Novel Selective PDE IV Inhibitors as Antiasthmatic Agents. Synthesis and Biological Activities of a Series of 1-Aryl-2,3-bis(hydroxymethyl)naphthalene Lignans

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A series of 1-aryl-2,3-bis(hydroxymethyl)naphthalene lignans have been synthesized and evaluated for their ability to selectively inhibit PDE IV isolated from guinea pig. Replacement of the 1-phenyl ring by a pyridone ring led to marked improvement of their selectivity for PDE IV over PDE III. The compounds that were most potent and selective involved those bearing an *N*-alkylpyridone ring at C-1. These compounds also showed potent antispasmogenic activity without causing significant changes in heart rate in the guinea pig. The most potent compound was 6,7-diethoxy-2,3-bis(hydroxymethyl)-1-[1-(2-methoxyethyl)-2-oxo-pyrid-4-yl]naphthalene (**17f**), ED_{50} values of histamine-induced and antigen-induced bronchoconstriction in the guinea pig being 0.08 and 2.3 mg/kg iv, respectively. This compound was chosen as a candidate for further pharmacological evaluation.

Introduction

Asthma is a complex disease characterized by airways obstruction and bronchial inflammation. Despite widespread use of antiasthmatic drugs, the mortality and morbidity due to asthma is increasing worldwide, suggesting the lack of really effective drugs for therapy.

Cyclic nucleotide phosphodiesterases (PDEs) are the enzymes hydrolyzing purine cyclic nucleotides, cAMP and cGMP, to form the respective 5′-mononucleotides. At least seven different gene families of PDEs are currently known to exist in mammalian tissues.[1] Inhibition of PDE activity results in the increase in cellular levels of second messengers, cAMP and cGMP. Elevation of these second messengers has been implicated in relaxation of airway smooth muscle.[2] There is also considerable evidence that elevated levels of cAMP in proinflammatory cells prevents their activation.[3]

An area of recent interest has been the search for selective PDE IV inhibitors as potential antiasthmatic agents.[4] The reported selective PDE IV inhibitors include catechol ethers, quinazolinediones, and xanthines.[4c,5] During our continued search for biologically active lignans, we found that arylnaphthalene lignans showed consistent PDE IV inhibitory activity as a class. Since inhibition of PDE III is reported to correlate with the induction of cardiovascular side effects,[6] we undertook a search for PDE IV inhibitors having minimal PDE III inhibitory activity in the lignan series. We report here the synthesis, structure−activity relationships, and biological activities of a series of novel 1-aryl-2,3-bis(hydroxymethyl)naphthalene lignans.

Chemistry

The various diols **7**, **15**, and **17** were synthesized via either Diels−Alder reactions of isobenzofurans **4**[7] (Scheme 1) or cyclization of lactones **21**[8] (Scheme 3). As shown in Scheme 1, the bromo acetals **1** were transformed into the cyclic acetals **3** via hydroxy acetals **2**. Being too unstable to be isolated, isobenzofurans **4** generated from the cyclic acetals **3** were treated directly with dimethyl maleate to give the adducts **5**. The adducts **5** were also prepared by the reaction of the hydroxy acetals **2** with dimethyl maleate in the presence of acetic acid in a one-pot procedure. Subsequent aromatization of the adducts **5** with boron trifluoride etherate or trifluoroacetic acid followed by reduction of the ester groups with lithium aluminum hydride (LAH) afforded the diols **7** (method A). The methylsulfonyl analog **7g** was obtained by oxidizing the corresponding sulfide **7gg** with *m*-chloroperbenzoic acid. The naphthalene **7e** was prepared by reduction of the corresponding ester **6**[9] with LAH. The preparation of the diol with a spacer methylene **7d** was as follows. Treatment of the hydroxy acetal **2** with dimethyl acetylenedicarboxylate in acetic acid afforded the olefin **8**. Subsequent catalytic hydrogenation of **8** gave the adduct **5** which was converted to the diol **7d** by the same reactions as described above.

The amino analog **7h** was synthesized by deprotection of the silyl ether **6a**, Zincke nitration[10] on the resulting **9**, and catalytic hydrogenation (method B). The acetamide analog **7i** was prepared by acylation of the corresponding amine **6i** with acetic anhydride followed by reduction with LAH. The *N*,*N*-dimethylcarbamoyl analog **7j** was obtained by transformation of the diol **7k** to the silyl derivative **11**, lithiation followed by carbonation, condensation with dimethylamine, and deprotection (method C).

The diols bearing a pyridone ring **15** and **17** were prepared by the methods shown in Scheme 2. Acetylation of the pyridines **7** prepared via the isobenzofurans **4** provided the acetates **13** which were oxidized with *m*-chloroperbenzoic acid to give the *N*-oxides **14**. Treatment of **14** with acetic anhydride followed by selective removal of the acetyl group of the C-1 substituent with ammonium hydroxide afforded the pyridones **15** (R^2 = Ac).[11] Alkylation of **15** (R^2 = Ac) with alkyl halides and sodium hydride gave the *N*-alkyl analogs **16**. Removal of the acetate protecting groups with sodium methoxide

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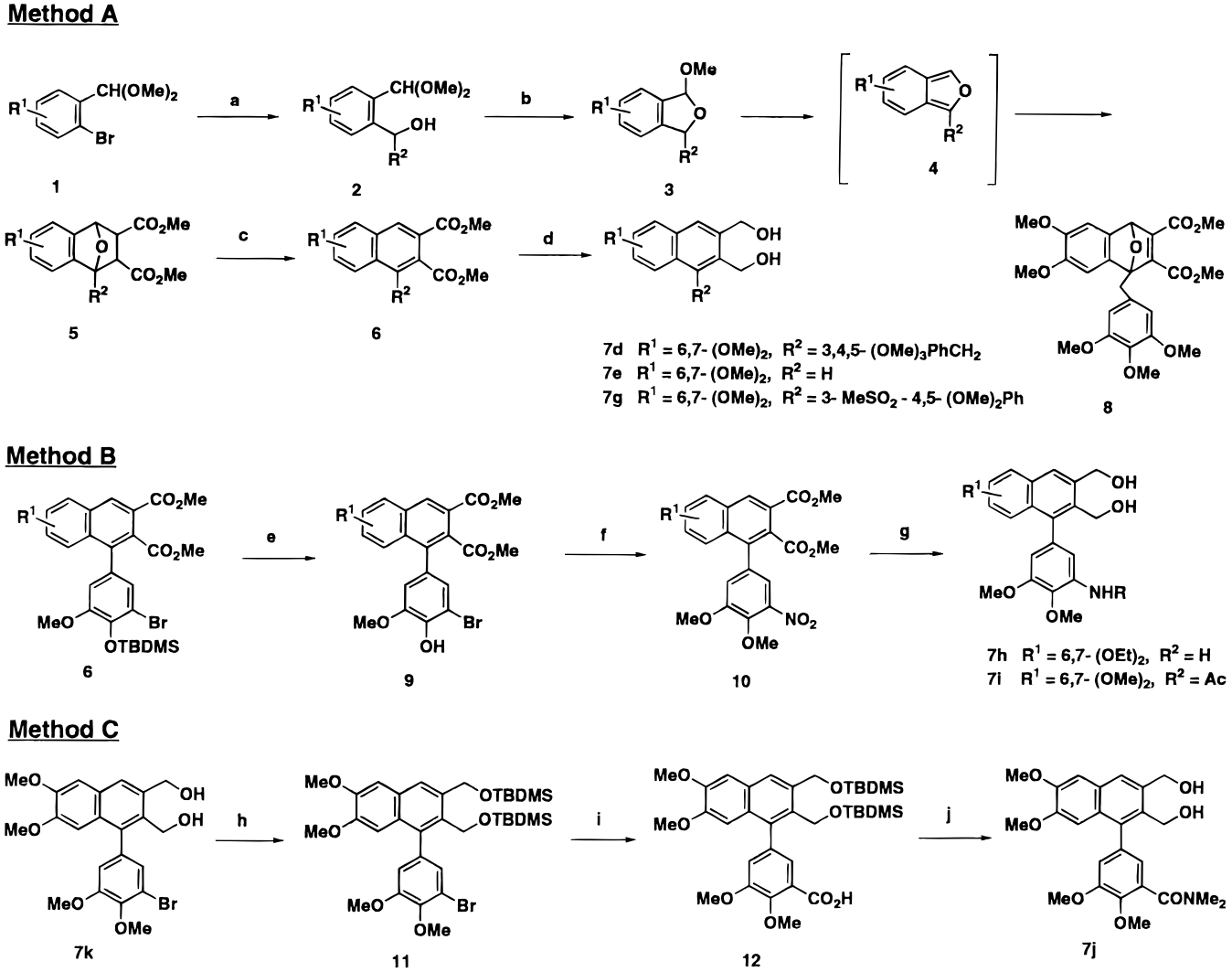
Scheme 1[a]



[a] Reagents and conditions: (a) *n*-BuLi, R^2CHO/THF, −70 °C; (b) dimethyl maleate, AcOH/toluene reflux; (c) TFA/$CHCl_3$, 25 °C or $BF_3{\cdot}OEt_2/CH_3CN$ reflux; (d) LAH/THF, 10 °C; (e) 10% aqueous HCl/THF, reflux, overnight; (f) (1) $NaNO_2$/AcOH; (2) Me_2SO_4, K_2CO_3/DMF; (g) (1) H_2, 10% Pd−C/THF−MeOH, 25 °C; (2) Ac_2O, Et_3N/THF, 25 °C; (3) LAH/THF, 10 °C; (h) TBDMSCI/pyridine, 25 °C; (i) *n*-BuLi, CO_2/Et_2O, −70 °C; (j) (1) CDI/THF, $HNMe_2$, 25 °C; (2) 10% aqueous HCl/THF, 25 °C.

provided the *N*-alkylpyridones **17** (method D). In an alternative synthesis of **17**, the diesters **6** were oxidized to the *N*-oxides **18**, which were converted into the pyridones **19**. Subsequent alkylation followed by reduction of the ester groups with sodium borohydride and methanol in THF[12] gave the *N*-alkylpyridones **17** (method E). The acetate **17h** was obtained by acylation of **17b** with acetic anhydride.

