Novel, Potent, and Selective Phosphodiesterase-4 Inhibitors as Antiasthmatic Agents: Synthesis and Biological Activities of a Series of 1-Pyridylnaphthalene Derivatives

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The structural requirements for potent and selective PDE4 inhibition were revealed in a 1-pyridylnaphthalene series, and the best compound (**3kg**, T-2585·HCl) was chosen for further biological evaluation (PDE4 inhibition IC_{50} = 0.13 nM, selectivity PDE3/4 ratio = 14 000). Compound **3kg** showed potent antispasmogenic activities (ED_{50} = 0.063 mg/kg for reduction of antigen-induced bronchoconstriction, intravenously; ED_{50} = 0.033 mg/kg for reduction of histamine-induced bronchoconstriction, intraduodenally) in guinea pigs with little cardiovascular effects. Furthermore, **3kg** induced significantly weaker emetic effects than RP73401 after oral administration in ferrets and intravenous administration in dogs (**3kg**, none of 4 ferrets vomited at a dose of 10 mg/kg, po and none of 8 dogs vomited at a dose of 0.3 mg/kg, iv; RP73401, 4 of 8 ferrets vomited at a dose of 3 mg/kg, po and 6 of 8 dogs vomited at a dose of 0.3 mg/kg, iv); that is compatible with the lower affinity for the high-affinity rolipram binding site (**3kg**, 2.6 nM; RP73401, 0.85 nM). This may imply that **3kg** has an improved therapeutic ratio because of a broad margin between the K_i value of binding affinity and the IC_{50} value of PDE4 inhibition (ratio = 0.050).

Introduction

Asthma is a chronic inflammatory disease of the airways, with the most characteristic symptoms being a variable airway obstruction and hyperresponsiveness. The development of highly effective drugs would be beneficial, because the mortality and morbidity due to asthma is increasing worldwide despite extensive treatment.

Cyclic nucleotide phosphodiesterases (PDEs) play a key role in the metabolism of purine cyclic nucleotides, cAMP and cGMP. PDEs have been classified into seven structurally, biochemically, and pharmacologically distinct families.[1] Among them, cAMP-PDE (PDE4), consisting of four gene products (PDE4A to PDE4D), is characterized by selective, high-affinity hydrolysis of cAMP.[2] Inhibition of PDE4 results in the increase in cellular levels of cAMP, which contributes to both the relaxation of airway smooth muscle and the prevention of proinflammatory cell activation.[3]

With a considerable amount of interest and excitement, a large number of selective PDE4 inhibitors have been reported.[4] The majority of them are classified into three categories: rolipram-related compounds, xanthine derivatives exemplified by theophilline, and nitraquazone analogues.[4a] Despite significant efforts to discover potential antiasthmatic agents based on selective PDE4 inhibition, side effects including emesis and cardiovascular effects have limited their therapeutic potential.[5]

A series of 1-arylnaphthalene lignans having a selective PDE4 inhibitory activity was reported by Iwasaki et al. as a new structural class.[6] In connection with our efforts in search of new naphthalene derivatives with an improved therapeutic ratio, we now disclose 1-pyridylnaphthalene derivatives having potent antispasmogenic activities with low emetic and cardiovascular effects.

Chemistry

1 (T-440), compound **2**, and rolipram-related compounds **4**−**8**[7] possess both an aromatic moiety and a carbonyl group (Scheme 1). A topological model of the PDE4 pharmacophore was reported by Marivet.[8] We envisaged that the three-dimensional space location of a carbonyl group relative to an aromatic ring is also desirable for the expression of PDE4 inhibitory activity in the 1-arylnaphthalene series.

To enhance the potency of PDE4 inhibition and improve the isozyme selectivity against the other types of PDEs, we designed compound **3** as a hybrid compound of **1** (T-440) and compound **2**, as shown in Scheme 1.[6] In this approach, (1) the naphthalene part (A,B-ring) was fixed, (2) the heterocyclic compound having a carbonyl group (D-ring) was introduced, and (3) the pyridyl group (C-ring) was selected on the basis of the scope of chemical modification.

Compound **3** was divided into four parts (A−D-rings), and the modification of each part was carried out in the following procedures: (i) introduction of heterocyclic compounds containing a carbonyl group as the D-ring, (ii) preparation of regioisomers of the pyridyl ring for the C-ring, (iii) conversion of substituents on the B-ring, and (iv) transformation of substituents on the A-ring. The desired compound **3** was obtained by means of the catalytic Ullmann reaction (method A, Scheme 3) or

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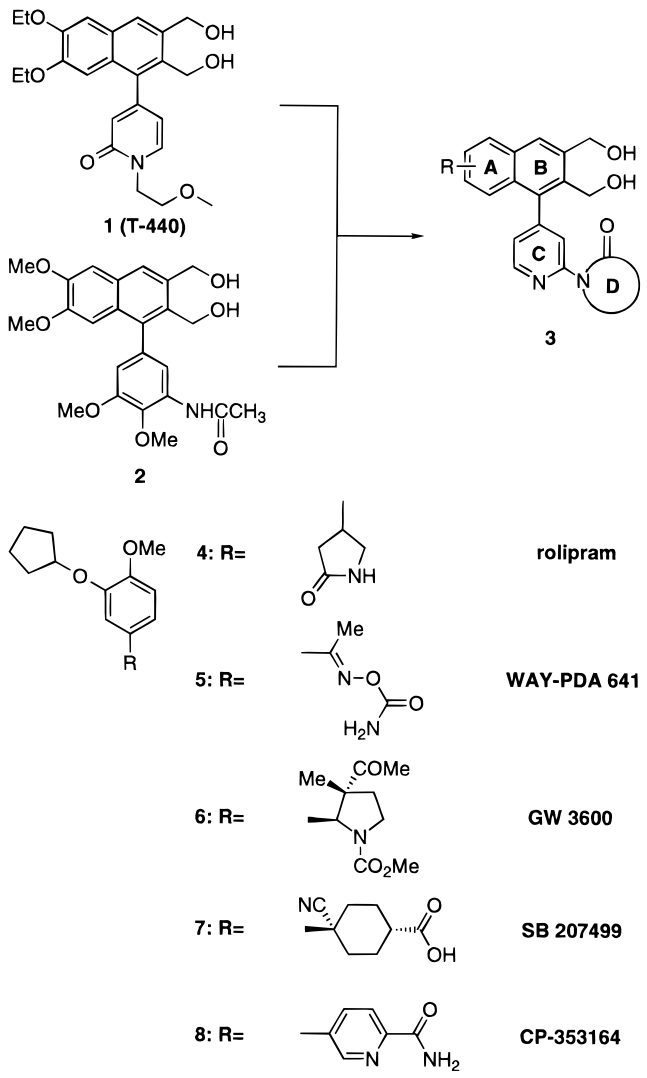
Scheme 1



phthalazinone cyclization (method B, Scheme 4) from the key intermediate 1-(halogenopyridyl)naphthalene (Scheme 2).

As shown in Scheme 2, hydroxy acetals **10** were prepared by the usual method from the bromo acetals **9**.[9] 1-(Halogenopyridyl)naphthalenes **11a**−**e**,**h**−**m** were synthesized by the Diels−Alder reaction of isobenzofurans generated from **10** with dimethyl fumarate or methyl acrylate, followed by aromatization with BF_3·Et_2O.[10]

Compounds **3aa**−**ah** were synthesized by reduction of the corresponding ester **11a** with $NaBH_4$−MeOH, followed by the Ullmann condensation with heterocyclic compounds having an −NH− moiety in the presence of a catalytic amount of CuI (Scheme 3).[11] Bis(methoxycarbonyl) analogue **13** was obtained from the corresponding **11a** by the catalytic Ullmann reaction. Bis(acetoxymethyl) analogue **14** was prepared by acetylation of the corresponding bis(hydroxymethyl) **3ag** with acetic anhydride. Regioisomers of pyridine (C-ring) (**15** and **16**) and **3dg** having no substituents on the C-6 and C-7 positions of naphthalene were prepared in a similar manner as described above. Method A is widely applicable to the synthesis of various compounds containing an −NH− moiety in the D-ring.

On the other hand, compounds having a phthalazinone moiety were effectively synthesized by method B. Compounds **3eg**,**gg**−**kg** having alkoxy substituents on the C-6 and C-7 positions were obtained by reduction of the corresponding esters **11e**,**g**−**k** with Red-Al, followed successively by the reaction with hydrazine hydrate and by cyclization with 2-(3-pyridinoyl)benzoic acid (Scheme 4). 3-Hydroxymethyl and 2-hydroxymethyl analogues **18lg**,**mg** were prepared by the same reactions as described above.

Biological Results and Discussion

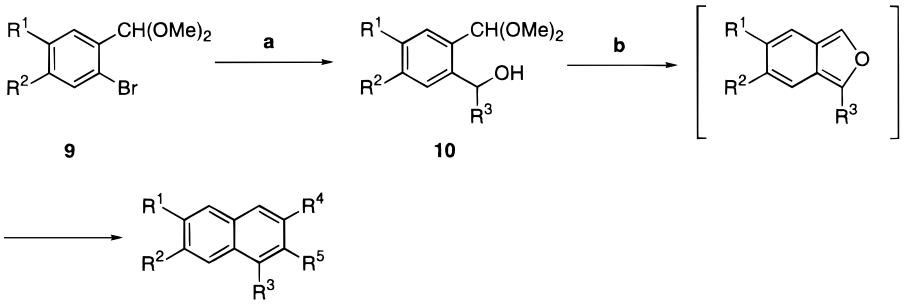
The compounds reported in this paper were evaluated by inhibitory activities to the five different forms of PDEs isolated from guinea pig cardiac ventricle (PDE1, -2, and -3) and lung (PDE4 and -5) in vitro (Table 1). Selected compounds on the basis of the PDE4 inhibitory activity were next evaluated for their potency to inhibit antigen-induced bronchoconstriction (intravenously) and histamine-induced bronchoconstriction (intraduodenally) 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). Third, further selected compounds based on antispasmogenic activities were evaluated for their affinity for the high-affinity rolipram binding site isolated from guinea pig brain and for emetic effects in ferrets and dogs after oral and intravenous administration, respectively (Table 3).

Phosphodiesterase Inhibition. In the transformation of the D-ring, PDE4 inhibitory activity increased in the order of monocyclic pyridone **3aa**, bicyclic quinolone **3ab**, and tricyclic phenanthridinone **3ac** (IC_{50}: **3aa** 80 nM, **3ab** 2.8 nM, **3ac** 0.20 nM; Table 1). The importance of the position of the carbonyl group in the D-ring is evident from the comparison of the potency of PDE4 inhibitory activity between **3ab** and **3ad**. 2-Quinolone derivative **3ab** was 14 times more potent than 4-quinolone derivative **3ad** (Table 1). The lead compound **3ae** having a phthalazinone moiety showed potent inhibitory activity against PDE4 (IC_{50} = 0.68 nM) and exhibited a moderate selectivity for PDE4 over PDE3 (selectivity ratio = 370).

Introduction of the pyridyl group on the 4-position of the phthalazinone moiety of the lead compound **3ae** afforded three regioisomeric 4-pyridylphthalazinone derivatives (**3af**−**ah**). 4-(3-Pyridyl)phthalazinone derivative **3ag** showed potent PDE4 inhibitory activity (IC_{50} = 0.63 nM) similar to 4-(2-pyridyl)phthalazinone and 4-(4-pyridyl)phthalazinone derivatives **3af**,**ah** (IC_{50} = 0.55, 0.49 nM) and exhibited virtually the same selectivity for PDE4 over PDE3 as **3af**,**ah** (Table 1). It was difficult to select a compound for further chemical modification among three regioisomers based on PDE inhibitions. From antispasmogenic activities and cardiovascular effects of **3af**−**ah** discussed in the next section (Table 2), **3ag** was chosen for further chemical modifications; that is, the 4-(3-pyridyl)phthalazinone moiety was fixed as the D-ring.

Bis(methoxycarbonyl) derivative **13** and bis(acetoxymethyl) derivative **14** showed remarkably reduced PDE4 inhibitory activities (IC_{50} = 150, 190 nM), compared with **3ag** (IC_{50} = 0.63 nM). Next, 3-hydroxymethyl

Scheme 2[a]



11a: $R^1=R^2$=MeO, R^3=2-bromo-4-pyridyl, $R^4=R^5$=COOMe
11b: $R^1=R^2$=MeO, R^3=2-bromo-5-pyridyl, $R^4=R^5$=COOMe
11c: $R^1=R^2$=MeO, R^3=2-bromo-6-pyridyl, $R^4=R^5$=COOMe
11d: $R^1=R^2$=H, R^3=2-bromo-4-pyridyl, $R^4=R^5$=COOMe
11e: $R^1=PhCH_2O$, R^2=MeO, R^3=2-chloro-4-pyridyl, $R^4=R^5$=COOMe
11h: R^1=MeO, $R^2=PhCH_2O$, R^3=2-chloro-4-pyridyl, $R^4=R^5$=COOMe
11i: R^1=EtO, R^2=MeO, R^3=2-chloro-4-pyridyl, $R^4=R^5$=COOMe
11j: R^1=MeO, R^2=EtO, R^3=2-chloro-4-pyridyl, $R^4=R^5$=COOMe
11k: $R^1=R^2$=EtO, R^3=2-chloro-4-pyridyl, $R^4=R^5$=COOMe
11l: $R^1=R^2$=MeO, R^3=2-chloro-4-pyridyl, R^4=COOMe, R^5=H
11m: $R^1=R^2$=MeO, R^3=2-chloro-4-pyridyl, R^4=H, R^5=COOMe

[a] Reagents and conditions: (a) *n*-BuLi, R^3CHO/THF, −70 °C; (b) (1) dimethyl fumarate or methyl acrylate, AcOH/toluene or xylene, reflux, (2) $BF_3{\cdot}Et_2O/CH_3CN$, reflux or 25 °C.

