzyl)-2*H*-1,2,3,4-tetrazol-5-yl]propionic acid. 3-[2-(4-Methoxybenzyl)-2*H*-1,2,3,4-tetrazol-5-yl]propionitrile (2.10 g, 8.6 mmol) was treated, to give the title compound (2.26 g, 8.6 mmol, 99%), in a similar manner described for **28**. MS (ESI) *m/z* 263 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.86–2.92 (2H, m), 3.16–3.24 (2H, m), 3.79 (3H, s), 5.64 (2H, s), 6.86–6.91 (2H, m), 7.29–7.35 (2H, m). IR (ATR) cm^{-1} 2931, 1712, 1610, 1512, 1440, 1294, 1244, 1213, 1030, 931, 796.

4.1.1.108. Methyl 3-[2-(4-methoxybenzyl)-2*H*-1,2,3,4-tetrazol-5-yl]propanoate. To a methanol solution (17 ml) of 3-[2-(4-methoxybenzyl)-2*H*-1,2,3,4-tetrazol-5-yl]propionic acid (447 mg, 1.70 mmol) was added tetramethylsilyldiazomethane (2 M hexane solution, 1.28 ml, 2.56 mmol) under ice-cooling, followed by stirring for 3 h. The solvent was distilled off under reduced pressure to give the title compound (372 mg, 1.35 mmol, 79%). MS (ESI) *m/z* 277 $(M+H)^+$.

^1H NMR ($CDCl_3$) δ 2.81–2.86 (2H, m), 3.17–3.22 (2H, m), 3.68 (3H, s), 3.80 (3H, s), 5.63 (2H, s), 6.82–6.95 (2H, m), 7.29–7.38 (2H, m). IR (ATR) cm^{-1} 2952, 1736, 1612, 1514, 1248, 1176, 1028, 841, 779.

4.1.1.109. Methyl 3-[2*H*-1,2,3,4-tetrazol-5-yl]propanoate. To a methanol solution (10 ml) of methyl 3-[2-(4-methoxybenzyl)-2*H*-1,2,3,4-tetrazol-5-yl]propanoate (379 mg, 1.37 mmol) were added 20% palladium hydroxide-carbon (150 mg) and a 4 N hydrochloric acid in 1,4-dioxane solution (5 ml). The resulting mixture was stirred in a hydrogen atmosphere for 6 h. The catalyst was removed by filtration through celite, and the filtrate was concentrated in vacuo. The residue was subjected to LH-20 column chromatography (methanol) to give the title compound (178 mg, 1.14 mmol, 83%). MS (ESI) *m/z* 157 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.82–2.91 (2H, m), 3.27–3.36 (2H, m), 3.75 (3H, s).

4.1.1.110. Methyl 3-(2-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-2*H*-1,2,3,4-tetrazol-5-yl)propanoate (34 h) and Methyl 3-(1-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3,4-tetrazol-5-yl)propanoate. In a similar manner described for **34f**, compound **26** (224 mg, 0.52 mmol) was treated using methyl 3-[2H-1,2,3,4-tetrazol-5-yl]propanoate (88 mg, 0.51 mmol), potassium carbonate (130 mg, 0.94 mmol) and tetrabutylammonium iodide (173 mg, 0.47 mmol) to give the title compounds, 2H-isomer **34h** (143 mg, 0.27 mmol, 51%) and 1H-isomer (57 mg, 0.11 mmol, 20%), respectively. 2H-Isomer **34h** (low polarity fraction): MS (ESI) *m/z* 560 $(M+Na)^+$. ^1H NMR ($CDCl_3$) δ 2.65–2.86 (2H, m), 3.14–3.22 (2H, m), 3.44 (3H, s), 3.48–3.51 (2H, m), 3.68 (3H, s), 3.86 (3H, s), 4.35–4.43 (1H, m), 4.81–4.94 (2H, m), 5.75 (1H, s), 6.28–6.34 (1H, m), 6.35–6.40 (1H, m), 6.70–6.73 (1H, m), 6.84–7.01 (1H, m), 7.07–7.12 (1H, m), 7.17–7.24 (1H, m), 7.28–7.40 (3H, m). IR (ATR) cm^{-1} 2937, 1736, 1489, 1431, 1277, 1171, 1059, 1028, 760, 715. 1H-Isomer (high polarity fraction): MS (ESI) *m/z* 538 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 2.55–2.77 (2H, m), 2.83–2.98 (2H, m), 2.99–3.14 (2H, m), 3.43 (3H, s), 3.66 (3H, s), 3.86 (3H, s), 4.36–4.42 (1H, m), 4.58–4.72 (2H, m), 5.75 (1H, s), 6.27–6.33 (1H, m), 6.37–6.41 (1H, m), 6.73 (1H, d, *J* = 2.2 Hz), 6.95–7.01 (1H, m), 7.10–7.13 (1H, m), 7.21 (1H, t, *J* = 8.1 Hz), 7.28–7.40 (3H, m). IR (ATR) cm^{-1} 2951, 1736, 1481, 1429, 1275, 1171, 1028, 1003, 760, 715.