Scheme 3 summarizes the synthesis of the diols **7** via the lactones **21**, which were prepared in three steps from aldehydes via Stobbe condensation.[13] Alkylation of the lactones **21** with aldehydes and lithium diisopropylamide followed by cyclization with trifluoroacetic acid gave the tetralins **23**. The diols **7** were obtained by aromatization of **23** with 2,3-dichloro-5,6-dicyanobenzoquinone and subsequent reduction with LAH (method F).

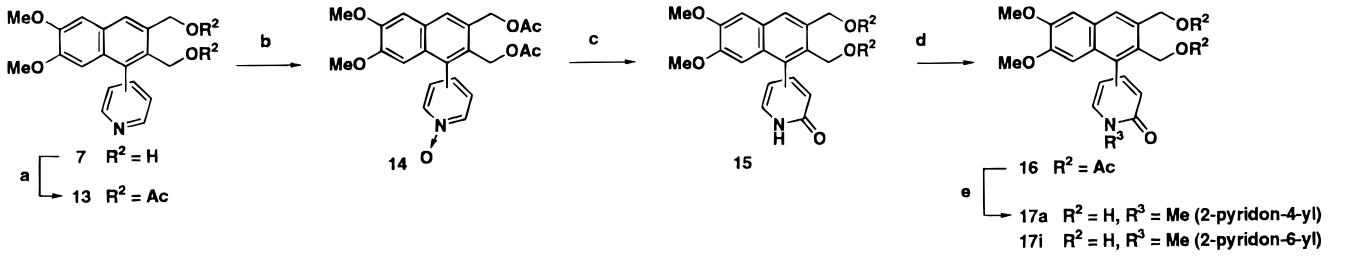
Biological Results and Discussion

The compounds reported in this paper were first evaluated as inhibitors of the four different forms of PDE isolated from guinea pig cardiac ventricle (PDE I and III) and lung (PDE IV and V) *in vitro* (Table 1). Secondly, we selected a group of compounds on the basis of the PDE IV inhibitory potency. These compounds were evaluated for their ability to inhibit intravenous histamine-induced and antigen-induced bronchospasm in anesthetized guinea pigs (Table 2). The effects of these compounds on heart rate were simultaneously investigated to assess the cardiovascular side effects reported to be produced by nonselective PDE inhibitors (Table 2).

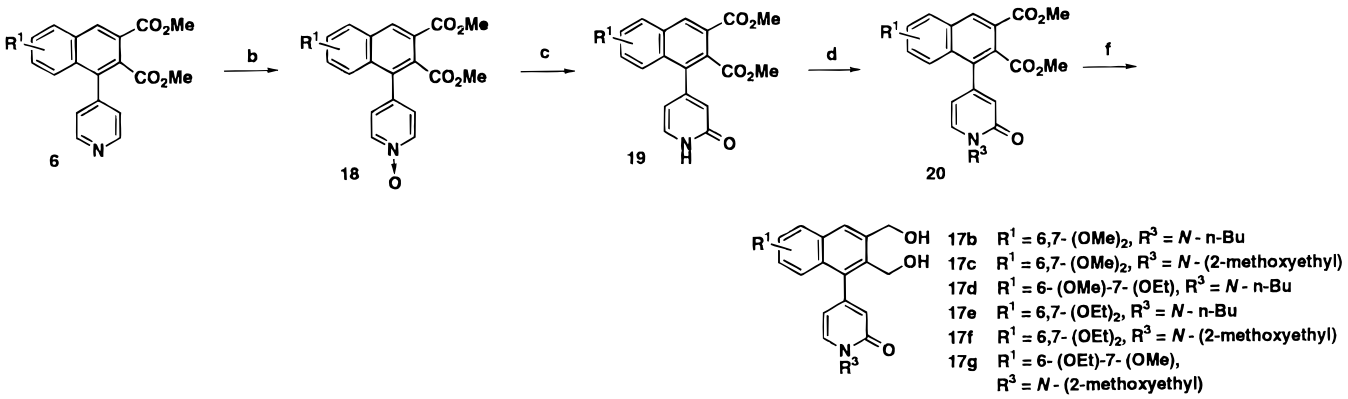
Phosphodiesterase Inhibition. The most potent inhibitors of PDE IV were found among the compounds carrying a 3,4,5-trisubstituted phenyl and a *N*-alkylated pyridone ring at C-1 (Table 1). In the trisubstituted phenyl series, the initial lead compound **7a** showed potent inhibitory activity against PDE IV (IC_{50} = 0.3 μM), though it exhibited poor selectivity for PDE IV over PDE III. In an attempt to define the structural parameters necessary for activity and selectivity, our strategy was to systematically change the substituents on the naphthalene ring of compound **7**. Replacement of the 6,7-dimethoxy group of **7a** to a 6,7-methylenedioxy group (**7b**) led to a decrease of PDE IV inhibitory activity. A drop in the activity was also observed when

Scheme 2[a]

Method D



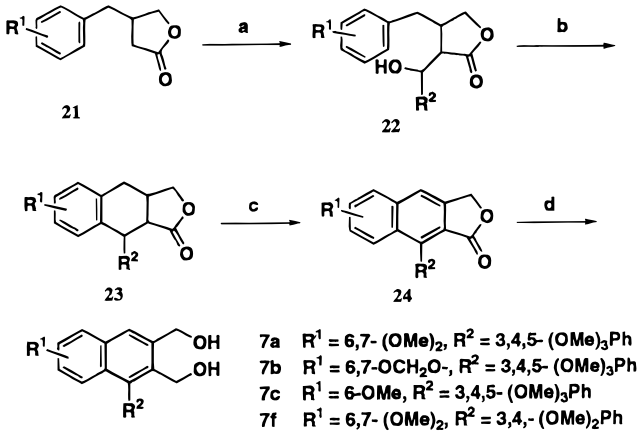
Method E



[a] Reagents and conditions: (a) Ac_2O, pyridine, 25 °C; (b) *m*-CPBA/CH_2Cl_2, 25 °C; (c) (1) Ac_2O, reflux; (2) NH_4OH/MeOH, 25 °C; (d) NaH, R^3I/DMF, 25 °C; (e) NaOMe/MeOH, 25 °C; (f) $NaBH_4$/THF−MeOH, reflux.

Scheme 3[a]

Method F



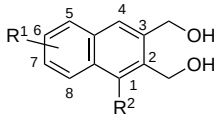
[a] Reagents and conditions: (a) LDA, R^2CHO/THF, −70 °C; (b) TFA, 25 °C; (c) DDQ/PhH, reflux; (d) LAH/THF, 10 °C.

the 7-methoxy group was replaced by a hydrogen atom (**7c**). Transformation of the 2,3-bis(hydroxymethyl) groups into a lactone function (**24a**)[14] retained the activity. Removal of the 3,4,5-trimethoxyphenyl group (**7e**) or introduction of a methylene group between the naphthalene ring and 1-phenyl ring (**7d**) resulted in a substantial loss in activity. The activity of **7a** was markedly enhanced, however, by changing the 3-methoxy group of the 3,4,5-trimethoxyphenyl moiety to other functional groups. The optimal activity was obtained when the 3-methoxy group was substituted with a *N*,*N*-dimethylcarbamoyl group (**7j**, IC_{50} = 0.005 μM) and either a methylsulfonyl (**7g**) or acetamido group (**7i**). Moreover, for analog **7i**, the ratio of the IC_{50} value for PDE III to PDE IV increases from 3 to 29. Thus, nature of the 3-substituent on the 1-phenyl ring had a marked effect on the potency and selectivity.

