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Discovery of atrop fixed alkoxy-aminobenzhydrol derivatives: Novel, highly potent and orally efficacious squalene synthase inhibitors

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ABSTRACT

We have recently reported the discovery of the new benzhydrol template, which has a highly potent inhibitory activity for squalene synthase, as typified by compound **1** (SSI IC_{50} = 0.85 nM). However, it was composed of a pair of easy rotatable atropisomers. In the effort to fix the isomerization, a highly potent alkoxy-aminobenzhydrol scaffold was developed. Some of these acquired compounds demonstrating strong cholesterol synthesis inhibitory activities in a rat hepatic cell. Moreover, two of the series compounds exhibited specific plasma lipid-lowering effects in in vivo animal models.

1. Introduction

Squalene synthase is one of the more promising pharmaceutical targets to treat hyperlipidemia. Inhibition of the squalene synthase causes the decrease of the hepatic cholesterol concentration, consequently the sterol response element binding protein (SREBP) is stimulated and it induces an expression of the low-density lipoprotein (LDL) receptor on the hepatic cell, thus leading to a reduction of serum LDL concentration.[1] Many clinical trials revealed that 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors had serum LDL cholesterol lowering effects and abilities to reduce the risk of coronary heart disease.[2]

Since squalene synthase is located in the downstream of HMG-CoA reductase in the cholesterol biosynthesis cascade,[3] the squalene synthase inhibitor[4] does not interfere with the biosynthesis of many non-steroidal essential isoprenoid molecules, such as geranylgeranyl pyrophosphate and ubiquinones.[5] It means that squalene synthase inhibitor is able to avoid some of the adverse effects of the HMG-CoA reductase inhibitor, such as mytotoxicity, muscle pain and, in very rare cases, rhabdomyolysis.[6] Additionally, the squalene synthase inhibitor was assumed to have a serum triglyceride lowering effect.[7]

To obtain alternative medicine for hyperlipidemia, we have investigated synthesizing orally active benzhydrol type squalene synthase inhibitors.[8] In the present article, we have reported the design, synthesis, and identification of highly potent benzhydrol derivatives, represented by compound **1**, as squalene synthase inhibitors. These compounds had hydroxyl group attached chiral carbons on their benzhydrol part, and furthermore, each stereo isomers were a mixture of easy rotatable atropisomers. As necessary, compound **1** consists of four stereo isomers (Fig. 1), which is not favored as a clinical candidate. The pair of atropisomers was created by a high rotational barrier around the C–N bond between the amide nitrogen and the aryl ring, because the amide was substituted by the bulky neopentyl alkyl and the *ortho*-substituted aryl ring (benzhydrol moiety). Moreover, isolated atropisomer had easily rotated and produced a specific ratio of atrop mixture in the solution state.

We had to dissolve these pending issues to obtain a clinical candidate. Thus, our research effort was forecast to obtain the single active isomer which had the highest potential among all isomers.

Based on our previously reported X-ray co-crystallography analysis of squalene synthase soluble domain with compound **1**, only (*S*)-hydroxy-(*aR*)-atropisomer was detected in the complex

Abbreviations: WSCI·HCl, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; HOBt, 1-hydroxybenzotriazole; MeOH, methanol; AcOEt, ethyl acetate; DMF, *N*,*N*-dimethylformamide; THF, tetrahydrofuran.

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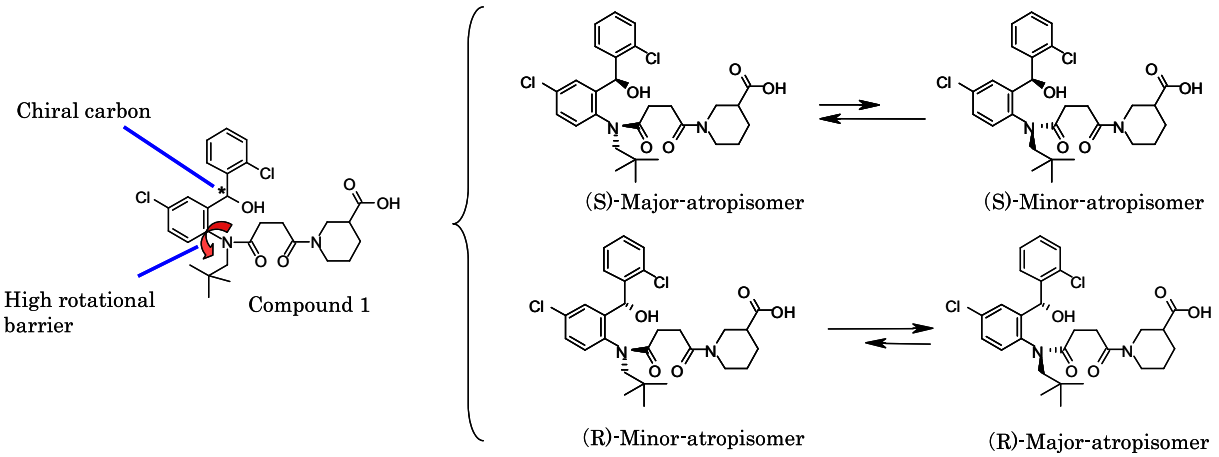


Figure 1. Compound **1** consists of four stereo isomers.

which formed 11 membered ring conformation with an intramolecular hydrogen bond, between the proton of hydroxyl group and the oxygen atom of side chain amide (Fig. 2).[9] Obviously, the isomer has the strongest inhibitory activity against squalene synthase among all four available isomers.

To meet the challenge of obtaining the most effective single isomer, two approaches were attempted. One was separation of the enantiomers of benzhydrol part by HPLC with the chiral column; the other was increasing the rotational barrier around the C–N bond by incorporating a new substituent to fix the atropisomerization and separate them.

In this paper, we will describe an investigation of atrop fixation that resulted in the attainment of novel alkoxy-aminobenzhydrol compounds, high potent oral efficacious squalene synthase inhibitors with plasma lipid lowering effects in in vivo animal models.

2. Result

2.1. Chemistry

Tertiary alcohol derivatives were prepared from benzophenone **2** as shown in Scheme 1. Commercially available **2** was treated with methyl magnesium bromide to form tertiary alcohol **3**, followed by reductive aminoalkylation and amidation with methyl succinic chloride gave amide **5**. Saponification of **5** led to the corresponding carboxylic acid **6**. Atrop mixture of succinic diamides were prepared by condensation of **6** with isonipecotic ester, further purification successively gave a pair of atropisomers **7** and **8**, individually.

Scheme 2 illustrates the general synthesis of *ortho*-substituted compounds. Amidation of **9a–c,j** with pivaloyl chloride afforded amides **10a–c,j**. Ethoxy and isopropyloxy compounds **10d,e** and 3-hydroxypropyloxy derivatives **10f,g** were prepared from phenol **10j** with alkylhalides or alkylalcohols. 2,2-Dimethyl-3-hydroxypropyloxy and neopentyloxy intermediates **10h,i** were led from 2-nitrophenol **11**. Coupling with pivaloyl amides **10a–i** and 2-methoxybenzaldehyde afforded benzhydrols **13a–i** via di- or tri-anion intermediates in good yields, followed by sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) reduction gave amines **14a–i**, at the time trifluoromethyl amide **13b** was reduced to methyl amide **14b**. Chiral aminobenzhydrols were separated by HPLC with the chiral column, except the chloro compound; which was separated after the diamide formation step. Monoamides **16a–i** were prepared by amidation with acid chloride, after the incorporation of the succinic part, major and minor atropisomers were identified by NMR. Following base hydrolysis and condensation with cyclic amines provided diamide esters **18a,d**, **19a–i** and **20a**. Hydrolysis of the esters gave final acids **21a,d**, **22a–i** and **23a**, successively. As we expected, we could prepare and purify major atropisomers of final ester and acid compounds in the most of all cases.

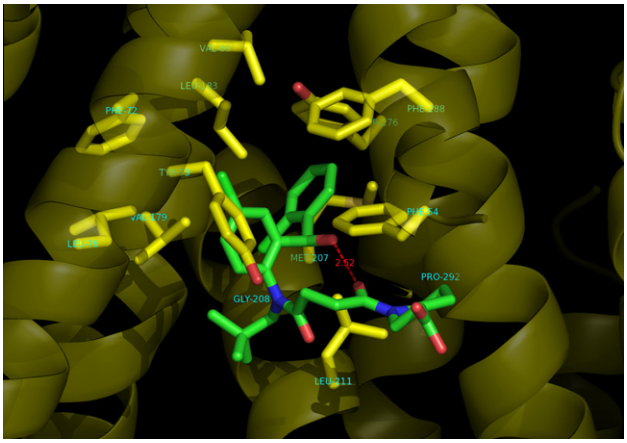


Figure 2. Crystal structure of **1** bound in squalene synthase.[9] Intramolecular hydrogen bond between the proton of hydroxyl group and the oxygen atom of side chain amide was highlighted. Only (*S*)-hydroxyl-(*aR*)-atropisomer was observed.

2.2. Evaluation and discussion

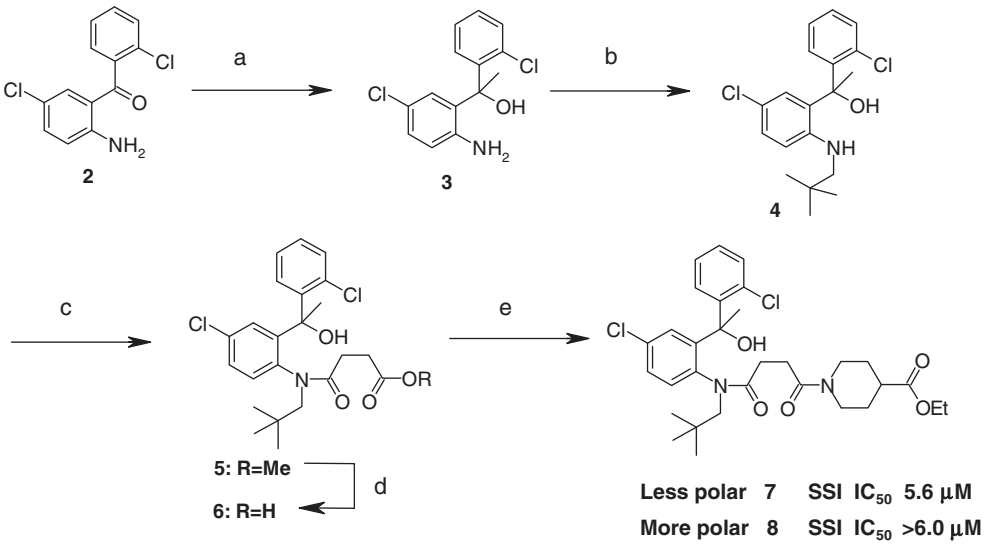
In order to get the structure–activity relationship (SAR), prepared derivatives were evaluated in terms of their squalene synthase inhibitory (SSI) activities and cholesterol synthesis inhibitory (CSI) activities in rat hepatic cells.[8] CSI activity was used as a potential parameter to predict in vivo CSI activity, and was considered more important than SSI activity as a guide to afford effective cholesterol-lowering medicine.

In an effort to fix the atropisomerization, an attempt was made to increase the rotational barrier around the C–N bond, by incorporation of bulky substitute near the bond.

There were three possible positions near the C–N bond to attach new substitute: first is an alcohol attached chiral carbon, second is a methylene carbon of neopentyl alkyl part, and third is an *ortho*-position of aryl ring (Fig. 3).

Initially, methyl substituent incorporation to the alcohol chiral carbon was attempted.

Although prepared tertiary alcohol compounds were a racemate, fixation and separation of the atropisomers were successful.



Scheme 1. Synthesis of *tert*-alcohol compounds. Reagents and conditions: (a) 3 equiv MeMgBr, THF, −78 °C to rt, 20 h; (b) *t*BuCHO, $NaBH_4$, AcOH, 0 °C, 10 min; (c) methyl 4-chloro-4-oxobutanoate, $NaHCO_3$, DCM, rt, 42 h; (d) K_2CO_3, MeOH–H_2O, 50 °C, 1 h; (e) ethyl isonipecotate, EDC, HOBt, DCM, rt, 17 h.

Only one of the pair of the atropisomers, compound **7**, showed SSI activity; however, the activity had fallen (IC_{50} = 5600 nM) compared with compound **1** (IC_{50} = 0.85 nM).[8]

Presumably, these tertiary alcohol compounds are unfit to form the unique active conformation, 11-membered ring formation with the intramolecular hydrogen bond, which might be very important to keep an active conformation to inhibit squalene synthase from our X-ray analysis study (Fig. 2).[9]

Subsequently, incorporation of methyl substituent to the joint methylene of neopentyl part was conducted, but it was not successful due to the high bulkiness of the neopentyl part.

Finally, substituent incorporation to *ortho*-position of aryl ring was investigated.

To begin with practical synthesis, *ortho*-methoxy substituted compounds were prepared from commercially available substrates.

To find more active chiral hydroxyl configuration, both of the hydroxyl enantiomers of *ortho*-methoxy derivatives were prepared as only major atropisomers by using HPLC, individually. After the incorporation of the succinic part. So as to obtain SAR for these new atrop-fixed compounds, various piperidine derivatives were prepared and evaluated their activities against squalene synthase.

As summarized in Table 1, final compounds **18–23a-isomer B** derived from the aminoalcohol enantiomers with the longer retention times, showed stronger inhibitory activities than the corresponding isomers **18–23a-isomer A** derived from the aminoalcohols enantiomers with the shorter retention times. According to the co-crystallized X-ray analysis of squalene synthase and compound **1**, the active enantiomers highly likely have (*S*)-hydroxy groups.

Successively, in order to verify each atropisomers' inhibitory activity, both the major and minor atropisomers of *ortho*-ethoxy substituted compounds **(*S*)-18,19,21,22d** were separately prepared, from the aminoalcohol enantiomer **(*S*)-15** which had longer retention time, and their activities were compared with each other. Fortunately, the major atropisomers **(*S*)-*major*-18,19,21,22d** showed stronger SSI activities than the corresponding minor atropisomers **(*S*)-*minor*-18,19,21,22d** (Table 2). Base on our X-ray analysis, these major atropisomers would be (*S*)-hydroxyl-(*aR*)-isomers.

Moreover, (*S*)-nipecotic acid compounds demonstrated the strongest CSI activities among both the methoxy and ethoxy derivatives. In our speculation, the CSI activities differentiation depending on the acid structure, might be due to recognition and selective uptake into hepatic cell by organic anion transporter.

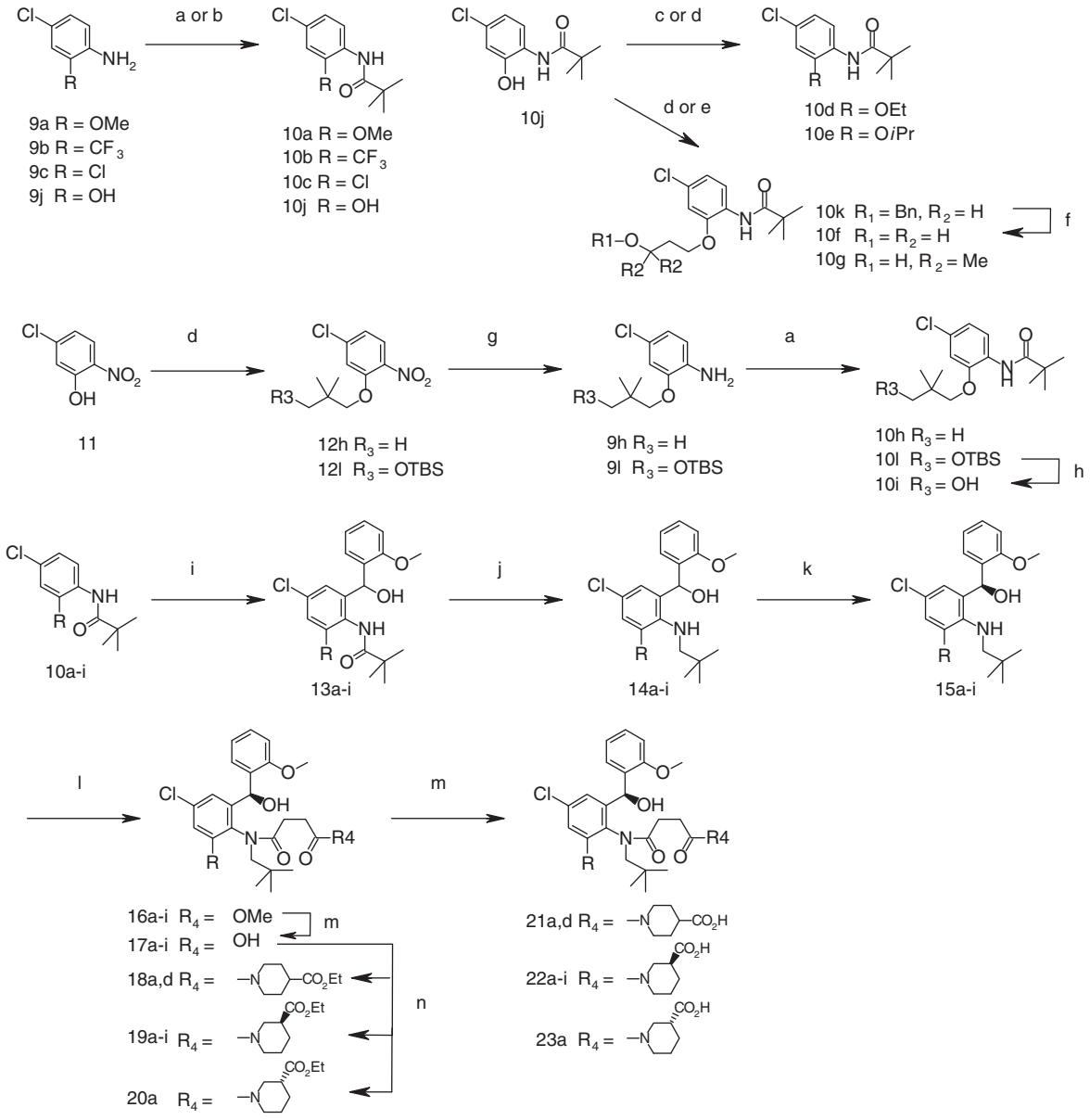
Our research focus then moved on to an optimization of the *ortho*-substituent of benzene ring. Methyl, chloro, variety alkoxy, and hydroxy propyloxy, which was expected to have more polar interaction with squalene synthase, substituted compounds were prepared and evaluated their inhibitory activities. As a result, all of these substituents could fix the atropisomerization.

As shown in Table 3, which was specifically methoxy and 2-propyloxy compounds **(*S*)-(*aR*)-22a,e** had strong SSI and CSI activities. Additionally, the 3-hydroxypropyloxy compound **(*S*)-22f** improved its solubility without decreasing strong SSI and CSI activities; however, its cell permeability had fallen.

Since there was a good prospect in the 3-hydroxypropyloxy derivatives, we tried to improve cell permeability by incorporating geminal dimethyl groups near the hydroxyl group. Prepared geminal dimethyl derivatives **(*S*)-22g,i** kept the inhibitory activities strong; however, their permeabilities were not high enough compared with other alkoxy compounds.

Measurement of hepatic (target organ) selectivity of alkoxy derivatives was required to predict their potential as an orally effective squalene synthase inhibitor. The high cell permeable neopentyloxy compound **(*S*)-(*aR*)-22h** was examined in a pharmaco kinetic study using hamsters, our first screening animal for the measurement of a plasma lipid lowering effect. As a result, it sustained high hepatic selectivity, a suitable PK profile was confirmed (Table 4).