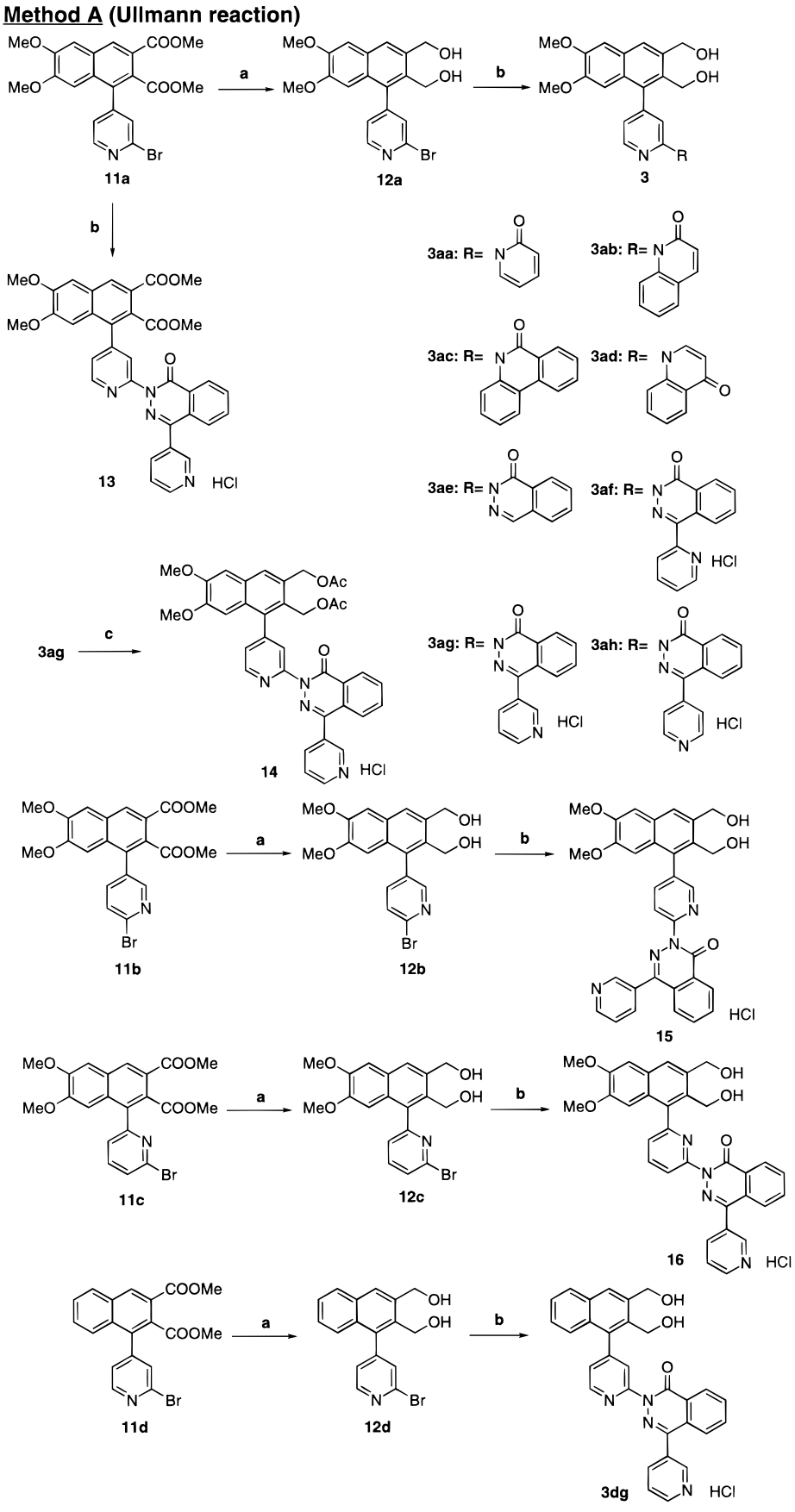
derivative **18lg** and 2-hydroxymethyl derivative **18mg** were synthesized to identify which hydroxymethyl group is necessary for the activity. **18lg** retained the activity (IC_{50} = 0.70 nM), though **18mg** resulted in a significant loss in activity (IC_{50} = 31 nM). From the above results, it is concluded that the 3-hydroxymethyl group of **3ag** plays an important role in PDE4 inhibitory activity.

Next we paid attention to regioisomers of the C-ring because of the importance of three-dimensional relationships between the carbonyl group in the D-ring and the 3-hydroxymethyl group on the B-ring. 2,5-Disubstituted pyridine derivative **15**, having the naphthyl and phthalazinyl groups in a para position to each other, showed a great decrease of activity (IC_{50} = 40 nM) compared with 2,4-disubstituted pyridine derivative **3ag**, having the naphthyl and phthalazinyl groups in a meta position to each other (IC_{50} = 0.63 nM). It was unexpected that a significant drop of activity was observed in 2,6-disubstituted pyridine derivative **16** (IC_{50} = 15 nM). This suggests that the conformation of **3ag** is very important to exert the potent activity, and the three-dimensional locations of the carbonyl group in the D-ring and the 3-hydroxymethyl group on the B-ring are properly controlled by both hydrogens on the 3- and 5-positions of the pyridine ring of **3ag**.

Finally we investigated the effects of substituents of the A-ring on PDE4 inhibitory activity. Removal of alkoxy substituents on the A-ring (**3dg**) resulted in a marked loss in activity (IC_{50} = 5000 nM), compared with 6,7-dimethoxy compound **3ag** (IC_{50} = 0.63 nM). Replacement of the 6,7-dimethoxy group of **3ag** with a 6-benzyloxy-7-methoxy group (**3eg**), a 6-cyclopentyloxy-7-methoxy group (**3gg**), which is a typical group of rolipram-related compounds, or a 6-methoxy-7-benzyloxy group (**3hg**) led to a significant decrease of PDE4 inhibitory activity. 6-Ethoxy-7-methoxy analogue **3ig** retained PDE4 inhibitory activity (IC_{50} = 0.90 nM), though it exhibited poor selectivity for PDE4 over PDE3 (selectivity ratio = 38). 6-Methoxy-7-ethoxy analogue **3jg** showed 4 times as much potent activity (IC_{50} = 0.16 nM) as **3ag**, and the ratio of the IC_{50} value for PDE3 to PDE4 increased from 460 to 3100. Among lower alkoxy analogues, 6,7-diethoxy compound **3kg** showed the best inhibitory activity against PDE4 (IC_{50} = 0.13 nM) with markedly improved selectivity against PDE1, -2, -3, and -5 isoforms; the PDE3 versus PDE4 selectivity is 14 000.

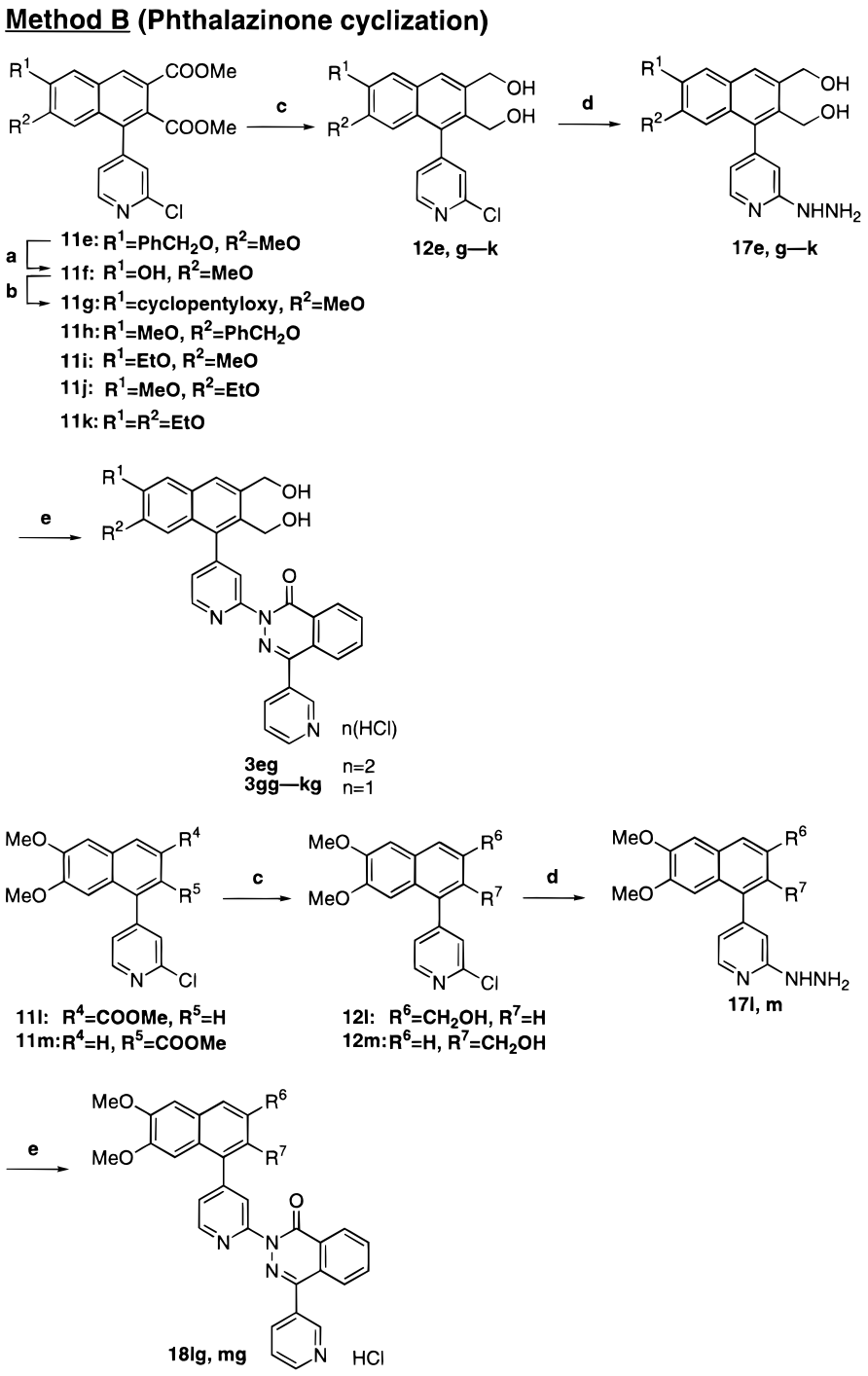
Antispasmogenic Activity. We selected 10 compounds on the basis of the PDE4 inhibitory potency (IC_{50} < 3 nM) for the evaluation of their ability to inhibit antigen-induced bronchoconstriction (iv) and histamine-induced bronchoconstriction (id) in anesthetized guinea pigs. RP73401[12] was selected as a reference compound (ED_{50} = 0.033 mg/kg for antigen response, iv; 0.20 mg/kg for histamine response, id). Among **3af**−**ah** having equipotent PDE4 inhibitions, **3ag** exhibited the best inhibitory activity on intravenously administered antigen-induced bronchoconstriction (ED_{50} (mg/kg): **3af** 0.18, **3ag** 0.022, **3ah** 0.17) with the least effect on heart rate (Table 2). **3ab**,**kg** also had excellent antispasmogenic activities for intravenously administered antigen response, with ED_{50} values of 0.12 and 0.063 mg/kg, respectively. 3-Hydroxymethyl analogue **18lg** showed a very weak reduction of antigen response (a 33% reduction at 1 mg/kg, iv), despite the fact that **18lg** had equipotent PDE4 inhibitory activity to 3,4-bis(hydroxymethyl) analogue **3ag** (IC_{50} = 0.70 nM). To assess the cardiovascular side effects, the effects of selected compounds on heart rate were simultaneously investigated, and it was confirmed that **3ab**,**ag**,**kg** induced little increase in heart rate at a dose of 0.1 mg/kg when administered intravenously (0, 1, and 3 beats/min, respectively). In the histamine-induced bronchoconstriction model, compound **3kg** proved to have the most potent antispasmogenic activity (ED_{50} = 0.033 mg/kg, id) among the selected compounds and greater activity than RP73401 (ED_{50} = 0.20 mg/kg, id). More detailed information on the antispasmogenic activity of **3kg** will be published elsewhere.