4.1.1.111. 3-(2-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-2*H*-1,2,3,4-tetrazol-5-yl)propanoic acid (35h). Compound **34h** (123 mg, 0.23 mmol) was treated using potassium carbonate (95 mg, 0.69 mmol) to give the title compound **35h** (75 mg, 0.14 mmol, 63%), in a similar manner described for **10**.

^1H NMR ($CDCl_3$) δ 2.64–2.90 (4H, m), 3.12–3.21 (2H, m), 3.44 (3H, s), 3.86 (3H, s), 4.36–4.46 (1H, m), 4.83–4.95 (2H, m), 5.75 (1H, s), 6.26–6.35 (1H, m), 6.36–6.40 (1H, m), 6.71–6.78 (1H, m), 6.91–7.04 (1H, m), 7.08–7.15 (1H, m), 7.18–7.24 (1H, m), 7.29–7.40 (3H, m). IR (ATR) cm^{-1} 3417, 2935, 1712, 1491, 1279, 1173, 1101, 1063, 823, 762, 717. Anal. Calcd for $C_{26}H_{26}ClN_5O_5 \cdot 0.75H_2O$: C,58.10; H,5.16; N,13.03. Found: C,58.30; H,4.95; N,12.82.

4.1.1.112. Ethyl 2-(2-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-2*H*-1,2,3,4-tetrazol-5-yl)-2-methylpropanoate (34i) and ethyl 2-(2-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3,4-tetrazol-5-yl)-2-methylpropanoate. In a similar manner described for **34f**, compound **26** (179 mg, 0.37 mmol) was treated with ethyl 2,2-dimethyl-2-(1*H*-tetrazol-5-yl)acetate (138 mg, 0.75 mmol) to give the title compounds, 2H-isomer **34i** (191 mg, 0.34 mmol, 90%) and 1H-isomer (28.7 mg, 0.05 mmol, 13%). 2H-Isomer **34i** (low polarity fraction): MS (ESI) *m/z* 566 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.14 (3H, t, *J* = 7.1 Hz), 1.64 (6H, s), 2.68–2.80 (2H, m), 3.44 (3H, s), 3.86 (3H, s), 4.10 (2H, q, *J* = 7.1 Hz), 4.36–4.39 (1H, m), 4.89–4.93 (2H, m), 5.76 (1H, s), 6.32–6.33 (1H, m), 6.39 (1H, t, *J* = 3.2 Hz), 6.71–6.72 (1H, m), 6.97 (1H, d, *J* = 8.1 Hz), 7.10–7.11 (1H, m), 7.22 (1H, t, *J* = 8.1 Hz), 7.31–7.41 (3H,m). 1H-Isomer (high polarity fraction): MS (ESI) *m/z* 566 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.15–1.19 (3H, m), 1.73 (6H, s), 2.65–2.80 (2H, m), 3.43 (3H, s), 3.87 (3H, s), 4.12–4.16 (2H, m), 4.33–4.39 (1H, m), 4.47–4.52 (2H, m), 5.74 (1H, s), 6.32–6.33 (1H, m), 6.38–6.40 (1H, m), 6.73–6.74 (1H, m), 6.97 (1H, d, *J* = 8.1 Hz), 7.11–7.12 (1H, m), 7.22 (1H, t, *J* = 8.1 Hz), 7.27–7.29 (1H, m), 7.34–7.41 (2H, m).