Due to strong CSI activities and high cell permeabilities, 2-propyloxy and neopentyloxy compounds **(*S*)-(*aR*)-22e,h** were selected and examined in an in vivo hamster orally repeated dose plasma lipid lowering test (Fig. 4). With a 2 week treatment to the hamster at dose of 100 mg/kg oral administration twice daily, the compounds **(*S*)-(*aR*)-22e,h** significantly reduced both of serum total cholesterol (−32% for **22e** and −24% for **22h**) and triglyceride levels (−35% for **22e** and −44%for **22h**), respectively. On the other hand, atorvastatin, a HMG-CoA reductase inhibitor, significantly reduced the total cholesterol; however, it did not have an effect on triglyceride. As a consequence, as far as hamster orally repeated dose serum lipid lowering test at higher dose, our squalene synthase inhibitors would present an advantage compared with the HMG-CoA reductase inhibitor in the serum triglyceride lowering effect.



Scheme 2. Synthesis of various upper ring compounds. Reagents: (a) pivaloyl chloride, Et_3N, DMAP, DCM, 0 °C to rt, 2 h; (b) pivaloyl chloride, $NaHCO_3$, CH_2Cl_2, rt, 1.5 h; (c) RI, K_2CO_3, DMF, rt, 19 h; (d) ROH, DEAD, PPh_3, THF, rt, 2 h (or rt to 60 °C, 2 h); (e) ROMs, K_2CO_3, DMF, rt, 60 °C, 6 h; (f) Pd–C, H_2, AcOEt, rt, 7 h; (g) Raney-Ni, H_2, EtOH, rt; (h)TBAF, THF, rt; (i) *s*BuLi, THF then 2-methoxybenzaldehyde, −78 °C to rt; (j) Red-Al, THF, rt; (k) HPLC separation by using CHIRALCEL OD (2-PrOH–hexane); (l) methyl 4-chloro-4-oxobutanoate, $NaHCO_3$, DCM, rt; (m) K_2CO_3, MeOH–H_2O, 50 °C; (n) amine, EDC, HOBt, DCM.

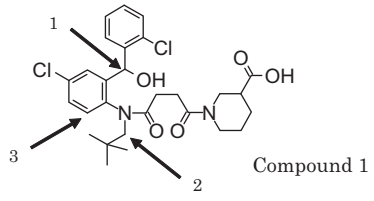


Figure 3. Three possible positions near the C–N bond to attach new substitute: (1) alcohol attached chiral carbon; (2) methylene carbon of neopentyl alkyl part; (3) *ortho*-position of aryl ring.

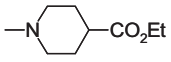
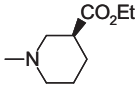
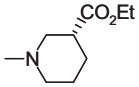
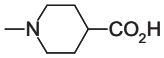
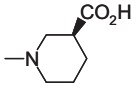
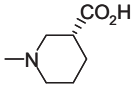
Furthermore, these two alkoxy compounds were evaluated in an in vivo marmoset, non rodent, repeated dose lipid lowering test (Fig. 5).

As a result, with treatment for five days to the marmoset at dose of 100 mg/kg/day, the 2-propyloxy compound **(*S*)-(*aR*)-22e** showed the statistically significant non-HDL cholesterol reducing effect (−34%). Moreover, the rate of change from the initial values of serum non-HDL cholesterol and triglyceride were significantly reduced. Furthermore, HDL cholesterol was not reduced; it was slightly increased. In contrast, the neopentyloxy compound **(*S*)-(*aR*)-22h** did not show efficient results for the marmoset. Nevertheless, we have successively obtained an orally effective squalene synthase inhibitor **(*S*)-(*aR*)-22e** with robust serum lipid lowering effects in in vivo models.

3. Conclusion

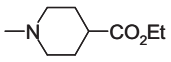
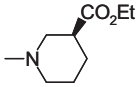
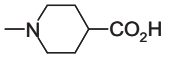
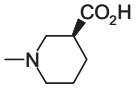
A number of atrop fixed aminobenzhydrol derivatives were explored in an effort to develop a highly potent and orally efficacious squalene synthase inhibitor. We succeeded in fixing the atropisomerization, the remaining issue of our aminobenzhydrol

Table 1
Evaluation of squalene synthase inhibitory (SSI) activities and cholesterol synthesis inhibitory (CSI) activities of major atropisomer of *ortho*-methoxy derivatives **18–23a**

		Isomer A from shorter retention time aminoalcohol		**Isomer B from longer** retention time aminoalcohol	
	R	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)
18a		72	–	1.3	–
19a		95	–	3.4	–
20a		90	–	2.5	–
21a		65	880	1.6	25
22a*		55	690	1.5	8.6
23a		50	830	1.6	15

SSI: Squalene synthase inhibitory activity. CSI: cholesterol synthase inhibitory activity in rat hepatic cell. –, not tested.
* Only major atropisomer.

Table 2
Evaluation of SSI and CSI activities of major and minor atropisomers of *ortho*-ethoxy derivatives **18**, **19**, **21** and **22d**

		(*S*)-hydroxyl-*major*-atropisomer		**(*S*)-hydroxyl-*minor*-atropisomer**	
	R	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)
18d		3.4	–	32	–
19d		4.5	–	>600	–
20d		4.5	150	40	–
22d		2.9	77	300	>300

SSI: Squalene synthase inhibitory activity. CSI: cholesterol synthase inhibitory activityin rat hepatic cell. –, not tested.

template, by incorporating an alkoxy substitute at an *ortho*-position of the aminobenzhydrol template. Consequently, high potent single isomers were obtained. Finally, the 2-propyloxy compound **(*S*)-(*aR*)-22e** demonstrated significance in in vivo serum lipid lowering effects in both the hamster and the marmoset. Further biological and toxicological evaluations of this compound will be reported in due course.

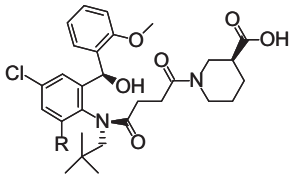
4. Experimental

4.1. Chemistry

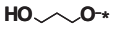
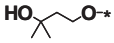
4.1.1. General

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. ^{1}H NMR

Table 3
Evaluation of SSI and CSI activities, solubilities, and cell permeabilities of (*S*)-hydroxyl-(*aR*)-atropisomers **22a–i**



(*S*)-hydroxyl-(*aR*)-atropisomer

	R	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)	Solubility (pH 1.2/6.8)	Caco-2 cell permeability ratio
22a	MeO	1.5	8.6	<3/980	24
22b	Me	11	310	<3/>1100	30
22c	Cl	9.7	270	—/—	—
22d	EtO	2.9	77	<3/1000	>30
22e	*i*PrO	1.3	6.6	<3/97	>30
22f[a]		2.5	8.4	92/440	2.6
22g[a]		3.8	18	37/280	3.6
22h		2.4	19	<3/110	>30
22i[a]		3.7	35	12/210	18.1

SSI: Squalene synthase inhibitory activity. CSI: cholesterol synthase inhibitory activity in rat hepatic cell. —, not tested. Solubility: μg/ml in pH 1.2 and 6.8 buffer. Caco-2 cell permeability ratio: atenorol = 1.
[a] Containing small amount of minor atropisomer.

Table 4
PK profile of compound to compound **(*S*)-(*aR*)-22h** in the hamster

Time after administration (h)	Plasma concn (ng/mL)	Liver concn (ng/g of liver)	K_p (liver/plasma)
4	486	24,867	54.5
7	244	19,707	79.8

100 mg/kg/5 mL p.o. Fed. hamster.

spectra were recorded on JEOL JNM-EX400 spectrometers, and chemical shifts are given in ppm from tetramethylsilane as an internal standard. Parenthetical peak derives from minor atropisomer. FAB mass spectra were recorded on a JEOL JMS-HX110 spectrometer. HR-FAB mass spectra were recorded on a JEOL JMS-700. ESI mass spectra were recorded on SCIEX API-150EX and Agilent Technologies Agilent 1100 series LC/MS. Column chromatography was performed with Merck Silica Gel 60 (particle size 0.060–0.200 or 0.040–0.063). Flash column chromatography was performed with YAMAZEN cartridge series or ultra pack series. Thin-layer chromatography (TLC) was performed on Merck precoated TLC glass sheets with silica gel 60F254 or Whatman Partisil PLK5F with silica gel 150 Å.

4.1.1.1. 1-(2-Amino-5-chlorophenyl)-1-(2-chlorophenyl)ethanol (3). A solution of 2-amino-5-chloro-2′-chlorobenzophenone (3.00 g, 11.3 mmol) in THF (30 ml) was added methylmagnesium bromide (0.93 mol/l in THF, 13.3 ml, 12 mmol) at −78 °C. The resulting mixture was gradually warmed to −40 °C, and recooled to −78 °C, then methylmagnesium bromide (0.93 mol/l in THF, 26.6 ml, 24.8 mmol) was added again. The solution was allowed to reach room temperature and stirred for 19 h, then saturated ammonium chloride solution was added. The organic material was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Then, the residue was purified by a silica gel column chromatography (*n*-hexane/AcOEt = 10:1 as eluent) to give compound **3** (0.82 g, 2.9 mmol, 26%) as a colorless syrup. ^{1}H NMR ($CDCl_3$) δ 2.00 (3H, s), 4.05 (2H, br s), 6.55 (1H, d, J = 8.3 Hz), 7.03–7.08 (2H, m), 7.23–7.37 (3H, m), 7.73 (1H, dd, J = 7.8, 1.3 Hz). IR (ATR) cm^{-1}

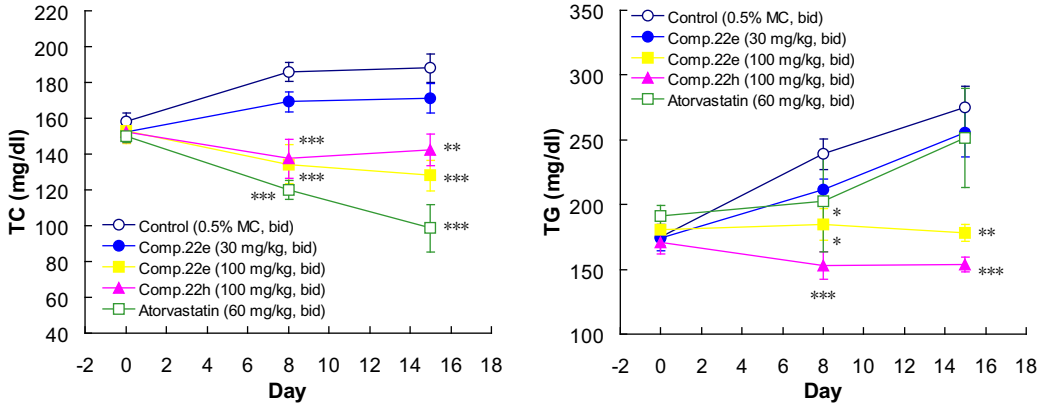


Figure 4. Effects of compounds **(*S*)-(*aR*)-22e**,**h** and atorvastatin on serum lipid in the hamster study of orally repeated doses for 14 days. TC: total cholesterol. TG: triglyceride.

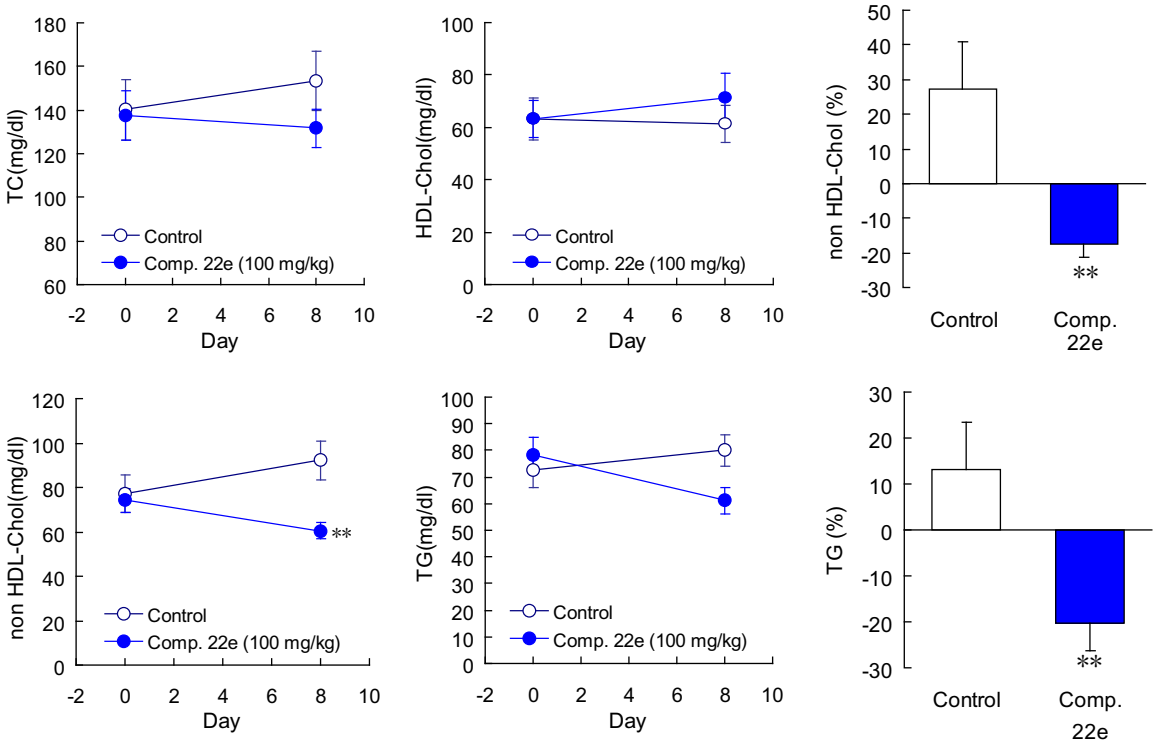


Figure 5. Effects of compound (***S*)-(*aR*)-22e** on serum lipid in the marmoset study of 100 mg/kg/day orally repeated doses for 7 days; change values (for total cholesterol, HDL cholesterol, non-HDL cholesterol, and triglyceride) and percent changes from initial values (for non-HDL cholesterol and tryglyceride).

3377, 1724, 1614, 1487, 1410, 1263, 1036, 868, 816, 758. MS (FAB) *m/z* 283 [(M+H)$^+$, $Cl_{35}Cl_{35}$], 285 [(M+H)$^+$, $Cl_{35}Cl_{37}$], 287 [(M+H)$^+$, $Cl_{37}Cl_{37}$].

4.1.1.2. 1-[5-Chloro-2-(2,2-dimethylpropylamino)phenyl]-1-(2-chlorophenyl)ethanol (4). To a solution of compound **3** (760 mg, 2.69 mmol) in acetic acid (30 ml), pivalaldehyde (321 μl, 2.96 mmol) was added, then stirred for 5 min at room temperature. To the resulting mixture, sodium borohydride (132 mg, 3.50 mmol) was added at 0 °C, and allowed to reach room temperature and then stirred for 24 h. The solution was removed in vacuo, and the residue was dissolved in AcOEt and H_2O. Then, the organic material was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Then, the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 10:1 as eluent) to give compound **4** (0.29 g, 0.82 mmol, 31%) as pale yellow syrup. ^{1}H-NMR ($CDCl_3$) δ 0.84 (9H, s), 1.97 (3H, s), 3.37 (1H, d, *J* = 14.6 Hz), 3.42 (1H, d, *J* = 14.6 Hz), 6.57 (1H, s), 6.97 (1H, d, *J* = 8.8 Hz), 7.09 (1H, dd, *J* = 8.8, 2.5 Hz), 7.11–7.34 (3H, m), 7.36–7.45 (2H, m). IR (ATR) cm^{-1} 3390, 2962, 1597, 1491, 1431, 1367, 1284, 1203, 1039, 879, 804, 760. MS (ESI) *m/z* 353 [(M+H)$^+$, $Cl_{35}Cl_{35}$], 355 [(M+H)$^+$, $Cl_{35}Cl_{37}$].

4.1.1.3. Methyl 4-[{4-chloro-2-[1-(2-chlorophenyl)-1-hydroxyethyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (5). To an ice-cooled solution of compound **4** (0.21 g, 0.59 mmol) in CH_2Cl_2 (6 ml), ethyl 4-chloro-4-oxobutanoate (0.15 g, 1.77 mmol) and $NaHCO_3$ (0.15 g, 1.77 mmol) were added. After being stirred for 14 h at room temperature, to the recooled reaction mixture, ethyl 4-chloro-4-oxobutanoate (0.11 g, 0.71 mmol) and $NaHCO_3$ (0.15 g, 1.77 mmol) were added. After being stirred for 14 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 chromatography (*n*-hexane/AcOEt = 10:1 as eluent) to give compound **5** (0.21 g, 0.45 mmol, 76%) as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.70 (0.88) (9H, s), 2.00–2.39 (2H, m), 2.41–2.71 (2H, m), (2.95) 3.56 (1H, d, *J* = 14.2 Hz), 4.06–4.18 (1H, m), 7.10–7.44 (5H, m), 7.61–8.02 (2H, m). IR (ATR) cm^{-1} 3396, 2951, 1736, 1635, 1475, 1435, 1365, 1167, 1034, 756. MS (ESI) *m/z* 466 [(M+H)$^+$, $Cl_{35}Cl_{35}$], 468 [(M+H)$^+$, $Cl_{35}Cl_{37}$], 470 [(M+H)$^+$, $Cl_{37}Cl_{37}$]. Anal. Calcd for $C_{24}H_{29}Cl_2N_1O_4{\cdot}0.4H_2O$: C, 60.87; H, 6.34; N, 2.96. Found: C, 60.99; H, 6.24; N, 2.81.

4.1.1.4. 4-[{4-Chloro-2-[1-(2-chlorophenyl)-1-hydroxyethyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (6). Compound **5** (0.20 g, 0.42 mmol) was suspended in a mixture of MeOH (4 ml) and water (2 ml), and K_2CO_3 (0.18 g, 1.26 mmol) was added at room temperature, followed by stirring for 14 h at the same temperature. The solvent was removed under reduced pressure and was added to 1 N hydrochloric acid (3.2 ml to pH 4) and CH_2Cl_2. The organics were extracted with CH_2Cl_2 (three 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 *n*-hexane to give compound **6** (0.15 g, 0.33 mmol, 78%) as a colorless powder. ^{1}H NMR (DMSO-d_6) δ 0.68 (0.74) (9H, s), 1.85 (3H, s), 1.89–2.68 (4H, m), 3.20–3.78 (2H, m), 6.07 (6.19) (1H, s), 7.16–7.50 (6H, m), 7.75–7.90 (1H, m). IR (ATR) cm^{-1} 3396, 2952, 1712, 1631, 1477, 1431, 1255, 1182, 1036, 827, 750. MS (ESI) *m/z* 452 [(M+H)$^+$, $Cl_{35}Cl_{35}$], 454 [(M+H)$^+$, $Cl_{35}Cl_{37}$]. Anal. Calcd for $C_{23}H_{27}Cl_2N_1O_4{\cdot}0.1H_2O$: C, 60.82; H, 6.04; N, 3.08. Found: C, 60.84; H, 6.06; N, 3.02.

