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Quantitative Structure–Activity Analyses of Novel Hydroxyphenylurea Derivatives as Antioxidants

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Abstract—A series of substituted hydroxyphenylureas was synthesized, the chemical structure of which was designed based on structures of natural antioxidants, vitamin E (α-tocopherol) and uric acid. They exhibited high inhibitory activity against lipid peroxidation. In order to gain an insight into the mechanism of the inhibition reaction, we analyzed their structure–activity relationships quantitatively. Electronic and steric effects of substituents on the phenolic hydroxyl group were shown to be of importance in governing the inhibitory potency. An increase in the electron donating property of substituents toward the phenolic hydroxyl group enhanced the antioxidative activity by the stabilization of an electron-deficient radical-type transition state. The steric shielding by *ortho*-substituents stabilized the phenoxy radicals formed following the transition state. Derivatives having the carboxyl group were only weakly active presumably because of an intermolecular ion-dipole interaction of the phenolic hydroxyl group with the carboxylate anion which could retard the formation of the transition state.

Introduction

Active oxygen species and free radicals have been recognized to play an important role in the initiation and/or progression of various diseases such as ischemia-reperfusion injury, atherosclerosis, and inflammatory injury.[1] Antioxidants are expected to be promising drugs for treatment of these diseases by removing oxidative stresses. For example, probucol **1**, a well-known reagent exhibiting antioxidative activity, is expected as a therapeutic agent for atherosclerosis.[2]

[probucol] [vitamin E] [uric acid]

1 Probucol — **2** α-Tocopherol (Vitamin E) — **3** Uric Acid

Key words: Quantitative structure–activity relationship; QSAR; hydroxyphenylurea; antioxidant.
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[derivative **14**] [diphenylurea]

[acetanilide **14**] [acetanilide]

[derivative **48**] [*N*-substituted phenylurea]

[acetanilied **12**]

We noted the chemical structures of α-tocopherol (vitamin E) **2** and uric acid **3**, both of which exhibit an

interesting antioxidative activity. α-Tocopherol terminates chain reactions of the lipid peroxidation by giving a hydrogen atom from its phenolic hydroxyl group to the peroxidized lipid radical and turns into the stable tocopheroxy radical.[3] For this mechanism, the *para*-alkoxyphenol structure is an essential component of α-tocopherol. Uric acid scavenges radical species and the resultant urate radical is stabilized by delocalization of the unpaired electron in the π electron system containing urea substructures.[4] The antioxidative nature of these compounds could be governed by the readiness in releasing the hydrogen as well as the stability of the produced radicals. Based on these considerations, we designed novel 2-hydroxy-5-methoxyphenylureas **4** by combining substructural features of α-tocopherol and uric acid as shown in Figure 1.

The corresponding radical species would be stabilized by delocalization of the odd electron in the benzene ring and the urea moiety. As we expected, the first synthesized compound, 1-(2-hydroxy-5-methoxyphenyl)-3-phenylurea **5**, exhibited antioxidative potency about 10 times higher than that of α-tocopherol. It was also revealed that the potency of the derivatives varied with substituent/structural modifications to various extents.

In this paper, we report the relationship between structure and activity in the inhibition of lipid peroxidation of variously substituted hydroxyphenylureas **5–58** quantitatively, using free–energy related substituent parameters as well as a quantum chemical index and regression analyses. On the basis of this result, we propose a physicochemical mechanism of their antioxidative activity.

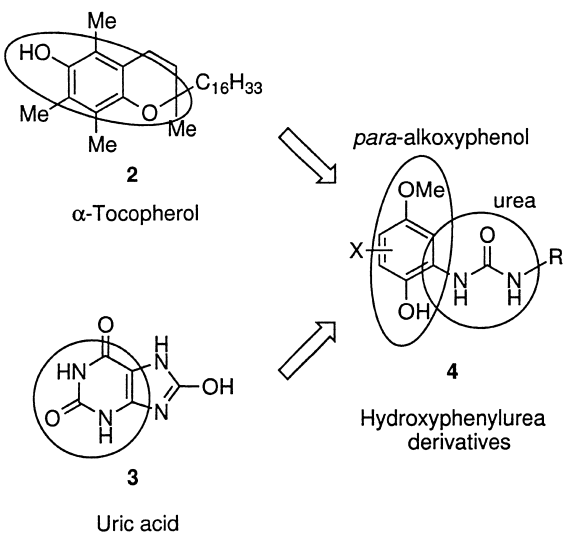


Figure 1. Design of hydroxyphenylurea derivatives.

Chemistry

The compounds **5–57** were synthesized by combining the substituted anilines **62** with the other substituted anilines or amines (R-NH_2) using triphosgene followed by removal of the protecting group with methanolic hydrogen chloride (Scheme 1).

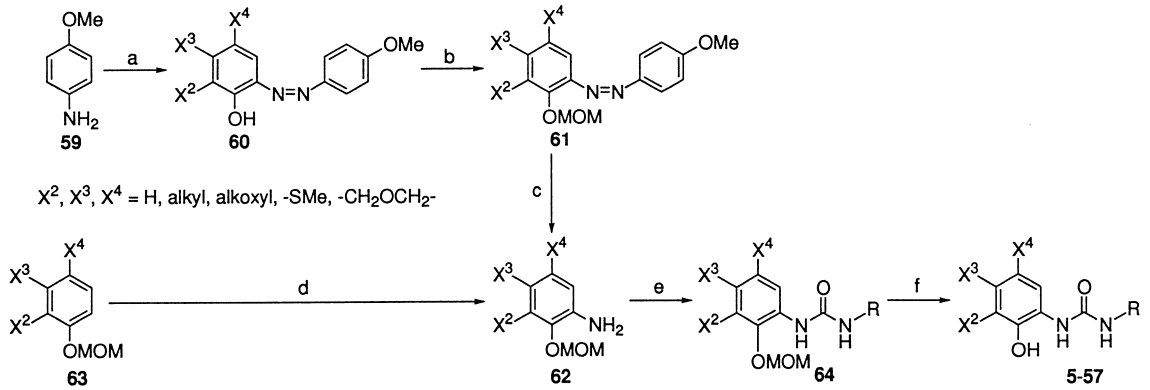
The substituted anilines **62** were prepared by hydrogenation of the substituted azobenzenes **61** or azidation of the substituted benzenes **63** followed by reduction. The amines (R-NH_2) were purchased from commercial sources or synthesized by alkylation and acylation of the corresponding alcohols, amines, and halides.

Tetrahydroquinazoline derivative **58** was synthesized by the synthetic route shown in Scheme 2. Cyclization of **69** was likewise carried out by using triphosgene under weakly basic conditions. Those reactions are described in the experimental section.

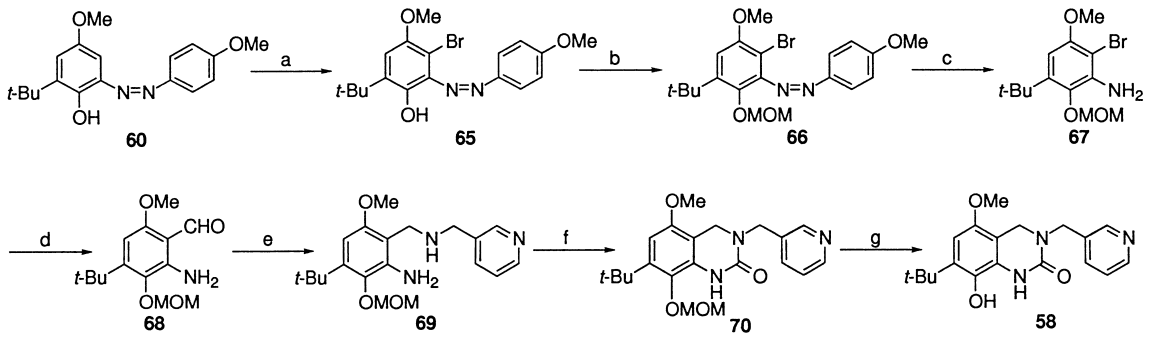
QSAR Parameters

Recently, Hansch and co-workers have shown that there are a number of examples in which substituted phenols display an inhibitory effect on biological reactions.[5,6] The inhibitory mechanism involves free radical reactions of substituted phenols which are governed mainly by electronic characters of substituents. The electronic effects of substituents are mostly represented by the σ^+ parameter, one of the variations of the Hammett σ including the through-resonance effect on the electron-deficient reaction center. It is defined according to the reaction constants for the solvolysis of the substituted *t*-cumyl chlorides.[7] In this study, we first examined the σ^+ value because we expected the antioxidative reaction mechanism to be similar to mechanisms found by Hansch and co-workers. In Table 1, the σ^+ values are listed along with the σ^0 values[8] which are supposed to represent for the effect of the substituents devoid of the through-resonance effect. The effect of *ortho*-substituents was analyzed by assuming that it was primarily equivalent with that of the corresponding *para*-substituents, which should be adjusted/corrected according to the reduced through-resonance effect with the use of an additional parameter, $\Delta\sigma_R^+ (= \sigma^+ - \sigma^0)$.[9] We used the combination of these electronic parameters to clarify the inhibitory mechanism of hydroxyphenylureas against lipid peroxidation.

To represent the steric effect of *ortho*-substituents on the phenolic hydroxyl group, the E_s(AMD) parameter derived from the rate constants for the acidic hydrolysis of *ortho*-substituted benzamides was used (Table 1).[10] The E_s(AMD) value of hydrogen is defined as the reference (zero).



Scheme 1. (a) (1) $NaNO_2$, HCl, H_2O, (2) substituted phenol, NaOH, H_2O; (b) MOMCl, NaH DMF; (c) H_2, Pd-C, EtOH; (d) (1) *sec*–BuLi, THF, (2) $TosN_3$, THF, (3) $Na_4P_2O_7$, aq., (4) $LiAlH_4$, THF; (e) R-NH_2, triphosgene, Et_3N,CH_2Cl_2; (f) concd HCl, MeOH.



Scheme 2. (a) Br_2, CS_2; (b) MOMCl, NaH, DMF; (c) H_2, Pd-C, MeOH; (d) (1) *n*–BuLi, Et_2O, (2) DMF; (e) (1) 3-(aminomethyl)pyridine, benzene, (2) $NaBH_3CN$, CH_3CN; (f) triphosgene, Et_3N, CH_2Cl_2; (g) concd HCl, MeOH.

The molecular hydrophobicity parameter, logP, of substituted diphenylureas (**5–29**) was estimated principally by our empirical method to calculate the logP value of substituted acetanilides.[11,12] The difference in the logP value, ΔlogP, between multisubstituted and unsubstituted diphenylureas (**5–18**) was assumed as being nearly equal to the ΔlogP between multisubstituted and unsubstituted acetanilides. Likewise, the ΔlogP value for compounds **19–29** was taken as the summation of the ΔlogP values for two substituted ring moieties. The reference logP value of diphenylurea (3.00) was cited from literature.[13] The ΔlogP value is not identical to $\Delta\pi$, in which π is the substituent hydrophobicity constant defined from partition coefficients of monosubstituted benzenes. The ΔlogP value of multisubstituted benzene is a composite of $\Sigma\pi$ and increments originated from electronic, steric and intramolecular hydrogen-bonding interactions between substituents. In compounds **30–56**, the logP value of corresponding phenylureas which have no substituents on the phenyl ring and miscellaneous substituents at the end of the urea moiety was calculated using the CLOGP procedure.[14,15] Thus, the logP value for the all compounds was estimated by the summation of ΔlogP and logP of diphenylurea or CLOGP of corresponding *N*-substituted phenylurea. The logP values are listed in Table 2. Regression analyses were performed by using the QREG93 program developed by Asao et al.[16]

Molecular Orbital Calculations

To clarify the effect of the urea moiety against the antioxidative activity and to assess the overall reactivity of the hydroxyl group in hydroxyphenylurea derivatives theoretically, quantum chemical calculations were performed. For *p*-methoxyphenol and probucol **1**, the crystal structures in Cambridge Structural Database[18] (entries MOPHLC[19] and HAXHET,[20] respectively) were used as their initial coordinates. An initial conformation of vitamin E **2** was constructed based on the crystal structure of 2,2,5,7,8-pentamethyl-6-hydroxychroman (entry MOPHLB[19]). Initial coordinates of all hydroxyphenylureas were constructed in the *syn–syn*

Table 1. Physicochemical parameters for substituents

Substituents	σ_m^{+a}	σ_p^{+a}	σ_m^{0b}	σ_p^{0b}	$\Delta\sigma_R^{+c}$	E_s (AMD)[d]
Me	−0.07	−0.31	−0.07	−0.13	−0.19	−1.16
Et	−0.06	−0.30	−0.07	−0.13	−0.17	−1.33
t-Bu	−0.06	−0.26	−0.07	−0.17	−0.09	−2.78[e]
C_8H_{17}	—	−0.29[f]	−0.08[f]	−0.16[f]	−0.13	−1.64[f]
OMe	0.05	−0.78	0.06	−0.16	−0.62	−0.40
OC_8H_{17}	—	−0.81[g]	0.04[g]	−0.14[g]	−0.67	−0.55[g]
SMe	0.16	−0.60	0.13	0.06	−0.66	−1.14
NHCONH-R	0.13[h]	−0.60[h]	0.21[h]	0.03[h]	−0.63	−0.61[i]

[a]Taken from ref. 7 or ref. 13.
[b]Taken from ref. 8 or ref. 17.
[c]$\Delta\sigma_R^+ = \sigma_p^+ - \sigma_p^0$.
[d]Taken from ref. 10.
[e]E_s(AMD) value of *t*-Bu was approximated by E_s value of *t*-Bu.
[f]The values of C_8H_{17} were approximated by the values of Bu.
[g]The values of OC_8H_{17} were approximated by the values of OBu.
[h]The values of these parameters were approximated by the values of NHAc.
[i]E_s(AMD) value of NHCONH-R was approximated by E_s value of NH_2.

conformation on the basis of the crystal structure of **24** shown in Figure 2.[18]

The geometry of compounds was refined by semi-empirical molecular orbital calculations with the PM3 Hamiltonian using the SPARTAN (version 4.1.1) software.[21] The calculations were performed with restricted Hartree–Fock method for the ground-state compounds and unrestricted Hartree–Fock for the radicals.