4.1.1.113. 2-(2-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)ethyl]-2*H*-1,2,3,4-tetrazol-5-yl}-2-methylpropanoic acid (35i). Compound **34i** (191 mg, 0.34 mmol) was treated using potassium carbonate (140 mg, 1.02 mmol) to give the title compound **35i** (154 mg, 0.29 mmol, 85%), in a similar manner described for **10**. MS (ESI) *m/z* 538 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.57–1.58 (6H, m), 2.61–2.78 (2H, m), 3.43 (3H, s), 3.85 (3H, s), 4.36–4.38 (1H, m), 4.81–4.93 (2H, m), 5.74 (1H, s), 6.29–6.32 (1H, m), 6.34–6.36 (1H, m), 6.71 (1H, d, *J* = 2.2 Hz), 6.94–6.96 (1H, m), 7.07–7.09 (1H, m), 7.19 (1H, t, *J* = 7.9 Hz), 7.29–7.39 (3H, m). Anal. Calcd for $C_{27}H_{28}N_5O_5Cl \cdot 2.5H_2O \cdot 0.3$ 1,4-dioxane: C, 55.57; H, 5.85; N, 11.49. Found: C, 55.66; H, 5.31; N, 10.99.

4.1.1.114. Ethyl 1-(2-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-2*H*-1,2,3,4-tetrazol-5-yl)cyclopropanecarboxylate (34j) and ethyl 1-(2-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3,4-tetrazol-5-yl)cyclopropanecarboxylate. In a similar manner described

for **34f**, compound **26** (179 mg, 0.37 mmol) was treated with ethyl 1-(2*H*-1,2,3,4-tetrazol-5-yl)cyclopropanecarboxylate (136 mg, 0.75 mmol) to give the title compounds, 2H-isomer **34j** (81 mg, 0.14 mmol, 38%) and 1H-isomer (65 mg, 0.12 mmol, 31%). 2H-Isomer **34j** (low polarity fraction): MS (ESI) *m/z* 564 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.15 (3H, t, J = 7.1 Hz), 1.39–1.43 (2H, m), 1.70–1.73 (2H, m), 2.68–2.83 (2H, m), 3.44 (3H, s), 3.86 (3H, s), 4.12 (2H, q, J = 7.1 Hz), 4.37–4.40 (1H, m), 4.89–4.93 (2H, m), 5.75 (1H, s), 6.32–6.33 (1H, m), 6.37–6.39 (1H, m), 6.72 (1H, d, J = 2.2 Hz), 6.97 (1H, dd, J = 8.1, 1.5 Hz), 7.10–7.11 (1H, m), 7.21 (1H, t, J = 8.1 Hz), 7.31–7.38 (3H, m). 1H-Isomer (high polarity fraction): MS (ESI) *m/z* 564 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.15 (3H, t, J = 7.1 Hz), 1.40–1.45 (1H, m), 1.51–1.56 (1H, m), 1.79–1.84 (2H, m), 2.72–2.79 (2H, m), 3.43 (3H, s), 3.86 (3H, s), 4.11 (2H, q, J = 7.1 Hz), 4.46–4.50 (1H, m), 4.52–4.57 (1H, m), 4.63–4.71 (1H, m), 5.75 (1H, s), 6.31–6.33 (1H, m), 6.38–6.40 (1H, m), 6.74–6.74 (1H, m), 6.96–6.98 (1H, m), 7.11–7.13 (1H, m), 7.16–7.23 (2H, m), 7.34–7.41 (2H, m).

4.1.1.115. 1-(2-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-2*H*-1,2,3,4-tetrazol-5-yl)cyclopropanecarboxylic acid (35j). Compound **34j** (80.9 mg, 0.143 mmol) and potassium carbonate (59.5 mg, 0.43 mmol) were treated, to give the title compound **35j** (70.8 mg, 0.132 mmol, 92%), in a similar manner described for **10**. MS (ESI) *m/z* 536 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.26–1.32 (1H, m), 1.36–1.41 (1H, m), 1.67–1.72 (2H, m), 2.57–2.74 (2H, m), 3.42 (3H, s), 3.85 (3H, s), 4.33–4.37 (1H, m), 4.80–4.86 (2H, m), 5.72 (1H, s), 6.26–6.29 (1H, m), 6.33–6.35 (1H, m), 6.69–6.71 (1H, m), 6.94 (1H, d, J = 8.1 Hz), 7.06–7.08 (1H, m), 7.18 (1H, t, J = 8.1 Hz), 7.28–7.35 (3H, m). Anal. Calcd for $C_{27}H_{26}N_5O_5Cl{\cdot}2H_2O{\cdot}0.075CHCl_3$: C, 56.67; H, 5.33; N, 12.10. Found: C, 56.87; H, 4.80; N, 11.61.

