1-Arylnaphthalene Lignan: A Novel Scaffold for Type 5 Phosphodiesterase Inhibitor

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1-Arylnaphthalene lignan, which had been reported as a PDE4 inhibitor by Iwasaki, was disclosed as a new structural class of PDE5 inhibitors. The structural requirements for potent and specific PDE5 inhibition were revealed in a 1-arylnaphthalene lignan series, in which 1-(3-bromo-4,5-dimethoxyphenyl)-5-chloro-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-2-(methoxycarbonyl)naphthalene hydrochloride (**27q**) showed the most potent and specific inhibition (PDE5 inhibition IC_{50} = 6.2 nM, selectivity for PDE5 against PDE1, -2, -3, and -4 >16 000). It is noteworthy that **27q** has the best selectivities against PDE isoforms among PDE5 inhibitors so far reported. Compound **27q** exhibited almost the same relaxant effects on rat aortic rings as sodium 1-[6-chloro-4-[(3,4-methylenedioxybenzyl)amino]quinazolin-2-yl]piperidine-4-carboxylate (**35**) (**27q**, EC_{50} = 0.10 μM; **35**, EC_{50} = 0.20 μM) and was selected for further biological evaluation.

Introduction

Cyclic nucleotide phosphodiesterases (PDEs) are key enzymes for catalyzing the hydrolysis of cyclic nucleotides, cAMP and cGMP, to their respective 5′-nucleoside monophosphates. PDEs have been classified into at least seven distinct isoenzyme families,[1] which have been distinguished by their substrate specificities, the mechanisms of regulation, and their sensitivity to various pharmacological agents. PDE5, cGMP-specific PDE, is distributed in lung, kidney, spleen, endothelial cells, smooth muscle cells, etc., and plays a key role for biological regulations by means of hydrolysis of cGMP in these tissues. Because cGMP mediates vasorelaxant actions, the potent and selective PDE5 inhibitor is an attractive target for treatment of hypertension, angina, congestive heart failure, and impotence.[2]

Potent and selective PDE5 inhibitors have been extensively reported, but a majority of them are classified into three categories: zaprinast-related inhibitors,[3] quinazoline derivatives,[4] and phthalazine derivatives.[5] Iwasaki et al. in our company reported a series of 1-aryl-2,3-bis(hydroxymethyl)naphthalene lignans as selective PDE4 inhibitors.[6] In connection with our efforts in search of biologically active lignans, we now disclose 1-arylnaphthalene lignans having potent and specific PDE5 inhibitory activities. It is noteworthy that both selective PDE4 and PDE5 inhibitors are derived from the common scaffold, 1-arylnaphthalene lignan, and the spectra of PDE inhibitions are entirely altered by the chemical modification of its substituents.

Chemistry

The key intermediates **9**, 1-aryl-2,3-bis(methoxycarbonyl)naphthalene lignans, were synthesized by the Diels−Alder reaction of isobenzofurans **7** with dimethyl fumarate, followed by acid-mediated ring opening of 1,4-epoxides **8** and subsequent dehydration[7] (Scheme 1). As shown in Scheme 1, the precursors of isobenzofuran (**3** and **6**) were prepared by the following two methods: bromoacetals **1** were transformed into cyclic acetals **3** via hydroxy acetals **2**[8] (method A), and lactols **6** were obtained from phthalides **5** which were converted from amides **4**[9] (method B). The Diels−Alder adducts **8** were afforded by the reaction of **3** or **6** with dimethyl fumarate as a dienophile in the presence of acetic acid in a one-pot procedure. Aromatization of **8** proceeded well by treatment with trifluoroacetic acid or BF_3·Et_2O via ring opening of 1,4-epoxides and subsequent dehydration to provide the key intermediates **9** in good yields.

9a was found to be a seed compound from the random screening of 1-arylnaphthalene lignans[6] on PDE5 inhibition. **9a** was divided into three parts (A−C rings), and the modification of each part was carried out in the following procedures: (i) transformation of the methoxycarbonyl moiety on 2,3-positions of arylnaphthalene (B ring); (ii) conversion of 1-aryl group and/or substituents on 1-aryl group as the C ring; and (iii) replacement of substituents on the A ring. The transformation of substituent on 2,3-positions of **9a** is outlined in Scheme 2. 3-Carboxylactone **11** was prepared by selective oxidation of the 3-hydroxymethyl group of diol **10** that was obtained from **9a** by the reduction of ester groups with Red-Al. Alkaline hydrolysis of the ester group of **9a** proceeded in a highly selective manner to provide 2-methoxycarbonyl-3-carboxy compound **12a** because of the steric hindrance of the 1-(3,4,5-trimethoxyphenyl) ring. Corresponding 2-carboxylactone **13** was selectively prepared by the reduction of **12a** with sodium borohydride via the activated mixed anhydride. 3-Amino-2-hydroxymethyl compound **14** was obtained by means of Curtius rearrangement of acyl azide derived from **12a,** followed by reduction of **13** with $LiAlH_4$.

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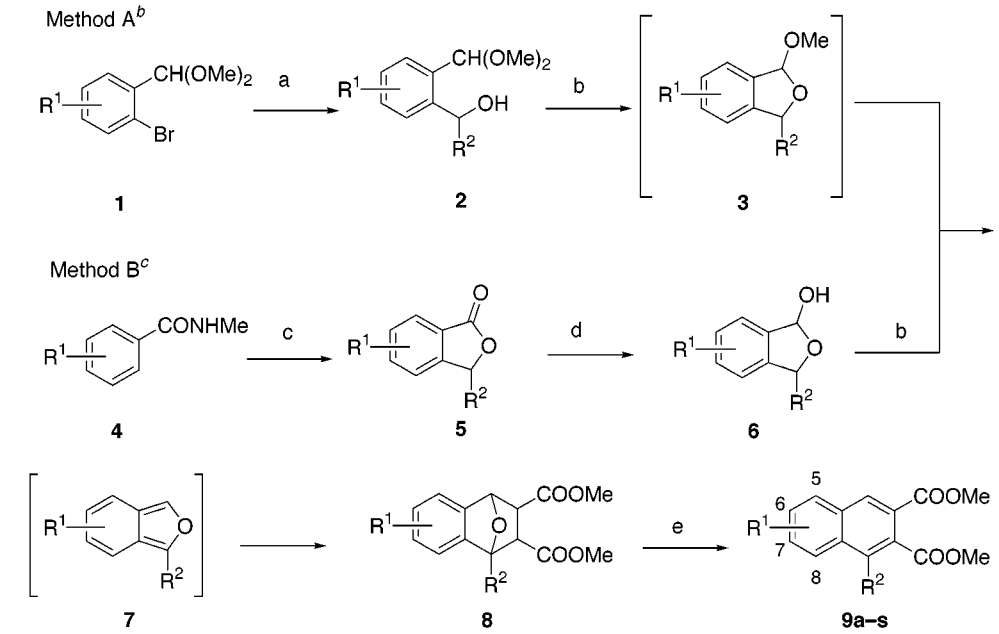
Scheme 1[a]



9a: R^1 = 6,7-$(OMe)_2$ R^2 = 3,4,5-$(OMe)_3$Ph
9b: R^1 = 6,7-$(OMe)_2$ R^2 = 3-H_2N-4,5-$(OMe)_2$Ph
9c: R^1 = 6,7-$(OMe)_2$ R^2 = 3-Cl-4,5-$(OMe)_2$Ph
9d: R^1 = 6,7-$(OMe)_2$ R^2 = 3-Br-4,5-$(OMe)_2$Ph
9e: R^1 = 6,7-$(OMe)_2$ R^2 = 3-Me-4,5-$(OMe)_2$Ph
9f: R^1 = 6,7-$(OMe)_2$ R^2 = 3,4-OCH_2O-
9g: R^1 = 6,7-$(OMe)_2$ R^2 = 3,4-Cl_2
9h: R^1 = 6,7-$(OMe)_2$ R^2 = 3,5-Cl_2
9i: R^1 = 6,7-$(OMe)_2$ R^2 = 3-NO_2
9j: R^1 = 6,7-$(OMe)_2$ R^2 = 2-Br-4-pyridyl
9k: R^1 = 6,7-$(OMe)_2$ R^2 = 2-thienyl
9l: R^1 = 6,7-$(OMe)_2$ R^2 = (E)-CH=CH-{3,4,5-$(OMe)_3$Ph}
9m: R^1 = 6-OEt-7-OMe R^2 = 3-Br-4,5-$(OMe)_2$Ph
9n: R^1 = 6,7,8-$(OMe)_3$ R^2 = 3-Br-4,5-$(OMe)_2$Ph
9o: R^1 = H R^2 = 3-Br-4,5-$(OMe)_2$Ph
9p: R^1 = 6-OMe R^2 = 3-Br-4,5-$(OMe)_2$Ph
9q: R^1 = 5-Cl R^2 = 3-Br-4,5-$(OMe)_2$Ph
9r: R^1 = 7-Cl R^2 = 3-Br-4,5-$(OMe)_2$Ph
9s: R^1 = 7-Me R^2 = 3-Br-4,5-$(OMe)_2$Ph

[a] Reagents: (a) *n*-BuLi, R^2CHO/THF, or *n*-BuLi then ClTi(O*i*-Pr)$_3$, R^2CHO/THF; (b) dimethyl fumarate, AcOH/toluene; (c) *s*-BuLi, TMEDA, R^2CHO/THF; (d) DIBAL/CH_2Cl_2; (e) TFA or BF_3·OEt_2. [b] **9a**−**p** were prepared by method A. [c] **9q**−**s** were prepared by method B.

Condensation of **12a** with ammonia or secondary amines afforded amides **16**, **18**−**24**, and **27a** in good yields, whereas that with methylamine resulted in providing a mixture of amide **17** and imide **28,** which were isolated by silica gel column chromatography. Alcohols **25** and **26** were obtained from the reduction of ketone **24** and ester **22** with $NaBH_4$ in good yields, respectively.

Scheme 3 summarizes the synthesis of reduced analogues of **27a**. Amine **31,** the reduced analogue of the amide on the 3-position of **27a**, was prepared from 2-methoxycarbonyl-3-methyl analogue **29**, which was produced by the Diels−Alder reaction of isobenzofuran **7a** with methyl crotonate. Bromination of **29** with *N*-bromosuccinimide was followed by substitution with 4-(2-hydroxyethyl)piperazine to provide amine **31** in a moderate yield. 2-Hydroxymethyl analogue **34**, accompanied by the excessively reduced amine **33**, was obtained from *O-tert*-butyldimethylsilyl compound **32** by treatment with $LiAlH_4$.

