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Novel Hydroxyphenylurea Dual Inhibitor Against Acyl-CoA: Cholesterol Acyltransferase (ACAT) and Low Density Lipoprotein (LDL) Oxidation as Antiatherosclerotic Agent

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Abstract—Novel hydroxyphenylurea derivatives were synthesized and their inhibitory potency evaluated against acyl-CoA: cholesterol acyltransferase (ACAT). Quantitative structure–activity relationship analysis revealed that their ACAT inhibitory activities were controlled by the hydrophobicity of the whole molecule, the substitution pattern of urea moiety, and the existence of carboxylic acid. The derivatives with strong activities inhibited foam cell formations. Moreover, these compounds showed antioxidative effects against low density lipoprotein (LDL), owing to their characteristic 3-*tert*-butyl-2-hydroxy-5-methoxyphenyl substructure. Based on the mechanism of atherosclerosis generation, this hydroxyphenylurea-type dual inhibitor against both ACAT and LDL oxidation is expected to be a promising drug for atherosclerosis.

Introduction

Atherosclerosis causes heart attack, stroke, and gangrene of the extremities.[1] In the early stage of atherosclerosis, the massive accumulation of foam cells is observed within the innermost layer of the artery wall. The foam cells are mainly developed from monocytes/macrophages, and filled with lipid droplets consisting of cholesteryl esters. The hypothetical mechanism of the formation of foam cells in the atherosclerotic lesions is illustrated in Figure 1.[2] Oxidized low density lipoprotein (ox-LDL), viruses, and toxins can injure the endothelial cells, which leads the adhesion of macrophages to the artery wall.[3] Then the macrophages migrate into the intima and become foam cells owing to the unregulated uptake of ox-LDL via the scavenger receptor.[4] The ox-LDL is hydrolyzed in the macrophages and the resulting cholesterol is acylated again to form cholesteryl ester by acyl-CoA: cholesterol acyltransferase (ACAT).[5] Cholesteryl ester forms lipid droplets in macrophages which finally turn into mature foam cells.

ACAT is the key enzyme in both the foam cell formation of macrophages and the cholesterol absorption in the intestine.[6] Since the inhibition of ACAT can lower plasma cholesterol level by the prevention of cholesterol absorption, the ACAT inhibitors are expected to have therapeutic effects for hypercholesterolemia. Moreover, the inhibitors can reduce the extent of atherosclerotic lesions by preventing macrophages from converting to foam cells. Various ACAT inhibitors having urea substructure (Fig. 2) are now under development for the treatment of hypercholesterolemia and atherosclerosis.[7,8]

Antioxidants are also promising as therapeutic agents for atherosclerosis.[9] The ox-LDL can play an important role in atherosclerosis by injuring endothelial cells of the artery wall and supplying cholesterol to macrophages. Antioxidants could decrease the amount of the ox-LDL production, which leads to the treatment for atherosclerosis. Vitamin E, a natural antioxidant, and probucol, the well-known drug for hypercholesterolemia (Fig. 3), have been known to reduce the progression of atherosclerosis by the suppression of oxidative stress.[10]

In our previous paper, we reported the antioxidantive activities of hydroxyphenylureas.[11] It was revealed that hydroxyphenylureas with strong antioxidative activity had electron-donating substituents on their phenol rings, bulky substituents at the *ortho*-positions of the phenolic

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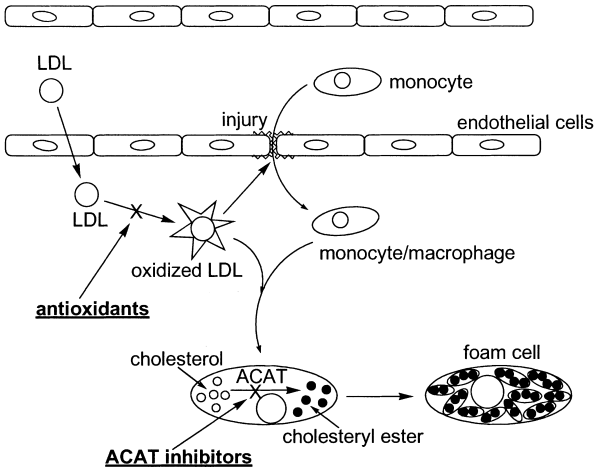


Figure 1. Hypothetical mechanism of the foam cell formation.

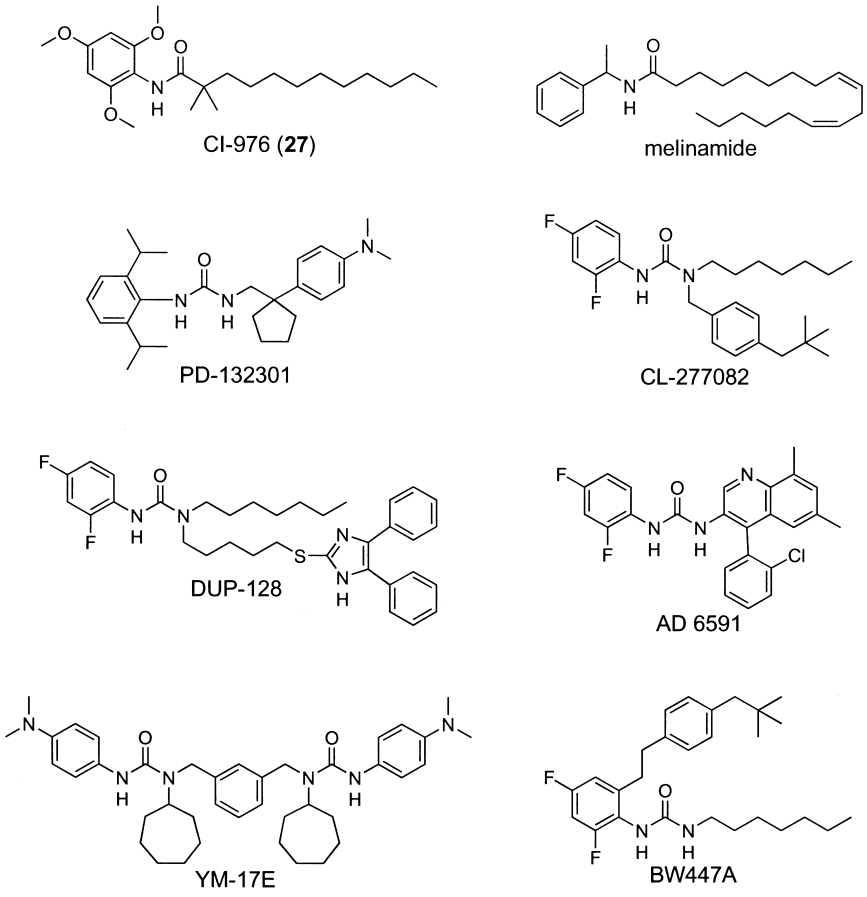


Figure 2. ACAT inhibitors.

hydroxyl group, and no carboxylate in the molecule. In the course of our random screening programs searching for useful biological effects of these hydroxyphenylureas, compound **15** was found to lower the amount of plasma cholesterol in rats. Because the hydroxyphenylurea **15** has a phenylurea moiety which is common to some ACAT inhibitors,[7,8] we assumed that it exhibited the biological activity by inhibiting ACAT in the intestine. Thus, we examined the inhibitory activity of the hydroxyphenylurea **15** against ACAT and found it to show moderate inhibition (14% inhibition at 1 μM). Then we obtained various hydroxyphenylurea derivatives and evaluated their ACAT inhibitory activities in order to get a dual inhibitor against both ACAT activity and LDL oxidation, which could be a promising drug for hypercholesterolemia and atherosclerosis. In this paper, we report the lead generation and optimization of hydroxyphenylureas as dual inhibitors against ACAT and LDL oxidation, and discuss their structure–activity relationships.