In the most stable conformation such as **24** (*a*) in Figure 3, an intramolecular hydrogen-bond formation is possible between the phenolic hydroxyl group and the urea carbonyl. Since hydrogen-bonded hydroxyl group may not be susceptible enough to react with the lipid peroxy radicals, quantum chemical properties were calculated for the meta-stable conformers such as **24** (*b*) where the intramolecular hydrogen-bond formation is not observed.

The electron-releasing reactivity index of phenolic oxygen, $R(O_{phenol})$, listed in Table 2, was calculated by eq (1).[22]

$$R(O_{phenol}) = f_r(O_{phenol})/ - E_{HOMO} \times 100 \qquad (1)$$

In eq (1), $f_r(O_{phenol})$ is the frontier electron density at the phenolic oxygen atom on the highest occupied molecular orbital (HOMO) and E_{HOMO} is the energy level of the HOMO in eV. The $R(O_{phenol})$ index approximates the superdelocalizability for comparisons of the reactivity of a corresponding position among a series of compounds.[23] The $R(O_{phenol})$ value was multiplied by 100 to scale them in an order similar to that of other parameters.

Results and Discussion

We designed and synthesized hydroxyphenylurea derivatives referring to the antioxidative potencies and the structural properties of vitamin E and uric acid. At first, to clarify the effect of the urea moiety against the inhibitory activity of lipid peroxidation, the stabilities of *p*-methoxyphenol, probucol **1**, vitamin E **2**, and hydroxyphenylurea **5** were compared. The stabilities were estimated by the energy differences between the ground-states and the corresponding radicals (Table 3). The energy difference of **5** was 2.3–5.1 kcal/mol less than the others. Thus, a phenol having a urea moiety was more stable in its radical form than those without ureas. Its stability presumably arised from the delocalization of an odd electron into the urea moiety. It was concluded that **5** has higher antioxidative activity than other phenolic derivatives owing to stabilization in the radical form.

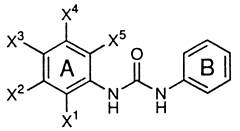
To examine the substituent effects on the reactivity of the phenolic hydroxyl group in transforming into the phenoxy radical, we analyzed the first set of diphenylureas with simple substituents such as alkyl, alkoxy, and methylthio groups on the benzene ring A, where the phenolic hydroxyl group is located. For 14 compounds (**5–18**), eq (2) was formulated with $\Sigma\sigma^+$ summed over *ortho*-, *meta*-, and *para*-substituents.

$$\log(1/IC_{50}) = -0.59(\pm0.41)\Sigma\sigma^+ - 0.24(\pm0.23)\Sigma E_s(AMD) + 4.98(\pm0.68)$$
$$n = 14,\ s = 0.30,\ r = 0.80,\ F_{2,11} = 9.91 \qquad (2)$$

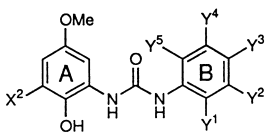
In this and the following equations, n is the number of compounds, s the standard deviation, r the correlation coefficient, and F the ratio between regression and residual variances. The figure in parentheses is the 95% confidence interval.

The quality of eq (2) was just marginal and not as good as one would like. Inspecting the correlation closely, we noted that the residual between observed and calculated activity values was generally large for compounds having the methoxyl group in the *ortho*-position. In these compounds, the phenolic hydroxyl group is sandwiched between the urea and methoxyl groups except for compound **18**. The through-resonance

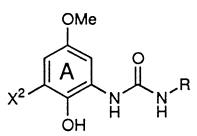
Table 2. Physicochemical parameters of hydroxyphenylurea derivatives



	Substituents									
No.	X^1	X^2	X^3	X^4	X^5	$\Sigma\sigma^{\#}$	ΣE_s(AMD)	R(O_{phenol})	logP	I_{COOR}
5	OH	H	H	OMe	H	−0.75	−0.61	0.787	1.95	0
6	OH	H	OMe	H	H	0.08	−0.61	0.341	1.92	0
7	OH	OMe	H	H	H	−0.13	−1.01	0.402	1.76	0
8	OH	H	H	OC_8H_{17}	H	−0.78	−0.61	0.803	5.23	0
9	OH	H	H	SMe	H	−0.57	−0.61	0.576	2.52	0
10	OH	Me	H	OMe	H	−0.87	−1.77	0.803	2.26	0
11	OH	Et	H	OMe	H	−0.88	−1.94	0.793	2.66	0
12	OH	*t*-Bu	H	OMe	H	−0.92	−3.39	0.837	3.43	0
13	OH	C_8H_{17}	H	OMe	H	−0.91	−2.25	0.795	5.48	0
14	OH	OMe	H	OMe	H	−0.91	−1.01	0.847	1.75	0
15	OH	OC_8H_{17}	H	OMe	H	−0.89	−1.16	0.911	5.03	0
16	OH	OMe	H	OC_8H_{17}	H	−0.94	−1.01	0.861	5.02	0
17	OH	OMe	OMe	OMe	H	−0.86	−1.01	0.723	0.99	0
18	OMe	H	OMe	OH	H	−0.81	−0.40	0.589	1.72	0



	Substituents										
No.	X^2	Y^1	Y^2	Y^3	Y^4	Y^5	$\Sigma\sigma^{\#}$	ΣE_s(AMD)	R(O_{phenol})	logP	I_{COOR}
19	H	H	CF_3	H	H	H	−0.75	−0.61	0.880	3.20	0
20	H	H	CO_2H	H	H	H	−0.75	−0.61	0.860	2.11	1
21	H	H	H	Me	H	H	−0.75	−0.61	0.703	2.48	0
22	H	H	H	CH=$CHCO_2H$(*trans*)	H	H	−0.75	−0.61	0.763	—[a]	1
23	H	H	H	Cl	H	H	−0.75	−0.61	0.726	2.90	0
24	H	H	H	OMe	H	H	−0.75	−0.61	0.490	1.94	0
25	H	H	H	OCH_2CO_2Et	H	H	−0.75	−0.61	0.838	1.99	1
26	*t*-Bu	H	H	NMe_2	H	H	−0.92	−3.39	0.476	—[a]	0
27	*t*-Bu	H	H	$O(CH_2)_3NBu_2$	H	H	−0.92	−3.39	0.598	5.93	0
28	*t*-Bu	*i*-Pr	H	H	H	*i*-Pr	−0.92	−3.39	0.853	4.48	0
29	*t*-Bu	F	H	F	H	H	−0.92	−3.39	0.898	3.55	0



	Substituents						
No.	X^2	R	$\Sigma\sigma^{\#}$	ΣE_s(AMD)	R(O_{phenol})	logP	I_{COOR}
30	*t*-Bu		−0.92	−3.39	0.905	2.92	0

(continued)

Table 2—*contd*

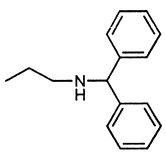
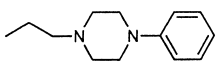
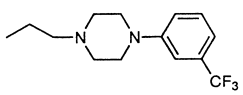
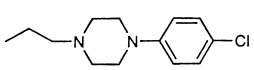
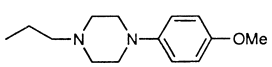
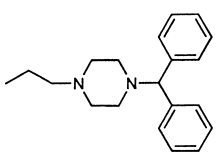
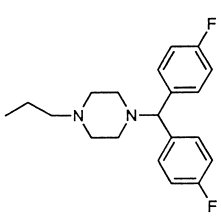
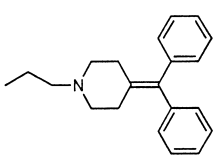
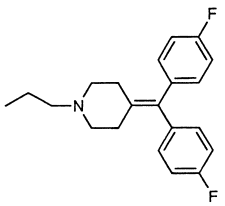
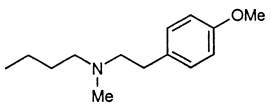
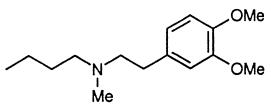
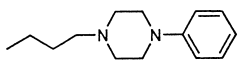
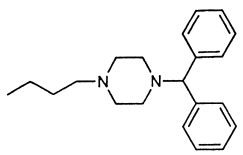
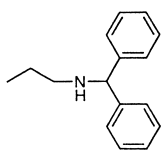
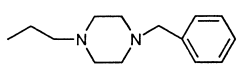
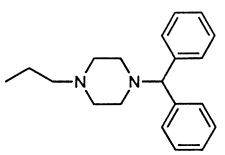
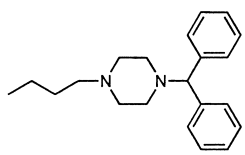
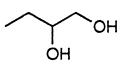
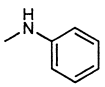
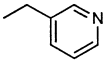
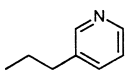
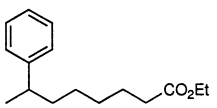
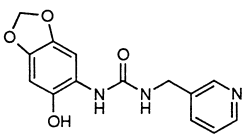
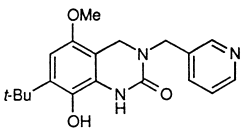
No.	X^2	R	$\Sigma\sigma^{\#}$	ΣE_s(AMD)	R(O_{phenol})	logP	I_{COOR}
31	*t*-Bu		−0.92	−3.39	0.896	2.92	0
32	*t*-Bu		−0.92	−3.39	0.928	2.92	0
33	*t*-Bu		−0.92	−3.39	0.931	3.56	0
34	H		−0.75	−0.61	0.903	3.06	0
35	H		−0.75	−0.61	0.902	2.89	0
36	H		−0.75	−0.61	0.889	4.07	0
37	H		−0.75	−0.61	0.903	3.77	0
38	H		−0.75	−0.61	0.901	2.91	0
39	H		−0.75	−0.61	0.892	4.19	0
40	H		−0.75	−0.61	0.902	4.47	0
41	H		−0.75	−0.61	0.901	4.69	0

Table 2—*contd*

42	H		−0.75	−0.61	0.901	4.98	0
43	H		−0.75	−0.61	0.901	1.56	0
44	H		−0.75	−0.61	0.901	1.10	0
45	H		−0.75	−0.61	0.902	2.56	0
46	H		−0.75	−0.61	0.902	3.85	0
47	OMe		−0.91	−1.01	0.986	2.86	0
48	*t*-Bu		−0.92	−3.39	0.934	4.32	0
49	*t*-Bu		−0.92	−3.39	0.977	5.67	0
50	*t*-Bu		−0.92	−3.39	0.932	5.33	0
51	*t*-Bu		−0.92	−3.39	0.946	2.12	0

(continued)

Table 2—*contd*

No.	X^2	R	$\Sigma\sigma^{\#}$	ΣE_s(AMD)	$R(O_{phenol})$	logP	I_{COOR}
52	*t*-Bu		−0.92	−3.39	0.944	0.71	0
53	*t*-Bu		−0.92	−3.39	0.949	2.84	0
54	*t*-Bu		−0.92	−3.39	0.941	1.80	0
55	*t*-Bu		−0.92	−3.39	0.929	1.98	0
56	*t*-Bu		−0.92	−3.39	0.933	5.21	1
57			—[a]	−0.61	0.651	—[a]	0
58			—[a]	−3.39	0.753	—[a]	0
1		probucol	—[a]	−5.56	0.489	—[a]	0
2		α-tocopherol	—[a]	−2.32	1.169	—[a]	0

[a]The values were not calculated because of missing parameters.

electronic effect between the *ortho*-methoxyl and the phenolic hydroxyl groups may not be complete because the coplanar conformation of the hydroxyl group may be taken only with difficulty. We therefore examined the use of the parameter, $\Delta\sigma_R^+$ for *ortho*-substituents defined above. In a way, this procedure is to apply the Yukawa–Tsuno's one[24] to the *ortho*-substituents. The importance of the through-resonance effect could be understood by comparison between the coefficient of $\Sigma\sigma^+$ and that of $\Sigma\Delta\sigma_R^+$.

$$\log(1/IC_{50}) = -1.06(\pm0.52)\Sigma\sigma^+ - 0.95(\pm0.79)\Sigma\Delta\sigma_R^+ - 0.16(\pm0.19)\Sigma E_s(\text{AMD}) + 5.16(\pm0.57)$$
$$n = 14,\ s = 0.24,\ r = 0.89,\ F_{3,10} = 12.60 \quad (3)$$

Equation (3) is improved significantly over eq (2), although the ΣE_s(AMD) term is not significant over the 95% level. In this equation, the coefficient of $\Sigma\Delta\sigma_R^+$ is nearly equal to that of $\Sigma\sigma^+$. This means that the through-resonance effect almost does not exist in 2,6-disubstituted phenols and that the effect does not control the reactivity of the phenolic hydroxyl group in transforming into their radical species.

Combining these two parameters, we used the $\Sigma\sigma^{\#}$ (sigma mixed),[9] the sum of the σ^+ for *meta*- and *para*- and the σ^0 for *ortho*-substituents, to formulate eq (4).

$$\log(1/IC_{50}) = -1.08(\pm0.49)\Sigma\sigma^{\#} - 0.16(\pm0.18)\Sigma E_s(\text{AMD}) + 5.25(\pm0.37) \quad (4)$$
$$n = 14,\ s = 0.23,\ r = 0.89,\ F_{2,11} = 20.15$$

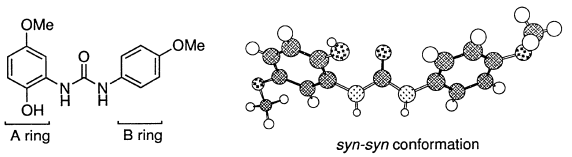


Figure 2. Crystal structure of **24**.