4.1.1.116. Methyl 2-(allyloxy)-2-methylpropanoate. Methyl 2-hydroxy-2-methylpropanoate (3.00 g, 25.4 mmol) was treated by sodium hydride (55% in oil, 1.22 g, 27.9 mmol) and allyl bromide (3.22 ml, 38.1 mmol) to give the title compound (4.02 g, 25.4 mmol, quant.), in a similar manner described for methyl 2,2-dimethyl-3-(prop-2-yn-1-yloxy)propanoate.

4.1.1.117. Methyl 2-methyl-2-(2-oxoethoxy)propanoate. Methyl 2-(allyloxy)-2-methylpropanoate (3.00 g, 19.0 mmol) was dissolved in dichloromethane (60 ml). Ozone was blown into the resulting solution for 30 min under ice-cooling. To the reaction mixture, dimethylsulfide (5 ml) was added at −78 °C. The resulting mixture was warmed slowly to room temperature overnight. The reaction mixture was concentrated in vacuo to give the title compound (3.04 g, 18.9 mmol, 99%). ^1H NMR ($CDCl_3$) δ 1.49 (6H, s), 3.74 (3H, s), 4.04–4.07 (2H, m), 9.75 (1H, s).

4.1.1.118. 2-(2-Methoxy-1,1-dimethyl-2-oxoethoxy)acetic acid. Methyl 2-methyl-2-(2-oxoethoxy)propanoate (3.04 g, 19.0 mmol) was dissolved in a mixture of *tert*-butanol (30 ml) and water (30 ml). Under ice-cooling, monosodium phosphate dihydrate (5.92 g, 37.9 mmol), sulfamic acid (5.52 g, 56.9 mmol) and sodium chlorite (5.15 g, 56.9 mmol) were added to the resulting solution, followed by stirring at room temperature for 30 min. To the reaction mixture, a 20% aqueous solution of sodium thiosulfate was added. The mixture was diluted with chloroform and washed with brine. The organic layer was dried over Na_2SO_4, and then concentrated to give the title compound (1.44 g, 8.17 mmol, 43%). ^1H NMR ($CDCl_3$) δ 1.50–1.51 (6H, m), 3.77–3.78 (3H, m), 4.10 (2H, s).

4.1.1.119. Methyl 2-{2-[(2-cyanoethyl)amino]-2-oxoethoxy}-2-methylpropanoate. 2-(2-Methoxy-1,1-dimethyl-2-oxoethoxy)acetic acid (1.44 g, 8.17 mmol) was dissolved in dichloromethane (30 ml). To the resulting solution were added 3-aminopropionitrile (0.90 ml12.3 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.88 g, 9.81 mmol), and 1-hydroxybenzotriazole (0.38 g, 2.45 mmol). The resulting mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with chloroform and washed with brine. The organic layer was dried over Na_2SO_4, and then concentrated to give the title compound (998 mg, 4.37 mmol, 54%). ^1H NMR ($CDCl_3$) δ 1.48 (6H, s), 2.67 (2H, t, J = 6.5 Hz), 3.59 (2H, q, J = 6.5 Hz), 3.76 (3H, s), 3.96 (2H, s).

4.1.1.120. Methyl 2-{[1-(2-cyanoethyl)-1*H*-1,2,3,4-tetrazol-5-yl]methoxy}-2-methylpropanoate. Methyl 2-{2-[(2-cyanoethyl)amino]-2-oxoethoxy}-2-methylpropanoate (921 mg, 4.04 mmol) was dissolved in acetonitrile (20 ml). Under a nitrogen atmosphere, sodium azide (393 mg, 6.05 mmol) and trifluoromethanesulfonic anhydride (1.02 ml, 6.05 mmol) were added to the solution at 0 °C and the resulting mixture was stirred overnight at room temperature. To the reaction mixture, satd $NaHCO_3$ aq was added. And the organic materials were extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column (ethyl acetate–*n*-hexane = 1:1) to give the title compound (221 mg, 0.87 mmol, 22%). ^1H NMR ($CDCl_3$) δ 1.55 (6H, s), 3.09 (2H, t, J = 7.2 Hz), 3.79 (3H, s), 4.93 (2H, s), 5.01 (2H, t, J = 7.2 Hz).