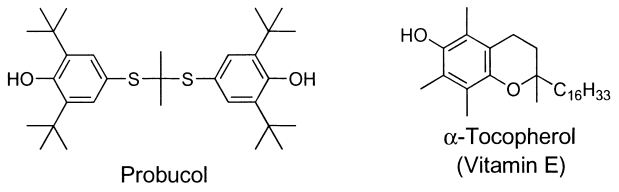


Figure 3. Antioxidants.

Chemistry

Our principles of molecular design of dual inhibitors against ACAT and LDL oxidation are shown in Figure 4. First, in order to maintain antioxidative activity, we selected the 3-*tert*-butyl-2-hydroxy-5-methoxyaniline group as the optimized substructure at the phenol ring (A-ring) position. In the previous article, we showed that it was able to modify hydroxyphenylureas around *N*-substituents on the opposite side of phenol ring (B-ring) part without any decrease in antioxidative activity.[11] Consequently, various substituents were introduced in order to obtain compounds with strong ACAT inhibitory potency. The syntheses of compounds **1**–**5** in Table 1 have been reported in the previous paper. The derivatives **6**–**26** were synthesized according to the procedure in Scheme 1. Secondary amines **30** were prepared by alkylation of **28**, followed by removal of the protecting group. Then, the *ortho*-hydroxyaniline **31** with the protected hydroxy group and the secondary amines **30** were combined by triphosgene to give the methoxymethoxyphenylureas **32**. By removing the protecting group by treatment with methanolic hydrogen chloride, trisubstituted ureas **6**–**26** were obtained in satisfactory yields. More detailed information is shown in the Experimental.

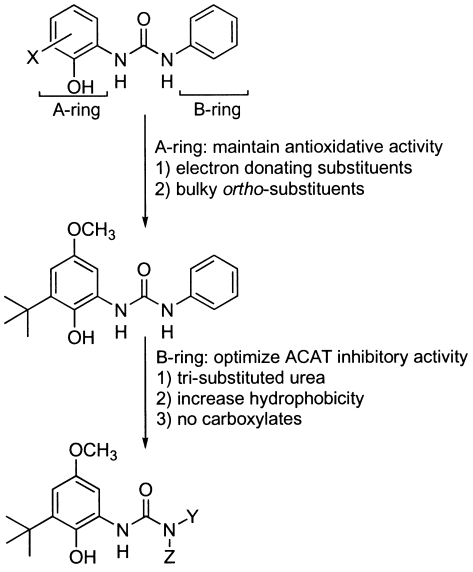
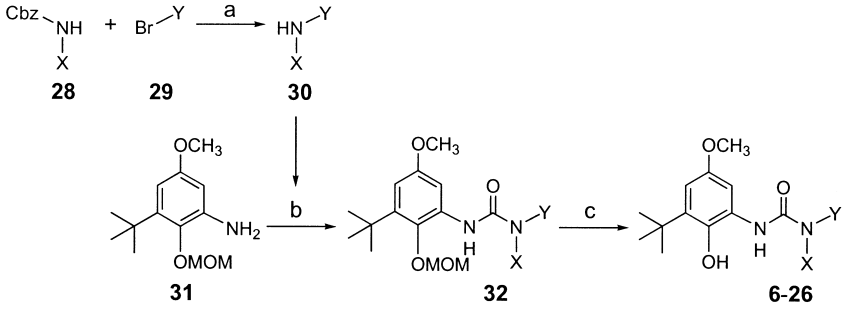


Figure 4. Principles of molecular design.

Results and Discussion

Inhibitory activity against ACAT

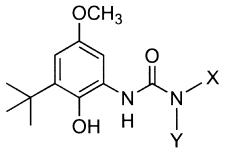
The ACAT inhibitory activities were shown by the decrease percentage (% inhibition) of the cholesteryl ester production by ACAT at 1 μM dosing. Compounds with strong inhibitory activity against ACAT had high percentage values. The inhibitory potencies of the 1,3-disubstituted ureas were very weak except for **1**, the logP value of which was comparatively high (4.48). CI-976 (**27**),[12] a well-known ACAT inhibitor, has also high logP value (6.17). The disubstituted ureas **2**–**8** might show low inhibitory activities because of their low hydrophobicity. In order to examine structural effects on ACAT inhibition, we analyzed quantitative structure–activity relationship (QSAR) of both di- and tri-substituted ureas. The ACAT inhibition potencies were transformed into their logit {logit = log[% inhibition/(100 − % inhibition)]}.[13] By this transformation, the value of % inhibition could correspond to the amount of compounds interacting with the enzymes. The ratio of % inhibition to (100 − % inhibition) could be proportional to the binding constants of compounds with the enzymes, and it was shown that logit could be successfully applicable as the indices of biological activity in QSAR studies.[13–15] Compounds with strong inhibitory potency had high logit values and low 50% inhibition concentration values (IC_{50}). The % inhibition value and logit of every compound, and moreover the IC_{50} values of rather high potent compounds, are shown in Table 2, as well as every compound's physicochemical parameters for QSAR analysis. The logP value, which was calculated based on the summation of hydrophobicity of substituents and the electronic and steric effects between substituents,[11] indicated the hydrophobicity of the whole molecule. The I_{TRI} and I_{COOH} terms were indicator variables, which take a value of unity for tri-substituted ureas and carboxylic acids, respectively, and zero for others. By the correlation analysis of these parameters, eq 1 was formulated.



Scheme 1. (a) (1) NaH, DMF, (2) H_2, Pd-C, EtOH; (b) triphosgene, Et_3N, CH_2Cl_2; (c) concd HCl, MeOH.

