was diluted to 50 mL with ethyl acetate, was washed successively with water, dilute sodium hydroxide, and brine, dried, and concentrated. Chromatography over 50 g of silica gel, with ethyl acetate as eluant, and recrystallization of the product from ethyl acetate–hexane afforded 0.40 g (56%) of **48**, mp 117–119 °C. Anal. ($C_{26}H_{30}N_2O_3$): C, H, N.

PAF-Binding Assay.[10,11] [^{3}H]PAF was obtained from the New England Nuclear Company. 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 minutes at 1000*g* yielded a platelet-rich pellet which was then washed by resuspension in phosphate-buffered saline, pH 7.3 (PBS) 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 using a Royco Cell-Crit 921.

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. A solution (0.05 mL) of [^{3}H]PAF (10 000 cpm, 45 Ci/mM) in ethanol 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% methanol. 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 which significantly inhibited specific PAF binding were reevaluated at three or more logarithmically spaced concentrations and IC_{50} values were determined by linear regression of 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 control 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.

Acknowledgment. We thank members of the Physical Chemistry Department, Hoffmann-La Roche, Inc., for determination of the spectral and microanalytical data for the compounds reported herein. We also thank Dr. R. W. Kierstead for his continued support and encouragement during the course of these studies.

Pentadienyl Carboxamide Derivatives as Antagonists of Platelet-Activating Factor

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A series of *N*-[4-(3-pyridinyl)butyl]-5,5-disubstituted-pentadienamides was prepared and evaluated for PAF-antagonist activity. Compounds were assayed in vitro in a PAF-binding assay employing washed, whole dog platelets as the receptor source and in vivo after intravenous or oral administration for their ability to prevent PAF-induced bronchoconstriction in guinea pigs. Criteria required for good oral activity in the latter model include an (*E*,*E*)-5-phenyl-2,4-pentadienamide, a second phenyl or a four- or five-carbon alkyl moiety in the 5-position of the diene, and an (*R*)-[1-alkyl-4-(3-pyridinyl)butyl] substituent on the carboxamide nitrogen atom. The alkyl substituent on this side chain can be methyl, ethyl, or cyclopropyl. Two members of this series, [*R*-(*E*)]-5,5-bis(4-methoxyphenyl)-*N*-[1-methyl-4-(3-pyridinyl)butyl]-2,4-pentadienamide (**31**) and [*R*-(*E*,*E*)]-5-(4-methoxyphenyl)-*N*-[1-methyl-4-(3-pyridinyl)butyl]-2,4-decadienamide (**58**), were selected for further pharmacological evaluation. Both were found to be substantially longer acting after oral administration than the corresponding *S* enantiomers in the guinea pig bronchoconstriction assay. A second in vivo model used to evaluate PAF antagonists determines the ability of test compounds to decrease the area of skin wheals induced by an intradermal injection of PAF. In this model, using both rats and guinea pigs, compounds **31** and **58** were found to be as active as the reference PAF antagonist 3-[4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-2-yl]-1-(4-morpholinyl)-1-propanone (**45**).

We have recently described the preparation and evaluation of two series of novel platelet-activating-factor (PAF) antagonists typified by the pyridoquinazolinecarboxamide **1**[1] and the biphenylcarboxamide **2**.[2] Key elements of these compounds were shown to be the aromatic ring marked "a", the carboxamide moiety, and the 3-substituted pyri-

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

(1) Tilley, J. W.; Burghardt, B.; Burghardt, C.; Mowles, T. F.; Lienweber, F.-J.; Klevans, L.; Young, R.; Hirkaler, G.; Fahrenholtz, K.; Zawoiski, S.; Todaro, L. J. *J. Med. Chem.* **1988**, *31*, 466–472.

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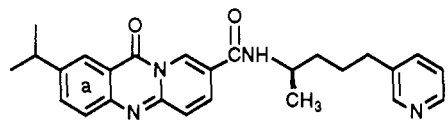

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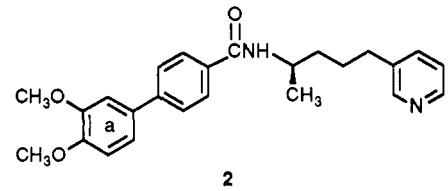

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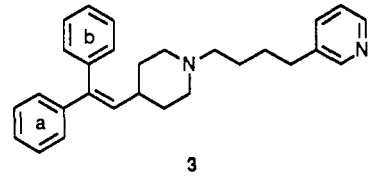

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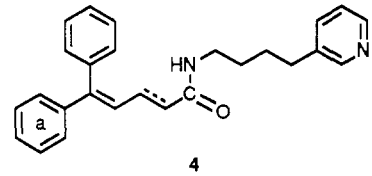


4

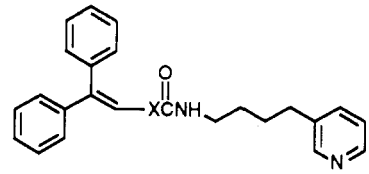
dine ring separated by the appropriate distances. In our search for new lead compounds, we have relied on a PAF-binding assay employing whole, washed dog platelets.[3] From this effort, the (diphenylethenyl)piperidine **3** was also identified as a relatively potent inhibitor of PAF binding (IC_{50} 100 nM) although it was devoid of activity in our in vivo tests used to profile PAF antagonists. Molecular modeling experiments indicated that low-energy conformations of **1**, **2**, and **3** exist in which the aromatic ring of **3** marked "a" is superimposed with the corresponding rings of **1** and **2** and the piperidine nitrogen is superimposed with the carboxamide nitrogen atoms of **1** and **2**, while the pyridine rings with their side chains are free to adopt the same conformation in all three molecules. When fit in this manner, a correspondence between the second aromatic ring of **3**, marked "b", and the pyridoquinazoline carbonyl group of **1** is also seen.

We thus hypothesized that all three molecules interact with the PAF receptor in a similar manner and were encouraged to consider ring-opened derivatives of **3**, such as **4**, as an approach to PAF antagonists with improved in vivo activity. In this paper, we describe the structure–activity studies carried out on compounds of the general structure **4** and detail the process which led to the selection of the orally active, long-acting PAF antagonist **58** for in-depth pharmacological study.

Chemistry

The diphenylalkenamides and the dienamides listed in Tables I–IV were obtained by acylation of the appropriate amines with various diphenylalkenoic acids or dienoic acids through the intermediacy of a mixed anhydride (method A), an acid chloride (method B), or a 4-nitrophenyl ester (method C). The physical properties of most of these amides are summarized in Table V; the remainder are described individually in the Experimental Section. Methods A and C were useful in the coupling of the heteroaromatic alkylamines described herein, although hindered alkylamines, such as the tertiary alkylamine **108**, required prolonged reaction times or elevated reaction temperatures when coupled via the active-ester method. Of the three methods, only the acid chloride procedure could be used successfully to acylate the anilines leading to **50** and **51**.

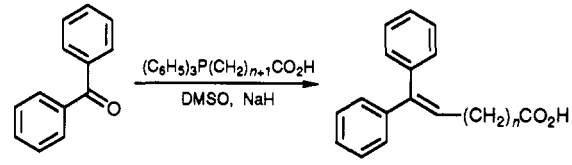
Table I. PAF-Antagonist Activity of *N*-[4-(3-Pyridinyl)butyl]alkenamides



no.	X	inhibn of PAF binding: IC_{50},[a] nM	guinea pig bronchoconstriction assay: % inhibn,[b] 0.5 mg/kg, iv	ID_{50},[a,b] mg/kg, iv	% inhibn,[c] 50 mg/kg, po
5	bond	450	66 ± 10	0.58	28 ± 4
6	CH_2	inact[d]			
7	$(CH_2)_2$	100	21 ± 2		
8	$(CH_2)_3$	inact[d]			
9	$(CH_2)_4$	550	15 ± 6		
10	$(CH_2)_5$	inact[d]			
11		400	−1 ± 2		
12		55	60 ± 8	0.62	35 ± 2

[a] IC_{50} and ID_{50} vaues were determined by linear-regression analysis; the correlation coefficient for each regression line was >0.95. [b] One-minute pretreatment time. [c] Two-hour pretreatment time. [d] Inact = no significant inhibition at 1000 nM.

The shorter chain diphenylalkenoic acids were prepared by literature procedures[4-6] and the remaining alkenoic acids **66–68** were available through a Wittig reaction in-



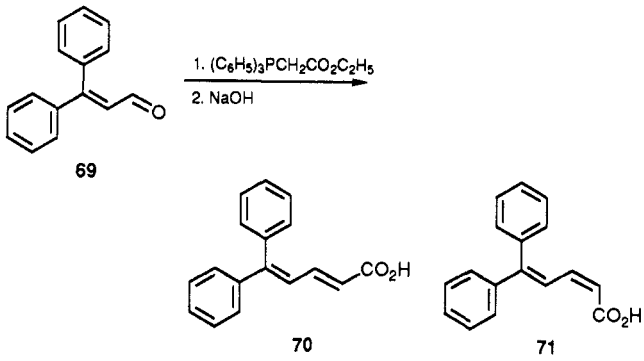
65

66: $n = 3$
67: $n = 4$
68: $n = 5$

volving condensation of benzophenone with the ylide derived from the action of dimsyl sodium on the appropriate (ω-carboxyalkyl)triphenylphosphonium bromide. A Wittig reaction between (carbethoxymethylene)triphenylphosphorane and the aldehyde **69** (method D) gave an isomeric mixture of esters which was separated by HPLC and hydrolyzed with sodium hydroxide to give the (*E*)- and (*Z*)-diphenylpentadienoic acids **70** and **71**.

The intermediate dienoic acids listed in Table VII were prepared from the starting carbonyl compounds in a two-stage synthetic approach that allowed sequential introduction of each double bond in the diene system. Since the dienoic acids can exist in as many as four isomeric forms, methods and reaction conditions were chosen that allowed some measure of stereochemical control around the newly formed double bonds. As shown in Scheme I, the initial stage, homologation of the ketones **72** into the α,β-unsaturated aldehydes **73**, was generally accomplished via a directed aldol condensation through reaction of the substrate with a lithioenaminophosphonate as described

(2) Tilley, J. W.; Clader, J. W.; Zawoiski, S.; Wirkus, M.; LeMahieu, R. A.; O'Donnell, M.; Crowley, H.; Welton, A. F. *J. Med. Chem.*, preceding paper in this issue.
(3) Janero, D. R.; Burghardt, B.; Burghardt, C. *Thrombosis Res.* **1988**, *50*, 789. Janero, D. R.; Burghardt, B.; Burghardt, C. *J. Pharmacol. Methods* **1988**, *20*, 237.
(4) Jorgenson, M.; Thatcher, A. *Org. Synth.* **1968**, *48*, 75.
(5) Borche, W. *Justus Liebigs Ann. Chem.* **1936**, *526*, 18.
(6) Puterbaugh, W. *J. Org. Chem.* **1962**, *27*, 4010.

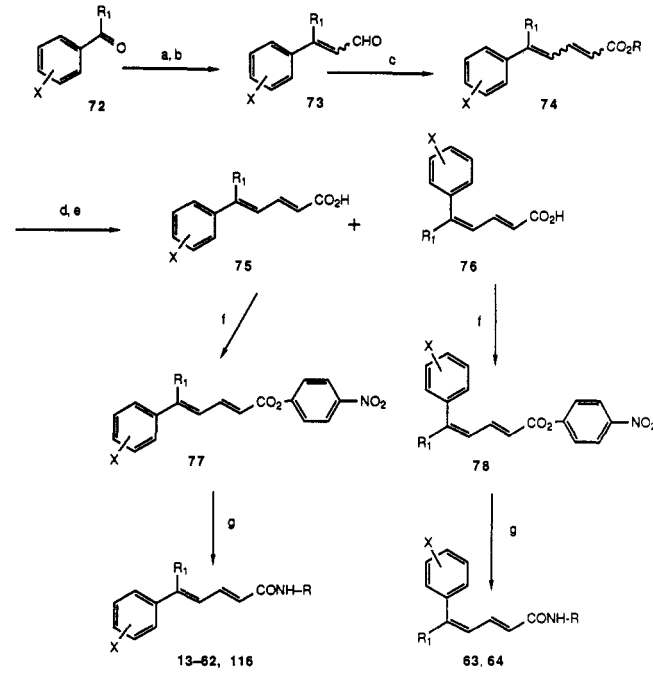


by Meyers[7] (method E). With the exception of *p*-methoxybenzaldehyde, which gave the corresponding (*E*)-cinnamaldehyde **73o** as the sole isolable product, unsymmetrical carbonyl compounds were transformed by this procedure into an isomeric mixture of α,β-unsaturated aldehydes with an *E*/*Z* ratio ranging between 3:2 and 2:3. In some of the cases, the individual isomers were isolated by HPLC, but in those instances in which the isomers could not be readily separated, the mixtures were carried on through the next synthetic step and the products then were separated as the corresponding dienoic acid esters. Structural assignment of the *E* and *Z* isomers was based on their proton NMR spectra through correlation of the observed chemical shifts for the aldehydic and vinylic protons with the values reported for those of closely related compounds.[8] Characteristically, in the 3-(4-methoxyphenyl)-2-alkenals, the aldehydic proton of the *E* isomers appeared at significantly lower field (δ 10.1–10.15) than the corresponding proton in the (*Z*)-alkenals (δ 9.45–9.48). This relative downfield shift was also noted in the signals of the vinylic proton (δ 6.25–6.39 vs 6.05–6.08) and of the ortho aromatic protons (δ 7.46–7.52 vs δ 7.17–7.22). Indirect confirmation of the above structure assignments for the isomeric aldehydes was obtained by single-crystal X-ray crystallographic analysis of (*E*,*E*)-decadienoic acid **75u** which had been prepared from the (*E*)-octenal **73u**.

Although most aldehydes listed in Table VI were attainable through this procedure, the reaction failed when attempted on the hindered substrate 2,2′-dimethoxybenzophenone (**79**). However, condensation of **79** with lithioacetonitrile produced the carbinol **80**, which after dehydration and reduction of the newly formed α,β-unsaturated nitrile with diisobutylaluminum hydride furnished the desired aldehyde **73f** in good yield (Scheme II). This alternate pathway assumed additional importance when it became apparent that larger amounts of (*E*)-3-(4-methoxyphenyl)-2-octenal (**73u**) would be needed in its role as an intermediate in the preparation of the development candidate **58**. It was found that the carbinol **82** obtained in 96% yield from the unsymmetrical ketone **81**, could be dehydrated with trifluoroacetic acid in dichloromethane to produce the unsaturated nitrile **83** predominantly as its *E* isomer (*E*/*Z* ratio >12:1). Since this high stereoisomeric ratio was preserved through the reduction step, HPLC purification of octenal **73u** was avoided and the crude material could be used directly in the synthesis of (*E*,*E*)-decadienoic acid **75u**.

