New Strong Fibrates with Piperidine Moiety

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New fibrates containing piperidine, 4-hydroxypiperidine, piperidin-3-ene, and piperazine moieties in the structures were synthesized and evaluated. Among the synthesized compounds, 2-[3-[1-(4-fluorobenzoyl)-piperidin-4yl]phenoxy]-2-methylpropanoic acid (9aA: AHL-157) showed very superior activities in decreasing triglyceride, cholesterol, and blood sugar compared to bezafibrate in mice and rats.

Key words fibrate; piperidine; hypolipidemic; hypoglycemic

2-Methyl-2-phenoxypropanoic acid (fibric acid) derivatives are called fibrates[1—3] and clinically useful in hyperlipidemic patients who show from middle to high levels of triglyceridemia. Although clofibrate,[4] one of the first generation fibrates, has been frequently used until quite recently, the second generation fibrates such as bezafibrate,[5—8] fenofibrate,[9—16] and gemfibrozil[4,17] have been developed and are now clinically used for the treatment of hyperlipidemia. Gemfibrozil having a 5-phenoxy-pentanoic acid moiety instead of the fibric acid moiety, is also called an exceptionally new fibrates because of having almost similar pharmacological activity as the other fibrates possessing fibric acid moieties.

Although these fibrates are clinically used, drugs significantly reducing cholesterol and triglyceride in the blood and possessing a more powerful hypoglycemic effect are desired.

By chance, we found that 2-[3-[1-[4-chloro(phenylsulfonyl)]-4-hydroxypiperidin-4-yl]-phenoxy]acetic acid (**4a**), which was synthesized during the development of thromboxane-receptor antagonists, has total cholesterol- and β-lipoprotein-lowering effects in mice. Since **4a** shows almost equipotent total cholesterol- and β-lipoprotein-lowering activities to bezafibrate used as a reference compound and has a similar structure to bezafibrate, we started to modify the chemical structure of **4a** in order to find new fibrates.

As shown in Chart 1, our strategy to synthesize and develop stronger fibrates consists of modifying four parts (A—D) of **4a**. First, we modified the phenoxyacetic acid moiety (A part) of **4a**, which was converted to the 2-methyl-2-phenoxypropanoic acid moiety (fibrate moiety). Since the product, 2-[3-[1-[(4-chlorophenyl)sulfonyl]-4-hydroxypiperidin-4-yl]phenoxy]-2-methylpropanoic acid (**4b**), has almost equipotent total cholesterol- and β-lipoprotein-lowering activities to **4a**, the *N*-phenylsulfonyl moiety (part C) was changed to the *N*-benzoyl moiety. Although the *N*-benzoyl derivative (**4c**) also has almost equipotent activities to **4a**, the derivatives when the 4-chloro group of part D was changed to the 4-fluoro group 2-[3-[1-(4-fluorobenzoyl)-4-hydroxypiperidin-4-yl]phenoxy]-2-methylpropanoic acid (**4d**) had about three times higher activity than **4a**. Finally, the derivatives with the modified 4-hydroxypiperidine moiety of **4d** into piperidine, piperidin-3-ene, and piperazine moieties were synthesized and evaluated. In this paper, we describe the synthesis and hypolipidemic activities of the derivatives.

Chemistry The 4-hydroxypiperidine derivatives (**4a—d**) were synthesized as shown in Chart 2. The reaction of the Grignard reagent prepared from 3-benzyloxybromobenzene with 1-benzyl-4-piperidone gave the 4-aryl-4-hydroxypiperidine derivative (**1**), which was transformed into the *O*,*N*-debenzylated 4-hdyroxypiperidine derivative (**2**) by the palladium-catalyzed hydrogenolysis. Compound **2** was allowed to react with 4-substituted benzenesulfonyl or benzoyl chlorides to afford the corresponding *N*-arylsulfonyl or *N*-benzoyl derivatives (**3a—c**). The reaction of **3a—c** with ethyl 2-bromoacetate and 2-bromo-2-methylpropanoate followed by alkaline hydrolysis gave the expected 2-phenoxy-2-methylpropanoic acids (**4a—d**).

The piperidine derivatives (**9**) were synthesized from 1-benzyl-4-piperidinone according to the scheme shown in Chart 3. The piperidin-3-ene derivatives (**5a—c**) were obtained from the reaction of 1-benzyl-4-piperidone with the Grignard reagents derived from the methoxybromobenzenes followed by dehydration using hydrochloric acid. The palladium-catalyzed hydrogenation and debenzylation of **5a—c** gave the piperidine derivatives (**6a—c**) which were demethylated with aqueous hydrobromic acid to the phenols (**7a—c**). The reaction of **7a—c** with benzoyl chlorides gave *N*-benzoylpiperidines (**8**), which were allowed to react with ethyl 2-bromo-2-methylpropanoate followed by hydrolysis to give the 2-phenoxy-2-methylpropanoic acids (**9**).

The piperidin-3-ene derivative (**12**) was synthesized from **3c** according to the scheme shown in Chart 4. Namely, the reaction of the phenol (**3c**) with ethyl 2-bromo-2-methylpropanoate gave 2-phenoxy-2-methylpropanoate (**10**), which was dehydrated with *p*-toluenesulfonic acid (TsOH) followed by alkaline hydrolysis to give the piperidin-3-ene derivative (**12**).

The piperazine derivative (**15**) was synthesized from the

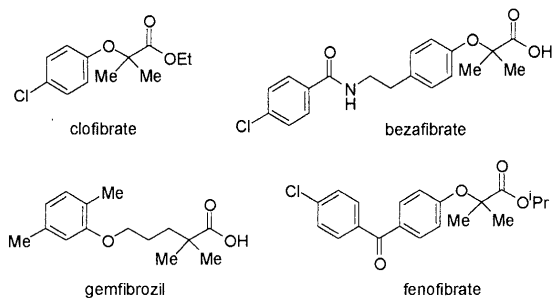

Fig. 1

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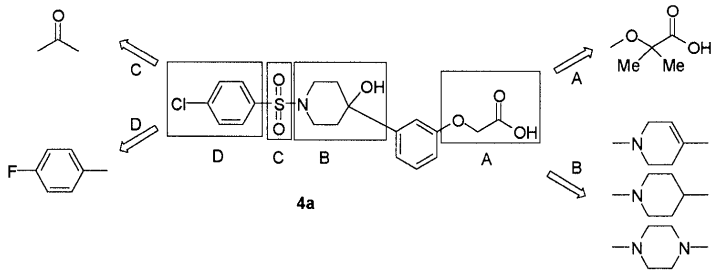


Chart 1

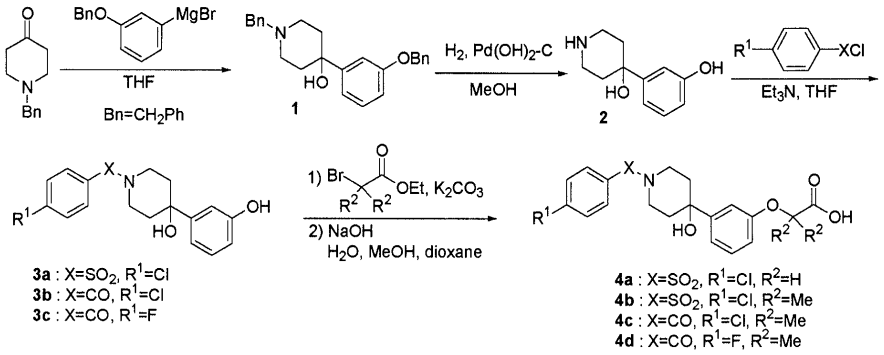
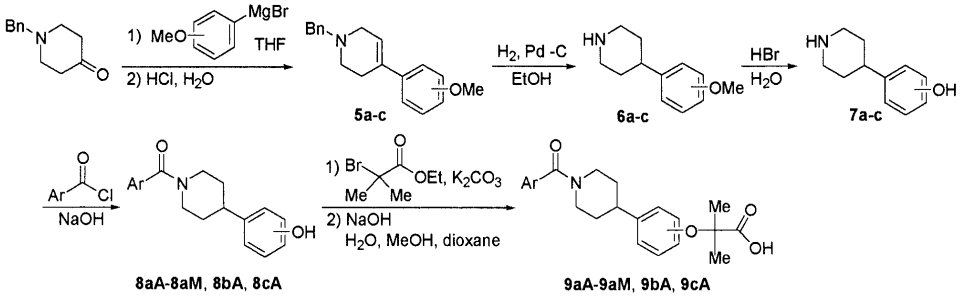


Chart 2



a: *m*-substituted; **b**: *o*-substituted; **c**: *p*-substituted
A: 4-FC_6H_4; **B**: 4-ClC_6H_4; **C**: 2-FC_6H_4; **D**: 4-BrC_6H_4; **E**: 4-$CF_3C_6H_4$; **F**: 2,4-$F_2C_6H_3$; **G**: 2,4,6-$F_3C_6H_2$; **H**: 3-FC_6H_4
I: 3,5-^{t}Bu-4-HOC_6H_2; **J**: 3-pyridinyl; **K**: 2,4,6-$Me_3C_6H_2$; **L**: C_6H_5; **M**: 4-MeC_6H_5

