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Syntheses of Fused Heterocyclic Compounds and Their Inhibitory Activities for Squalene Synthase

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Abstract—A variety of fused heterocyclic compounds (**2**–**11**) were synthesized as a modification of the lead compound **1a** and evaluated for their inhibition of squalene synthase. 4,1-Benzothiazepine derivative **2**, 1,4-benzodiazepine derivative **6**, 1,3-benzodiazepine derivative **7**, 1-benzazepine derivative **9**, and 4,1-benzoxazocine derivative **10** potently inhibited squalene synthase activity, whereas the 4,1-benzoxazepine derivatives **1** was the most potent inhibitor. 4,1-Benzothiazepine *S*-oxide derivative **4**, 1,4-benzodiazepine derivative **5**, 1,3,4-benzotriazepine derivative **8**, and 1,2,3,4-tetrahydroquinoline derivative **11** were found to be weakly active. Comparison of the X-ray structures of these compounds (**1a**, **2**, **4**, **5**, **7** and **10**) suggests that orientation of the 5- (or 6)-phenyl group is important for activity.

Introduction

Adequate control of serum cholesterol level is very important for prophylaxis and therapy of diseases related to atherosclerosis[1] such as ischemic cardiopathy and cerebral infarction, which are the major causes of death in industrialized countries. Hypercholesterolaemia is related to the development and progression of coronary heart disease, and great efforts have been made at discovering agents to lower plasma cholesterol in order to prevent and treat hypercholesterolemia.[2]

As pharmaceutical preparations for controlling cholesterol biosynthesis, 3-hydroxy-3-methyl glutaryl-coenzyme A (HMG-CoA) reductase inhibitors such as pravastatin,[3a] lovastatin,[3b] simvastatin,[3c] fluvastatin,[3d] and atorvastatin,[3e] are available for clinical use.[4] HMG-CoA reductase inhibitors block an early step in the cholesterol biosynthetic pathway. These agents are therefore thought to inhibit the biosynthesis of not only cholesterol but also biologically important isoprenoids such as dolicol, ubiquinone and isoprenyl tRNA. Thus, the occurrence of undesirable side effects arising from the inhibition of isoprenoid synthesis is feared.

Since farnesyl pyrophosphate is the final common precursor in the biosynthesis pathway of cholesterol and other non-steroidal isoprenoids, drugs which inhibit the step beyond that involving farnesyl pyrophosphate are desirable as cholesterol biosynthesis inhibitors. Inhibitors of squalene synthase, squalene epoxidase, and oxidosqualene cyclase have therefore been targeted by many laboratories.[2]

Squalene synthase [EC2.5.1.21], which catalyzes the formation of squalene from farnesyl pyrophosphate, participates in the first committed step in sterol synthesis. Farnesyl pyrophosphate, the substrate for squalene synthase, is water-soluble and may be readily metabolized for excretion in urine.[5] It has been reported that inhibition of squalene synthase plays a role in feedback regulation of HMG-CoA reductase.[6] We therefore suspected that squalene synthase inhibitors might be safe and effective in the treatment of hyperlipidemia.

Several classes of squalene synthase inhibitors have recently been reported,[7,8] such as cationic intermediate analogues (containing ammonium ions or sulfonium ions), substrate analogues (phosphorus-containing compounds, bisphosphonates, and α-phosphonosulfonic acids), quinuclidine derivatives, 2,8-dioxabicyclo[3.2.1]octane derivatives[8,9] (Squalestatins, Zaragozic acids, TAN-1607A[10]), and others.[11]

From random screening for squalene synthase inhibitors, we found that a novel class of inhibitor, benzene fused lactam derivative, (3,5-*trans*)-5-phenyl-2-oxo-4,1-benzoxazepine-3-acetic acid derivative **1a** (Fig. 1),

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exhibited potent inhibition of rat enzyme ($IC_{50} = 0.072\,\mu M$) and HepG2 enzyme ($IC_{50} = 0.024\,\mu M$).

Benzene fused seven-membered heterocycles such as 1,4-benzodiazepines,[12a–h] 1,5-benzothiazepines,[12i] 1,4-benzothiazepines,[12j] 1-benzazepines,[12k,l] and so on,[12m–q] are important components of a number of pharmacologically active compounds. A variety of benzene fused seven-membered heterocycles have been reported, and the conformations of these skeletons are likely to be significantly different from one another. Since the main determinant of side-chain orientation is the conformation of the seven-membered ring, we thought that this conformation would also determine the selectivity towards the biological target, and we therefore assumed that the spatial positions of 5-phenyl, 3-acetic acid and 1-alkyl groups side chains of **1a** were important for potent inhibitory activity. Thus, as a chemical modification of compound **1a**, we first synthesized heterocyclic seven-membered lactam derivatives to find an optimal template for inhibition of squalene synthase.[13] In order to assess the effect of ring size on the biological activity, six- and eight-membered lactam compounds were also synthesized.

Chemistry

The medium-sized ring systems having acetic acid side chain prepared in this study are shown in Figure 1. As seven-membered heterocyclic compounds, the 4,1-benzothiazepine-3-acetic acid derivatives **2**, 1,4-benzodiazepine-3-acetic acid derivatives **5** and **6**, 1,3-benzodiazepine-3-acetic acid derivative **7**, 1,3,4-benzotriazepine-3-acetic acid derivative **8** and 1-benzazepine-3-acetic acid derivative **9** were synthesized. The 4,1-benzoxazocine-3-acetic acid derivative **10** having an eight-membered ring and quinoline-3-acetic acid derivative **11** with a six-membered ring were also prepared (vide infra).

Preparation of 4,1-benzoxazepine-3-acetic acid derivatives

The syntheses of the 4,1-benzoxazepine-3-acetic acid derivatives **1a**,**b** are shown in Scheme 1.[14] Reduction of 2-aminobenzophenone **12** with sodium borohydride ($NaBH_4$) yielded aminoalcohol **13**,[14] which were treated with aldehydes and sodium cyano borohydride ($NaBH_3CN$) to afford the alkylated compounds **14a**,**b**. After condensation of **14a**,**b** and fumaric acid chloride monoethyl ester, intramolecular Michael addition of the obtained amides **15a**,**b** afforded the 4,1-benzoxazepine-3-acetates **16a**,**b**. In this reaction, thermodynamically stable 3,5-*trans*-isomers were obtained. Hydrolysis of the esters **16a**,**b** gave the carboxylic acids **1a**,**b**.

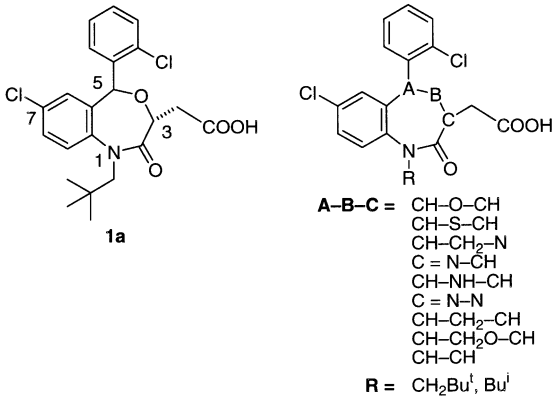
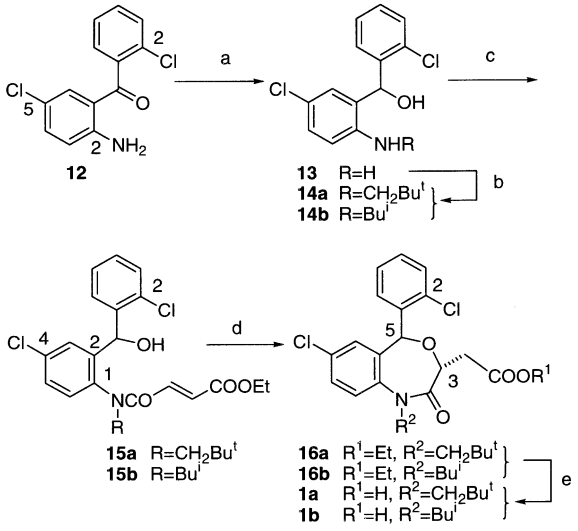


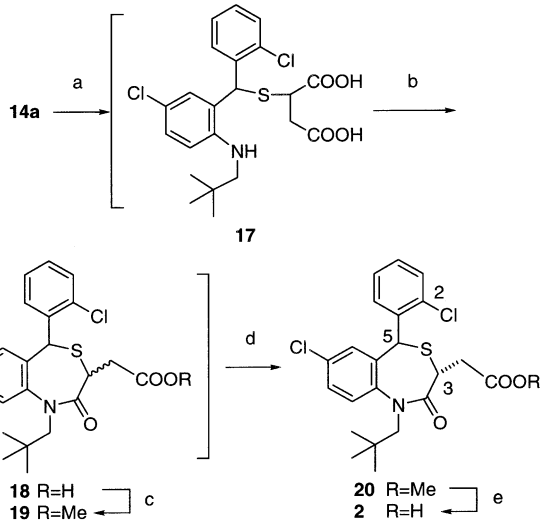
Figure 1. Structures of benzene fused heterocyclic compounds.

Preparation of 4,1-benzothiazepine-3-acetic acid derivatives

The synthesis of the 4,1-benzothiazepine-3-acetic acid derivative **2** is outlined in Scheme 2. The dicarboxylic acid derivative **17** was obtained by treatment of **14a** and thiomalic acid in a mixture of concentrated hydrochloric acid and acetic acid. Intramolecular cyclization of **17** by refluxing in xylene afforded the 4,1-benzothiazepine-3-acetic acid derivative **18** as a ca. 1:1 mixture of *cis* and *trans* isomers.[15] Esterification of **18** led to the methyl ester **19**, which was epimerized with potassium carbon-



Scheme 1. Reagents and conditions: (a) $NaBH_4$; (b) isobutylaldehyde or pivalaldehyde, $NaBH_3CN$, AcOH; (c) fumaric acid chloride monoethyl ester, $NaHCO_3$; (d) K_2CO_3, EtOH, (e) NaOH.



Scheme 2. Reagents and conditions: (a) thiomalic acid, concd HCl–AcOH; (b) xylene, reflux; (c) MeOH, cat H_2SO_4; (d) K_2CO_3, MeOH; (e) NaOH.

ate in methanol to give the thermodynamically stable *trans*-isomer **20**. The ester **20** was hydrolyzed to give the desired 4,1-benzothiazepine-3-acetic acid derivative **2**.

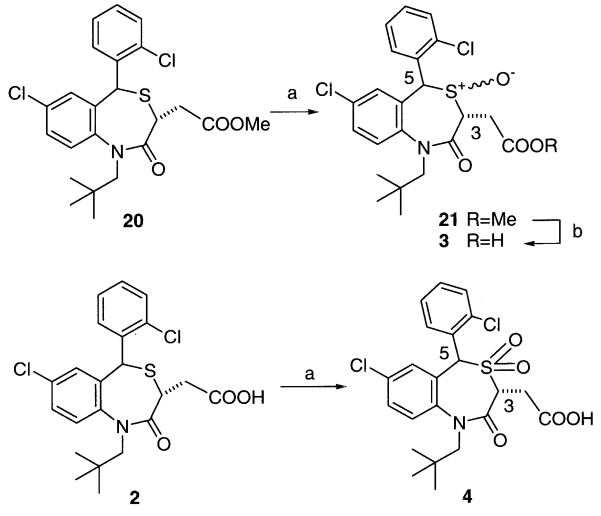
Oxidation of the methyl ester **20** with 1.0 equivalent of *m*-chloroperbenzoic acid (MCPBA), followed by alkaline hydrolysis of the obtained sulfoxide **21**, afforded the 4,1-benzothiazepine-3-acetic acid *S*-oxide **3**. This oxidation proceeded asymmetrically to yield only one isomer, the stereochemistry of which has not yet been determined. The *S*-dioxide **4**[16] was prepared by oxidation of the carboxylic acid derivative **2** with 2.2 equivalents of MCPBA (Scheme 3).

Preparation of 1,4-benzodiazepine-3-acetic acid derivatives

Condensation of β-methyl *N*-benzyloxycarbonyl-DL-aspartate[17] with the aminobenzophenone derivative **12** by the mixed anhydride method gave the amide **23**, but condensation of that DL-aspartic acid derivative with the *N*-neopentylated aminobenzophenone **22** did not proceed. Removal of the benzyloxycarbonyl group by hydrogenolysis, followed by treatment with acetic acid, afforded the 1,4-benzodiazepine-3-acetic acid derivative **24**. Treatment of compound **24** and isobutyl bromide with sodium hydride (NaH) gave the 1-isobutyl analogue **25**. On the other hand, alkylation of **24** with neopentyl bromide yielded a trace of an alkylated compound. Compound **25** was hydrolyzed to give the desired 1,4-benzodiazepine-3-acetic acid derivative **5**. The 2,3,4,5-tetrahydro-1*H*-4,1-benzodiazepine-3-acetic acid derivative **6** was prepared by reduction of the C=N double bond by $NaBH_4$ (Scheme 4).