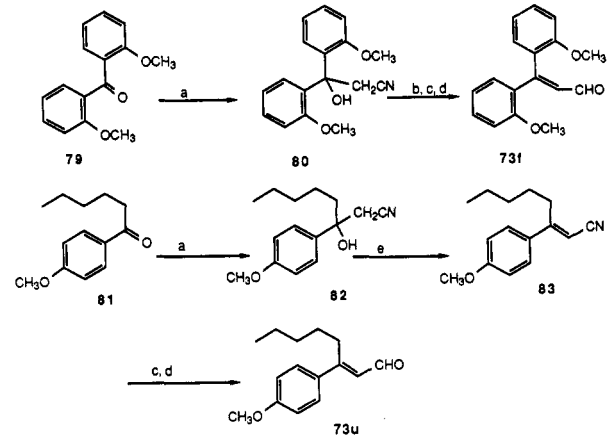
As noted above, the pentadienoic acids **75** were readily available through reaction of the α,β-unsaturated aldehydes **73** with the stabilized ylides, (carbomethoxymethylene)- or (carbethoxymethylene)triphenylphosphorane. While use of a polar reaction medium such as methanol or ethanol in the Wittig reaction resulted in mixtures of isomers with an *E*/*Z* ratio as high as 3:2,

Scheme I[a]



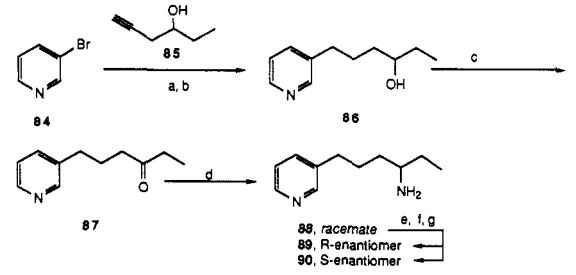
[a] Reagents: (a) $(EtO)_2POCH_2CH{=}N\text{-}t\text{Bu}$, LDA; (b) oxalic acid; (c) $(C_6H_5)_3P{=}CHCO_2C_2H_5$; (d) separate isomers; (e) NaOH; (f) DCC, 4-nitrophenol; (g) RNH_2.

Scheme II[a]



[a] Reagents: (a) LDA, CH_3CN, THF; (b) $SOCl_2$; (c) DIBAL-H, −40 °C, toluene; (d) H_2SO_4; (e) CF_3CO_2H, CH_2Cl_2.

Scheme III[a]

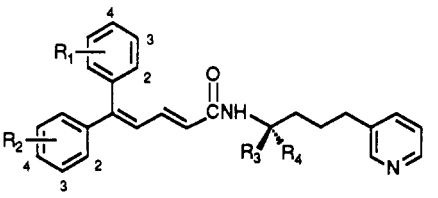


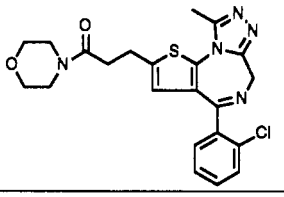
[a] Reagents: (a) $[(C_6H_5)_3P]_2PdCl_2$, NEt_3, CH_2Cl_2; (b) H_2, Pd(C), EtOH; (c) DMSO, oxalic acid, NEt_3, CH_2Cl_2; (d) $CH_3CO_2NH_4$, $NaCNBH_3$, MeOH; (e) (*R*)-mandelic acid, DCC, HOBT; (f) separate diastereomers; (g) 6 N HCl, reflux.

(7) Meyers, A.; Tamioka, K.; Fleming, M. *J. Org. Chem.* **1978**, *43*, 3789.

(8) Quinkert, G.; Hintzmann, M.; Michaelis, P.; Jürges, P.; Appelt, H.; Kruger, U. *Justus Liebigs Ann. Chem.* **1971**, *748*, 38.

Table II. PAF-Antagonist Activity of (*E*)-*N*-[4-(3-Pyridinyl)butyl]-5,5-diphenylpentadienamides



no.	R_1	R_2	R_3	R_4	inhibn of PAF binding: IC_{50},[a] nM	guinea pig bronchoconstriction assay: % inhibn,[b] iv, 1.0 mg/kg	ID_{50},[a,b] mg/kg, iv	% inhibn, 50 mg/kg, po: 2 h	6 h	ID_{50},[a,c] po
13	3-F	3-F	H	H	20	71 ± 17[b]	0.34	37 ± 24		50
14	4-F	4-F	H	H	40	91 ± 0	0.38	89 ± 9		28
15	3-Cl	3-Cl	H	H	25	76 ± 14	0.47	23 ± 7		
16	4-Cl	4-Cl	H	H	60	95 ± 2[b]	0.18	54 ± 11		50
17	3-NO_2	3-NO_2	H	H	115	78 ± 6[b]	0.26			
18	2-OCH_3	2-OCH_3	H	H	40	40 ± 2				
19	3-OCH_3	3-OCH_3	H	H	2	69 ± 9[b]	0.36	31 ± 11		80
20	4-OCH_3	4-OCH_3	H	H	25	92 ± 3	0.25	82 ± 12	71 ± 8	12
21	3,4-$(OCH_3)_2$	3,4-$(OCH_3)_2$	H	H	55	78 ± 6	0.54	71 ± 12	17 ± 11	27
22	4-CH_3	4-CH_3	H	H	60	95 ± 1	0.26	67 ± 15	11 ± 6	43
23	3-F	3-OCH_3	H	H	40	90 ± 5	0.25	1 ± 8		
24	3-OCH_3	3-F	H	H	25	88 ± 4	0.46	25 ± 14		
25	3-F	3-F	CH_3	H	170	73 ± 6	0.22	91 ± 3	87 ± 9	37
26	3-F	3-F	H	CH_3	250	34 ± 7[d]		46 ± 15		
27	4-F	4-F	CH_3	H	250	70 ± 9[d]	0.31	53 ± 22		
28	4-F	4-F	H	CH_3	275	21 ± 10				
29	3-OCH_3	3-OCH_3	CH_3	H	35	88 ± 3	0.21	86 ± 11	12 ± 7	29
30	3-OCH_3	3-OCH_3	H	CH_3	300	36 ± 4		10 ± 8		
31	4-OCH_3	4-OCH_3	CH_3	H	65	98 ± 0	0.25	98 ± 1	93 ± 4	4
32	4-OCH_3	4-OCH_3	H	CH_3	200	59 ± 12	0.84	90 ± 2	56 ± 18	29
33	4-OCH_3	4-OCH_3	CH_3	CH_3	85	97 ± 0	0.27	54 ± 9		55
34	H	4-OCH_3	CH_3	H	2	89 ± 4	0.16	95 ± 1	53 ± 10	
35	4-OCH_3	H	CH_3	H	4	74 ± 11	0.50	0 ± 2		
36	3,4-$(OCH_3)_2$	3,4-$(OCH_3)_2$	CH_3	H	50	99 ± 1	0.14	67 ± 19	2 ± 8	26
37	4-CH_3	4-CH_3	CH_3	H	250	97 ± 2	0.30	91 ± 7	14 ± 16[f]	18
38	4-OCH_3	4-OCH_3	C_2H_5	H	120	99 ± 4	0.16	99 ± 1	85 ± 12[f]	6
39	4-OCH_3	4-OCH_3	H	C_2H_5	400	44 ± 8				
40	4-OCH_3	4-OCH_3	C_3H_7[e]	H	>1000	24 ± 13				
41	4-OCH_3	4-OCH_3	$CH(CH_3)_2$[e]	H	800	87 ± 7	0.43	57 ± 19		26
42	4-OCH_3	4-OCH_3		H	60	98 ± 1	0.20	99 ± 0.3	82 ± 12	6
43	4-OCH_3	4-OCH_3	C_4H_9[e]	H	>1000	42 ± 7				
44	4-OCH_3	4-OCH_3		H	>1000	19 ± 14				
45	WEB 2086				200	99 ± 1	0.03	100 ± 0	100 ± 0	1

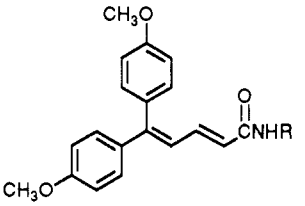
[a] IC_{50} and ID_{50} values were determined by linear-regression analysis; the correlation coefficient for each regression line was >0.95. [b] One-minute pretreatment time. [c] Two-hour pretreatment time. [d] Screening dose of 0.5 mg/kg, iv. [e] Racemic. [f] Eight-hour pretreatment time.

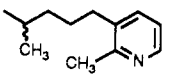
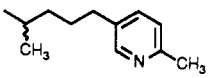
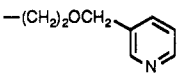
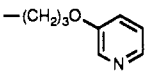
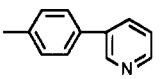
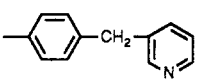
formation of the *Z*-isomer could be minimized (<7%) through the use of an aprotic reaction solvent, e.g., dichloromethane or benzene. The desired 2-(*E*)-isomers were separated by HPLC at this stage and subjected to base hydrolysis to afford the acids **75**. The acids thus prepared are listed in Table VII. In preparation for their conversion to the target carboxamides via method C, the (*E*)- and (*Z*)-pentadienoic acids were condensed with *p*-nitrophenol in the presence of dicyclohexylcarbodiimide to yield the highly reactive *p*-nitrophenyl esters **77** and **78** respectively listed in Table VIII (method F).

The new (±)-α-substituted-3-pyridinebutanamines were available by two general methods. The first sequence, shown in Scheme III, makes use of strategies that had been developed for the synthesis of closely related heteroaromatic alkylamines.[9] Palladium-catalyzed coupling of the hexynol **85** with 3-bromopyridine (**84**) afforded the alkynol **86**, which was subjected to sequential hydrogenation and Swern oxidation to give the ketone **87**. Reductive amination of the ketone with sodium cyanoborohydride then furnished the racemic amine **88**. Resolution was achieved through fractional crystallization of the diastereoisomeric (*R*)-mandelamides. When the racemic amine was coupled with (*R*)-mandelic acid in dimethylformamide in the presence of 1-hydroxybenzotriazole and dicyclohexylcarbodiimide, the diastereoisomerically pure (*R**,*R*)-mandelamide crystallized directly from the reaction

(9) Tilley, J. W.; Levitan, P.; Lind, J.; Welton, A.; Crowley, H.; Tobias, L.; O'Donnell, M. *J. Med. Chem.* **1987**, *30*, 185.

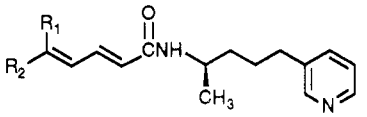
Table III. PAF-Antagonist Activity of (*E*)-*N*-Substituted-5,5-bis(4-methoxyphenyl)pentadienamides



no.	R	inhibn of PAF binding: IC_{50},[a] nM	guinea pig bronchoconstriction assay: % inhibn,[b] iv, 1.0 mg/kg	ID_{50},[a,b] mg/kg, iv	% inhibn, 50 mg/kg, po: 2 h	% inhibn, 50 mg/kg, po: 6 h	ID_{50},[a,c] mg/kg, po
46		30	47 ± 10	1.1			
47		700	5 ± 6				
48		250	48 ± 7				
49		300	43 ± 7				
50		10	97 ± 1	0.15	82 ± 12	77 ± 16	29
51		250	3 ± 7				

[a] IC_{50} and ID_{50} values were determined by linear-regression analysis; the correlation coefficient for each regression line was >0.95. [b] One-minute pretreatment time. [c] Two-hour pretreatment time.

Table IV. PAF-Antagonist Activity of (*E*)-*N*-[4-(3-Pyridinyl)butyl]-5,5-bis(4-methoxyphenyl)pentadienamides



no.	R_1	R_2	inhibition of PAF binding, IC_{50}, nM[a]	guinea pig bronchoconstriction assay: % inhibn,[b] iv, 1.0 mg/kg	ID_{50},[a,b] mg/kg, iv[a,b]	% inhibn, 50 mg/kg, po: 2 h	% inhibn, 50 mg/kg, po: 6 h	ID_{50},[a,c] mg/kg, po[a,c]
52	H	4-$CH_3OC_6H_4$	30	−17 ± 13				
53	CH_3	4-$CH_3OC_6H_4$	25	42 ± 16				
54	C_2H_5	4-$CH_3OC_6H_4$	30	72 ± 13	0.68	84 ± 2	9 ± 11	35
55	C_3H_7	4-$CH_3OC_6H_4$	50	86 ± 7	0.52	9 ± 13		
56	$CH(CH_3)_2$	4-$CH_3OC_6H_4$	40	89 ± 3	0.41	71 ± 14	20 ± 5	30
57	C_4H_9	4-$CH_3OC_6H_4$	14	99 ± 1	0.68	98 ± 1	69 ± 15	12
58	C_5H_{11}	4-$CH_3OC_6H_4$	40	99 ± 1	0.05	100 ± 0.5	71 ± 4	16
59	$CH_3(CH_2)_5$	4-$CH_3OC_6H_4$	9	100 ± 1	0.07	96 ± 1	14 ± 10	8
60	$CH_3(CH_2)_7$	4-$CH_3OC_6H_4$	5	98 ± 1	0.10	84 ± 8	27 ± 10	13
61	C_5H_{11}	C_5H_{11}	100	78 ± 7	0.64	4 ± 4		
62	C_6H_{11}	4-$CH_3OC_6H_4$	20	73 ± 17	0.21	97 ± 1	12 ± 10	10
63	4-$CH_3OC_6H_4$	C_5H_{11}	10	57 ± 1	0.78	13 ± 7		
64	4-$CH_3OC_6H_4$	C_6H_{11}	20	18 ± 12				

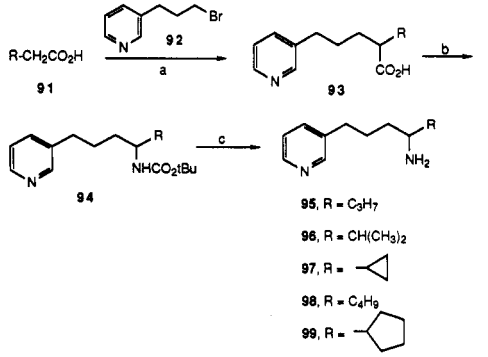
[a] IC_{50} and ID_{50} values were determined by linear regression analysis; the correlation coefficient for each regression line was >0.95. [b] One-minute pretreatment time. [c] Two-hour pretreatment time.

mixture along with the byproduct dicyclohexylurea. The more soluble *R*,S* diastereomer was isolated from the mother liquor and purified by crystallization from 2-propanol. Acid hydrolysis of the optically pure mandelamides provided the resolved (*R*)- and (*S*)-α-ethyl amines **89** and **90**, respectively. Stereochemical assignment was based on analogy with the corresponding α-methyl amines.[1]

For the preparation of higher homologues, the appropriate carboxylic acid **91** was treated with 2 equiv of lithium diisopropylamide and the resulting dianion was alkylated with 3-(3-bromopropyl)pyridine[10] to furnish the α-substituted 3-pyridinepentanoic acids **93** in 61–85% yield. Conversion of the acids to the amines **95–99** was achieved in 70–80% yield via a Curtius reaction involving reaction of the acid with diphenyl phosphorazidate in

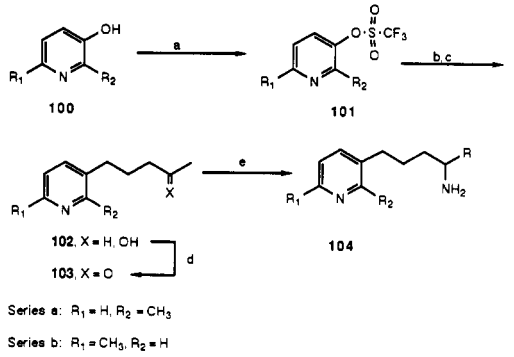
(10) Hawes, E.; Davis, H. *J. Heterocycl. Chem.* **1973**, *10*, 39.