Scheme 3[a]



[a] Reagents and conditions: (a) $NaBH_4$/THF−MeOH, reflux; (b) (1) RH or 4-(3-pyridyl)-1(2*H*)-phthalazinone, CuI, K_2CO_3/DMF, 120 °C, (2) 2 N aqueous HCl/$CHCl_3$−MeOH; (c) (1) Ac_2O, Et_3N/CH_2Cl_2, (2) 2 N aqueous HCl/$CHCl_3$−MeOH.

Scheme 4[a]



[a] Reagents and conditions: (a) H_2, 10% Pd−C/AcOH−dioxane, 45 psi, 25 °C; (b) cyclopentyl bromide, NaH/DMF, 25 °C; (c) Red-Al/THF, 0 °C; (d) $NH_2NH_2 \cdot H_2O$, reflux; (e) (1) 2-(3-pyridinoyl)benzoic acid/ethylene glycol, 150 °C, (2) 2 N aqueous HCl/$CHCl_3$−MeOH.

Affinity for the High-Affinity Rolipram Binding Site and Emetic Effects. We finally selected three compounds (**3ab**,**ag**,**kg**) on the basis of antispasmogenic activity for the evaluation of emetic effects in ferrets and dogs and affinity for the high-affinity rolipram binding site. As shown in Table 3, **3ab**,**ag**,**kg** did not induce emetic effects at a dose of 10 or 30 mg/kg, po, though RP73401 clearly caused emesis at a dose of 3 mg/kg, po. **3kg** also showed a considerably weaker emetic effect than RP73401 in dogs when administered intravenously at a dose of 0.3 mg/kg (**3kg**, none of 8 tested animals vomited; RP73401, 6 animals of 8 tested animals vomited).

The affinities for the high-affinity rolipram binding site of selected compounds (**3ab**,**ag**,**kg**) and RP73401 were investigated and compared with emetic effects (Table 3). **3ab**,**ag**,**kg** exhibited comparatively lower affinities than RP73401 for the high-affinity rolipram binding site (K_i value (nM): **3ab** 6.2, **3ag** 3.5, **3kg** 2.6, RP73401 0.85). It is important that **3kg** showed the broadest margin between the K_i value of binding affinity and the IC_{50} value of PDE4 inhibition (ratio = 0.050),

Table 1. PDE Inhibitory Activities of Pyridylnaphthalene Derivatives

compd	method[a]	PDE inhibition, IC_{50}[b] (nM) 1	2	3	4	5	selectivity 3/4
3aa	A	50000		2000	80	40000	25
3ab	A	2000		330 ± 90	2.8 ± 0.3	2000	120
3ac	A			41 ± 4	0.20 ± 0.04		210
3ad	A	9000		400	40	20000	10
3ae	A	5000		250 ± 80	0.68 ± 0.26	20000	370
3af	A	4000		170 ± 50	0.55 ± 0.16	9000	310
3ag	A	2000		290 ± 40	0.63 ± 0.04	4000	460
3ah	A	2000		100 ± 10	0.49 ± 0.06	4000	200
13	A			29000	150		190
14	A			3500	190		18
18lg	B			81 ± 11	0.70 ± 0.04	200	120
18mg	B			700	31		23
15	A	>100000		80000	40	40000	2000
16	A			5600	15		370
3dg	A	>100000		50000	5000	10000	10
3eg	B			>100000	700		>140
3gg	B			690	30		23
3hg	B			16000	17		940
3ig	B	20000		34 ± 1	0.90 ± 0.24	1000	38
3jg	B	3000		490 ± 60	0.16 ± 0.05	800	3100
3kg (T-2585·HCl)	B	10000 ± 1100	1300 ± 220	1800 ± 290	0.13 ± 0.016	200 ± 5.8	14000
(±)-rolipram		>100000	>100000	>300000	500 ± 60	>100000	>600
RP73401		>100000	40000	>100000	0.31 ± 0.017	14000 ± 3800	>320000

[a] Method A: Ullmann reaction. Method B: phthalazinone cyclization. [b] Values given ± SEM are the means of three experiments.

Table 2. Bronchial and Cardiovascular Effects of Selected Compounds

compd	dose (mg/kg, iv)	*n*	antigen-induced bronchoconstriction % reduction[a]	antigen-induced bronchoconstriction ED_{50}[b] (mg/kg)	heart rate[c] (Δbeats/min)	histamine-induced bronchoconstriction ED_{50}[d] (mg/kg, id)	histamine-induced bronchoconstriction *n*
3ab	0.03	2	−11	0.12	3	0.40	4
	0.1	2	68	(0.013−1.13)	0	(0.12−1.35)	
	1	2	86		−4		
	3	1	90		27		
3ac	1	2	38	1.2	18		
	3	2	91	(1.09−1.34)	15		
3ae	0.1	2	25	0.24	16		
	1	2	87	(0.10−0.58)	11		
	3	2	91		55		
3af	0.03	3	−25	0.18	3 ± 2		
	0.1	3	40	(0.022−1.44)	5 ± 1		
	0.3	3	78		7 ± 4		
	1	2	87		22		
3ag	0.01	4	34	0.022	1 ± 2	1.1	4
	0.03	4	61	(0.0098−0.050)	3 ± 2	(0.44−2.80)	
	0.1	4	73		1 ± 5		
3ah	0.1	3	15	0.17	12 ± 4		
	0.3	3	82	(0.014−2.08)	10 ± 4		
	1	2	92		29		
3ig	0.1	4	23	0.17	7 ± 4		
	0.3	2	77	(0.073−0.41)	18		
3jg	0.1	5	39	0.18	3 ± 5		
	0.3	4	69	(0.059−0.37)	7 ± 3		
3kg (T-2585·HCl)	0.03	4	37	0.063	4 ± 1	0.033	3
	0.1	4	57	(0.037−0.107)	3 ± 5	(0.01−0.11)	
	0.3	3	84		2 ± 3		
18lg	1	2	33				
RP73401	0.01	2	24	0.033	4	0.20	3
	0.03	3	56	(0.0090−0.12)	3 ± 3	(0.11−0.34)	
	0.1	4	63		2 ± 5		

[a] Percent inhibition of antigen-induced bronchoconstriction in guinea pigs. [b] The dose which inhibits antigen-induced bronchoconstriction in guinea pigs by 50%. ED_{50} values were determined from the dose−inhibition curve. The values in parentheses are 95% confidence limits. [c] Changes in heart rate between basal value and the value observed after administration of test compounds in guinea pigs. Basal values for heart rate were 230−330 beats/min. [d] The dose which inhibits histamine-induced bronchoconstriction in guinea pigs by 50%. ED_{50} values were determined from the dose−inhibition curve (at least three doses). The values in parentheses are 95% confidence limits.

which may imply an improved therapeutic ratio among the PDE4 inhibitors reported so far.[4b]

Conclusion

Novel 1-pyridylnaphthalene derivatives were disclosed as a new structural class of potent and selective PDE4 inhibitors. Among the analogues, compound **3kg** (PDE4 inhibition IC_{50} = 0.13 nM, PDE3/4 ratio = 14 000) showed potent antispasmogenic activities (ED_{50} = 0.063 mg/kg for reduction of antigen-induced bronchoconstriction, iv; ED_{50} = 0.033 mg/kg for reduction of histamine-induced bronchoconstriction, id) without sig-

Table 3. Rolipram Binding Affinity, PDE4 Inhibitory Activity, and Emetic Effects of Selected Compounds

compd	[^{3}H]rolipram binding, K_i[a] (nM), GP[b] brain (A) ($n = 4$)	PDE4 inhibition, IC_{50}[a] (nM), GP[b] lung (B) ($n = 3$)	ratio B/A	emesis (vomiting/tested) ferret (po) 0.3	1	3	10	30	100 (mg/kg)	dog (iv) 0.1	0.3	1 (mg/kg)
3ab	6.2 ± 1.2	2.8 ± 0.3	0.45					0/4	1/4			
3ag	3.5 ± 0.9	0.63 ± 0.04	0.18				0/6	0/4	3/4			
3kg (T-2585·HCl)	2.6 ± 0.4	0.13 ± 0.02	0.050				0/4[c]	4/4			0/8	3/4
RP73401	0.85 ± 0.09	0.31 ± 0.02	0.36	0/4[d]	1/8	4/8	6/6			0/4	6/8	
(±)-rolipram	3.8 ± 1.1	500 ± 60	130									

[a] Mean ± SEM. [b] Guinea pig. [c] C_{max} and AUC_{0-4h} of **3kg** at a threshold dose which did not induce the emetic effect: $C_{max} = 18.4$ ng/mL, $AUC_{0-4h} = 50.0$ ng/mL [mean value ($n = 4$)]. [d] C_{max} and AUC_{0-4h} of RP73401 at a threshold dose which did not induce the emetic effect: $C_{max} = 9.2$ ng/mL, $AUC_{0-4h} = 25.5$ ng/mL [mean value ($n = 4$)].

nificant changes in heart rate. Compound **3kg**-induced weak emetic effects on both orally administered ferrets and intravenously administered dogs correlated with the affinity for the high-affinity rolipram binding site (binding affinity $K_i = 2.6$ nM).

On the basis of the potency, selectivity, and low side effects, compound **3kg** (T-2585·HCl) was selected for further evaluation as an antiasthmatic agent.

Experimental Section

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 Perkin-Elmer 1640 spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker AC-200 (200 MHz) spectrometer with Me_4Si as an internal standard. Mass spectra were obtained on a Hitachi M-2000A double-focusing mass spectrometer. 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 2,3-Bis(methoxycarbonyl)-1-pyridylnaphthalenes 11a−e,h−m (Scheme 2). Compounds **11a−e,h−m** were all prepared by essentially the same procedure (Scheme 1). The sequence is illustrated for **11a**, followed by analytical data for **11b−e,h−m**.

2,3-Bis(methoxycarbonyl)-1-(2-bromo-4-pyridyl)-6,7-dimethoxynaphthalene (11a). To a stirred solution of **9** (R^1,R^2═OMe) (86.1 g, 0.296 mol) in THF (500 mL) was added *n*-BuLi (194 mL, 0.310 mol) 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 2-bromoisonicotinaldehyde (55.0 g, 0.296 mol) in THF (100 mL). The resulting mixture was stirred at the same temperature for 30 min and poured into a mixture of water and AcOEt. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. A solution of the residue **10** (R^1,R^2═OMe), dimethyl fumarate (42.7 g, 0.296 mol), and acetic acid (100 mL) in xylene (200 mL) was heated under reflux for 2 h. The solvent was removed by evaporation to give 2,3-bis(methoxycarbonyl)-1-(2-bromo-4-pyridyl)-6,7-dimethoxy-1,4-epoxy-1,2,3,4-tetrahydronaphthalene as a syrup. This crude product was used in the next step. A solution of the crude products and BF_3·Et_2O (110 mL, 0.894 mol) in CH_3CN (200 mL) was heated under reflux for 3 h. The reaction mixture was allowed to cool to room temperature and poured into a mixture of saturated aqueous $NaHCO_3$ and $CHCl_3$. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from MeOH gave **11a** (81.7 g, 60%): mp 192−194 °C; IR (KBr) 1732, 1720, 1248, 1133 cm^{-1}; ^{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), 7.27 (s, 1H), 7.31 (dd, 1H, $J = 5.0$, 1.4 Hz), 7.55 (s, 1H), 8.50 (s, 1H), 8.51 (d, 1H, $J = 5.0$ Hz); EIMS *m*/*z* 461/459 (M^+, base), 430/428.

2,3-Bis(methoxycarbonyl)-1-(2-bromo-5-pyridyl)-6,7-dimethoxynaphthalene (11b): yield 48%; mp 186−188 °C; IR (KBr) 1730, 1712, 1251, 1135 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 3.79 (s, 3H), 3.95 (s, 3H), 4.04 (s, 3H), 6.64 (s, 1H), 7.28 (s, 1H), 7.58−7.68 (m, 2H), 8.37−8.42 (m, 1H), 8.51 (s, 1H); EIMS *m*/*z* 461/459 (M^+, base), 430/428.

2,3-Bis(methoxycarbonyl)-1-(2-bromo-6-pyridyl)-6,7-dimethoxynaphthalene (11c): yield 51%; mp 199−200 °C; IR (KBr) 1727, 1254, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H), 3.82 (s, 3H), 3.94 (s, 3H), 4.03 (s, 3H), 6.93 (s, 1H), 7.24 (s, 1H), 7.48 (dd, 1H, $J = 7.5$, 1.0 Hz), 7.57 (dd, 1H, $J = 7.9$, 1.0 Hz), 7.71 (dd, 1H, $J = 7.9$, 7.5 Hz), 8.46 (s, 1H); EIMS *m*/*z* 461/459 (M^+, base), 430/428.

