Bioorganic & Medicinal Chemistry 17 (2009) 4636–4646

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Synthesis and structure–activity relationships of *N*-(4-amino-2,6-diisopropylphenyl)-*N*'-(1,4-diarylpiperidine-4-yl)methylureas as anti-hyperlipidemic agents

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ARTICLE INFO

Article history:
Received 18 March 2009
Revised 27 April 2009
Accepted 28 April 2009
Available online 3 May 2009

Keywords:
ACAT inhibitor
LDL receptor up-regulator
1,4-Diarylpiperidine-4-methylureas
Antihyperlipidemic agent
Solubility

ABSTRACT

Based on 1,4-diarylpiperidine-4-methylureas, a new class of ACAT inhibitors, we examined in the study the SAR of a series of compounds prepared by replacing the substituent at the three aromatic parts. Introduction of long alkoxy group onto the phenyl moiety at the B-part was effective in improving both the inhibitory activity for ACAT and the up-regulatory activity for LDL-R expression. Particularly, 3-hydroxypropoxy group (**43**) on the phenyl moiety of B-part led to improved solubility, while keeping both biological activities. Compound **43** inhibited ACAT activity with an IC_{50} value of 18 nM, which is superior to that of a known ACAT inhibitor, CI-1011. In addition, compound **43** revealed an LDL-R up-regulatory activity comparable to that of SMP-797. We therefore expect this compound to be a novel ACAT inhibitor.

1. Introduction

Hyperlipidemia and related cardiovascular diseases, such as atherosclerosis, are risk factors for stroke and coronary heart diseases, which are among the leading causes of death in many industrialized countries. Acyl-coenzyme A: cholesterol acyltransferase (ACAT), which catalyzes intracellular cholesterol esterification,[1,2] plays important roles in several physiological processes, such as absorption of dietary and biliary cholesterol in the small intestine,[3,4] secretion of very low-density lipoprotein (VLDL) in the liver,[5–7] and accumulation of cholesteryl esters in macrophages in the arterial wall.[8–10] It is therefore believed that inhibition of ACAT may lower plasma cholesterol level and help prevent atherosclerosis.

It is known that expression of hepatic low-density lipoprotein receptor (LDL-R) is extremely important for lipid homeostasis. Statins, which are HMG-CoA reductase inhibitors that increase hepatic LDL-R expression, are known to be effective in lowering total cholesterol and LDL cholesterol levels in hyperlipidemic patients.[11] Accordingly, it is believed that dual effectors of ACAT and LDL-R expression may be promising agents in the treatment of hyperlipidemia and related cardiovascular diseases.

We have previously reported a novel ACAT inhibitor, SMP-797 (Fig. 1), with potent cholesterol-lowering activity and direct regressive effect on atherosclerotic lesions.[12] We have also shown that SMP-797, unlike other ACAT inhibitors, such as Avasimibe (CI-1011) and F12511,[12,13] up-regulates hepatic LDL-R expression. Furthermore, SMP-797 at a concentration much higher than that needed for LDL-R up-regulation had no effect on cholesterol synthesis in HepG2 cells. These findings strongly suggest that SMP-797 up-regulation of LDL-R is independent from its ACAT inhibitory activity. Therefore, we expect SMP-797 to be a next generation anti-hyperlipidemic agent.

In a previous paper, we have identified a series of 1,4-diarylpiperidine-4-methylurea compounds as novel ACAT inhibitors.[14] In particular, we have shown that a methoxy group as R^1 in part-A and as R^2 at the *o*-position in part-B, and an amino group as R^3 in part-C are essential for both ACAT inhibition and LDL-R up-regulation, (Table 1).This is quite interesting because the piperidine-based structure of these urea compounds is completely different from the 1,8-naphthyridine moiety in SMP-797. Here we report in details the structure activity relationship (SAR) of this series of compounds, particularly their effects on ACAT inhibition and LDL-R up-regulation.

2. Chemistry

We initially synthesized the precursor nitriles **3–4**, **6–12**, and **15–19** to afford the ureas **1**, **21–31**, and **37–46**. These nitriles were

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doi:10.1016/j.bmc.2009.04.059

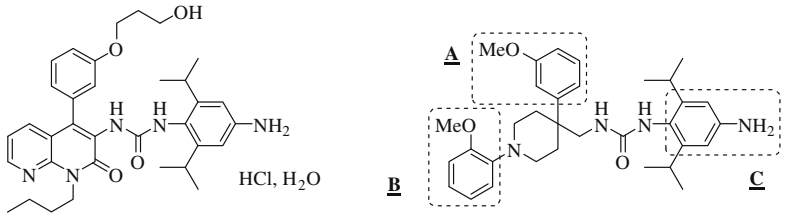
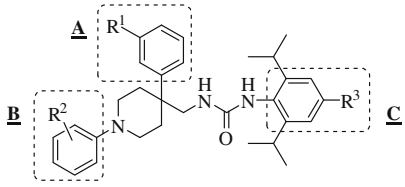


Figure 1. Structures of SMP-797 and compound **1**.

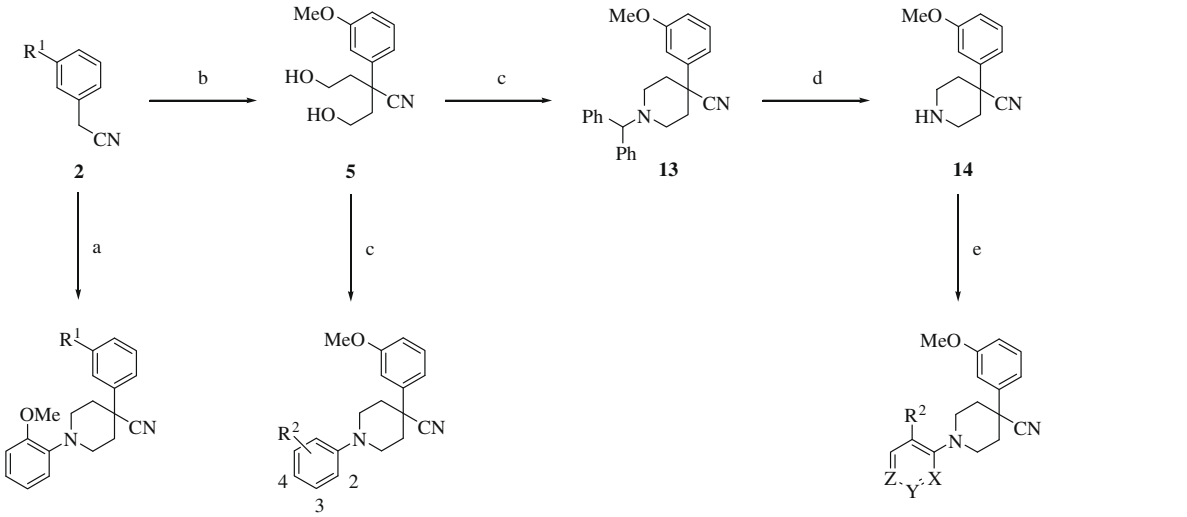
Table 1
Effects of different substituents at the phenyl moiety (A, B, or C-part) on compounds biological activity towards ACAT and LDL-R



Compds	R^1	R^2	R^3	ACAT[a] IC_{50} (nM)	LDL-R[b]@10^{-7} M
21	OMe	H	H	35	–[c]
22	OMe	H	NH_2	40	–[c]
1	OMe	2-OMe	NH_2	37	+
23	OMe	3-OMe	NH_2	48	–
24	OMe	4-OMe	NH_2	142	–
25	H	2-OMe	NH_2	82	–
CI-1011				479[d]	–
SMP-797				31	++

[a] Inhibitory activity for ACAT in rat macrophages.
[b] Effect on LDL-R expression in $HepG_2$.
[c] 10^{-5} M.
[d] In-house data.

prepared by three synthetic methods using different functional groups (Scheme 1). The first synthetic method was conversion of the substituent on the phenyl ring in part A. The nitriles **3** and **4** were prepared by dialkylation of the commercially available phenylacetonitriles **2** with *N,N*-bis(2-chloroethyl)anisidine[15] in the presence of a catalytic amount of phosphonium bromide.[16] The second synthetic method was conversion of the *N*-(substituted phenyl)piperidines in part B. The diol **5** was prepared by common dialkylation of the (3-methoxyphenyl)acetonitrile with the commercially available 2-(2-bromoethoxyl)tetrahydro-*2H*-pyran using NaH in DMF followed by methanolysis. The diol **5** thus obtained was converted to the nitriles **6-13** by cyclization via bis-triflate with the appropriate amines ($R^2C_6H_4NH_2$ or Ph_2CHNH_2).[17] Cyclization of the corresponding dimesylate or dibromide, which were easily prepared by common mesylation or bromination from the diol **5**, did not give the desired compounds in sufficient yields, probably due to different reactivity of the leaving group. The third synthetic method was conversion of the *N*-(substituted pyridyl)piperidines in part B. The benzohydryl group on the nitrogen of the compound **13** was removed by palladium-catalyzed hydrogenation to give the unsubstituted piperidine **14**. The piperidine **14** thus obtained was converted to the *N*-pyridylpiperidines **15–**



3 R^1=H
4 R^1=OBn

6 R^2=H
7 R^2=2-OMe
8 R^2=3-OMe
9 R^2=4-OMe
10 R^2=2-OCF_3
11 R^2=2-OCH_2CF_3
12 R^2=2-OBn

15	R^2=H	X=N	Y=CH	Z=CH
16	R^2=H	X=CH	Y=N	Z=CH
17	R^2=H	X=CH	Y=CH	Z=N
18	R^2=OMe	X=N	Y=CH	Z=CH
19	R^2=OBn	X=N	Y=CH	Z=CH

Scheme 1. Synthesis of nitriles **3**, **4**, **6–12**, and **15–19**. Reagents and conditions: (a) *N,N*-bis(2-chloroethyl)anisidine, $CH_3(CH_2)15P^+Bu_3{\cdot}Br^-$, 50% $NaOH_{aq}$, 100 °C; (b) (1) $BrCH_2CH_2OTHP$, NaH, DMF, 0 °C→rt; (2) *p*-TsOH monohydrate, MeOH, rt; (c) (1) triflic anhydride, *N,N*-diisopropylethylamine, EtOAc, −30 °C; (2) $R^2C_6H_4NH_2$, or Ph_2CHNH_2, *N,N*-diisopropylethylamine, −30 °C→rt; (d) 10% Pd/C, HCO_2NH_4, EtOH, reflux; (e) pyridyl halide, $Pd_2(dba)_3$, (*S*)-(−)-BINAP, NaO^tBu, toluene, 80 °C.

