2p, 128113-14-4; **2q**, 128113-15-5; **2r**, 128113-16-6; **2s**, 128113-17-7; **2t**, 128113-18-8; **2u**, 128113-19-9; **2v**, 128113-20-2; **2w**, 128113-21-3; **2x**, 128113-22-4; **3a**, 20621-51-6; **3b**, 99009-49-1; **3c**, 21814-53-9; **3d**, 21814-48-2; **3e**, 21814-67-5; **4a**, 128113-23-5; **4b**, 128113-24-6; **4c**, 128113-25-7; **4d**, 128113-26-8; **4e**, 128113-27-9; **5a**, 76181-06-1; **5b**, 128113-28-0; **5c**, 128113-29-1; **5d**, 128113-30-4; **5e**, 128113-31-5; **5f**, 128113-32-6; **6**, 55776-14-2; $H_2N(CH_2)_2NMe_2$, 108-00-9; $H_2N(CH_2)_2NEt_2$, 100-36-7; $H_2N(CH_2)_2NH(CH_2)_2OH$, 111-41-1; $H_2N(CH_2)_3NMe_2$, 109-55-7; 4-chloroaniline, 106-47-8; 2,6-dichloro-3-nitrobenzoic acid, 55775-97-8.

Propenyl Carboxamide Derivatives as Antagonists of Platelet Activating Factor

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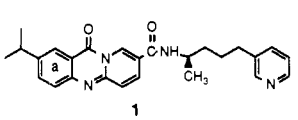
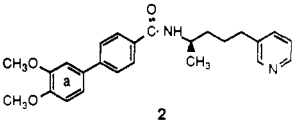
A series of *N*-[4-(3-pyridinyl)butyl] 3-substituted propenyl carboxamide derivatives bearing an unsaturated bicyclic moiety in the 3-position was prepared and evaluated for PAF (platelet activating factor) antagonist activity. These compounds represent conformationally constrained direct analogues of the corresponding potent 5-arylpentadienecarboxamides (**5**). Most of the new compounds were active in a PAF-binding assay employing whole, washed dog platelets as the receptor source and inhibited PAF-induced bronchoconstriction in guinea pigs after intravenous administration. However, oral activity in the PAF-induced bronchoconstriction model was highly sensitive to the nature and substitution of the bicyclic ring system. The most interesting compounds included [*R*-(*E*)]-(1-butyl-6-methoxy-2-naphthyl)-*N*-[1-methyl-4-(3-pyridinyl)butyl]-2-propenamide (**4b**), [*R*-(*E*)]-(3-butyl-6-methoxy-2-benzo[*b*]thiophene-yl)-*N*-[1-methyl-4-(3-pyridinyl)butyl]-2-propenamide (**4k**), and [*R*-(*E*)]-(3-butyl-6-methoxy-1-methyl-2-indolyl)-*N*-[1-ethyl-4-(3-pyridinyl)butyl]-2-propenamide (**4l**) which inhibited PAF-induced bronchoconstriction in guinea pigs with IC_{50}s of 3.0–5.4 mg/kg, when the animals were challenged 2 h after drug treatment. They were also highly effective 6 h after a 50 mg/kg oral dose. This study supports the notion that the key remote aromatic ring present in the 5-arylpentadienecarboxamides (**5**) is preferentially coplanar with the diene system for good PAF antagonist activity.

In the relatively short period since the discovery of platelet activating factor (PAF), considerable effort has been invested in determining the pathophysiological role of this ether phospholipid, particularly as a mediator of allergic[1-4] and inflammatory disease states.[5,6] The search for PAF antagonists has led to the identification of a wide assortment of structural types that exhibit potent inhibitory activity in both in vitro and in vivo screening models. Several of these PAF antagonists are currently being evaluated in man.[7]

In preceding papers from these laboratories,[8-10] we have described the synthesis and pharmacological evaluation of several related series of PAF antagonists exemplified by pyridoquinazolinecarboxamide **1**, biphenyl carboxamide



1



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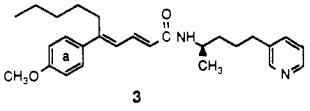

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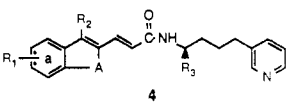
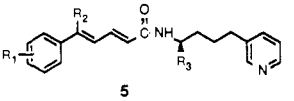


4

2, and (*E*,*E*)-5-phenyl-2,4-pentadienamide **3**, a compound that was ultimately selected for clinical development. In these reports, we discussed in detail the key structural features common to **1–3** that are apparently required for PAF inhibition. These include an aromatic ring "a" attached through an extended π-system to a carboxamide group, connected in turn with an appropriate spacer to a 3-pyridyl moiety.

The pyridoquinazolines in which the key aromatic ring "a" is part of a planar heteroaromatic ring are generally less potent PAF antagonists than the biphenylcarboxamides or the pentadienamides in which rotation of the corresponding aromatic ring out of conjugation with the remainder of the π-system is possible. We were thus interested to determine the effect of constraining analogues of **3** such that the aromatic ring would be held in conjugation with the olefin and amide portions of the molecule. In the present study, we have prepared a number of propenamide derivatives of general formula **4** in which an ortho position of the aromatic ring has been fused to C_4 of the pentadienamide moiety through a one or two atom linking unit "A".

Much of the information elicited from structure–activity studies on the 5-phenyl-2,4-pentadienamide series was available when the present program was initiated. With reference to **5**, structural elements shown to be required



5

† Chemistry Research Department.
‡ Department of Pharmacology and Chemotherapy.

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0022-2623/90/1833-2856$02.50/0

Table I. PAF Antagonist Activity of (*E*)-*N*-[4-(3-Pyridinyl)butyl]-2-propenamides

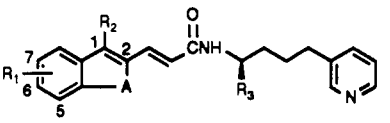
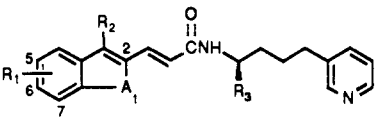
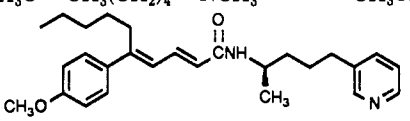
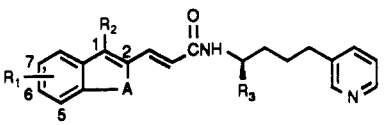
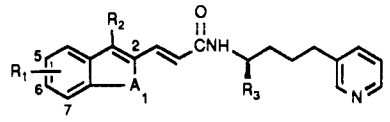
					PAF-binding inhibition:	PAF-induced bronchoconstriction assay (guinea pig): % inhibn				
						iv		50 mg/kg, po		
no.	R_1	R_2	A	R_3	IC_{50}, nM	1.0 mg/kg	ID_{50} mg/kg	2 h	6 h	ID_{50} mg/kg
										
4a	6-CH_3O	4-CH_3OPh	CH=CH	CH_3	55	92 ± 3	0.18	79 ± 2	55 ± 19	12
4b	6-CH_3O	$CH_3(CH_2)_3$	CH=CH	CH_3	7	95 ± 1	0.45	92 ± 2	71 ± 10	4.2
4c	5-CH_3O	$CH_3(CH_2)_3$	CH=CH	CH_3	6	50 ± 12	1.0	4 ± 2		
4d	7-CH_3O	$CH_3(CH_2)_3$	CH=CH	CH_3	15	0				
4e	7-CH_3O	$CH_3(CH_2)_3$	CH_3OC=CH	CH_3	3	80 ± 12	0.44	16 ± 8		
4f	H	$CH_3(CH_2)_3$	CH_3OC=CH	CH_3	1	90 ± 5	0.11	95 ± 2	52 ± 15	2.8
4g	6-CH_3O	4-CH_3OPh	CH_2CH_2	CH_3	30	95 ± 2	0.15	75 ± 2	1 ± 10	17
4h	6-CH_3O	$CH_3(CH_2)_3$	CH_2CH_2	CH_3	90	94 ± 2	0.46	50 ± 2		50
										
4i	6-CH_3O	$CH_3(CH_2)_4$	CH_2	CH_3	33	96 ± 1	0.05	0		
4j	6-CH_3O	$CH_3(CH_2)_4$	O	CH_3	40	89 ± 1	0.06	0		
4k	6-CH_3O	$CH_3(CH_2)_4$	S	CH_3	24	98 ± 1	0.11	97 ± 1	97 ± 1	5.4
4l	6-CH_3O	$CH_3(CH_2)_4$	NCH_3	CH_3CH_2	26	98 ± 0	0.07	99 ± 1	96 ± 2	3.0
3					40	99 ± 1	0.05	100 ± 1	71 ± 4	4.1

Table II. Propenamides

						%				
no.	R_1	R_2	A	R_3	method	yield	mp, °C	solvent	formula	anal.
										
