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Discovery of a new 2-aminobenzhydrol template for highly potent squalene synthase inhibitors

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ABSTRACT

To obtain small and efficient squalene synthase inhibitors, a flexible 2-aminobenzhydrol open form structure was designed and showed potent inhibitory activity comparable to 4,1-benzoxazepin compounds. Further chemical modification led to the discovery of a novel template with a strong squalene synthase inhibitory activity, and its basic structure–activity relationship was revealed. The X-ray crystallographic data of compound **12** bound to the active site of squalene synthase provided an important insight into the binding mode of this alternative template that formed 11-membered ring conformations with an intramolecular hydrogen bond.

1. Introduction

The serum level of low-density lipoprotein (LDL) is one of the important factors associated with coronary heart disease (CHD). In industrialized countries, CHD remains one of the most common causes of mortality. Patients who have higher serum levels of LDL cholesterol are generally treated with statins,[1] which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in hepatic cholesterol biosynthesis.

However, statins also have a potential risk of adverse effects, such as mytotoxicity, muscle pain and in very rare cases, rhabodmyolysis.[2] These adverse effects might be caused from the inhibition of HMG-CoA reductase not only to block the synthesis of cholesterol, but also to inhibit the biosynthesis of physiologically essential isoprenoid-derived molecules. As a general trend, statins have become increasingly recognized as an imperfect medicine for all types of hypercholesterolemia, and an alternative antihyperlipidemic agent which does not inhibit isoprenoid biosynthesis is desired in medical practice.

It is known that squalene synthase converts two molecules of farnesyl pyrophosphates into a squalene, which is downstream of HMG-CoA reductase in the cholesterol biosynthesis cascade.[3] This indicates that an inhibitor of the enzyme does not interfere with the biosynthesis of many highly demanded non-steroidal isoprenoid molecules, such as geranylgeranyl pyrophosphate and ubiquinone (coenzyme Q).[4] Therefore, squalene synthase is an interesting target for the development of a safer cholesterol-lowering medicine, and we have started to explore this field.[5]

Our research group already disclosed a series of novel squalene synthase inhibitors, as exemplified by compound **1**, which has a sub-nano molar grade of IC_{50} against rat squalene synthase.[6] Although these inhibitors have strong inhibitory activities in vitro, they failed to show sufficient efficacy in vivo at reasonable doses. This is presumably because of their extremely high protein binding affinities, which is due to their high lipophilicity and flat naphthalene rings, to inhibit cholesterol biosynthesis sufficiently in hepatic cells in vivo.

In 2001, the X-ray crystal structures of squalene synthase soluble domain with inhibitors, compound **1**, and Takeda's compound **2** (Fig. 1)[7] were reported by our research group.[8]

From the analytical data, two aryl rings of compounds **1** and **2** crossed each other. These aromatic rings were finely superimposed and similarly interacted with the lipophilic pockets of squalene

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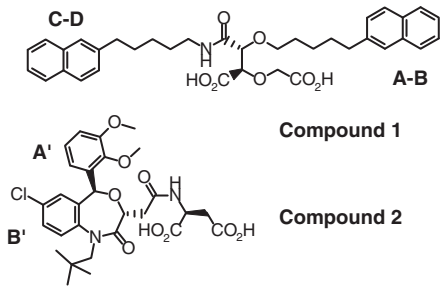


Figure 1.

synthase (Figs. 2a and b). Ring **A**–**B** of compound **1** and Ring **B**′ of compound **2** were surrounded by the residues of Val 179, Leu 183, Met 207, Gly 208, Leu 211, Tyr 276, Phe 288, and Pro292. Ring **C**–**D** of compound **1** and Ring **A**′ of compound **2** were also bound within a lipophilic cavity formed by the residues of Phe 54, Val 69, Phe 72, Tyr 73, Leu 76, Val 179, Leu 183, and Phe 288.

These two lipophilic cavities are important targets for the inhibition of squalene synthase. Thus, it appears to be a rational approach to identify alternative inhibitors that directly link these two aromatic rings (Scheme 1). Therefore, we designed and synthesized a flexible, two aromatic rings linked, open form template to afford a small and efficacious squalene synthase inhibitor. To prevent a repeat of the failure of compound **1**, lower lipophilic inhibitors were designed such that phenyl rings were selected instead of naphthalene rings and the exposed hydroxyl group was incorporated to increase hydrophilicity.

In this article, we will describe in detail the discovery of the open form template, which possesses a 2-aminobenzhydrol core structure, as well as its structure–activity relationship (SAR) as a squalene synthase inhibitor.

2. Results

2.1. Chemistry

A series of the novel open form squalene synthase inhibitors were prepared from benzophenone as shown in Scheme 2. Commercially available aminobenzophenone **3** was reduced by sodium borohydrate ($NaBH_4$) to afford 2-aminobenzhydrol **4**, followed by

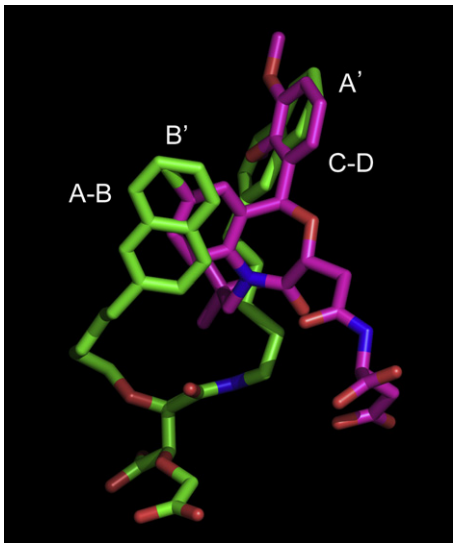


Figure 2b. X-ray crystal structure of compound **1** (green carbons, PDB code: 3Q30) overlaid with the bound crystal structure of **2** (magenta carbons, PDB code: 3Q2Z) (protein not shown).

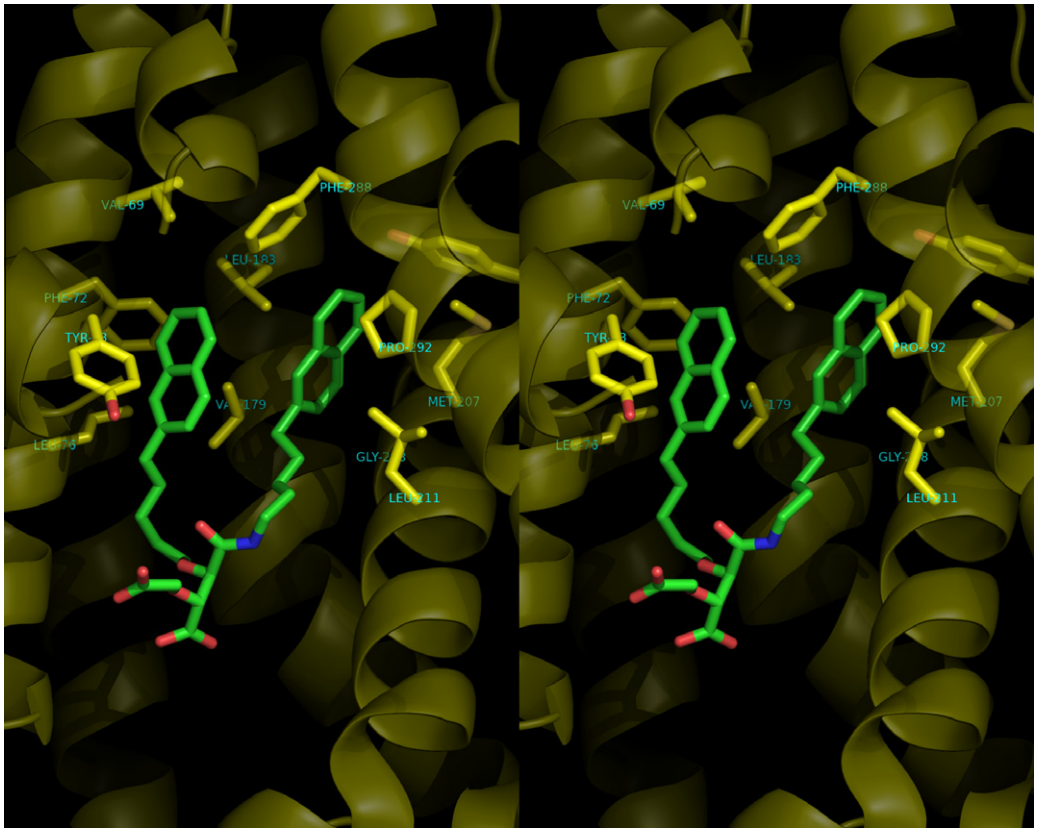
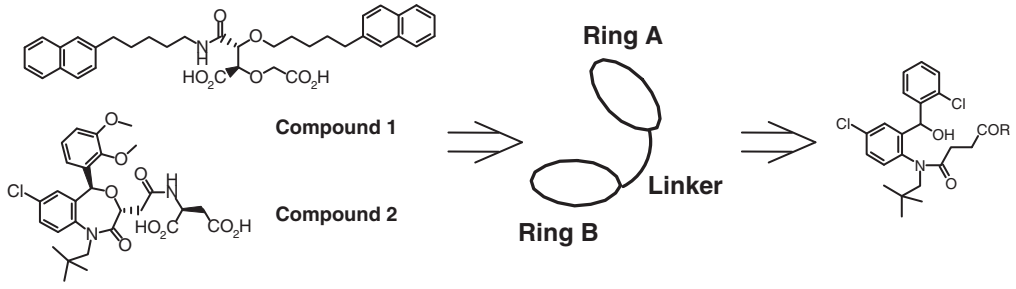
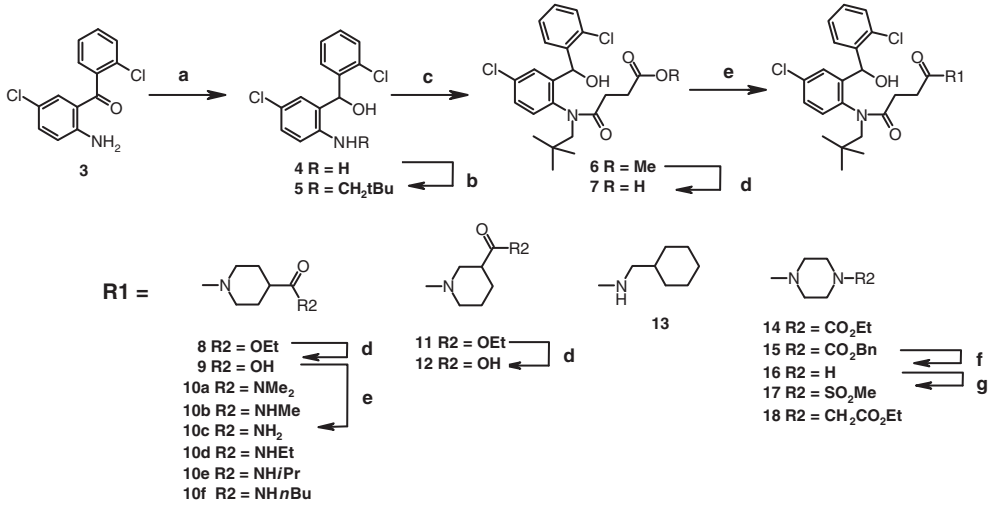


Figure 2a. Crystal structure of compound **1** bound in two lipophilic pockets of squalene synthase (PDB code: 3Q30).



Scheme 1.



Scheme 2. Synthesis of open form compounds **8**–**18**. Reagents and conditions: (a) $NaBH_4$, MeOH; (b) *t*BuCHO, $NaBH_4$, AcOH; (c) methyl 4-chloro-4-oxobutanoate, $NaHCO_3$, DCM; (d) K_2CO_3, MeOH–H_2O; (e) amine, EDC, HOBt, DCM; (f) H_2, Pd–C, MeOH, rt; (g) MsCl, Et_3N, DCM.

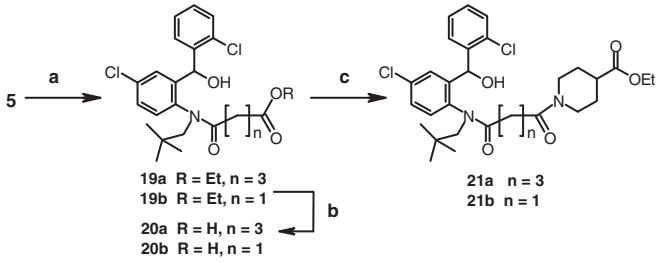
reductive aminoalkylation to obtain neopentyl amine **5** in good yield. Amide **6** was produced by the treatment of **5** with methyl succinyl chloride. Saponification of **6** afforded the desired carboxylic acid **7**. Succinic diamide **8** was prepared by the condensation of **7** with isonipecotic ester using *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide (EDC), and subsequent hydrolysis provided acid **9**. EDC coupling of **9** with various amines afforded a series of amides **10a**–**f**. Nipecotic acid derivatives **11** and **12** were also prepared similarly.

Piperazine derivatives **14**–**18** were prepared from acid **7**. Hydrogenation of benzyl carbamate **15** using 10% Pd/C as a catalyst furnished amine **16**, and the following methanesulfonylation gave **17**. Amine **18** was produced by the condensation of acid **7** and 4-ethoxycarbonylmethyl piperazine.

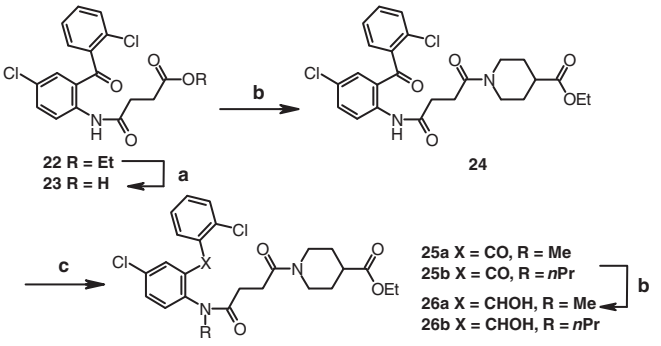
Neopentyl amine **5** was coupled with malonyl chloride and glutaryl chloride to afford amides **19a** and **19b**, respectively. Sequential hydrolysis and amidation with ethyl isonipecotate yielded **21a** and **21b** (Scheme 3).

N-Methyl and *N*-propyl derivatives **26a** and **26b** were prepared as outlined in Scheme 4. Saponification of **22**, followed by condensation gave isonipecotate **24**. N-Alkylation of **24** with alkyl iodides and sodium hydride afforded **25a** and **25b**, and the following $NaBH_4$ reduction led to the desired benzhydroles **26a** and **26b**, respectively.

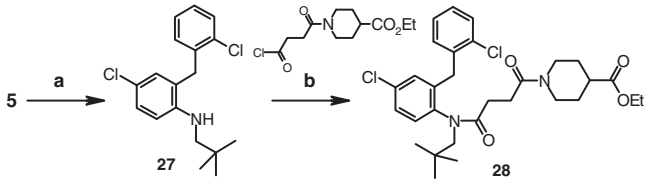
Dehydroxy analog **28** was prepared from benzhydrol **5**. The key dehydration was carried out by triphenylphosphine oxide, trifluoromethanesulfonic anhydride, and $NaBH_4$ in 87% yield (Scheme 5).[9] The upper ring-modified compounds were prepared similarly from benzophenones **29A**–**C** and aniline **32** as shown in Scheme 6.



Scheme 3. Synthesis of various length compounds. Reagents and conditions: (a) acid chloride, $NaHCO_3$, DCM; (b) Na_2CO_3, MeOH–H_2O, rt; (c) amine, EDC, HOBt, DCM.



Scheme 4. Synthesis of smaller alkyl compounds. Reagents and conditions: (a) K_2CO_3, MeOH–H_2O, 60 °C; (b) amine, EDC, HOBt, DCM; (c) alkyl iodide, NaH, DMF, 0 °C; (d) $NaBH_4$, EtOH, 0 °C.



Scheme 5. Synthesis of non-hydroxyl compounds. Reagents and conditions: (a) Ph_3PO, Tf_2O, $NaBH_4$, DCM, 87%; (b) acid chloride, $NaHCO_3$, DCM.

2-Aminobenzhydrols **34D–K** were prepared from various aldehydes and pivaloyl amide **33**.

2.2. Evaluation and discussion

The biological activities of the new compounds are shown in Table 1. The initially prepared 2-aminobenzhydrol compound **6** and its acid **7** had very weak squalene synthase inhibitory (SSI) activities[10] (IC_{50} = 1.7 and 6.5 μM, respectively) compared with 4,1-benzoxazapin compounds (IC_{50} = 11 nM in Takeda's patent,[7] which might be ascribed to the relative conformational change of their lipophilic parts.

From the X-ray crystal structure studies,[8] the carboxylic acid of compound **7** seems to face the solvent side through the active domain pocket of squalene synthase, the shape resembles a valley. We then attempted to incorporate a cyclic substituent into the carboxylic acid unit by an amide bond, which was expected to interact with the side walls of the pocket.

Isonipecotic ester **8** showed dramatically improved SSI activity (IC_{50} = 0.85 nM) even though the precursor acid **7** had less activity. A novel template with potent activity comparable to 4,1-benzoxazepin compounds has been found.

To obtain the structure–activity relationship (SAR), prepared derivatives were evaluated in terms of their SSI activities and cholesterol synthesis inhibitory (CSI) activities in rat hepatic cells. 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. Hence, the early stage of our research effort was focused on improving both SSI and CSI activities.

Interestingly, the SSI activity of isonipecotic acid **9** was dramatically reduced from its ester **8**. In contrast, nipecotic acid **12** and its ester **11** showed an inverse relationship in which acid **12** had more potent SSI activity than ester **11**. For SSI activity, the lipophilic substituent, like the ester group, might favor the 4th position of the piperidine ring; and the hydrophilic substitute, like carboxylic acid, might favor the 3rd position of the piperidine ring.

Surprisingly, the CSI activity of acid **9** was seven-fold stronger than that of ester **8**, even though the SSI activity of ester **8** was one hundred fifty-fold stronger than that of acid **9**. With regard to the CSI/SSI ratio, carboxylic acid **9** and **12** showed better value.

In our speculation, the carboxylic part of **9** and **12** might be recognized by a cell surface anion transporter,[11] and these compounds were well ingested into hepatic cells. In contrast, extremely high lipophilic compound **13** showed good CSI/SSI ratio; however, it could be due to its high cell permeability. Further investigation needs to be performed to verify our hypothesis.

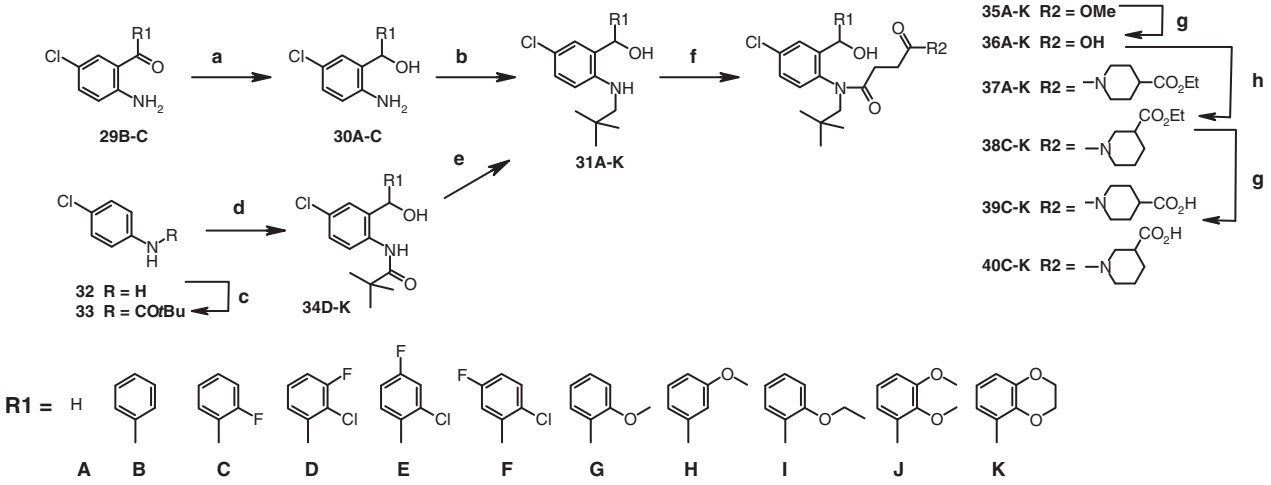
As a result of the modification of the isonipecotic acid part, all compounds showed moderate to strong SSI activities. The activities of mono-substituted isonipecotic amides (**10b**, **d**, **e**, **f**) were ten-fold higher than those of non- and di-substituted amides (**10a**, **c**). These data revealed that SSI activity does not depend on the size of the alkyl substituents of isonipecotic amides.