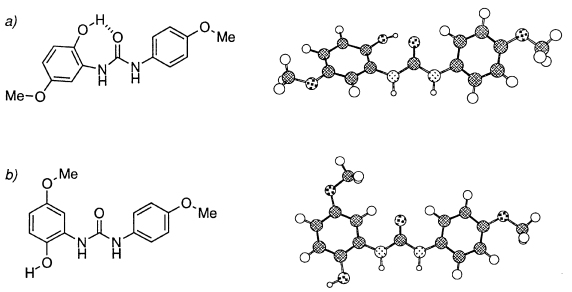


Figure 3. Stable conformers of **24**.

In eq (3) and (4), the ΣE_s(AMD) term is not deleted since it is significant above the 95% level for the larger set of compounds as will be shown below. The negative coefficient of $\Sigma\sigma^{\#}$ shows that the electron-donating effect including the through-resonance effect from *para*- and *meta*-, but not from *ortho*-, substituents on the electron-deficient phenoxy radical enhances the inhibitory activity. The mechanistic interpretation of this effect is shown in Figure 4.

On approaching to the lipid peroxide radical, one of the electrons of the O–H bond of the hydroxyphenylurea tends to shift to the radical. In the transition complex, phenolic oxygen is positively charged more or less.[25,26] Enhancement of the electron-donating property of substituents could reduce the activation energy of this process, leading to compounds showing the higher inhibitory activity against the propagation of lipid peroxidation.

The E_s(AMD) value of *ortho*-substituents is defined so that the bulkier are the substituents, the more negative

Table 3. Conformational energies and differences

No.	E_{gr}[a]	E_{rd}[b]	(kcal/mol) ΔE[c]
p-Methoxyphenol	−58.99	−36.54	22.45
1	−107.53	−85.74	21.79
2	−178.67	−158.95	19.72
5	−63.88	−46.49	17.39

[a]The energies in the ground state.
[b]The energies in the radical forms.
[c]$\Delta E = E_{rd} - E_{gr}$.

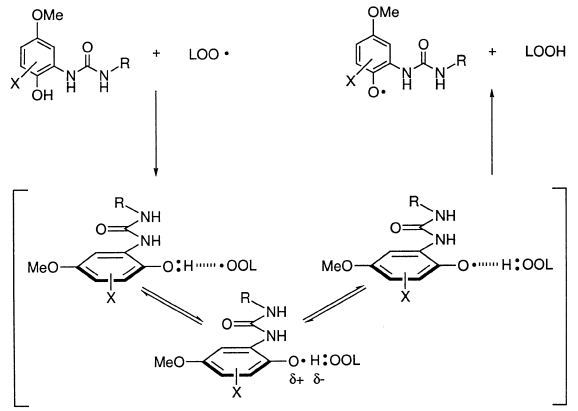


Figure 4. Mechanism of termination of radical chain reaction by hydroxyphenylurea derivatives.

are the values. The negative coefficient of the ΣE_s(AMD) term in eq (4) indicates that the hydroxyphenylureas with the bulkier *ortho*-substituents show higher inhibitory activity, although the steric effect is not very important. After passing through the intermediate state, the hydroxyphenylureas are transformed to the corresponding phenoxy radicals. The phenoxy radicals generated are stabilized more effectively by the shielding effect of the bulkier *ortho*-substituents so that it is less reactive to radicalize another lipid molecule. Thus, the more sterically hindered hydroxyphenylureas could have the higher antioxidative activity. In eq (4), the $\Sigma\sigma^{\#}$ term seems to represent the electron-donating effect on increasing the reactivity of the phenolic hydroxyl group turning into the corresponding phenoxy radical and the ΣE_s(AMD) term appears to show the steric effect of substituents on the stability of the resultant phenoxy radical.

The addition of the logP term did not improve the quality of the correlation, although the highly lipophilic atmosphere of lipid peroxidation reaction expected to imply the contribution of hydrophobicity of their inhibitors. The use of the $\Sigma\sigma^0$ value, instead of $\Sigma\sigma^+$ and $\Sigma\sigma^{\#}$, gave poorer correlations ($s = 0.33$, $r = 0.73$) and in the correlation equation the ΣE_s(AMD) term was entirely insignificant (equations not shown).

To obtain more detailed information, we included 11 diphenylureas (**19–29**) having various substituents on the non-phenolic benzene ring B. The electronic and steric effects of substituents Y^1–Y^5 of the B ring on the reactivity of the phenolic hydroxyl group of the A ring were regarded as being insignificant because of their distant location. Thus, the electronic and steric parameters of substituted phenylureido groups were taken to be unchanged regardless of the substitution patterns on the B ring to yield eq (5).

$$\log(1/IC_{50}) = -1.14(\pm0.39)\Sigma\sigma^{\#} - 0.14(\pm0.09)\Sigma E_s(AMD) - 1.19(\pm0.27)I_{COOR} + 5.30(\pm0.29)$$
$$n = 25, s = 0.20, r = 0.95, F_{3,21} = 63.36 \quad (5)$$

The quality of the correlation in eq (5) formulated for 25 diphenylureas was much improved over that of eq (4). The $\Sigma\sigma^{\#}$ and ΣE_s(AMD) terms, now significant above the 95% level, are similar to those in eq (4). In eq (5), however, the addition of an indicator variable, I_{COOR}, is required for an acceptable correlation. I_{COOR} takes a value of unity for compounds having either carboxyl or ester substituent on the B ring, and takes zero otherwise. The ester substituents are probably hydrolyzed into carboxylates by esterases involved during incubation for 15 h with brain homogenate. The I_{COOR} term in eq (5) shows that carboxylate derivatives are about ten times less potent than derivatives otherwise equivalent. Carboxylate exists in ionic form in the buffer solution and an intermolecular ion-dipole interaction between the carboxylate anion and the phenolic hydroxyl is possible. The carboxylate could prevent phenolic hydroxyl from formation of the transition state with lipid peroxides by the intermolecular ion-dipole association. This effect of carboxylates was represented by the indicator variable I_{COOR} in eq (5).

The facts that the coefficients of the electronic and steric terms in eq (5) is almost equivalent to those in eq (4) and that no hydrophobicity term is significant again in eq (5) indicates that any structural variations beyond the urea moiety may be made without significant variations in the activity if the substitution pattern is optimized on the ring A. Thus, in order to examine the structural conversion around the ring B without decrease of the inhibitory activity, we synthesized various substituted-ureido compounds (**30–56**) in which variations in electronic and steric effects of those substituents on the phenolic hydroxyl on the A ring are also regarded as being unchanged. The correlation analysis including these compounds gave eq (6).

$$\log(1/IC_{50}) = -1.20(\pm0.48)\Sigma\sigma^{\#} - 0.14(\pm0.07)\Sigma E_s(AMD) - 1.17(\pm0.28)I_{COOR} + 5.25(\pm0.35)$$
$$n = 52, s = 0.26, r = 0.88, F_{3,48} = 56.81 \quad (6)$$

The inhibitory activity against the lipid peroxidation of 52 compounds was correlated with the same set of parameters as those in previous equations for diphenylureas. Although logP values of these compounds were widely spread between 0.71 (**52**) and 5.93 (**27**), no hydrophobic effect was observed and the observed activities of compounds **30–56** were identical to their estimated ones within the range of experimental errors. The surroundings in the brain homogenate where the hydroxyphenylurea derivatives inhibit lipid peroxidation are hydrophobic. Then it had been expected that the hydrophobic derivatives would have approached to the site of inhibition reaction more easily than the less hydrophobic ones and that the former would have exhibited higher potency. However the variations in the hydrophobicity of compounds do not participate in the activity variations.

It was revealed that the inhibitory activities of hydroxyphenylurea derivatives were governed by electronic steric effects on the ring A and that any structural conversion around the ring B was rather tolerable except for the negative effect of carboxylates. These findings were very important to rationally design novel compounds with various pharmacological effects as well as high antioxidative activities by modification around the ring B. For example, 1-(3-*tert*-butyl-2-hydroxy-5-methoxyphenyl)-3-(2-cyclohexylethyl)-3-(4-dimethylaminophenyl)urea, one of the hydroxyphenylurea derivatives, was found to inhibit low density lipoprotein oxidation and acyl CoA: cholesterol acyltransferase.[27]

The minute analyses of electronic effects of hydroxyphenylureas gave the mechanistic interpretation illustrated in Figure 4. This mechanism implies that the reactivity index $R(O_{phenol})$ derived from the frontier electron density at the HOMO level could work as the parameter for the electronic effect of substituents on the hydroxyl group. In order to validate this mechanistic hypothesis, we performed correlation analysis using the $R(O_{phenol})$ index. For 25 diphenylurea derivatives used for eq (5), eq (7) was formulated with almost equivalent coefficients of ΣE_s(AMD) and I_{COOR} terms and the intercept in eq (5).

$$\log(1/IC_{50}) = 1.36(\pm0.67)R(O_{phenol}) - 0.21(\pm0.10)\Sigma E_s(AMD) - 1.28(\pm0.34)I_{COOR} + 5.08(\pm0.48)$$
$$n = 25, s = 0.24, r = 0.92, F_{3,21} = 41.13 \quad (7)$$

For 54 hydroxyphenylureas including two compounds **57**, **58** for which the $\Sigma\sigma^{\#}$ parameters of substituents were not available, eq (8) was formulated which is practically equivalent to eq (7).

$$\log(1/IC_{50}) = 1.01(\pm0.57)R(O_{phenol}) - 0.20(\pm0.07)\Sigma E_s(AMD) - 1.16(\pm0.31)I_{COOR} + 5.26(\pm0.46)$$
$$n = 54, s = 0.30, r = 0.85, F_{3,50} = 41.91 \quad (8)$$

The ΣE_s(AMD) term is significant in eq (7) and (8) and its coefficient is almost equivalent with that in eq (5) and

(6), indicating that the steric effect of substituents on A ring really exists inspite of its instability in eq (1)–(4).

The antioxidative potencies, $\log(1/IC_{50})$, of probucol **1** and α-tocopherol **2** lacking the urea moiety were calculated by eq (8), as being 6.87 and 6.90, respectively. On the average, these values overestimate the potencies about 1.5 log unit higher than the observed values (Table 3). Since eq (8) is derived based on QSAR of hydroxyphenylureas, these differences are due to the stabilization in the radical form by urea moiety as discussed previously. Thus, the introduction of the urea moiety is expected to contribute to the activity enhancement by about 30 times.

Conclusion

We designed and synthesized novel hydroxyphenylureas based on the structures of natural antioxidants, vitamin E and uric acid. Quantitative analyses of their electronic effects on the inhibition of lipid peroxidation gave us a mechanistic interpretation. The structural requirements for high antioxidative activity of hydroxyphenylureas are: (1) electron-donating substituents on the benzene ring where the phenolic hydroxyl group is located, (2) bulky substituents at the *ortho*-positions of the phenolic hydroxyl group, and (3) neither carboxylates nor esters in their structures. The urea moiety seems to contribute to the activity enhancement with a factor of 30 by stabilizing its radical. Some of the hydroxyphenylurea compounds studied here are now under pharmacological investigation for the possibility as therapeutic agents of diseases mentioned earlier in this paper.

Experimental

Inhibitory activity of lipid peroxidation

Probucol **1** was purchased from Daiichi Seiyaku Co. Ltd. (Tokyo, Japan), and Deferoxamine mesylate (Desferal) was from Chiba-Geigy Japan Ltd. (Hyogo, Japan). α-Tocopherol **2**, 2-thiobarbituric acid sodium salt (TBA) and 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) were purchased from Nacalai Tesque Co. Ltd. (Kyoto, Japan). All other chemicals and materials used were of the analytical grade available from local commercial sources.

Adult male Sprague Dawley rats weighing 250–300 g were obtained from Charles River, Japan Ltd. (Shizuoka, Japan). Rats were sacrificed by decapitation and exsanguination. The entire brain was removed and homogenized in 4 vol of cold 1/15 M phosphate buffered saline (PBS, pH 7.4) and stored at −80 °C until use.

Table 4. Inhibitory activities of lipid peroxidation of hydroxyphenylurea derivatives

No.	IC_{50} (μM)	$\log(I/IC_{50})$ Obsd.	Calcd. (eq (6))	Dev.	Calcd. (eq (8))	Dev.
5	0.43	6.37	6.24	0.13	6.18	0.19
6	6.00	5.22	5.24	−0.02	5.73	−0.51
7	2.80	5.55	5.55	0.00	5.87	−0.32
8	0.37	6.43	6.27	0.16	6.19	0.24
9	0.81	6.09	6.02	0.07	5.96	0.13
10	0.39	6.41	6.54	−0.13	6.43	−0.02
11	0.28	6.55	6.58	−0.03	6.45	0.10
12	0.14	6.85	6.83	0.02	6.78	0.07
13	0.44	6.36	6.66	−0.30	6.51	−0.15
14	0.25	6.60	6.48	0.12	6.32	0.28
15	0.30	6.52	6.48	0.04	6.41	0.11
16	0.33	6.48	6.52	−0.04	6.33	0.15
17	0.65	6.19	6.42	−0.23	6.19	0.00
18	2.40	5.62	6.28	−0.66	5.93	−0.31
19	0.30	6.52	6.24	0.28	6.27	0.25
20	10.10	5.00	5.07	−0.07	5.09	−0.09
21	0.31	6.51	6.24	0.27	6.09	0.42
22	6.50	5.19	5.07	0.12	4.99	0.20
23	0.44	6.36	6.24	0.12	6.12	0.24
24	0.59	6.23	6.24	−0.01	5.88	0.35
25	11.30	4.95	5.07	−0.12	5.07	−0.12
26	0.13	6.89	6.83	0.06	6.42	0.47
27	0.14	6.85	6.83	0.02	6.54	0.31
28	0.16	6.80	6.83	−0.03	6.80	0.00
29	0.15	6.82	6.83	−0.01	6.85	−0.03
30	0.13	6.89	6.83	0.06	6.85	0.04
31	0.16	6.80	6.83	−0.03	6.84	−0.04
32	0.07	7.15	6.83	0.32	6.88	0.27
33	0.15	6.82	6.83	−0.01	6.88	−0.06
34	0.42	6.38	6.24	0.14	6.29	0.09
35	1.30	5.89	6.24	−0.35	6.29	−0.40
36	2.40	5.62	6.24	−0.62	6.28	−0.66
37	0.41	6.39	6.24	0.15	6.29	0.10
38	1.50	5.82	6.24	−0.42	6.29	−0.47
39	0.54	6.27	6.24	0.03	6.28	−0.01
40	0.16	6.80	6.24	0.56	6.29	0.51
41	1.20	5.92	6.24	−0.32	6.29	−0.37
42	1.20	5.92	6.24	−0.32	6.29	−0.37
43	0.26	6.59	6.24	0.35	6.29	0.30
44	1.10	5.96	6.24	−0.28	6.29	−0.33
45	0.85	6.07	6.24	−0.17	6.29	−0.22
46	0.15	6.82	6.24	0.58	6.29	0.53
47	0.09	7.05	6.48	0.57	6.46	0.59
48	0.16	6.80	6.83	−0.03	6.88	−0.08
49	0.16	6.80	6.83	−0.03	6.92	−0.12
50	0.14	6.85	6.83	0.02	6.88	−0.03
51	0.16	6.80	6.83	−0.03	6.89	−0.09
52	0.38	6.42	6.83	−0.41	6.89	−0.47
53	0.15	6.82	6.83	−0.01	6.90	−0.08
54	0.15	6.82	6.83	−0.01	6.89	−0.07
55	0.19	6.72	6.83	−0.11	6.88	−0.16
56	2.00	5.70	5.66	0.04	5.72	−0.02
57	2.60	5.59	—[a]	—[a]	6.04	−0.45
58	0.38	6.42	—[a]	—[a]	6.70	−0.28
1	4.40	5.36	—[a]	—[a]	6.87	−1.51
2	4.13	5.38	—[a]	—[a]	6.90	−1.52

[a]The values were not calculated because of missing parameters.