Preparation of 1,3-benzodiazepine-3-acetic acid derivatives

Scheme 5 shows the preparation of the 1,3-benzodiazepine-3-acetic acid derivative **7**. Treatment of methyl 2-chlorophenylacetate **26** and 4-chloro-1,2-dinitrobenzene with NaH gave the phenylacetic acid derivative **27**. Reduction of **27** with lithium borotetrahydride ($LiBH_4$) led to the 2-phenylethanol derivative **28**. Swern's oxidation of **28**, and subsequent reductive amination of the resulting aldehyde **29** with ethyl glycinate afforded the aminoacetic acid derivative **30**. Acylation of **30** with trifluoroacetic anhydride led to the amide **31**. The amine **32** was synthesized by reduction of a nitro group of compound **31**. Treatment of **32** with pivaladehyde, followed by $NaBH_3CN$ gave the *N*-alkylated compound **33**. Deprotection of **33** afforded the diamine **34.** The synthesis of the 1,3-benzodiazepine-3-acetic acid derivative **7** was accomplished via compound **35** by treatment of **34** with triphosgene and subsequent alkaline hydrolysis.



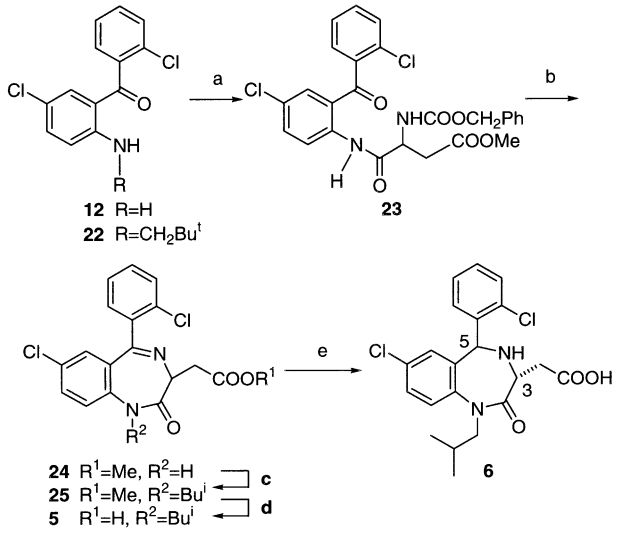
Scheme 3. Reagents and conditions: (a) mCPBA; (b) K_2CO_3, MeOH–H_2O.

Preparation of 1,3,4-benzotriazepine-3-acetic acid derivatives

The preparation of the 1,3,4-benzotriazepine-3-acetic acid derivative **8** is shown in Scheme 6. Treatment of the aminobenzophenone derivative **22** and Lawesson's reagent gave the thione **36**. Reaction of compound **36** with ethyl hydrazineacetate afforded a mixture of two geometrical isomers **37a**,**b**, which was separated by silica gel column chromatography to give the less polar isomer **37a** and the polar isomer **37b**. Compound **37a** was convertible to the cyclized compound **38** by treatment with triphosgene. Compound **38** was then hydrolyzed to give the desired 1,3,4-benzotriazepine-3-acetic acid derivative **8**. On the other hand, treatment of the polar isomer **37b** with triphosgene gave a complex mixture. It appears that **37a** is an (*E*)-isomer which is advantageous for cyclization and **37b** is a (*Z*)-isomer which undergoes only minimal cyclization.

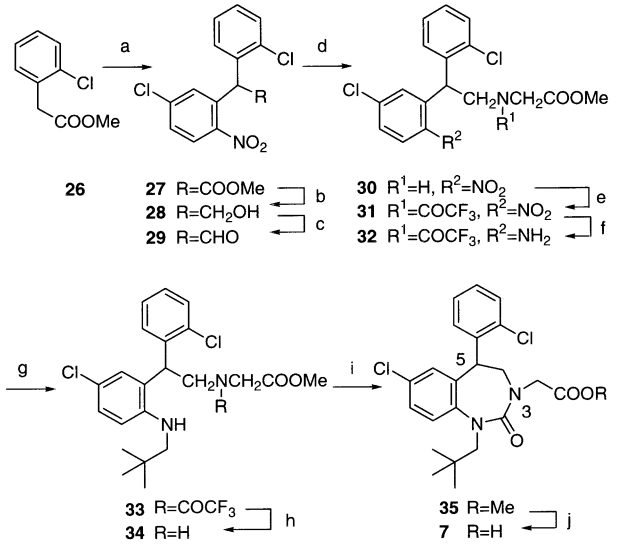
Preparation of 1-benzazepine-3-acetic acid derivatives

The synthesis of the 1-benzazepine-3-acetic acid derivative **9** is outlined in Scheme 7. Condensation of 2-chlorobenzophenone **39** and diethyl succinate afforded alkylidenesuccinic acid derivative **40** by Stobbe condensation.[18] Compound **40** was converted successively to the 4-phenylbutyric acid derivative **41** by dec-

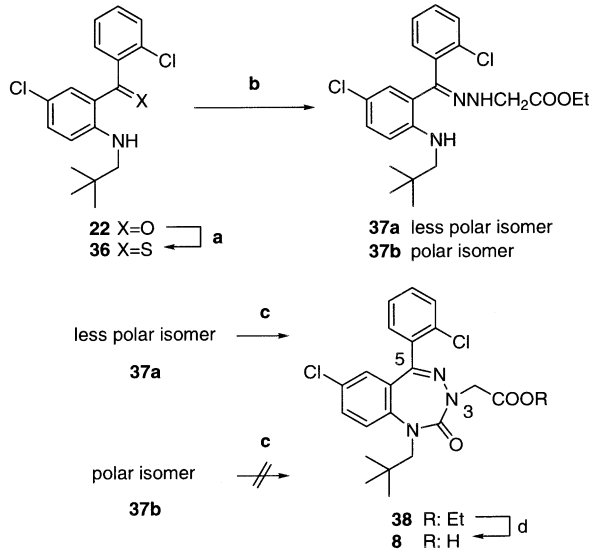


Scheme 4. Reagents and conditions: (a) β-methyl *N*-benzyloxycarbonyl-DL-aspartate, Bu^iOCOCl, *N*-methylmorpholine; (b) (1) H_2, Pd–C; (2) AcOH, DMF; (c) Bu-Br, NaH, DMF; (d) K_2CO_3, MeOH, H_2O; (e) $NaBH_4$.

arboxylation, hydrogenation of double bond and treatment with p-toluenesulfonic acid in ethanol. The α-tetralone derivative **42** was prepared by alkaline hydolysis of **41** and subsequent intramolecular Friedel–Crafts acylation. Beckmann rearrangement of the oxime compound derived from **42** afforded the 1-benzazepine derivative **43**.[19] After alkylation at the 1-position, the obtained 1-isobutyl derivative **44** was halogenated to 7-chloro derivative **45** by treatment with *N*-chlorosuccinimide. Alkylation of **43** with neopentyl bromide yielded a trace of an alkylated compoumd. Treatment of compound **45** with lithium diisopropylamide (LDA) and ethyl iodoacetate afforded the ethyl ester **46**. Hydrolysis of **46** gave the desired 3-acetic acid derivative **9** as a ca. 2:1 mixture of *cis* and *trans* isomers.



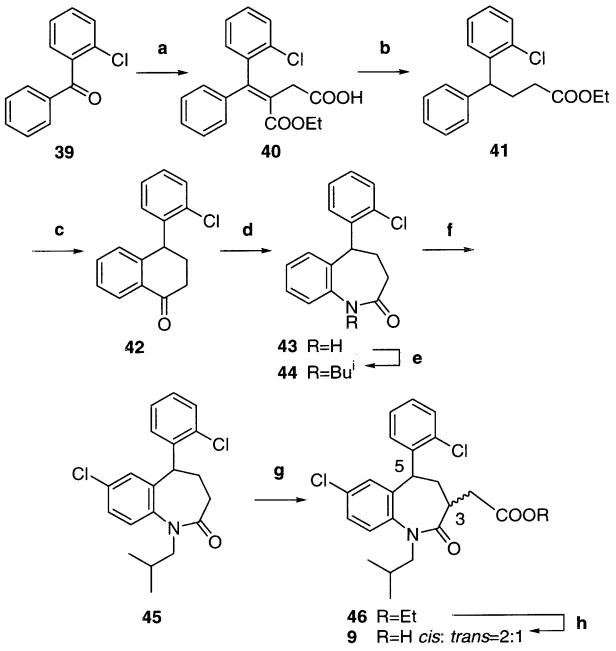
Scheme 5. Reagents and conditions: (a) 4-chloro-1,2-dinitrobenzene, NaH, DMF; (b) $LiBH_4$; (c) $(COCl)_2$, DMSO, NEt_3; (d) glycine methyl ester hydrochloride, AcONa, $NaBH_3CN$; (e) $(CF_3CO)_2O$; (f) H_2, Pd–C; (g) pivalaldehyde, AcOH, $NaBH_3CN$; (h) concd HCl; (i) triphosgene, NEt_3; (j) NaOH.



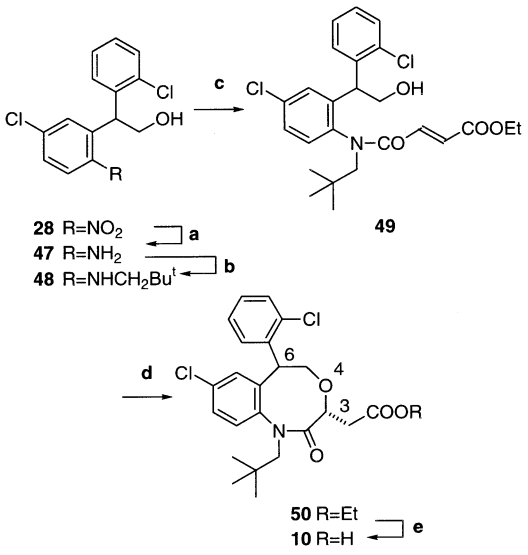
Scheme 6. Reagents and conditions: (a) Lawesson's reagent; (b) ethyl hydrazinoacetate hydrochloride, K_2CO_3; (c) triphosgene, NEt_3; (d) NaOH.

Preparation of 4,1-benzoxazocine-3-acetic acid derivatives

The preparation of the 4,1-benzoxazocine-3-acetic acid derivative **10** is shown in Scheme 8. The 2-phenylethanol derivative **28** was led to the amino analogue **47** by reduction of a nitro group. Reductive alkylation of compound **47**, followed by treatment of the resulting compound **48** with fumaryl chloride monoethyl ester afforded the amide **49**. Unlike 4,1-benzoxazepine derivatives, compound **49** was hardly cyclized to a 4,1-benzoxazocine derivative by treatment with potassium carbonate in ethanol. When the amide **49** was treated with potassium carbonate in the presence of 18-crown-6



Scheme 7. Reagents and conditions: (a) diethyl succinate, ButOK; (b) (1) HBr–AcOH; (2) H_2, Pd–C; (3) EtOH, *p*-TsOH; (c) (1) 1 N NaOH; (2) $SOCl_2$ then $AlCl_3$; (d) (1) NH_2OH; (2) PPA, 120 °C; (e) Bu-^{i}Br, NaH; (f) NCS; (g) (1) LDA; (2) ICH_2COOEt; (h) NaOH.



Scheme 8. Reagents and conditions: (a) Raney–Ni, NH_2NH_2; (b) pivalaldehyde, $NaBH_3CN$, AcOH; (c) fumalyl chloride monoethyl ester, $NaHCO_3$; (d) K_2CO_3, CH_2Cl_2, 18-Crown-6; (e) concd HCl.

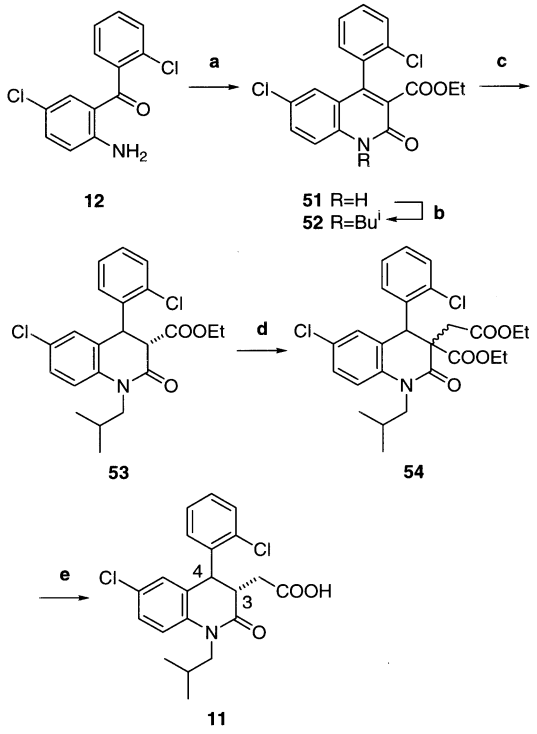
in dichloromethane, the 4,1-benzoxazocine-3-acetic acid derivative **50** was obtained in 24% yield.[14] In this reaction, only one isomer could be isolated. Acid hydrolysis of compound **50** gave the desired acid **10**. Alkaline hydrolysis was unable to yield **10** because of ring-opening reaction. The relative configrations of **10** and **50** were determined to be 3,6-*trans* by X-ray diffraction analysis of the compound **10**.

Preparation of 1,2,3,4-tetrahydroquinoline-3-acetic acid derivatives

The synthesis of the 1,2,3,4-tetrahydroquinoline-3-acetic acid derivative **11** was carried out as follows (Scheme 9). Heating of the aminobenzophenone derivative **12** and diethyl malonate with 1,8-diazabicyclo-[5. 4. 0]-7-undecene (DBU) afforded the quinoline derivative **51**.[20] Compound **51** was led to the isobutyl analogue **52** by alkylation at the 1-position. Treatment of **51** with neopentyl bromide yielded a trace of a neopentyl analogue. The C=C double bond in **52** was reduced selectively by lithium alminium hydride to give the *trans* ester **53**. The diester **54** was prepared by treatment of **53** with NaH, followed by reaction with ethyl bromoacetate. Compound **54** was converted to the 1,2,3,4-tetrahydroquinoline-3-acetic acid derivative **11** by decarboxylation, esterification, purification by column chromatography and then alkaline hydrolysis.