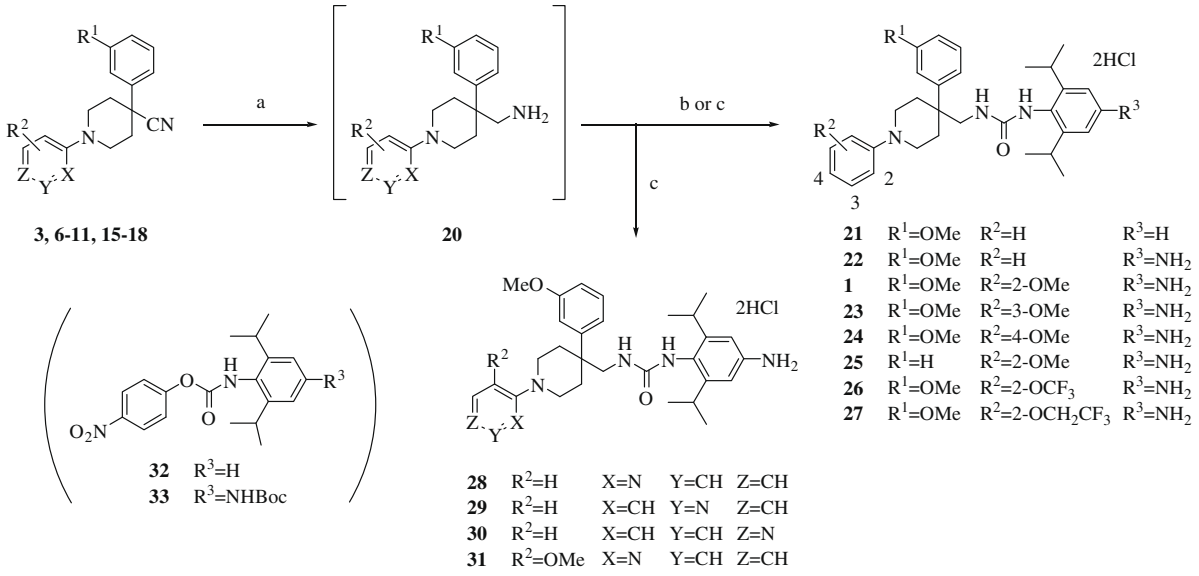
19 by coupling reaction with appropriate pyridyl halide in the presence of $Pd_2(dba)_3$ and (*S*)-(−)-BINAP.[18]

Synthesis of the desired ureas **1** and **21–31** was achieved as illustrated in Scheme 2. Reduction of the nitriles **3**, **6–11**, and **15–18** using $LiAlH_4$ followed by coupling reaction with the corresponding phenylcarbamates **32** or **33**[14,19] afforded the desired urea compounds. The primary amines **20** were used for the urea generation step without purification because of their high polarity. In the case of ureas **1** and **22–31** the Boc group was removed by 10% methanolic HCl in the final step to afford the desired compounds as HCl salt.

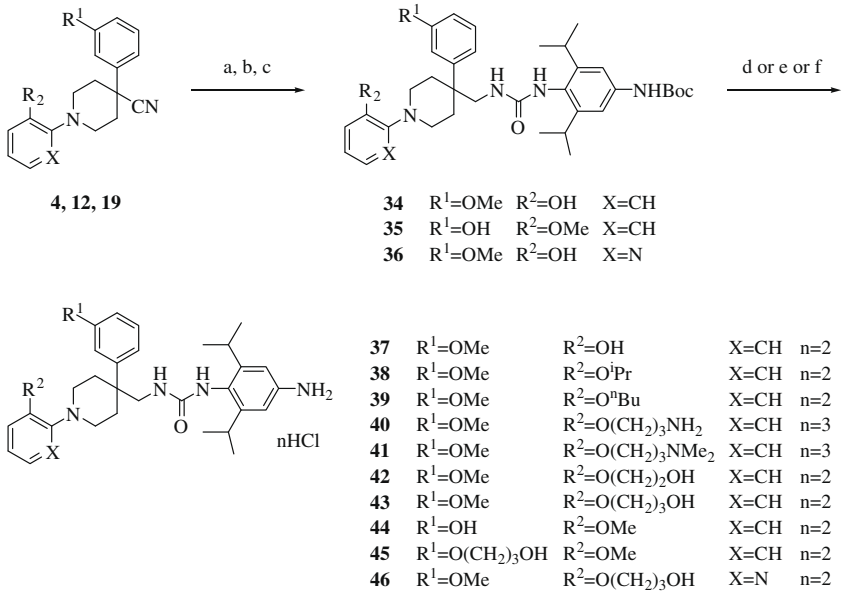
The various alkoxy-substituted compounds **37–46** on the aryl moiety in A or B-part (Fig. 1) were prepared as illustrated in Scheme 3. Reduction of the nitrile **4**, **12**, or **19** followed by coupling reaction with **33** produced urea derivatives, which underwent deprotection of the benzyl group over $Pd(OH)_2/C$ under hydrogen atmosphere to afford the intermediates **34–36** in good yield. Alkylation of the hydroxyl group of **34–36** with an appropriate alkylhalide using cesium carbonate as base followed by deprotection of the benzyl and/or Boc group provided the desired compounds **37–46**.

3. Results and discussion

Although compound **1** had an ACAT inhibitory activity comparable to that of SMP-797, its up-regulatory activity for LDL-R was weaker than that of SMP-797 (Table 1). Therefore, to improve both biological activities of compound **1**, we designed further structural modifications. The common structural moiety in compound **1** and SMP-797 is the 4-amino-2,6-diisopropylphenylurea (Fig. 1). In the course of our SAR study of SMP-797 derivatives, we found that introduction of a long alkyl chain to *N*(1)-position of 1,8-naph-



Scheme 2. Synthesis of ureas **1** and **21–31**. Reagents and conditions: (a) $LiAlH_4$, THF, reflux; (b) **32**, THF, rt; (c) (1) **33**, THF, rt; (2) 10% HCl/MeOH, rt.



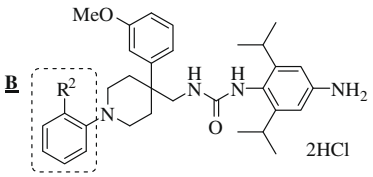
Scheme 3. Synthesis of ureas **37–46**. Reagents and conditions: (a) $LiAlH_4$, THF, reflux; (b) **33**, THF, rt; (c) 20% $Pd(OH)_2/C$, H_2 (0.3 MPa), MeOH, rt; (d) 10% HCl/MeOH, rt; (e) (1) alkyl halide, Cs_2CO_3, DMF, 60 °C; (2) 10% HCl/MeOH, rt; (f) (1) alkyl halide, Cs_2CO_3, DMF, 60 °C; (2) 20% $Pd(OH)_2/C$, 5 N HCl_{aq}, H_2 (0.45 MPa), MeOH, rt; (3) 10% HCl/MeOH, rt.

thyridine enhanced ACAT inhibitory activity.[20] Thus, we hypothesized that the 1-arylpiperidine part of compound **1** and the 1,8-naphthyridine part of SMP-797 play a similar role in ACAT inhibitory activity. Accordingly, we assumed that modification of the methoxy group (R^2) may translate to improvement of this biological activity.

Replacement of the methoxy group at R^2 with other alkoxy groups gave compounds with ACAT inhibitory activity comparable to that of SMP-797 and improved up-regulatory activity for LDL-R expression (Table 2). Except for compound **26**, compounds **1**, **27**, and **38–39** inhibited ACAT with IC_{50} values similar to that of SMP-797, suggesting that elongation of the alkyl chain has no beneficial effect on ACAT inhibitory activity. Surprisingly, the up-regulatory activity for LDL-R expression tended to increase by alkyl chain elongation. In particular, compound **39** showed biological activities comparable to those of SMP-797 but better than those of compound **1**. From these findings we concluded that lipophilicity and/or substituent size are important for good LDL-R up-regulatory activity. Although compound **39** looked promising, its solubility was low (0.0003 mg/mL, at pH 7.4), which is a drawback for oral bioavailability. We therefore focused on the substituent size and designed compounds with a hydrophilic group in the alkyl chain.

To improve the solubility we introduced an amino, dimethylamino, or a hydroxyl group as hydrophilic functional group to the alkoxy moiety at the phenyl moiety (A or B-part). In addition prepared the phenol compounds **37** and **44** and used them as reference. ACAT inhibitory activity, LDL-R up-regulatory activity, and solubility of the synthesized compounds (**37** and **39–45**) are summarized in Table 3. Compounds **37** and **44** with a phenolic hydroxyl group had decreased ACAT inhibitory activity. Similarly, the aminopropoxyl compounds **40** and **41** showed decreased inhibitory activity against ACAT. These findings indicate that a basic substituent at the R^2 position is not favorable for ACAT inhibition. The hydroxyalkoxy compounds **42** and **43** showed an LDL-R up-regulatory activity equivalent to that of the lipophilic compound **39**, and their ACAT inhibitory activity increased in accordance with elongation of the alkyl-chain. With these findings we speculated that size of the substituent is important for LDL-R up-regulatory activity. Particularly, compound **43** showed a more potent ACAT inhibitory activity than that of **39** or SMP-797. Furthermore and as expected, the solubility of **43** was improved by 70-fold compared to that of **39** (0.022 mg/mL versus 0.0003 mg/mL, at pH 7.4). Actually, the calculated clogP value supported this finding (**43**; *c*log *P* = 5.91 vs **39**; *c*log *P* = 7.70).[21] Based on SAR information of SMP-797, introduction of a 3-hydroxypropoxyl group onto the A-part (compound **45**) gave a biological activity inferior to that of **1** or **43**.

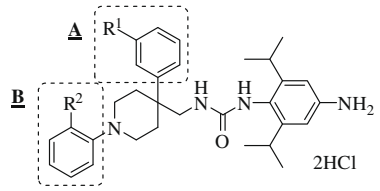
Table 2
Effects of the alkoxy substituent at the phenyl moiety (B-part) on compounds biological activity towards ACAT and LDL-R



Compds	R^2	ACAT[a] IC_{50} (nM)	LDL-R[b]@10^{-7} M
1	OMe	37	+
26	OCF_3	68	++
27	OCH_2CF_3	48	++
38	O^iPr	37	+
39	O^nBu	32	++
SMP-797		31	++

[a] Inhibitory activity for ACAT in rat macrophages.
[b] Effect on LDL-R expression in $HepG_2$.

Table 3
Effects of substitution of the alkoxy group at the phenyl moiety (A or B-part) with a hydrophilic group on compounds biological activity towards ACAT and LDL-R and solubility

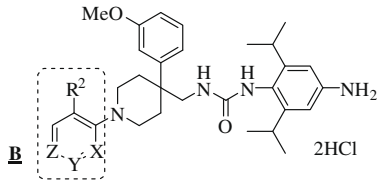


Compds	R^1	R^2	ACAT[a] IC_{50} (nM))	LDL-R[b]@10^{-7} M	Solubility (mg/ml)@ pH 7.4
39	OMe	O^nBu	32	++	0.0003
37	OMe	OH	246	–	Nt[d]
40[c]	OMe	$O(CH_2)_3NH_2$	195	++	0.032
41[c]	OMe	$O(CH_2)_3NMe_2$	239	Nt[d]	>0.25
42	OMe	$O(CH_2)_2OH$	96	++	Nt[d]
43	OMe	$O(CH_2)_3OH$	18	++	0.022
44	OH	OMe	797	–	Nt[d]
45	$O(CH_2)_3OH$	OMe	62	+	Nt[d]
SMP-797			31	++	0.010

[a] Inhibitory activity for ACAT in rat macrophages.
[b] Effect on LDL-R expression in $HepG_2$.
[c] 3HCl salts.
[d] Nt: not tested.