Immediately before the assay, the brain homogenate was diluted to the fourfold volume with the PBS. Ten microliters of each of the solutions containing various amounts of antioxidants in dimethylsulfoxide (DMSO) were added to and mixed with 1 mL of the brain homogenate. The mixture was incubated with aeration at 37 °C for 15 h. The lipid peroxidation level in the incubated homogenate was measured as that of malonaldehyde formed by peroxidation of unsaturated lipids. The amount of malonaldehyde was measured as that of a red pigment formed by the condensation with thiobarbituric acid (TBA test) according to a method modified from that of Ohkawa et al.[28] Five hundred microliters of aqueous Desferal solution (final concentration: 1 mM) and 250 μL of BHT solution dissolved in DMSO (final concentration: 1 mM), both of which work as quenchers of further peroxidation, were mixed with 1 mL of 20% acetic acid and 1 mL of 1% aqueous TBA solution. The quenching solution (2.75 mL) was added to and mixed with the incubated homogenate. The mixture was heated at 95 °C for 20 min followed by cooling and extraction with 4 mL of *n*-butanol. The fluorescence of the *n*-butanol layer was measured at 536 nm (excitation) and 552 nm (emission). The inhibition percentage of the peroxidation was calculated from the difference in the fluorescence intensity between solutions from control and treated homogenates. The IC_{50} value was calculated by the Probit method from inhibitory percentage values at the concentrations of 0, 0.1, 1, and 10 μM using an appropriate commercial computer program.

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 Hitachi R-90 (90 MHz) or 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.

Preparation of the aniline 62

3-*tert*-Butyl-5-methoxy-2-methoxymethoxyaniline (62; X^2 = OMe, X^3 = H, X^4 = *t*-Bu). To a solution of *p*-anisidine (**59**, 153 g, 1.24 mol) in 25% HCl aq (1200 mL) was added slowly $NaNO_2$ (94 g, 1.36 mol) in water (300 mL) under cooling with ice-water. The mixture was added dropwise to a solution of 3-*tert*-butyl-4-hydroxyanisole (BHA, 212 g, 1.18 mol) in NaOH aq (248 g in 1000 mL of water) at 10 °C and stirred at the same temperature for 15 min. The mixture was acidified to pH 3 with concd HCl, the resulting crystals were collected by filtration, washed with water and dried. The crude crystals were recrystallized from $CHCl_3$–EtOH to yield 217 g (59%) of **60** (X^2 = OMe, X^3 = H, X^4 = *t*-Bu). The solid of **60** (217 g, 0.691 mol) was added portionwise to a suspension of sodium hydride (NaH, 31.8 g, 0.829 mol, 60% mineral oil suspended) in *N,N*-dimethylformamide (DMF, 860 mL) at 0 °C and stirred for 10 min at rt. To the reaction mixture was added chloromethyl methyl ether (MOMCl, 63 mL, 0.829 mol) dropwise at 0 °C and the resulting mixture was stirred at rt for 1 h. After evaporation of DMF, the residue was extracted with ethyl acetate (AcOEt), and the organic layer was washed with brine, dried ($MgSO_4$), and concd in vacuo. The resulting crystals were recrystallized from Et_2O-hexane to afford **61** (X^2 = OMe, X^3 = H, X^4 = *t*-Bu, 168 g, 68%). A mixture of **61** (168 g, 0.468 mol), 10% palladium on carbon (3.0 g) and MeOH (1600 mL) was subjected to hydrogenation using Parr apparatus (H_2, 3.5 atm) for 2.5 h at room temperature. After removal of catalyst by filtration, the filtrate was concentrated in vacuo. The residue was purified on silica gel chromatography using $CHCl_3$/AcOEt (10:1) to afford **62** (X^2 = OMe, X^3 = H, X^4 = *t*-Bu, 95.6 g, 85%): syrup; ^{1}H NMR (δ in $CDCl_3$) 1.35 (s, 9H, CH_3), 3.63 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 4.24 (br, 2H, NH_2), 4.95 (s, 2H, CH_2), 6.18 (δ, 1H, J = 3 Hz, ArH-4), 6.26 (d, 1H, J = 3 Hz, ArH-6); EIMS m/z 239 (M^+).

3,4,5-Trimethoxy-2-methoxymethoxyaniline (62; X^2 = OMe, X^3 = OMe, X^4 = OMe). To a solution of **63** (X^2 = OMe, X^3 = OMe, X^4 = OMe, 4.1 g, 18.0 mmol) in tetrahydrofuran (THF, 40 mL) was added dropwise *sec*-butyllithium (1.875 M in cyclohexane, 10.5 mL, 19.8 mmol) at −78 °C under nitrogen atmosphere and the mixture was stirred for 45 min at the same temperature. To the reaction mixture was added dropwise a solution of *p*-toluenesulfonyl azide ($TosN_3$, 3.9 g, 19.8 mmol) in THF (10 mL) at −78 °C under nitrogen atmosphere. The mixture was stirred at the same temperature for 2.5 h and poured onto aqueous sodium pyrophosphate ($Na_4P_2O_7$ aq, 60 mL) at 0 °C. After stirring the mixture for 2 h at the same temperature, the insoluble materials were removed by filtration, and the filtrate was extracted with AcOEt. The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified with silica gel chromatography using hexane/AcOEt (9:1). The fractions were collected and concentrated in vacuo. The residue was dissolved to THF (50 mL), added to a suspension of lithium aluminum hydride ($LiAlH_4$, 1.15 g) in THF (50 mL) at 0 °C and stirred for 40 min at the same temperature. To the mixture was added water (2.7 mL), 15% NaOH aq (2.7 mL), and water (8.1 mL) in this order. After the insoluble materials were removed by filtration, the filtrate

was concentrated in vacuo and the residue was diluted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was chromatographed on silica gel using hexane/AcOEt (2:1) as an eluent to give **62** (X^2 = OMe, X^3 = OMe, X^4 = OMe, 2.5 g, 57%): syrup; ^{1}H NMR (δ in $CDCl_3$) 3.57 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 5.03 (s, 2H, CH_2), 6.08 (s, 1H, ArH-6); EIMS *m*/*z* 243 (M^+).

In the same manner, the other substituted methoxymethoxyanilines were obtained.

Preparation of the amine (R-NH_2)

Commercially unavailable amines were synthesized by alkylation or acylation of the corresponding alcohols, amines and halides. The procedures are exemplified by the syntheses of 4-(3-dibutylaminopropyl)oxyaniline, and 2-(4-benzylpiperazin-1-yl)ethylamine as follows.

4-(3-Dibutylaminopropyl)oxyaniline. To a suspension of NaH (1.15 g, 29.6 mmol, 60% mineral oil suspended) in DMF (30 mL) was added dropwise *p*–aminophenol (3.2 g, 29 mmol) and the mixture was stirred for 30 min at room temperature. To the suspension was added slowly *N,N*-dibutyl-3-chloropropylamine (6.0 g, 29 mmol) at 0 °C and the reaction mixture was stirred for 2 h at room temperature. After the mixture was concentrated in vacuo, the residue was extracted with 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 $CHCl_3$/EtOH (20:1) to afford 4-(3-dibutylaminopropyl)oxyaniline (3.6 g, 44%): syrup; ^{1}H NMR (δ in $CDCl_3$) 0.89 (t, 6H, *J* = 7 Hz, CH_3), 1.19–1.49 (m, 8H, CH_2), 1.79–1.93 (m, 2H, CH_2), 2.40 (t, 4H, *J* = 7 Hz, CH_2), 2.57 (t, 2H, *J* = 7 Hz, CH_2), 3.40 (br, 2H, NH_2), 3.92 (t, 2H, *J* = 6 Hz, CH_2), 6.58–6.66 (m, 2H, ArH-2 and -6), 6.70–6.78 (m, 2H, ArH-3 and -5); EIMS *m*/*z* 279 ($M^+ + 1$).

2-(4-Benzylpiperazin-1-yl)ethylamine. A mixture of *N*-benzyloxycarbonyl-2-iodoethylamine (6.9 g, 22.7 mmol), *N*-benzylpiperazine (4.0 g, 22.7 mmol), and K_2CO_3 (15.7 g, 114 mmol) in hexamethylphosphoric triamide (HMPA, 40 mL) was stirred overnight at room temperature. The reaction mixture was diluted with water and extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo, and the residue was purified on silica gel chromatography using $CHCl_3$/EtOH (15:1) to afford *N*-benzyloxycarbonyl-2-(4-benzylpiperazin-1-yl)ethylamine (5.6 g, 70%). A solution of *N*-benzyloxycarbonyl-2-(4-benzylpiperazin-1-yl)ethylamine (2.3 g, 6.5 mmol) in 30% HBr-AcOH (50 mL) was stirred at room temperature for 1 h. To the solution was added Et_2O and the resulting solid was collected by filtration. The solid was dissolved in saturated $NaHCO_3$ aq and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to give 2-(4-benzylpiperazin-1-yl)ethylamine (1.2 g, 83%): syrup; ^{1}H NMR (δ in $CDCl_3$) 2.35–2.60 (m, 10H, CH_2), 2.78 (t, 2H, *J* = 6 Hz, CH_2), 3.51 (s, 2H, CH_2), 7.20–7.35 (m, 5H, ArH); EIMS *m*/*z* 219 (M^+).

Urea formation and removal of the methoxymethyl protecting group

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-(3-pyridylmethyl)urea (54). To a solution of triphosgene (5.58 g) in CH_2Cl_2 (450 mL), the solution of 3-*tert*-butyl-5-methoxy-2-methoxymethoxyaniline **62** (11.25 g, 47 mmol) and triethylamine (20 mL) in CH_2Cl_2 (150 mL) were added dropwise at −78 °C and the reaction mixture was warmed up to rt for 30 min. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (200 mL) and the solution of 3-picolylamine (5.1 g, 47 mmol) and triethylamine (10 mL) in CH_2Cl_2 (100 mL) was added dropwise at rt. After stirring at the same temperature for 1 h, the reaction mixture was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo, and the residue was chromatographed on silica using $CHCl_3$/MeOH (15:1). The crude crystals were recrystallized from *i*-Pr_2O-AcOEt to yield 14.0 g (80%) of 1-(3-*tert*-butyl-5-methoxy-2-methoxymethoxyphenyl)-3-(3-pyridylmethyl)urea (**72**). To a solution of **72** (14.0 g, 37.4 mmol) in MeOH (150 mL) was added concd HCl (6.8 mL) and the mixture was stirred at room temperature for 1 h. The resulting mixture was concd in vacuo and the crude crystals were recrystallized from EtOH to give **54** (11.2 g, 82%): mp 165–167 °C; IR (KBr) 3311, 3200, 1653, 1600 cm^{-1}; ^{1}H NMR (δ in DMSO-d_6) 1.33 (s, 9H, CH_3), 3.64 (s, 3H, CH_3), 4.45–4.6 (m, 2H, CH_2), 6.47 (d, 1H, *J* = 3 Hz, ArH-4), 6.85 (d, 1H, *J* = 3 Hz, ArH-6), 7.5–7.7 (m, 1H, NH), 7.95–8.1 (dd, 1H, *J* = 5, 8 Hz, PyH-5), 8.46 (d, 1H, *J* = 8 Hz, PyH-4), 8.75–8.9 (m, 3H, PyH-2, -6 and NH or OH); EIMS *m*/*z* 329 (M^+); Anal. Calcd for $C_{18}H_{23}N_3O_3$·HCl: C 59.09, H 6.61, N 11.49. Found: C 58.87, H 6.70, N 11.29.

In the same manner the following compounds were obtained.

1-(2-Hydroxy-5-methoxyphenyl)-3-phenylurea (5). Mp 158–159 °C; IR (KBr) 3310, 1604, 1565 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$ + DMSO-d_6) 3.76 (s, 3H, CH_3), 6.49–6.54 (dd, 1H, *J* = 3, 9 Hz, ArH-4), 6.85 (d, 1H, *J* = 9 Hz, ArH-3), 6.93–7.05 (m, 1H, ArH-4′), 7.10 (d, 1H, *J* = 3 Hz, ArH-6), 7.25–7.34 (m, 2H, ArH-3′ and -5′), 7.43–7.48 (m, 2H, ArH-2′ and -6′), 8.16 (br, 1H, NH or OH), 8.57

(br, 1H, NH or OH); EIMS *m/z* 258 (M^+); Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11, H, 5.46, N, 10.85. Found: C, 65.25, H, 5.36, N, 10.74.

