Quantitative Structure–Activity Relationship of Catechol Derivatives Inhibiting 5-Lipoxygenase

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Various catechol derivatives (β-substituted 3,4-dihydroxystyrenes, 1-substituted 3,4-dihydroxybenzenes, and 6-substituted 2,3-dihydroxynaphthalenes) were synthesized and their inhibition of 5-lipoxygenase was assayed. Their structure–activity relationships were examined quantitatively with substituent and structural parameters and regression analysis. The variations in the inhibitory activity were explained in bilinear hydrophobic parameter (log *P*) terms, and steric (molecular thickness) and electronic (proton nuclear magnetic resonance (^{1}H-NMR) chemical shift of the proton adjacent to the catechol group) parameter terms. The hydrophobicity of the inhibitor molecule was important, and the optimum value of log *P* was about 4.3—4.6, beyond which inhibition did not increase further. A lower electron density of the aromatic ring containing the catechol group and the greater thickness of the lipophilic side chains were unfavorable to the activity. The results added a physicochemical basis for the selection of candidate compounds for developmental studies.

Keywords quantitative structure–activity relationship; Kubinyi's Bilinear-model; Hansch–Fujita analysis; 5-lipoxygenase; 5-lipoxygenase inhibition; 1-(3,4-dihydroxyphenyl)-1-octen-3-one; caffeic acid octyl amide

Arachidonate 5-lipoxygenase is a key enzyme in the biosynthesis of leukotrienes, which seem to be related to many diseases such as allergic asthma,[1] psoriasis,[2] and myocardial infraction.[3] Therefore, potent inhibitors of this enzyme are candidate drugs for the treatment of these diseases.

Caffeic acid and its methyl ester are potent inhibitors of 5-lipoxygenase.[4] We have studied[5] the structure–activity relationships of 3,4-dihydroxystyrenes modified by various substituents at the β-position (series I; see Chart 1). Hoping to understand the physicochemical background of the structural effects of the side chains as well as the ring systems on the inhibition, we synthesized a number of 1-substituted 3,4-dihydroxybenzenes (series II) and 6-substituted 2,3-dihydroxynaphthalenes (series III) with various substituents and measured their inhibition of 5-lipoxygenase (Table I). Together with the results for the previously reported 3,4-dihydroxystyrenes, the structure–activity relationships were examined quantitatively with their substituent and structural parameters and by regression analysis.

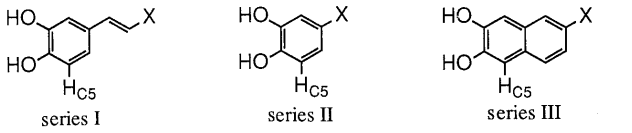


Chart 1

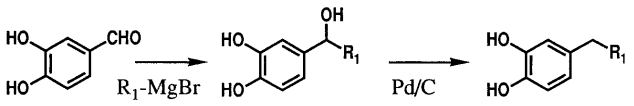
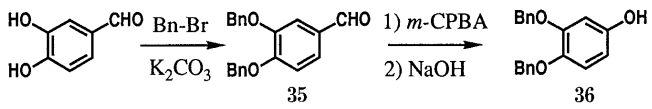


Chart 2

Synthesis

Some of the series I compounds (**3**, **5**, **6**, and **12**—**18**) were newly synthesized by a reported procedure.[5] Compounds **26**—**28** of series II were prepared similarly to compounds **7**—**11**.[5]

The 4-alkyl-1,2-dihydroxybenzene derivatives **32**—**34** were obtained by catalytic hydrogenation (palladium on carbon: Pd/C) of the corresponding benzylalcohols, **29**—**31**, which were prepared by the Grignard reaction of protocatechualdehyde (Chart 2). 4-Alkoxycatechols were prepared as shown in Chart 3. Baeyer–Villiger oxidation of the dibenzyl ether of protocatechualdehyde, **35**, with 3-chloroperoxybenzoic acid (*m*-CPBA) followed by hydrolysis with 3 N NaOH gave phenol **36**. The phenol was alkylated with alkyl bromide followed by debenzylation with Pd/C to yield 4-alkoxycatechols (**37**, **38**). The β-phenoxyacrylamides



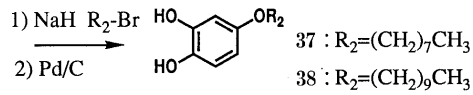
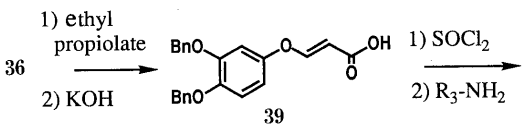


Chart 3



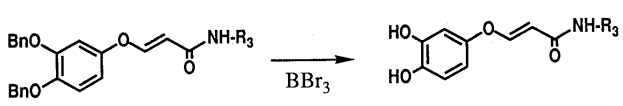


Chart 4

TABLE I. Physicochemical and Biological Data of the Compounds of Series I, II, and III

No.	Substituents X	mp (°C)[a]	Recrystn solvent[b]	Formula	Analysis (%) Calcd (Found) C	H	N	I_{50}[c] (M)
Series I								
1	$CO_2CH_2CH_3$	142—143	A	$C_{11}H_{12}O_4$	63.45 (63.36	5.81 5.77)		1.65×10^{-7}
2	$CO_2(CH_2)_3CH_3$	111—111.5	B	$C_{13}H_{16}O_4$	66.09 (65.94	6.83 6.84)		6.70×10^{-8}
3	$CO_2(CH_2)_4CH_3$	125—127	B	$C_{14}H_{18}O_4$		250.1204[d] (250.1219)		7.70×10^{-8}
4	$CO_2(CH_2)_8CH_3$	107—108	B	$C_{18}H_{26}O_4$	70.56 (70.41	8.55 8.76)		1.88×10^{-7}
5	$CONHCH_2CH_3$	Amorph.		$C_{11}H_{13}NO_3$		208.0972 (208.0968)		1.50×10^{-6}
6	$CONH(CH_2)_3CH_3$	Amorph.		$C_{13}H_{17}NO_3$		236.1286 (236.1306)		7.00×10^{-7}
7	$CONH(CH_2)_5CH_3$	141—143	A	$C_{15}H_{21}NO_3$	68.42 (68.34	8.04 8.07	5.32 5.22)	1.30×10^{-7}
8	$CONH(CH_2)_7CH_3$	126—128.5	A	$C_{17}H_{25}NO_3$	70.07 (70.10	8.65 8.92	4.81 5.08)	4.20×10^{-8}
9	$CONH(CH_2)_9CH_3$	Amorph.		$C_{19}H_{29}NO_3$		320.2224 (320.2222)		4.50×10^{-8}
10	$CONH(CH_2)_{11}CH_3$	124—125	A	$C_{21}H_{33}NO_3$		348.2536 (348.2534)		6.50×10^{-8}
11	$CONH(CH_2)_{13}CH_3$	119—120	A	$C_{23}H_{37}NO_3$		375.2712 (375.2792)		1.55×10^{-7}
12	$CONHCH_2Ph$	164—167	A	$C_{16}H_{15}NO_3$		270.1130 (270.1160)		1.15×10^{-7}
13	$CONH(CH_2)_2Ph$	157—159	A	$C_{17}H_{17}NO_3$	72.07 (72.30	6.05 6.19	4.94 4.78)	1.50×10^{-7}
14	CONHPh(4-butyl)	204—205.5	A	$C_{19}H_{21}NO_3$		312.1598 (312.1561)		8.10×10^{-8}
15	CONHPh(4-octyl)	173.5—175	A	$C_{23}H_{29}NO_3$		368.2224 (368.2180)		8.40×10^{-8}
16	CONHPh(3,4-OCH_3)	201—202	C	$C_{17}H_{17}NO_5$	64.75 (64.46	5.43 5.41	4.44 4.35)	1.20×10^{-7}
17	$CONHCH_2$Ph(3,4-OCH_3)	203—206	A	$C_{18}H_{19}NO_5$	65.64 (65.43	5.81 5.92	4.25 4.03)	1.70×10^{-7}
18	$CONH(CH_2)_2$Ph(3,4-OCH_3)	97—99	A	$C_{19}H_{20}NO_5$		344.1496 (344.1456)		2.60×10^{-7}
19	$CO(CH_2)_2CH_3$	131—132	D	$C_{12}H_{14}O_3$	69.89 (69.62	6.84 6.89)		2.75×10^{-7}
20	$CO(CH_2)_4CH_3$	130—131	D	$C_{14}H_{18}O_3$	71.77 (71.71	7.74 7.81)		3.50×10^{-8}
21	$CO(CH_2)_6CH_3$	115—116.5	D	$C_{16}H_{22}O_3$	73.25 (72.96	8.45 8.62)		5.80×10^{-8}
22	$CO(CH_2)_5OH$	Amorph.		$C_{14}H_{18}O_4$	67.18 (67.06	7.25 7.13)		5.95×10^{-7}
23	CH_2CH_3[e]	Liquid		$C_{10}H_{12}O_2$		165.0915 (165.0950)		9.50×10^{-8}
24	$(CH_2)_3CH_3$[e]	Liquid		$C_{12}H_{16}O_2$		193.1227 (193.1195)		1.20×10^{-8}
25	$(CH_2)_5CH_3$[e]	Liquid		$C_{14}H_{20}O_2$		221.1540 (221.1524)		1.50×10^{-8}
Series II								
26	$CONH(CH_2)_5CH_3$	139—140	E	$C_{13}H_{19}NO_3$	65.80 (65.52	8.07 8.21	5.90 5.89)	4.00×10^{-7}
27	$CONH(CH_2)_9CH_3$	129.5—130	A	$C_{17}H_{27}NO_3$	69.59 (69.61	9.28 9.25	4.77 4.69)	1.80×10^{-7}
28	$CONH(CH_2)_{11}CH_3$	119.5—120	E	$C_{19}H_{31}NO_3$	70.99 (70.80	9.72 9.74	4.36 4.35)	4.50×10^{-7}
29	$CH(OH)(CH_2)_2CH_3$	137—139	A	$C_{10}H_{14}O_3$	65.92 (65.88	7.74 7.75)		1.80×10^{-6}
30	$CH(OH)(CH_2)_4CH_3$	108—110	A	$C_{12}H_{18}O_3$	68.55 (68.44	8.63 8.68)		1.20×10^{-6}
31	$CH(OH)(CH_2)_6CH_3$	120—122.5	A	$C_{14}H_{22}O_3$	70.56 (70.46	9.30 9.56)		3.20×10^{-7}