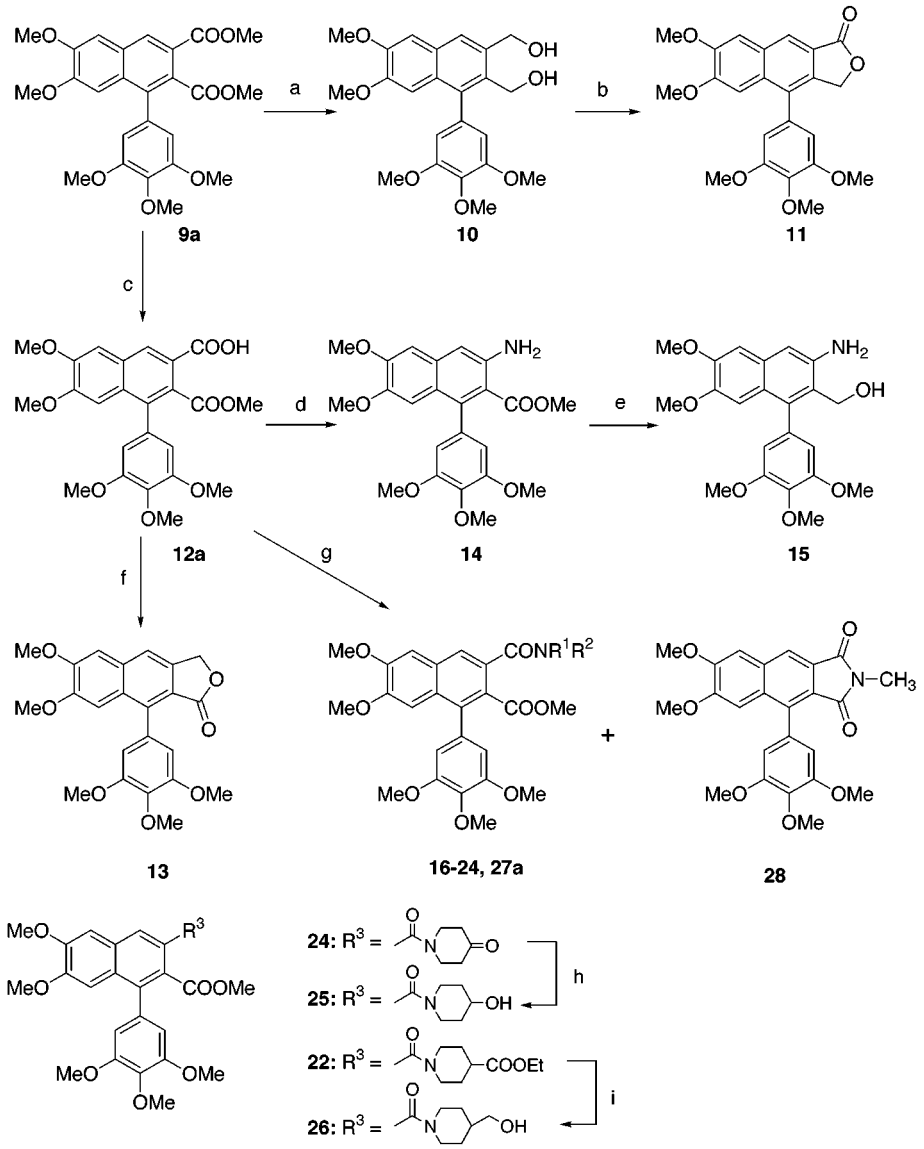
Biological Results and Discussion

The compounds reported in this paper were first evaluated for inhibitory activities against the three different forms of PDEs isolated from canine cardiac ventricle (PDE1 and -3) and lung (PDE5) in vitro (Tables 1−3).

Compounds selected on the basis of the PDE5 inhibitory activity were next evaluated for the relaxant effects on rat aortic rings and additionally investigated for the two different forms of PDEs isolated from canine adrenal gland (PDE2) and lung (PDE4) (Table 4). From the random screening of 1-arylnaphthalene lignans on PDE inhibition, we found that **9a** had a relatively selective PDE5 inhibitory activity (IC_{50} = 2.1 μM, selectivity for PDE5 over PDE1 and -3 > 50).

Transformation of the substituents on the 2,3-positions of **9a** was first examined (Table 1). The importance of both or either ester group on the 2,3-positions of **9a** is evident from the comparison of PDE5 inhibitory activities and isozyme selectivities between **9a** and bis(hydroxymethyl) compound **10**, the corresponding reduced product of **9a**. Both 2-carboxy and 3-carboxy lactones **11** and **13**, the imide **28**, and amides **16**−**18**, having carbonyl groups on 2- and/or 3-positions, were synthesized to investigate the structure−activity relationships (SAR) of 1-arylnaphthalene lignans. 3-Carboxylactone **11** was 30 times more potent than **9a** (IC_{50} = 0.068 μM), though it exhibited remarkably worse selectivities for PDE5 over PDE1 and -3 than **9a**. 2-Carboxylactone **13**, the corresponding regioisomer of **11**, showed drastically changed PDE inhibition spectra and potent PDE1 and -3 inhibitory activities, with less PDE5 activity. The imide **28**, 2-methoxycarbonyl-3-amide **16**, and 2-methoxycarbonyl-3-methylamide **17** markedly lost PDE5 inhibitory activities (IC_{50} > 100 μM), whereas 2-methoxycarbonyl-3-dimethylamide **18**

Scheme 2[a]



[a] Reagents: (a) Red-Al/THF; (b) $AgCO_3$/benzene; (c) $NaOH_{aq}$/MeOH; (d) (1) ClCOOEt, NEt_3/THF, (2) NaN_3, (3) heat/toluene, (4) concd HCl; (e) $LiAlH_4$/THF; (f) (1) ClCOOEt, NEt_3/THF, (2) $NaBH_4$, (3) NaH/DMF; (g) amine, NH_3, or CH_3NH_2, EDCl·HCl−HOBt or CDI; (h) $NaBH_4$/EtOH; (i) $NaBH_4$/MeOH−THF.

showed an improved PDE5 inhibitory activity (IC_{50} = 0.23 μM) with retained isozyme selectivities.

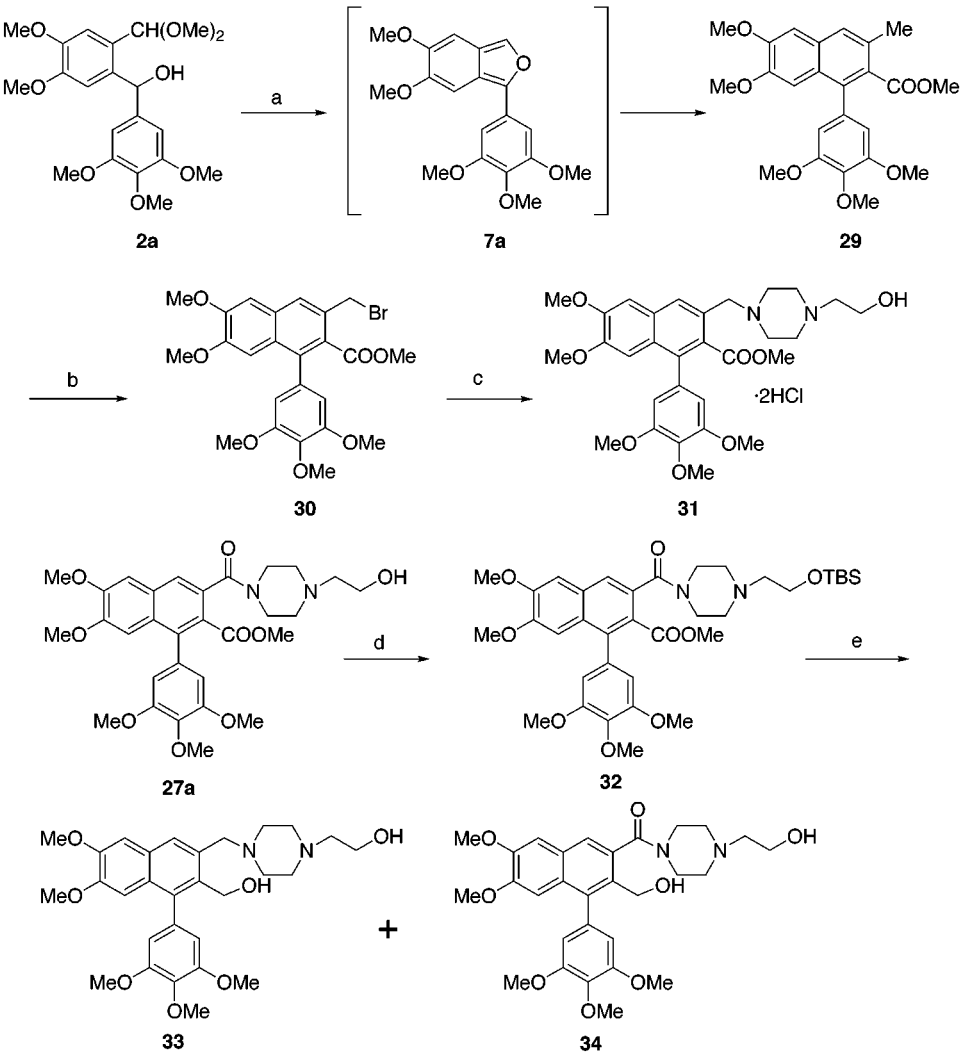
Next we focused on the synthesis of 3-tertiary amides **19** and **20** based on the above results. Morpholino, 4-oxopiperidino, 4-hydroxypiperidino, and 4-(hydroxymethyl)piperidino amides **23**−**26**, having oxygen atom in, on, or close to the 4-position of the six-membered ring, exhibited similar PDE5 inhibitory activities to dimethyl amide **18** and improved isozyme selectivities. Among the cyclic amides, 3-(2-hydroxyethyl)piperazino amide **27a** showed a potent PDE5 inhibitory activity (IC_{50} = 0.094 μM) and improved selectivities for PDE5 over PDE1 and -3 (selectivity ratios: 436 and 1063, respectively).

27a was selected as a lead compound, and the corresponding reduced products of **27a** were synthesized in order to confirm the role of the carbonyl group on 2- and/or 3-positions toward PDE5 inhibitory activity. 4-(2-Hydroxyethyl)piperazinomethyl analogue **31**, the reduction product of amide carbonyl, resulted in a considerable loss of activity (IC_{50} = 2.4 μM). On the other hand, 2-hydroxymethyl analogue **34**, the reduction product of methyl ester, exhibited marked loss of PDE1, -3, and -5 inhibitiory activities (IC_{50} > 100 μM for PDE1, -3, and -5). The 2-methoxycarbonyl and 3-[4-(2-hydroxyethyl)piperazino]carbonyl groups were fixed from the results of the above SAR study about the substituent on 2,3-positions of **27a**.

Next we looked at the replacement of the 1-aryl group, 1-(3,4,5-trimethoxyphenyl) group, with the phenyl group having a variety of substituents, the heteroaryl group, or the *trans*-styryl group (Table 2). Among mono-, di-, and trisubstituted phenyl compounds, 3-halogeno-4,5-dimethoxyphenyl derivatives **27c** and **27d** only possessed increased potencies compared with 3,4,5-trimethoxyphenyl **27a** (**27c**, IC_{50} = 0.049 μM; **27d**, IC_{50} = 0.024 μM; **27a**, IC_{50} = 0.094 μM). Replacement by heteroaryl groups (**27j** and **27k**) and the *trans*-styryl group (**27l**) led to remarkable loss of PDE5 inhibitory activities (IC_{50} >100 μM).

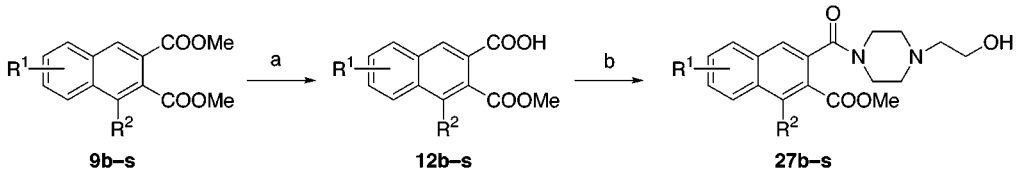
Finally we investigated the effects of substituent on the A ring toward PDE5 inhibitory activity (Table 3).

Scheme 3[a]



[a] Reagents: (a) (1) *n*-BuLi, 3,4,5-$(OMe)_3$PhCHO/THF, (2) methyl crotonate, AcOH/toluene, (3) TFA; (b) NBS, $(PhCO)_2O_2/CCl_4$; (c) 1-(2-hydroxyethyl)piperazine/THF; (d) TBS-Cl, imidazole/THF; (e) $LiAlH_4$/THF.

Scheme 4[a]



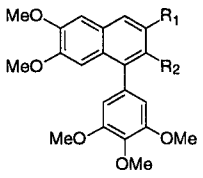
b: R^1 = 6,7-$(OMe)_2$	R^2 = 3-H_2N-4,5-$(OMe)_2$Ph	**k**: R^1 = 6,7-$(OMe)_2$	R^2 = 2-thienyl
c: R^1 = 6,7-$(OMe)_2$	R^2 = 3-Cl-4,5-$(OMe)_2$Ph	**l**: R^1 = 6,7-$(OMe)_2$	R^2 = (E)-CH=CH-{3,4,5-$(OMe)_3$Ph}
d: R^1 = 6,7-$(OMe)_2$	R^2 = 3-Br-4,5-$(OMe)_2$Ph	**m**: R^1 = 6-OEt-7-OMe	R^2 = 3-Br-4,5-$(OMe)_2$Ph
e: R^1 = 6,7-$(OMe)_2$	R^2 = 3-Me-4,5-$(OMe)_2$Ph	**n**: R^1 = 6,7,8-$(OMe)_3$	R^2 = 3-Br-4,5-$(OMe)_2$Ph
f: R^1 = 6,7-$(OMe)_2$	R^2 = 3,4-OCH_2O-	**o**: R^1 = H	R^2 = 3-Br-4,5-$(OMe)_2$Ph
g: R^1 = 6,7-$(OMe)_2$	R^2 = 3,4-Cl_2	**p**: R^1 = 6-OMe	R^2 = 3-Br-4,5-$(OMe)_2$Ph
h: R^1 = 6,7-$(OMe)_2$	R^2 = 3,5-Cl_2	**q**: R^1 = 5-Cl	R^2 = 3-Br-4,5-$(OMe)_2$Ph
i: R^1 = 6,7-$(OMe)_2$	R^2 = 3-NO_2	**r**: R^1 = 7-Cl	R^2 = 3-Br-4,5-$(OMe)_2$Ph
j: R^1 = 6,7-$(OMe)_2$	R^2 = 2-Br-4-pyridyl	**s**: R^1 = 7-Me	R^2 = 3-Br-4,5-$(OMe)_2$Ph

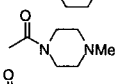
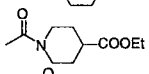
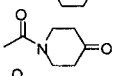
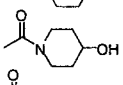
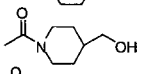
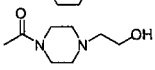
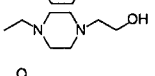
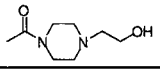
[a] Reagents: (a) $NaOH_{aq}$/MeOH; (b) 1-(2-hydroxyethyl)piperazine, DCC, HOBt/CH_2Cl_2.