From the above results, it may be concluded that the amide group on the C-1 phenyl ring of **7j** plays an important role in PDE IV inhibitory activity. Therefore, we next designed the diols bearing a pyridone ring at C-1 (**15a** and **17a**−**i**), which has an amide group in the ring. Among them, *N*-alkylated pyridones (**17d**−**f**) showed the best inhibitory activity against PDE IV (IC_{50} = 0.03−0.07 μM) with good selectivity for the PDE I, III, and V isozymes; the PDE III vs PDE IV selectivity ratio is between 714 and 1667 for these compounds. It is evident from Table 1 that in general, the change of the phenyl ring to the pyridone ring markedly improved the selectivity ratio. Replacement of the 6,7-diethoxy groups in **17e** and **17f** by 6,7-dimethoxy groups resulted in a severe loss of PDE IV inhibitory activity (**17b**,**c**); however, the 6-methoxy-7-ethoxy analog (**17d**) retained activity. The 2,3-bis(hydroxymethyl) groups seem to be essential for the activity because replacement of 2,3-bis(hydroxymethyl) groups with 2,3-bis(acetoxymethyl) groups resulted in a large loss of activity (**17h**).

Antispasmogenic Activity. We selected 11 compounds on the basis of the PDE IV inhibitory potency for the evaluation of their ability to reverse histamine-induced bronchoconstriction in anesthetized guinea pigs when given intravenously. Rolipram[4a] was selected as a reference compound (ED_{50} = 0.01 mg/kg iv).[15] As shown in Table 2, compounds with the *N*,*N*-dimethylcarbamoyl (**7j**) and *N*-(2-methoxyethyl) (**17f**) substituents had excellent antispasmogenic activity with ED_{50} values of 0.03 and 0.08 mg/kg, respectively. The most potent compound was *N*-(2-methoxyethyl) derivative **17f**

Table 1. Physical Properties and PDE Inhibitory Activities of Lignans



						PDE inhibition, IC_{50}, μM[e]				selectivity
compd	R^1	R^2	method	formula[a]	mp, °C	I	III	IV	V	III/IV
7a	6,7-$(OMe)_2$	3,4,5-$(OMe)_3$Ph	F	$C_{23}H_{26}O_7$	124−126	60	0.9	0.3	3	3
7b	6,7-OCH_2O−	3,4,5-$(OMe)_3$Ph	F	$C_{22}H_{22}O_7$	254−255	>100	>100	>30	>30	3
7c	6-OMe	3,4,5-$(OMe)_3$Ph	F	$C_{22}H_{24}O_6$	124−125	30	20	40	8	0.5
7d	6,7-$(OMe)_2$	3,4,5-$(OMe)_3PhCH_2$	A	$C_{24}N_{28}O_7$	182−184	40	8	5	20	2
7e	6,7-$(OMe)_2$	H	A	$C_{14}H_{16}O_4$	190−192	>100	>100	20	>100	5
7f	6,7-$(OMe)_2$	3,4-$(OMe)_2$Ph	F	$C_{22}H_{24}O_6$	186−187	70	1	0.2	3	5
7g	6,7-$(OMe)_2$	3-$MeSO_2$-4,5-$(OMe)_2$Ph	A	$C_{23}H_{26}O_8S$[b]	187−189	100	0.09	0.05	53	2
7h	6,7-$(OEt)_2$	3-H_2N-4,5-$(OMe)_2$Ph·HCl	B	$C_{24}H_{29}NO_6$·HCl·$1.6H_2O$	200−210	50	20	0.05	30	400
7i	6,7-$(OMe)_2$	3-CH_3CONH-4,5-$(OMe)_2$Ph	B	$C_{24}H_{27}NO_7$	200−201	100	2	0.07	100	29
7j	6,7-$(OMe)_2$	3-Me_2NCO-4,5-$(OMe)_2$Ph	C	$C_{25}H_{29}NO_7$	162−163	>100	0.06	0.005	30	12
24a[c]	6,7-$(OMe)_2$	3,4,5-$(OMe)_3$Ph	F	$C_{22}H_{20}O_6$	205−206	9	0.3	0.5	1	1
15a	6,7-$(OMe)_2$	2-oxopyrid-4-yl	D	$C_{19}H_{19}NO_5$	242−244	>100	20	0.2	10	100
17a	6,7-$(OMe)_2$	*N*-Me-2-oxopyrid-4-yl	D	$C_{20}H_{21}NO_5$	176−178	>100	20	0.6	20	33
17b	6,7-$(OMe)_2$	*N*-Bu-2-oxopyrid-4-yl	E	$C_{23}H_{27}NO_4$	159−161	>100	30	0.3	20	100
17c	6,7-$(OMe)_2$	*N*-(2-methoxyethyl)-2-oxopyrid-4-yl	E	$C_{22}H_{25}NO_6$	124−126	>100	14	0.5	22	28
17d	5-OMe-7-OEt	*N*-Bu-2-oxopyrid-4-yl	E	$C_{24}H_{29}NO_5$	164−166	>100	50	0.07	8	714
17e	6,7-$(OEt)_2$	*N*-Bu-2-oxopyrid-4-yl	E	$C_{25}H_{31}NO_5$	149−150	>100	50	0.03	9	1667
17f	6,7-$(OEt)_2$	*N*-(2-methoxyethyl)-2-oxopyrid-4-yl	E	$C_{24}H_{29}NO_6$	126−127	>100	57	0.057	22	1000
17g	6-OEt-7-OMe	*N*-(2-methoxyethyl)-2-oxopyrid-4-yl	E	$C_{23}H_{27}NO_6$	162−164	>100	7	0.45	24	17
17h[d]	6,7-$(OMe)_2$	*N*-Bu-2-oxopyrid-4-yl	E	$C_{27}H_{31}NO_7$	134−135	>100	80	20	4	4
17i	6,7-$(OMe)_2$	*N*-Me-2-oxopyrid-6-yl	D	$C_{20}H_{21}NO_5$	238−240	>100	30	0.6	30	50
rolipram						>100	>100	1.9	>100	>53

[a] C, H, N, S, and Cl analyses were within ±0.4% of the theoretical values, unless otherwise noted. [b] S: calcd, 6.93; found, 7.51. [c] 6,7-Dimethoxy-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-1(3*H*)-one. [d] 2,3-Bis(acetoxymethyl)-1-(*N*-butyl-2-oxopyrid-4-yl)-6,7-dimethoxynaphthalene. [e] Data shown are the result of single determination.

Table 2. Bronchial and Cardiovascular Effects of Selected Compounds

	PDE inhibition, IC_{50}, μM[d]			histamine-induced[a] bronchoconstriction			antigen-induced[c] bronchoconstriction,
compd	III	IV	dose, mg/kg iv	% reduction	ED_{50}, mg/kg	heart rate[b] Δbeats/min	ED_{50}, mg/kg
7a	0.9	0.3	3	89		79	4.6
7g	0.09	0.05	0.03	34	0.093	3	
			0.1	57		1	
			0.3	71		−7	
7h	20	0.05	0.3	45	0.39	−4	>10
			1	69		1	
			3	90		2	
7j	0.06	0.005	0.03	59	0.03	1	
			0.1	83		28	
			0.3	69		50	
17b	30	0.3	3	79		1	>10
17c	14	0.5	0.1	34	0.16	1	
			0.3	70		3	
17d	50	0.07	0.3	40	0.42	7	
			1	75		6	
			3	92		4	
17e	50	0.03	0.3	47		−5	>10
17f	57	0.057	0.1	60	0.08	5	2.3
			0.3	92		5	
			1	98		5	
17g	7	0.45	0.3	30	0.51	4	4.1
			1	76		7	
			3	98		6	
17i	30	0.6	3	81		11	>10
rolipram	>100	1.9	0.1	79	0.01	9	19
			1	72		3	

[a] Precent inhibition of histamine-induced bronchoconstriction in guinea pigs. [b] Difference in heart rate between basal value and the value observed after test compound administration in guinea pigs. Basal values for heart rate were 230−330 beats/min. [c] The dose which inhibits antigen-induced bronchoconstriction in guinea pigs by 50%. [d] Data shown are the result of single determination.

which showed a 98% reduction of the histamine response at 1 mg/kg, and rolipram exhibited a 72% reduction at the same dose. The *N*-butyl analog **17e** was 4-fold less potent than compound **17f** in inhibition of bronchoconstriction despite the fact that **17e** was 2-fold more potent than **17f** as an inhibitor of PDE IV.

In the guinea pig antigen-induced bronchoconstriction model, compound **17f** (ED_{50} = 2.3 mg/kg iv) proved to have activity greater than rolipram (ED_{50} = 19 mg/kg iv).[16] More detailed information on the antispasmogenic activity of **17f** in this model will be published elsewhere.

To assess the cardiovascular side effects, the effects of selected compounds on heart rate were investigated. Increasing effects of these compounds on heart rate correlate with the inhibitory effects of those on PDE III activity. Among the compounds showing potent antispasmogenic activity, the *N*-(2-methoxyethyl) analog **17f** exhibited minimal effects on increase in heart rate, reflecting the high III/IV selectivity ratio (1000). By contrast, the *N*,*N*-dimethylcarbamoyl analog **7j** possessing poor selectivity ratio (12) induced significant increase in heart rate. However, this correlation did not hold for the methylsulfonyl analog **7g** (ED_{50} = 0.093 mg/kg iv) having very poor selectivity ratio (2), where it was found that compound **7g** showed negligible changes in heart rate, though the reason for this is not clear.