Piperazine carbamates **14**, **15** and ethoxy carbonyl methyl piperazine **18**, which has a basic nitrogen, were more potent than the non-substituted piperazine **16** and methyl sulfonamide **17**.

To identify the essential part of compound **8** for enzyme inhibition, the following conversions were attempted: adjustment of the length of the methylene side chain between two amide residues, replacement of the large neopentyl part to less lipophilic methyl or propyl groups, and the removal of the hydroxyl group.

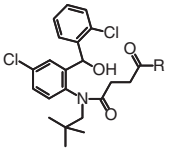
Extended three-carbon-linked pentanoic amide **21a** and shortened one-carbon-linked maronic amide **21b**, in addition to the smaller alkyl compounds **26a**, **b**, showed very weak SSI activities compared with compound **8**. Dehydroxy compound **28** also showed weak SSI activity (Table 2). It would appear that the two-carbon-linked succinic amide side chain and the bulky alkyl part are necessary to maintain the appropriate conformation of this template.

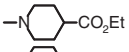
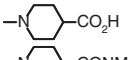
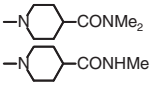
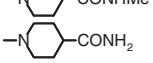
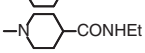
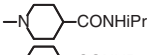
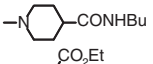
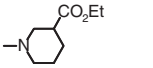
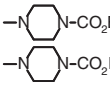
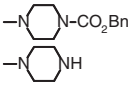
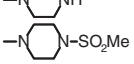
To investigate the effect of substituents on the upper benzene ring, a series of compounds were prepared and evaluated (Table 3). Compound **37A**, which has no upper ring, and non-substituted benzene compound **37B** showed no measurable and very weak SSI activities, respectively. On the other hand, 2-fluorobenzene isonipecotic ester **37C** demonstrated the highest SSI activity with an



Scheme 6. Synthesis of various upper ring compounds. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C; (b) *t*BuCHO, $NaBH_4$, AcOH; (c) pivaloyl chloride, DMAP, Et_3N, DCM; (d) *sec*BuLi, THF then aldehyde −78 °C to rt; (e) Red-Al, THF, rt; (f) methyl 4-chloro-4-oxobutanoate, $NaHCO_3$, DCM, rt; (g) K_2CO_3, MeOH–H_2O, 50 °C; (h) amine, EDC, HOBt, DCM.

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



Compound	R	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)	CSI/SSI ratio
6	OMe	1700	—	—
7	OH	6500	—	—
8		0.85	1700	200
9		130	250	1.9
10a		97	—	—
10b		1.3	900	692
10c		280	—	—
10d		2.4	—	—
10e		3.7	1600	432
10f		1.6	2000	1250
11		410	—	—
12		20	270	13.5
13		220	2600	11.8
14		2.3	—	—
15		1.1	—	—
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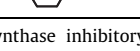
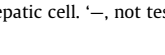
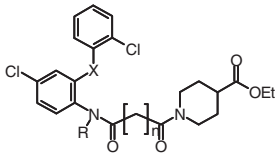
17		260	—	—
18		7.9	1400	177

SSI: Squalene synthase inhibitory activity. CSI: cholesterol synthase inhibitory activity in rat hepatic cell. '—, not tested'.

Table 2
Evaluation of squalene synthase inhibitory (SSI) activities and cholesterol synthesis inhibitory (CSI) activities (part 2)



Compound	X	R	*n*	SSI (IC_{50}, nM)
8	CHOH	$CH_2{}^tBu$	2	8.5
21a	CHOH	$CH_2{}^tBu$	3	>6000
21b	CHOH	$CH_2{}^tBu$	1	>600
26a	CHOH	Me	2	21,000
26b	CHOH	*n*Pr	2	600
28	CH_2	$CH_2{}^tBu$	2	650

IC_{50} value of 0.45 nM. The other 2-fluorobernzene derivatives **38–40C** showed lower SSI activities than 2-chlorobenzene compounds.

2-Chloro-3-fluorobenzene series **D** showed higher SSI activities than 2-chloro compounds. However, 2-chloro-4-fluorobenzene series **E** demonstrated drastically decreased inhibitory potency and 2-chloro-5-fluorobenzene series **F** showed no SSI activities. These results suggest that substitution on the 4- and 5-positions of the upper benzene ring would sterically disfavor the lipophilic cavity of squalene synthase.

Furthermore, 2-methoxy, 2,3-dimethoxybenzene, and 1,4-benzodioxane derivatives (**G**, **J**, **K**) showed strong SSI activities. In particular, 2-methoxybenzene and 1,4-benzodioxane derivatives (**G**, **K**) had excellent CSI activities as well. In general, there was a tendency for lower *C* log *P* compounds to have stronger CSI activities.

As described above, the present results suggest that the upper ring is crucial for the inhibition of squalene synthase. Also the hydroxyl part, succinic amide side chain lengths, and a large alkyl substituent (e.g., neopentyl part) are very important for maintaining strong SSI activity.

Most benzhydrol derivatives, as represented by compound **9**, were composed of a pair of atrop isomers.[12] These two rotamers are created by a high rotational barrier around the C–N bond between the amide nitrogen and the aryl ring because the bulky neopentyl group and *ortho*-substituted aryl ring are located on the nitrogen of the amide bond.

To elucidate the absolute structure of the active isomer, we carried out X-ray structure analysis of squalene synthase co-crystallized with racemic inhibitor **12**. The results showed that only the (*S*)-hydroxyl-(*aR*)-atrop isomer was buried in the squalene synthase lipophilic cavities (Fig. 3).[13] Surprisingly, an intramolecular hydrogen bonding interaction between the proton of the hydroxyl group and the oxygen atom of the side chain amide was observed. Thus, it can be predicted that the improvement of SSI activity depends on the formation of this intramolecular hydrogen bond, which results from the increased dipole moment of the carbonyl part, due to the formation of an amide bond by the introduction of the nipecotin and iso-nipecotin parts.

3. Conclusion

We designed a novel 2-aminobenzhydrol template and revealed its high potential as a squalene synthase inhibitor. The finding of compound **8**, showing strong inhibitory activity comparable to 4,1-benzoxazepin compounds, was taken as a starting point for our research. In subsequent investigations to clarify the SAR of our newly synthesized template, carboxylic acid compounds showed higher CSI activities in rat hepatic cells. In particular, 2-methoxybenzene and 1,4-benzodioxane derivatives demonstrated strong SSI and CSI activities. Finally, the unique active binding formation of our new template was elucidated. The X-ray analysis of squalene synthase co-crystallized with racemic atrop mixture **12** showed that the (*S*)-hydroxyl-(*aR*)-atrop isomer of **12** was buried in the lipophilic cavity of the enzyme, and formed 11-membered ring conformations with an intramolecular hydrogen bond between the hydroxyl group and the side chain amide carbonyl oxygen. Further structure optimization and biological evaluations of the new template will be reported in due course.

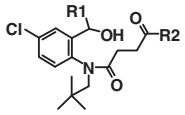
4. Experimental

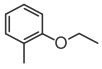
4.1. Chemistry

4.1.1. General

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. ^1H NMR spectra were recorded on JEOL JNM-EX400 spectrometers, and chemical shifts are given in ppm from tetramethylsilane as an internal standard. FAB mass spectra were recorded on a JEOL JMS-HX110 spectrometer. HR-FAB mass spectra were recorded

Table 3
Evaluation of squalene synthase inhibitory (SSI) activities and cholesterol synthesis inhibitory (CSI) activities (part 3)



	Compound R1	Compound R2						
		37A-K	38C-K	39C-K		40C-K		
		SSI (nM)	SSI (nM)	SSI (nM)	CSI (nM)	SSI (nM)	CSI (nM)	*C* log *P*
		0.85	410	130	250	20	270	2.98
A	H	>6000	—	—	—	—	—	1.81
B		770	—	—	—	—	—	2.42
C		0.45	>600	1700	>10,000	290	200	2.52
D		7.2	28	17	920	8.4	1300	3.00
E		2	>600	>600	—	190	—	3.28
F		>600	>600	>600	—	>600	—	2.8
G		1.1	2.6	1.7	600	1.3	84	2.81
H		210	>600	>600	—	>600	—	2.35
I		410	>600	>600	—	>600	—	3.32
J		1.1	1.3	2.8	1600	2.0	1500	2.25
K		10	13	7	230	6.8	170	1.87

SSI: Squalene synthase inhibitory activity. CSI: Cholesterol synthase inhibitory activity in rat liver cell. '— not tested'. *C* log *P* was calculated using ACD/labs ver. 11.00. ACD/log *P* DB.

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 pre-coated TLC glass sheets with silica gel 60F254 or Whatman Partisil PLK5F with Silica gel 150 Å.

4.1.2. Methyl 4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (6)

An ice-cooled solution of {5-chloro-2-[(2,2-dimethylpropyl)amino]phenyl}(2-chlorophenyl)methanol (0.50 g, 1.5 mmol) in CH_2Cl_2 (50 ml) was added ethyl 4-chloro-4-oxobutanoate (0.23 g, 1.7 mmol) and $NaHCO_3$ (0.37 g, 4.4 mmol). After being stirred for 2 h at room temperature, the reaction was quenched with water. The organic material was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1:2–1:1 as eluent) to give compound **6** (0.41 g, 0.90 mmol, 61%) as a colorless powder. ^{1}H NMR ($CDCl_3$) δ 0.87 (0.88) (9H, s), 2.23–2.39 (3H, m), 2.80–2.90 (1H, m), 3.02 (2.98) (1H, d, J = 13.8 Hz), 3.66 (3.57)(3H, s), 4.44 (4.50) (1H, d, 13.8 Hz), 4.56–4.57 (1H, m), 6.13 (6.33) (1H, br s), 7.03 (1H, br s), 7.21–7.37 (5H, m), 7.73–7.78 (1H, m). IR (ATR) cm^{-1} 3359, 2950, 1745, 1650, 1432, 1168, 1027, 752, 420. Mp 130–132 °C. MS (FAB) m/z 452 $(M+H)^+$. Anal. Calcd for $C_{23}H_{27}NO_4Cl_2$: C, 61.07; H, 6.02; N, 3.10; Cl, 15.67. Found: C, 61.09; H, 6.04; N, 3.00; Cl, 15.78.

4.1.3. 4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (7)

Compound **6** (0.20 g, 0.44 mmol) was suspended in a mixture of MeOH (10 ml) and water (5 ml), and K_2CO_3 was added at room temperature, followed by stirring for 12 h at same temperature.

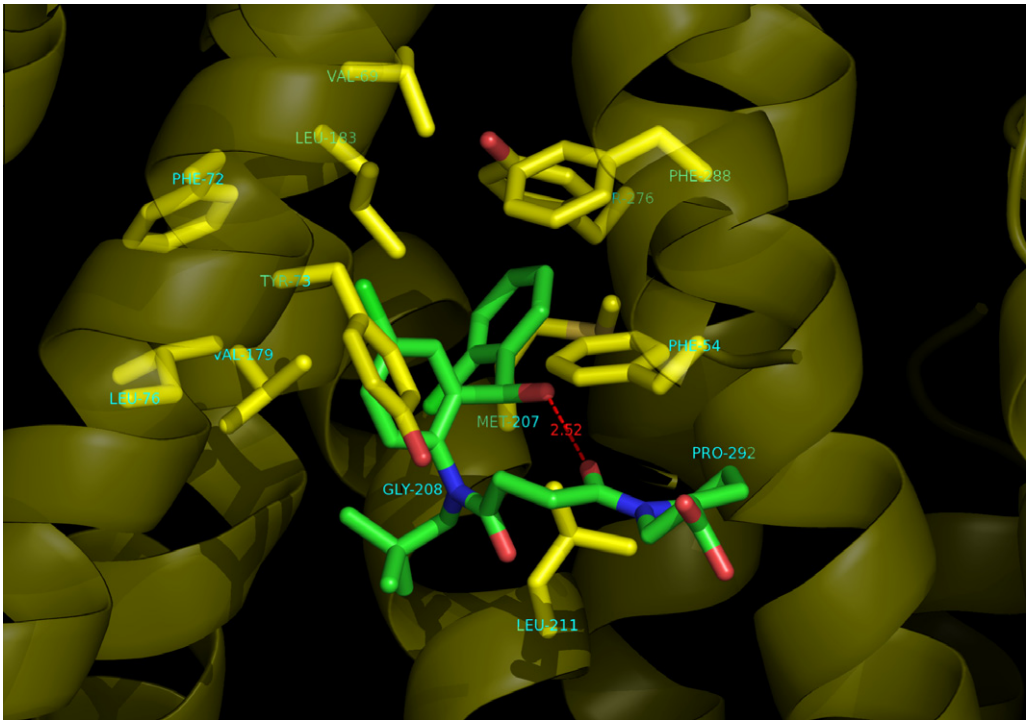


Figure 3. Crystal structure of compound **12** bound in squalene synthase. The intramolecular hydrogen bond between the proton of the hydroxyl group and the oxygen atom of side chain amide are highlighted (PDB code: 3ASX).

The solvent was removed under reduced pressure and was adding 1 N hydrochloric acid and CH_2Cl_2. The organics were extracted with CH_2Cl_2 (3 times). The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Then, the residue was washed with diethyl ether and hexane to give compound **7** as a colorless powder. ^{1}H NMR (DMSO-d_6) δ 0.76 (0.84) (9H, s), 1.06–1.27 (1H, m), 1.71–2.48 (3H, m), 2.54(3.03) (1H, d, J = 13.7 Hz), 4.20 (4.40) (1H, d, J = 13.7 Hz), 5.89 (6.09) (1H, br s), 6.27 (1H, br), 7.07 (1H, d, J = 2.4 Hz), 7.28–7.61 (6H, m). IR (ATR) cm^{-1} 2954, 1710, 1641, 1477, 1396, 1168, 1027, 750. Mp 78–80 °C. MS (ESI) m/z 438 (M+H)$^+$. Anal. Calcd for $C_{23}H_{27}NO_4Cl_2 \cdot 0.25H_2O$: C, 59.67; H, 5.80; N, 3.16; Cl, 16.01. Found: C, 59.36; H, 5.96; N, 2.96; Cl, 16.30.

4.1.4. Ethyl 1-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-4-carboxylate (8)

To a solution of compound **7** (0.16 g, 0.37 mmol) and isonipecotic acid ethyl ester (0.086 ml, 0.56 mmol) in CH_2Cl_2 was added WSCI·HCl (0.11 g) and HOBt (0.085 g), and then the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with water and the organics were extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, then concentrated in vacuo, and then the residue was purified with silica gel column chromatography (0–5% MeOH–CH_2Cl_2 as eluent) to give compound **8** (0.16 g, 0.28 mmol, 76%) as a colorless powder. ^{1}H NMR ($CDCl_3$) δ 0.91 (9H, s), 1.24 (1.26) (3H, t, J = 7.0 Hz), 1.80–1.97 (3H, m), 2.11–2.22 (2H, m), 2.38–2.52 (2H, m), 2.68–2.89 (2H, m), 3.07–3.19 (2H, m), 3.29 (3.28) (1H, d, J = 13.9 Hz), 3.83–3.84 (1H, m), 4.12 (4.14) (2H, q, J = 7.3 Hz), 4.26–4.40 (1H, m), 4.50 (4.51) (1H, d, J = 13.7 Hz), 6.16 (1H, s), 6.40 (6.30) (1H, d, J = 5.0 Hz), 6.98 (1H. d, J = 1.2 Hz), 7.30–7.42 (5H, m), 7.92–7.95 (1H, m). IR (ATR) cm^{-1} 3320, 2950, 1731, 1664, 1625, 1394, 1166, 1041, 746, 478. Mp 138–140 °C. MS (ESI) m/z 577 (M+H)$^+$. Anal. Calcd for $C_{30}H_{38}N_2O_5Cl_2$: C, 62.39; H, 6.63; N, 4.85; Cl, 12.28. Found: C, 62.24; H, 6.63; N, 4.79; Cl, 12.05.

4.1.5. 1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (9)

Compound **9** was prepared in a similar manner described for **8** in 88% yield as a colorless powder. ^{1}H NMR (DMSO-d_6) δ 0.73 (0.81) (9H, s), 1.27–1.46 (2H, m), 1.73–1.81 (2H, m), 1.96–2.17 (1H, m), 2.29–2.69 (5H, m), 2.97–3.06 (2H, m), 4.12–4.38 (3H, m), 5.88 (6.07) (1H, br s), 6.26 (1H, br s), 7.02 (1H, s), 7.26 (1H, s), 7.34–7.60 (5H, m). IR (ATR) cm^{-1} 2952, 1727, 1658, 1621, 1475, 1396, 1170, 1020, 744, 541, 420. Mp 168–170 °C. MS (ESI) m/z 549 (M+H)$^+$. Anal. Calcd for $C_{28}H_{34}N_2O_5Cl_2$: C, 61.20; H, 6.24; N, 5.10; Cl, 12.90. Found: C, 60.96; H, 6.29; N, 4.89; Cl, 12.69.

4.1.6. 1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-*N*,*N*-dimethylpiperidine-4-carboxamide (10a)

Compound **10a** was prepared from **9** in a similar manner described for **8** in 57% yield as a colorless powder. ^{1}H NMR ($CDCl_3$) δ 0.91 (9H, s), 1.69–1.76 (3H, m), 2.11–2.24 (2H, m), 2.41–2.49 (1H, m), 2.66–2.75 (2H, m), 2.93 (3H, s), 3.06 (3H, s), 3.10–3.17 (3H, m), 3.29 (3.27) (1H, d, J = 13.7 Hz), (3.95) 4.50 (1H, d, J = 13.7 Hz), 4.45–4.57 (1H, m), 6.15–6.18 (1H, m), 6.42 (6.25) (1H, d, J = 5.0 Hz), 6.97–6.99 (1H, m), 7.22–7.42 (5H, m), 7.95 (7.91) (1H, d, J = 7.7 Hz). IR (ATR) cm^{-1} 3278, 2948, 1639, 1617, 1398, 1276, 1027, 750, 482. Mp 197–199 °C. MS (FAB) m/z 576 (M+H)$^+$. Anal. Calcd for $C_{30}H_{39}N_3O_4Cl_2 \cdot 1.5H_2O$: C, 59.70; H, 7.01; N, 6.96; Cl, 11.75. Found: C, 59.96; H, 6.76; N, 6.84; Cl, 11.84.

4.1.7. 1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-*N*-methylpiperidine-4-carboxamide (10b)

Compound **10b** was prepared from **9** in a similar manner described for **8** in 61% yield as a colorless powder. ^{1}H NMR ($CDCl_3$) δ 0.90(0.91) (9H, s), 1.61–1.87 (3H, m), 2.11–2.47 (5H, m), 2.63–2.70 (1H, m), 2.81 (3H, s), 3.03–3.14 (2H, m), 3.28 (3.94) (1H, d,

J = 13.7 Hz), 4.49 (4.50) (1H, d, J = 13.8 Hz), 4.11–4.57 (1H, m), 5.42 (5.58) (1H, br), 6.14–6.17 (1H, m), 6.37 (6.28) (1H, d, J = 5.1 Hz), 6.98 (6.99) (1H, s), 7.22–7.41 (5H, m), 7.91–7.95 (1H, m). IR (ATR) cm^{-1} 3266, 2948, 1652, 1627, 1475, 1407, 1168, 1027, 833, 746, 534. Mp 130–132 °C. MS (FAB) m/z 562 $(M+H)^+$. Anal. Calcd for $C_{29}H_{37}N_3O_4Cl_2{\cdot}0.5H_2O$: C, 60.94; H, 6.70; N, 7.35; Cl, 12.41. Found: C, 60.84; H, 6.64; N, 7.21; Cl, 12.42.