4a	6-CH_3O	4-CH_3OPh	CH=CH	CH_3	A	78.8	amorphous solid		$C_{31}H_{32}N_2O_3 \cdot 0.25H_2O$	C, H, N, H_2O
4b	6-CH_3O	$CH_3(CH_2)_3$	CH=CH	CH_3	A	78.5	159–160	CH_2Cl_2–EtOAc	$C_{28}H_{34}N_2O_2$	C, H, N
4c	5-CH_3O	$CH_3(CH_2)_3$	CH=CH	CH_3	A	84.1	138–139	EtOAc–hexane	$C_{28}H_{34}N_2O_2$	C, H, N
4d	7-CH_3O	$CH_3(CH_2)_3$	CH=CH	CH_3	A	82.6	127–128	EtOAc–hexane	$C_{28}H_{34}N_2O_2$	C, H, N
4e	7-CH_3O	$CH_3(CH_2)_3$	CH_3OC=CH	CH_3	A	81.5	168–169	EtOAc–hexane	$C_{29}H_{36}N_2O_3$	C, H, N
4f	H	$CH_3(CH_2)_3$	CH_3OC=CH	CH_3	A	81.7	133–134	EtOAc–hexane	$C_{28}H_{34}N_2O_2$	C, H, N
4g	6-CH_3O	4-CH_3OPh	CH_2CH_2	CH_3	A	82.5	amorphous solid		$C_{31}H_{34}N_2O_3 \cdot 0.25H_2O$	C, H, N, H_2O
4h	6-CH_3O	$CH_3(CH_2)_3$	CH_2CH_2	CH_3	A	89.9	amorphous solid		$C_{28}H_{36}N_2O_2 \cdot 0.20H_2O$	C, H, N, H_2O
										
4i	6-CH_3O	$CH_3(CH_2)_4$	CH_2	CH_3	B	90.2	104–105.5	Et_2O–hexane	$C_{28}H_{36}N_2O_2$	C, H, N
4j	6-CH_3O	$CH_3(CH_2)_4$	O	CH_3	A	81.0	122–124	EtOAc–hexane	$C_{27}H_{34}N_2O_3$	C, H, N
4k	6-CH_3O	$CH_3(CH_2)_4$	S	CH_3	A	91.0	132–133	EtOAc	$C_{27}H_{34}N_2O_2S$	C, H, S
4l	6-CH_3O	$CH_3(CH_2)_4$	NCH_3	CH_3CH_2	B	59.5	147–148	Et_2O	$C_{29}H_{39}N_3O_2$	C, H, N

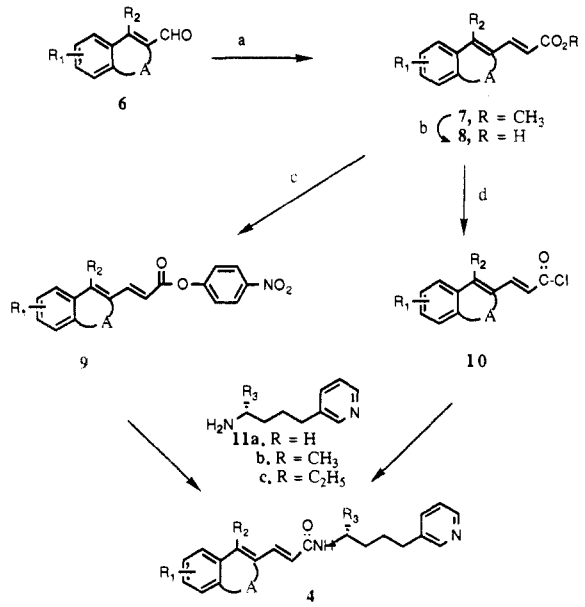
for good oral activity included (i) a methoxy substituent (R_1) in the 3- or 4-position of the phenyl ring, (ii) either an anisyl ring or a four or five carbon alkyl chain (R_2) at the 5-position of the pentadienamide system, and (iii) a methyl, ethyl, or cyclopropyl moiety (R_3) in the *R* configuration on the carbon α to the carboxamide nitrogen atom. Thus in the present work, the substitution patterns of the target compounds were generally confined within these parameters while varying the nature of the linking group "A".

Compounds in which "A" represents either a two carbon bridge or a heteroatom were evaluated both in vitro in a PAF-binding assay using washed dog platelets as the receptor and in vivo for their ability to inhibit PAF-induced bronchoconstriction in guinea pigs when administered intravenously or orally. Several of these compounds compare favorably with **3** as orally active PAF antagonists with long durations of action.

Chemistry

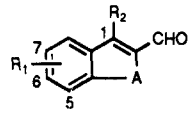
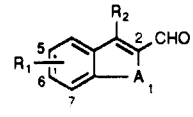
The carboxamides listed in Tables I and II were prepared by the general route shown in Scheme I. Reaction of the appropriate aldehydes **6** with (carbomethoxymethylene)triphenylphosphorane in CH_2Cl_2 and subsequent saponification of the intermediate esters **7** furnished the corresponding (*E*)-propenoic acid derivatives **8**. Con-

Scheme I[a]



[a] Reagents: (a) $Ph_3P{=}CHCO_2CH_3$, CH_2Cl_2; (b) NaOH; (c) DCC, 4-nitrophenol; (d) $(COCl)_2$.

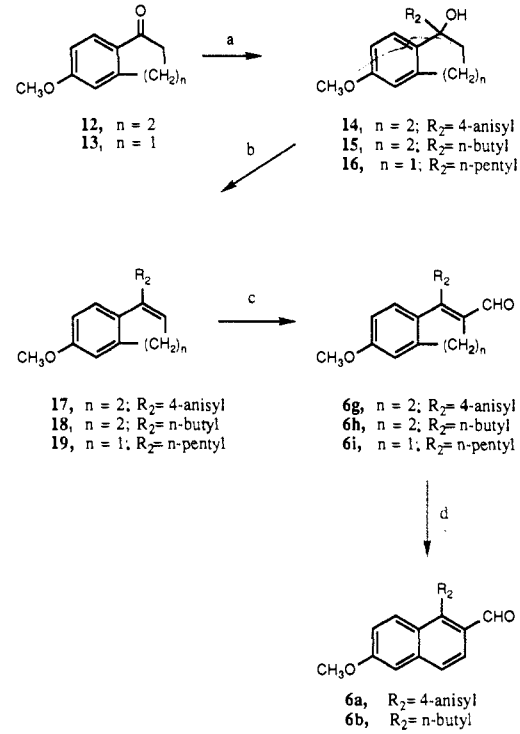
Table III. Carboxaldehydes

no.	R_1	R_2	A	method
				
6a	6-CH_3O	4-CH_3OPh	CH=CH	F
6b	6-CH_3O	$CH_3(CH_2)_3$	CH=CH	F
6c	5-CH_3O	$CH_3(CH_2)_3$	CH=CH	H
6d	7-CH_3O	$CH_3(CH_2)_3$	CH=CH	H
6e	7-CH_3O	$CH_3(CH_2)_3$	CH_3OC=CH	G
6f	H	$CH_3(CH_2)_3$	CH_3OC=CH	G
6g	6-CH_3O	4-CH_3OPh	CH_2CH_2	E
6h	6-CH_3O	$CH_3(CH_2)_3$	CH_2CH_2	E
				
6i	6-CH_3O	$CH_3(CH_2)_4$	CH_2	E
6j	6-CH_3O	$CH_3(CH_2)_4$	O	G
6k	6-CH_3O	$CH_3(CH_2)_4$	S	E
6l	6-CH_3O	$CH_3(CH_2)_4$	NCH_3	I

densation of either the derived *p*-nitrophenyl esters **9** (method C) or the acid chlorides **10** (method D) with 3-pyridinebutanamines **11**[8,10,11] gave the target carboxamides **4**.