Finally, to obtain further improvement in the solubility, we replaced the phenyl moiety of the B-part by a pyridyl one. The inhibitory activity for ACAT of the prepared compounds **1**, **28–31**, **43**, and **46** and their up-regulation of LDL-R are summarized in Table 4. ACAT inhibitory activity of the 2-pyridyl compound **28** was much higher than that of the 3-pyridyl **29** or the 4-pyridyl **30**. Based on SAR information obtained so far, introduction of an alkoxy group to position 3 of the pyridyl moiety in **28** was viewed as a good way to improve both biological activities. As expected, compounds **31** and **46** showed more potent inhibitory activity against ACAT than to the corresponding compound **1** and **43**, respectively. Unfortunately, these compounds had no up-regulatory activity for LDL-R expression. These findings indicate that the pyridine ring is not suitable as B-part for LDL-R up-regulation

Table 4
Effects of substitution at the phenyl or the pyridyl moiety (B-part) on compounds biological activity towards ACAT and LDL-R



Compds	X	Y	Z	R^2	ACAT[a] IC_{50} (nM)	LDL-R[b]@10^{-7} M
1	CH	CH	CH	OMe	37	+
43	CH	CH	CH	$O(CH_2)_3OH$	18	++
28	N	CH	CH	H	32	–
29	CH	N	CH	H	466	Nt[d]
30	CH	CH	N	H	>1000	Nt[d]
31	N	CH	CH	OMe	6	+[c]
46	N	CH	CH	$O(CH_2)_3OH$	4	–
SMP-797					31	++

[a] Inhibitory activity for ACAT in rat macrophages.
[b] Effect on LDL-R expression in $HepG_2$.
[c] 10^{-5} M.
[d] Nt: not tested.

probably due to its basicity and/or hydrophilicity. It is therefore suggested that the mechanisms of ACAT inhibition and LDL-R up-regulation are completely different.

4. Conclusion

Based on the 1,4-diarylpiperidine-4-methylurea **1**, a new ACAT inhibitor, we examined in this study the SAR of a series of compounds prepared by replacing the substituent at A or B-part of **1**. Introduction of long alkoxy group was effective in improving both ACAT inhibitory activity and LDL-R up-regulatory activity. Particularly, 3-hydroxypropoxy group on the phenyl moiety of B-part led to improved solubility, while keeping both biological activities. Compound **43** inhibited ACAT with an IC_{50} value of 18 nM, which is superior to that of a known ACAT inhibitor, CI-1011 (IC_{50} = 479 nM, Table 1). In addition, **43** revealed an LDL-R up-regulatory activity comparable to that of SMP-797. We therefore expect **43** to be a novel ACAT inhibitor. Although in this study we were able to synthesize compounds that have improved LDL-R up-regulatory activity, the mechanism of this up-regulation is still unclear. Studies to unveil this mechanism are now underway.

5. Experimental

5.1. Chemistry

Melting points (MP) were determined on an electrothermal apparatus without correction. IR spectra were recorded on a JEOL JIR-SPX60 spectrometer as ATR. NMR spectra were recorded on a JEOL JNM-LA300 spectrometer. Chemical shifts (σ) are given in parts per million, and TMS was used as the internal standard for spectra obtained in DMSO-d_6 and $CDCl_3$. All J values are given in Hz. Mass spectra were recorded on a Bruker Daltonics esquire 3000plus and a Thermo Fisher Scientific LTQ orbitrap Discovery MS equipment. Elemental analysis was performed on a CE Instrument EA1110 and a Yokokawa analytical system IC7000. Reagents and solvents were used as obtained from commercial suppliers without further purification. Column chromatography was carried out using a Yamazen W-prep system, and performed using pre-packed silica gel or amino silica gel. Reaction progress was determined by TLC analysis on silica gel or amino silica gel coated glass plate. Visualization was done with UV light (254 nm) or iodine. All reactions were carried out under a nitrogen atmosphere unless otherwise mentioned.

5.1.1. 1-(2-Methoxyphenyl)-4-phenylpiperidine-4-carbonitrile (3)

To a solution of phenylacetonitrile (117 mg, 1.0 mmol) and *N,N*-bis(2-chloroethyl)anisidine (248 mg, 1.0 mmol) in 50% NaOH solution (1.2 mL) was added hexadecyltributylphosphonium bromide (25.4 mg, 0.050 mmol), and the mixture was stirred at 100 °C for 2 h. The reaction was quenched by adding H_2O, and the mixture was extracted with Et_2O. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuo, and the residue was purified by silica gel column chromatography. The solvent was removed in vacuo, and the resulting solid was triturated with MeOH to give **3** (164 mg, 56%) as white needle-like crystal. Mp 97–98 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (2H, m), 2.36 (2H, m), 3.12 (2H, m), 3.59 (2H, m), 3.89 (3H, s), 6.91 (1H, m), 6.98 (1H, m), 7.03 (2H, m), 7.32 (1H, m), 7.43 (2H, m), 7.56 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.9, 42.9, 48.5, 55.4, 111.1, 118.8, 121.1, 122.0, 123.5, 125.7, 128.1, 129.0, 140.2, 141.0, 152.2; IR (ATR) 2238, 1597, 1585 cm^{-1}; MS (ESI) *m/z* 293 (M+1). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.91; H, 6.90; N, 9.58.

5.1.2. 1-(2-Methoxyphenyl)-4-(3-benzyloxyphenyl)piperidine-4-carbonitrile (4)

Compound **4** was prepared from (3-benzyloxyphenyl)acetonitrile in a manner similar to that described for compound **3** with a yield of 77% as white needle-like crystals (MeOH). Mp 102–103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.21 (2H, m), 2.36 (2H, m), 3.11 (2H, m), 3.57 (2H, m), 3.88 (3H, s), 5.08 (2H, s), 6.87–6.98 (3H, m), 7.05 (2H, m), 7.18 (1H, m), 7.20 (1H, m), 7.24–7.46 (6H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.8, 42.8, 48.5, 55.4, 70.1, 111.1, 112.8, 114.1, 118.2, 118.8, 121.0, 121.9, 123.4, 127.5, 128.0, 128.6, 130.0, 136.6, 140.9, 141.8, 152.1, 159.2; IR (ATR) 2239, 1579, 1504 cm^{-1}; MS (ESI) *m/z* 399 (M+1). Anal. Calcd for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.32; H, 6.40; N, 7.15.

5.1.3. 4-Hydroxy-2-(2-hydroxyethyl)-2-(3-methoxyphenyl)butanenitrile (5)

To a suspension of 55% NaH disparaged in mineral oil (3.26 g, 0.075 mol) in dry DMF (50 mL) was added dropwise a solution of (3-methoxyphenyl)acetonitrile (5.0 g, 0.034 mol) and (2-bromoethyl)tetrahydropyranyl ether (14.9 g, 0.0713 mol) in dry Et_2O at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was then poured into saturated NH_4Cl solution, and the resulting mixture was extracted with Et_2O. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuo. The residue was dissolved in MeOH (50 mL), and *p*-TsOH monohydrate (646 mg, 3.4 mmol) was added and stirred at room temperature for 1 h. The solvent was removed in vacuo, and the residue was diluted with EtOAc and saturated NH_4Cl solution. The organic layer was separated, washed with saturated $NaHCO_3$ solution, brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuo, and the resulting solid was triturated with Et_2O to give **5** (5.94 g, 74%) as a pale yellow solid. Mp 89–90 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.17 (4H, m), 3.18 (2H, m), 3.37 (2H, m), 3.76 (3H, s), 4.59 (2H, t, J = 5.1 Hz), 6.92 (1H, d, J = 8.0 Hz), 6.96 (1H, s), 7.00 (1H, d, J = 8.0 Hz), 7.33 (1H, dd, J = 8.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.3, 42.9, 55.2, 57.3, 111.7, 112.6, 117.8, 122.1, 130.0, 139.8, 159.5; IR (ATR) 3243, 2237, 1610, 1585 cm^{-1}; MS (APCI) *m/z* 236 (M+1). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.46; H, 7.34; N, 5.91.

5.1.4. 4-(3-Methoxyphenyl)-1-phenylpiperidine-4-carbonitrile (6)

To a solution of **5** (470 mg, 2.0 mmol) in dry EtOAc (10 mL) at −30 °C was slowly added trifluoromethanesulfonic anhydride (704 μL, 4.2 mmol) followed by addition of *N,N*-diisopropylethylamine (730 μL, 4.2 mmol). After 15 min, aniline (218 μL, 2.4 mmol) was added, followed by addition of *N,N*-diisopropylethylamine (730 μL, 4.2 mmol). The reaction mixture was kept at −30 °C for 1 h and at room temperature for 2 h. The reaction was then quenched by adding water and the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuo, and the residue was purified by silica gel column chromatography and triturated with MeOH to give **6** (488 mg, 84%) as white needle-like crystal. Mp 86–87 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (4H, m), 3.24 (2H, m), 3.76 (2H, m), 3.84 (3H, s), 6.90 (2H, m), 7.02 (2H, m), 7.07 (1H, m), 7.12 (1H, m), 7.30 (2H, m), 7.34 (1H, dd, J = 7.9, 7.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.3, 42.7, 47.5, 55.4, 112.0, 113.2, 117.0, 117.8, 120.4, 121.6, 129.2, 130.1, 141.5, 151.0, 160.1; IR (ATR) 2227, 1601, 1581 cm^{-1}; MS (ESI) *m/z* 293 (M+1). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.14; H, 6.83; N, 9.67.

5.1.5. 1-(2-Methoxyphenyl)-4-(3-methoxyphenyl)piperidine-4-carbonitrile (7)

Compound **7** was prepared from **5** and 2-methoxyaniline in a manner similar to that described for compound **6** with a yield of 77% as white needle-like crystal (MeOH). Mp 110–111 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (2H, m), 2.37 (2H, m), 3.12 (2H, m), 3.58 (2H, m), 3.84 (3H, s), 3.89 (3H, s), 6.91 (2H, m), 6.93 (1H, m), 7.04 (2H, m), 7.10 (1H, m), 7.18 (1H, m), 7.34 (1H, dd, J = 8.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.3, 42.9, 48.5, 55.3, 55.4, 111.1, 111.7, 113.4, 117.9, 118.8, 121.1, 122.0, 123.5, 130.0, 140.9, 141.8, 152.2, 160.0; IR (ATR) 2233, 1608, 1583 cm^{-1}; MS (ESI) m/z 323 (M+1). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.28; H, 6.87; N, 8.70.

5.1.6. 1,4-Bis(3-methoxyphenyl)piperidine-4-carbonitrile (8)

Compound **8** was prepared from **5** and 3-methoxyaniline in a manner similar to that described for compound **6** with a yield of 89% as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.23 (4H, m), 3.26 (2H, m), 3.76 (2H, m), 3.81 (3H, s), 3.84 (3H, s), 6.51 (1H, d, J = 8.1 Hz), 6.58 (1H, s), 6.63 (1H, d, J = 8.1 Hz), 6.90 (1H, m), 7.06 (1H, m), 7.12 (1H, m), 7.21 (1H, dd, J = 8.0, 8.0 Hz), 7.34 (1H, dd, J = 8.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.0, 42.7, 47.6, 55.2, 55.3, 103.5, 107.1, 109.7, 111.9, 113.3, 117.8, 121.2, 123.9, 130.0, 130.1, 141.3, 160.1, 160.6; IR (ATR) 2235, 1601, 1583 cm^{-1}; MS (ESI) m/z 323 (M+1). Anal. Calcd for $C_{20}H_{22}N_2O_2 \cdot 1/5H_2O$: C, 73.68; H, 6.93; N, 8.59. Found: C, 74.07; H, 6.86; N, 8.64.

5.1.7. 4-(3-Methoxyphenyl)-1-(4-methoxyphenyl)piperidine-4-carbonitrile (9)

Compound **9** was prepared from **5** and 4-methoxyaniline in a manner similar to that described for compound **6** with a yield of 87% as white needle-like crystals (MeOH). Mp 101–102 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.23 (2H, m), 2.27 (2H, m), 3.17 (2H, m), 3.49 (2H, m), 3.78 (3H, s), 3.84 (3H, s), 6.86 (1H, m), 6.88 (2H, d, J = 9.2 Hz), 6.89 (1H, m), 6.96 (2H, d, J = 9.2 Hz), 7.09 (1H, m), 7.14 (1H, m), 7.34 (1H, dd, J = 8.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.6, 42.6, 49.0, 55.3, 55.5, 111.9, 113.2, 114.4, 117.8, 119.3, 121.7, 130.0, 141.6, 145.4, 154.3, 160.0; IR (ATR) 2239, 1608, 1583 cm^{-1}; MS (ESI) m/z 323 (M+1). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.46; H, 6.85; N, 8.77.