Chart 3

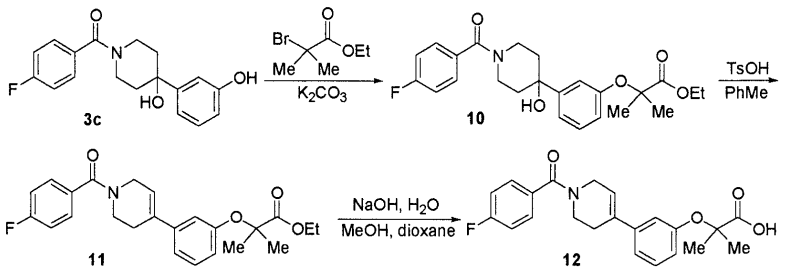


Chart 4

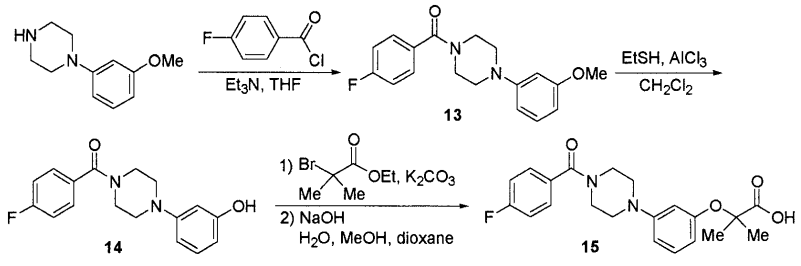


Chart 5

Table 1. Hypolipidemic Activities of **4**, **9**, **12**, **15**, and Bezafibrate in High-Cholesterol Diet-Fed Mice

Compound	T-CHOL (MED: mg/kg)	β-LP (MED: mg/kg)
Bezafibrate	100	100
9aA	0.3	0.3
9aB	1	1
9aC	1	1
9aD	3	3
9aE	3	3
9aF	3	3
9aG	3	3
9aH	3	3
9aI	30	30
9aJ	30	30
9aK	30	30
9aL	NT	NT
9aM	NT	NT
9bA	10	10
9cA	100	100
4a	100	100
4b	100	100
4c	100	100
4d	30	30
12	10	10
15	100	100

Mice ($n=6$) were given high-cholesterol diet (1% cholesterol and 0.5% cholic acid) for 7 d. Drugs were orally administered on days 6 and 7. Each value represents the MED (minimum effective dose, reducing 15% in T-CHOL and 20% in β-LP, respectively). NT: Not tested.

Table 2. T-CHOL, β-LP, and TG Reducing Effects of **9aD**, **9aE**, **9aJ**, **9aL**, and **9aM** on Serum Lipids of Normal Mice

Treatment	T-CHOL (mg/dl)	β-LP (mg/dl)	TG (mg/dl)
Control	198±8	294±23	227±23
9aD	137±4**(69)	58±7**(20)	66±3**(29)
9aE	136±16**(69)	78±11**(27)	87±7**(38)
9aJ	178±15 (90)	253±28 (86)	214±22 (94)
9aL	181±14 (91)	116±14**(39)	102±8**(45)
9aM	130±12**(66)	110±17**(37)	103±14**(45)

Drugs were orally administrated 10 mg/kg for 3 d. Blood was taken about 24 h after the final administration. Each value represents the mean±S.E. ($n=5$). Percent of control is indicated in parentheses. * and **: Significantly different from the control at $p<0.05$ and $p<0.01$ (2-side).

Table 3. T-CHOL and TG Reducing Effect of 9aA and Bezafibrate in High-Cholesterol Diet-Fed Rats

Drugs	(%)	T-CHOL (mg/dl)	TG (mg/dl)
Normal		62±2	141±4
Control		174±9## (281)	130±11 (92)
9aA	0.001	125±7** (72)	120±11 (92)
	0.003	110±4** (63)	86±7* (66)
	0.01	133±7** (76)	78±10* (60)
Bezafibrate	0.01	149±6 (86)	127±17 (98)
	0.03	123±13* (71)	72±9* (55)
	0.1	138±14 (79)	78±12 (60)

Rats were given a high-cholesterol diet (1.5% cholesterol, 0.5% cholic acid) for 2 weeks. Each value represents the mean±S.E. ($n=5$). Percent of control is indicated in parentheses. ##: Significantly different from the normal group ($p<0.01$, 2-side). *, **: Significantly different from the control group ($p<0.05$, $p<0.01$, 2-side).

commercially available 1-(3-methoxyphenyl)piperazine as shown in Chart 5. The *N*-benzoylpiperazine derivative (**13**) prepared by the acylation of 1-(3-methoxyphenyl)piperazine with 4-fluorobenzoyl chloride was demethylated using ethanethiol and aluminum chloride to give the phenol (**14**) which was reacted with ethyl 2-bromo-2-methylpropanoate followed by alkaline hydrolysis to yield the 2-phenoxypropanoic acid (**15**).

Pharmacological Activity The pharmacological activity of **4b** having the phenoxyacetic acid moiety of **4a** replaced with the 2-phenoxy-2-methylpropanoic acid moiety, which is common to fibrate-type compounds, was evaluated. The potency of reducing cholesterol and β-lipoprotein (β-LP) in serum did not change when compared with **4a**. Compound **4c**, having the sulfonyl group replaced with the benzoyl group, showed almost equipotent activity to **4b**. Compound **4d**, having the chlorine group of the phenyl ring of **4c** replaced with the fluorine group, showed a stronger total cholesterol (T-CHOL)- and β-LP-lowering effect than **4a**—**c** or bezafibrate.

Among the compounds (**4d**, **9aA**, **12**, **15**) having a 4-hydroxypiperidine, piperidine, piperidin-3-ene, or piperazine moiety, **9aA** showed the strongest activity. When the substitution position of the 2-methylpropanoic acid moiety on the phenyl group was changed from *meta* to *ortho* or *para*, the *meta*-substituted compound (**9aA**) showed the strongest activity among the derivatives.

Although several compounds (**9aB**—**9aM**) had the 4-fluorobenzoyl group of **9aA** replaced with other substituted benzoyl or 3-pyridinecarbonyl groups, **9aA** showed the most potent activity in reducing the T-CHOL and β-LP in serum. As shown in Table 1, compounds **9aL** and **9aM** were not tested in the high-cholesterol diet-fed mice, but they were estimated using normal mice and the results are shown in Table 2. They showed the reducing potencies between those of **9aD** (or **9aE**) and **9aJ** on β-LP and triglyceride (TG) in serum.

The pharmacological profiles of **9aA** were studied in rats and mice. First, the reducing effects of **9aA** on the serum TG and T-CHOL levels were estimated in high-cholesterol diet-fed rats in comparison with bezafibrate (Table 3). Second, the reducing effects of **9aA** on the serum TG were estimated in fructose-induced hypertriglycemic rats and compared with bezafibrate, fenofibrate and gemfibrozil (Table 4). The reducing effects of **9aA** on the serum glucose and TG were then estimated in KK-A^y mice and compared with bezafibrate (Table 5). As a result, the reducing activity of **9aA** on the TG and T-CHOL levels was greater than 10 times more potent than that of bezafibrate. The hypoglycemic effects of **9aA** in KK-A^y mice were also greater than 10 times more potent than those of bezafibrate.

Now, Patients with NIDDM (non-insulin-dependent diabetes mellitus) commonly have dyslipiedaemia (especially hypertriglyceridaemia and low HDL (high density lipoprotein) cholesterol levels) and are at high risk of coronary heart disease.[8] In this paper, **9aA** improved the lipid profile in several animal models, additionally this compound showed hypoglycemic effect in a spontaneous NIDDM mouse model. These results indicate that **9aA** may be a useful therapeutic candidate for NIDDM patients with hyperlipidaemia.

As mentioned above, after evaluation of several pharmacological studies, it was clarified that **9aA** possesses an additional hypoglycemic effect along with the strong reducing effect on serum cholesterol and TG. Detailed studies of the mechanism and action of **9aA** will be reported separately.

Since 2-[3-[1-(4-fluorobenzoyl)piperidin-4-yl]phenoxy]-2-methylpropanoic acid (**9aA**: AHL-157) was selected as a novel synthesized fibrate-type compound as described above, we examined the procedure for the large scale synthesis of **9aA**. The transformation of **8a** to **9aA** was effectively achieved under the reaction conditions[18] using acetone, chloroform, and sodium hydroxide as shown in Chart 6.

Table 4. TG Reducing Effects of **9aA**, Bezafibrate, Fenofibrate, and Gemfibrozil in Fructose-Induced Hypertriglyceridemia in Rat

Drugs	Dose (mg/kg/d)	TG (mg/dl)	Inhibition (%)
Normal Control		100.9±12.0	
Control		186.4±25.0#	
9aA	0.03	182.9±37.6	(1.9%)
	0.1	191.5±47	(−2.7%)
	0.3	121.7±18	(34.7%)
	1.0	80.1±11**	(57.0%)
Bezafibrate	0.3	161.6±14	(13.3%)
	1.0	179.5±30.5	(3.7%)
	3.0	156.3±12	(16.1%)
	10.0	98.1±14*	(47.4%)
Fenofibrate	0.3	189.3±20	(−1.6%)
	1.0	221.1±26.6	(−18.6%)
	3.0	129.6±18	(30.5%)
	10.0	110.2±15	(40.9%)
Gemfibrozil	0.3	222.3±26.5	(−19.3%)
	1.0	188.1±23.0	(−0.9%)
	3.0	126.2±16	(32.3%)
	10.0	95.9±9.1*	(48.6%)

Rats (n=8) were given 25% fructose solution for 21 d, and drugs were orally administered once a day for the latter 7 d of the experimental period at each dose. Blood samples were drawn from inferior vena cava 24 h after the last administration. Each data represents the mean±S.E. #: Significantly different from Normal control by Aspin-Welch t-test (p<0.05, 2-side). *, **: Significantly different from the control by Dunnett's test (p<0.05, p<0.01, 2-side). The % TG lowering action relative to control are shown in parentheses.