Removal of substituents (**27o**) and introduction of an alkoxy, alkyl, and/or chloro substituent on 5,6,7-positions (**27m**,**q**−**s**) showed potent PDE5 inhibitory activities similar to **27d**. Introduction of the methoxy group on the 8-position (**27n**) resulted in marked loss of not only PDE5 but also PDE1 inhibitory activity (IC_{50} > 100 μM). From the modification of the substituent on the A ring, 5-chloro analogue **27q** showed the best inhibitory activity against PDE5 (IC_{50} = 0.0062 μM), with markedly improved selectivities against PDE1 and -3 isoforms.

We selected seven compounds on the basis of the

Table 1. Structures and PDE Inhibitions

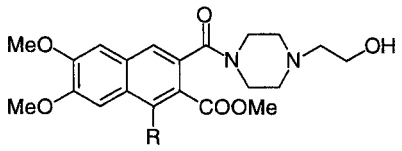


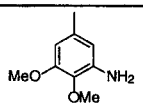
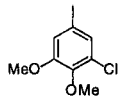
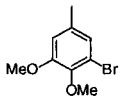
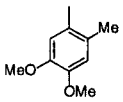
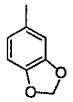
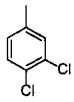
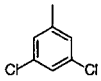
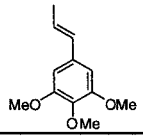
			PDE inhibition, IC_{50}, μM[a]		
compd	R_1	R_2	I	III	V
9a	COOMe	COOMe	>100	>100	2.1
10	CH_2OH	CH_2OH	18	0.88	13
15	NH_2	CH_2OH	2.1	3.5	13
11			0.43	0.84	0.068
13			0.82	0.32	5.7
28			>100	>100	>100
16	$CONH_2$	COOMe	0.82	0.32	>100
17	CONHMe	COOMe	>100	2.9	>100
18	$CONMe_2$	COOMe	35	16	0.23
19		COOMe	29	77	0.78
20		COOMe	27	>100	2.1
21		COOMe	69	>100	1.4
22		COOMe	24	60	2.0
23		COOMe	>100	>100	0.39
24		COOMe	88	>100	0.50
25		COOMe	74	>100	0.17
26		COOMe	45	>100	0.32
27a		COOMe	41	>100	0.094
31		COOMe	26	>100	2.4
34		CH_2OH	>100	>100	>100

[a] IC_{50} values were determined from the logarithmic concentration−inhibition curve (at least four points). The value is given as the mean of three experiments, where the variation from the mean value is ±20% or less.

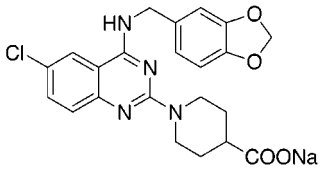
PDE5 inhibitory potency and isozyme selectivities for the evaluation of their relaxant effects on rat aortic rings and inhibitory activities of two additional and different forms of PDEs (PDE2 and -4), as shown in Table 4. Sodium 1-[6-chloro-4-[(3,4-methylenedioxybenzyl)amino]quinazolin-2-yl]piperidine-4-carboxylate (**35**) was selected as a reference compoud. These compounds were examined for relaxant effects on isolated rat aortic rings precontracted with phenylephrine (3 μM). The EC_{50} values of these compounds were well-correlated with the inhibitory activities toward PDE5 as shown in Table 4.

Table 2. Structures and PDE Inhibitions



		PDE inhibition, IC_{50}, μM[a]		
compd	R	I	III	V
27b		>100	>100	30
27c		26	>100	0.049
27d		11	>100	0.024
27e		97	>100	52
27f		55	>100	33
27g		89	>100	53
27h		>100	>100	54
27i		>100	>100	>100
27j		75	>100	>100
27k		77	>100	>100
27l		13	>100	>100

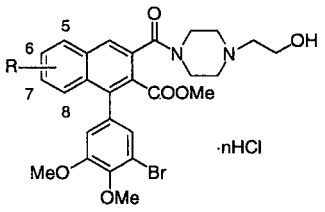
[a] IC_{50} values were determined from the logarithmic concentration−inhibition curve (at least four points). The value is given as the mean of three experiments, where the variation from the mean value is ±20% or less.



35

It was ascertained that **27q** exhibited a highly selective PDE5 inhibitory activity against not only PDE1 and -3 but also PDE2 and -4 (>16 000). It is noteworthy that

Table 3. Structures and PDE Inhibitions



		PDE inhibition, IC_{50}, μM[a]		
compd	R	I	III	V
27m	6-OEt-7-OMe	61	>100	0.017
27n	6,7,8-$(OMe)_3$	>100	>100	>100
27o	H	3.4	>100	0.025
27p	6-OMe	13	>100	0.012
27q	5-Cl	>100	>100	0.0062
27r	7-Cl	1.1	>100	0.021
27s	7-Me	3.5	>100	0.051

[a] IC_{50} values were determined from the logarithmic concentration−inhibition curve (at least four points). The value is given as the mean of three experiments, where the variation from the mean value is ±20% or less.

Table 4. PDE Inhibitions and Relaxant Effects on Rat Aorta for Selected Compounds

	PDE inhibition, IC_{50}, μM[a]					relaxant effect
compd	I	II	III	IV	V	EC_{50}, μM[b]
27a	41	>100	>100	>100	0.094	2.0
27c	26	>100	>100	>100	0.049	1.3
27d	11	>100	>100	>100	0.024	0.46
27m	61	>100	>100	>100	0.017	0.30
27o	3.4	>100	>100	>100	0.025	0.79
27p	13	>100	>100	>100	0.012	0.56
27q	>100	>100	>100	>100	0.0062	0.10
35	4.7	15	>100	3.4	0.0016	0.20

[a] IC_{50} values were determined from the logarithmic concentration−inhibition curve (at least four points). The value is given as the mean of three experiments, where the variation from the mean value is ±20% or less. [b] EC_{50} values were determined from the logarithmic concentration−relaxation curve. The value is given as the average of two experiments, where the variation from the mean value is ±30% or less.

27q showed the best selectivities against PDE isoforms (PDE1, -2, -3, and -4), among PDE5 inhibitors so far reported.

Conclusion

We discovered that 1-arylnaphthalene lignans have potent and specific PDE5 inhibitory activities and indicated that the spectra of PDE inhibitions are entirely altered by the chemical modification of substitutents on the common scaffold, 1-arylnaphthalene lignan. This finding will be beneficial for the design of specific PDE5 inhibitors in the other structural class. Among the analogues, **27q** showed the most potent and specific PDE5 inhibitory activity (IC_{50} = 6.2 nM, isozyme selectivities > 16 000) and exhibited potent effects on relaxation of rat aortic rings (EC_{50} = 0.10 μM). **27q** was selected for further evaluation as a treatment of cardiovascular diseases.

Experimental Section

General. Melting points were determined on a Büchi 535 capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400II analyzer. IR spectra were recorded on a Shimadzu IR-420 spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker AC-200 instrument (200 MHz) with TMS as an internal standard. Mass spectra were recorded on a Hitachi M-2000A spectrometer. Column chromatography was performed with silica gel (E. Merck, 70−230 mesh). Reactions were monitored by TLC using 0.25-mm silica gel F-254 (E. Merck) glass plates. *n*-Butyllithium was the 1.6 M solution in hexane and *sec*-butyllithium was the 1.3 M solution in cyclohexane supplied by Asia Lithium Co.

General Procedure for the Preparation of Dimethyl Ester of 1-Arylnaphthalene Derivatives 9. Method A (Scheme 1). Compounds **9a,c−h,j−p** were essentially prepared by the same procedure. The sequence is illustrated for **9a**, followed by analytical data for **9c−h,j−p**.

6,7-Dimethoxy-2,3-bis(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (9a). To a solution of acetal **1** [R_1 = 4,5-$(OMe)_2$] (58.2 g, 0.20 mol) in THF (300 mL) was added *n*-BuLi (131 mL, 0.21 mol) at −78 °C under a nitrogen atmosphere. After the mixture stirred at the same temperature for 30 min, a solution of the 3,4,5-trimethoxybenzaldehyde (39.2 g, 0.20 mol) in THF (100 mL) was added, and the reaction mixture was stirred at the same temperature for 30 min. The mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. A mixture of the residue, dimethyl fumarate (28.8 g, 0.20 mol), and acetic acid (100 mL) in toluene (100 mL) was heated under reflux for 2 h. After cooling to room temperature, TFA (5 mL) was added to the reaction mixture and the mixture was stirred at room temperature overnight. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from Et_2O gave **9a** (49.8 g, 53%): mp 186−187 °C; ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.95 (s, 6H), 4.03 (s, 3H), 6.61 (s, 2H), 6.95 (s, 1H), 7.25 (s, 1H), 8.46 (s, 1H); EIMS *m/z* 470 (M^+, base), 455, 439, 344.

1-(3-Chloro-4,5-dimethoxyphenyl)-6,7-dimethoxy-2,3-bis(methoxycarbonyl)naphthalene (9c): yield 43%; mp 165−168 °C; ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 4.03 (s, 3H), 6.80−6.90 (m, 2H), 7.02 (d, 1H, *J* = 1.9 Hz), 7.25 (s, 1H), 8.47 (s, 1H).

1-(3-Bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2,3-bis(methoxycarbonyl)naphthalene (9d): yield 37%; mp 178−179 °C; ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 4.03 (s, 3H), 6.86 (s, 1H), 6.68 (d, 1H, *J* = 1.9 Hz), 6.89 (d, 1H, *J* = 1.9 Hz), 7.25 (s, 1H), 8.46 (s, 1H); EIMS *m/z* 518/520 (M^+, base), 487/489.

6,7-Dimethoxy-2,3-bis(methoxycarbonyl)-1-(2-methyl-4,5-dimethoxyphenyl)naphthalene (9e): yield 63%; mp 162−164 °C; ^{1}H NMR ($CDCl_3$) δ 1.93 (s, 3H), 3.61 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 4.03 (s, 3H), 6.65 (s, 1H), 6.73 (s, 1H), 6.81 (s, 1H), 7.27 (s, 1H), 8.47 (s, 1H); EIMS *m/z* 454 (M^+, base), 422, 407.

6,7-Dimethoxy-2,3-bis(methoxycarbonyl)-1-(3,4-methylenedioxyphenyl)naphthalene (9f): yield 57%; mp 169−170 °C; ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.79 (s, 3H), 3.94 (s, 3H), 4.02 (s, 3H), 6.03 (d, 1H, *J* = 1.4 Hz), 6.07 (d, 1H, *J* = 1.4 Hz), 6.72−6.99 (m, 4H), 7.23 (s, 1H), 8.44 (s, 1H); EIMS *m/z* 424 (M^+, base), 393.

1-(3,4-Dichlorophenyl)-6,7-dimethoxy-2,3-bis(methoxycarbonyl)naphthalene (9g): yield 75%; mp 185−187 °C; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 3.79 (s, 3H), 3.94 (s, 3H), 4.03 (s, 3H), 6.72 (s, 1H), 7.18−7.31 (m, 2H), 7.49 (d, 1H, *J* = 2.0 Hz), 7.56 (d, 1H, *J* = 8.2 Hz), 8.47 (s, 1H); EIMS *m/z* 448 (M^+, base), 417.