5.1.8. 4-(3-Methoxyphenyl)-1-[2-(trifluoromethoxy)phenyl]piperidine-4-carbonitrile (10)

Compound **10** was prepared from **5** and 2-trifluoromethoxyaniline in a manner similar to that described for compound **6** with a yield of 26% as white needle-like crystal (Et_2O). Mp 101–102 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (2H, m), 2.22 (2H, m), 3.17 (2H, m), 3.41 (2H, m), 3.78 (3H, s), 6.84 (1H, dd, J = 8.0, 2.3 Hz), 6.95–7.22 (6H, m), 7.28 (1H, dd, J = 8.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.6, 42.5, 48.8, 55.4, 112.1, 113.2, 117.9, 120.6, 121.8, 122.0, 123.4, 127.7, 130.1, 141.5, 142.5, 160.0; IR (ATR) 2233, 1605, 1585 cm^{-1}; MS (ESI) m/z 377 (M+1). Anal. Calcd for $C_{20}H_{19}F_3N_2O_2$: C, 63.82; H, 5.09; F, 15.14; N, 7.44. Found: C, 63.48; H, 5.05; F, 15.16; N, 7.51.

5.1.9. 4-(3-Methoxyphenyl)-1-[2-(2,2,2-trifluoroethoxy)phenyl]piperidine-4-carbonitrile (11)

Compound **11** was prepared from **5** and 2-(2′,2′,2′-trifluoroethoxy)aniline[22,23] in a manner similar to that described for compound **6** with a yield of 50% as white needle-like crystal (MeOH). Mp 84–85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (2H, m), 2.27 (2H, m), 3.14 (2H, m), 3.55 (2H, m), 3.83 (3H, s), 4.37 (2H, q, J = 8.2 Hz), 6.89 (2H, m), 6.98–7.10 (3H, m), 7.14 (1H, m), 7.34 (1H, dd, J = 8.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.6, 42.6, 48.4, 55.2, 66.7 (q), 111.9, 113.1, 115.0, 117.8, 119.4, 121.8, 123.2, 123.7, 130.0, 141.6, 142.1, 150.0, 160.0; IR (ATR) 2241, 1608, 1601, 1583 cm^{-1}; MS (ESI) m/z 391 (M+1). Anal. Calcd for $C_{21}H_{21}F_3N_2O_2$: C, 64.61; H, 5.42; F, 14.60; N, 7.18. Found: C, 64.32; H, 5.41; F, 14.63; N, 7.31.

5.1.10. 4-(3-Methoxyphenyl)-1-(2-benzyloxyphenyl)piperidine-4-carbonitrile (12)

Compound **12** was prepared from **5** and 2-benzyloxyaniline in a manner similar to that described for compound **6** with a yield of 82% as white needle-like crystal (MeOH). Mp 103–104 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.19 (2H, m), 2.27 (2H, m), 3.14 (2H, m), 3.64 (2H, m), 3.82 (3H, s), 5.13 (2H, s), 6.89 (1H, m), 6.94–7.06 (5H, m), 7.12 (1H, m), 7.28–7.40 (4H, m), 7.43 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.6, 42.7, 48.3, 55.2, 70.3, 111.7, 113.1, 113.3, 117.7, 118.9, 121.5, 121.8, 123.1, 127.1, 127.7, 128.4, 129.9, 137.1, 141.4, 141.7, 151.4, 159.9; IR (ATR) 2235, 1601, 1583 cm^{-1}; MS (ESI) m/z 399 (M+1). Anal. Calcd for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.53; H, 6.59; N, 7.23.

5.1.11. 4-(3-Methoxyphenyl)-1-diphenylmethylpiperidine-4-carbonitrile (13)

Compound **13** was prepared from **5** and benzohydrylamine in a manner similar to that described for compound **6** with a yield of 82% as white needle-like crystal (MeOH). Mp 127–128 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.06 (2H, m), 2.13 (2H, m), 2.34 (2H, m), 2.94 (2H, m), 3.78 (3H, s), 4.32 (1H, s), 6.83 (1H, dd, J = 7.9, 2.0 Hz), 7.01 (1H, d, J = 2.0 Hz), 7.06 (1H, d, J = 7.9 Hz), 7.15 (2H, m), 7.24 (5H, m), 7.38 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.8, 42.9, 49.5, 55.3, 76.1, 112.0, 113.1, 117.9, 122.2, 127.1, 127.8, 128.6, 130.0, 141.9, 142.6, 160.0; IR (ATR) 2229, 1599 cm^{-1}; MS (ESI) m/z 383 (M+1). Anal. Calcd for $C_{26}H_{26}N_2O$: C, 81.64; H, 6.85; N, 7.32. Found: C, 81.30; H, 6.78; N, 7.40.

5.1.12. 4-(3-Methoxyphenyl)piperidine-4-carbonitrile (14)

To a solution of **13** (5.0 g, 0.0131 mol) in MeOH (50 mL) and THF (50 mL) were added ammonium formate (10 g) and 10% Pd/C (50% wet, 1.0 g), and the mixture was stirred at reflux for 1 h and then filtered through Celite. The filtrate was concentrated, and the residue was purified by amino silica gel column chromatography to give **14** (1.76 g, 62%) as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (1H, dd, J = 8.1, 8.1 Hz), 7.10 (1H, m), 7.04 (1H, m), 6.86 (1H, m), 3.83 (3H, s), 3.17 (4H, m), 2.07 (2H, m), 1.98 (2H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 37.2, 43.2, 43.9, 55.3, 111.8, 113.1, 117.8, 122.1, 130.0, 142.1, 160.0; IR (ATR) 3342, 2233, 1601, 1583 cm^{-1}; MS (ESI) m/z 217 (M+1). Anal. Calcd for $C_{13}H_{16}N_2O \cdot 1/2H_2O$: C, 69.31; H, 7.61; N, 12.43. Found: C, 69.44; H, 7.42; N, 12.55.

5.1.13. 4-(3-Methoxyphenyl)-1-pyridin-2-ylpiperidine-4-carbonitrile (15)

To a solution of **14** (200 mg, 0.925 mmol) in toluene (4.0 mL) were added 2-bromopyridine (98.0 μL, 1.02 mmol), $Pd_2(dba)_3$ (84.7 mg, 0.0925 mmol), (*S*)-(−)-BINAP (115 mg, 0.185 mmol), and sodium *tert*-butoxide (178 mg, 1.85 mmol), and the mixture was stirred at 90 °C for 2 h and filtered through Celite. The filtrate was diluted with EtOAc and water. The organic layer was separated, washed with brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuo, and the residue was purified by silica gel column chromatography to give **15** (224 mg, 82%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (1H, m), 7.52 (1H, m), 7.33 (1H, dd, J = 8.0, 8.0 Hz), 7.09 (1H, m), 7.03 (1H, m), 6.88 (1H, m), 6.72 (1H, d, J = 8.6 Hz), 6.67 (1H, m), 4.49 (2H, m), 3.83 (3H, s), 3.32 (2H, m), 2.19 (2H, m), 2.09 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.9, 43.1, 43.2, 55.3, 107.2, 112.0, 113.2, 113.7, 117.8, 121.7, 130.1, 137.7, 141.5, 148.1, 158.9, 160.0; IR (ATR) 2233, 1591, 1562 cm^{-1}; MS (ESI) $m/$

z 294 (M+1). Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.47; H, 6.47; N, 14.20.

5.1.14. 4-(3-Methoxyphenyl)-1-pyridin-3-ylpiperidine-4-carbonitrile (16)

Compound **16** was prepared from **14** and 3-bromopyridine in a manner similar to that described for compound **15** with a yield of 67% as a pale yellow crystal (Et_2O). Mp 105–106 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (1H, d, J = 2.8 Hz), 8.14 (1H, dd, J = 4.4, 1.5 Hz), 7.34 (1H, dd, J = 8.0, 8.0 Hz), 7.24 (1H, m), 7.18 (1H, dd, J = 8.3, 4.4 Hz), 7.10 (1H, m), 7.06 (1H, m), 6.88 (1H, dd, J = 8.0, 2.1 Hz), 3.82 (3H, s), 3.75 (2H, m), 3.25 (2H, m), 2.23 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.0, 42.5, 46.8, 55.4, 112.0, 113.3, 117.7, 121.4, 123.3, 123.7, 130.2, 139.2, 141.0, 141.1, 146.7, 160.1; IR (ATR) 2227, 1608, 1579, 1566 cm^{-1}; MS (ESI) *m/z* 294 (M+1). Anal. Calcd for $C_{18}H_{19}N_3O{\cdot}1/4H_2O$: C, 72.58; H, 6.60; N, 14.11. Found: C, 72.73; H, 6.40; N, 14.05.

5.1.15. 4-(3-Methoxyphenyl)-1-pyridin-4-ylpiperidine-4-carbonitrile (17)

Compound **17** was prepared from **14** and 4-iodopyridine in a manner similar to that described for compound **15** with a yield of 50% as white needle-like crystal (Et_2O). Mp 112–113 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (2H, d, J = 6.4 Hz), 7.34 (1H, dd, J = 8.0, 8.0 Hz), 7.05 (1H, d, J = 8.0 Hz), 7.02 (1H, dd, J = 2.1, 2.1 Hz), 6.89 (1H, dd, J = 8.0, 2.1 Hz), 6.73 (2H, d, J = 6.4 Hz), 4.03 (2H, m), 3.83 (3H, s), 3.33 (2H, m), 2.20 (2H, m), 2.09 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.5, 42.8, 44.1, 55.4, 108.8, 112.0, 113.3, 117.6, 121.2, 130.3, 140.8, 150.6, 154.3, 160.1; IR (ATR) 2241, 1591 cm^{-1}; MS (ESI) *m/z* 294 (M+1). Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.30; H, 6.45; N, 14.31.

5.1.16. 4-(3-Methoxyphenyl)-1-(3-methoxypyridin-2-yl)piperidine-4-carbonitrile (18)

Compound **18** was prepared from **14** and 2-bromo-3-methoxypyridine in a manner similar to that described for compound **15** with a yield of 97% as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.18 (2H, m), 2.27 (2H, m), 3.29 (2H, m), 3.80 (3H, s), 3.85 (3H, s), 4.12 (2H, m), 6.86 (2H, m), 7.04–7.12 (3H, m), 7.30 (1H, dd, J = 8.0, 8.0 Hz), 7.88 (1H, dd, J = 4.9, 1.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.0, 42.8, 45.6, 55.0, 77.2, 111.6, 112.9, 117.1, 117.3, 117.6, 121.7, 129.8, 138.5, 141.6, 146.5, 151.2, 159.7; IR (ATR) 2233, 1601, 1587 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{19}H_{21}N_3O_2$: 324.1707. Found: 324.1704 (Δ = −0.78 ppm).

5.1.17. 1-[3-(Benzyloxy)pyridine-2-yl]-4-(3-methoxyphenyl)piperidine-4-carbonitrile (19)

Compound **19** was prepared from **14** and 2-bromo-3-benzyloxypyridine[24] in a manner similar to that described for compound **15** with a yield of 99% as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.11 (2H, m), 2.21 (2H, m), 3.33 (2H, m), 3.81 (3H, s), 4.20 (2H, m), 5.09 (2H, s), 6.82 (1H, dd, J = 7.9, 4.8 Hz), 6.86 (1H, m), 7.04–7.14 (3H, m), 7.31 (1H, dd, J = 8.0, 8.0 Hz), 7.32–7.44 (5H, m), 7.91 (1H, dd, J = 4.8, 1.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.2, 43.0, 45.8, 55.3, 70.5, 111.9, 113.0, 117.0, 117.8, 119.7, 121.9, 127.2, 128.1, 128.6, 129.9, 136.3, 139.4, 141.9, 145.7, 151.8, 159.9; IR (ATR) 2244, 1601, 1585 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{25}H_{25}N_3O_2$: 400.2020. Found: 400.2015 (Δ = −1.25 ppm).