Conclusion

Novel fibrates with 4-hydroxypiperidine, piperidine, piperidin-3-ene, and piperazine moieties in the center of the structure were synthesized. It was found that 1) **9aA** with the piperidine moiety showed a strong total cholesterol- and β-LP-lowering effect in mice, 2) the reducing activity of **9aA** on TG in rats and mice is greater than 10 times more potent than that of bezafibrate, and 3) the hypoglycemic effect of **9aA** in KK-A^y mice is also greater than 10 times more potent than that of bezafibrate. **9aA** was finally selected as the most

Table 5. Glucose and TG Reducing Effects of **9aA** and Bezafibrate in KK-A^y Mice

		Glucose (mg/dl)	TG (mg/dl)
Control		551.6±15.3	868.9±65.1
9aA	0.003%	469.7±34.9 (85.2)	708.3±72.2 (81.5)
	0.01%	398.4±23.8** (72.2)	536.0±29.1** (61.7)
	0.03%	414.7±31.6** (75.2)	594.0±52.7** (68.4)
Bezafibrate	0.03%	496.0±39.5 (89.9)	746.9±83.2 (86.0)
	0.1%	440.7±22.7* (79.9)	661.0±24.8 (76.1)
	0.3%	258.1±18.6** (46.8)	451.4±18.4** (52.0)

Mice were given drug containing diet (0.003% to 0.3%) for 14 d. Each value represents the mean±S.E. of 8 mice. The values in parentheses represent percent of control. *, **: Significantly different from the control by Dunnett's test (p<0.05, p<0.01, 2-side).

Table 6. Yields, Melting Points, Mass Spectral and Analytical Data for **4**, **9**, **12**, and **15**

Compd. No.	Yield (%)	mp (°C)	Formula	FAB-MS (m/z)	*Anal.* Calcd (Found)		
					C	H	N
4a	80	143—144	$C_{19}H_{20}ClNO_6S$	426 (M^++1, ^{35}Cl), 428 (M^++3, ^{37}Cl)	53.58 (53.77)	4.73 (4.76)	3.29 (3.46)
4b	45	181—182	$C_{21}H_{24}ClNO_6S$	454 (M^++1, ^{35}Cl), 456 (M^++3, ^{37}Cl)	55.56 (55.41)	5.33 (5.28)	3.09 (2.95)
4c	67	158—159	$C_{22}H_{24}ClNO_5\cdot 0.2H_2O$	418 (M^++1, ^{35}Cl), 420 (M^++3, ^{37}Cl)	62.70 (62.75)	5.83 (5.87)	3.32 (3.32)
4d	67	77—79	$C_{22}H_{24}FNO_5\cdot 0.25H_2O$	402 (M^++1)	65.10 (64.96)	6.08 (6.16)	3.45 (3.47)
9aA	60	138—139	$C_{22}H_{24}FNO_4$	386 (M^++1)	68.56 (68.56)	6.28 (6.45)	3.63 (3.40)
9aB	73	140—141	$C_{22}H_{24}ClNO_4$	402 (M^++1, ^{35}Cl), 404 (M^++3, ^{37}Cl)	65.75 (65.71)	6.02 (5.92)	3.49 (3.40)
9aC	71	121—122	$C_{22}H_{24}FNO_4$	386 (M^++1)	68.56 (68.60)	6.28 (6.07)	3.63 (3.72)
9aD	81	153—154	$C_{22}H_{24}BrNO_4$	446 (M^++1, ^{79}Br), 448 (M^++3, ^{81}Br)	59.20 (59.01)	5.42 (5.66)	3.14 (3.05)
9aE	61	148—149	$C_{23}H_{24}F_3NO_4\cdot 0.25H_2O$	436 (M^++1)	62.79 (62.93)	5.61 (5.71)	3.18 (3.13)
9aF	78	110—112	$C_{22}H_{23}F_2NO_4$	404 (M^++1)	65.50 (65.41)	5.75 (5.77)	3.47 (3.36)
9aG	55	115—116	$C_{22}H_{22}F_3NO_4$	422 (M^++1)	62.70 (62.45)	5.26 (5.27)	3.32 (3.34)
9aH	58	122—123	$C_{22}H_{24}FNO_4$	386 (M^++1)	68.56 (68.37)	6.28 (6.28)	3.63 (3.55)
9aI	80	148—150	$C_{30}H_{41}NO_5\cdot 0.25H_2O$	496 (M^++1)	72.04 (71.85)	8.36 (8.46)	2.80 (2.81)
9aJ	45	149—150	$C_{21}H_{24}N_2O_4$	369 (M^++1)	68.46 (68.55)	6.57 (6.52)	7.60 (7.74)
9aK	72	168—169	$C_{25}H_{31}NO_4\cdot 0.25H_2O$	410 (M^++1)	72.53 (72.72)	7.67 (7.67)	3.38 (3.33)
9aL	84	122—123	$C_{22}H_{25}NO_4$	368 (M^++1)	71.91 (72.03)	6.86 (7.01)	3.81 (3.91)
9aM	85	124—125	$C_{23}H_{27}NO_4\cdot 0.2H_2O$	382 (M^++1)	71.74 (71.98)	7.17 (7.38)	3.64 (3.64)
9bA	56	185—186	$C_{22}H_{24}FNO_4$	386 (M^++1)	68.56 (68.69)	6.28 (6.29)	3.63 (3.52)
9cA	63	174—175	$C_{22}H_{24}FNO_4$	386 (M^++1)	68.56 (68.44)	6.28 (6.32)	3.63 (3.52)
12	75 (3 steps)	129—130	$C_{22}H_{22}FNO_4$	384 (M^++1)	68.92 (68.85)	5.78 (5.94)	3.65 (3.66)
15	48	143—144	$C_{21}H_{23}FN_2O_4$	387 (M^++1)	65.27 (65.29)	6.00 (6.00)	7.25 (7.25)

