Design, Synthesis, and Structure−Activity Relationship Studies of Novel 1-[(1-Acyl-4-piperidyl)methyl]-1*H*-2-methylimidazo[4,5-*c*]pyridine Derivatives as Potent, Orally Active Platelet−Activating Factor Antagonists

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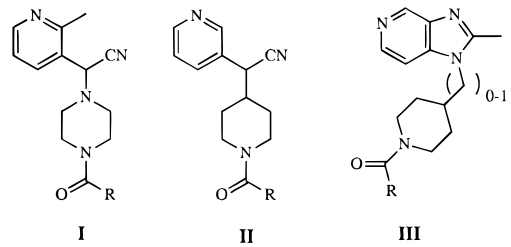
Replacement of the polar head of our previous series of 1-acyl-4-[(2-methyl-3-pyridyl)-cyanomethyl]piperazines with a 2-methylimidazo[4,5-*c*]pyridine group has led to the identification of a new series of 1-[(1-acyl-4-piperidyl)methyl]-1*H*-2-methylimidazo[4,5-*c*]pyridine derivatives as potent, orally active platelet-activating factor (PAF) antagonists. On the basis of the general structure−activity relationship trends found for the acyl substituent in our earlier series, five groups of compounds were tested, diaryl- or alkylarylpropanoyl derivatives, their 3-hydroxy-substituted analogues, and urea, carbamate and amino acid derivatives. The optimal compound **19** (UR-12670), bearing the 3,3-diphenylpropanoyl moiety, exhibited very high in vitro and in vivo potency (IC_{50} = 0.0076 μM for the in vitro PAF-induced platelet aggregation assay, ID_{50} = 0.0086 mg/kg for the in vivo PAF-induced hypotension test in normotensive rats, and ID_{50} = 0.092 mg/kg po and 0.0008 mg/kg iv for the PAF-induced mortality test in mice). Compound **19** also showed long duration of activity. It gave 100% protection against PAF-induced mortality in mice 7 h after iv administration of a single dose of 1 mg/kg and also provided 100% inhibition of PAF-induced aggregation in dog whole blood 6 h after iv administration of the same dose. The lead structure **19** has been selected for in-depth pharmacological evaluation.

Introduction

Earlier work in our laboratory led to the discovery of (pyridylcyanomethyl)piperazines and -piperidines of general formula I and II as a new class of potent platelet-activating factor (PAF) antagonists and to the selection of UR-12460 (**1**) and UR-12519 (**2**) for development (see Table 1).[1] These compounds, which have demonstrated to be fairly stable as solids, were found to suffer a relatively rapid hydrolysis of the (cyanomethyl)amino group in aqueous solution. This fact together with a short duration of action in vivo led us to discontinue them and initiate a search for a surrogate polar head within the same skeleton.

A structural feature of many PAF antagonists is the presence of an sp^2 nitrogen at a given distance from and orientation to an amide or other isosteric groups.[2] We demonstrated that piperazinic derivatives I and their carba analogues II featured essentially the same activity in in vitro and iv in vivo tests (see **1** vs **3** in Table 1), showing that the piperazinic nitrogen serves merely as a framework.[1] The presence of the cyano group, on the other hand, was essential for activity, suggesting that in addition to the requisite named above another feature may be important in the interaction of this type of compound with the PAF receptor, namely, a third coordination center close to the pyridine sp^2 nitrogen. Inspection of the molecular model for the imidazo[4,5-*c*]pyridine moiety, which is present in different PAF antagonists,[3] indicates that the two more distant nitrogens might also fulfill the latter requisite. Accordingly, structures like III resulting from the replacement of the (cyanomethyl)pyridyl moiety of II with 2-methylimidazo-[4,5-*c*]pyridine appear to be interesting candidates. This hypothesis is illustrated in Figure 1, which shows the MM2-optimized modeled structures[4] for (cyanomethyl)-pyridine II (R = CH_3) and the proposed imidazopyridine series III (R = CH_3) overlaid with the three indicated coordination centers of both molecules superimposed. In order to test our hypothesis, compounds **4**−**7**, with the heterocyclic head linked directly to the piperidine ring or through a methylene bridge, were prepared (see Table 1). The activities of the longer compounds **4** and **5** were very close to those of their analogues **1**−**3**, and preliminary chemical stability studies indicated that the new skeleton was free of hydrolysis problems. With this result on hand, we proceeded to the fine optimization of the acyl radical following the trends found in previous series. The present report provides an account of the synthesis and pharmacological evaluation of 1-[(1-acyl-4-piperidyl)methyl]-1*H*-2-methylimidazo[4,5-*c*]pyridine derivatives, from which a new lead, **19**, has been selected.