Scheme IV[a]



[a] Reagents: (a) 2 equiv of LDA, THF; (b) diphenylphosphoryl azide, Et_3N, tBuOH; (c) 1 N HCl.

Scheme V[a]



[a] Reagents: (a) phenyltriflimide, NEt_3, CH_2Cl_2; (b) $[(C_6H_5)_3P]_2PdCl_2$, NEt_3, DMF; (c) H_2, Pd/C, EtOH; (d) DMSO, oxalic acid, NEt_3, CH_2Cl_2; (e) $CH_3CO_2NH_4$, $NaCNBH_3$, MeOH.

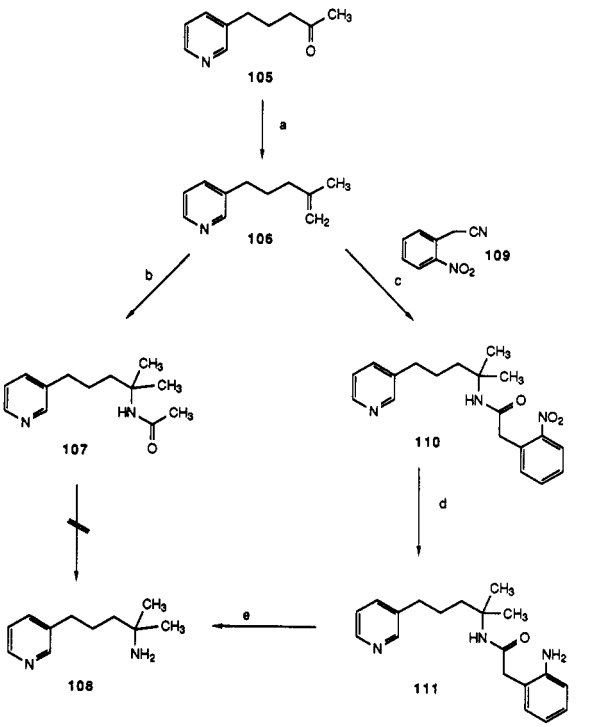
tert-butanol and subsequent mild acid hydrolysis of the intermediate carbamate[11] as shown in Scheme IV.

Pyridinebutanamines **104** bearing a methyl group in the 2- or 6-positions were available from the pyridinols **100** (Scheme V). Treatment with phenyltriflimide gave the corresponding triflic esters **101**, which underwent a palladium-catalyzed coupling reaction with pentyn-4-ol followed by catalytic hydrogenation to yield the alkynes **102**.[12] The subsequent steps of Swern oxidation and reductive amination were identical with those employed for the synthesis of **88**.

The α,α-dimethyl-3-pyridinebutanamine (**108**) was prepared as shown in Scheme VI. A Wittig reaction was used to transform 5-(3-pyridinyl)-2-pentanone[1] (**105**) into the methylene derivative **106**. Treatment with acetonitrile and sulfuric acid under Ritter conditions smoothly afforded the acetamide **107**; however, the hindered amide was stable to the usual acid or base catalyzed hydrolysis conditions, and more rigorous conditions resulted in extensive degradation of the product. When the Ritter reaction was repeated with 2-nitrophenylacetonitrile as the nitrile component, the (2-nitrophenyl)acetamide **110** was formed in 74% yield. Removal of the benzoyl group was readily achieved by hydrogenation over palladium on carbon in acetic acid[13] to give the aniline **111**, which underwent a subsequent intramolecular cyclization to form oxindole and simultaneously to free the amine **108** in 78% yield.

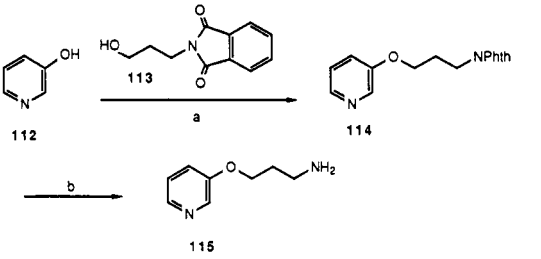
Condensation of 3-hydroxypyridine **112** and *N*-(3-hydroxypropyl)phthalimide **113** under Mitsunobu conditions[14] followed by cleavage of the phthalimide provided the aminopropyl ether **115** (Scheme VII).

Scheme VI[a]



[a] Reagents: (a) $(C_6H_5)_3P{=}CH_2$; (b) CH_3CN, H_2SO_4; (c) H_2SO_4; (d) H_2, Pd/C, HOAc; (e) HOAc, Δ.

Scheme VII[a]



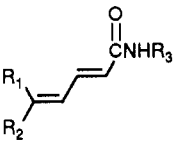
[a] Reagents: (a) $(C_6H_5)_3P$, diethyldiazodiacarboxylate; (b) H_2N-NH_2.

Results and Discussion

In order to determine whether compounds of structure **4** might be useful as PAF antagonists, the derivatives listed in Table I were evaluated in a PAF-binding assay employing washed dog platelets as previously described.[1,3] The compounds which had binding IC_{50}s of ≤500 nM were further evaluated in guinea pigs for their ability to prevent PAF-induced bronchoconstriction. In this model, groups of five guinea pigs were administered 1 mg/kg of the drug substance intravenously 1 min prior to iv challenge with a maximally constrictory dose of PAF (1 μg/kg) and the ability of the drug (n = 4) to inhibit the ensuing bronchoconstriction relative to control animals (n = 4) was determined. Compounds which caused a ≥50% inhibition of the response were further evaluated at lower doses to determine an intravenous ID_{50} and were tested orally at a trial dose of 50 mg/kg, 2 h prior to PAF challenge. It is our practice to further profile compounds which caused a ≥50% inhibition of the response in the initial oral screen

(11) Haeflinger, W.; Klöppner *Helv. Chem. Acta* **1982**, *65*, 1837.
(12) Tilley, J. W.; Zawoiski, S. *J. Org. Chem.* **1988**, *53*, 386.
(13) Cuiban, F. *Rev. Roum. Chim.* **1973**, *18*, 449.
(14) (a) Bittner, S.; Assaf, Y. *Chem. Ind. (London)* **1975**, 281. (b) Manhas, M.; Hoffmann, W.; Lal, B.; Bose, A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 461.

Table V. Data for Dienamides



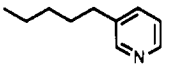
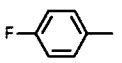
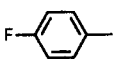
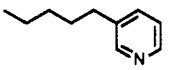
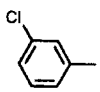
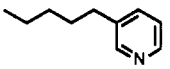
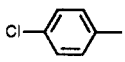
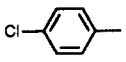
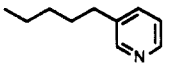
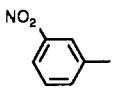
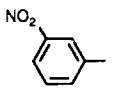
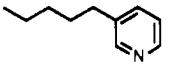
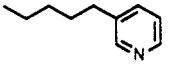
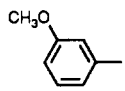
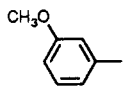
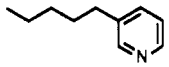
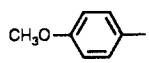
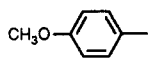
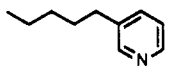
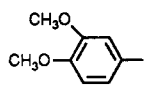
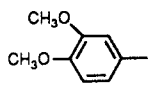
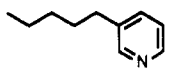
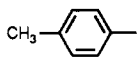
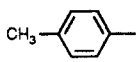
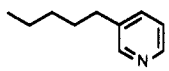
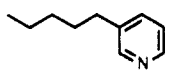
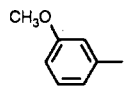
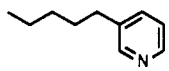
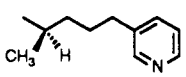
no.	R_1	R_2	R_3	method	% yield	mp, °C	solvent	formula	anal.
13				C	89	103–104	EtOAc–hex.	$C_{26}H_{24}F_2N_2O$	C, H, F, N
14				C	94	155–156	EtOAc–hex.	$C_{26}H_{24}F_2N_2O$	C, H, F, N
15				C	78	100–102	EtOAc–hex.	$C_{26}H_{24}Cl_2N_2O$	C, H, Cl, N
16				C	82	146–147	EtOAc–hex.	$C_{26}H_{24}Cl_2N_2O$	C, H, Cl, N
17				C	84	158–159	EtOAc–hex.	$C_{26}H_{24}N_2O_5$	C, H, N
18				C	81	103.5–104.5	Et_2O	$C_{28}H_{30}N_2O_3$	C, H, N
19				C	88	86–88	EtOAc–Et_2O	$C_{28}H_{30}N_2O_3$	C, H, N
20				C	81	76–77	EtOAc–hex.	$C_{28}H_{30}N_2O_3$	C, H, N
21				C	72	145–146	EtOAc–hex.	$C_{30}H_{34}N_2O_5$	C, H, N
22				C	72	144.5–145.5	EtOAc–hex.	$C_{28}H_{30}N_2O$	C, H, N
23				C	75	98–100	EtOAc–hex.	$C_{27}H_{27}FN_2O_2$	C, H, F, N
24				C	86	58–60	EtOAc–hex.	$C_{27}H_{27}FN_2O_2$	C, H, F, N
25				C	83	137–139	EtOAc–hex.	$C_{27}H_{26}F_2N_2O$	C, H, F, N
26				C	92	135–136	EtOAc–hex.	$C_{27}H_{26}F_2N_2O$	C, H, F, N
27				C	83	160.5–161.5	EtOAc–hex.	$C_{27}H_{26}F_2N_2O$	C, H, F, N
28				C	93	155–156	EtOAc–hex.	$C_{27}H_{26}F_2N_2O$	C, H, F, N
29				C	83	109–110	EtOAc–hex.	$C_{29}H_{32}N_2O_3$	C, H, N
30				C	88	105–108	EtOAc–hex.	$C_{29}H_{32}N_2O_3$	C, H, N
31				C	99	amorphous solid[a]		$C_{29}H_{32}N_2O_3$[b]	C, H, N
32				C	98	amorphous solid[a]		$C_{29}H_{32}N_2O_3$	C, H, N

Table V (Continued)

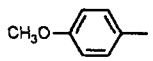
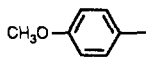
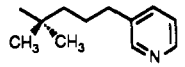
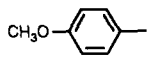
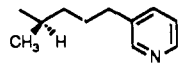
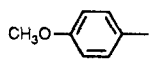
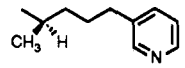
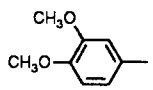
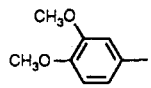
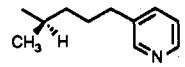
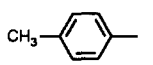
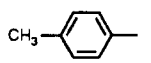
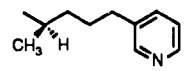
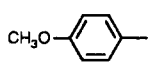
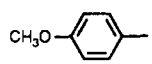
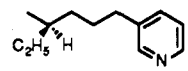
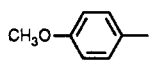
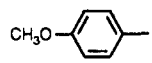
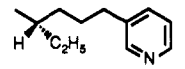
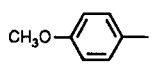
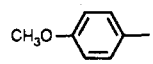
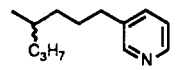
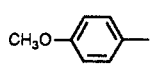
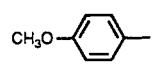
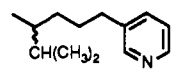
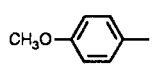
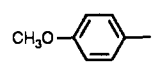
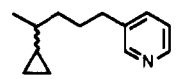
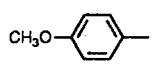
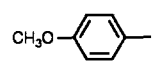
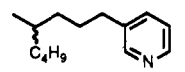
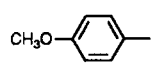
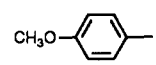
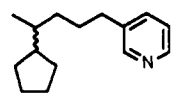
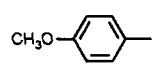
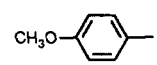
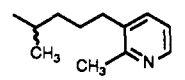
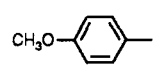
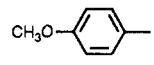
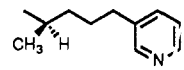
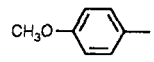
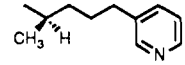
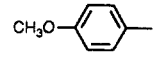
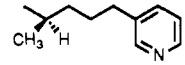
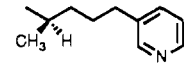
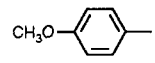
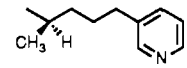
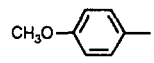
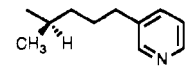
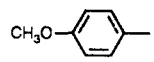
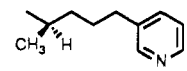
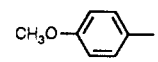
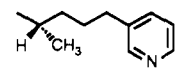
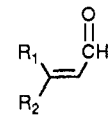
no.	R_1	R_2	R_3	method	% yield	mp, °C	solvent	formula	anal.
33				C	82	144–145	EtOAc–hex.	$C_{30}H_{34}N_2O_3$	C, H, N
34				C	94	amorphous solid[a]		$C_{28}H_{30}N_2O_2$	C, H, N
35				C	60	129.5–131	EtOAc–hex.	$C_{28}H_{30}N_2O_2$	C, H, N
36				C	89	140.5–141.5	EtOAc	$C_{31}H_{36}N_2O_5$	C, H, N
37				C	72	144.5–145.5	EtOAc–hex.	$C_{28}H_{30}N_2O$	C, H, N
38				C	80	amorphous solid[a]		$C_{30}H_{34}N_2O_3$	C, H, N
39				C	91	amorphous solid[a]		$C_{30}H_{34}N_2O_3$	H, N[c]
40				C	87	glass[a]		$C_{31}H_{36}N_2O_3$	C, H, N
41				C	86	amorphous solid[a]		$C_{31}H_{36}N_2O_3$	C, H, N
42				C	87	amorphous solid[a]		$C_{31}H_{34}N_2O_3$	H, N[d]
43				C	86	amorphous solid[a]		$C_{32}H_{38}N_2O_3$	C, H, N
44				C	88	amorphous solid[a]		$C_{33}H_{38}N_2O_3$	C, H, N
46				C	83	amorphous solid[a]		$C_{30}H_{34}N_2O_3$	C, H, N
47				C	63	amorphous solid[a]		$C_{30}H_{34}N_2O_3$[e]	C, H, N
48				C	80	amorphous solid[a]		$C_{27}H_{28}N_2O_4$	C, H, N
49				C	90	146–147	EtOAc–hex.	$C_{27}H_{28}N_2O_4$	C, H, N
50				B	61	210–212	Me_2CO-EtOAc	$C_{30}H_{26}N_2O_3$	C, H, N
51				B	60	185–186	Me_2CO-EtOAc	$C_{31}H_{28}N_2O_3$	C, H, N
52	H			C	90	186.5–187.5	EtOAc	$C_{22}H_{26}N_2O_2$	C, H, N
53	CH_3			C	91	107.5–108.5	EtOAc–hex.	$C_{23}H_{28}N_2O_2$	C, H, N
54	CH_3CH_2			C	71	107–109	Et_2O	$C_{24}H_{30}N_2O_2$	C, H, N
55	$CH_3(CH_2)_2$			C	73	amorphous solid[a]		$C_{25}H_{32}N_2O_2$	H, N[f]
56	$(CH_3)_2CH$			C	76	oil[a]		$C_{25}H_{32}N_2O_2$	C, H, N
57	$CH_3(CH_2)_3$			C	68	89–91	Et_2O	$C_{26}H_{34}N_2O_2$	C, H, N