4.1.1.121. Methyl 2-[(2-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-2*H*-1,2,3,4-tetrazol-5-yl)methoxy]-2-methylpropanoate (35k) and Methyl 2-[(2-{2-[(4*R*,6*S*)-8-chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-1*H*-1,2,3,4-tetrazol-5-yl)methoxy]-2-methylpropanoate. Methyl 2-{[1-(2-cyanoethyl)-1*H*-1,2,3,4-tetrazol-5-yl]methoxy}-2-methylpropanoate (221 mg, 0.87 mmol) was dissolved in dichloromethane (4 ml). To the solution, 1,8-diazabicyclo[5,4,0]undec-7-ene (0.326 ml, 2.18 mmol) was added at room temperature. The resulting mixture was stirred overnight at room temperature. The solution was concentrated to give the crudely purified methyl 2-methyl-2-(1*H*-1,2,3,4-tetrazol-5-ylmethoxy)propanoate. This crude compound and compound **26** (179 mg, 0.37 mmol) were dissolved in *N*,*N*-dimethylformamide (4 ml). To the resulting solution, potassium carbonate (155 mg, 1.12 mmol) and tetrabutylammonium iodide (138 mg, 0.37 mmol) were added. The resulting mixture was stirred at 80 °C for 4 h. The reaction mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by preparative thin layer chromatography on silica gel (ethyl acetate–*n*-hexane = 1:2) to give 2H-isomer **34k** (100 mg, 0.17 mmol, 45%) and 1H-isomer (68.9 mg, 0.12 mmol, 31%). 2H-Isomer **34k** (low polarity fraction): MS (ESI) *m/z* 582 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.51 (6H, d, J = 2.2 Hz), 2.73–2.81 (2H, m), 3.44 (3H, s), 3.75 (3H, s), 3.86 (3H, s), 4.40–4.44 (1H, m), 4.75 (2H, s), 4.91–4.95 (2H, m), 5.75 (1H, s), 6.32–6.35 (1H, m), 6.38–6.40 (1H, m), 6.72 (1H, d, J = 2.0 Hz), 6.95–6.98 (1H, m), 7.09–7.12 (1H, m), 7.21 (1H, t, J = 8.1 Hz), 7.32–7.38 (3H, m). 1H-Isomer (high polarity fraction): MS (ESI) *m/z* 582 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.45 (6H, d, J = 1.5 Hz), 2.65–2.76 (2H, m), 3.43 (3H, s), 3.65 (3H, s), 3.76 (2H, s), 3.86 (3H, s), 4.48–4.52 (1H, m), 4.87–4.88 (2H, m), 5.75 (1H, s), 6.31–6.33 (1H, m), 6.37–6.38 (1H, m), 6.74 (1H, d, J = 2.2 Hz), 6.96 (1H, dd, J = 8.1, 1.5 Hz), 7.10–7.11 (1H, m), 7.18 (1H, t, J = 8.1 Hz), 7.32–7.39 (3H, m).

4.1.1.122. 2-[(2-{2-[(4*R*,6*S*)-8-Chloro-6-(2,3-dimethoxyphenyl)-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl]ethyl}-2*H*-1,2,3,4-tetrazol-5-yl)methoxy]-2-methylpropanoic acid (35k). Com-

pound **34k** (100 mg, 0.17 mmol) and potassium carbonate (71.3 mg, 0.52 mmol) were treated, to give the title compound **35k** (64 mg, 0.11 mmol, 65%), in a similar manner described for **10**. MS (ESI) *m/z* 568 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 1.46–1.48 (6H, m), 2.62–2.78 (2H, m), 3.43 (3H, s), 3.85 (3H, s), 4.38–4.42 (1H, m), 4.72 (2H, s), 4.85–4.89 (2H, m), 5.73 (1H, s), 6.29–6.31 (1H, m), 6.35–6.37 (1H, m), 6.71 (1H, d, J = 2.0 Hz), 6.94–6.97 (1H, m), 7.08–7.09 (1H, m), 7.19 (1H, t, J = 7.9 Hz), 7.29–7.37 (3H, m). Anal. Calcd for $C_{28}H_{30}N_5O_6Cl{\cdot}1.9H_2O{\cdot}0.5EtOH{\cdot}0.1CHCl_3$: C, 54.84; H, 5.85; N, 10.99. Found: C, 55.23; H, 5.21; N, 10.52.