Results and Discussion

The compounds synthesized were evaluated for inhibition of activity of squalene synthase prepared from rat liver and human hepatoma (HepG2) cells. Inhibitory activity was measured according to the method of Cohen et al. with a slight modification.[21]



Scheme 9. Reagents and conditions: (a) diethyl malonate, DBU; (b) BuiBr, NaH, KI; (c) $LiAlH_4$; (d) $BrCH_2COOEt$, NaH; (e) (1) KOH, EtOH–H_2O; (2) MeI; (3) K_2CO_3, MeOH–H_2O.

Table 1 shows inhibitory activities of the fused heterocyclic compounds (**1**–**11**). The 4,1-benzoxazepine derivative **1a** and its 1-isobutyl analogue **1b** showed the same level of potency. The 4,1-benzothiazepine derivative **2** was ca. 2.5-fold less potent for rat enzyme than that of **1a** and had the same potency for human enzyme as **1a**. Oxidation of the sulfur atom of **2** led to the *S*-oxide **3**, which exhibited ca. 10-fold less potent for both enzymes than **1a**. The *S*-dioxide **4** was found to exhibit only a moderate inhibitor of rat enzyme, with an IC_{50} value of 3.3 μM. The 1-benzazepine derivative **9** [*cis*–*trans* (2:1) mixture] exhibited 5-fold weaker activity for both enzymes than **1a**. Because the *cis* isomer appeared to be inactive,[22] we assumed that the pure form of *trans* isomer would have 3-fold more potent activity than the *cis*–*trans* (2:1) mixture. The 1,3-benzodiazepine derivative **7** exhibited 5-fold weaker activity for rat and human enzymes than **1a**. The 1,4-benzodiazepine derivative **5** and 1,3,4-benzotriazepine derivative **8** had poor activities for rat enzyme, with IC_{50} values of 3.9 and 8.7 μM, respectively. Reduction of a C=N double bond of **5** led to **6**, the activity of which was found to be the same as that of **7** and the 4,1-benzoxazocine derivative **10**. The 1,2,3,4-tetrahydroquinoline derivative **11** was found to be only weakly active. The above results indicate that the 4,1-benzoxazepine derivatives exhibited the most potent inhibition of both rat and human enzymes.

It is expected that these fused heterocycles will play an important roles in determination of relative spatial positions of the substituents which are predicted to attach to the enzyme binding site. In order to compare conformations, the X-ray structures of some compounds were overlaid (Figs 2–4). We found that the 6–7 ring systems analyzed here have similar overall conformations. We assume that these conformations are especially stable and very similar to the active conformation. Actually, these conformations are similar to the conformation of 5-naphtyl-4,1-benzoxazepine derivative[11a–d] in the crystal of protein–inhibitor complex.[11d]

The 4,1-benzoxazepine derivative **1a**, 4,1-benzothiazepine derivative **2**, 1,3-benzodiazepine derivative **7** and 4,1-benzoxazocine derivative **10** had potent inhibitory activities [IC_{50} = 0.072–0.42 μM (rat), 0.024–0.13 μM (human)]. We found that the 1-neopentyl groups and the 5-phenyl rings in the compounds with a seven-membered ring (**1a**, **2** and **7**) are superimposed well (Fig. 2). The conformation of the eight-membered ring of **10** is different from that of the seven-membered ring. Interestingly, however, the substituents of **10** superimposed well on those of **1a**, **2** and **7**. Although the positions of the carboxymethyl part differ in the X-ray structures, it can be seen that this flexible part occupies a specific region when the compounds bind to the enzyme.

The 1,4-benzodiazepine derivative **5** exhibited only moderate activity [IC_{50} = 3.9 μM (rat), 2.3 μM (human)]. Superimposition of the X-ray structures of **1a**

and **5** may explain this decrease in activity. As shown in Figure 3, the orientations of the 5-phenyl rings of these compounds were different, because the bond angle of a sp^3 carbon is different from that of a sp^2 carbon. Actually, reduction of the double bond of **5** resulted in 10-fold increase in activity (Table 1, compound **6**). It is likely that the orientation of the 5-phenyl ring of the 1,3,4-benzotriazepine derivative **8** [$IC_{50} = 8.7$ μM (rat enzyme)], which has a sp^2 carbon at the 5-position, is similar to that of **5**.

Overlaying of the X-ray structures of the 4,1-benzoxazepine derivative **1a** and the 4,1-benzothiazepine *S*-dioxide derivative **4** revealed that the orientation of the 5-phenyl ring of **4** was different from that of **1a** due to steric interaction with oxygen atoms (Fig. 4). It is assumed that similar steric hindrance would result in a change in orientation of the 5-substituent of the *S*-oxide **3**. We also assume that the conformation of **11** with the six-membered ring would be quite different from that of compounds with a seven-membered ring since **11** was only weakly active.

Conclusion

Various fused heterocyclic compounds were prepared and their inhibitions of squalene synthase were investigated. The 4,1-benzoxazepine nucleus is optimal template for inhibitory activity. The results of superimposition of the X-ray structures of some compounds prepared in this study revealed that the orientations of the 5-phenyl (6-phenyl) group on the rings strongly affected activity.

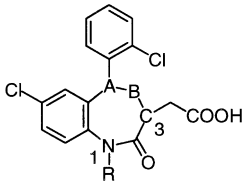
Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer (with tetramethylsilane as an internal standard). Infrared (IR) absorption spectra were recorded on a Jasco IR-810. TLC analyses were carried out on Merck Kieselgel 60 F_{254} plates. Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd., and are within ±0.4% of the theoretical values unless otherwise noted. For column chromatography, Merck Kieselgel 60 (70–230 mesh ASTM) was used. Yields were not maximized. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

5-Chloro-α-(2-chlorophenyl)-2-(neopentylamino)benzyl-alcohol (14a). $NaBH_3CN$ (0.69 g, 11.2 mmol) was added to an ice-cooled solution of 2-amino-5-chloro-α-(2′-chlorophenyl)benzyl alcohol **13** (2.0 g, 7.46 mmol), pivalaldehyde (0.71 g, 8.21 mmol) and AcOH (0.90 g, 14.9 mmol) in MeOH (20 mL). After being stirred for 1.5 h at room temperature, the reaction was quenched with 5% $KHSO_4$. The mixture was extracted with AcOEt (50 mL, twice). The extract was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and then concentrated *in vacuo* to give **14a** (2.4 g, 7.09 mmol, 95%) as colorless prisms. Mp 110–111 °C. ^{1}H NMR ($CDCl_3$) δ 0.92 (9H, s), 2.83 (2H, s), 6.15 (1H, s), 6.61 (1H, d, $J = 8.4$ Hz), 6.97 (1H, d, $J = 2.6$ Hz), 7.12–7.45 (5H, m). Anal. calcd for $C_{18}H_{21}Cl_2NO$: C, 63.91; H, 6.29; N, 4.14. Found: C,64.12; H, 6.30; N,4.31.

5-Chloro-α-(2-chlorophenyl)-2-(isobutylamino)benzyl-alcohol (14b). 14b (3.6 g, 11.1 mmol, quant) was obtained in a similar procedure from **13** (2.9 g, 10.8 mmol) and isobutylaldehyde (0.71 g, 7.90 mmol) as colorless prisms. Mp 87–88 °C. ^{1}H NMR ($CDCl_3$) δ 0.92 (6H, d, $J = 6.6$ Hz), 1.77–1.97 (1H, m), 2.90 (2H, d,

Table 1. Inhibitory activities for squalene synthase of the fused heterocyclic compounds



Compounds	A–B–C	R	IC_{50} (μM)[a]	
			Rat enzyme	HepG2 enzyme
1a (3,5-*trans*)	CH–O–CH	CH_2Bu^t	0.072	0.024
1b (3,5-*trans*)	CH–O–CH	Bu^i	0.061	0.034
2 (3,5-*trans*)	CH–S–CH	CH_2Bu^t	0.18	0.039
3 (3,5-*trans*)	CH–SO–CH	CH_2Bu^t	0.70	0.25
4 (3,5-*trans*)	CH–SO_2–CH	CH_2Bu^t	3.3	—[b]
5	C=N–CH	Bu^i	3.9	2.3
6 (3,5-*trans*)	CH–NH–CH	Bu^i	0.43	0.16
7	CH–CH_2–N	CH_2Bu^t	0.42	0.13
8	C=N–N	CH_2Bu^t	8.7	—
9 (*cis*–*trans* = 2:1)	CH–CH_2–CH	Bu^i	0.39	0.12
10 (3,6-*trans*)	CH–CH_2O–CH	CH_2Bu^t	0.13	0.083
11 (3,4-*trans*)	CH–CH	Bu^i	> 10 (10.6)[c]	—

[a]IC_{50} values were determined by a single experiment run in duplicate.
[b]Not tested.
[c]Value of % inhibition at 10 μM is given in parentheses.

$J=7.0$ Hz), 6.13 (1H, s), 6.58 (1H, d, $J=8.6$ Hz), 6.91 (1H, d, $J=2.6$ Hz), 5.99 (1H, s), 7.12–7.47 (5H, m). Anal. calcd for $C_{17}H_{19}Cl_2NO$: C, 62.97; H, 5.91; N, 4.32. Found: C, 62.97; H, 6.05; N, 4.44.

Ethyl 3-[*N*-[4-chloro-2-(2-chloro-α-hydroxybenzyl)phenyl]-*N*-neopentylcarbamoyl]acrylate (15a). A solution of fumaric acid chloride monoethyl ester (1.3 g, 7.96 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of **14a** (2.4 g, 7.09 mmol) and $NaHCO_3$ (0.91 g, 10.9 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred for 2 h at room temperature and filtered. The filtrate was washed with water, dried over Na_2SO_4 and then concentrated under reduced pressure to give **15a** (3.0 g, 6.46 mmol, 91%) as colorless prisms. Mp 153–154 °C. IR ν_{max} (KBr) cm^{-1}: 3420 (OH); 1720, 1650, 1625 (C=O, C=C). ^1H NMR ($CDCl_3$) δ 0.86 (1/3×9H, s), 0.93 (2/3×9H, s), 1.23 (2/3×3H, t, $J=7.0$ Hz), 1.25 (1/3×3H, t, $J=7.0$ Hz), 2.87 (1/3×1H, d, $J=13.4$ Hz), 3.14 (2/3×1H, d, $J=13.4$ Hz), 4.10 (2/3×2H, q, $J=7.0$ Hz), 4.27 (1/3×2H, q, $J=7.0$ Hz), 4.44 (1/3×1H, d, $J=13.4$ Hz), 4.57 (2/3×1H, d, $J=13.4$ Hz), 6.10 (1/3×1H, s), 6.22 (2/3×1H, d, $J=15.0$ Hz), 6.30 (2/3×1H, s), 6.40 (2/3×1H, d, $J=15.0$ Hz), 6.75–7.71 (7H + 1/3×2H, m). Anal. calcd for $C_{24}H_{27}Cl_2NO_4$: C, 62.07; H, 5.86; N, 3.02. Found: C, 62.18; H, 6.12; N,3.14.

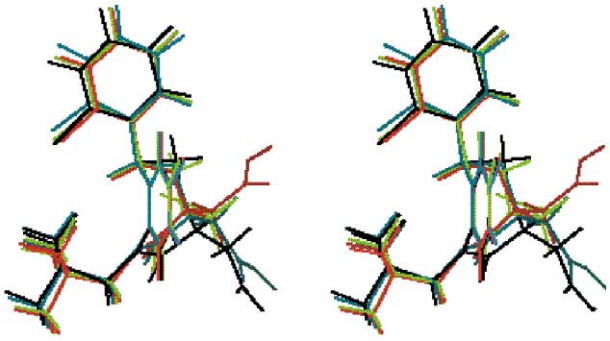


Figure 2. Overlay of the X-ray structures of 1a (red), 2 (blue), 7 (green) and 10 (black).

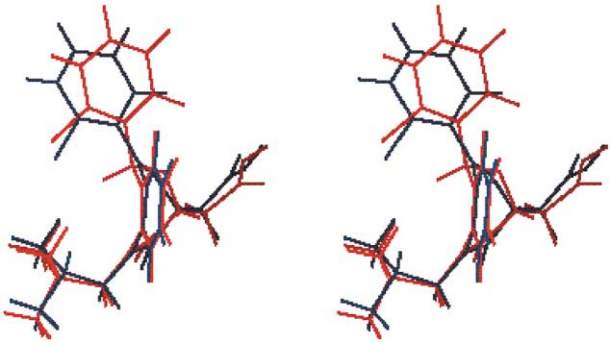


Figure 3. Overlay of the X-ray structures of 1a (red) and 5 (blue).

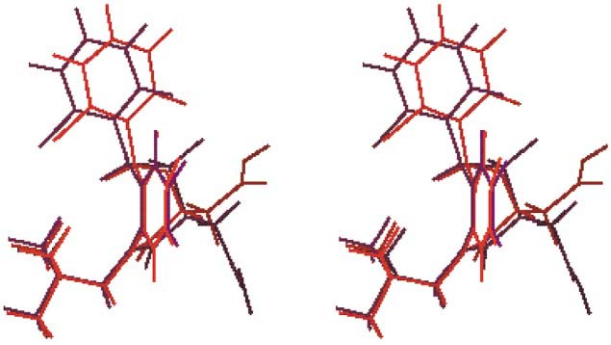


Figure 4. Overlay of the X-ray structures of 1a (red) and 4 (purple).