4.1.8. 1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxamide (10c)

Compound **10c** was prepared from **9** in a similar manner described for **8** in 34% yield as a colorless powder. ^1H NMR ($CDCl_3$) δ 0.91 (9H, s), 1.84–1.95 (3H, m), 2.11–2.22 (2H, m), 2.35–2.48 (2H, m), 2.68–2.74 (2H, m), 3.03–3.17 (2H, m), 3.28 (3.27) (1H, d, J = 13.8 Hz), (3.94) 4.49 (1H, d, J = 13.8 Hz), 4.48–4.55 (1H, m), 5.28 (1H, br), 5.41 (5.60) (1H, br), 6.15–6.17 (1H, m), 6.34 (6.27) (1H, d, J = 5.0 Hz), 6.98 (1H, d, J = 1.7 Hz), 7.23–7.52 (4H, m), 7.91–7.94 (1H, m). IR (ATR) cm^{-1} 3324, 2950, 1677, 1654, 1614, 1475, 1402, 1270, 1027, 763, 570. Mp 90–92 °C. MS (ESI) m/z 548 $(M+H)^+$. Anal. Calcd for $C_{28}H_{35}N_3O_4Cl_2{\cdot}1.0H_2O$: C, 59.36; H, 6.58; N, 7.42; Cl, 12.52. Found: C, 59.12; H, 6.64; N, 7.21; Cl, 12.31.

4.1.9. 1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-*N*-ethylpiperidine-4-carboxamide (10d)

Compound **10d** was prepared from **9** in a similar manner described for **8** in 42% yield as a colorless powder. ^1H NMR ($CDCl_3$) δ 0.91 (0.90) (9H, s), 1.12 (1.14) (3H, t, J = 7.1 Hz), 1.78–2.66 (8H, m), 2.93–3.10 (3H, m), 3.29 (2H, q, J = 7.1 Hz), 3.26–3.31 (1H, m), 3.94 (1H, br d, J = 11.7 Hz), 4.50 (4.51) (1H, d, J = 13.6 Hz), 4.45–4.53 (1H, m), 5.38 (5.50) (1H, br), 6.15–6.17 (1H, m), 6.37 (6.28) (1H, d, J = 5.0 Hz), 6.98 (1H, s), 7.23–7.42 (5H, m), 7.91–7.95 (1H, m). IR (ATR) cm^{-1} 3266, 2954, 1662, 1625, 1475, 1394, 1180, 1029, 744, 576, 480. Mp 148–150 °C. MS (FAB) m/z 576 $(M+H)^+$. Anal. Calcd for $C_{30}H_{39}N_3O_4Cl_2{\cdot}0.5H_2O$: C, 61.53; H, 6.89; N, 7.18; Cl, 12.11. Found: C, 61.56; H, 6.81; N, 7.12; Cl, 12.22.

4.1.10. 1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-*N*-isopropylpiperidine-4-carboxamide (10e)

Compound **10e** was prepared from **9** in a similar manner described for **8** in 38% yield as a colorless powder. ^1H NMR ($CDCl_3$) δ 0.91 (9H, s), 1.12–1.16 (6H, m), 1.76–1.87 (3H, m), 2.11–2.66 (5H, m), 3.02–3.13 (3H, m), 3.28 (3.27) (1H, d, J = 13.8 Hz), 3.93 (1H, br d, J = 14.2 Hz), 4.03–4.06 (1H, m), 4.51 (4.50) (1H, d, J = 13.7 Hz), 4.48–4.56 (1H, m), 5.20 (5.29) (1H, br), 6.16 (1H, br), 6.37 (6.27) (1H, br), 6.98 (1H, s), 7.24–7.52 (5H, m), 7.91–7.95 (1H, m). IR (ATR) cm^{-1} 3282, 2958, 1662, 1623, 1473, 1394, 1166, 1027, 744, 541, 480. Mp 148–150 °C. MS (ESI) m/z 590 $(M+H)^+$. Anal. Calcd for $C_{31}H_{41}N_3O_4Cl_2{\cdot}0.25H_2O$: C, 62.57; H, 7.03; N, 7.06; Cl, 11.91. Found: C, 62.69; H, 6.98; N, 7.04; Cl, 11.53.

4.1.11. *N*-Butyl-1-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-4-carboxamide (10f)

Compound **10f** was prepared from **9** in a similar manner described for **8** in 45% yield as a colorless powder. ^1H NMR ($CDCl_3$) δ 0.91 (9H, s), 1.30–1.55 (7H, m), 1.78–1.88 (3H, m), 2.11–2.45 (4H, m), 2.64–2.70 (1H, m), 3.03–3.30 (6H, m), 3.94 (1H, br d, J = 13.2 Hz), 4.51 (4.50) (1H, d, J = 13.6 Hz), 4.48–4.51 (1H, m), 5.38 (5.51) (1H, br), 6.16 (1H, t, J = 4.9 Hz), 6.38 (6.28) (1H, d, J = 4.9 Hz), 6.98 (1H, d, J = 2.0 Hz), 7.22–7.42 (5H, m), 7.91–7.95 (1H, m). IR (ATR) cm^{-1} 3259, 2956, 1662, 1623, 1473, 1394, 1180, 1027, 744, 478, 422. Mp 178–180 °C. MS (ESI) m/z 604 $(M+H)^+$. Anal. Calcd for $C_{32}H_{43}N_3O_4Cl_2{\cdot}0.25H_2O$: C, 63.10; H, 7.20; N, 6.90; Cl, 11.64. Found: C, 63.09; H, 7.14; N, 6.88; Cl, 11.87.

4.1.12. Ethyl 1-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-3-carboxylate (11)

Compound **11** was prepared from **7** in a similar manner described for **8** in 85% yield as a colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.91 (0.90) (9H, s), 1.25 (1.26) (3H, t, J = 7.08 Hz), 1.35–2.21 (4H, m), 2.32–3.53 (6H, m), 3.73–4.19 (5H, m), 4.51 (4.50) (1H, d, J = 13.7 Hz), 4.48–4.75 (1H, m), 6.16–6.18 (1H, m), 6.28–6.40 (1H, m), 6.98 (1H, d, J = 1.95 Hz), 7.24–7.43 (5H, m), 7.91–7.96 (1H, m). IR (ATR) cm^{-1} 3345, 2950, 1727, 1627, 1168, 1027, 750, 480. MS (ESI) m/z 577 $(M+H)^+$. Anal. Calcd for $C_{30}H_{38}N_2O_5Cl_2$: C, 62.39; H, 6.63; N, 4.85; Cl, 12.28. Found: C, 62.02; H, 6.69; N, 4.71; Cl, 11.99.

4.1.13. 1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (12)

Compound **12** was prepared from **11** in a similar manner described for **7** in 68% yield as a colorless powder. ^1H NMR (DMSO-d_6) δ 0.69–0.86 (9H, m), 1.09–3.96 (13H, m), 4.08–4.42 (2H, m), 5.76–6.30 (2H, m), 6.98–7.73 (7H, m). IR (ATR) cm^{-1} 3326, 2952, 1621, 1475, 1394, 1168, 1029, 748, 480, 420. Mp 153–155 °C. MS (ESI) m/z 549 $(M+H)^+$. Anal. Calcd for $C_{28}H_{34}N_2O_5Cl_2{\cdot}2.1H_2O$: C, 57.26; H, 6.56; N, 4.77; Cl, 12.07. Found: C, 56.99; H, 6.32; N, 4.49; Cl, 11.86.

4.1.14. *N*-{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]-phenyl}-*N*′-(cyclohexylmethyl)-*N*-(2,2-dimethylpropyl)succinamide (13)

Compound **13** was prepared from **7** in a similar manner described for **8** in 65% yield as a colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.87 (9H, s), 0.88–1.68 (11H, m), 2.09–2.17 (1H, m), 2.23–2.28 (1H, m), 2.46–2.54 (1H, m), 2.63–2.77 (1H, m), 2.94–3.03 (1H, m), 3.03 (1H, d, J = 13.8 Hz), 3.14–3.21 (1H, m), 4.42 (4.52) (1H, d, J = 13.8 Hz), 5.70 (1H, m), 5.89 (1H, d, J = 5.3 Hz), 6.07 (1H, d, J = 5.3 Hz), 7.11 (1H, d, J = 2.20 Hz), 7.21–7.38 (5H, m), 7.81–7.83 (1H, m). IR (ATR) cm^{-1} 3330, 2923, 1639, 1475, 1394, 1276, 1168, 1027, 748, 478, 422. MS (ESI) m/z 533 $(M+H)^+$. Anal. Calcd for $C_{29}H_{38}N_2O_3Cl_2{\cdot}0.9H_2O{\cdot}0.3$ether: C, 63.42; H, 7.54; N, 4.90; Cl, 12.40. Found: C, 63.77; H, 7.28; N, 4.81; Cl, 12.07.

4.1.15. Ethyl 4-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperazine-1-carboxylate (14)

Compound **14** was prepared from **7** in a similar manner described for **8** in quantum yield as a colorless powder. ^1H NMR ($CDCl_3$) δ 0.91 (0.89) (9H, s), 1.27 (1.21) (3H, t, J = 7.1 Hz), 2.13–2.49 (3H, m), 3.05–3.14 (1H, m), 3.28 (2.94) (1H, d, J = 13.7 Hz), 3.33–3.66 (8H, m), 4.15 (2H, q, J = 7.1 Hz), 4.50 (4.46) (1H, d, J = 13.7 Hz), 6.15–6.18 (2H, m), 6.98 (1H, dd, J = 2.0, 0.73 Hz), 7.21–7.43 (4H, m), 7.92 (1H, dd, J = 7.8, 1.5 Hz). IR (ATR) cm^{-1} 3332, 2948, 1700, 1662, 1635, 1423, 1234, 1184, 1027, 750. Mp 177–179 °C. MS (ESI) m/z 578 $(M+H)^+$. Anal. Calcd for $C_{29}H_{37}N_3O_5Cl_2$: C, 60.21; H, 6.45; N, 7.26; Cl, 12.26. Found: C, 60.07; H, 6.46; N, 7.30; Cl, 12.18.

4.1.16. Benzyl 4-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperazine-1-carboxylate (15)

Compound **15** was prepared from **7** in a similar manner described for **8** in 69% yield as a colorless powder. ^1H NMR ($CDCl_3$) δ 0.91 (9H, s), 2.15–2.45 (2H, m), 3.09–3.62 (11H, m), 4.50 (1H, d, J = 14.9 Hz), 5.15 (2H, s), 6.15 (2H, m), 6.98 (1H, br s), 7.26–7.36

(10H, m), 7.93 (1H, m). IR (ATR) cm^{-1}: 3345, 2960, 1695, 1664, 0625, 1427, 1222, 1020, 748, 696, 574. Mp 129–132 °C. MS (ESI) *m*/*z* 640 $(M+H)^+$. Anal. Calcd for $C_{34}H_{39}N_3O_5Cl_2$: C, 63.75; H, 6.14; N, 6.56; Cl, 11.07. Found: C, 63.58; H, 6.18; N, 6.33; Cl, 11.22.

4.1.17. *N*-{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]-phenyl}-*N*-(2,2-dimethylpropyl)-4-oxo-4-piperazin-1-ylbutanamide (16)

A suspension of **15** (0.15 g, 0.23 mmol) and 10% Palladium on carbon (50% water, 30 mg) in MeOH (30 ml) was hydrogenated for 2 h. The reaction mixture was filtrated and concentrated in vacuo to give **16** (0.12 g, *quant*.) as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.87 (9H, s), 2.14–2.25 (2H, m), 2.54–3.98 (11H, m), 4.35–4.60 (1H, m), 5.79–6.28 (2H, m), 7.00 (1H, s), 7.24–7.37 (5H, m), 7.81 (1H, s). IR (ATR) cm^{-1} 3338, 2952, 1637, 1392, 1247, 1024, 700, 561, 509. Mp 148–150 °C. MS (FAB) *m*/*z* 506 $(M+H)^+$. HRMS (FAB) *m*/*z* 506.1951 (calcd for $C_{26}H_{34}O_3N_3Cl_2$: 506.1977). Anal. Calcd for $C_{26}H_{33}N_3O_3Cl_2{\cdot}1.5H_2O{\cdot}0.25$hexane·0.20ether: C, 59.65; H, 7.34; N, 7.37; Cl, 12.44. Found: C, 59.77; H, 7.72; N, 7.46; Cl, 12.56.

4.1.18. *N*-{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]-phenyl}-*N*-(2,2-dimethylpropyl)-4-[4-(methylsulfonyl)-piperazin-1-yl]-4-oxobutanamide (17)

Compound **17** was dissolved in CH_2Cl_2, followed by the addition of Et_3N (0.028 ml, 0.20 mmol) and methane sulfonyl chloride (0.013 ml, 0.16 mmol). The reaction mixture was stirred at room temperature for 18 h. The mixture was diluted with water and CH_2Cl_2. The organics were extracted with CH_2Cl_2, the extract was washed with brine, and then dried with Na_2SO_4. The organic solvent was removed under reduced pressure and the residue was purified with silica gel column chromatography (5–7% MeOH–CH_2Cl_2) to give compound **17** (49 mg, 0.083 mmol, 62%) as colorless powder. ^1H NMR (DMSO-d_6) δ 0.76–0.86 (9H, m), 2.04–2.71 (5H, m), 2.87 (3H, s), 2.92–3.12 (4H, m), 3.37–3.54 (4H, m), 4.08–4.42 (1H, m), 5.63–6.21 (2H, m), 7.02–7.69 (7H, m). IR (ATR) cm^{-1} 3388, 2954, 1635, 1324, 1157, 958, 775, 516. Mp 104–106 °C. MS (FAB) *m*/*z* 584 $(M+H)^+$. HRMS (FAB) *m*/*z* 584.1714 (calcd for $C_{27}H_{36}O_5N_3Cl_2S$: 584.1753).

4.1.19. Ethyl (4-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperazin-1-yl)acetate (18)

Compound **18** was prepared from **7** in a similar manner described for **8** in 71% yield as a colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.91 (9H, s), 1.27 (3H, t, *J* = 7.10 Hz), 2.11–2.22 (2H, m), 2.38–2.66 (5H, m), 3.05–3.12 (1H, m), 3.20 (2H, s), 3.27 (1H, d, *J* = 13.7 Hz), 3.48–3.72 (4H, m), 4.18 (2H, q, *J* = 7.10 Hz), 4.50 (1H, d, *J* = 13.7 Hz), 6.15 (1H, d, *J* = 5.0 Hz), 6.28 (1H, d, *J* = 5.0 Hz), 6.97 (1H, s), 7.24–7.41 (5H, m), 7.92 (1H, d, *J* = 7.6 Hz). IR (ATR) cm^{-1} 3266, 2962, 1749, 1664, 1625, 1440, 1180, 1160, 746. MS (ESI) *m*/*z* 592 $(M+H)^+$. Anal. Calcd for $C_{30}H_{39}N_3O_5Cl_2{\cdot}0.5H_2O$: C, 59.90; H, 6.70; N, 6.99; Cl, 11.79. Found: C, 60.04; H, 6.61; N, 6.93; Cl, 12.03.

4.1.20. Ethyl 5-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-5-oxopentanoate (19a)

Compound **19a** was prepared from **5** in a similar manner described for **6** in quantum yield as a colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.91 (9H, s), 1.17–1.28 (3H, m), 1.77–2.56 (6H, m), 4.00–4.16 (2H, m), 4.35 (1H, d, *J* = 13.7 Hz), 4.53 (1H, d, *J* = 13.7 Hz), 6.11 (1H, br s), 6.34 (1H, s), 7.19–7.76 (7H, m). MS (FAB) *m*/*z* 480 $(M+H)^+$. HRMS (FAB) *m*/*z* 480.1682 (calcd for $C_{29}H_{37}O_5N_2Cl_2$: 480.1708).

4.1.21. 5-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-5-oxopentanoic acid (20a)

Compound **20a** was prepared from **19a** in a similar manner described for **7** in quantum yield as a colorless amorphous. ^1H NMR (DMSO-d_6) δ 0.77–0.86 (9H, m), 0.93–3.03 (6H, m), 4.22 (1H, brd, *J* = 13.3 Hz), 4.40 (1H, brd, *J* = 13.3), 5.84–6.20 (2H, m), 6.76–7.62 (7H, m), 11.97 (1H, br). IR (ATR) cm^{-1} 2954, 1706, 1635, 1475, 1396, 1166, 1025, 754, 418. Mp 65–67 °C. MS (ESI) *m*/*z* 452 $(M+H)^+$. Anal. Calcd for $C_{23}H_{27}NO_4Cl_2{\cdot}0.3H_2O{\cdot}0.2$ether: C, 60.49; H, 6.31; N, 2.96; Cl, 15.00. Found: C, 60.83; H, 6.27; N, 2.80; Cl, 14.71.

4.1.22. Ethyl 1-{5-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-5-oxopentanoyl}-piperidine-4-carboxylate (21a)

Compound **21a** was prepared from **20a** in a similar manner described for **8** in 86% yield as a colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.81–0.90 (9H, s), 1.26 (3H, t, *J* = 7.1 Hz), 1.41–2.31 (8H, m), 2.48–3.21 (6H, m), 3.68–3.81 (1H, m), 4.12–4.18 (2H, m), 4.27–4.53 (2H, m), 5.84–6.33 (2H, m), 7.17–7.74 (7H, m). IR (ATR) cm^{-1} 2952, 1727, 1639, 1475, 1170, 1037, 755, 418. Mp 58–60 °C. MS (ESI) *m*/*z* 591$(M+H)^+$. Anal. Calcd for $C_{31}H_{40}N_2O_5Cl_2{\cdot}0.4H_2O{\cdot}0.2$ether: C, 62.25; H, 7.03; N, 4.57; Cl, 11.56. Found: C, 62.52; H, 6.97; N, 4.46; Cl, 11.16.

4.1.23. Ethyl 1-{3-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-3-oxopropanoyl}-piperidine-4-carboxylate (21b)

Compound **21b** was prepared from **5** in a similar manner described for **21a** in 78% yield from **5** as a colorless amorphous. ^1H NMR (DMSO-d_6) δ 0.74–0.84 (9H, m), 1.15 (3H, t, *J* = 7.1 Hz), 1.32–1.78 (3H, m), 2.23–3.74 (8H, m), 4.04 (2H, q, *J* = 7.2 Hz), 4.10–4.38 (2H, m), 5.86–6.03 (1H, m), 6.34 (1H, br), 6.98 (1H, dd, *J* = 11.2, 2.4 Hz), 7.30–7.53 (6H, m). IR (ATR) cm^{-1} 3345, 2952, 1727, 1623, 1475, 1166, 1029, 748, 586, 418. Mp 90–92 °C. MS (FAB) *m*/*z* 563 $(M+H)^+$. HRMS (FAB) *m*/*z* 563.2100 (calcd for $C_{29}H_{37}O_5N_2Cl_2$: 563.2080). Anal. Calcd for $C_{29}H_{37}N_2O_5Cl_2$: C, 61.81; H, 6.44; N, 4.96; Cl, 12.58. Found: C, 61.45; H, 6.46; N, 4.85; Cl, 12.54.

4.1.24. Ethyl 4-({4-chloro-2-[(2-chlorophenyl)carbonyl]-phenyl}amino)-4-oxobutanoate (22)

Compound **22** was prepared from **3** in a similar manner described for **6** as a colorless amorphous. ^1H NMR ($CDCl_3$) δ 1.27 (3H, t, *J* = 7.1 Hz), 2.74–2.77 (2H, m), 2.81–2.85 (2H, m), 4.17 (2H, q, *J* = 7.1 Hz), 7.29–7.33 (2H, m), 7.39–7.42 (1H, m), 7.48–7.53 (3H, m), 8.78 (1H, d, *J* = 9.3 Hz), 11.48 (1H, br s). IR (ATR) cm^{-1} 3291, 1735, 1698, 1637, 1577, 1425, 1398. MS (ESI) *m*/*z* 396 $[(M+H)^+, {}^{37}Cl]$, 394 $[(M+H)^+, {}^{35}Cl]$. Anal. Calcd for $C_{19}H_{17}Cl_2NO_4$: C, 57.88; H, 4.35; Cl, 17.99; N, 3.55; found: C, 57.84; H, 4.34; Cl, 17.97; N, 3.42.

4.1.25. 4-({4-Chloro-2-[(2-chlorophenyl)carbonyl]phenyl}-amino)-4-oxobutanoic acid (23)

Compound **23** was prepared from **22** in a similar manner described for **7** in 67% yield as a colorless crystal. ^1H NMR ($CDCl_3$) δ 2.79–2.85 (4H, m), 7.26–7.34 (2H, m), 7.39–7.43 (1H, m), 7.48–7.54 (3H, m), 8.76 (1H, d, *J* = 9.3 Hz), 11.50 (1H, br s). Mp 152–155 °C. MS (ESI) *m*/*z* 366 $[(M+H)^+, {}^{35}Cl]$.