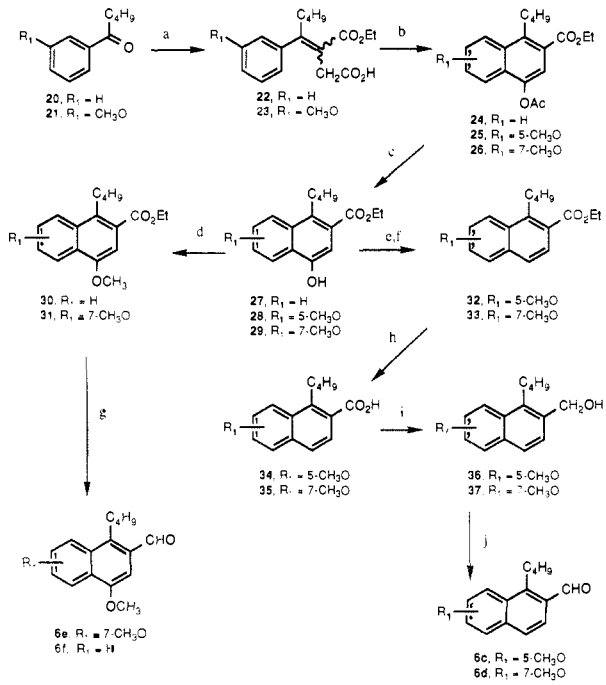
Aldehydes **6**, listed in Table III and employed as starting materials in Scheme I, were available through a variety of methods. 6-Methoxynaphthalene-2-carboxaldehydes **6a,b** and related compounds **6g–i** were prepared according to the sequence outlined in Scheme II. Reaction of 6-methoxytetralone (**12**) with (4-methoxyphenyl)magnesium bromide or butyllithium gave mixtures of the starting ketone and the desired carbinols **14** and **15**, respectively. Acid-catalyzed dehydration of the crude reaction products followed by chromatographic separation gave the 1-substituted 3,4-dihydronaphthalenes **17** and **18**, which were then transformed into the corresponding dihydro-

Scheme II[a]



[a] Reagents: (a) 4-$CH_3OPhMgBr$ or BuLi; (b) H^+; (c) $POCl_3$, DMF; (d) DDQ.

Scheme III[a]



[a] Reagents: (a) $(CH_2CO_2Et)_2$, KO-*t*-Bu; (b) NaOAc, Ac_2O; (c) ethanolic HCl; (d) MeI, K_2CO_3; (e) 1-chloro-5-phenyltetrazole, K_2CO_3; (f) H_2, Pd/C; (g) *N*-methylpiperazine-modified SMEAH; (h) NaOH; (i) BH_3–THF; (j) DMSO, oxalic acid, NEt_3, CH_2Cl_2.

naphthalene-2-carboxaldehydes **6g** and **6h** under Vilsmeier conditions (method E). In a similar manner, 6-methoxy-1-indanone (**13**) was converted to aldehyde **6i**. Dehydrogenation of the dihydronaphthalenecarboxaldehydes **6g,h** using DDQ gave 6-methoxynaphthalene-2-carboxaldehydes **6a** and **6b** (method F). Preparation of conformationally constrained carboxamides that are formally derived from the 5,5-bis(3-methoxyphenyl)-2,4-pentadienamides necessitated the synthesis of both 5- and 7-methoxy-2-

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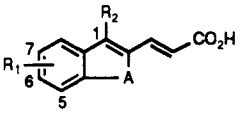
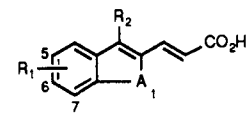
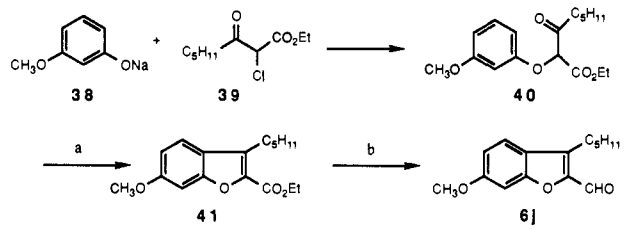
Table IV. Propenoic Acids

no.	R_1	R_2	A	% yield[a]	mp, °C	solvent	formula	anal.
								
8a	6-CH_3O	4-CH_3OPh	CH=CH	52.1	248–249	CH_2Cl_2–EtOAc	$C_{21}H_{18}O_4$	C, H
8b	6-CH_3O	$CH_3(CH_2)_3$	CH=CH	87.1	163–164	MeOH	$C_{18}H_{20}O_3$	C, H
8c	5-CH_3O	$CH_3(CH_2)_3$	CH=CH	88.7	202–204	Et_2O	$C_{18}H_{20}O_3$	C, H
8d	7-CH_3O	$CH_3(CH_2)_3$	CH=CH	74.9	160.5–161.5	Et_2O	$C_{18}H_{20}O_3$	C, H
8e	7-CH_3O	$CH_3(CH_2)_3$	CH_3OC=CH	61.2	174–176	Et_2O–hexane	$C_{19}H_{22}O_4$	C, H
8f	H	$CH_3(CH_2)_3$	CH_3OC=CH	83.0	166–167	Et_2O	$C_{18}H_{20}O_3$	C, H
8g	6-CH_3O	4-CH_3OPh	CH_2CH_2	63.1	222–224	CH_2Cl_2–EtOAc	$C_{21}H_{20}O_4$	C, H
8h	6-CH_3O	$CH_3(CH_2)_3$	CH_2CH_2	72.6	oil		$C_{18}H_{22}O_3$	*b*
								
8i	6-CH_3O	$CH_3(CH_2)_4$	CH_2	48.0	165–166	EtOAc–hexane	$C_{18}H_{22}O_3$	C, H
8j	6-CH_3O	$CH_3(CH_2)_4$	O	68.4	146–147	EtOAc	$C_{17}H_{20}O_4$	C, H
8k	6-CH_3O	$CH_3(CH_2)_4$	S	84.5	209–210	i-PrOH	$C_{17}H_{20}O_3S$	C, H, S
8l	6-CH_3O	$CH_3(CH_2)_4$	NCH_3	42.0	157–158	Et_2O	$C_{18}H_{23}NO_3$	C, H, N

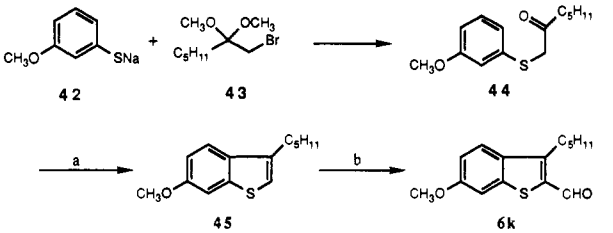
[a] From corresponding aldehyde **6**. [b] Characterized as its *p*-nitrophenyl ester (see Table V).

Scheme IV[a]



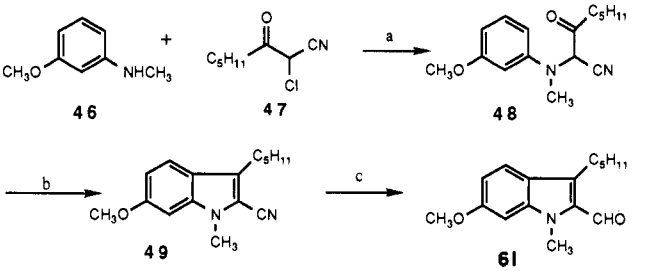
[a] Reagents: (a) H_2SO_4; (b) *N*-methylpiperazine-modified SMEAH.

Scheme V[a]



[a] Reagents; (a) H_2SO_4; (b) $POCl_3$–DMF.

Scheme VI[a]



[a] Reagents: (a) EtOH, reflux; (b) CF_3CO_2H; (c) DiBAH.

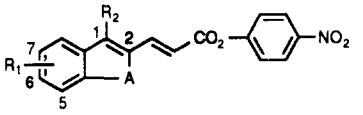
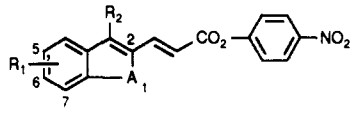
naphthaldehydes **6c** and **6d**. The route used to prepare these compounds illustrated in Scheme III also allowed entry into the electronically equivalent 4-methoxy isomer **6f**. Thus Stobbe condensation of diethyl succinate with valerophenones **20** and **21** afforded 4-phenyl-3-carbethoxy-3-butenoic acids **22** and **23**, respectively as mixtures of *E* and *Z* isomers which were employed directly in the next step. Cyclization of **22** in the presence of Ac_2O–$NaOAc$[12] provided 4-acetoxy-2-naphthoic acid ester **24**, while under the same conditions **23** furnished an isomeric mixture (~2:5) of 5- and 7-methoxy-4-acetoxy-2-naphthoic acid esters **25** and **26** that were readily separated by HPLC. Treatment of the 4-acetoxy compounds with ethanolic HCl furnished the corresponding 4-hydroxynaphthoic acid esters **27–29**, two of which, **27** and **29**, were reacted with methyl iodide and potassium carbonate to yield 4-methoxy- and 4,7-dimethoxynaphthoic acid esters **30** and **31**, respectively. To prepare 5-methoxy- and 7-methoxynaphthoic acid esters **32** and **33**, the 4-hydroxy substituent in **28** and **29** was removed by hydrogenolysis of the corresponding 1-phenyl-5-tetrazolyl ethers over palladium on carbon.[13] Transformation of 2-naphthoic acid esters **30** and **31** into the corresponding 2-naphthaldehydes **6f** and **6e** was accomplished by direct reduction of the esters with sodium bis(2-methoxyethoxy)aluminum hydride modified with *N*-methylmorpholine[14] (method G). However, in a more reliable procedure, esters **32** and **33** were hydrolyzed to the corresponding acids (**34** and **35**) and reduced with borane–tetrahydrofuran complex, and the resulting carbinols (**36** and **37**) were subjected to a Swern oxidation[15] to afford carboxaldehydes **6c** and **6d** (method H).