1-(3,5-Dichlorophenyl)-6,7-dimethoxy-2,3-bis(methoxycarbonyl)naphthalene (9h): yield 65%; mp 153−155 °C; ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H), 3.81 (s, 3H), 3.94 (s, 3H), 4.03 (s, 3H), 6.72 (s, 1H), 7.20−7.36 (m, 3H), 7.47 (t, 1H, *J* = 1.9 Hz), 8.47 (s, 1H); EIMS *m/z* 448 (M^+, base), 417.

1-(2-Bromo-4-pyridyl)-6,7-dimethoxy-2,3-bis(methoxy-

carbonyl)naphthalene (9j):[10] yield 60%; mp 192−194 °C; ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.80 (s, 3H), 3.95 (s, 3H), 4.04 (s, 3H), 6.65 (s, 1H), 7.3−7.37 (m, 2H), 7.55 (d, 1H, J = 0.7 Hz), 8.48−8.58 (m, 2H); EIMS m/z 459/461 (M^+, base), 428/430.

6,7-Dimethoxy-2,3-bis(methoxycarbonyl)-1-(3,4,5-trimethoxystyryl)naphthalene (9l): yield 57%; mp 166−168 °C; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 3.90 (s, 3H), 3.92 (s, 6H), 3.95 (s, 3H), 3.98 (s, 3H), 4.04 (s, 3H), 6.76 (s, 2H), 6.81 (d, 1H, J = 16.5 Hz), 7.23 (s, 1H), 7.32 (d, 1H, J = 18.1 Hz), 7.37 (s, 1H), 8.38 (s, 1H); EIMS m/z 496 (M^+, base).

1-(3-Bromo-4,5-dimethoxyphenyl)-6-ethoxy-7-methoxy-2,3-bis(methoxycarbonyl)naphthalene (9m): yield 42%; mp 171−173 °C; ^{1}H NMR ($CDCl_3$) δ 1.56 (t, 3H, J = 7.0 Hz), 3.69 (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 4.25 (q, 2H, J = 7.0 Hz), 6.86 (S, 1H), 6.89 (d, 1H, J = 1.9 Hz), 7.18 (d, 1H, J = 1.9 Hz),7.23 (s, 1H), 8.44 (s, 1H); EIMS m/z 532/534 (M^+, base).

1-(3-Bromo-4,5-dimethoxyphenyl)-6,7,8-trimethoxy-2,3-bis(methoxycarbonyl)naphthalene (9n): yield 66%; mp 199−202 °C; ^{1}H NMR ($CDCl_3$) δ 3.36 (s, 3H), 3.61 (s, 3H), 3.83 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 4.01 (s, 3H), 6.83 (d, 1H, J = 1.9 Hz), 7.05−7.15 (m, 2H), 8.46 (s, 1H); EIMS m/z 548/550 (M^+, base), 470.

1-(3-Bromo-4,5-dimethoxyphenyl)-2,3-bis(methoxycarbonyl)naphthalene (9o): yield 56%; mp 153−156 °C; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H), 3.84 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 6.88 (d, 1H, J = 1.9 Hz), 7.16 (d, 1H, J = 1.9 Hz), 7.50−7.70 (m, 3H), 7.93−8.09 (m, 1H), 8.63 (s, 1H); EIMS m/z 458/460 (M^+, base), 443/445, 427/429.

1-(3-Bromo-4,5-dimethoxyphenyl)-2,3-bis(methoxycarbonyl)-6-methoxynaphthalene (9p): yield 22%; mp 151−153 °C; ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.83 (s, 3H), 3.95 (s, 9H), 6.86 (d, 1H, J = 1.9 Hz), 7.14 (d, 1H, J = 1.9 Hz), 7.19−7.29 (m, 2H), 7.53 (d, 1H, J = 9.1 Hz), 8.50 (s, 1H); EIMS m/z 488/490 (M^+, base), 457/459.

1-(3-Amino-4,5-dimethoxyphenyl)-6,7-dimethoxy-2,3-bis(methoxycarbonyl)naphthalene (9b):[6] yield 81%; mp 196−198 °C; ^{1}H NMR ($CDCl_3$) δ 1.50−1.70 (br s, 2H), 3.68 (s, 3H), 3.80 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 4.02 (s, 3H), 6.33 (d, 1H, J = 1.8 Hz), 6.39 (d, 1H, J = 1.9 Hz), 6.70 (s, 1H), 7.22 (s, 1H), 8.42 (s, 1H).

6,7-Dimethoxy-2,3-bis(methoxycarbonyl)-1-(3-nitrophenyl)naphthalene (9i). To a solution of acetal **1** [R_1 = 4,5-$(OMe)_2$] (5.82 g, 20 mmol) in THF (40 mL) was added *n*-BuLi (12.5 mL, 20 mmol) at −78 °C under a nitrogen atmosphere. After stirring at the same temperature for 30 min, ClTi-(O*i*-Pr)$_3$ (1 M in hexane, 20 mL, 20 mmol) was added and the mixture was stirred at the same temperature for 30 min. After 3-nitrobenzaldehyde (3.02 g, 0.20 mol) in 20 mL of THF was added, the reaction mixture was warmed to room temperature. After stirring for 30 min, the mixture was poured into diluted hydrochloric acid and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. A mixture of the residue, dimethyl fumarate (2.88 g, 20 mmol), and acetic acid (10 mL) in toluene (30 mL) was heated under reflux for 2 h. After evaporation of the solvent, the residue was dissolved in a mixture of $CHCl_3$ (50 mL) and TFA (10 mL). After stirring at room temperature overnight, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was crystallized from Et_2O to afford **9i** (4.6 g, 54%): mp 194−196 °C; ^{1}H NMR ($CDCl_3$) δ 3.62 (s, 3H), 3.74 (s, 3H), 3.95 (s, 3H), 4.04 (s, 3H), 6.63 (s, 1H), 7.29 (s, 1H), 7.62−7.80 (m, 2H), 8.25−8.40 (m, 2H), 8.52 (s, 1H); EIMS m/z 425 (M^+, base), 394.

General Procedure for the Preparation of Dimethyl Ester of 1-Arylnaphthalene Derivatives 9. Method B (Scheme 1). Compounds **9q**−**s** were essentially prepared by the same procedure. The sequence is illustrated for **9q**, followed by analytical data for **9r,s**.

3-(3-Bromo-4,5-dimethoxyphenyl)-7-chlorophthalide (5q). To a stirred mixture of 2-chloro-*N*-methylbenzamide (**4a**) (12.5 g, 73.8 mmol) and *N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (22.3 mL, 148 mmol) in THF (30 mL) was added *s*-BuLi (125 mL, 163 mmol) at −78 °C under a nitrogen atmosphere, and the mixture was stirred at the same temperature for 15 min. To this mixture was added dropwise 3,4,5-trimethoxybenzaldehyde (18.1 g, 73.8 mol) in 300 mL of THF. After stirring at the same temperature for 30 min, the reaction mixture was poured into a mixture of H_2O and AcOEt. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. A solution of the residue in concentrated hydrochloric acid (10 mL)−dioxane (100 mL) was heated under reflux for 2 h. After evaporation of the organic solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was crystallized from Et_2O to give **5q** (19.2 g, 68%): mp 165−168 °C; ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 3.86 (s, 3H), 6.26 (s, 1H), 6.69 (d, 1H, J = 1.9 Hz), 7.07 (d, 1H, J = 1.9 Hz), 7,34−7.35 (m, 1H), 7,50−7.60 (m, 1H), 7.90 (d, 1H, J = 8.2 Hz); EIMS m/z 384/382 (M^+, base), 303.

1-(3-Bromo-4,5-dimethoxyphenyl)-5-chloro-2,3-bis-(methoxycarbonyl)naphthalene (9q). To a stirred solution of **5q** (5.0 g, 13 mmol) in CH_2Cl_2 (50 mL) was added diisobutylaluminum hydride (DIBAL) (1.5 M in toluene, 9.6 mL, 14.3 mmol) at −78 °C under a nitrogen atmosphere, and the mixture was stirred at the same temperature for 30 min. After addition of 1 mL of acetic acid, the reaction mixture was washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. A mixture of the residue, dimethyl fumarate (1.87 g, 13 mmol), and acetic acid (8 mL) in toluene (24 mL) was refluxed for 3 h. After evaporation of the solvent, the residue was diluted with AcOEt and washed successively with aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give 1-(3-bromo-4,5-dimethoxyphenyl)-5-chloro-2,3-bis(methoxycarbonyl)-1,4-epoxy-1,2,3,4-tetrahydronaphthalene. The crude product was used in the next step without further purification. A mixture of the crude product and boron trifluoride etherate (BF_3·Et_2O) (3.2 mL, 26 mmol) in CH_3CN (50 mL) was heated at 50 °C for 5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from *i*-Pr_2O gave **9q** (3.45 g, 54%): mp 133−135 °C; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H), 3.84 (s, 3H), 3.96 (s, 3H), 4.00 (s, 3H), 6.85 (d, 1H, J = 1.9 Hz), 7.13 (d, 1H, J = 1.9 Hz), 7.41−7.62 (m, 2H), 7.70 (dd, 1H, J = 7.0, 1.6 Hz), 9.06 (d, 1H, J = 0.7 Hz); EIMS m/z 492/494 (M^+, base), 461/463.

1-(3-Bromo-4,5-dimethoxyphenyl)-7-chloro-2,3-bis-(methoxycarbonyl)naphthalene (9r): yield 39%; mp 145−148 °C; ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H), 3.85 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 6.84 (d, 1H, J = 1.9 Hz), 7.13 (d, 1H, J = 1.9 Hz), 7.50−7.62 (m, 2H), 7.94 (m, 1H), 8.60 (s, 1H); EIMS m/z 492/494 (M^+, base).

1-(3-Bromo-4,5-dimethoxyphenyl)-2,3-bis(methoxycarbonyl)-7-methylnaphthalene (9s): yield 83%; mp 120−122 °C; ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 6.86 (d, 1H, J = 1.8 Hz), 7.14 (d, 1H, J = 1.8 Hz), 7.35 (s, 1H), 7.44 (dd, 1H, J = 8.3, 1.4 Hz), 7.89 (d, 1H, J = 8.3 Hz), 8.58 (s, 1H); EIMS m/z 472/474 (M^+, base), 457/459, 441/443.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)naphthalene (10). To a stirred suspension of **3a** (2.0 g, 4.25 mmol) in THF (20 mL) was added dropwise Red-Al (70% in toluene, 3.07 g, 10.6 mmol) at −10 °C, and the mixture was stirred at 0 °C for 1 h. After dropwise addition of MeOH (1 mL) and 20% aqueous NaOH (6 mL), the mixture was stirred at 50 °C for 30 min. The reaction mixture was poured into a mixture of H_2O and AcOEt and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$−MeOH = 10:1) gave **10** (1.47 g, 83%): mp 124−126 °C; ^{1}H NMR ($CDCl_3$)

δ 3.59−4.15 (br s, 2H), 3.75 (s, 3H), 3.84 (s, 6H), 3.96 (s, 3H), 4.01 (s, 3H), 4.65 (s, 2H), 4.93 (s, 2H), 6.59 (s, 2H), 6.79 (s, 1H), 7,14 (s, 1H), 7.73 (s, 1H); EIMS *m/z* 414 (M^+, base), 396.

2-(Hydroxymethyl)-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)naphthalene-3-carboxylic Acid Lactone (11). A mixture of **10** (1.5 g, 3.62 mmol) and $AgCO_3$ (3.0 g, 10.9 mmol) in benzene (30 mL) was refluxed for 3 h. The solid was filtered off and washed with $CHCl_3$. The filtrate was concentrated under reduced pressure, and the residue obtained was crystallized from AcOEt to give **11** (1.1 g, 74%): mp 240−242 °C; ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 3.87 (s, 3H), 3.98 (s, 3H), 4.06 (s, 3H), 5.27 (s, 2H), 6.60 (s, 2H), 7.14 (s, 1H), 7.32 (s, 1H), 8.33 (s, 1H); EIMS *m/z* 410 (M^+, base), 395, 379.

General Procedure for the Preparation of 12. Compounds **12a**−**s** were essentially prepared by the same procedure. The sequence is illustrated for **12a**, followed by analytical data for **12b**−**s**.