4.1.26. Ethyl 1-[4-({4-chloro-2-[(2-chlorophenyl)carbonyl]-phenyl}amino)-4-oxobutanoyl]piperidine-4-carboxylate (24)

Compound **24** was prepared from **23** in a similar manner described for **8** in 95% yield as a colorless crystal. ^1H NMR ($CDCl_3$) δ 1.26 (3H, t, *J* = 7.1 Hz), 1.59–1.78 (2H, m), 1.89–2.05 (2H, m), 2.51–2.57 (1H, m), 2.72–2.90 (5H, m), 3.14–3.21 (1H, m),

3.87–3.94 (1H, m), 4.13 (2H, q, J = 7.1 Hz), 4.37–4.43 (1H, m), 7.26–7.33 (2H, m), 7.37–7.43 (1H, m), 7.47–7.54 (3H, m), 8.78 (1H, d, J = 9.1 Hz), 11.50 (1H, br s). IR (ATR) cm^{-1} 3300, 3200, 1727, 1702, 1641, 1598, 1577, 1504, 1432, 1398, 1375, 1315, 1240, 1162, 1101. Mp 155–157 °C (AcOEt–Hexane). MS (ESI) m/z 507 [(M+H)$^+$, ^{37}Cl], 505 [(M+H)$^+$, ^{35}Cl]. HRMS (FAB) m/z 507.1316 (calcd for $C_{25}H_{27}Cl_2N_2O_5$: 507.1297). Anal. Calcd for $C_{25}H_{26}Cl_2N_2O_5$: C, 59.41; H, 5.19; Cl, 14.03; N, 5.54; found: C, 59.41; H, 5.13; Cl, 13.87; N, 5.61.

4.1.27. Ethyl 1-{4-[{4-chloro-2-[(2-chlorophenyl)carbonyl]-phenyl}(methyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (25a)

To the solution of compound **24** (0.52 g, 1.03 mmol) in *N,N*-dimethylformamide (10 ml) was added sodium hydride (60%net, 45 mg, 1.13 mmol) at 0 °C, and stirred for 10 min. Then, the reaction mixture was added diazomethane (0.79 ml, 0.73 g, 5.15 mmol) and stirred for 50 min at the same temperature. The reaction mixture was diluted with AcOEt and organics were washed with brine. The extract was dried over Na2SO4 and then concentrated in vacuo, and the residue was purified with silica gel column chromatography (0–5% MeOH- CH_2Cl_2 as eluent) to give compound **25a** (0.51 g, 0.98 mmol, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.1 Hz), 1.55–1.74 (2H, m), 1.86–1.97 (2H, m), 2.16–2.25 (1H, m), 2.34–2.62 (3H, m), 2.76–2.90 (2H, m), 2.99 (3.28) (3H, s), 3.82–3.90 (1H, m), 4.14 (2H, q, J = 7.1 Hz), 4.31–4.40 (1H, m), 7.40–7.59 (7H, m). MS (ESI) m/z 521 [(M+H)$^+$, ^{37}Cl], 519 [(M+H)$^+$, ^{35}Cl].

4.1.28. Ethyl 1-{4-[{4-chloro-2-[(2-chlorophenyl)carbonyl]-phenyl}(propyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (25b)

Compound **25b** was prepared from **24** in a similar manner described for **25a** in 68% yield as a pale yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 0.83 (0.89) (3H, t, J = 7.6 Hz), 1.25 (3H, t, J = 7.1 Hz), 1.40–1.77 (4H, m), 1.86–1.97 (2H, m), 2.14–2.25 (1H, m), 2.36–2.54 (3H, m), 2.76–2.91 (3H, m), 3.06–3.15 (1H, m), 3.86–3.91 (1H, m), 3.95–4.02 (1H, m), 4.13 (2H, q, J = 7.1 Hz), 4.29–4.37 (1H, m), 7.27–7.47 (6H, m), 7.54 (7.55) (1H, d, J = 8.3 Hz). MS (ESI) m/z 549 [(M+H)$^+$, ^{37}Cl], 547 [(M+H)$^+$, ^{35}Cl]. HRMS (FAB) m/z 547.1789 (calcd for $C_{28}H_{33}Cl_2N_2O_5$: 547.1767).

4.1.29. Ethyl 1-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)-methyl]phenyl}(methyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (26a)

Compound **26a** was prepared from **25a** in a similar manner described for **4** in 83% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 1.22–1.27 (3H, m), 1.50–1.72 (2H, m), 1.82–2.04 (3H, m), 2.20–2.25 (1H, m), 2.48–2.67 (2H, m), 2.80–2.96 (1H, m), 3.08–3.22 (2H, m), 3.37 (3.38) (3H, s), 3.82–3.89 (1H, m), 4.10–4.17 (2H, m), 4.26–4.40 (1H, m), 6.25–6.28 (1H, m), 6.56 (0.45H, d, J = 5.6 Hz, exchangeable with D_2O), 6.66 (0.55H, d, J = 5.9 Hz, exchangeable with D_2O), 6.94 (1H, d, J = 2.5 Hz), 7.05–7.08 (1H, m), 7.26–7.32 (3H, m), 7.39–7.43 (1H, m), 7.98–8.01 (1H, m). MS (ESI) m/z 523 [(M+H)$^+$, ^{37}Cl], 521 [(M+H)$^+$, ^{35}Cl]. HRMS (FAB) m/z 521.1636 (calcd for $C_{26}H_{31}Cl_2N_2O_5$: 521.1610).

4.1.30. Ethyl 1-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)-methyl]phenyl}(propyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (26b)

Compound **26b** was prepared from **25b** in a similar manner described for **4** in 79% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, J = 7.3 Hz), 1.20–1.28 (4H, m), 1.40–1.75 (3H, m), 1.82–2.03 (5H, m), 2.44–2.55 (2H, m), 2.73–2.90 (1H, m), 3.05–3.29 (2.4H, m), 3.81–3.89 (0.6H, m), 4.11–4.41 (2H, m), 6.23–6.26 (1H, m), 6.51 (0.4H, d, J = 5.6 Hz), 6.59 (0.6H, d, J = 2.4 Hz), 7.01–7.04 (1H, m), 7.26–7.35 (3H, m), 7.39–7.43 (1H, m), 7.77–8.00 (1H, m). MS (ESI) m/z 551 [(M+H)$^+$, ^{37}Cl], 549 [(M+H)$^+$, ^{35}Cl]. HRMS (FAB) m/z 549.1901 (calcd for $C_{28}H_{35}Cl_2N_2O_5$: 549.1923).

4.1.31. 4-Chloro-2-(2-chlorobenzyl)-*N*-(2,2-dimethylpropyl)-aniline (27)

A solution of triphenylphosphineoxide (329 mg, 1.18 mmol) in CH_2Cl_2 (5.0 ml) was cooled to 0 °C, added trifulic anhydride (109 μl, 0.65 mmol), and stirred for 1 h. At the same temperature, the mixture was added [5-chloro-2-(2,2-dimethylpropylamino)phenyl](2-chlorophenyl)methanol (200 mg, 0.591 mmol) and stirred for 2 h. Then, the reaction mixture was added sodium borohydrate (89.5 mg, 2.36 mmol) and allowed to warm to room temperature for 2 h. The solution was removed under reduced pressure, the residue was extracted with AcOEt, and then saturated NH_4Claq. The organic layer was washed with brine and dried over Na_2SO_4. The solution was concentrated in vacuo and the residue was purified by column chromatography (*n*-hexane/AcOEt = 1:0–0:1) to give the title compound (166 mg, 87%). ^{1}H NMR ($CDCl_3$) δ 0.81 (9H, s), 2.77 (2H, s), 3.34 (1H, br s), 3.94 (2H, s), 6.55 (1H, d, J = 8.8 Hz), 6.97–7.03 (2H, m), 7.10–7.18 (3H, m), 7.38–7.42 (1H, m). MS (ESI) m/z 322 (M+H)$^+$.

4.1.32. Ethyl 1-(4-{[4-chloro-2-(2-chlorobenzyl)phenyl](2,2-dimethylpropyl)amino}-4-oxobutanoyl)piperidine-4-carboxylate (28)

A solution of 1-(3-carboxypropionyl)piperidine-4-carboxylic acid ethyl ester (100 mg, 0.384 mmol) in CH_2Cl_2 (3.0 ml) was added *N,N*-dimethylformamide (50 μl) and cooled to −15 °C. The mixture was added oxalyl chloride (40.2 μl, 0.471 mmol) and stirred for 1 h. The solution was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (3.0 ml) and added [4-chloro-2-(2-chlorobenzyl)phenyl](2,2-dimethylpropyl)amine (82.5 mg, 0.256 mmol) at 0 °C, 4-dimethylaminopyridine (47.0 mg, 0.384 mmol) and diisopropylethylamine (66.9 μl, 0.384 mmol). The reaction mixture was stirred for 12 h and treated with H_2O. The organic layer was washed with brine and dried over Na_2SO_4. The solution was concentrated in vacuo and the residue was purified by column chromatography (*n*-hexane/AcOEt = 1:0–0:1) to give the title compound (45.3 mg, 32%). ^{1}H NMR ($CDCl_3$) δ 0.92 (9H, s), 1.25 (3H, t, J = 7.2 Hz), 1.53–1.75 (2H, m), 1.85–1.95 (2H, m), 1.95–2.13 (1H, m), 2.40–2.82 (6H, m), 3.05–3.13 (1H, m), 3.79–3.89 (1H, m), 3.95–4.06 (2H, m), 4.14 (2H, q, J = 7.2 Hz), 4.32–4.40 (2H, m), 6.87–6.92 (1H, m), 7.15–7.27 (3H, m), 7.36–7.45 (1H, m). MS (ESI) m/z 561 (M+H)$^+$. Anal. Calcd for $C_{30}H_{38}Cl_2N_2O_4$: C, 64.17; H, 6.82; N, 4.99; found: C, 64.10; H, 7.25; N, 4.63.

4.1.33. {5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}-methanol (31A)

Compound **31A** was prepared from **30A** in a similar manner described for **5** in 73% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s), 2.88 (2H, s), 4.64 (2H, d, J = 3.2 Hz), 4.85 (1H, br s), 6.58 (1H, d, J = 8.5 Hz), 7.02 (1H, d, J = 2.4 Hz), 7.14 (1H, dd, J = 8.5, 2.4 Hz). IR (ATR) cm^{-1} 3568, 2954, 1604, 1581, 1508, 1475, 1200, 1001, 872, 802. MS (ESI) m/z 228 [(M+H)$^+$, Cl_{35}], 230 [(M+H)$^+$, Cl_{37}].

4.1.34. Methyl 4-{[4-chloro-2-(hydroxymethyl)phenyl](2,2-dimethylpropyl)amino}-4-oxobutanoate (35A)

Compound **35A** was prepared from **31A** in a similar manner described for **6** in 85% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.89 (9H, s), 2.09–2.42 and 2.80–2.90 (4H, m), 2.68 (4.26) (1H, d, J = 13.4 Hz), 3.14–3.20 (1H, m), 3.66 (3H, s), 4.49 (4.51) (1H, d, J = 12.9 Hz), 4.67 (4.68) (1H, d, J = 12.9 Hz), 7.21 (1H, d, J = 8.3 Hz), 7.29 (1H, dd, J = 8.1, 2.2 Hz), 7.66 (1H, d, J = 2.2 Hz). IR (ATR) cm^{-1}

3450, 2952, 1736, 1645, 1479, 1406, 1365, 1236, 1169, 1045, 847. MS (ESI) *m*/*z* 342 [(M+H)$^+$, Cl_{35}], 364 [(M+Na)$^+$, Cl_{35}].

4.1.35. 4-{[4-Chloro-2-(hydroxymethyl)phenyl](2,2-dimethylpropyl)amino}-4-oxobutanoic acid (36A)

Compound **36A** was prepared from **35A** in a similar manner described for **7** in 98% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90 (9H, s), 2.15–2.45 and 2.77–2.90 (4H, m), 2.68 (1H, d, *J* = 13.5 Hz), 4.29 (1H, d, *J* = 13.5 Hz), 4.50 (1H, d, *J* = 13.5 Hz), 4.65 (1H, d, *J* = 13.5 Hz), 7.20 (1H, d, *J* = 8.5 Hz), 7.30 (1H, dd, *J* = 8.5, 2.4 Hz), 7.64 (1H, d, *J* = 2.4 Hz). IR (ATR) cm^{-1} 3423, 2954, 1712, 1639, 1477, 1394, 1246, 1171, 1093, 1043, 829. MS (ESI) *m*/*z* 328 (M+H)$^+$.

4.1.36. 1-(4-{[4-Chloro-2-(hydroxymethyl)phenyl](2,2-dimethylpropyl)amino}-4-oxobutanoyl)piperidine-4-carboxylate (37A)

Compound **37A** was prepared from **36A** in a similar manner described for **8** in 81% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.89 (9H, s), 1.24 (1.26) (3H, t, *J* = 7.1 Hz), 1.70–2.05 (5H, m), 2.06–2.21 (1H, m), 2.29–2.54 (2H, m), 2.60 (2.63) (1H, d, *J* = 13.4 Hz), 2.70–2.85 (1H, m), 2.92–3.19 (2H, m), 3.78–3.87 (1H, m), 4.13 (4.14) (2H, q, *J* = 7.1 Hz), 4.18–4.40 (2H, m), 4.30 (1H, d, *J* = 13.6 Hz), 4.67 (1H, d, *J* = 13.6 Hz), 4.75–4.94 (1H, m), 7.10–7.31 (2H, m), 7.65 (1H, s). IR (ATR) cm^{-1} 3440, 2952, 1728, 1630, 1477, 1392, 1273, 1173, 1039. MS (ESI) *m*/*z* 467 [(M+H)$^+$, Cl_{35}], 469 [(M+H)$^+$, Cl_{37}]. Anal. Calcd for $C_{24}H_{35}ClN_2O_5 \cdot 0.2H_2O$: C, 61.25; H, 7.58; Cl, 7.53; N, 5.95; found: C, 61.06; H, 7.56; Cl, 7.76; N, 5.65.

4.1.37. (2-Amino-5-chlorophenyl)(phenyl)methanol (30B)

Compound **30B** was prepared from **29B** in a similar manner described for **4** in 91% yield as a colorless crystal. ^{1}H NMR ($CDCl_3$) δ 3.94 (1H, br s), 5.81 (1H, s), 6.59 (1H, dd, *J* = 8.8, 1.0 Hz), 7.02–7.09 (2H, m), 7.27–7.41 (5H, m). IR (ATR) cm^{-1} 3213, 1603, 1485, 1448, 1417, 1257, 1200, 1028, 906, 854, 823, 686. MS (ESI) *m*/*z* 234 [(M+H)$^+$, Cl_{35}], 236 [(M+H)$^+$, Cl_{37}]. Anal. Calcd for $C_{13}H_{12}ClNO \cdot 0.05H_2O$: C, 66.56; H, 5.20; Cl, 15.11; N, 5.97; found: C, 66.58; H, 5.15; Cl, 15.03; N, 5.90.

4.1.38. {5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}-(phenyl)methanol (31B)

Compound **31B** was prepared from **30B** in a similar manner described for **5** in 45% yield as a pale yellow syrup. ^{1}H NMR ($CDCl_3$) δ 0.81 (9H, s), 2.45 (1H, br s), 2.72 and 2.73 (2H, both s), 4.34 (1H, br s), 5.78 (1H, br s), 6.55 (1H, d, *J* = 8.8 Hz), 7.08 (1H, d, *J* = 2.4 Hz), 7.14 (1H, dd, *J* = 8.6, 2.4 Hz), 7.25–7.40 (5H, m). IR (ATR) cm^{-1} 3409, 2954, 1600, 1579, 1508, 1475, 1252, 1170, 1018, 804, 700. MS (ESI) *m*/*z* 304 [(M+H)$^+$, Cl_{35}], 306 [(M+H)$^+$, Cl_{37}].

4.1.39. Methyl 4-[{4-chloro-2-[hydroxy(phenyl)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35B)

Compound **35B** was prepared from **31B** in a similar manner described for **6** in 85% yield as a colorless syrup. ^{1}H NMR ($CDCl_3$) δ (0.70–0.82 and 1.73–1.82) 2.07–2.19 and 2.23–2.44 and 2.94–3.04 (4H, m), 0.90 (0.92) (9H, s), 2.55 (2.86) (1H, d, *J* = 13.3 Hz), 3.58 (3.69) (3H, s), 4.45 (4.48) (1H, d, *J* = 13.3 Hz), 4.71 (4.72) (1H, br s), 5.81 (5.88) (1H, s), 7.22–7.43 (7H, m), 7.93 (1H, d, *J* = 2.2 Hz). IR (ATR) cm^{-1} 3423, 2952, 1736, 1664, 1475, 1238, 1167, 1024, 835, 700, 501. MS (ESI) *m*/*z* 418 [(M+H)$^+$, Cl_{35}], 420 [(M+H)$^+$, Cl_{37}].

4.1.40. 4-[{4-Chloro-2-[hydroxy(phenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (36B)

Compound **36B** was prepared from **35B** in a similar manner described for **7** in quantum yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.87 (0.92) (9H, s), 1.80–1.89 and 2.00–2.24 and 2.33–2.47 and 2.91–2.99 (4H, m), 2.48 (2.90) (1H, d, *J* = 13.4 Hz), 4.39 (4.49) (1H, d, *J* = 13.4 Hz), 5.79 (5.84) (1H, s), 7.15–7.43 (7H, m), 8.00 (1H, d, *J* = 2.7 Hz). MS (ESI) *m*/*z* 404 [(M+H)$^+$, Cl_{35}], 406 [(M+H)$^+$, Cl_{37}].

4.1.41. Ethyl 1-{4-[{4-chloro-2-[hydroxy(phenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37B)

Compound **37B** was prepared from **36B** in a similar manner described for **8** in 53% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.92 (9H, s), 1.24 (1.25) (3H, t, *J* = 7.1 Hz), 1.47–1.73 (2H, m), 1.75–1.99 (2H, m), 2.00–2.09 (1H, m), 2.14–2.23 (1H, m), 2.36–2.55 (2H, m), 2.66 (1H, d, *J* = 13.7 Hz), 2.70–2.89 (1H, m), 3.05–3.19 (2H, m), 3.79–3.89 (1H, m), 4.12 (4.14) (2H, q, *J* = 7.1 Hz), 4.23–4.40 (1H, m), 4.50 (4.52) (1H, d, *J* = 13.7 Hz), 5.89–5.95 (1H, m), 6.08–6.19 (1H, m), 7.18–7.43 (8H, m). IR (ATR) cm^{-1} 3388, 2952, 1728, 1626, 1475, 1392, 1274, 1169, 1038, 700. MS (ESI) *m*/*z* 543 [(M+H)$^+$, Cl_{35}], 445 [(M+H)$^+$, Cl_{37}]. Anal. Calcd for $C_{30}H_{39}ClN_2O_5$: C, 66.35; H, 7.24; N, 5.16; Cl, 6.53; found: C, 66.41; H, 7.25; N, 4.96; Cl, 6.83.

4.1.42. (2-Amino-5-chlorophenyl)(2-fluorophenyl)methanol (30C)

Compound **30C** was prepared from **29C** in a similar manner described for **4** in 88% yield as a colorless crystal. ^{1}H NMR ($CDCl_3$) δ 4.10 (1H, br s), 6.10 (1H, s), 6.62 (1H, d, *J* = 8.5 Hz), 7.00 (1H, s), 7.04–7.13 (2H, m), 7.19 (1H, dd, *J* = 7.6 Hz), 7.22–7.27 (1H, m), 7.29–7.37 (1H, m), 7.43 (1H, dd, *J* = 7.6 Hz). IR (ATR) cm^{-1} 3307, 1618, 1585, 1483, 1454, 1279, 1217, 1026, 802, 748. MS (ESI) *m*/*z* 252 [(M+H)$^+$, Cl_{35}], 254 [(M+H)$^+$, Cl_{37}]. Anal. Calcd for $C_{13}H_{11}ClFNO$: C, 61.32; H, 4.43; Cl, 14.04; F, 7.52; N, 5.55; found: C, 61.69; H, 4.38; Cl, 13.96; F, 7.43; N, 5.47.

4.1.43. {5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}-(2-fluorophenyl)methanol (31C)

Compound **31C** was prepared from **30C** in a similar manner described for **5** in 62% yield as a pale yellow syrup. ^{1}H NMR ($CDCl_3$) δ 0.94 (9H, s), 2.49 (1H, br s), 2.82 (2H, s), 4.59 (1H, br s), 6.07 (1H, s), 6.59 (1H, d, *J* = 8.8 Hz), 7.00 (1H, d, *J* = 2.2 Hz), 7.05–7.18 (4H, m), 7.28–7.35 (1H, m), 7.38 (1H, ddd, *J* = 7.6, 7.6, 1.7 Hz). MS (ESI) *m*/*z* 322 [(M+H)$^+$, Cl_{35}], 324 [(M+H)$^+$, Cl_{37}].