Scheme IV illustrates the procedure used to prepare 6-methoxy-3-benzofurancarboxaldehyde (**6j**). Sodium 3-methoxyphenolate (**38**) was condensed with 2-chloro-3-oxooctanoic acid ethyl ester (**39**) to yield the corresponding 3-anisyl ether **40**. Dehydrative cyclization of **40** in sulfuric acid and reduction of the intermediate ester **41** with the modified sodium bis(2-methoxyethoxy)aluminum hydride reagent as in method G, provided the carboxaldehyde **6j**.

The attempt to use a similar sequence to synthesize 6-methoxy-2-benzo[*b*]thiophenecarboxaldehyde (**6k**) was

(12) Baddar, F. G.; El-Assal, L. S.; Baghos, V. B. *J. Chem. Soc.* **1985**, 1714.
(13) Musliner, W. J.; Gates, W. *J. Am. Chem. Soc.* **1966**, *88*, 4271.
(14) Kanazawa, R.; Tokoroyama, T. *Synthesis* **1976**, 526.
(15) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

Table V. 4-Nitrophenyl Esters

no.	R_1	R_2	A	% yield	mp, °C	solvent	formula	anal.
								
9a	6-CH_3O	4-CH_3OPh	CH=CH	83.4	160–161	*i*-PrOH	$C_{27}H_{21}NO_6$	C, H, N
9b	6-CH_3O	$CH_3(CH_2)_3$	CH=CH	86.5	140–141	*i*-PrOH	$C_{24}H_{23}NO_5$	C, H, N
9c	5-CH_3O	$CH_3(CH_2)_3$	CH=CH	75.7	115–116	Et_2O	$C_{24}H_{23}NO_5$	C, H, N
9d	7-CH_3O	$CH_3(CH_2)_3$	CH=CH	93.1	114–115	Et_2O	$C_{24}H_{23}NO_5$	C, H, N
9e	7-CH_3O	$CH_3(CH_2)_3$	CH_3OC=CH	>99	144–145.5	*i*-PrOH	$C_{25}H_{25}NO_6$	C, H, N
9f	H	$CH_3(CH_2)_3$	CH_3OC=CH	92.1	121.5–122.5	*i*-PrOH	$C_{24}H_{23}NO_5$	C, H, N
9g	6-CH_3O	4-CH_3OPh	CH_2CH_2	44.0	151–152	*i*-PrOH	$C_{27}H_{23}NO_6$	C, H, N
9h	6-CH_3O	$CH_3(CH_2)_3$	CH_2CH_2	65.1	94–95	Et_2O-*i*-PrOH	$C_{24}H_{25}NO_5$	C, H, N
								
9j	6-CH_3O	$CH_3(CH_2)_4$	O	86.7	120–121.5	*i*-PrOH	$C_{23}H_{23}NO_6$	C, H, N
9k	6-CH_3O	$CH_3(CH_2)_4$	S	82.3	111–113	CH_2Cl_2-*i*-PrOH	$C_{23}H_{23}NO_5S$	C, H, N, S

unsuccessful since sodium thiophenolate **42** failed to produce the expected 3-methoxyphenyl thioether when reacted with the 2-chloro β-ketoester **39**. However, as outlined in Scheme V, reaction of thiophenolate **42** with 1-bromo-2,2-dimethoxyheptane (**43**), followed by cyclization of the intermediate **44** in sulfuric acid, furnished a modest yield of 6-methoxy-3-pentylbenzo[*b*]thiophene (**45**). Finally, treatment of **45** under Vilsmeier conditions furnished the target carboxaldehyde **6k**.

As shown in Scheme VI, reaction of 3-methoxy-*N*-methylaniline (**46**) with 2-chloro-3-oxooctanenitrile (**47**) gave 2-anilino-β-ketonitrile **48**, which was then cyclized in trifluoroacetic acid to afford 2-cyanoindole (**49**). Reduction of nitrile **49** with diisobutylaluminum hydride in toluene (method I) furnished 6-methoxy-*N*-methyl-3-pentylindole (**6k**).

Results and Discussion

The testing protocols used to evaluate carboxamides **4a–l** as potential inhibitors of PAF-mediated events have been described previously.[8-10] These compounds were screened initially in vitro in a PAF-binding assay utilizing prewashed dog platelets as the receptor source[16,17] and were subsequently tested for their ability to prevent PAF-induced bronchoconstriction in guinea pigs. In this model, guinea pigs were administered 1 mg/kg of the drug substance 1 min prior to intravenous challenge with a maximally constrictory dose of PAF (1 μg/kg), and the ability of the drug to inhibit the ensuing bronchoconstriction relative to control animals was determined. Compounds which caused a ≥50% inhibition of the response was further evaluated at multiple doses to determine an intravenous ID_{50} and were tested at a trial dose of 50 mg/kg, orally, 2 h prior to PAF challenge. Oral ID_{50} values and the percent inhibition 6 h after a 50 mg/kg po dose were also determined for compounds which caused a ≥50% inhibition of the bronchoconstriction response in the initial oral screen.

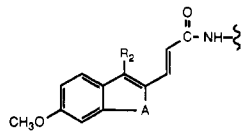
Since the carboxamides listed in Table I by design bear a close structural relationship to the more active members of the pentadienamide series of PAF antagonists **5**, it was not unexpected that most showed high levels of activity in the binding assay. Comparison of in vivo efficacy among the naphthalenepropenamides (**4a–f**) reveals that oral PAF antagonist activity is highly sensitive to the position of the methoxy group. All of these compounds except **4d** effectively attenuated the response to PAF after intravenous administration. However, after oral administration, compounds bearing a methoxy group in the 4- or 6-positions were highly efficacious while those substituted in the 5- or 7-positions, including the 4,7-dimethoxy analogue **4e**, were devoid of activity. The profound sensitivity of oral bioavailability to the position of methoxy substitution was not seen in the more flexible pentadienamide series and may be related to changes in metabolic pathways. Dihydronaphthalene derivatives **4g** and **4h** were approximately equipotent to the corresponding naphthalenes **4a** and **4b** after intravenous administration, but were less potent or shorter acting after oral dosing.

Those substances in which the linking unit "A" is included in a 5-membered carbocyclic (**4i**) or heteroaromatic ring structure (**4j–l**) exhibited levels of inhibition in the binding assay and after intravenous administration that essentially mirrored those found for the lead pentadienamide **3**. However, when these compounds were examined for oral activity, the indene (**4i**) and benzofuran (**4j**) derivatives were totally inactive while benzothiophene **4k** and indole **4l** were among the most potent and long-acting agents of this class yet encountered.

This limited study has further defined the requirements for activity in the class of PAF antagonists that include the pyridoquinazolinecarboxamides, the biphenylcarboxamides, and the pentadienecarboxamides. Compounds **4a–l** may be considered as direct, conformationally restricted analogues of pentadienamide **3** varying in the nature of the linking group "A". The naphthalenes monosubstituted with methoxy groups in the 4- and 6-positions, benzothiophene **4k**, and indole **4l** all show profiles of activity similar to that of the lead compound. These results are consistent with a model of the active conformation of both the phenylpentadienamides and the biphenylcarboxamides, in which the aromatic ring "a" in structures **2** and **3** is coplanar with the extended π-system and brings into question the relatively inferior levels of potency found in the pyridoquinazolinecarboxamides, wherein the corresponding phenyl ring is part of a rigid planar heteroaromatic ring system. We speculate that this

(16) Janero, D. R.; Burghardt, B.; Burghardt, C. *Thromb. Res.* **1988**, *50*, 789.
(17) Janero, D. R.; Burghardt, B.; Burghardt, C. *J. Pharmacol. Methods* **1988**, *20*, 237.

may be due to unfavorable effects of the electron-withdrawing pyridine nitrogen atom and carbonyl groups present in the pyridoquinazoline heteroaromatic system. A second possibility is that the connecting π-system may be preferably in the *s*-cis conformation as in partial structure **50** for good PAF antagonist activity rather than



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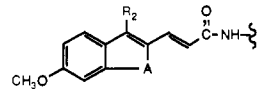

51

the *s*-trans conformation (**51**). If valid, this steric requirement could be readily accommodated by both the phenylpentadienamides and the biphenylcarboxamides but obviously not by the pyridoquinazolinecarboxamides.