TABLE I. (continued)

No.	Substituents X	mp (°C)[a]	Recrystn solvent[b]	Formula	Analysis (%) Calcd (Found) C	H	N	I_{50}[c] (M)
32	$(CH_2)_3CH_3$	Amorph.		$C_{10}H_{14}O_2$	72.26 (72.23	8.49 8.60)		6.30×10^{-7}
33	$(CH_2)_5CH_3$	Amorph.		$C_{12}H_{18}O_2$	74.19 (73.90	9.34 9.07)		2.50×10^{-7}
34	$(CH_2)_7CH_3$	60—61	F	$C_{14}H_{22}O_2$	75.63 (75.40	9.97 10.23)		1.90×10^{-7}
37	$O(CH_2)_7CH_3$	108—109	A	$C_{14}H_{22}O_3$	70.56 (70.33	9.30 9.31)		3.00×10^{-7}
38	$O(CH_2)_9CH_3$	112—113	A	$C_{16}H_{26}O_3$	72.14 (72.29	9.84 9.90)		1.60×10^{-7}
43	$OCH=CHCONH(CH_2)_5CH_3$	103—104	E	$C_{15}H_{21}NO_4$		280.1547 (280.1527)		2.50×10^{-7}
44	$OCH=CHCONH(CH_2)_7CH_3$	139—140	E	$C_{17}H_{25}NO_4$	66.43 (66.21	8.20 8.47	4.56 4.38)	1.70×10^{-7}
45	$OCH=CHCONH(CH_2)_9CH_3$	110—111	E	$C_{19}H_{29}NO_4$	68.03 (67.74	8.71 8.69	4.18 4.03)	7.20×10^{-8}
Series III								
50	$COCH_3$	169—170	E	$C_{12}H_{10}O_3$	71.28 (71.23	4.98 4.89)		3.00×10^{-6}
51	$CO(CH_2)_2CH_3$	180—181	E	$C_{14}H_{14}O_3$		231.1021 (231.1062)		4.60×10^{-7}
52	$CO(CH_2)_4CH_3$	173—174	E	$C_{16}H_{18}O_3$	74.40 (74.17	7.02 7.05)		2.00×10^{-7}
56	CH_2CH_3	148—149.5	E	$C_{12}H_{12}O_2$	76.57 (76.46	6.43 6.31)		3.00×10^{-6}
57	$(CH_2)_3CH_3$	137.5—139	E	$C_{14}H_{16}O_2$	77.75 (77.68	7.46 7.47)		8.00×10^{-7}
58	$(CH_2)_5CH_3$	138.5—139.5	E	$C_{16}H_{20}O_2$	78.65 (78.35	8.25 8.29)		9.00×10^{-7}
63	$CONH(CH_2)_3CH_3$	193.5—194	G	$C_{15}H_{17}NO_3$	69.48 (69.38	6.61 6.73	5.40 5.37)	5.00×10^{-6}
64	$CONH(CH_2)_5CH_3$	181—181.5	G	$C_{17}H_{21}NO_3$	71.06 (70.97	7.37 7.27	4.87 4.89)	1.40×10^{-6}
65	$CONH(CH_2)_7CH_3$	186—187.5	G	$C_{19}H_{25}NO_3$		316.1911 (316.1883)		2.00×10^{-7}
68	OCH_2CH_3	131—132	A	$C_{12}H_{12}O_3$	70.58 (70.38	5.92 5.88)		1.30×10^{-6}
69	$O(CH_2)_3CH_3$	141.5—143	A	$C_{14}H_{16}O_3$	72.39 (72.15	6.94 6.97)		4.00×10^{-7}
70	$O(CH_2)_5CH_3$	130.5—132	A	$C_{16}H_{20}O_3$	73.82 (73.98	7.74 7.84)		5.60×10^{-7}

a) Compounds that did not show a sharp mp are denoted "Amorph". *b*) Solvents: A, AcOEt–hexane; B, Et_2O–hexane; C, CH_3CN–Et_2O; D, EtOH–H_2O; E, $CHCl_3$–hexane; F, hexane; G, $CHCl_3$–MeOH. *c*) Concentration for 50% inhibition of 5-lipoxygenase from guinea pig leukocytes. Each value represents the mean of at least two experiments. *d*) High mass data. The upper value was calculated and the lower one was that found. The values are for $M+H^+$ (measured by the SIMS-positive mode) except for compounds **3** and **11**, where M^+ (measured by the EI-mode) was measured. *e*) The sample is a *cis–trans* mixture, although the *cis* isomer is generally predominant.

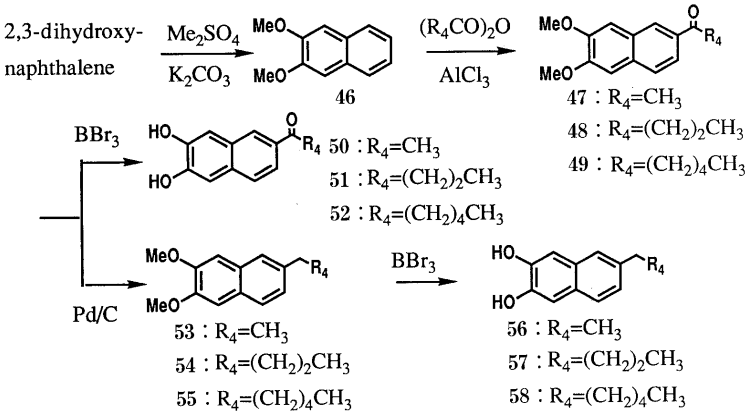


Chart 5

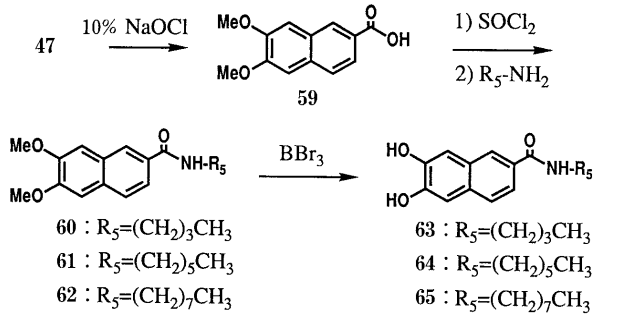


Chart 6

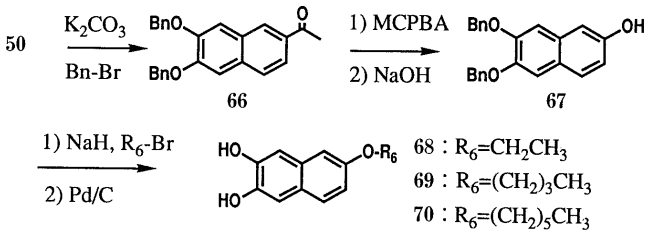


Chart 7

43—**45** were prepared[6] by the addition of phenol **36** to ethyl propiolate followed by amidation giving compounds **40**—**42**, which were debenzylated with boron tribromide as shown in Chart 4. The 6-acyl-2,3-dihydroxynaphthalenes **50**—**52** were prepared by the Friedel–Crafts reaction of 2,3-dimethoxynaphthalene, **46**, with acid anhydrides and aluminum chloride followed by demethylation by use of boron tribromide (Chart 5). The 6-alkyl-2,3-dihydroxynaphthalenes **56**—**58** were prepared by the reduction of the acyl derivatives **47**—**49** by catalytic hydrogenation followed by demethylation (Chart 5). The *N*-alkyl-6,7-dihydroxy-2-naphthamides **63**—**65** were prepared by procedures similar to those for compounds **43**—**45** from 6,7-dimethoxy-2-naphthoic acid, **59**, which was prepared by the Haloform reaction of **47** by use of a sodium hypochlorite solution (Chart 6). The 6-alkoxy-2,3-dihydroxynaphthalenes **68**—**70** were prepared similarly to the 4-alkoxy-2,3-dihydroxybenzene derivatives **37**, **38** (Chart 7).

All compounds used in this study are listed in Table I.

Biological Results and Discussion

The 50% inhibitory concentration of each compound (I_{50}) was measured against the production of leukotriene B_4 and 5-hydroxyeicosatetraenoic acid from arachidonic acid. The measurement was done by use of a reported procedure[5] in a $10000 \times g$ supernatant fraction from guinea-pig polymorphonuclear leukocytes. Inhibition of the enzyme by compounds of series I—III is listed in Table I.

In general, the series I compounds caused greater inhibition than series II or III compounds with the corresponding substituents X. The styrene double bond seemed favorable for inhibition. Within each series, the activity varied depending upon the substituents X. The physicochemical background for variations in the strength of inhibition was examined by quantitative structure–activity analysis with pI_{50} ($-\log I_{50}$) as the dependent variable.

First, analysis was made of the series I compounds (**1**—**25**) with the use of single parameters. The results

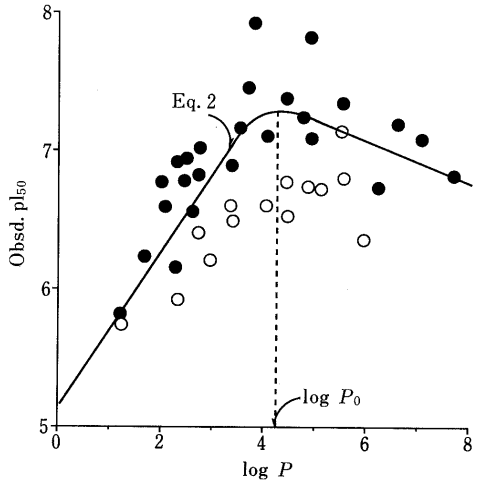


Fig. 1. Plots of pI_{50} *versus* log P
●, series I; ○, series II.

indicated that the activity was parabolically related to the hydrophobic parameter (log P), as shown in Eq. 1. P is the partition coefficient measured in the 1-octanol/water system.[7] The log P of some compounds with different chain lengths was estimated from the observed log P value of homologs by use of the $\pi(CH_3)$ value ($=0.54$).[8]

$$pI_{50} = -0.10(\log P)^2 + 1.02 \log P + 4.87 \quad (1)$$
$$(0.04) \qquad (0.34) \qquad (0.66)$$

$n=25$, $r=0.82$, $s=0.28$, $F=23.24$, $\log P_0=5.1$

In this and the following equations, n is the number of compounds, r is the correlation coefficient, s is the standard deviation, F is the ratio between regression and residual variances, and $\log P_0$ is the optimum log P value.