4.1.44. Methyl 4-[{4-chloro-2-[(2-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35C)

Compound **35C** was prepared from **31C** in a similar manner described for **6** in 87% yield as a colorless syrup. ^{1}H NMR ($CDCl_3$) δ 0.91 (0.93) (9H, s), (1.18–1.27 and 1.93–2.03) 2.14–2.49 and 2.95–3.04 (4H, m), 2.95 (2.97) (1H, d, *J* = 13.7 Hz), 3.58 (3.61) (3H, s), 4.51 (4.52) (1H, d, *J* = 13.7 Hz), 5.05–5.09 (1H, m), 6.08–6.18 (1H, m), 6.99–7.06 (2H, m), 7.13–7.17 (1H, m), 7.22–7.39 (3H, m), 7.69–7.78 (1H, m). IR (ATR) cm^{-1} 2954, 1736, 1579, 1508, 1367, 1230, 1144, 985, 806, 756, 696. MS (ESI) *m*/*z* 436 [(M+H)$^+$, Cl_{35}], 438 [(M+H)$^+$, Cl_{37}].

4.1.45. 4-[{4-Chloro-2-[(2-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (36C)

Compound **36C** was prepared from **35C** in a similar manner described for **7** in quantum yield as a light green amorphous. ^{1}H NMR ($CDCl_3$) δ 0.91 (0.92) (9H, s), (1.25–1.35 and 1.95–2.10) 2.20–2.50 and 2.85–2.95 (4H, m), 2.87 (2.98) (1H, d, *J* = 13.6 Hz), 4.47 (4.53) (1H, d, *J* = 13.6 Hz), 6.06 (6.17) (1H, s), 6.96–7.07 (1H, m), 7.09–7.17 (1H, m), 7.20–7.39 (4H, m), 7.70–7.77 (1H, m). MS (ESI) *m*/*z* 422 (M+H)$^+$.

4.1.46. Ethyl 1-{4-[{4-chloro-2-[(2-fluorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-4-carboxylate (37C)

Compound **37C** was prepared from **36C** in a similar manner described for **8** in 78% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.90) 0.93 (9H, s), 1.24 (1.25) (3H, t, J = 6.8 Hz), 1.48–1.72 (2H, m), 1.80–1.99 (2H, m), 2.04–2.21 (2H, m), 2.34–2.55 (2H, m), 2.74–2.90 (1H, m), 3.03–3.20 (3H, m), 3.79–3.88 (1H, m), 4.12 (4.14) (2H, q, J = 6.8 Hz), 4.21–4.41 (1H, m), 4.53 (4.56) (1H, d, J = 13.7 Hz), 6.09–6.16 (1H, m), (6.54) 6.55 (1H, d, J = 5.1 Hz), 6.95–7.03 (1H, m), 7.10–7.14 (1H, m), 7.19–7.34 (4H, m), 7.90–7.97 (1H, m). IR (ATR) cm^{-1} 3322, 2952, 1728, 1662, 1624, 1477, 1392, 1167, 1038, 756. MS (ESI) m/z 562 $(M+H)^+$. Anal. Calcd for $C_{30}H_{38}ClFN_2O_5 \cdot 0.1CH_2Cl_2 \cdot 0.2H_2O$: C, 63.07; H, 6.79; N, 4.89; Cl, 7.42; F, 3.31; found: C, 63.24; H, 6.74; N, 4.70; Cl, 7.15; F, 3.33.

4.1.47. Ethyl 1-{4-[{4-chloro-2-[(2-fluorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-3-carboxylate (38C)

Compound **38C** was prepared from **36C** in a similar manner described for **8** in 93% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.94 (9H, s), 1.19–1.29 (3H, m), 1.30–1.88 (2H, m), 1.90–2.22 (2H, m), 2.26–2.52 (2H, m), 2.57–2.74 (1H, m), 2.86–3.28 (3H, m), 3.47–4.02 (2H, m), 4.06–4.19 (2H, m), 4.34–4.57 (2H, m), 6.13 (1H, s), 6.48–6.60 (8H, m), 6.96–7.03 (1H, m), 7.06–7.15 (1H, m), 7.19–7.34 (4H, m), 7.92–7.99 (1H, m). IR (ATR) cm^{-1} 3321, 2951, 1728, 1662, 1624, 1475, 1248, 1169, 1030, 756. MS (ESI) m/z 561 [$(M+H)^+$, Cl_{35}], 563 [$(M+H)^+$, Cl_{37}]. Anal. Calcd for $C_{30}H_{38}ClFN_2O_5 \cdot 0.1H_2O$: C, 64.01; H, 6.84; N, 4.98; Cl, 6.30; F, 3.38; found: C, 64.10; H, 6.68; N, 4.83; Cl, 6.40; F, 3.40.

4.1.48. 1-{4-[{4-Chloro-2-[(2-fluorophenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (39C)

Compound **39C** was prepared from **37C** in a similar manner described for **9** in quantum yield as a light green amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90 (0.94) (9H, s), 1.24–1.76 (3H, m), 1.77–2.04 (2H, m), 2.05–2.22 (1H, m), 2.28–47 (1H, m), 2.49–2.65 (1H, m), 2.70–2.97 (1H, m), 2.98–3.23 (2H, m), 3.68–3.88 (1H, m), 4.24–4.39 (1H, m), 4.43–4.57 (1H, m), 6.13 (6.19) (1H, br s), 6.95–7.06 (1H, m), 7.08–7.18 (1H, m), 7.22–7.45 (7.61–7.67 and 7.90–7.97) (5H, m). IR (ATR) cm^{-1} 3346, 2952, 1728, 1620, 1477, 1396, 1169, 1030, 756. MS (ESI) m/z 533 [$(M+H)^+$, Cl_{35}], 535 [$(M+H)^+$, Cl_{37}]. Anal. Calcd for $C_{28}H_{34}ClFN_2O_5 \cdot 1.0H_2O$: C, 61.03; H, 6.58; N, 5.08; found: C, 60.86; H, 6.28; N, 4.85.

4.1.49. 1-{4-[{4-Chloro-2-[(2-fluorophenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (40C)

Compound **40C** was prepared from **38C** in a similar manner described for **9** in 96% yield as a light green amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90 (0.93) (9H, s), 1.19–1.47 (1H, m), 1.50–1.88 (2H, m), 1.98–2.22 (2H, m), 2.25–3.22 (7H, m), 3.40–4.07 (2H, m), 4.40–4.58 (2H, m), 6.00–6.21 (2H, m), 6.90–7.04 (1H, m), 7.06–7.46 (4H, m), 7.53–7.67 (1H, m), 7.84–7.97 (1H, m). IR (ATR) cm^{-1} 3500–3200, 2952, 1728, 1620, 1477, 1396, 1169, 756. MS (ESI) m/z 531 [$(M+H)^+$, Cl_{35}], 533 [$(M+H)^+$, Cl_{37}]. HRMS (FAB) m/z 533.2195 (calcd for $C_{28}H_{35}ClFN_2O_5$ 533.2219). Anal. Calcd for $C_{28}H_{34}ClFN_2O_5 \cdot 0.2CH_2Cl_2 \cdot 0.3H_2O$: C, 60.98; H, 6.35; N, 5.04; found: C, 61.09; H, 5.96; N, 4.85.

4.1.50. *N*-(4-Chlorophenyl)-2,2-dimethylpropanamide (33)

To a solution of 4-Chloroaniline (**32**, 2.592 g, 20.32 mmol) in CH_2Cl_2 (40 ml) was added 4-(dimethylamino)pyridine (273 mg, 2.23 mmol), triethylamine (3.11 ml, 22.3 mmol), and pivaloyl chloride (2.63 ml, 251.3 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. After water was added, the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was recrystallized from n-hexane and CH_2Cl_2 to afford the title compound (**33**, 3.912 g, 18.48 mmol, 91%) as a colorless crystal. ^{1}H NMR ($CDCl_3$) δ 1.31 (9H, s), 7.26–7.30 (2H, m), 7.45–7.52 (2H, m). IR (ATR) cm^{-1} 3294, 2966, 1655, 1593, 1523, 1491, 1396, 1309, 1244, 1173, 827. MS (ESI) m/z 212 $(M+H)^+$. Anal. Calcd for $C_{11}H_{14}ClNO$: C, 62.41; H, 6.67; Cl, 16.75; N, 6.62; found: C, 62.37; H, 6.71; Cl, 16.59; N, 6.55.

4.1.51. 2-Chloro-3-fluorobenzaldehyde

To a solution of 2-chloro-3-fluoro-benzoic acid (1.00 g, 5.73 mmol) in THF (40 ml) was added borane–tetrahydrofuran complex (1.0 M solution, 20.1 ml, 20.1 mmol) at 0 °C. The mixture was stirred under reflux overnight and then cooled with crushed ice. After 1 N HClaq and AcOEt were added to the reaction mixture, the two layers were separated. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, and then alcohol residue was obtained. Separately, to the solution of oxalyl chloride (737 μl, 8.60 mmol) in CH_2Cl_2 (50 ml) was dropped dimethylsulfoxide (1.22 ml, 17.2 mmol) at −78 °C. The mixture was stirred for 5 min at the same temperature. Then, the residue described above was added with CH_2Cl_2 (15 ml) to the reaction mixture at −78 °C. The solution was stirred for 1 h at −40 °C, and then triethylamine (3.97 ml, 28.7 mmol) was added. The mixture was stirred and warmed to room temperature. After 0.5 N HClaq was added, the two layers were separated. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed (*n*-hexane/AcOEt = 50:1) to give the title compound (500 mg, 55%). ^{1}H NMR ($CDCl_3$) δ 7.35–7.43 (2H, m), 7.72–7.78 (1H, m), 10.47 (1H, s).

4.1.52. *N*-{4-Chloro-2-[(2-chloro-3-fluorophenyl)hydroxymethyl]-phenyl}-2,2-dimethylpropionamide (34D)

N-Pivaloyl-4-chloroaniline (**33**, 595 mg, 2.81 mmol) was dissolved in THF (50 ml), and the solution was added *sec*-butyl lithium *c*-hexane, *n*-hexane solution (0.99 M, 5.96 ml, 6.18 mmol) at −78 °C, and then stirred at 0 °C for 2 h. The mixture was added 2-chloro-3-fluoro-benzaldehyde (490 mg, 3.09 mmol) at the same temperature for 30 min. The reaction mixture was poured saturated with NH_4Claq and AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (*n*-hexane/AcOEt = 9:1) to give the title compound (676 mg, 65%) as light yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.27 (9H, s), 3.85 (1H, d, J = 3.5 Hz), 4.81 (1H, br s), 6.95 (1H, d, J = 3.5 Hz), 7.08–7.17 (1H, m), 7.28–7.32 (3H, m), 7.72 (1H, d, J = 8.8 Hz), 8.39 (1H, br s). MS (FAB) m/z 370 $(M+H)^+$.

4.1.53. [5-Chloro-2-(2,2-dimethylpropylamino)phenyl]-(2-chloro-3-fluorophenyl)methanol (31D)

A solution of *N*-{4-chloro-2-[(2-chloro-3-fluorophenyl)hydroxymethyl]phenyl}-2,2-dimethylpropionamide (**34D**, 670 mg, 1.81 mmol) was dissolved in THF (30 ml). To the solution was added dropwise a toluene solution of sodium bis(2-methoxyethoxy)aluminum hydride (35%, 3.37 ml, 10.9 mmol) at 0 °C. The mixture was stirred for 2 h at room temperature. The reaction mixture was added saturated (+)-tartaric acid sodium potassium solution and stirred for 5 min. The mixture was added AcOEt and separated with a funnel. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography

(*n*-hexane/AcOEt = 20:1) to give the title compound (300 mg, 47%) as light yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.94 (9H, s), 2.85 (2H, s), 6.14 (1H, s), 6.62 (1H, d, J = 8.8 Hz), 6.88 (1H, d, J = 2.4 Hz), 7.10–7.18 (2H, m), 7.24–7.30 (2H, m). MS (FAB) m/z 357 $(M+H)^+$.

4.1.54. Methyl 4-[{4-chloro-2-[(2-chloro-3-fluorophenyl)-(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35D)

Compound **35D** was prepared from **31D** in a similar manner described for **6** in 55% yield as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 0.90 (0.94) (9H, s), 2.18–2.27 (1H, m), 2.23–2.47 (2H, m), 2.87–2.96 (1H, m), 3.07 (1H, d, J = 16.3 Hz), 3.66 (3.69) (3H, s), 4.49 (1H, d, J = 16.3 Hz), 6.14 (1H, s), 7.00–7.06 (1H, m), 7.14–7.21 (1H, m), 7.27–7.32 (1H, m), 7.23–7.39 (2H, m), 7.63 (1H, d, J = 7.8 Hz). IR (ATR) cm^{-1} 3411, 2956, 2869, 1743, 1648, 1577, 1469, 1434, 1409, 1351, 1263, 1232, 1164, 1114, 1068, 1043, 998, 948, 904, 873, 846, 809. MS (FAB) m/z 470 $(M+H)^+$.

4.1.55. 4-[{4-Chloro-2-[(2-chloro-3-fluorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (36D)

Compound **36D** was prepared from **35D** in a similar manner described for **7** in 86% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.89 (0.90) (9H, s), (1.56–1.58 and 2.05–2.10) 2.24–2.48 and 2.78–2.86 (4H, m), 2.96 (3.08) (1H, d, J = 13.4 Hz), 4.45 (4.50) (1H, d, J = 13.4 Hz), 6.05 (6.29) (1H, s), 6.92 (1H, d, J = 2.2 Hz), 7.09–7.17 (1H, m), 7.24–7.32 (4H, m), 7.50–7.59 (1H, m). IR (ATR) cm^{-1} 2956, 2869, 1708, 1637, 1579, 1467, 1442, 1396, 1365, 1322, 1263, 1168, 1114, 1101, 1043, 968, 946, 902, 875, 833, 808. MS (FAB) m/z 456 $(M+H)^+$. Anal. Calcd for $C_{22}H_{24}Cl_2FNO_4 \cdot 0.4CHCl_3$: C, 53.81; H, 4.83; N, 2.75; found: C, 53.90; H, 4.99; N, 2.65.

4.1.56. Ethyl 1-{4-[{4-chloro-2-[(2-chloro-3-fluorophenyl)-(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37D)

Compound **37D** was prepared from **36D** in a similar manner described for **8** in 58% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.89) 0.91 (9H, s), 1.24 (1.26) (3H, t, J = 7.1 Hz), 1.75–2.00 and 2.05–2.20 (3H, m), 2.41–2.56 (2H, m), (2.69–2.91) 3.00–3.21 (3H, m), 3.12 (1H, d, J = 13.5 Hz), 3.67–3.82 (1H, m), 4.10–4.18 (3H, m), 4.22–4.50 (1H, m), 4.52 (4.53) (1H, d, J = 13.5 Hz), 6.13–6.16 (1H, m), 6.45–6.71 (6.51–6.54) (1H, m), 6.96 (1H, s), 7.14–7.20 and 7.33–7.40 (3H, m), 7.73–7.80 (1H, m). IR (ATR) cm^{-1} 3318, 2954, 2865, 1727, 1625, 1577, 1467, 1442, 1392, 1365, 1313, 1263, 1168, 1097, 1039, 987, 970, 946, 902, 875, 833, 808. MS (FAB) m/z 595 $(M+H)^+$. Anal. Calcd for $C_{30}H_{37}Cl_2FN_2O_5 \cdot 0.5H_2O$: C, 59.60; H, 6.34; N, 4.63; found: C, 59.26; H, 6.20; N, 4.46.

4.1.57. Ethyl 1-{4-[{4-chloro-2-[(2-chloro-3-fluorophenyl)-(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate (38D)

Compound **38D** was prepared from **36D** in a similar manner described for **8** in 80% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.91) 0.92 (9H, s), 1.23 (1.24) (3H, t, J = 7.3 Hz), (1.65–1.73) 1.90–2.14 (4H, m), 2.20–2.52 and 2.55–2.70 (3H, m), (2.79–2.88) 2.93–3.18 (2H, m), 3.19–3.28 (3.49–3.56) (1H, m), 3.70–3.86 (3.92–3.99) (4.35–4.44) (4.70–4.73) (2H, m), 4.07–4.19 (2H, m), 4.52 (1H, d, J = 13.7 Hz), 6.16 (6.32) (1H, d, J = 4.1 Hz), 6.93–7.00 (1H, m), 7.14–7.19 (2H, m), 7.28–7.41 (2H, m), 7.72–7.78 (1H, m). IR (ATR) cm^{-1} 3332, 2950, 2865, 1727, 1625, 1579, 1467, 1442, 1392, 1365, 1309, 1261, 1170, 1114, 1068, 1031, 1006, 946, 900, 875, 856, 833, 808. MS (FAB) m/z 595 $(M+H)^+$. Anal. Calcd for $C_{30}H_{37}Cl_2FN_2O_5 \cdot 0.5H_2O$: C, 59.60; H, 6.34; N, 4.63; found: C, 59.26; H, 6.19; N, 4.46.

4.1.58. 1-{4-[{4-Chloro-2-[(2-chloro-3-fluorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-4-carboxylic acid (39D)

Compound **39D** was prepared from **37D** in a similar manner described for **9** in 87% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.89) 0.91 (9H, s), 1.36–1.74 (3H, m), 1.75–2.27 (3H, m), 2.28–2.62 (3H, m), 2.68–3.28 (3H, m), 3.71–3.87 (1H, m), 4.20–4.52 (2H, m), 6.14 (1H, s), (6.31) 6.94 (1H, d, J = 8.6 Hz), 7.00–7.46 (4H, m), (7.53–7.58) 7.67–7.77 (1H, m). IR (ATR) cm^{-1} 2954, 2865, 1727, 1623, 1467, 1444, 1396, 1365, 1263, 1170, 1105, 1031, 948, 929, 902, 875, 833, 808. MS (FAB) m/z 567 $(M+H)^+$. Anal. Calcd for $C_{28}H_{33}Cl_2FN_2O_5$: C, 59.26; H, 5.86; N, 4.94; found: C, 59.49; H, 6.10; N, 4.58.

4.1.59. 1-{4-[{4-Chloro-2-[(2-chloro-3-fluorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-3-carboxylic acid (40D)

Compound **40D** was prepared from **38D** in a similar manner described for **9** in 92% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.88) 0.90 (9H, s), 1.46–1.87 (2H, m), 1.88–2.25 (3H, m), 2.30–2.70 (1H, m), 2.77–3.22 (3H, m), (3.40–3.49) 3.55–4.15 (4.29–4.44) (4.57–4.64) (4H, m), 4.45–4.56 (1H, m), 6.10–6.14 (6.23–6.31) (1H, m), 6.97 (1H, s), 7.01–7.41 (7.42–7.60) (4H, m), 7.62–7.73 (1H, m). IR (ATR) cm^{-1} 2950, 2867, 1727, 1619, 1579, 1467, 142, 1396, 1365, 1261, 1170, 1116, 1043, 1008, 977, 948, 900, 873, 856, 833, 808. MS (FAB) m/z 567 $(M+H)^+$. Anal. Calcd for $C_{28}H_{33}Cl_2FN_2O_5$: C, 59.26; H, 5.86; N, 4.94; found: C, 59.04; H, 5.98; N, 4.63.

4.1.60. {5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}-(2-chloro-4-fluorophenyl)methanol (31E)

Compound **31E** was prepared from **33** in a similar manner described for **31D** in 14% yield in two steps as a pale yellow amorphous. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (9H, s), 2.84 (2H, s), 6.11 (1H, s), 6.61 (1H, d, J = 8.8 Hz), 6.95 (1H, d, J = 2.4 Hz), 6.96–7.05 (1H, m), 7.13–7.18 (2H, m), 7.38–7.42 (1H, m). MS (FAB) m/z 356 $(M+H)^+$.

4.1.61. Methyl 4-[{4-chloro-2-[(2-chloro-4-fluorophenyl)-(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35E)

Compound **35E** was prepared from **31E** in a similar manner described for **6** in 60% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.89 (0.90) (9H, s), 2.18–2.25 (1H, m), 2.32–2.49 (2H, m), 2.88–2.98 (1H, m), 3.02 (1H, d, J = 13.7 Hz), (3.60) 3.68 (3H, s), 4.48 (1H, d, J = 13.7 Hz), 4.80 (1H, d, J = 5.8 Hz), 6.10 (6.30) (1H, d, J = 5.8 Hz), 7.02 (1H, d, J = 2.0 Hz), 7.08–7.16 (2H, m), 7.28–7.37 (2H, m), (7.68–7.70) 7.78–7.83 (1H, m). IR (ATR) cm^{-1} 3392, 2960, 1739, 1646, 1600, 1481, 1434, 1411, 1396, 1351, 1288, 1226, 1164, 1112, 1054, 1031, 998, 962, 937, 912, 863, 835, 804. MS (FAB) m/z 470 $(M+H)^+$.