1-(2-Hydroxy-4-methoxyphenyl)-3-phenylurea (6). Mp 164–166 °C; IR (KBr) 3285, 1620, 1562 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.67 (s, 3H, CH_3), 6.30–6.43 (dd, 1H, *J* = 3, 9 Hz, ArH-5), 6.48 (d, 1H, *J* = 3 Hz, ArH-3), 6.85–7.02 (m, 1H, ArH-4′), 7.17–7.34 (m, 2H, ArH-3′ and -5′), 7.42–7.52 (m, 2H, ArH-2′ and 6′), 7.85 (d, 1H, *J* = 9 Hz, ArH-6), 7.96 (s, 1H, NH or OH), 9.12 (s, 1H, NH or OH), 9.92 (s, 1H, NH or OH); EIMS *m/z* 258 (M^+); Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11, H, 5.46, N, 10.85. Found: C, 64.94, H, 5.35, N, 10.91.

1-(2-Hydroxy-3-methoxyphenyl)-3-phenylurea (7). Mp 153–155 °C; IR (KBr) 3533, 3310, 1642, 1563 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.79 (s, 3H, CH_3), 6.56–6.74 (m, 2H, ArH-4 and -5), 6.82–7.03 (m, 1H, ArH-4′), 7.18–7.35 (m, 2H, ArH-3′ and -5′), 7.42–7.52 (m, 2H, ArH-2′ and -6′), 7.68–7.80 (dd, 1H, *J* = 3, 9 Hz, ArH-6), 8.21 (s, 1H, NH or OH), 9.06 (br, 1H, NH or OH), 9.34 (s, 1H, NH or OH); EIMS *m/z* 258 (M^+); Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11, H, 5.46, N, 10.85. Found: C, 65.32, H, 5.45, N, 10.82.

1-(2-Hydroxy-5-octyloxyphenyl)-3-phenylurea (8). Mp 146–147 °C; IR (Nujol) 3300, 3150, 1620, 1600 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 0.70–2.00 (m, 15H, CH_3 and CH_2), 3.85 (t, 2H, *J* = 6 Hz, CH_2), 6.29–6.42 (dd, 1H, *J* = 3, 9 Hz, ArH-4), 6.73 (d, 1H, *J* = 9 Hz, ArH-3), 6.86–7.02 (m, 1H, ArH-4′), 7.17–7.35 (m, 2H, ArH-3′ and -5′), 7.43–7.53 (m, 2H, ArH-2′ and -6′), 7.77 (d, 1H, *J* = 3 Hz, ArH-6), 8.17 (s, 1H, NH or OH), 9.33 (s, 1H, NH or OH), 9.40 (s, 1H, NH or OH); EIMS *m/z* 356 (M^+); Anal. Calcd for $C_{21}H_{28}N_2O_3$: C, 70.76, H, 7.92, N, 7.86. Found: C, 70.85, H, 7.89, N, 7.89.

1-(2-Hydroxy-5-methylthiophenyl)-3-phenylurea (9). Mp 162–164 °C; IR (KBr) 3311, 1598, 1560 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 2.40 (s, 3H, CH_3), 6.79–6.82 (m, 2H, ArH-3, and -4), 6.88–7.05 (m, 1H, ArH-4′), 7.19–7.36 (m, 2H, ArH-3′ and -5′), 7.43–7.53 (m, 2H, ArH-2′ and -6′), 8.15 (s, 1H, ArH-6), 8.21 (s, 1H, NH or OH), 9.31 (s, 1H, NH or OH), 10.0 (br, 1H, NH or OH); EIMS *m/z* 274 (M^+); Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29, H, 5.14, N, 10.21. Found: C, 61.35, H, 4.95, N, 10.13.

1-(2-Hydroxy-5-methoxy-3-methylphenyl)-3-phenylurea (10). Mp 173–176 °C; IR (Nujol) 3300, 1635 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 2.20 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 6.33 (d, 1H, *J* = 3 Hz, ArH-4), 6.86–7.02 (m, 1H, ArH-4′), 7.18–7.35 (m, 2H, ArH-3′ and -5′), 7.43–7.53 (m, 2H, ArH-2′ and -6′), 7.58 (d, 1H, *J* = 3Hz, ArH-6), 8.25 (s, 1H, NH or OH), 8.30 (s, 1H, NH or OH), 9.37 (s, 1H, NH or OH); EIMS *m/z* 272 (M^+); Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16, H, 5.92, N, 10.29. Found: C, 66.06, H, 5.79, N, 10.18.

1-(3-Ethyl-2-hydroxy-5-methoxyphenyl)-3-phenylurea (11). Mp 150–152 °C; IR (Nujol) 3350, 3300, 1620 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.19 (t, 3H, *J* = 7.6 Hz, CH_3), 2.64 (q, 2H, *J* = 7.6 Hz, CH_2), 3.66 (s, 3H, CH_3), 6.38 (d, 1H, *J* = 3 Hz, ArH-4), 6.56 (d, 1H, *J* = 3 Hz, ArH-6), 7.02 (s, 1H, NH or OH), 7.07–7.16 (m, 1H, ArH-4′), 7.16 (s, 1H, NH or OH), 7.22–7.33 (m, 4H, ArH-2′, -3′, -5′ and -6′), 7.78 (s, 1H, NH or OH); EIMS *m/z* 286 (M^+); Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12, H, 6.34, N, 9.78. Found: C, 66.95, H, 6.10, N, 9.88.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-phenylurea (12). Mp 147–149 °C; IR (Nujol) 3400, 3350, 1670 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.40 (s, 9H, CH_3), 3.67 (s, 3H, CH_3), 6.38 (d, 1H, *J* = 3 Hz, ArH-4), 6.77 (d, 1H, *J* = 3 Hz, ArH-6), 6.84 (s, 1H, NH or OH), 7.05 (s, 1H, NH or OH), 7.08–7.15 (m, 1H, ArH-4′), 7.23–7.33 (m, 4H, ArH-2′, -3′, -5′ and -6′), 7.65 (s, 1H, NH or OH); EIMS *m/z* 314 (M^+); Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77, H, 7.05, N, 8.91. Found: C, 68.52, H, 6.90, N, 8.96.

1-(2-Hydroxy-5-methoxy-3-octylphenyl)-3-phenylurea (13). Mp 100–101 °C; IR (Nujol) 3500, 3270, 1632, 1620 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 0.83–0.95 (m, 3H, CH_3), 1.15–1.65 (m, 12H, CH_2), 2.50–2.59 (m, 2H, CH_2), 3.66 (s, 3H, CH_3), 6.30 (d, 1H, *J* = 3 Hz, ArH-4), 6.92–6.99 (m, 1H, ArH-4′), 7.23–7.31 (m, 2H, ArH-3′ and -5′), 7.43–7.47 (m, 2H, ArH-2′ and -6′), 7.50 (d, 1H, *J* = 3 Hz, ArH-6), 8.16 (s, 1H, NH or OH), 8.29 (s, 1H, NH or OH), 9.34 (s, 1H, NH or OH); SIMS *m/z* 371 ($M^+ + 1$); Anal. Calcd for $C_{22}H_{30}N_2O_3$: C, 71.32, H, 8.16, N, 7.56. Found: C, 71.23, H, 8.11, N, 7.44.

1-(2-Hydroxy-3,5-dimethoxyphenyl)-3-phenylurea (14). Mp 172–174 °C; IR (Nujol) 3400, 3300, 1640 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.68 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 6.25 (d, 1H, *J* = 3 Hz, ArH-4), 6.91–6.99 (m, 1H, ArH-4′), 7.23–7.31 (m, 2H, ArH-3′ and -5′), 7.42–7.46 (m, 2H, ArH-2′ and -6′), 7.45 (d, 1H, *J* = 3Hz, ArH-6), 8.24 (s, 1H, NH or OH), 8.57 (s, 1H, NH or OH), 9.38 (s, 1H, NH or OH); SIMS *m/z* 289 ($M^+ + 1$); Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49, H, 5.59, N, 9.72. Found: C, 62.19, H, 5.36, N, 9.64.

1-(2-Hydroxy-5-methoxy-3-octyloxyphenyl)-3-phenylurea (15). Mp 66–68 °C; IR (Nujol) 3400, 1670 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 0.80–1.90 (m, 15H, CH_3 and CH_2), 3.67 (s, 3H, CH_3), 3.96 (t, 2H, *J* = 6 Hz, CH_2), 6.22 (d, 1H, *J* = 3 Hz, ArH-4), 6.85–7.03 (m, 1H, ArH-4′), 7.18–7.34 (m, 2H, ArH-3′ and -5′), 7.42–7.52 (m, 2H, ArH-2′ and -6′), 7.48 (d, 1H, *J* = 3 Hz, ArH-6), 8.20 (s, 1H, NH or OH), 8.27 (s, 1H, NH or OH), 9.40 (s,

1H, NH or OH); EIMS *m/z* 386 (M^+); Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37, H, 7.82, N, 7.25. Found: C, 68.15, H, 7.80, N, 7.32.

1-(2-Hydroxy-3-methoxy-5-octyloxyphenyl)-3-phenylurea (16). Mp 115–117 °C; IR (Nujol) 3300, 1660 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 0.80–1.90 (m, 15H, CH_3 and CH_2), 3.77 (s, 3H, CH_3), 3.87 (t, 2H, J = 6 Hz, CH_2), 6.23 (d, 1H, J = 3 Hz, ArH-4), 6.85–7.03 (m, 1H, ArH-4′), 7.17–7.34 (m, 2H, ArH-3′ and -5′), 7.42–7.52 (m, 2H, ArH-2′ and -6′), 7.47 (d, 1H, J = 3 Hz, ArH-6), 8.23 (s, 1H, NH or OH), 8.51 (s, 1H, NH or OH), 9.38 (s, 1H, NH or OH); EIMS *m/z* 386 (M^+); Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37, H, 7.82, N, 7.25. Found: C, 68.29, H, 7.88, N, 7.19.

1-(2-Hydroxy-3,4,5-trimethoxyphenyl)-3-phenylurea (17). Mp 123–125 °C; IR (Nujol) 3350, 3300, 1670 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.75 (s, 6H, CH_3), 3.80 (s, 3H, CH_3), 6.87–7.03 (m, 1H, ArH-4′), 7.19–7.35 (m, 2H, ArH-3′ and -5′), 7.43–7.53 (m, 2H, ArH-2′ and -6′), 7.65 (s, 1H, ArH-6), 8.16 (s, 1H, NH or OH), 8.90 (s, 1H, NH or OH), 9.31 (s, 1H, NH or OH); EIMS *m/z* 318 (M^+); Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37, H, 5.70, N, 8.80. Found: C, 60.15, H, 5.66, N, 8.74.

1-(5-Hydroxy-2,4-dimethoxyphenyl)-3-phenylurea (18). Mp 162–164 °C; IR (KBr) 3372, 3280, 1664, 1597 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.76 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 6.70 (s, 1H, ArH-3), 6.86–7.03 (m, 1H, ArH-4′), 7.18–7.35 (m, 2H, ArH-3′ and -5′), 7.42–7.53 (m, 2H, ArH-2′ and -6′), 7.71 (s, 1H, ArH-6), 7.97 (s, 1H, NH or OH), 8.49 (s, 1H, NH or OH), 9.16 (s, 1H, NH or OH); EIMS *m/z* 288 (M^+); Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49, H, 5.59, N, 9.72. Found: C, 62.36, H, 5.49, N, 9.70.

1-(3-Trifluoromethylphenyl)-3-(2-hydroxy-5-methoxyphenyl)urea (19). Mp 155–157 °C; IR (Nujol) 3300, 1630 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.68 (s, 3H, CH_3), 6.38 (dd, 1H, J = 3, 9 Hz, ArH-4), 6.75 (d, 1H, J = 9 Hz, ArH-3), 7.20–7.53 (m, 3H, ArH-4′, -5′ and -6′), 7.75 (d, 1H, J = 3 Hz, ArH-6), 8.01 (s, 1H, NH or OH), 8.22 (s, 1H, ArH-2′), 9.45 (s, 1H, NH or OH), 9.67 (s, 1H, NH or OH); EIMS *m/z* 326 (M^+); Anal. Calcd for $C_{15}H_{13}N_2O_3F_3 \cdot H_2O$: C, 52.33, H, 4.39, N, 8.14. Found: C, 52.38, H, 4.29, N, 8.07.

1-(3-Carboxyphenyl)-3-(2-hydroxy-5-methoxyphenyl)urea (20). Mp 173–175 °C; IR (Nujol) 3310, 1670, 1600 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.66 (s, 3H, CH_3), 6.39 (dd, 1H, J = 3, 9 Hz, ArH-4), 6.76 (d, 1H, J = 9 Hz, ArH-3), 7.24–7.32 (m, 1H, ArH-5′), 7.56–7.62 (m, 2H, ArH-4′ and -6′), 7.76 (d, 1H, J = 3 Hz, ArH-6), 8.13 (s, 1H, ArH-2′), 8.59 (s, 1H, NH or OH), 9.75 (s, 1H, NH or OH); SIMS *m/z* 303 ($M^+ + 1$); Anal. Calcd for $C_{15}H_{14}N_2O_5 \cdot 0.25CHCl_3 \cdot H_2O$: C, 52.31, H, 4.68, N, 8.00. Found: C, 52.64, H, 4.46, N, 8.01.

1-(2-Hydroxy-5-methoxyphenyl)-3-(4-methylphenyl)urea (21). Mp 163–165 °C; IR (KBr) 3302, 1606 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 2.23 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 6.26–6.39 (dd, 1H, J = 3, 9 Hz, ArH-4), 6.72 (d, 1H, J = 9 Hz, ArH-3), 7.03 (d, 2H, J = 9 Hz, ArH-3′ and -5′), 7.31 (d, 2H, J = 9 Hz, ArH-2′ and -6′), 7.75 (d, 1H, J = 3 Hz, ArH-6), 8.10 (s, 1H, NH or OH), 9.18 (s, 1H, NH or OH), 9.36 (s, 1H, NH or OH); EIMS *m/z* 272 (M^+); Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16, H, 5.92, N, 10.29. Found: C, 66.10, H, 5.85, N, 10.35.