The plots of pI_{50} versus log P are shown in Fig. 1. The shape of the relationship shown in Fig. 1 is a skewed "parabola." The "slope" of the ascending side of the parabola is steeper than that on the descending side. We examined the correlation using the bilinear model of Kubinyi.[9] Equation 2 (Table II) was derived as the counterpart of Eq. 1. The optimum value of log P was calculated to be 4.3, slightly lower than that calculated from Eq. 1. The quality of the correlation of Eq. 2 was better than that of Eq. 1, so further analyses were conducted using the bilinear model with respect to the log P value of compounds.

Next, we looked at incorporating the series II compounds (**26**—**34**, **37**, **38**, and **43**—**45**) into the series I compounds. The pI_{50} values of the series II compounds are also plotted in Fig. 1. They almost invariably deviated downward from the bilinear regression line for the series I compounds. By use of an indicator variable, D_{II}, which is unity for the series II compounds, Eq. 3, of good quality, was derived (Table II). The situation is summarized in Fig. 2.

Finally, analysis of series III compounds (**50**—**52**, **56**—**58**, **63**—**65**, and **68**—**70**) was attempted together with series I and II compounds. The inhibition caused by series III compounds was again lower than that of the series I compounds with the same log P values (Fig. 2). By consideration of a second indicator variable, D_{III}, which is unity for series III compounds, Eq. 4, which was of excellent

TABLE II. Correlation Equations for the 5-Lipoxygenase Inhibitory Activity of Compounds $pI_{50}=h(\log P)+i\log(\beta 10^{\log P}+1)+jD_{II}+kD_{III}+\text{const.}$

Eq. no.	Series	h	i	j	k	Const.	$\log P_0$[a]	$-\log\beta$[b]	n[c]	r[d]	s[e]	$F_{m,n-m-1}$[f]
2	I	0.64	−0.84			5.18	4.30	3.79	25	0.84	0.27	16.64
		(0.19)[g]	(0.29)			(0.52)						
3	I, II	0.52	−0.72	−0.61		5.47	4.50	4.11	39	0.87	0.25	26.57
		(0.12)	(0.22)	(0.17)		(0.36)						
4	I, II, III	0.49	−0.75	−0.62	−1.13	5.50	4.63	4.33	51	0.89	0.27	36.17
		(0.11)	(0.22)	(0.18)	(0.20)	(0.33)						

a) Optimum log *P* value. *b*) Estimated log *P* values where the slope changes from ascending to descending. *c*) Number of points used for calculation. *d*) Correlation coefficient. *e*) Standard deviation. *f*) *F* value of the correlation; *m* stands for the number of independent variables including β; theoretical *F* values are: $F_{3,21;\alpha=0.05}=3.07$ for Eq. 2, $F_{4,30;\alpha=0.05}=2.69$ for Eq. 3, and $F_{5,40;\alpha=0.05}=2.45$ for Eq. 4. *g*) Figures in parentheses are 95% confidence intervals.

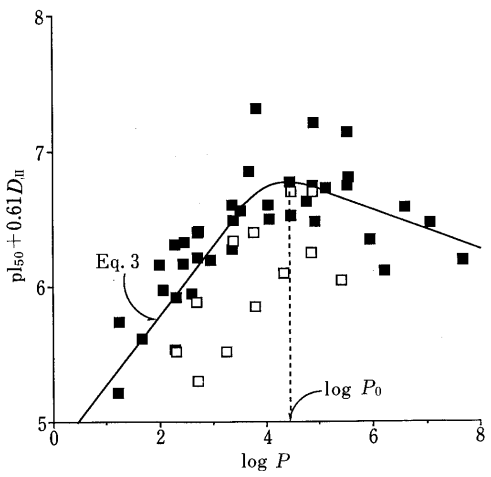


Fig. 2. Plots of $pI_{50}+0.61D_{II}$ *versus* log *P*

■, series I and II; □, series III.

TABLE III. Development of Eq. 4

Intercept	D_{III}	log *P*	D_{II}	$\log(\beta 10^{\log P}+1)$	s	r	$F_{X,Y}$[a]
6.79	−0.74				0.48	0.55	$F_{1,49}=21.72$
6.18	−0.73	0.16			0.42	0.69	$F_{1,48}=15.40$
6.33	−0.91	0.16	−0.49		0.37	0.78	$F_{1,47}=15.36$
5.50	−1.13	0.49	−0.62	−0.75	0.27	0.89	$F_{2,45}=22.14$

a) *F* statistic for the significance of the addition of each parameter; theoretical *F* values are: $F_{1,40,\alpha=0.05}=4.08$, $F_{1,60,\alpha=0.05}=4.00$, $F_{2,40,\alpha=0.05}=3.23$, and $F_{2,60,\alpha=0.05}=3.15$.

TABLE IV. Simple Correlation Matrix (r^2) for the Parameters of Eq. 4

	log *P*	$\log(\beta 10^{\log P}+1)$	D_{II}	D_{III}
log *P*	1.000			
$\log(\beta 10^{\log P}+1)$	0.769	1.000		
D_{II}	0.003	0.000	1.000	
D_{III}	0.000	0.021	0.116	1.000

quality, was formulated (Table II).

If differences in the skeletal structure were not considered, hydrophobicity was most important in governing the variations in activity. The effect of the skeletal structures was reflected in the terms D_{II} and D_{III} in Eq. 4. The styrene structure of series I compounds was most favorable to activity; in series II compounds, the deletion of the double bond lowered the activity. The naphthalene skeleton, which seems to involve a styrene-like substructure, further lowered the activity of series III compounds. The slope of the log *P* term in the ascending part in Eq. 4 is close to 0.5, suggesting that these compounds may interact with a hydrophobic protein surface, but are not engulfed in a hydrophobic pocket[10] until the log *P* value reaches about 4.3. Beyond this point, the inhibition did not increase, but decreased. The slope of the decrease, however, was not very steep. The compounds whose log *P* value was higher than the optimum generally had side chains longer than 8 or 10 bond units when the styrene double bond in series I compounds and the $\alpha\beta$ bond in series III compounds were included. The end of the side chain in these longer-chain compounds may not interact so tightly with the region where the shorter side-chain compounds are hydrophobically bound. Furthermore, the inhibitory mode of the binding of the shorter-chain region may be released by some conformational change in the enzyme structure caused by the additional hydrophobicity of the compounds. Another possibility is that the bilinear correlation equation may reflect pharmacokinetic processes being governed by the hydrophobicity of the compounds.[9] Enzyme preparation is considered to involve a number of "impurities." The compounds in which log *P* is beyond the optimum may be trapped with hydrophobic impurities to a higher extent than those with a lower log *P* value. The stepwise development of Eq. 4 for the 51 compounds studied here is shown in Table III. The intercorrelation between independent variables for the 51 derivatives in Eq. 4 was insignificant except for that between log *P* and $\log(\beta 10^{\log P}+1)$ (Table IV). The pI_{50} values and physicochemical independent variables of the compounds are listed in Table V.

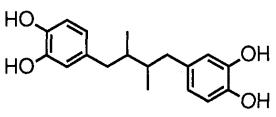
Although Eq. 4 explains variations in the inhibitory activity fairly well, the physicochemical meaning of the indicator variables D_{II} and D_{III} should be clarified. When one or both of the hydroxy groups were replaced by a methoxy group in **20**, one of the most potent inhibitors, the activity was significantly decreased,[5] suggesting that a catechol structure with two vicinally located hydroxy groups is essential for strong inhibition; this is probably the pharmacophore of these compounds.

Recently, compounds containing catechol, such as nordihydroguaiaretic acid (see Chart 8), which is one of the most efficient inhibitors of lipoxygenase, have been shown to reduce the catalytically active ferric form of soybean lipoxygenase-1 to an inactive ferrous form.[12] The inhibition is increased by the introduction of electron-releasing substituents into catechol derivatives.[12] Thus, we analyzed variations in the activity of our compounds in terms of their electronic structure using the chemical shift of the proton at the C_5 position of the 3,4-dihydroxystyrene skeleton (see Chart 1) measured by proton nuclear magnetic

TABLE V. Inhibitory Activity and Physicochemical Parameters of the Compounds of Series I, II, and III