4.1.62. 4-[{4-Chloro-2-[(2-chloro-4-fluorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (36E)

Compound **36E** was prepared from **35E** in a similar manner described for **7** in 86% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.88 (0.90) (9H, s), (1.38–1.46) (2.01–2.09) 2.21–2.49 (2.77–2.86) (4H, m), 2.89 (3.03) (1H, d, J = 13.7 Hz), 4.43 (4.51) (1H, d, J = 13.7 Hz), 6.02 (6.28) (1H, s), 6.93–7.14 and 7.27–7.36 (5H, m), 7.62–7.68 (1H, m). IR (ATR) cm^{-1} 2954, 1710, 1639, 1600, 1477, 1394, 1326, 1259, 1226, 1166, 1114, 1052, 1029, 981, 912, 860, 833. MS (FAB) m/z 456 $(M+H)^+$. Anal. Calcd for $C_{22}H_{24}Cl_2FNO_4 \cdot 0.5H_2O$: C, 56.78; H, 5.41; N, 3.01; found: C, 56.56; H, 5.25; N, 3.07.

4.1.63. Ethyl 1-{4-[{4-chloro-2-[(2-chloro-4-fluorophenyl)-(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37E)

Compound **37E** was prepared from **36E** in a similar manner described for **8** in 76% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.89) 0.90 (9H, s), 1.23 (1.26) (3H, t, J = 7.1 Hz), (1.28–1.39) 1.49–1.71 (1H, m), 1.78–1.98 (2H, m), 2.06–2.66 (4H, m), 2.69–2.90 (1H, m), 2.94–3.21 (3.63–3.85) (3H, m), 4.05–4.13 (2H, m), 4.18–4.51 (2H, m), 6.06–6.09 (6.28–6.30) (6.37–6.40) (6.42–6.48) (1H, m), 6.95 (1H, d, J = 2.0 Hz), 7.08–7.12 (2H, m), 7.17–7.39 (2H, m), (7.66–7.68) 7.84–7.91 (1H, m). IR (ATR) cm^{-1} 2952, 2867, 1727, 1627, 1475, 1448, 1392, 1365, 1313, 1272, 1220, 1168, 1112, 1033, 946, 912, 858, 833, 804, 752. MS (FAB) m/z 595 (M+H)$^+$. Anal. Calcd for $C_{30}H_{37}Cl_2FN_2O_5{\cdot}0.5H_2O$: C, 59.60; H, 6.34; N, 4.63; found: C, 59.44; H, 6.18; N, 4.58.

4.1.64. Ethyl 1-{4-[{4-chloro-2-[(2-chloro-4-fluorophenyl)-(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate (38E)

Compound **38E** was prepared from **36E** in a similar manner described for **8** in 63% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.89) 0.90 (9H, s), 1.23 (1.25) (3H, t, J = 7.1 Hz), (1.30–1.46) 1.50–1.85 (3H, m), 1.90–2.26 (3H, m), 2.27–3.15 (5H, m), 3.16–3.26 (3.46–3.52) (1H, m), 3.62–3.87 (3.94–4.00) (4.32–4.40) (4.69–4.73) (2H, m), (4.43) 4.48 (1H, d, J = 13.7 Hz), 6.07–6.12 (6.28–6.31) (6.35–6.40) (6.43–6.47) (1H, m), 6.95 (1H, s), 7.05–7.12 (2H, m), 7.19–7.46 (2H, m), (7.63–7.71) 7.83–7.93 (1H, m). IR (ATR) cm^{-1} 2950, 2865, 1727, 1627, 1475, 1442, 1392, 1309, 1280, 1255, 1220, 1174, 1114, 1031, 912, 856, 833, 804, 754. MS (FAB) m/z 595 (M+H)$^+$. Anal. Calcd for $C_{30}H_{37}Cl_2FN_2O_5{\cdot}0.5H_2O$: C, 59.60; H, 6.34; N, 4.63; found: C, 59.44; H, 6.18; N, 4.58.

4.1.65. 1-{4-[{4-Chloro-2-[(2-chloro-4-fluorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-4-carboxylic acid (39E)

Compound **39E** was prepared from **37E** in a similar manner described for **9** in 83% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.89) 0.90 (9H, s), (1.20–1.38) 1.50–1.72 (2H, m), 1.75–2.02 (3H, m), 2.05–2.60 (3H, m), 2.70–2.92 (1H, m), 2.96–3.37 (3H, m), 3.67–3.88 (1H, m), 4.21–4.56 (2H, m), 6.10(6.29) (1H, s), 6.94 (1H, d, J = 7.2 Hz), 7.03–7.16 (2H, m), 7.20–7.34 (7.37–7.43) (2H, m), (7.62–7.67) 7.82–7.93 (1H, m). IR (ATR) cm^{-1} 2956, 2867, 1724, 1621, 1602, 1477, 1396, 1365, 1265, 1222, 1168, 1112, 1029, 912, 858, 833, 804, 750. MS (FAB) m/z 567 (M+H)$^+$. Anal. Calcd for $C_{28}H_{33}Cl_2FN_2O_5{\cdot}0.5H_2O$: C, 55.01; H, 5.33; N, 4.42; found: C, 55.35; H, 5.58; N, 4.39.

4.1.66. 1-{4-[{4-Chloro-2-[(2-chloro-4-fluorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-3-carboxylic acid (40E)

Compound **40E** was prepared from **38E** in a similar manner described for **9** in 83% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.89 (9H, s), 1.18–1.90 (5H, m), 1.91–2.69 (4H, m), 2.80–3.22 (3.36–3.55) (3H, m), 3.69–3.92 (3.96–4.09) (1H, m), 4.30–4.69 (2H, m), 6.00–6.12 (6.20–6.3) (1H, m), 6.83–7.48 (5H, m), (7.56–7.70) 7.80–7.95 (1H, m). IR (ATR) cm^{-1} 2952, 2867, 1725, 1623, 1602, 1475, 1396, 1365, 1286, 1255, 1222, 1174, 1114, 1052, 1031, 912, 858, 833. MS (FAB) m/z 567 (M+H)$^+$. Anal. Calcd for $C_{28}H_{33}Cl_2FN_2O_5{\cdot}0.4CHCl_3$: C, 55.79; H, 5.43; N, 4.52; found: C, 55.59; H, 5.58; N, 4.29.

4.1.67. 2-Chloro-5-fluorobenzaldehyde

The solution of 2-chloro-5-fluoro-benzoic acid (4.00 g, 23.0 mmol) in THE (200 ml) was added triethylamine (4.14 ml, 29.9 mmol). At −30 °C, the mixture was added ethyl chloroformate (2.62 ml, 27.8 mmol) and stirred for 10 min. The solution was added sodium borohydrate (2.60 g, 68.9 mmol) and stirred for 5 min. The mixture was added H_2O (10 ml) and stirred for 20 min at room temperature. The solution was concentrated in vacuo and the residue was added $CHCl_3$ and 1 N HClaq. The organic layer was washed with 1 N NaOHaq and dried over Na_2SO_4. The solution was removed in reduced pressure. The residue was washed with n-hexane to give alcohol as a colorless solid. To the CH_2Cl_2 suspention of dimethylsulfoxide (2.43 ml, 34.2 mmol) was added a solution of oxalyl chloride (1.47 ml, 17.1 mmol) in 50 ml of dry CH_2Cl_2 at −78 °C, and the resulting mixture was stirred for 20 min. CH_2Cl_2 (15 ml) solution of the alcohol was added at −78 °C. The mixture was allowed to warm to −40 °C for 1 h. The mixture was added triethylamine (7.89 ml, 57.0 mmol), allowed to warm to room temperature, and was treated with 0.1 N HClaq. The organic layer was washed with saturated Na_2CO_3aq, dried over Na2SO4, and concentrated in vacuo to give the title compound (1.33 g, 37%) as a colorless solid after trituration with n-hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.28 (1H, m), 7.41–7.47 (1H, m), 7.58–7.64 (1H, m), 10.42 (1H, d, J = 3.2 Hz). MS (EI) m/z 158 M$^+$.

4.1.68. *N*-{4-Chloro-2-[(2-chloro-5-fluorophenyl)(hydroxy)-methyl]phenyl}-2,2-dimethylpropanamide (34F)

Compound **34F** was prepared from **33** in a similar manner described for **34D** in 46% yield as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (9H, s), 3.90 (1H, d, J = 3.5 Hz), 5.99 (1H, d, J = 3.5 Hz), 6.93 (1H, br s), 6.98–7.04 (1H, m), 7.27–7.36 (3H, m), 7.63 (1H, d, J = 8.8 Hz), 8.21 (1H, br s). MS (FAB) m/z 371 (M+H)$^+$.

4.1.69. {5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}(2-chloro-5-fluorophenyl)methanol (31F)

Compound **31F** was prepared from **34F** in a similar manner described for **31D** in 87% yield as a pale yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (9H, s), 2.85 (2H, s), 6.09 (1H, s), 6.63 (1H, d, J = 8.8 Hz), 6.90 (1H, d, J = 2.4 Hz), 6.98–7.07 (1H, m), 7.14–7.21 (2H, m), 7.37 (1H, dd, J = 5.1, 8.8 Hz). MS (FAB) m/z 357 (M+H)$^+$.

4.1.70. Methyl 4-[{4-chloro-2-[(2-chloro-5-fluorophenyl)-(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35F)

Compound **35F** was prepared from **31F** in a similar manner described for **6** in 67% yield as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 0.90 (0.92) (9H, s), 2.17–2.24 (1H, m), 2.33–2.45 (2H, m), 2.88–2.98 (1H, m), 3.16 (1H, d, J = 13.7 Hz), (3.61) 3.69 (3H, s), 4.50 (1H, d, J = 13.7 Hz), 4.97 (1H, d, J = 5.4 Hz), 6.07 (6.30) (1H, d, J = 5.4 Hz), 6.94 (1H, d, J = 2.0 Hz), 6.97–7.03 (1H, m), 7.27–7.35 (3H, m), 7.60–7.64 (1H, m). IR (ATR) cm^{-1} 3338, 3266, 2950, 1729, 1625, 1587, 1465, 1434, 1396, 1357, 1290, 1263, 1199, 1170, 1114, 1064, 1031, 998, 943, 904, 873, 819. MS (FAB) m/z 470 (M+H)$^+$.

4.1.71. 4-[{4-Chloro-2-[(2-chloro-5-fluorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (36F)

Compound **36F** was prepared from **35F** in a similar manner described for **7** in 97% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90 (0.91) (9H, s), (1.50–1.58) (2.08–2.15) 2.22–2.49 (2.78–2.88) (4H, m), 3.04 (3.07) (1H, d, J = 13.7 Hz), 4.48 (4.53) (1H, d, J = 13.7 Hz), 6.01 (6.25) (1H, s), 6.88 (1H, d, J = 2.2 Hz), 6.94–7.07 (7.08–7.14) (2H, m), 7.20–7.33 (2H, m), 7.48–7.51 (7.58–7.60) (1H, m). IR (ATR) cm^{-1} 2954, 1710, 1637, 1587, 1469, 1396, 1324, 1261, 1170, 1112, 1052, 1027, 966, 941, 902, 885, 813. MS (FAB) m/z 456 (M+H)$^+$. Anal. Calcd for $C_{22}H_{24}Cl_2FNO_4{\cdot}0.3CHCl_3$: C, 54.75; H, 4.94; N, 2.83; found: C, 54.58; H, 5.02; N, 2.91.

4.1.72. Ethyl 1-{4-[{4-chloro-2-[(2-chloro-5-fluorophenyl)-(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37F)

Compound **37F** was prepared from **36F** in a similar manner described for **8** in 71% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.89) 0.92 (9H, s), 1.24 (1.26) (3H, t, J = 7.1 Hz), (1.48–1.74) 1.78–1.99 (3H, m), 2.07–2.23 (2H, m), 2.33–2.54 (2H, m), (2.55–2.65) 2.71–2.96 (2H, m), 3.00–3.19 (2H, m), 3.33 (1H, d, J = 13.4 Hz), 3.72–3.87 (1H, m), 4.07–4.16 (2H, m), 4.18–4.43 (1H, m), 4.52 (4.54) (1H, d, J = 13.4 Hz), 6.04–6.09 (6.22–6.26) (1H, m), (6.55) 6.62 (1H, d, J = 5.2 Hz), 6.90 (1H, s), 6.92–7.11 (1H, m), (7.05–7.17) 7.20–7.32 (7.40–7.52) (2H, m), 7.69–7.75 (1H, m). IR (ATR) cm^{-1} 3330, 2952, 2863, 1727, 1625, 1467, 1392, 1365, 1313, 1261, 1170, 1112, 1035, 946, 902, 875, 813. MS (FAB) m/z 595 (M+H)$^+$. Anal. Calcd for $C_{30}H_{37}Cl_2FN_2O_5$: C, 60.37; H, 6.27; N, 4.71; found: C, 60.50; H, 6.26; N, 4.70.

4.1.73. Ethyl 1-{4-[{4-chloro-2-[(2-chloro-5-fluorophenyl)-(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate (38F)

Compound **38F** was prepared from **36F** in a similar manner described for **8** in 73% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.89) 0.92 (9H, s), 1.18–1.28 (3H, m), (1.30–1.45) 1.47–1.86 (3H, m), 1.96–2.23 (3H, m), 2.28–2.51 (2.55–2.72) (2H, m), 2.83–3.24 (2H, m), 3.27–3.36 (3.46–3.53) (1H, m), 3.68–3.87 (3.94–4.02) (4.33–4.46) (4.68–4.73) (2H, m), 4.48–4.54 (2H, m), 6.04–6.12 (6.24–6.29) (1H, m), 6.54–6.65 (1H, m), 6.90 (1H, s), 6.92–7.02 (1H, m), (7.03–7.14) 7.18–7.30 (7.36–7.57) (2H, m), 7.69–7.77 (1H, m). IR (ATR) cm^{-1} 3320, 2950, 2865, 1727, 1625, 1467, 1392, 1365, 1309, 1278, 1249, 1172, 1112, 1029, 960, 902, 813. MS (FAB) m/z 595 (M+H)$^+$. Anal. Calcd for $C_{30}H_{37}Cl_2FN_2O_5$: C, 60.50; H, 6.26; N, 4.70; found: C, 60.48; H, 6.33; N, 4.64.

4.1.74. 1-{4-[{4-Chloro-2-[(2-chloro-5-fluorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-4-carboxylic acid (39F)

Compound **39F** was prepared from **37F** in a similar manner described for **9** in 64% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.92 (9H, s), 1.50–1.75 (2H, m), 1.77–2.04 (3H, m), 2.07–2.29 (2H, m), 2.30–2.70 (2H, m), 2.72–3.40 (3H, m), 3.71–3.90 (1H, m), 4.18–4.58 (2H, m), 5.99–6.27 (1H, m), 6.46–7.09 (3H, m), 7.11–7.54 (2H, m), 7.60–7.83 (1H, m). IR (ATR) cm^{-1} 2950, 2865, 1725, 1619, 1587, 1469, 1407, 1365, 1265, 1170, 1112, 1029, 964, 929, 902, 875, 813. MS (FAB) m/z 567 (M+H)$^+$. Anal. Calcd for $C_{28}H_{33}Cl_2FN_2O_5 \cdot 0.3CHCl_3$: C, 56.60; H, 5.53; N, 4.62; found: C, 56.85; H, 5.72; N, 4.57.

4.1.75. 1-{4-[{4-Chloro-2-[(2-chloro-5-fluorophenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-3-carboxylic acid (40F)

Compound **40F** was prepared from **38F** in a similar manner described for **9** in 80% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.91 (9H, s), 1.18–1.90 (5H, m), 1.91–3.55 (7H, m), 3.71–4.07 (1H, m), 4.34–4.70 (2H, m), 6.01–6.16 (6.19–6.28) (1H, m), 6.85–7.10 (2H, m), 7.13–7.54 (3H, m), 7.63–7.79 (1H, m). IR (ATR) cm^{-1} 2952, 2865, 1725, 1619, 1587, 1469, 1409, 1365, 1249, 1172, 1112, 1052, 1029, 960, 902, 875, 813. MS (FAB) m/z 567 (M+H)$^+$. Anal. Calcd for $C_{28}H_{33}Cl_2FN_2O_5 \cdot 0.4CHCl_3$: C, 55.79; H, 5.43; N, 4.52; found: C, 55.41; H, 5.57; N, 4.43.

4.1.76. *N*-{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-phenyl}-2,2-dimethylpropanamide (34G)

Compound **34G** was prepared from **33** in a similar manner described for **34D** in 76% yield as a colorless crystal. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (9H, s), 3.93 (3H, s), 4.10 (1H, d, J = 4.4 Hz), 5.99 (1H, d, J = 4.6 Hz), 6.82–6.93 (2H, m), 6.96–7.00 (2H, m), 7.28–7.35 (2H, m), 8.20 (1H, d, J = 8.8 Hz), 9.20 (1H, br). IR (ATR) cm^{-1} 3313, 2958, 1645, 1510, 1394, 1254, 1039, 818, 746, 654. MS (ESI) m/z 348 (M+H)$^+$.

4.1.77. {5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}-(2-methoxyphenyl)methanol (31G)

Compound **31G** was prepared from **34G** in a similar manner described for **31D** in 49% yield as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 0.92 (9H, s), 2.83 (2H, s), 3.27 (1H, br s), 3.89 (3H, s), 4.86 (1H, br s), 5.99 (1H, s), 6.58 (1H, d, J = 8.5 Hz), 6.91–7.00 (3H, m), 7.09–7.15 (2H, m), 7.28–7.34 (1H, m). IR (ATR) cm^{-1} 3421, 2954, 1601, 1508, 1464, 1240, 1026, 752. MS (ESI) m/z 334 (M+H)$^+$.

4.1.78. Methyl 4-[{4-chloro-2-[hydroxy(2-methoxyphenyl)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35G)

Compound **35G** was prepared from **31G** in a similar manner described for **6** in 79% yield as a colorless solid. ^{1}H NMR ($CDCl_3$) δ (0.91) 0.93 (9H, s), (0.95–1.10) (1.76–1.88) 2.15–2.47 (3H, m), (2.64–2.70) 2.78–2.94 (1H, m), (2.95) 3.05 (1H, d, J = 13.4 Hz), (3.58) 3.68 (3H, s), 3.73 (3.82) (3H, s), 4.41–4.47 (1H, m), 4.60 (1H, d, J = 5.1 Hz), 6.09 (6.23) (1H, d, J = 5.1 Hz), 6.84–6.91 (2H, m), 7.05–7.11 (2H, m), 7.16–7.18 (1H, m), 7.21–7.35 (1H, m), 7.65–7.69 (7.82–7.85) (1H, m). IR (ATR) cm^{-1} 3373, 2949, 1738, 1635, 1242, 1167, 1038, 748. MS (ESI) m/z 448 (M+H)$^+$. Anal. Calcd for $C_{24}H_{30}ClNO_5$: C, 64.35; H, 6.75; Cl, 7.91; N, 3.13; found: C, 64.27; H, 6.76; Cl, 8.02; N, 3.13.

4.1.79. 4-[{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (36G)

Compound **36G** was prepared from **35G** in a similar manner described for **7** in 93% yield as a colorless amorphous. ^{1}H NMR (DMSO-d_6) δ 0.85 (9H, s), (0.90–1.05) (1.73–1.86) 2.07–2.40 (4H, m), 2.81 (3.01) (1H, d, J = 14.0 Hz), 3.65 (3.66) (3H, s), 4.27 (4.34) (1H, d, J = 13.5 Hz), 5.75 (5.81) (1H, s), 5.85 (6.06) (1H, d, J = 4.9 Hz), 6.86–7.08 (3H, m), 7.17–7.61 (4H, m). IR (ATR) cm^{-1} 3421, 2964, 1734, 1643, 1475, 1394, 1246, 1169, 1028, 756. MS (ESI) m/z 434 (M+H)$^+$. Anal. Calcd for $C_{23}H_{28}ClNO_5 \cdot 0.1CH_2Cl_2$: C, 62.71; H, 6.42; Cl, 9.62; N, 3.17; found: C, 63.03; H, 6.44; Cl, 9.37; N, 3.12.