Table 1. Structures and chemical data of hydroxyphenylureas

Substituents



No.	X	Y	Formula	mp (°C)	Anal.[a]
1[b]	2,6-Diisopropylphenyl	H	$C_{24}H_{34}N_2O_3$	193–195	CHN
2[b]	2,4-Difluorophenyl	H	$C_{18}H_{20}N_2O_3F_2$	153–154	CHN
3[b]	Cyclohexyl	H	$C_{18}H_{28}N_2O_3$	147–148	CHN
4[b]	Anilino	H	$C_{18}H_{28}N_3O_3$	160–162	CHN
5[b]	3-Pyridylmethyl	H	$C_{18}H_{23}N_3O_3{\cdot}HCl$	165–167	CHN
6	$(CH_2)_3CO_2C_2H_5$	H	$C_{18}H_{28}N_2O_5$	69–71	CHN
7	$C(CH_3)(CH_2OH)_2$	H	$C_{16}H_{26}N_2O_5$	137–139	CHN
8	$C(CH_2OH)_3$	H	$C_{16}H_{26}N_2O_6$	169–170	CHN
9	$(CH_2)_2CO_2C_2H_5$	C_6H_5	$C_{23}H_{30}N_2O_5$	68–70	CHN
10	$(CH_2)_3CO_2C_2H_5$	C_6H_5	$C_{24}H_{32}N_2O_5{\cdot}1/4CHCl_3$	Syrup	CHN
11	$(CH_2)_3CONHC_2H_5$	C_6H_5	$C_{24}H_{33}N_3O_4$	156–158	CHN
12	$(CH_2)_3CON(C_2H_5)_2$	C_6H_5	$C_{26}H_{37}N_3O_4$	131–133	CHN
13	$(CH_2)_3CO$-Morpholino	C_6H_5	$C_{26}H_{35}N_3O_5$	129–131	CHN
14	$(CH_2)_3CONHCH_2CH(OH)CH_2OH$	C_6H_5	$C_{25}H_{35}N_3O_6$	102–105	CHN
15	$(CH_2)_3CO_2H$	C_6H_5	$C_{22}H_{28}N_2O_5$	127–128	CHN
16	$(CH_2)_4CO_2H$	C_6H_5	$C_{23}H_{30}N_2O_5$	132–133	CHN
17	$(CH_2)_6CO_2H$	C_6H_5	$C_{25}H_{34}N_2O_5$	86–89	CHN
18	$(CH_2)_3CO_2C_2H_5$	4-Dimethylaminophenyl	$C_{26}H_{37}N_3O_5$	77–79	CHN
19	$(CH_2)_3CO_2C_2H_5$	2,4-Difluorophenyl	$C_{24}H_{30}N_2O_5F_2$	115–116	CHNF
20	$(CH_2)_3CO_2C_2H_5$	1-Naphthyl	$C_{28}H_{34}N_2O_5$	104–105	CHN
21	$(CH_2)_3CO_2C_2H_5$	Cyclohexyl	$C_{24}H_{38}N_2O_5$	113–115	CHN
22	$(CH_2)_3CO_2C_2H_5$	Cycloheptyl	$C_{25}H_{40}N_2O_5$	99–101	CHN
23	Cyclohexyl	$CH_2C_6H_5$	$C_{25}H_{34}N_2O_3$	140–141	CHN
24	Cycloheptyl	4-Dimethylaminophenyl	$C_{27}H_{39}N_3O_3{\cdot}HCl{\cdot}C_2H_5OH$	140–142	CHNCl
25	$CH_2C_6H_5$	4-Dimethylaminophenyl	$C_{27}H_{33}N_3O_3{\cdot}HCl$	183–185	CHNCl
26	2-Cyclohexylethyl	4-Dimethylaminophenyl	$C_{28}H_{41}N_3O_3{\cdot}1/4H_2O$	124–125	CHN

[a]Deviation between calculated and observed values were less than 0.4%.
[b]Reported in our previous paper, ref 11.

$$\begin{aligned}\text{logit} &= 0.30\,(\pm 0.11)\ \text{logP} + 0.62\,(\pm 0.39)\ I_{TRI} \\ &\quad - 1.28\,(\pm 0.51)\ I_{COOH} - 0.98\,(\pm 0.38) \qquad (1)\\ n &= 26,\ s = 0.39,\ r = 0.90,\ F_{3,22} = 31.90\end{aligned}$$

In this equation, n is the number of tested compounds, s the standard deviation, r the correlation coefficient, and F the ratio between regression and residual variances. The figures in parentheses are the 95% confidence intervals.

The coefficient of the logP term was positive, indicating that compounds with higher hydrophobicity showed stronger inhibitory activities against ACAT. In the assay system used in this study, ACAT was obtained as the hydrophobic microsome fraction from the homogenate of rabbit intestinal mucosal scrapings by sequential centrifugation. Cholesterol, which is highly hydrophobic (logP = 9.52 estimated by CLOGP software[16,17]), is acylated by ACAT under a hydrophobic environment like microsome fractions. The hydrophobic character of hydroxyphenylurea ACAT inhibitors is thought to be necessary so that inhibitor molecules could approach the enzyme in the hydrophobic micrsomes.

The coefficient of the I_{TRI} term was positive, and it was revealed that tri-substituted ureas showed about four times stronger activity than di-substituted ones on the average. DeVries et al. reported the similar results: in the case of their ACAT inhibitors having phenylurea moiety, tri-substituted ureas inhibited the ACAT activity stronger than did the di-substituted derivatives.[18] The effect of the substitution pattern shown quantitatively by I_{TRI} term coincides with the results by DeVries et al. However, it remains unclear at the molecular level why the number of substituents can affect the affinity between the enzyme and the inhibitor.

The coefficient of the I_{COOH} term in eq 1 was negative. The hydroxyphenylurea with a carboxylic acid moiety would exhibit 20 times lower activity than was expected. The negative charge or the local hydrophilicity of carboxylate might prevent the inhibitor from interacting with the enzyme.

Inhibition of the foam cell formation

Compounds with strong inhibitory activities against ACAT were examined for the inhibitory potency of the foam cell formation of macrophages. Compound **26** inhibited the transformation of macrophages to foam cells stronger than CI-976. Compound **12** and **24** were as potent as CI-976. They had the proper hydrophobic character (their logP values were more than 3 as shown in Table 2), and could permeate into macrophage cells. Compounds with weak inhibitory activity against the foam cell formation had weak ACAT inhibitory activity, which might indicate that the foam cell formation of macrophages was mainly controlled by ACAT activity.