2,3-Bis(methoxycarbonyl)-1-(2-bromo-4-pyridyl)naphthalene (11d): yield 43%; mp 162−163 °C; IR (KBr) 1732, 1711, 1278, 1136 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H), 3.98 (s, 3H), 7.23−7.32 (m, 1H), 7.40−7.52 (m, 1H), 7.58 (s, 1H), 7.58−7.70 (m, 2H), 8.03 (dd, 1H, $J = 6.0$, 2.4 Hz), 8.50 (dd, 1H, $J = 6.0$, 0.6 Hz), 8.67 (s, 1H); EIMS *m*/*z* 401/399 (M^+, base), 370/368.

6-Benzyloxy-2,3-bis(methoxycarbonyl)-1-(2-chloro-4-pyridyl)-7-methoxynaphthalene (11e): yield 16%; mp 260−261 °C dec; IR (KBr) 1730, 1715, 1237, 1137 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.54 (s, 3H), 3.70 (s, 3H), 3.88 (s, 3H), 5.28 (s, 2H), 6.70 (s, 1H), 7.37−7.58 (m, 7H), 7.87 (s, 1H), 8.53−8.60 (m, 2H); EIMS *m*/*z* 493/491 (M^+, 48), 402/400, 91 (base).

7-Benzyloxy-2,3-bis(methoxycarbonyl)-1-(2-chloro-4-pyridyl)-6-methoxynaphthalene (11h): yield 40%; mp 149−153 °C; IR (KBr) 1735, 1721, 1252, 1132 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 3H), 3.93 (s, 3H), 4.05 (s, 3H), 5.10 (s, 2H), 6.60 (s, 1H), 7.04 (dd, 1H, $J = 5.0$, 1.4 Hz), 7.13−7.42 (m, 7H), 8.41−8.52 (m, 2H); EIMS *m*/*z* 493/491 (M^+, 8), 402/400, 91 (base).

2,3-Bis(methoxycarbonyl)-1-(2-chloro-4-pyridyl)-6-ethoxy-7-methoxynaphthalene (11i): yield 54%; mp 205−208 °C; IR (KBr) 1723, 1245, 1135 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.57 (t, 3H, $J = 7.0$ Hz), 3.67 (s, 3H), 3.78 (s, 3H), 3.95 (s, 3H), 4.26 (q, 2H, $J = 7.0$ Hz), 6.64 (s, 1H), 7.26 (s, 1H), 7.28 (dd, 1H, $J = 5.0$, 1.4 Hz), 7.39 (d, 1H, $J = 0.6$ Hz), 8.48 (s, 1H), 8.53 (d, 1H, $J = 5.0$ Hz); EIMS *m*/*z* 431/429 (M^+, base), 372/370.

2,3-Bis(methoxycarbonyl)-1-(2-chloro-4-pyridyl)-7-ethoxy-6-methoxynaphthalene (11j): yield 58%; mp 196−198 °C; IR (KBr) 1728, 1248, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 (t, 3H, $J = 7.0$ Hz), 3.67 (s, 3H), 3.95 (s, 3H), 3.96 (q, 2H, $J = 7.0$ Hz), 4.03 (s, 3H), 6.63 (s, 1H), 7.21−7.32 (m, 2H), 7.37−7.42 (m, 1H), 8.49 (s, 1H), 8.52 (dd, 1H, $J = 5.0$, 0.5 Hz); EIMS *m*/*z* 431/429 (M^+, base), 372/370.

2,3-Bis(methoxycarbonyl)-1-(2-chloro-4-pyridyl)-6,7-diethoxynaphthalene (11k): yield 56%; mp 154−156 °C; IR (KBr) 1745, 1712, 1249, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 (t, 3H, $J = 7.0$ Hz), 1.55 (t, 3H, $J = 7.0$ Hz), 3.67 (s, 3H), 3.94 (s, 3H), 3.95 (q, 2H, $J = 7.0$ Hz), 4.23 (q, 2H, $J = 7.0$ Hz), 6.63 (s, 1H), 7.24 (s, 1H), 7.27 (dd, 1H, $J = 5.0$, 1.4 Hz), 7.39 (s, 1H), 8.46 (s, 1H), 8.52 (d, 1H, $J = 5.0$ Hz); EIMS *m*/*z* 445/443 (M^+, base), 358/356.

1-(2-Chloro-4-pyridyl)-6,7-dimethoxy-3-methoxycarbonylnaphthalene (11l): yield 2%; mp 203−206 °C; IR (KBr) 1706, 1246, 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 3.98

(s, 3H), 4.04 (s, 3H), 7.07 (s, 1H), 7.29 (s, 1H), 7.40 (dd, 1H, J = 5.0, 1.4 Hz), 7.48− 7.56 (m, 1H), 7.86 (d, 1H, J = 1.4 Hz), 8.45− 8.58 (m, 2H); EIMS m/z 359/357 (M^+, base), 328/326.

1-(2-Chloro-4-pyridyl)-6,7-dimethoxy-2-methoxycarbonylnaphthalene (11m): yield 53%; mp 141−143 °C; IR (KBr) 1723, 1265, 1118 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (s, 3H), 3.74 (s, 3H), 4.04 (s, 3H), 6.59 (s, 1H), 7.19 (s, 1H), 7.21 (dd, 1H, J = 5.0, 1.4 Hz), 7.31 (s, 1H), 7.80 (d, 1H, J = 8.6 Hz), 7.93 (d, 1H, J = 8.6 Hz), 8.52 (d, 1H, J = 5.0 Hz); EIMS m/z 359/357 (M^+, base), 328/326.

General Procedure for Synthesis of 2,3-Bis(hydroxymethyl)-1-pyridyl-6,7-dimethoxynaphthalenes 12a−d. Method A (Scheme 3). Compounds **12a**−**d** were all prepared by essentially the same procedure (Scheme 2). The sequence is illustrated for **12a**, followed by analytical data for **12b**−**d**.

2,3-Bis(hydroxymethyl)-1-(2-bromo-4-pyridyl)-6,7-dimethoxynaphthalene (12a). To a stirred suspension of **11a** (266 g, 0.578 mol) and $NaBH_4$ (65.5 g, 1.73 mol) in THF (1.5 L) was added MeOH (350 mL) dropwise under reflux over 1 h, and the mixture was stirred under reflux for another 1 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was poured into a mixture of aqueous $NaHCO_3$ and $CHCl_3$, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from AcOEt gave **12a** (168 g, 72%): mp 190−192 °C; IR (KBr) 3440 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.61 (s, 3H), 3.89 (s, 3H), 4.21 (dd, 1H, J = 11.7, 5.0 Hz), 4.32 (dd, 1H, J = 11.7, 5.0 Hz), 4.84 (d, 2H, J = 5.0 Hz), 4.87 (t, 1H, J = 5.0 Hz), 5.30 (t, 1H, J = 5.0 Hz), 6.47 (s, 1H), 7.40 (s, 1H), 7.44 (dd, 1H, J = 5.0, 1.3 Hz), 7.66 (s, 1H), 7.94 (s, 1H), 8.54 (d, 1H, J = 5.0 Hz); EIMS m/z 405/403 (M^+, base), 387/385.

2,3-Bis(hydroxymethyl)-1-(2-bromo-5-pyridyl)-6,7-dimethoxynaphthalene (12b): yield 84%; mp 197−199 °C; IR (KBr) 3185 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.61 (s, 3H), 3.89 (s, 3H), 4.27 (s, 2H), 4.72−5.02 (m, 3H), 5.30 (t, 1H, J = 5.3 Hz), 6.49 (s, 1H), 7.40 (s, 1H), 7.74 (dd, 1H, J = 8.1, 1.7 Hz), 7.83 (d, 1H, J = 8.1 Hz), 7.93 (s, 1H), 8.35 (d, 1H, J = 1.7 Hz); EIMS m/z 405/403 (M^+, base), 387/385.

2,3-Bis(hydroxymethyl)-1-(2-bromo-6-pyridyl)-6,7-dimethoxynaphthalene (12c): yield 80%; mp 107−108 °C; IR (KBr) 3424 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85 (br s, 2H), 3.78 (s, 3H), 4.01 (s, 3H), 4.30−4.70 (m, 2H), 4.79−5.09 (m, 2H), 6.76 (s, 1H), 7.14 (s, 1H), 7.55 (dd, 1H, J = 7.9, 0.9 Hz), 7.61 (dd, 1H, J = 7.9, 0.9 Hz), 7.71−7.85 (m, 2H); EIMS m/z 405/403 (M^+, 62), 359/357 (base).

2,3-Bis(hydroxymethyl)-1-(2-bromo-4-pyridyl)naphthalene (12d): yield 94%; mp 108−109 °C; IR (KBr) 3388 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.60 (br s, 2H), 4.53, 4.61 (ABq, 2H, J = 12.1 Hz), 4.98 (s, 2H), 7.21−7.38 (m, 2H), 7.33−7.60 (m, 3H), 7.87 (dd, 1H, J = 7.5, 1.4 Hz), 7.92 (s, 1H), 8.49 (dd, 1H, J = 5.0, 0.5 Hz); EIMS m/z 345/343 (M^+, 56), 327/325 (base).

General Procedure for Ullmann Reactions. Method A (Scheme 3). Compounds **3aa**−**ah**,**dg**, **13**, **15**, and **16** were all prepared by essentially the same procedure (Scheme 3). The sequence is illustrated for **3aa**, followed by analytical data for **3ab**−**ah**,**dg**, **13**, **15**, and **16**.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-[2-(2(1*H*)-pyridon-1-yl)-4-pyridyl]naphthalene (3aa). A mixture of **12a** (2.0 g, 4.95 mmol), 2-hydroxypyridine (518 mg, 5.44 mmol), CuI (95 mg, 0.50 mmol), and K_2CO_3 (752 mg, 5.44 mmol) in DMF (20 mL) was heated at 120 °C for 5 h. The reaction mixture was allowed to cool to room temperature and poured into a mixture of concentrated NH_4OH and 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), followed by crystallization from AcOEt, gave **3aa** (1.3 g, 63%): mp 205−208 °C; IR (KBr) 3373, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (br s, 1H), 3.82 (s, 3H), 4.01 (s, 3H), 4.38 (br s, 1H), 4.45 (d, 1H, J = 13.0 Hz), 4.52−4.71 (m, 1H), 4.71−4.90 (m, 1H), 5.04 (d, 1H, J = 13.0 Hz), 6.37 (ddd, 1H, J = 6.9, 6.7, 1.2 Hz), 6.61 (d, 1H, J = 9.2 Hz), 6.84 (s, 1H), 7.16 (s, 1H), 7.31−7.52 (m, 2H), 7.77 (s, 1H), 7.96 (s, 1H), 8.05 (dd, 1H, J = 7.1, 1.7 Hz), 8.73 (d, 1H, J = 5.0 Hz); EIMS m/z 418 (M^+, 48), 400 (base). Anal. ($C_{24}H_{22}N_2O_5$) C, H, N.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-[2-(2(1*H*)-quinolon-1-yl)-4-pyridyl]naphthalene (3ab): yield 58%; mp >250 °C; IR (KBr) 3386, 1646 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.69 (s, 3H), 3.89 (s, 3H), 4.30 (dd, 1H, J = 11.6, 5.5 Hz), 4.53 (dd, 1H, J = 11.6, 5.5 Hz), 4.87 (d, 2H, J = 5.5 Hz), 4.92 (t, 1H, J = 5.5 Hz), 5.31 (t, 1H, J = 5.5 Hz), 6.60−6.80 (m, 3H), 7.28 (dd, 1H, J = 7.3, 6.8 Hz), 7.39 (s, 1H), 7.40−7.55 (m, 1H), 7.54 (s, 1H), 7.66 (dd, 1H, J = 5.0, 1.4 Hz), 7.80 (d, 1H, J = 6.8 Hz), 7.93 (s, 1H), 8.07 (d, 1H, J = 9.6 Hz), 8.89 (d, 1H, J = 5.0 Hz); EIMS m/z 468 (M^+, 26), 450 (base). Anal. ($C_{28}H_{24}N_2O_5 \cdot 0.25H_2O$) C, H, N.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-[2-(6(5*H*)-phenanthridinon-5-yl)-4-pyridyl]naphthalene (3ac): yield 36%; mp 245−248 °C dec; IR (KBr) 3381, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.47 (br s, 1H), 3.88 (br s, 1H), 3.89 (s, 3H), 4.00 (s, 3H), 4.65 (s, 2H), 4.92 (s, 2H), 6.78 (dd, 1H, J = 7.3, 2.2 Hz), 6.84 (s, 1H), 7.13 (s, 1H), 7.25−7.42 (m, 2H), 7.52 (s, 1H), 7.58 (dd, 2H, J = 5.0, 1.4 Hz), 7.75 (s, 1H), 7.69−7.89 (m, 1H), 8.22−8.39 (m, 2H), 8.46 (dd, 1H, J = 8.0, 1.4 Hz), 8.91 (d, 1H, J = 5.0 Hz); EIMS m/z 518 (M^+, base). Anal. ($C_{32}H_{26}N_2O_5 \cdot 0.75H_2O$) C, H, N.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-[2-(4(1*H*)-quinolon-1-yl)-4-pyridyl]naphthalene (3ad): yield 61%; mp 113−115 °C; IR (KBr) 3379, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.22 (br s, 2H), 3.77 (s, 3H), 4.01 (s, 3H), 4.51, 4.70 (ABq, 2H, J = 11.6 Hz), 4.88, 5.05 (ABq, 2H, J = 11.6 Hz), 6.35 (d, 1H, J = 8.0 Hz), 6.60 (s, 1H), 7.17 (s, 1H), 7.29 (dd, 1H, J = 8.0, 6.2 Hz), 7.39−7.60 (m, 3H), 7.68 (s, 1H), 7.79 (s, 1H), 7.98 (d, 1H, J = 8.0 Hz), 8.28 (d, 1H, J = 6.2 Hz), 8.81 (d, 1H, J = 5.0 Hz); SIMS m/z 469 ($M^+ + 1$, base). Anal. ($C_{28}H_{24}N_2O_5 \cdot 1.75H_2O$) Calcd: C, 67.26; H, 5.54; N, 5.60. Found: C, 66.90; H, 5.08; N, 5.26.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-[2-(1(2*H*)-phthalazinon-2-yl)-4-pyridyl]naphthalene (3ae): yield 75%; mp 201−203 °C; IR (KBr) 3426, 3375, 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.49 (br s, 1H), 3.82 (s, 3H) 3.87 (br s, 1H), 4.02 (s, 3H), 4.50−4.79 (m, 2H), 4.79−4.99 (m, 1H), 4.99−5.15 (m, 1H), 6.85 (s, 1H), 7.17 (s, 1H), 7.47 (dd, 1H, J = 5.0, 1.4 Hz), 7.71−7.98 (m, 5H), 8.42 (s, 1H), 8.46 (d, 1H, J = 8.4 Hz), 8.85 (d, 1H, J = 5.0 Hz); EIMS m/z 469 (M^+, 79), 340 (base). Anal. ($C_{27}H_{23}N_3O_5$) C, H, N.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-{2-[1(2*H*)-phthalazinon-4-(2-pyridyl)-2-yl]-4-pyridyl}naphthalene Hydrochloride (3af). To a solution of the free base of **3af** (1.0 g, 1.8 mmol) in $CHCl_3$ (50 mL) and MeOH (30 mL) was added a solution of 2 N aqueous HCl (0.9 mL, 1.8 mmol), and the mixture was concentrated under reduced pressure. Crystallization of the residual hydrochloride from EtOH gave **3af** (1.0 g, 95%): mp 162−164 °C dec; IR (KBr) 3405, 1683 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.70 (s, 3H), 3.91 (s, 3H), 4.30, 4.50 (ABq, 2H, J = 11.7 Hz), 4.47 (br s, 3H), 4.87 (s, 2H), 6.76 (s, 1H), 7.41 (s, 1H), 7.53−7.70 (m, 2H), 7.77 (s, 1H), 7.85−8.15 (m, 5H), 8.30−8.52 (m, 2H), 8.81 (d, 2H, J = 5.3 Hz); SIMS m/z 547 ($M^+ + 1 -$ HCl, 90), 529 (base). Anal. ($C_{32}H_{26}N_4O_5 \cdot$HCl$\cdot 0.5H_2O$) C, H, N.