4.1.80. Ethyl 1-{4-[{4-chloro-2-[hydroxy(2-methoxyphenyl)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-4-carboxylate (37G)

Compound **37G** was prepared from **36G** in a similar manner described for **8** in 91% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.91) 0.97 (9H, s), 1.14–1.28 (4H, m), 1.55–1.71 (1H, m), 1.74–1.98 (2H, m), 2.02–2.23 (2H, m), 2.34–2.53 (2H, m), 2.66–2.90 (2H, m), 2.96–3.19 (2H, m), 3.21–3.34 (1H, m), 3.69 (3H, s), 3.73–3.89 (1H, m), 4.12 (2H, q, J = 7.0 Hz), 4.19–4.55 (2H, m), 6.04–6.41 (1H, m), 6.85 (1H, d, J = 8.3 Hz), 7.03–7.13 (2H, m), 7.15–7.34 (2H, m), 7.79–7.92 (1H, m).

IR (ATR) cm^{-1} 3309, 2964, 1730, 1660, 1624, 1444, 1394, 1240, 1176, 1028, 750. MS (ESI) m/z 573 (M+H)$^+$. Anal. Calcd for $C_{31}H_{41}ClN_2O_6$: C, 64.97; H, 7.21; Cl, 6.19; N, 4.89; found: C, 64.71; H, 7.22; Cl, 6.59; N, 4.90.

4.1.81. Ethyl 1-{4-[{4-chloro-2-[hydroxy(2-methoxyphenyl)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-3-carboxylate (38G)

Compound **38G** was prepared from **36G** in a similar manner described for **8** in 69% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.97 (9H, s), 1.14–1.39 (4H, m), 1.55–1.84 (2H, m), 1.89–2.88 (6H, m), 2.94–3.35 (3H, m), 3.40–3.90 (2H, m), 3.69 (3H, s), 3.94–4.19 (2H, m), 4.33–4.58 (2H, m), 6.05–6.41 (2H, m), 6.85 (1H, d, J = 8.8 Hz), 7.02–7.13 (2H, m), 7.17–7.35 (3H, m),

7.80–7.94 (1H, m). IR (ATR) cm^{-1} 3354, 2954, 1732, 1664, 1628, 1473, 1406, 1242, 1163, 1030, 752. MS (ESI) *m*/*z* 573 $(M+H)^+$. Anal. Calcd for $C_{31}H_{41}ClN_2O_6$: C, 64.97; H, 7.21; Cl, 6.19; N, 4.89; found: C, 64.93; H, 7.26; Cl, 6.37; N, 4.87.

4.1.82. 1-{4-[{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (39G)

Compound **39G** was prepared from **37G** in a similar manner described for **9** in 92% yield as a colorless amorphous. ^1H NMR (DMSO-d_6) δ (0.85) 0.86 (5H, s), 0.88–1.04 (1H, m), 1.20–1.55 (2H, m), 1.69–1.89 (2H, m), 2.03–2.20 (1H, m), 2.26–2.76 (4H, m), 2.84–3.14 (2H, m), 3.53–3.86 (1H, m), (3.66) 3.67 (3H, s), 4.05–4.20 (1H, m), 4.29 (4.34) (1H, d, *J* = 13.7 Hz), 5.79–6.09 (2H, m), 6.86–7.10 (2H, m), 7.17–7.27 (1H, m), 7.29–7.43 (2H, m), 7.49–7.60 (2H, m). IR (ATR) cm^{-1} 2952, 1726, 1620, 1483, 1396, 1284, 1242, 1171, 1030, 750. MS (ESI) *m*/*z* 545 $(M+H)^+$. Anal. Calcd for $C_{29}H_{37}ClN_2O_6$: C, 63.90; H, 6.84; Cl, 6.50; N, 5.14; found: C, 63.84; H, 6.91; Cl, 6.63; N, 5.03.

4.1.83. 1-{4-[{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (40G)

Compound **40G** was prepared from **38G** in a similar manner described for **9** in 90% yield as a colorless amorphous. ^1H NMR (DMSO-d_6) δ (0.85) 0.86 (7H, s), 0.94–1.34 (1H, m), 1.45–1.72 (2H, m), 1.83–2.24 (3H, m), 2.26–2.71 (3H, m), 2.84–3.09 (2H, m), 3.15–3.88 (2H, m), 3.67 (3H, s), 4.24–4.42 (2H, m), 5.80–6.09 (2H, m), 6.86–7.10 (2H, m), 7.17–7.28 (1H, m), 7.29–7.42 (2H, m), 7.47–7.60 (2H, m). IR (ATR) cm^{-1} 2951, 1728, 1622, 1475, 1396, 1240, 1167, 1115, 1030, 756. MS (ESI) *m*/*z* 545 $(M+H)^+$. Anal. Calcd for $C_{29}H_{37}ClN_2O_6$: C, 63.90; H, 6.84; Cl, 6.50; N, 5.14; found: C, 64.03; H, 7.09; Cl, 6.49; N, 4.90.

4.1.84. *N*-{4-Chloro-2-[hydroxy(3-methoxyphenyl)methyl]-phenyl}-2,2-dimethylpropanamide (34H)

Compound **34H** was prepared from **33** in a similar manner described for **34D** in quantum yield. ^1H NMR ($CDCl_3$) δ 1.09 (9H, s), 3.35–3.38 (1H, m), 3.76 (3H, s), 5.79 (1H, br s), 6.80–6.94 (1H, m), 7.08 (1H, d, *J* = 2.5 Hz), 7.22–7.30 (2H, m), 8.11 (1H, d, *J* = 8.8 Hz), 8.72 (1H, br s). MS (ESI) *m*/*z* 348 $(M+H)^+$.

4.1.85. {5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}-(3-methoxyphenyl)methanol (31H)

Compound **31H** was prepared from **34H** in a similar manner described for **31D** in quantum yield. ^1H NMR ($CDCl_3$) δ 0.83 (9H, s), 2.58 (1H, br s), 2.73 (2H, s), 3.78 (3H, s), 4.37 (1H, br s), 5.72 (1H, s), 6.55 (1H, d, *J* = 8.6 Hz), 6.82–6.85 (1H, m), 6.82–6.85 (1H, m), 7.06 (1H, d, *J* = 2.5 Hz), 7.06 (1H, d, *J* = 2.5 Hz), 7.13 (1H, dd, *J* = 8.6, 2.7 Hz,), 7.24–7.28 (1H, m). MS (ESI) *m*/*z* 334 $(M+H)^+$.

4.1.86. Methyl 4-[{4-chloro-2-[hydroxy(3-methoxyphenyl)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35H)

Compound **35H** was prepared from **31H** in a similar manner described for **6** in 86% yield. ^1H NMR ($CDCl_3$) δ (0.90) 0.91 (9H, s), (1.81–1.91) 2.09–2.22 and 2.23–2.44 (2.63–2.78) (2.93–3.05) (4H, m), 2.60 (2.86) (1H, d, *J* = 13.5 Hz), 3.59 (3.69) (3H, s), (3.78) 3.82 (3H, s), (4.47) 4.49 (1H, d, *J* = 13.5 Hz), (4.66–4.75), 5.76–5.88 (1H, m), 6.77–6.90 (6.92–6.97), (7.03–7.06) (2H, m), 7.32–7.19 (4H, m), (7.40) 7.89 (1H, d, *J* = 2.0 Hz). MS (ESI) *m*/*z* 448 $(M+H)^+$. Anal. Calcd for $C_{24}H_{30}ClNO_5 \cdot 0.25H_2O$: C, 63.71; H, 6.79; N, 3.09; found: C, 63.83; H, 6.77; N, 2.66.

4.1.87. 4-[{4-Chloro-2-[hydroxy(3-methoxyphenyl)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (36H)

Compound **36H** was prepared from **35H** in a similar manner described for **7** in quantum yield. ^1H NMR ($CDCl_3$) δ (0.88) 0.91 (9H, s), 2.06 (1H, d, *J* = 12.5 Hz), (1.88–1.98) 2.08–2.25 (2H, m), 2.30–2.45 (2.63–2.76) (2H, m), (2.51) 2.90 (1H, d, *J* = 13.5 Hz), 3.76 (3H, s), (3.80) 3.82 (3H, s), (4.39) 4.48 (1H, d, *J* = 13.5 Hz), 4.67 (1H, s), (5.78) 5.74 (1H, s), 6.75–6.87 (3H, m), 6.91–6.98 (1H, m), 7.32–7.17 (2H, m), (7.39) 7.90 (1H, d, *J* = 2.5 Hz). MS (ESI) *m*/*z* 434 $(M+H)^+$. Anal. Calcd for $C_{23}H_{28}ClNO_5$: C, 63.66; H, 6.50; N, 3.23; found: C, 63.47; H, 6.70; N, 2.76.

4.1.88. Ethyl 1-{4-[{4-chloro-2-[hydroxy(3-methoxyphenyl)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-4-carboxylate (37H)

Compound **37H** was prepared from **36H** in a similar manner described for **8** in 98% yield. ^1H NMR ($CDCl_3$) δ (0.89) 0.93 (9H, s), (1.21–1.29) 1.48–1.62 (2H, m), 1.77–2.10 (3H, m), 2.13–2.28 (1H, m), 2.36–2.60 (2H, m), 2.69 (1H, d, *J* = 13.0 Hz), (2.95–3.21) 2.72–2.91 (2H, m), (3.78) 3.82 (3H, s), 4.08–4.19 (2H, m), 4.22–4.47 (1H, m), 4.51 (4.53) (1H, d, *J* = 13.5 Hz), 5.80–5.93 (1H, m), 6.12 (1H, d, *J* = 5.6 Hz), 6.17 (1H, d, *J* = 5.1 Hz), 6.75–6.92 (2H, m), 7.07–7.11 (1H, m), 7.17–7.38 (7.83–7.74) (3H, m). MS (ESI) *m*/*z* 573 $(M+H)^+$. Anal. Calcd for $C_{31}H_{41}ClN_2O_6$: C, 64.97; H, 7.21; N, 4.89; found: C, 64.78; H, 7.26; N, 4.83.

4.1.89. Ethyl 1-{4-[{4-chloro-2-[hydroxy(3-methoxyphenyl)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-3-carboxylate (38H)

Compound **38H** was prepared from **36H** in a similar manner described for **8** in 95% yield. ^1H NMR ($CDCl_3$) δ (0.89) 0.93 (9H, s), 1.20–1.31 (1H, m), 1.32–1.88 (3H, m), 1.92–2.12 (3H, m), 2.13–2.52 (2H, m), 2.54–2.86 (2H, m), 2.89–3.29 (3.47–3.56) (2H, m), (3.77) 3.82 (3H, s), 4.06–4.20 (2H, m), (4.64–4.72) 4.29–4.60 (2H, m), 5.80–5.92 (1H, m), 6.08–6.21 (1H, m), 6.75–6.91 (3H, m), 7.06–7.12 (1H, m), 7.19–7.30 (2H, m), 7.31–7.40 (7.81–7.72) (1H, m). MS (ESI) *m*/*z* 573 $(M+H)^+$. Anal. Calcd for $C_{31}H_{41}ClN_2O_6$: C, 64.97; H, 7.21; N, 4.89; found: C, 64.75; H, 7.25; N, 4.71.

4.1.90. 1-{4-[{4-Chloro-2-[hydroxy(3-methoxyphenyl)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (39H)

Compound **39H** was prepared from **37H** in a similar manner described for **9** in quantum yield. ^1H NMR ($CDCl_3$) δ (0.89) 0.92 (9H, s), (1.07–1.17) 1.48–1.74 (2H, m), 1.77–2.11 (3H, m), 2.14–2.30 (1H, m), 2.37–2.61 (2H, m), 2.65–2.90 (2H, m), 2.97–3.21 (2H, m), (3.77) 3.82 (3H, s), 4.23–4.40 (2H, m), (4.51) 4.53 (1H, d, *J* = 13.2 Hz), 5.83 (1H, s), 5.90 (1H, d, *J* = 4.2 Hz), 6.75–6.91 (3H, m), 7.06–7.10 (1H, m), 7.18–7.30 (2H, m), 7.32–7.39 (7.81–7.77) (1H, m). MS (ESI) *m*/*z* 545 $(M+H)^+$. Anal. Calcd for $C_{29}H_{37}ClN_2O_6$: C, 63.90; H, 6.84; N, 5.14; found: C, 63.64; H, 7.16; N, 4.79.

4.1.91. 1-{4-[{4-Chloro-2-[hydroxy(3-methoxyphenyl)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (40H)

Compound **40H** was prepared from **38H** in a similar manner described for **9** in quantum yield. ^1H NMR ($CDCl_3$) δ 0.89 (0.93) (9H, s), 1.02–1.58 (2H, m), 1.60–1.90 (1H, m), 1.96–2.59 (5H, m), 2.62–2.91 (1H, m), 2.93–3.27 (2H, m), 3.30–3.94 (1H, m), (3.78) 3.82 (3H, s), 4.31–4.55 (2H, m), 5.78–5.92 (1H, m), 6.75–6.92 (3H, m), 7.04–7.10 (1H, m), 7.17–7.31 (7.70–7.82) (2H, m), 7.32–7.41 (1H, m). MS (ESI) *m*/*z* 545 $(M+H)^+$. Anal. Calcd for $C_{29}H_{37}ClN_2O_6$: C, 63.90; H, 6.84; N, 5.14; found: C, 64.03; H, 7.15; N, 4.87.

4.1.92. *N*-{4-Chloro-2-[(2-ethoxyphenyl)(hydroxy)methyl]-phenyl}-2,2-dimethylpropanamide (34I)

Compound **34I** was prepared from **33** in a similar manner described for **34D** in quantum yield. ^{1}H NMR ($CDCl_3$) δ 1.10 (9H, s), 1.44 (3H, d, J = 7.2 Hz), 4.05–4.25 (2H, m), 4.29 (1H, d, J = 4.4 Hz), 5.99 (1H, d, J = 3.7 Hz), 6.80–6.93 (1H, m), 6.96 (1H, d, J = 8.1 Hz), 7.01 (1H, d, J = 2.5 Hz), 7.23–7.33 (2H, m), 8.20 (1H, d, J = 8.8 Hz), 9.19 (1H, br s). MS (ESI) m/z 362 $(M+H)^+$.

4.1.93. {5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}-(2-ethoxyphenyl)methanol (31I)

Compound **31I** was prepared from **34I** in a similar manner described for **31D** in quantum yield. ^{1}H NMR ($CDCl_3$) δ 0.91 (9H, s), 1.40 (3H, t, J = 6.9 Hz), 2.82 (2H, s), 3.37 (1H, br s), 4.06–4.16 (2H, m), 4.78 (1H, s), 5.98 (1H, s), 6.57 (1H, d, J = 8.6 Hz), 6.85–6.96 (2H, m), 6.99 (1H, d, J = 2.7 Hz,), 7.09–7.14 (1H, m), 7.23–7.30 (1H, m). MS (ESI) m/z 348 $(M+H)^+$.

4.1.94. Methyl 4-[{4-chloro-2-[(2-ethoxyphenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35I)

Compound **35I** was prepared from **34I** in a similar manner described for **6** in 91% yield. ^{1}H NMR ($CDCl_3$) δ 0.89 (9H, s), 0.90 (10H, s), 1.29 (3H, t, J = 7.4 Hz), 1.47 (10H, t, J = 7.1 Hz), (0.72–0.83) 1.66–1.76 (1H, m), (2.08–2.18) 2.23–2.34 and 2.36–2.52 (2.73–2.83) (3H, m), 2.80 (2.89) (1H, d, J = 13.7 Hz), 2.93 (4.15) (1H, d, J = 5.4 Hz), (3.57) 3.68 (3H, s), 3.99–4.17 (2H, m), 4.37 (4.45) (1H, d, J = 13.5 Hz), (6.11) 6.19 (1H, d, J = 5.1 Hz), 6.81–6.91 (2H, m), 6.98–7.04 (1H, m), 7.17–7.33 (7.45–7.51) (7.96–7.94) (4H, m). MS (ESI) m/z 462 $(M+H)^+$. Anal. Calcd for $C_{25}H_{32}ClNO_5$: C, 65.00; H, 6.98; N, 3.03; found: C, 64.65; H, 7.05; N, 2.84.

4.1.95. 4-[{4-Chloro-2-[(2-ethoxyphenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (36I)

Compound **35I** was prepared from **34I** in a similar manner described for **7** in quantum yield. ^{1}H NMR ($CDCl_3$) δ 0.88 (0.92) (9H, s), 1.30 (1.48) (3H, t, J = 7.1 Hz), (1.76–1.86) 1.95–2.14 (1H, m), 2.31–2.47 (2H, m), 2.51–2.60 (2.62–2.72) (2H, m), 2.74 (2.92) (1H, d, J = 13.7 Hz), 3.97–4.14 (2H, m), 4.36 (4.48) (1H, d, J = 13.7 Hz), 6.06 (6.23) (1H, s), 6.83–6.92 (2H, m), 6.97–7.03 (2H, m), 7.13–7.40 (8.03–7.99) (4H, m). MS (ESI) m/z 448 $(M+H)^+$. Anal. Calcd for $C_{24}H_{30}ClNO_5 \cdot 0.25H_2O$: C, 63.71; H, 6.79; N, 3.09; found: C, 63.78; H, 6.73; N, 2.96.

4.1.96. Ethyl 1-{4-[{4-chloro-2-[(2-ethoxyphenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-4-carboxylate (37I)

Compound **37I** was prepared from **36I** in a similar manner described for **8** in 99% yield. ^{1}H NMR ($CDCl_3$) δ (0.94) 0.94 (9H, s), 1.17–1.28 (6H, m), (1.44–1.72) 1.76–1.99 (3H, m), 2.10–2.29 (2H, m), 2.37–2.54 (2H, m), 2.72–2.92 (1H, m), 2.95–3.19 (3H, m), 3.78–3.89 (1H, m), 4.02–4.18 (4H, m), 4.22–4.32 (1H, m), 4.36–4.45 (1H, m), 4.48 (1H, d, J = 13.7 Hz), (5.89) 6.08 (1H, d, J = 5.1 Hz), 6.12–6.18 (1H, m), 6.86 (1H, d, J = 8.3 Hz), 6.98–7.09 (1H, m), 7.12–7.16 (1H, m), 7.19–7.31 (7.92–7.73) (4H, m). MS (ESI) m/z 587 $(M+H)^+$. Anal. Calcd for $C_{32}H_{43}ClN_2O_6$: C, 65.46; H, 7.38; N, 4.77; found: C, 65.37; H, 7.47; N, 4.66.

4.1.97. Ethyl 1-{4-[{4-chloro-2-[(2-ethoxyphenyl)(hydroxy)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-3-carboxylate (38I)

Compound **38I** was prepared from **36I** in a similar manner described for **8** in 93% yield. ^{1}H NMR ($CDCl_3$) δ (0.90) 0.94 (9H, s), 1.17–1.31 (6H, m), 1.33–1.86 (3H, m), 1.93–2.53 (4H, m), 2.55–2.93 (2H, m), 2.95–3.29 (3H, m), (3.47) 3.49 (1H, d, J = 13.5 Hz), 3.56–3.90 (1H, m), 4.02–4.21 (4H, m), 4.32–4.60 (4.70–4.78) (1H, m), 4.47 (4.49) (1H, d, J = 13.5 Hz), (5.92) 6.01 (1H, d, J = 5.1 Hz), (6.09) 6.12–6.20 (1H, m), 6.81–6.89 (1H, m), 6.97–7.09 (1H, m), 7.11–7.40 (4H, m), 7.74–7.83 (7.92–7.89) (1H, m). MS (ESI) m/z 587 $(M+H)^+$. Anal. Calcd for $C_{32}H_{43}ClN_2O_6$: C, 65.46; H, 7.38; N, 4.77; found: C, 65.33; H, 7.48; N, 4.55.

4.1.98. 1-{4-[{4-Chloro-2-[(2-ethoxyphenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (39I)

Compound **39I** was prepared from **37I** in a similar manner described for **9** in quantum yield. ^{1}H NMR ($CDCl_3$) δ (0.90) 0.94 (9H, s), 1.20 (1.47) (3H, t, J = 7.1 Hz), 1.51–1.72 (2H, m), 1.76–2.02 (3H, m), 2.13–2.31 (2H, m), 2.36–2.59 (2H, m), 2.68–2.85 (1H, m), 2.89 (3.13) (1H, d, J = 13.5 Hz), 2.94–3.11 (3.63–3.73) (1H, m), 3.78–3.90 (1H, m), 4.23–4.43 (1H, m), (3.42–3.48) 4.00–4.12 (2H, m), 4.48 (4.49) (1H, d, J = 13.5 Hz), 6.16 (1H, d, J = 7.4 Hz), 6.80–6.89 (2H, m), 6.98–7.09 (1H, m), 7.11–7.39 (3H, m), 7.74–7.80 (7.92–7.88) (1H, m). MS (ESI) m/z 559 $(M+H)^+$. Anal. Calcd for $C_{30}H_{39}ClN_2O_6$: C, 64.45; H, 7.03; N, 5.01; found: C, 64.49; H, 7.17; N, 4.80.