4.1.1.5. Ethyl 1-{4-[{4-chloro-2-[1-(2-chlorophenyl)-1-hydroxyethyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}-piperidine-4-carboxylate (less polar 7 and more polar 8). To a solution of compound **6** (94 mg, 0.21 mmol) and ethyl isonipecotate (42 μl, 0.27 mmol) in CH_2Cl_2, WSCI·HCl (60 mg, 0.31 mmol)

and HOBt (14 mg, 0.11 mmol) were added, and then the mixture was stirred at room temperature for 17 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 the residue was purified with thin-layer silica gel chromatography (1 mm × 20 cm × 20 cm × 2, 5% MeOH–CH_2Cl_2 as eluent) to give less polar compound **7** (21.5 mg, 17%) and more polar compound **8** (73 mg, 59%) as a colorless powder. *Less polar* **7**: ^{1}H NMR ($CDCl_3$) δ 0.78–1.00(1H, m), 0.97 (9H, s), 1.21–1.30 (3H, m), 1.48–2.00 (4H, m), 2.03 (3H, s), 2.03–2.23 (2H, m), 2.28–2.55 (2H, m), 2.73–3.19 (3H, m), 3.08 (1H, d, J = 13.6 Hz), 3.79–3.91 (1H, m), 4.37–4.45 (1H, m), 4.10–4.18 (2H, m), 429 (1H, d, J = 13.6 Hz), 5.93 and 6.15 (1H, s), 7.01–7.07 (1H, m), 7.18–7.33 (4H, m), 7.36–7.42 (1H, m), 8.14–8.20 (1H, m). IR (ATR) cm^{-1} 3315, 2927, 1730, 1651, 1620, 1473, 1281, 1171, 1034, 835, 756. MS (ESI) *m/z* 591 [(M+H)$^+$, $Cl_{35}Cl_{35}$], 593 [(M+H)$^+$, $Cl_{35}Cl_{37}$]. HRMS (FAB) *m/z* 591.2407 (calcd for $C_{31}H_{41}Cl_2N_2O_5$ 591.2393). Anal. Calcd for $C_{31}H_{40}Cl_2N_2O_5$: C, 62.94; H, 6.82; N, 4.74. Found: C, 63.17; H, 6.88; N, 4.51. *More polar* **8**: ^{1}H NMR ($CDCl_3$) δ 0.66 (9H, s), 0.86–0.98 (1H, m), 1.20–1.28 (3H, m), 1.38–1.78 (1H, m), 1.83–1.98 (2H, m), 2.06 (3H, s), 2.09–2.56 (4H, m), 2.76–2.94 (2H, m), 3.06–3.17 (1H, m), 3.36–3.49 (1H, m), 3.87 (1H, J = 14.2 Hz), 4.09–4.18 (2H, m), 4.28–4.48 (1H, m), 4.56–4.72 (1H, m), 7.10–7.51 (6H, m), 7.74 (1H, dd, J = 11.5, 2.4 Hz), 7.88 (1H, d, J = 7.6 Hz). IR (ATR) cm^{-1} 3300, 2947, 1734, 1660, 1624, 1475, 1277, 1182, 1038, 841, 764. MS (ESI) *m/z* 591 [(M+H)$^+$, $Cl_{35}Cl_{35}$], 593 [(M+H)$^+$, $Cl_{35}Cl_{37}$]. Anal. Calcd for $C_{31}H_{40}Cl_2N_2O_5$: C, 62.94; H, 6.82; Cl, 11.99; N, 4.74. Found: C, 63.05; H, 6.91; Cl, 11.74; N, 4.68.

4.1.1.6. *N*-(4-Chloro-2-methoxyphenyl)-2,2-dimethylpropanamide (10a). Triethylamine (6.70 ml, 48.2 mmol), pivaloyl chloride (2.92 g, 24.1 mmol) and 4-dimethylaminopyridine (0.267 g, 2.19 mmol) were added to an ice-cooled solution of 4-chloro-2-methoxyaniline hydrochloride (**9a**, 4.25 g, 21.9 mmol) in CH_2Cl_2 (100 ml). After being stirred for 16 h at room temperature, the solvent was concentrated, and the residue was dissolved in AcOEt and water. The organic material was extracted with AcOEt. 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 (*n*-hexane/AcOEt = 8:2–3:1 as eluent) to give compound **10a** (5.22 g, 21.6 mmol, 98%) as a colorless powder. ^{1}H NMR ($CDCl_3$) δ 1.31 (9H, s), 3.89 (3H, s), 6.85 (1H, d, J = 2.2 Hz), 6.93 (1H, dd, J = 8.8, 2.2 Hz), 8.01 (1H, br), 8.34 (1H, d, J = 8.8 Hz). IR (ATR) cm^{-1} 3442, 2954, 1668, 1521, 1403, 1251, 1037, 862, 796, 613, 584. MS (ESI) *m/z* 242 (M+H)$^+$. Anal. Calcd for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.35; H, 6.52; N, 5.81.

4.1.1.7. *N*-{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}-2,2-dimethylpropanamide (13a). Compound **10a** (2.22 g, 9.21 mmol) was dissolved in THF (100 ml). To the solution *sec*-butyl lithium (0.99 mol/l in *c*-hexane and *n*-hexane, 21.0 ml, 21.0 mmol) was added at −78 °C, and stirred at 0 °C for 15 min then at rt for 15 min. The mixture was cooled to −78 °C again, and 2-methoxybenzaldehyde (1.22 ml, 10.1 mmol) was added. The reaction mixture was stirred at −50 °C for 1.5 h, and poured saturated with NH_4Cl aq and AcOEt. The organic material was extracted with AcOEt. Combined 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 = 3:1–1:1 as eluent) to give compound **13a** (3.08 g, 88%) as colorless powder. ^{1}H NMR ($CDCl_3$) δ 1.30 (9H, s), 3.68 (3H, s), 3.82 (3H, s), 4.37 (1H, d, J = 3.2 Hz), 5.97 (1H, s, J = 2.7 Hz), 6.79–6.83 (3H, m), 7.02 (1H, t, J = 7.6 Hz), 7.24–7.29 (1H, m), 7.56–7.58 (1H, m). IR (ATR) cm^{-1} 3266, 1639, 1461, 1240, 1008, 761, 640. MS (ESI) *m/z* 360 (M−OH)$^+$. Anal. Calcd for $C_{20}H_{24}ClNO_4$: C, 63.57; H, 6.40; N, 3.71; Cl, 9.38. Found: C, 63.20; H, 6.35; N, 3.64; Cl, 9.39.

4.1.1.8. {5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-methoxyphenyl}(2-methoxyphenyl)methanol (14a). A solution of compound **13a** (15.5 g, 40.9 mmol) was dissolved in THF (100 ml). Sodium bis(2-methoxyethoxy)aluminum hydride (60% in toluene, 62 ml) was added to the solution at 0 °C. The mixture was stirred for 4 h at 50 °C. The reaction mixture was added to saturated (+)-tartaric acid sodium potassium solution and stirred for 5 min. The mixture was added to 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 **14a** (13.3 g, 36.5 mmol, 89%) as as colorless powder. ^{1}H NMR ($CDCl_3$) δ 0.965 (9H, s), 2.69 (1H, d, J = 11.2 Hz), 2.76 (1H, d, J = 11.2 Hz), 3.83 (3H, s), 3.84 (3H, s), 4.35 (1H, br), 6.31 (1H, s), 6.59 (1H, d, J = 2.0 Hz), 6.76 (1H, d, J = 2.2 Hz), 6.91–6.99 (2H, m), 7.28–7.31 (2H, m). IR (ATR) cm^{-1} 3353, 2942, 1602, 1587, 1459, 1236, 1024, 829, 757, 607. MS (ESI) *m/z* 364 (M+H)$^+$. Anal. Calcd for $C_{20}H_{26}ClNO_3$: C, 66.01; H, 7.20; N, 3.85. Found: C, 65.72; H, 7.13; N, 3.95.

4.1.1.9. (*R*) and (*S*)-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-methoxyphenyl}(2-methoxyphenyl)methanol ((*R*)-15a and (*S*)-15a). From *rac*-compound **14a** (3.00 g, 8.24 mmol), the enantiomers were separated by HPLC with a Chiralcel OD (Φ20 × 250 mm) at flow rate of 20 ml/min at room temperature using 25% 2-propanol–*n*-hexane (254 nm detection) to give peak 1 (isomer A, **(*R*)-15a**, 1.5 g) at retention time (t_R) = 4 min, and peak 2 (isomer B, **(*S*)-15a**, 1.5 g) at t_R = 8 min. The peaks similar to the racemate were obtained by ^{1}H NMR ($CDCl_3$).

4.1.1.10. Methyl 4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)-methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-16a). Methyl 4-chloro-4-oxobutanoate (0.203 ml, 1.65 mmol) and $NaHCO_3$ (345 mg, 4.11 mmol) were added to an ice-cooled solution of **(*S*)-15a** (500 mg, 1.37 mmol) in CH_2Cl_2 (20 ml). After being stirred for 1 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 (*n*-hexane/AcOEt = 2:1–1:2 as eluent) to give compound **(*S*)-16a** (611 mg, 1.28 mmol, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.89 (9H, s), 2.22–2.34 (2H, m), 2.52–2.65 (1H, m), 2.90–3.00 (1H, m), 3.09 (1H, d, J = 13.6 Hz), 3.67 (3H, s), 3.73 (3H, s), 3.86 (3H, s), 4.45 (1H, d, J = 13.6 Hz), 4.79 (1H, d, J = 5.4 Hz), 6.11 (1H, d, J = 5.1 Hz), 6.70 (1H, d, J = 2.1 Hz), 6.82 (1H, d, J = 2.1 Hz), 6.87 (1H, d, J = 7.8 Hz), 7.05–7.09 (1H, m), 7.29–7.34 (1H, m), 7.70 (1H, d, J = 7.6 Hz). MS (ESI) *m/z* 460 (M−OH)$^+$.

4.1.1.11. 4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-17a). Compound **(*S*)-16a** (500 mg, 1.05 mmol) was suspended in a mixture of MeOH (10 ml) and water (5 ml), and K_2CO_3 (0.361 g, 2.62 mmol) was added at room temperature, followed by stirring for 2.5 h at 60 °C. The solvent was removed under reduced pressure, and was added 1 N citric acid solution and AcOEt. The organics were extracted with AcOEt (3 times). The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was washed with diethyl ether and *n*-hexane to give compound **(*S*)-17a** (486 mg, 1.05 mmol, quant.) as a colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.84 (0.88, 9H, s), 2.28–2.86 (4H, m), 2.89 (1H, d, J = 13.6 Hz), 3.75 (3.82, 3H, s), 3.87 (3.83, 3H, s), 4.39 (1H, d, J = 13.6 Hz), 6.06 (6.31, 1H, s), 6.77 (1H,

d, J = 2.2 Hz), 6.85–6.89 (2H, m), 7.02 (1H, t, J = 7.4 Hz), 7.30–7.34 (1H, m), 7.45–7.47 (1H, m). IR (ATR) cm^{-1} 3409, 2952, 1712, 1637, 1394, 1240, 1025, 754. MS (ESI) m/z 446 $(M-OH)^+$. Anal. Calcd for $C_{24}H_{309}NO_6Cl{\cdot}1.0H_2O$: C, 59.81; H, 6.69; N, 2.91. Found: C, 59.78; H, 6.58; N, 2.66.

4.1.1.12. Ethyl 1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)-methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate ((*S*)-18a). To a solution of compound **(*S*)-17a** (100 mg, 0.216 mmol) and isonipecotic acid ethyl ester (42.0 mg, 0.270 mmol) in CH_2Cl_2 (5 ml), WSCI·HCl (52.0 mg, 0.270 mmol) and HOBt (41.0 mg, 0.270 mmol) were added, and then the mixture was stirred at room temperature for 2.5 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, The residue was purified with silica gel column chromatography (*n*-hexane/AcOEt = 1:1–1:2 as eluent) to give compound **(*S*)-18a** (72.2 mg, 0.120 mmol, 56%) as a colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.93 (9H, s), 1.24 (3H, t, J = 7.1 Hz), 1.53–1.92 (4H, m), 2.05–2.20 (2H, m), 2.46–2.85 (3H, m), 3.07–3.14 (2H, m), 3.30 (1H, d, J = 13.4 Hz), 3.70 (3H, s), 3.85 (3H, s), 3.81–3.85 (1H, m), 4.12 (2H, q, J = 7.1 Hz), 4.38–4.41 (1H, m), 4.50 (1H, d, J = 13.4 Hz), 6.14–6.16 (1H, m), 6.35–6.42 (1H, m), 6.63 (1H, d, J = 2.1 Hz), 6.78 (1H, d, J = 2.1 Hz), 6.85 (1H, d, J = 8.5 Hz), 7.08–7.11 (1H, m), 7.28–7.33 (1H, m), 7.87–7.90 (1H, m). IR (ATR) cm^{-1} 3369, 2950, 1727, 1660, 1623, 1241, 1174, 1031, 754, 576. MS (ESI) m/z 603 $(M+H)^+$. Anal. Calcd for $C_{32}H_{43}N_2O_7Cl$: C, 63.72; H, 7.19; N, 4.64. Found: C, 63.42; H, 7.26; N, 4.64.

4.1.1.13. (*aR*)-1-{4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)-methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid ((*S*)-(*aR*)-21a). Compound **(*S*)-21a** was prepared from **(*S*)-18a** in a similar manner described for **(*S*)-17a**. Then, the obtained amorphous was washed with diethyl ether and *n*-hexane to give compound **(*S*)-(*aR*)-21a** in 68% yield as a colorless powder. ^1H NMR (CD_3OD) δ 0.87 (9H, m), 1.28–1.97 (6H, m), 2.31–3.26 (5H, m), 3.03 (1H, d, J = 13.6 Hz), 3.74 (3H, s), 3.89 (3H, s), 3.89–3.93 (1H, m), 4.26–4.27 (1H, m), 4.34 (1H, d, J = 13.6 Hz), 6.02 (1H, s), 6.62 (1H, d, J = 2.2 Hz), 6.98 (1H, d, J = 8.3 Hz), 7.03–7.07 (2H, m), 7.32–7.36 (1H, m), 7.56–7.59 (1H, m). IR (ATR) cm^{-1} 3407, 2950, 1718, 1614, 1282, 1025, 750, 578.MS (ESI) m/z 575 $(M+H)^+$. Anal. Calcd for $C_{30}H_{39}N_2O_7Cl{\cdot}0.33H_2O$: C, 62.01; H, 6.88; N, 4.82. Found: C, 62.09; H, 6.88; N, 4.77.

4.1.1.14. Ethyl (3*S*)-1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-19a). Compound **(*S*)-19a** was prepared from **(*S*)-17a** in a similar manner described for **(*S*)-18a** in 74% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.93 (9H, s), 1.20–1.28 (3H, m), 1.61–1.69 (4H, m), 2.11–3.32 (10H, m), 3.70 (3H, s), 3.84 (3H, s), 4.08–4.16 (2H, m), 4.48–4.56 (1H, m), 6.15 (1H, t, J = 5.2 Hz), 6.35 (1H, d, J = 5.1 Hz), 6.63 (1H, t, J = 2.5 Hz), 6.78 (1H, t, J = 2.5 Hz), 6.85 (1H, d, J = 8.1 Hz), 7.09 (1H, t, J = 7.6 Hz), 7.28–7.33 (1H, m), 7.88 (1H, t, J = 5.6 Hz). ^{13}C NMR ($CDCl_3$) δ 14.26, 24.32, 24.72, 27.40 (27.44), 28.00 (27.57), 28.08, 34.43, 41.04 (42.36), 44.04, 45.88, 47.24, 54.90, 55.49, 60.66 (60.95), 64.85 (64.90), 110.14, 111.03 (110.99), 120.73, 120.93, 127.89, 128.32, 129.54 (129.48), 130.28 (130.25), 134.65, 145.30 (145.23), 155.77, 156.32, 171.13 (170.98), 172.86, 173.50 (173.39). IR (ATR) cm^{-1} 3330, 2942, 1727, 1660, 1625, 1461, 1241, 1178, 1029, 754, 576. MS (ESI) m/z 603 $(M+H)^+$. Anal. Calcd for $C_{32}H_{43}N_2O_7Cl{\cdot}0.33H_2O$: C, 63.10; H, 7.22; N, 4.60. Found: C, 63.27; H, 7.25; N, 4.46.

4.1.1.15. (*aR*)-(3*S*)-1-{4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-22a) Compound **(*S*)-(*aR*)-22a** was prepared from **(*S*)-19a** in a similar manner described for **(*S*)-(*aR*)-21a** in 97% yield as colorless powder. ^1H NMR (DMSO-d_6) δ 0.81 (9H, s), 1.26–1.42 (1H, m), 1.48–1.69 (2H, m), 1.88–1.98 (1H, m), 2.11–2.48 (4H, m), 2.51–2.70 (1H, m), 2.81–3.00 (1H, s), 2.93 (1H, d, J = 13.3 Hz), 3.23–3.31 (2H, m), 3.67 (3H, s), 3.70–3.83 (1H, m), 3.85 (3H, s), 4.28 (1H, d, J = 13.3 Hz), 5.83–5.84 (1H, m), 5.92 (1H, m), 6.44 (1H, s), 6.99 (1H, d, J = 8.3 Hz), 7.05 (1H, t, J = 7.3 Hz), 7.11 (1H, d, J = 2.2 Hz), 7.29–7.34 (1H, m), 7.57 (1H, d, J = 7.3 Hz), 12.38 (1H, s). IR (ATR) cm^{-1} 2948, 1727, 1621, 1587, 1461, 1407, 1241, 1178, 1029, 754, 576, 489. MS (ESI) m/z 575 $(M+H)^+$. Anal. Calcd for $C_{30}H_{39}N_2O_7Cl$: C, 62.65; H, 6.84; N, 4.87. Found: C, 62.37; H, 7.06; N, 4.62.

4.1.1.16. Ethyl (3*R*)-1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-20a). Compound **(*S*)-20a** was prepared from **(*S*)-17a** in a similar manner described for **(*S*)-18a** in 76% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.93 (9H, s), 1.21–1.27 (3H, m), 1.76–2.33 (8H, m), 2.54–2.67 (1H, m), 3.01–3.19 (2H, m), 3.22–3.32 (1H, m), 3.46–3.51 (1H, m), 3.70 (3H, s), 3.70–3.82 (1H, m), 3.85 (3H, s), 4.07–4.15 (2H, m), 4.48–4.53 (1H, m), 6.15 (1H, d, J = 5.4 Hz), 6.43 (6.39, 1H, d, J = 5.2 Hz), 6.62–6.64 (1H, m), 6.78–6.79 (1H, m), 6.85 (1H, d, J = 8.5 Hz), 7.07–7.12 (1H, m), 7.28–7.32 (1H, m), 7.89 (1H, d, J = 7.6 Hz). IR (ATR) cm^{-1} 3353, 2924, 1727, 1658, 1625, 1461, 1241, 1176, 1029, 755, 576, 489. MS (ESI) m/z 603 $(M+H)^+$. Anal. Calcd for $C_{32}H_{43}N_2O_7Cl$: C, 63.72; H, 7.19; N, 4.64. Found: C, 63.58; H, 7.35; N, 4.39.

4.1.1.17. (*aR*)-(3*R*)-1-{4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-23a). Compound **(*S*)-(*aR*)-23a** was prepared from **(*S*)-20a** in a similar manner described for **(*S*)-(*aR*)-21a** in 92% yield as colorless powder. ^1H NMR (CD_3OD) δ 0.87 (9H, s), 1.28 (1H, m), 1.49–1.52 (1H, m), 1.63 (1H, m), 1.77–1.80 (1H, m), 1.98 (2H, m), 2.33–2.59 (3H, m), 2.71–2.83 (2H, m), 2.99–3.05 (1H, m), 3.47 (1H, m), 3.74 (3H, s), 3.89 (3H, s), 3.77–3.85 (1H, m), 4.34 (1H, d, J = 13.7 Hz), 6.02 (1H, s), 6.63 (1H, d, J = 6.3, 2.2 Hz), 6.98–7.06 (3H, m), 7.31–7.36 (1H, m), 7.55–7.58 (1H, m). IR (ATR) cm^{-1} 2944, 1727, 1621, 1461, 1409, 1286, 1241, 1178, 1029, 754, 576, 489. MS (ESI) m/z 575 $(M+H)^+$. Anal. Calcd for $C_{30}H_{39}N_2O_7Cl{\cdot}0.33H_2O$: C, 62.01; H, 6.88; N, 4.82. Found: C, 62.20; H, 7.05; N, 4.59.