In the same manner, other pyridylnaphthalene hydrochlorides **3ag**,**ah**,**dg**, **13**, **15**, and **16** were obtained.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-4-pyridyl}naphthalene hydrochloride (3ag): yield 87%; mp 212−215 °C dec; IR (KBr) 3380, 1677 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.69 (s, 3H), 3.91 (s, 3H), 4.31, 4.49 (ABq, 2H, J = 11.6 Hz), 4.88 (s, 2H), 5.42 (br s, 3H), 6.74 (s, 1H), 7.42 (s, 1H), 7.62 (dd, 1H, J = 5.0, 1.4 Hz), 7.76 (s, 1H), 7.75−7.90 (m, 1H), 7.92−8.19 (m, 4H), 8.41−8.56 (m, 1H), 8.71 (dd, 1H, J = 6.5, 1.4 Hz), 8.81 (d, 1H, J = 5.0 Hz), 9.04 (dd, 1H, J = 5.0, 1.4 Hz), 9.18 (d, 1H, J = 1.4 Hz); SIMS m/z 547 ($M^+ + 1 -$ HCl, 64), 529 (base). Anal. ($C_{32}H_{26}N_4O_5 \cdot$HCl$\cdot 2H_2O$) C, H, N.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-{2-[1(2*H*)-phthalazinon-4-(4-pyridyl)-2-yl]-4-pyridyl}naphthalene hydrochloride (3ah): yield 44%; mp 220−223 °C dec; IR (KBr) 3408, 1674 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.69 (s, 3H), 3.91 (s,

3H), 4.31, 4.48 (ABq, 2H, J = 11.6 Hz), 4.87 (s, 2H), 5.18 (br s, 3H), 6.74 (s, 1H), 7.42 (s, 1H), 7.62 (dd, 1H, J = 5.0, 1.4 Hz), 7.75 (s, 1H), 7.78−7.90 (m, 1H), 7.95 (s, 1H), 7.98−8.18 (m, 4H), 8.41−8.55 (m, 1H), 8.80 (d, 1H, J = 5.0 Hz), 8.97 (s, 1H), 9.00 (s, 1H); SIMS m/z 547 ($M^+ + 1$ − HCl, base). Anal. ($C_{32}H_{26}N_4O_5 \cdot HCl \cdot 2.5H_2O$) Calcd: C, 61.19; H, 5.14; N, 8.92. Found: C, 61.72; H, 4.84; N, 8.28.

2,3-Bis(hydroxymethyl)-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-4-pyridyl}naphthalene dihydrochloride (3dg): yield 67%; mp 242−243 °C dec; IR (KBr) 3442, 1674 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.32−4.56 (m, 2H), 4.95 (br s, 4H), 4.93 (s, 2H), 7.33 (d, 1H, J = 8.0 Hz), 7.40−7.65 (m, 3H), 7.71−7.90 (m, 2H), 7.92−8.11 (m, 4H), 8.12 (s, 1H), 8.42−8.55 (m, 1H), 8.67 (d, 1H, J = 8.0 Hz), 8.79 (d, 1H, J = 5.0 Hz), 8.95−9.10 (m, 1H), 9.10−9.28 (m, 1H); SIMS m/z 487 ($M^+ + 1$ − 2HCl, base). Anal. ($C_{30}H_{22}N_4O_3 \cdot 2HCl \cdot 3.25H_2O$) C, H, N.

2,3-Bis(methoxycarbonyl)-6,7-dimethoxy-1-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-4-pyridyl}naphthalene hydrochloride (13): yield 17%; mp 184−186 °C; IR (KBr) 1723, 1675, 1253, 1120 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.60 (s, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 4.13 (br s, 1H), 6.93 (s, 1H), 7.50 (dd, 1H, J = 5.0, 1.5 Hz), 7.65−7.83 (m, 3H), 7.86 (dd, 1H, J = 7.8, 5.0 Hz), 8.00 (d, 1H, J = 3.5 Hz), 8.02 (d, 1H, J = 3.5 Hz), 8.31−8.55 (m, 2H), 8.60 (s, 1H), 8.79 (d, 1H, J = 5.0 Hz), 8.90 (d, 1H, J = 3.5 Hz), 9.02 (d, 1H, J = 1.4 Hz); SIMS m/z 603 ($M^+ + 1$ − HCl, base). Anal. ($C_{34}H_{26}N_4O_7 \cdot HCl \cdot 2.75H_2O$) C, H, N.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-5-pyridyl}naphthalene hydrochloride (15): yield 42%; mp 212−213 °C dec; IR (KBr) 3422, 1671 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.61 (s, 3H), 3.91 (s, 3H), 4.34 (s, 2H), 4.88 (s, 2H), 5.13 (br s, 3H), 6.58 (s, 1H), 7.43 (s, 1H), 7.82 (dd, 1H, J = 6.0, 3.0 Hz), 7.55−8.15 (m, 6H), 8.45−8.55 (m, 3H), 8.93 (d, 1H, J = 4.3 Hz), 9.09 (s, 1H); SIMS m/z 547 ($M^+ + 1$ − HCl, base). Anal. ($C_{32}H_{26}N_4O_5 \cdot HCl \cdot 0.75H_2O$) C, H, N.

2,3-Bis(hydroxymethyl)-6,7-dimethoxy-1-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-6-pyridyl}naphthalene hydrochloride (16): yield 26%; mp 225−229 °C dec; IR (KBr) 3428, 1672 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.56 (s, 3H), 3.88 (s, 3H), 3.93 (br s, 3H), 4.25, 4.50 (ABq, 2H, J = 11.6 Hz), 4.85 (s, 2H), 6.77 (s, 1H), 7.36 (s, 1H), 7.68−7.81 (m, 3H), 7.84 (d, 1H, J = 7.4 Hz), 7.91 (s, 1H), 7.95−8.10 (m, 2H), 8.18−8.31 (m, 2H), 8.45 (dd, 1H, J = 6.0, 3.0 Hz), 8.84 (dd, 1H, J = 5.0, 1.4 Hz), 8.93 (d, 1H, J = 1.4 Hz); SIMS m/z 547 ($M^+ + 1$ − HCl, 68), 529 (base). Anal. ($C_{32}H_{26}N_4O_5 \cdot HCl \cdot 1.5H_2O$) C, H, N.

2,3-Bis(acetoxymethyl)-6,7-dimethoxy-1-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-4-pyridyl}naphthalene Hydrochloride (14). To a stirred solution of the free base of **3ag** (1.5 g, 2.7 mmol) in CH_2Cl_2 (20 mL) were added acetic anhydride (1.6 mL, 17.0 mmol) and triethylamine (3.1 mL, 22.2 mmol) at 0 °C. The mixture was stirred overnight at room temperature. The reaction mixture was washed 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), followed by crystallization from AcOEt, gave the free base of **14** (1.3 g, 75%). To a solution of the free base of **14** (932 mg, 1.5 mmol) in $CHCl_3$ (15 mL) and MeOH (5 mL) was added a solution of 2 N aqueous HCl (0.74 mL, 1.5 mmol), and the mixture was concentrated under reduced pressure. Crystallization of the residual hydrochloride from EtOH gave **14** (893 mg, 91%): mp 161−163 °C dec; IR (KBr) 1733, 1674 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.94 (s, 3H), 2.10 (s, 3H), 3.68 (s, 3H), 3.92 (s, 3H), 4.92, 5.03 (ABq, 2H, J = 12.2 Hz), 5.34 (s, 2H), 5.53 (br s, 1H), 6.71 (s, 1H), 7.48 (s, 1H), 7.54 (dd, 1H, J = 5.0, 1.4 Hz), 7.70−7.89 (m, 2H), 7.89−8.10 (m, 4H), 8.40−8.58 (m, 2H), 8.81 (d, 1H, J = 5.0 Hz), 8.94 (dd, 1H, J = 5.0, 1.4 Hz), 9.07 (d, 1H, J = 1.4 Hz); SIMS m/z 631 ($M^+ + 1$ − HCl, 74), 571 (base). Anal. ($C_{36}H_{30}N_4O_7 \cdot HCl \cdot 1.5H_2O$) C, H, N.

Method B (Scheme 4). 2,3-Bis(methoxycarbonyl)-1-(2-chloro-4-pyridyl)-6-hydroxy-7-methoxynaphthalene (11f). A solution of **11e** (6.6 g, 13.4 mmol) in AcOH (1 L) and dioxane (1 L) was hydrogenated over 10% Pd−C (2.0 g) at 45 psi and 25 °C for 20 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in a mixture of aqueous $NaHCO_3$ and $CHCl_3$, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from EtOH gave **11f** (3.4 g, 63%): mp 231−233 °C dec; IR (KBr) 3401, 1726, 1711, 1236, 1128 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.53 (s, 3H), 3.71 (s, 3H), 3.87 (s, 3H), 6.66 (s, 1H), 7.40 (dd, 1H, J = 5.0, 1.4 Hz), 7.48 (s, 2H), 8.45 (s, 1H), 8.57 (d, 1H, J = 5.0 Hz), 10.24 (br s, 1H); EIMS m/z 403/401 (M^+, base), 372/370.