Ethyl 3-[*N*-[4-chloro-2-(2-chloro-α-hydroxybenzyl)phenyl]-*N*-isobutylcarbamoyl]acrylate (15b). 15b (4.2 g, 9.33 mmol, 84%) was obtained in a similar procedure from **14b** (3.6 g, 11.1 mmol) as colorless prisms. Mp 136–138 °C. IR ν_{max} (KBr) cm^{-1}: 3360 (OH); 1725, 1655, 1610 (C=O, C=C). ^1H NMR ($CDCl_3$) δ 0.75 (1/3×3H, d, $J=6.6$ Hz), 0.89–0.98 (3H + 2/3×3H, m), 1.23 (2/3×3H, t, $J=7.0$ Hz), 1.25 (1/3×3H, t, $J=7.0$ Hz), 1.7–1.9 (1H, m), 2.65 (1/3×1H, dd, $J=4.8$, 13.2 Hz), 3.03 (2/3×1H, dd, $J=4.6$, 13.2 Hz), 4.34–4.47 (4H, m), 6.11 (2/3×1H, d, $J=15.0$ Hz), 6.12 (1/3×1H, d, $J=5.0$ Hz), 6.27 (2/3×1H, d, $J=5.0$ Hz), 6.40 (2/3×1H, d, $J=15.0$ Hz), 6.69 (1/3×1H, d, $J=15.0$ Hz), 6.81 (1/3×1H, d, $J=15.0$ Hz), 6.96–7.72 (7H, m). Anal. calcd for $C_{23}H_{25}Cl_2NO_4$: C, 61.34; H, 5.59; N, 3.11. Found: C,61.26; H, 5.71; N,3.06.

Ethyl (3,5-*trans*)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate (16a). A mixture of **15a** (3.0 g, 6.46 mmol) and K_2CO_3 (1.1 g, 7.73 mmol) in EtOH (60 mL) was stirred for 24 h. The reaction mixture was diluted with AcOEt, washed with water, dried over Na_2SO_4 and then concentrated. The residue was subjected to column chromatography [eluent: hexane–AcOEt (3:1, v/v)] and recrystallized from AcOEt–hexane (1:3, v/v) to give **16a** (2.5 g, 5.438 mmol, 83%) as colorless prisms. Mp 101–102 °C. IR ν_{max} (KBr) cm^{-1}: 1740, 1670 (C=O). ^1H NMR ($CDCl_3$) δ 0.94 (9H, s), 1.25 (3H, t, $J=7.2$ Hz), 2.80 (1H, dd, $J=16.6$, 6.2 Hz), 3.04 (1H, dd, $J=16.6$, 7.2 Hz), 3.40 (1H, d, $J=14.0$ Hz), 4.14 (2H, dq, $J=7.2$, 1.8 Hz), 4.43 (1H, dd, $J=7.2$, 6.2 Hz), 4.52 (1H, d, $J=14.0$ Hz), 6.26 (1H, s), 6.52 (1H, s), 7.37–7.74 (6H, m). Anal. calcd for $C_{24}H_{27}Cl_2NO_4$: C, 62.07; H, 5.86; N, 3.02. Found: C,62.36; H, 5.87; N,2.99.

Ethyl (3,5-*trans*)-7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate (16b). 16b (4.0 g, 8.88 mmol, 95%) was obtained in a similar procedure from **15b** (4.2 g, 9.33 mmol) as a colorless oil. IR ν_{max} (KBr) cm^{-1}: 1740, 1670 (C=O). ^1H NMR ($CDCl_3$) δ 0.93 (3H, d, $J=6.6$ Hz), 1.03 (3H, d, $J=6.6$ Hz), 1.25 (3H, t, $J=7.2$ Hz), 1.90–2.10 (1H, m), 2.80 (1H, dd, $J=16.6$, 6.2 Hz), 3.06 (1H, dd, $J=16.6$, 7.2 Hz), 3.44 (1H, dd, $J=5.6$, 14.0 Hz), 4.14 (2H, q, $J=7.2$ Hz), 4.32 (1H, dd, $J=14.0$, 8.4 Hz), 4.44 (1H, dd, $J=7.2$, 6.2 Hz), 6.14 (1H, s), 6.51 (1H, d, $J=2.2$ Hz), 7.26–7.72 (6H, m).

(3,5-*trans*)-7-Chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (1a). A mixture of **16a** (2.5 g, 5.38 mmol), K_2CO_3 (0.91 g, 6.56 mmol), MeOH (30 mL) and water (10 mL) was stirred overnight at room temperature. The reaction mixture was diluted with water, acidified, extracted with

AcOEt. The extract was washed with water, dried over Na_2SO_4 and then concentrated under reduced pressure to give **1a** (1.8 g, 4.13 mmol, 77%) as colorless prisms. Mp 247–248 °C. IR ν_{max} (KBr) cm^{-1}: 3600–2200 (br, COOH), 1710, 1685 (C=O). ^1H NMR ($CDCl_3$) δ 0.94 (9H, s), 2.86 (1H, dd, $J=16.8$, 5.8 Hz), 3.09 (1H, dd, $J=16.8$, 7.4 Hz), 3.41 (1H, d, $J=14.0$ Hz), 4.39 (1H, dd, $J=7.4$, 5.8 Hz), 4.52 (1H, d, $J=14.0$ Hz), 6.26 (1H, s), 6.54 (1H, d, $J=1.4$ Hz), 7.36–7.74 (6H, m). Anal. calcd for $C_{22}H_{23}Cl_2NO_4$: C, 60.56; H, 5.31; N, 3.21. Found: C, 60.55; H, 5.47; N,3.11.

(3,5-*trans*)-7-Chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (1b). **1b** (3.2 g, 7.58 mmol, 85%) was obtained in a similar procedure from **16b** (4.0 g, 8.88 mmol) as colorless prisms. Mp 220–221 °C. IR ν_{max} (KBr) cm^{-1}: 3600–2200 (br, COOH), 1720, 1680 (C=O). ^1H NMR ($CDCl_3$) δ 0.93 (3H, d, $J=6.6$ Hz), 1.03 (3H, d, $J=6.6$ Hz), 1.91–2.05 (1H, m), 2.86 (1H, dd, $J=16.6$, 5.8 Hz), 3.10 (1H, dd, $J=16.8$, 7.4 Hz), 3.46 (1H, dd, $J=14.0$, 5.4 Hz), 4.32 (1H, dd, $J=14.0$, 8.4 Hz), 4.38 (1H, dd, $J=7.4$, 5.8 Hz), 6.13 (1H, s), 6.53 (1H, d, $J=2.4$ Hz), 7.26–7.74 (6H, m). Anal. calcd for $C_{21}H_{21}Cl_2NO_4$: C, 59.73; H, 5.01; N, 3.32. Found: C,59.98; H, 5.24; N,3.14.

Methyl (3,5-*trans*)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzothiazepine-3-acetate (20). A mixture of **14a** (6.5 g, 19.2 mmol), thiomalic acid (2.85 g, 19.0 mmol), concentrated HCl (10 mL) and AcOH (10 mL) was stirred for 30 min at 100 °C. The reaction mixture was cooled, and a 10% NaOH (200 mL) was added. The mixture (pH = 3) was extracted with CH_2Cl_2–THF (9:1, v/v) (100 mL, twice). The extracts were washed with saturated NH_4Cl (150 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was dissolved in xylene (200 mL) and the solution was refluxed overnight. The reaction mixture was concentrated in vacuo. The residue was dissolved in MeOH (100 mL), and concentrated H_2SO_4 (0.5 mL) was added. This mixture was refluxed for 3 h and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL), washed with saturated $NaHCO_3$ (100 mL) and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was subjected to column chromatography [eluent: hexane–AcOEt (1:1, v/v)] to give **19** as 3,5-*cis* and -*trans* mixtures. K_2CO_3 (1.4 g, 10.1 mmol) was added to a solution of **19** in MeOH (50 mL). After stirring overnight at room temperature, the reaction mixture was diluted with AcOEt (150 mL). The solution was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was chromatographed [eluent: hexane–AcOEt (3:1, v/v)] and recrystallized from CH_2Cl_2–petroleum ether (1:10, v/v) to give **20** (4.4 g, 9.43 mmol, 49%) as colorless prisms. Mp 133–136 °C (CH_2Cl_2-petroleum ether). IR ν_{max}(KBr) cm^{-1}: 1730 (C=O), 1680 (C=O). ^1H NMR ($CDCl_3$) δ 0.98 (9H, s), 2.42 (1H, dd, $J=3.8$, 17.0 Hz), 3.13 (1H, dd, $J=10.4$, 17.0 Hz), 3.30 (1H, d, $J=14.0$ Hz), 3.66 (3H, s), 3.78 (1H, dd, $J=3.8$, 10.4 Hz), 4.42 (1H, d, $J=14.0$ Hz), 6.34 (1H, s), 6.75 (1H, d, $J=1.6$ Hz), 7.27-7.92 (6H, m). Anal. calcd for $C_{23}H_{25}Cl_2NO_3S$: C, 59.23; H, 5.40; N, 3.00; S, 6.87. Found: C,59.36; H, 5.30; N,2.84; S, 6.86.

(3,5-*trans*)-7-Chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzothiazepine-3-acetic acid (2). An aqueous solution of NaOH (1 N, 0.4 mL) was added to a solution of **20** (0.15 g, 0.322 mmol) in MeOH (4 mL). After stirring for 3 h at 60 °C, the reaction mixture was concentrated. The residue was diluted with H_2O (20 mL), acidified, and extracted with CH_2Cl_2 (20 mL, twice). The extracts were washed with saturated NH_4Cl, dried over Na_2SO_4 and then concentrated in vacuo. The residue was recrystallized from CH_2Cl_2–petroleum ether (1:2, v/v) to give **2** (0.11 g, 0.243 mmol, 75%) as colorless needles. Mp 269–271 °C (CH_2Cl_2–petroleum ether). IR ν_{max}(KBr) cm^{-1}: 3600–2400 (br, COOH), 1750 (C=O), 1645 (C=O). ^1H NMR ($CDCl_3$) δ 0.98 (9H, s), 2.51 (1H, dd, $J=3.8$, 16.8 Hz), 3.12 (1H, dd, $J=10.2$, 16.8 Hz), 3.30 (1H, d, $J=13.8$ Hz), 3.73 (1H, dd, $J=3.8$, 10.2 Hz), 4.42 (1H, d, $J=13.8$ Hz), 6.33 (1H, s), 6.75 (1H, s), 7.33–7.48, 7.86–7.91 (total 6H, m). Anal. calcd for $C_{22}H_{23}Cl_2NO_3S$: C, 58.41; H, 5.12; N, 3.10; S, 7.09. Found: C, 58.39; H, 5.19; N, 2.84; S, 6.78.

Methyl (3,5-*trans*)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzothiazepine-3-acetate *S*-oxide (21). MCPBA (0.37 g, 2.14 mmol) was added to an ice-cooled solution of **20** (1 g, 2.14 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 10 min at room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHSO_3$, saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was recrystallized from CH_2Cl_2–hexane (1:3, v/v) to give **21** (0.59 g, 1.22 mmol, 57%) as a colorless powder. Mp 166–169 °C (CH_2Cl_2–hexane). IR ν_{max}(KBr) cm^{-1}: 1730, 1670 (C=O), 1055 (S^+-O^-). ^1H NMR ($CDCl_3$) δ 1.01 (9H, s), 2.83 (1H, dd, $J=5.2$, 17.6 Hz), 3.38 (1H, dd, $J=9.6$, 17.6 Hz), 3.44 (1H, d, $J=14.2$ Hz), 3.68 (3H, s), 3.81 (1H, dd, $J=5.2$, 9.6 Hz), 4.50 (1H, d, $J=14.2$ Hz), 5.91 (1H, s), 6.93–6.95, 7.26–7.55, 7.85–7.89 (7H, m). Anal. calcd for $C_{23}H_{25}Cl_2NO_4S{\cdot}1.7H_2O$: C, 53.85; H, 5.58; N, 2.73. Found: C, 53.70; H, 5.27; N, 2.36.

(3,5-*trans*)-7-Chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzothiazepine-3-acetic acid *S*-oxide (3). An aqueous solution (5 mL) of K_2CO_3 (0.17 g, 1.23 mmol) was added to a solution of **21** (0.5 g, 1.04 mmol) in MeOH (10 mL). The mixture was stirred for 2 h at 60 °C. The reaction mixture was diluted with water (50 mL), acidified, and then extracted with CH_2Cl_2 (50 mL, twice). The extracts were washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was recrystallized from CH_2Cl_2–hexane (1:1, v/v) to give **3** (0.38 g, 0.811 mmol, 78%) as a colerless powder. Mp 230–235 °C (dec) (CH_2Cl_2–hexane). IR ν_{max}(KBr) cm^{-1}: 3600–2400 (br, COOH), 1740, 1660 (C=O), 1050 (S^+-O^-). ^1H NMR ($CDCl_3$) δ 1.00 (9H, s), 2.86 (1H, dd, $J=4.8$, 17.2 Hz), 3.41 (1H, dd, $J=9.6$, 17.2 Hz), 3.45 (1H, d, $J=13.6$ Hz), 3.78 (1H, dd, $J=4.8$, 9.6 Hz), 4.51 (1H, d, $J=13.6$ Hz), 5.93 (1H, s), 6.96 (1H, brs), 7.27–7.56, 7.87–7.91

(6H, m). Anal. calcd for $C_{22}H_{23}Cl_2NO_4S$: C, 56.41; H, 4.95; N, 2.99. Found: C, 56.36; H, 5.04; N, 3.04.