4.1.1.18. (*aS*)-Methyl 4-[{4-chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*R*)-16a). Compound **(*R*)-16a** was prepared in a similar manner described for **(*S*)-16a** in 98% yield as colorless oil. ^1H NMR ($CDCl_3$) δ 0.890 (9H, s), 2.23–2.34 (2H, m), 2.52–3.00 (2H, m), 3.09 (1H, d, J = 13.7 Hz), 3.67 (3H, s), 3.73 (3H, s), 3.86 (3H, s), 4.45 (1H, d, J = 13.7 Hz), 4.78 (1H, d, J = 5.4 Hz), 6.11 (1H, d, J = 4.9 Hz), 6.71 (1H, d, J = 2.2 Hz), 6.82 (1H, d, J = 2.2 Hz), 6.87 (1H, d, J = 8.1 Hz), 7.06–7.09 (1H, m), 7.30–7.34 (1H, m), 7.71 (1H, d, J = 7.6 Hz). IR (ATR) cm^{-1} 3419, 2944, 1731, 1644, 1324, 1282, 1031, 757, 499. MS (ESI) m/z 460 $(M-OH)^+$.

4.1.1.19. 4-[{4-Chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*R*)-17a). Compound **(*R*)-17a** was prepared in a similar manner described for **(*S*)-17a** in quantum yield as colorless amorphous. ^1H NMR (DMSO-d_6) δ 0.80 (9H, s), 2.16–2.42 (4H, m), 2.83 (1H, d, J = 13.4 Hz), 3.68 (3H, s), 3.86 (3H, s), 4.26 (1H, d, J = 13.4 Hz), 5.82 (1H, s), 6.49 (1H, d, J = 2.4 Hz), 6.99–7.06 (3H,

m), 7.13 (1H, d, J = 2.4 Hz), 7.30–7.35 (1H, m), 7.50 (1H, dd, J = 7.4, 1.6 Hz). IR (ATR) cm^{-1} 3380, 2946, 1737, 1643, 1286, 1247, 1174, 1025, 863, 757, 574. MS (ESI) m/z 446 $(M-OH)^+$.

4.1.1.20. Ethyl 1-{4-[{4-chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)-methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate ((*R*)-18a). Compound **(*R*)-18a** was prepared from **(*R*)-17a** in a similar manner described for **(*S*)-18a** in 56% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.927 (9H, s), 1.24 (3H, t, J = 7.3 Hz), 1.48–1.96 (4H, m), 2.04–2.21 (2H, m), 2.46–2.51 (1H, m), 2.54–2.62 (1H, m), 2.73–2.88 (1H, m), 3.06–3.17 (2H, m), 3.30 (1H, d, J = 13.5 Hz), 3.70 (3H, s), 3.85 (3H, s), 3.81–3.85 (1H, m), 4.12 (2H, q, J = 7.3 Hz), 4.24–4.40 (1H, m), 4.51 (1H, d, J = 13.5 Hz), 6.14–6.16 (1H, m), 6.34–6.42 (1H, m), 6.63 (1H, d, J = 2.3 Hz), 6.78–6.79 (1H, m), 6.85 (1H, d, J = 8.3 Hz), 7.08–7.11 (1H, m), 7.29–7.32 (1H, m), 7.87–7.90 (1H, m). IR (ATR) cm^{-1} 3343, 2950, 1727, 1660, 1623, 1241, 1176, 1031, 755, 576. MS (ESI) m/z 603 $(M+H)^+$. Anal. Calcd for $C_{32}H_{43}N_2O_7Cl{\cdot}0.33H_2O$: C, 63.10; H, 7.22; N, 4.60. Found: C, 63.23; H, 7.01; N, 4.74.

4.1.1.21. (*aS*)-1-{4-[{4-Chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)-methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid ((*R*)-(*aS*)-21a). Compound **(*R*)-(*aS*)-21a** was prepared from **(*R*)-18a** in a similar manner described for **(*S*)-(*aR*)-21a** in 99% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.926 (9H, s), 1.48–1.99 (4H, m), 2.12–2.22 (2H, m), 2.49–2.61 (2H, m), 2.74–2.81 (1H, m), 3.04–3.22 (2H, m), 3.31 (1H, t, J = 14.2 Hz), 3.70 (3H, s), 3.85 (3H, s), 3.80–3.85 (1H, m), 4.32–4.41 (1H, m), 4.51 (1H, d, J = 14.2 Hz), 6.16 (1H, d, J = 3.2 Hz), 6.61–6.62 (1H, m), 6.78 (1H, d, J = 2.3 Hz), 6.84–6.86 (1H, m), 7.08–7.11 (1H, m), 7.29–7.32 (1H, m), 7.84–7.88 (1H, m). IR (ATR) cm^{-1} 3340, 2950, 1727, 1623, 1461, 1176, 1027, 754, 491. MS (ESI) m/z 575 $(M+H)^+$. Anal. Calcd for $C_{30}H_{39}N_2O_7Cl$: C, 62.65; H, 6.84; N, 4.87. Found: C, 62.37; H, 7.13; N, 4.57.

4.1.1.22. Ethyl (3*S*)-1-{4-[{4-chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*R*)-19a). Compound **(*R*)-19a** was prepared from **(*R*)-17a** in a similar manner described for **(*S*)-18a** in 19% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ (0.89) 0.90 (9H, s), 1.17–1.24 (3H, m), 1.42–1.53 (1H, m), 1.68–1.80 (1H, m), 1.85–2.44 (7H, m), 2.91–3.15 (2H, m), 3.41–3.48 (2H, m), (3.67) 3.67 (3H, s), 3.81 (3H, s), 4.03–4.14 (2H, m), 4.41–4.51 (1H, m), 4.68–4.77 (1H, m), 6.09–6.13 (1H, m), 6.35–6.43 (1H, m), 6.59 (6.60) (1H, d, J = 2.3 Hz), 6.73–6.77 (1H, m), 6.79–6.85 (1H, m), 7.02–7.10 (1H, m), 7.25–7.32 (1H, m), 7.89–7.82 (1H, m). IR (ATR) cm^{-1} 3349, 2942, 1727, 1658, 1623, 1461, 1241, 1176, 1029, 755, 576. MS (ESI) m/z 603 $(M+H)^+$. Anal. Calcd for $C_{32}H_{43}N_2O_7Cl{\cdot}0.33H_2O$: C, 63.10; H, 7.22; N, 4.60. Found: C, 63.11; H, 7.04; N, 4.73.

4.1.1.23. (3*S*)-1-{4-[{4-Chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)-methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*R*)-(aS)-22a). Compound **(*R*)-(*aS*)-22a** was prepared from **(*R*)-19a** in a similar manner described for **(*S*)-(*aR*)-21a** in 93% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ (0.87) 0.90 (9H, s), 1.18–1.41 (1H, m), 1.43–1.83 (2H, m), 1.95–2.27 (4H, m), (2.29–2.44) 2.48–2.71 (2.77–2.97) (2H, m), 3.00–3.16 (2H, m), (3.18) 3.27 (1H, d, J = 13.7 Hz), 3.37–3.47 (3.85–3.93),(1H, m), (3.67) 3.69 (3H, s), 3.82 (3H, s), 4.39–4.51 (4.54–4.61) (1H, m), 6.10 (1H, s), (6.59) 6.61 (1H, d, J = 2.0 Hz), 6.73–6.77 (1H, m), 6.79–6.85 (1H, m), 7.03–7.09 (1H, m), 7.25–7.30 (1H, m), 7.87–7.77 (1H, m). IR (ATR) cm^{-1} 3347, 2950, 1727, 1621, 1461, 1241, 1178, 1029, 754, 576, 491. MS (ESI) m/z 575 $(M+H)^+$. Anal. Calcd for $C_{30}H_{39}N_2O_7Cl{\cdot}0.33H_2O$: C, 62.01; H, 6.88; N, 4.82. Found: C, 62.06; H, 7.07; N, 4.55.

4.1.1.24. Ethyl (3*R*)-1-{4-[{4-chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*R*)-20a). Compound **(*R*)-20a** was prepared from **(*R*)-17a** in a similar manner described for **(*S*)-18a** in 31% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.931 (0.925, 9H, s), 1.25 (1.22, 3H, t, J = 7.3 Hz), 1.62–2.20 (5H, m), 2.29–2.85 (4.42–4.75, 2H, m), 2.99–3.22 (3.46–3.50, 3.74–3.81, 3.89–4.04, 2H, m), 3.30 (3.28, 1H, d, J = 13.5 Hz), 3.70 (3H, s), 3.85 (3H, s), 4.14 (4.09, 2H, q, J = 7.3 Hz), 4.51 (4.50, 1H, d, J = 13.5 Hz), 6.14–6.17 (1H, m), 6.34–6.42 (1H, m), 6.62–6.64 (1H, m), 6.78–6.79 (1H, m), 6.85 (1H, d, J = 8.2 Hz), 7.08–7.11 (1H, m), 7.30 (1H, d, J = 7.8 Hz), 7.87–7.89 (1H, m). IR (ATR) cm^{-1} 3382, 2950, 1720, 1639, 1284, 1180, 1031, 856, 754, 572, 422. MS (ESI) m/z 603 $(M+H)^+$. Anal. Calcd for $C_{32}H_{43}N_2O_7Cl$: C, 63.72; H, 7.19; N, 4.64. Found: C, 63.60; H, 6.99; N, 4.68.

4.1.1.25. (3*R*)-1-{4-[{4-Chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)-methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*R*)-(*aS*)-23a). Compound **(*R*)-(*aS*)-23a** was prepared from **(*R*)-20a** in a similar manner described for **(*S*)-(*aR*)-21a** in 89% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ (0.88) 0.89 (9H, s), 1.18–1.42 (1H, m), 1.57–1.85 (2.07–2.22) (3H, m), 2.34–2.47 (1H, m), 2.48–2.69 (2H, m), 2.78–2.98 (1H, m), 3.00–3.30 (4H, m), 3.44–3.53 (1H, m), 3.67 (3.68) (3H, s), 3.71–3.90 (1H, m), (3.80) 3.81 (3H, s), 4.39–4.51 (2H, m), 6.11 (1H, d, J = 7.0 Hz), (6.59) 6.61 (1H, d, J = 2.3 Hz), 6.74–6.77 (1H, m), 6.79–6.85 (1H, m), 7.05 (1H, t, J = 7.8 Hz), 7.24–7.30 (1H, m), 7.86–7.77 (1H, m). IR (ATR) cm^{-1} 3355, 2950, 1727, 1623, 1241, 1178, 1029, 754, 576, 489. MS (ESI) m/z 575 $(M+H)^+$. Anal. Calcd for $C_{30}H_{39}N_2O_7Cl{\cdot}0.33H_2O$: C, 62.01; H, 6.88; N, 4.82. Found: C, 62.15; H, 7.03; N, 4.57.

4.1.1.26. *N*-[4-Chloro-2-(trifluoromethyl)phenyl]-2,2-dimethylpropanamide (10b). Compound **10b** was prepared in a similar manner described for **10a** in 37% yield as colorless crystal. ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (9H, s), 7.51 (1H, dd, J = 8.9, 2.3 Hz), 7.58 (1H, d, J = 2.3 Hz), 7.75 (1H, br), 8.24 (1H, d, J = 8.8 Hz). IR (ATR) cm^{-1} 3288, 2974, 1645, 1496, 1304, 1138, 1053, 816, 607. MS (ESI) m/z 280 $(M+H)^+$.

4.1.1.27. *N*-{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-6-(trifluoromethyl)phenyl}-2,2-dimethylpropanamide (13b). Compound **13b** was prepared in a similar manner described for **13a** in 25% yield as colorless crystal. ^1H NMR ($CDCl_3$) δ 1.32 (9H, s), 3.67 (3H, s), 4.05 (1H, d, J = 3.2 Hz), 5.98 (1H, d, J = 2.9 Hz), 6.82 (1H, d, J = 8.1 Hz), 7.03–7.08 (1H, m), 7.27–7.33 (1H, m), 7.44 (1H, d, J = 2.2 Hz), 7.57–7.62 (1H, m), 7.56 (1H, d, J = 2.4 Hz). IR (ATR) cm^{-1} 3284, 2952, 1655, 1510, 1468, 1311, 1242, 1161, 1128, 881, 760. MS (ESI) m/z 398 $(M+H)^+$.

4.1.1.28. {5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-methylphenyl}(2-methoxyphenyl)methanol (14b). Compound **14b** was prepared in a similar manner described for **14a** in 66% yield as colorless crystal. ^1H NMR ($CDCl_3$) δ 0.98 (9H, s), 2.29 (3H, s), 2.61 (1H, d, J = 11.2 Hz), 2.65 (1H, d, J = 11.2 Hz), 3.84 (3H, s), 6.20 (1H, s), 6.86–7.02 (3H, m), 7.07 (1H, d, J = 2.4 Hz), 7.18–7.36 (2H, m). MS (ESI) m/z 348 $(M+H)^+$.

4.1.1.29. (*S*)-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-methylphenyl}(2-methoxyphenyl)methanol (15b). Compound **(*S*)-15b** was separated in a similar manner described for **(*S*)-15a** using HPLC with a Chiralcel OD as colorless crystal.

4.1.1.30. Methyl 4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methylphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-16b). Compound **(*S*)-16b** was prepared in a similar manner described for **(*S*)-16a** in 88% yield as colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.87 (0.95) (9H, s), 1.92–2.02 and 2.11–2.21 (1H, m), 2.24–2.37 (1H, m), 2.40–2.50 (1H, m), 2.45 (3H, s), 2.51–2.62 (2.71–2.74) (1H, m), 2.75–2.89 (1H, m), 3.06 (3.36) (1H, d, J = 13.7 Hz), (3.56) 3.68 (3H, s), 3.77 (3.86) (3H, s), (3.91) 4.12 (0H, q, J = 7.2 Hz), 4.31 (1H, d, J = 13.7 Hz), 4.42 (1H, d, J = 4.9 Hz), 6.06 (6.39) (1H, d, J = 5.4 Hz), 6.83–6.94 (1H, m), 6.99–7.09 (2H, m), 7.20 (1H, d, J = 2.4 Hz), 7.28–7.35 (1H, m), 7.51–7.56 (7.74–7.71) (1H, m). IR (ATR) cm^{-1} 3410, 2952, 1736, 1647, 1437, 1238, 1167, 1030, 754. MS (FAB) m/z 462 (M+H)$^+$. MS (ESI, neg) m/z 460 (M−H)$^-$.

4.1.1.31. 4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methylphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-17b). Compound **(*S*)-17b** was prepared in a similar manner described for **(*S*)-17a** in 92% yield as colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.84 (9H, s), 2.15–2.35 (2H, m), 2.43 (3H, s), 2.47–2.64 (2H, m), 2.72–2.84 (1H, m), 2.92 (1H, d, J = 13.4 Hz), 3.79 (3H, s), 4.26 (1H, d, J = 13.7 Hz), 6.03 (1H, s), 6.91 (1H, d, J = 7.8 Hz), 6.97–7.04 (1H, m), 7.11 (1H, d, J = 2.4 Hz), 7.23 (1H, d, J = 2.4 Hz), 7.30–7.26 (1H, m), 7.34 (2H, d, J = 7.8 Hz). MS (ESI) m/z 430 (M−OH)$^+$. MS (ESI, neg) m/z 446 (M−H)$^-$.

4.1.1.32. Ethyl (3*S*)-1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methylphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-19b). Compound **(*S*)-19b** was prepared from **(*S*)-17b** in a similar manner described for **(*S*)-18a** in 72% yield as colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 and 0.94 (9H, s), 1.20–1.31 (5H, m), 1.59–1.84 (2H, m), 2.00–2.13 (2H, m), 2.16–2.38 (2H, m), 2.43 (3H, d, J = 2.4 Hz), 2.44–2.74 (2H, m), 2.83–3.16 (2H, m), 3.18–3.36 (2H, m), 3.71 (3H, s), 4.06–4.20 (2H, m), 4.35–4.55 (2H, m), 6.07–6.13 (1H, m), 6.86 (1H, d, J = 7.8 Hz), 6.92–6.97 (1H, m), 7.07 (1H, t, J = 7.4 Hz), 7.17–7.12 (1H, m), 7.34–7.28 (1H, m), 7.80 (1H, t, J = 7.4 Hz). IR (ATR) cm^{-1} 3325, 2952, 1728, 1658, 1624, 1458, 1240, 1178, 1032, 754. 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, 65.53; H, 7.69; N, 4.50.

4.1.1.33. (*aR*)-(3*S*)-1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methylphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-22b). Compound **(*S*)-(*aR*)-22b** was prepared from **(*S*)-19b** in a similar manner described for **(*S*)-(*aR*)-21a** in 78% yield as colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.91 and 0.92 (9H, s), 1.21–1.33 (2H, m), 1.59–1.87 (2H, m), 1.95–2.32 (3H, m), 2.42 and 2.43 (3H, s), 2.45–2.67 (2H, m), 2.91–3.16 (2H, m), 3.20–3.29 (1H, m), 3.39–3.54 (1H, m), 3.71 snd 3.72 (3H, s), 3.73–4.06 (1H, m), 4.35–4.52 (1H, m), 6.08 (1H, d, J = 5.1 Hz), 6.82–6.90 (1H, m), 6.95–7.01 (1H, m), 7.06 (1H, t, J = 7.4 Hz), 7.13–7.17 (1H, m), 7.27–7.35 (1H, m), 7.78–7.70 (1H, m). IR (ATR) cm^{-1} 2952, 1728, 1622, 1460, 1240, 1180, 1032, 754. 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, 64.32; H, 7.33; N, 4.71.

4.1.1.34. *N*-(2,4-Dichlorophenyl)-2,2-dimethylpropanamide (10c). Compound **10c** was prepared in a similar manner described for **10a** in 78% yield as colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.34 (9H, s), 7.23–7.26 (1H, m), 7.38 (1H, d, J = 2.4 Hz), 7.95 (1H, br), 8.38 (1H, d, J = 9.0 Hz). MS (ESI) m/z 246 (M+H)$^+$.

4.1.1.35. *N*-{2,4-Dichloro-6-[hydroxy(2-methoxyphenyl)methyl]-phenyl}-2,2-dimethylpropanamide (13c). Compound **13c** was prepared in a similar manner described for **13a** in 47% yield as colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 1.28 (9H, s), 3.75 (3H, s), 5.97 (1H, d, J = 3.7 Hz), 6.86 (1H, d, J = 8.1 Hz), 6.98–7.02 (1H, m), 7.13 (1H, d, J = 2.4 Hz), 7.27–7.32 (1H, m), 7.37 (1H, d, J = 2.2 Hz), 7.38–7.41 (1H, m), 7.51 (1H, br). IR (ATR) cm^{-1} 3289, 2962, 1668, 1484, 1465, 1230, 1016, 869, 755, 489. MS (ESI) m/z 365 (M−OH)$^+$. Anal. Calcd for $C_{19}H_{21}Cl_2NO_3{\cdot}0.3Et_2O$: C, 59.98; H, 5.98; N, 3.46, found: C, 60.37; H, 5.72; N, 3.77.

4.1.1.36. {3,5-Dichloro-2-[(2,2-dimethylpropyl)amino]phenyl}-(2-methoxyphenyl)methanol (14c). Compound **14c** was prepared in a similar manner described for **14a** in 64% yield as pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.98 (9H, s), 2.76 (2H, s), 3.84 (3H, s), 4.32 (1H, br), 6.29 (1H, s), 6.29–7.00 (3H, m), 7.23–7.34 (3H, m). IR (ATR) cm^{-1} 3380, 2952, 1459, 1240, 1027, 858, 752, 568. MS (ESI) m/z 350 (M−OH)$^+$.

4.1.1.37. Methyl 4-[{2,4-dichloro-6-[hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (16c). Compound **16c** was prepared in a similar manner described for **16a** in 49% yield as colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.958 (9H, s), 2.32–2.61 (3H, m), 2.96–3.04 (1H, m), 3.19 (1H, d, J = 13.7 Hz), 3.68 (3H, s), 3.74 (3H, s), 4.43 (1H, d, J = 13.7 Hz), 4.99 (1H, d, J = 5.6 Hz), 6.10 (1H, d, J = 5.4 Hz), 6.89 (1H, d, J = 8.3 Hz), 7.05–7.10 (2H, m), 7.32–7.36 (1H, m), 7.40 (1H, d, J = 2.4 Hz), 7.70 (1H, dd, J = 8.0, 1.3 Hz). MS (ESI) m/z 464 (M−OH)$^+$. Anal. Calcd for $C_{24}H_{29}Cl_2NO_5$: C, 59.76; H, 6.06; N, 2.90. Found: C, 60.07; H, 6.08; N, 2.77.