Table 2. Biological activities and physicochemical parameters of hydroxyphynylureas

No.	ACAT Inhibitory activity							Physicochemical parameters		
		Logit[a]				Foam cell formation inhibition	LDL oxidation inhibition			
	% Inhibition at 1 μM	Obsd.	Calcd[b]	Dev.	IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)	logP[c]	I_{TRI}[d]	I_{COOH}[e]
1	92	1.06	0.39	0.67	0.06	4.4	0.09	4.48	0	0
2	42	−0.14	0.10	−0.24	—	—	—	3.55	0	0
3	43	−0.12	0.10	−0.22	—	—	—	3.56	0	0
4	42	−0.14	−0.12	−0.02	—	—	—	2.84	0	0
5	23	−0.52	−0.45	−0.07	—	—	—	1.80	0	0
6	19	−0.63	−0.36	−0.27	—	—	—	2.08	0	0
7	7	−1.12	−0.87	−0.25	—	—	—	0.46	0	0
8	13	−0.83	−1.23	0.40	—	—	—	−0.69	0	0
9	62	0.21	0.80	−0.59	—	—	—	3.82	1	0
10	96	1.38	0.70	0.68	—	> 10	—	3.48	1	0
11	83	0.69	0.30	0.39	—	> 10	—	2.22	1	0
12	85	0.75	0.56	0.19	0.08	1.1	0.11	3.03	1	0
13	84	0.72	0.30	0.42	0.27	4.4	0.20	2.20	1	0
14	22	−0.55	−0.22	−0.33	—	—	—	0.54	1	0
15	14	−0.79	−0.88	0.09	—	—	—	2.54	1	1
16	4	−1.38	−0.72	−0.66	—	—	—	3.07	1	1
17	60	0.18	−0.39	0.57	—	—	—	4.12	1	1
18	80	0.60	0.76	−0.16	0.20	> 10	—	3.68	1	0
19	76	0.50	0.91	−0.41	—	—	—	4.16	1	0
20	92	1.06	1.07	−0.01	0.05	7.6	0.06	4.66	1	0
21	84	0.72	0.78	−0.06	0.26	> 10	—	3.74	1	0
22	88	0.87	0.96	−0.09	0.17	> 10	—	4.30	1	0
23	96	1.38	1.22	0.16	0.04	3.9	0.12	5.13	1	0
24	97	1.51	1.47	0.04	0.05	1.5	0.22	5.96	1	0
25	90	0.95	1.19	−0.24	0.10	3.0	0.12	5.06	1	0
26	95	1.28	1.55	−0.27	0.07	0.44	0.79	6.39	1	0
27	87	0.83	—	—	0.09	1.4	—	6.17	—	–

[a]logit = log{% inhibition/(100 − % inhibition)}.
[b]Calculated by eq 1.
[c]Calculated by our method, ref 11.
[d]Indicator variable for trisubstituted ureas.
[e]Indicator variable for carboxylic acids.

LDL oxidation inhibition

All compounds in this report have a 3-*tert*-butyl-2-hydroxy-5-methoxyphenylurea moiety which was optimized for the strong antioxidative activity. Therefore, those hydroxyphenylureas were expected to inhibit LDL oxidation. Compouds with strong inhibitory activities against the foam cell formation (**1**, **13**, **14**, **20**, and **23**–**26**) were examined for their LDL oxidation inhibitory potency. As we expected, all of the eight derivatives inhibited the endothelial cell-induced oxidation of LDL at the submicromolar level. Thus, we obtained dual inhibitors against ACAT and LDL oxidation by the rational structural evolution of the hydroxyphenylurea antioxidant.

Conclusion

We obtained hydroxyphenylureas with strong inhibitory activities against both ACAT and LDL oxidation. According to the result of QSAR analysis, it was revealed that the ACAT inhibition depended on the hydrophobicity of the whole molecule, the number of substituents at the urea nitrogens, and the existence of carboxylates. Some of these compounds exhibited comparable ACAT inhibition with CI-976, a well-known ACAT inhibitors. These compounds were also potent in the inhibition of the foam cell formation. Owing to the characteristic phenolic substructure, hydroxyphenylureas could potently inhibit LDL oxidation. These hydroxyphenylureas were dual inhibitors of ACAT and LDL oxidation, which are important for the treatment of atherosclerosis. Further improvement and development of hydroxyphenylureas are now being undertaken.[19,20]

Experimental

Inhibitory activities of ACAT and the foam cell formation of macrophages

ACAT enzyme was prepared from the intestines of male Japanese White rabbits (Oriental Yeast, Japan). Intestinal mucosal scrapings were suspended in 0.25 M sucrose solution, and the suspension was homogenized in 0.154 M potassium phosphate buffer (pH 6.2) with a Teflon Potter homogenizer (Iuchi, Japan). The microsomes were obtained from the mucosal homogenate by sequential centrifugation, and used for ACAT assay. ACAT activity was determined by measuring the incorporation of [^{14}C]oleoyl-CoA into cholesteryl oleate according to the methods of Heider et al.[6]

The foam cell formation was evaluated by measuring the incorporation of [^{14}C]oleic acid into cholesteryl ester in the whole cells by the method of Tabas et al.[21] The murine macrophage cell line J774A.1 cells were obtained from America Type Tissue Culture Collection (ATCC; Camden, NJ, USA), grown in a 6-well plate (Iwaki Glass, Japan), maintained in Dulbecco's modified Eagle's medium (DMEM; Nissui Pharmaceutical Co., Ltd, Tokyo), and supplemented with 10% fetal bovine serum (FBS; CSL Ltd, Rarville, Australia), penicillin (100 IU/mL), streptomycin (100 μg/mL), and glutamine (292 μg/mL) at 37 °C in a 5% CO_2 humidified atmosphere. Monolayers of J774A.1 cells and mouse peritoneal macrophages were preincubated for 2 h in DMEM containing 10% lipoprotein deficient serum and then incubated for 18 h in the presence of 30 μg/mL of oxidized LDL with [^{14}C]oleate-albumin complex, and the lipid extracts of these cells were assayed for cholesteryl [^{14}C]oleate. Tested compounds were added with [^{14}C]oleate-albumin complex.

Inhibition against LDL oxidation

The effects of hydroxyphenylureas on the endothelial cell-induced oxidation of LDL were assessed by the increase in the thiobarbituric acid reactive substance (TBARS) production.[22–24] Bovine aortic endothelial cells were isolated from the aorta with a scrape and cultured in Eagle's minimum essential medium (Nissui Pharmaceutical Co., Ltd, Tokyo) a supplemented with 10% FBS, penicillin (100 IU/mL) and streptomycin (100 μg/mL) at 37 °C in a 5% CO_2 humidified atmosphere. The endothelial cell-induced oxidation of LDL was achieved by incubating 100 μg/mL protein of LDL for 18 h at 37 °C in the presence of confluent endothelial cells in serum-free Ham's F10 medium. Tested compounds were dissolved in DMSO and added at the indicated concentration simultaneously with the LDL. The amounts of TBARS were calculated as nanomole equivalents of malondialdehyde.

Synthesis

Melting points were determined on Yamato melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1640 IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AC-200 (200 MHz) spectrometer with tetramethylsilane as the internal standard. Mass spectra were recorded on a Hitachi M-2000A spectrometer. Elemental analyses were performed on a Perkin–Elmer 2400 II. Column chromatography was accomplished by using Kieselgel 60 (230–400 mesh, E. Merck) with the indicated solvent system.