(3,5-*trans*)-7-Chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzothiazepine-3-acetic acid *S*-dioxide (4). MCPBA (0.25 g, 1.46 mmol) was added to an ice-cooled solution of **2** (0.3 g, 0.663 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 2h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ (50 mL) and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was recrystallized from CH_2Cl_2–hexane (1:2, v/v) to give **4** (0.14 g, 0.289 mmol, 44%) as a colerless powder. Mp 245–249 °C (dec) (CH_2Cl_2–hexane). IR ν_{max} (KBr) cm^{-1}: 3600–2400 (br, COOH), 1710, 1680 (C=O), 1315, 1135 (SO_2). ^1H NMR ($CDCl_3$ + 1drop of DMSO-d_6) δ 0.93 (9H, s), 2.88 (1H, dd, J = 3.0, 17.2 Hz), 3.44 (1H, d, J = 14.0 Hz), 3.46 (1H, dd, J = 10.6, 17.2 Hz), 4.40 (1H, dd, J = 3.0, 10.6 Hz), 4.51 (1H, d, J = 14.0 Hz), 6.37 (1H, s), 7.40–7.59, 8.29–8.34 (7H, m). Anal. calcd for $C_{22}H_{23}NO_5SCl_2 \cdot 0.2H_2O$: C, 54.15; H, 4.83; N, 2.87. Found: C, 54.08; H, 4.83; N, 2.65.

Methyl 3-benzyloxycarbonylamino-3-[*N*-[4-chloro-2-(2-chlorobenzoyl)phenyl]carbamoyl]propionate (23). *N*-Methylmorpholine (1.6 g, 16 mmol) and isobutylchloroformate (2.2 g, 16 mmol) was added to a stirred solution of β-methyl *N*-benzyloxycarbonyl-DL-aspartate (4.3 g, 15.3 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was stirred for 10 min at room temperature and then warmed to reflux. A solution of **12** (4.1 g, 15.4 mmol) in CH_2Cl_2 (20 mL) was added to the refluxing reaction mixture. Heating was continued for 20 min. The mixture was then cooled to room temperature, stirred for 2 days, and diluted with CH_2Cl_2 (100 mL). The mixture was washed with 10% citric acid, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was chromatographed [eluent: hexane–AcOEt (3:1)] to give **23** (3.7 g, 6.99 mmol, 45%) as a colorless amorphous powder. IR ν_{max} (KBr) cm^{-1}: 3400 (NH), 1735, 1710, 1690, 1650 (C=O). ^1H NMR ($CDCl_3$) δ 2.82 (1H, dd, J = 4.8, 17.6 Hz), 3.31 (1H, dd, J = 4.4, 17.6 Hz), 3.69 (3H, s), 4.84 (1H, m), 5.15 (1H, d, J = 12.2 Hz), 5.27 (1H, d, J = 12.2 Hz), 7.24–7.56 (11H, m), 8.76 (1H, d, J = 8.8 Hz). Anal. calcd for $C_{26}H_{22}Cl_2N_2O_6$: C, 58.99; H, 4.19; N, 5.29. Found: C, 58.81; H, 4.19; N, 5.16.

Methyl 7-chloro-5-(2-chlorophenyl)-2-oxo-2,3-dihydro-1*H*-1,4-benzodiazepine-3-acetate (24). A 10% Pd–C catalyst (0.5 g) and concentrated HCl (0.59 mL) was added to a stirred solution of **23** (3.7 g, 6.99 mmol) in MeOH (60 mL). The apparatus was filled with hydrogen and the mixture was stirred for 30 min at room temperature. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2–THF (9:1, v/v) (100 mL) and washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was dissolved in DMF (20 mL). After addition of AcOH (1 mL), the mixture was stirred for 2 h at 60 °C, diluted with AcOEt (50 mL), washed with 5% $KHSO_4$, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was crystallized with Et_2O to give **24** (2.7 g, 7.16 mmol, quant) as a colorless amorphous powder. IR ν_{max} (KBr) cm^{-1}: 3280 (NH), 1720, 1690 (C=O), 1610 (C=N). ^1H NMR ($CDCl_3$) δ 3.22 (1H, dd, J = 7.0, 16.8 Hz), 3.44 (1H dd, J = 7.4, 16.8 Hz), 3.74 (3H, s), 4.23 (1H, t, J = 7.1 Hz), 7.08 (1H, d, J = 2.2 Hz), 7.38–7.48 (6H, m), 8.72 (1H, br). Anal. calcd for $C_{18}H_{14}Cl_2N_2O_3 \cdot 0.75H_2O$: C, 55.33; H, 4.00; N, 7,17. N, 7.17. Found: C, 54.92; H, 3.60; N, 7.21.

Methyl 7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-2,3-dihydro-1*H*-1,4-benzodiazepine-3-acetate (25). NaH (36 mg, 1.50 mmol) was added to a solution of **24** (0.52 g, 1.38 mmol) in DMF (5 mL) at 0 °C. The mixture was stirred for 5 min at 0 °C, followed by addition of isobutyl bromide (0.23 g, 1.7 mmol). The reaction mixture was stirred for 1 h at room temperature, and diluted with AcOEt (50 mL). The solution was washed with 5% $KHSO_4$, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was subjected to column chromatography [eluent: hexane–AcOEt (4:1, v/v)] to give **25** (0.3 g, 0.692 mmol, 50%) as a pale yellow oil. IR ν_{max} (neat) cm^{-1}: 1740, 1680 (C=O), 1600 (C=N). ^1H NMR ($CDCl_3$) δ 0.80 (3H, d, J = 6.4 Hz), 0.88 (3H, d, J = 6.6 Hz), 1.76 (1H, m), 3.22 (1H, dd, J = 7.0, 16.8 Hz), 3.44 (1H, dd, J = 7.4, 16.8 Hz), 3.53 (1H, qd, J = 4.8, 14.2 Hz), 3.72 (3H, s), 4.17 (1H, t, J = 7.1 Hz), 4.33 (1H, dd, J = 10.0, 14.2 Hz), 7.08 (1H, d, J = 2.4 Hz), 7.37–7.53 (6H, m).

7-Chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-2,3-dihydro-1*H*-1,4-benzodiazepine-3-acetic acid (5). An aqueous solution (2 mL) of K_2CO_3 (0.11 g, 0.82 mmol) was added to a solution of **25** (0.23 g, 0.531 mmol) in MeOH (4 mL). The mixture was stirred for 1 h at 60 °C, diluted with water (50 mL), acidified with 1 N HCl, and extracted with CH_2Cl_2 (50 mL, twice). The extracts were washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was recrystallized from CH_2Cl_2–petroleum ether (1:3, v/v) to give **5** (0.11 g, 0.262 mmol, 49%) as a colorless powder. Mp 175–178 °C (CH_2Cl_2–petroleum ether). IR ν_{max} (KBr) cm^{-1}: 3600–2400 (br, COOH), 1710 (C=O), 1670 (C=O), 1600 (C=N). ^1H NMR ($CDCl_3$) δ 0.79 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.8 Hz), 1.75 (1H, m), 3.23 (1H, dd, J = 6.4, 16.8 Hz), 3.36 (1H, dd, J = 6.4, 16.8 Hz), 3.55 (1H, qd, J = 4.6, 14.0 Hz), 4.11 (1H, t, J = 6.4 Hz), 4.34 (1H, dd, J = 9.8, 14.0 Hz), 7.10 (1H, d, J = 2.4 Hz), 7.37–7.55 (6H, m). Anal. calcd for $C_{21}H_{20}Cl_2N_2O_3 \cdot 0.2H_2O$: C, 59.65; H, 4.86; N, 6.62. Found: C, 59.65; H, 4.96; N, 6.62.

(3,5-*trans*)-7-Chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-3-acetic acid (6). $NaBH_4$ (10 mg) was added to a solution of **5** (30 mg, 0.0715 mmol) in MeOH–H_2O (6:1, v/v) (0.7 mL). The mixture was stirred for 2 h at room temperature, diluted with water, neutralized with 1 N HCl, and extracted with CH_2Cl_2 (50 mL, twice). The extracts were washed with brine, dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was

recrystallized from CH_2Cl_2–petroleum ether (1:10, v/v) to give **6** (17 mg, 0.0403 mmol, 56%) as a colorless powder. Mp 184–188 °C (dec) (CH_2Cl_2–petroleum ether). IR ν_{max} (KBr) cm^{-1}: 3600–2400 (br, COOH), 1705, 1665 (C=O). ^1H NMR ($CDCl_3$) δ 0.918 (3H, d, $J=6.6$ Hz), 1.035 (3H, d, $J=6.6$ Hz), 1.940 (1H, m), 2.668 (1H, dd, $J=5.4$, 16.4 Hz), 2.877 (1H, dd, $J=7.8$, 16.4 Hz), 3.419 (1H, dd, $J=5.2$, 13.6 Hz), 3.685 (1H, dd, $J=5.4$, 7.8 Hz), 4.245 (1H, dd, $J=8.8$, 13.6 Hz), 5.634 (1H, s), 5.56–5.92 (1H, br), 6.479 (1H, d, $J=2.2$ Hz), 7.22–7.44, 7.93–7.96 (6H, m). Anal. calcd for $C_{21}H_{22}Cl_2N_2O_3\cdot H_2O$: C, 57.41; H, 5.50; N, 6.38. Found: C, 57.56; H, 5.16; N, 6.40.

Methyl 5-chloro-α-(2-chlorophenyl)-2-nitrophenylacetate (27). A mixture of NaH (oil-free, 3.4 g, 0.141 mol), **26** (28 g, 0.152 mol) and 4-chloro-1,2-dinitrobenzene (27 g, 0.133 mol) in DMF (100 mL) was stirred for 1 h at 0 °C. The reaction mixture was poured into 1 N HCl (300 mL) and the resulting aqueous solution was extracted with AcOEt (200 mL, twice). The extracts were washed with brine, dried over Na_2SO_4 and evaporated to give an oil, which was chromatographed [eluent: hexane–AcOEt (10:1, v/v)] to give **27** (26.3 g, 77.3 mmol, 58%) as a yellow powder. Mp 96–97 °C (hexane). IR ν_{max} (KBr) cm^{-1}: 1740 (C=O), 1515, 1340 (NO_2). ^1H NMR ($CDCl_3$) δ 3.80 (3H, s), 6.07 (1H, s), 6.90 (1H, d, $J=2.2$ Hz), 7.22–7.49 (5H, m), 8.06 (1H, d, $J=8.4$ Hz). Anal. calcd for $C_{15}H_{11}Cl_2NO_4$: C, 52.96; H, 3.26; N, 4.12. Found: C, 53.04; H, 3.34; N, 4.06.

2-(2-Chlorophenyl)-2-(5-chloro-2-nitrophenyl)ethanol (28). A mixture of **27** (26 g, 76.4 mmol) and $LiBH_4$ (2 g) in THF (200 mL) was stirred for 4 h at room temperature. The mixture was poured into 20% AcOH (50 mL) and the resulting aqueous solution was extracted with AcOEt (200 mL, twice). The extracts were washed with brine, dried over Na_2SO_4 and evaporated to give an oil, which was chromatographed [eluent: hexane–AcOEt (3:1, v/v)] to give **28** (11 g, 35.2 mmol, 46%) as a brown oil. ^1H NMR ($CDCl_3$) δ 1.90 (1H, br), 4.15–4.33 (2H, m), 5.27 (1H, t, $J=6.2$ Hz), 7.20–7.40 (6H, m), 7.87 (1H, d, $J=8.4$ Hz).

5-Chloro-α-(2-chlorophenyl)-2-nitrophenylacetaldehyde (29). A solution of DMSO (6.7 mL, 94.2 mmol) in CH_2Cl_2 (30 mL) was added to a solution of oxalyl chloride (6.2 mL, 70.8 mmol) in CH_2Cl_2 (300 mL) at −78 °C, and the resulting mixture was stirred for 10 min at −78 °C. After addition of a solution of **28** (11 g, 35.2 mmol) in CH_2Cl_2 (100 mL), the whole mixture was stirred for 15 min at −78 °C. After addition of NEt_3 (37 mL, 0.26 mol), the mixture was allowed to warm to 0 °C, washed with saturated NH_4Cl (124 mL) and brine, and dried over Na_2SO_4, and then concentrated. The residue was chromatographed [eluent: hexane–AcOEt (3:1, v/v)] to give **29** (9.1 g, 29.3 mmol, 83%) as a brown oil. ^1H NMR ($CDCl_3$) δ 6.30 (1H, s), 6.84 (1H, d, $J=2.2$ Hz), 7.14–7.65 (5H, m), 8.10 (1H, d, $J=8.8$ Hz), 9.89 (1H, s).

Methyl *N*-[2-(2-chlorophenyl)-2-(5-chloro-2-nitrophenyl)-ethyl]glycinate (30). Methyl glycinate hydrochloride (0.69 g, 5.5 mmol) and AcONa (0.45 g, 5.5 mmol) was added to a solution of **29** (1.7 g, 5.48 mmol) in MeOH (15 mL). After stirring for 30 min at room temperature, $NaBH_3CN$ (0.35 g, 5.5 mmol) was added to the mixture. After stirring for 3 h at 50 °C, 1 N NaOH (50 mL) was added and the solution was extracted with CH_2Cl_2 (50 mL, twice). The extracts were washed with brine, dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was subjected to column chromatography [eluent: hexane–AcOEt (3:1, v/v)] to give **30** (1.1 g, 2.87 mmol, 52%) as a pale yellow oil. IR ν_{max} (neat) cm^{-1}: 3600–3200 (br, NH), 1740 (C=O), 1520 (NO_2), 1345 (NO_2). ^1H NMR ($CDCl_3$) δ 3.20 (1H, dd, $J=6.8$, 12.2 Hz), 3.37 (1H, dd, $J=7.6$, 12.2 Hz), 3.48 (2H, s), 3.73 (3H, s), 5.26 (1H, t, $J=7.2$ Hz), 7.22–7.44 (6H, m), 7.85 (1H, d, $J=8.6$ Hz).