4.1.99. 1-{4-[{4-Chloro-2-[(2-ethoxyphenyl)(hydroxy)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (40I)

Compound **40I** was prepared from **38I** in a similar manner described for **9** in quantum yield. ^{1}H NMR ($CDCl_3$) δ (0.90) 0.92 (9H, s), 1.16–1.25 (1.42–1.49) (3H, m), 1.57–1.87 (2H, m), 1.96–2.13 (1H, m), 2.14–2.32 (1H, m), 2.32–2.58 (2H, m), 2.61–3.27 (4H, m), 3.39–3.67 (1H, m), 3.69–3.92 (1H, m), 3.96–4.12 (2H, m), 4.32–4.56 (4.61–4.69) (1H, m), 6.09–6.19 (1H, m), 6.79–6.89 (2H, m), 6.97–7.08 (1H, m), 7.10–7.42 (3H, m), 7.67–7.81 (7.93–7.87) (1H, m). MS (ESI) m/z 559 $(M+H)^+$. Anal. Calcd for $C_{30}H_{39}ClN_2O_6$: C, 64.45; H, 7.03; N, 5.01; found: C, 64.48; H, 7.41; N, 4.68.

4.1.100. [5-Chloro-2-(2,2-dimethylpropylamino)phenyl]-(2,3-dimethoxyphenyl)methanol (31J)

Compound **31J** was prepared from **32** in a similar manner described for **31D**. ^{1}H NMR ($CDCl_3$) δ 0.92 (9H, s), 2.83 (2H, s), 3.83 (3H, s), 3.88 (3H, s), 5.99 (1H, s), 6.57 (1H, d, J = 8.5 Hz), 6.80 (1H, dd, J = 7.8, 1.5 Hz), 6.90 (1H, dd, J = 8.3, 1.5 Hz), 6.99 (1H, d, J = 2.4 Hz), 7.03 (1H, dd, J = 8.1, 7.8 Hz), 7.10 (1H, dd, J = 8.5, 2.4 Hz). Mp 118–119 °C (AcOEt–Hexane). MS (ESI) m/z 362 $(M+H)^+$.

4.1.101. *N*-{4-Chloro-2-[(2,3-dimethoxyphenyl)hydroxymethyl]-phenyl}-*N*-(2,2-dimethylpropyl)succinamic acid methyl ester (35J)

Compound **35J** was prepared from **31J** in a similar manner described for **6** in 96% yield. ^{1}H NMR ($CDCl_3$) δ 0.91 (0.94) (9H, s), (1.25–1.35) (1.85–1.95) 2.10–2.25 (3H, m), 2.82–2.93 (1H, m), 2.97 (3.08) (1H, d, J = 13.7 Hz), 3.59 (3.60) (3H, s), 3.68 (3.78) (3H, s), 3.83 (3.88) (3H, s), 4.46 (4.47) (1H, d, J = 13.7 Hz), 4.64 (1H, d, J = 5.1 Hz), 6.04 (6.09) (1H, d, J = 5.1 Hz), 6.73–7.74 (6H, m). MS (ESI) m/z 478 $(M+H)^+$.

4.1.102. *N*-{4-Chloro-2-[(2,3-dimethoxyphenyl)hydroxymethyl]-phenyl}-*N*-(2,2-dimethylpropyl)succinamic acid (36J)

Compound **36J** was prepared from **35J** in a similar manner described for **7** in quantum yield. ^{1}H NMR ($CDCl_3$) δ (0.91) 0.92 (9H, s), 1.18–1.39 (3.44–3.52) (1H, m), (1.91–2.01) 2.19–2.34 (2H, m), 2.38–2.53 (2.73–2.84) (2H, m), (2.96) 2.98 (1H, d, J = 13.9 Hz), 3.62 (3.78) (3H, s), (3.83) 3.87 (3H, s), (4.43) 4.47 (1H, d, J = 24.7 Hz), (6.05) 6.08 (1H, s), 6.70–7.23 (7.83–7.79) (6H, m). MS (ESI) m/z 464 $(M+H)^+$.

4.1.103. 1-{3-[{4-Chloro-2-[(2,3-dimethoxyphenyl)hydroxymethyl]phenyl}-(2,2-dimethylpropyl)carbamoyl]propionyl}piperidine-4-carboxylic acid ethyl ester (37J)

Compound **37J** was prepared from **36J** in a similar manner described for **8** in 62% yield. ^{1}H NMR ($CDCl_3$) δ 0.94 (9H, s), 1.21–1.25 (3H, m), 1.47–1.97 (4H, m), 2.09–2.22 (2H, m), 2.37–2.51 (2H, m), 2.73–2.92 (1H, m), 3.02–3.18 (2H, m), 3.28 (3.29) (1H, d, J = 13.7 Hz), 3.56 (3.57) (3H, s), 3.79–3.86 (1H, m), 3.87 (3H, s), 4.10–4.16 (2H, m), 4.22–4.28 (4.37–4.43) (1H, m), 4.51 (4.53) (1H, d, J = 13.7 Hz), 6.11 (6.12) (1H, d, J = 5.1 Hz), 6.28 (6.39) (1H, d, J = 5.1 Hz), 6.91–6.94 (1H, m), 7.09–7.24 (4H, m), 7.48–7.52 (1H, m). IR (ATR) cm^{-1} 3316 (br), 3000–2850 (br), 1733, 1662, 1625, 1477, 1442, 1394, 1317. Mp 152–153 °C (AcOEt–Hexane). MS (ESI) m/z 606, 604 (M+H)$^+$. Anal. Calcd for $C_{32}H_{43}ClN_2O_7$: C, 63.72; H, 7.19; Cl, 5.88; N, 4.64; found: C, 63.55; H, 7.26; Cl, 5.96; N, 4.51.

4.1.104. 1-{3-[{4-Chloro-2-[(2,3-dimethoxyphenyl)hydroxymethyl]phenyl}-(2,2-dimethylpropyl)carbamoyl]propionyl}piperidine-3-carboxylic acid ethyl ester (38J)

Compound **38J** was prepared from **36J** in a similar manner described for **8** in 51% yield. ^{1}H NMR ($CDCl_3$) δ 0.97 (9H, s), 1.2–1.33 (3H, m), 1.5–3.8 (13H, m), 3.56 (3.57) (3H, s), 3.87 (3H, s), 4.0–4.8 (4H, m), 6.12–6.13 (1H, m), 6.27–6.30, 6.35–6.39 (1H, m), 6.91 (6.93) (1H, s), 7.08–7.09 (1H, m), 7.15–7.25 (3H, m), 7.48–7.51 (1H, m). IR (ATR) cm^{-1} 3345, 3000–2800 (br), 1731, 1654, 1625, 1475, 1438, 1411, 1367, 1303, 1274. Mp 127–129 °C (AcOEt–Hexane). MS (ESI) m/z 606, 604 (M+H)$^+$. HRMS (FAB) m/z 603.2834 (calcd for $C_{32}H_{44}ClN_2O_7$: 603.2837). Anal. Calcd for $C_{32}H_{43}ClN_2O_7 \cdot 0.33C_6H_{14}$: C, 64.63; H, 7.60; Cl, 5.61; N, 4.43; found: C, 64.46; H, 7.70; Cl, 5.64; N, 4.26.

4.1.105. 1-{3-[{4-Chloro-2-[(2,3-dimethoxyphenyl)hydroxymethyl]phenyl}-(2,2-dimethylpropyl)carbamoyl]propionyl}piperidine-4-carboxylic acid (39J)

Compound **39J** was prepared from **37J** in a similar manner described for **9** in 91% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90 (0.97) (9H, s), 1.3–3.3 (13H, m), 3.562 (3.76) (3H, s), 3.83 (3.87) (3H, s), 4.25–4.6 (2H, m), 6.06 (6.12) (1H, s), 6.7–7.7 (6H, m). IR (ATR) cm^{-1} 2952 (br), 1727, 1625, 1477, 1270. MS (ESI) m/z 578, 576 (M+H)$^+$. Anal. Calcd for $C_{30}H_{39}ClN_2O_7 \cdot 0.3H_2O$: C, 62.07; H, 6.88; Cl, 6.11; N, 4.83; found: C, 62.06; H, 6.87; Cl, 6.10; N, 4.64.

4.1.106. 1-{3-[{4-Chloro-2-[(2,3-dimethoxyphenyl)hydroxymethyl]phenyl}-(2,2-dimethylpropyl)carbamoyl]propionyl}piperidine-3-carboxylic acid (40J)

Compound **40J** was prepared from **40J** in a similar manner described for **9** in 89% yield. ^{1}H NMR ($CDCl_3$) δ 0.90, 0.91, 0.95, 0.96 (total 9H, s each), 1.3–4.9 (20H, m), 4.3–4.7 (1H, m), 6.04–6.14 (1H, m), 6.7–7.7 (6H, m). IR (ATR) cm^{-1} 3050–2850 (br), 1727, 1623, 1477, 1272. MS (ESI) m/z 578, 576 (M+H)$^+$. Anal. Calcd for $C_{30}H_{39}ClN_2O_7 \cdot 0.3H_2O$: C, 62.07; H, 6.88; Cl, 6.11; N, 4.83; found: C, 62.12; H, 6.87; Cl, 6.03; N, 4.65.

4.1.107. *N*-{4-Chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl-(hydroxy)methyl]phenyl}-2,2-dimethylpropanamide (34K)

Compound **34K** was prepared from **33** in a similar manner described for **34D** in 77% yield as a pale yellow amorphous. ^{1}H NMR ($CDCl_3$) δ 1.16 (9H, s), 3.82 (1H, br s), 4.25–4.40 (4H, m), 5.97 (1H, s), 6.48–6.53 (1H, m), 6.78–6.82 (1H, m), 6.88–6.90 (1H, m), 6.97 (1H, s), 7.28–7.33 (1H, m), 8.17 (1H, d, J = 8.8 Hz), 9.15 (1H, br s). MS (CI) m/z 375 M$^+$.

4.1.108. {5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}-(2,3-dihydro-1,4-benzodioxin-5-yl)methanol (31K)

Compound **31K** was prepared from **34K** in a similar manner described for **31D** in 78% yield as a colorless syrup. ^{1}H NMR ($CDCl_3$) δ 0.95 (9H, s), 2.84 (2H, s), 4.27–4.36 (4H, m), 5.95 (1H, s), 6.59 (1H, d, J = 8.5 Hz), 6.70–6.78 (1H, m), 6.80–6.89 (2H, m), 6.93 (1H, d, J = 2.4 Hz), 7.10–7.14 (1H, m). MS (CI) m/z 361 M$^+$.

4.1.109. Methyl 4-[{4-chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35K)

Compound **35K** was prepared from **31K** in a similar manner described for **6** in 89% yield as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 0.89 (0.90) (9H, s), (1.80–1.88) 2.15–2.28 and 2.31–2.45 (2.82–2.90) (4H, m), 2.90 (2.99) (1H, d, J = 13.7 Hz), (3.59) 3.67 (3H, s), (4.08–4.15) 4.17–4.29 (4.29–4.38) (4H, m), 4.42 (4.44) (1H, d, J = 13.7 Hz), 4.50–4.53 (1H, m), 6.05 (6.23) (1H, d, J = 4.9 Hz), (6.63–6.69) 6.70–6.77 (1H, m), 6.83–6.92 (1H, m), 7.18–7.23 (2H, m), 7.87 (1H, s). IR (ATR) cm^{-1} 3409, 2952, 2875, 1735, 1644, 1600, 1473, 1407, 1363, 1324, 1280, 1241, 1193, 1166, 1087, 1039, 993, 956, 921, 889, 817. MS (FAB) m/z 476 (M+H)$^+$.

4.1.110. 4-[{4-Chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl-(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (36K)

Compound **36K** was prepared from **35K** in a similar manner described for **7** in 88% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.87) 0.91 (9H, s), (1.05–1.14) (1.87–1.96) 2.12–2.52 (2.76–2.83) (4H, m), 2.86 (2.94) (1H, d, J = 13.7 Hz), 4.10–4.33 (4H, m), (4.36) 4.47 (1H, d, J = 13.7 Hz), (6.00) 6.24 (1H, s), (6.61–6.64) 6.72–6.79 (1H, m), 6.82–6.90 (6.97–7.01) (1H, m), 7.15–7.33 (3H, m), 7.89 (1H, d, J = 2.4 Hz). IR (ATR) cm^{-1} 2950, 2875, 1710, 1637, 1602, 1473, 1396, 1280, 1257, 1193, 1168, 1087, 1051, 956, 921, 889, 817. MS (FAB) m/z 462 (M+H)$^+$. Anal. Calcd for $C_{23}H_{27}ClNO_5 \cdot 0.3CHCl_3$: C, 58.93; H, 5.69; N, 2.79; found: C, 59.38; H, 5.87; N, 2.83.

4.1.111. Ethyl 1-{4-[{4-chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37K)

Compound **37K** was prepared from **36K** in a similar manner described for **8** in 57% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.90) 0.93 (9H, s), 1.23 (1.25) (3H, t, J = 7.1 Hz), (1.59–1.80) 1.80–1.97 (3H, m), 2.07–2.32 (1H, m), 2.35–2.52 (3H, m), 2.68–3.30 (3H, m), 3.66–3.87 (1H, m), 4.02–4.52 (8H, m), 6.05–6.10 (1H, m), 6.18–6.21 (6.30–3.33)(1H, m), (6.61–6.66) 6.70–6.76 (1H, m), (6.82–6.84) 6.88–6.97 (1H, m), 7.12–7.42 (3H, m), 7.79–7.82 (7.97–8.00) (1H, m). IR (ATR) cm^{-1} 3340, 2950, 2873, 1727, 1625, 1473, 1392, 1363, 1313, 1280, 1259, 1170, 1089, 1039, 958, 921, 887, 817. MS (FAB) m/z 601 (M+H)$^+$. Anal. Calcd for $C_{32}H_{41}ClN_2O_7$: C, 63.94; H, 6.87; N, 4.66; found: C, 63.61; H, 6.86; N, 4.93.

4.1.112. Ethyl 1-{4-[{4-chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate (38K)

Compound **38K** was prepared from **36K** in a similar manner described for **8** in 84% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ (0.90) 0.93 (9H, s), 1.12–1.28 (3H, m), (1.32–1.45) 1.55–1.90 (3H, m), 1.92–2.52 (4H, m), 2.54–3.30 (3H, m), (3.42–3.52) 3.60–3.89 (1H, m), 4.10–4.37 (7H, m), 4.40–4.59 (4.68–4.4.74) (1H, m), 6.03–6.10 (1H, m), 6.16–6.34 (1H, m), 6.61–6.77 (1H, m), 6.78–6.977 (1H, m), 7.09–7.46 (7.78–7.82) (4H, m). IR (ATR) cm^{-1} 3322, 2948, 2867, 1727, 1625, 1473, 1392, 1363, 1311, 1280, 1257, 1174, 1114, 1087, 1051, 956, 921,

887, 817. MS (FAB) *m*/*z* 601 $(M+H)^+$. Anal. Calcd for $C_{32}H_{41}ClN_2O_7$: C, 63.94; H, 6.87; N, 4.66; found: C, 63.60; H, 6.91; N, 4.76.

4.1.113. 1-{4-[{4-Chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (39K)

Compound **39K** was prepared from **37K** in a similar manner described for **9** in 87% yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90 (0.93) (9H, s), 1.39–2.00 (4H, m), 2.06–2.59 (4H, m), 2.65–3.41 (4H, m), 3.62–3.89 (1H, m), 3.96–4.52 (6H, m), 6.10 (6.22) (1H, s), 6.53–6.78 (1H, m), 6.79–6.99 (1H, m), 7.00–7.43 (3H, m), 7.76–7.83 (1H, m). IR (ATR) cm^{-1} 2950, 2933, 2869, 1725, 1621, 1473, 1396, 1365, 1311, 1280, 1259, 1170, 1087, 1031, 956, 921, 889, 815. MS (FAB) *m*/*z* 573 $(M+H)^+$. Anal. Calcd for $C_{30}H_{37}ClN_2O_7 \cdot 0.4CHCl_3$: C, 59.13; H, 6.03; N, 4.48; found: C, 59.48; H, 6.27; N, 4.50.

4.1.114. 1-{4-[{4-Chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (40K)

Compound **40K** was prepared from **38K** in a similar manner described for **9** in quantum yield as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.90 (0.98) (9H, s), 1.18–1.92 (4H, m), 1.95–2.69 (4H, m), 2.71–3.34 (3H, m), 3.36–3.89 (2H, m), 3.90–4.62 (6H, m), 6.07 (6.20) (1H, s), 6.60–6.98 (2H, m), 6.99–7.43 (3H, m), 7.72–7.83 (1H, m). IR (ATR) cm^{-1} 2948, 2867, 1725, 1619, 1473, 1396, 1363, 1280, 1255, 1170, 1116, 1087, 1051, 1008, 956, 921, 889, 815. MS (FAB) *m*/*z* 573 $(M+H)^+$. Anal. Calcd for $C_{30}H_{37}ClN_2O_7 \cdot 0.6CHCl_3$: C, 57.48; H, 5.81; N, 4.30; found: C, 57.80; H, 6.10; N, 4.35.

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

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.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.01.065. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Tobert, J. A. *Nat. Rev. Drug. Disc.* **2003**, *2*, 517; (b) Havel, R. J.; Rapaport, E. *N. Eng. J. Med.* **1995**, *332*, 1491; (c) Shepherd, J. et al *N. Eng. 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. (a) Abe, I.; Tomesch, J. C.; Wattanasin, S.; Prestwich, G. D. *Nat. Prod. Rep.* **1994**, *11*, 279; (b) Rosenberg, S. H. *Expert Opin. Ther. Pat.* **1998**, *8*, 521.
4. One of the original squalene synthase inhibitors, zaragozic acid A, caused acidosis in rats and dogs; however, the adverse effect was not shown in monkeys. It might be species-dependent toxicity. Please refer the following articles: (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.
5. (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) Ishihara, T.; Kakuta, H.; Moritani, H.; Ugawa, T.; Yanagisawa, I. *Bioorg. Med. Chem.* **2004**, *12*, 5899; (c) Ishihara, T.; Kakuta, H.; Moritani, H.; Ugawa, T.; Sakamoto, S.; Tsukamoto, S.; Yanagisawa, I. *Bioorg. Med. Chem.* **2003**, *11*, 2403; (d) Miki, T.; Kori, M.; Mabuchi, H.; Tozawa, R.; Nishimoto, T.; Sugiyama, Y.; Teshima, K.; Yukimasa, H. *J. Med. Chem.* **2002**, *45*, 4571; (e) Miki, T.; Kori, M.;

Mabuchi, H.; Banno, H.; Tozawa, R.; Nakamura, M.; Itokawa, S.; Sugiyama, Y.; Yukimasa, H. *Bioorg. Med. Chem.* **2002**, *10*, 401.
6. Usui, H.; Kagechika, K.; Nagashima, H. WO1998/029380.
7. Yukimasa, H.; Sugiyama, Y.; Tozawa, R. WO1997/010224.
8. Usui, H.; Katakura, S.; Suzuki, M. *Jpn. Kokai Tokkyo Koho*. **2001**, 131 (JP 2001/354587). The atomic coordinates have been deposited with Protein Data Bank (PDB code: 3Q30 and 3Q2Z).
9. Hendrickson, J. B.; Singer, M.; Hussoin, M. S. *J. Org. Chem.* **1993**, *58*, 6913.
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) Ieiri, I.; Sugiyama, Y.; Higuchi, S. *Expert Opin. Drug Metab. Toxicol.* **2009**, *5*, 703; (b) Shitara, Y.; Horie, T.; Sugiyama, Y. *Eur. J. Pharm. Sci.* **2006**, *27*, 425.
12. (a) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398; (b) Oki, M. *Top. Stereochem.* **1983**, *14*, 1; (c) Kitagawa, O.; Taguchi, T. *Yuki Gosei Kagaku Kyokaishi.* **2001**, *59*, 680.
13. The atomic coordinates have been deposited with Protein Data Bank (PDB code: 3ASX).