Table V (Continued)

no.	R_1	R_2	R_3	method	% yield	mp, °C	solvent	formula	anal.
58	$CH_3(CH_2)_4$			C	93	88–89	EtOAc–hex.	$C_{27}H_{36}N_2O_2$	C, H, N
59	$CH_3(CH_2)_5$			C	43	71.5–73	Et_2O–hex.	$C_{28}H_{38}N_2O_2$	C, H, N
60	$CH_3(CH_2)_7$			C	78	92.5–94	Et_2O–hex.	$C_{30}H_{42}N_2O_2$	C, H, N
61	$CH_3(CH_2)_4$	$CH_3(CH_2)_4$		C	78	oil		$C_{25}H_{40}N_2O$	H, N[g]
62				C	62	142.5–143.5	EtOAc–hex.	$C_{28}H_{36}N_2O_2$	C, H, N
63		$CH_3(CH_2)_4$		C	86	oil[a]		$C_{27}H_{36}N_2O_2$	C, H, N
64				C	86	147–148.5	EtOAc–hex.	$C_{28}H_{36}N_2O_2$	C, H, N
116	$CH_3(CH_2)_4$			C	89	88–89	Et_2O	$C_{27}H_{36}N_2O_2$	C, H, N

[a] Compound purified by HPLC and then lyophilized from benzene. [b] 0.4 M hydrate. [c] C: calcd, 76.57; found, 76.08. [d] C: calcd, 77.15; found, 76.71. [e] 0.4 M hydrate. [f] C: calcd, 75.49; found, 75.95. [g] C: calcd, 78.07; found, 77.66.

Table VI. Data for α,β-Unsaturated Aldehydes[a]



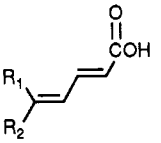
no.	R_1	R_2	% yield[b]	mp, °C	solvent	formula	anal.
69	C_6H_5	C_6H_5	96	45–46.5	hex.	$C_{15}H_{12}O$	C, H
73a	3-FC_6H_4	3-FC_6H_4	78	52–54	hex.	$C_{15}H_{10}F_2O$	C, H, F
73b	4-FC_6H_4	4-FC_6H_4	79	58–59.5	pent	$C_{15}H_{10}F_2O$	C, H, F
73c	3-ClC_6H_4	3-ClC_6H_4	87[c]	75–77	Et_2O–hex.	$C_{15}H_{10}Cl_2O$	C, H, Cl
73d	4-ClC_6H_4	4-ClC_6H_4	87[c]	oil		$C_{15}H_{10}Cl_2O$	*d*
73e	3-$NO_2C_6H_4$	3-$NO_2C_6H_4$	70	134–136	CH_2Cl_2–hex.	$C_{15}H_{10}N_2O_5$	C, H, N
73f	2-$CH_3OC_6H_4$	2-$CH_3OC_6H_4$	97	59.5–61.5	Et_2O–hex.	$C_{17}H_{16}O_3$	C, H
73g	3-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$	96[c]	oil		$C_{17}H_{16}O_3$	H[e]
73h	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	85	56–57	Et_2O–hex.	$C_{17}H_{16}O_3$	C, H
73i	C_6H_5	4-$CH_3OC_6H_4$	39	oil		$C_{16}H_{14}O_2$	C, H
73j	4-$CH_3OC_6H_4$	C_6H_5	32	oil		$C_{16}H_{14}O_2$	C, H
73k	3,4-$(CH_3O)_2C_6H_3$	3,4-$(CH_3O)_2C_6H_3$	75	129–130	Et_2O	$C_{19}H_{20}O_5$	C, H
73l	4-$CH_3C_6H_3$	4-$CH_3C_6H_3$	77	93–94	hex.	$C_{19}H_{18}O_2$	C, H
73m	3-FC_6H_4	3-$CH_3OC_6H_4$	*f*			$C_{16}H_{13}FO_2$	
73n	3-$CH_3OC_6H_4$	3-FC_6H_4	*f*			$C_{16}H_{13}FO_2$	
73o	H	4-$CH_3OC_6H_4$	77	58.5–60	Et_2O–hex.	$C_{10}H_{10}O_2$	C, H
73p	CH_3	4-$CH_3OC_6H_4$	49	42.5–45	Et_2O–hex.	$C_{11}H_{12}O_2$	C, H
73q	CH_3CH_2	4-$CH_3OC_6H_4$	37	oil		$C_{12}H_{14}O_2$	*g*
73r	$CH_3(CH_2)_2$	4-$CH_3OC_6H_4$	30	oil		$C_{13}H_{16}O_2$	*h*
73s	$(CH_3)_2CH$	4-$CH_3OC_6H_4$	*f*			$C_{13}H_{16}O_2$	*h*
73t	$CH_3(CH_2)_3$	4-$CH_3OC_6H_4$	46	oil		$C_{14}H_{18}O_2$	H[i]
73u	$CH_3(CH_2)_4$	4-$CH_3OC_6H_4$	40	oil		$C_{15}H_{20}O_2$	C, H
73v	4-$CH_3OC_6H_4$	$CH_3(CH_2)_4$	36	oil		$C_{15}H_{20}O_2$	C, H
73w	$CH_3(CH_2)_5$	4-$CH_3OC_6H_4$	*f*	oil		$C_{16}H_{22}O_2$	
73x	$CH_3(CH_2)_7$	4-$CH_3OC_6H_4$	*f*	oil		$C_{18}H_{26}O_2$	
73y	C_6H_{11}	4-$CH_3OC_6H_4$	23	oil		$C_{16}H_{20}O_3$	*j*
73z	4-$CH_3OC_6H_4$	C_6H_{11}	30	oil		$C_{16}H_{20}O_2$	*j*
73aa	$CH_3(CH_2)_4$	$CH_3(CH_2)_4$	65	oil		$C_{13}H_{24}O$	*k*

[a] The aldehydes listed, with the exception of **73f**, were obtained by method E. Compound **73f** was prepared via the corresponding nitrile as outlined in Scheme II. Both methods were used to prepare **73u** (see the Experimental Section). [b] Unless indicated otherwise, refers to isolated yield after crystallization of the product or after HPLC separation of the geometric isomers if applicable. [c] Crude yield. [d] Attempted crystallization of the oily aldehyde **73d** with MeOH resulted in formation of the corresponding dimethyl acetal, mp 89–90 °C. Anal. ($C_{17}H_{16}Cl_2O_2$) C, H, N. [e] C: calcd, 76.10; found, 75.64. [f] Mixture of isomeric aldehydes not separated prior to conversion to the dienoic acids. [g] MS *m/z* 190 (M^+). [h] MS *m/z* 204 (M^+). [i] C: calcd, 77.03; found, 76.58. [j] MS *m/z* 244 (M^+). [k] MS *m/z* 196 (M^+).

by determining oral ID_{50} values and the percent inhibition 6 h after a 50 mg/kg oral dose.

Of the compounds in Table I, compounds **5** and **12** met our threshold activity criteria both in the binding assay and after intravenous administration. Furthermore, both showed a modest but significant inhibition of PAF-induced bronchoconstriction after oral administration which was sufficient to encourage us to pursue each series. In this

Table VII. Data for Pentadienoic Acids



no.	R_1	R_2	% yield	mp, °C	solvent	formula	anal.
70	C_6H_5	C_6H_5	61	193–194[a]	CH_2Cl_2–hex.	$C_{17}H_{14}O_2$	C, H
75a	3-FC_6H_4	3-FC_6H_4	87	163.5–165	Et_2O–hex.	$C_{17}H_{12}F_2O_2$	C, H, F
75b	4-FC_6H_4	4-FC_6H_4	81	187–188[b]	Et_2O–hex.	$C_{17}H_{12}F_2O_2$	C, H, F
75c	3-ClC_6H_4	3-ClC_6H_4	57	167–168	Et_2O–hex.	$C_{17}H_{12}Cl_2O_2$	C, H, Cl
75d	4-ClC_6H_4	4-ClC_6H_4	56	214–215[c]	*i*-PrOH	$C_{17}H_{12}Cl_2O_2$	C, H, Cl
75e	3-$NO_2C_6H_4$	3-$NO_2C_6lH_4$	75	237–238	$CHCl_3$–EtOH	$C_{17}H_{12}N_2O_6$[d]	C, H, N
75f	2-$CH_3OC_6H_4$	2-$CH_3OC_6H_4$	64	196–197	*i*-PrOH	$C_{19}H_{18}O_4$	C, H
75g	3-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$	69	179–180.5	CH_2Cl_2–hex.	$C_{19}H_{18}O_4$	C, H
75h	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	82	189.5–190.5[e]	CH_2Cl_2–hex.	$C_{19}H_{18}O_4$	C, H
75i	C_6H_5	4-$CH_3OC_6H_4$	51	209–211	*i*-PrOH	$C_{18}H_{16}O_3$	C, H
75j	4-$CH_3OC_6H_4$	C_6H_5	62	183–184	*i*-PrOH–hex.	$C_{18}H_{16}O_3$	C, H
75k	3,4-$(CH_3O)_2C_6H_3$	3,4-$(CH_3O)_2C_6H_3$	85	174–175.5	CH_2Cl_2–*i*-PrOH	$C_{21}H_{22}O_6$	C, H
75l	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	68	224.5–226.5	*i*-PrOH	$C_{19}H_{18}O_2$	C, H
75m	3-FC_6H_4	3-$CH_3OC_6H_4$	24[f]	152.5–153.5	EtOAc–hex.	$C_{18}H_{15}FO_3$	C, H, F
75n	3-$CH_3OC_6H_4$	3-FC_6H_4	16[f]	156–157	Et_2O–hex.	$C_{18}H_{15}FO_3$	C, H, F
75o	H	4-$CH_3OC_6H_4$	61	133.5–135	*i*-PrOH	$C_{12}H_{12}O_3$	C, H
75p	CH_3	4-$CH_3OC_6H_4$	76	174–175	*i*-PrOH	$C_{13}H_{14}O_3$	C, H
75q	CH_3CH_2	4-$CH_3OC_6H_4$	62	135–137	*i*-PrOH–hex.	$C_{14}H_{16}O_3$	C, H
75r	$CH_3(CH_2)_2$	4-$CH_3OC_6H_4$	68	151–152.5	*i*-PrOH–hex.	$C_{15}H_{18}O_3$	C, H
75s	$(CH_3)_2CH$	4-$CH_3OC_6H_4$	25[g]	140.5–141.5	cyclohex–hex.	$C_{15}H_{18}O_3$	C, H
75t	$CH_3(CH_2)_3$	4-$CH_3OC_6H_4$	52	138–139.5	*i*-PrOH–hex.	$C_{16}H_{20}O_3$	C, H
75u	$CH_3(CH_2)_4$	4-$CH_3OC_6H_4$	80	126–127.5	*i*-PrOH	$C_{17}H_{22}O_3$	C, H
75w	$CH_3(CH_2)_5$	4-$CH_3OC_6H_4$	29[h]	88–89.5	hex.	$C_{18}H_{24}O_3$	C, H
75x	$CH_3(CH_2)_7$	4-$CH_3OC_6H_4$	28[i]	109–110	hex.	$C_{20}H_{28}O_3$	C, H
75y	C_6H_{11}	4-$CH_3OC_6H_4$	53	130.5–131.5	cyclohex–hex.	$C_{18}H_{22}O_3$	C, H
75aa	$CH_3(CH_2)_4$	$CH_3(CH_2)_4$		oil		$C_{15}H_{26}O_2$	C, H
76v	4-$CH_3OC_6H_4$	$CH_3(CH_2)_4$	46	86.5–87.5	Et_2O–hex.	$C_{17}H_{22}O_3$	C, H
76z	4-$CH_3OC_6H_4$	C_6H_{11}	45	185–186	*i*-PrOH–hex.	$C_{18}H_{22}O_3$	C, H

[a] Lit.[22] mp 192–193 °C. [b] Lit.[22] mp 180–185 °C. [c] Lit.[22] mp 212–216 °C. [d] Hydrate (0.25H_2O). [e] Lit.[22] mp 186–189 °C. [f] Starting from an isomeric mixture of aldehydes (E/Z ~1:1). [g] Starting from an isomeric mixture of aldehydes (E/Z ~2:3). [h] Starting from an isomeric mixture of aldehydes (E/Z ~11:9). [i] Starting from an isomeric mixture of aldehydes (E/Z ~3:2).

paper, we describe a series of pentadienamide analogues based on the lead provided by **12**.