4.2. Biological evaluation procedure of inhibitory effects on cholesterol synthesis in rat hepatic cell

4.2.1. Preparation of rat primary hepatocytes

Shechter's method[10] was slightly modified. This study consisted of three experiments, and the effects of inhibitors at each concentration were evaluated in triplicate. One animal was used to prepare the hepatocytes for each experiment.

Under anesthesia by thiopental sodium (0.1 g/kg, ip), a plastic catheter was introduced through the portal vein. The liver was perfused with Ca^{2+}, Mg^{2+} free Hanks' balanced salts solution (pH 7.2) containing 2% albumin, 0.5 mM EGTA, 10 mM HEPES, and 41.7 mM $NaHCO_3$ at 37 °C for 10 min at 19–21 ml/min; and then with Ca^{2+}, Mg^{2+} free Hanks' balanced salts solution (pH 7.5) containing 0.05% collagenase, 4 mM $CaCl_2$, 10 mM HEPES, and 41.7 mM $NaHCO_3$ for another 15 min. Liver cells were dispersed in DMEM supplemented with 100 U/ml penicillin and 100 μg/ml streptomycin by dissection and gentle pipetting. After filtration through a 70 μm nylon mesh filter (Cell Strainer, BD Falcon), hepatocytes were obtained by repeated centrifugation (3 times) at 600 rpm (centrifuge; 5930, swinging bucket rotor: RS-3011M) for 1 min at 4 °C. After the last centrifugation, the medium was changed to DMEM supplemented with 10% LPDS, 100 U/ml penicillin, and 100 μg/ml streptomycin. Then, viability was determined by staining with trypan blue. Hepatocytes with over 80% viability were cultured in 6-well cell culture plates (10^6 cells/well).

4.2.2. Measurement of cholesterol biosynthetic activity of rat hepatocytes

One day later, the medium was replaced with media supplemented with 5% LPDS, 25 mM HEPES, and inhibitors (final concentrations: 0, 1, 3, 10, 30, 100, 300, 1000, and 3000 nM). After incubation for 1 h at 37 °C, 10 μl of [^{14}C]mevalonolactone (5 μCi/ml) was added into the media, and the incubation was continued for another 1 h. The cells were washed with D-PBS (3 times) and dissolved in 1 ml of 0.1 M NaOH. Ten micro liters of the cell lysates were transferred to a 96-well plate to determine the protein concentration in duplicate. Eight hundred microliters of the remains were saponified for 1 h at 75 °C by adding 2 ml of ethanol and 0.5 ml of 50 (w/v)% KOH. After the addition of 50 or 100 μl of [^{3}H]cholesterol (0.45 μCi/ml) as an internal standard, the nonsaponifiable lipids were extracted with 4.5 ml of petroleum ether. Water layer was frozen in dry ice and ethanol, and the upper layer was transferred to another tube. The extracts in the tubes were dried under N_2 gas at 40 °C. The residue was dissolved in 50 μl of dichloromethane–methanol (2:1) solution including 10 mg/ml cholesterol, applied onto TLC plastic sheets (Silica gel 60), and developed with a solvent (toluene–ethyl acetate, 3:1). The radio activities incorporated into the cholesterol fractions in Aquasol-2 were counted with a liquid scintillation counter.

The protein concentration was determined using a BCA Protein Assay Kit.

The radioactivities incorporated into the cholesterol fractions were corrected from the formula as follows:

Radioactivities incorporated (dpm/μg protein) = Radioactivities of [^{14}C]cholesterol (dpm) × 50,000 (dpm)/radioactivities of [^{3}H]cholesterol (dpm)/protein content (μg).

Referring to the mean radioactivity of the cells in the three wells treated with 0 nM of inhibitors, inhibition (%) of cholesterol synthesis at each concentration was calculated by the following equation:

Inhibition (%) = (1 − arithmetic mean radioactivity incorporated of three wells at each concentration/arithmetic mean radioactivity incorporated of three wells at 0 nM) × 100

4.3. Rat single-dose in vivo hepatic cholesterol synthesis inhibitory activity

A rat single-dose liver-cholesterol synthesis inhibitory effect was measured as described below.