In conclusion, we have prepared a series of novel PAF antagonists that may be considered conformationally constrained analogues of the orally active 5-phenylpentadienamide class of PAF antagonists **5**. Potency of these compounds in the PAF binding assay and their intravenous inhibitory activity in the PAF-induced bronchoconstriction assay seem to be independent of the nature of the constraining group "A". The most interesting analogues, **4b**,**4k** and **4l**, show oral activity and durations of action that compare favorably with pentadienamide **3**, a compound which has been selected for clinical development.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The proton NMR spectra were recorded on a Varian XL-100, XL-200, or XL-400 spectrometer, IR spectra were obtained on a Beckman IR-9 or IR-12 spectrometer, electron-impact mass spectra were taken on a CEC 21-110 mass spectrometer at 70 eV. NMR, IR, and MS spectra were recorded for each new compound reported herein and were consistent with the assigned structures. Preparative high-pressure liquid chromatography (HPLC) was performed on silica gel Prep-Pak 500 cartridges with a Waters Associates Prep LC 500A instrument. Column chromatography was accomplished on Kieselgel 60 (35–70 mesh) from E. Merck. Kieselgel 60 F_{254} plates from E. Merck were used for TLC, and compounds were visualized with UV light or iodine vapor. Bulb-to-bulb distillation was performed on a Büchi Kugelrohr apparatus and was carried out at the reported air bath temperatures until distillation ceased. Dry CH_2Cl_2 was distilled from P_2O_5; $(i\text{-Pr})_2NH$ and Et_3N were distilled from CaH_2 while DMF and THF were dried over Linde 3A sieves.

Method A. (*E*)-3-(1-Butyl-6-methoxy-2-naphthalenyl)-2-propenoic Acid Methyl Ester (7b). A solution of **6b** (1.6 g, 6.6 mmol) and (carbomethoxymethylene)triphenylphosphorane (2.45 g, 7.33 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 40 h. The solvent was removed in vacuo and the residue was triturated with a mixture of Et_2O (20 mL) and hexane (50 mL). After the resulting solid was filtered off, the filtrate was evaporated and the residue was passed through a column of silica gel (20 g) made up in Et_2O–hexane (1:9). Evaporation of the appropriate fractions furnished 1.75 g (88.9%) of **7b**. A sample was crystallized from hexane to give the analytical sample, mp 71–72 °C. Anal. ($C_{19}H_{22}O_3$) C, H.

(*E*)-3-(1-Butyl-6-methoxy-2-naphthalenyl)-2-propenoic Acid (8b). A solution of **7b** (1.7 g, 5.7 mmol) in MeOH (10 mL) was treated with 2 N NaOH (4.5 mL) and the mixture was stirred at reflux for 1 h. The warm reaction mixture was acidified with 1 N HCl (9.2 mL). After the mixture cooled, the resulting solid was collected by filtration to provide 1.6 g (98%) of **8b**. Crystallization of a portion from MeOH gave the analytical specimen, mp 163–164 °C. Anal. ($C_{18}H_{20}O_3$) C, H.

Method B. (*E*)-3-(1-Butyl-6-methoxy-2-naphthalenyl)-2-propenoic Acid 4-Nitrophenyl Ester (9b). A stirred mixture of **8b** (1.5 g, 5.28 mmol) and 4-nitrophenol (0.81 g, 5.83 mmol) in CH_2Cl_2 was cooled in an ice bath, during the addition of a solution of dicyclohexylcarbodiimide (1.1 g, 5.34 mmol) in CH_2Cl_2 (5 mL), and the reaction was stirred at room temperature over a weekend. After the precipitated dicyclohexylurea was removed by filtration, the filtrate was concentrated and applied to a column of silica gel (25 g) made up in CH_2Cl_2–hexane (2:1). Elution with the same solvent mixture and concentration of the appropriate fractions yielded 2 g of **9b**. Crystallization of the material from *i*-PrOH gave 1.85 g (86.5%) of the active ester, mp 140–141 °C. Anal. ($C_{24}H_{23}NO_5$) C, H, N.

Method C. [*R*-(*E*)]-3-(1-Butyl-6-methoxy-2-naphthalenyl)-*N*-[1-methyl-4-(3-pyridinyl)butyl]-2-propenamide (4b). A solution of **9b** (1.8 g, 4.44 mmol) and (*R*)-α-methyl-3-pyridinebutanamine (**11b**; 0.73 g, 4.44 mmol) in THF (25 mL) was maintained at room temperature for 42 h. After the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 (75 mL) and washed with 0.5 N NaOH (3 × 50 mL). The aqueous layers were extracted in turn with CH_2Cl_2 (50 mL), then the combined extracts were dried (K_2CO_3) and evaporated. The crude product was purified by HPLC (EtOAc) and subsequent crystallization from CH_2Cl_2–EtOAc to yield 1.5 g (78.5%) of **4b**, mp 159–160 °C. Anal. ($C_{28}H_{34}N_2O_2$), C, H, N.

Method D. [*R*-(*E*)]-3-(6-Methoxy-3-pentylinden-2-yl)-*N*-[1-methyl-4-(3-pyridinyl)butyl]-2-propenamide (4i). A suspension of (*E*)-3-(6-methoxy-3-pentyl-1*H*-inden-2-yl)-2-propenoic acid (**8i**; 1.43 g, 5 mmol) in $PhCH_3$ (15 mL) at 0 °C was treated dropwise with a solution of oxalyl chloride (1.09 mL, 12.5 mmol) in $PhCH_3$ (5 mL) and the reaction was stirred at room temperature for 20 min. After the mixture was concentrated to ca. half-volume in vacuo, the resulting solution of crude acid chloride was added dropwise with stirring to a chilled (−75 °C) solution of (*R*)-α-methyl-3-pyridinebutanamine (0.825 g, 5.02 mmol) in $PhCH_3$ (25 mL). The cooling bath was removed and after 1.5 h at room temperature the reaction mixture was diluted with $PhCH_3$ (50 mL) and was washed with 1 N NaOH solution. The dried (K_2CO_3) $PhCH_3$ layer was evaporated and the residue was crystallized two times from Et_2O–hexane to furnish 1.55 g (72%) of **4i**, mp 104–105.5 °C. Anal. ($C_{28}H_{36}N_2O_2$) C, H, N.

Method E. 1-Butyl-3,4-dihydro-6-methoxy-2-naphthalenecarboxaldehyde (6h). $POCl_3$ (16.6 mL) was added dropwise with stirring to DMF (70 mL) at −5 °C. After the addition was completed, the mixture was stirred at 0 °C for 15 min, then a solution of **18** (34.9 g, 0.161 mol) in DMF (30 mL) was added slowly over 15 min while the temperature of the reaction mixture was maintained at 0 °C. The cooling bath was then withdrawn and after the mixture had stirred at room temperature for 1.5 h, a few chips of ice were added followed, after 5 min, by 10 N NaOH (200 mL). The reaction mixture was heated to 110 °C, resulting in the vigorous evolution of dimethylamine from the mixture, and after 10 min the reaction was cooled, diluted with H_2O (750 mL), and extracted with CH_2Cl_2 (1 × 500 mL, 2 × 300 mL). The organic layers were washed in turn with H_2O (2 × 200 mL) and then were combined, dried ($MgSO_4$), and evaporated to furnish an amber oil that was passed through a short column of silica gel (200 g) in CH_2Cl_2. The fractions containing the product were evaporated to yield 39.4 g (~100%) of crude **6h** as an oil.

Method F. 1-Butyl-6-methoxy-2-naphthalenecarboxaldehyde (6b). A mixture of **6h** (4.6 g, 18.83 mmol) and DDQ (5.43 g, 23.92 mmol) in PhH (100 mL) was stirred at reflux for 5.5 h. The reaction was then cooled and after the precipitated hydroquinone was removed, the filtrate was washed with 1 N NaOH (3 × 75 mL). Each aqueous layer was extracted with PhH (50 mL), then the combined organic extracts were dried ($MgSO_4$) and evaporated to provide 4.2 g of crude product. Crystallization from *i*-PrOH afforded 3.1 g (68%) of **6b** as a light tan solid, mp 56–57 °C. A sample was recrystallized from the same solvent to yield the analytical specimen, mp 57–58 °C. Anal. ($C_{16}H_{18}O_2$) C, H.

Method G. 1-Butyl-4,7-dimethoxy-2-naphthalenecarboxaldehyde (6e). *N*-Methylpiperazine (8.3 mL, 76.8 mmol) in $PhCH_3$ (15 mL) was added dropwise over 5 min to a chilled (−5 °C) mixture of SMEAH in $PhCH_3$ (3.4 M, 20.6 mL, 70 mmol) and $PhCH_3$ (25 mL). This solution was added to a stirred solution of **31** (4 g, 12.64 mmol) in $PhCH_3$ (50 mL) at −40 °C. After 5 h, the cooling bath was removed and the reaction was allowed to

warm to −15 °C over 45 min, whereupon concentrated HCl (30 mL) was added slowly to destroy excess reagent. The mixture was diluted with ice-cold 1 N HCl (200 mL), and after the phases were separated, the aqueous layer was extracted with $PhCH_3$ (2 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to yield 1.35 g (42%) of crude **6e** as an oil. This material was used in subsequent reactions without further purification.