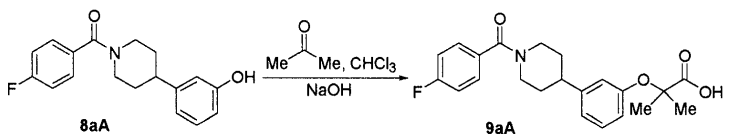


Chart 6

Table 7. ^{1}H-NMR and IR Spectral Data for **4**, **9**, **12**, and **15**

Compd.	^{1}H-NMR ($CHCl_3$) δ	IR (KBr) cm^{-1}
4a	1.57—1.68 (2H, m), 1.90—2.04 (2H, m), 2.60—2.72 (2H, m), 3.51—3.60 (2H, m), 4.64 (2H, s), 4.94 (1H, s), 6.75 (1H, dd, J=7.8, 2.4 Hz), 6.99 (1H, s), 7.00 (1H, d, J=7.8 Hz), 7.21 (1H, t, J=7.8 Hz), 7.24 (2H, d, J=8.6 Hz), 7.81 (2H, d, J=8.6 Hz), 12.80—14.30 (1H, br) [DMSO-d_6]	3500 1725
4b	1.49 (6H, s), 1.58—1.70 (2H, m), 1.84—1.97 (2H, m), 2.60—2.72 (2H, m), 3.50—3.62 (2H, m), 4.93 (1H, s), 6.66 (1H, dd, J=8.0, 2.0 Hz), 6.92 (1H, t, J=2.0 Hz), 7.01 (1H, d, J=8.0 Hz), 7.19 (1H, t, J=8.0 Hz), 7.74 (2H, d, J=8.8 Hz), 7.80 (2H, d, J=8.8 Hz), 13.30—14.20 (1H, br) [DMSO-d_6]	3448 1712
4c	1.55—2.20 (4H, m), 1.60 (6H, s), 3.15—4.00 (4H, m), 4.45—4.72 (1H, br), 6.81 (1H, dd, J=8.1, 2.0 Hz), 7.07 (1H, t, J=2.0 Hz), 7.11 (1H, d, J=8.1 Hz), 7.24 (1H, t, J=8.1 Hz), 7.36 (2H, d, J=8.8 Hz), 7.39 (2H, d, J=8.8 Hz)	3400 1722 1595
4d	1.50—2.16 (4H, m), 1.58 (6H, s), 3.10—3.40 (1H, m), 3.40—3.80 (2H, m), 4.37—4.62 (1H, m), 4.62—5.17 (2H, br), 6.78 (1H, dd, J=7.8, 2.0 Hz), 7.02—7.12 (4H, m), 7.20 (1H, t, J=7.8 Hz), 7.36—7.46 (2H, m)	3422 1734 1605
9aA	1.50 (6H, s), 1.50—1.65 (2H, m), 1.70—1.90 (2H, m), 2.72—2.83 (1H, m), 2.90—3.10 (2H, m), 3.70—4.50 (2H, br), 6.69 (1H, dd, J=7.8, 2.0 Hz), 6.77 (1H, t, J=2.0 Hz), 6.89 (1H, d, J=7.8 Hz), 7.18 (1H, t, J=7.8 Hz), 7.20—7.30 (2H, m), 7.45—7.55 (2H, m), 11.5—13.5 (1H, br) [DMSO-d_6]	1734 1605
9aB	1.45—1.65 (2H, m), 1.50 (6H, s), 1.65—1.98 (2H, m), 2.68—2.80 (1H, m), 2.80—3.25 (2H, m), 3.45—3.80 (1H, m), 4.40—4.80 (1H, m), 6.65 (1H, dd, J=8.0, 2.0 Hz), 6.75 (1H, t, J=2.0 Hz), 6.88 (1H, d, J=8.0 Hz), 7.18 (1H, t, J=8.0 Hz), 7.45 (2H, d, J=8.3 Hz), 7.50 (2H, d, J=8.3 Hz), 12.75—13.00 (1H, br) [DMSO-d_6]	1734 1597
9aC	1.47—1.90 (3H, m), 1.59 (6H, s), 1.90—2.00 (1H, m), 2.65—2.80 (1H, m), 2.80—2.95 (1H, m), 3.02—3.18 (1H, m), 3.61—3.77 (1H, br), 4.83—5.00 (1H, m), 5.00—6.00 (1H, br), 6.76 (1H, dd, J=8.4, 2.2 Hz), 6.80 (1H, s), 6.90 (1H, d, J=8.4 Hz), 7.10 (1H, t, J=8.4 Hz), 7.17—7.26 (2H, m), 7.34—7.50 (2H, m)	1724 1599
9aD	1.48—2.00 (4H, m), 1.59 (6H, s), 2.66—2.78 (1H, m), 2.78—3.00 (1H, m), 3.00—3.24 (1H, m), 3.63—3.97 (1H, m), 4.68—4.96 (1H, m), 6.74 (1H, dd, J=7.8, 2.0 Hz), 6.80 (1H, t, J=2.0 Hz), 6.88 (1H, d, J=7.8 Hz), 7.19 (1H, t, J=7.8 Hz), 7.31 (2H, d, J=8.3 Hz), 7.54 (2H, d, J=8.3 Hz)	1736 1587
9aE	1.48 (6H, s), 1.50—1.65 (2H, m), 1.65—1.95 (2H, m), 2.70—2.80 (1H, m), 2.80—3.00 (1H, m), 3.30—3.75 (2H, m), 4.45—4.75 (1H, m), 6.66 (1H, dd, J=7.8, 2.0 Hz), 6.75 (1H, s), 6.86 (1H, d, J=7.8 Hz), 7.16 (1H, t, J=7.8 Hz), 7.65 (2H, d, J=8.1 Hz), 7.81 (2H, d, J= 8.1 Hz) [DMSO-d_6]	1721 1595
9aF	1.50—1.90 (3H, m), 1.60 (6H, s), 1.90—2.04 (1H, m), 2.65—2.80 (1H, m), 2.80—2.95 (1H, m), 3.05—3.30 (1H, m), 3.60—3.70 (1H, m), 4.83—4.95 (1H, m), 6.77 (1H, dd, J=8.0, 2.0 Hz), 6.80 (1H, t, J=2.0 Hz), 6.83—6.88 (1H, m), 6.92 (1H, d, J=8.0 Hz), 6.93—6.98 (1H, m), 7.21 (1H, t, J=8.0 Hz), 7.26—7.44 (1H, m)	1740 1602
9aG	1.60 (6H, s), 1.60—1.80 (2H, m), 1.80—1.90 (1H, m), 1.90—2.02 (1H, m), 2.68—2.80 (1H, m), 2.80—2.95 (1H, m), 3.15—3.23 (1H, m), 3.58—3.70 (1H, m), 4.86—4.96 (1H, m), 6.67—6.83 (4H, m), 6.91 (1H, d, J=7.8 Hz), 7.22 (1H, t, J=7.8 Hz)	1754 1614
9aH	1.50—2.05 (4H, m), 1.60 (6H, s), 2.70—2.80 (1H, m), 2.80—3.00 (1H, m), 3.00—3.23 (1H, m), 3.85—3.96 (1H, m), 4.71—4.98 (1H, m), 6.67 (1H, dd, J=8.0, 2.0 Hz), 6.81 (1H, t, J=2.0 Hz), 6.92 (1H, d, J=8.0 Hz), 7.06—7.18 (2H, m), 7.18—7.24 (2H, m), 7.34—7.46 (1H, m)	1724 1597
9aI	1.39 (18H, s), 1.42 (6H, s), 1.43—1.62 (2H, m), 1.73—1.86 (1H, m), 2.63—2.78 (1H, m), 2.83—3.05 (1H, m), 3.05—3.50 (2H, m), 3.92—4.50 (1H, br), 6.69 (1H, d, J=7.8 Hz), 6.72 (1H, s), 6.75 (1H, d, J=7.8 Hz), 7.08 (1H, t, J=7.8 Hz), 7.17 (2H, s), 7.17—7.33 (1H, br) [DMSO-d_6]	3448 1602
9aJ	1.52—2.04 (4H, m), 1.62 (6H, s), 2.68—2.80 (1H, m), 2.80—2.97 (1H, m), 3.08—3.28 (1H, m), 3.66—3.87 (1H, m), 4.74—4.94 (1H, m), 6.78 (1H, d, J=7.8 Hz), 6.81 (1H, s), 6.84 (1H, d, J=7.8 Hz), 7.18 (1H, t, J=7.8 Hz), 7.44 (1H, dd, J=7.7, 4.8 Hz), 7.87 (1H, d, J=7.7 Hz), 8.00—9.20 (1H, br), 8.68 (1H, d, J=4.8 Hz), 8.73 (1H, s)	1718 1631
9aK	1.45—1.59 (1H, m), 1.60 (6H, S), 1.60—1.75 (1H, m), 1.75—1.83 (1H, m), 1.95—2.05 (1H, m), 2.18 (3H, s), 2.28 (3H, s), 2.30 (3H, s), 2.65—2.77 (1H, m), 2.80—2.90 (1H, m), 3.00—3.13 (1H, m), 3.45—3.57 (1H, m), 4.90—5.00 (1H, m), 6.74 (1H, dd, J=7.8, 2.1 Hz), 6.77 (1H, t, J=2.1 Hz), 6.83 (1H, d, J=7.8 Hz), 6.85 (1H, s), 6.88 (1H, s), 7.18 (1H, t, J=7.8 Hz)	1722 1574
9aL	1.40—2.15 (4H, m), 1.59 (6H, s), 2.60—3.40 (3H, m), 3.68—4.05 (1H, m), 4.20—5.60 (2H, br), 6.76 (1H, dd, J=7.8, 2.0 Hz), 6.81 (1H, t, J=2.0 Hz), 6.90 (1H, d, J=7.8 Hz), 7.20 (1H, t, J=7.8 Hz), 7.35—7.55 (5H, m)	1741 1594
9aM	1.48—1.75 (2H, m), 1.59 (6H, s), 1.75—2.03 (2H, m), 2.38 (3H, s), 2.65—2.80 (1H, m), 2.80—3.25 (2H, m), 3.58—4.24 (1H, m), 4.24—5.37 (2H, br), 6.76 (1H, dd, J=7.8, 2.0 Hz), 6.81 (1H, t, J=2.0 Hz), 6.89 (1H, d, J=7.8 Hz), 7.19 (1H, t, J=7.8 Hz), 7.21 (2H, d, J=8.3 Hz), 7.33 (2H, d, J=8.3 Hz)	1718 1578
9bA	1.53—2.05 (4H, m), 1.63 (6H, S), 2.76—3.00 (1H, m), 3.00—3.32 (2H, m), 3.78—4.00 (1H, m), 4.70—5.00 (1H, m), 6.75 (1H, d, J=7.3 Hz), 6.98 (1H, t, J=7.3 Hz), 7.05—7.15 (3H, m), 7.17 (1H,dd, J=7.3, 1.5 Hz), 7.38—7.50 (2H, m)	1708 1600
9cA	1.58 (6H, S), 1.50—2.05 (4H, m), 2.68—2.80 (1H, m), 2.80—3.00 (1H, m), 3.00—3.24 (1H, m), 3.77—3.97 (1H, m), 4.77—4.95 (1H, m), 6.86 (2H, d, J=8.8 Hz), 7.05—7.17 (4H, m), 7.40—7.50 (2H, m)	1715 1569
12	1.60 (6H, S), 2.45—2.66 (2H, m), 3.50—3.70 (1H, m), 3.85—4.05 (1H, m), 4.05—4.20 (1H, m), 4.25—4.45 (1H, m), 5.82—6.20 (1H, m), 6.84 (1H, dd, J=8.3, 2.0 Hz), 6.96 (1H, s), 7.02—7.18 (3H, m), 7.24 (1H, t, J= 8.3 Hz), 7.40—7.50 (2H, m)	1732 1603
15	1.59 (6H, S), 3.00—3.37 (4H, m), 3.43—4.10 (4H, m), 4.80—6.00 (1H, br), 6.45 (1H, dd, J=8.1, 2.2 Hz), 6.52 (1H, t, J=2.2 Hz), 6.63 (1H, dd, J=8.1, 2.2 Hz), 7.05—7.20 (3H, m), 7.40—7.50 (2H, m)	1724 1603

promising candidate of our new fibrate, and is now in preclinical stage.

Experimental

Melting points were determined on a Yanaco micro melting point apparatus without correction. IR spectra were measured with a Perkin-Elmer 1600 FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-EX400 FT-NMR spectrometer in $CDCl_3$ or dimethyl sulfoxide (DMSO)-d_6 using tetramethylsilane as the internal reference. The following abbreviations were used: s=singlet, d=doublet, dd=double doublet, dt=double triplet, t=triplet, q=quartet, m=multiplet and br=broad. FAB-MS, electron ionization mass spectrometry (EI-MS) or high-resolution mass spectrometry (HR-MS) were obtained using JEOL JMS-DX303 or JEOL JMS-AX500 mass spectrometer. TLC was performed by using Silica gel $60F_{254}$ (Merck). Column chromatography was performed with Silica gel 60 (70—230 mesh)

(Merck). Sodium sulfate was employed as the drying agent. Palladium hydroxide [20 wt.%, Pd (dry basis) on carbon, wet] was obtained from Aldrich Chemical Company, Inc. The yields, physical and spectral data for **4a**—**d**, **9aA**—**9aM**, **9bA**, **9cA**, **12** and **15** are shown in Tables 6 and 7.

1-Benzyl-4-[3-(benzyloxy)phenyl]-4-hydroxypiperidine (1) A solution of 3-benzyloxy bromobenzene (13.0 g, 49.4 mmol) in tetrahydrofuran (THF) (50 ml) was dropwise added to a stirred mixture of Mg (1.21 g, 49.8 mmol) and I_2 (catalytic amount) in THF (30 ml) at 40 °C over 30 min, and the mixture was stirred at reflux for 2 h. After cooling, a solution of 1-benzyl-4-piperidone (7.20 g, 37.7 mmol) in THF (50 ml) was added dropwise to the stirred mixture at room temperature over a 30 min period, and then stirred at reflux for 2 h. After cooling, aq. sat. NH_4Cl. (50 ml) was added dropwise, and the reaction mixture was extracted with Et_2O. The organic layer was dried, concentrated *in vacuo* to give a pale brown oil which was purified by column chromatography on silica gel, eluting with 50% AcOEt in *n*-hexane to give **1** (10.3 g, 73%) as a pale yellow viscous liquid. ^{1}H-NMR ($CDCl_3$) δ: 1.50—3.00 (1H, br), 1.67—1.80 (2H, m), 2.08—2.23 (2H, m), 2.42—2.55 (2H, m), 2.73—2.85 (2H, m), 3.58 (2H, s), 5.05 (2H, s), 6.86 (1H, dd, J=7.8, 2.0 Hz), 7.09 (1H, dd, J=7.8, 2.0 Hz), 7.18 (1H, t, J=2.0 Hz), 7.22—7.50 (11H, m). EI-MS m/z: 373 (M^+). HR-MS *m/z*: 373.2026 (Calcd for $C_{25}H_{27}NO_2$: 373.2042). IR ν (neat) cm^{-1}: 3380.