No.	Substituents X	log P[a]	D_{II}[b]	D_{III}[c]	ΔH_{C5}[d]	$E_{1/2}$[e]	ΔT_{max}[f]	pI_{50} Obsd.	pI_{50} Calcd[g]	pI_{50} (Δ)[h]
Series I										
1	$CO_2CH_2CH_3$	2.45[i]	0	0	1.5	1.40	0.60[m]	6.78	6.71	(0.07)
2	$CO_2(CH_2)_3CH_3$	3.53	0	0	1.5	1.40	0.60[m]	7.17	7.20	(−0.03)
3	$CO_2(CH_2)_4CH_3$	4.07[i]	0	0	1.5	1.40	0.60[m]	7.11	7.37	(−0.26)
4	$CO_2(CH_2)_8CH_3$	6.23[i]	0	0	1.5	1.40	0.60[m]	6.73	7.16	(−0.43)
5	$CONHCH_2CH_3$	1.21[i]	0	0	1.3	1.05	0.60[m]	5.82	6.10	(−0.28)
6	$CONH(CH_2)_3CH_3$	2.29[i]	0	0	1.3	1.05	0.60[m]	6.15	6.63	(−0.48)
7	$CONH(CH_2)_5CH_3$	3.37	0	0	1.3	1.05	0.60[m]	6.89	7.13	(−0.24)
8	$CONH(CH_2)_7CH_3$	4.45[i]	0	0	1.3	1.05	0.60[m]	7.38	7.43	(−0.05)
9	$CONH(CH_2)_9CH_3$	5.53[i]	0	0	1.3	1.05	0.60[m]	7.35	7.32	(0.03)
10	$CONH(CH_2)_{11}CH_3$	6.61[i]	0	0	1.3	1.05	0.60[m]	7.19	7.07	(0.12)
11	$CONH(CH_2)_{13}CH_3$	7.69[i]	0	0	1.3	1.05	0.60[m]	6.81	6.80	(0.01)
12	$CONHCH_2Ph$	2.48	0	0	1.3	1.05	0.60[m]	6.94	6.72	(0.22)
13	$CONH(CH_2)_2Ph$	2.72	0	0	1.3	1.05	0.60[m]	6.82	6.84	(−0.02)
14	CONHPh(4-butyl)	4.92[j]	0	0	1.3	1.05	0.60[m]	7.09	7.42	(−0.33)
15	CONHPh(4-octyl)	7.08[i]	0	0	1.3	1.05	0.60[m]	7.08	6.95	(0.13)
16	$CONHPh(3,4\text{-}OCH_3)$	2.30	0	0	1.3	1.05	0.60[m]	6.92	6.63	(0.29)
17	$CONHCH_2Ph(3,4\text{-}OCH_3)$	1.99	0	0	1.3	1.05	0.60[m]	6.77	6.48	(0.29)
18	$CONH(CH_2)_2Ph(3,4\text{-}OCH_3)$	2.07	0	0	1.3	1.05	0.60[m]	6.59	6.52	(0.07)
19	$CO(CH_2)_2CH_3$	2.61	0	0	1.6	1.25	0.60[m]	6.56	6.78	(−0.22)
20	$OC(CH_2)_4CH_3$	3.69[i]	0	0	1.6	1.25	0.60[m]	7.46	7.26	(0.20)
21	$CO(CH_2)_6CH_3$	4.77[i]	0	0	1.6	1.25	0.60[m]	7.24	7.43	(−0.19)
22	$CO(CH_2)_5OH$	1.67	0	0	1.6	1.25	0.60[m]	6.23	6.32	(−0.09)
23	CH_2CH_3	2.74[i]	0	0	0.9	0.525	0.60[m]	7.02	6.85	(0.17)
24	$(CH_2)_3CH_3$	3.82	0	0	0.9	0.525	0.60[m]	7.92	7.30	(0.62)
25	$(CH_2)_5CH_3$	4.90[i]	0	0	0.9	0.525	0.60[m]	7.82	7.42	(0.40)
Series II										
26	$CONH(CH_2)_5CH_3$	2.71	1	0	1.2	—[l]	2.07[n]	6.40	6.21	(0.19)
27	$CONH(CH_2)_9CH_3$	4.87[i]	1	0	1.2	—[l]	2.07[n]	6.74	6.80	(−0.06)
28	$CONH(CH_2)_{11}CH_3$	5.95[i]	1	0	1.2	—[l]	2.07[n]	6.35	6.60	(−0.25)
29	$CH(OH)(CH_2)_2CH_3$	1.24[i]	1	0	0.2	—[l]	2.17[o]	5.74	5.49	(0.25)
30	$CH(OH)(CH_2)_4CH_3$	2.32	1	0	0.2	—[l]	2.17[o]	5.92	6.02	(−0.10)
31	$CH(OH)(CH_2)_6CH_3$	3.40[i]	1	0	0.2	—[l]	2.17[o]	6.49	6.52	(−0.03)
32	$(CH_2)_3CH_3$	2.96	1	0	0	—[l]	2.17[p]	6.20	6.33	(−0.13)
33	$(CH_2)_5CH_3$	4.04[i]	1	0	0	—[l]	2.17[p]	6.60	6.74	(−0.14)
34	$(CH_2)_7CH_3$	5.12[i]	1	0	0	—[l]	2.17[p]	6.72	6.77	(−0.05)
37	$O(CH_2)_7CH_3$	4.47[k]	1	0	−0.2	—[l]	2.07[q]	6.52	6.81	(−0.29)
38	$O(CH_2)_9CH_3$	5.55[i]	1	0	−0.2	—[l]	2.07[q]	6.80	6.69	(0.11)
43	$OCH{=}CHCONH(CH_2)_5CH_3$	3.36	1	0	1	—[l]	2.07[q]	6.60	6.51	(0.09)
44	$OCH{=}CHCONH(CH_2)_7CH_3$	4.44[i]	1	0	1	—[l]	2.07[q]	6.77	6.81	(−0.04)
45	$OCH{=}CHCONH(CH_2)_9CH_3$	5.52[i]	1	0	1	—[l]	2.07[q]	7.14	6.70	(0.44)
Series III										
50	$COCH_3$	2.32	0	1	5.5	—[l]	0.71[r]	5.52	5.52	(0.00)
51	$CO(CH_2)_2CH_3$	3.40[i]	0	1	5.5	—[l]	0.71[r]	6.34	6.02	(0.32)
52	$CO(CH_2)_4CH_3$	4.48[i]	0	1	5.5	—[l]	0.71[r]	6.70	6.30	(0.40)
56	CH_2CH_3	3.25	0	1	4.3	—[l]	0.71[r]	5.52	5.95	(−0.43)
57	$(CH_2)_3CH_3$	4.33[i]	0	1	4.3	—[l]	0.71[r]	6.10	6.29	(−0.19)
58	$(CH_2)_5CH_3$	5.41[i]	0	1	4.3	—[l]	0.71[r]	6.05	6.22	(−0.17)
63	$CONH(CH_2)_3CH_3$	2.72	0	1	5.3	—[l]	0.71[r]	5.30	5.71	(−0.41)
64	$CONH(CH_2)_5CH_3$	3.80[i]	0	1	5.3	—[l]	0.71[r]	5.85	6.17	(−0.32)
65	$CONH(CH_2)_7CH_3$	4.88[i]	0	1	5.3	—[l]	0.71[r]	6.70	6.30	(0.40)
68	OCH_2CH_3	2.70	0	1	3.9	—[l]	0.71[r]	5.89	5.70	(0.19)
69	$O(CH_2)_3CH_3$	3.78[i]	0	1	3.9	—[l]	0.71[r]	6.40	6.16	(0.24)
70	$O(CH_2)_5CH_3$	4.86[i]	0	1	3.9	—[l]	0.71[r]	6.25	6.30	(−0.05)

a) Values were measured, unless otherwise noted. *b*) Indicator variable that is unity for the series II compounds. *c*) Indicator variable that is unity for the series III compounds. *d*) Calculated from the equation $\Delta H_{C5} = \{H_{C5}(R) - H_{C5}(\text{pyrocatechol})\} \times 10$. The value of $H_{C5}(R)$ indicated a ^{1}H-NMR chemical shift of the proton adjacent to the catechol (see Chart 1). The parameters of compounds **2**, **7**, **20**, **24**, **27**, **30**, **33**, **38**, **43**, **50**, **57**, **63**, and **70** were used for the derivatives **1**—**4**, **5**—**18**, **19**—**22**, **23**—**25**, **26**—**28**, **29**—**31**, **32**—**34**, **37**—**38**, **43**—**45**, **50**—**52**, **56**—**58**, **63**—**65**, and **68**—**70**, respectively. *e*) All values were scaled by 0.01 and the parameters of compounds **2**, **8**, **20**, **24**, **26**, **29**, **32**, **38**, and **44** were used for the derivatives **1**—**4**, **5**—**18**, **19**—**22**, **23**—**25**, **26**—**28**, **29**—**31**, **32**—**34**, **37**—**38**, and **43**—**45**, respectively. *f*) Values were estimated by use of a program or a brochure, both of which were provided by Dr. A. Verloop. All values were used as values relative to that of *H*. *g*) Estimated from Eq. 4. *h*) Δ, difference between observed and calculated values. *i*) Estimated from the observed log P values of each derivative by calculation of $\pi(CH_3)(=0.54)$.[8] *j*) Estimated from the measured log P value of caffeic acid phenyl amide (log P=2.78) by the addition of $\pi(n\text{-Bu})(=2.14)$.[11] *k*) Estimated from the measured log P value of 4-*n*-hexyloxycatechol (log P=3.39). *l*) Not listed because the values were unstable for series II compounds. Not obtained reversible anodic waves for series III compounds. *m*) B_1 parameter of vinyl was used. *n*) B_5 parameter of $CONH_2$ was used. *o*) B_5 parameter of $CH(OH)CH_3$ was used. *p*) B_5 parameter of CH_2CH_3 was used. *q*) B_5 parameter of OCH_3 was used. *r*) B_1 parameter of naphthyl was used.



nordihydroguaiaretic acid

Chart 8

resonance (^{1}H-NMR) and the half-wave potential ($E_{1/2}$).[15] For series I compounds, almost equivalent Eqs. 5 and 6 were formulated.

$$\underset{(0.16)}{pI_{50}=0.62\log P}\underset{(0.25)}{-0.81\log(\beta 10^{\log P}+1)}\underset{(0.49)}{-0.71\Delta H_{C5}}\underset{(0.82)}{+6.19} \quad (5)$$

$$n=25,\ r=0.89,\ s=0.23,\ F=19.37,\ -\log\beta=3.81,\ F_{1,20}=8.39$$

$$\underset{(0.16)}{pI_{50}=0.63\log P}\underset{(0.24)}{-0.82\log(\beta 10^{\log P}+1)}\underset{(0.38)}{-0.63E_{1/2}}\underset{(0.62)}{+5.89} \quad (6)$$

$$n=25,\ r=0.90,\ s=0.22,\ F=21.31,\ -\log\beta=3.77,\ F_{1,20}=10.13$$

For simplicity, the chemical shift parameter was used in Eq. 5 as the value relative to that of pyrocatechol $\{\Delta H_{C5}=H_{C5}(R)-H_{C5}(\text{pyrocatechol})\}$. The ΔH_{C5} and $E_{1/2}$ used were the values of representative compounds for each of the homologous derivatives, because the length of alkane side chains did not significantly affect these parameters (see Table V); these values were multiplied by 10 and 0.01, respectively, to place them on a scale similar to that of $\log P$ in these equations. The ΔH_{C5} and $E_{1/2}$ parameters are highly correlated with each other ($r=0.95$).

The fact that the addition of the electronic term improved the quality of the correlation significantly over that of Eq. 2 is consistent with observations of nordihydroguaiaretic acid and its derivatives. The enzyme inhibition is governed not only by hydrophobicity but also by the electronic structure of the catechol skeleton. Equations 5 and 6 show that the lower the proton chemical shift or the $E_{1/2}$ value, the more potent is the activity, so high electron density at the catechol moiety is indeed necessary for potent inhibition. For the series I—III compounds, analysis was done by use of $\log P$ and ΔH_{C5}, and gave Eq. 7. The $E_{1/2}$ values for series II compounds were unstable and those for series III compounds were not measurable because irreversible anodic waves arose from these compounds.

$$\underset{(0.13)}{pI_{50}=0.47\log P}\underset{(0.25)}{-0.68\log(\beta 10^{\log P}+1)}\underset{(0.23)}{-0.82D_{II}}\underset{(0.06)}{-0.29\Delta H_{C5}}\underset{(0.39)}{+5.91} \quad (7)$$

$$n=51,\ r=0.86,\ s=0.31,\ F=24.92,\ \log\beta=-4.30,\ \log P_0=4.65$$

Equation 7 shows that the indicator variable D_{III} in Eq. 4 could be replaced by the parameter ΔH_{C5}, and that the D_{III} term reflects variations in the electron density of the catechol moiety.