1-[4-(*trans*-Carboxyvinyl)phenyl]-3-(2-hydroxy-5-methoxyphenyl)urea (22). Mp 206 °C; IR (Nujol) 3350, 1670, 1600 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.66 (s, 3H, CH_3), 6.38 (d, 1H, J = 16 Hz, CH), 6.39 (dd, 1H, J = 3, 9 Hz, ArH-4), 6.74 (d, 1H, J = 9 Hz, ArH-3), 7.49 (d, 2H, J = 9 Hz, ArH-3′ and -5′), 7.53 (d, 1H, J = 16 Hz, CH), 7.61 (d, 2H, J = 9 Hz, ArH-2′ and -6′), 7.77 (d, 1H, J = 3 Hz, ArH-6), 8.26 (s, 1H, NH or OH), 9.50 (s, 1H, NH or OH), 9.60 (s, 1H, NH or OH), 12.22 (s, 1H, CO_2H); EIMS *m/z* 328 (M^+); Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19, H, 4.91, N, 8.53. Found: C, 61.94, H, 4.81, N, 8.47.

1-(4-Chlorophenyl)-3-(2-hydroxy-5-methoxyphenyl)urea (23). Mp 184–186 °C; IR (Nujol) 3300, 1620, 1595, 1570 cm^{-1}; ^1H NMR (δ in $CDCl_3$ + DMSO-d_6) 3.71 (s, 3H, CH_3), 6.33–6.46 (dd, 1H, J = 3, 9 Hz, ArH-4), 6.77 (d, 1H, J = 9 Hz, ArH-3), 7.18 (d, 2H, J = 9 Hz, ArH-3′ and -5′), 7.42 (d, 2H, J = 9 Hz, ArH-2′ and -6′), 7.53 (d, 1H, J = 3 Hz, ArH-6), 8.12 (s, 1H, NH or OH), 8.80 (s, 1H, NH or OH), 8.95 (s, 1H, NH or OH); EIMS *m/z* 292 (M^+); Anal. Calcd for $C_{14}H_{13}N_2O_3Cl$: C, 57.45, H, 4.48, N, 9.57. Found: C, 57.43, H, 4.43, N, 9.49.

1-(2-Hydroxy-5-methoxyphenyl)-3-(4-methoxyphenyl)urea (24). Mp 150–152 °C; IR (Nujol) 3300, 3200, 1620 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.66 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 6.26–6.40 (dd, 1H, J = 3, 9 Hz, ArH-4), 6.72 (d, 1H, J = 9 Hz, ArH-3), 6.83 (d, 2H, J = 9 Hz, ArH-3′ and -5′), 7.34 (d, 2H, J = 9 Hz, ArH-2′ and -6′), 7.75 (d, 1H, J = 3 Hz, ArH-6), 8.05 (s, 1H, NH or OH), 9.12 (s, 1H, NH or OH), 9.36 (s, 1H, NH or OH); EIMS *m/z* 288 (M^+); Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49, H, 5.59, N, 9.72. Found: C, 62.48, H, 5.40, N, 9.74.

1-(4-Ethoxycarbonylmethoxyphenyl)-3-(2-hydroxy-5-methoxyphenyl)urea (25). Mp 143–144 °C; IR (KBr) 3350, 1740, 1680, 1600 cm^{-1}; ^1H NMR (δ in $CDCl_3$ + DMSO-d_6) 1.29 (t, 3H, J = 7 Hz, CH_3), 3.71 (s, 3H, CH_3), 4.24 (q, 2H, J = 7 Hz, CH_2), 4.55 (s, 2H, CH_2), 6.39–6.52 (dd, 1H, J = 3, 9 Hz, ArH-4), 6.80 (d, 1H, J = 9 Hz, ArH-3), 6.81 (d, 2H, J = 9 Hz, ArH-3′ and -5′), 7.10 (d, 1H,

$J = 3$ Hz, ArH-6), 7.32 (d, 2H, $J = 9$ Hz, ArH-2′ and -6′), 8.01 (s, 1H, NH or OH), 8.40 (s, 1H, NH or OH), 8.97 (br, 1H, NH or OH); EIMS m/z 360 (M^+); Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99, H, 5.59, N, 7.76. Found: C, 59.61, H, 5.55, N, 7.58.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-(4-dimethylaminophenyl)urea (26). Mp 196–199 °C; IR (KBr) 2957, 2557, 1677, 1572 cm^{-1}; ^{1}H NMR (δ in DMSO-d_6) 1.36 (s, 9H, CH_3), 3.10 (s, 6H, CH_3), 3.68 (s, 3H, CH_3), 6.48 (d, 1H, $J = 3$ Hz, ArH-4), 7.19 (d, 1H, $J = 3$ Hz, ArH-6), 7.55–7.65 (m, 4H, ArH-2′, -3′, -5′ and -6′), 8.65 (s, 1H, NH or OH), 9.75 (s, 1H, NH or OH); EIMS m/z 357 (M^+); Anal. Calcd for $C_{20}H_{27}N_3O_3$·HCl: C, 60.98, H, 7.16, N, 10.67. Found: C, 60.94, H, 7.15, N, 10.54.

1-[4-(3-Dibutylaminopropyl)oxyphenyl]-3-(3-*tert*-butyl-2-hydroxy-5-methoxyphenyl)urea (27). Mp 150–153 °C; IR (KBr) 2960, 1670, 1610 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 0.88 (t, 6H, $J = 7.2$ Hz, CH_3), 1.20–1.35 (m, 4H, CH_2), 1.41 (s, 9H, CH_3), 1.60–1.80 (m, 4H, CH_2), 2.10–2.30 (m, 2H, CH_2), 2.90–3.05 (m, 4H, CH_2), 3.10–3.25 (m, 2H, CH_2), 3.63 (t, 2H, CH_2), 3.72 (s, 3H, CH_3), 6.54 (d, 1H, $J = 3$ Hz, ArH-4), 6.55 (d, 2H, $J = 9$ Hz, ArH-3′ and -5′), 6.70 (d, 1H, $J = 3$ Hz, ArH-6), 7.36 (d, 2H, $J = 9$ Hz, ArH-2′ and -6′), 8.65 (s, 1H, NH or OH), 9.08 (s, 1H, NH or OH); EIMS m/z 515 (M^+); Anal. Calcd for $C_{29}H_{45}N_3O_4$·HCl·0.25H_2O: C, 64.42, H, 8.67, N, 7.77. Found: C, 64.42, H, 8.44, N, 7.97.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-(2,6-diisopropylphenyl)urea (28). Mp 193–195 °C; IR (KBr) 3323, 2965, 1639, 1556 cm^{-1}; ^{1}H NMR (δ in DMSO-d_6) 1.16 (d, 12H, $J = 7$ Hz, CH_3), 1.34 (s, 9H, CH_3), 3.10–3.24 (m, 2H, CH), 3.65 (s, 3H, CH_3), 6.46 (d, 1H, $J = 3$ Hz, ArH-4), 7.07–7.31 (m, 4H, ArH-6, -3′, -4′ and -5′), 8.19 (s, 1H, NH or OH), 8.56 (s, 1H, NH or OH), 8.61 (s, 1H, NH or OH); EIMS m/z 398 (M^+); Anal. Calcd for $C_{24}H_{34}N_2O_3$: C, 72.33, H, 8.60, N, 7.03. Found: C, 72.33, H, 8.59, N, 6.92.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-(2,4-difluorophenyl)urea (29). Mp 153–154 °C; IR (KBr) 3334, 1640 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 1.40 (s, 9H, CH_3), 3.71 (s, 3H, CH_3), 6.48 (d, 1H, $J = 3$ Hz, ArH-4), 6.76–6.88 (m, 2H, ArH-5′ and -6′), 6.80 (d, 1H, $J = 3$ Hz, ArH-6), 6.90 (s, 1H, NH or OH), 7.02 (s, 1H, NH or OH), 7.12 (s, 1H, NH or OH), 7.80–7.95 (m, 1H, ArH-3′); EIMS m/z 350 (M^+); Anal. Calcd for $C_{18}H_{20}N_2O_3F_2$: C, 61.71, H, 5.75, N, 8.00. Found: C, 61.80, H, 5.71, N, 7.84.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-(2-pyridyl)urea (30). Mp 185–187 °C; IR (KBr) 3096, 1696, 1652, 1540 cm^{-1}; ^{1}H NMR (δ in DMSO-d_6) 1.36 (s, 9H, CH_3), 3.69 (s, 3H, CH_3), 6.55 (d, 1H, $J = 3$ Hz, ArH-4), 7.22 (m, 1H, PyH-5), 7.26 (d, 1H, $J = 3$ Hz, ArH-6), 7.48 (d, 1H, $J = 8$ Hz, PyH-3), 8.0–8.15 (m, 1H, PyH-4), 8.25–8.35 (m, 1H, PyH-6), 9.93 (s, 1H, NH or OH), 11.25 (s, 1H, NH or OH); EIMS m/z 315 (M^+); Anal. Calcd for $C_{17}H_{21}N_3O_3$·HCl: C, 58.04, H, 6.30, N, 11.94. Found: C, 57.91, H, 6.34, N, 11.70.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-(3-pyridyl)urea (31). Mp 200–202 °C; IR (Nujol) 3170, 1715 cm^{-1}; ^{1}H NMR (δ in DMSO-d_6) 1.36 (s, 9H, CH_3), 3.68 (s, 3H, CH_3), 6.52 (d, 1H, $J = 3$ Hz, ArH-4), 7.24 (d, 1H, $J = 3$ Hz, ArH-6), 7.93 (dd, 1H, $J = 5$, 9 Hz, PyH-5), 8.36 (d, 1H, $J = 9$ Hz, PyH-4), 8.50 (d, 1H, $J = 5$ Hz, PyH-6), 8.81 (s, 1H, NH or OH), 9.13 (d, 1H, $J = 2$ Hz, PyH-2), 10.72 (s, 1H, NH or OH); EIMS m/z 315 (M^+); Anal. Calcd for $C_{17}H_{21}N_3O_3$·HCl: C, 58.04, H, 6.30, N, 11.94. Found: C, 58.13, H, 6.55, N, 11.85.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-(4-pyridyl)urea (32). Mp 193–195 °C; IR (KBr) 3520, 3480, 2952, 1723, 1610, 1587 cm^{-1}; ^{1}H NMR (δ in DMSO-d_6) 1.36 (s, 9H, CH_3), 3.69 (s, 3H, CH_3), 6.55 (d, 1H, $J = 3$ Hz, ArH-4), 7.23 (d, 1H, $J = 3$ Hz, ArH-6), 7.95 (d, 2H, $J = 7.2$ Hz, PyH-2 and -6), 8.05 (br, 1H, NH or OH), 8.59 (d, 2H, $J = 7.2$ Hz, PyH-3 and -5), 8.98 (s, 1H, NH or OH), 11.59 (s, 1H, NH or OH); EIMS m/z 315 (M^+); Anal. Calcd for $C_{17}H_{21}N_3O_3$·HCl·1.5H_2O: C, 53.90, H, 6.65, N, 11.09. Found: C, 53.88, H, 6.58, N, 10.73.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-cyclohexylurea (33). Mp 147–148 °C; IR (KBr) 3375, 2932, 1572 cm^{-1}; ^{1}H NMR (δ in $CDCl_3$) 1.12–2.00 (m, 10H, CH_2), 1.41 (s, 9H, CH_3), 3.50–3.70 (m, 1H, CH), 3.64 (s, 3H, CH_3), 5.24 (d, 1H, $J = 7.8$ Hz, NH), 6.06 (d, 1H, $J = 3$ Hz, ArH-4), 6.33 (s, 1H, NH or OH), 6.73 (d, 1H, $J = 3$ Hz, ArH-6), 8.70 (s, 1H, NH or OH); EIMS m/z 320 (M^+); Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47, H, 8.81, N, 8.74. Found: C, 67.42, H, 9.02, N, 9.00.

1-(2-Hydroxy-5-methoxyphenyl)-3-diphenylmethylaminoethylurea (34). Mp 198–201 °C; IR (Nujol) 3350, 3290, 1670, 1650 cm^{-1}; ^{1}H NMR (δ in DMSO-d_6) 2.80–3.00 (m, 2H, CH_2), 3.30–3.50 (m, 2H, CH_2), 3.62 (s, 3H, CH_3), 5.40 (s, 1H, CH), 6.32 (dd, 1H, $J = 3$, 9 Hz, ArH-4), 6.74 (d, 1H, $J = 9$ Hz, ArH-3), 7.10–7.80 (m, 12H, ArH and NH or OH), 7.66 (d, 1H, $J = 3$ Hz, ArH-6), 8.06 (s, 1H, NH or OH), 9.43 (s, 1H, NH or OH); SIMS m/z 392 ($M^+ + 1$); Anal. Calcd for $C_{23}H_{25}N_3O_3$·HCl·0.25H_2O: C, 63.88, H, 6.18, N, 9.72. Found: C, 64.03, H, 6.09, N, 9.67.

1-(2-Hydroxy-5-methoxyphenyl)-3-[2-(4-phenylpiperadin-1-yl)ethyl]urea (35). Mp 172–174 °C; IR (Nujol) 3350, 1670, 1650, 1610 cm^{-1}; ^{1}H NMR (δ in DMSO-d_6) 3.10–3.35 (m, 6H, CH_2), 3.50–3.70 (m, 4H, CH_2), 3.63 (s, 3H, CH_3), 3.81 (d, 2H, $J = 9$ Hz, CH_2), 6.34 (dd, 1H, $J = 3$,

8.8 Hz, ArH-4), 6.74 (d, 1H, $J=8.8$ Hz, ArH-3), 6.86 (t, 1H, $J=7$ Hz, ArH-4′), 6.99 (d, 2H, $J=8$ Hz, ArH-3′ and -5′), 7.26 (m, 2H, ArH-2′ and -6′), 7.38 (br, 1H, NH or OH), 7.64 (d, 1H, $J=3$ Hz, ArH-6), 8.12 (s, 1H, NH or OH), 11.01 (s, 1H, NH or OH); EIMS m/z 370 (M^+); Anal. Calcd for $C_{20}H_{26}N_4O_3$·HCl: C, 59.03, H, 6.69, N, 13.77. Found: C, 58.78, H, 6.66, N, 13.61.