To each the compounds of the present invention was added a necessary amount of a 0.5% methyl cellulose solution immediately before use. Then, an equivalent molar amount of sodium hydroxide or sodium hydrogen carbonate was added to dissolve or suspend it in the resulting solution. To 6-week-old Wistar male rats were orally administered each of the compounds of the present invention (3 mg/kg, n = 4–6), while only a 0.5% methyl cellulose solution was administered to a control group. One hour later, physiological saline of mevalonic acid (5 μCi/5 ml/kg) labeled with a radioisotope ^{14}C was intraperitoneally administered. The rats were sacrificed 1 h later. To 1 g of the liver thus obtained from the rats was added 5 ml of a 15% KOH ethanol solution and the resulting mixture was left to stand for 15 h. After heating at 75 °C for 2 h, the reaction mixture was extracted with 5 ml of water and 10 ml of petroleum ether. The petroleum ether layer was collected, evaporated to dryness and then dissolved in 50 μl of a chloroform/acetone = 2:1 solution. The cholesterol band was separated by silica gel thin layer chromatography (Art.5748, toluene/ethyl acetate = 3:1) and cut out. It was put in a vial container, followed by the addition of 10 ml of Aquasol-2 (product of Packard BioScience Company). The radioactivity was measured using a liquid scintillation counter. A ratio of the radioactivity relative to that of a control group was determined and liver-cholesterol synthesis inhibitory activity (%) was calculated.

4.4. Plasma lipid lowering studies in common marmosets

Male and female common marmosets (305–410 g) were purchased from Clea Japan (Tokyo, Japan), and fed a commercial chow diet (CMS-1M; Clea Japan) and allowed access to water ad libitum. All animal experiments were carried out according to the Daiichi Sankyo Animal Care Guidelines.

Before the experiment, blood samples were collected under nonfasted conditions. Plasma total cholesterol and triglyceride were measured as described above. High-density lipoprotein (HDL) was separated by precipitation reagents (Wako Pure Chemical Industries). And then the cholesterol was measured enzymatically. Non-HDL-cholesterol was calculated by subtracting HDL-cholesterol from total cholesterol.

Common marmosets were divided into two groups (control vs prepared compound, 100 mg/kg, n = 8); groups were matched for body weight, plasma total cholesterol, triglyceride, HDL cholesterol and non-HDL cholesterol. Drugs were suspended in 0.5% methylcellulose solution and administered orally at 5 ml/kg once a day (9–10AM) for 7 days. Next morning after the final administration of drugs, blood samples were collected under nonfasted conditions and plasma parameters were measured.