4.1.1.38. 4-[{2,4-Dichloro-6-[hydroxy(2-methoxyphenyl)methyl]-phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (17c). Compound **17c** was prepared in a similar manner described for **17a** in 96% yield as colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.915 (9H, s), 2.43–2.55 (3H, m), 2.95–2.99 (1H, m), 2.99 (1H, d, J = 13.6 Hz), 3.76 (3H, s), 4.37 (1H, d, J = 13.6 Hz), 6.06 (1H, s), 6.90 (1H, d, J = 8.5 Hz), 7.02–7.06 (1H, m), 7.11 (1H, d, J = 2.2 Hz), 7.33–7.37 (1H, m), 7.43 (1H, d, J = 2.4 Hz), 7.49 (1H, d, J = 7.3 Hz). MS (ESI) m/z 450 (M−OH)$^+$. Anal. Calcd for $C_{23}H_{27}Cl_2NO_5$: C, 58.98; H, 5.81; N, 2.99. Found: C, 59.02; H, 5.90; N, 3.20.

4.1.1.39. Ethyl (3*S*)-1-{4-[{2,4-dichloro-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-19c). Compound **19c** was prepared in a similar manner described for **(*S*)-18a** in 88% yield as colorless amorphous. Then, the enantiomers were separated by HPLC with a Chiralcel OD (Φ20 × 250 mm) at flow rate of 7 ml/min at room temperature using 10% 2-propanol–*n*-hexane (254 nm detection) to give peak 1 (**(*R*)-19c**) at t_R = 21 min, and peak 2 (**(*S*)-19c**) at t_R = 26 min. **(*S*)-19c**; ^{1}H NMR ($CDCl_3$) δ 1.00 (9H, s), 1.19–1.29 (3H, m), 1.63–1.79 (3H, m), 2.07–2.66 (5H, m), 2.86–3.39 (4H, m), 3.71 (3H, s), 3.71–3.79 (1H, m), 4.01–4.19 (2H, m), 4.38–4.50 (2H, m), 6.12–6.14 (1H, m), 6.57–6.59 (1H, m), 6.87 (1H, d, J = 8.1 Hz), 6.97 (1H, t, J = 2.7 Hz), 7.08–7.20 (1H, m), 7.30–7.36 (2H, m), 7.86–7.88 (1H, m). IR (ATR) cm^{-1} 3345, 2952, 1727, 1670, 1556, 1448, 1238, 1180, 1029, 754, 578. MS (ESI) m/z 607 (M+H)$^+$. (**(*R*)-19c**; the peak similar to the enantiomer was obtained.)

4.1.1.40. (*aR*)-(3*S*)-1-{4-[{2,4-Dichloro-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-22c). Compound **(*S*)-(*aR*)-22c** was prepared from **(*S*)-19c** in a similar manner described for **(*S*)-(*aR*)-21a** in 48% yield as colorless powder (minor atropisomer **(*S*)-(*aS*)-22c** was separated in 12% yield.) **(*S*)-(*aR*)-22c**; ^{1}H NMR ($CDCl_3$) δ 0.97 (0.91, 9H, s), 1.12–2.55 (9H, m), 3.00–3.51 (4H, m), 3.70 (3.68, 3H, s), 3.72–3.87 (1H, m), 4.43 (4.34, 1H, d, J = 13.7 Hz), 5.59 (1H, br), 6.10 (1H, s), 6.84–6.87

(1H, m), 6.93–7.11 (2H, m), 7.22–7.39 (2H, m), 7.85 (7.64, 1H, d, J = 7.45 Hz). IR (ATR) cm^{-1} 3316, 2950, 1619, 1448, 1390, 1238, 1184, 1031, 754, 514. MS (ESI) m/z 579 $(M+H)^+$. Anal. Calcd for $C_{29}H_{36}N_2O_6Cl_2{\cdot}1.5H_2O$: C, 57.43; H, 6.48; N, 4.62. Found: C, 57.29; H, 6.21; N, 4.46. **(*S*)-(*aS*)-22c**; ^1H NMR ($CDCl_3$) δ 0.93 (0.92, 9H, s), 1.26–1.35 (1H, m), 1.58–2.04 (4H, m), 2.17–2.57 (3H, m), 2.70–3.48 (5H, m), 3.65 (3.72, 3H, s), 3.55–3.84 (1H, m), 4.21–4.44 (1H, m), 6.06–6.26 (1H, m), 6.79–6.92 (2H, m), 7.16–7.70 (4H, m). MS (ESI) m/z 579 $(M+H)^+$. Anal. Calcd for $C_{29}H_{36}N_2O_6Cl_2{\cdot}1.5H_2O$: C, 57.43; H, 6.48; N, 4.62. Found: C, 57.04; H, 6.40; N, 4.22.

4.1.1.41. *N*-(4-Chloro-2-hydroxyphenyl)-2,2-dimethylpropanamide (10j). 2-Amino-4-chlorophenol (25.32 g, 176.4 mmol) was dissolved in CH_2Cl_2 (1500 ml). To the solution at 0 °C, and $NaHCO_3$ (44.45 g, 529.1 mmol) and pivaloyl chloride (23.89 ml, 194.0 mmol) were added. The mixture was gradually wormed to room temperature for 1.5 h. 1 N HClaq (360 ml) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, and dried over Na_2SO_4. The solvent was removed in a reduced presser, and the residue was recrystallized with diethyl ether and *n*-hexane to give compound **10j** (29.30 g, 128.7 mmol, 73%) as pale purple crystal. ^1H NMR ($CDCl_3$) δ 1.35 (9H, s), 6.83 (1H, dd, J = 8.5, 2.4 Hz), 6.90 (1H, d, J = 8.5 Hz), 7.02 (1H, d, J = 2.4 Hz), 7.53 (1H, br), 9.07 (1H, s). IR (ATR) cm^{-1} 3425, 2958, 1641, 1583, 1537, 1514, 1410, 1371, 1265, 1205, 935, 841. MS (ESI) m/z 228 $[(M+H)^+, Cl_{35}]$, 230 $[(M+H)^+, Cl_{37}]$.

4.1.1.42. *N*-(4-Chloro-2-ethoxyphenyl)-2,2-dimethylpropanamide (10d). Compound **10j** (303 mg, 1.33 mmol) was dissolved in DMF (10 ml). K_2CO_3 (139 mg, 1.00 mmol) and iodoethane (160 μl, 2.00 mmol) were added to the solution, and the mixture was stirred at room temperature for 19 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in AcOEt (20 ml), 1 N HClaq (2 ml) and H2O (15 ml). The layers were separated, and 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 = 8:1) to give compound **10d** (325 mg, 1.27 mmol, 95%) as pale yellow oil. ^1H NMR ($CDCl_3$) δ 1.31 (9H, s), 1.47 (3H, t, J = 7.1 Hz), 4.08 (2H, q, J = 7.1 Hz), 6.84 (1H, d, J = 2.2 Hz), 6.92 (1H, dd, J = 8.5, 2.2 Hz), 8.10 (1H, br), 8.33 (1H, d, J = 8.5 Hz). IR (ATR) cm^{-1} 3440, 2974, 1674, 1601, 1514, 1389, 1255, 1124, 1038, 943, 820, 586. MS (ESI) m/z 256 $[(M+H)^+, Cl_{35}]$, 258 $[(M+H)^+, Cl_{37}]$.

4.1.1.43. *N*-{4-Chloro-2-ethoxy-6-[hydroxy(2-methoxyphenyl)-methyl]phenyl}-2,2-dimethylpropanamide (13d). Compound **13d** was prepared in a similar manner described for **13a** in 66% yield as colorless crystal. ^1H NMR ($CDCl_3$) δ 1.31 (9H, s), 1.41 (3H, t, J = 7.1 Hz), 4.01 (2H, q, J = 7.1), 4.44 (1H, d, J = 3.5 Hz), 5.98 (1H, d, J = 3.5 Hz), 6.77 (1H, d, J = 2.2 Hz), 6.79 (1H, d, J = 2.2 Hz), 6.80 (1H, dd, J = 8.4, 1.0 Hz), 7.01 (1H, td, J = 7.5, 1.0 Hz), 7.21–7.29 (1H, m), 7.57 (1H, dd, J = 7.5, 1.0 Hz). IR (ATR) cm^{-1} 3429, 3248, 2974, 1660, 1585, 1493, 1389, 1292, 1228, 1043, 758. MS (ESI) m/z 374 $[(M+H)^+, Cl_{35}]$, 376 $[(M+H)^+, Cl_{37}]$. MS (ESI, neg) m/z 390 $[(M-H)^-, Cl_{35}]$, 392 $[(M-H)^-, Cl_{37}]$. Anal. Calcd for $C_{21}H_{26}ClNO_4{\cdot}0.5H_2O$: C, 62.92; H, 6.79; N, 3.49. Found: C, 63.15; H, 6.69; N, 3.58.

4.1.1.44. {5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-ethoxyphenyl}(2-methoxyphenyl)methanol (14d). Compound **14d** was prepared in a similar manner described for **14a** in 84% yield as colorless crystal. ^1H NMR ($CDCl_3$) δ 0.98 (9H, s), 1.44 (3H, t, J = 7.0 Hz), 2.67 (1H, d, J = 11.2 Hz), 2.78 (1H, d, J = 11.2 Hz), 3.84 (3H, s), 4.02 (2H, q, J = 7.0 Hz), 6.36 (1H, s), 6.55 (1H, d, J = 2.2 Hz), 6.74 (1H, d, J = 2.2 Hz), 6.92 (1H, d, J = 7.5 Hz), 6.98 (1H, td, J = 7.3, 1.0 Hz), 7.30 (1H, td, J = 7.8, 1.7 Hz), 7.32 (1H, dd, J = 7.3, 1.7 Hz). IR (ATR) cm^{-1} 3246, 2945, 1591, 1462, 1390, 1292, 1236, 1188, 1039, 903, 822, 752. MS (ESI) m/z 378 $[(M+H)^+, Cl_{35}]$, 380 $[(M+H)^+, Cl_{37}]$. Anal. Calcd for $C_{21}H_{28}ClNO_3$: C, 66.74; H, 7.47; N, 3.71. Found: C, 67.07; H, 7.54; N, 3.59.

4.1.1.45. (*S*)-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-ethoxyphenyl}(2-methoxyphenyl)methanol (15d). Compound **(*S*)-15d** was separated in a similar manner described for **(*S*)-15a** using by HPLC with a Chiralcel OD as colorless crystal.

4.1.1.46. Methyl 4-[{4-chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-16d). Compound **(*S*)-16d** was prepared in a similar manner described for **(*S*)-16a** in quantum yield as colorless oil. ^1H NMR ($CDCl_3$) δ (0.89) 0.91 (9H, s), 1.48 (3H, t, J = 7.0 Hz), (1.16–1.29 and 1.72–1.83 and 2.12–2.25) 2.24–2.36 and 2.53–2.64 and 2.87–3.02 (4H, m), (2.90) 3.09 (1H, d, J = 13.5 Hz), (3.56) 3.67 (3H, s), 3.73 (3.82) (3H, s), 3.94–4.14 (2H, m), (4.39) 4.44 (1H, d, J = 13.5 Hz), 4.78 (1H, d, J = 5.4 Hz), 6.10 (6.26) (1H, d, J = 5.4 Hz), 6.70 (1H, d, J = 2.2 Hz), 6.81 (1H, d, J = 2.2 Hz), 6.82–7.18 (2H, m), 7.19–7.29 (1H, m), (7.45–7.54) 7.70 (1H, d, J = 7.6 Hz). IR (ATR) cm^{-1} 3411, 2951, 1736, 1645, 1579, 1466, 1392, 1286, 1238, 1161, 1030, 754. MS (ESI) m/z 474 $[(M-OH)^+, Cl_{35}]$, 476 $[(M-OH)^+, Cl_{37}]$, 492 $[(M+H)^+, Cl_{35}]$, 494 $[(M+H)^+, Cl_{37}]$, 514 $[(M+Na)^+, Cl_{35}]$, 516 $[(M+Na)^+, Cl_{37}]$.

4.1.1.47. 4-[{4-Chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)-methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-17d). Compound **(*S*)-17d** was prepared in a similar manner described for **(*S*)-17a** in 99% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.88 (0.90) (9H, s), (1.41) 1.47 (3H, t, J = 7.0), (1.10–1.17 and 1.92–2.11) 2.30–2.65 and 2.77–2.96 (4H, m), 2.89 (1H, d, J = 13.7 Hz), 3.76 (3.83) (3H, s), 3.98–4.17 (2H, m), 4.38 (1H, d, J = 13.7 Hz), 5.30 (1H, s), 6.05 (6.31) (1H, s), 6.76 (1H, d, J = 2.2 Hz), 6.84 (1H, d, J = 2.2 Hz), 7.70–7.87 (1H, m), 6.99–7.08 (1H, m), 7.20–7.38 (1H, m), 7.43–7.50 (7.55–7.60) (1H, m). IR (ATR) cm^{-1} 3415, 2952, 1712, 1639, 1466, 1392, 1289, 1240, 1174, 1028, 754. MS (ESI) m/z 460 $[(M-OH)^+, Cl_{35}]$, 462 $[(M-OH)^+, Cl_{37}]$, 478 [(M+H)+, Cl_{35}], 480 $[(M+H)^+, Cl_{37}]$. MS (ESI, neg) m/z: 476 $[(M-H)^-, Cl_{35}]$, 478 $[(M-H)^-, Cl_{37}]$.

4.1.1.48. (*aR*)-Ethyl and (a*S*)-ethyl 1-{4-[{4-chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate ((*S*)-(*aR*)-18d, (*S*)-(a*S*)-18d). Compound **(*S*)-(*aR*)-18d** and **(*S*)-(*aS*)-18d** were prepared from **(*S*)-17d** in a similar manner described for **(*S*)-18a**. Purification using preparative TLC (1 mm × 20 cm × 20 cm, CH_2Cl_2/MeOH = 15:1) gave **(*S*)-(*aR*)-18d** (87%) and **(*S*)-(*aS*)-18d** (7%) as colorless amorphous. **(*S*)-(*aR*)-18d**; ^1H NMR ($CDCl_3$) δ 0.95 (9H, s), 1.21–1.33 (6H, m), 1.46 (3H, t, J = 7.1 Hz), 1.57–1.73 (1H, m), 1.75–1.98 (2H, m), 2.08–2.26 (2H, m), 2.42–2.66 (2H, m), 2.71–2.92 (1H, m), 3.04–3.19 (2H, m), 3.30 (1H, dd, J = 13.7, 2.9 Hz), 3.70 (3H, s), 3.78–3.90 (1H, m), 3.96–4.17 (4H, m), 4.50 (1H, dd, J = 13.4, 6.3 Hz), 6.10–6.16 (1H, m), 6.62 (1H, d, J = 2.0 Hz), 6.77 (1H, d, J = 2.2 Hz), 6.85 (1H, d, J = 7.8 Hz), 7.09 (1H, t, J = 7.4 Hz), 7.27–7.33 (1H, m), 7.91–7.85 (1H, m). IR(ATR) cm^{-1} 3348, 2952, 1728, 1660, 1624, 1466, 1392, 1242, 1174, 1034, 754. MS (ESI) m/z 617 $[(M+H)^+, Cl_{35}]$, 619$[(M+H)^+, Cl_{37}]$. Anal. Calcd for $C_{33}H_{45}ClN_2O_7{\cdot}0.25H_2O$: C, 63.76; H, 7.38; N, 4.51. Found: C, 63.74; H, 7.44; N, 4.24. **(*S*)-(*aS*)-18d**; ^1H NMR ($CDCl_3$) δ 0.89 (9H, s), 1.22–1.30 (3H, m), 1.38–1.46 (3H, m), 1.49–1.77 (2H, m), 1.81–1.90 (2H, m), 2.12–2.25 (1H, m), 2.29–2.52 (2H, m), 2.61–2.85 (2H, m), 2.86–3.00 (2H, m), 3.62–3.74 (1H, m), 3.84 (3H, s), 3.96–4.19

(4H, m), 4.22–4.32 (1H, m), 4.39 (1H, d, *J* = 13.4 Hz), 6.21 (1H, s), 6.82–6.88 (3H, m), 6.98–7.05 (1H, m), 7.15–7.25 (1H, m), 7.41 (1H, dd, *J* = 10.3, 2.0 Hz). IR(ATR) cm^{-1} 3381, 2951, 1635, 1466, 1392, 1242, 1180, 1036, 754. Anal. Calcd for $C_{33}H_{45}ClN_2O_7$: C, 64.22; H, 7.35; N, 4.54. Found: C, 64.16; H, 7.47; N, 4.38.

4.1.1.49. (*aR*)-1-{4-[{4-chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid ((*S*)-(*aR*)-21d). Compound **(*S*)-(*aR*)-21d** was prepared from **(*S*)-(*aR*)-18d** in a similar manner described for **(*S*)-(*aR*)-21a** in 80% yield as colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.95 (9H, s), 1.47 (3H, t, *J* = 7.0 Hz), 1.51–1.73 (4H, m), 1.80–2.03 (2H, m), 2.09–2.27 (2H, m), 2.49–2.67 (2H, m), 2.74–2.88 (1H, m), 3.03–3.22 (2H, m), 3.32 (1H, dd, *J* = 13.5, 7.0 Hz), 3.71 (3H, d, *J* = 2.2 Hz), 3.80–3.91 (1H, m), 3.96–4.15 (2H, m), 4.51 (1H, dd, *J* = 13.5, 9.2 Hz), 6.14 (1H, s), 6.61 (1H, d, *J* = 2.2 Hz), 6.76–6.79 (1H, m), 6.82–6.88 (1H, m), 7.05–7.13 (1H, m), 7.28–7.33 (1H, m), 7.90–7.84 (1H, m). IR (ATR) cm^{-1} 2952, 1736, 1658, 1620, 1466, 1392, 1288, 1242, 1028, 754. MS (ESI) *m/z* 571 [$(M-OH)^+$, Cl_{35}], 589[$(M+H)^+$, Cl_{35}]. Anal. Calcd for $C_{31}H_{41}ClN_2O_7 \cdot 0.25H_2O$: C, 62.72; H, 7.05; N, 4.72. Found: C, 62.61; H, 7.08; N, 4.55.

4.1.1.50. (a*S*)-1-{4-[{4-chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid ((a*S*)-(*S*)-21d). Compound **(*S*)-(*aS*)-21d** was prepared from **(*S*)-(*aS*)-18d** in a similar manner described for **(*S*)-(*aR*)-21a** in 36% yield as colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.92 (9H, s), 0.96 (3H, s), 1.27–1.31 (1H, m), 1.40–1.50 (4H, m), 1.72–1.94 (2H, m), 2.15–2.28 (2H, m), 2.30–2.46 (2H, m), 2.48–2.68 (4H, m), 2.72–2.87 (1H, m), 2.89–3.03 (1H, m), 3.78 (3H, s), 3.84–3.89 (2H, m), 6.20–6.29 (1H, m), 6.32–6.41 (1H, m), 6.83–6.92 (1H, m), 7.03–7.10 (1H, m), 7.25–7.28 (1H, m), 7.32–7.36 (1H, m), 7.42–7.52 (1H, m), 7.75–7.67 (1H, m). IR (ATR) cm^{-1} 2951, 1726, 1624, 1466, 1392, 1286, 1242, 1182, 1030, 754. MS (ESI) *m/z* 589 [$(M+H)^+$, Cl_{35}], 591[$(M+H)^+$, Cl_{37}]. Anal. Calcd for $C_{31}H_{41}ClN_2O_7 \cdot 0.25H_2O$: C, 62.72; H, 7.05; N, 4.72. Found: C, 62.79; H, 7.15; N, 4.48.