Series III compounds contain a closed-ring styrene as a substructural feature in common with series I compounds. Thus, we expected the indicator variable D_{II} assigned to series II compounds to reflect the absence of the $\alpha\beta$ "double" bond. This factor could be steric. We examined various steric parameters to find if they could replace the D_{II} term and concluded that the STERIMOL width parameter[13] of the $\alpha\beta$ moiety works best when conformational factors are considered. That is, the vinyl group in series I compounds is likely to be coplanar with the benzene ring because of π electron resonance, as is the $\alpha\beta$-bond in series III (naphthalene) compounds. In series II compounds, the functional groups probably rotate around the bond which is connected directly with the benzene ring more easily than in series I compounds. Considering these conformational features, we used the maximum thickness, T_{max}, of the $\alpha\beta$-moiety from the ring plane as the steric parameter. For series I and III compounds, the half thickness, B_1, of the vinyl group and the naphthalene ring was used as the parameter. For the amides (**26**—**28**), benzylalcohols (**29**—**31**), alkanes (**32**—**34**), ethers (**37, 38**), and β-oxyacrylates (**43**—**45**), the maximum thickness, B_5, of the $CONH_2$, $CH(OH)CH_3$, CH_2CH_3, OCH_3, and OCH_3 groups, respectively, were used as the parameter, T_{max}. With the steric parameter estimated for these side chains, relative to that of H, ΔT_{max}, good correlation was obtained (Eq. 8).

$$\underset{(0.13)}{pI_{50}=0.47\log P}\underset{(0.25)}{-0.69\log(\beta 10^{\log P}+1)}$$
$$\underset{(0.15)}{-0.55\Delta T_{max}}\underset{(0.06)}{-0.28\Delta H_{C5}}\underset{(0.40)}{+6.24} \quad (8)$$

$$n=51,\ r=0.86,\ s=0.30,\ F=26.49,\ -\log\beta=4.30,\ \log P_0=4.64$$

Equation 8 shows that indicator variable D_{II} could be replaced by the ΔT_{max} parameter. The D_{II} term in Eqs. 3 and 4 probably accounts for the largest thickness of the atomic group at the α and β positions of the catechol moiety.

In our previous paper,[5] compound **20** was shown to inhibit the enzyme non-competitively. Other catechol derivatives, such as circiliol, have also been indicated as non-competitive inhibitors.[14] Thus, compounds included in this study could also be non-competitive. In this work, they were suggested to interact with a hydrophobic milieu of the 5-lipoxygenase. Although the slope of the $\log P$ term (*ca.* 0.5) suggests that the interaction could occur on the hydrophobic proteinous surface but not in the hydrophobic pocket, the essential catechol part of the molecule, but not the side chain, may be engulfed in the pocket where the two hydroxy groups could chelate with prosthetic metal ions to inhibit the function of the oxygenase.

Based on the above results from analysis of the quantitative structure–activity relationships, the structural requirements for maximum potency can be summarized as follows.

(1) Hydrophobicity close to $\log P=4.3$—4.7 is preferable.
(2) High electron density of the catechol moiety caused by electron-releasing side chains, not by the fused ring with delocalization of electrons, is preferable.
(3) Thickness of the lipophilic side chains close to the catechol benzene ring ($\alpha\beta$) is unfavorable to the activity.

The compounds that should cause the greatest inhibition, as predicted by Eqs. 4 and 8, are compounds **8** and **20**, both of series I with a $\log P$ value close to the optimum. The results were helpful in giving a physicochemical base for the selection of candidate compounds for developmental studies.

Experimental

5-Lipoxygenase Inhibitory Activity Inhibition by 5-lipoxygenase was assayed as described previously.[5]

Measurement of Substituent Parameters 1) log *P*: The partition ratio *P* (apparent partition coefficient), was measured by the flask-shaking method[7] at 25±3 °C with 1-octanol and water. After the partitioning equilibrium was reached, the concentration of each compound in the aqueous phase was measured by its ultraviolet (UV) absorbance.

2) H_{C5}: The ^{1}H-NMR chemical shift of the proton adjacent to the catechol group was measured on a Bruker AC-200 NMR in dimethyl sulfoxide-d_6 (DMSO-d_6) with tetramethylsilane (TMS) as an internal standard. The values for series III were assigned by use of nuclear Overhauser effect (NOE) analyses.

3) $E_{1/2}$: The half-wave potential (mV *vs.* a saturated calomel reference electrode) was measured as the midpoint of the cathodic and anodic peak potentials of cyclic voltammograms recorded as reported elsewhere,[15] except that a carbon-disk (i.d. = 3 mm) electrode (BAS Co.) was used as the working electrode. The carbon electrode surface was polished before each measurement with 0.05 μm alumina powder (Union Carbide, U.S.A.). Concentrations of about 1 mM of each sample in 50% EtOH that contained 0.1 M NaH_2PO_4–Na_2HPO_4 (pH 7.4) were used for voltammetric measurements.

Analyses Melting points were determined with a Yanaco melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured on a Bruker AC-200 NMR or a Hitachi R-24B NMR spectrometer with TMS as the internal standard; chemical shifts are given on the δ (ppm) scale. Infrared (IR) spectra were obtained on a Shimadzu IR-420 spectrometer.

The physicochemical data are summarized in Table I. The analytical data of previously prepared compounds are included here, because they were not given in our earlier report.[5]

Compounds and Syntheses: Caffeic Acid *n*-Pentyl Ester (3) Yield 20%. mp 125—127 °C. IR (KBr) cm^{-1}: 3480, 3310, 1675, 1635, 1600. ^{1}H-NMR (DMSO-d_6): 0.88 (3H, t, J=6.8 Hz), 1.2—1.7 (6H, m), 4.10 (2H, t, J=6.6 Hz), 6.26 (1H, d, J=15.9 Hz), 6.76 (1H, d, J=8.0 Hz), 7.01 (1H, dd, J=8.0, 1.8 Hz), 7.05 (1H, d, J=1.8 Hz), 7.47 (1H, d, J=15.9 Hz), 9.14 (1H, OH), 9.60 (1H, OH).

Caffeic Acid Ethyl Amide (5) Yield 29%. Amorphous solid. IR (KBr) cm^{-1}: 3480, 3370, 1645, 1578. ^{1}H-NMR (DMSO-d_6, $CDCl_3$): 1.16 (3H, t, J=7 Hz), 3.27 (2H, q, J=7 Hz), 6.31 (1H, d, J=16 Hz), 6.7—7.1 (3H, m), 7.41 (1H, d, J=16 Hz), 8.47 (1H, NH).

Caffeic Acid *n*-Butyl Amide (6) Yield 25%. Amorphous solid. IR (KBr) cm^{-1}: 3260, 1650. ^{1}H-NMR (DMSO-d_6, $CDCl_3$): 0.92 (3H, t, J=7 Hz), 1.15—1.7 (4H, m), 3.24 (2H, dt, J=4, 6 Hz), 6.38 (1H, d, J=16 Hz), 6.7—7.1 (3H, m), 7.32 (1H, d, J=16 Hz), 7.88 (1H, t, J=4 Hz, NH), 9.00 (2H, OH).

Caffeic Acid Benzyl Amide (12) Yield 37%. mp 164—167 °C. IR (KBr) cm^{-1}: 3250, 1670, 1640. ^{1}H-NMR (DMSO-d_6, $CDCl_3$): 4.42 (2H, d, J=6 Hz), 6.36 (1H, d, J=15 Hz), 6.65—7.5 (4H, m), 7.25 (5H, s), 8.27 (1H, t, J=6 Hz, NH), 8.80 (1H, OH), 9.00 (1H, OH).

Caffeic Acid Phenethyl Amide (13) Yield 24%. mp 157—159 °C. IR (KBr) cm^{-1}: 3450, 3300, 1640, 1600. ^{1}H-NMR (DMSO-d_6): 2.76 (2H, t, J=7.7 Hz), 3.40 (2H, m), 6.31 (1H, d, J=15.7 Hz), 6.73 (1H, d, J=8.1 Hz), 6.83 (1H, dd, J=8.1, 1.8 Hz), 6.93 (1H, d, J=1.8 Hz), 7.1—7.4 (6H, m), 8.07 (1H, t, J=5.8 Hz, NH), 9.12 (1H, OH), 9.36 (1H, OH).

Caffeic Acid 4-*n*-Butylphenyl Amide (14) Yield 31%. mp 204—205.5 °C. IR (KBr) cm^{-1}: 3490, 3390, 1660, 1620, 1600. ^{1}H-NMR (DMSO-d_6, $CDCl_3$): 0.90 (3H, t, J=6 Hz), 1.1—1.9 (4H, m), 2.52 (2H, t, J=6 Hz), 6.43 (1H, d, J=16 Hz), 6.7—7.8 (9H, m), 7.38 (1H, d, J=16 Hz), 9.58 (1H, NH).

Caffeic Acid 4-*n*-Octylphenyl Amide (15) Yield 37%. mp 173.5—175 °C. IR (KBr) cm^{-1}: 3260, 1655, 1620, 1600. ^{1}H-NMR (DMSO-d_6): 0.85 (3H, t, J=6.6 Hz), 1.1—1.7 (12H, m), 2.51 (2H, t, J=7.9 Hz), 6.53 (1H, d, J=15.7 Hz), 6.77 (1H, d, J=8.1 Hz), 6.8—7.0 (2H, m), 7.12 (2H, d, J=8.3 Hz), 7.38 (1H, d, J=15.7 Hz), 7.58 (2H, d, J=8.3 Hz), 9.19 (1H, OH), 9.44 (1H, OH), 9.98 (1H, NH).

Caffeic Acid 3,4-Dimethoxyphenyl Amide (16) Yield 27%. mp 201—202 °C. IR (KBr) cm^{-1}: 3250, 1650, 1600. ^{1}H-NMR (DMSO-d_6): 3.72 (3H, s), 3.74 (3H, s), 6.50 (1H, d, J=15.4 Hz), 6.7—7.4 (7H, m), 9.19 (1H, OH), 9.44 (1H, OH), 9.94 (1H, NH).