6,7-Dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene-3-carboxylic Acid (12a). A solution of **3a** (30 g, 63.8 mmol) in a mixture of MeOH (200 mL) and 2 N aqueous NaOH (63.8 mL) was refluxed for 30 min. After evaporation of the organic solvent, the residue was acidified with 2 N hydrochloric acid and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from Et_2O gave **12a** (27.4 g, 94%): mp 222−224 °C; ^{1}H NMR (DMSO-d_6) δ 3.54 (s, 3H), 3.70 (s, 3H), 3.758 (s, 3H), 3.762 (s, 6H), 3.93 (s, 3H), 6.61 (s, 2H), 6.97 (s, 1H), 7.65 (s, 1H), 8,48 (s, 1H), 13,14 (br s, 1H); SIMS *m/z* 456 (M^+),425 (base).

1-(3-Amino-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-(methoxycarbonyl)naphthalene-3-carboxylic acid (12b): yield 97%; ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.81 (s, 3H), 3.81 (s, 3H), 3.92 (s, 3H), 4.03 (s, 3H), 5.66 (br s, 3H), 6.36 (d, 1H, J = 1.8 Hz), 6.41 (d, 1H, J = 1.9 Hz), 7.00 (s, 1H), 7.24 (s, 1H), 8.52 (s, 1H); EIMS *m/z* 441 (M^+), 423, 409 (base).

1-(3-Chloro-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-(methoxycarbonyl)naphthalene-3-carboxylic acid (12c): yield 84%; mp 209−212 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.53 (s, 3H), 3.70 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 3.93 (s, 3H), 6.85 (s, 1H), 6.92−7.01 (m, 2H), 7.67 (s, 1H), 8.50 (s, 1H), 13.08−13.30 (br s, 1H); SIMS *m/z* 4460 ($M^+ + 1$), 429 (base).

1-(3-Bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-(methoxycarbonyl)naphthalene-3-carboxylic acid (12d): yield 98%; mp 228−230 °C; ^{1}H NMR (DMSO-d_6) δ 3.54 (s, 3H), 3.70 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 6.86 (s, 1H), 7.02 (d, 1H, J = 1.9 Hz), 7.08 (d, 1H, J = 1.9 Hz), 7.67 (s, 1H), 8.51 (s, 1H), 13.00−13.40 (br s, 1H).

6,7-Dimethoxy-2-(methoxycarbonyl)-1-(2-methyl-4,5-dimethoxyphenyl)naphthalene-3-carboxylic acid (12e): yield 87%; mp 202−204 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3H), 3.62 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 3.96 (s, 3H), 4.04 (s, 3H), 6.66 (s, 1H), 6.74 (s, 1H), 6.82 (s, 1H), 7.29 (s, 1H), 8.57 (s, 1H); EIMS *m/z* 440 (M^+), 408 (base).

6,7-Dimethoxy-2-(methoxycarbonyl)-1-(3,4-methylenedioxyphenyl)naphthalene-3-carboxylic acid (12f): yield 99%; mp 255−256 °C; ^{1}H NMR (DMSO-d_6) δ 3.51 (s, 3H), 3.67 (s, 3H), 3.93 (s, 3H), 6.13 (d, 2H, J = 2.0 Hz), 6.73 (dd, 1H, J = 7.9, 1.7 Hz), 6.81 (s, 1H), 6.84 (d, 1H, J = 1.5 Hz), 7.04 (d, 1H, J = 7.9 Hz), 7.64 (s, 1H), 8.48 (s, 1H), 13.17 (br s, 1H); EIMS *m/z* 410 (M^+), 378 (base).

1-(3,4-Dichlorophenyl)-6,7-dimethoxy-2-(methoxycarbonyl)naphthalene-3-carboxylic acid (12g): yield 98%; mp 248−250 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.51 (s, 3H), 3.68 (s, 3H), 3.93 (s, 3H), 6.70 (s, 1H), 7.32 (dd, 1H, J = 8.3, 2.0 Hz), 7.57 (d, 1H, J = 2.0 Hz), 7.69 (s, 1H), 7.78 (d, 1H, J = 8.3 Hz), 8.53 (s, 1H); EIMS *m/z* 434 (M^+), 402 (base).

1-(3,5-Dichlorophenyl)-6,7-dimethoxy-2-(methoxycarbonyl)naphthalene-3-carboxylic acid (12h): yield 95%; mp 239−241 °C; ^{1}H NMR (DMSO-d_6) δ 3.52 (s, 3H), 3.69 (s, 3H), 3.94 (s, 3H), 6.69 (s, 1H), 7.37 (d, 2H, J = 1.9 Hz), 7.69 (s, 1H), 7.77 (t, 1H, J = 1.9 Hz), 8.54 (s, 1H), 13.24 (br s, 1H); EIMS *m/z* 434 (M^+), 402 (base).

6,7-Dimethoxy-2-(methoxycarbonyl)-1-(3-nitrophenyl)naphthalene-3-carboxylic acid (12i): yield 93%; mp 249−250 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.47 (s, 3H), 3.64 (s, 3H), 3.94 (s, 3H), 6.64 (s, 1H), 7.71 (s, 1H), 7.75−7.90 (m, 2H), 8.08−8.15 (m, 1H), 8.29−8.43 (m, 1H), 8.57 (s, 1H), 13.27 (br s, 1H); EIMS *m/z* 411 (M^+), 379 (base).

1-(2-Bromo-4-pyridyl)-6,7-dimethoxy-2-(methoxycarbonyl)naphthalene-3-carboxylic acid (12j): yield 98%; mp 223−225 °C dec; ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H), 3.81 (s, 3H), 4.05 (s, 3H), 6.67 (s, 1H), 7.30 (s, 1H), 7.34 (dd, 1H, J = 5.0, 1.4 Hz), 7.56−7.62 (m, 1H), 8.55 (d, 1H, J = 5.0 Hz), 8.61 (s, 1H); EIMS *m/z* 445/447 (M^+), 413/415 (base).

6,7-Dimethoxy-2-(methoxycarbonyl)-1-(2-thienyl)naphthalene-3-carboxylic acid (12k): yield 99%; mp 225−227 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.54 (s, 3H), 3.69 (s, 3H), 3.93 (s, 3H), 6.99 (s, 1H), 7.11 (dd, 1H, J = 3.5, 1.2 Hz), 7.22 (dd, 1H, J = 5.1, 3.5 Hz), 7.67 (s, 1H), 7.78 (dd, 1H, J = 5.1, 1.2 Hz), 8.54 (s, 1H), 13.04−13.45 (br s, 1H); EIMS *m/z* 372 (M^+), 340 (base).

6,7-Dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxystyryl)naphthalene-3-carboxylic acid (12l): yield 93%; mp 239−240 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.69 (s, 3H), 3.74 (s, 3H), 3.85 (s, 6H), 3.92 (s, 3H), 3.93 (s, 3H), 6.77 (d, 1H, J = 16 Hz), 6.96 (s, 2H), 7.43 (s, 1H), 7.58 (d, 1H, J = 16 Hz), 7.61 (s, 1H), 8.40 (s, 1H), 13.12 (br s, 1H); SIMS *m/z* 482 (M^+, base), 451.

1-(3-Bromo-4,5-dimethoxyphenyl)-6-ethoxy-7-methoxy-2-(methoxycarbonyl)naphthalene-3-carboxylic acid (12m): yield 86%; mp 223−224 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.57 (t, 3H, J = 6.9 Hz), 3.70 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 3.96 (s, 3H), 4.26 (q, 2H, J = 7.0 Hz), 6.87 (s, 1H), 6.91 (d, 1H, J = 1.9 Hz), 7.19 (d, 1H, J = 1.9 Hz), 7.26 (s, 1H), 8.55 (s, 1H); EIMS *m/z* 518/520 (M^+), 486/488 (base).

1-(3-Bromo-4,5-dimethoxyphenyl)-6,7,8-trimethoxy-2-(methoxycarbonyl)naphthalene-3-carboxylic acid (12n): yield 93%; mp 231−232 °C dec; ^{1}H NMR ($CDCl_3$) δ 3.36 (s, 3H), 3.61 (s, 3H), 3.83 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 4.02 (s, 3H), 6.84 (d, 1H, J = 1.9 Hz), 7.10 (d, 1H, J = 1.9 Hz), 7.13 (s, 1H), 8.56 (s, 1H); EIMS *m/z* 534/536 (M^+), 502/504 (base), 424.

1-(3-Bromo-4,5-dimethoxyphenyl)-2-(methoxycarbonyl)naphthalene-3-carboxylic acid (12o): yield 83%; mp 188−191 °C; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H), 3.85 (s, 3H), 3.97 (s, 3H), 6.90 (d, 1H, J = 1.9 Hz), 7.17 (d, 1H, J = 1.9 Hz), 7.54−7.73 (m, 3H), 7.98−8.10 (m, 1H), 8.75 (s, 1H), 10.00−10.78 (br s, 1H); EIMS *m/z* 444/446 (M^+), 412/414 (base).

1-(3-Bromo-4,5-dimethoxyphenyl)-6-methoxy-2-(methoxycarbonyl)naphthalene-3-carboxylic acid (12p): yield 93%; mp 206−208 °C; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H), 3.85 (s, 3H), 3.96 (s, 6H), 6.88 (d, 1H, J = 1.9 Hz), 7.15 (d, 1H, J = 1.9 Hz), 7.21−7.35 (m, 2H), 7.55 (d, 1H, J = 9.1 Hz), 8.52 (s, 1H); EIMS *m/z* 474/476 (M^+), 442/444 (base).

1-(3-Bromo-4,5-dimethoxyphenyl)-5-chloro-2-(methoxycarbonyl)naphthalene-3-carboxylic acid (12q): yield 93%; mp 202−204 °C; ^{1}H NMR (DMSO-d_6) δ 3.57 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 7.03 (d, 1H, J = 1.9 Hz), 7.10 (d, 1H, J = 1.9 Hz), 7.50−7.76 (m, 2H), 7.93 (dd, 1H, J = 7.3, 1.1 Hz), 8.90 (s, 1H); EIMS *m/z* 478/480 (M^+), 446/448 (base).

1-(3-Bromo-4,5-dimethoxyphenyl)-7-chloro-2-(methoxycarbonyl)naphthalene-3-carboxylic acid (12r): yield 71%; mp 215−217 °C dec; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H), 3.86 (s, 3H), 3.98 (s, 3H), 6.86 (d, 1H, J = 1.9 Hz), 7.14 (d, 1H, J = 1.9 Hz), 7.52−7.65 (m, 2H), 7.97 (d, 1H, J = 7.9 Hz), 8.71 (s, 1H); EIMS *m/z* 478/480 (M^+), 446/448 (base).

1-(3-Bromo-4,5-dimethoxyphenyl)-2-(methoxycarbonyl)-7-methylnaphthalene-3-carboxylic acid (12s): yield 83%; mp 214−216 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H), 3.70 (s, 3H), 3.85 (s, 3H), 3.98 (s, 3H), 6.88 (d, 1H, J = 1.9 Hz), 7.15 (d, 1H, J = 1.9 Hz), 7.36 (s, 1H), 7.46 (dd, 1H, J = 8.4, 1.4 Hz), 7.93 (d, 1H, J = 8.3 Hz), 8.70 (s, 1H); EIMS *m/z* 458/460 (M^+), 426/428 (base).

3-Amino-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (13). To a mixture of **12a** (15.0 g, 35 mmol) and triethylamine (21.2 g, 210 mmol) in THF

(300 mL) was added dropwise ethyl chloroformate (7.6 g, 70 mmol) in 50 mL of THF at −50 °C. After the mixture stirred at 0 °C for 30 min, 6.8 g of NaN_3 in H_2O (50 mL) was added to the mixture in one portion. After the mixture stirred at room temperature for 30 min, the mixture was diluted with $CHCl_3$ and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in toluene (100 mL) and refluxed for 1 h. After cooling to room temperature, 70 mL of concentrated hydrochloric acid (70 mL) was added and the mixture was heated at 100 °C for 10 min. The reaction mixture was extracted with $CHCl_3$ and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (*n*-hexane−AcOEt = 1:1) gave **13** (8.9 g, 59%): mp 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 3.47 (s, 3H), 3.73 (s, 3H), 3.83 (s, 6H), 3.94 (s, 6H), 4.21 (br s, 2H), 6.57 (s, 2H), 6.86 (s, 1H), 6.91 (s, 2H); EIMS *m*/*z* 427 (M^+).