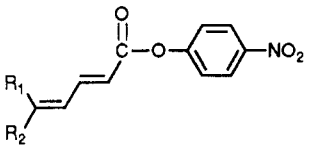
Compounds **13–24**, direct analogues of **12** bearing various substituents on the aromatic rings are reported in Table II. From this limited data set, it is apparent that potency in the PAF binding assay and iv PAF inhibitory activity are relatively independent of substitution in the 3- and 4-positions. This result is consistent with our findings in the related pyridoquinazoline (**1**) and biphenyl (**2**) series of PAF antagonists. A number of these compounds also demonstrated oral activity with the variations being primarily due to differences in absorption and metabolism. The bis-4-methoxy analogue **20** is of particular interest as it is not only one of the most potent members of this series but also retained a high level of inhibition 6 h after oral dosing.

In our earlier work with compounds **1** and **2**, we had found that the introduction of an alkyl substituent on the carbon atom α to the carboxamide nitrogen results in a stereoselective enhancement of oral potency, presumably due to selective resistance to enzymatic degradation.[1,2] In order to test the generality of this concept, compounds **25–43** (Table II) were prepared. Comparison, particularly of the in vivo data for several pairs of enantiomeric α methyl analogues (**25** and **26**, **27** and **28**, **29** and **30**, **31** and **32**) provides convincing evidence that compounds of the *R* configuration have superior activity as PAF antagonists with the corresponding *S* enantiomers having significant but considerably diminished potency. The analogue **33** with two α methyl groups is less potent orally than either of the corresponding monomethyl enantiomers **31** or **32**. In order to probe the steric limitations of the α-alkyl substituent, several examples (**38–44**) in the bis-4-methoxyphenyl series were prepared which incorporated homologous alkyl substituents. From the data it is apparent that ethyl in the *R*, but not the *S*, configuration and cyclopropyl are tolerated very well but that activity falls off rapidly as alkyl substituents of greater size are introduced. Thus a decrease in activity is seen as the size of the alkyl group is increased from cyclopropyl to isopropyl and the *n*-propyl and *n*-butyl derivatives have only minimal activity.

Compounds **46** and **47** (Table III) were prepared in order to test a proposal that the pyridinyl carbon–nitrogen double bond of this class of PAF antagonists mimics the acetoxy carbonyl group of PAF at its receptor. According to our speculation, positions 1 and 2 of the pyridine would correspond to the acetoxy carbonyl and the carbon atom in the pyridine 3-position, which is bound to the side chain, would correspond to the glycerol-bound acetoxy oxygen atom of PAF. Given the tight steric requirements of the PAF acetyl group, we anticipated that the 2-methylpyridinyl analogue **46** would be more active than the 6-methylpyridinyl analogue **47** and this proved to be the case, although neither compound was as active as the corresponding unsubstituted derivative **32**.

The other compounds in Table III were prepared to further characterize the limitations on the pyridinealkanamine side chain. The poor activity of the ethers **48** and **49** are consistent with our previous conclusion that an all-carbon side chain is optimal.[1] The relatively high potency of the 3-pyridinyl anilide **50** was a surprise. This finding combined with the observation that the homologue **51** is virtually inactive in vivo is useful in defining the

Table VIII. Data for Pentadienoic Acid 4-Nitrophenyl Esters



no.	R_1	R_2	% yield	mp, °C	solvent	formula	anal.
77a	3-FC_6H_4	3-FC_6H_4	92	129.5–130.5	CH_2Cl_2–hex.	$C_{23}H_{15}F_2NO_4$	C, H, F, N
77b	4-FC_6H_4	4-FC_6H_4	78	112.5–114	*i*-PrOH	$C_{23}H_{15}F_2NO_4$	C, H, F, N
77c	3-ClC_6H_4	3-ClC_6H_4	87	99–100	Et_2O–*i*-PrOH	$C_{23}H_{15}Cl_2NO_4$	C, H, Cl, N
77d	4-ClC_6H_4	4-ClC_6H_4	89	121–122	*i*-PrOH	$C_{23}H_{15}Cl_2NO_4$	C, H, Cl, N
77e	3-$NO_2C_6H_4$	3-$NO_2C_6H_4$	92	161.5–162.5	*i*-PrOH–hex.	$C_{23}H_{15}N_3O_8$	C, H, N
77f	2-$CH_3OC_6H_4$	2-$CH_3OC_6H_4$	88	141.5–143	*i*-PrOH	$C_{25}H_{21}NO_6$	C, H, N
77g	3-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$	89	99–100	CH_2Cl_2–hex.	$C_{25}H_{21}NO_6$	C, H, N
77h	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	85	125–126	Et_2O	$C_{25}H_{21}NO_6$	C, H, N
77i	C_6H_5	4-$CH_3OC_6H_4$	56	113–115	Et_2O–hex.	$C_{24}H_{19}NO_5$	C, H, N
77j	4-$CH_3OC_6H_5$	C_6H_5	82	oil[a]		$C_{24}H_{19}NO_5$	C, H, N
77k	3,4-$(CH_3O)_2C_6H_3$	3,4-$(CH_3O)C_6H_3$	64	140–142	Et_2O	$C_{27}H_{25}NO_8$	C, H, N
77l	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	86	153.5–154.5	*i*-PrOH	$C_{25}H_{21}NO_4$	C, H, N
77m	3-FC_6H_4	3-$CH_3OC_6H_4$	98	134–135	*i*-PrOH	$C_{24}H_{18}NFO_5$	C, H, N, F
77n	3-$CH_3OC_6H_4$	3-FC_6H_4	95	146.5–147.5	*i*-PrOH	$C_{24}H_{18}NFO_5$	C, H, N, F
77o	H	4-$CH_3OC_6H_4$	78	200.5–202	THF-Et_2O	$C_{18}H_{15}NO_5$	C, H, N
77p	CH_3	4-$CH_3OC_6H_4$	67	176–177	CH_2Cl_2–*i*-PrOH	$C_{19}H_{17}NO_5$	C, H, N
77q	CH_3CH_2	4-$CH_3OC_6H_4$	73	112.5–113.5	*i*-PrOH	$C_{20}H_{19}NO_5$	C, H, N
77r	$CH_3(CH_2)_2$	4-$CH_3OC_6H_4$	68	90–92	*i*-PrOH	$C_{21}H_{21}NO_5$	C, H, N
77s	$(CH_3)_2CH$	4-$CH_3OC_6H_4$	80	95–96.5	*i*-PrOH–hex.	$C_{21}H_{21}NO_5$	C, H, N
77t	$CH_3(CH_2)_3$	4-$CH_3OC_6H_4$	78	78–80	*i*-PrOH	$C_{22}H_{23}NO_5$	C, H, N
77u	$CH_3(CH_2)_4$	4-$CH_3OC_6H_4$	76	75–76	*i*-PrOH	$C_{23}H_{25}NO_5$	C, H, N
77w	$CH_3(CH_2)_5$	4-$CH_3OC_6H_4$	85	oil[a]		$C_{24}H_{27}NO_5$	C, H, N
77x	$CH_3(CH_2)_7$	4-$CH_3OC_6H_4$	89	oil[a]		$C_{26}H_{31}NO_5$	C, H, N
77y	C_6H_{11}	4-$CH_3OC_6H_4$	77	136–137	*i*-PrOH	$C_{24}H_{25}NO_5$	C, H, N
77aa	$CH_3(CH_2)_4$	$CH_3(CH_2)_4$	80	oil[a]		$C_{21}H_{29}NO_4$	C, H[b]
78v	4-$CH_3OC_6H_4$	$CH_3(CH_2)_4$	89	oil[a]		$C_{23}H_{25}NO_5$	C, H, N
78z	4-$CH_3OC_6H_4$	C_6H_{11}	76	117–119	*i*-PrOH–hex.	$C_{24}H_{25}NO_5$	C, H, N

[a] Analytical sample purified by HPLC.

distance requirements between the amido moiety and the pyridine nitrogen atom. However, it also suggests that binding-site models which attempt to relate the receptor binding of the *N*-[4-(3-pyridinyl)butyl] carboxamides to that of PAF itself, with the carboxamide mimicking the PAF ether oxygen atom and the pyridine ring, mimicking the acetyl moiety, are invalid due to impossible distance constraints.

At this point, **31** was selected for profiling in additional models of PAF-induced symptomatology; however, concerns about the possible toxicological implications of its extended electron-rich π-system prompted us to consider analogues in which one or both of the anisole rings were replaced with an alkyl moiety. As the data in Table IV indicate, when the anisole ring which is syn to the amide is replaced with an alkyl group, iv activity in the bronchoconstriction assay increases to a maximum as the alkyl chain length is increased from zero to five carbon atoms and remains relatively constant as the chain is further extended to eight carbon atoms. Oral activity, particularly when measured at the 6-h time point after dosing, is more sensitive to alkyl chain length in this series; maximal activity is seen with the *n*-butyl and *n*-pentyl derivatives **57** and **58**, respectively. This is presumably due to differences in metabolism and absorption among the different homologues. Two compounds (**63** and **64**) were prepared in which the anti aromatic ring was replaced by an alkyl group; both were substantially less potent in the guinea pig bronchoconstriction assay than their geometric isomers **58** and **62**, respectively.

The triazolothienodiazepine **45** is among the most potent PAF antagonists yet described in the literature.[15] Data

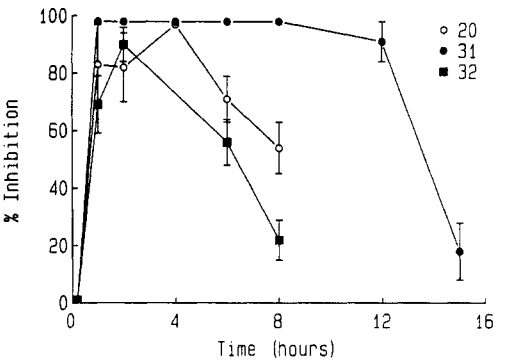
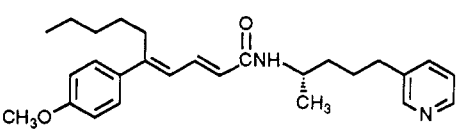


Figure 1. Time-course for oral **20**, **31**, and **32** inhibition of PAF-induced bronchoconstriction in guinea pigs. The compounds were administered orally at a dose of 50 mg/kg. Each point represents the mean ± SEM for determinations made on six animals.

from the PAF-induced bronchoconstriction test for **45** are shown in Table II and indicate that the more active compounds in the pentadienamide series are only 2–5-fold less potent intravenously and 4–10-fold less potent orally.

The two most interesting compounds to emerge from this work, **31** and **58**, were selected for further characterization. Duration of action studies for **31** were carried out for longer periods in comparison with the corresponding des-α-methyl and *S*-α-methyl analogues as shown in Figure 1 and for **58** in comparison with its *S* enantiomer **116** as



116

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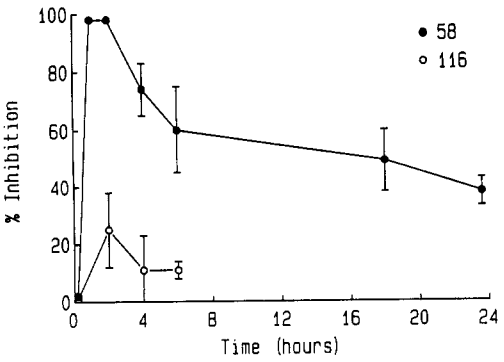

Figure 2. Time-course for oral **58** and **116** inhibition of PAF-induced bronchoconstriction in guinea pigs. The compounds were administered orally at a dose of 50 mg/kg. Each point represents the mean ± SEM for determinations made on six animals.

Table IX. Inhibitory Effect of **31**, **58** and **45** on PAF-Induced Capillary-Permeability Changes in Rats and Guinea Pigs

	rat skin test		guinea pig skin test	
compd	ID_{50}, iv	ID_{50}, po	ID_{50}, iv	ID_{50}, po
31	2.0	25	15	75
58	1.7	70	3.0	65
45	0.64	45	2.5	35

shown in Figure 2. These results confirm the importance of an appropriately configured side-chain alkyl substituent in promoting a long duration of action in this class of PAF antagonists.

A second model used to profile the lead PAF antagonists determined the ability of the drugs to block capillary-permeability changes induced in rat and guinea pig skin by intradermally injected PAF. These skin models are of particular interest because, while PAF-induced bronchoconstriction in the guinea pig occurs secondary to platelet activation,[16] the PAF-mediated increase in vascular permeability in these species is independent of the platelet response.[17] In this assay, animals were treated intravenously or orally with the test substances and challenged with an intradermal injection of PAF either immediately or after a 2-h interval, respectively. The PAF-induced increase in capillary permeability causes an extravasation of serum protein, resulting in the formation of a skin wheal which is visualized on the reflected skin surface with the aid of intravenously administered Evan's blue dye given following the PAF challenge. Inhibition was determined by comparison of the mean area of the skin wheals from the drug-treated animals with that from the corresponding control animals. ID_{50} values calculated from linear-regression analysis of dose-response curves and are summarized in Table IX. Both **31** and **58** as well as the reference PAF antagonist **45**[15] are effective in this model and all three are similar in potency.

In conclusion, we have described a new series of orally effective, long-acting PAF antagonists which are members of the class characterized by a *N*-[4-(3-pyridinyl)butyl] carboxamide attached to an unsaturated, lipophilic moiety. These results, combined with our previous findings,[1,2] suggest that the binding site for these agents comprises a large lipophilic region, possibly at the receptor protein–membrane interface, which is tolerant of steric bulk but provides recognition for the aromatic ring marked "a" in structures **1–4**. More specific recognition comes from a polar interaction with the carboxamide moiety and either a π-interaction with the pyridine ring or an association of receptor elements with the pyridine nitrogen lone pair. The lead structure **58** was selected for in-depth pharmacological evaluation, the details of which will be reported elsewhere.

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, and shifts are reported in ppm downfield from TMS (internal standard). The IR spectra were obtained on a Beckman IR-9 or IR-12 spectrometer and are consistent with the proposed structures. Mass spectra were taken on a CEC 21-110 mass spectrometer at 70 eV. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. Preparative high-pressure liquid chromatography (HPLC) was performed with silica gel Prep-Pak 500 cartridges on a Waters Associates Prep LC 500A instrument. Column chromatography was accomplished on Kieselgel 60, 35–70 mesh, from E. Merck, Darmstadt. 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, and DMF and THF were dried over Linde 3A sieves.