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References and notes

1. (a) Tobert, J. A. *Nat. Rev. Drug. Disc.* **2003**, *2*, 517; (b) Havel, R. J.; Rapaport, E. *New Eng. J. Med.* **1995**, *332*, 1491; (c) Shepherd, J. et al *N. Engl. J. Med.* **1995**, *333*, 1301.
2. (a) Hodel, C. *Toxicol. Lett.* **2002**, *128*, 159; (b) Thompson, P. D.; Clarkson, P.; Karas, R. H. *JAMA* **2003**, *289*, 1681.
3. Furberg, C. D.; Pitt, B. *Curr. Control Trials Cardiovasc. Med.* **2001**, *2*, 205.
4. (a) Ishihara, T.; Kakuta, H.; Moritani, H.; Ugawa, T.; Yanagisawa, I. *Bioorg. Med. Chem.* **2004**, *12*, 5899; (b) Ishihara, T.; Kakuta, H.; Moritani, H.; Ugawa, T.; Sakamoto, S.; Tsukamoto, S.; Yanagisawa, I. *Bioorg. Med. Chem.* **2003**, *11*, 2403; (c) Miki, T.; Kori, M.; Mabuchi, H.; Tozawa, R.; Nishimoto, T.; Sugiyama, Y.; Teshima, K.; Yukimasa, H. *J. Med. Chem.* **2002**, *45*, 4571; (d) Miki, T.; Kori, M.; Mabuchi, H.; Banno, H.; Tozawa, R.; Nakamura, M.; Itokawa, S.; Sugiyama, Y.; Yukimasa, H. *Bioorg. Med. Chem.* **2002**, *10*, 401.
5. (a) Biller, S. A.; Neuenschwander, K.; Ponpipom, M. M.; Poulter, C. D. *Curr. Pharm. Des.* **1996**, *2*, 1; (b) Gonzalez-Pacanowska, D.; Arison, B.; Havel, C. M.; Watson, J. A. *J. Biol. Chem.* **1988**, *263*, 1301; (c) Bergstrom, J. D.; Kurtz, M. M.; Rew, D. J.; Amend, A. M.; Karakas, J. D.; Bostedor, R. G.; Bansal, V. S.; Dufresne, C.; VanMiddlesworth, F. L.; Hensens, O. D. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 80; (d) Bostedor, R. G.; Karkas, J. D.; Arison, B. H.; Bansal, V. S.; Vaidya, S.; Germershausen, J. I.; Kurtz, M. M.; Bergstrom, J. D. *J. Biol. Chem.* **1997**, *272*, 9197.
6. (a) Hiyoshi, H.; Yanagimachi, M.; Ito, M.; Saeki, T.; Yoshida, I.; Okada, T.; Ikuta, H.; Shinmyo, D.; Tanaka, K.; Kurusu, N.; Tanaka, H. *Eur. J. Pharmacol.* **2001**, *431*, 345; (b) Brown, G. R.; Butlin, R. J.; Chapman, S.; Eakin, M. A.; Foubister, A. J.; Freeman, S.; Griffiths, D.; Harrison, P. J.; Johnson, M. C.; Mallion, K. B.; McTaggart, F.; Reid, A. C.; Smith, G. J.; Taylor, M. J.; Walker, R. P.; Whittamore, P. R. *J. Med. Chem.* **1995**, *38*, 4157; (c) Brown, G. R.; Clarke, D. S.; Foubister, A. J.; Freeman, S.; Harrison, P. J.; Johnson, M. C.; Mallion, K. B.; McCormick, J.; McTaggart, F.; Reid, A. C.; Smith, G. J.; Taylor, M. J. *J. Med. Chem.* **1996**, *39*, 2971; (d) Usui, H.; Kagechika, K.; Nagashima, H. WO1998/029380.; (e) Usui, H.; Katakura, S.; Suzuki, M. Jpn. Kokai Tokkyo Koho. **2001**, 131p (JP 2001/354587).
7. Ichikawa, M.; Yokomizo, A.; Itoh, M.; Sugita, K.; Usui, H.; Shimizu, H.; Suzuki, M.; Terayama, K.; Kanda, A. *Bioorg. Med. Chem.* **2011**, *19*, 1930.
8. Ichikawa, M.; Yokomizo, A.; Itoh, M.; Haginoya, N.; Sugita, K.; Usui, H.; Terayama, K.; Kanda, A. *Bioorg. Med. Chem.* **2011**, *19*, 5207.
9. Yukimasa, H.; Sugiyama, Y.; Tozawa, R. WO1997/010224.
10. Shechter, I.; Klinger, E.; Rucker, M. L.; Engstrom, R. G.; Spirito, J. A.; Islam, M. A.; Boettcher, B. R.; Weinstein, D. B. *J. Biol. Chem.* **1992**, *267*, 8628.
11. (a) Brown, M. S.; Goldstein, J. L. *Cell* **1997**, *89*, 331; (b) Brown, M. S.; Goldstein, J. L. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 11041.
12. The atomic coordinates have been deposited with Protein Data Bank (PDB code: 3V66).
13. (a) Griebenow, N.; Flessner, T.; Buchmueller, A.; Raabe, M.; Bischoff, H.; Kolkhof, P. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2554; (b) Griebenow, N.; Buchmueller, A.; Kolkhof, P.; Schamberger, J.; Bischoff, H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3648.
14. Pandit, J.; Danley, D. E.; Schulte, G. K. *J. Biol. Chem.* **2000**, *275*, 30610.
15. Ref. 4c.
16. Figure 5 in Ref. 8.
17. Hulcoop, D. G.; Lautens, M. *Org. Lett.* **2007**, *9*, 1761.
18. Leroux, F.; Castagnetti, E.; Schlosser, M. *J. Org. Chem.* **2003**, *68*, 4693.
19. Alig, L.; Hadvary, P.; Hürzeler, M.; Müller, M.; Steiner, B.; Weller, T. US5378712 A1.
20. Linz, G.; Himmelsbach, F.; Pieper, H.; Austel, V.; Guth, B.; Weisenberger, J. US5817677 A1, 1998.
21. Isobe, Y.; Kurimoto, A; Hashimoto, K.; Nakamura, T.; Nakamura, Kei. WO 2007/034917.
22. Marlowe, C. K.; Scarborough, R. M.; Zhu, B. WO1998/046591.
23. Nakayama, K.; Ohtsuka, M.: Kawato, H.; Okumura, R.; Hoshino, K.; Watokins, W.; Zhang, J.; Palme, M.; Cho, A.; WO2002/087589.