I II III

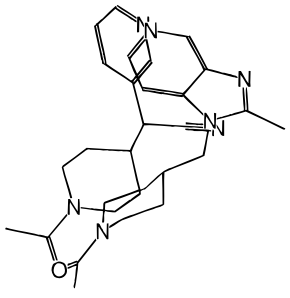


Figure 1. Overlay of (cyanomethyl)pyridine II (R = Me) and imidazopyridine III (R = Me).

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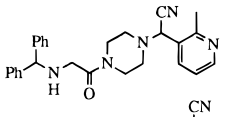
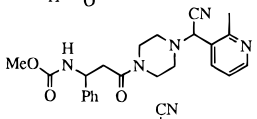
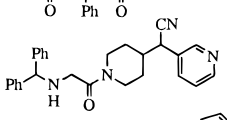
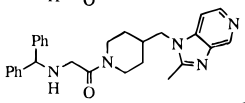
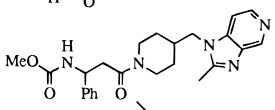
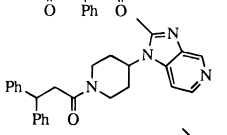
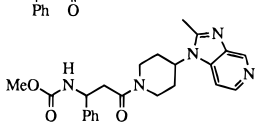
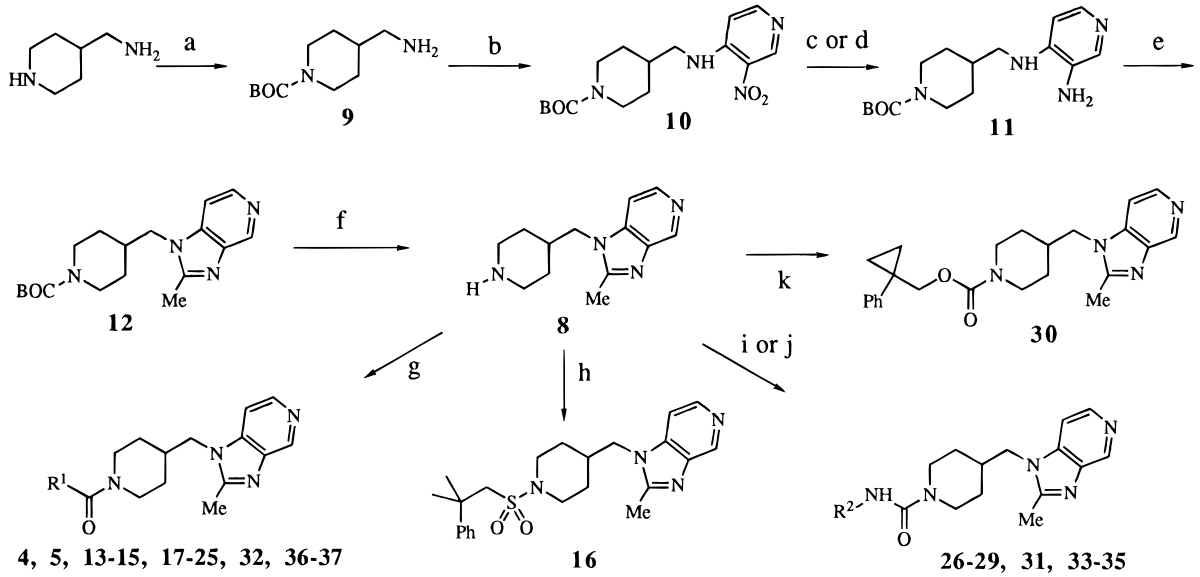
Table 1. Comparison of (Cyanomethyl)pyridines with Imidazopyridines

comp	R	PAF-induced platelet aggregation IC_{50},[a] μM	PAF-induced hypotension ID_{50},[b] mg/kg iv	PAF-induced mortality ID_{50},[c] mg/kg iv	PAF-induced mortality ID_{50},[d] mg/kg po	mp, °C (cryst solvent)[e]	formula[f]
1		0.040 (0.030-0.053)	0.021 (0.015-0.031)	0.009 (0.008-0.011)	0.30 (0.16-0.54)		
2		0.041 (0.031-0.055)	0.015 (0.011-0.021)	0.0055 (0.0009-0.031)	0.044 (0.023-0.091)		
3		0.024 (0.015-0.039)	0.030 (0.019-0.047)		2.6 (0.72-9.3)		
4		0.013 (0.009-0.017)	0.067 (0.036-0.13)	0.0041 (0.0014-0.012)	0.3-1	77-79	$C_{28}H_{31}N_5O.1/2H_2O$
5		0.012 (0.009-0.017)	0.035 (0.027-0.045)	0.0027 (0.0009-0.0078)	0.03-0.1	97-100	$C_{24}H_{29}N_5O_3.1/2H_2O$
6		0.10 (0.05-0.2)	0.41 (0.31-0.55)		>3	95-100	$C_{27}H_{28}N_4O.1/4\ H_2O$
7		1.30 (1.0-1.75)	0.56 (0.27-1.14)			102-105	$C_{23}H_{27}N_5O_3.H_2O$