3-Amino-2-(hydroxymethyl)-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)naphthalene (14). To a stirred suspension of lithium aluminum hydride ($LiAlH_4$) (72 mg, 1.88 mmol) in THF (10 mL) was added **13** (400 mg, 0.94 mmol) in 10 mL of THF at 5 °C, and the mixture was stirred at the same temperature for 1 h. H_2O (0.07 mL), 15% aqueous NaOH (0.07 mL), and H_2O (0.21 mL) were added dropwise to the reaction mixture successively, and the resultant mixture was stirred at room temperature overnight. The precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. Crystallization of the residue from *n*-hexane−AcOEt (1:1) gave **14** (320 mg, 85%): mp 114−115 °C; ^{1}H NMR ($CDCl_3$) δ 3.50−4.30 (m, 3H), 3.66 (s, 3H), 3.78 (s, 6H), 3.93 (s, 6H), 4.57 (s, 2H), 6.50 (s, 2H), 6.65 (s, 1H), 6.88 (s, 1H), 6.92 (s, 1H); EIMS *m*/*z* 400 (M^+), 381.

3-(Hydroxymethyl)-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)naphthalene-2-carboxylic Acid Lactone (15). To mixture of **12a** (2.0 g, 4.38 mmol) and triethylamine (443 mg, 4.38 mmol) in THF (20 mL) was added dropwise ethyl chloroformate (475 mg, 4.38 mmol) in 10 mL of THF at −5 to 0 °C. After stirring at 0 °C for 10 min, the precipitate was filtered off and washed with THF. The filtrate was added dropwise to a solution of $NaBH_4$ (414 mg, 10.6 mmol) in 50% H_2O−THF (v/v) (20 mL) at 0−5 °C. After stirring at room temperature for 1 h, the reaction mixture was poured into H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. To a solution of the obtained residue in DMF (25 mL) was added NaH (62% dispersion in mineral oil, 204 mg, 5.26 mmol) at room temperature, and the mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with the addition of H_2O and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from Et_2O gave **15** (1.52 g, 85%): mp 233−235 °C; ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 3.86 (s, 3H), 3.98 (s, 3H), 4.06 (s, 3H), 5.41 (s, 2H), 6.62 (s, 2H), 7.15 (s, 1H), 7.20 (s, 1H), 7.73 (s, 1H); EIMS *m*/*z* 410 (M^+, base), 395.

6,7-Dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)-3-naphthalenecarboxamide (16). To a mixture of **12a** (500 mg, 1.1 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) (230 mg, 1.2 mmol), and 1-hydroxybenzotriazole hydrate (HOBt·$1H_2O$) (184 mg, 1.2 mmol) in DMF (5 mL) was added 28% aqueous NH_3 (167 μL, 1.2 mmol), and the mixture was stirred at room temperature for 3 h. The mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$−MeOH = 20:1) gave **16** (330 mg, 66%): mp 206−207 °C; ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.95 (s, 3H), 4.02 (s, 3H), 5.70−6.42 (br s, 2H), 6.61 (s, 2H), 6.97 (s, 1H), 7.20 (s, 1H), 8.02 (s, 1H); SIMS *m*/*z* 456 ($M^+ + 1$), 439, 424 (base). Anal. ($C_{24}H_{25}NO_8$) Calcd: C, 60.88; H, 5.75; N, 2.96. Found: C, 61.05; H, 5.30; N, 2.87.

***N*-Methyl-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)-3-naphthalenecarboxamide (17) and 6,7-Dimethoxy-2-phenyl-9-(3,4,5-trimethoxyphenyl)benz[*f*]isoindole-1,3-dione (28).** To a mixture of **12a** (500 mg, 1.1 mmol), EDCI·HCl (230 mg, 1.2 mmol), and HOBt·$1H_2O$ (184 mg, 1.2 mmol) in DMF (5 mL) was added 40% aqueous $MeNH_2$ (103 μL, 1.2 mmol), and the mixture was stirred at room temperature for 2 h. The mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (from $CHCl_3$−acetone = 10:1 to $CHCl_3$−MeOH = 20:1) gave **17** (23 mg, 4%) and **28** (320 mg, 67%), respectively.

17: mp 219−220 °C; ^{1}H NMR ($CDCl_3$) δ 3.03 (d, 3H, J = 4.8 Hz), 3.62 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.94 (s, 3H), 4.02 (s, 3H), 6.14−6.32 (br d, 1H), 6.60 (s, 2H), 6.97 (s, 1H), 7.17 (s, 1H), 7.91 (s, 1H); EIMS *m*/*z* 469 (M^+), 437 (base), 422. Anal. ($C_{25}H_{27}NO_7$·$1.4H_2O$) Calcd: C, 60.69; H, 6.07; N, 2.83. Found: C, 60.67; H, 5.62; N, 2.82.

28: mp >250 °C; ^{1}H NMR ($CDCl_3$) δ 3.15 (s, 3H), 3.81 (s, 3H), 3.86 (s, 6H), 3.99 (s, 3H), 4.07 (s, 3H), 6.62 (s, 2H), 7.14 (s, 1H), 7.32 (s, 1H), 8.19 (s, 1H); EIMS *m*/*z* 437 (M^+ base), 422.

***N*,*N*-Dimethyl-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)-3-naphthalenecarboxamide (18).** To a solution of **12a** (500 mg, 1.1 mmol) in DMF (5 mL) was added 1,1′-carbonyldiimidazole (CDI) (213 mg, 1.31 mmol). After stirring at room temperature for 1 h, 50% aqueous Me_2-NH (118 mg, 1.31 mmol) was added and the mixture was stirred at room temperature overnight. The mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$−acetone = 10:1) afforded **18** (396 mg, 75%): mp 190−192 °C; ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 6H), 3.55 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.95 (s, 3H), 4.03 (s, 3H), 6.60 (s, 2H), 7.03 (s, 1H), 7.14 (s, 1H), 7.64 (s, 1H); EIMS *m*/*z* 483 (M^+), 439 (base).

General Procedure for the Preparation of 19−24. Compounds **19**−**24** were essentially prepared by the same procedure. The sequence is illustrated for **19**, followed by analytical data for **20**−**24**.

6,7-Dimethoxy-2-(methoxycarbonyl)-3-(1-pyrrolidinylcarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (19). To a mixture of **12a** (500 mg, 1.1 mmol), EDCI·HCl (230 mg, 1.2 mmol), and HOBt·$1H_2O$ (184 mg, 1.2 mmol) in DMF (5 mL) was added pyrrolidine (100 μL,1.2 mmol), and the mixture was stirred at room temperature overnight. The mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$−MeOH = 20:1) gave **19** (506 mg, 91%): mp 196−198 °C; ^{1}H NMR ($CDCl_3$) δ 1.83−2.08 (m, 4H), 3.39−3.78 (m, 4H), 3.56 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.94 (s, 3H), 4.03 (s, 3H), 6.59 (s, 2H), 7.02 (s, 1H), 7.15 (s, 1H), 7.69 (s, 1H); EIMS *m*/*z* 509 (M^+), 477, 439 (base).

6,7-Dimethoxy-2-(methoxycarbonyl)-3-(piperidinocarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (20): yield 90%; mp 170−172 °C; ^{1}H NMR ($CDCl_3$) δ 1.50−1.80 (m, 6H), 3.34−3.90 (m, 4H), 3.57 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.94 (s, 3H), 4.03 (s, 3H), 6.60 (s, 2H), 7.03 (s, 1H), 7.14 (s, 1H), 7.61 (s, 1H); EIMS *m*/*z* 523 (M^+), 491, 439 (base).

6,7-Dimethoxy-2-(methoxycarbonyl)-3-(4-methyl-1-piperazinylcarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (21): yield 65%; mp 136−138 °C; ^{1}H NMR ($CDCl_3$) δ 2.31−2.60 (m, 4H), 2.35 (s, 3H), 3.45−3.61 (m, 2H), 3.57 (s, 3H), 3.69−3.90 (m, 2H), 3.79 (s, 3H), 3.84 (s, 6H), 3.94 (s, 3H), 4.03 (s, 3H), 6.59 (s, 2H), 7.02 (s, 1H), 7.15 (s, 1H), 7.62 (s, 1H); EIMS *m*/*z* 538 (M^+), 455 (base), 439.

6,7-Dimethoxy-2-(methoxycarbonyl)-3-[4-(ethoxycarbonyl)piperidinocarbonyl]-1-(3,4,5-trimethoxyphenyl)-

naphthalene (22): yield 96%; mp 137−139 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.13 Hz), 1.50−2.10 (m, 5H), 2.50−2.70 (m, 1H), 2.95−3.32 (m, 2H), 3.57 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.94 (s, 3H), 4.03 (s, 3H), 4.17 (q, 2H, J = 7.13 Hz), 4.46−4.68 (m, 1H), 6.59 (s, 2H), 7.03 (s, 1H), 7.15 (s, 1H), 7.60 (s, 1H); EIMS m/z 595 (M^+), 563, 439 (base).

6,7-Dimethoxy-2-(methoxycarbonyl)-3-(morpholinocarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (23): yield 88%; mp 196−198 °C; ^{1}H NMR ($CDCl_3$) δ 3.45−3.61 (m, 2H), 3.57 (s, 3H), 3.62−3.90 (m, 6H), 3.79 (s, 3H), 3.84 (s, 6H), 3.95 (s, 3H), 4.03 (s, 3H), 6.59 (s, 2H), 7.03 (s, 1H), 7.15 (s, 1H), 7.61 (s, 1H); EIMS m/z 525 (M^+), 439 (base).

6,7-Dimethoxy-2-(methoxycarbonyl)-3-(4-oxopiperidinocarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (24): yield 92%; mp 188−190 °C; ^{1}H NMR ($CDCl_3$) δ 2.50−2.70 (m, 4H), 3.53 (s, 3H), 3.70−4.11 (m, 4H), 3.80 (s, 3H), 3.84 (s, 6H), 3.95 (s, 3H), 4.04 (s, 3H), 6.59 (s, 2H), 7.05 (s, 1H), 7.16 (s, 1H), 7.68 (s, 1H); EIMS m/z 537 (M^+), 439 (base). Anal. ($C_{29}H_{33}NO_9$) Calcd: C, 64.80; H, 5.81; N, 2.61. Found: C, 64.77; H, 5.98; N, 3.05.

6,7-Dimethoxy-2-(methoxycarbonyl)-3-(4-hydroxypiperidinocarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (25). To a stirred suspension of **24** (2.0 g, 3.72 mmol) in EtOH (20 mL) was added $NaBH_4$ (70 mg, 1.86 mmol) at 0 °C, and the mixture was stirred at the same temperature for 30 min. The mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from AcOEt gave **25** (1.80 g, 90%): yield 90%; mp 224−227 °C; ^{1}H NMR ($CDCl_3$) δ 1.52−2.09 (m, 5H), 3.21−3.59 (m, 2H), 3.55 (s, 3H), 3.62−3.92 (m, 2H), 3.79 (s, 3H), 3.84 (s, 6H), 3.94 (s, 3H), 4.03 (s, 3H), 4.09−4.34 (m, 1H), 6.59 (s, 2H), 7.03 (s, 1H), 7.14 (s, 1H), 7.61 (s, 1H); EIMS m/z 539 (M^+), 507, 439 (base).

6,7-Dimethoxy-2-(methoxycarbonyl)-3-(4-hydroxymethylpiperidinocarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (26). To a stirred mixture of **22** (2.0 g, 3.36 mmol) and $NaBH_4$ (254 mg, 6.72 mmol) in THF (5 mL) was added dropwise MeOH (2.1 mL) under reflux over 1 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was poured into H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$−acetone = 2:1) gave **26** (1.45 g, 78%): mp 218−220 °C; ^{1}H NMR ($CDCl_3$) δ 1.23−1.49 (m, 2H), 1.61−1.99 (m, 3H), 2.70−3.28 (m, 2H), 3.48−3.68 (m, 3H), 3.56 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.94 (s, 3H), 4.03 (s, 3H), 4.62−4.89 (m, 1H), 6.59 (s, 2H), 7.02 (s, 1H), 7.14 (s, 1H), 7.61 (s, 1H); EIMS m/z 553 (M^+), 521, 439 (base).