5.1.18. *N*-(2,6-Diisopropylphenyl)-*N*′-{[4-(3-methoxyphenyl)-1-phenylpiperidin-4-yl]methyl}urea (21)

To a solution of **6** (146 mg, 0.50 mmol) in dry THF (3.0 mL) was added lithium aluminum hydride (37.9 mg, 1.0 mmol), and the mixture was stirred at reflux for 1 h, and quenched with NaOH solution. The resulting mixture was stirred at room temperature for 1 h, dried over anhydrous magnesium sulfate, and filtered through Celite. The filtrate was concentrated to give an amine. The amine was dissolved in dry THF (3.0 mL), then 4-nitrophenyl(2,6-diisopropylphenyl)carbamate **32** (205 mg, 0.60 mmol) was added to the solution, and the mixture was stirred at room temperature for 1 h. The reaction was then quenched by adding saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuo, and the residue was purified by amino silica gel column chromatography to give **21** (229 mg, 92%) as a white amorphous. ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.10 (12H, d, J = 6.8 Hz), 1.98 (2H, m), 2.08 (2H, m), 3.02 (2H, m), 3.07 (2H, m), 3.36 (2H, m), 3.38 (2H, d, J = 6.1 Hz), 3.77 (3H, s), 6.79 (1H, dd, J = 7.2, 7.2 Hz), 6.82 (1H, m), 6.90 (2H, m), 6.92 (1H, m), 6.98 (1H, m), 7.07 (2H, d, J = 7.2 Hz), 7.16 (3H, m), 7.28 (1H, dd, J = 8.0, 8.0 Hz), 7.31 (1H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.2, 27.5, 31.9, 40.6, 44.7, 48.2, 54.7, 110.9, 112.8, 115.1, 118.0, 118.7, 122.4, 126.5, 128.6, 129.1, 132.8, 146.0, 146.5, 150.8, 156.6, 159.2; IR (ATR) 3315, 1668, 1637, 1598 cm^{-1}; MS (ESI) *m/z* 500 (M+1). Anal. Calcd for $C_{32}H_{41}N_3O_2$: C, 76.92; H, 8.27; N, 8.41. Found: C, 76.64; H, 8.23; N, 8.56.

5.1.19. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[4-(3-methoxyphenyl)-1-phenylpiperidin-4-yl]methyl}urea dihydrochloride (22)

To a solution of **6** (146 mg, 0.50 mmol) in dry THF (3.0 mL) was added lithium aluminum hydride (37.9 mg, 1.0 mmol), and the mixture was stirred at reflux for 1 h and quenched with NaOH solution. The resulting mixture was stirred at room temperature for 1 h, dried over anhydrous magnesium sulfate, and filtered through Celite. The filtrate was concentrated to give an amine. The amine was dissolved in dry THF (3.0 mL), then *tert*-butyl 4-nitrophenyl(2,6-diisopropyl-1,4-phenylene)biscarbamate **33** (274 mg, 0.60 mmol) was added to the solution, and the mixture was stirred at room temperature for 1 h. The reaction was quenched by adding saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuo, and the residue was purified by amino silica gel column chromatography to give urea as a white amorphous. The urea was added to 10% HCl–MeOH (5.0 mL) at room temperature, and the mixture was stirred for 3 days. The solvent was removed in vacuo, and the resulting solid was triturated with *i*PrOH/Et_2O to give **22** (250 mg, 91%) as a yellow solid. Mp 197–198 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.09 (12H, d, J = 7.0 Hz), 2.33 (2H, m), 2.54 (2H, m), 3.05 (2H, m), 3.35 (2H, m), 3.56 (2H, s), 3.77 (2H, m), 3.81 (3H, s), 6.89 (1H, m), 6.99 (1H, m), 7.04 (1H, d, J = 8.0 Hz), 7.10 (2H, s), 7.33 (1H, dd, J = 8.0, 8.0 Hz), 7.37 (1H, m), 7.48 (2H, m), 7.68 (1H, s), 7.71(2H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.9, 27.8, 30.1, 50.8, 54.8, 111.6, 112.4, 117.5, 118.3, 120.5, 123.8, 127.5, 129.2, 129.5, 130.0, 132.8, 143.6, 148.3, 156.7, 159.3; IR (ATR) 2964, 2600, 1655, 1551 cm^{-1}; MS (ESI) *m/z* 515 (M+1). Anal. Calcd for $C_{32}H_{42}N_4O_2{\cdot}2HCl{\cdot}3/2H_2O$: C, 62.53; H, 7.71; N, 9.12. Found: C, 62.84; H, 7.55; N, 9.30.

5.1.20. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[1-(2-methoxyphenyl)-4-(3-methoxyphenyl)piperidin-4-yl]methyl}urea dihydrochloride (1)

Compound **1** was prepared from **7** in a manner similar to that described for compound **22** with a yield of 90% as a pale yellow solid (*i*PrOH/Et_2O). Mp 238–240 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.07 (12H, d, J = 6.7 Hz), 2.35 (2H, m), 2.50 (2H, m), 3.08 (2H, m), 3.52 (4H, m), 3.75 (5H, br), 3.81 (3H, s), 6.92 (1H, dd, J = 8.0, 2.2 Hz), 7.01 (3H, m), 7.11 (2H, s), 7.23 (1H, d,

J = 8.3 Hz), 7.36 (1H, dd, J = 8.0, 8.0 Hz), 7.44 (1H, m), 7.72 (1H, s), 8.02 (1H, d, J = 7.8 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.0, 27.8, 29.9, 49.1, 54.9, 55.9, 111.6, 112.7, 114.0, 117.5, 118.6, 121.0, 122.8, 129.3, 130.0, 130.2, 130.5, 132.8, 148.3, 151.9, 156.7, 159.4; IR (ATR) 2956, 2600, 1655, 1605, 1551 cm^{-1}; MS (ESI) m/z 545 (M+1). Anal. Calcd for $C_{33}H_{44}N_4O_3{\cdot}2HCl{\cdot}3/2H_2O$: C, 61.48; H, 7.66; N, 8.69. Found: C, 61.36; H, 7.47; N, 8.74.

5.1.21. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[1,4-bis(3-methoxyphenyl)piperidin-4-yl]methyl}urea dihydrochloride (23)

Compound **23** was prepared from **8** in a manner similar to that described for compound **22** with a yield of 86% as a pale yellow solid (*i*PrOH/Et_2O). Mp 195–196 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.07 (12H, d, J = 7.0 Hz), 2.23 (2H, m), 2.44 (2H, m), 3.07 (2H, m), 3.25 (2H, m), 3.52 (2H, s), 3.69 (2H, m), 3.76 (3H, s), 3.80 (3H, s), 6.82 (1H, d, J = 8.0 Hz), 6.87 (1H, dd, J = 8.0, 2.2 Hz), 6.97 (1H, s), 7.02 (1H, d, J = 8.0 Hz), 7.09 (2H, s), 7.14 (2H, m), 7.32 (1H, dd, J = 8.0, 8.0 Hz), 7.63 (1H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.0, 27.8, 30.5, 54.8, 55.2, 111.3, 111.4, 112.5, 117.4, 118.4, 120.0, 127.2, 129.2, 130.2, 131.8, 132.7, 135.7, 148.3, 156.7, 159.3, 159.9; IR (ATR) 2964, 2600, 1655, 1601, 1551 cm^{-1}; MS (ESI) m/z 545 (M+1). Anal. Calcd for $C_{33}H_{44}N_4O_3{\cdot}2HCl{\cdot}3/2H_2O$: C, 61.48; H, 7.66; N, 8.69. Found: C, 61.47; H, 7.57; N, 8.89.

5.1.22. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[4-(3-methoxyphenyl)-1-(4-methoxyphenyl)piperidin-4-yl]methyl}urea dihydrochloride (24)

Compound **24** was prepared from **9** in a manner similar to that described for compound **22** with a yield of 87% as a pale yellow solid (*i*PrOH/Et_2O). Mp 207–208 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.07 (12H, d, J = 6.8 Hz), 2.32 (2H, m), 2.54 (2H, m), 3.06 (2H, m), 3.31 (2H, m), 3.56 (2H, s), 3.70(2H, m), 3.77 (3H, s), 3.81 (3H, s), 6.89 (1H, m), 7.05 (6H, m), 7.33 (1H, dd, J = 7.9, 7.9 Hz), 7.63 (1H, s), 7.68 (2H, d, J = 8.3 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.0, 27.8, 30.1, 51.6, 54.8, 55.4, 110.4, 111.6, 112.4, 114.7, 117.0, 118.2, 121.1, 122.1, 129.2, 130.8, 136.0, 148.3, 156.8, 158.7, 159.3; IR (ATR) 2964, 2569, 1653, 1602, 1558, 1514 cm^{-1}; MS (ESI) m/z 545 (M+1). Anal. Calcd for $C_{33}H_{44}N_4O_3{\cdot}2HCl{\cdot}2H_2O$: C, 60.63; H, 7.71; N, 8.57. Found: C, 60.28; H, 7.63; N, 8.73.

5.1.23. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[1-(2-methoxyphenyl)-4-phenylpiperidin-4-yl]methyl}urea dihydrochloride (25)

Compound **25** was prepared from **3** in a manner similar to that described for compound **22** with a yield of 86% as a white solid (*i*PrOH/Et_2O). Mp 220–222 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.09 (12H, d, J = 6.8 Hz), 2.33 (2H, m), 2.50 (2H, m), 3.07 (2H, m), 3.48 (4H, br), 3.72 (5H, br), 7.03 (1H, dd, J = 7.9, 7.9 Hz), 7.06 (2H, s), 7.20 (1H, d, J = 8.1 Hz), 7.31 (1H, m), 7.37–7.46 (5H, m), 7.70 (1H, s), 7.91 (1H, d, J = 7.7 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.0, 27.7, 30.0, 48.9, 55.8, 113.9, 117.4, 121.0, 122.4, 126.1, 126.4, 128.3, 129.8, 130.2, 130.9, 132.7, 148.2, 151.9, 156.7; IR (ATR) 2962, 2580, 1654, 1558 cm^{-1}; MS (ESI) m/z 515 (M+1). Anal. Calcd for $C_{32}H_{42}N_4O_2{\cdot}2HCl{\cdot}2H_2O$: C, 61.63; H, 7.76; N, 8.98. Found: C, 61.32; H, 7.62; N, 8.92.

5.1.24. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-({4-(3-methoxyphenyl)-1-[2-(trifluoromethoxy)phenyl]piperidin-4-yl}methyl)urea dihydrochloride (26)

Compound **26** was prepared from **10** in a manner similar to that described for compound **22** with a yield of 83% as a white solid (*i*PrOH/Et_2O). Mp 193–195 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.09 (12H, d, J = 7.0 Hz), 2.04 (2H, m), 2.15 (2H, m), 2.89 (2H, m), 3.07 (2H, m), 3.19 (2H, m), 3.37 (2H, s), 3.78 (3H, s), 6.84 (1H, dd, J = 8.1, 2.2 Hz), 6.95–7.05 (3H, m), 7.12 (3H, m), 7.24 (2H, m), 7.29 (1H, dd, J = 8.1, 8.1 Hz), 7.65 (1H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.9, 27.8, 32.5, 40.6, 47.2, 48.5, 54.7, 111.1, 112.9, 117.6, 118.8, 120.3, 121.5, 122.4, 125.1, 127.8, 129.1, 129.9, 133.0, 141.3, 146.0, 148.3, 156.6, 159.3; IR (ATR) 2956, 2600, 1655, 1604, 1558 cm^{-1}; MS (ESI) m/z 599 (M+1). Anal. Calcd for $C_{33}H_{41}F_3N_4O_3{\cdot}2HCl{\cdot}4/5H_2O$: C, 57.78; H, 6.55; N, 8.17. Found: C, 58.11; H, 6.50; N, 7.97.