Conclusion

Novel arylnaphthalene lignans bearing a *N*-alkylpyridone ring have been shown to be very potent PDE IV inhibitors with high PDE III vs PDE IV selectivity ratios. Of the analogs, compound **17f** (PDE IV IC_{50} = 0.057 μM, PDE III/IV ratio 1000) showed potent antispasmogenic activity (ED_{50} = 0.08 mg/kg iv) without producing the significant changes in heart rate with the use of histamine-induced bronchospasm assay. Compound **17f** was 8-fold less active than rolipram (ED_{50} = 0.01 mg/kg iv) in the above assay system, whereas in the guinea pig antigen-induced bronchoconstriction model, **17f** (ED_{50} = 2.3 mg/kg iv) was 8-fold more active than rolipram (ED_{50} = 19 mg/kg iv).

On the basis of the potency, selectivity, and favorable effect on cardiovascular systems, compound **17f** was selected for further evaluation as an antiasthmatic agent.

Experimental Section

Melting points were determined on a Yamato MP-21 capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained at 200 MHz with a Bruker AC-200 instrument. Chemical shifts were reported in ppm (δ) using Me_4Si as standard. Mass spectra were obtained on a Hitachi M-60 mass spectrometer. Elemental analyses were carried out in this laboratory. Column chromatography was performed with silica gel (E. Merck, 70−230 mesh). Reactions were monitored by TLC using 0.25 mm silica gel F254 (E. Merck) glass plates. *n*-Butyllithium was the 1.6 M solution in hexane supplied by Asia Lithium Co.

General Procedure for the Synthesis of Diols 7. Method A (Scheme 1). Compounds **7d**,**e**,**g** were all prepared by essentially the same procedure (Scheme 1). The sequence is illustrated for **7g**, followed by analytical data for **7d** and **7e**.

6,7-Dimethoxy-2,3-bis(methoxycarbonyl)-1-[3-(methylthio)-4,5-dimethoxyphenyl]naphthalene (6g). To a stirred solution of **1** [R^1 = 4,5-$(OMe)_2$] (5.82 g, 20 mmol) in THF (40 mL) was added BuLi (13.1 mL, 21 mmol) at −70 °C under an atmosphere of nitrogen. The mixture was stirred at the same temperature for 30 min. To this mixture was added a solution of the 3,4-dimethoxy-5-(methylthio)benzaldehyde (4.24 g, 20 mmol) in THF (15 mL). The resulting mixture was stirred at the same temperature for 2 h and poured into a mixture of water (50 mL) and AcOEt (100 mL). The organic layer was separated, washed with water (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. A solution of the residue, dimethyl maleate (3.46 g, 24 mmol), and acetic acid (10 mL) in toluene (20 mL) was heated under reflux for 5 h. The solvent was removed by evaporation to give 1,4-epoxy-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[3-(methylthio)-4,5-dimethoxyphenyl]-2,3-bis(methoxycarbonyl)naphthalene (**5g**) as a syrup. This crude product was used in the next step without purification. To a solution of **5g** in $CHCl_3$ (50 mL) was added trifluoroacetic acid (TFA) (10 mL), and the mixture was stirred at room temperature for 3 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Crystallization of the residue from Et_2O gave **6g** (4.08 g, 42%): mp 164−166 °C; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.65 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 4.01 (s, 3H), 6.73 (s, 2H), 6.91 (s, 1H), 7.21 (s, 1H), 8.42 (s, 1H); MS *m*/*z* 489, 488, 487, 486 (M^+). Anal. ($C_{25}H_{26}O_8S$) C, H, S.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-[3-(methylthio)-3,4-dimethoxyphenyl]naphthalene (7gg). To a suspension of lithium aluminum hydride (LAH) (340 mg, 8.8 mmol) in THF (40 mL) was added a solution of the **6g** (2.14 g, 4.4 mmol) in THF (60 mL) at −20 °C. The mixture was gradually warmed to 10 °C during 1 h and stirred at the same temperature for 1 h. To this mixture was added dropwise water (0.34 mL), 15% aqueous NaOH (0.34 mL), and water (1.0 mL) successively at 10 °C, and the resulting 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 Et_2O gave **7gg** (1.84 g, 97%): mp 141−142 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 1.5H), 2.03 (s, 1.5H), 2.34 (s, 3H), 3.30−3.80 (br s, 2H), 3.73 (s, 3H), 3.80 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 4.10 (q, J = 7.1 Hz, 1H), 4.59 (s, 2H), 4.85 (s, 2H), 6.69 (s, 2H), 6.75 (s, 1H), 7.09 (s, 1H), 7.64 (s, 1H); MS *m*/*z* 432, 431, 430 (M^+). Anal. ($C_{23}H_{26}O_6S$·0.5AcOEt) C, H, S.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-[3-(methylsulfonyl)-4,5-dimethoxyphenyl]naphthalene (7g). To a stirred solution of **7gg** (2.3 g, 5.3 mmol) in $CHCl_3$ (100 mL) was added *m*-chloroperbenzoic acid (*m*-CPBA) (2.0 g, 11.7 mmol), and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed with 1 N aqueous NaOH (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from AcOEt−Et_2O gave **7g** (1.6 g, 68%): mp 187−189 °C; ^{1}H NMR ($CDCl_3$) δ 3.27 (s, 3H), 3.40−3.90 (br s, 2H), 3.70 (s, 3H), 3.88 (s, 3H), 3.96 (s, 3H), 4.09 (s, 3H), 4.39 (AB q, J = 12.0 Hz, 1H), 4.59 (AB q, J = 12.0 Hz, 1H), 4.63 (AB q, J = 13.0 Hz, 1H), 4.90 (AB q, J = 13.0 Hz, 1H), 6.59 (s, 1H), 7.07 (s, 1H), 7.23 (d, J = 1.5 Hz, 1H), 7.47 (d, J = 1.5 Hz, 1H), 7.63 (s, 1H); MS *m*/*z* 464, 463, 462 (M^+). Anal. ($C_{23}H_{26}O_8S$) C, H; S: calcd, 6.93; found, 7.51.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-(3,4,5-trimethoxybenzyl)naphthalene (7d): yield 53%; mp 182−184 °C; ^{1}H NMR ($CDCl_3$) δ 3.30 (br s, 2H), 3.65 (s, 3H), 3.75 (s, 6H), 3.82 (s, 3H), 3.93 (s, 3H), 4.43 (s, 2H), 4.83 (s, 4H), 6.30 (s, 2H), 7.03 (s, 1H), 7.18 (s, 1H), 7.53 (s, 1H); MS *m*/*z* 428 (M^+). Anal. ($C_{24}H_{28}O_7$) C, H.

6,7-Dimethoxy-2,3-bis(hydroxymethyl)naphthalene (7e): yield 53%; mp 190−192 °C; ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 6H), 4.75 (d, J = 6.0 Hz, 4H), 5.00 (t, J = 6.0 Hz, 2H), 7.12 (s, 2H), 7.67 (s, 1H); MS *m*/*z* 248 (M^+). Anal. ($C_{14}H_{16}O_4$) C, H.

1,4-Epoxy-1,4-dihydro-6,7-dimethoxy-1-(3,4,5-trimethoxybenzyl)-2,3-bis(methoxycarbonyl)naphthalene (8). This compound was prepared as described for **6g** except for using dimethyl acetylenedicarboxylate in lieu of dimethyl maleate: yield 17%; ^{1}H NMR ($CDCl_3$) δ 3.65 (d, J = 1.5 Hz, 2H), 3.69 (s, 6H), 3.72 (s, 3H), 3.80 (s, 3H), 3.84 (s, 6H), 3.88 (s, 3H), 5.90 (s, 1H), 6.55 (s, 2H), 7.17 (d, J = 1.5 Hz, 2H); MS *m*/*z* 500 (M^+). Anal. ($C_{26}H_{28}O_{10}$) C, H.

1,4-Epoxy-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4,5-trimethoxybenzyl)-2,3-bis(methoxycarbonyl)naphthalene (5d). A solution of **8** (300 mg, 0.6 mmol) in AcOEt (20 mL) was hydrogenated over 10% Pd−C (150 mg) at atmospheric pressure and 25 °C for 5 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give **5d** as an oil (280 mg, 93%): ^{1}H NMR ($CDCl_3$) δ 3.30−

4.20 (m, 4H), 3.47 (s, 6H), 3.49 (s, 6H), 3.80 (s, 3H), 3.86 (s, 6H), 5.38 (d, J = 5.0 Hz, 1H), 6.53 (s, 2H), 6.86 (s, 2H); MS m/z 502 (M^+). Anal. ($C_{26}H_{30}O_{10}$) C, H.