2,3-Bis(methoxycarbonyl)-1-(2-chloro-4-pyridyl)-6-cyclopentyloxy-7-methoxynaphthalene (11g). To a solution of **11f** (890 mg, 2.2 mmol) in DMF (20 mL) was added NaH (60%, 106 mg, 2.6 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. Cyclopentyl bromide (0.28 mL, 2.6 mmol) was added to the mixture at 0 °C, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of aqueous NH_4Cl and $CHCl_3$, and 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), followed by crystallization from AcOEt, gave **11g** (680 mg, 65%): mp 179−181 °C; IR (KBr) 1732, 1714, 1238, 1133 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45−2.20 (m, 8H), 3.67 (s, 3H), 3.75 (s, 3H), 3.95 (s, 3H), 4.88−5.00 (m, 1H), 6.62 (s, 1H), 7.24 (s, 1H), 7.27 (dd, 1H, J = 5.0, 1.4 Hz), 7.38 (s, 1H), 8.47 (s, 1H), 8.52 (d, 1H, J = 5.0 Hz); EIMS m/z 471/469 (M^+, 11), 403/401 (base).

General Procedure for Synthesis of 2,3-Bis(hydroxymethyl)-1-pyridyl-6,7-dimethoxynaphthalenes 12e,g−m. Method B (Scheme 4). Compounds **12e,g−m** were all prepared by essentially the same procedure (Scheme 4). The sequence is illustrated for **12e**, followed by analytical data for **12g−m**.

6-Benzyloxy-2,3-bis(hydroxymethyl)-1-(2-chloro-4-pyridyl)-7-methoxynaphthalene (12e). To a solution of **11e** (3.0 g, 6.1 mmol) in THF (30 mL) was added Red-Al (34%, sodium bis(2-methoxyethoxy)aluminum hydride in toluene, 5.0 mL, 17 mmol) in THF (10 mL) dropwise at 0 °C, and the mixture was stirred at room temperature for 1 h. To the reaction mixture were added dropwise MeOH (2 mL) and 2 N aqueous NaOH (20 mL) at 10 °C, and the resulting mixture was stirred at 40 °C for 30 min. The mixture was poured into a mixture of H_2O and CH_2Cl_2, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from EtOH−Et_2O gave **12e** (1.6 g, 60%): mp 215−217 °C dec; IR (KBr) 3356 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85 (br s, 1H), 3.09 (br s, 1H), 3.75 (s, 3H), 4.53 (s, 2H), 4.93 (s, 2H), 5.29 (s, 2H), 6.55 (s, 1H), 7.18 (s, 1H), 7.22−7.58 (m, 7H), 7.70 (s, 1H), 8.55 (dd, 1H, J = 5.0, 0.5 Hz); SIMS m/z 438/436 ($M^+ + 1$, 9), 420/418, 91 (base).

2,3-Bis(hydroxymethyl)-1-(2-chloro-4-pyridyl)-6-cyclopentyloxy-7-methoxynaphthalene (12g): yield 61%; mp 200−201 °C; IR (KBr) 3410 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.45−1.92 (m, 6H), 1.85−2.19 (m, 2H), 3.59 (s, 3H), 4.20 (dd, 1H, J = 11.6, 5.0 Hz), 4.31 (dd, 1H, J = 11.6, 5.0 Hz), 4.71−4.92 (m, 3H), 4.89−5.07 (m, 1H), 5.28 (t, 1H, J = 5.5 Hz), 6.47 (s, 1H), 7.36 (s, 1H), 7.40 (dd, 1H, J = 5.0, 1.4 Hz), 7.52 (s, 1H), 7.92 (s, 1H), 8.57 (d, 1H, J = 5.0 Hz); EIMS m/z 415/413 (M^+, 34), 347/345, 329/327 (base).

7-Benzyloxy-2,3-bis(hydroxymethyl)-1-(2-chloro-4-pyridyl)-6-methoxynaphthalene (12h): yield 59%; mp 146−148 °C; IR (KBr) 3331 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (br s, 2H), 4.03 (s, 3H), 4.49 (s, 2H), 4.91 (s, 2H), 5.07 (s, 2H), 6.48 (s, 1H), 7.06 (dd, 1H, J = 5.0, 1.4 Hz), 7.10−7.48 (m, 7H), 7.74 (s, 1H), 8.46 (d, 1H, J = 5.0 Hz); EIMS m/z 437/435 (M^+, 44), 91 (base).

2,3-Bis(hydroxymethyl)-1-(2-chloro-4-pyridyl)-6-ethoxy-7-methoxynaphthalene (12i): yield 59%; mp 150−153 °C; IR (KBr) 3318 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (t, 3H, J = 7.0 Hz), 3.14 (br s, 1H), 3.29 (br s, 1H), 3.73 (s, 3H), 4.23 (q, 2H,

J = 7.0 Hz), 4.53 (s, 2H), 4.93 (s, 2H), 6.52 (s, 1H), 7.14 (s, 1H), 7.29 (dd, 1H, J = 5.0, 1.4 Hz), 7.40 (d, 1H, J = 0.5 Hz), 7.74 (s, 1H), 8.53 (dd, 1H, J = 5.0, 0.5 Hz); EIMS *m/z* 375/373 (M^+, base), 357/355.

2,3-Bis(hydroxymethyl)-1-(2-chloro-4-pyridyl)-7-ethoxy-6-methoxynaphthalene (12j): yield 87%; mp 123−126 °C; IR (KBr) 3414 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (t, 3H, J = 7.0 Hz), 3.24 (br s, 1H), 3.40 (br s, 1H), 3.90 (q, 2H, J = 7.0 Hz), 3.99 (s, 3H), 4.52 (d, 2H, J = 4.5 Hz), 4.92 (d, 2H, J = 4.5 Hz), 6.52 (s, 1H), 7.14 (s, 1H), 7.28 (dd, 1H, J = 5.0, 1.4 Hz), 7.40 (dd, 1H, J = 1.4, 0.5 Hz), 7.74 (s, 1H), 8.53 (dd, 1H, J = 5.0, 0.5 Hz); EIMS *m/z* 375/373 (M^+, base), 357/355.

2,3-Bis(hydroxymethyl)-1-(2-chloro-4-pyridyl)-6,7-diethoxynaphthalene (12k): yield 97%; mp 148−150 °C; IR (KBr) 3268 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (t, 3H, J = 7.0 Hz), 1.53 (t, 3H, J = 7.0 Hz), 3.25 (br s, 1H), 3.40 (br s, 1H), 3.90 (q, 2H, J = 7.0 Hz), 4.21 (q, 2H, J = 7.0 Hz), 4.52 (s, 2H), 4.91 (s, 2H), 6.52 (s, 1H), 7.13 (s, 1H), 7.28 (dd, 1H, J = 5.0, 1.4 Hz), 7.39 (d, 1H, J = 0.5 Hz), 7.71 (s, 1H), 8.52 (dd, 1H, J = 5.0, 0.5 Hz); EIMS *m/z* 389/387 (M^+, base), 371/369.

1-(2-Chloro-4-pyridyl)-6,7-dimethoxy-3-hydroxymethylnaphthalene (12l): yield 24%; mp 115−118 °C; IR (KBr) 3422 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.93 (br s, 1H), 3.86 (s, 3H), 4.02 (s, 3H), 4.86 (s, 2H), 7.05 (s, 1H), 7.19 (s, 1H), 7.28 (d, 1H, J = 1.4 Hz), 7.40 (dd, 1H, J = 5.0, 1.4 Hz), 7.51 (s, 1H), 7.76 (s, 1H), 8.50 (d, 1H, J = 5.0 Hz); EIMS *m/z* 331/329 (M^+, base), 302/300.

1-(2-Chloro-4-pyridyl)-6,7-dimethoxy-2-hydroxymethylnaphthalene (12m): yield 83%; mp 132−135 °C; IR (KBr) 3373 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (t, 1H, J = 5.5 Hz), 3.75 (s, 3H), 4.02 (s, 3H), 4.51 (d, 2H, J = 5.5 Hz), 6.56 (s, 1H), 7.18 (s, 1H), 7.20−7.32 (m, 1H), 7.38 (s, 1H), 7.55 (d, 1H, J = 8.4 Hz), 7.80 (d, 1H, J = 8.4 Hz), 8.55 (dd, 1H, J = 5.0, 0.6 Hz); EIMS *m/z* 331/329 (M^+, base), 302/300.

General Procedure for Synthesis of Hydrazinopyridylnaphthalenes 17e,g−m. Method B (Scheme 4). Compounds **17e**,**g**−**m** were all prepared by essentially the same procedure (Scheme 4). The sequence is illustrated for **17e**, followed by analytical data for **17g**−**m**.

6-Benzyloxy-2,3-bis(hydroxymethyl)-1-(2-hydrazino-4-pyridyl)-7-methoxynaphthalene (17e). A mixture of **12e** (1.6 g, 3.6 mmol) and $NH_2NH_2 \cdot H_2O$ (20 mL) was heated under reflux for 2 h. The reaction mixture was allowed to cooled to room temperature and poured into water. The precipitate was collected by filtration and washed with water and successive EtOH to give **17e** (1.4 g, 88%): mp 155−157 °C dec; IR (KBr) 3324 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.61 (s, 3H), 4.15 (br s, 2H), 4.34 (d, 2H, J = 4.3 Hz), 4.76 (t, 1H, J = 5.1 Hz), 4.83 (d, 2H, J = 5.1 Hz), 5.23 (s, 2H), 5.27 (t, 1H, J = 5.1 Hz), 6.52 (dd, 1H, J = 5.0, 1.4 Hz), 6.62 (s, 1H), 6.69 (s, 1H), 7.28−7.52 (m, 7H), 7.83 (s, 1H), 8.11 (d, 1H, J = 5.0 Hz); SIMS *m/z* 432 (M^+ + 1, 22), 91 (base).

2,3-Bis(hydroxymethyl)-6-cyclopentyloxy-1-(2-hydrazino-4-pyridyl)-7-methoxynaphthalene (17g): yield 99%; mp 127−130 °C; IR (KBr) 3312 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.48−1.90 (m, 6H), 1.85−2.21 (m, 2H), 3.58 (s, 3H), 4.14 (s, 2H), 4.34 (d, 2H, J = 5.0 Hz), 4.75 (t, 1H, J = 5.0 Hz), 4.83 (d, 2H, J = 5.0 Hz), 4.85−5.08 (m, 1H), 5.26 (t, 1H, J = 5.0 Hz), 6.52 (d, 1H, J = 5.1 Hz), 6.62 (s, 1H), 6.66 (s, 1H), 7.32 (s, 1H), 7.52 (s, 1H), 7.84 (s, 1H), 8.11 (d, 1H, J = 5.1 Hz); EIMS *m/z* 409 (M^+, 33), 293 (base).

7-Benzyloxy-2,3-bis(hydroxymethyl)-1-(2-hydrazino-4-pyridyl)-6-methoxynaphthalene (17h): yield 83%; mp 199−202 °C; IR (KBr) 3352 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.89 (s, 3H), 4.13 (br s, 2H), 4.34 (s, 2H), 4.78 (br s, 1H), 4.83 (s, 2H), 4.91 (s, 2H), 5.27 (br s, 1H), 6.41 (d, 1H, J = 5.1 Hz), 6.56 (s, 1H), 6.75 (s, 1H), 7.20−7.45 (m, 6H), 7.54 (s, 1H), 7.85 (s, 1H), 8.10 (d, 1H, J = 5.1 Hz); SIMS *m/z* 432 (M^+ + 1, 74), 91 (base).

2,3-Bis(hydroxymethyl)-6-ethoxy-1-(2-hydrazino-4-pyridyl)-7-methoxynaphthalene (17i): yield 89%; mp 130−134 °C; IR (KBr) 3350 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.39 (t, 3H, J = 6.9 Hz), 3.60 (s, 3H), 4.05−4.28 (m, 4H), 4.35 (d, 2H, J = 5.0 Hz), 4.75 (t, 1H, J = 5.0 Hz), 4.83 (t, 2H, J = 5.0 Hz), 5.26 (t, 1H, J = 5.0 Hz), 6.52 (dd, 1H, J = 5.0, 1.4 Hz), 6.62 (s, 1H), 6.67 (s, 1H), 7.33 (s, 1H), 7.51 (s, 1H), 7.84 (s, 1H), 8.11 (d, 1H, J = 5.0 Hz); EIMS *m/z* 369 (M^+, 33), 351 (base).

2,3-Bis(hydroxymethyl)-7-ethoxy-1-(2-hydrazino-4-pyridyl)-6-methoxynaphthalene (17j): yield 86%; 197−200 °C; IR (KBr) 3311 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.28 (t, 3H, J = 6.9 Hz), 3.79 (q, 2H, J = 6.9 Hz), 3.89 (s, 3H), 4.14 (s, 2H), 4.34 (d, 2H, J = 4.7 Hz), 4.75 (t, 1H, J = 4.7 Hz), 4.83 (d, 2H, J = 5.3 Hz), 5.26 (t, 1H, J = 5.3 Hz), 6.51 (dd, 1H, J = 5.1, 1.4 Hz), 6.61 (s, 1H), 6.65 (s, 1H), 7.35 (s, 1H), 7.52 (s, 1H), 7.85 (s, 1H), 8.10 (d, 1H, J = 5.1 Hz); EIMS *m/z* 369 (M^+, 27), 351 (base).