4-Hydroxy-4-(3-hydroxyphenyl)piperidine (2) A solution of **1** (10.0 g, 26.8 mmol) in MeOH (100 ml) was hydrogenated in the presence of $Pd(OH)_2$ (3.0 g) under a H_2 atmosphere (4 atm) at room temperature for 6 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give **2** (4.00 g, 77%) as a white solid. mp 188—189 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.42—1.52 (2H, m), 1.66—1.80 (2H, m), 2.62—2.76 (2H, m), 2.84—2.97 (2H,m), 4.40—4.80 (1H, br), 6.54—6.60 (1H, m), 6.85 (1H, dd, J=7.8, 2.0 Hz), 6.89 (1H, t, J=2.0 Hz), 7.07 (1H, t, J=7.8 Hz), 8.00—10.00 1H, br). EI-MS *m/z*: 193 (M^+). HR-MS *m/z*: 193.1097 (Calcd for $C_{11}H_{15}NO_2$: 193.1102). IR ν (KBr) cm^{-1}: 3273.

1-[4-Halobenzoyl or (4-Chlorophenyl)sulfonyl]-4-hydroxy-4-(3-hydroxyphenyl)piperidine (3) (General Procedure A) A solution of a benzoyl or phenylsulfonyl chloride (44 mmol) in THF (20 ml) was added dropwise to a stirred solution of **2** (20 mmol) and Et_3N (43 mmol) in THF (80 ml) at 0 °C over a 15 min period, and then was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, and concentrated *in vacuo*. The residue was dissolved in a mixture of 1 N NaOH (50 ml), MeOH (50 ml) and 1,4-dioxane (50 ml), then stirred at room temperature for 30 min. The mixture was acidified with dil. HCl to pH 3 at 0 °C. The mixture was extracted with $CHCl_3$, washed with sat. aq. $NaHCO_3$ and H_2O, dried, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with 5% MeOH in $CHCl_3$ to give **3** as a white solid.

1-[(4-Chlorophenyl)sulfonyl]-4-hydroxy-4-(3-hydroxyphenyl)piperidine (**3a**): mp 195—196 °C. Yield 75%. ^{1}H-NMR (DMSO-d_6) δ: 1.52—1.70 (2H, m), 1.82—2.00 (2H, m), 2.57—2.76 (2H, m), 3.48—3.68 (2H, m), 4.84 (1H, s), 6.80 (1H, d, J=7.8 Hz), 6.86 (1H, t, J=2.0 Hz), 7.08 (1H, t, J=7.8 Hz), 7.24 (2H, d, J=8.8 Hz), 7.80 (2H, d, J=8.8 Hz), 9.19 (1H, s). EI-MS *m/z*: 367 (M^+). HR-MS *m/z*: 367.0627 (Calcd for $C_{17}H_{18}ClNO_4S$: 367.0645). IR ν (KBr) cm^{-1}: 3444, 3340.

1-(4-Chlorobenzoyl)-4-hydroxy-4-(3-hydroxyphenyl)piperidine (**3b**): mp 168—170 °C. Yield 80%. ^{1}H-NMR ($CHCl_3$) δ: 1.53—1.70 (1H, m), 1.70—1.93 (2H, m), 1.93—2.15 (1H, m), 3.16—3.43 (2H, m), 3.43—3.63 (2H, m), 4.40—4.58 (1H, m), 6.66 (1H, dd, J=7.9, 2.0 Hz), 6.84 (1H, d, J=7.9 Hz), 6.88 (1H, t, J=2.0 Hz), 7.11 (1H, t, J=7.9 Hz), 7.30 (2H, d, J=8.3 Hz), 7.33 (2H, d, J=8.3 Hz). EI-MS *m/z*: 331 (M^+). HR-MS *m/z*: 331.0987 (Calcd for $C_{18}H_{18}ClNO_3$: 331.0975). IR ν (KBr) cm^{-1}: 3227, 1614.

1-(4-Fluorobenzoyl)-4-hydroxy-4-(3-hydroxyphenyl)piperidine (**3c**): mp 195—196 °C. Yield 87%. ^{1}H-NMR ($CDCl_3$) δ: 1.60—2.00 (3H, m), 2.00—2.20 (1H, m), 3.22—3.45 (1H, m), 3.45—3.78 (2H, m), 4.45—4.70 (1H, m), 6.74 (1H, dd, J=8.0, 2.0 Hz), 6.92 (1H, d, J=8.0 Hz), 6.96 (1H, t, J=2.0 Hz), 7.07—7.16 (2H, m), 7.20 (1H, t, J=8.0 Hz), 7.40—7.48 (2H, m). EI-MS *m/z*: 315 (M^+). HR-MS *m/z*: 315.1268 (Calcd for $C_{17}H_{18}FNO_3$: 315.1271). IR ν (KBr) cm^{-1}: 3241, 1615.

2-[3-[1-[4-Halobenzoyl or (4-Chlorophenyl)sulfonyl]-4-hydroxypiperidin-4-yl]phen-oxy]acetic or -2-Methylpropanoic Acid (4) (General Procedure B) A mixture of **3** (10 mmol), ethyl 2-bromo-2-methylpropanoate (0.1 mol) and K_2CO_3 (30 mmol) was stirred at 100 °C for 8 h. The mixture was poured into H_2O and extracted with $CHCl_3$, and the $CHCl_3$ layer was concentrated *in vacuo*. The residue was dissolved in a mixture of 1 N NaOH (50 ml), MeOH (50 ml), and 1,4-dioxane (50 ml), and then stirred for 1 h at room temperature. The mixture was poured into H_2O, acidified with dil. HCl to pH 3, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with 5% MeOH in $CHCl_3$ to give an oil which was crystallized from Et_2O to give **4** as a white solid.

1-Benzyl-4-(methoxyphenyl)-1,2,3,6-tetrahydropyridine·HCl (5) (General Procedure C) A solution of methoxybromobenzene (1.10 mol) in THF (350 ml) was added dropwise to a stirred mixture of Mg (1.10 mol) and I_2 (catalytic amount) in THF (100 ml) at 40 °C over a 1 h period, then stirred at reflux for 1 h. After cooling, a solution of 1-benzyl-4-piperidinone (1.0 mol) in THF (250 ml) was added dropwise to the stirred mixture at room temperature over a 1 h period, and then stirred at reflux for 1 h. After cooling, sat. aq. NH_4Cl (400 ml) and H_2O (200 ml) were added to the mixture, then allowed to stand for a short time. The mixture was partitioned between THF and H_2O, and the organic layer was washed with brine, then concentrated *in vacuo*. The residue was dissolved in a mixture of 1,4-dioxane (500 ml) and 6 N HCl (1000 ml), then refluxed for 3 h. After cooling, the mixture was concentrated *in vacuo*, and the residue was triturated with Et_2O to give **5** as a white solid.

1-Benzyl-4-(3-methoxyphenyl)-1,2,3,6-tetrahydropyridine·HCl (**5a**): mp 193—195 °C. Yield 62%. ^{1}H-NMR (DMSO-d_6) δ: 2.64—2.83 (1H, m), 2.83—3.02 (1H, m), 3.10—3.30 (1H, m), 3.47—3.62 (1H, m), 3.62—3.80 (2H, m), 3.77 (3H, s), 4.30—4.50 (2H, m), 6.13—6.18 (1H, br), 6.89 (1H, dd, J=8.1, 2.0 Hz), 6.98 (1H, t, J=2.0 Hz), 7.03 (1H, d, J=8.1 Hz), 7.29 (1H, t, J=8.1 Hz), 7.42—7.52 (3H, m), 7.66—7.76 (2H, m), 11.20—11.60 (1H, br). EI-MS *m/z*: 279 (M^+). HR-MS *m/z*: 279.1606 (Calcd for $C_{19}H_{21}NO$: 279.1623). IR ν (KBr) cm^{-1}: 2515.

1-Benzyl-4-(2-methoxyphenyl)-1,2,3,6-tetrahydropyridine·HCl (**5b**): mp 163—165 °C. Yield 86%. ^{1}H-NMR (DMSO-d_6) δ: 2.52—2.65 (1H, m), 2.75—3.00 (1H, m), 3.10—3.30 (1H, m), 3.30—3.50 (1H, m), 3.60—3.80 (2H, m), 3.78 (3H, s), 4.35—4.50 (2H, m), 5.75—5.80 (1H, m), 6.94 (1H, t, J=7.8 Hz), 7.02 (1H, d, J=7.8 Hz), 7.15 (1H, dd, J=7.8, 1.5 Hz), 7.29 (1H, dt, J=7.8, 1.5 Hz), 7.36—7.54 (3H, m), 7.60—7.75 (2H, m), 10.90—11.20 (1H, br). EI-MS *m/z*: 279 (M^+). HR-MS *m/z*: 279.1635 (Calcd for $C_{19}H_{21}NO$: 279.1623). IR ν (KBr) cm^{-1}: 2498.

1-Benzyl-4-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridine·HCl (**5c**): mp 228—229 °C. Yield 69%. ^{1}H-NMR (DMSO-d_6) δ: 2.65—2.80 (1H, m), 2.80—2.95 (1H, m), 3.10—3.30 (1H, m), 3.50—3.62 (1H,m), 3.62—3.78 (2H, m), 3.76 (3H, s), 4.35—4.48 (2H, m), 6.01—6.06 (1H, m), 6.93 (2H, d, J=8.8 Hz), 7.40 (2H, d, J=8.8 Hz), 7.43—7.50 (3H, m), 7.65—7.72 (2H, m), 11.01—11.30 (1H, br). EI-MS *m/z*: 279 (M^+). HR-MS *m/z*: 279.1609 (Calcd for $C_{19}H_{21}NO$: 279.1623). IR ν (KBr) cm^{-1}: 2484.