4.1.1.51. (*aR*) and (a*S*)-ethyl (3*S*)-1-{4-[{4-chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-(*aR*)-19d, (*S*)-(a*S*)-19d). Compound **(*S*)-(*aR*)-19d** (74%) and **(*S*)-(*aS*)-19d** (7%) were prepared from **(*S*)-17d** in a similar manner described for **(*S*)-(*aR*)-18d** as colorless amorphous. **(*S*)-(*aR*)-19d**; ^{1}H NMR ($CDCl_3$) δ 0.94 and 0.95 (9H, s), 1.22 and 1.26 (3H, t, *J* = 7.1 Hz), 1.28–1.82 (2H, m), 1.46 (3H, t, *J* = 7.0 Hz), 2.00–2.36 (3.5H, m), 2.42–2.44 (2H, m), 2.77–2.87 (0.5H, m), 2.96–3.22 (2H, m), 3.26–3.33 (2H, m), 3.70 (3H, s), 3.72–3.84 (1H, m), 3.96–4.19 (5H, m), 4.42–4.58 (2H, m), 6.11–6.17 (1H, m), 6.36 (1H, d, *J* = 4.9 Hz), 6.60–6.63 (1H, m), 6.76–6.78 (1H, m), 6.83–6.87 (1H, m), 7.07–7.12 (1H, m), 7.28–7.33 (1H, m), 7.86–7.91 (1H, m). IR (ATR) cm^{-1} 3330, 2945, 1660, 1626, 1466, 1392, 1288, 1242, 1178, 1113, 1030, 754. MS (ESI) *m/z* 617 [$(M+H)^+$, Cl_{35}], 619[$(M+H)^+$, Cl_{37}]. Anal. Calcd for $C_{33}H_{45}ClN_2O_7$: C, 64.22; H, 7.35; N, 4.54. Found: C, 64.28; H, 7.49; N, 4.35. **(*S*)-(*aS*)-19d**; ^{1}H NMR ($CDCl_3$) δ 0.89 (9H, s), 1.18–1.28 (3H, m), 1.28–1.51 (3H, m), 1.43 (3H, t, *J* = 7.1 Hz), 1.60–1.82 (3H, m), 1.97–2.09 (1H, m), 2.13–2.26 (1H, m), 2.27–2.48 (2H, m), 2.64–2.94 (3H, m), 3.15 (1H, dd, *J* = 13.7, 10.0 Hz), 3.54–3.79 (1H, m), 3.83 (3H, s), 3.84 (3H, s), 3.96–4.20 (4H, m), 4.39 (1H, dd, *J* = 13.4, 4.2 Hz), 4.47–4.57 (1H, m), 6.19–6.25 (1H, m), 6.79–6.90 (3H, m), 6.98–7.07 (1H, m), 7.15–7.25 (1H, m), 7.43–7.37 (1H, m). IR(ATR) cm^{-1} 3317, 2935, 1728, 1660, 1626, 1475, 1529, 1219, 1176, 1032, 1003, 760. MS (ESI) *m/z* 617 [$(M+H)^+$, Cl_{35}], 619[$(M+H)^+$, Cl_{37}]. Anal. Calcd for $C_{33}H_{45}ClN_2O_7$: C, 64.22; H, 7.35; N, 4.54. Found: C, 64.11; H, 7.42; N, 4.44.

4.1.1.52. (*aR*)-(3*S*)-1-{4-[{4-chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-22d). Compound **(*S*)-(*aR*)-22d** was prepared from **(*S*)-(*aR*)-19d** in a similar manner described for **(*S*)-(*aR*)-21a** in 87% yield as colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.93 (9H, s), 1.22–1.31 (1H, m), 1.43–1.49 (3H, m), 1.59–1.84 (2H, m), 1.94–2.66 (7H, m), 2.86–3.52 (3H, m), 3.70 (3H, s), 3.71–3.90 (1H, m), 3.94–4.14 (3H, m), 4.43–4.53 (2H, m), 6.13 (1H, d, *J* = 6.1 Hz), 6.64 (1H, d, *J* = 2.2 Hz), 6.75–6.79 (1H, m), 6.81–6.88 (1H, m), 7.05–7.12 (1H, m), 7.27–7.34 (1H, m), 7.87–7.81 (1H, m). IR (ATR) cm^{-1} 2951, 1728, 1622, 1466, 1392, 1286, 1241, 1180, 1030, 754. MS (ESI) *m/z* 589 [$(M+H)^+$, Cl_{35}], 591[$(M+H)^+$, Cl_{37}]. Anal. Calcd for $C_{31}H_{41}ClN_2O_7$: C, 63.20; H, 7.01; N, 4.76. Found: C, 62.91; H, 7.20; N, 4.58.

4.1.1.53. (a*S*)-(3*S*)-1-{4-[{4-Chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(a*S*)-22d). Compound **(*S*)-(*aS*)-22d** was prepared from **(*S*)-(*aS*)-19d** in a similar manner described for **(*S*)-(*aR*)-21a** in 93% yield as colorless amorphous. ^{1}H NMR ($CDCl_3$) δ 0.89 (9H, s), 1.35–1.46 (4H, m), 1.59–1.89 (3H, m), 1.98–2.12 (1H, m), 2.14–2.27 (1H, m), 2.29–2.49 (2H, m), 2.71–3.02 (3H, m), 3.09–3.28 (1H, m), 3.44–3.63 (1H, m), 3.83 (3H, s), 3.96–4.13 (2H, m), 4.30–4.44 (1H, m), 6.21 (1H, s), 6.81–6.90 (3H, m), 6.98–7.08 (1H, m), 7.24–7.16 (1H, m), 7.41 (1H, d, *J* = 2.0 Hz). IR (ATR) cm^{-1} 2954, 1724, 1618, 1464, 1392, 1286, 1242, 1111, 1039, 754. MS (ESI) *m/z* 589 [$(M+H)^+$, Cl_{35}], 591 [$(M+H)^+$, Cl_{37}]. Anal. Calcd for $C_{31}H_{41}ClN_2O_7$: C, 63.20; H, 7.01; N, 4.76. Found: C, 63.09; H, 7.16; N, 4.63.

4.1.1.54. *N*-[4-Chloro-2-(propan-2-yloxy)phenyl]-2,2-dimethylpropanamide (10e). To a stirred solution of **10j** (4.01 g, 17.6 mmol) in tetrahydrofuran (200 mL) at 0 °C, 2-propanol (2.02 ml, 26.4 mmol) and triphenylphosphine (6.92 g, 26.4 mmol) was added, followed by a drop in diethyl azodicarboxylate (40% in toluene, 11.5 g, 26.4 mmol). After 2 h, a saturated aqueous solution of ammonium chloride was added and the mixture was extracted with AcOEt. 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 (*n*-hexane/AcOEt = 10:1 as eluent) to give compound **10e** (4.40 g, 16.3 mmol, 93%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.31 (9H, s), 1.39 (6H, d, *J* = 6.1 Hz), 4.52–4.59 (1H, m), 6.86 (1H, d, *J* = 2.2 Hz), 6.92 (1H, dd, *J* = 8.8, 2.2 Hz), 8.13 (1H, s), 8.36 (1H, dd, *J* = 13.4, 8.8 Hz). IR (ATR) cm^{-1} 3428, 2976, 1684, 1595, 1508, 1479, 1408, 1246, 1119, 962, 819, 586. MS (ESI) *m/z* 270 [$(M+H)^+$, Cl_{35}], 272 [$(M+H)^+$, Cl_{37}].

4.1.1.55. *N*-{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-6-(propan-2-yloxy)phenyl}-2,2-dimethylpropanamide (13e). Compound **13e** was prepared in a similar manner described for **13a** in 40% yield as colorless crystal. ^{1}H NMR ($CDCl_3$) δ 1.31 (9H, s), 1.34 (6H, dd, *J* = 23.4, 11.7 Hz), 4.49–4.52 (2H, m), 5.97 (1H, d, *J* = 3.4 Hz), 6.78 (1H, s), 6.81 (1H, d, *J* = 7.3 Hz), 7.01–7.04 (1H, m), 7.23–7.26 (3H, m), 7.60–7.62 (1H, m). IR (ATR) cm^{-1} 3523, 2972, 1670, 1585, 1491, 1319, 1111, 1047, 1014, 831, 754. MS (ESI, neg) *m/z* 404 $(M-H)^-$.

4.1.1.56. {5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-(propan-2-yloxy)phenyl}(2-methoxyphenyl)methanol (14e). Compound **14e** was prepared in a similar manner described for **14a** in 37% yield as colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.99 (9H, s), 1.35 (6H, dd, *J* = 5.5, 2.7 Hz), 2.63 (1H, d, *J* = 11.0 Hz), 2.76 (1H, d, *J* = 11.0 Hz), 3.83 (3H, s), 4.48–4.57 (1H, m), 6.33 (1H, s), 6.48 (1H, d,

J = 2.2 Hz), 6.75 (1H, d, J = 2.2 Hz), 6.92 (1H, d, J = 8.3 Hz), 6.98 (1H, t, J = 7.4 Hz), 7.29 (1H, td, J = 15.3, 7.6 Hz), 7.35 (1H, dd, J = 7.4, 1.6 Hz). IR (ATR) cm^{-1} 2952, 1587, 1464, 1240, 1113, 1028, 752. MS (ESI) m/z 392 $(M+H)^+$.

4.1.1.57. (*S*)-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-(propan-2-yloxy)phenyl}(2-methoxyphenyl)methanol (15e). Compound **(*S*)-15e** was separated in a similar manner described for **(*S*)-15a** using HPLC with a Chiralcel OD as colorless crystal.

4.1.1.58. Methyl 4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(propan-2-yloxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-16e). Compound **(*S*)-16e** was prepared in a similar manner described for **(*S*)-16a** in 99% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ (0.90) 0.91 (9H, s), 1.37–1.44 (6H, m), 2.16–2.38 (2H, m), 2.51–2.66 (1H, m), 2.88–3.00 (1H, m), 3.05 (1H, d, J = 13.7 Hz), 3.56 (0H, s), 3.67 (3H, s), 3.74 (3H, s), 3.83 (1H, s), 4.42 (1H, d, J = 13.2 Hz), 4.55–4.66 (1H, m), 4.70 (1H, d, J = 5.1 Hz), 6.09 (6.24–6.28) (1H, d, J = 5.4 Hz (and m)), 6.69 (1H, d, J = 2.2 Hz), 6.79 and 6.82 (1H, d, J = 2.5 Hz), 6.84–6.93 (1H, m), 7.03–7.09 (1H, m), 7.20–7.25 (1H, m), 7.29–7.35 (1H, m), 7.41–7.44 (1H, m), 7.65–7.70 (1H, m). IR (ATR) cm^{-1} 3410, 2951, 1736, 1645, 1466, 1284, 1238, 1163, 1113, 1020, 754. MS (ESI) m/z 488 $(M-OH)^+$, 506 $(M+H)^+$.

4.1.1.59. 4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(propan-2-yloxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-17e). Compound **(*S*)-17e** was prepared in a similar manner described for **(*S*)-17a** in 93% yield as colorless amorphous. $^{1H\ NMR}$ ($CDCl_3$) δ (0.87) 0.92 (9H, s), 1.27–1.66 (2H, m), 1.36–1.43 (6H, m), 2.31–2.62 (3H, m), 2.72–2.83 (1H, m), 2.86 (1H, d, J = 13.5 Hz), 3.78 (3.84) (3H, s), 4.36 (1H, d, J = 13.5 Hz), 4.54–4.67 (1H, m), 6.04 (1H, s), 6.75 (1H, d, J = 2.2 Hz), 6.83 (1H, d, J = 2.7 Hz), 6.90 (1H, d, J = 7.2 Hz), 6.99–7.05 (1H, m), 7.29–7.36 (1H, m), 7.39–7.45 (7.55–7.50) (1H, m). IR (ATR) cm^{-1} 2949, 1712, 1637, 1581, 1464, 1389, 1284, 1240, 1174, 1113, 1022, 754. MS (ESI) m/z 492 $(M+H)^+$. MS (ESI, neg) m/z 490 $(M-H)^-$.

4.1.1.60. (*aR*)-Ethyl (3*S*)-1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methxyphenyl)methyl]-6-(propan-2-yloxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-(*aR*)-19e). Compound **(*S*)-(*aR*)-19e** was prepared from **(*S*)-17e** in a similar manner described for **(*S*)-(*aR*)-18d** in 68% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.95 and 0.96 (9H, s), 1.19–1.33 (2H, m), 1.26 (3H, t, J = 7.3 Hz), 1.36–1.42 (6H, m), 1.57–1.81 (2H, m), 2.01–2.36 (4H, m), 2.42–2.67 (2H, m), 2.83 (0.5H, dd, J = 13.1, 10.6 Hz), 2.96–3.22 (2H, m), 3.29 (1H, dd, J = 13.4, 7.3 Hz), 3.71 (3H, s), 3.73–3.82 (0.5H, m), 4.01–4.19 (2H, m), 4.42–4.64 (3H, m), 6.13 (1H, t, J = 5.1 Hz), 6.34 (1H, d, J = 5.1 Hz), 6.59 (1H, t, J = 2.3 Hz), 6.72–6.76 (1H, m), 6.85 (1H, d, J = 7.8 Hz), 7.09 (1H, t, J = 7.6 Hz), 7.27–7.33 (1H, m), 7.91–7.83 (1H, m). IR(ATR) cm^{-1} 3350, 2941, 1728, 1660, 1626, 1464, 1286, 1242, 1178, 1115, 1018, 754. MS (ESI) m/z 613 $(M-OH)^+$, 631 $(M+H)^+$. Anal. Calcd for $C_{34}H_{47}ClN_2O_7$: C, 64.70; H, 7.51; N, 4.44. Found: C, 64.78; H, 7.69; N, 4.22.

4.1.1.61. (*aR*)-(3*S*)-1-{4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(propan-2-yloxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-22e). Compound **(*S*)-(*aR*)-22e** was prepared from **(*S*)-(*aR*)-19e** in a similar manner described for **(*S*)-(*aR*)-21d** in 99% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.94 and 0.95 (9H, s), 1.36–1.43 (6H, m), 1.58–1.82 (2H, m), 1.96–2.43 (3H, m), 2.51–2.67 (2H, m), 2.73–2.88 (1H, m), 2.94–3.37 (3H, m), 3.70 and 3.71 (3H, s), 3.74–3.86 (1H, m), 3.93 (0.5H, dd, J = 13.4, 3.2 Hz), 4.11–4.23 (0.5H, m), 4.42–4.51 (1H, m), 4.53–4.64 (2H, m), 6.12 (1H, d, J = 7.8 Hz), 6.60 (1H, d, J = 2.5 Hz), 6.73–6.76 (1H, m), 6.84 (1H, t, J = 7.8 Hz), 7.03–7.11 (1H, m), 7.25–7.33 (1H, m), 7.87–7.79 (1H, m). IR (ATR) cm^{-1} 2947, 1728, 1624, 1464, 1410, 1284, 1242, 1180, 1115, 1009, 754. MS (ESI) m/z 585 $(M-OH)^+$, 603 $(M+H)^+$. Anal. Calcd for $C_{32}H_{43}ClN_2O_7$: C, 63.72; H, 7.19; N, 4.64. Found: C, 63.79; H, 7.51; N, 4.43.

4.1.1.62. *N*-{2-[3-(Benzyloxy)propoxy]-4-chlorophenyl}-2,2-dimethylpropanamide (10k). Compound **10k** was prepared from **10j** in a similar manner described for **10e** in 89% yield as pale yellow oil. ^1H NMR ($CDCl_3$) δ 1.25 (9H, s), 2.10–2.17 (2H, m), 3.62–3.67 (2H, m), 4.13–4.18 (2H, m), 4.53 (2H, s), 6.86 (1H, d, J = 2.2 Hz), 6.93 (1H, dd, J = 8.8, 2.2 Hz), 7.27–7.34 (5H, m), 7.99 (1H, br), 8.33 (1H, d, J = 8.8 Hz). IR (ATR) cm^{-1} 3444, 2958, 2868, 1684, 1567, 1512, 1412, 1248, 1117, 922, 812, 735.

MS (ESI) m/z 376 $(M+H)^+$.

4.1.1.63. *N*-[4-Chloro-2-(3-hydroxypropoxy)phenyl]-2,2-dimethylpropanamide (10f). A solution of **10k** (4.76 g, 12.7 mmol) and 10% palladium on carbon (50% water, 650 mg) in AcOEt (120 ml) was hydrogenated for 7 h. The reaction mixture was filtrated and concentrated in vacuo to give **10f** (3.16 g, 11.1 mmol, 87%) as colorless crystal. ^1H NMR ($CDCl_3$) δ 1.31 (9H, s), 2.07–2.14 (2H, m), 3.88 (2H, q, J = 5.6 Hz), 4.16–4.20 (2H, m), 6.88 (1H, d, J = 2.2 Hz), 6.94 (1H, dd, J = 8.6, 2.2 Hz), 8.05 (1H, br s), 8.32 (1H, d, J = 8.6 Hz). IR (ATR) cm^{-1} 3431, 3342, 2964, 1658, 1601, 1514, 1392, 1255, 1061, 1020, 839, 588. MS (ESI) m/z 286 $(M+H)^+$.

4.1.1.64. *N*-{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxypropoxy)phenyl}-2,2-dimethylpropanamide (13f) Compound **13f** was prepared from **10f** in a similar manner described for **13a**, using 3.5 equiv *sec*-butyl lithium, in 43% yield as colorless needle crystal. ^1H NMR ($CDCl_3$) δ 1.18 (9H, s), 1.97–2.04 (2H, m), 2.63 (1H, t, J = 6.2 Hz), 3.78–3.83 (2H, m), 3.82 (3H, s), 4.07–4.09 (1H, m), 4.16 (2H, t, J = 5.9 Hz), 5.96–5.99 (1H, m), 6.81 (1H, d, J = 2.2 Hz), 6.87–7.01 (3H, m), 7.18–7.24 (1H, m), 7.27–7.33 (1H, m), 7.77 (1H, br). IR (ATR) cm^{-1} 3367, 2960, 1653, 1587, 1489, 1234, 1034, 833, 756. MS (ESI) m/z 404 [$(M-OH)^+$, Cl_{35}], 406 [$(M-OH)^+$, Cl_{37}].

4.1.1.65. 3-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-[hydroxy-(2-methoxyphenyl)methyl]phenoxy}propan-1-ol (14f). Compound **14f** was prepared in a similar manner described for **14a** in quantum yield as colorless oil. ^1H NMR ($CDCl_3$) δ 0.97 (9H, s), 2.04–2.11 (2H, m), 2.69 (1H, d, J = 11.3 Hz), 2.77 (1H, d, J = 11.0 Hz), 3.82–3.90 (2H, m), 3.84 (3H, s), 4.07–4.17 (2H, m), 6.29 (1H, s), 6.59 (1H, d, J = 2.2 Hz), 6.80 (1H, d, J = 2.5 Hz), 6.90–7.01 (2H, m), 7.27–7.39 (2H, m). IR (ATR) cm^{-1} 3338, 2951, 1587, 1462, 1240, 1028, 889, 831, 752. MS (ESI) m/z 408 $(M+H)^+$.

4.1.1.66. 3-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenoxy}propan-1-ol ((*S*)-15f). Compound **(*S*)-15f** was separated in a similar manner described for **(*S*)-15a** using by HPLC with a Chiralcel OD as colorless needle crystal.

4.1.1.67. Methyl 4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxypropoxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-16f). Compound **(*S*)-16f** was prepared in a similar manner described for **(*S*)-16a** in quantum yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.87 (0.89) (9H, s), 1.83 (1H, t, J = 4.8 Hz), 2.01–2.23 (2H, m), 2.24–2.45 (2H, m), 2.48–2.65 (2H, m), 2.75–2.86 (1H, m), 2.99 (1H, d, J = 13.7 Hz), (3.60) 3.68 (3H, s), 3.76 (3.82) (3H, s), 3.80–3.93 (2H, m), 4.04–

4.14 (1H, m), 4.15–4.24 (1H, m), 4.34–4.42 (2H, m), 6.08 (6.29) (1H, d, J = 4.9 Hz), 6.78 (1H, d, J = 2.2 Hz), 6.84–6.94 (2H, m), 6.99–7.11 (1H, m), 7.29–7.35 (1H, m), (7.47–7.51) 7.60–7.55 (1H, m). IR (ATR) cm^{-1} 3423, 2952, 1736, 1643, 1579, 1464, 1286, 1238, 1165, 1026, 754. MS (ESI) m/z 504 $(M-OH)^+$, 522 $(M+H)^+$.