6,6-Diphenyl-5-hexenoic Acid (66). In an inert atmosphere, NaH (56% dispersion in oil, 8.6 g, 0.20 mol) was triturated with pentane and then was dispersed in dry DMSO (100 mL). The mixture was stirred at 70 °C for 1 h, then it was cooled to 0 °C and (carboxybutyl)triphenylphosphonium bromide (36.5 g, 0.0823 mol) was added in several portions over 5 min. After the resulting deep-red solution was stirred at 0–5 °C for 15 min, a solution of benzophenone (18 g, 0.099 mol) in dry THF (100 mL) was added at such a rate that the reaction temperature did not exceed 25 °C. The mixture was stirred at room temperature for 4.5 h, then it was diluted with H_2O (400 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The organic layers were discarded, and the aqueous layer was acidified with 6 N HCl (40 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The extracts were washed with H_2O (3 × 100 mL) and then were combined, dried ($MgSO_4$), and evaporated. The residue was crystallized from hexane to give 16.5 g (75.3%) of **66**, mp 111–112.5 °C (lit.[18] mp 113–113.5 °C). Anal. ($C_{18}H_{18}O_2$) C, H.

7,7-Diphenyl-6-heptenoic acid (67) was prepared as above. Benzophenone (18 g, 0.0988 mol) when reacted with the phosphorane derived from (carboxypentyl)triphenylphosphonium bromide[19] (37.64 g, 0.0823 mol) furnished 16.3 g (70.3%) of **67**, mp 71.5–72.5 °C. Recrystallization from hexane gave the analytical sample, mp 72.5–73.5 °C (lit.[20] mp 70.5–71.5 °C). Anal. ($C_{19}H_{20}O_2$) C, H.

8,8-Diphenyl-7-octenoic acid (68) was prepared as above. Benzophenone (17.5 g, 0.096 mol) was treated with the phosphorane derived from (carboxyhexyl)triphenylphosphonium bromide (37.7 g, 0.08 mol) and crystallization of the crude from hexane afforded 16.6 g (70.6%) of **68**, mp 88–89 °C. Anal. ($C_{20}H_{22}O_2$) C, H.

Method A. 3,3-Diphenyl-*N*-[4-(3-pyridinyl)butyl]-2-propenamide (5). To a stirred solution of 3,3-diphenyl-2-propenoic acid[4] (6.23 g, 27.8 mmol) and Et_3N (4.25 mL, 30.5 mmol) in dry THF (40 mL) at 0 °C was added a solution of ethyl chloroformate (2.74 mL, 27.8 mmol) in THF (20 mL) dropwise such that the reaction temperature was maintained at 0 °C. After the addition was completed, the mixture was stirred at 0 °C for 15 min before 3-pyridinebutanamine[10] (4.38 g, 29.2 mmol) in THF (20 mL) was added dropwise. The reaction was stirred at 0 °C

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for 1 h and then at room temperature for 2 h before the precipitated Et_3N·HCl was removed by filtration. The evaporated filtrate was partitioned between 1 N HCl (80 mL) and Et_2O (80 mL) and, after the ethereal extract was discarded, the aqueous phase was basified with 4 N NaOH (30 mL) and extracted with Et_2O (4 × 100 mL). Evaporation of the dried (K_2CO_3) organic extracts and purification of the residual material by HPLC (EtOAc) yielded 7.42 g (74.9%) of **5**. A portion was crystallized from Et_2O to give the analytical sample, mp 78–80 °C. Anal. ($C_{24}H_{24}N_2O$) C, H, N.

Method B. 5,5-Diphenyl-*N*-[4-(3-pyridinyl)butyl]-4-pentenamide (7). A solution of 5,5-diphenyl-4-pentenoic acid[6] (30.3 g, 0.12 mol) in $SOCl_2$ (30 mL, 0.414 mol) was stirred at room temperature for 15 min, then $PhCH_3$ (200 mL) was added, and the solvents were evaporated under reduced pressure. A solution of the residual acid chloride in CH_2Cl_2 (125 mL) was added over 15 min to a stirred solution of 3-pyridinebutanamine[10] (18 g, 0.12 mol) in CH_2Cl_2 (125 mL) maintained at 0 °C. The mixture was allowed to equilibrate to room temperature over 1 h and then excess 1 N NaOH solution was added, and the phases were separated. The organic phase was washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue was purified by HPLC (EtOAc–Et_3N, 49:1) to give 45.1 g (97.7%) of **7** as a pale yellow oil. Anal. ($C_{26}H_{28}N_2O$) C, H, N.

Method C. [*R*-(*E*,*E*)]-5-(4-Methoxyphenyl)-*N*-[1-methyl-4-(3-pyridinyl)butyl]-2,4-decadienamide (58). In an inert atmosphere, a solution of **77u** (79.09 g, 0.2 mol) and (*R*)-α-methyl-3-pyridinebutanamine[2] (35.5 g, 0.2 mol) in THF (300 mL) was stirred at room temperature overnight and then was heated at reflux for 3 h to consume the last traces of starting materials. After the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 (700 mL) and the solution was washed with 0.5 N NaOH (3 × 500 mL). The aqueous layers were back-washed in turn with CH_2Cl_2 (300 mL) and then the combined organic phases were dried (K_2CO_3) and evaporated. The residual oil was dissolved in Et_2O (600 mL) and the product was allowed to crystallize from solution. The colorless solid was recovered by filtration, washed with Et_2O (3 × 100 mL), and dried to afford 78.0 g (92.7%) of **58**, mp 88–89 °C; $[\alpha]_D$ −28.48° (*c* 1.0, MeOH). Recrystallization of the amide from EtOAc–hexane provided the analytical sample, mp 88–89 °C; $[\alpha]_D$ −28.65° (*c* 1.0, MeOH). Anal. ($C_{27}H_{36}N_2O_2$) C, H, N.

Method D. 3,3-Diphenyl-2-propenal[7] (69). In an argon atmosphere, 1.6 M *n*-BuLi in hexane (862 mL, 1.38 mol) was added to a stirred solution of (*i*-Pr)$_2$NH (193.2 mL, 1.38 mol) in dry THF (1 L) cooled in an Me_2CO–dry ice bath. The mixture was stirred at −78 °C for 30 min before the dropwise addition of acetaldehyde *N*-*tert*-butylimine[21] (88.5 mL, 0.60 mol) over 10 min. The reaction mixture was maintained at −78 °C for an additional 30 min, and then diethyl chlorophosphonate (101.2 mL, 0.6 mol) was added at such a rate that the temperature did not exceed −65 °C. After 1 h, the cooling bath was removed, and the mixture was allowed to warm to −10 °C over 45 min and then benzophenone (109.3 g, 0.6 mol) was added in one portion via a Gooch tube. The reaction mixture was stirred at room temperature overnight, and then the solvents were removed under reduced pressure, and the residue was taken up in a solution of oxalic acid dihydrate (175 g) in H_2O (1.5 L) and $PhCH_3$ was added (1.5 L). After the mixture was stirred vigorously overnight at room temperature, the layers were separated, and the organic phase was washed sequentially with 5% oxalic acid solution (750 mL), brine (750 mL), and saturated $NaHCO_3$ (750 mL). The dried ($MgSO_4$) organic extract was concentrated to ~250 mL under reduced pressure and then placed on a short column of silica gel (500 g) and eluted with CH_2Cl_2 to provide the crude aldehyde. Crystallization from hexane gave 109.3 g (87.5%) of **69**, mp 45–46.5 °C. Concentration of the mother liquor gave a second crop of impure aldehyde, which after two recrystallizations from hexane afforded an additional 10.1 g (8.1%) of **69**, mp 44.5–46 °C (Table VI).

Method E. (*E*)-5,5-Diphenyl-2,4-pentadienoic Acid (70) and (*Z*)-5,5-Diphenyl-2,4-pentadienoic Acid (71). A solution of **69** (18.73 g, 0.09 mol) and (carboxymethylene)triphenylphosphorane (33.1 g, 0.095 mol) in EtOH (500 mL) was stirred for 1 h at room temperature. After the solvent was removed in vacuo, the residue was dispersed in a mixture of Et_2O (125 mL) and hexane (250 mL) and stirred at 50 °C for 10 min to ensure complete digestion of the solids. The cooled mixture was filtered and the filter cake was washed with hexane–Et_2O (2:1, 2 × 50 mL). Evaporation of the filtrate gave an oil that was passed through a short column of silica gel (200 g) and then purified by HPLC (CH_2Cl_2–hexane, 1:1) to yield 4.2 g (16.8%) of the less polar (*Z*)-5,5-diphenyl-2,4-pentadienoic acid ethyl ester that crystallized on standing (mp 36–37 °C), as well as 20.2 g (80.7%) of (*E*)-5,5-diphenyl-2,4-pentadienoic acid ethyl ester as an oil. A portion of the *E* isomer was crystallized from Et_2O to give the dienoic acid ester as a colorless solid, mp 34–35 °C.

A mixture of the (*Z*)-dienoic acid ester (3.5 g, 12.6 mmol) in MeOH (20 mL) and 4 N KOH (5 mL) in H_2O was stirred at reflux for 30 min. Most of the solvent was removed under reduced pressure and the concentrate was poured over a stirred mixture of ice and 3 N HCl (10 mL). The resulting solid was filtered off, washed with H_2O, dried, and then crystallized from CH_2Cl_2–hexane to provide 3.05 g (96.9%) of the (*Z*)-dienoic acid **71**, mp 175–176.5 °C. Anal. ($C_{17}H_{14}O_2$) C, H.

The (*E*)-dienoic acid ester (15 g, 53.9 mmol) was saponified under the same conditions and crystallization of the crude acid from *i*-PrOH furnished 11.7 g (86.7%) of the (*E*)-dienoic acid **70**, mp 193–194 °C (lit.[22] mp 192–193 °C). Anal. ($C_{17}H_{14}O_2$) C, H.

Method F. (*E*,*E*)-5-(4-Methoxyphenyl)-2,4-decadienoic Acid 4-Nitrophenyl Ester (77u). To a mixture of **75u** (174.2 g, 0.635 mol) and 4-nitrophenol (106 g, 0.762 mol) in CH_2Cl_2 (800 mL) cooled to 0–5 °C was added a solution of DCC (137.6 g, 0.667 mol) in CH_2Cl_2 (400 mL) in one portion. The reaction was stirred at 0–5 °C for 60 min and then at room temperature overnight before the precipitated solid was filtered off and washed with a mixture (1:1) of CH_2Cl_2 and hexane (2 × 200 mL). Evaporation of the combined filtrates gave a yellow oil that was applied to a short column of silica gel (1 kg) and eluted with CH_2Cl_2–hexane (3:2) to yield ~240 g of the crude ester **77u** as a yellow solid. Crystallization of the product from *i*-PrOH furnished 219.2 g (87.3%) of **77u**, mp 75–76 °C. Anal. ($C_{23}H_{25}NO_5$) C, H, N.

β-Hydroxy-β-(2-methoxyphenyl)-2-methoxybenzenepropanenitrile (80) was prepared by the method described for the preparation of **82** below. Thus, 2,2′-dimethoxybenzophenone (24.2 g, 0.1 mol) yielded 26.4 g (93.2%) of **80**, mp 178–180 °C. A sample was crystallized from MeOH to provide the analytical specimen, mp 181–182 °C. Anal. ($C_{17}H_{17}NO_3$) C, H, N.

3,3-Bis(2-methoxyphenyl)propenal (73f). $SOCl_2$ (4.5 mL, 0.062 mol) was added to a suspension of **80** (13.4 g, 0.0475 mol) in pyridine (70 mL) maintained at 10 °C during the addition. The reaction was stirred at room temperature for 2 h and then was diluted with ice–H_2O and extracted with CH_2Cl_2 (200 mL). The organic phase was washed in turn with 3 N HCl (1 × 150 mL, 1 × 20 mL) and brine and then was dried ($MgSO_4$) and evaporated. Crystallization of the residue from *i*-PrOH–hexane gave 9.0 g (71.5%) of 3,3-bis(2-methoxyphenyl)-2-propenenitrile, mp 99–100 °C and recrystallization of a sample from the same solvents provided the analytical sample, mp 100.5–101.5 °C. Anal. ($C_{17}H_{15}NO_2$) C, H, N.

Reduction of 3,3-bis(2-methoxyphenyl)-2-propenenitrile was carried out as described below for the preparation of **73u**. From 7.3 g (27.5 mmol) of nitrile, there was obtained 7.2 g (97.5%) of **73f**, mp 59.5–61.5 °C. Anal. ($C_{17}H_{16}O_3$) C, H.

(*R*,*S*)-3-Hydroxy-3-(4-methoxyphenyl)octanenitrile (82). A solution of freshly distilled (*i*-Pr)$_2$NH (72.5 mL, 0.52 mol) in dry THF (250 mL) was cooled to −10 °C and was maintained at that temperature during the dropwise addition, over 20 min, of *n*-BuLi in hexane (2.5 M, 207 mL). After the mixture had been stirred at −10 °C for 15 min, it was cooled to −70 °C and held at that temperature during the dropwise addition of dry MeCN (30 mL, 0.56 mol) over 10 min, followed after 5 min, by the addition of a solution of 4′-methoxyhexanophenone (93.2 g; 0.45 mol) in dry THF (250 mL) within 15 min. The cooling bath was removed, and the reaction was allowed to equilibrate to −35 °C over 15 min, and then a mixture of HOAc (60 g, 0.50 mol) and H_2O (60 mL) was added carefully in a dropwise manner. The temperature of

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the reaction mixture rose fairly rapidly to 0 °C and after stirring for 5 min a mixture of H_2O and brine (2:1, 300 mL) was added in one portion. After separation of the phases, the organic layer was washed with brine (300 mL), and the aqueous phases were extracted in turn with CH_2Cl_2 (2 × 300 mL), and then the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give 112.8 g of the crude carbinol. Crystallization of the product from Et_2O–hexane furnished 107.8 g (96%) of **82**, mp 45–47 °C. Anal. ($C_{15}H_{21}NO_2$) C, H, N.

(*E*)-3-(4-Methoxyphenyl)-2-octenenitrile (83). A solution of **82** (107.8 g, 0.436 mol) in CH_2Cl_2 (540 mL) and CF_3CO_2H (21.6 mL) was refluxed for 6.5 h. After standing overnight at room temperature, the solution was washed successively with H_2O (250 mL), 1 N NaOH (500 mL), and brine (100 mL). The aqueous washes were extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to provide 99.2 g (99%) of a mixture of **83** and the corresponding *Z* isomer. The *E*/*Z* ratio was determined to be >12:1 by NMR ($CDCl_3$) and the material was used in the subsequent step without further purification. A small sample from a previous experiment was purified by HPLC (CH_2Cl_2–hexane, 1:1) and distilled to afford the analytical specimen, bp 130 °C (0.05 mm). Anal. ($C_{15}H_{19}NO$) C, H, N.