[a] Concentration required to inhibit PAF-induced maximum aggregation by 50%. Parentheses contain 95% confidence limits. [b] Dose required to reduce the lowering of the arterial blood pressure caused by PAF by 50%. Parentheses contain 95% confidence limits. [c] Dose required to inhibit PAF-induced mortality by 50% (intravenous route). [d] Dose required to inhibit PAF-induced mortality by 50% (oral administration). [e] Compounds were purified by chromatography and triturated with ether. [f] Satisfactory elemental analyses (±0.4%) were obtained for C, H, and N for all compounds except for the following products (compd, element, calcd (found value)): **7** N, 15.93 (15.34).

Scheme 1[a]



[a] (a) BOC_2O, $CHCl_3$, room temperature, 18 h; (b) 4-chloro-3-nitropyridine, Et_3N, CH_3Cl, reflux for 18 h, 64% (two steps); (c) H_2, 10% Pd/C, MeOH, 18 h; (d) $Na_2S_2O_4$, pyridine/H_2O, room temperature, 18 h; (e) ethyl acetimidate hydrochloride, EtOH, reflux, 18 h, 62% (two steps); (f) 6.5 N HCl_g/dioxane, MeOH, room temperature, 18 h, 78%; (g) R^1COOH, DCC, HOBT, DMF, room temperature, 18 h; (h) $Ph(CH_3)_2CCH_2SO_2Cl$, Et_3N, $CHCl_3$, room temperature, 18 h; (i) R^2COOH, $(PhO)_3$, Et_3N, benzene, 90 °C, 2 h and then 8 was added, 90 °C, 18 h; (j) $R^2NHCOOPh$, pyr, 130 °C, 18 h; (k) $Ph(C_3H_4)CH_2OCOOPh$, pyr, 130 °C, 18 h.

Chemistry

All the (piperidylmethyl)imidazopyridines were prepared from a common intermediate, amine **8**, which was synthesized according to Scheme 1. BOC-protection of the secondary amine of 4-(aminomethyl)piperidine followed by alkylation of the primary amine with 4-chloro-3-nitropyridine[5] gave nitropyridine **10**. This compound was reduced with $Na_2S_2O_4$ in pyridine/H_2O[6] or alternatively hydrogenated over 10% Pd/C to diamine **11**, which was cyclized to the imidazopyridine **12** using

ethyl acetimidate hydrochloride. Deprotection of the secondary amine of **12** afforded amine **8**.

Amide derivatives **13**−**15**, **17**−**25**, **32**, **36**, and **37** were obtained by reacting **8** with the corresponding carboxylic acid (R^1COOH) via DCC coupling in the presence of HOBT. Ureas **26**−**29**, **31**, and **33**−**35** were obtained by two methods: either by reaction of **8** with the isocyanate generated through treatment of the corresponding R^2-COOH with diphenyl phosphorazidate or by coupling **8** with the appropiate phenyl carbamate ($R^2NHCOOPh$) in pyridine heating at reflux. Similar conditions were used for the reaction of **8** with $Ph(C_3H_4)CH_2OCOPh$ to give **30**. Sulfonamide **16** was prepared by reaction of **9** with $Ph(CH_3)_2CH_2SO_2Cl$.[7] The carboxylic acids are commercially available or were prepared by known methods.[8] Compounds **6** and **7** were obtained from 1-(4-piperidyl)-1*H*-2-methylimidazo[4,5-*c*]pyridine. This intermediate was synthesized as described for amine **8** starting from 1-(*tert*-butoxycarbonyl)-4-aminopiperidine.

Results and Discussion

Several different assays were used to evaluate the potency of the PAF antagonists described here: the in vitro PAF-induced platelet aggregation assay,[9] the in vivo PAF-induced hypotension test in normotensive rats,[10] and the PAF-induced mortality test in mice[11] (po and iv administration). Along with the standard reference compound WEB-2086, we used BB-882, also an imidazopyridine derivative and one of the most advanced PAF antagonists presently in clinical trials. On the basis of the general structure−activity relationship (SAR) trends found for the acyl substituent in our earlier series, five groups of compounds were tested, diaryl- or alkylarylpropanoyl derivatives **13**−**22**, their 3-hydroxy-substituted analogues **23**−**25**, the urea and carbamate derivatives **26**−**30**, and amino acid derivatives **31**−**37** (Table 2). Diphenyl- or alkylphenylpropanoyl derivatives **13**−**15** and **19** gave potent activities in the three tests involving the in vitro assay and iv in vivo tests, 3,3-diphenylpropanoyl derivative **19** being the most active. As we found that unsubstituted 3-phenylpropanoyl derivative **17** showed a significant loss of activity, we infer that branched substitution on the acyl moiety seems to be important for activity. Introduction of a methoxy group at the 2-position of the aromatic ring, as in compound **18**, also enhanced potency. Considering unsaturated derivatives **20** and **21**, we found that the ethyl derivative **21** was more favored and comparable to its ether analogue **22**. While few compounds (**13**−**15** and **21**) showed modest activities in the oral test, 3,3-diphenylpropanoyl derivative **19** was found to show the highest potency comparable to reference compound BB-882. Interestingly, replacing the amide group in compound **15** with a sulfonamide moiety (compound **16**) was detrimental to oral activity.