Caffeic Acid 3,4-Dimethoxybenzyl Amide (17) Yield 51%. mp 203—206 °C. IR (KBr) cm^{-1}: 3480, 1650, 1585. ^{1}H-NMR (DMSO-d_6, $CDCl_3$): 3.80 (6H, s), 4.38 (2H, d, J=6 Hz), 6.38 (1H, d, J=15 Hz), 6.6—7.2 (6H, m), 7.39 (1H, d, J=15 Hz), 7.85 (1H, NH), 8.0—8.3 (2H, OH).

Caffeic Acid 2-(3,4-Dimethoxyphenyl)ethyl Amide (18) Yield 10%. mp 97—99 °C. IR (KBr) cm^{-1}: 3300, 1650, 1600. ^{1}H-NMR (DMSO-d_6): 2.7 (2H, m), 3.4 (2H, m), 3.71 (3H, s), 3.73 (3H, s), 6.32 (1H, d, J=16 Hz), 6.7—7.0 (6H, m), 7.22 (1H, d, J=16 Hz), 8.02 (1H, NH), 9.12 (1H, OH), 9.35 (1H, OH).

***N*-*n*-Hexyl-3,4-dihydroxybenzamide (26)** Yield 20%. mp 139—140 °C. IR (KBr) cm^{-1}: 3480, 3350, 3150, 1615, 1580, 1540. ^{1}H-NMR (DMSO-d_6): 0.86 (3H, t, J=6.6 Hz), 1.2—1.8 (8H, m), 3.1—3.2 (2H, m), 6.73 (1H, d, J=8.2 Hz), 7.16 (1H, dd, J=8.2, 2.0 Hz), 7.26 (1H, d, J=2.0 Hz), 8.09 (1H, NH), 9.0—9.5 (2H, br, OH).

***N*-*n*-Decyl-3,4-dihydroxybenzamide (27)** Yield 16%. mp 129.5—130 °C. IR (KBr) cm^{-1}: 3480, 3350, 3180, 1610, 1580, 1540. ^{1}H-NMR (DMSO-d_6): 0.85 (3H, t, J=6.6 Hz), 1.2—1.8 (16H, m), 3.1—3.2 (2H, m), 6.73 (1H, d, J=8.4 Hz), 7.16 (1H, dd, J=8.4, 2.0 Hz), 7.26 (1H, d, J=2.0 Hz), 8.07 (1H, NH), 9.06 (1H, OH), 9.39 (1H, OH).

***N*-*n*-Dodecyl-3,4-dihydroxybenzamide (28)** Yield 13%. mp 119.5—120.0 °C. IR (KBr) cm^{-1}: 3480, 3350, 3150, 1615, 1580, 1540. ^{1}H-NMR (DMSO-d_6): 0.85 (3H, t, J=6.7 Hz), 1.2—1.8 (20H, m), 3.1—3.2 (2H, m), 6.73 (1H, d, J=8.2 Hz), 7.16 (1H, dd, J=8.2, 2.0 Hz), 7.26 (1H, d, J=2.0 Hz), 8.07 (1H, NH), 9.06 (1H, OH), 9.39 (1H, OH).

1-(3,4-Dihydroxyphenyl)-*n*-octanol (31) To a solution of *n*-heptylmagnesium bromide (prepared from 1.6 g of magnesium turnings and 9.4 ml of *n*-heptyl bromide in 100 ml of tetrahydrofuran (THF)) was added dropwise protocatechualdehyde (2.5 g) in THF (10 ml) at 0 °C for 10 min. The resultant solution was stirred at 0 °C for 30 min and then poured into ice water. The mixture was acidified to pH 2 with 1 N HCl and extracted with AcOEt. The extract was washed with water and brine in that order, and dried over $MgSO_4$. After evaporation of the solvent, **31** was collected by recrystallization from AcOEt–hexane (2.4 g, 57%). mp 120—122.5 °C. IR (KBr) cm^{-1} 3450, 3100, 1610, 1520. ^{1}H-NMR (DMSO-d_6, $CDCl_3$): 0.87 (3H, t, J=6 Hz), 1.1—2.0 (12H, m), 4.3—4.5 (2H, m), 6.5—7.0 (3H, m), 8.12 (2H, OH).

1-(3,4-Dihydroxyphenyl)-*n*-butanol (29) The procedure used for the preparation of **31** was repeated with protocatechualdehyde and *n*-propylmagnesium bromide to obtain **29** (2.3 g, 43%). mp 137—139 °C. IR (KBr) cm^{-1}: 3450, 3100, 1615, 1520. ^{1}H-NMR (DMSO-d_6, $CDCl_3$): 0.87 (3H, t, J=6 Hz), 1.1—2.0 (4H, m), 3.6 (1H, OH), 4.48 (1H, m), 6.5—7.0 (3H, m), 7.5—7.9 (2H, OH).

1-(3,4-Dihydroxyphenyl)-*n*-hexanol (30) The procedure used for the preparation of **31** was repeated with protocatechualdehyde and *n*-pentylmagnesium bromide to obtain **30** (2.8 g, 67%). mp 108—110 °C. IR (KBr) cm^{-1}: 3450, 3100, 1610, 1520. ^{1}H-NMR (DMSO-d_6): 0.83 (3H, t, J=6.5 Hz), 1.1—1.7 (8H, m), 4.29 (1H, m), 4.82 (1H, d, J=4.1 Hz, OH), 6.51 (1H, dd, J=8.0, 1.9 Hz), 6.63 (1H, d, J=8.0 Hz), 6.69 (1H, d, J=1.9 Hz), 8.62 (1H, OH), 8.72 (1H, OH).

4-*n*-Octylcatechol (34) Compound **31** (1.9 g) in EtOH (40 ml) containing five drops of 12 N HCl was hydrogenated over 10% Pd/C (380 mg) under atmospheric pressure at room temperature for 2 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was extracted with AcOEt and the extract was washed with water and brine in that order, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane. Compound **34** was recrystallized from hexane (510 mg, 29%). mp 60—61 °C. IR (KBr) cm^{-1}: 3460, 3310, 1600, 1520. ^{1}H-NMR ($CDCl_3$): 0.86 (3H, t, J=6.0 Hz), 1.2—1.8 (12H, m), 2.42 (2H, t, J=7.0 Hz), 5.92 (2H, OH), 6.4—6.8 (3H, m).

4-*n*-Butylcatechol (32) The procedure used for the preparation of **34** was repeated with **29** to obtain **32** (1.1 g, 80%). Amorphous solid. IR (KBr) cm^{-1}: 3480, 3350, 1610, 1520. ^{1}H-NMR ($CDCl_3$): 0.86 (3H, t, J=6.0 Hz), 1.2—1.8 (4H, m), 2.42 (2H, t, J=7.0 Hz), 5.68 (2H, OH), 6.4—6.8 (3H, m).

4-*n*-Hexylcatechol (33) The procedure used for the preparation of **34** was repeated with **30** to obtain **33** (1.4 g, 91%). Amorphous solid. IR (KBr) cm^{-1}: 3480, 3350, 1610, 1520. ^{1}H-NMR (DMSO-d_6): 0.85 (3H, t, J=6.6 Hz), 1.2—1.7 (8H, m), 2.38 (2H, t, J=7.7 Hz), 6.40 (1H, dd, J=7.9, 2.0 Hz), 6.54 (1H, d, J=2.0 Hz), 6.61 (1H, d, J=7.9 Hz), 8.57 (1H, OH), 8.65 (1H, OH).

4-*n*-Octyloxycatechol (37) 1) Protocatechualdehyde Dibenzyl Ether (**35**): A solution of protocatechualdehyde (10 g), K_2CO_3 (20 g), and benzyl bromide (20 ml) in dimethylformamide (DMF) (200 ml) was stirred at 150 °C for 4 h. After the reaction mixture was cooled to 0 °C, it was poured into Et_2O. The organic layer was washed with water and brine in that order, and dried over $MgSO_4$. After evaporation of the solvent, **35** was collected by precipitation from AcOEt–hexane (18 g, 78%). IR (KBr) cm^{-1}: 1675, 1575, 1495. ^{1}H-NMR ($CDCl_3$): 5.20 (2H, s), 5.24 (2H, s),

7.00 (1H, d, J=8.2 Hz), 7.2—7.5 (12H, m), 9.80 (1H, s).

2) 3,4-Dibenzyloxyphenol (**36**): A solution of **35** (18 g) and *m*-CPBA (15 g) in AcOEt (200 ml) was stirred at room temperature for 6 h, and then AcOEt (300 ml) was added. The organic layer was washed with aqueous $NaHCO_3$, water and brine, in that order, and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in dioxane (50 ml). To this solution was added 3 N NaOH (50 ml), and the solution was stirred at room temperature for 30 min. The resultant solution was acidified with 3 N HCl to pH 2 at 0 °C and extracted with AcOEt. The extract was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, **36** was collected by precipitation from $CHCl_3$–hexane (9.2 g, 53%). IR (KBr) cm^{-1}: 3300, 1600, 1500. ^{1}H-NMR ($CDCl_3$): 5.04 (2H, s), 5.05 (2H, s), 6.27 (1H, dd, J=8.5, 2.8 Hz), 6.47 (1H, d, J=2.8 Hz), 6.77 (1H, d, J=8.5 Hz), 7.2—7.5 (10H, m).

3) 4-*n*-Octyloxycatechol (**37**): To a cooled (0 °C) solution of **36** (0.7 g) in DMF (10 ml) was added NaH (140 mg) and 1-bromooctane (0.6 ml), in that order. The resultant solution was stirred at room temperature for 30 min, and cooled to 0 °C. Water was carefully added to the solution and the resultant mixture was extracted with AcOEt. The extract was washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel (AcOEt–hexane). The obtained compound in AcOEt (10 ml) was hydrogenated over 10% Pd/C (500 mg) under atmospheric pressure at room temperature for 15 h. Then, the catalyst was removed by filtration. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane. Compound **37** was recrystallized from AcOEt–hexane (230 mg, 42%). mp 108—109 °C. IR (KBr) cm^{-1}: 3400, 3300, 1615, 1525, 1510. ^{1}H-NMR (DMSO-d_6): 0.86 (3H, t, J=6.7 Hz), 1.2—1.8 (12H, m), 3.78 (2H, t, J=6.4 Hz), 6.16 (1H, dd, J=8.6, 2.9 Hz), 6.32 (1H, d, J=2.9 Hz), 6.60 (1H, d, J=8.6 Hz), 8.33 (1H, OH), 8.83 (1H, OH).