1-{2-[4-(3-Trifluoromethylphenyl)piperadin-1-yl]ethyl}-3-(2-hydroxy-5-methoxyphenyl)urea (36). Mp 181–182 °C; IR (Nujol) 3300, 1660 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.15–3.30 (m, 8H, CH_2), 3.53–3.56 (m, 2H, CH_2), 3.63 (s, 3H, CH_3), 3.96–4.01 (m, 2H, CH_2), 6.32 (dd, 1H, $J=3$, 9 Hz, ArH-4), 6.71 (d, 1H, $J=9$ Hz, ArH-3), 7.16 (d, 1H, $J=7.6$ Hz, ArH-6′), 7.28–7.32 (m, 2H, ArH-2′ and -4′), 7.48 (t, 1H, $J=8$ Hz, ArH-5′), 7.65 (d, 1H, $J=3$ Hz, ArH-6), 8.07 (s, 1H, NH or OH), 9.41 (s, 1H, NH or OH), 10.56 (br, 1H, NH or OH); EIMS m/z 438 (M^+); Anal. Calcd for $C_{21}H_{25}N_4O_3F_3$·HCl: C, 53.11, H, 5.52, N, 11.80. Found: C, 53.11, H, 5.48, N, 11.85.

1-{2-[4-(4-Chlorophenyl)piperadin-1-yl]ethyl}-3-(2-hydroxy-5-methoxyphenyl)urea (37). Mp 183–186 °C; IR (Nujol) 3250, 1660, 1590 cm^{-1}; ^1H NMR (δ in D_2O + TFA + DMSO-d_6) 3.40–3.50 (m, 4H, CH_2), 3.60–3.75 (m, 8H, CH_2), 3.76 (s, 3H, CH_3), 6.65–6.71 (dd, 1H, $J=3$, 9 Hz, ArH-4), 6.90 (d, 1H, $J=9$ Hz, ArH-3), 7.19 (d, 1H, $J=3$ Hz, ArH-6), 7.26 (d, 2H, $J=9$ Hz, ArH-3′ and -5′), 7.46 (d, 2H, $J=9$ Hz, ArH-2′ and -6′); EIMS m/z 404(M^+); Anal. Calcd for $C_{20}H_{25}N_4O_3$ Cl·HCl: C, 54.43, H, 5.94, N, 12.69. Found: C, 54.36, H, 5.94, N, 12.69.

1-(2-Hydroxy-5-methoxyphenyl)-3-{2-[4-(4-methoxyphenyl)piperain-1-yl]ethyl}urea (38). Mp 183–185 °C; IR (Nujol) 3350, 3300, 3200, 1640 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.10–3.45 (m, 6H, CH_2), 3.50–3.80 (m, 6H, CH_2), 3.63 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 6.33 (dd, 1H, $J=3$, 9 Hz, ArH-4), 6.73 (d, 1H, $J=9$ Hz, ArH-3), 6.88 (d, 2H, $J=9$ Hz, ArH-3′ and -5′), 7.03 (d, 2H, $J=9$ Hz, ArH-2′ and -5′), 7.33 (br, 1H, NH or OH), 7.64 (d, 1H, $J=3$ Hz, ArH-6), 8.09 (s, 1H, NH or OH), 10.90 (br, 1H, NH or OH); EIMS m/z 400 (M^+); Anal. Calcd for $C_{21}H_{28}N_4O_4$·2.0HCl: C, 53.28, H, 6.39, N, 11.83. Found: C, 53.39, H, 6.29, N, 11.73.

1-(2-Hydroxy-5-methoxyphenyl)-3-[2-(4-diphenylmethylpiperadin-1-yl)ethyl]urea (39). Mp 200–202 °C; IR (Nujol) 3390, 3260, 2400, 1665 cm^{-1}; ^1H NMR (δ in DMSO-d_6 + D_2O) 2.70–2.90 (br, 4H, CH_2), 3.15–3.30 (m, 2H, CH_2), 3.35–3.50 (m, 6H, CH_2), 3.64 (s, 3H, CH_3), 4.80 (s, 1H, CH), 6.38 (dd, 1H, $J=3$, 9 Hz, ArH-4), 6.73 (d, 1H, $J=9$ Hz, ArH-3), 7.24–7.41 (m, 6H, ArH), 7.53–7.56 (m, 4H, ArH), 7.58 (d, 1H, $J=3$ Hz, ArH-6); EIMS m/z 460 (M^+); Anal. Calcd for $C_{27}H_{32}N_4O_3$·2.0HCl·H_2O: C, 58.80, H, 6.58, N, 10.16. Found: C, 59.08, H, 6.41, N, 10.27.

1-{2-[4-Bis(4-fluorophenyl)methylpiperadin-1-yl]ethyl}-3-(2-hydroxy-5-methoxyphenyl)urea (40). Mp 203–205 °C; IR (KBr) 3389, 3230, 2310, 1664 cm^{-1}; ^1H NMR (δ in DMSO-d_6 + D_2O) 2.55–2.80 (br, 4H, CH_2), 3.20–3.30 (m, 2H, CH_2), 3.35–3.50 (m, 6H, CH_2), 3.64 (s, 3H, CH_3), 4.75 (s, 1H, CH), 6.38 (dd, 1H, $J=3$, 9 Hz, ArH-4), 6.73 (d, 1H, $J=9$ Hz, ArH-3), 7.19 (t, 4H, $J=9$ Hz, ArH), 7.53 (dd, 4H, $J=6$, 9 Hz, ArH), 7.58 (d, 1H, $J=3$ Hz, ArH-6); SIMS m/z 497 ($M^+ + 1$); Anal. Calcd for $C_{27}H_{30}N_4O_3F_2$·2.0HCl·H_2O: C, 55.20, H, 5.83, N, 9.54. Found: C, 55.31, H, 5.57, N, 9.49.

1-(2-Hydroxy-5-methoxyphenyl)-3-[2-(4-diphenylmethylenepiperidin-1-yl)ethyl]urea (41). Mp 124–127 °C; IR (Nujol) 3380, 3300, 1680 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 2.25–2.50 (m, 10H, CH_2), 3.15–3.30 (m, 2H, CH_2), 3.62 (s, 3H, CH_3), 6.30 (dd, 1H, $J=3$, 9 Hz, ArH-4), 6.66 (d, 1H, $J=9$ Hz, ArH-3), 6.85–6.95 (m, 1H, NH), 7.05–7.15 (m, 4H, ArH), 7.15–7.35 (m, 6H, ArH), 7.60 (d, 1H, $J=3$ Hz, ArH-6), 8.02 (s, 1H, NH or OH), 9.32 (s, 1H, NH or OH); EIMS m/z 457 (M^+); Anal. Calcd for $C_{28}H_{31}N_3O_3$: C, 73.49, H, 6.83, N, 9.18. Found: C, 73.09, H, 6.71, N, 8.99.

1-{2-[4-Bis(4-fluorophenyl)methylenepiperidin-1-yl]ethyl}-3-(2-hydroxy-5-methoxyphenyl)urea (42). Mp 128–131 °C; IR (Nujol) 3380, 3300, 1680, 1600, 1595 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 2.25–2.35 (m, 4H, CH_2), 2.35–2.60 (m, 6H, CH_2), 3.15–3.25 (m, 2H, CH_2), 3.62 (s, 3H, CH_3), 6.30 (dd, 1H, $J=3$, 9 Hz, ArH-4), 6.67 (d, 1H, $J=9$ Hz, ArH-3), 6.85–6.95 (m, 1H, NH), 7.15–7.25 (m, 8H, ArH), 7.60 (d, 1H, $J=3$ Hz, ArH-6), 8.02 (s, 1H, NH or OH), 9.31 (s, 1H, NH or OH); SIMS m/z 494 ($M^+ + 1$); Anal. Calcd for $C_{28}H_{29}N_3O_3F_2$: C, 68.14, H, 5.92, N, 8.51. Found: C, 67.83, H, 5.96, N, 8.38.

1-(2-Hydroxy-5-methoxyphenyl)-3-[*N*-2-(4-methoxyphenyl)ethyl-*N*-methyl]aminopropylurea (43). Mp 185–187 °C; IR (Nujol) 3240, 2620, 1670, 1600 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 1.80–1.95 (m, 2H, CH_2), 2.79 (s, 3H, CH_3), 2.92–3.18 (m, 8H, CH_2), 3.62 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 6.32 (dd, 1H, $J=3$, 9 Hz, ArH-4), 6.70 (d, 1H, $J=9$ Hz, ArH-3), 6.88 (d, 2H, $J=9$ Hz, ArH-2′ and -6′), 7.12 (m, 1H, NH), 7.21 (d, 2H, $J=9$ Hz, ArH-3′ and -5′), 7.63 (d, 1H, $J=3$ Hz, ArH-6), 8.00 (s, 1H, NH or OH), 9.42 (s, 1H, NH or OH); SIMS m/z 388 ($M^+ + 1$); Anal. Calcd for $C_{21}H_{29}N_3O_4$·HCl: C, 59.50, H, 7.13, N, 9.91. Found: C, 59.47, H, 7.19, N, 9.90.

1-(2-Hydroxy-5-methoxyphenyl)-3-[*N*-2-(3,4-dimethoxyphenyl)ethyl-*N*-methyl]aminopropylurea (44). Mp 143–144 °C; IR (KBr) 3260, 2950, 2630, 1670, 1610 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 1.85–1.95 (m, 2H, CH_2), 2.79 (d,

3H, $J=4$ Hz, CH_3), 2.93–3.23 (m, 8H, CH_2), 3.62 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 6.32 (dd, 1H, $J=3$, 9 Hz, ArH-4), 6.71 (d, 1H, $J=9$ Hz, ArH-3), 6.77–6.82 (dd, 1H, $J=2$, 8 Hz, ArH-6′), 6.88 (d, 1H, $J=8$ Hz, ArH-5′), 6.91 (d, 1H, $J=2$ Hz, ArH-2′), 7.16 (m, 1H, NH), 7.62 (d, 1H, $J=3$ Hz, ArH-6), 8.02 (s, 1H, NH or OH), 9.45 (s, 1H, NH or OH); SIMS m/z 418 ($M^+ + 1$); Anal. Calcd for $C_{22}H_{31}N_3O_5 \cdot HCl$: C, 58.21, H, 7.11, N, 9.26. Found: C, 57.91, H, 7.16, N, 9.13.

1-(2-Hydroxy-5-methoxyphenyl)-3-[3-(4-phenylpiperadin-1-yl)propyl]urea (45). Mp 189–191 °C; IR (Nujol) 3350, 3150, 1650 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 1.90–2.10 (m, 2H, CH_2), 3.10–3.30 (m, 6H, CH_2), 3.40–3.70 (m, 4H, CH_2), 3.63 (s, 3H, CH_3), 3.70–3.90 (m, 2H, CH_3), 6.32 (dd, 1H, $J=3$, 9 Hz, ArH-4), 6.71 (d, 1H, $J=9$ Hz, ArH-3), 6.86 (t, 1H, $J=7$ Hz, ArH-4′), 7.00 (d, 2H, $J=8$ Hz, ArH-3′ and -5′), 7.14 (br, 1H, NH), 7.20–7.30 (m, 2H, ArH-2′ and -6′), 7.63 (d, 1H, $J=3$ Hz, ArH-6), 8.00 (s, 1H, NH or OH), 10.81 (br, 1H, NH or OH); EIMS m/z 384 (M^+); Anal. Calcd for $C_{21}H_{28}N_4O_3 \cdot HCl$: C, 59.92, H, 6.94, N, 13.31. Found: C, 59.73, H, 7.05, N, 13.32.

1-(2-Hydroxy-5-methoxyphenyl)-3-[3-(4-diphenylmethylpiperadin-1-yl)propyl]urea (46). Mp 181–183 °C; IR (Nujol) 3380, 3280, 1660 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.8–1.95 (m, 2H, CH_2), 2.30–2.55 (m, 2H, CH_2), 2.80–2.95 (m, 2H, CH_2), 3.05–3.20 (m, 6H, CH_2), 3.40–3.55 (m, 2H, CH_2), 3.62 (s, 3H, CH_3), 4.45 (s, 1H, CH), 6.31 (dd, 1H, $J=3$, 9 Hz, ArH-4), 6.70 (d, 1H, $J=9$ Hz, ArH-3), 7.10–7.15 (m, 1H, NH), 7.20–7.35 (m, 6H, ArH), 7.42–7.46 (m, 4H, ArH), 7.61 (d, 1H, $J=3$ Hz, ArH-6), 7.99 (s, 1H, NH or OH), 9.42 (s, 1H, NH or OH); SIMS m/z 475 ($M^+ + 1$); Anal. Calcd for $C_{28}H_{34}N_4O_3 \cdot 2.0HCl \cdot H_2O$: C, 59.47, H, 6.77, N, 9.91. Found: C, 59.55, H, 6.70, N, 10.08.