Methyl *N*-[2-(2-chlorophenyl)-2-(5-chloro-2-nitrophenyl)-ethyl]-*N*-trifluoroacetylglycinate (31). Trifluoroacetic anhydride (3.0 g, 14.2 mmol) was added to a solution of **30** (4.9 g, 12.8 mmol) and pyridine (3.0 g, 38.4 mmol) in CH_2Cl_2 (50 mL). This mixture was stirred for 10 min at room temperature, duluted with CH_2Cl_2 (50 mL). The solution was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was subjected to column chromatography [eluent: hexane–AcOEt (5:1, v/v)] to give **31** (5.9 g, 12.3 mmol, 96%) as a yellow oil. IR ν_{max} (neat) cm^{-1}: 1750, 1700 (C=O), 1525, 1350 (NO_2). ^1H NMR ($CDCl_3$) δ: 3.79 (3H, s), 4.14 (1H, dd, $J=7.0$, 14.0 Hz), 4.22 (2H, s), 4.43 (1H, dd, $J=8.8$, 14.0 Hz), 5.47 (1H, dd, $J=7.0$, 8.8 Hz), 7.27–7.52 (6H, m), 7.87 (1H, d, $J=8.4$ Hz).

Methyl *N*-[2-(2-amino-5-chlorophenyl)-2-(2-chlorophenyl)-ethyl]-N-trifluoroacetylglycinate (32). A 10% Pd–C catalyst (100 mg) was added to a solution of **31** (1 g, 2.09 mmol) in AcOEt (20 mL). The apparatus was filled with hydrogen and the mixture was stirred at room temperature for 8 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was subjected to column chromatography [eluent: hexane–AcOEt (4:1, v/v)] to give **32** (0.39 g, 0.868 mmol, 42%) as a yellow oil. IR ν_{max}(neat) cm^{-1}: 3460 (NH_2), 3380 (NH_2), 1750, 1695 (C=O). ^1H NMR ($CDCl_3$) δ 3.71 (1/4×3H, s), 3.74 (3/4×3H, s), 3.47–4.25 (4H, m), 4.72–4.80 (1/4×1H, m), 4.87 (3/4×1H, dd, $J=5.8$, 9.4 Hz), 6.57–6.63 (1H, m), 7.05–7.44 (6H, m).

Methyl *N*-[2-(5-chloro-2-neopentylaminophenyl)-2-(2-chlorophenyl)ethyl]-*N*-trifluoroacetylglycinate (33). A solution of **32** (0.39 g, 0.868 mmol), AcOH (0.05 mL), and pivalaldehyde (78 mg, 0.90 mmol) in MeOH (5 mL) was stirred for 30 min at room temperature, followed by addition of $NaBH_3CN$ (57 mg, 0.90 mmol) at 0 °C. The mixture was stirred for 1 h at room temperature, diluted with CH_2Cl_2 (50 mL), washed with 1 N NaOH and brine, dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was subjected to column chromatography [eluent: hexane–AcOEt (5:1, v/v)] to give **33** (0.27 g, 0.520 mmol, 60%) as a pale yellow oil. IR ν_{max} (neat) cm^{-1}: 3420 (br, NH), 1755, 1700 (C=O). ^1H NMR ($CDCl_3$) δ 0.85 (9H, s), 2.65–2.83 (2H, m), 3.32 (1/4×1H, d, $J=17.4$ Hz), 3.51–3.60 (1H, m), 3.70 (1/4×3H,

s), 3.75 (3/4×3H, s), 3.87 (1H, dd, $J=9.8$, 13.4 Hz), 4.06 (3/4×1H, d, $J=17.8$ Hz), 4.27 (1H, dd, $J=5.8$, 13.4 Hz), 4.72–4.86 (1H, m), 6.53–6.60 (1H, m), 7.11–7.40 (6H, m).

Methyl *N*-[2-(5-chloro-2-neopentylaminophenyl)-2-(2-chlorophenyl)ethyl]glycinate (34). Concentrated HCl (0.6 mL) was added to a solution of **33** (0.2 g, 0.385 mmol) in MeOH (3 mL). The mixture was refluxed overnight, followed by addition of 1 N NaOH (8 mL). The solution was extracted with CH_2Cl_2 (50 mL, twice). The extracts were washed with brine, dried over Na_2SO_4 and then concentrated in vacuo to give **34** (72 mg, 0.170 mmol, 44%) as a brown oil. IR ν_{max} (neat) cm−1: 3420 (NH), 1740 (C=O). ^{1}H NMR ($CDCl_3$) δ 0.82 (9H, s), 2.66 (1H, d, $J=11.2$ Hz), 2.77 (1H, d, $J=11.2$ Hz), 3.03 (1H, dd, $J=5.2$, 11.8 Hz), 3.28 (1H, dd, $J=8.4$, 11.8 Hz), 3.43 (1H, d, $J=17.6$ Hz), 3.53 (1H, d, $J=17.6$ Hz), 3.74 (3H, s), 4.56 (1H, dd, $J=5.2$, 8.4 Hz), 6.54 (1H, d, $J=8.8$ Hz), 6.99–7.42 (6H, m).

Methyl 7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,4,5-tetrahydro-3*H*-1,3-benzodiazepine-3-acetate (35). Triphosgene (0.14 g, 0.472 mmol) was added to a solution of **34** (0.47 g, 1.11 mmol) and NEt_3 (0.21 g, 2.08 mmol) in toluene (5 mL). The mixture was stirred for 5 h at 70 °C, diluted with CH_2Cl_2 (50 mL), washed with 1 N HCl and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was crystallized with hexane to give **35** (0.30 g, 0.668 mmol, 60%) as a colorless powder. Mp 142–148 °C (hexane). IR ν_{max} (KBr) cm^{-1}: 1750 (C=O), 1640 (C=O). ^{1}H NMR ($CDCl_3$) δ 0.94 (9H, s), 3.49 (1H, d, $J=14.4$ Hz), 3.64 (1H, d, $J=17.2$ Hz), 3.72 (3H, s), 3.88 (2H, d, $J=8.6$ Hz), 4.04 (1H, d, $J=17.2$ Hz), 4.31 (1H, d, $J=14.4$ Hz), 5.32 (1H, t, $J=8.6$ Hz), 6.65 (1H, d, $J=1.8$ Hz), 7.14–7.50 (6H, m).

7-Chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,4,5-tetrahydro-3*H*-1,3-benzodiazepine-3-acetic acid (7). A mixture of **35** (0.3 g, 0.668 mmol) and 1 N NaOH (0.7 mL) in MeOH (3 mL) was stirred for 30 min at 70 °C. The reaction mixture was diluted with water (50 mL), acidified with 1 N HCl, extracted with CH_2Cl_2 (50 mL, twice). The extracts were washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was recrystallized from CH_2Cl_2–hexane (1:10, v/v) to give **7** (0.21 g, 0.482 mmol, 72%) as colorless prisms. Mp 228–231 °C (CH_2Cl_2–hexane). IR ν_{max} (KBr) cm^{-1}: 3400–2400 (br, COOH), 1755 (C=O), 1600 (C=O). ^{1}H NMR ($CDCl_3$) δ 0.94 (9H, s), 3.41 (1H, d, $J=14.2$ Hz), 3.44 (1H, d, $J=16.0$ Hz), 3.84 (2H, d, $J=8.8$ Hz), 4.24 (1H, d, $J=16.0$ Hz), 4.53 (1H, d, $J=14.2$ Hz), 5.28 (1H, t, $J=8.8$ Hz), 6.62 (1H, s), 7.20–7.53 (6H, m). Anal. calcd for $C_{22}H_{24}Cl_2N_2O_3$: C, 60.70; H, 5.56. N, 6.43. Found: C, 60.37; H, 5.49; N, 6.15.

[5-Chloro-2-(neopentylamino)phenyl](2-chlorophenyl)methanethione (36). Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] (0.3 g, 0.743 mmol) was added to a solution of **22** (0.5 g, 1.49 mmol) in toluene (5 mL). After being refluxed for 2 h, the mixture was diluted with AcOEt (50 mL). The solution was washed with water and brine, dried over Na_2SO_4, and then concentrated under reduced pressure to give **36** (0.54 g, 1.53 mmol, quant) as a red oil. IR ν_{max} (neat) cm^{-1}: 1235 (C=S).

Ethyl [2-[5-chloro-2-(neopentylamino)phenyl](2-chlorophenyl)methylene]hydrazino]acetate (37a,b). Ethyl hydrazinoacetate hydrochloride (0.23 g, 1.49 mmol) and K_2CO_3 (0.11 g, 0.765 mmol) was added to a solution of **36** (0.54 g, 1.53 mmol) in EtOH (7 mL). The mixture was stirred overnight at 70 °C. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water and brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was chromatographed [eluent: hexane–AcOEt (15:1, v/v)] to give **37a** (less polar isomer) (0.16 g, 0.367 mmol, 24%) as a colorless oil from the first fraction and **37b** (polar isomer) (0.26 g, 0.596 mmol, 39%) as colorless prisms from the second fraction.

37a. IR ν_{max} (neat) cm^{-1}: 3400 (NH), 1740 (C=O). ^{1}H NMR ($CDCl_3$) δ: 0.95 (9H, s), 1.27 (3H, t, $J=7.2$ Hz), 2.96 (2H, d, $J=5.8$ Hz), 4.04–4.27 (4H, m), 5.97 (1H, t, $J=5.8$ Hz), 6.68 (1H, d, $J=9.0$ Hz), 6.88 (1H, d, $J=2.6$ Hz), 7.15–7.50 (5H, m).

37b. Mp 116–118 °C (CH_2Cl_2–petroleum ether). IR ν_{max} (KBr) cm^{-1}: 3280 (NH), 1735 (C=O). ^{1}H NMR ($CDCl_3$) δ 1.07 (9H, s), 1.25 (3H, t, $J=6.8$ Hz), 3.01 (2H, d, $J=4.8$ Hz), 3.89 (1H, dd, $J=3.8$, 17.6 Hz), 4.09 (1H, dd, $J=7.8$, 17.6 Hz), 4.16 (2H, q, $J=6.8$ Hz), 5.25 (1H. dd, $J=4.4$, 7.4 Hz), 6.50 (1H, d, $J=2.6$ Hz), 6.62 (1H, d, $J=8.8$ Hz), 7.06 (1H, dd, $J=2.6$, 8.8 Hz), 7.30–7.62 (4H, m), 8.38 (1H, br).

Ethyl 7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepine-3-acetate (38). Triphosgene (54 mg, 0.184 mmol) was added to a solution of **37a** (0.16 g, 0.367 mmol) and NEt_3 (90 mg, 0.891 mmol) in toluene (2 mL). After being stirred for 1 h at 70 °C, the reaction mixture was diluted with AcOEt (50 mL), washed with water and brine, dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was subjected to column chromatography [eluent: hexane–AcOEt (3:1, v/v)] to give **38** (0.16 g, 0.346 mmol, 94%) as a pale yellow oil. IR ν_{max} (neat) cm^{-1}: 1750, 1680 (C=O). ^{1}H NMR ($CDCl_3$) δ 0.88 (9H, s), 1.24 (3H, t, $J=7.0$ Hz), 3.38 (1H, d, $J=14.0$ Hz), 4.18 (2H, q, $J=7.0$ Hz), 4.32 (1H, d, $J=16.8$ Hz), 4.36 (1H, d, $J=14.0$ Hz), 4.48 (1H, d, $J=16.8$ Hz), 6.86 (1H, d, $J=2.6$ Hz), 7.20–7.50 (6H, m).

7-Chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepine-3-acetic acid (8). An aqueous solution of NaOH (1 N, 0.3 mL) was added to a solution of **38** (0.16 g, 0.346 mmol) in EtOH (3 mL). After being stirred at room temperature for 4 h, the reaction mixture was diluted with water (50 mL), acidified with 1 N HCl, and concentrated. The residue was extracted with CH_2Cl_2 (50 mL, twice). The extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallized

from CH_2Cl_2-petroleum ether (1:10, v/v) to give **8** (91 mg, 0.21 mmol, 61%) as a colorless powder. Mp 181–183 °C (CH_2Cl_2–petroleum ether). IR ν_{max} (KBr) cm^{-1}: 3600–2400 (br, COOH), 1720, 1680 (C=O). ^1H NMR ($CDCl_3$) δ 0.86 (9H, s), 3.39 (1H, d, J = 14.6 Hz), 4.43–4.41 (3H, m), 6.88 (1H, d, J = 2.6 Hz), 7.22–7.47 (6H, m). Anal. calcd for $C_{21}H_{21}Cl_2N_3O_3$: C, 58.07; H, 4.87. N, 9.67. Found: C, 57.90; H, 5.13; N, 9.46.