The procedures of syntheses and the spectral data of compounds **1**–**5** were described in our previous article.[11]

Preparation of disubstituted amines 30

Ethyl 4-(1-naphthylamino)butyrate (30; X = $(CH_2)_3CO_2C_2H_5$, Y = 1-naphthyl). To a suspension of NaH (3.17 g, 79.3 mmol, 60% mineral oil suspended) in *N*,*N*-dimethylformamide (DMF, 100 mL) was added dropwise *N*-benzyloxycarbonyl-*N*-(1-naphthyl)amine (**28**, 20.0 g, 72.1 mmol) at 0 °C under nitrogen atmosphere and the mixture was stirred for 90 min at rt. To the suspension was added slowly a solution of ethyl 4-bromobutyrate (**29**, 14.8 g, 75.7 mmol) in DMF (50 mL) at 0 °C under nitrogen atmosphere and the reaction mixture was stirred for 90 min at rt. After the mixture was concentrated in vacuo, the residue was extracted with ethyl acetate (AcOEt), the organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified on silica gel chromatography using hexane/AcOEt (3:1) to afford ethyl 4-[*N*-benzyloxycarbonyl-*N*-(1-naphthyl)amino]butyrate (25.5 g, 90%): syrup; IR (film) 2981, 1706, 1597 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 1.17 (t, 3H, J = 7 Hz, CH_3), 1.93 (m, 2H, CH_2), 2.29–2.36 (m, 2H, CH_2), 4.00–4.11 (m, 4H, CH_2), 5.03 (s, 2H, CH_2), 6.95–7.52 (m, 9H, ArH, NapH-3, -4, -6, and -7), 7.73–7.89 (m, 3H, NapH-2, -5, and -8); EIMS m/z 391 (M^+). A mixture of ethyl 4-[*N*-benzyloxycarbonyl-*N*-(1-naphthyl)amino]butyrate (25.5 g, 65.1 mmol), 10% palladium on carbon (5.0 g) and EtOH (400 mL) was subjected to hydrogenation using Parr apparatus (H_2, 3.5 atm) for 6 h at rt. After removal of catalyst by filtration, the filtrate was concentrated in vacuo. The residue was purified on silica gel chromatography using hexane/AcOEt (3:1) to afford **30** (X = $(CH_2)_3CO_2C_2H_5$, Y = 1-naphthyl, 11.1 g, 66%): syrup; IR (film) 2981, 1732, 1583 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 1.24 (t, 3H, J = 7 Hz, CH_3), 2.04–2.17 (m, 2H, CH_2), 2.51 (t, 2H, J = 7 Hz, CH_2), 3.33 (t, 2H, J = 6.6 Hz, CH_2), 4.14 (q, 2H, J = 7 Hz, CH_2), 6.58 (d, 1H, J = 7.2 Hz, NH), 7.19–7.51 (m, 4H, ArH, NapH-3, -4, -6, and -7), 7.75–7.87 (m, 3H, NapH-2, -5, and -8); EIMS m/z 257 (M^+).

In the same manner, the other disubstituted amines were obtained.

Urea formation and removal of the methoxymethyl protecting group

3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-(3-ethoxycarbonylpropyl)-1-(1-naphthyl)urea (20). To a solution of triphosgene (2.63 g) in CH_2Cl_2 (150 mL), the solution of 3-*tert*-butyl-5-methoxy-2-methoxymethoxyaniline **31** (6.1 g, 25.3 mmol) and triethylamine (10.6 mL) in CH_2Cl_2 (100 mL) were added dropwise at −78 °C and the reaction mixture was warmed up to rt for 1 h. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (150 mL) and the solution of ethyl 4-(1-naphthylamino)-butyrate (**30**; X = $(CH_2)_3CO_2C_2H_5$, Y = 1-naphthyl, 6.5 g, 25.3 mmol) and triethylamine (5.3 mL) in CH_2Cl_2 (100 mL) was added dropwise at rt. After stirring at the same temperature for 10 h, the reaction mixture was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo, and the residue was chromatographed on silica gel using hexane/AcOEt (3:1) to yield 3.52 g (27%) of 3-(3-*tert*-butyl-5-methoxy-2-methoxymethoxyphenyl)-1-(3-ethoxycarbonylpropyl)-1-(1-naphthyl)urea (**32**; X = $(CH_2)_3CO_2C_2H_5$, Y = 1-naphthyl): syrup; IR (film) 2957, 1736, 1677, 1592 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 1.77 (t, 3H, J = 7 Hz, CH_3), 1.22 (s, 9H, CH_3), 1.93–2.04 (m, 2H, CH_2), 2.27–2.47 (m, 2H, CH_2), 2.63 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 4.01–4.44 (m, 6H, CH_2), 6.50 (d, 1H,

$J=3$ Hz, ArH), 7.12 (s, 1H, NH), 7.54–7.58 (m, 4H, NapH-3, -4, -6, and -7), 7.83 (d, 1H, $J=3$ Hz, ArH), 7.93–7.98 (m, 3H, NapH-2, -5, and -8); EIMS m/z 522 (M^+). To a solution of **32** (R = 3-C$(CH_3)_3$-5-OCH_3, X = $(CH_2)_3$ $CO_2C_2H_5$, Y = 1-naphthyl, 3.52 g, 6.74 mmol) in MeOH (30 mL) was added concd HCl (3.0 mL) and the mixture was stirred at rt for 1 h. The resulting mixture was concentrated in vacuo and the crude crystals were recrystallized from AcOEt-diisopropylether to give **20** (940 mg, 29%): IR (KBr) 3350, 2951, 1732 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.21 (t, 3H, $J=7$ Hz, CH_3), 1.40 (s, 9H, CH_3), 1.96–2.03 (m, 2H, CH_2), 2.36–2.45 (m, 2H, CH_2), 3.46–3.53 (m, 1H, CH_2), 3.57 (s, 3H, CH_3), 4.09 (q, 2H, $J=7$ Hz, CH_2), 4.16–4.30 (m, 1H, CH_2), 5.77 (d, 1H, $J=3$ Hz, ArH), 6.00 (s, 1H, NH or OH), 6.66 (d, 1H, $J=3$ Hz, ArH), 7.56–7.67 (m, 4H, NapH-3, -4, -6, and -7), 7.90–7.99 (m, 3H, NapH-2, -5, and -8), 8.75 (s, 1H, NH or OH); EIMS m/z 478 (M^+). Anal. calcd for $C_{28}H_{34}N_2O_5$: C 70.27, H 7.16, N 5.85. Found: C 69.98, H 7.16, N 5.73.