Method B (Scheme 1). 1-(3-Bromo-4-hydroxy-5-methoxyphenyl)-6,7-diethoxy-2,3-bis(methoxycarbonyl)naphthalene (9h). To a solution of **6h** (5.3 g, 8.2 mmol) in THF (45 mL) was added 10% aqueous HCl (30 mL), and the mixture was heated at 70 °C overnight. The reaction mixture was allowed to cool to room temperature and extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from Et_2O gave **9h** (1.8 g, 41%): mp 165−167 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (t, J = 7.0 Hz, 3H), 1.54 (t, J = 7.0 Hz, 3H), 3.69 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 3.96−4.04 (m, 2H), 4.24 (t, J = 7.0 Hz, 2H), 6.05 (s, 1H), 6.83 (d, J = 2.0 Hz, 1H), 6.84 (s, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.23 (s, 1H), 8.42 (s, 1H); MS m/z 533 (M^+). Anal. ($C_{25}H_{25}BrO_8$) C, H; Br: calcd, 14.98; found, 14.35.

6,7-Diethoxy-2,3-bis(methoxycarbonyl)-1-(3-nitro-4,5-dimethoxyphenyl)naphthalene (10h). To a stirred suspension of **9h** (14 g, 26 mmol) in AcOH (90 mL) was added $NaNO_2$ (5.4 g, 78 mmol) portionwise so that the reaction temperature does not exceed 20 °C over 1 h, and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water (100 mL), and the precipitate was collected by filtration and washed with water. The precipitate was dissolved in $CHCl_3$ (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. To a solution of the residue in DMF (150 mL) were added Me_2SO_4 (4.4 mL, 47 mmol) and K_2CO_3 (7.1 g, 52 mmol), and the mixture was stirred at room temperature overnight. The resulting precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), washed with 2 N aqueous NaOH, followed by water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from diisopropyl ether gave **10h** (7.74 g, 58%): mp 183−184 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (t, J = 7.0 Hz, 3H), 1.54 (t, J = 7.0 Hz, 3H), 3.69 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 3.96−4.04 (m, 2H), 4.05 (s, 3H), 4.24 (t, J = 7.0 Hz, 2H), 6.81 (s, 1H), 7.15 (d, J = 2.0 Hz, 1H), 7.26 (s, 1H), 7.38 (d, J = 2.0 Hz, 1H), 8.50 (s, 1H); MS m/z 513 (M^+). Anal. ($C_{26}H_{27}NO_{10}$) C, H, N.

1-(3-Amino-4,5-dimethoxyphenyl)-6,7-diethoxy-2,3-bis(hydroxymethyl)naphthalene Hydrochloride (7h). A solution of **10i** (8.0 g, 15 mmol) in THF (150 mL) and MeOH (75 mL) was hydrogenated over 10% Pd−C (2.0 g) at 40 psi and 25 °C for 7 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give an oil. To a suspension of LAH (1.1 g, 29 mmol) in THF (100 mL) was added a solution of the oil in THF (500 mL) at 10 °C, and the mixture was stirred at the same temperature for 1 h. To this reaction mixture were added dropwise water (1.1 mL), 15% aqueous NaOH (1.1 mL), and water (3.3 mL) successively at 10 °C, and the mixture was stirred at room temperature for 2 h. The resulting precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. Crystallization of the residue from Et_2O gave a solid. To a solution of the solid in AcOEt (50 mL) and MeOH (2 mL) was added a solution of HCl in 1,4-dioxane (24.1%, 3.8 mL, 15 mmol), and the mixture was concentrated under reduced pressure. Recrystallization of the residual hydrochloride from MeOH−Et_2O gave **7h** (3.7 g, 53%): mp 200−210 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 3H), 1.40 (t, J = 7.0 Hz, 3H), 3.30−4.00 (m, 4H), 3.78 (s, 3H), 3.91 (s, 3H), 3.93 (q, J = 7.0 Hz, 2H), 4.19 (q, J = 7.0 Hz, 2H), 4.59 (d, J = 12.0 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 6.28 (d, J = 2.0 Hz, 1H), 6.35 (d, J = 2.0 Hz, 1H), 6.82 (s, 1H), 7.10 (s, 1H), 7.84 (s, 1H); MS m/z 427 (M^+). Anal. ($C_{24}H_{29}NO_6 \cdot HCl \cdot 1.6H_2O$) C, H, N, Cl.

1-(3-Acetamido-4,5-dimethoxyphenyl)-2,3-bis(hydroxymethyl)-6,7-dimethoxynaphthalene (7i). A solution of **10i** (8.0 g, 15 mmol) in THF (150 mL) and MeOH (75 mL) was hydrogenated with H_2/Pd−C as in the case of **7h** and gave 1-(3-amino-4,5-dimethoxyphenyl)-6,7-dimethoxy-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene **(6i)** as a syrup. To a solution of **6i**, 4-(dimethylamino)pyridine (0.1 g), and triethylamine (1.4 mL, 10 mmol) in THF (50 mL) was added acetic anhydride (570 mg, 5.0 mmol) at 10 °C. The mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was dissolved in AcOEt (100 mL), washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$:acetone = 10:1) gave 1-(3-acetamido-4,5-dimethoxyphenyl)-6,7-dimethoxy-2,3-bis(methoxycarbonyl)-6,7-dimethoxynaphthalene **(6ii)** as a yellow foam which was reduced with LAH as in the case of **7h**. Crystallization of the products from AcOEt gave **7i** (4.80 g, 75%): mp 200−201 °C; ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H), 3.36−3.70 (br s, 2H), 3.75 (s, 3H), 3.85 (s, 3H), 4.00 (s, 6H), 4.60 (s, 2H), 4.83 (d, J = 12.0 Hz, 1H), 4.96 (d, J = 12.0 Hz, 1H), 6.72 (d, J = 1.7 Hz, 1H), 6.85 (s, 1H), 7.13 (s, 1H), 7.71 (s, 1H), 7.88 (br s, 2H); MS m/z 427 (M^+). Anal. ($C_{24}H_{27}NO_7$) C, H, N.

Method C (Scheme 1). 1-(3-Bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2,3-bis[(*tert*-butyldimethylsiloxy)methyl]naphthalene (11). To a stirred solution of **7k** (4.1 g, 8.9 mmol) in pyridine (10 mL) was added *tert*-butyldimethylsilyl chloride (3.44 g, 22.8 mmol) at 10 °C, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and a solution of the residue in Et_2O (50 mL) was washed with 5% aqueous citric acid and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from hexane gave **11** (4.5 g, 74%): mp 132−134 °C; ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6H), 0.21 (s, 6H), 0.90 (s, 9H), 1.05 (s, 9H), 3.76 (s, 3H), 3.86 (s, 3H), 3.96 (s, 3H), 4.03 (s, 3H), 4.53 (br s, 2H), 5.09 (br s, 2H), 6.72 (s, 1H), 6.85 (d, J = 1.5 Hz, 1H), 7.17 (s, 1H), 7.18 (d, J = 1.5 Hz, 1H), 7.90 (s, 1H); MS m/z 692 (M^+). Anal. ($C_{34}H_{51}BrO_6Si_2$) C, H, Br.

2,3-Bis[(*tert*-butyldimethylsiloxy)methyl]-1-(3-carboxy-4,5-dimethoxyphenyl)-6,7-dimethoxynaphthalene (12). To a stirred solution of **11** (2.0 g, 2.9 mmol) in Et_2O (50 mL) was added BuLi (2.0 mL, 3.2 mmol) at −70 °C under an atmosphere of nitrogen, and the mixture was stirred at the same temperature for 20 min. The mixture was bubbled with CO_2 gas (200 mL/min, 20 min) and stirred at the same temperature for 2 h. The reaction mixture was poured into a mixture of water (20 mL) and AcOEt (30 mL), and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from hexane gave **12** (1.8 g, 93%): mp 156−157 °C; ^{1}H NMR ($CDCl_3$) δ −0.08 (s, 3H), −0.05 (s, 3H), 0.16 (s, 3H), 0.18 (s, 3H), 0.82 (s, 9H), 1.02 (s, 9H), 3.70 (s, 3H), 3.87 (s, 3H), 4.00 (s, 3H), 4.13 (s, 3H), 4.40 (br s, 2H), 4.58 (br s, 2H), 6.60 (s, 1H), 7.13 (s, 1H), 7.15 (s, 1H), 7.66 (s, 1H), 7.90 (s, 1H), 12.25 (br s, 1H); MS m/z 656 (M^+). Anal. ($C_{35}H_{52}O_8Si_2$) C, H.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-[3-(*N*,*N*-dimethylcarbamoyl)-4,5-dimethoxyphenyl]naphthalene (7j). To a stirred solution of **12** (2.6 g, 4.0 mmol) in THF (30 mL) was added carbonyldiimidazole (CDI) (771 mg, 4.8 mmol) at 10 °C, and the mixture was stirred at room temperature for 20 min. To the mixture was added dimethylamine (50% MeOH solution, 2.0 mL, 20 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. To the residue was added a mixture of brine (20 mL) and $CHCl_3$ (30 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (hexane:AcOEt = 1:1) gave 1.7 g of a foam. To a stirred solution of the foam in THF (20 mL) was added 10% aqueous HCl (10 mL), and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the solution of the residue in $CHCl_3$ (50 mL) was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (hexane:AcOEt = 1:1) and crystallization from Et_2O gave **7j** (850 mg, 47%): mp 162−163 °C; ^{1}H NMR ($CDCl_3$) δ 2.95 (s, 3H), 3.07 (s, 3H), 3.30−3.80 (br s, 2H), 3.70 (s, 3H), 3.83 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 4.55 (s, 2H), 4.82 (s, 2H), 6.73 (s, 1H), 6.82 (s, 1H), 6.96 (s, 1H), 7.10 (s, 1H), 7.65 (s, 1H); MS m/z 455 (M^+). Anal. ($C_{25}H_{29}NO_7$) C, H, N.