5.1.25. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-({4-(3-methoxyphenyl)-1-[2-(2,2,2-trifluoroethoxy)phenyl]piperidin-4-yl}methyl)urea dihydrochloride (27)

Compound **27** was prepared from **11** in a manner similar to that described for compound **22** with a yield of 80% as a white solid (*i*PrOH/Et_2O). Mp 210–212 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.07 (12H, d, J = 6.8 Hz), 2.28 (2H, br), 2.41 (2H, br), 3.08 (2H, m), 3.30 (2H, br), 3.45 (2H, br), 3.60 (2H, br), 3.79 (3H, s), 4.77 (2H, q, J = 8.6 Hz), 6.87 (1H, m), 6.97 (1H, s), 7.02 (1H, m), 7.11 (3H, m), 7.22–7.34 (3H, m), 7.65 (2H, br); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.9, 27.8, 30.9, 48.6, 54.7, 65.0, 65.5, 111.4, 112.6, 115.3, 117.5, 118.5, 122.8, 129.2, 130.0, 132.9, 148.3, 149.6, 156.6, 159.4; IR (ATR) 2964, 2602, 1655, 1605, 1558 cm^{-1}; MS (ESI) m/z 613 (M+1). Anal. Calcd for $C_{34}H_{43}F_3N_4O_3{\cdot}2HCl{\cdot}H_2O$: C, 58.03; H, 6.73; F, 8.10; N, 7.96. Found: C, 58.35; H, 6.71; F, 7.69; N, 7.91.

5.1.26. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[4-(3-methoxyphenyl)-1-pyridin-2-ylpiperidin-4-yl]methyl}urea dihydrochloride (28)

Compound **28** was prepared from **15** in a manner similar to that described for compound **22** with a yield of 72% as a white solid (*i*PrOH/Et_2O). Mp 183–185 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.07 (12H, d, J=6.8 Hz), 1.98 (2H, m), 2.15 (2H, m), 3.06 (2H, m), 3.39 (2H, m), 3.52 (2H, m), 3.79 (3H, s), 3.95 (2H, m), 6.11 (1H, s), 6.82–6.90 (2H, m), 6.95 (1H, s), 7.01 (1H, d, J = 7.9 Hz), 7.09 (2H, s), 7.31 (2H, m), 7.68 (1H, s), 7.89–7.97 (2H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.8, 23.7, 28.0, 31.7, 41.2, 43.1, 48.1, 54.9, 111.4, 112.1, 112.4, 113.0, 117.6, 118.9, 129.5, 130.1, 133.1, 137.3, 143.4, 145.2, 148.4, 151.8, 156.8, 159.4; IR (ATR) 3284, 2590, 1639, 1603, 1541 cm^{-1}; MS (ESI) m/z 516 (M+1). Anal. Calcd for $C_{31}H_{41}N_5O_2{\cdot}2HCl{\cdot}3/2H_2O$: C, 60.48; H, 7.53; N, 11.38. Found: C, 60.13; H, 7.47; N, 11.20.

5.1.27. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[4-(3-methoxyphenyl)-1-pyridin-3-ylpiperidin-4-yl]methyl}urea dihydrochloride (29)

Compound **29** was prepared from **16** in a manner similar to that described for compound **22** with a yield of 78% as a pale yellow solid (*i*PrOH/Et_2O). Mp 183–185 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.07 (12H, d, J = 7.0 Hz), 1.96 (2H, m), 2.15 (2H, m), 3.06 (2H, m), 3.21 (2H, m), 3.37 (2H, d, J = 4.0 Hz), 3.63 (2H, m), 3.78 (3H, s), 6.11 (1H, br), 6.82 (1H, dd, J = 8.0, .2.2 Hz), 6.95 (1H, d, J = 2.2 Hz), 7.00 (1H, d, J = 8.0 Hz), 7.29 (1H, dd, J = 8.0, 8.0 Hz), 7.70 (1H, s), 7.74 (1H, dd, J = 9.0, 5.3 Hz), 8.00 (1H, dd, J = 9.0, 2.6 Hz), 8.07 (1H, d, J = 5.3 Hz), 8.36 (1H, d, J = 2.6 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.9, 23.7, 31.4, 40.9, 43.2, 54.9, 111.3, 113.1, 117.5, 119.0, 126.7, 127.0, 128.6, 128,7, 129.4, 130.3, 133.1, 145.2, 148.1, 148.4, 156.8, 159.4; IR (ATR) 3284, 2590, 1653, 1603, 1552 cm^{-1}; MS (ESI) m/z 516 (M+1). Anal. Calcd for $C_{31}H_{41}N_5O_2{\cdot}2HCl{\cdot}7/4H_2O$: C, 60.04; H, 7.56; N, 11.29. Found: C, 59.77; H, 7.50; N, 11.28.

5.1.28. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[4-(3-methoxyphenyl)-1-pyridin-4-ylpiperidin-4-yl]methyl} urea dihydrochloride (30)

Compound **30** was prepared from **17** in a manner similar to that described for compound **22** with a yield of 73% as a white solid

(*i*PrOH/Et_2O). Mp 208–210 °C (dec.); ^1H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.07 (12H, d, J = 6.8 Hz), 1.96 (2H, m), 2.14 (2H, m), 3.05 (2H, m), 3.38 (2H, d, J = 4.8 Hz), 3.43 (2H, m), 3.78 (3H, s), 3.88 (2H, m), 6.20 (1H, br), 6.84 (1H, dd, J = 8.0, 2.2 Hz), 6.95 (1H, d, J = 2.2 Hz), 7.01 (1H, d, J = 8.0 Hz), 7.07 (2H, s), 7.16 (2H, d, J = 7.7 Hz), 7.30 (1H, dd, J = 8.0, 8.0 Hz), 7.72 (1H, s), 8.16 (1H, d, J = 7.7 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.9, 23.7, 28.0, 32.0, 41.4, 43.0, 54.9, 107.4, 111.4, 113.0, 117.4, 118.9, 129.5, 130.6, 132.8, 139.4, 145.2, 148.3, 156.2, 156.9, 159.4; IR (ATR) 3234, 2594, 1641, 1601, 1541 cm^{-1}; MS (ESI) m/z 516 (M+1). Anal. Calcd for $C_{31}H_{41}N_5O_2{\cdot}2HCl{\cdot}2H_2O$: C, 59.61; H, 7.58; N, 11.21. Found: C, 59.46; H, 7.47; N, 11.20.

5.1.29. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[4-(3-methoxyphenyl)-1-(3-methoxypyridin-2-yl)piperidin-4-yl]-methyl}urea dihydrochloride (31)

Compound **31** was prepared from **18** in a manner similar to that described for compound **22** with a yield of 80% as a pale yellow solid (*i*PrOH/Et_2O). Mp 201–203 °C (dec.); ^1H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.08 (12H, d, J = 7.0 Hz), 2.00 (2H, m), 2.18 (2H, m), 3.08 (2H, m), 3.38 (2H, m), 3.41 (2H, m), 3.45 (3H, s), 3.86 (2H, m), 3.90 (3H, s), 6.14 (1H, s), 6.83 (1H, dd, J = 8.0, 2.0 Hz), 6.96 (1H, s), 7.02 (1H, d, J = 8.0 Hz), 7.04 (1H, dd, J = 7.5, 6.0 Hz), 7.11 (2H, s), 7.30 (1H, dd, J = 8.0, 8.0 Hz), 7.57 (1H, d, J = 7.5 Hz), 7.69 (1H, d, J = 6.0 Hz), 7.73 (1H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.9, 23.7, 28.0, 32.3, 41.1, 45.4 54.9, 56.7, 111.3, 113.1, 115.6, 117.7, 119.0, 121.9, 129.4, 129.7, 130.1, 133.2, 145.4, 147.0, 147.5, 148.4, 156.9, 159.4; IR (ATR) 3284, 2590, 1647, 1599, 1552 cm^{-1}; MS (ESI) m/z 546 (M+1). Anal. Calcd for $C_{32}H_{43}N_5O_3{\cdot}2HCl{\cdot}3/4H_2O$: C, 60.80; H, 7.41; N, 11.08. Found: C, 60.61; H, 7.44; N, 11.02.

5.1.30. *tert*-Butyl (4-{[({[1-(2-hydroxyphenyl)-4-(3-methoxyphenyl)piperidin-4-yl]methyl}amino)carbonyl]-amino}-3,5-diisopropylphenyl)carbamate (34)

To a suspension of lithium aluminum hydride (253 mg, 6.7 mmol) in dry THF (40 mL) was added **12** (1.33 g, 3.3 mmol), and the mixture was stirred at reflux for 1 h and quenched with NaOH solution. The resulting mixture was stirred at room temperature for 1 h, added anhydrous magnesium sulfate, and filtered through Celite. The filtrate was concentrated to give an amine. The amine was dissolved in dry THF (40 mL), added *tert*-butyl 4-nitrophenyl(2,6-diisopropyl-1,4-phenylene)biscarbamate **33** (1.83 g, 4.0 mmol), and stirred at room temperature for 1 h. The reaction was then quenched by adding saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuo, and the residue was purified by amino silica gel column chromatography to give urea (2.15 g) as a colorless amorphous. To a solution of the amorphous in MeOH (43 ml) was added 20% $Pd(OH)_2/C$ (50% wet, 215 mg), and stirred at room temperature for 1 h under hydrogen atmosphere (0.3 MPa). The reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was purified by silica gel column chromatography to give **34** (1.90 g, 90%) as a colorless amorphous. ^1H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.07 (12H, d, J = 6.8 Hz), 1.47 (9H, s), 2.00 (2H, m), 2.11 (2H, m), 2.78 (2H, m), 3.00 (2H, m), 3.05 (2H, m), 3.37 (2H, d, J = 5.5 Hz), 3.77 (3H, s), 6.66 (1H, m), 6.74–6.85 (4H, m), 6.91 (2H, m), 7.18 (2H, s), 7.19 (1H, s), 7.25 (1H, m), 8.47 (1H, br), 8.92 (1H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.1, 27.6, 27.9, 32.7, 40.3, 47.0, 48.3, 54.6, 110.8, 112.8, 113.0, 115.1, 118.6, 118.7, 119.1, 122.7, 129.0, 137.9, 140.1, 146.7, 147.9, 150.1, 152.6, 156.9, 159.2; IR (ATR) 3385, 1654, 1602 cm^{-1}; HRMS (ESI) m/z Calcd for $C_{37}H_{51}N_4O_5$ 631.3854; found 631.3832 (Δ = −3.42 ppm).