General Procedure for the Preparation of 27a−n. Compounds **27a−n** were essentially prepared by the same procedure. The sequence is illustrated for **27a**, followed by analytical data for **27b−n**.

3-[4-(2-Hydroxyethyl)-1-piperazinylcarbonyl]-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (27a). To a mixture of **12a** (59.4 g, 0.13 mol), 1-(2-hydroxyethyl)piperazine (17.5 mL, 0.143 mol), and HOBt·$1H_2O$ (21.9 g, 0.143 mol) in CH_2Cl_2 (300 mL) was added 1,3-dicyclohexylcarbodiimide (DCC) (29.5 g, 0.143 mol), and the mixture was stirred at room temperature overnight. The precipitate was filtered off and washed with CH_2Cl_2. The filtrate was washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$−MeOH = 20:1) gave **27a** (32.0 g, 88%): mp 173−176 °C;^{1}H NMR ($CDCl_3$) δ 2.45−2.74 (m, 7H), 3.42−4.00 (m, 6H), 3.57 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.94 (s, 3H), 4.03 (s, 3H), 6.59 (s, 2H), 7.03 (s, 1H), 7.15 (s, 1H), 7.61 (s, 1H); SIMS m/z 569 ($M^+ + 1$, base), 537, 469.

1-(3-Amino-4,5-dimethoxy)-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (27b): yield 38%; mp 113−117 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.54−2.30 (br s, 2H), 2.40−2.72 (m, 7H), 3.40−4.18 (m, 4H), 3.57 (s, 3H), 3.65 (t, 2H, J = 5.4 Hz), 3.80 (s, 3H), 3.81 (s, 3H), 3.91 (s, 3H), 4.02 (s, 3H), 6.33 (d, 1H, J = 1.8 Hz), 6.38, (d, 1H, J = 1.8 Hz), 7.09 (s, 1H), 7.12 (s, 1H), 7.58 (s, 1H); SIMS m/z 554 ($M^+ + 1$), 522, 424 (base).

1-(3-Chloro-4,5-dimethoxy)-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (27c): yield 87%; mp 155−158 °C; ^{1}H NMR ($CDCl_3$) δ 1.50−2.41 (m, 2H), 2.58−2.84 (m, 5H), 3.47−3.93 (m, 6H), 3.57 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 3.97 (s, 3H), 4.03 (s, 3H), 6.83 (d, 1H, J = 1.8 Hz), 6.91 (s, 1H), 6.97 (d, 1H, J = 1.8 Hz), 7.15 (s, 1H), 7.62 (s, 1H); SIMS m/z 573 ($M^+ + 1$), 541, 443 (base).

1-(3-Bromo-4,5-dimethoxy)-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (27d): yield 78%; mp 167−168 °C; ^{1}H NMR ($CDCl_3$) δ 2.45−2.80 (m, 7H), 3.40−4.00 (m, 6H), 3.59 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 3.95 (s, 3H), 4.03 (s, 3H), 6.88 (d, 1H, J = 1.9 Hz), 6.91 (s, 1H), 7.13−7.15 (m, 2H), 7.62 (s, 1H); EIMS m/z 616/618 (M^+), 585/587, 487/489, 99 (base).

3-[4-(2-Hydroxyethyl)-1-piperazinylcarbonyl]-6,7-dimethoxy-2-(methoxycarbonyl)-1-(2-methyl-4,5-dimethoxyphenyl)naphthalene (27e): yield 55%; mp 120−122 °C; ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 3H), 2.45−2.71 (m, 7H), 3.41−4.01 (m, 6H), 3.54 (s, 3H), 3.73 (s, 3H), 3.80 (s, 3H), 3.95 (s, 3H), 4.03 (s, 3H), 6.67 (s, 1H), 6.69 (s, 1H), 6.82 (s, 1H), 7.15 (s, 1H), 7.63 (s, 1H); EIMS m/z 552 (M^+), 534, 521, 439, 423 (base).

3-[4-(2-Hydroxyethyl)-1-piperazinylcarbonyl]-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4-methylenedioxyphenyl)naphthalene (27f): yield 94%; mp 186−188 °C; ^{1}H NMR ($CDCl_3$) δ 2.43−2.78 (m, 7H), 3.40−4.00 (m, 6H), 3.59 (s, 3H), 3.79 (s, 3H), 4.02 (s, 3H), 6.03 (d, 1H, J = 1.3 Hz), 6.07 (d, 1H, J = 1.3 Hz), 6.71−7.01 (m, 4H), 7.14 (s, 1H), 7.61 (s, 1H); EIMS m/z 522 (M^+), 504, 491, 409, 393 (base).

1-(3,4-Dichlorophenyl)-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-6,7-dimethoxy-2-(methoxycarbonyl)naphthalene (27g): yield 69%; mp 179−180 °C; ^{1}H NMR ($CDCl_3$) δ 2.43−2.72 (m, 7H), 3.49−3.94 (m, 6H), 3.58 (s, 3H), 3.78 (s, 3H), 4.03 (s, 3H), 6.76 (s, 1H), 7.15 (s, 1H), 7.21 (dd, 1H, J = 8.2, 2.0 Hz), 7.46 (d, 1H, J = 1.9 Hz), 7.56 (d, 1H, J = 8.2 Hz), 7.65 (s, 1H); EIMS m/z 546 (M^+), 528, 515, 417 (base).

1-(3,5-Dichlorophenyl)-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-6,7-dimethoxy-2-(methoxycarbonyl)naphthalene (27h): yield 67%; mp 126−128 °C; ^{1}H NMR ($CDCl_3$) δ 2.43−2.72 (m, 7H), 3.39−4.00 (m, 6H), 3.59 (s, 3H), 3.80 (s, 3H), 4.03 (s, 3H), 6.75 (s, 1H), 7.15 (s, 1H), 7.26 (s, 2H), 7.46 (t, 1H, J = 1.9 Hz), 7.65 (s, 1H); EIMS m/z 546 (M^+), 528, 515, 417 (base).

3-[4-(2-Hydroxyethyl)-1-piperazinylcarbonyl]-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3-nitrophenyl)naphthalene (27i): yield 52%; mp 147−150 °C; ^{1}H NMR ($CDCl_3$) δ 2.26−2.90 (m, 7H), 3.47−4.15 (m, 6H), 3.52 (s, 3H), 3.72 (s, 3H), 4.04 (s, 3H), 6.65 (s, 1H), 7.19 (s, 1H), 7.62−7.80 (m, 3H), 8.23 (d, 1H, J = 1.0 Hz), 8.28−8.41 (m, 1H); EIMS m/z 523 (M^+), 505, 492, 394 (base).

1-(2-Bromo-4-pyridyl)-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-6,7-dimethoxy-2-(methoxycarbonyl)naphthalene (27j): yield 59%; mp 204−205 °C; ^{1}H NMR ($CDCl_3$) δ 2.46−2.74 (m, 7H), 3.40−3.99 (m, 6H), 3.59 (s, 3H), 3.78 (s, 3H), 4.04 (s, 3H), 6.66 (s, 1H), 7.16 (s, 1H), 7.21−7.35 (m, 1H), 7.51 (s, 1H), 7.68 (s, 1H), 9.51 (d, 1H, J = 5.0 Hz); EIMS m/z 557/559 (M^+), 539/541, 526/528, 428/430 (base).

3-[4-(2-Hydroxyethyl)-1-piperazinylcarbonyl]-6,7-dimethoxy-2-(methoxycarbonyl)-1-(2-thienyl)naphthalene (27k): yield 83%; mp 190−192 °C; ^{1}H NMR ($CDCl_3$) δ 2.46−2.74 (m, 7H), 3.43−3.93 (m, 6H), 3.59 (s, 3H), 3.82 (s, 3H), 4.03 (s, 3H), 7.05−7.22 (m, 4H), 7.49 (dd, 1H, J = 5.1, 1.2 Hz), 7.64 (s, 1H); SIMS m/z 485 ($M^+ + 1$), 453, 355 (base).

3-[4-(2-Hydroxyethyl)-1-piperazinylcarbonyl]-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxystyryl)naphthalene (27l): yield 73%; mp 123−125 °C; ^{1}H NMR ($CDCl_3$) δ 2.42−2.74 (m, 7H), 3.41−3.60 (m, 2H), 3.65 (t, 1H,

J = 5.1 Hz), 3.78−3.90 (m, 2H), 3.81 (s, 3H), 3.89 (s, 3H), 3.92 (s, 6H), 3.97 (s, 3H), 4.03 (s, 3H), 6.68 (d, 1H, J = 16 Hz), 6.76 (s, 2H), 7.13 (s, 1H), 7.42 (s, 1H), 7.51 (d, 1H, J = 16 Hz), 7.55 (s, 1H); EIMS m/z 594 (M^+), 99 (base).

1-(3-Bromo-4,5-dimethoxyphenyl)-6-ethoxy-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-7-methoxy-2-(methoxycarbonyl)naphthalene (27m): yield 85%; mp 110−112 °C; ^{1}H NMR ($CDCl_3$) δ 1.56 (t, 3H, J = 7.0 Hz), 2.42−2.73 (m, 7H), 3.41−4.02 (m, 6H), 3.59 (s, 3H), 3.79 (s, 3H), 3.85 (s, 3H), 3.95 (s, 3H), 4.25 (q, 2H, J = 7.0 Hz), 6.88 (d, 1H, J = 1.8 Hz), 6.91 (s, 1H), 7.13 (s, 1H), 7.14 (s, 1H), 7.60 (s, 1H); EIMS m/z 630/632 (M^+), 599/601, 501/503, 99, 56 (base).

1-(3-Bromo-4,5-dimethoxyphenyl)-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-6,7,8-trimethoxy-2-(methoxycarbonyl)naphthalene (27n): yield 81%; mp 148−150 °C; ^{1}H NMR ($CDCl_3$) δ 2.41−2.76 (m, 7H), 3.30−4.10 (m, 4H), 3.35 (s, 3H), 3.50 (s, 3H), 3.64 (t, 2H, J = 5.2 Hz), 3.83 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 4.00 (s, 3H), 6.84 (d, 1H, J = 1.8 Hz), 6.98 (s, 1H), 7.07 (d, 1H, J = 1.8 Hz), 7.61 (s, 1H); EIMS m/z 646/648 (M^+), 615/618, 517/519 (base), 439.

General Procedure for the Preparation of 27o−s. Compounds **27o−s** were essentially prepared by the same procedure. The sequence is illustrated for **27o**, follwed by analytical data for **27p−s**.

1-(3-Bromo-4,5-dimethoxyphenyl)-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-2-(methoxycarbonyl)naphthalene Hydrochloride (27o). To a mixture of **12o** (2.0 g, 4.49 mmol), 1-(2-hydroxyethyl)piperazine (660 μL, 4.94 mol), and HOBt·1H_2O (668 mg, 4.94 mmol) in CH_2Cl_2 (40 mL) was added DCC (1.02 g, 4.94 mmol), and the mixture was stirred at room temperature overnight. The precipitate was filtered off and washed with CH_2Cl_2. The filtrate was washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$−MeOH = 20:1) gave 1-(3-bromo-4,5-dimethoxyphenyl)-3-[4-(2-hydroxyethyl)piperazinocarbonyl]-2-(methoxycarbonyl)-naphthalene. After addition of 2 N hydrochloric acid (2.05 mL, 4.1 mmol) to a solution of the obtained free base (1.9 g, 3.41 mmol) in $CHCl_3$ (40 mL), the mixture was concentrated under reduced pressure. Crystallization of the residual salt from AcOEt gave **27o** (1.76 g, 66%): mp 173−175 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.90−3.96 (m, 11H), 3.54 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 4.40−4.59 (m, 1H), 5.39 (br s, 1H), 7.04 (s, 1H), 7.07 (s, 1H), 7.59−7.81 (m, 3H), 8.07−8.18 (m, 1H), 8.33 (s, 1H), 11.04 (br s, 1H); SIMS m/z 557/559 (M^+ + 1−HCl), 525/527, 427/429 (base).

1-(3-Bromo-4,5-dimethoxyphenyl)-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-7-methoxy-2-(methoxycarbonyl)-naphthalene hydrochloride (27p): yield 57%; mp 159−162 °C; ^{1}H NMR (DMSO-d_6) δ 2.91−4.08 (m, 11H), 3.52 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 3.92 (s, 3H), 4.41−4.69 (m, 1H), 5.41 (br s, 1H), 7.00 (s, 1H), 7.04 (s, 1H), 7.29 (dd, 1H, J = 9.2, 2.6 Hz), 7.44−7.61 (m, 2H), 8.00 (s, 1H), 10.97 (br s, 1H); EIMS m/z 586/588 (M^+ − HCl), 568/570, 555/557, 457/459 (base).