4-(Methoxyphenyl)piperidine·HCl (6) (General Procedure D) A solution of **5** (0.5 mol) in a mixture of MeOH (440 ml) and H_2O (360 ml) was hydrogenated in the presence of 5% Pd–C (32.0 g) under a H_2 atmosphere (1 atm) at room temperature for 16 h. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to give **6** as a white solid.

4-(3-Methoxyphenyl)piperidine·HCl (**6a**): mp 171—172 °C. Yield *ca.* 100%. ^{1}H-NMR (DMSO-d_6) δ: 1.81—2.00 (4H, m), 2.71—2.86 (1H, m), 2.86—3.06 (2H, m), 3.23—3.40 (2H, m), 3.74 (3H, s), 6.74—6.86 (3H, m), 7.25 (1H, t, J=7.8 Hz), 9.00—9.46 (2H, br). EI-MS *m/z*: 191 (M^+). HR-MS *m/z*: 191.1306 (Calcd for $C_{12}H_{17}NO$: 191.1310). IR ν (KBr) cm^{-1}: 2490.

4-(2-Methoxyphenyl)piperidine·HCl (**6b**): mp 228—230 °C. Yield 74%. ^{1}H-NMR (DMSO-d_6) δ: 1.78—2.00 (4H, m), 2.90—3.08 (2H, m), 3.09—3.22 (1H, m), 3.24—3.38 (2H, m), 3.80 (3H, s), 6.94 (1H, t, J=7.7 Hz), 6.99 (1H, d, J=7.7 Hz), 7.14 (1H, dd, J=7.7, 1.5 Hz), 7.21 (1H, dt, J=7.7, 1.5 Hz), 9.00—9.30 (2H, br). EI-MS *m/z*: 191 (M^+). HR-MS *m/z*: 191.1324 (Calcd for $C_{12}H_{17}NO$: 191.1310). IR ν (KBr) cm^{-1}: 2506.

4-(4-Methoxyphenyl)piperidine·HCl (**6c**): mp 205—206 °C. Yield 81%. ^{1}H-NMR (DMSO-d_6) δ: 1.80—1.95 (4H, m), 2.75—2.85 (1H, m), 2.85—3.00 (2H, m), 3.20—3.30 (2H, m), 3.73 (3H, s), 6.89 (2H, d, J=8.8 Hz), 7.14 (2H, d, J=8.8 Hz), 9.08—9.34 (2H, m). EI-MS *m/z*: 191 (M^+). HR-MS *m/z*: 191.1320 (Calcd for $C_{12}H_{17}NO$: 191.1310). IR ν (KBr) cm^{-1}: 2502.

4-(Hydroxyphenyl)piperidine (7) (General Procedure E) A mixture of **6** (500 mmol) and 47% hydrobromic acid (300 g, 1.74 mol) was refluxed with stirring for 2 h. The mixture was concentrated *in vacuo* and the residue was dissolved in H_2O, then made alkaline to pH 9.5 with aq. NaOH. The resulting precipitate (**7**) was collected by filtration as a white solid.

4-(3-Hydroxyphenyl)piperidine (**7a**): mp 227—228 °C. Yield 89%. ^{1}H-NMR (DMSO-d_6) δ: 1.34—1.55 (2H, m), 1.55—1.75 (2H, m), 2.36—2.62 (3H, m), 2.62—3.80 (1H, br), 2.90—3.07 (2H, m), 6.52—6.66 (3H, m), 7.05 (1H, t, J=7.8 Hz), 8.40—10.20 (1H, br). EI-MS *m/z*: 177 (M^+). HR-MS *m/z*: 177.1146 (Calcd for $C_{11}H_{15}NO$: 177.1154). IR ν (KBr) cm^{-1}: 3265.

4-(2-Hydroxyphenyl)piperidine (**7b**): mp 172—173 °C. Yield 68%. ^{1}H-NMR ($CDCl_3$) δ: 1.70—1.93 (4H, m), 2.70—2.90 (2H, m), 2.95—3.10 (1H, m), 3.10—3.32 (2H, m), 4.00—5.20 (2H, br), 6.70 (1H, dd, J=7.7, 1.4 Hz),

6.84 (1H, dt, J=7.7, 1.4 Hz), 7.04 (1H, dt, J=7.7, 1.4 Hz), 7.14 (1H, dd, J=7.7, 1.4 Hz). EI-MS m/z: 177 (M^+). HR-MS m/z: 177.1155 (Calcd for $C_{11}H_{15}NO$: 177.1154). IR ν (KBr) cm^{-1}: 3312.

4-(4-Hydroxyphenyl)piperidine (**7c**): mp 218—220 °C. Yield 67%. ^{1}H-NMR (DMSO-d_6) δ: 1.30—1.50 (2H, m), 1.50—1.70 (2H, m), 2.30—2.65 (3H, m), 2.90—3.10 (2H, m), 6.70 (2H, d, J=8.3 Hz), 6.99 (2H, d, J=8.3 Hz). EI-MS m/z: 177 (M^+). HR-MS m/z: 177.1138 (Calcd for $C_{11}H_{15}NO$: 177.1154). IR ν (KBr) cm^{-1}: 3300.

(1-Aroyl-4-hydroxyphenyl)piperidine (8) (General Procedure F) An aroyl chloride (0.5 mol) was dropwise added to a stirred solution of **7** (0.45 mol), NaOH (21.6 g, 0.54 mol), isopropanol (240 ml), and H_2O (240 ml) at 40 °C over a 15 min period, then the mixture was stirred at 40 °C for 1 h. A solution of MeOH (400 ml) and aq. NaOH (20% w/w) (59.7 g, 0.498 mol) was next added to the mixture, then stirred at 50 °C for 1 h. After cooling, the mixture was acidified with aq. HCl to pH 4, and the resulting precipitate (**8**) was collected by filtration as a white solid.

Compounds **8** except **8aI** and **8aK** were synthesized according to general procedure F. Compound **8aI** was synthesized from **7a** according to the procedure for the synthesis of **13** and the compound **8aK** was synthesized from **7a** according to general procedure A.

1-(4-Fluorobenzoyl)-4-(3-hydroxyphenyl)piperidine (**8aA**): mp 163—164 °C. Yield *ca.* 100%. ^{1}H-NMR ($CHCl_3$) δ: 1.40—2.15 (4H, m), 2.65—3.32 (3H, m), 3.70—4.10 (1H, m), 4.70—5.05 (1H, m), 5.82—6.36 (1H, br), 6.65—6.73 (2H, m), 6.75 (1H, d, J=8.0 Hz), 7.06—7.13 (2H, m), 7.16 (1H, t, J=8.0 Hz), 7.40—7.50 (2H, m). EI-MS m/z: 299 (M^+). HR-MS m/z: 299.1327 (Calcd for $C_{18}H_{18}FNO_2$: 299.1321). IR ν (KBr) cm^{-1}: 3449, 1602.

1-(4-Chlorobenzoyl)-4-(3-hydroxyphenyl)piperidine (**8aB**): mp 142—143 °C. Yield *ca.* 100%. ^{1}H-NMR ($CHCl_3$) δ: 1.40—2.15 (4H, m), 2.60—2.80 (1H, m), 2.80—3.00 (1H, m), 3.00—3.30 (1H, m), 3.68—4.03 (1H, m), 4.65—5.08 (1H, m), 6.42—6.60 (1H, br), 6.60—6.80 (3H, m), 7.15 (1H, t, J=8.2 Hz), 7.32—7.43 (4H, m). EI-MS m/z: 315 (M^+). HR-MS m/z: 315.1040 (Calcd for $C_{18}H_{18}ClNO_2$: 315.1026). IR ν (KBr) cm^{-1}: 3226, 1610.

1-(2-Fluorobenzoyl)-4-(3-hydroxyphenyl)piperidine (**8aC**): mp 149—150 °C. Yield 96%. ^{1}H-NMR ($CHCl_3$) δ: 1.62—2.10 (4H, m), 2.63—2.80 (1H, m), 2.80—2.97 (1H, m), 3.00—3.36 (1H, br), 3.60—3.75 (1H, m), 4.85—5.00 (1H, m), 6.63—6.80 (3H, m), 6.95—7.27 (4H, m), 7.33—7.50 (2H, m). EI-MS m/z: 299 (M^+). HR-MS m/z: 299.1322 (Calcd for $C_{18}H_{18}FNO_2$: 299.1321). IR ν (KBr) cm^{-1}: 3270, 1620.

1-(4-Bromobenzoyl)-4-(3-hydroxyphenyl)piperidine (**8aD**): mp 163—164 °C. Yield 93%. ^{1}H-NMR ($CHCl_3$) δ: 1.43—2.15 (4H, m), 2.63—2.80 (1H, m), 2.80—3.00 (1H, m), 3.00—3.30 (1H, m), 3.70—4.00 (1H, m), 4.73—5.00 (1H, m), 6.15 (1H, s), 6.64—6.72 (2H, m), 6.74 (1H, d, J=7.8 Hz), 7.16 (1H, t, J=7.8 Hz), 7.31 (2H, d, J=8.3 Hz), 7.55 (2H, d, J=8.3 Hz). EI-MS m/z: 359 (M^+). HR-MS m/z: 359.0501 (Calcd for $C_{18}H_{18}BrNO_2$: 359.0520). IR ν (KBr) cm^{-1}: 3208, 1614.