We next introduced a polar group with the ability to establish hydrogen bonding in the 3,3-diaryl- or 3,3-arylalkylpropanoyl chain, a strategy that had increased bioavailability in previous series. Among compounds **23**−**25**, which carry a hydroxy group on position 3, **24** and **25** were only slightly less active than **19** in the in vitro and iv in vivo tests and compounds **23** and **25** proved to be 3 times more active than either **19** or BB-882 in the oral test. Replacing the amide with urea or carbamate was in general well tolerated (compounds **26**−**30**) except in the oral test, where only cyclopropyl derivative **29** showed acceptable activity. It was interesting to note that the enantiomer of **27**, **28**, was significally less active. Taking into account that we found activity in urea derivatives, we tried compounds with the urea function as the linker between the piperidine and the leucine ethyl ester, moiety present in BB-882 (see compound **31**), in comparison with ethyl phenylglycines **33** and **34** and the racemic carba analogue **32**. Good results were obtained for **31**, **33**, and its ether analogue **35** in the first three screening tests, but only ether **35** showed modest activity in the oral test. α-Amino amide **36**, which had the advantage of lacking chiral centers, showed diminished activity that again increased in the presence of a 2-methoxy substituent in the aromatic ring (see compound **37**); however, this compound proved orally inactive.

To facilitate the final selection of a lead structure from the most interesting compounds that have emerged from this work (**15**, **19**, **24**, **25**, **27**, and **37**), duration of activity studies in two animal species were carried out (see Table 3). All the new compounds showed better results than our previous leader **1** showing that the isosteric replacement of the (cyanomethyl)pyridine moiety with 2-methylimidazo[4,5-*c*]pyridine produced a substantial increase in the duration of activity. Compound **19** showed the longest duration of activity. It gave 100% protection against PAF-induced mortality in mice 7 h after iv administration of a single dose of 1 mg/kg and also provided 100% inhibition of PAF-induced aggregation in dog whole blood[12] 6 h after iv administration of the same dose.

In conclusion, we have found that replacement of the (cyanomethyl)pyridine moiety present in our previous series with 2-methylimidazo[4,5-*c*]pyridine results in compounds of greater PAF antagonist activity. Among the different types of acyl radicals tested, the 3,3-diphenylpropanoyl substituent of **19** was found to confer the highest potency and the longest duration of activity. The lead structure **19** has been selected for in-depth pharmacological evaluation.

Experimental Section

Chemistry. Melting points were determined with a Mettler FP 80 central processor melting-point apparatus and are uncorrected. ^1H NMR (80 MHz) and ^{13}C NMR (20.1 MHz) spectra were recorded on a Brücker AC80 spectrometer, and ^1H NMR (250 MHz) spectra were recorded on an AVANCE DPX spectrometer and are reported in ppm on the δ scale from the indicated reference. Mass spectra were measured on an HP-5988 quadrupole mass spectrometer. Combustion analyses were performed with a Carlo Erba 1106 analyzer. Liquid chromatography was performed with a forced flow (flash chromatography) of the indicated solvent system on SDS silica gel chromagel 60 a C.C. (230−400 mesh). Unless otherwise specified, all nonaqueous reactions were conducted under a rigorously dried argon atmosphere, using oven-dried glassware. C-18-PAF acether was synthesized from (*S*)-batyl alcohol[13] following a published procedure.[14]

1-(*tert*-Butoxycarbonyl)-4-(aminomethyl)piperidine (9). To a cooled (0 °C) solution of 4-(aminomethyl)piperidine (150 g, 1.3 mol) in $CHCl_3$ (800 mL) was added a solution of BOC_2O (147 g, 0.65 mol) in $CHCl_3$ (500 mL), and the mixture was stirred for 18 h. After adding H_2O (400 mL), the organic phase was separated, dried (Na_2SO_4), and evaporated. The resulting material was used directly in the next step: ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 4.11 (br d, J = 13.4 Hz, 2H), 2.69 (m, 2H), 2.58 (d, J = 5.5 Hz, 2H), 1.45 (s, 9H), 1.8−0.8 (m, 7H).