In the same manner, the following compounds were obtained.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-(3-ethoxycarbonylpropyl)urea (6). IR (KBr) 3386, 2954, 1735, 1578 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.25 (t, 3H, $J=7$ Hz, CH_3), 1.41 (s, 9H, CH_3), 1.77—1.91 (m, 2H, CH_2), 2.37 (t, 2H, $J=7$ Hz, CH_2), 3.22–3.32 (dd, 2H, $J=6.1$, 6.7 Hz, CH_2), 3.72 (s, 3H, CH_3), 4.07–4.18 (q, 2H, $J=7$ Hz, CH_2), 5.30 (m, 1H, NH or OH), 6.40 (d, 1H, $J=3$ Hz, ArH), 6.76 (d, 1H, $J=3$ Hz, ArH), 6.76 (s, 1H, NH or OH), 8.15 (s, 1H, NH or OH); EIMS m/z 352 (M^+). Anal. calcd for $C_{18}H_{28}N_2O_5$: C 61.35, H 8.01, N 7.95. Found: C 61.50, H 8.14, N 8.13.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-[1,1-bis(hydroxymethyl)ethyl]urea (7). IR (KBr) 3384, 2949, 1651, 1558 cm^{-1}; ^1H NMR (δ in $CDCl_3$ + DMSO-d_6) 1.24 (s, 3H, CH_3), 1.41 (s, 9H, CH_3), 2.32 (br, 1H, OH), 3.64–3.78 (m, 4H, CH_2), 3.72 (s, 3H, CH_3), 4.34 (br, 1H, OH), 6.34 (s, 1H, NH or OH), 6.40 (d, 1H, $J=3$ Hz, ArH), 6.68 (d, 1H, $J=3$ Hz, ArH), 8.01 (s, 1H, NH or OH), 8.84 (s, 1H, NH or OH); SIMS m/z 327 $(M+H)^+$. Anal. calcd for $C_{16}H_{26}N_2O_5$: C 58.88, H 8.03, N 8.58. Found: C 58.73, H 8.13, N 8.71.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-[1,1-bis(hydroxymethyl)-2-hydroxyethyl]urea (8). IR (KBr) 3349, 2955, 1732, 1567 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 1.34 (s, 9H, CH_3), 3.59 (d, 6H, $J=5.5$ Hz, CH_2), 3.64 (s, 3H, CH_3), 4.73 (t, 3H, $J=5.5$ Hz, OH), 6.36 (s, 1H, NH or OH), 6.47 (d, 1H, $J=3$ Hz, ArH), 6.57 (d, 1H, $J=3$ Hz, ArH), 8.62 (s, 1H, NH or OH), 9.23 (s, 1H, NH or OH); SIMS m/z 343 $(M+H)^+$. Anal. calcd for $C_{16}H_{26}N_2O_6$: C 56.13, H 7.66, N 8.18. Found: C 56.08, H 7.71, N 8.20.

3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-(2-ethoxycarbonylethyl)-1-phenylurea (9). IR (KBr) 3358, 2954, 1729 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.21 (t, 3H, $J=7$ Hz, CH_3), 1.41 (s, 9H, CH_3), 2.66 (t, 2H, $J=7.2$ Hz, CH_2), 3.67 (s, 3H, CH_3), 4.02–4.13 (q, 2H, $J=7$ Hz, CH_2), 4.02–4.09 (t, 2H, $J=7.2$ Hz, CH_2), 6.06 (d, 1H, $J=3$ Hz, ArH), 6.22 (s, 1H, NH or OH), 6.70 (d, 1H, $J=3$ Hz, ArH), 7.34–7.57 (m, 5H, ArH), 8.55 (s, 1H, NH or OH); EIMS m/z 414 (M^+). Anal. calcd for $C_{23}H_{30}N_2O_5$: C 66.65, H 7.30, N 6.76. Found: C 66.53, H 7.28, N 6.69.

3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-(3-ethoxycarbonylpropyl) - 1-phenylurea (10). IR (film) 2955, 1732 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.22 (t, 3H, $J=7.2$ Hz, CH_3), 1.41 (s, 9H, CH_3), 1.84–1.98 (m, 2H, CH_2), 2.38 (t, 2H, $J=7.4$ Hz, CH_2), 3.66 (s, 3H, CH_3), 3.79 (t, 2H, $J=7.4$ Hz, CH_2), 4.05–4.16 (q, 2H, $J=7.2$ Hz, CH_2), 6.07 (d, 1H, $J=3$ Hz, ArH), 6.26 (s, 1H, NH or OH), 6.70 (d, 1H, $J=3$ Hz, ArH), 7.34–7.56 (m, 5H, ArH), 8.71 (s, 1H, NH or OH); EIMS m/z 428 (M^+). Anal. calcd for $C_{24}H_{32}N_2O_5 \cdot 1/4CHCl_3$: C 63.54, H 7.09, N 6.11. Found: C 63.38, H 7.11, N 6.04.

4-[3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-phenylureido]butanoic acid (15). IR (KBr) 2955, 1734 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.41 (s, 9H, CH_3), 1.84–1.98 (m, 2H, CH_2), 2.44 (t, 2H, $J=7.4$ Hz, CH_2), 3.67 (s, 3H, CH_3), 3.81 (t, 2H, $J=7.2$ Hz, CH_2), 6.08 (d, 1H, $J=3$ Hz, ArH), 6.17 (s, 1H, NH or OH), 6.70 (d, 1H, $J=3$ Hz, ArH), 7.34–7.57 (m, 5H, ArH), 8.50 (s, 1H, NH or OH); SIMS m/z 401 $(M+H)^+$. Anal. calcd for $C_{22}H_{28}N_2O_5$: C 65.98, H 7.05, N 7.00. Found: C 65.95, H 6.97, N 6.79.

5-[3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-phenylureido]pentanoic acid (16). IR (KBr) 2955, 1714 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.41 (s, 9H, CH_3), 1.64–1.68 (m, 4H, CH_2), 2.38 (m, 2H, CH_2), 3.67 (s, 3H, CH_3), 3.74–3.81 (m, 2H, CH_2), 6.03 (d, 1H, $J=3$ Hz, ArH), 6.08 (s, 1H, NH or OH), 6.70 (d, 1H, $J=3$ Hz, ArH), 7.34–7.57 (m, 5H, ArH), 8.68 (s, 1H, NH or OH); SIMS m/z 415 $(M+H)^+$. Anal. calcd for $C_{23}H_{30}N_2O_5$: C 66.65, H 7.30, N 6.76. Found: C 66.99, H 7.36, N 6.63.