5.1.31. *tert*-Butyl (4-{[({[4-(3-hydroxyphenyl)-1-(2-methoxyphenyl)piperidin-4-yl]methyl}amino)carbonyl]-amino}-3,5-diisopropylphenyl)carbamate (35)

Compound **35** was prepared from **4** in a manner similar to that described for compound **34** with a yield of 76% as a pale yellow amorphous. ^1H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.09 (12H, d, J = 7.0 Hz), 1.48 (9H, s), 1.96 (2H, m), 2.06 (2H, m), 2.82 (2H, m), 3.05 (2H, m), 3.12 (2H, m), 3.34 (2H, d, J = 5.5 Hz), 3.77 (3H, s), 6.66 (1H, m), 6.83 (4H, m), 6.89 (2H, m), 7.15 (1H, dd, J = 7.6, 7.6 Hz), 7.20 (2H, s), 7.24 (1H, s), 8.93 (1H, s), 9.10 (1H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.2, 27.7, 28.0, 32.7, 40.3, 46.7, 48.7, 55.2, 78.5, 112.2, 112.7, 113.0, 117.1, 117.8, 120.7, 121.8, 127.2, 128.9, 137.9, 141.8, 146.2, 146.8, 151.9, 152.6, 157.0, 157.3; IR (ATR) 3281, 1716, 1699, 1655, 1597, 1522 cm^{-1}; HRMS (ESI) m/z Calcd for $C_{37}H_{51}N_4O_5$ 631.3854; found 631.3831 (Δ = −3.71 ppm).

5.1.32. *tert*-Butyl (4-{[({[1-(3-hydroxypyridin-2-yl)-4-(3-methoxyphenyl)piperidin-4-yl]methyl}amino)carbonyl]-amino}-3,5-diisopropylphenyl)carbamate (36)

Compound **36** was prepared from **19** in a manner similar to that described for compound **34** with a yield of 82% as a white amorphous. ^1H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.06 (12H, d, J = 6.8 Hz), 1.47 (9H, s), 1.95 (2H, m), 2.06 (2H, m), 3.03 (2H, m), 3.11 (2H, m), 3.35 (2H, d, J = 5.5 Hz), 3.50 (2H, m), 3.76 (3H, s), 5.54 (1H, br), 6.67 (1H, dd, J = 7.7, 4.8 Hz), 6.80 (1H, d, J = 7.9 Hz), 6.90 (1H, s), 6.92 (1H, m), 6.98 (1H, dd, J = 7.7, 1.7 Hz), 7.18 (3H, s), 7.26 (1H, dd, J = 7.9, 7.9 Hz), 7.63 (1H, dd, J = 4.8, 1.7 Hz), 8.93 (1H, s), 9.25 (1H, br); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.1, 27.7, 28.0, 32.3, 41.0, 43.8, 48.6, 54.6, 78.5, 110.8, 112.8, 113.0, 116.1, 118.7, 121.3, 127.2, 129.0, 137.1, 137.9, 143.7, 146.5, 146.7, 151.1, 152.6, 156.9, 159.1; IR (ATR) 1697, 1653, 1597, 1522 cm^{-1}; HRMS (ESI) m/z Calcd for $C_{36}H_{50}N_5O_5$ 632.3806; found 632.3789 (Δ = −2.70 ppm).

5.1.33. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[1-(2-hydroxyphenyl)-4-(3-methoxyphenyl)piperidin-4-yl]methyl}-urea dihydrochloride (37)

The urea **34** (158 mg, 0.25 mmol) was added to 10% HCl–MeOH (5.0 mL) at room temperature, and the mixture was stirred for 3 days. The solvent was removed in vacuo, and the resulting solid was triturated with *i*PrOH/Et_2O to give **37** (139 mg, 92%) as a white solid. Mp 216–218 °C (dec.); ^1H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.08 (12H, d, J = 7.0 Hz), 2.35 (2H, m), 2.50 (2H, m), 3.07 (2H, m), 3.51 (4H, m), 3.81 (3H, s), 3.85 (2H, m), 6.89 (1H, m), 6.99–7.09 (5H, m), 7.25 (1H, dd, J = 7.9, 7.9 Hz), 7.34 (1H, dd, J = 7.9, 7.9 Hz), 7.66 (1H, s), 7.85 (1H, d, J = 7.9 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.0, 27.8, 29.9, 49.2, 54.8, 111.6, 112.5, 117.2, 117.7, 118.4, 119.4, 122.5, 128.8, 129.3, 130.0, 130.6, 132.5, 148.3, 150.3, 156.7, 159.4; IR (ATR) 2962, 2571, 1652, 1602, 1558 cm^{-1}; MS (ESI) m/z 531 (M+1). Anal. Calcd for $C_{32}H_{42}N_4O_3{\cdot}2HCl{\cdot}2H_2O$: C, 60.09; H, 7.56; N, 8.76. Found: C, 60.05; H, 7.49; N, 8.76.

5.1.34. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[1-(2-isopropoxyphenyl)-4-(3-methoxyphenyl)piperidin-4-yl]methyl}-urea dihydrochloride (38)

To a solution of **34** (158 mg, 0.25 mmol) in dry *N*,*N*-dimethylformamide (1.5 mL) were added cesium carbonate (122 mg, 0.38 mmol) and 2-propyl iodide (27.5 μL, 0.28 mmol), and the mixture was stirred at 60 °C for 4 h. The reaction was quenched by adding saturated ammonium hydrochloride solution and the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuo, and the residue was purified by amino silica gel column chromatography to give 2-isopropoxyl derivative (139 mg) as colorless oil. The 2-isopropoxyl derivative was added to 10% HCl–MeOH (5.0 mL) at room temperature and

stirred for 3 days. The solvent was removed in vacuo, and the resulting solid was triturated with *i*PrOH/Et_2O to give **38** (112 mg, 69%) as a white solid. Mp 226–228 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.08 (12H, d, J = 7.0 Hz), 1.09 (6H, br), 2.40 (2H, m), 2.52 (2H, m), 3.08 (2H, m), 3.45 (2H, m), 3.57 (2H, m), 3.60 (2H, br), 3.81 (3H, s), 4.73 (1H, br), 6.88 (1H, dd, J = 8.1, 2.2 Hz), 7.01 (3H, m), 7.09 (2H, s), 7.22 (1H, d, J = 8.4 Hz), 7.35 (2H, m), 7.66 (1H, s), 8.10 (1H, br); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.8, 23.0, 27.7, 29.8, 31.4, 33.8, 48.9, 54.8, 70.5, 111.6, 112.7, 115.1, 116.3, 117.3, 118.5, 120.4, 123.6, 129.4, 130.1, 132.6, 148.2, 150.1, 156.6, 159.5; IR (ATR) 2968, 2549, 1637, 1606, 1558 cm^{-1}; MS (ESI) *m/z* 573 (M+1). Anal. Calcd for $C_{35}H_{48}N_4O_3{\cdot}2HCl{\cdot}2H_2O$: C, 61.66; H, 7.98; N, 8.22. Found: C, 61.36; H, 7.91; N, 8.56.

5.1.35. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[1-(2-butoxyphenyl)-4-(3-methoxyphenyl)piperidin-4-yl]methyl}-urea dihydrochloride (39)

Compound **39** was prepared from **34** and 1-butyl iodide in a manner similar to that described for compound **38** with a yield of 92% as a pale yellow solid (*i*PrOH/Et_2O). Mp 193–194 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 0.88 (3H, t, J = 7.3 Hz), 1.08 (12H, d, J = 6.8 Hz), 1.30 (2H, br), 1.51 (2H, br), 2.39 (2H, m), 2.51 (2H, m), 3.08 (2H, m), 3.45 (2H, m), 3.56 (2H, m), 3.60 (2H, br), 3.81 (3H, s), 3.98 (2H, m), 6.89 (1H, m), 7.01 (3H, m), 7.10 (2H, s), 7.21 (1H, d, J = 8.1 Hz), 7.36 (2H, m), 7.67 (1H, s), 8.07 (1H, br); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 13.2, 18.4, 23.0, 27.7, 29.8, 29.9, 33.8, 49.0, 54.8, 68.4, 111.6, 112.6, 114.4, 117.3, 118.4, 120.7, 123.1, 129.3, 130.0, 130.3, 132.7, 148.2, 151.2, 156.6, 159.4; IR (ATR) 2960, 2568, 1653, 1606, 1558 cm^{-1}; MS (ESI) *m/z* 587 (M+1). Anal. Calcd for $C_{36}H_{50}N_4O_3{\cdot}2HCl{\cdot}9/4H_2O$: C, 61.75; H, 8.13; N, 8.00. Found: C, 61.62; H, 8.01; N, 7.99.

5.1.36. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[1-[2-(3-aminopropoxy)phenyl]-4-(3-methoxyphenyl)piperidin-4-yl]-methyl}urea trihydrochloride (40)

Compound **40** was prepared from **34** and *tert*-butyl *N*-(3-bromopropyl)carbamate in a manner similar to that described for compound **38** with a yield of 57% as a pale yellow solid (*i*PrOH/Et_2O). Mp 203–205 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.07 (12H, d, J = 6.8 Hz), 2.00 (2H, m), 2.37 (2H, m), 2.53 (2H, m), 2.90 (2H, m), 3.07 (2H, m), 3.47 (4H, m), 3.75 (2H, m), 3.81 (3H, s), 4.20 (2H, m), 6.17 (1H, br), 6.89 (1H, m), 7.02 (3H, m), 7.10 (2H, s), 7.24 (1H, m), 7.35 (2H, m), 7.77 (1H, s), 7.85 (1H, br), 8.20 (3H, br); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.8, 23.6, 26.3, 28.0, 30.0, 35.8, 49.6, 55.0, 64.9, 65.8, 111.7, 112.9, 114.6, 117.7, 118.4, 121.3, 122.7, 129.6, 130.2, 133.0, 148.4, 151.2, 156.9, 159.4; IR (ATR) 3307, 2603, 1652, 1606, 1581, 1558 cm^{-1}; MS (ESI) *m/z* 588 (M+1). Anal. Calcd for $C_{35}H_{49}N_5O_3{\cdot}3HCl{\cdot}9/4H_2O$: C, 56.98; H, 7.72; N, 9.49. Found: C, 56.75; H, 7.63; N, 9.45.

5.1.37. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[1-{2-(3-(dimethylamino)propoxy]phenyl}-4-(3-methoxyphenyl)piperidin-4-yl]methyl}urea trihydrochloride (41)

Compound **41** was prepared from **34** and 3-chloro-*N*,*N*-dimethylpropylamine hydrochloride in a manner similar to that described for compound **38** with a yield of 36% as a pale yellow solid (*i*PrOH/Et_2O). Mp 193–195 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.08 (12H, d, J = 6.8 Hz), 2.13 (2H, m), 2.26 (2H, m), 2.53 (2H, m), 2.70 (6H, s), 3.04 (2H, m), 3.20 (2H, m), 3.31 (2H, m), 3.50 (2H, m), 3.73 (2H, m), 3.85 (3H, s), 4.17 (2H, m), 5.98 (1H, br), 6.88 (1H, d, J = 8.1 Hz), 7.01 (3H, m), 7.05 (2H, s), 7.18 (1H, m), 7.34 (2H, m), 7.65 (1H, s), 7.67 (1H, br), 10.66 (1H, br); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.8, 23.3, 23.6, 28.0, 29.9, 41.8, 49.5, 53.6, 55.0, 66.1, 111.8, 112.4, 117.7, 118.2, 121.3, 123.2, 129.6, 130.2, 130.7, 132.9, 148.3, 151.2, 157.0, 159.4; IR (ATR) 3307, 2598, 1655, 1605, 1579, 1545 cm^{-1}; MS (ESI) *m/z* 616 (M+1). Anal. Calcd for $C_{37}H_{53}N_5O_3{\cdot}3HCl{\cdot}3H_2O$: C, 57.03; H, 8.02; N, 8.99. Found: C, 56.85; H, 7.95; N, 8.97.