Table 2. PAF Antagonist Activities of Compounds **13**–**37**

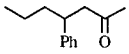
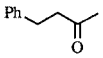
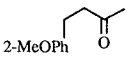
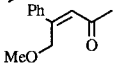
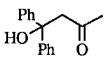
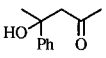
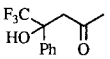
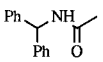
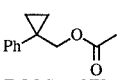
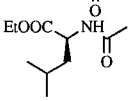
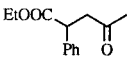
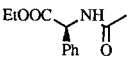
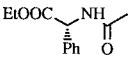
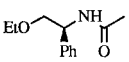
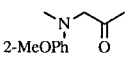
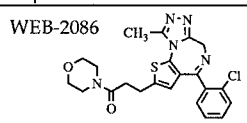
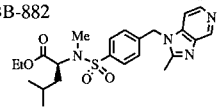
comp	R	PAF-induced platelet aggregation IC_{50},[a] μM	PAF-induced hypotension ID_{50},[b] mg/kg iv	PAF-induced mortality ID_{50},[c] mg/kg iv	PAF-induced mortality ID_{50},[d] mg/kg po	mp, °C (cryst solvent)[e]	formula[f]
13		0.012 (0.007-0.019)	0.033 (0.021-0.052)	0.001-0.003	0.3-1	132-135	$C_{23}H_{28}N_4O.H_2O$
14		0.011 (0.0095-0.012)	0.0079 (0.005-0.012)	0.003-0.01	0.5-1	110-115	$C_{25}H_{32}N_4O.3/4H_2O$
15		0.0067 (0.0058-0.0077)	0.012 (0.010-0.14)	0.0027 (0.0018-0.0042)	0.3-1	147-148	$C_{24}H_{30}N_4O.1/2H_2O$
16		0.0062 (0.0051-0.0075)	0.087 (0.054-0.014)	50% inh at 0.01 mg/kg	>1	165-166 (A)	$C_{23}H_{30}N_4SO_2$
17		0.060 (0.054-0.065)	>5	0.013 (0.011-0.015)	>1	53-57	$C_{22}H_{26}N_4O.3/4H_2O$
18		0.015 (0.014-0.007)	0.045 (0.028-0.0072)	0.0033 (0.0028-0.0039)	>1	54-56	$C_{23}H_{28}N_4O_2.1/2H_2O$
19		0.0076 (0.006-0.011)	0.0086 (0.0063-0.012)	0.0008 (0.0006-0.0010)	0.092 (0.060-0.140)	207-208 (B)	$C_{28}H_{30}N_4O$
20		0.24 (0.17-0.35)	0.011 (0.008-0.014)	0.0037 (0.0020-0.0069)	>1	86-91	$C_{28}H_{28}N_4O.1/4H_2O$
21		0.013 (0.011-0.017)	0.0054 (0.002-0.014)	50% inh at 0.03 mg/kg	0.3-1	59-62	$C_{24}H_{28}N_4O.1/2H_2O$
22		0.018 (0.011-0.029)	0.022 (0.015-0.032)	0.0079 (0.0031-0.020)	>1	63-67	$C_{24}H_{28}N_4O_2.H_2O$
23		0.64 (0.50-0.85)	0.013 (0.010-0.016)	0.01-0.03	0.02-0.03	210-211	$C_{28}H_{30}N_4O_2.1/2H_2O$
24		0.0069 (0.0035-0.013)	0.043 (0.034-0.054)	0.0029 (0.0017-0.0050)	0.3-1	199-200	$C_{23}H_{28}N_4O_2.1/4H_2O$
25		0.036 (0.028-0.045)	0.013 (0.010-0.015)	0.0029 (0.0019-0.0044)	0.032 (0.023-0.046)	210-211 (C)	$C_{23}H_{25}F_3N_4O_2.1/2H_2O$
26		0.0081 (0.0062-0.011)	0.14 (0.10-0.18)	>0.03	>1	211-212 (D)	$C_{27}H_{29}N_5O.1/2H_2O$
27		0.013 (0.012-0.016)	0.017 (0.012-0.025)	0.0047 (0.0042-0.0052)	0.3-1	80-84	$C_{22}H_{27}N_5O.1/2H_2O$
28		0.041 (0.033-0.051)	0.21 (0.13-0.35)	45% inh at 0.03 mg/kg	>1	79-83	$C_{22}H_{27}N_5O.1/2H_2O$
29		0.017 (0.013-0.024)	0.021 (0.013-0.035)	0.0020 (0.0020-0.0020)	0.2-0.3	227-228	$C_{23}H_{27}N_5O.1/4H_2O$
30		0.035 (0.026-0.045)	0.014 (0.011-0.016)	0.012 (0.002-0.070)	>1	138-140	$C_{24}H_{28}N_4O_2.1/2H_2O$
31		0.012 (0.008-0.019)	0.030 (0.020-0.046)	0.0027 (0.0012-0.0063)	>1	60-63	$C_{22}H_{33}N_5O_3.3/4H_2O$
32		0.012 (0.0091-0.015)	0.17 (0.09-0.33)	45% inh at 0.03 mg/kg		173-174	$C_{25}H_{30}N_4O_3.3/2H_2O$
33		0.016 (0.012-0.020)	0.061 (0.031-0.12)	50% inh at 0.01 mg/kg	>1	153-154	$C_{24}H_{29}N_5O_3.1/2H_2O$
34		0.15 (0.12-0.19)	0.069 (0.041-0.11)	0.01-0.02	>1	78-80	$C_{24}H_{29}N_5O_3.1/2H_2O$
35		0.017 (0.013-0.023)	0.019 (0.012-0.029)	0.003-0.01	0.3-1	68-70	$C_{24}H_{31}N_5O_2.1/2H_2O$
36		0.023 (0.012-0.044)	0.31 (0.23-0.43)	>0.03	>1	74-78	$C_{22}H_{27}N_5O.5/4H_2O$
37		0.014 (0.011-0.017)	0.063 (0.043-0.091)	0.0066 (0.0031-0.0143)	>1	59-64	$C_{23}H_{29}N_5O_2.1/2H_2O$