4.1.1.68. 4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)-methyl]-6-(3-hydroxypropoxy)phenyl}(2,2-dimethylpropyl)-amino]-4-oxobutanoic acid ((*S*)-17f). Compound **(*S*)-17f** was prepared in a similar manner described for **(*S*)-16a** in 99% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.84 (0.89) (9H, s), 1.98–2.23 (2H, m), 2.38–2.70 (4H, m), 2.85 (2.96) (1H, d, J = 13.7 Hz), 3.74–3.90 (3H, m), 3.78 (3.83) (3H, s), 4.04–4.24 (2H, m), 4.32 (1H, d, J = 13.7 Hz), 4.36 (1H, d, J = 13.2 Hz), 6.03 (6.31) (1H, s), 6.84 (1H, dd, J = 13.4, 3.6 Hz), 6.87–6.94 (2H, m), 6.99–7.05 (7.05–7.09) (1H, m), 7.29–7.37 (1H, m), 7.39 (7.55) (1H, dd, J = 7.6, 1.5 Hz). IR (ATR) cm^{-1} 3381, 2951, 1712, 1637, 1464, 1392, 1286, 1240, 1174, 1026, 754. MS (ESI) m/z 490 $(M-OH)^+$, 508 $(M+H)^{+\cdot}$ MS (ESI, neg) m/z 506 $(M-H)^+$.

4.1.1.69. Ethyl (3*S*)-1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxypropoxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-19f). Compound **(*S*)-19f** was prepared from **(*S*)-17f** in a similar manner described for **(*S*)-18a** in 88% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.91 and 0.93 (9H, s), 1.19–1.33 (5H, m), 1.57–1.82 (2H, m), 1.87–1.94 (1H, m), 1.97–2.15 (3H, m), 2.17–2.41 (2H, m), 2.42–2.61 (1H, m), 2.63–2.88 (1H, m), 2.90–3.09 (1H, m), 3.14–3.28 (1H, m), 3.72 and 3.73 (3H, s), 3.74–3.88 (3H, m), 3.96–4.23 (4H, m), 4.30–4.59 (2H, m), 5.80 (0.5H, d, J = 5.1 Hz), 5.96 (0.5H, d, J = 5.1 Hz), 6.12 (1H, t, J = 5.5 Hz), 6.68 (1H, dd, J = 12.4, 2.3 Hz), 6.82–6.90 (2H, m), 7.02–7.11 (1H, m), 7.28–7.35 (1H, m), 7.83–7.72 (1H, m). IR(ATR) cm^{-1} 3365, 2951, 1728, 1624, 1464, 1286, 1242, 1180, 1026, 754. MS (ESI) m/z 629 $(M-OH)^+$, 647 $(M+H)^+$. Anal. Calcd for $C_{34}H_{47}ClN_2O_8 \cdot 0.25H_2O$: C, 63.15; H, 7.49; N, 4.21. Found: C, 63.23; H, 7.74; N, 4.15.

4.1.1.70. (*aR*)-(3*S*)-1-{4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxypropoxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-22f). Compound **(*S*)-22f** was prepared from **(*S*)-19f** in a similar manner described for **(*S*)-21a** in 86% yield containing small amount of minor atropisomer as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.89 and 0.91 (9H, s), 1.22–1.47 (2H, m), 1.55–1.85 (2H, m), 1.92–2.15 (3H, m), 2.22–2.61 (4H, m), 2.90–3.19 (3H, m), 3.43–3.54 (1H, m), 3.72 and 3.74 (3H, s), 3.77–3.95 (4H, m), 4.01–4.12 (1H, m), 4.14–4.25 (1H, m), 4.36–4.48 (1H, m), 6.10 (1H, d, J = 9.8 Hz), 6.71 (1H, d, J = 2.2 Hz), 6.82–6.90 (2H, m), 7.02–7.11 (1H, m), 7.27–7.35 (1H, m), 7.74–7.64 (1H, m). IR (ATR) cm^{-1} 3377, 2945, 1720, 1631, 1464, 1284, 1246, 1182, 1030, 752. MS (ESI) m/z 601 $(M-OH)^+$, 619 (M+H)+. MS (ESI, neg) m/z 617 $(M-H)^-$. Anal. Calcd for $C_{32}H_{43}ClN_2O_8 \cdot 0.75H_2O$: C, 60.75; H, 7.09; N, 4.43. Found: C, 60.44; H, 6.72; N, 4.41.

4.1.1.72. 3-Hydroxy-3-methylbutyl methanesulfonate. 3-Methyl-1,3-butandiol (3.83 g, 36.8 mmol) was dissolved in CH_2Cl_2 (150 ml). Triethylamine (6.66 ml, 47.8 mmol) and methanesulfonyl chloride (3.13 ml, 40.5 mmol) were added to the ice-cooled solution, and stirred for 7.5 h at room temperature. Water (100 ml) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. Then, combined organic layer was washed with brine, and dried over Na_2SO_4. The solvent was removed in a reduced presser to give title compound (4.79 g, 26.3 mmol, 72%) as colorless oil. ^1H NMR ($CDCl_3$) δ 1.30 (6H, s), 1.96 (2H, t, J = 6.8 Hz), 3.02 (3H, s), 4.42 (2H, t, J = 6.8 Hz)

4.1.1.73. *N*-[4-Chloro-2-(3-hydroxy-3-methylbutoxy)phenyl]-2,2-dimethylpropanamide (10g). Compound **10j** (4.60 g, 20.2 mmol) was dissolved in DMF (50 ml). To the solution, 3-hydroxy-3-methylbutyl methanesulfonate (4.79 g, 26.3 mmol) and sodium carbonate (8.38 g, 60.7 mmol) were added, and stirred at 60 °C for 6 h. The solvent was removed in vacuo, and the residue was diluted in AcOEt (100 ml) and water (80 ml). The layers were separated, and the aqueous layer was extracted with AcOEt. Combined organic layer was washed with brine, and dried over Na_2SO_4. The solvent was removed in a reduced presser, and the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 4:1–3:1) to give compound **10g** (5.73 g, 18.3 mmol, 90%) as colorless oil. ^1H NMR ($CDCl_3$) δ 1.30 (9H, s), 1.35 (6H, s), 2.03 (2H, t, J = 6.6 Hz), 4.21 (2H, t, J = 6.6 Hz), 6.89 (1H, d, J = 2.2 Hz), 6.94 (1H, dd, J = 8.7, 2.2 Hz), 8.04 (1H, s), 8.34 (1H, d, J = 8.7 Hz).

4.1.1.74. *N*-{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxy-3-methylbutoxy)phenyl}-2,2-dimethylpropanamide (13g). Compound **13g** was prepared from **10g** in a similar manner described for **13f** in 80% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 1.23 (9H, s), 1.30 (3H, s), 1.31 (3H, s), 1.98 (2H, td, J = 6.3, 1.9 Hz), 2.32 (1H, s), 3.76 (3H, s), 4.15–4.22 (3H, m), 5.97 (1H, d, J = 3.4 Hz), 6.81 (1H, d, J = 2.2 Hz), 6.86 (1H, d, J = 8.3 Hz), 6.88 (1H, d, J = 2.2 Hz), 6.98 (1H, td, J = 7.5, 1.1 Hz), 7.25–7.30 (1H, m), 7.36 (1H, dd, J = 7.5, 1.1 Hz), 7.55 (1H, s).

4.1.1.75. 4-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-[hydroxy(2-methoxyphenyl)methyl]phenoxy}-2-methylbutan-2-ol (14g). Compound **14g** was prepared in a similar manner described for **14a** in 92% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.97 (9H, s), 1.33 (6H, s), 2.02 (2H, t, J = 6.6 Hz), 2.69 (1H, d, J = 11.3 Hz), 2.76 (1H, d, J = 11.3 Hz), 3.84 (3H, s), 4.11–4.20 (2H, m), 4.96 (1H, br), 6.30 (1H, s), 6.58 (1H, d, J = 2.2 Hz), 6.81 (1H, d, J = 2.2 Hz), 6.92 (1H, dd, J = 8.6, 1.0 Hz), 6.98 (1H, td, J = 7.6, 1.0 Hz), 7.28–7.33 (2H, m). IR (ATR) cm^{-1} 3329, 3234, 2956, 1587, 1460, 1240, 1186, 1147, 1016, 833, 756. MS (ESI) m/z 436 $(M+H)^+$.

4.1.1.76. 4-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenoxy}-2-methylbutan-2-ol ((*S*)-15g). Compound **(*S*)-15g** was separated in a similar manner described for **(*S*)-15a** using by HPLC with a Chiralcel OD as colorless crystal.

4.1.1.77. Methyl 4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)-methyl]-6-(3-hydroxy-3-methylbutoxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-16g). Compound **(*S*)-16g** was prepared in a similar manner described for **(*S*)-16a** in 98% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ (0.89) 0.89 (9H, s), (1.27) 1.32 (3H, s), (1.31) 1.34 (3H, s), 1.99–2.14 (2H, m), 2.18–2.39 (2H, m), 2.50–2.68 (1H, m), 2.84–2.97 (1H, m), 3.06 (1H, d, J = 13.7 Hz), (3.58) 3.67 (3H, s), 3.74 (3.82) (3H, s), 4.08–4.27 (2H, m), (4.32) 4.41 (1H, d, J = 13.5 Hz), 4.68 (1H, d, J = 5.1 Hz), 6.09 (6.26) (1H, d, J = 5.1 Hz), 6.73 (1H, d, J = 2.2 Hz), 6.83–6.98 (3H, m), 7.03–7.10 (1H, m), 7.32 (1H, td, J = 7.8, 1.6 Hz), (7.47 (0.2H, d, J = 2.5 Hz),) 7.69–7.64 (1H, m). IR (ATR) cm^{-1} 3423, 2952, 1720, 1643, 1466, 1286, 1238, 1169, 1026, 754. MS (ESI) m/z 550 $(M+H)^+$.

4.1.1.78. 4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)-methyl]-6-(3-hydroxy-3-methylbutoxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-17g). Compound **(*S*)-17g** was prepared in a similar manner described for **(*S*)-17a** in 97% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.85 (0.89) (9H, s), (1.27) 1.31 (3H, s), (1.28) 1.33 (3H, s), 1.84–2.18 (2H, m), 2.31–2.41 (1H, m), 2.42–2.59 (2H, m), 2.68–2.79 (1H, m), 2.88 (2.96) (1H, d, J = 13.7 Hz), 3.76 (3.82) (3H, s), 4.07–4.26 (2H, m),

4.34 (4.36) (1H, d, J = 13.5 Hz), 6.04 (6.30) (1H, s), (6.63) 6.78 (1H, d, J = 2.2 Hz), 6.85–6.94 (2H, m), 6.99–7.07 (1H, m), 7.32 (1H, td, J = 7.8, 1.6 Hz), 7.44 (7.56–7.52) (1H, dd, J = 7.6, 1.5 Hz). IR (ATR) cm^{-1} 3390, 1712, 1639, 1466, 1392, 1286, 1240, 1171, 1026, 754. MS (ESI) m/z 536 $(M+H)^+$.

4.1.1.79. Ethyl (3*S*)-1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxy-3-methylbutoxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-19g). Compound **(*S*)-19g** was prepared from **(*S*)-17g** in a similar manner described for **(*S*)-18a** in 81% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ (0.88 and 0.89) 0.93 and 0.94 (9H, s), (1.22) 1.26 (3H, t, J = 7.4 Hz), 1.32 (3H, s), 1.33 (3H, s), 1.36–1.50 (1H, m), 1.58–1.80 (2H, m), 2.00–2.11 (3H, m), 2.12–2.27 (2H, m), 2.27–2.37 (1H, m), 2.43–2.52 (1H, m), 2.52–2.64 (1H, m), 2.68–2.87 (1H, m), 2.92–3.32 (3H, m), 3.71 (3H, s), (3.73–3.85) 3.99–4.26 (5H, m), 4.39–4.58 (2H, m), 6.13 (1H, t, J = 5.4 Hz), 6.23 (1H, dd, J = 16.9, 5.1 Hz), 6.62–6.66 (1H, m), 6.82–6.88 (6.90–6.94) (2H, m), (6.99–7.05) 7.05–7.12 (1H, m), 7.30 (1H, td, J = 7.7, 1.6 Hz), (7.39–7.43) 7.88–7.81 (1H, m). MS (FAB) m/z 675 $(M+H)^+$. Anal. Calcd for $C_{36}H_{51}ClN_2O_8 \cdot 0.5H_2O \cdot 0.25n$-hexane: C, 63.81; H, 7.93; N, 3.97. Found: C, 64.01; H, 7.99; N, 3.70.

4.1.1.80. (*aR*)-(3*S*)-1-{4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxy-3-methylbutoxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-22g). Compound **(*S*)-(*aR*)-22g** was prepared from **(*S*)-19g** in a similar manner described for **(*S*)-21a** in 89% yield containing small amount of minor atropisomer as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.91 (9H, s), 1.30 and 1.31 (3H, s), 1.32 and 1.33 (3H, s), 1.55–1.84 (2H, m), 1.92–2.15 (4H, m), 2.16–2.32 (2H, m), 2.40–2.63 (4H, m), 2.89–3.02 (1H, m), 3.03–3.25 (3H, m), 3.61–3.69 (0.5H, m), 3.71 (3H, s), 3.87–3.98 (0.5H, m), 4.05–4.30 (3H, m), 4.44 (1H, d, J = 13.5 Hz), 6.10 (1H, d, J = 2.9 Hz), 6.66 (1H, dd, J = 6.1, 2.2 Hz), 6.82–6.90 (2H, m), 7.04–7.11 (1H, m), 7.27–7.33 (1H, m), 7.82–7.72 (1H, m). IR (ATR) cm^{-1} 3371, 2954, 1712, 1635, 1464, 1408, 1244, 1182, 1028, 752. MS (FAB) m/z 647 $(M+H)^+$.

Anal. Calcd for $C_{34}H_{47}ClN_2O_8 \cdot 0.25H_2O$: C, 62.66; H, 7.35; N, 4.30. Found: C, 62.49; H, 7.37; N, 4.14.

4.1.1.81. 4-Chloro-2-(2,2-dimethylpropoxy)-1-nitrobenzene (12h). Compound **12h** was prepared from **11** in a similar manner described for **10e** in 83% yield as brown crystal. ^1H NMR ($CDCl_3$) δ 1.08 (9H, s), 3.72 (2H, s), 6.98 (1H, dd, J = 8.6, 2.0 Hz), 7.04 (1H, d, J = 2.0 Hz), 7.84 (1H, d, J = 8.8 Hz). IR (ATR) cm^{-1} 3113, 2952, 1604, 1568, 1512, 1471, 1398, 1335, 1250, 1003, 908, 748. MS (FAB) m/z 244 [$(M+H)^+$, Cl_{35}], 246 [$(M+H)^+$, Cl_{37}].

4.1.1.82. 4-Chloro-2-(2,2-dimethylpropoxy)aniline (9h). A solution of **12h** (4.76 g, 12.7 mmol) and Raney nickel catalyst (600 mg) in AcOEt (120 ml) was hydrogenated for 7 h. The reaction mixture was filtrated and concentrated in vacuo to give **9h** (3.16 g, 11.1 mmol, 87%) as colorless crystal. ^1H NMR ($CDCl_3$) δ 1.06 (9H, d, J = 1.2 Hz), 3.61 (2H, d, J = 1.0 Hz), 3.76 (2H, br), 6.62 (1H, dd, J = 8.8, 1.2 Hz), 6.71–6.76 (2H, m). IR (ATR) cm^{-1} 3431, 3342, 2964, 1658, 1601, 1514, 1392, 1255, 1061, 1020, 839, 588. MS (ESI) m/z 286 $(M+H)^+$.

4.1.1.83. *N*-[4-Chloro-2-(2,2-dimethylpropoxy)phenyl]-2,2-dimethylpropanamide (10h). Compound **10h** was prepared from **9h** in a similar manner described for **10a** in 66% yield as pale yellow needle crystal. ^1H NMR ($CDCl_3$) δ 1.06 (9H, d, J = 1.2 Hz), 3.61 (2H, d, J = 1.0 Hz), 3.76 (2H, br), 6.62 (1H, dd, J = 8.8, 1.2 Hz), 6.71–6.76 (2H, m). IR (ATR) cm^{-1} 3448, 2956, 1693, 1595, 1516, 1475, 1396, 1207, 1018, 924, 806, 579. MS (ESI) m/z 298 $(M+H)^+$.

4.1.1.84. *N*-{4-Chloro-2-(2,2-dimethylpropoxy)-6-[hydroxy(2-meth-oxyphenyl)methyl]phenyl}-2,2-dimethylpropanamide (13h). Compound **13h** was prepared from **10h** in a similar manner described for **13a** in 47% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 1.05 (9H, s), 1.30 (9H, s), 3.60 (2H, dd, J = 15.4, 8.6 Hz), 3.71 (3H, s), 4.41 (1H, d, J = 3.2 Hz), 5.96–5.99 (1H, m), 6.79 (1H, dd, J = 4.2, 2.0 Hz), 6.83 (1H, d, J = 7.6 Hz), 7.02 (1H, td, J = 7.6, 0.7 Hz), 7.23–7.29 (1H, m), 7.32 (1H, s), 7.55 (1H, dd, J = 7.6, 1.0 Hz). IR (ATR) cm^{-1} 3371, 2956, 1647, 1591, 1490, 1421, 1240, 1072, 1014, 895, 758. MS (ESI) m/z 416 $(M-OH)^+$. MS (ESI, neg) m/z 432 $(M-H)^-$.

4.1.1.85. {5-Chloro-3-(2,2-dimethylpropoxy)-2-[(2,2-dimethylpropyl)amino]phenyl}(2-methoxyphenyl)methanol (14h). Compound **14h** was prepared in a similar manner described for **14a** in 50% yield as colorless powder. ^1H NMR ($CDCl_3$) δ 1.00 (9H, s), 1.07 (9H, s), 2.76 (2H, s), 3.55–3.73 (2H, m), 3.83 (3H, s), 5.35 (1H, bs), 6.35 (1H, s), 6.49 (1H, d, J = 2.2 Hz), 6.75 (1H, d, J = 2.2 Hz), 6.93 (1H, d, J = 8.1 Hz), 6.96–7.04 (1H, m), 7.23–7.36 (2H, m). IR (ATR) cm^{-1} 3361, 2954, 1591, 1464, 1236, 1186, 1045, 889, 752. MS (ESI) m/z 420 $(M+H)^+$.

4.1.1.86. (*S*)-{5-Chloro-3-(2,2-dimethylpropoxy)-2-[(2,2-dimethylpropyl)amino]phenyl}(2-methoxyphenyl)methanol (15h). Compound **(*S*)-15h** was separated in a similar manner described for **(*S*)-15a** using HPLC with a Chiralcel OD as colorless crystal.

4.1.1.87. Methyl 4-[{4-chloro-2-(2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-16h). Compound **(*S*)-16h** was prepared in a similar manner described for **(*S*)-16a** in quantum yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.92 (9H, s), 1.08 (9H, s), 2.21–2.37 (2H, m), 2.55–2.65 (1H, m), 2.87–2.97 (1H, m), 3.10 (1H, d, J = 13.5 Hz), 3.57 (1H, d, J = 8.6 Hz), 3.67 (3H, d, J = 1.0 Hz), 3.75–3.75 (1H, m), 3.75 (3H, d, J = 0.7 Hz), 4.36 (1H, d, J = 13.7 Hz), 4.64 (1H, d, J = 5.1 Hz), 5.30 (1H, d, J = 1.2 Hz), 6.09 (1H, d, J = 5.1 Hz), 6.75–6.77 (1H, m), 6.86–6.94 (2H, m), 7.06 (1H, t, J = 7.5 Hz), 7.32 (1H, t, J = 7.6 Hz), 7.65 (1H, d, J = 7.4 Hz). IR (ATR) cm^{-1} 3415, 2952, 1736, 1647, 1577, 1464, 1286, 1238, 1171, 1026, 754.