5.1.38. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[1-[2-(2-hydroxyethoxy)phenyl]-4-(3-methoxyphenyl)piperidin-4-yl]-methyl}urea dihydrochloride (42)

To a solution of **34** (158 mg, 0.25 mmol) in dry *N*,*N*-dimethylformamide (1.5 mL) were added cesium carbonate (122 mg, 0.38 mmol) and 2-benzyloxyethylbromide (43.6 μL, 0.28 mmol), and the mixture was stirred at 60 °C for 6 h. The reaction was quenched by adding H_2O, and the mixture was extracted with EtOAc. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuo, and the residue was purified by amino silica gel column chromatography to give 2-benzyloxyethoxy derivative (159 mg) as colorless oil. To a solution of the 2-benzyloxyethoxy derivative in MeOH (3.0 mL) were added 5 N HCl solution (1 drop) and 20% $Pd(OH)_2$/C (50% wet, 32 mg), and the mixture was stirred at room temperature for 20 h under hydrogen atmosphere (0.45 MPa). The reaction mixture was filtered through Celite, and the filtrate was concentrated.The residue was purified by silica gel column chromatography to give 2-hydroxyethoxy derivative (120 mg) as a white amorphous. The 2-hydroxyethoxy derivative was added to 10% HCl–MeOH (5.0 mL) at room temperature, and stirred for 3 days. The solvent was removed in vacuo, and the resulting solid was triturated with *i*PrOH/Et_2O to give **42** (118 mg, 72%) as a white solid. Mp 206–208 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.08 (12H, d, J = 7.0 Hz), 2.34 (2H, m), 2.55 (2H, m), 3.08 (2H, m), 3.49 (2H, m), 3.55 (2H, br), 3.67 (2H, br), 3.81 (3H, s), 4.00 (2H, br), 4.10 (2H, t, J = 4.6 Hz), 6.88 (1H, dd, J = 8.0, 2.2 Hz), 7.01 (3H, m), 7.09 (2H, s), 7.23 (1H, d, J = 7.5 Hz), 7.34 (1H, dd, J = 8.0, 8.0 Hz), 7.40 (1H, m), 7.71 (1H, s), 7.96 (1H, d, J = 7.9 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.0, 27.8, 29.9, 49.3, 54.8, 59.0, 70.9, 111.6, 112.4, 114.6, 117.3, 118.3, 120.9, 122.5, 129.3, 130.1, 130.4, 132.5, 148.3, 151.4, 156.9, 159.4; IR (ATR) 3346, 2966, 2602, 1662, 1606, 1551 cm^{-1}; MS (ESI) *m/z* 575 (M+1). Anal. Calcd for $C_{34}H_{46}N_4O_4{\cdot}2HCl{\cdot}7/4H_2O$: C, 60.12; H, 7.64; N, 8.25. Found: C, 60.24; H, 7.33; N, 8.00.

5.1.39. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[1-[2-(3-hydroxypropoxy)phenyl]-4-(3-methoxyphenyl)piperidin-4-yl]-methyl}urea dihydrochloride (43)

Compound **43** was prepared from **34** and 3-benzyloxypropylbromide in a manner similar to that described for compound **42** with a yield of 76% as a white solid (*i*PrOH/Et_2O). Mp 186–188 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.08 (12H, d, J = 6.8 Hz), 1.68 (2H, br), 2.38 (2H, m), 2.50 (2H, m), 3.08 (2H, m), 3.43 (4H, br), 3.55 (2H, br), 3.76 (2H, br), 3.81 (3H, s), 4.09 (2H, m), 6.88 (1H, dd, J = 8.1, 2.2 Hz), 7.00 (3H, m), 7.10 (2H, s), 7.20 (1H, d, J = 8.1 Hz), 7.33 (1H, dd, J = 8.1, 8.1 Hz), 7.39 (1H, dd, J = 7.5, 7.5 Hz), 7.68 (1H, s), 8.02 (1H, d, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.0, 27.8, 30.0, 31.3, 49.2, 54.8, 57.1, 66.1, 111.5, 112.7, 114.3, 117.3, 118.4, 120.7, 122.8, 129.4, 130.1, 130.3, 132.7, 148.3, 151.5, 156.7, 159.5; IR (ATR) 3290, 2962, 2563, 1653, 1606, 1558 cm^{-1}; MS (ESI) *m/z* 589 (M+1). Anal. Calcd for $C_{35}H_{48}N_4O_4{\cdot}2HCl{\cdot}2H_2O$: C, 60.25; H, 7.80; N, 8.03. Found: C, 60.05; H, 7.74; N, 8.05.

5.1.40. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*′-{[4-(3-hydroxyphenyl)-1-(2-methoxyphenyl)piperidin-4-yl]methyl}-urea dihydrochloride (44)

Compound **44** was prepared from **35** in a manner similar to that described for compound **37** with a yield of 89% as a white solid (*i*PrOH/Et_2O). Mp 224–226 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C,

300 MHz) δ 1.09 (12H, d, J = 6.8 Hz), 2.29 (2H, m), 2.48 (2H, m), 3.08 (2H, m), 3.48 (4H, br), 3.76 (5H, br), 6.77 (1H, m), 6.87 (2H, m), 7.04 (1H, dd, J = 7.7, 7.7 Hz), 7.11 (2H, s), 7.21 (1H, d, J = 7.7 Hz), 7.22 (1H, dd, J = 8.1, 8.1 Hz), 7.40 (1H, dd, J = 7.7, 7.7 Hz), 7.70 (1H, s), 7.93 (1H, d, J = 7.7 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.0, 27.8, 30.0, 48.9, 55.9, 113.2, 113.6, 113.9, 116.8, 117.4, 121.0, 122.5, 129.2, 130.0, 130.2, 130.7, 132.7, 148.3, 151.9, 156.8, 157.5; IR (ATR) 3215, 2580, 1655, 1603, 1554, 1508 cm^{-1}; MS (ESI) m/z 531 (M+1). Anal. Calcd for $C_{32}H_{42}N_4O_3 \cdot 2HCl \cdot 3/2H_2O$: C, 60.94; H, 7.51; N, 8.88. Found: C, 60.97; H, 7.22; N, 8.96.

5.1.41. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*'-{[4-[3-(3-hydroxypropoxy)phenyl]-1-(2-methoxyphenyl)piperidin-4-yl]-methyl}urea dihydrochloride (45)

Compound **45** was prepared from **35** and 3-benzyloxypropylbromide in a manner similar to that described for compound **42** with a yield of 44% as a pale yellow solid (iPrOH/Et_2O). Mp 194–196 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.09 (12H, d, J = 7.0 Hz), 1.89 (2H, dt, J = 6.4, 6.4 Hz), 2.30 (2H, m), 2.50 (2H, m), 3.09 (2H, m), 3.49 (4H, br), 3.58 (2H, t, J = 6.4 Hz), 3.75 (5H, br), 4.10 (2H, t, J = 6.4 Hz), 6.88 (1H, dd, J = 8.0, 2.0 Hz) 7.01 (3H, m), 7.09 (2H, s), 7.19 (1H, d, J = 7.5 Hz), 7.34 (1H, dd, J = 8.0, 8.0 Hz), 7.39 (1H, dd, J = 7.5, 7.5 Hz), 7.68 (1H, s), 7.91 (1H, d, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.0, 27.8, 30.1, 32.1, 48.9, 55.8, 57.2, 64.5, 112.1, 113.2, 113.9, 117.3, 118.4, 121.0, 122.4, 129.3, 129.8, 130.3, 131.0, 132.6, 148.3, 151.2, 156.7, 158.9; IR (ATR) 3300, 2576, 2654, 2606, 1556, 1500 cm^{-1}; MS (ESI) m/z 589 (M+1). Anal. Calcd for $C_{35}H_{48}N_4O_4 \cdot 2HCl \cdot 5/2H_2O$: C, 59.48; H, 7.84; N, 7.93. Found: C, 59.69; H, 7.58; N, 9.96.

5.1.42. *N*-(4-Amino-2,6-diisopropylphenyl)-*N*'-{[1-[3-(3-hydroxypropoxy)pyridin-2-yl]-4-(3-methoxyphenyl)piperidin-4-yl]methyl}urea dihydrochloride (46)

Compound **46** was prepared from **36** and 3-benzyloxypropylbromide in a manner similar to that described for compound **42** with a yield of 49% as a pale yellow solid (iPrOH/Et_2O). Mp 173–175 °C (dec.); ^{1}H NMR (DMSO-d_6, 60 °C, 300 MHz) δ 1.07 (12H, d, J = 6.8 Hz), 1.91 (2H, tt, J = 6.1, 6.1 Hz), 2.02 (2H, m), 2.19 (2H, m), 3.07 (2H, m), 3.40 (2H, s), 3.47 (2H, m), 3.58 (2H, t, J = 6.1 Hz), 3.79 (3H, s), 3.83 (2H, m), 4.18 (2H, t, J = 6.1 Hz), 6.14 (1H, s), 6.83 (1H, dd, J = 8.0, 2.0 Hz), 6.96–7.03 (2H, m), 7.04 (1H, dd, J = 7.9, 5.3 Hz), 7.13 (2H, s), 7.30 (1H, dd, J = 8.0, 8.0 Hz), 7.60 (1H, d, J = 7.9 Hz), 7.67 (1H, d, J = 5.3 Hz), 7.76 (1H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.9, 23.7, 28.0, 31.7, 32.4, 41.1, 45.5, 48.4, 54.9, 57.1, 66.6, 111.3, 113.1, 115.6, 117.8, 118.9, 122.5, 129.2, 129.5, 130.1, 133.2, 145.5, 146.7, 146.9, 148.4, 156.9, 159.4; IR (ATR) 3284, 2598, 1653, 1628, 1599, 1551 cm^{-1}; MS (ESI) m/z 590 (M+1). Anal. Calcd for $C_{34}H_{47}N_5O_4 \cdot 2HCl \cdot 5/4H_2O$: C, 59.60; H, 7.58; N, 10.22. Found: C, 59.41; H, 7.58; N, 10.25.

5.2. Biology

5.2.1. Acyl-coenzyme A: cholesterol acyltransferase activity in rat macrophages

The amount of cholesterol esterification (an estimate of whole-cell ACAT activity) was determined by measuring incorporation of an extracellular ^{3}H-oleic acid-BSA complex into the intracellular cholesteryl ester.[25] Resident peritoneal rat macrophages (2×10^6 cells/mL/well) were incubated in medium containing liposomes, the ^{3}H-oleic acid–BSA complex, and various concentrations of the synthesized compounds for 24 h in a humidified incubator (5% CO_2) at 37 °C. Lipids were then extracted from the cells with hexane/2-propanol (3:2, v/v). The organic solvent was evaporated, and the cholesteryl ^{3}H-oleate was isolated by thin-layer chromatography. The band corresponding to cholesteryl ^{3}H-oleate was scraped and the radioactivity counted. The remaining cellular protein was dissolved in 0.1 N NaOH. Protein concentration was determined by the method of Lowry et al.[26]

5.2.2. Measurement of hepatic low-density lipoprotein receptor expression

$HepG_2$ cells treated with the synthesized compound were lysed with lysis buffer (125 mM Tris–HCl (pH 8.0), 2 mM $CaCl_2$, 1% Triton X-100, Complete™ (Boehringer Ingelheim Co., Ltd, Ingelheim, Germany)) and centrifuged.[27] Immunoblot analysis was performed using mouse monoclonal antibody against LDL-R (clone IgG-C7) (PROGEN Biotechnik GmbH, Heidelberg, Germany).

Acknowledgments

We are grateful to Ms. K. Bando for performing the elemental analysis, and Ms. I. Taoka for recording MS spectra.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.04.059.

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