Method H. 1-Butyl-5-methoxy-2-naphthalenecarboxaldehyde (6c). A mixture of DMSO (0.54 mL, 7.56 mmol) in dry CH_2Cl_2 (3 mL) was added with stirring to a chilled (<−60 °C) mixture of oxalyl chloride (0.59 mL, 6.93 mmol) in dry CH_2Cl_2 (15 mL) at such a rate that the reaction temperature did not exceed −60 °C. After 15 min a solution of alcohol **36** (1.54 g, 6.3 mmol) in CH_2Cl_2 (6 mL) was added while the reaction temperature was maintained below −60 °C. The reaction was allowed to proceed for 15 min, then Et_3N (2.9 mL, 20.8 mmol) was added to the chilled reaction. After an additional 20 min, the cooling bath was removed and the mixture was allowed to warm to room temperature. Then 2 N HCl (225 mL) was added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to yield 1.6 g (>99%) of carboxaldehyde **6c**. Sublimation of a portion (50 °C, 0.1 mm) furnished the analytical sample, mp 61.5–62.5 °C. Anal. ($C_{16}H_{18}O_2$) C, H.

3,4-Dihydro-6-methoxy-1-(4-methoxyphenyl)naphthalene (17). A solution of (4-methoxyphenyl)magnesium bromide, freshly prepared in the normal manner in THF (200 mL) from 4-bromoanisole (101 g, 0.537 mol) and magnesium metal (14.5 g, 0.597 mol), was added over 45 min with stirring to a chilled (0 °C) solution of 6-methoxytetralone (**12**, 85 g, 0.482 mol) in dry THF (500 mL). After the addition was completed, the reaction was stirred at room temperature for 2 h and the excess reagent was destroyed by the careful addition of H_2O (50 mL). Most of the solvent was removed in vacuo and the concentrate was partitioned between EtOAc and 1 N NaOH. After the resultant solids were filtered off, the layers were separated, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give 123 g of crude carbinol **14** as an oil.

A solution of **14** (100 g) in $PhCH_3$ (800 mL) containing *p*-toluenesulfonic acid (1 g) was refluxed for 3 h in a flask equipped with a Dean–Stark trap. The cooled solution was washed with 10% $NaHCO_3$ and with brine, dried ($MgSO_4$), and evaporated. The residual material was passed through a short column of silica gel (250 g) made up in CH_2Cl_2–hexane (1:3), and the product was eluted with CH_2Cl_2–hexane (1:1). Evaporation of the appropriate fractions and crystallization of the residue twice from $PhCH_3$–hexane gave 37.1 g of **17** (36%), mp 100.5–102 °C.

1-Butyl-3,4-dihydro-6-methoxynaphthalene (18). A solution of 2.5 M *n*-BuLi in hexane (160 mL) was added to a stirred mixture of 6-methoxytetralone (**12**, 70.5 g, 0.4 mol) in Et_2O (500 mL) maintained at 10 °C. The reaction mixture was stirred at room temperature overnight, then H_2O (20 mL) was added dropwise over several minutes followed by 2 N HCl (200 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2 × 250 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give 80 g of a mixture (~1:1) of 1-butyl-1-hydroxy-6-methoxytetralin (**15**) and the starting ketone as an oil.

A solution of the crude material (80 g) in $CHCl_3$ (250 mL) containing trifluoroacetic acid (25 mL) was stirred at ambient temperature for 16 h, then the solvents were removed under reduced pressure. The residue was partitioned between CH_2Cl_2 (500 mL) and 1 N NaOH (200 mL), and the separated aqueous layer was extracted with CH_2Cl_2 (100 mL). The organic extracts were washed in turn with brine, then were combined, dried ($MgSO_4$), and concentrated in vacuo. The resulting oil was passed through a column of silica gel (400 g) made up in hexane and eluted with hexane. Evaporation of the fractions (3 × 500 mL) containing the less polar product furnished 34.9 g (40.3%) of **18** and a sample was crystallized from *i*-PrOH to provide the analytical specimen, mp 101–102 °C. Anal. ($C_{18}H_{18}O_2$) C, H.

3,4-Dihydro-6-methoxy-1-(4-methoxyphenyl)-2-naphthalenecarboxaldehyde (6g). As in method E, dihydronaphthalene derivative **17** (17 g, 63.8 mmol) was added to the reagent formed from the addition of $POCl_3$ (6.54 mL) to DMF (35 mL) at −5 °C. The cooling bath was then withdrawn, and after the mixture had stirred at 35 °C for 1.5 h, a few chips of ice were added followed after 5 min by 10 N NaOH (70 mL). After the reaction was heated to 110 °C for 10 min, the mixture was cooled and the resulting solid was removed by filtration, washed with H_2O, and dried in vacuo to give 18.75 g (99%) of **6g**, mp 104–105 °C. Crystallization of a portion from Et_2O furnished the pure aldehyde, mp 105–106 °C. Anal. ($C_{19}H_{18}O_3$) C, H.

6-Methoxy-1-(4-methoxyphenyl)-2-naphthalenecarboxaldehyde (6a). Aldehyde **6g** (9.7 g, 33 mmol) and DDQ (9.36 g, 41.2 mmol) were stirred together in PhH (150 mL) at reflux for 17 h and was worked up according to the procedure described in method F to yield 9.5 g (98%) of crude product which was crystallized from *i*-PrOH to give **6a**, mp 99–101 °C. Anal. ($C_{19}H_{16}O_3$) C, H.

4-Acetoxy-1-butyl-5-methoxy-2-naphthalenecarboxylic Acid Ethyl Ester (25) and 4-Acetoxy-1-butyl-7-methoxy-2-naphthalenecarboxylic Acid Ethyl Ester (26). To a solution of KO-*t*-Bu (25 g, 0.223 mol) in *t*-BuOH (180 mL) at 60 °C was added a mixture of diethyl succinate (52.3 g, 0.3 mol) and 1-(3-methoxyphenyl)pentanone (**21**; 38.8 g, 0.2 mol) at a rapid dropwise rate, and the reaction mixture was refluxed with stirring for 2.5 h. After the solvent was removed under reduced pressure, the residue was dissolved in H_2O (250 mL) and extracted with Et_2O (3 × 150 mL) to remove neutral materials. The aqueous layer was then acidified and extracted with CH_2Cl_2 (3 × 200 mL) to yield, after evaporation of the dried ($MgSO_4$) organic extracts, 61.3 g of a mixture of the isomeric 3-(ethoxycarbonyl)-4-(3-methoxyphenyl)-3-octenoic acids **23** as an oil.

A solution of the above mixture of acids (15 g, 46.8 mmol) and NaOAc (3.9 g, 46.4 mmol) in Ac_2O (90 mL) was heated at reflux for 4 h. The solvent was removed in vacuo and the residue was partitioned between CH_2Cl_2 (200 mL) and 10% K_2CO_3 solution (100 mL). The dried ($MgSO_4$) organic layer was concentrated and the resulting mixture was separated by using HPLC (Et_2O–hexane, 1:3). Evaporation of the appropriate fractions furnished two isomeric compounds weighing 7.2 and 2.7 g (42.7% and 16% from **23**), respectively.

Crystallization of the major component from hexane afforded 7-methoxynaphthoic acid ester **26**, mp 70–71.5 °C. Anal. ($C_{20}H_{24}O_5$) C, H.

Crystallization of the more polar minor isomer from hexane gave the corresponding 5-methoxy isomer **25**, mp 86–88 °C. Anal. ($C_{20}H_{24}O_5$) C, H.

1-Butyl-4-hydroxy-5-methoxy-2-naphthalenecarboxylic Acid Ethyl Ester (28). A solution of **25** (3.3 g, 9.58 mmol) in 1.05 M ethanolic HCl (35 mL) was heated at reflux for 1.5 h and the solvent was removed under reduced pressure. Crystallization of the residual material from hexane provided 2.5 g (86.3%) of **28**, mp 80–82 °C. Anal. ($C_{18}H_{22}O_4$) C, H.

1-Butyl-4-hydroxy-2-naphthalenecarboxylic Acid Ethyl Ester (27). As in the sequence described above for the preparation of **25** and **26**, 1-phenylpentanone (**20**; 50 g, 0.308 mol) was heated with diethyl succinate (80.5 g, 0.462 mol) in *t*-BuOH at 60 °C for 6 h in the presence of KO-*t*-Bu (38 g, 0.334 mol). The normal workup furnished 81 g of a mixture of the isomeric 3-(ethoxycarbonyl)-3-octenoic acids **22** as an oil. The acids (79.4 g, 0.273 mol) were cyclized as above by refluxing in acetic anhydride (500 mL) containing NaOAc (22.5 g, 0.273 mol) for 9 h. After workup, the crude product was passed through a short column of silica gel (650 g) made up in CH_2Cl_2–hexane (2:1) to give 60 g of 4-acetoxy compound **24** as an oil. A solution of **24** (60 g) in 1 M ethanolic HCl (500 mL) was heated at reflux for 0.75 h and after the solvent was evaporated, the residue was crystallized from hexane to give 46.6 g of ethyl ester **27**, mp 117–120 °C (57% from **20**). Recrystallization of a portion from hexane gave the pure ester, mp 118–119 °C. Anal. ($C_{17}H_{20}O_3$) C, H.