1-(2-Hydroxy-3,5-dimethoxyphenyl)-3-(2-diphenylmethylaminoethyl)urea (47). Mp 183–185 °C; IR (KBr) 3300, 1670 cm^{-1}; ^1H NMR (δ in D_2O + TFA + DMSO-d_6) 3.10–3.20 (m, 2H, CH_2), 3.50–3.60 (m, 2H, CH_2), 3.75 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 5.57 (s, 1H, CH), 6.42 (d, 1H, $J=2.5$ Hz, ArH-4), 6.96 (d, 1H, $J=2.5$ Hz, ArH-6), 7.44–7.56 (m, 10H, ArH); SIMS m/z 422 ($M^+ + 1$); Anal. Calcd for $C_{24}H_{27}N_3O_4 \cdot HCl$: C, 62.95, H, 6.16, N, 9.18. Found: C, 62.59, H, 6.17, N, 8.92.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-[2-(4-benzylpiperadin-1-yl)ethyl]urea (48). Mp 134–135 °C; IR (Nujol) 3350, 3300, 1610 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.42 (s, 9H, CH_3), 2.4–2.7 (m, 10H, CH_2), 3.2–3.4 (m, 2H, CH_2), 3.48 (s, 2H, CH_2), 3.74 (s, 3H, CH_3), 5.45 (m, 1H, NH), 6.42 (d, 1H, $J=3$ Hz, ArH-4), 6.77 (d, 1H, $J=3$ Hz, ArH-6), 7.29 (m, 7H, ArH); SIMS m/z 441 ($M^+ + 1$); Anal. Calcd for $C_{25}H_{36}N_4O_3$: C, 68.15, H, 8.24, N, 12.72. Found: C, 67.99, H, 8.45, N, 12.57.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-[2-(4-diphenylmethylpiperadin-1-yl)ethyl]urea (49). Mp 169–175 °C; IR (KBr) 3312, 1655 cm^{-1}; ^1H NMR (δ in DMSO-d_6 + D_2O) 1.34 (s, 9H, CH_3), 2.60–2.80 (br, 4H, CH_2), 3.20–3.35 (m, 2H, CH_2), 3.35–3.55 (m, 6H, CH_2), 3.65 (s, 3H, CH_3), 4.68 (s, 1H, CH), 6.52 (d, 1H, $J=3$ Hz, ArH-4), 6.78 (d, 1H, $J=3$ Hz, ArH-6), 7.23–7.53 (m, 10H, ArH); EIMS m/z 516 (M^+); Anal. Calcd for $C_{31}H_{40}N_4O_3 \cdot 2.0HCl \cdot H_2O$: C, 61.28, H, 7.30, N, 9.22. Found: C, 61.36, H, 7.44, N, 8.95.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-[3-(4-diphenylmethylpiperadin-1-yl)propyl]urea (50). Mp 173–175 °C; IR (Nujol) 3270, 1655, 1600 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.36 (s, 9H, CH_3), 1.9–2.1 (m, 2H, CH_2), 2.5–3.5 (m, 12H, CH_2), 3.68 (s, 3H, CH_3), 4.24 (s, 1H, CH), 6.55 (d, 1H, $J=3$ Hz, ArH-4), 6.67 (d, 1H, $J=3$ Hz, ArH-6), 7.1–7.35 (m, 11H, ArH and NH or OH), 8.50 (s, 1H, NH or OH), 8.90 (s, 1H, NH or OH); SIMS m/z 531 ($M^+ + 1$); Anal. Calcd for $C_{32}H_{42}N_4O_3 \cdot HCl$: C, 67.77, H, 7.64, N, 9.88. Found: C, 67.60, H, 7.62, N, 9.92.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-(2-chloroethyl)urea (51). Mp 126–128 °C; IR (KBr) 3353, 2961, 1628 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.40 (s, 9H, CH_3), 3.5–3.7 (m, 4H, CH_2), 3.71 (s, 3H, CH_3), 5.51 (br, 1H, NH or OH), 6.41 (d, 1H, $J=3$ Hz, ArH-4), 6.68 (s, 1H, NH or OH), 6.78 (d, 1H, $J=3$ Hz, ArH-6); EIMS m/z 300 (M^+); Anal. Calcd for $C_{14}H_{21}N_2O_3Cl$: C, 55.91, H, 7.04, N, 9.31. Found: C, 56.07, H, 7.28, N, 9.11.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-(2,3-dihydroxypropyl)urea (52). Mp 118–123 °C; IR (Nujol) 3350, 3300, 2850, 1630, 1610 cm^{-1}; ^1H NMR (δ in $CDCl_3$ + DMSO-d_6) 1.40 (s, 9H, CH_3), 2.30 (br, 2H, CH_2), 3.3–3.5 (m, 2H, CH_2), 3.55–3.7 (m, 2H, CH_2), 3.72 (s, 3H, CH_3), 3.99 (m, 1H, CH), 6.2–6.4 (m, 1H, NH), 6.41 (d, 1H, $J=3$ Hz, ArH-4), 6.68 (d, 1H, $J=3$ Hz, ArH-6), 7.93 (s, 1H, NH or OH), 8.81 (s, 1H, NH or OH); SIMS m/z 313 ($M^+ + 1$); Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68, H, 7.74, N, 8.97. Found: C, 57.62, H, 7.76, N, 8.80.

4-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-1-phenylsemicarbazide (53). Mp 160–162 °C; IR (Nujol) 3370, 3340, 1660, 1605 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.41 (s, 9H, CH_3), 3.69 (s, 3H, CH_3), 6.34 (d, 1H, $J=3$ Hz, ArH-4), 6.59 (s, 1H, NH), 6.75 (d, 1H, $J=3$ Hz, ArH-6), 3.89 (d, 2H, $J=7$ Hz, ArH-3′ and -5′), 7.01 (t, 1H, $J=7$ Hz, ArH-4′), 7.26 (s, 1H, NH or OH), 7.26–7.34 (m, 2H, ArH-2′ and -6′), 7.83 (s, 1H, NH or OH); EIMS m/z 329 (M^+); Anal. Calcd for $C_{18}H_{23}N_3O_3$: C,

65.63, H, 7.04, N, 12.76. Found: C, 65.51, H, 7.38, N, 12.49.

1-(3-*tert*-Butyl-2-hydroxy-5-methoxyphenyl)-3-(3-pyridylethyl)urea (55). Mp 172–175 °C; IR (KBr) 3350, 1636 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 1.32 (s, 9H, CH_3), 2.92–3.08 (m, 2H, CH_2), 3.40–3.55 (m, 2H, CH_2), 3.63 (s, 3H, CH_3), 6.45 (d, 1H, J = 3 Hz, ArH-4), 6.73 (d, 1H, J = 3 Hz, ArH-6), 7.00–7.15 (m, 1H, NH), 8.01 (dd, 1H, J = 5, 8 Hz, PyH-5), 8.50 (d, 1H, J = 8 Hz, PyH-4), 8.69 (s, 1H, NH or OH), 8.80 (d, 1H, J = 5 Hz, PyH-6), 8.88 (s, 1H, PyH-2); EIMS m/z 343 (M^+); Anal. Calcd for $C_{19}H_{25}N_3O_3$·HCl: C, 60.07, H, 6.90, N, 11.06. Found: C, 59.86, H, 6.86, N, 10.97.

Ethyl 7-[3-(3-*tert*-butyl-2-hydroxy-5-methoxyphenyl) ureido]-7-phenylheptanoate (56). Mp 93–95 °C; IR (KBr) 3320, 2940, 1642 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 1.24 (t, 3H, J = 7 Hz, CH_3), 1.2–1.9 (m, 8H, CH_2), 1.39 (s, 9H, CH_3), 2.27 (t, 2H, J = 7 Hz, CH_2), 3.67 (s, 3H, CH_3), 4.11 (q, 2H, J = 7 Hz, CH_2), 4.6–4.8 (m, 1H, CH), 5.40 (d, 1H, J = 7 Hz, NH), 6.17 (s, 1H, NH or OH), 6.47 (s, 1H, ArH-4), 6.73 (d, 1H, J = 3 Hz, ArH-6), 7.2–7.4 (m, 5H, ArH), 8.24 (s, 1H, NH or OH); SIMS m/z 471 ($M^+ + 1$); Anal. Calcd for $C_{27}H_{38}N_2O_5$: C, 68.91, H, 8.14, N, 5.95. Found: C, 68.95, H, 8.42, N, 5.74.

1-(2-Hydroxy-4,5-methylenedioxyphenyl)-3-(3-pyridylmethyl)urea (57). Mp 167–170 °C; IR (KBr) 3050, 1663 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 4.45 (d, 2H, J = 5 Hz, CH_2), 5.84 (s, 2H, CH_2), 6.50 (s, 1H, ArH-3), 7.38–7.55 (m, 1H, NH), 7.46 (s, 1H, ArH-6), 7.97 (dd, 1H, J = 5, 8 Hz, PyH-5), 8.03 (s, 1H, NH or OH), 8.39 (d, 1H, J = 8 Hz, PyH-4), 8.73–8.82 (m, 2H, PyH-2 and -6), 9.58 (br, 1H, NH or OH); SIMS m/z 288 ($M^+ + 1$); Anal. Calcd for $C_{14}H_{13}N_3O_4$·HCl: C, 51.94, H, 4.36, N, 12.98. Found: C, 51.99, H, 4.31, N, 12.87.

7-*tert*-Butyl-8-hydroxy-5-methoxy-2-oxo-3-(3-pyridylmethyl)-1,2,3,4-tetrahydroquinazoline (58). To a solution of **60** (X^2 = OMe, X^3 = H, X^4 = *t*-Bu, 28.4 g, 0.10 mol) in carbon disulfide (CS_2, 500 mL) was added dropwise bromine (6.0 mL, 0.10 mol) at room temperature. After stirring at the same temperature for 2 h, the reaction mixture was diluted with Et_2O, washed with water and brine, dried ($MgSO_4$), filtered and concentrated in vacuo to afford **65** (29.5 g, 81%). In the same manner as the alkylation by MOMCl and the hydrogenation as described above, **67** was obtained from **65**. To a solution of **67** (15.3 g, 48 mmol) in Et_2O (300 mL) was added *n*-butyllithium (2.3 M in hexane, 54.5 mL, 125 mmol) dropwise at −78 °C and the mixture was stirred for 1 h at the same temperature. To the resulting mixture was added a solution of DMF (9.6 mL, 124 mmol) at −78 °C. After the reaction mixture was stirred for 45 min at the same temperature, 10% acetic acid aq (100 mL) was added and extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was chromatographed on silica gel using hexane/AcOEt (10:1) as an eluent to give **68** (5.1 g, 40%): mp 62–64 °C; ^1H NMR (δ in $CDCl_3$) 1.37 (s, 9H, CH_3), 3.65 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 4.91 (s, 2H, CH_2), 6.03 (s, 1H, ArH), 10.34 (s, 1H, CHO); EIMS m/z 267 (M^+). A mixture of **68** (5.0 g, 18.7 mmol) and 3-(aminomethyl)pyridine (3.0 g, 28.1 mmol) was stirred at 95 °C for 3 h. After the mixture had cooled to room temperature, acetonitrile (40 mL) and molecular sieves 3A were added to remove water in the mixture. To the mixture was added sodium cyanoborohydride (2.35 g, 37.4 mmol) at 0 °C. The mixture was neutralized with 15% HCl/dioxane (pH 6.5–7.0). After stirring for 4 h, molecular sieves were removed by filtration and the filtrate was concentrated in vacuo. The residue was diluted with AcOEt and washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was chromatographed on silica gel using $CHCl_3$/EtOH (20:1) as an eluent to give **69** (2.2 g, 33%): mp 60–65 °C; ^1H NMR (δ in $CDCl_3$) 1.37 (s, 9H, CH_3), 3.65 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.81 (s, 2H, CH_2), 3.87 (s, 2H, CH_2), 4.95 (s, 2H, CH_2), 6.22 (s, 1H, ArH), 7.21–7.25 (m, 1H, PyH-5), 7.65–7.70 (m, 1H, PyH-4), 8.49–8.56 (m, 2H, PyH-2 and -6); EIMS m/z 359 (M^+). To the solution of **69** (2.12 g, 5.9 mmol) and triethylamine (3.3 mL) in CH_2Cl_2 (200 mL) was added a solution of triphosgene (610 mg, 2.1 mmol) in CH_2Cl_2 (10 mL) dropwise at −78 °C and the reaction mixture was warmed to room temperature for 30 min. The reaction mixture was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo, and the residue was chromatographed on silica using $CHCl_3$/EtOH (20:1). The crude crystals were recrystallized from Et_2O to yield 735 mg (32%) of **70**. To a solution of **70** (560 mg, 1.45 mmol) in MeOH (15 mL) was added concd HCl (1.0 mL) and the mixture was stirred at 35 °C for 4 h. The resulting mixture was concentrated in vacuo and the crude crystals were recrystallized from EtOH to give **58** (410 mg, 75%): mp 228–231 °C; IR (Nujol) 1665, 1610 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 1.34 (s, 9H, CH_3), 3.69 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 4.75 (s, 2H, CH_2), 6.39 (s, 1H, ArH), 7.95–8.10 (dd, 1H, J = 5, 8 Hz, PyH-5), 8.44 (s, 1H, PyH-2), 8.50 (d, 1H, J = 8 Hz, PyH-4), 8.85 (d, 1H, J = 5 Hz, PyH-6), 8.89 (s, 1H, NH or OH); EIMS m/z 341 (M^+); Anal. Calcd for $C_{19}H_{23}N_3O_3$·HCl: C, 60.39, H, 6.40, N, 11.12. Found: C, 60.21, H, 6.37, N, 10.98.

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Example 1.

$$\begin{aligned}\Delta\log P &= \log P([\text{derivative } \mathbf{14}]) - \log P([\text{diphenylurea}])\\ &= \log P([\text{acetanilide } \mathbf{14}])^{a} - \log P([\text{acetanilide}])^{b}\\ &= (-0.09) - 1.16 = -1.25\\ \log P([\text{derivative } \mathbf{14}]) &= \log P([\text{diphenylurea}])^{c} + \Delta\log P\\ &= 3.00 + (-1.25) = 1.75\end{aligned}$$

Example 2.

$$\begin{aligned}\Delta\log P &= \log P([\text{derivative } \mathbf{48}]) - \log P([N\text{-substituted phenylurea}])\\ &= \log P([\text{acetanilide } \mathbf{12}])^{a} - \log P([\text{acetanilide}])^{b}\\ &= 1.59 - 1.16 = 0.43\\ \log P([\text{derivative } \mathbf{48}]) &= \text{CLOGP}([N\text{-substituted phenylurea}])^{d} + \Delta\log P\\ &= 3.89 + 0.43 = 4.32\end{aligned}$$

[a]Estimated by our empirical method. [b]Measured value (Fujita, T.; Iwasa, J.; Hansch, C. *J. Am. Chem. Soc.* **1964**, *86*, 5175–5180). [c]Cited from reference 13. [d]Calculated by CLOGP method.

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