(*E*)-3-(4-Methoxyphenyl)-2-octenal (73u). To a solution of crude **83** (99.2 g, 0.43 mol) in dry $PhCH_3$ (960 mL) cooled in a MeCN–dry ice bath, a solution of DiBAH in hexane (1.5 M, 385 mL) was added dropwise over 30 min as the reaction temperature was maintained between −40 and −35 °C. After 1 h at −40 °C, the reaction was allowed to warm slowly to −12 °C over 1 h before a solution of 5% H_2SO_4 (1.4 L) was added slowly over 45 min while maintaining the temperature at −10 °C. When the addition was completed, the mixture was warmed to 40 °C and was stirred rapidly for 2.5 h to effect hydrolysis of the intermediate imine. After the reaction was cooled to room temperature, the layers were separated, and the aqueous phase was extracted with $PhCH_3$ (2 × 250 mL). The organic layers were washed in turn with H_2O (250 mL) and brine (250 mL) and then were dried (Na_2SO_4), filtered through a pad of Celite, and evaporated to give an essentially quantitative recovery (100.2 g) of a mixture of **73u** and the corresponding *Z* aldehyde **73v**. The *E*/*Z* ratio was established as >12:1 by NMR ($CDCl_3$) and the material was used in the subsequent step without further purification.

(*E*)-3-(4-Methoxyphenyl)-2-octenal (73u) and (*Z*)-3-(4-methoxyphenyl)-2-octenal (73v) were prepared as a mixture of isomers by method D described above except that the reaction was allowed to proceed for 5 days. Thus, 4′-methoxyhexanophenone (20.6 g, 0.1 mol) provided 23.3 g of crude product containing **73u** and **73v** in an *E*/*Z* ratio of ~3:2. The mixture was separated by HPLC (Et_2O–hexane, 1:7) to afford 8.1 g (36.1%) of the less-polar *Z* isomer **73v** as an oil and 9.0 g (40.1%) of the *E* isomer **73u**.

A small portion of the *E* isomer was purified by bulb-to-bulb distillation to give the analytical sample, bp 170–180 °C (0.2 mm). Anal. ($C_{15}H_{20}O$) C, H, N.

In the same way, bulb-to-bulb distillation of a sample of the *Z* isomer **73v** provided the analytical sample, bp 160–175 °C (0.2 mm). Anal. ($C_{15}H_{20}O$) C, H, N.

(*E*,*E*)-5-(4-Methoxyphenyl)-2,4-decadienoic Acid (75u). A mixture of crude **73u** containing ~8% of the corresponding *Z* aldehyde **73v** (100.2 g, 0.43 mol) and (carbomethoxymethylene)triphenylphosphorane (158 g, 0.47 mol) in CH_2Cl_2 (500 mL) was stirred for three days at room temperature. After the reaction was worked up as in the previous example, the crude product was passed through a short column of silica gel (750 g) and eluted with CH_2Cl_2 to yield 116.3 g of the (*E*,*E*)-dienoic ester contaminated by minor amounts of the isomeric dienoic esters as a yellow oil.

The oil (116.3 g, 0.40 mol) was stirred for 30 min in a refluxing solution of MeOH (660 mL) and H_2O (550 mL) containing NaOH (32 g, 0.80 mol), and after the MeOH was distilled off, ice (550 g) was added followed by concentrated HCl (82 mL, 0.98 mol). The mixture was extracted three times with CH_2Cl_2 (1 × 1.2 L and 2 × 500 mL), and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The resulting solid residue was triturated with hexane (450 mL), and after the mixture was cooled to ~30 °C, the yellow crystalline solid was filtered off, washed with hexane (3 × 70 mL), and dried to provide 93.9 g (79.6%) of isomerically pure (*E*,*E*)-dienoic acid **75u**, mp 125.5–126.5 °C. A portion was crystallized from Et_2O–hexane to afford the analytical sample, mp 126.5–127.5 °C. Anal. ($C_{17}H_{22}O_3$) C, H.

(*R*,*S*)-(α)-Ethyl-3-pyridinebutanol (86). Under an inert atmosphere, $(Ph_3P)_2PdCl_2$ (17.56 g, 0.025 mol) and CuI (1.7 g, 0.0089 mol) were added to a stirred solution of (±)-5-hexyn-3-ol (259.3 g, 2.64 mol), 3-bromopyridine (395 g, 2.5 mol), and Et_3N (418 mL, 3.0 mol) in CH_2Cl_2 (1.5 L). After 1.5 h, the mildly exothermic reaction reached reflux temperature, and when the gentle reflux had subsided (30 min), external heat was applied to maintain reflux for an additional 5 h. The cooled reaction was stirred overnight at ambient temperature, then H_2O (500 mL) and ice (500 g) were added, followed by concentrated HCl (275 mL) and the mixture was stirred for 10 min. After the phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 750 mL) and each organic layer was back-washed in turn with 1 N HCl (500 mL) before being discarded. The combined aqueous layers were basified with 10 N NaOH and extracted with three portions of CH_2Cl_2 (1 × 1.5 L and 2 × 750 mL). The combined extracts were dried (K_2CO_3) and evaporated to constant weight under reduced pressure to afford 361.5 g of crude (*R*,*S*)-α-ethyl-4-(3-pyridinyl)-3-butynol as an oil.

A solution of the above alcohol (361.5 g, 2.06 mol) was hydrogenated over PtO_2 (15 g) in EtOH (3 L) at room temperature and atmospheric pressure. After the catalyst was filtered off, the solvent was removed under reduced pressure and the residual oil was evaporatively distilled to provide 357 g (79.6%) of **86**, bp 120–130 °C (0.1 mm). Anal. ($C_{11}H_{17}NO$) H, N, C: calcd, 73.70; found, 74.14.

6-(3-Pyridinyl)-3-hexanone (87). A stirred solution of oxalyl chloride (265 g, 2.088 mol) in CH_2Cl_2 (1.75 L) was cooled to −78 °C under argon, then a mixture of DMSO (170 g, 2.18 mol) in CH_2Cl_2 (200 mL) was added dropwise over 75 min such that the reaction temperature did not exceed −72 °C. The mixture was stirred at −75 °C for 10 min and then **86** (356.6 g, 1.99 mol) in CH_2Cl_2 (150 mL) was added dropwise over 1 h while the reaction temperature was maintained below −70 °C. After the addition of substrate was completed, the mixture was stirred at −75 °C for another 30 min, then Et_3N (630 mL, 4.5 mol) was added slowly over 1 h while the reaction temperature was kept between −70 and −65 °C. The cooling bath was removed, and after the mixture was allowed to equilibrate to room temperature over 1 h, H_2O (1.2 L) was added, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 1 L), and then the organic phase and extracts were washed in turn with 1.5 N NaOH (1 L) and 10% NaCl (1 L). The combined CH_2Cl_2 layers were dried (K_2CO_3) and concentrated, and the crude product was distilled to yield 327.9 g (92.9%) of **87**, bp 110–115 °C (0.1 mm). Anal. ($C_{11}H_{15}NO$) C, H, N.

(*R*,*S*)-α-Ethyl-3-pyridinebutanamine (88). A mixture of **87** (327.9 g, 1.85 mol), $NaBH_3CN$ (116.5 g, 1.854 mol) and NH_4OAc (1426 g, 18.5 mol) in dry MeOH (6.5 L) was stirred at room temperature for 72 h, then ~4 L of solvent was distilled off under reduced pressure (internal temperature <30 °C). The reaction was cooled in an ice bath as 6 N HCl (4.5 L) was added slowly over 2 h, and stirring was continued overnight. In an argon atmosphere, the reaction was made strongly basic by the addition of 12.5 N NaOH (2.5 L) and extracted three times with CH_2Cl_2 (1 × 2 L and 2 × 1 L). The combined extracts were dried (K_2CO_3) and evaporated, and the crude amine was distilled to afford 289.4 g (87.7%) of **88**, bp 95–100 °C (0.1 mm). Anal. ($C_{11}H_{18}N_2$) C, H, N.

(*R*)-α-Ethyl-3-pyridinebutanamine (89) and (*S*)-α-Ethyl-3-pyridinebutanamine (90). A solution of DCC (367.4 g, 1.78 mol) in DMF (500 mL) was added to a stirred solution of the racemic amine **88** (289 g, 1.67 mol), (*R*)-mandelic acid (259 g, 1.7 mol) and 1-hydroxybenzotriazole hydrate (274 g, 1.79 mol) in DMF (1.7 L) maintained at −10 °C during the addition. After it was stirred at −5 °C for 3 h and then at room temperature overnight, the mixture was rechilled to 0 °C for 2 h and the precipitate was filtered off and washed in turn with cold DMF (3 × 150 mL) and EtOAc (3 × 200 mL). The solid, a mixture of dicyclohexylurea (DCU) and the less-soluble (*R*,*R**)-α-hydroxy-*N*-[1-ethyl-4-(3-pyridinyl)butyl]benzeneacetamide, was dispersed in 1 N HCl (2 L) and stirred at room temperature for 4 h. The

undissolved solid (DCU) was removed by filtration and washed with dilute HCl (200 mL) and with H_2O. The filtrate was basified with 6 N NaOH and the resulting colorless, crystalline material was collected by filtration, washed well with H_2O, and dried in vacuo to provide 195.4 g (77.2%) of (*R,R**)-α-hydroxy-*N*-[1-ethyl-4-(3-pyridinyl)butyl]benzeneacetamide, mp 161.5–163 °C, $[\alpha]_D$ −14.9° (*c* 1.0, MeOH). Anal. ($C_{19}H_{24}N_2O_2$) C, H, N.

The original DMF mother liquor and washings from above were evaporated, and the residue was partitioned between CH_2Cl_2 (2 L) and 2 N NaOH (1.5 L). The separated organic phase was washed with 1 N NaOH (2 × 500 mL), and then each aqueous layer was washed in turn with CH_2Cl_2 (2 × 800 mL). The organic phases were extracted with three portions of 1 N HCl (1 × 1.5 L and 2 × 600 mL), and then were discarded. The combined acidic layers were basified with 10 N NaOH (400 mL) and extracted with CH_2Cl_2 (1 × 2 L and 2 × 600 mL). The organic extracts were combined, dried (K_2CO_3), and evaporated, and the residual solid was triturated with hot hexane (1 L). The solid was collected by filtration to give 265 g of mandelamide rich (~7:1) in the more soluble (*S*,R*)-α-hydroxy-*N*-[1-ethyl-4-(3-pyridinyl)butyl]-benzeneacetamide, $[\alpha]_D$ −37.3° (*c* 1.0, MeOH). Fractional crystallization of the material from *i*-PrOH furnished 147 g (58.6%), mp 122–124 °C, $[\alpha]_D$ −41.2° (*c* 1.0, MeOH). Anal. ($C_{19}H_{24}N_2O_2$) C, H, N.

A solution of (*R,R**)-α-hydroxy-*N*-[1-ethyl-4-(3-pyridinyl)butyl]benzeneacetamide (195 g, 1.094 mol) in 6 N HCl (1.1 L) containing concentrated HCl (104 mL) was stirred at reflux for 48 h. After most of the solvent had been removed under reduced pressure, the residue was made strongly basic by the addition of 10 N NaOH in an argon atmosphere and extracted with CH_2Cl_2 (1 × 1.5 L and 2 × 800 mL). The combined extracts were dried (K_2CO_3) and evaporated and the crude product was distilled to give 109 g of **89**, bp 105 °C (0.2 mm), $[\alpha]_D$ −11.9° (*c* 1.0, MeOH). Anal. ($C_{11}H_{18}N_2$) C, H, N.

(*S*)-α-Ethyl-3-pyridinebutanamine (**90**) was prepared as described for **89**. Thus, hydrolysis of (*R*,S*)-α-hydroxy-*N*-[1-ethyl-4-(3-pyridinyl)butyl]benzeneacetamide (31.2 g, 76.6 mmol) and distillation furnished 16.4 g (92%) of **90**, bp 95–98 °C (0.1 mm), $[\alpha]_D$ +11.75° (*c* 1.0, MeOH). Anal. ($C_{11}H_{18}N_2$) C, H, N.

(±)-α-Propyl-3-pyridinepentanoic Acid (93a). In an inert atmosphere, 1.6 M *n*-BuLi in hexane (26.4 mL, 42 mmol) was added to a stirred solution of $(i\text{-Pr})_2NH$ (5.9 mL, 42 mol) in dry THF (20 mL) cooled in an Me_2CO–dry ice bath. The mixture was stirred at −78 °C for 30 min, and then a solution of pentanoic acid (2.04 g, 20 mmol) in THF (10 mL) was added over 3 min. The reaction was allowed to equilibrate to ambient temperature and then was heated at 50 °C for 1 h to complete formation of the dianion. The mixture was recooled to −78 °C and a solution of 3-(3-bromopropyl)pyridine[10] (**92**, 4.0 g, 20 mmol, freshly liberated from its HBr salt) in THF (20 mL) was added. The cooling bath was removed and the reaction was stirred at 50 °C for 7 h, and then, after the solvents were removed in vacuo, the residue was dissolved in 1 N HCl (100 mL) and the solution was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were back-washed with 1 N HCl (2 × 25 mL), and then the combined acidic layers were basified with 10 N NaOH (17 mL) and washed with CH_2Cl_2 (3 × 100 mL) to remove the residual **92**. The aqueous phase was acidified with the addition of HOAc (3 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The extracts were washed with brine and then were combined, dried (Na_2SO_4), and evaporated to give 3.5 g of crude **93a**. Crystallization of the product from Et_2O–hexane afforded 2.7 g (61%) of **93a**, mp 56–57 °C. Anal. ($C_{13}H_{19}NO_2$) C, H, N.

(*R,S*)-α-(1-Methylethyl)-3-pyridinepentanoic acid (93b) was obtained as described above for **93a**. From isovaleric acid (2.04 g, 20 mmol) there was obtained, after crystallization of the crude from Et_2O–hexane, 2.8 g (63.3%) of **93b**, mp 52–55 °C. Recrystallization of a sample from the same solvents furnished the analytical specimen, mp 54–56 °C. Anal. ($C_{13}H_{19}NO_2$) C, H, N.