Ethyl 4-(2-chlorophenyl)-4-phenylbutyrate (41). A mixture of **40**[19] (27 g, 78.3 mmol) and 47% HBr (80 mL) in AcOH (100 mL) was refluxed overnight. The resulting mixture was diluted with AcOEt. The solution was washed with brine, dried over Na_2SO_4 and then concentrated to give ethyl 4-(2-chlorophenyl)-4-phenylbut-3-enoate (21 g). A solution of this compound in AcOEt (150 mL) was hydrogenated over 10% Pd–C (50% wet, 2 g) under atomospheric pressure until the absorption of hydrogen stopped. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. A mixture of the residue, p-TsOH·H_2O (0.5 g) and EtOH (150 mL) was refluxed overnight. After removal of the sovent under reduced pressure, the mixture was dissolved in AcOEt. The solution was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated. The residue was chromatographed [eluent: hexane–AcOEt (10:1, v/v)] to give **41** (8.0 g, 26.4 mmol, 34%) as a colorless oil. IR ν_{max} (neat) cm^{-1}: 1730 (C=O). ^1H NMR ($CDCl_3$) δ: 1.23 (3H, t, J = 7.1 Hz), 2.2–2.5 (4H, m), 4.10 (2H, q, J = Hz), 4.45–4.6 (1H, m), 7.0–7.4 (9H, m).

4-(2-Chlorophenyl)-1-tetralone (42). An aqueous solution of NaOH (1 N, 40 mL) was added to a solution of **41** (8.0 g, 26.4 mmol) in EtOH (80 mL). After being stirred for 1 h, the mixture was concentrated in vacuo. The residue was dissolved in water (100 mL). The solution was washed with Et_2O (50 mL). The aqueous layer was acidified with concentrated HCl and extracted with AcOEt (150 mL). The extract was washed with water, dried over $MgSO_4$, and concentrated. A mixture of the residue, $SOCl_2$ (4.0 mL) and DMF (0.05 mL) in toluene (50 mL) was heated for 1 h at 80 °C, and then concentrated in vacuo. $AlCl_3$ (2.9 g, 21.8 mmol) was added to an ice-cooled solution of the residue in 1,2-dichloroethane (50 mL) in portions. After being stirred for 1 h at room temperature, the reaction was quenched with 1 N HCl. The solution was washed with 1 N NaOH, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed [eluent: hexane–AcOEt (10:1, v/v)] to give **42** (4.5 g, 17.5 mmol, 66%) as a colorless oil. IR ν_{max} (neat) cm^{-1}: 1685 (C=O). ^1H NMR ($CDCl_3$) δ 2.2–2.5 (2H, m), 2.6–2.8 (2H, m), 4.85 (1H, t, J = 5.9 Hz), 6.7–7.5 (7H, m), 8.05–8.20 (1H, m).

5-(2-Chlorophenyl)-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (43). A solution of NH_2OH·HCl (1.3 g, 19.2 mmol) and AcONa (2.2 g, 26.3 mmol) in water (30 mL) was added to a solution of **42** (4.5 g, 17.5 mmol) in EtOH (100 mL). After being refluxed for 2 h, the mixture was concentrated in vacuo. The residue was dissolved in AcOEt. The solution was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated. The residue was crystallized with hexane–Et_2O to give the oxime (3.9 g, 82%) as colorless needles (mp 114–115 °C). A mixture of the oxime (3.9 g, 27.7 mmol) and polyphosphoric acid (30 g) was heated for 20 min at 120 °C. Water was added to the mixture and the deposited powder was collected, chromatographed [eluent: hexnae–CH_2Cl_2–AcOEt (1:1:1, v/v)] to give **43** (3.0 g, 11.0 mmol, 63%) as colorless prisms. Mp 226–227 °C (hexane–AcOEt). IR ν_{max} (KBr) cm^{-1}: 1670 (C=O). ^1H NMR ($CDCl_3$) δ 2.4–2.7 (4H, m), 4.7–4.9 (1H, m), 6.55–6.7 (1H, m), 6.95–7.6 (8H, m). Anal. calcd for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.15. Found: C, 70.94; H, 5.20; N, 5.20.

5-(2-Chlorophenyl)-1-isobutyl-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (44). NaH (0.82 g, 60% in oil, 20.6 mmol) was added to an ice-cooled solution of **43** (2.8 g, 10.3 mmol) and isobutylbromide (2.2 mL, 20.6 mmol) in DMF (20 mL). After being stirred for 4 h at room temperature, the mixture was diluted with AcOEt. The solution was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated. The residue was chromatographed [eluent: hexane–AcOEt (5:1, v/v)] to give **44** (3.0 g, 9.15 mmol, 89%) as cololess prisms. Mp 139–140 °C (hexane–AcOEt). IR ν_{max} (KBr) cm^{-1}: 1660 (C=O). ^1H NMR ($CDCl_3$) δ 0.92 (3H, d, J = 6.7 Hz), 1.08 (3H, d, J = 6.5 Hz), 1.8–2.1 (1H, m), 2.3–2.6 (4H, m), 3.44 (1H, dd, J = 13.7, 4.9 Hz), 4.23 (1H, dd, J = 13.7, 9.0 Hz), 4.65–4.8 (1H, m), 6.54 (1H, d, J = 7.3 Hz), 6.95–7.10 (1H, m), 7.2–7.6 (6H, m). Anal. calcd for $C_{20}H_{22}ClNO$: C, 73.27; H, 6.76; N, 4.27. Found: C, 73.08; H, 6.69; N, 4.36.

7-Chloro-5-(2-chlorophenyl)-1-isobutyl-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (45). A mixture of **44** (2.7 g, 8.24 mmol) and *N*-chlorosuccinimide (1.7 g, 12.4 mmol) in DMF (10 mL) was stirred for 7 h at 70 °C. The mixture was diluted with AcOEt. The solution was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated. The residual solid was recrystallzed from hexane–AcOEt to give **45** (2.4 g, 6.62 mmol, 80%) as colorless prisms. Mp 152–154 °C (hexane–AcOEt). IR ν_{max} (KBr) cm^{-1}: 1655 (C=O). ^1H NMR ($CDCl_3$) δ 0.92 (3H, d, J = 6.8 Hz), 1.07 (3H, d, J = 6.6 Hz), 1.8–2.1 (1H, m), 2.3–2.6 (4H, m), 3.38 (1H, dd, J = 13.7, 4.8 Hz), 4.71 (1H, dd, J = 13.7, 9.1 Hz), 4.6–4.8 (1H, m), 6.51 (1H, d, J = 2.0 Hz), 7.2–7.55 (6H, m). Anal. calcd for $C_{20}H_{21}Cl_2NO$: C, 66.30; H, 5.84; N, 3.87. Found: C, 66.59; H, 5.88; N, 4.12.

Ethyl 7-chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-3-acetate (46). *n*-BuLi (1.14 mL, 1.58 M in hexane, 1.79 mmol) was added to a solution of Pr^i_2NH (0.25 mL, 1.79 mmol) in dry THF (5 mL) at −15 °C. The mixture was stirred for 45 min at −15 °C. After addition of **45** (0.5 g, 1.38 mmol) in THF (5 mL), the mixture was stirred for 15 min at 0 °C. The mixture was cooled to −78 °C and ICH_2COOEt (0.25 mL, 2.07 mmol) was added. After being stirred for 15 min at −78 °C and for 1 h at 0 °C, the mixture was quenched by 1 N HCl (50 mL). The mixture was extracted with AcOEt (50 mL). The extract was washed with

saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography [eluent: hexane–AcOEt (2:1, v/v)] to give **46** (0.10 g, 0.223 mmol, 16%, *cis*:*trans* = ca. 2:1) as a colorless oil. IR ν_{max} (neat) cm^{-1}: 1730, 1660 (C=O). ^1H NMR ($CDCl_3$) δ 0.5–1.15 (6H, m), 1.15–1.4 (3H, m), 1.7–3.1 (5H, m), 3.1–3.9 (2H, m), 4.0–4.2 (2H, m), 4.4–4.8 (1H, m), 6.4–7.6 (7H, m). SIMS (*m*/*z*): 449 (MH^+). In this reaction, the starting material (0.38 g, 76%) was recovered.

7-Chloro-5-(2-chlorophenyl)-1-isobutyl-2-oxo-2,3,4,5-tetrahydo-1*H*-1-benzazepine-3-acetic acid (9). An aqueous solution of NaOH (1 N, 1 mL) was added to a solution of **46** (0.09 g, 0.201 mmol) in EtOH (3 mL). After stirring for 20 min, the mixture was diluted with water (30 mL), washed with Et_2O (20 mL), acidified with 1 N HCl (30 mL), and extracted with AcOEt (30 mL). The extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo to give **9** (50 mg, 0.119 mmol, 59%) as colorless crystals. Mp 165–171 °C (hexane–AcOEt). IR ν_{max} (KBr) cm^{-1}: 1730, 1710, 1650, 1625 (C=O). ^1H NMR ($CDCl_3$) δ 0.5–1.15 (6H, m), 1.6–2.0 (1H, m), 2.1–3.1 (5H, m), 3.1–4.3 (2H, m), 4.4–4.8 (1H, m), 6.5–7.65 (7H, m). Anal. calcd for $C_{22}H_{23}Cl_2NO_3$: C, 62.86; H, 5.51; N, 3.33. Found: C, 62.77; H, 5.61; N, 3.29.

2-(2-Amino-5-chlorophenyl)-2-(2-chlorophenyl)ethanol (47). Hydrazine hydrate (3.4 g, 67.2 mmol) and Raney Ni (0.1 g) was added to a solution of **28** (7.0 g, 22.4 mmol) in EtOH (70 mL). After being stirred for 30 min at room temperature, the catalyst was removed by filtration and the solvent was removed in vacuo. The residue was chromatographed [eluent: hexane–AcOEt (2:1, v/v)] to give **47** (4.4 g, 15.6 mmol, 70%) as a brown oil. IR ν_{max} (neat) cm^{-1}: 3450 (NH_2), 3370 (NH_2), 3600-3200 (br, OH). ^1H NMR ($CDCl_3$) δ 4.11 (2H, d, J = 6.6 Hz), 4.59 (1H, t, J = 6.6 Hz), 6.60 (1H, d, J = 8.4 Hz), 7.01–7.43 (6H, m).

2-(5-Chloro-2-neopentylaminophenyl)-2-(2-chlorophenyl)-ethanol (48). AcOH (1.4 mL), and pivalaldehyde (2.0 g, 23.6 mmol) was added to a solution of **47** (4.4 g, 15.6 mmol) in MeOH (50 mL). After being stirred for 30 min at room temperature, $NaBH_3CN$ (1.5 g, 23.6 mmol) was added. The reaction mixture was stirred for 1 h at room temperature, diluted with CH_2Cl_2 (100 mL). The solution was washed with 1 N NaOH and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was chromatographed [eluent: hexane–AcOEt (4:1, v/v)] to give **48** (5.5 g, 15.6 mmol, quant) as a brown oil. IR ν_{max} (neat) cm^{-1}: 3600–3100 (br, NH, OH). ^1H NMR ($CDCl_3$) δ 0.81 (9H, s), 2.65 (1H, d, J = 11.4 Hz), 2.77 (1H, d, J = 11.4 Hz), 4.11–4.15 (2H, m), 4.59 (1H, t, J = 6.3 Hz), 6.55 (1H, d, J = 8.6 Hz), 7.01–7.44 (6H, m).

Ethyl 3-[*N*-[4-Chloro-2-[1-(2-chlorophenyl)-2-hydroxyethyl]phenyl]-*N*-neopentylcarbamoyl]acrylate (49). Fumaryl chloride monoethyl ester (2.6 g, 16.0 mmol) was added dropwise to a suspension of **48** (5.5 g, 15.6 mmol) and $NaHCO_3$ (1.7 g, 20.2 mmol) in CH_2Cl_2 (30 mL). After being stirred for 1 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL). The solution was washed with water and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The recidue was chromatographed [eluent: hexane–AcOEt (5:1, v/v)] to give **49** (6.8 g, 14.2 mmol, 91%) as a brown oil. IR ν_{max} (neat) cm^{-1}: 3600–3200 (br, OH), 1720, 1660, (C=O), 1625 (C=C). ^1H NMR ($CDCl_3$) δ 0.68 (1/2×9H, s), 0.94 (1/2×9H, s), 1.21 (1/2×3H, t, J = 7.2 Hz), 1.25 (1/2×3H, t, J = 7.2 Hz), 2.30 (1/2×1H, d, J = 13.8 Hz), 2.88 (1/2×1H, d, J = 13.4 Hz), 3.96–4.29 (4H + 1/2×1H, m), 4.60–4.67 (1H, m), 4.82 (1/2×1H, t, J = 7.0 Hz), 5.86 (1/2×1H, d, J = 15.2 Hz), 6.17 (1/2 1H, d, J = 15.2 Hz), 6.69–7.81 (8H, m).

Ethyl (3,6-*trans*)-8-chloro-6-(2-chlorophenyl)-1-neopentyl-2-oxo-2,3,5,6-tetrahydro-1*H*-4,1-benzoxazocine-3-acetate (50). A mixture of **49** (6.8 g, 14.2 mmol), 18-crown-6 (3.8 g, 14.3 mmol) and K_2CO_3 (2.0 g, 14.3 mmol) in CH_2Cl_2 (70 mL) was stirred for 3 days at room temperature. After removal of the solvent, the residue was chromatographed [eluent: hexane–AcOEt (5:1, v/v)] to give **50** (1.6 g, 3.34 mmol, 24%) as a colorless amorphous powder. IR ν_{max} (KBr) cm^{-1}: 1725, 1670 (C=O). ^1H NMR ($CDCl_3$) δ 1.03 (9H, s), 1.23 (3H, t, J = 7.2 Hz), 2.74 (1H, dd, J = 6.6, 17.2 Hz), 2.97 (1H, dd, J = 7.8, 17.2 Hz), 3.72 (1H, d, J = 13.4 Hz), 3.94–4.14 (5H, m), 4.42 (1H, dd, J = 1.4, 11.4 Hz), 4.67 (1H, dd, J = 1.4, 8.8 Hz), 7.01 (1H, d, J = 2.2 Hz), 7.23–7.43 (6H, m).