1-Butyl-4-methoxy-2-naphthalenecarboxylic Acid Ethyl Ester (30). A solution of **27** (27 g, 99 mmol) and iodomethane (17 mL, 0.25 mol) in Me_2CO (200 mL) containing K_2CO_3 (13.8 g, 0.1 mol) was stirred at room temperature for 24 h. After the reaction mixture was filtered, the filtrate was concentrated to dryness and the residue was partitioned between CH_2Cl_2 (350 mL) and H_2O (200 mL). The dried ($MgSO_4$) organic layer was evaporated and the residual material was distilled on a Kugelrohr

apparatus (135–138 °C, 0.1 mm) to provide 25.8 g (91%) of **30** as an oil. Anal. ($C_{18}H_{22}O_3$) C, H.

1-Butyl-4,7-dimethoxy-2-naphthalenecarboxylic Acid Ethyl Ester (31). As described above for the preparation of **30**, naphthol **29** (6.5 g, 21.5 mmol) was allowed to react with iodomethane (7 mL, 112 mmol) in acetone (65 mL) containing K_2CO_3 (5 g, 36.2 mmol) with stirring at room temperature for 64 h. The crude product obtained after the usual workup was crystallized from *i*-PrOH to yield 5.35 g (78.7%) of **31**, mp 44–45 °C. Anal. ($C_{19}H_{24}O_4$) C, H.

1-Butyl-5-methoxy-2-naphthalenecarboxylic Acid Ethyl Ester (32). KO-*t*-Bu (2.3 g, 20.5 mmol) was added to a solution of 4-naphthol derivative **28** (5.39 g, 17.83 mmol) and 5-chloro-1-phenyl-1*H*-tetrazole (3.48 g, 18.72 mmol) in DMF (20 mL), and the reaction mixture was stirred at room temperature for 1.25 h. After the solvent was removed in vacuo, the residual material was partitioned between CH_2Cl_2 (150 mL) and H_2O (75 mL). The separated aqueous layer was reextracted with CH_2Cl_2, and after each organic extract was washed with H_2O, the extracts were combined, dried (Na_2SO_4), and evaporated. Crystallization of the crude product from Et_2O–hexane gave 6.7 g of the corresponding 1-phenyltetrazolyl ether as a brown solid, mp 143–145 °C.

A solution of the above tetrazolyl ether (6.65 g, 14.89 mmol) in a mixture of THF (25 mL) and EtOH (75 mL) was hydrogenated over 10% Pd/C (1.3 g) at 50 °C under a H_2 pressure of 50 psi. After the uptake of H_2 had stopped, the catalyst was removed by filtration and the filtrate was concentrated to dryness. The resulting material was dissolved in Et_2O (150 mL) and the solution was extracted with 1 N NaOH (2 × 50 mL). After the base washes were extracted with Et_2O, the combined organic layers were dried ($MgSO_4$) and evaporated to yield 3.6 g (70.5%) of **32** as an oil. A portion was distilled on a Kugelrohr apparatus (140 °C, 0.1 mm) to furnish the analytical sample. Anal. ($C_{18}H_{22}O_3$) H; C: calcd, 75.50; found, 75.02.

1-Butyl-5-methoxy-2-naphthalenecarboxylic Acid (34). Ethyl ester **32** (3.45 g, 12 mmol) in MeOH (40 mL) was saponified with 2 N NaOH (10 mL) at reflux for 1.75 h. The usual workup afforded 3.1 g (99%) of **34**, mp 151–153 °C, and crystallization of a sample from Et_2O–hexane gave the analytical sample, mp 154–155 °C. Anal. ($C_{16}H_{18}O_3$) C, H.

1-Butyl-5-methoxy-2-naphthalenemethanol (36). A solution of BH_3 in THF (1 M, 10 mL) was added to a solution of naphthoic acid **34** (2.0 g, 7.74 mmol) in THF (15 mL) at 0–5 °C and the mixture was stirred at room temperatue for 3 h. After the solvent was evaporated, the reaction was diluted with 1 N NaOH and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), evaporated, and crystallized from hexane to give 1.58 g (83.5%) of alcohol **36**, mp 100–102 °C. Recrystallization of a portion from Et_2O–hexane afforded the analytical sample, 101–102 °C. Anal. ($C_{16}H_{20}O_2$) C, H.

1-Butyl-7-methoxy-2-naphthalenecarboxaldehyde (6d). As described for the preparation of **6c**, hydrolysis of **26** in 1.05 M ethanolic HCl furnished the deacetylated material **29** (mp 114–115 °C), which was converted to the corresponding 1-phenyltetrazolyl ether (mp 95.5–96.5 °C) and then hydrogenolyzed and saponified to give acid **35** (mp 123–125 °C). Reduction of **35** with BH_3 afforded carbinol **37** (mp 52–53 °C), and subsequent Swern oxidation (method G) provided aldehyde **6d** as an oil. Distillation of a sample on a Kugelrohr apparatus (138–140 °C, 0.1 mm) gave the analytical specimen. Anal. ($C_{16}H_{18}O_2$) C, H.

1-Butyl-4-methoxy-2-naphthalenecarboxaldehyde (6f). As in method G, ethyl ester **30** (8.6 g, 30 mmol) in $PhCH_3$ (100 mL) was treated with the reagent formed from the addition of *N*-methylpiperazine (19.6 mL, 0.182 mol) to a mixture of SMEAH in $PhCH_3$ (3.4 M, 49 mL) and $PhCH_3$ (90 mL) at −45 °C for 2 h and then at −15 °C for 1 h. The usual workup gave 7.5 g of crude aldehyde, which was crystallized from *i*-PrOH to provide 4.1 g (56%) of **6f**, mp 51–52 °C. Anal. ($C_{16}H_{18}O_2$) C, H.

6-Methoxy-3-pentyl-1*H*-indene (19). A solution of pentylmagnesium bromide (2 M; 83 mL) was added with stirring to a chilled (−5 °C) solution of 5-methoxy-1-indenone (**13**; 24.33 g, 0.15 mol) in dry THF (100 mL) and the mixture was stirred at room temperature for 1.5 h. A few chips of ice were added to destroy excess reagent and after the solvents had been removed under reduced pressure, the residue was taken up in a mixture of CH_2Cl_2 (250 mL) and 2 N HCl and stirred at room temperature for 3 h. The separated aqueous phase was extracted with CH_2Cl_2 (150 mL), then the combined organic layers were dried ($MgSO_4$) and evaporated to provide 30 g of crude product as an oil. Purification of the material by HPLC (CH_2Cl_2–hexane, 2:5) gave 21.62 g (66.6%) of **19** as an oil.

6-Methoxy-3-pentyl-1*H*-indene-2-carboxaldehyde (6i). According to method E, **19** (21.6 g, 0.1 mol) was reacted with the reagent formed from the addition of $POCl_3$ (10.25 mL, 0.11 mol) to DMF (70 mL) at −5 °C. The cooling bath was withdrawn and after the reaction was stirred at room temperature for 1.5 h, excess reagent was destroyed by the addition of a few ice chips followed in 5 min by the addition of 10 N NaOH (70 mL). The reaction was heated to 110 °C for 10 min, then it was worked up in the described manner to give a complex mixture of products. Purification of the crude by HPLC (CH_2Cl_2–hexane, 3:2) gave 8.6 g of **6i** as an oil. A sample was subjected to bulb-to-bulb distillation (180–190 °C, 0.1 mm) to give the analytical sample. Anal. ($C_{16}H_{20}O_2 \cdot 0.3H_2O$) C, H.

2-Chloro-3-oxooctanoic Acid Ethyl Ester (39). Sulfuryl chloride (39 mL, 0.465 mol) was added dropwise over 75 min to 3-oxooctanoic acid ethyl ester (85 g, 0.456 mol) with stirring at −10 °C. The mixture was left overnight at ambient temperature, and after the remaining gaseous HCl and SO_2 were removed (water aspirator), the crude chloro compound was distilled in vacuo (71–74 °C, 0.15 mm) to yield 96.2 g of **39** (95.6%) as a colorless oil.

6-Methoxy-3-pentyl-2-benzofurancarboxylic Acid Ethyl Ester (41). A mixture of 2-chloro-3-oxooctanoic acid ethyl ester (**39**; 51.5 g, 0.235 mol) and sodium 3-methoxyphenolate (**38**; 35 g, 0.239 mol) was refluxed with stirring in PhH (250 mL) for 7 h and then stirred at room temperature overnight. The cooled reaction was washed with H_2O (2 × 250 mL), and the dried ($MgSO_4$) organic layer was evaporated to give 70 g of a brown oil. The crude product was purified by HPLC (Et_2O–hexane, 1:19) to give 30.45 g (42%) of the intermediate **40** as a colorless oil.