4-*n*-Decyloxycatechol (38) The procedure used for the preparation of **37** was repeated with **36** and 1-bromodecane to give **38** (270 mg, 44%). mp 112—113 °C. IR (KBr) cm^{-1}: 3400, 3300, 1615, 1525, 1510. ^{1}H-NMR (DMSO-d_6): 0.86 (3H, t, J=6.7 Hz), 1.2—1.8 (16H, m), 3.78 (2H, t, J=6.4 Hz), 6.16 (1H, dd, J=8.6, 2.9 Hz), 6.32 (1H, d, J=2.9 Hz), 6.59 (1H, d, J=8.6 Hz), 8.33 (1H, OH), 8.82 (1H, OH).

***trans*-*N*-*n*-Hexyl-β-(3,4-dihydroxyphenoxy)acrylamide (43)** 1) *trans*-β-(3,4-Dibenzyloxyphenoxy)acrylic Acid (**39**): By the procedure of Fujinami *et al.*,[6] **36** was converted to **39** (3.4 g, 42%). IR (KBr) cm^{-1}: 3020, 2550, 1655, 1590, 1510. ^{1}H-NMR ($CDCl_3$): 5.13 (2H, s), 5.15 (2H, s), 5.43 (1H, d, J=12.2 Hz), 6.57 (1H, dd, J=8.8, 2.8 Hz), 6.68 (1H, d, J=2.8 Hz), 6.89 (1H, d, J=8.8 Hz), 7.2—7.5 (10H, m), 7.78 (1H, d, J=12.2 Hz).

2) *trans*-*N*-*n*-Hexyl-β-(3,4-dibenzyloxyphenoxy)acrylamide (**40**): A solution of **39** (0.9 g), $SOCl_2$ (5 ml), and one drop of DMF was heated at reflux for 2 h. After the excess of $SOCl_2$ was removed by distillation, the residue obtained was dissolved in $CHCl_3$ (5 ml) and cooled to 0 °C. To the cooled solution was added triethylamine (0.4 ml) and *n*-hexylamine (0.4 ml), in that order, and the resultant solution was stirred at room temperature for 1 h. After the reaction, the solution was diluted with AcOEt. The organic layer was washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane to give **40** (200 mg, 18%). IR (KBr) cm^{-1}: 3300, 1665, 1615, 1595. ^{1}H-NMR ($CDCl_3$): 0.89 (3H, t, J=6.5 Hz), 1.2—1.8 (8H, m), 3.2—3.4 (2H, m), 5.12 (2H, s), 5.13 (2H, s), 5.39 (1H, d, J=12.2 Hz), 6.56 (1H, dd, J=8.8, 2.8 Hz), 6.68 (1H, d, J=2.8 Hz), 6.88 (1H, d, J=8.8 Hz), 7.2—7.5 (10H, m), 7.67 (1H, d, J=12.2 Hz).

3) *trans*-*N*-*n*-Hexyl-β-(3,4-dihydroxyphenoxy)acrylamide (**43**): To a solution of **40** (200 mg) in dry CH_2Cl_2 (10 ml) was added dropwise 1 M BBr_3 in CH_2Cl_2 (2.6 ml) at −70 °C. After the addition, the reaction mixture was stirred at −70 °C for 10 min, and poured into ice water. The resultant mixture was extracted with AcOEt and the extract was washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane, and recrystallized from $CHCl_3$–hexane to give **43** (30 mg, 25%). mp 103—104 °C. IR (KBr) cm^{-1}: 3460, 3100, 1670, 1595, 1520. ^{1}H-NMR (DMSO-d_6): 0.86 (3H, t, J=6.6 Hz), 1.2—1.8 (8H, m), 3.0—3.1 (2H, m), 5.50 (1H, d, J=12.1 Hz), 6.37 (1H, dd, J=8.5, 2.8 Hz), 6.49 (1H, d, J=2.8 Hz), 6.71 (1H, d, J=8.5 Hz), 7.41 (1H, d, J=12.1 Hz), 7.74 (1H, NH), 8.88 (1H, OH), 9.25 (1H, OH).

***trans*-*N*-*n*-Octyl-β-(3,4-dihydroxyphenoxy)acrylamide (44)** The procedure used for the preparation of **43** was repeated with **39** and *n*-octylamine to obtain **44** (60 mg, 8% yield from **39**). mp 139—140 °C. IR (KBr) cm^{-1}: 3400, 3230, 1660, 1620, 1575. ^{1}H-NMR (DMSO-d_6): 0.86 (3H, t, J=6.7 Hz), 1.2—1.8 (12H, m), 3.0—3.1 (2H, m), 5.50 (1H, d, J=12.1 Hz), 6.37 (1H, dd, J=8.5, 2.8 Hz), 6.49 (1H, d, J=2.8 Hz), 6.71 (1H, d, J=8.5 Hz), 7.41 (1H, d, J=12.1 Hz), 7.74 (1H, NH), 8.88 (1H, OH), 9.25 (1H, OH).

***trans*-*N*-*n*-Decyl-β-(3,4-dihydroxyphenoxy)acrylamide (45)** The procedure used for the preparation of **43** was repeated with **39** and *n*-decylamine to obtain **45** (70 mg, 8% yield from **39**). mp 110—111.0 °C. IR (KBr) cm^{-1}: 3450, 3300, 1660, 1620, 1580. ^{1}H-NMR (DMSO-d_6): 0.85 (3H, t, J=6.6 Hz), 1.2—1.8 (16H, m), 3.0—3.1 (2H, m), 5.50 (1H, d, J=12.1 Hz), 6.37 (1H, dd, J=8.5, 2.9 Hz), 6.49 (1H, d, J=2.9 Hz), 6.71 (1H, d, J=8.5 Hz), 7.41 (1H, d, J=12.1 Hz), 7.74 (1H, NH), 8.88 (1H, OH), 9.25 (1H, OH).

6-Acetyl-2,3-dihydroxynaphthalene (50) 1) 2,3-Dimethoxynaphthalene (**46**): The procedure used for preparation of **35** was repeated with 2,3-dihydroxynaphthalene (20 g), dimethyl sulfate (26 ml), and K_2CO_3 (50 g) in DMF (200 ml) to obtain **46** (10 g, 42%). IR (KBr) cm^{-1}: 1620, 1595. ^{1}H-NMR ($CDCl_3$): 4.00 (6H, s), 7.12 (2H, s), 7.35 (2H, dd, J=6.9, 3.6 Hz), 7.69 (2H, dd, 2H, J=6.9, 3.6 Hz).

2) 6-Acetyl-2,3-dimethoxynaphthalene (**47**): $AlCl_3$ (39 g) was added in portions to a solution of **46** (14.0 g), and acetic anhydride (11.5 ml) in nitrobenzene (80 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h and poured into ice water. The mixture was extracted with Et_2O and the extract was washed with water, aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. After evaporation of the solvent, **47** was collected by precipitation from AcOEt–hexane (7.1 g, 41%). IR (KBr) cm^{-1}: 1675, 1620, 1600. ^{1}H-NMR ($CDCl_3$): 2.59 (3H, s), 3.91 (6H, s), 7.00 (1H, s), 7.06 (1H, s), 7.52 (1H, d, J=9.0 Hz), 7.78 (1H, dd, J=9.0, 2.0 Hz), 8.15 (1H, d, J=2.0 Hz).

3) 6-Acetyl-2,3-dihydroxynaphthalene (**50**): The procedure used for the preparation of **43** was repeated with **47** (7.1 g) in CH_2Cl_2 (150 ml) and 1 M BBr_3 (123 ml), except that the reaction temperature was −40 to 0 °C. After the reaction, **50** was recrystallized from $CHCl_3$–hexane (3.5 g, 56%). mp 169—170.0 °C. IR (KBr) cm^{-1}: 3300, 1640, 1525. ^{1}H-NMR (DMSO-d_6): 2.62 (3H, s), 7.16 (1H, s), 7.30 (1H, s), 7.63 (1H, d, J=9.0 Hz), 7.70 (1H, dd, J=9.0, 2.0 Hz), 8.32 (1H, d, J=2.0 Hz), 9.81 (1H, OH), 10.00 (1H, OH).

6-*n*-Butyloyl-2,3-dihydroxynaphthalene (51) The procedure used for the preparation of **50** was repeated with **46** and butyric anhydride to obtain **51** (230 mg, 3% yield from **46**). mp 180—181 °C. IR (KBr) cm^{-1}: 3500, 3300, 1660, 1625, 1600. ^{1}H-NMR (DMSO-d_6): 0.95 (3H, t, J=7.5 Hz), 1.67 (2H, qt, J=7.5, 7.1 Hz), 3.05 (2H, t, J=7.1 Hz), 7.16 (1H, s), 7.30 (1H, s), 7.63 (1H, d, J=8.6 Hz), 7.70 (1H, dd, J=8.6, 1.5 Hz), 8.32 (1H, d, J=1.5 Hz) 9.79 (1H, OH), 9.97 (1H, OH).

6-*n*-Hexanoyl-2,3-dihydroxynaphthalene (52) The procedure used for the preparation of **50** was repeated with **46** and hexanoic anhydride to obtain **52** (230 mg, 4% yield from **46**). mp 173—174 °C. IR (KBr) cm^{-1}: 3480, 3290, 1665, 1625, 1595. ^{1}H-NMR (DMSO-d_6): 0.88 (3H, t, J=6.8 Hz), 1.2—1.8 (6H, m), 3.06 (2H, t, J=7.2 Hz), 7.16 (1H, s), 7.30 (1H, s), 7.63 (1H, d, J=8.7 Hz), 7.70 (1H, dd, J=8.7, 1.5 Hz), 8.32 (1H, d, J=1.5 Hz), 9.80 (1H, OH), 9.95 (1H, OH).