Method D (Scheme 2). 2,3-Bis(acetoxymethyl)-6,7-dimethoxy-1-(4-pyridyl)naphthalene (13a). To a stirred solution of **7l** (6.5 g, 20 mmol) in CH_2Cl_2 (50 mL) were added acetic anhydride (6.12 g, 60 mmol) and triethylamine (6.1 g, 60 mmol) at 10 °C. The mixture was stirred at room temperature overnight. The reaction mixture was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from AcOEt/hexane gave **13a** (6.7 g, 82%): mp 112−114 °C; ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3H), 2.10 (s, 3H), 3.67 (s, 3H), 3.98 (s, 3H), 4.98 (s, 2H), 5.30 (s, 2H), 6.49 (s, 1H), 7.14 (s, 1H), 7.20−7.70 (m, 2H), 7.80 (s, 1H), 8.50−8.70 (m, 2H); MS *m*/*z* 409 (M^+). Anal. ($C_{23}H_{23}NO_6$) C, H, N.

2,3-Bis(acetoxymethyl)-6,7-dimethoxy-1-(4-pyridyl)-naphthalene *N*-Oxide (14a). To a stirred solution of **13a** (61.4 g, 0.15 mol) in CH_2Cl_2 (500 mL) was added *m*-CPBA (31.4 g, 0.18 mol) at 10 °C, and the mixture was stirred at room temperature for 3 h. The reaction mixture was successively washed with 10% aqueous $NaHSO_3$, saturated aqueous K_2CO_3, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from Et_2O gave **14a** (60.56 g, 95%): mp 210−212 °C; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H), 2.12 (s, 3H), 3.75 (s, 3H), 4.02 (s, 3H), 5.04 (s, 2H), 5.34 (s, 2H), 6.54 (s, 1H), 7.18 (s, 1H), 7.20−7.40 (m, 2H), 7.85 (s, 1H), 8.30−8.50 (m, 2H); MS *m*/*z* 425 (M^+). Anal. ($C_{23}H_{23}NO_7$) C, H, N.

2,3-Bis(acetoxymethyl)-6,7-dimethoxy-1-(2-oxopyrid-4-yl)naphthalene (15b). A mixture of **14a** (62.0 g, 0.146 mol) and acetic anhydride (300 mL) was heated under reflux overnight. The acetic anhydride was removed by evaporation. To a solution of the residue in MeOH (500 mL) was added 28% aqueous NH_3 (20 mL), and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and the residue was poured into a mixture of water (500 mL) and $CHCl_3$ (1 L). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Crystallization of the residue from AcOEt gave **15b** (47.2 g, 76%): mp 241−243 °C; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3H), 2.12 (s, 3H), 3.79−3.95 (m, 1H), 3.83 (s, 3H), 4.01 (s, 3H), 5.16 (s, 2H), 5.34 (s, 2H), 6.32 (s, 1H), 6.63 (s, 1H), 6.81 (s, 1H), 7.18 (s, 1H), 7.58 (s, 1H), 7.83 (br s, 1H); MS *m*/*z* 425 (M^+). Anal. ($C_{23}H_{23}NO_7$) C, H, N.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-(2-oxopyrid-4-yl)naphthalene (15a). To a solution of 10% NH_3 in MeOH (200 mL) was added **15b** (2.88 g, 6.8 mmol), and the mixture was stirred at room temperature overnight. The resulting mixture was concentrated under reduced pressure, and crystallization of the residue from Et_2O gave **15a** (1.5 g, 65%): mp 242−244 °C; ^{1}H NMR (DMSO-d_6) δ 3.74 (s, 3H), 3.93 (s, 3H), 4.20−4.60 (m, 2H), 4.52 (s, 2H), 4.86 (s, 2H), 6.16 (dd, J = 1.5, 7.0 Hz, 1H), 6.42 (d, J = 1.5 Hz, 1H), 6.80 (s, 1H), 7.21 (s, 1H), 7.43 (d, J = 7.0 Hz, 1H), 7.82 (s, 1H), 11.43−11.70 (m, 1H); MS *m*/*z* 341 (M^+). Anal. ($C_{19}H_{19}NO_5$) C, H, N.

2,3-Bis(acetoxymethyl)-6,7-dimethoxy-1-(1-methyl-2-oxopyrid-4-yl)naphthalene (16a). To a suspension of NaH (60%, 440 mg, 11 mmol) in DMF (30 mL) was added a solution of **15b** (4.25 g, 10 mmol) in DMF (70 mL) at 10 °C, and the mixture was stirred at room temperature for 30 min. Methyl iodide (2.13 g, 15 mmol) was added to the mixture at 10 °C, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was poured into a mixture of water (50 mL) and AcOEt (100 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$:acetone = 10:1) gave **16a** as a syrup (2.24 g, 51%): ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3H), 2.12 (s, 3H), 3.13 (s, 3H), 3.75 (s, 3H), 4.01 (s, 3H), 4.55 (s, 2H), 4.84 (s, 2H), 6.13 (dd, J = 1.5, 7.0 Hz, 1H), 6.47 (d, J = 1.5 Hz, 1H), 6.80 (s, 1H), 7.11 (s, 1H), 7.45 (d, J = 7.0 Hz, 1H), 7.81 (s, 1H); MS *m*/*z* 439 (M^+). Anal. ($C_{24}H_{25}NO_7$) C, H, N.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-(1-methyl-2-oxopyrid-4-yl)naphthalene (17a). To a solution of **16a** (878 mg, 2 mmol) in MeOH (30 mL) was added NaOMe (270 mg, 5 mmol), and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added acetic acid (300 mg, 5 mmol), and the solution was concentrated under reduced pressure. Purification of the residue by silica gel chromatography ($CHCl_3$:MeOH = 10:1) followed by crystallization from AcOEt gave **17a** (227 mg, 32%): mp 176−178 °C; ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 3H), 3.73 (s, 3H), 3.95 (s, 3H), 4.23 (br s, 2H), 4.57 (br s, 2H), 4.84 (br s, 2H), 6.10 (m, 1H), 6.41 (br s, 1H), 6.70 (s, 1H), 7.00 (s, 1H), 7.35 (s, 1H), 7.62 (s, 1H); MS *m*/*z* 355 (M^+). Anal. ($C_{20}H_{21}NO_5$) C, H, N.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-(1-methyl-2-oxopyrid-6-yl)naphthalene (17i): yield 54%; mp 177−178 °C; ^{1}H NMR ($CDCl_3$) δ 3.13 (s, 3H), 3.75 (s, 3H), 3.97 (s, 3H), 4.50 (br s, 2H), 4.61 (s, 2H), 4.88 (s, 2H), 6.25 (d, J = 7.0 Hz, 1H), 6.50 (s, 1H), 6.63 (d, J = 9.0 Hz, 1H), 7.13 (s, 1H), 7.43 (dd, J = 7.0, 9.0 Hz, 1H), 7.79 (s, 1H); MS *m*/*z* 355 (M^+). Anal. ($C_{20}H_{21}NO_5$) C, H, N.

Method E (Scheme 2). 6,7-Diethoxy-2,3-bis(methoxycarbonyl)-1-(4-pyridyl)naphthalene *N*-Oxide (18f). This compound was prepared as described for **14:** yield 94%; mp 177−178 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (t, J = 7.0 Hz, 3H), 1.56 (t, J = 7.0 Hz, 3H), 3.70 (s, 3H), 3.95 (s, 3H), 3.96 (q, J = 7.0 Hz, 2H), 4.25 (q, J = 7.0 Hz, 2H), 6.65 (s, 1H), 7.26 (s, 1H), 7.31 (s, 1H), 7.34 (s, 1H), 8.34 (s, 1H), 8.38 (s, 1H), 8.47 (s, 1H); MS *m*/*z* 425 (M^+). Anal. ($C_{23}H_{23}NO_7$) C, H, N.

6,7-Diethoxy-2,3-bis(methoxycarbonyl)-1-(2-oxopyrid-4-yl)naphthalene (19f). This compound was prepared as described for **15**: yield 60%; mp 234−235 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.48 (t, J = 7.0 Hz, 3H), 3.79 (s, 3H), 3.94 (s, 3H), 3.90−4.20 (m, 2H), 4.25 (q, J = 7.0 Hz, 2H), 6.36 (dd, J = 1.5, 6.6 Hz, 1H), 6.65 (d, J = 1.0 Hz, 2H), 6.89 (s, 1H), 7.24 (s, 1H), 7.51 (d, J = 6.6 Hz, 1H), 8.44 (s, 1H); MS *m*/*z* 425 (M^+). Anal. ($C_{22}H_{23}NO_7$) C, H, N.