(*R,S*)-α-Cyclopropyl-3-pyridinepentanoic acid (93c) was obtained as described above for **93a**. Thus cyclopropaneacetic acid (2.5 g, 25 mmol) yielded 4.6 g (83.9%) of **93c** as a colorless solid. Crystallization of a portion from Et_2O–hexane provided the analytical sample, mp 82–84 °C. Anal. ($C_{13}H_{17}NO_2$) C, H, N.

(*R,S*)-α-Butyl-3-pyridinepentanoic acid (93d) was prepared as described above for **93a**. Thus, hexanoic acid (2.32 g, 20 mmol) afforded 4.0 g (85%) of **93d** as an oil: MS *m/z* 235 (M^+).

(*R,S*)-α-Cyclopentyl-3-pyridinepentanoic acid (93e) was obtained as described above for **93a**. From cyclopentaneacetic acid (2.56 g, 20 mmol) there was obtained 4 g (80.9%) of crude **93e**, which was crystallized from Et_2O–hexane to provide 3.1 g of the title compound as a colorless solid, mp 95–97 °C. Anal. ($C_{15}H_{21}NO_2$) C, H, N.

(*R,S*)-α-Propyl-3-pyridinebutanamine (95). A solution of **93a** (2.5 g, 11.3 mmol), diphenyl phosphorazidate (2.45 mL, 11.37 mmol), and Et_3N (1.6 mL, 11.5 mmol) in *t*-BuOH (25 mL) was stirred at reflux overnight. After the solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (100 mL) and washed with 1 N NaOH (2 × 50 mL). The aqueous layers were back-extracted with CH_2Cl_2 (50 mL), and then the combined extracts were dried (K_2CO_3) and evaporated, and the residual oil was purified by HPLC (EtOAc) to afford 2.75 g (83.3%) of the carbamate **94a** as an oil.

A solution of the carbamate **94a** (1.8 g, 6.16 mmol) in 1 N HCl (25 mL) was heated on a steam bath for 75 min and then was cooled and extracted with Et_2O (40 mL). In an atmosphere of argon, the acidic layer was treated with 10 N NaOH (3 mL) and extracted with CH_2Cl_2 (2 × 50 mL). Evaporation of the dried (K_2CO_3) extracts yielded 1.15 g (97%) of **95** as an oil. A portion was purified by bulb-to-bulb distillation to afford the analytical sample, bp 110 °C (0.1 mm). Anal. ($C_{12}H_{20}N_2$) C, H, N.

(*R,S*)-α-(1-Methylethyl)-3-pyridinebutanamine (96) was prepared as described above for **95**. Thus the acid **93b** (2.3 g, 10.4 mmol) gave 2.5 g (82.2%) of the carbamate **94b**, of which 1.7 g (5.8 mmol) was hydrolyzed to give 1.1 g (98%) of the amine **96**, bp 110–115 °C (0.1 mm). Anal. ($C_{12}H_{20}N_2$) H, N, C: calcd 74.95; found 74.45.

(*R,S*)-α-Cyclopropyl-3-pyridinebutanamine (97) was prepared as described above for **95**. The acid **93c** (4.2 g, 19.15 mmol) was converted to 4.8 g (86.3%) of the carbamate **94c**. Acid hydrolysis of **94c** (4.4 g, 15.15 mmol) afforded 2.8 g (97%) of the crude amine **97**. This material was used without further purification in subsequent reactions.

(*R,S*)-α-Butyl-3-pyridinebutanamine (98) was prepared as described above for **95**. The acid **93d** (3.7 g, 15.7 mmol) provided 3.6 g (74.8%) of the carbamate **94d**, of which 2.2 g (7.18 mmol) was hydrolyzed to give 1.35 g (91%) of the amine **98**, bp 115 °C (0.1 mm). Anal. ($C_{13}H_{22}N_2$) C, H, N.

(*R,S*)-α-Cyclopentyl-3-pyridinebutanamine (99) was prepared as described above for **95**. The acid **93e** (2.8 g, 11.32 mmol) was converted to 2.5 g (69.3%) of the purified carbamate **94e**. Hydrolysis of **94e** (1.6 g, 5.02 mmol) gave, after bulb-to-bulb distillation of the product, 1.05 g (93.9%) of the amine **99**, bp 120–130 °C (0.1 mm). Anal. ($C_{14}H_{22}N_2 \cdot 0.25H_2O$) C, H, N.

2-Methyl-3-pyridinyl Trifluoromethanesulfonate (101). A mixture of 3-hydroxy-2-methylpyridine (**100**) (7.65 g, 0.07 mol) and bis[(trifluoromethyl)sulfonyl]benzenimide (25 g, 0.07 mol) in CH_2Cl_2 (175 mL) was cooled in an ice bath as dry Et_3N (10.25 mL, 0.074 mol) was added dropwise over 10 min. The reaction was stirred for 1 h at 0 °C then was allowed to equilibrate to room temperature over 1 h. The mixture was washed in turn with 1 N NaOH (2 × 50 mL), half-saturated K_2CO_3 (50 mL), and brine (2 × 50 mL) and then was dried (K_2CO_3) and evaporated to give 16.7 g of crude **101** as an oil. Distillation of the product afforded 14.34 g (84.9%) of **101**, bp 73–76 °C (3.75 mm). Anal. ($C_7H_6F_3NO_3S$) C, H, F, N, S.

(*R,S*)-α,2-Dimethyl-3-pyridinebutanol (102a). After argon was passed through a solution of **101** (10 g, 41.4 mmol) and (±)-4-pentyn-2-ol (5.18 g, 61.2 mmol) in DMF (125 mL) and Et_3N (40 mL) for 35 min, $(Ph_3P)_2PdCl_2$ (0.888 g, 1.23 mmol) was added and the reaction mixture was stirred at 90 °C for 3 h and then at room temperature overnight. The mixture was cooled in an ice bath and was acidified by the dropwise addition of 6 N HCl (150 mL) and then was extracted with Et_2O (3 × 150 mL). The aqueous layer was made basic with 10 N NaOH and extracted with EtOAc (3 × 150 mL). The combined EtOAc extracts were washed with brine, dried (K_2CO_3), and evaporated, and the resulting brown oil was passed through a plug of silica gel (EtOAc–hexane, 7:3) to provide 7.0 g of (*R,S*)-5-(2-methyl-3-pyridinyl)-4-pentyn-2-ol as an oil.

A solution of the above alcohol (7.0 g, 40.4 mmol) in EtOH (70 mL) was hydrogenated over 10% Pd/C (0.78 g) at room temperature and atmospheric pressure until the uptake of hydrogen had stopped. After the catalyst was filtered off, the solution was evaporated and the residual oil was evaporatively distilled to provide 6.0 g (80.7%) of **102a**, bp 110–115 °C (0.15 mm). Anal. ($C_{11}H_{17}NO \cdot 0.133H_2O$) C, H, N, H_2O.

5-(2-Methyl-3-pyridinyl)-2-pentanone (103a) was prepared under the conditions described above for **87**. From 5.54 g (31 mmol) of **102a** there was obtained 4.96 g (89.7%) of **102a** after bulb-to-bulb distillation, bp 100–105 °C (0.15 mm). Anal. ($C_{11}H_{15}NO \cdot 0.06H_2O$) C, H, N, H_2O.

5-(6-Methyl-3-pyridinyl)-2-pentanone (103b) was prepared under conditions similar to those described for **87**. Oxidation of **102b**[12] (10.25 g, 57.2 mmol) furnished 7.4 g (73%) of **103b** after purification of the crude product by HPLC (EtOAc–hexane, 1:1) followed by bulb-to-bulb distillation, bp 88–90 °C (0.05 mm). Anal. ($C_{11}H_{15}NO$) C, H, N.

***(R,S)*-α,2-Dimethyl-3-pyridinebutanamine (104a)** was prepared under the conditions described for **88**. The reductive amination of **103a** (15.14 g, 85 mmol) provided, after distillation of the crude amine, 12.6 g (83.2%) of **104a**, bp 85 °C (0.005 mm).

***(R,S)*-α,6-Dimethyl-3-pyridinebutanamine (104b)** was prepared as described for **88**. Reductive amination of **103b** (7.27 g, 41 mmol) yielded, after distillation of the crude product, 4.31 g (59%) of **104b**, bp 98–101 °C (0.005 mm). Anal. ($C_{11}H_{18}N_2$) H, N; C: calcd, 74.11; found, 73.54.

3-(4-Methyl-4-pentenyl)pyridine (106). In an argon atmosphere, NaH (60% dispersion in oil, 7 g, 0.175 mol) was triturated with pentane and then was dispersed in dry DMSO (75 mL). The mixture was stirred at 75 °C for 45 min and then was cooled and methyltriphenylphosphonium bromide (61 g, 0.17 mol) was added, followed after 30 min by a solution of 5-(3-pyridinyl)-2-pentanone[1] (**105**, 25 g, 0.153 mol) in DMSO (125 mL). After the reaction mixture was stirred overnight at room temperature, 1 N HCl (1 L) was added and the precipitated triphenylphosphine oxide was removed by filtration. The filtrate was made basic by the addition of 10 N NaOH (110 mL) and then extracted with CH_2Cl_2 (4 × 300 mL). The extracts were washed with brine and then were combined, dried (K_2CO_3), and evaporated to give 25 g of the crude olefin **106**. The material was purified by HPLC (EtOAc–hexane, 1:1) to yield 17.5 g (70.9%) of **106** as a colorless oil. Anal. ($C_{11}H_{15}N$) H, N; C: calcd, 81.94; found, 81.20.

***N*-[1,1-Dimethyl-4-(3-pyridinyl)butyl]-2-nitrobenzeneacetamide (110).** A mixture of **106** (22.7 g, 0.14 mol) and 2-nitrophenylacetonitrile (**109**, 22.8 g, 0.14 mol) in HOAc (80 mL) was cooled to 12 °C, then concentrated H_2SO_4 (16 mL) was added dropwise over 6 min. The reaction was stirred for 2 h at room temperature, and then after the HOAc was removed in vacuo, H_2O (1 L) was added and the mixture was extracted with CH_2Cl_2 (400 mL) to remove the neutral impurities. The aqueous layer was basified with 10 N NaOH, extracted with CH_2Cl_2 (4 × 200 mL) and evaporation of the dried (K_2CO_3) extracts afforded 35.6 g (74.1%) of **110**. A portion was crystallized from EtOAc–hexane to provide the analytical sample, mp 117–118.5 °C. Anal. ($C_{19}H_{23}N_3O_3$) C, H, N.

α,α-Dimethyl-3-pyridinebutanamine (108). A solution of **110** (35.2 g, 0.103 mol) in HOAc (250 mL) was hydrogenated over 10% Pd/C (3.5 g) at atmospheric pressure and ambient temperature. The reaction was exothermic and stopped abruptly after the uptake of the theoretical amount of H_2 (7.5 L). The catalyst was filtered off and the filtrate was heated at reflux for 90 min. Concentrated HCl (10 mL) was added to the cooled reaction and the solvent was evaporated under reduced pressure. The residual material was dispersed in H_2O (1 L) and extracted with EtOAc (4 × 200 mL) to remove the byproduct, oxindole. The aqueous layer was basified with 10 N NaOH and extracted with CH_2Cl_2 (3 × 300 mL) to give, after evaporation of the dried (K_2CO_3) extracts, 15 g of the amine **108** as an oil. The material was purified by bulb-to-bulb distillation (95 °C, 0.1 mm) to yield 14.3 g (77.8%) of **108**. Anal. ($C_{11}H_{18}N_2$) C, H, N.

2-[3-(3-Pyridinyloxy)propyl]-1*H*-isoindole-1,3(2*H*)-dione (114). A mixture of 3-hydroxypyridine (**112**, 5.0 g, 52.5 mmol), *N*-(3-hydroxypropyl)phthalimide (**113**, 10.5 g, 52.5 mmol), and Ph_3P (13.5 g, 51.5 mmol) in DMF at 0 °C was treated with diethyl azidocarboxylate (9 mL, 57.15 mmol) and the reaction was stirred overnight at room temperature. After the solvent was removed in vacuo, the residue was taken up in CH_2Cl_2 and the solution was washed with H_2O (5×), dried (Na_2SO_4), and evaporated. The residual material was purified by HPLC (EtOAc–hexane, 1:1) and crystallized from CH_2Cl_2–Et_2O to afford 6.3 g (43.3%) of **114**, mp 112–115 °C. Anal. ($C_{16}H_{14}N_2O_3$) C, H, N.

3-(3-Pyridinyloxy)-1-propanamine (115). A 40% aqueous solution of CH_3NH_2 (5 mL) was added to a solution of **114** (1.0 g, 3.5 mmol) in EtOH (20 mL) and the reaction was stirred overnight at room temperature. The solvents were evaporated; the residue was partioned between saturated brine and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (4×), dried (K_2CO_3), and evaporated to give 0.40 g (80%) of **115** as a yellow oil, which was used without further purification.

[*S*-(*E*,*E*)]-5-(4-Methoxyphenyl)-*N*-[1-methyl-4-(3-pyridinyl)butyl]-2,4-decadienamide (116). Under the conditions of method C, the *p*-nitrophenyl ester **77u** (7.9 g, 20 mmol) was reacted with (*S*)-α-methyl-3-pyridinebutanamine[2] (3.35 g, 0.2 mol) in THF (75 mL). After the usual workup, the product was crystallized from Et_2O–hexane to furnish 7.19 g (86%) of **116**, mp 88–89 °C; $[\alpha]_D$ +28.6° (*c* 1.0, MeOH). Anal. ($C_{27}H_{36}N_2O_2$) C, H, N.

In Vivo Assay for PAF-Induced Increase in Capillary Permeability. For the PAF challenge, groups of five Sprague–Dawley rats or Charles River guinea pigs were anesthetized with ether and pretreated with an antihistamine (50 mg/kg ip of pyrilamine maleate) and a serotonin antagonist (4 mg/kg ip of methylsergide maleate). After 30 min, 0.05 mL of a saline solution containing 5 ng of PAF was injected intradermally at four sites per animal. Evan's blue dye (0.5%) was then injected intravenously into the tail vein of the rat or the ear vein of the guinea pig in order to assist in visualization of the skin wheals formed at each site of PAF injection. Thirty minutes later, the animals were sacrificed by cervical dislocation, and the increase in capillary permeability induced by PAF was determined by measuring the average diameter of each wheal on the dorsal rat or guinea pig skin with a metric vernier caliper. ID_{50} values for active compounds were determined by linear regression of log dose–response curves generated by at least three doses that caused a reduction in area of the PAF-induced skin wheals of between 10 and 90%. The correlation coefficient for the regression line of each antagonist was always greater than 0.95.

Acknowledgment. We thank members of the Physical Chemistry Department, Hoffmann-La Roche, Inc., for determination of the spectral and microanalytical data for the compounds reported herein.