The above oil (21.5 g, 70 mmol) was added over 1 h with stirring to H_2SO_4 (22 mL) at −10 °C. After 1 h at −10 °C, the reaction was diluted carefully with ice (400 g) and extracted with Et_2O (2 × 400 mL). The organic extracts were washed in turn with saturated $NaHCO_3$ and with brine and then were combined, dried ($MgSO_4$), and evaporated. The crude reaction product was crystallized from hexane to give 10.86 g (53.5%) of ethyl ester **41**, mp 38–41 °C. A sample was recrystallized from EtOH–H_2O to furnish the analytical specimen, mp 39.5–41.5 °C. Anal. ($C_{17}H_{22}O_4$) C, H.

6-Methoxy-3-pentyl-2-benzofurancarboxaldehyde (6j). As described in method G, SMEAH in $PhCH_3$ (3.4 M, 33.6 mL) and $PhCH_3$ (30 mL) pretreated with *N*-methylpiperazine (13.5 mL, 0.125 mol) in $PhCH_3$ (20 mL) was reacted with ester **41** (6 g, 20.66 mmol) in $PhCH_3$ (90 mL) for 30 min at −45 °C. The previously described workup yielded 4.82 g (~95%) of aldehyde **6j** as an oil contaminated with a minor amount of the corresponding carbinol. A portion was purified by HPLC (CH_2Cl_2–hexane, 4:1) and then distilled (Kugelrohr; 180 °C, 0.1 mm) to give the pure aldehyde as an oil. Anal. ($C_{15}H_{18}O_3$) C, H.

6-Methoxy-3-pentylbenzo[*b*]thiophene (45). To a stirred solution of 3-methoxythiophenolate (**42**; 45 g, 0.277 mol) in H_2O (100 mL) at 15 °C was added dropwise over 20 min 1-bromo-2,2-dimethoxyheptane (**43**; 54.5 g). The reaction mixture was stirred for 1 h at room temperature then was extracted with Et_2O (2 × 250 mL). The ether extracts were washed in turn with H_2O (2 × 100 mL) and 1 N HCl (2 × 100 mL). The dried ($MgSO_4$) organic layers were combined and evaporated to yield crude 1-[(3-methoxyphenyl)thio]-2-heptanone (**44**; 67 g).

Crude ketone **44** (65 g) was added over 30 min with stirring to H_2SO_4 at −10 °C. After 30 min at −5 °C, the reaction mixture was diluted carefully with ice (200 g) and the resulting solid was filtered off, washed with H_2O, and dried to give 40 g of crude cyclized material **45**. Crystallization of material from hexane furnished 18.4 g (30.4%) of **45**, (mp 43–45 °C) and a sample was recrystallized from hexane to provide the analytical specimen, mp 45–47 °C. Anal. ($C_{14}H_{18}OS$) C, H, S.

6-Methoxy-3-pentyl-2-benzo[*b*]thiophenecarboxaldehyde (6k). As in method E, benzothiophene **45** (9.37 g, 40 mmol) was reacted with the reagent formed from the addition of $POCl_3$ (4.1 mL, 44 mmol) to DMF (25 mL) at −5 °C. The cooling bath was

withdrawn and after the reaction stirred at room temperature for 3 h and then at 45 °C overnight, excess reagent was destroyed by the addition of a few ice chips followed in 5 min by the addition of 10 N NaOH (50 mL). The reaction was heated to 110 °C for 10 min, then it was worked up in the described manner to give 9 g of crude aldehyde. Crystallization of the reaction product from hexane gave 7.83 g (75%) of **6k**, mp 44–46 °C. Recrystallization of a portion from ether furnished the pure aldehyde, mp 48.5–50 °C. Anal. ($C_{15}H_{18}O_2S$) C, H, S.

6-Methoxy-1-methyl-3-pentyl-2-indolecarbonitrile (49). A solution of 3-methoxy-*N*-methylaniline (**46**; 9.8 g, 55.4 mmol) and 2-chloro-3-oxooctanenitrile (**47**; 6.2 g, 53.25 mmol) in EtOH (25 mL) was heated at reflux for 17 h, then the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL) and was washed with 1 N HCl (3 × 50 mL). The aqueous layers were extracted in turn with CH_2Cl_2 (50 mL), and the combined organic layers were dried (K_2CO_3) and evaporated. The residual oil was purified by HPLC (Et_2O–hexane, 3:7) to yield 6.42 g of 2-(3-methoxy-*N*-methylanilino)-3-oxooctanenitrile (**48**) as an oil.

The above material was dissolved in trifluoroacetic acid (15 mL) and the solution was allowed to stand overnight at ambient temperature. The solvent was then evaporated and the residue was partitioned between CH_2Cl_2 (100 mL) and 1 N NaOH (100 mL). The dried (K_2CO_3) organic layer was evaporated and the residue was purified by HPLC (Et_2O–hexane, 1:1) to give 3.2 g (31.2%) of **49** as an oil.

6-Methoxy-1-methyl-3-pentyl-2-indolecarboxaldehyde (6l). A solution of diisobutylaluminum hydride in $PhCH_3$ (1.5 M, 8.5 mL) was added with stirring to a chilled (−40 °C) solution of nitrile **49** (2.85 g, 11.12 mmol) in dry $PhCH_3$ (25 mL). After 10 min, the cooling bath was removed and the reaction was stirred at room temperature for 2 h followed by the careful addition of 5% H_2SO_4 (100 mL). The mixture was heated at 40 °C for 45 min and then was cooled and diluted with $PhCH_3$ (75 mL), and the layers separated. The dried (Na_2SO_4) organic layer was evaporated to afford 2.81 g (97%) of aldehyde **6l** as an oil.

PAF-Binding Assay.[16,17] [^{3}H]PAF was obtained from the New England Nuclear Co. Platelet-rich plasma was prepared by centrifugation of citrate-treated dog blood. Acidification to pH 6.5 with 0.15 M citric acid and centrifugation for 10 min at 1000*g* yielded a platelet-rich pellet which was then washed by resuspension in phosphate-buffered saline (PBS), pH 7.3, containing 1 mM EDTA and recentrifugation. The washed platelet preparation was adjusted to 2×10^7 platelets/0.05 mL in 0.1% BSA–PBS. Platelet counting was done with a Royco Cell-Crit 921 instrument.

To a 0.40-mL Microfuge tube containing 0.05 mL of silicone oil was added buffer and a PAF standard or a test drug to bring the aqueous volume to 0.15 mL. Then, 0.05 mL of a solution of [^{3}H]PAF (10000 cpm, 45 Ci/mM) in EtOH was added followed by 2×10^7 dog platelets. After mixing, incubation for 10 min at room temperature, and centrifugation for 1 min in a Beckman Microfuge B (8000*g*), the pellet was removed by clipping off the tip of the tube and the platelets were washed out of the tip with 0.20 mL of 50% MeOH. For counting, 10 mL of Aquasol was added, and the radioactivity in the samples was determined with a Searle Mark III liquid-scintillation counter linked to an Iso-Data microprocessor.

Experiments were run in triplicate; compounds were initially evaluated at a concentration of 1 μM and percent specific inhibition was determined. Those drugs that significantly inhibited specific PAF binding were reevaluated at three or more logarithmically spaced concentrations and IC_{50} values were determined by linear regression from log plots of concentration vs specific inhibition. The correlation coefficient for the regression line of each antagonist was always greater than 0.95.

In Vivo PAF-Induced Bronchoconstriction Assay. Male guinea pigs (Hartley strain, Charles River) weighing 400–600 g were anesthetized with urethane (2 g/kg) given intraperitoneally, and a polyethylene cannula was inserted into the jugular vein for intravenous drug administration. Tracheal pressure (centimeters of water) was recorded from a Statham pressure transducer (P 32 AA). Propanolol was administered 5 min before PAF challenge. Two minutes later, spontaneous breathing was arrested with succinylcholine chloride (1.2 mg/kg) administered intravenously, and the animals were ventilated with a Harvard Model 680 small-animal respirator set at 40 breaths/min and a 4.0 cm^3 stroke volume.

For intravenous drug dosing, test drug or vehicle were administered through the cannula into the jugular vein 1 min before the animals were challenged with a maximum constrictory dose of PAF (1 μg/kg) given intravenously. The change in tracheal pressure was averaged for four contol and four drug-treated animals and the percent inhibition was calculated. For oral drug dosing, animals were dosed with the test compound or vehicle at the appropriate interval prior to intravenous challenge with PAF as noted above. ID_{50} values for active compounds were determined by linear regression of log dose–response curves generated by at least three doses that caused statistically significant inhibition of the PAF-induced bronchoconstriction of between 10 and 90%. The correlation coefficient for the regression line of each antagonist was always greater than 0.95.

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