Table 2 (Continued)

comp	R	PAF-induced platelet aggregation IC_{50},[a] μM	PAF-induced hypotension ID_{50},[b] mg/kg iv	PAF-induced mortality ID_{50},[c] mg/kg iv	PAF-induced mortality ID_{50},[d] mg/kg po	mp, °C (cryst solvent)[e]	formula[f]
WEB-2086		0.091 (0.071-0.12)	0.17 (0.12-0.27)	0.084 (0.042-0.167)	1.24 (0.70-2.21)		
BB-882		0.0036 (0.0021-0.0063)	0.0037 (0.0024-0.0057)	0.0021 (0.0010-0.0040)	0.11 (0.07-0.19)		

[a–d] See corresponding footnotes to Table 1. [e] A, EtOAc/hexane; B, EtOAc/MeOH; C, EtOAc/ether; D, EtOAc. All other compounds were purified by chromatography and triturated with ether. [f] Satisfactory elemental analyses (±0.4%) were obtained for C, H, and N for all compounds except for the following products (compd, element, calcd (found value)): **17** N, 14.90 (15.79); **31**, N, 16.32 (15.64).

Table 3. Duration of Activity of Compounds **15**, **19**, **24**, **25**, **27**, and **37**[a]

	PAF-induced mortality in mice, inh (%) at 1 mg/kg iv			PAF-induced platelet aggregation, inh (%) at 1 mg/kg iv	
compd	3 h	5 h	7 h	4 h	6 h
15		88	50	100	100
19	100	100	100	100	100
24		80	60	59	43
25		90	70		
27		56	22	100	77
37		90	70	100	87
1	30	15		39	
WEB-2086	55	27	31	100	55
BB-882	100	95	56	100	100

[a] Percent protection of PAF-induced mortality in mice and percent inhibition of PAF-induced platelet aggregation in dog whole blood.

4-[[[1-(*tert*-Butoxycarbonyl)-4-piperidyl]methyl]amino]-3-nitropyridine (10). To a mixture of $POCl_3$ (120 mL) and PCl_5 (112 g) heated at 65 °C was added slowly 4-hydroxy-3-nitropyridine (75 g, 0.535 mol). This mixture was stirred at 130 °C for 18 h. The solution was reduced in vacuo to an oil that was redisolved in $CHCl_3$ (700 mL). After cooling to 0 °C, a solution of **9** (0.65 mol) and Et_3N (110 mL) in $CHCl_3$ (500 mL) was added and the mixture heated at reflux for 18 h. It was then evaporated, and the residue was partitioned between 1 N NaOH and EtOAc. The aqueous phase was reextracted twice with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and concentrated to a total volume of 400 mL. After cooling (−20 °C) overnight, a yellow solid was collected and dried (115 g, 64% for two steps): mp 131−138 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 9.20 (s, 1H), 8.30 (d, J = 5.5 Hz, 1H), 8.19 (m, 1H), 6.72 (d, J = 5.5 Hz, 1H), 4.18 (br d, J = 13.4 Hz, 2H), 3.26 (t, J = 5.9 Hz, 2H), 2.72 (br t, J = 12.7 Hz, 2H), 1.46 (s, 9H), 1.8−0.8 (m, 5H). Anal. ($C_{16}H_{24}N_4O_4$) C, H, N.