(3,6-*trans*)-8-Chloro-6-(2-chlorophenyl)-1-neopentyl-2-oxo-2,3,5,6-tetrahydro-1*H*-4,1-benzoxazocine-3-acetic Acid (10). Concentrated HCl (10 mL) was added to a solution of **50** (1.2 g, 2.51 mmol) in dioxane (20 mL). After being refluxed for 3 h, the mixture was diluted with CH_2Cl_2 (100 mL), washed with water and brine, dried over Na_2SO_4 and then concentrated in vacuo. The residue was recrystallized from CH_2Cl_2–petroleum ether (1:10, v/v) to give **10** (0.23 g, 0.511 mmol, 20%) as colorless needles. Mp 127–133 °C (CH_2Cl_2–petroleum ether). IR ν_{max} (KBr) cm^{-1}: 3600–2400 (br, COOH), 1710, 1660 (C=O). ^1H NMR ($CDCl_3$) δ 1.03 (9H, s), 2.81 (1H, dd, J = 6.6, 17.4 Hz), 2.97 (1H, dd, J = 7.0, 17.4 Hz), 3.73 (1H, d, J = 13.8 Hz), 3.93–4.09 (3H, m), 4.43 (1H, d, J = 11.0 Hz), 4.66 (1H, d, J = 8.2 Hz), 7.00 (1H, d, J = 2.6 Hz), 7.23–7.44 (6H, m). Anal. calcd for $C_{23}H_{25}Cl_2NO_4 \cdot H_2O$: C, 58.98; H, 5.81; N, 2.99. Found: C, 58.82; H, 5.43; N, 2.97.

Ethyl 6-chloro-4-(2-chlorophenyl)-2-oxo-1,2-dihyroquinoline-3-carboxylate (51). A mixture of **12** (5 g, 18.8 mmol), diethyl malonate (4.5 mL, 26.3 mmol) and DBU (0.28 mL, 2.6 mmol) was heated for 8 h at 190–200 °C. The resulting mixture was diluted with AcOEt. The solution was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated. The residue was chromatographed [eluent: hexane–AcOEt (3:2, v/v)] to give **51** (4.3 g, 11.9 mmol, 63%) as colorless crystals. IR ν_{max} (KBr) cm^{-1}: 1730, 1710, 1650(C=O). ^1H NMR ($CDCl_3$) δ: 0.97 (3H, t, J = 7.2 Hz), 4.0–4.2 (2H, m), 7.02 (1H, d, J = 2.1 Hz), 7.2–7.6 (6H, m), 12.6 (1H, br).

Ethyl 6-chloro-4-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (52). A mixture of **51** (2.5 g, 6.90 mmol), isobutylbromide (1.5 mL, 13.8 mmol), KI (2.2 g, 10.4 mmol), K_2CO_3 (1.9 g, 13.8 mmol) and DMF (20 mL) was stirred for 3 days at room teperature. The resulting mixture was diluted with AcOEt. The solution was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography [eluent: hexane–AcOEt (3:2, v/v)] to give **52** (1.4 g, 3.35 mmol, 49%) as colorless prisms. Mp 117–119 °C (hexane–AcOEt). IR ν_{max} (KBr) cm^{-1}: 1730, 1645 (C=O). ^1H NMR ($CDCl_3$) δ: 0.9–1.2 (9H, m), 2.1–2.4 (1H, m), 3.9–4.35 (4H, m), 7.03 (1H, d, $J=2.4$ Hz), 7.25–7.60 (6H, m). Anal. calcd for $C_{22}H_{21}Cl_2NO_3$: C, 63.17; H, 5.06; N, 3.35. Found : C, 63.03; H, 5.34; N, 3.17.

Ethyl (3,4-*trans*)-6-chloro-4-(2-chlorophenyl)-1-isobutyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (53). $LiAlH_4$ (0.18 g, 4.84 mmol) was added to an ice-cooled solution of **52** (1.4 g, 3.35 mmol) in THF (20 mL). The mixture was stirred for 20 min at ice-bath temperature. Water (2 mL) was added to the mixture. The resulting mixture was diluted with AcOEt. The mixture was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography [eluent: hexane–AcOEt (10:1, v/v)] to give **53** (0.65 g, 1.55 mmol, 46%) as a colorless oil. IR ν_{max} (neat) cm^{-1}: 1740, 1680 (C=O). ^1H NMR ($CDCl_3$) δ 0.95 (3H, d, $J=6.8$ Hz), 1.00 (3H, d, $J=6.8$ Hz), 1.11 (3H, t, $J=7.1$ Hz), 2.0–2.25 (1H, m), 3.76 (1H, dd, $J=14.2$, 7.2 Hz), 3.94 (1H, dd, $J=14.2$, 7.4 Hz), 4.02 (1H, d, $J=7.4$ Hz), 4.0–4.2 (2H, m), 5.09 (1H, d, $J=7.4$ Hz), 6.9–7.5 (7H, m).

Ethyl 6-chloro-4-(2-chlorophenyl)-3-ethoxycarbony-1-isobutyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-acetate (54). NaH (68 mg, 1.70 mmol) was added to an ice-cooled solution of **53** (0.65 g, 1.55 mmol) and $BrCH_2COOEt$ (0.22 mL, 2.17 mmol) in DMF (10 mL). After being stirred for 8 h at room temperature, the mixture was diluted with AcOEt. The mixture was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography [eluent: hexane–AcOEt (5:1, v/v)] to give **54** (0.65 g, 1.28 mmol, 83%) as a colorless oil. IR ν_{max} (neat) cm^{-1}: 1730, 1665 (C=O). ^1H NMR ($CDCl_3$) δ 0.9–1.1 (9H, m), 1.23 (3H, t, J=7.1 Hz), 2.0–2.3 (1H, m), 2.66 (1H, d, $J=17.7$ Hz), 3.22 (1H, d, $J=17.7$ Hz), 3.78 (1H, dd, $J=14.2$, 6.2 Hz), 3.9–4.3 (5H, m), 5.73 (1H, s), 6.63 (1H, s), 6.95–7.6 (6H, m). MS (m/e) 505 (M+).

(3,4-*trans*)-6-Chloro-4-(2-chlorophenyl)-3-ethoxycarbony-1-isobutyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-acetic acid (11). A mixture of **54** (0.65 g, 1.28 mmol), 85% KOH (0.42 g, 6.42 mmol), EtOH (10 mL) and water (10 mL) was refluxed overnight. The mixture was acidified with 1 N HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and then concentrated. The residue was subjected to column chromatography [eluent: hexane–CH_2Cl_2 MeOH (5:5:1, v/v)] to give crude **11**. A mixture of the crude **11**, MeI (0.08 mL, 1.28 mmol), K_2CO_3 (0.18 g, 7.62 mmol) and DMF (10 mL) was stirred for 1 h. The mixture was diluted with AcOEt. The mixture was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated. The residue was chromatographed [eluent: hexane–AcOEt (5:1, v/v)] to give the methyl ester of **11** (0.31 g, 0.738 mmol). A mixture of the methyl ester, K_2CO_3 (0.2 g, 1.48 mmol), MeOH (10 mL) and water (10 mL) was refluxed for 1 h. The resulting mixture was acidified with 1 N HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and then concentrated to give **11** (0.20 g, 0.492 mmol, 38%) as colorless crystals. Mp 131–133 °C (hexane–AcOEt). IR ν_{max} (KBr) cm^{-1}: 1715, 1665 (C=O). ^1H NMR ($CDCl_3$) δ 0.93 (3H, d, $J=6.6$ Hz), 0.96 (3H, d, $J=7.0$ Hz), 1.9–2.2 (1H, m), 2.34 (1H, dd, $J=16.4$, 4.0 Hz), 2.62 (1H, dd, $J=14.4$, 8.8 Hz), 3.35–3.55 (1H, m), 4.08 (1H, dd, $J=14.4$, 8.8 Hz), 4.75 (1H, d, $J=13.4$ Hz), 6.5–6.6 (1H, m), 6.9–7.6 (6H, m). Anal. calcd for $C_{21}H_{21}Cl_2NO_3$: C, 62.08; H, 5.21; N, 3.45. Found : C, 62.18; H, 5.42; N, 3.34.

Single-crystal X-ray analysis of 1a, 2, 4, 5, 7 and 10

Crystals of **1a**, **2**, **4**, **5**, **7** and **10** were grown from methanol. Data were collected on a diffractometer, Rigaku AFC5R, and corrected for Lorentz and polarization factors. Absorption correction was not applied. The structures were determined by direct methods with the aid of TEXSAN[23] and refined by CRYLSQ[24] in the XTAL package. The parameters refined include the coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were included using a riding model in which the distances from the bonded carbon atoms were fixed at 1.09 Å. Thermal parameters of hydrogen atoms were taken from their bonded atoms as U_{iso} and fixed through the next several cycles of refinement. The final R factors were 0.063, 0.082, 0.048, 0.053, 0.073 and 0.085, respectively. In the case of compound **10**, the chloro atom existed on both sides of the 6-phenyl ring in the ratio of 4:1. It was suggested that two comformers resulted from turnover of the 6-phenyl ring existed in a single crystal, and the ratio of these comformers was 4:1. Figure 2 shows only the chloro atom of major comformer. Crystal data, conditions of data collection, atomic coordinates, thermal parameters, bond distances, bond angles, and torsion angles are available as supporting information.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 164786 (**1a**), CCDC164787 (**2**), CCDC164788 (**4**), CCDC164789 (**5**), CCDC164790 (**7**) and CCDC164791 (**10**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

Animals and materials

Animals were supplied by Clea, Japan, Inc. RS-[2-^{14}C] mevalonolactone and [1-^3H]-farnesyl pyrophosphate

were purchased from New England Nuclear. [2-^{14}C] mevalonic acid was synthesized from [2-^{14}C] mevalonolactone by saponification with potassium hydroxide. [2-^{14}C] Sodium acetate was purchased from Amersham. Farnesyl pyrophosphate was synthesized by the method described by V. J. Davisson and coworkers[25] (Nemoto & Co.). HepG2 cells were supplied by ATCC. Fetal bovine serum (FBS) and Dulbecco's modified Eagle's medium (DMEM) were purchased from GIBCO. Human lipoprotein deficient serum (human LPDS) was purchased from Sigma. All other reagents were supplied by Wako Pure Chemical Industries.

Preparation of rat squalene synthase

An SD male rat (6 weeks old) was killed by bleeding, and its liver was excised. About 10 g of the liver was washed with a saline solution cooled with ice, which was then homogenized in 15 mL of an ice-cooled buffer solution [100 mM potassium phosphate (pH 7.4), 15 mM nicotinamide, 2 mM $MgCl_2$], followed by centrifugation for 20 minutes at 10,000*g* (4 °C). The supernatant layer was separated and subjected to further centrifugation for 90 min at 105,000*g* (4 °C). The sediment was then suspended in an ice-cooled 100 mM potassium phosphate buffer solution (pH 7.4), which was again subjected to centrifugation for 90 min at 105,000*g* (4 °C). The sediment thus obtained (microsome fraction) was suspended in an ice-cooled 100 mM potassium phosphate buffer (pH 7.4) (about 40 mg/mL protein concentration, determined using BCA protein assay kit of Pierce Co., Ltd.). This suspension was used as the enzyme solution.

Preparation of human squalene synthase

HepG2 cells (about 1×10^9 cells) obtained by incubation (37 °C in the presence of 5% CO_2) in a DMEM contains 10% FBS, penicillin G (100 units/mL) and streptomycin (10 μg/mL) were suspended in 10 mL of ice-cooled buffer solution [100 mM potassium phosphate buffer (pH 7.4), 30 mM nicotinamide and 2.5 mM $MgCl_2$]. The cells were crashed by means of ultrasonication (for 30 s, twice). From the sonicate thus obtained, the microsome fraction was obtained by the same procedure as in preparation of rat-derived enzyme, which was suspended in an ice-cooled 100 mM potassium phosphate buffer (pH 7.4) (about 4 mg/mL protein concentration). This suspension was used as the enzyme solution.

Assay of squalene synthase inhibitory activity

Squalene synthase activity was monitored by the formation of [^{3}H]squalene from [1-^{3}H]FPP. Fifty microliter of assay mixture included 5 μM [1-^{3}H]FPP (25 μCi/mol), 1 mM NADPH, 5 mM $MgCl_2$, 6 mM glutathione, 100 mM buffer solution of potassium phosphate (pH 7.4), the test compound dissolved in DMSO (a final concentration of DMSO was 2%) and enzyme solution prepared from rat or HepG2 cells (protein content 0.8 μg). The assay ran 45 min at 37 °C and stopped by adding 150 μL of $CHCl_3$–MeOH (1:2) containing 0.2% cold squalene as carrier. Aqueous solution of 3 N NaOH (50 μM) and $CHCl_3$ (50 μM) were added to the mixture. The chloroform layer containing the reaction mixture having squalene as the principal component and 3 mL of toluene-based liquid scintillator were mixed, and its radioactivuty was determined by means of a liquid scintillation counter. The squalene synthase inhibitory activity was expressed in terms of the concentration of the test compound inhibiting by 50% the radioactivity taken into the chloroform layer [IC_{50}, molar concentration (M)].

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