6-Ethyl-2,3-dihydroxynaphthalene (56) 1) 6-Ethyl-2,3-dimethoxynaphthalene (**53**): The procedure used for the preparation of **34** was repeated with **47** (1.0 g), 10% Pd/C (1.0 g), and 12 N HCl (2 ml) in dioxane (15 ml) to obtain **53** (850 mg, 91%). IR (KBr) cm^{-1}: 1605, 1510. ^{1}H-NMR ($CDCl_3$): 1.31 (3H, t, J=7.6 Hz), 2.77 (2H, q, J=7.6 Hz), 3.99 (6H, s), 7.08 (1H, s), 7.09 (1H, s), 7.21 (1H, dd, J=8.3, 1.7 Hz), 7.49 (1H, d, J=1.7 Hz), 7.61 (1H, d, J=8.3 Hz).

2) 6-Ethyl-2,3-dihydroxynaphthalene (**56**): The procedure used for the preparation of **50** was repeated with **53** (600 mg) in CH_2Cl_2 (20 ml) and 1 M BBr_3 (5.5 ml) to obtain **56** (340 mg, 65%). mp 148—149.5 °C. IR (KBr) cm^{-1}: 3400, 1605, 1520. ^{1}H-NMR (DMSO-d_6): 1.21 (3H, t, J=7.6 Hz), 2.66 (2H, q, J=7.6 Hz), 7.03 (1H, s), 7.05 (1H, s), 7.05 (1H, m), 7.34 (1H, m), 7.48 (1H, d, J=8.4 Hz), 9.39 (2H, OH).

6-*n*-Butyl-2,3-dihydroxynaphthalene (57) The procedure used for the preparation of **56** was repeated with **48** to obtain **57** (140 mg, 48% yield from **48**). mp 137.5—139 °C. IR (KBr) cm^{-1}: 3400, 1605, 1520. ^{1}H-NMR (DMSO-d_6): 0.90 (3H, t, J=7.3 Hz), 1.2—1.7 (4H, m), 2.63 (2H, t, J=7.7 Hz), 7.02 (1H, s), 7.04 (1H, s), 7.03 (1H, m), 7.33 (1H, m), 7.47 (1H, d, J=8.4 Hz), 9.36 (1H, OH), 9.41 (1H, OH).

6-*n*-Hexyl-2,3-dihydroxynaphthalene (58) The procedure used for the preparation of **56** was repeated with **49** to obtain **58** (120 mg, 28% yield from **49**). mp 138.5—139.5 °C. IR (KBr) cm^{-1}: 3300, 1610, 1520. ^{1}H-NMR (DMSO-d_6): 0.85 (3H, t, J=6.6 Hz), 1.2—1.7 (8H, m), 2.62 (2H, t, J=7.7 Hz), 7.02 (1H, s), 7.04 (1H, s), 7.03 (1H, m), 7.32 (1H, m), 7.46 (1H, d, J=8.4 Hz), 9.39 (2H, OH).

***N*-*n*-Butyl-6,7-dihydroxy-2-naphthamide (63)** 1) 6,7-Dimethoxy-2-naphthoic Acid (**59**): A solution of **47** (10.8 g) and sodium hypochlorite

solution (available chlorine, min. 5%, 120 ml) was stirred at 100—115 °C for 1 h. After being cooled to room temperature, the solution was washed with Et_2O and cooled to 0 °C. The solution was acidified with 12 N HCl to pH 2 and extracted with AcOEt. The organic layer was washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvent, **59** was precipitated from AcOEt–hexane (7.2 g, 66%). IR (KBr) cm^{-1}: 2600, 1680, 1620. ^{1}H-NMR (DMSO-d_6, $CDCl_3$): 3.9 (6H, s), 7.11 (1H, s), 7.21 (1H, s), 7.58 (1H, d, J=9 Hz), 7.76 (1H, dd, J=9, 2 Hz), 8.3 (1H, d, J=2 Hz).

2) *N*-*n*-Butyl-6,7-dimethoxy-2-naphthamide (**60**): The procedure used for the preparation of **40** was repeated with **59** (740 mg) and *n*-butylamine. After the reaction, the mixture was extracted with $CHCl_3$ and the extract was concentrated under reduced pressure to give **60** (650 mg, 71%). IR (KBr) cm^{-1}: 3300, 1620, 1540. ^{1}H-NMR ($CDCl_3$): 0.98 (3H, t, J=6.5 Hz), 1.2—1.8 (4H, m), 3.51 (2H, m), 3.99 (3H, s), 4.01 (3H, s), 6.30 (1H, NH), 7.13 (1H, s), 7.16 (1H, s), 7.66 (1H, dd, J=8.5, 1.5 Hz), 7.72 (1H, d, J=8.5 Hz), 8.15 (1H, d, J=1.5 Hz).

3) *N*-*n*-Butyl-6,7-dihydroxy-2-naphthamide (**63**): The procedure used for the preparation of **50** was repeated with **60** (600 mg) in CH_2Cl_2 (20 ml) and 1 M BBr_3 (6.7 ml). After the reaction, the solution was extracted with AcOEt and the residue obtained was chromatographed on silica gel ($CHCl_3$–MeOH) and recrystallized from $CHCl_3$–MeOH to give **63** (320 mg, 59%). mp 193.5—194 °C. IR (KBr) cm^{-1}: 3500, 3400, 3050, 1620, 1600, 1540. ^{1}H-NMR (DMSO-d_6): 0.91 (3H, t, J=7.2 Hz), 1.2—1.8 (4H, m), 3.28 (2H, m), 7.14 (1H, s), 7.18 (1H, s), 7.55—7.65 (2H, m), 8.10 (1H, m), 8.38 (1H, t, J=5.6 Hz, NH), 9.71 (1H, OH), 9.79 (1H, OH).

***N*-*n*-Hexyl-6,7-dihydroxy-2-naphthamide (64)** The procedure used for the preparation of **63** was repeated with **59** and *n*-hexylamine to obtain **64** (180 mg, 27%). mp 181—181.5 °C. IR (KBr) cm^{-1}: 3500, 3150, 1615, 1595, 1520. ^{1}H-NMR (DMSO-d_6): 0.87 (3H, t, J=7.2 Hz), 1.2—1.8 (8H, m), 3.27 (2H, m), 7.14 (1H, s), 7.18 (1H, s), 7.55—7.65 (2H, m), 8.10 (1H, m), 8.38 (1H, t, J=5.6 Hz, NH), 9.71 (1H, OH), 9.79 (1H, OH).

***N*-*n*-Octyl-6,7-dihydroxy-2-naphthamide (65)** The procedure used for the preparation of **63** was repeated with **59** and *n*-octylamine to obtain **65** (90 mg, 14%). mp 186—187.5 °C. IR (KBr) cm^{-1}: 3500, 3350, 3150, 1615, 1595, 1520. ^{1}H-NMR (DMSO-d_6): 0.86 (3H, t, J=6.5 Hz), 1.2—1.8 (12H, m), 3.26 (2H, m), 7.14 (1H, s), 7.18 (1H, s), 7.55—7.65 (2H, m), 8.09 (1H, m), 8.38 (1H, t, J=5.6 Hz, NH), 9.70 (1H, OH), 9.78 (1H, OH).

6-Ethoxy-2,3-dihydroxynaphthalene (68) 1) 6-Acetyl-2,3-dibenzyloxynaphthalene (**66**): The procedure used for the preparation of **35** was repeated with **50** (6.3 g), benzyl bromide (9.2 ml), and K_2CO_3 (12.8 g) in DMF (50 ml) to give **66** (5.2 g, 44%). IR (KBr) cm^{-1}: 1660, 1610. ^{1}H-NMR ($CDCl_3$): 2.62 (3H, s), 5.23 (4H, s), 7.1—7.7 (14H, m), 8.17 (1H, m).

2) 6,7-Dibenzyloxy-2-naphthol (**67**): The procedure used for the preparation of **36** was repeated with **66** (2.9 g), *p*-toluenesulfonic acid (1.0 g), and *m*-CPBA (2.6 g) in CH_2Cl_2 (30 ml). After the reaction, the residue obtained was chromatographed on silica gel (AcOEt–hexane) to give **67** (580 mg, 21%). IR (KBr) cm^{-1}: 3300, 1625, 1600. ^{1}H-NMR ($CDCl_3$): 5.24 (2H, s), 5.26 (2H, s), 6.91 (1H, dd, J=8.7, 2.4 Hz), 6.97 (1H, d, J=2.4 Hz), 7.05 (1H, s), 7.15 (1H, s), 7.2—7.5 (11H, m).

3) 6-Ethoxy-2,3-dihydroxynaphthalene (**68**): The procedure used for the preparation of **37** was repeated with **67** (0.25 g) and 1-bromoethane to obtain **68** (35 mg, 24%). mp 131—132 °C. IR (KBr) cm^{-1}: 3350, 1610, 1525. ^{1}H-NMR (DMSO-d_6): 1.35 (3H, t, J=7.0 Hz), 4.05 (2H, q, J=7.0 Hz), 6.82 (1H, dd, J=8.8, 2.5 Hz), 7.00 (1H, s), 7.02 (1H, s), 6.98 (1H, m), 7.45 (1H, d, J=8.8 Hz), 9.2—9.5 (2H, OH).

6-*n*-Butoxy-2,3-dihydroxynaphthalene (69) The procedure used for the preparation of **68** was repeated with **67** and 1-bromobutane to obtain **69** (25 mg, 13%). mp 141.5—143 °C. IR (KBr) cm^{-1}: 3350, 1610, 1525. ^{1}H-NMR (DMSO-d_6): 0.95 (3H, t, J=7.3 Hz), 1.4—1.8 (4H, m), 3.99 (2H, t, J=6.5 Hz), 6.82 (1H, dd, J=8.8, 2.5 Hz), 7.00 (1H, s), 7.01 (1H, s), 7.00 (1H, m), 7.45 (1H, d, J=8.8 Hz), 9.4 (2H, OH).

6-*n*-Hexyloxy-2,3-dihydroxynaphthalene (70) The procedure used for the preparation of **68** was repeated with **67** and 1-bromohexane to obtain **70** (50 mg, 27%). mp 130.5—132 °C. IR (KBr) cm^{-1}: 3350, 1610, 1525. ^{1}H-NMR (DMSO-d_6): 0.88 (3H, t, J=6.8 Hz), 1.3—1.8 (8H, m), 3.98 (2H, t, J=6.5 Hz), 6.82 (1H, dd, J=8.8, 2.5 Hz), 7.00 (1H, s), 7.02 (1H, s), 6.99 (1H, m), 7.45 (1H, d, J=8.8 Hz), 9.4 (2H, OH).

Acknowledgments We thank the staff of the Central Research Laboratories, Green Cross Corporation, for their cooperation in the biological and analytical examinations.

References and Notes

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