2,3-Bis(hydroxymethyl)-6,7-diethoxy-1-(2-hydrazino-4-pyridyl)naphthalene (17k): yield 62%; mp 225−230 °C dec; IR (KBr) 3277 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.28 (t, 3H, J = 6.9 Hz), 1.40 (t, 3H, J = 6.9 Hz), 3.81 (q, 2H, J = 6.9 Hz), 4.14 (s, 2H), 4.16 (q, 2H, J = 6.9 Hz), 4.34 (d, 2H, J = 4.6 Hz), 4.74 (t, 1H, J = 4.6 Hz), 4.82 (d, 2H, J = 5.3 Hz), 5.25 (t, 1H, J = 5.3 Hz), 6.51 (d, 1H, J = 5.0 Hz), 6.61 (s, 1H), 6.66 (s, 1H), 7.34 (s, 1H), 7.52 (s, 1H), 7.83 (s, 1H), 8.10 (d, 1H, J = 5.0 Hz); EIMS *m/z* 383 (M^+, 26), 365 (base).

6,7-Dimethoxy-1-(2-hydrazino-4-pyridyl)-3-hydroxymethylnaphthalene (17l): yield 69%; mp 139−144 °C; IR (KBr) 3329 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (s, 3H), 3.90 (s, 3H), 4.18 (s, 2H), 4.64 (d, 2H, J = 5.6 Hz), 5.28 (t, 1H, J = 5.6 Hz), 6.69 (dd, 1H, J = 5.0, 1.4 Hz), 6.83 (s, 1H), 7.21 (s, 1H), 7.23 (d, 1H, J = 1.4 Hz), 7.38 (s, 1H), 7.52 (s, 1H), 7.72 (s, 1H), 8.10 (d, 1H, J = 5.0 Hz); SIMS *m/z* 326 (M^+ + 1, base).

6,7-Dimethoxy-1-(2-hydrazino-4-pyridyl)-2-hydroxymethylnaphthalene (17m): yield 96%; mp 84−88 °C; IR (KBr) 3346 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (s, 3H), 4.00 (s, 3H), 4.52 (s, 2H), 6.00 (br s, 1H), 6.65 (dd, 1H, J = 5.0, 1.4 Hz), 6.69 (s, 1H), 6.72 (s, 1H), 7.14 (s, 1H), 7.53 (d, 1H, J = 8.4 Hz), 7.74 (d, 1H, J = 8.4 Hz), 8.21 (d, 1H, J = 5.0 Hz); EIMS *m/z* 325 (M^+, base).

General Procedure for Synthesis of Phthalazinopyridylnaphthalenes 3eg,gg−kg and 18lg,mg. Method B (Scheme 4). Compounds **3eg**,**gg**−**kg** and **18lg**,**mg** were all prepared by essentially the same procedure (Scheme 4). The sequence is illustrated for **3eg**, followed by analytical data for **3gg**−**kg** and **18lg**,**mg**.

6-Benzyloxy-2,3-bis(hydroxymethyl)-7-methoxy-1-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-4-pyridyl}-naphthalene Dihydrochloride (3eg). A mixture of **17e** (1.3 g, 3.0 mmol) and 2-(3-pyridinoyl)benzoic acid (710 mg, 3.1 mmol) in ethylene glycol (10 mL) was heated at 120 °C for 4 h. The reaction mixture was allowed to cool to room temperature and poured into water. The precipitate was collected by filtration and washed with water and MeOH successively to give the free base of **3eg** (1.0 g, 55%). To a solution of the free base of **3eg** (250 mg, 0.4 mmol) in $CHCl_3$ (3 mL) and MeOH (1 mL) was added a solution of 2 N aqueous HCl (0.4 mL, 0.8 mmol), and the mixture was concentrated under reduced pressure. Crystallization of the residual dihydrochloride from EtOH gave **3eg** (144 mg, 55%): mp 219−221 °C dec; IR (KBr) 3426, 1629 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.69 (s, 3H), 4.13 (br s, 4H), 4.29, 4.48 (ABq, 2H, J = 11.7 Hz), 4.86 (s, 2H), 5.25 (s, 2H), 6.76 (s, 1H), 7.29−7.69 (m, 7H), 7.69−7.88 (m, 2H), 7.87−8.12 (m, 4H), 8.40−8.59 (m, 2H), 8.80 (d, 1H, J = 5.0 Hz), 8.94 (d, 1H, J = 4.3 Hz), 9.08 (s, 1H); SIMS *m/z* 623 (M^+ + 1 − 2HCl, 18), 91 (base). Anal. ($C_{38}H_{30}N_4O_5 \cdot 2HCl \cdot 2.5H_2O$) C, H, N.

2,3-Bis(hydroxymethyl)-6-cyclopentyloxy-7-methoxy-1-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-4-pyridyl}-naphthalene hydrochloride (3gg): yield 73%; mp 215−217 °C dec; IR (KBr) 3422, 1674 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.51−1.90 (m, 6H), 1.89−2.21 (m, 2H), 3.66 (s, 3H), 4.05 (br s, 3H), 4.29, 4.48 (ABq, 2H, J = 11.7 Hz), 4.86 (s, 2H), 4.88−5.07 (m, 1H), 6.73 (s, 1H), 7.38 (s, 1H), 7.60 (dd, 1H, J = 5.0, 1.4 Hz), 7.73 (s, 1H), 7.75−7.88 (m, 1H), 7.88−8.12 (m, 4H), 8.42−8.60 (m, 2H), 8.79 (d, 1H, J = 5.0 Hz), 8.94 (dd, 1H, J = 5.0, 1.4 Hz), 9.08 (d, 1H, J = 1.4 Hz); SIMS *m/z* 601 (M^+ + 1 − HCl, 17), 61 (base). Anal. ($C_{36}H_{32}N_4O_5 \cdot HCl \cdot 2H_2O$) C, H, N.

7-Benzyloxy-2,3-bis(hydroxymethyl)-6-methoxy-1-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-4-pyridyl}naphthalene hydrochloride (3hg): yield 71%; mp 205−208 °C dec; IR (KBr) 3414, 1672 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.91 (s, 3H), 4.02 (br s, 3H), 4.29, 4.47 (ABq, 2H, J = 11.7 Hz), 4.86 (s, 2H), 4.96, 5.14 (ABq, 2H, J = 11.7 Hz), 6.83 (s, 1H), 7.19−7.40 (m, 5H), 7.42 (s, 1H), 7.48 (dd, 1H, J = 5.0, 1.4 Hz), 7.75 (s, 1H), 7.72−8.13 (m, 5H), 8.41−8.53 (m, 2H), 8.79 (d, 1H, J = 5.0 Hz), 8.92 (dd, 1H, J = 5.0, 1.4 Hz), 9.08 (d, 1H, J = 1.4 Hz); SIMS m/z 623 (M^+ + 1 − HCl, 60), 91 (base). Anal. ($C_{38}H_{30}N_4O_5$·HCl·1.75H_2O) C, H, N.

2,3-Bis(hydroxymethyl)-6-ethoxy-7-methoxy-1-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-4-pyridyl}naphthalene hydrochloride (3ig): yield 55%; mp 204−207 °C dec; IR (KBr) 3416, 1672 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (t, 3H, J = 6.9 Hz), 3.68 (s, 3H), 4.17 (q, 2H, J = 6.9 Hz), 4.30, 4.48 (ABq, 2H, J = 11.7 Hz), 4.86 (s, 2H), 5.13 (br s, 3H), 6.73 (s, 1H), 7.40 (s, 1H), 7.61 (dd, 1H, J = 5.0, 1.4 Hz), 7.75 (s, 1H), 7.81 (dd, 1H, J = 6.0, 3.0 Hz), 7.93 (s, 1H), 7.95−8.21 (m, 3H), 8.47 (dd, 1H, J = 6.0, 3.0 Hz), 8.60−8.73 (m, 1H), 8.80 (d, 1H, J = 5.0 Hz), 9.02 (dd, 1H, J = 5.0, 1.4 Hz), 9.16 (d, 1H, J = 1.4 Hz); SIMS m/z 561 (M^+ + 1 − HCl, base). Anal. ($C_{33}H_{29}N_4O_5$·HCl·2H_2O) C, H, N.

2,3-Bis(hydroxymethyl)-7-ethoxy-6-methoxy-1-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-4-pyridyl}naphthalene hydrochloride (3jg): yield 44%; mp 211−215 °C dec; IR (KBr) 3389, 1677 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.26 (t, 3H, J = 6.9 Hz), 3.70−4.10 (m, 2H), 3.90 (s, 3H), 4.31, 4.47 (ABq, 2H, J = 11.7 Hz), 4.87 (s, 2H), 5.40 (br s, 3H), 6.70 (s, 1H), 7.41 (s, 1H), 7.59 (d, 1H, J = 5.0 Hz), 7.75 (s, 1H), 7.80 (dd, 1H, J = 6.0, 3.0 Hz), 7.94 (s, 1H), 7.95−8.18 (m, 3H), 8.47 (dd, 1H, J = 6.0, 3.0 Hz), 8.65 (d, 1H, J = 8.0 Hz), 8.79 (d, 1H, J = 5.0 Hz), 9.00 (d, 1H, J = 5.0 Hz), 9.14 (s, 1H); SIMS m/z 561 (M^+ + 1 − HCl, 82), 543 (base). Anal. ($C_{33}H_{28}N_4O_5$·HCl·0.75H_2O) C, H, N.

2,3-Bis(hydroxymethyl)-6,7-diethoxy-1-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-4-pyridyl}naphthalene hydrochloride (3kg): yield 80%; mp 207−211 °C dec; IR (KBr) 3426, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.26 (t, 3H, J = 6.9 Hz), 1.40 (t, 3H, J = 6.9 Hz), 3.75−4.08 (m, 2H), 4.18 (q, 2H, J = 6.9 Hz), 4.31, 4.47 (ABq, 2H, J = 11.6 Hz), 4.86 (s, 2H), 6.02 (br s, 3H), 6.70 (s, 1H), 7.40 (s, 1H), 7.59 (dd, 1H, J = 5.0, 1.4 Hz), 7.75 (s, 1H), 7.80 (dd, 1H, J = 6.0, 3.0 Hz), 7.93 (s, 1H), 7.93−8.13 (m, 3H), 8.47 (dd, 1H, J = 6.0, 3.0 Hz), 8.56−8.70 (m, 1H), 8.79 (d, 1H, J = 5.0 Hz), 9.00 (dd, 1H, J = 5.0, 1.4 Hz), 9.14 (d, 1H, J = 1.4 Hz); SIMS m/z 575 (M^+ + 1 − HCl, 45), 557 (base). Anal. ($C_{34}H_{30}N_4O_5$·HCl·2H_2O) C, H, N.

6,7-Dimethoxy-3-hydroxymethyl-1-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-4-pyridyl}naphthalene hydrochloride (18lg): yield 63%; mp >250 °C; IR (KBr) 3419, 1679 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.81 (s, 3H), 3.91 (s, 3H), 4.00 (br s, 2H), 4.68 (s, 2H), 7.33 (s, 1H), 7.38 (d, 1H, J = 1.4 Hz), 7.43 (s, 1H), 7.65−7.93 (m, 4H), 7.93−8.18 (m, 3H), 8.32−8.47 (m, 1H), 8.50 (dd, 1H, J = 6.0, 3.0 Hz), 8.78 (d, 1H, J = 5.0 Hz), 8.90 (dd, 1H, J = 5.0, 1.4 Hz), 9.01 (d, 1H, J = 1.4 Hz); EIMS m/z 516 (M^+ − HCl, base). Anal. ($C_{31}H_{24}N_4O_4$·HCl·1.5H_2O) C, H, N.

6,7-Dimethoxy-2-hydroxymethyl-1-{2-[1(2*H*)-phthalazinon-4-(3-pyridyl)-2-yl]-4-pyridyl}naphthalene hydrochloride (18mg): yield 50%; mp 200−213 °C dec; IR (KBr) 3412, 1682 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.69 (s, 3H), 3.90 (s, 3H), 4.40 (br s, 2H), 4.41 (s, 2H), 6.79 (s, 1H), 7.41 (s, 1H), 7.52−7.70 (m, 2H), 7.70−8.18 (m, 6H), 8.40−8.58 (m, 2H), 8.79 (d, 1H, J = 5.0 Hz), 8.93 (dd, 1H, J = 5.0, 1.4 Hz), 9.06 (d, 1H, J = 1.4 Hz); SIMS m/z 517 (M^+ + 1 − HCl, base). Anal. ($C_{31}H_{24}N_4O_4$·HCl·1.25H_2O) C, H, N.