4.1.1.88. (*aR*)-4-[{4-Chloro-2-(2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-(*aR*)-17h). Compound **(*S*)-(*aR*)-17h** was prepared in a similar manner described for **(*S*)-17a** in 87% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.88 (9H, s), 1.07 (9H, s), 2.28–2.47 (2H, m), 2.55–2.66 (1H, m), 2.73–2.83 (1H, m), 2.93 (1H, d, J = 13.5 Hz), 3.57 (1H, d, J = 8.6 Hz), 3.76 (1H, d, J = 7.8 Hz), 3.77 (3H, s), 4.29 (1H, d, J = 13.5 Hz), 6.05 (1H, s), 6.81 (1H, d, J = 2.2 Hz), 6.87–6.93 (2H, m), 7.05–6.98 (1H, m), 7.35–7.29 (1H, m), 7.40 (1H, dd, J = 7.5, 1.3 Hz). IR (ATR) cm $^{-1}$ 2954, 1712, 1641, 1464, 1402, 1286, 1240, 1186, 1055, 1026, 754. MS (ESI) m/z 502 $(M-OH)^+$, 520 $[(M+H)^+$, 542 $[(M+Na)^+$.

4.1.1.89. (*aR*)-Ethyl (3*S*)-1-{4-[{4-chloro-2-(2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-(*aR*)-19h). Compound **(*S*)-(*aR*)-19h** was prepared from **(*S*)-(*aR*)-17h** in a similar manner described for **(*S*)-18a** in 92% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.96 and 0.97 (9H, s), 1.08 (9H, s), 1.22 and 1.26 (3H, t, J = 7.4 Hz), 1.28–1.41 (2H, m), 1.58–1.84 (2H, m), 1.99–2.37 (3H, m), 2.43–2.69 (2H, m), 2.79–3.25 (2H, m), 3.32 (1H, dd, J = 13.4, 4.5 Hz), 3.55 (1H, d,

J = 8.8 Hz), 3.70 (3H, s), 3.75 (2H, d, *J* = 8.8 Hz), 3.98–4.05 (1H, m), 4.06–4.19 (4H, m), 4.45 (1H, dd, *J* = 13.5, 3.7 Hz), 4.49–4.58 (0H, m), 6.09–6.16 (6.22–6.30) (1H, m), 6.26 (1H, dd, *J* = 13.5, 5.4 Hz), 6.66 (1H, d, *J* = 2.2 Hz), 6.82–6.89 (2H, m), 7.08 (1H, t, *J* = 7.5 Hz), 7.33–7.27 (1H, m), 7.86 (1H, d, *J* = 7.4 Hz). IR(ATR) cm^{-1} 3354, 2954, 1728, 1662, 1630, 1464, 1288, 1244, 1180, 1026, 756. MS (FAB) *m/z* 659 $(M+H)^+$, 681 $(M+Na)^+$.

4.1.1.90. (*aR*)-(3*S*)-1-{4-[{4-Chloro-2-(2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-22h). Compound **(*S*)-(*aR*)-22h** was prepared from **(*S*)-(*aR*)-19h** in a similar manner described for **(*S*)-21a** in 90% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.95 and 0.96 (9H, s), 1.08 (9H, s), 1.22–1.44 (2H, m), 1.59–1.82 (2H, m), 1.96–2.28 (3H, m), 2.36–2.67 (2H, m), 2.84–3.20 (3H, m), 3.27 (1H, dd, *J* = 13.5, 4.0 Hz), 3.33–3.44 (0.5H, m), 3.56 (1H, dd, *J* = 8.5, 1.7 Hz), 3.70 and 3.71 (3H, s), 3.75 (1H, d, *J* = 8.5 Hz), 3.86–3.95 (0.5H, m), 4.06–4.15 (0.5H, m), 4.43 (1H, dd, J = 13.5, 10.1 Hz), 4.47–4.55 (0.5H, m), 6.11 (1H, d, *J* = 5.1 Hz), 6.67–6.71 (1H, m), 6.82–6.88 (2H, m), 7.03–7.11 (1H, m), 7.34–7.27 (1H, m), 7.80 (1H, d, *J* = 7.8 Hz). IR (ATR) cm^{-1} 2954, 1728, 1624, 1464, 1402, 1244, 1026, 754. MS (FAB) *m/z* 631 $(M+H)^+$, 653 $(M+Na)^+$. Anal. Calcd for $C_{34}H_{47}ClN_2O_7 \cdot 0.5H_2O$: C, 63.79; H, 7.56; N, 4.38. Found: C, 63.97; H, 7.23; N, 4.29.

4.1.1.91. 3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,2-dimethylpropan-1-ol. 2,2-Dimethyl-1,3-propandiol (1.60 g, 15.4 mmol) was dissolved in CH_2Cl_2 (150 ml). To the ice-cooled solution, imidazole (2.55 g, 16.9 mmol) and *tert*-butyldimethylsilyl chloride (1.36 g, 20.0 mmol) were added, and stirred at room temperature for 1 h. Water (40 ml) was added, and the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4. The solvent was removed in a reduced presser, and the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 9:1) to give title compound (2.57 g, 11.8 mmol, 77%) as colorless oil. ^1H NMR ($CDCl_3$) δ 0.07 (6H, s), 0.89 (6H, s), 0.90 (9H, s), 2.85 (1H, t, *J* = 5.9 Hz), 3.46–3.48 (4H, m). IR (ATR) cm^{-1} 3415, 2954, 2858, 1471, 1252, 1093, 1045, 833, 773. MS (ESI) *m/z* 219 $(M+H)^+$.

4.1.1.92. *tert*-Butyl[3-(5-chloro-2-nitrophenoxy)-2,2-dimethylpropoxy]dimethylsilane (12l). Compound **12l** was prepared from **11** in a similar manner described for **10e** in 97% yield as colorless oil. ^1H NMR ($CDCl_3$) δ 0.02 (6H, s), 0.87 (9H, s), 1.02 (6H, s), 3.48 (2H, s), 3.85 (2H, s), 6.99 (1H, dd, *J* = 8.8, 2.0 Hz), 7.09 (1H, d, *J* = 2.0 Hz), 7.86 (1H, d, *J* = 8.6 Hz). IR (ATR) cm^{-1} 2954 1604, 1522, 1342, 1259, 1093, 1022, 835, 773. MS (FAB) *m/z* 374 $(M+H)^+$.

4.1.1.93. 2-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,2-dimethylpropoxy)-4-chloroaniline (9l). Compound **9l** was prepared from **12l** in a similar manner described for **9h** in 99% yield as pale yellow oil. ^1H NMR ($CDCl_3$) δ 0.01 (6H, s), 0.88 (9H, s), 1.00 (6H, s), 3.45 (2H, s), 3.72 (2H, s), 3.75 (2H, br), 6.61 (1H, d, *J* = 7.8 Hz), 6.74 (1H, dd, *J* = 7.8, 2.2 Hz), 6.77 (1H, d, *J* = 2.2 Hz). IR (ATR) cm^{-1} 2954, 2856, 1614, 1504, 1462, 1223, 1092, 833, 773. MS (ESI) *m/z* 344 $(M+H)^+$.

4.1.1.94. *N*-[2-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,2-dimethylpropoxy)-4-chlorophenyl]-2,2-dimethylpropanamide (10l). Compound **10l** was prepared from **9l** in a similar manner described for **10a** in 94% yield as pale red oil. ^1H NMR ($CDCl_3$) δ 0.01 (6H, s), 0.87 (9H, s), 1.02 (6H, s), 1.32 (9H, s), 3.46 (2H, s), 3.78 (2H, s), 6.85 (1H, d, *J* = 2.2 Hz), 6.92 (1H, dd, *J* = 8.8, 2.2 Hz), 8.07 (1H, s), 8.35 (1H, d, *J* = 8.5 Hz). IR (ATR) cm^{-1} 2956, 1687, 1597, 1512, 1396, 1248, 1093, 833, 773. MS (ESI) *m/z* 428 $(M+H)^+$.

4.1.1.95. *N*-[4-Chloro-2-(3-hydroxy-2,2-dimethylpropoxy)-phenyl]-2,2-dimethylpropanamide (10i). Tetrabutylanmonium fluoride (1.00 mol/l in THF, 6.46 ml, 6.46 mmol) was added to ice-cooled THF (45 ml) solution of compound **10l** (2.30 g, 5.38 mmol), the mixture was stirred and gradually warmed to room temperature for 2 h. The solution was removed in vacuo, the residue was diluted with water and AcOEt, and the layers were separated. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with brine, dried over Na_2SO_4. The solvent was removed in a reduced presser to give compound **10i** (1.63 g, 5.1 mmol, 96%) as colorless oil. ^1H NMR ($CDCl_3$) δ 1.08 (6H, s), 1.32 (9H, s), 3.52–3.58 (2H, m), 3.83 (2H, s), 6.88 (1H, d, *J* = 2.2 Hz), 6.94 (1H, dd, *J* = 8.6, 2.2 Hz), 8.04 (1H, s), 8.32 (1H, d, *J* = 8.8 Hz). IR (ATR) cm^{-1} 3481, 2960, 1660, 1593, 1523, 1402, 1032, 926, 798, 613. MS (ESI) *m/z* 314 $(M+H)^+$.

4.1.1.96. *N*-{4-Chloro-2-(3-hydroxy-2,2-dimethylpropoxy)-6-[hydroxy(2-methoxyphenyl)methyl]phenyl}-2,2-dimethylpropanamide (13i). Compound **13i** was prepared in a similar manner described for **13f** in 88% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.97 (3H, s), 0.99 (3H, s), 1.15 (9H, s), 3.03 (1H, t, *J* = 6.9 Hz), 3.37 (1H, dd, *J* = 11.0, 6.6 Hz), 3.46 (1H, dd, *J* = 11.0, 6.6 Hz), 3.74 (1H, d, *J* = 8.3 Hz), 3.82 (1H, d, *J* = 8.3 Hz), 3.86 (3H, s), 4.05 (1H, d, *J* = 3.9 Hz), 5.97 (1H, d, *J* = 3.9 Hz), 6.79 (1H, d, *J* = 2.0 Hz), 6.90–6.97 (3H, m), 7.09 (1H, d, *J* = 7.6 Hz), 7.26–7.32 (1H, m), 7.95 (1H, s). IR (ATR) cm^{-1} 3467, 3309, 2958, 1628, 158, 1518, 1466, 1240, 1011, 1061, 897, 761. MS (ESI) *m/z* 432 $(M-OH)^+$.

4.1.1.97. 3-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-[hydroxy-(2-methoxyphenyl)methyl]phenoxy}-2,2-dimethylpropan-1-ol (14i). Compound **14i** was prepared in a similar manner described for **14a** in 77% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.99 (9H, s), 1.06 (3H, s), 1.06 (3H, s), 2.73–2.83 (2H, m), 3.53–3.58 (2H, m), 3.73 (3H, s), 3.84–3.84 (2H, m), 6.31 (1H, s), 6.55 (1H, d, *J* = 2.2 Hz), 6.81 (1H, d, *J* = 2.2 Hz), 6.93 (1H, dd, *J* = 8.6, 1.0 Hz), 6.95–7.01 (1H, m), 7.26–7.38 (2H, m). IR (ATR) cm^{-1} 3485, 2949, 1585, 1460, 1396, 1248, 1026, 823, 750. MS (ESI) *m/z* 436 $(M+H)^+$.

4.1.1.98. 3-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenoxy}-2,2-dimethylpropan-1-ol ((*S*)-15i).. Compound **(*S*)-15i** was separated in a similar manner described for **(*S*)-15a** using by HPLC with a Chiralcel OD as pale yellow crystal.

4.1.1.99. Methyl 4-[{4-chloro-2-(3-hydroxy-2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-16i). Compound **(*S*)-16i** was prepared in a similar manner described for **(*S*)-16a** in 99% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.88 and 0.94 (9H, s), (0.98) 1.05 (3H, s), (1.00) 1.06 (3H, s), (1.58–1.68) 2.20 (1H, t, *J* = 4.8 Hz), (2.04–2.15) 2.35–2.47 (2H, m), 2.48–2.59 (1H, m), (2.62–2.65) 2.66–2.77 (1H, m), 3.02 (3.19) (1H, d, *J* = 13.4 Hz), (3.29) 3.46 (1H, dd, *J* = 10.4, 4.3 Hz), (3.58–3.71) 3.79–3.86 (2H, m), 3.68 (3H, s), 3.78 (3H, s), (3.90) 4.17 (1H, d, *J* = 4.6 Hz), (4.06) 4.26 (1H, d, *J* = 13.4 Hz), 6.07 (6.37) (1H, d, *J* = 4.6 Hz), 6.83 (1H, d, *J* = 2.0 Hz), 6.85–6.94 (2H, m), 6.97 (1H, d, *J* = 2.2 Hz), 6.98 (1H, d, *J* = 2.0 Hz), 6.99–7.09 (1H, m), 7.29–7.36 (1H, m), 7.65 (7.50) (1H, d, *J* = 6.8 Hz). IR (ATR) cm^{-1} 3425, 2952, 1720, 1645, 1464, 1238, 1169, 1026, 889, 754. MS (ESI) *m/z* 550 $(M+H)^+$.

4.1.1.100. 4-[{4-Chloro-2-(3-hydroxy-2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-17i). Compound **(*S*)-17i** was prepared in a similar manner described for **(*S*)-17a** in 97% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.85 (9H, s),

(0.94 and 0.98) 1.03 (6H, s), (1.11–1.28 and 1.71–1.81 and 1.97–2.07 and 2.18–2.29) 2.43–2.63 (4H, m), 2.94 (3.17) (1H, d, J = 13.7 Hz), (3.30) 3.41 (1H, d, J = 10.3 Hz), (3.55) 3.64 (1H, d, J = 10.8 Hz), 3.67–3.76 (1H, m), 3.77 (3H, s), 3.79 (3H, s), 3.81–3.87 (2H, m), (4.13) 4.18 (1H, d, J = 13.7 Hz), 6.04 (6.38) (1H, s), (6.65) 6.86 (1H, d, J = 2.7 Hz), 6.88–6.93 (1H, m), 6.96–7.09 (2H, m), 7.36–7.30 (7.59–7.49) (2H, m). IR (ATR) cm^{-1} 3415, 2954, 1712, 1464, 1392, 1240, 1174, 1026, 754. MS (ESI) *m/z* 518 $(M-OH)^+$.

4.1.1.101. Ethyl (3*S*)-1-{4-[{4-chloro-2-(3-hydroxy-2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-19i). Compound **(*S*)-19i** was prepared from **(*S*)-17i** in a similar manner described for **(*S*)-18a** in 87% yield as colorless amorphous. ^1H NMR ($CDCl_3$) δ (0.91) 0.94 (9H, s), (1.03) 1.06 (6H, s), (1.23) 1.26 (3H, t, J = 6.9 Hz), 1.34–1.45 (1H, m), 1.48–1.82 (2H, m), 1.99–2.11 (1H, m), 2.21–2.60 (2H, m), 2.66–2.87 (1H, m), 2.89–3.07 (1H, m), 3.09–3.32 (2H, m), 3.42–3.53 (2H, m), 3.56–3.66 (2H, m), 3.73 (3H, s), 3.74 (3H, s), 3.76–3.89 (3H, m), 3.90–4.04 (1H, m), 4.05–4.20 (2H, m), 4.23–4.49 (4.50–4.60) (2H, m), (5.65) 6.10 (1H, d, J = 4.7 Hz), 6.73 (1H, dd, J = 17.0, 2.3 Hz), 6.87 (2H, d, J = 8.6 Hz), 6.90–6.94 (1H, m), (6.96–7.01) 7.02–7.10 (1H, m), 7.28–7.34 (1H, m), (7.46–7.53) 7.76–7.64 (1H, m). IR (ATR) cm^{-1} 3388, 2952, 1728, 1626, 1462, 1242, 1180, 1028, 754. MS (FAB) *m/z* 675 $(M+H)^+$. Anal. Calcd for $C_{36}H_{51}ClN_2O_8$: C, 64.03; H, 7.61; N, 4.15. Found: C, 63.91; H, 7.86; N, 3.89.

4.1.1.102. (*aR*)-(3*S*)-1-{4-[{4-chloro-2-(3-hydroxy-2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}-(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-22i). Compound **(*S*)-22i** was prepared from **(*S*)-19i** in a similar manner described for **(*S*)-(*aR*)-21a** in 86% yield containing small amount of minor atropisomer as colorless amorphous. ^1H NMR ($CDCl_3$) δ 0.90 (9H, s), 1.05 (6H, s), 1.24–1.48 (1H, m), 1.52–1.84 (3H, m), 1.90–2.11 (1H, m), 2.26–2.40 (1H, m), 2.43–2.62 (3H, m), 2.82–3.01 (1H, m), 3.03–3.24 (2H, m), 3.29–3.52 (2H, m), 3.58–3.73 (2H, m), 3.74 and 3.74 (3H, s), 3.77–3.86 (2H, m), 3.87–3.94 (1H, m), 4.27–4.47 (1H, m), 6.08 (1H, d, J = 13.7 Hz), 6.74 (1H, dd, J = 10.8, 2.2 Hz), 6.83–6.91 (1H, m), 6.92–6.96 (1H, m), 7.10–6.97 (1H, m), 7.35–7.27 (1H, m), 7.67–7.58 (1H, m). IR (ATR) cm^{-1} 3280, 2945, 1712, 1637, 1464, 1242, 1182, 1051, 1022, 750. Anal. Calcd for $C_{34}H_{47}ClN_2O_8 \cdot 0.5H_2O$: C, 62.23; H, 7.37; N, 4.27. Found: C, 62.00; H, 6.94; N, 4.22.

4.2. Biochemical analysis of plasma lipids[10]

4.2.1. Animals

Male Syrian hamsters (6 weeks) were purchased from Charles River (Kingston, NY). They were fed a commercial chow diet (F2; Funabashi Farm, Funabashi, Japan) and allowed access to water ad libitum. Male and female common marmosets (305–410 g) were purchased from Clea Japan (Tokyo, Japan), and fed a commercial chow diet (CMS-1M; Clea Japan) and allowed access to water ad libitum. All animal experiments were carried out according to the Daiichi Sankyo Animal Care Guidelines.

4.2.2. Hamsters study

Before the experiment, blood samples were collected under nonfasted conditions. Plasma total cholesterol and triglyceride were measured enzymatically (Cholesterol E test Wako, Triglyceride E test Wako; Wako Pure Chemical Industries, Osaka, Japan). Hamsters were divided into five groups matched for body weight, plasma total cholesterol and triglyceride (n=8). These five groups were assigned to receive vehicle (0.5% methylcellulose solution) or compounds **22e,h** (30, 100 mg/kg). Compounds were suspended in 0.5% methylcellulose solution by Teflon homogenizer, and vehicle and compounds suspension were administered orally at 10 mL/kg twice a day (9 AM and 4 PM) for 14 days. The following morning after the seventh and the final administrations, blood samples were collected and plasma parameters were measured.

4.2.3. Common marmosets study

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

Common marmosets were divided into two groups (control vs Compound **22e**, 100 mg/kg, n = 8); groups were matched for body weight, plasma total cholesterol, triglyceride, HDL cholesterol and non-HDL cholesterol. Drugs were suspended in 0.5% methylcellulose solution and administered orally at 5 mL/kg once a day (9–10 AM) for 7 days. Next morning after the final administration of drugs, blood samples were collected under nonfasted conditions and plasma parameters were measured.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.07.007. These data include MOL files and InChiKeys of the most important compounds described in this article.

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