3-Amino-4-[[[1-(*tert*-butoxycarbonyl)-4-piperidyl]methyl]amino]pyridine (11). A mixture of **10** (26.2 g, 0.077 mol) and 10% Pd/C (3.83 g) in MeOH (500 mL) was hydrogenated at atmospheric pressure for 18 h. The insoluble material was removed by filtration and the filtrate evaporated to give 22.9 g (96%) of an oil: ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.99 (d, J = 5.5 Hz, 1H), 7.94 (s, 1H), 6.56 (d, J = 5.5 Hz, 1H), 4.20 (br d, J = 13.4 Hz, 2H), 3.19 (m, 5H), 2.81 (br t, J = 12.0 Hz, 2H), 1.58 (s, 9H), 2.1−1 (m, 5H).

Alternatively, **11** was prepared as follows. To a solution of **10** (82.2 g, 0.244 mol) in pyridine (400 mL) was added a solution of $Na_2S_2O_4$ (170 g, 0.976 mol) in H_2O (500 mL). The mixture was stirred at room temperature for 24 h and then partitioned between EtOAc (800 mL) and 5 N NaOH (450 mL). The organic phase was separated, dried ($MgSO_4$), and evaporated to give a yellow solid (101 g), which still contained pyridine.

1-[[1-(*tert*-Butoxycarbonyl)-4-piperidyl]methyl]-1*H*-2-methylimidazo[4,5-*c*]pyridine (12). A solution of crude product **11** (0.24 mol) and ethyl acetimidate hydrochloride (60.3 g, 0.488 mol) in EtOH (930 mL) was refluxed for 18 h. More ethyl acetimidate hydrochloride (30.15 g, 0.24 mol) was added, and the mixture was heated for an additional 18 h. The solvent was removed in vacuo and the residue partitioned between 2 N NaOH and EtOAc. The organic phase was dried (Na_2SO_4) and concentrated to an oil that was purified by chromatography on silica gel ($CHCl_3$:MeOH, 4%) to give a creamy solid (49 g, 62% for two steps): ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.90 (s, 1H), 8.30 (d, J = 5.5 Hz, 1H), 7.13 (d, J = 5.5 Hz, 1H), 4.10 (br d, J = 13.4 Hz, 2H), 3.90 (d, J = 7.3 Hz, 2H), 2.55 (s, 3H), 2.54 (br t, J = 12.7 Hz, 2H), 1.46 (s, 9H), 2.2−1.0 (m, 5H).

1-(4-Piperidylmethyl)-1*H*-2-methylimidazo[4,5-*c*]pyridine (8). To a cooled solution (0 °C) of **12** (45.1 g, 0.136 mol) in MeOH (470 mL) was added dropwise 6.2 N HCl(g)/dioxane solution (93 mL). After the addition was completed, the cooling bath was removed and the mixture was stirred at room temperature for 18 h. It was then evaporated and the residue partitioned between cooled 2 N NaOH solution and $CHCl_3$. The aqueous phase was reextracted twice with $CHCl_3$, and the combined organic extracts were dried (Na_2SO_4) and evaporated to give a creamy solid (24.3 g, 78%): mp 128−129 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.96 (s, 1H), 8.35 (d, J = 5.5 Hz, 1H), 7.20 (d, J = 5.5 Hz, 1H), 3.95 (d, J = 7.3 Hz, 2H), 3.06 (br d, J = 12.0 Hz, 2H), 2.61 (s, 3H), 2.51 (br t, J = 12.7 Hz, 2H), 2.2−1.0 (m, 6H). Anal. ($C_{13}H_{18}N_4 \cdot {}^1/_4H_2O$).

1-[[1-[(2-Methyl-2-phenylpropyl)sulfonyl]-4-piperidyl]-methyl]-1*H*-2-methylimidazo[4,5-*c*]pyridine (16). To a solution of amine **8** (1 g, 4 mmol) and Et_3N (0.6 mL) in $CHCl_3$ (20 mL) was added 2-methyl-2-phenylpropanesulfonyl chloride[7] (2.32 g, 10 mmol), and the mixture was stirred at room temperature overnight. The resulting solution was diluted with $CHCl_3$, washed with 0.5 N NaOH, dried, and concentrated. The residue was purified by chromatography on silica gel ($CHCl_3$:MeOH, 5%) to afford a white solid which was recrystallized from EtOAc (0.4 g, 25%): mp 165−166 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.98 (s, 1H), 8.38 (d, J = 5.5 Hz, 1H), 7.32 (m, 5H), 7.17 (d, J = 5.5 Hz, 1H), 3.94 (d, J = 6.9 Hz, 2H), 3.65 (br d, J = 12.0 Hz, 2H), 3.16 (s, 2H), 2.60 (s, 3H), 2.18 (br t, J = 12.0 Hz, 2H), 1.58 (s, 6H), 1.48 (m, 5H). Anal. ($C_{23}H_{30}N_4O_2S$) C, H, N.