4-(3-Hydroxyphenyl)-1-[4-(trifluoromethyl)benzoyl]piperidine (**8aE**): mp 156—157 °C. Yield 76%. ^{1}H-NMR ($CHCl_3$) δ: 1.47—1.68 (1H, m), 1.68—1.90 (2H, m), 1.90—2.10 (1H, m), 2.66—2.70 (1H, m), 2.70—3.00 (1H, m), 3.05—3.27 (1H, m), 3.67—3.86 (1H, m), 4.78—5.04 (1H, m), 5.80—7.10 (1H, m), 6.64—6.72 (2H, m), 6.74 (1H, d, J=7.8 Hz), 7.15 (1H, t, J=7.8 Hz), 7.54 (2H, d, J=8.1 Hz), 7.68 (2H, d, J=8.1 Hz). EI-MS m/z: 349 (M^+). HR-MS m/z: 349.1295 (Calcd for $C_{19}H_{18}F_3NO_2$: 349.1290). IR ν (KBr) cm^{-1}: 3260, 1620.

1-(2,4-Difluorobenzoyl)-4-(3-hydroxyphenyl)piperidine (**8aF**): mp 147—148 °C. Yield *ca.* 100%. ^{1}H-NMR ($CHCl_3$) δ: 1.40—1.90 (3H, m), 1.90—2.05 (1H, m), 2.63—2.80 (1H, m), 2.80—2.95 (1H, m), 3.00—3.35 (1H, m), 3.58—3.62 (1H, m), 4.82—5.00 (1H, m), 5.80—6.30 (1H, br), 6.63—6.71 (2H, m), 6.74 (1H, d, J=7.8 Hz), 6.79—6.90 (1H, m), 6.90—6.99 (1H, m), 7.16 (1H, t, J=7.8 Hz), 7.35—7.48 (1H, m). EI-MS m/z: 317 (M^+). HR-MS m/z: 317.1241 (Calcd for $C_{18}H_{17}F_2NO_2$: 317.1228). IR ν (KBr) cm^{-1}: 3194, 1614.

4-(3-Hydroxyphenyl)-1-(2,4,6-trifluorobenzoyl)piperidine (**8aG**): mp 168—169 °C. Yield *ca.* 100%. ^{1}H-NMR ($CHCl_3$) δ: 1.55—1.80 (2H, m), 1.80—1.92 (1H, m), 1.92—2.05 (1H, m), 2.67—2.80 (1H, m), 2.82—2.96 (1H, m), 3.15—3.28 (1H, m), 3.57—3.68 (1H, m), 4.87—4.97 (1H, m), 6.15—6.45 (1H, br), 6.63—6.78 (5H, m), 7.15 (1H, t, J=8.1 Hz). EI-MS m/z: 335 (M^+). HR-MS m/z: 335.1149 (Calcd for $C_{18}H_{16}F_3NO_2$: 335.1133). IR ν (KBr) cm^{-1}: 3245, 1616.

1-(3-Fluorobenzoyl)-4-(3-hydroxyphenyl)piperidine (**8aH**): mp 155—156 °C. Yield *ca.* 100%. ^{1}H-NMR ($CHCl_3$) δ: 1.40—2.10 (4H, m), 2.65—2.80 (1H, m), 2.80—3.00 (1H, m), 3.00—3.25 (1H, m), 3.70—3.95 (1H, m), 4.72—5.00 (1H, m), 5.60—6.10 (1H, br), 6.65—6.73 (2H, m), 6.76 (1H, d, J=7.8 Hz), 7.08—7.24 (3H, m), 7.35—7.44 (2H, m). EI-MS m/z: 299 (M^+). HR-MS m/z: 299.1335 (Calcd for $C_{18}H_{18}FNO_2$: 299.1322). IR ν (KBr) cm^{-1}: 3187, 1598.

1-[3,5-Di(*tert*-butyl)-4-hydroxybenzoyl]-4-(3-hydroxyphenyl)piperidine (**8aI**): mp 263—265 °C. Yield 24%. ^{1}H-NMR ($CHCl_3$) δ: 1.43 (18H, s), 1.56—2.12 (4H, m), 2.67—2.80 (1H, m), 2.80—3.25 (2H, m), 3.84—4.30 (1H, m), 4.60—5.05 (1H, m), 5.40 (1H, s), 6.68 (1H, dd, J=7.8, 2.0 Hz), 6.73 (1H, s), 6.77 (1H, d, J=7.8 Hz), 7.17 (1H, t, J=7.8 Hz), 7.27 (2H, s). EI-MS m/z: 409 (M^+). HR-MS m/z: 409.2597 (Calcd for $C_{26}H_{35}NO_3$: 409.2616). IR ν (KBr) cm^{-1}: 3568, 3169, 1598.

4-(3-Hydroxyphenyl)-1-(3-pyridinecarbonyl)piperidine (**8aJ**): mp 188—189 °C. Yield 48%. ^{1}H-NMR ($CHCl_3$) δ: 1.46—2.10 (4H, m), 2.66—2.80 (1H, m), 2.80—3.00 (1H, m), 3.05—3.32 (1H, m), 3.65—3.92 (1H, m), 4.70—4.92 (1H, m), 6.65—6.76 (5H, m), 7.15 (1H, t, J=7.8 Hz), 7.42 (1H, dd, J=8.1, 4.9 Hz), 7.82 (1H, dt, J=8.1, 1.6 Hz). EI-MS m/z: 282 (M^+). HR-MS m/z: 282.1369 (Calcd for $C_{17}H_{18}N_2O_2$: 282.1368). IR ν (KBr) cm^{-1}: 3200, 1631.

4-(3-Hydroxyphenyl)-1-(2,4,6-trimethylbenzoyl)piperidine (**8aK**): mp 194—195 °C. Yield 72%. ^{1}H-NMR ($CHCl_3$) δ: 1.43—1.58 (1H, m), 1.62—1.85 (2H, m), 1.92—2.05 (1H, m), 2.19 (3H, s), 2.27 (3H, s), 2.29 (3H, s), 2.60—2.74 (1H, m), 2.76—2.92 (1H, m), 2.98—3.12 (1H, m), 3.46—3.56 (1H, m), 4.96—5.06 (1H, m), 6.60—6.74 (1H, m), 6.84 (1H, s), 6.85 (1H, s), 6.91 (1H, s), 7.12 (1H, t, J=8.1 Hz). EI-MS m/z: 323 (M^+). HR-MS m/z: 323.1895 (Calcd for $C_{21}H_{25}NO_2$: 323.1885). IR ν (KBr) cm^{-1}: 3198, 1607.

1-Benzoyl-4-(3-hydroxyphenyl)piperidine (**8aL**): mp 189—190 °C. Yield *ca.* 100%. ^{1}H-NMR ($CHCl_3$) δ: 1.30—2.15 (4H, m), 2.62—2.80 (1H, m), 2.80—3.00 (1H, m), 3.00—3.25 (1H, m), 3.76—4.05 (1H, m), 4.72—5.05 (1H, m), 5.55—6.25 (1H, br), 6.65—6.73 (2H, m), 6.76 (1H, d, J=7.8 Hz), 7.16 (1H, t, J=7.8 Hz), 7.36—7.49 (5H, m). EI-MS m/z: 281 (M^+). HR-MS m/z: 281.1409 (Calcd for $C_{18}H_{19}NO_2$: 281.1416). IR ν (KBr) cm^{-1}: 3154, 1614.

4-(3-Hydroxyphenyl)-1-(4-methylbenzoyl)piperidine (**8aM**): mp 137—138 °C. Yield 93%. ^{1}H-NMR ($CHCl_3$) δ: 1.48—2.12 (4H, m), 2.37 (3H, s), 2.65—2.80 (1H, m), 2.80—3.00 (1H, m), 3.00—3.28 (1H, m), 3.79—4.08 (1H, m), 4.73—5.02 (1H, m), 6.56—6.66 (1H, br), 6.66—6.78 (3H, m), 7.14 (1H, t, J=7.8 Hz), 7.20 (2H, d, J=7.8 Hz), 7.34 (2H, d, J=7.8 Hz). EI-MS m/z: 295 (M^+). HR-MS m/z: 295.1575 (Calcd for $C_{19}H_{21}NO_2$: 295.1572). IR ν (KBr) cm^{-1}: 3184, 1593.

1-(4-Fluorobenzoyl)-4-(2-hydroxyphenyl)piperidine (**8bA**): mp 211—212 °C. Yield 70%. ^{1}H-NMR ($CHCl_3$) δ: 1.43—2.08 (5H, m), 2.76—3.02 (1H, m), 3.05—3.28 (1H, m), 3.75—4.00 (1H, m), 4.74—4.98 (1H, m), 5.70—6.20 (1H, m), 6.74 (1H, dd, J=7.6, 1.0 Hz), 6.89 (1H, dt, J=7.6, 1.0 Hz), 7.01—7.17 (4H, m), 7.40—7.50 (2H, m). EI-MS m/z: 299 (M^+). HR-MS m/z: 299.1334 (Calcd for $C_{18}H_{18}FNO_2$: 299.1321). IR ν (KBr) cm^{-1}: 3133, 1601.

1-(4-Fluorobenzoyl)-4-(4-hydroxyphenyl)piperidine (**8cA**): mp 183—185 °C. Yield 79%. ^{1}H-NMR (DMSO-d_6) δ: 1.40—1.60 (2H, m), 1.60—1.90 (2H, m), 2.60—2.75 (1H, m), 2.75—3.30 (2H, m), 3.50—4.00 (1H, m), 4.50—4.80 (1H, m), 6.68 (2H, d, J=8.5 Hz), 7.05 (2H, d, J=8.5 Hz), 7.22—7.30 (2H, m), 7.42—7.56 (2H, m), 8.95—9.20 (1H, br). EI-MS m/z: 299 (M^+). HR-MS m/z: 299.1325 (Calcd for $C_{18}H_{18}FNO_2$: 299.1321). IR ν (KBr) cm^{-1}: 3126, 1607.

(1-Aroylpiperidin-4-yl)phenoxy]-2-methylpropanoic Acid (9) Compounds **9** were synthesized from **8** according to general procedure B.