Biological Methods. Isolation of Phosphodiesterase Isozymes. The method of Reeves et al.[13] was modified to isolate PDE isozymes. Briefly, male guinea pigs were killed with pentobarbital, 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 3 volumes of 20 mM Bis-Tris/2 mM EDTA/5 mM 2-mercaptoethanol/2 mM benzamidine/10 μM leupeptin/10 μM pepstatin A, pH 6.5, by using a Polytron PT-20. Phenylmethanesulfonyl fluoride (PMSF) dissolved in dimethyl sulfoxide (DMSO) was added to the buffer immediately before homogenization to give a final concentration of 0.1 mM. The homogenate was then centrifuged for 45 min at 35000*g* and the resulting supernatant applied to a column of Resource-Q. The PDEs were eluted from the column by using a continuous 50−1000 mM sodium acetate gradient (pH 6.5, containing 20 mM Bis-Tris, 2 mM EDTA, 5 mM 2-mercaptoethanol, 2 mM benzamidine, 0.1 mM PMSF). Fractions were collected and assayed for cAMP and cGMP PDE activity. Fractions containing high levels of type 1, 2, or 3 PDE activity from cardiac ventricle and type 4 or 5 PDE activity from lung were pooled. The combined PDE fractions were diluted to 77% 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.[14] The reaction mixture contained 50 mM Tris-HCl, pH 8.0, 5 mM $MgCl_2$, 4 mM 2-mercaptoethanol. In evaluation of the inhibitor effects of the different agents examined in types 1−5 PDE, the protein concentration in the assay was adjusted to ensure that hydrolysis of substrate ([^3H]cAMP or [^3H]cGMP) did not exceed 20% of the available substrate in the absence of an 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 30 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/stroke of air at a rate of 60 strokes/min (Harvard model 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 (OA) rabbit antiserum was prepared from rabbits (2.0−2.5 kg; Japan KBL) which had been immunized by injecting 10 mg of OA emulsified with Freund's complete adjuvant intramuscularly 4 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 >10 000 times as determined by the guinea pig 4-h PCA reaction test. Male Hartley guinea pigs (Japan SLC, Inc.) weighing 250−700 g were used. Guinea pigs were sensitized by iv administration of anti-OA rabbit antiserum (0.5 mL/kg); 20−28 h later, animals were challenged by antigen (30 μg/kg, iv). Guinea pigs were cannulated in the trachea under anesthesia with α-chloralose (120 mg/kg, iv) and ventilated with 10 mL/kg/stroke of air at a rate of 60 strokes/min (Harvard model 683). Spontaneous breathing was abolished with gallamine triethiodide (5 mg/kg, iv). The changes of pulmonary mechanics were measured by the method of Konzett and Rössler[15] 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 are expressed as the dose which suppressed antigen-induced bronchoconstriction by 50% (ED_{50}).

Rolipram Binding Studies. Male Hartley guinea pig brains were homogenized in 10 volumes of ice-cold 20 mM Tris HCl (pH 7.4) buffer containing 2 mM $MgCl_2$ and 0.1 mM DTT in a Polytron PT-10 homogenizer (Kinematica). The resulting homogenate was centrifuged at 45000*g* for 30 min at 4 °C. The pellet was washed by resuspension in 10 mL of buffer and recovered by centrifugation as before. The final pellet was suspended in Tris buffer and stored at −80 °C until use. Competition binding assays were performed after incubation of the mixture with 3 nM [^{3}H]-(±)-rolipram (Amersham), drugs, and 200 mg of membrane preparation for 60 min at 30 °C in reaction buffer (25 mM Tris HCl (pH 7.4), 5 mM $MgCl_2$, 0.05 mM 5′-AMP). Bound and free radioligand were separated by rapid filtration of mixture onto Unifilter Plate GF/B 96 (Packard Instrument). The membranes were washed four times with ice-cold buffer (25 mM Tris HCl (pH 7.4), 5 mM $MgCl_2$). Plates were dried immediately, and the bound radioactivity was counted via a TopCount microplate scintillation counter. Nonspecific binding was determined in the presence of 10 μM (±)-rolipram.

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References

(1) (a) Weishaar, R. E.; Cain, M. H.; Bristol, J. A. A New Generation of Phosphodiesterase Inhibitors: Multiple Molecular Forms of Phosphodiesterase and the Potential for Drug Selectivity. *J. Med. Chem.* **1985**, *28*, 537−545. (b) Beavo, J. A.; Reifsnyder, D. H. Primary Sequence of Cyclic Nucleotide Phosphodiesterase Isozymes and the Design of Selective Inhibitors. *Trends Pharmacol. Sci.* **1990**, *11*, 150−155. (c) Beavo, J. A. Cyclic Nucleotide Phosphodiesterases: Functional Implications of Multiple Isoforms. *Physiol. Rev.* **1995**, *75*, 725−748.

(2) Müller, T.; Engels, P.; Fozard, J. R. Subtypes of the Type 4 cAMP Phosphodiesterases: Structure, Regulation and Selective Inhibition. *Trends Pharmacol. Sci.* **1996**, *17*, 294−298.

(3) (a) Torphy, T. J. Action of Mediators on Airway Smooth Muscle Functional Antagonism as a Mechanism for Bronchodilator Drugs. *Agents Actions* **1988**, *23* (Suppl.), S37−53. (b) Giembycz, M. A.; Dent, G. Prospects for Selective Cyclic Nucleotide Phosphodiesterase Inhibitors in the Treatment of Bronchial Asthma. *Clin. Exp. Allergy* **1992**, *22*, 337−344. (c) Torphy, T. J.; Livi, G. P.; Christensen, S. B. Novel Phosphodiesterase Inhibitors for the Therapy of Asthma. *Drug News Perspect.* **1993**, *6*, 203−214.

(4) (a) Christensen, S. B.; Torphy, T. Isozyme-selective Phosphodiesterase Inhibitors as Antiasthmatic Agents. *Annu. Rep. Med. Chem.* **1994**, *29*, 185−194. (b) Hughes, B.; Owens, R.; Perry, M.; Warrellow, G.; Allen, R. PDE 4 Inhibitors: the Use of Molecular Cloning in the Design and Development of Novel Drugs. *Drug Discov. Today* **1997**, *2*, 89−101. (c) Palfreyman, M. N. Phosphodiesterase Type IV Inhibitors as Antiinflammatory Agents. *Drugs Future* **1995**, *20*, 793−804.

(5) (a) Hebenstriet, G. F.; Fellerer, K.; Fichte, K.; Fischer, G.; Geyer, N.; Meya, U.; Sastre-y-Hernández, M.; Schöny, W.; Schratzer, M.; Soukop, W.; Trampitsch, E.; Varosanec, S.; Zawada, E.; Zöchling, R. Rolipram in Major Depressive Disorder: Results of a Double-Blind Comparative Study with Imipramine *Pharmacopsychiatry* **1989**, *22*, 156−160. (b) Carpenter, D. O.; Briggs, D. B.; Knox, A. P.; Strominger, N. Excitation of Area Postrema Neurons by Transmitters, Peptides, and Cyclic Nucleotides. *J. Neurophys.* **1988**, *59*, 358−369. (c) Hood, W. B. Controlled and Uncontrolled Studies of Phosphodiesterase III Inhibitors in Contemporary Cardiovascular Medicine. *Am. J. Cardiol.* **1989**, *63*, 46−53A. (d) Heaslip, R. J.; Buckley, S. K.; Sickels, B. D.; Grimes, D. Bronchial vs Cardiovascular Activities of Selective Phosphodiesterase Inhibitors in the Anesthetized Beta-blocked Dog. *J. Pharmacol. Exp. Ther.* **1991**, *257*, 741−747.

(6) Iwasaki, T.; Kondo, K.; Kuroda, T.; Moritani, Y.; Yamagata, S.; Sugiura, M.; Kikkawa, H.; Kaminuma, O.; Ikezawa, K. Novel Selective PDE IV Inhibitors as Anti-asthmatic Agents. Synthesis and Biological Activities of a Series of 1-Aryl-2,3-bis(hydroxymethyl)naphthalene Lignans. *J. Med. Chem.* **1996**, *39*, 2696−2704.

(7) (a) Torphy, T. J.; Undem, B. J. Phosphodiesterase Inhibitors: New Opportunities for the Treatment of Asthma. *Thorax* **1991**, *46*, 512−523. (b) Heaslip, R. J.; Lombardo, L. J.; Golankiewicz, J. M.; Ilsemann, B. A.; Evans, D. Y.; Sickels, B. D.; Mudrick, J. K.; Bagli, J.; Weichman, B. M. Phosphodiesterase-IV Inhibition, Respiratory Muscle Relaxation and Bronchodilation by WAY−PDA-641. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 888−896. (c) Stafford, J. A.; Veal, J. M.; Feldman, P. L.; Valvano, N. L.; Bear, P. G.; Brackeen, M. F.; Brawley, E. S.; Connolly, K. M.; Domanico, P. L.; Han, B.; Rose, D. A.; Rutkowske, R. D.; Sekut, L.; Stimpson, S. A.; Strickland, A. B.; Verghese, M. W. Introduction of a Conformational Switching Element on a Pyrrolidine Ring. Synthesis and Evaluation of (R*, R*)-(±)-Methyl 3-acetyl-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-pyrrolidinecarboxylate, a Potent and Selective Inhibitor of cAMP-Specific Phosphodiesterase. *J. Med. Chem.* **1995**, *38*, 4972−4975. (d) Christensen, S. B.; Guider, A.; Forster, C. J.; Gleason, J. G.; Bender, P. E.; Karpinski, J. M.; DeWolf, W. E., Jr.; Barnette, M. S.; Underwood, D. C.; Griswold, D. E.; Cieslinski, L. B.; Burman, M.; Bochnowicz, S.; Osborn, R. R.; Manning, C. D.; Grous, M.; Hillegas, L. M.; Bartus, J. O.; Ryan, M. D.; Eggleston, D. S.; Haltiwanger, R. C.; Torphy, T. J. 1,4-Cyclohexanecarboxylates: Potent and Selective Inhibitors of Phosphodiesterase 4 for the Treatment of Asthma. *J. Med. Chem.* **1998**, *41*, 821−835. (e) Chambers, R. J.; Marfat, A.; Cheng, J. B.; Cohan, V. L.; Damon, D. B.; Duplantier, A. J.; Hibbs, T. A.; Jenkinson, T. H.; Johnson, K. L. Biarylcarboxamide Inhibitors of Phosphodiesterase IV and Tumor Necrosis factor-α. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 739−744.

(8) Marivet, M. C.; Bourguignon, J.-J.; Lugnier, C.; Mann, A.; Stoclet, J.-C.; Wermuth, C.-G. Inhibition of Cyclic Adenosine-3',5'-phosphate Phosphodiesterase from Vascular Smooth Muscle by Rolipram Analogues. *J. Med. Chem.* **1989**, *32*, 1450−1457.

(9) (a) Rodrigo, R. A Stereo- and Regiocontrolled Synthesis of Podophyllum Lignans. *J. Org. Chem.* **1980**, *45*, 4538−4540. (b) Forsey, S. P.; Rajapaksa, D.; Taylor, N. J.; Rodrigo, R. Comprehensive Synthetic Route to Eight Diastereomeric Podophyllum Lignans. *J. Org. Chem.* **1989**, *54*, 4280−4290.

(10) Sugahara, M.; Moritani, Y.; Terakawa, Y.; Ogiku, T.; Ukita, T.; Iwasaki, T. A Synthesis of 1-Pyridylnaphthalene Lignan Analogues. *Tetrahedron Lett.* **1998**, *39*, 1377−1380.

(11) Sugahara, M.; Ukita, T. A Facile Copper-Catalyzed Ullmann Condensation: N−Arylation of Heterocyclic Compounds Containing an −NHCO− Moiety. *Chem. Pharm. Bull.* **1997**, *45*, 719−721.

(12) Ashton, M. J.; Cook, D. C.; Fenton, G.; Karlsson, J.-A.; Palfreyman, M. N.; Raeburn, D.; Ratcliff, A. J.; Souness, J. E.; Thurairatnam, S.; Vicker, N. Selective Type IV Phosphodiesterase Inhibitors as Antiasthmatic Agents. The Syntheses and Biological Activities of 3-(Cyclopentyloxy)-4-methoxybenzamides and Analogues. *J. Med. Chem.* **1994**, *37*, 1696−1703.

(13) Reeves, M. L.; Leigh, B. K.; England, P. J. The Identification of a New Cyclic Nucleotide Phosphodiesterase Activity in the Human and Guinea-pig Cardiac Ventricle. *Biochem. J.* **1987**, *241*, 535−541.

(14) Thompson, W. J.; Terasaki, W.; Epstein, P. M.; Strada, S. J. Assay of Cyclic Nucleotide Phosphodiesterase and Resolution of Multiple Molecular Forms of the Enzyme. *Adv. Cycl. Nucleotide Res.* **1979**, *10*, 69−72.

(15) Konzett, H.; Rössler, R. Experimental Procedure for the Investigation of Bronchial Muscle. *Naunyn-Schmiedeberg's Arch. Exp. Pathol. Pharmacol.* **1940**, *195*, 71−74.

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