6,7-Diethoxy-2,3-bis(methoxycarbonyl)-1-[1-(2-methoxyethyl)-2-oxopyrid-4-yl]naphthalene (20f). This compound was prepared as described for **16**: yield 55%; mp 103−104 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.45 (t, J = 7.0 Hz, 3H), 1.55 (t, J = 6.9 Hz, 3H), 3.36 (s, 3H), 3.75 (s, 6H), 3.65−3.85 (m, 2H), 3.98−4.33 (m, 6H), 6.17 (dd, J = 1.9, 6.9 Hz, 1H), 6.59 (d, J = 1.6 Hz, 1H), 6.91 (s, 1H), 7.22 (s, 1H), 7.44 (d, J = 7.0 Hz, 1H), 8.42 (s, 1H); MS *m*/*z* 483 (M^+). Anal. ($C_{26}H_{29}NO_8$) C, H, N.

6,7-Diethoxy-2,3-bis(hydroxymethyl)-1-[1-(2-methoxyethyl)-2-oxopyrid-4-yl]naphthalene (17f). To a stirred suspension of **20f** (2.56 g, 5.3 mmol) and $NaBH_4$ (1.0 g, 26.5 mmol) in THF (42 mL) was added MeOH (8.5 mL) dropwise under reflux over 1 h, and the mixture was stirred under reflux for another 1 h. The reaction mixture was allowed to cooled to room temperature and concentrated under reduced pressure. The residue was poured into a mixture of 10% aqueous HCl (50 mL) and $CHCl_3$ (100 mL), and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from Et_2O followed by recrystallization from EtOH−H_2O gave **17f** as colorless needles (1.97 g, 87%): mp 126−127 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.42 (t, J = 7.0 Hz, 3H), 1.54 (t, J = 7.0 Hz, 3H), 3.37 (s, 3H), 3.75 (t, J = 5.0 Hz, 2H), 3.79−4.34 (m, 7H), 4.61−4.71 (m, 2H), 4.78−4.97 (m, 3H), 6.13 (dd, J = 1.8, 6.8 Hz, 1H), 6.49 (d, J = 1.8 Hz, 1H), 6.71 (s, 1H), 7.06 (s, 1H), 7.45 (d, J = 6.8 Hz, 1H), 7.66 (s, 1H); MS *m*/*z* 427 (M^+). Anal. ($C_{24}H_{29}NO_6$) C, H, N.

1-(1-Butyl-2-oxopyrid-4-yl)-6,7-dimethoxy-2,3-bis(hydroxymethyl)naphthalene (17b): yield 36%; mp 159−161 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 7.3 Hz, 3H), 1.33−1.90 (m, 4H), 3.75 (s, 3H), 3.90−4.12 (m, 5H), 3.99 (s, 3H), 4.20−4.43 (m, 2H), 4.58−5.00 (m, 2H), 6.38 (dd, J = 1.8, 6.8 Hz, 1H), 6.42 (d, J = 1.8 Hz, 1H), 6.61 (s, 1H),7.03 (s, 1H), 7.35 (d, J = 6.8 Hz, 1H), 7.67 (s, 1H); MS *m*/*z* 397 (M^+). Anal. ($C_{23}H_{27}NO_4$) C, H, N.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-[1-(2-methoxyethyl)-2-oxopyrid-4-yl]naphthalene (17c): yield 33%; mp 124−126 °C; ^{1}H NMR (DMSO-d_6) δ 3.31 (s, 3H), 3.57−3.80 (m, 2H), 3.68 (s, 3H), 3.91 (s, 3H), 4.10−4.55 (m, 4H), 4.80−4.93 (m, 3H), 5.29 (t, J = 5.2 Hz, 2H), 6.17 (d, J = 6.8 Hz, 1H), 6.39 (s, 1H), 6.76 (s, 1H), 7.38 (s, 1H), 7.74 (d, J = 6.8 Hz, 1H), 7.90 (s, 1H); MS *m*/*z* 399 (M^+). Anal. ($C_{22}H_{25}NO_6$) C, H, N.

1-(1-Butyl-2-oxopyrid-4-yl)-7-ethoxy-2,3-bis(hydroxymethyl)-6-methoxynaphthalene (17d): yield 88%; mp 164−166 °C dec; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.21−1.44 (m, 2H), 1.30 (t, J = 6.9 Hz, 3H), 1.59−1.82 (m, 2H), 3.80−4.08 (m, 4H), 3.89 (s, 3H), 4.29−4.53 (m, 2H), 4.76−4.89 (m, 3H), 5.27 (t, J = 10.8 Hz, 1H), 6.15 (dd, J = 1.8, 6.8 Hz, 1H), 6.34 (d, J = 1.8 Hz, 1H), 6.72 (s, 1H), 7.36 (s, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.87 (s, 1H); MS m/z 411 (M^+), 393 (M − 18). Anal. ($C_{24}H_{29}NO_5$) C, H, N.

1-(1-Butyl-2-oxopyrid-4-yl)-6,7-diethoxy-2,3-bis(hydroxymethyl)naphthalene (17e): yield 88%; mp 149−150 °C dec; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.21−1.44 (m, 2H), 1.30 (t, J = 6.9 Hz, 3H), 1.54 (t, J = 7.0 Hz, 3H), 1.59−1.82 (m, 4H), 3.80−4.08 (m, 4H), 4.29−4.53 (m, 2H), 4.76−4.89 (m, 4H), 5.27 (t, J = 10.8 Hz, 1H), 6.15 (dd, J = 1.8, 6.8 Hz, 1H), 6.34 (d, J = 1.8 Hz, 1H), 6.72 (s, 1H), 7.36 (s, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.87 (s, 1H); MS m/z 425 (M^+). Anal. ($C_{25}H_{31}NO_5$) C, H, N.

6-Ethoxy-2,3-bis(hydroxymethyl)-7-methoxy-1-[1-(2-methoxyethyl)-2-oxopyrid-4-yl]naphthalene (17g): yield 87%; mp 162−164 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 7.0 Hz, 3H), 3.29 (s, 3H), 3.60−3.75 (m, 2H), 3.66 (s, 3H), 4.06−4.24 (m, 4H), 4.30−4.55 (m, 2H), 4.77−4.92 (m, 3H), 5.27 (t, J = 5.3 Hz, 1H), 6.15 (dd, J = 1.8, 6.8 Hz, 1H), 6.38 (d, J = 1.8 Hz, 1H), 6.75 (s, 1H), 7.35 (s, 1H), 7.72 (d, J = 6.8 Hz, 1H), 7.86 (s, 1H); MS m/z 413 (M^+), 355. Anal. ($C_{23}H_{27}NO_6$) C, H, N.

2,3-Bis(acetoxymethyl)-1-(1-butyl-2-oxopyrid-4-yl)-6,7-dimethoxynaphthalene (17h). This compound was prepared as described for **16a**: yield 77%; mp 134−135 °C; ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 3H), 1.33−1.56 (m, 2H), 1.73−1.95 (m, 2H), 1.92 (s, 3H), 2.04 (s, 3H), 3.82 (s, 3H), 4.01 (s, 3H), 3.96−4.12 (m, 2H), 5.03 (d, J = 12.2 Hz, 1H), 5.20 (d, J = 12.2 Hz, 1H), 5.33 (s, 2H), 6.13 (dd, J = 1.8, 6.8 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 6.79 (s, 1H), 7.16 (s, 1H), 7.38 (d, J = 6.8 Hz, 1H), 7.81 (s, 1H); MS m/z 481 (M^+). Anal. ($C_{27}H_{31}NO_7 \cdot 0.3$ AcOEt) C, H, N.

Method F (Scheme 3). 3a,4,9,9a-Tetrahydro-6-methoxy-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (23c). To a stirred solution of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) [prepared from diisopropylamine (6.34 g, 58.2 mmol) and BuLi (36.4 mL, 58.2 mmol) in THF (30 mL)] was added a solution of **21** (R^1 = 2-MeO, 10.0 g, 48.5 mmol) in THF (30 mL) at −70 °C under an atmosphere of nitrogen. The mixture was stirred at the same temperature for 10 min. To this mixture was added a solution of 3,4,5-trimethoxybenzaldehyde (9.51 g, 48.5 mmol) in THF (30 mL), and the resulting mixture was stirred at the same temperature for 30 min. The reaction mixture was poured into a mixture of 10% aqueous HCl (100 mL) and AcOEt (200 mL). The organic layer was separated, washed with water (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. To the solution of the residue in CH_2Cl_2 (300 mL) was added trifluoroacetic acid (TFA) (30 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was washed with water (100 mL) and saturated aqueous $NaHCO_3$ (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from AcOEt gave **23c** (7.08 g, 38%): mp 195−196 °C; ^{1}H NMR ($CDCl_3$) δ 2.30−2.80 (m, 2H), 2.80−3.20 (m, 2H), 3.72, (s, 6H), 3.80−4.20 (m, 2H), 3.90 (s, 6H), 4.30−4.70 (m, 1H), 6.30 (s, 2H), 6.40−6.80 (m, 3H), MS m/z 384 (M^+). Anal. ($C_{22}H_{24}O_6$) C, H.