1-(3-Bromo-4,5-dimethoxyphenyl)-5-chloro-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-2-(methoxycarbonyl)naphthalene hydrochloride (27q): yield 67%; mp 230−235 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.96−4.06 (m, 11H), 3.56 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 4.35−4.67 (m, 1H), 5.38 (br s, 1H), 7.06 (s, 1H), 7.11 (d, 1H, J = 1.5 Hz), 7.58−7.71 (m, 2H), 7.88−8.01 (m, 1H), 8.31 (s, 1H), 11.15 (br s, 1H); SIMS m/z 591/593 (M^+ + 1 − HCl, base), 559/561, 491/493.

1-(3-Bromo-4,5-dimethoxyphenyl)-7-chloro-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-2-(methoxycarbonyl)naphthalene hydrochloride (27r): yield 66%; mp 156−158 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.89−4.01 (m, 11H), 3.53 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 4.40−4.70 (m, 1H), 5.40 (br s, 1H), 7.06 (s, 1H), 7.11 (s, 1H), 7.56 (d, 1H, J = 1.9 Hz), 7.77 (dd, 1H, J = 8.7, 2.1 Hz), 8.10−8.26 (m, 2H), 10.77 (br s, 1H); SIMS m/z 591/593 (M^+ + 1 − HCl, base), 559/561, 461/463.

1-(3-Bromo-4,5-dimethoxyphenyl)-3-[4-(2-hydroxyethyl)-1-piperazinylcarbonyl]-2-(methoxycarbonyl)-7-methylnaphthalene hydrochloride (27s): yield 77%; mp 230−231 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.43 (s, 3H), 2.90−4.06 (m, 11H), 3.52 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 4.40−4.68 (m, 1H), 5.40 (br s, 1H), 7.02 (s, 1H), 7.06 (d, 1H, J = 1.6 Hz), 7.40 (s, 1H), 7.56 (d, 1H, J = 8.4 Hz), 8.01 (d, 1H, J = 8.4 Hz), 8.10 (s, 1H), 11.24 (br s, 1H); SIMS m/z 571/573 (M^+ + 1 − HCl), 539/541, 441/443 (base).

3-Methyl-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (29). To a solution of acetal **1** [R_1 = 4,5-$(OMe)_2$] (169 g, 0.58 mol) in THF (400 mL) was added dropwise n-BuLi (400 mL, 0.64 mol) at −78 °C under a nitrogen atmosphere, and the mixture was stirred at the same temperature for 30 min. A solution of 3,4,5-trimethoxybenzaldehyde (114 g, 0.58 mol) in THF (300 mL) was added dropwise at −70 °C over 30 min. After stirring at the same temperature for 1 h, the mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. A mixture of the obtained residue, methyl crotonate (67.7 mL, 0.64 mol), and acetic acid (180 mL) in toluene (180 mL) was heated under reflux for 1 h. After the addition of TFA (30 mL), the mixture was further refluxed for 2 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (n-hexane−$CHCl_3$−AcOEt = 10:5:1) gave **29** (10.7 g, 4.3%): mp 175−183 °C dec;^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 3.60 (s, 3H), 3.78 (s, 3H), 3.84 (s, 6H), 3.94 (s, 3H), 4.01 (s, 3H), 6.63 (s, 2H), 6.99 (s, 1H), 7.09 (s, 1H), 7.54 (s, 1H); EIMS m/z 426 (M^+, base), 411.

3-(Bromomethyl)-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (30). A mixture of **29** (8.4 g, 19.7 mmol), N-bromosuccinimide (NBS) (3.86 g, 21.7 mmol), and benzoyl peroxide (200 mg) in CCl_4 (300 mL) was heated under reflux overnight. The mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (n-hexane−AcOEt = 5:3) gave **30** (1.45 g, 14.6%): mp 180−181 °C; ^{1}H NMR ($CDCl_3$) δ 3.59 (s, 3H), 3.79 (s, 3H), 3.85 (s, 6H), 3.95 (s, 3H), 4.03 (s, 3H), 4.78 (s, 2H), 6.61 (s, 2H), 7.02 (s, 1H), 7.14 (s, 1H), 7.76 (s, 1H); EIMS m/z 504/506 (M^+), 425 (base), 410, 94.

3-[4-(2-Hydroxyethyl)piperazinomethyl]-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene Dihydrochloride (31). To a stirred suspension of **30** (0.82 g, 1.62 mmol) in THF (10 mL) was added 1-(2-hydroxyethyl)piperazine (0.40 mL, 3.24 mmol) at room temperature, and the mixture was stirred at room temperature for 4.5 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$−MeOH = 10:1) gave 3-[4-(2-hydroxyethyl)piperazinomethyl]-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (0.85 g, 95%): ^{1}H NMR ($CDCl_3$) δ 2.32−2.61 (m, 10H), 3.42−3.80 (m, 5H), 3.52 (s, 3H), 3.80 (s, 3H), 3.85 (s, 6H), 3.94 (s, 3H), 4.02 (s, 3H), 6.62 (s, 2H), 7.05 (s, 1H), 7.13 (s, 1H), 7.59 (s, 1H); EIMS m/z 554 (M^+), 536, 523, 425 (base).

After addition of 4 N HCl−dioxane (0.94 mL, 3.76 mmol) to a solution of the above free base (0.85 g, 1.5 mmol) in 10 mL of dioxane, the mixture was concentrated under reduced pressure. The residue was triturated with ether and the product **31** (0.86 g) was collected in 82% yield: mp 123−130 °C dec; ^{1}H NMR (D_2O) δ 2.44−4.02 (s, 13H), 3.21−3.37 (m, 2H), 3.62 (s, 3H), 3.68 (s, 3H), 3.73 (s, 6H), 3.80 (s, 2H), 3.94 (s, 3H), 3.98 (s, 3H), 6.47 (s, 2H), 6.76 (s, 1H), 7.04 (s, 1H), 7.40 (s, 1H); EIMS m/z 554 (M^+ − 2HCl), 536, 523, 425 (base).

3-[4-(2-*tert*-Butyldimethylsilyloxyethyl)piperazinomethyl]-6,7-dimethoxy-2-(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)naphthalene (32). To a stirred suspen-

sion of **27a** (11.4 g, 20 mmol) in THF (40 mL) were added imidazole (2.04 g, 30 mmol) and *tert*-butyldimethylsilyl chloride (4.52 g, 30 mmol), and the mixture was stirred at room temperature overnight. The mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed successively with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was triturated with *n*-hexane, and the product **32** (13.1 g) was obtained in 96% yield: mp 95−98 °C; ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 2.43−2.72 (m, 6H), 3.40−3.93 (m, 6H), 3.57 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.94 (s, 3H), 4.03 (s, 3H), 6.59 (s, 2H), 7.02 (s, 1H), 7.15 (s, 1H), 7.61 (s, 1H); EIMS *m*/*z* 682 (M^+), 537, 439 (base).

3-[4-(2-Hydroxyethyl)piperazinomethyl]-2-(hydroxymethyl)-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)naphthalene (33) and 3-[4-(2-Hydroxyethyl)piperazinocarbonyl]-2-(hydroxymethyl)-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)naphthalene (34). To a stirred suspension of $LiAlH_4$ (2.67 g, 70.3 mmol) in THF (50 mL) was added dropwise **32** (12.0 g, 17.6 mmol) in 20 mL of THF at room temperature, and the mixture was stirred for 3 h. H_2O (8.5 mL) and 2 N aqueous NaOH (5.7 mL) were added dropwise successively, and the resultant mixture was stirred at room temperature for 30 min. The precipitate was removed through a Celite pad, and the filtrate was concentrated under reduced pressure. Purification of the residue by silica gel chromatography (from $CHCl_3$−MeOH = 20:1 to $CHCl_3$−MeOH = 1:2) gave **33** (3.5 g, 38%) and **34** (1.5 g, 16%), respectively.

33: ^{1}H NMR ($CDCl_3$) δ 1.51−1.92 (br s, 1H), 2.31−2.90 (m, 10H), 3.50−3.90 (m, 5H), 3.75 (s, 3H), 3.85 (s, 6H), 3.96 (s, 3H), 4.01 (s, 3H), 4.50 (s, 2H), 6.61 (s, 2H), 6.85 (s, 1H), 7.13 (s, 1H), 7.60 (s, 1H); EIMS *m*/*z* 526 (M^+), 396, 131 (base).

34: mp 188−191 °C; ^{1}H NMR (CD_3OD) δ 2.64 (t, 2H, J = 5.8 Hz), 2.68−3.00 (m, 8H), 3.64−3.78 (m, 2H), 3.70 (s, 3H), 3.83 (s, 3H), 3.84 (s, 6H), 3.95 (s, 3H), 3.97 (s, 2H), 6.77 (s, 2H), 6.95 (s, 1H), 7.25 (s, 1H), 7.82 (s, 1H); SIMS *m*/*z* 541 (M^+ + 1, base), 411.

Biological Methods. Isolation of Phosphodiesterase Isozymes. The method of Reeves et al.[11] was modified to isolate PDE isozymes: 1.0 g of lung, heart, or adrenal gland of 56-week-old beagle dog was homogenized in 10 mL ice-cold homogenization buffer (20 mM Tris/HCl, pH 7.8, 2 mM magnesium acetate, 0.3 mM $CaCl_2$, 1 mM dithiothreitol, 40 μM leupeptin, 1.3 mM benzamidine, 0.2 mM phenylmethanesulfonyl fluoride, and 1 mM NaN_3) in a Polytron homogenizer for 1 min at medium speed. The homogenate was centrifuged at 6000*g* for 20 min, and the supernatant was recentrifuged at 100000*g* for 60 min. The cytosolic fraction isolated above was applied to a DEAE-Sephadex column (Pharmacia) equilibrated in elution buffer (20 mM Tris/HCl, pH 7.8, 1 mM dithiothreitol, 1 mM $CaCl_2$, 2 μM leupeptin, and 5 mM benzamidine). The column was washed with 10 mL of elution buffer, and the PDEs were then eluted from the column by running a linear NaCl gradient (0−400 mM, 50 mL; 400−2000 mM, 10 mL) in elution buffer. Fractions (1 mL each) were collected on ice and assayed for cGMP and cAMP hydrolytic PDE activity.

Assay of Phosphodiesterase Activity. PDE activity was determined by a modification of the method of Thompson et al.[12] The assay buffer contained 50 mM Tris-HCl, pH 8.0, 5 mM $MgCl_2$, 4 mM 2-mercaptoethanol, 1 μM unlabeled cGMP or cAMP, and 22 nM [^{3}H]cGMP or [^{3}H]cAMP. The reaction was started by mixing 0.1−10 μM enzyme solution into 500 μL of assay buffer, and tubes were incubated at 37 °C for 30 min. After boiling for 1.5 min, the mixture was added to 100 μL of 1 mg/mL *Crotalus atrox* snake venom and incubated at 37 °C for 30 min. The reaction was quenched by the addition of 500 μL of methanol, and the resultant solution was applied to a Dowex (1 × 8-400) column. Aqueous scintillation cocktails were added to each elute, and the radioactivity was measured.

Relaxing Effect on Isolated Coronary Arteries Precontracted with Phenylephrine. Relaxing effect was determined by a modification of the method of Ignarro et al.[13] Porcine coronary arteries were removed, cleaned of adjacent tissues, and cut into rings with special care not to damage the endothelium. The rings were longitudinally opened and mounted in organ baths containing 10 mL of Krebs−Henseleit solution (37 °C, pH 7.4, bubbled with 95% O_2−5% CO_2). The coronary arterial strips were allowed to equilibrate under a resting tension of 1 g. The presence of intact endothelial cells was confirmed by bradykinin (final concentration, 7×10^{-9} M)-induced relaxation of strips precontracted with KCl (final concentration, 50 mM). The strips were contracted with phenylephrine (final concentration, 3×10^{-6} M), and after the attainment of a plateau contraction, cumulative concentration−relaxation curves for a tested compound were constructed. Relaxation was calculated as a percentage of the contractile response to papaverine.

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