7-[3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-phenylureido]heptanoic acid (17). IR (KBr) 3415, 2940, 1705 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.34–1.61 (m, 8H, CH_2), 1.41 (s, 9H, CH_3), 2.32 (t, 2H, $J=7.4$ Hz, CH_2), 3.66 (s, 3H, CH_3), 3.73 (t, 2H, $J=7.2$ Hz, CH_2), 6.03 (d, 1H, $J=3$ Hz, ArH), 6.07 (s, 1H, NH or OH), 6.70 (d, 1H, $J=3$ Hz, ArH), 7.33–7.56 (m, 5H, ArH), 8.77 (s, 1H, NH or OH); EIMS m/z 442 (M^+). Anal. calcd for $C_{25}H_{34}N_2O_5$: C 67.85, H 7.74, N 6.33. Found: C 67.76, H 7.76, N 6.13.

3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-(4-*N*, *N*-dimethylaminophenyl)-1-(3-ethoxycarbonylpropyl)urea (18). IR (KBr) 3336, 2944, 1724 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.23 (t, 3H, $J=7.2$ Hz, CH_3), 1.41 (s, 9H, CH_3), 1.82–1.97 (m, 2H, CH_2), 2.37 (t, 2H, $J=7.4$ Hz, CH_2), 3.02 (s, 6H, CH_3), 3.67 (s, 3H, CH_3), 3.72 (t, 2H, $J=7.4$ Hz, CH_2), 4.05–4.16 (q, 2H, $J=7.2$ Hz, CH_2), 6.02 (d, 1H, $J=3$ Hz, ArH), 6.22 (s, 1H, NH or OH), 6.69 (d, 1H, $J=3$ Hz, ArH), 6.78 (d, 2H, $J=9.2$ Hz, ArH), 7.18 (d, 2H, $J=9.2$ Hz, ArH), 9.03 (s, 1H, NH or OH); EIMS m/z 471 (M^+). Anal. calcd for $C_{26}H_{37}N_3O_5$: C 66.22, H 7.91, N 8.91. Found: C 66.18, H 7.92, N 8.79.

3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-(3-ethoxycarbonylpropyl)-1-(2,4-difluorophenyl)urea (19). IR (KBr) 3324, 2952, 1732 cm^{-1}; ^1H NMR (δ in $CDCl_3$)

1.24 (t, 3H, $J=7$ Hz, CH_3), 1.41 (s, 9H, CH_3), 1.85–1.99 (m, 2H, CH_2), 2.40 (t, 2H, $J=7$ Hz, CH_2), 3.71 (s, 3H, CH_3), 3.71–3.77 (m, 2H, CH_2), 4.08–4.18 (q, 2H, $J=7$ Hz, CH_2), 6.25 (d, 1H, $J=3$ Hz, ArH), 6.59 (br, 1H, NH or OH), 6.73 (d, 1H, $J=3$ Hz, ArH), 6.98–7.08 (m, 2H, ArH), 7.34–7.45 (m, 1H, ArH), 8.24 (s, 1H, NH or OH); EIMS m/z 464 (M^+). Anal. calcd for $C_{24}H_{30}N_2O_5F_2$: C 62.06, H 6.51, N 6.03, F 8.18. Found: C 62.14, H 6.51, N 6.02, F 8.02.

3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-cyclohexyl-1-(3-ethoxycarbonylpropyl) urea (21). IR (KBr) 3341, 2936, 1712 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.27 (t, 3H, $J=7.2$ Hz, CH_3), 1.43 (s, 9H, CH_3), 1.12–2.00 (m, 12H, CH_2), 2.39–2.45 (m, 2H, CH_2), 3.17–3.25 (m, 2H, CH_2), 3.74 (s, 3H, CH_3), 4.12–4.23 (q, 2H, $J=7.2$ Hz, CH_2), 4.12–4.23 (m, 1H, CH), 6.58 (d, 1H, $J=3$ Hz, ArH), 6.74 (d, 1H, $J=3$ Hz, ArH), 8.07 (s, 1H, NH or OH), 9.35 (s, 1H, NH or OH); SIMS m/z 435 $(M+H)^+$. Anal. calcd for $C_{24}H_{38}N_2O_5$: C 66.33, H 8.81, N 6.45. Found: C 66.29, H 8.82, N 6.34.

3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-cycloheptyl-1-(3-ethoxycarbonylpropyl) urea (22). IR (KBr) 3347, 2928, 1712 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.27 (t, 3H, $J=7.2$ Hz, CH_3), 1.43 (s, 9H, CH_3), 1.43–2.04 (m, 14H, CH_2), 2.39–2.45 (m, 2H, CH_2), 3.17–3.25 (m, 2H, CH_2), 3.74 (s, 3H, CH_3), 4.12–4.23 (q, 2H, $J=7.2$ Hz, CH_2), 4.33 (m, 1H, CH), 6.57 (d, 1H, $J=3$ Hz, ArH), 6.74 (d, 1H, $J=3$ Hz, ArH), 8.04 (s, 1H, NH or OH), 9.38 (s, 1H, NH or OH); EIMS m/z 448 (M^+). Anal. calcd for $C_{25}H_{40}N_2O_5$: C 66.94, H 8.99, N 6.25. Found: C 67.07, H 9.03, N 6.19.

3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-benzyl-1-cyclohexylurea (23). IR (KBr) 3375, 2939, 1621 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.39 (s, 9H, CH_3), 1.39–1.88 (m, 10H, CH_2), 3.58 (s, 3H, CH_3), 4.38 (m, 1H, CH), 4.52 (s, 2H, CH_2), 5.57 (d, 1H, $J=3$ Hz, ArH), 6.14 (s, 1H, NH or OH), 6.66 (d, 1H, $J=3$ Hz, ArH), 7.34–7.47 (m, 5H, ArH), 8.90 (s, 1H, NH or OH); SIMS m/z 411 $(M+H)^+$. Anal. calcd for $C_{25}H_{34}N_2O_3$: C 73.14, H 8.35, N 6.82. Found: C 73.37, H 8.42, N 6.82.

3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-cycloheptyl-1-(4-*N*,*N*-dimethylaminophenyl)urea (24). IR (KBr) 3397, 2927, 2430, 1657 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.39 (s, 9H, CH_3), 1.39–2.01 (m, 12H, CH_2), 3.18 (s, 6H, CH_3), 3.68 (s, 3H, CH_3), 4.53 (m, 1H, CH), 6.01 (s, 1H, NH or OH), 6.25 (d, 1H, $J=2.4$ Hz, ArH), 6.68 (d, 1H, $J=2.4$ Hz, ArH), 7.47 (d, 2H, $J=8$ Hz, ArH), 7.87 (d, 2H, $J=8$ Hz, ArH); SIMS m/z 454 $(M+H)^+$. Anal. calcd for $C_{27}H_{39}N_3O_3{\cdot}HCl{\cdot}C_2H_5OH$: C 64.97, H 8.65, N 7.84, Cl 6.61. Found: C 64.76, H 8.66, N 7.90, Cl 6.94.