Modified Synthetic Procedure of 9aA NaOH (60.0 g, 2.50 mol) was added in small portions to a stirred solution of **8aA** (30.0 g, 0.1 mol) in acetone (420 g, 7.23 mol) at room temperature over a 15 min period, and then stirred at 35 °C for 30 min. $CHCl_3$ (53.9 g, 0.451 mol) was added dropwise to the stirred mixture in such a way as to maintain the reaction temperature at 35 °C for 1 h. The entire mixture was stirred at 35 °C for 1 h, and then concentrated *in vacuo*. The residue was dissolved in H_2O, and the mixture was washed with $CHCl_3$ and acidified with dilute HCl to pH 3. The resulting precipitate was collected by filtration and dissolved in $CHCl_3$. The $CHCl_3$ solution was extracted with aq. Na_2CO_3 and the aqueous layer was acidified with dilute HCl to pH 3 again, and the resulting precipitate was collected by filtration and washed with H_2O. The solid was recrystallized from toluene to give **9aA** (29.4 g, 76%) as a white solid.

Ethyl 2-[3-[1-(4-Fluorobenzoyl)-4-hydroxypiperidin-4-yl]phenoxy]-2-methylpropanoate (10) A mixture of **3c** (4.44 g, 14.1 mmol), ethyl 2-bromo-2-methylpropanoate (12.5 g, 64.1 mmol) and K_2CO_3 (4.50 g, 32.6 mmol) was stirred at 100 °C for 14 h. The mixture was poured into H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and concentrated *in vacuo* to give **10** (6.05 g, *ca.* 100%) as a white solid. mp 103—104 °C. ^{1}H-NMR ($CHCl_3$) δ: 1.25 (3H, t, J=7.0 Hz), 1.45—2.25 (4H, m), 1.60 (6H, s), 3.20—3.86 (3H, m), 4.24 (2H, q, J=7.0 Hz), 4.50—4.77

(1H, m), 6.71 (1H, dd, J=8.1, 2.0 Hz), 7.03 (1H, t, J=2.0 Hz), 7.05—7.15 (3H, m), 7.23 (1H, t, J=8.1 Hz), 7.40—7.49 (2H, m). EI-MS m/z: 429 (M^+). HR-MS m/z: 429.1936 (Calcd for $C_{24}H_{28}FNO_5$: 429.1952). IR ν (KBr) cm^{-1}: 3403, 1732, 1607.

Ethyl 2-[3-[1-(4-Fluorobenzoyl)-1,2,3,6-tetrahydropyridin-4-yl]phenoxy]-2-methylpropanoate (11) A mixture of **10** (1.38 g, 3.22 mmol), TsOH acid monohydrate (700 mg, 3.68 mmol), and toluene (50 ml) was refluxed with stirring using a condenser attached to a water separator for 3 h. After cooling, the reaction mixture was washed with sat. aq. $NaHCO_3$ and H_2O, dried, and concentrated *in vacuo* to give **11** (1.12 g, 85%) as a pale yellow viscous liquid. ^{1}H-NMR ($CHCl_3$) δ: 1.25 (3H, t, J=7.0 Hz), 1.60 (6H, s), 2.42—2.68 (2H, m), 3.45—3.72 (1H, m), 3.83—4.00 (1H, m), 4.00—4.20 (1H, m), 4.24 (2H, q, J=7.0 Hz), 4.25—4.50 (1H, m), 5.76—6.24 (1H, m), 6.73 (1H, dd, J=8.1, 2.0 Hz), 6.90 (1H, s), 7.01 (1H, d, J=8.1 Hz), 7.06—7.17 (2H, m), 7.20 (1H, t, J=8.1 Hz), 7.42—7.51 (2H, m). EI-MS m/z: 411 (M^+). HR-MS m/z: 411.1842 (Calcd for $C_{24}H_{26}FNO_4$: 411.1845). IR ν (KBr) cm^{-1}: 1731, 1633.

2-[3-[1-(4-Fluorobenzoyl)-1,2,3,6-tetrahydropyridin-4-yl]phenoxy]-2-methylpropanoic Acid (12) A solution of **11** (1.00 g, 2.43 mmol) in a mixture of 1 N NaOH (10 ml), MeOH (10 ml), and 1,4-dioxane (10 ml) was stirred at room temperature for 1 h. The mixture was acidified with dilute HCl to pH 3 and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and concentrated *in vacuo* to give an oil which was crystallized from Et_2O to give **12** (820 mg, 88%) as a white solid.

1-(4-Fluorobenzoyl)-4-(3-methoxyphenyl)piperazine (13) A solution of 4-fluorobenzoyl chloride (1.80 g, 11.4 mmol) in THF (20 ml) was dropwise added to a stirred solution of 1-(3-methoxyphenyl)piperazine (2.0 g, 10.2 mmol) and Et_3N (3.0 ml, 21.6 mmol) in THF (40 ml) at 0 °C over a 15 min period, and the mixture was stirred at room temperature for 1 h. The mixture was concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with 3% MeOH in $CHCl_3$ to give **13** (3.10 g, 97%) as a pale yellow viscous liquid. ^{1}H-NMR ($CHCl_3$) δ: 3.00—3.36 (4H, m), 3.43—4.12 (4H, m), 3.79 (3H, s), 6.43—6.50 (2H, m), 6.54 (1H, dd, J=8.2, 2.0 Hz), 7.07—7.15 (2H, m), 7.19 (1H, t, J=8.2 Hz), 7.40—7.50 (2H, m). EI-MS m/z: 314 (M^+). HR-MS m/z: 314.1439 (Calcd for $C_{18}H_{19}FN_2O_2$: 314.1431). IR ν (KBr) cm^{-1}: 1632.

1-(4-Fluorobenzoyl)-4-(3-hydroxyphenyl)piperazine (14) $AlCl_3$ (4.0 g, 29.9 mmol) was added in small portions to a stirred solution of **13** (3.14 g, 10.0 mmol) and ethanethiol (4.0 ml, 53.5 mmol) in CH_2Cl_2 (120 ml) at 0 °C over a 5 min period, and the mixture was stirred at room temperature for 8 h and concentrated *in vacuo*. The residue was dissolved in H_2O, and the aqueous mixture was extracted with $CHCl_3$–MeOH (15 : 1). The organic layer was washed with H_2O, dried, and concentrated *in vacuo* to give an oil which was purified by column chromatography on silica gel, eluting with 3% MeOH in $CHCl_3$ to give **14** (2.10 g, 70%) as a white solid. mp 134—135 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.00—3.20 (4H, m), 3.40—3.85 (4H, m), 6.25 (1H, dd, J=8.1, 2.0 Hz), 6.33 (1H, t, J=2.0 Hz), 6.38 (1H, dd, J=8.1, 2.0 Hz), 6.99 (1H, t, J=8.1 Hz), 7.23—7.35 (2H, m), 7.45—7.55 (2H, m), 9.09 (1H, s). EI-MS m/z: 300 (M^+). HR-MS m/z: 300.1270 (Calcd for $C_{17}H_{17}FN_2O_2$: 300.1274). IR ν (KBr) cm^{-1}: 3092, 1576.

2-[3-[4-(4-Fluorobenzoyl)piperadino]phenoxy]-2-methylpropanoic Acid (15) Compound **15** was synthesized from **14** according to general procedure B.

Animals Male ICR mice and male SD rats were obtained from Charles River Japan, Inc. (Tokyo, Japan). Male KK-A^y mice were also obtained from CLEA Japan Inc. (Tokyo, Japan).

Chemicals Bezafibrate, fenofibrate, and gemfibrozil were purchased from Sigma (St. Louis, U.S.A.). For oral administration, the compounds were suspended in a vehicle (0.5% carboxymethylcellulose sodium solution containing 0.05% Tween 80). For the admixture in diet, normal-chow diet (MF; Oriental Yeast Co., Ltd., Tokyo, Japan), high-cholesterol diet (MF supplemented with 1.5% cholesterol and 0.5% cholic acid) and high-cholesterol diets containing 0.001, 0.003, and 0.01% **9aA**, and 0.01, 0.03, and 0.1% bezafibrate were prepared (Oriental Yeast Co., Ltd., Tokyo, Japan). Serum T-CHOL, TG, β-LP, and glucose levels were measured with commercially available kits (Wako Chemicals Japan).

Hypolipidemic Activities in Normal or Hypercholesterolemic Mice In the case of normal mice, drugs were orally administered to male ICR mice (7-weeks old, n=5) for 3 d. In the case of hypercholesterolemic mice, the high-cholesterol diet (1% cholesterol and 0.5% cholic acid) was given to male ICR mice (7-weeks old, n=6) for 7 d, and drugs were orally administered on days 6 and 7. The T-CHOL, β-LP, and TG levels in the serum were measured.

Hypolipidemic Effect in Hypecholesterolemic Rats Male SD rats (7 weeks old, n=5) were given the high-cholesterol diet (1.5% cholesterol and 0.5% cholic acid) or high-cholesterol diet containing drugs for 2 weeks. The T-CHOL and TG levels in serum were measured.

Hypolipidemic Effect in Fructose-Induced Hypertriglyceridemic Rats Male SD rats (6 weeks old) were given 25% fructose in drinking water during the experimental period. After 12 d, rats were divided into the control and treatement groups (n=8), and were orally administered with **9aA**, bezafibrate, fenofibrate, and gemfibrozil for 7 d. Twenty-four hours after the final administration, the serum TG levels were measured.

Hypoglycemic Effect in KK-A^y mice Male KK-A^y mice (13 weeks old, n=8) were administered **9aA** (0.003%, 0.01%, and 0.03%) and bezafibrate (0.03%, 0.1%, and 0.3%) admixture in their diets for 2 weeks. The serum glucose and TG levels were measured.

Statistical Analysis Data were expressed as mean±S.E. A statistical analysis of difference between the groups was performed with Dunnett's multiple comparison test followed by Bartlett's test. A Student's t-test or Aspin–Welch t-test were also used for comparison between the two groups. A p-value level less than 0.05 (2-side) was considered as statistically significant.

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