6-Methoxy-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]-furan-1(3*H*)-one (24c). A mixture of **23c** (7.68 g, 20 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (10.0 g, 44 mmol) in benzene (100 mL) was heated under reflux for 8 h. After cooling, the mixture was concentrated under reduced pressure. To the residue was added a mixture of $CHCl_3$ (300 mL) and water (150 mL), and resulting precipitate was removed by filtration through celite. The organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL × 3) and water (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from MeOH gave **24c** (3.88 g, 51%): mp 189−190 °C; ^{1}H NMR (DMSO-d_6) δ 3.75 (s, 6H), 3.88 (s, 6H), 5.30 (s, 2H), 6.45 (s, 1H), 6.90−7.30 (m, 3H), 7.50-7.80 (m, 2H); MS m/z 380 (M^+). Anal. ($C_{22}H_{20}O_6$) C, H.

6,7-Dimethoxy-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (24a). This compound was prepared as described for **24c**: yield 64%; mp 228−229 °C (reported[14] mp 238−239 °C); ^{1}H NMR (DMSO-d_6) δ 3.70 (s, 3H), 3.79 (s, 3H), 3.80 (s, 6H), 3.96 (s, 3H), 6.70 (s, 2H), 7.12 (s, 2H), 7.50 (s, 1H), 7.95 (s, 1H), 8.31 (s, 1H); MS m/z 410 (M^+). Anal. ($C_{22}H_{20}O_6$) C, H.

2,3-Bis(hydroxymethyl)-6-methoxy-1-(3,4,5-trimethoxyphenyl)naphthalene (7c). This compound was prepared as described for **7gg**: yield 60%; mp 124−125 °C; ^{1}H NMR (DMSO-d_6) δ 3.25 (s, 3H), 3.70 (s, 6H), 3.80 (s, 3H), 4.28 (d, J = 6.0 Hz, 2H), 4.63 (t, J = 6.0 Hz, 1H), 4.80 (d, J = 6.0 Hz, 2H), 5.20 (t, J = 6.0 Hz, 1H), 6.46 (s, 2H), 6.80−7.00 (m, 1H), 7.00−7.30 (m, 2H), 7.76 (s, 1H); MS m/z 384 (M^+). Anal. ($C_{22}H_{24}O_6$) C, H.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)naphthalene (7a): yield 79%; mp 124−126 °C; ^{1}H NMR ($CDCl_3$) δ 3.30−4.10 (m, 2H), 3.70 (s, 3H), 3.80 (s, 6H), 3.93 (s, 3H), 3.96 (s, 3H), 4.60 (s, 2H), 4.85 (s, 2H), 6.55 (s, 2H), 6.76 (s, 1H), 7.08 (s, 1H), 7.64 (s, 1H); MS m/z 410 (M^+). Anal. ($C_{23}H_{26}O_7$) C, H.

2,3-Bis(hydroxymethyl)-6,7-(methylenedioxy)-1-(3,4,5-trimethoxyphenyl)naphthalene (7b): yield 85%; mp 254−255 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.68 (s, 9H), 4.10−4.40 (m, 2H), 4.50−4.87 (m, 3H), 5.00−5.23 (m, 1H), 5.92 (s, 2H), 6.44 (s, 3H), 7.16 (s, 1H), 7.67 (s, 1H); MS m/z 398 (M^+), 380 (M − 18). Anal. ($C_{22}H_{22}O_7$) C, H.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-(3,4-dimethoxyphenyl)naphthalene (7f): yield 69%; mp 186−187 °C; ^{1}H NMR ($CDCl_3$) δ 2.80−3.50 (m, 2H), 3.62 (s, 3H), 3.75 (s, 3H), 3.88 (s, 6H), 4.50 (br s, 2H), 4.80 (br s, 2H), 6.50−7.10 (m, 5H), 7.50 (s, 1H); MS m/z 384 (M^+). Anal. ($C_{22}H_{24}O_6$) C, H.

Biological Methods. Isolation of Phosphodiesterase Isozymes. The method of Reeves *et al.*[17] was modified to isolate PDE isozymes. Briefly, male guinea pigs were killed by decapitation, and the hearts and lungs were immediately excised and rinsed in ice-cold saline. Samples of cardiac ventricle and lung were frozen on solid CO_2 after removal and stored at −80 °C until use. Tissue samples were minced and homogenized in 4 volumes of 20 mM Bis-tris/5 mM 2-mercaptoethanol/50 mM sodium acetate/2 mM benzamidine/3 mM EDTA/2 mM EGTA/2000 units/mL aprotinin/10 μM leupeptin/10 μM pepstatin A, pH 6.5, by using a Polytron PT-20. Phenylmethanesulfonyl fluoride dissolved in dimethyl sulfoxide (DMSO) was added to the buffer immediately before homogenization to give a final concentration of 0.2 mM. The homogenate was then centrifuged for 30 min at 25000G and the resulting supernatant applied to a column of DEAE-Sepharose CL-6B. The PDEs were eluted from the column by using a continuous 50−1000 mM sodium acetate gradient (pH 6.5, containing 2-mercaptoethanol). Fractions were collected and assayed for cAMP and cGMP PDE activity. Fractions containing high levels of type I or type III PDE activity from cardiac ventricle, and type IV or type V PDE activities from lung were pooled. The combined PDE fractions were diluted to 70% with ethylene glycol and stored at −20 °C.

Assay of Phosphodiestrase Activity. PDE activity was determined by a modification of the method of Thompson *et al.*[18] The reaction mixture contained 40 mM Tris-HCl, pH 8.0, 5 mM $MgCl_2$, and 4 mM 2-mercaptoethanol. In evaluation of the inhibitor effects of the different agents examined in type I, type III, type IV, and type V PDE, the protein concentration in the assay was adjusted to ensure that hydrolysis of substrate ([^{3}H]cAMP or [^{3}H]cGMP) did not exceed 20% of the available substrate in the absence of inhibitor. The concentration of substrate was 1.0 μM for these studies. All agents examined were dissolved in DMSO. Following addition of the substrate, the contents were mixed and incubated for 20 min at 30 °C. Assays were performed in triplicate at three to four different inhibitor concentrations, the mean of the determinations at each concentration was plotted, and the IC_{50} values were determined graphically. IC_{50} values presented are from representative experiments.

Histamine-Induced Bronchoconstriction in Anesthetized Guinea Pigs. Male Hartley guinea pigs (Japan SLC, Inc.) weighing 250−700 g were used. Guinea pigs were cannulated in the trachea under anesthesia with α-chloralose (120 mg/kg, iv) and ventilated with 10 mL/kg per stroke of air at a rate of 60 strokes/min (Harvard 683). Spontaneous breathing was abolished with gallamine triethiodide (5 mg/kg, iv). Pulmonary inflation pressure (PIP), an index of bronchospasm, was measured with a pressure transducer (Nihonkoden TP-400T) and recorded on a Linearcorder (Graphtec WR3701). At the same time, heart rate was monitored by cardiotachography utilizing the R wave of ECG (standard limb lead II) as trigger. Bronchoconstriction was induced by intravenous injection of histamine dihydrochloride (2 μg/kg) *via* the lateral saphenous vein at 10 min intervals. Test compounds were suspended in saline with the aid of Tween 80 and administered intravenously 1 min before histamine injection.

Antigen-Induced Bronchoconstriction in Anesthetized Guinea Pigs. Anti-ovalbumin (anti-OA) rabbit antiserum was prepared from rabbits (2.0−2.5 kg, Japan KBL) which had been immunized by injecting an 10 mg of OA emulsified with Freund's complete adjuvant intramuscularly four times weekly. The serum was obtained 7 days after the last immunization and frozen at <−70 °C until use. The antibody titers of antiserum thus obtained were $>10^4$ times as determined by the guinea pig 4 h PCA reaction test. Guinea pigs were sensitized by iv administration of anti-OA rabbit antiserum (0.5 mL/kg). Twenty to 28 h later, animals were challenged by antigen (30 μg/kg, iv).

The animals were anesthetized, cannulated, and immobilized in the same way as for histamine challenge except that they were ventilated at a rate of 15 mL/kg per stroke. The changes of pulmonary mechanics were measured by the method of Konzett and Rössler[19] using a differential pressure transducer (Nihon Kohden, model TP-602) connected to the tracheal cannula. The increase in the respiratory overflow volume provoked by antigen challenge was expressed as a percentage of the maximum overflow volume obtained by clamping off the trachea. Test compounds were administered iv 2 min before antigen challenge. The effects of drugs were expressed as the dose which suppressed antigen-induced bronchoconstriction by 50% (ED_{50}).

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