3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-benzyl-1-(4-*N*,*N*-dimethylaminophenyl)urea (25). IR (KBr) 3385, 3059, 2376, 1607 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 1.31 (s, 9H, CH_3), 3.02 (s, 6H, CH_3), 3.65 (s, 3H, CH_3), 4.93 (s, 2H, CH_2), 6.48 (d, 1H, $J=3$ Hz, ArH), 7.01 (d, 1H, $J=3$ Hz, ArH), 7.19–7.34 (m, 9H, ArH), 7.67 (s, 1H, NH or OH); EIMS m/z 447 (M^+). Anal. calcd for $C_{27}H_{33}N_3O_3{\cdot}HCl$: C 67.00, H 7.08, N 8.68, Cl 7.32. Found: C 67.08, H 7.04, N 8.59, Cl 7.41.

3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-(2-cyclohexylethyl)-1-(4-*N*,*N*-dimethylaminophenyl)urea (26). IR (KBr) 3404, 2922, 1639 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 0.80–0.95 (m, 2H, CH_2), 1.00–1.40 (m, 6H, CH_2), 1.28 (s, 9H, CH_3), 1.55–1.65 (m, 5H, CH_2 and CH), 2.95 (s, 6H, CH_3), 3.55–3.65 (m, 2H, CH_2), 3.63 (s, 3H, CH_3), 6.41 (d, 1H, $J=3$ Hz, ArH), 6.79 (d, 2H, $J=9$ Hz, ArH), 7.05 (d, 1H, $J=3$ Hz, ArH), 7.15 (d, 2H, $J=9$ Hz, ArH), 7.24 (s, 1H, NH or OH), 8.02 (s, 1H, NH or OH); EIMS m/z 467 (M^+). Anal. calcd for $C_{28}H_{41}N_3O_3{\cdot}1/4H_2O$: C 71.23, H 8.86, N 8.90. Found: C 71.01, H 8.49, N 8.88.

Synthesis of the derivatives including amide substructure 11–14

Compounds **11**–**14** were obtained from 3-(3-*tert*-butyl-5-methoxy-2-methoxymethoxyphenyl)-1-(3-ethoxycarbonylpropyl)-1-phenylurea **32** (R = 3-$C(CH_3)_3$-5-OCH_3, X = $(CH_2)_3CO_2C_2H_5$, Y = phenyl). They were hydrolyzed with 10% NaOH aq, made amide formation with the corresponding amines by 1, 3-dicyclohexylcarbodiimide and *N*-hydroxysuccinimide, and removed their methoxymethyl protecting group on the phenolic hydroxyl with methanolic hydrogen chloride.

***N*-Ethyl-4-[3-(3-*tert*-butyl-2-hydroxy-5-methoxyphenyl)-1-phenylureido]-butyramide (11).** IR (KBr) 3303, 2940, 1631 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.13 (t, 3H, $J=7.2$ Hz, CH_3), 1.41 (s, 9H, CH_3), 1.84–1.97 (m, 2H, CH_2), 2.27 (d, 2H, $J=6.8$ Hz, CH_2), 3.21–3.35 (m, 2H, CH_2), 3.68 (s, 3H, CH_3), 3.81 (t, 2H, $J=6.8$ Hz, CH_2), 6.12 (d, 1H, $J=3$ Hz, ArH), 6.13 (br, 1H, NH or OH), 6.43 (br, 1H, NH or OH), 6.72 (d, 1H, $J=3$ Hz, ArH), 7.33–7.57 (m, 5H, ArH), 8.67 (s, 1H, NH or OH); SIMS m/z 428 $(M+H)^+$. Anal. calcd for $C_{24}H_{33}N_3O_4$: C 67.42, H 7.78, N 9.83. Found: C 67.52, H 7.95, N 9.64.

***N*,*N*-Diethyl-4-[3-(3-tert-butyl-2-hydroxy-5-methoxyphenyl)-1-phenylureido]-butyramide (12).** IR (KBr) 2964, 1615 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.06–1.26 (m, 6H, CH_3), 1.41 (s, 9H, CH_3), 1.93–2.07 (m, 2H, CH_2), 2.38 (t, 2H, $J=6.8$ Hz, CH_2), 3.24–3.42 (m, 4H, CH_2), 3.70 (s, 3H, CH_3), 3.75–3.82 (m, 2H, CH_2), 6.32 (d, 1H, $J=3$ Hz, ArH), 6.71 (d, 1H, $J=3$ Hz, ArH), 7.33–7.51 (m, 6H, ArH, NH or OH), 8.85 (s, 1H, NH or OH); SIMS m/z 456 $(M+H)^+$. Anal. calcd for $C_{26}H_{37}N_3O_4$: C 68.54, H 8.19, N 9.22. Found: C 68.51, H 8.30, N 9.31.

3-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-(3-morpholinocarbonylpropyl)-1-phenylurea (13). IR (KBr) 2946, 1642 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.41 (s, 9H, CH_3), 1.94–2.04 (m, 2H, CH_2), 2.40 (t, 2H, $J=7$ Hz, CH_2), 3.43–3.47 (m, 2H, CH_2), 3.62–3.68 (m, 6H, CH_2), 3.68 (s, 3H, CH_3), 3.81 (d, 2H, $J=7$ Hz, CH_2), 6.17 (d, 1H, $J=3$ Hz, ArH), 6.71 (d, 1H, $J=3$ Hz, ArH), 6.72 (br, 1H, NH or OH), 7.34–7.54 (m, 5H, ArH), 8.77 (s, 1H, NH or OH); SIMS m/z 470 $(M+H)^+$. Anal. calcd for $C_{26}H_{35}N_3O_5$: C 66.50, H 7.51, N 8.95. Found: C 66.80, H 7.69, N 9.18.

***N*-(2,3-Dihydroxypropyl)-4-[3-(3-tert-butyl-2-hydroxy-5-methoxyphenyl)-1-phenylureido]-butyramide (14).** IR (KBr) 3322, 2952, 1638 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.40 (s, 9H, CH_3), 1.67 (br, 2H, OH), 1.86–1.93 (m, 2H, CH_2), 2.35 (t, 2H, $J = 6.8$ Hz, CH_2), 3.03 (m, 1H, CH), 3.35–3.41 (m, 2H, CH_2), 3.51–3.53 (m, 2H, CH_2), 3.68 (s, 3H, CH_3), 3.81 (t, 2H, $J = 6.8$ Hz, CH_2), 6.18 (d, 1H, $J = 3$ Hz, ArH), 6.30 (s, 1H, NH or OH), 6.70 (d, 1H, $J = 3$ Hz, ArH), 6.72 (br, 1H, NH or OH), 7.35–7.58 (m, 5H, ArH), 8.25 (s, 1H, NH or OH); SIMS *m*/*z* 474 $(M+H)^+$. Anal. calcd for $C_{25}H_{35}N_3O_6$: C 63.41, H 7.45, N 8.87. Found: C 63.39, H 7.58, N 9.01.

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