1-[[1-(3,3-Diphenylpropanoyl)-4-piperidyl]methyl]-1*H*-2-methylimidazo[4,5-*c*]pyridine (19). To a cooled solution (0 °C) of **8** (19.9 g, 0.083 mol), 3,3-diphenylpropanoic acid (18.7 g, 0.083 mol), and HOBT (11.18 g, 0.083 mol) in DMF (300 mL) was added DCC (17.2 g, 0.083 mol). After the solution was stirred at room temperature for 18 h, the solid material was separated and the filtrate concentrated. The residue was partitioned between $NaHCO_3$ solution and $CHCl_3$. The organic phase was dried (Na_2SO_4) and concentrated to an oil that was purified by chromatography on silica gel ($CHCl_3$:MeOH, 4%) to give a white solid (35 g). Recrystallization from EtOAc afforded a white solid (23.4 g, 68%): mp 207−208 °C; ^{1}H NMR

(250 MHz, $CDCl_3$) δ (TMS) 8.90 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 7.23 (m, 11H), 4.67 (t, J = 7.4 Hz, 1H), 4.65 (m, 1H), 3.85 (t, J = 7.0 Hz, 2H), 3.83 (m, 1H), 3.07 (q of d, J = 13, 8.1 Hz, 2H), 2.75 (br t, J = 11.8 Hz, 1H), 2.62 (s, 3H), 2.37 (br t, J = 11.8 Hz, 1H), 1.98 (m, 1H), 1.58 (br d, J = 11.8 Hz, 1H), 1.41 (br d, J = 11.8 Hz, 1H), 1.08 (q of d, J = 11, 0.4 Hz, 1H), 0.66 (q of d, J = 11, 0.4 Hz, 1H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ (TMS) 169.25, 153.17, 143.78, 143.37, 140.85, 140.71, 139.84, 138.97, 127.93, 127.58, 127.19, 125.87, 104.74, 48.62, 47.11, 44.90, 40.88, 38.00, 36.32, 29.66, 29.03, 13.37. Anal. ($C_{28}H_{30}N_4O$) C, H, N.

1-[[1-[[(1-Phenylcyclopropyl)amino]carbonyl]-4-piperidyl]methyl]-1*H*-2-methylimidazo[4,5-*c*]pyridine (29). Diphenyl phosphorazidate (2.14 mL, 0.01 mol) was added dropwise to a solution of 1-phenyl-1-cyclopropanecarboxylic acid (1.6 g, 0.01 mol) and Et_3N (1.14 mL) in benzene (40 mL). The mixture was heated at 90 °C for 2 h. Amine **8** (1.6 g, 0.0068 mol) was then added, and the mixture was heated at 90 °C for 18 h more. After cooling the mixture was partitioned between EtOAc and 1 N NaOH solution. The aqueous phase was reextracted twice with EtOAc, and the combined organic phases were dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography on silica gel ($CHCl_3$:MeOH, 10%) to give a white solid (1.2 g, 46%): mp 227−228 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.98 (s, 1H), 8.38 (d, J = 5.5 Hz, 1H), 7.20 (m, 6H), 5.44 (s, 1H), 3.97 (d, J = 7.3 Hz, 2H), 3.95 (m, 2H), 2.62 (s, 3H), 2.60 (br t, J = 12.7 Hz, 2H), 2.2−1.0 (m, 5H), 1.22 (s, 4H). Anal ($C_{23}H_{27}N_5O\cdot{}^1/_4H_2O$) C, H, N.

1-[[1-[[(1-Pheny-1-cyclopropyl)methoxy]carbonyl]-4-piperidyl]methyl]-1*H*-2-methylimidazo[4,5-*c*]pyridine (30). Amine **8** (0.72 g, 0.0031 mol) was added to a solution of phenyl [(1-phenyl-1-cyclopropyl)methyl]carbonate (prepared from reaction of (1-phenyl-1-cyclopropyl)methanol with phenyl chloroformate; 1.1 g, 0.0041 mol) in pyridine (30 mL). The mixture was refluxed for 18 h. After removal of the solvent in vacuo, the residue was partitioned between $CHCl_3$ and 1 N NaOH. The aqueous phase was reextracted twice with $CHCl_3$, and the combined organic phases were dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography on silica gel ($CHCl_3$:MeOH:NH_3, 60:2:0.2) to give a white solid (0.3 g, 25%): mp 138−140 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.97 (s, 1H), 8.37 (d, J = 5.5 Hz, 1H), 7.27 (s, 5H), 7.19 (d, J = 5.5 Hz, 1H), 4.16 (s, 2H), 4.15 (br d, J = 13.6 Hz, 2H), 3.94 (d, J = 7.21 Hz, 2H), 2.60 (s, 3H), 2.60 (m, 2H), 2.3−0.8 (m, 5H), 0.92 (s, 4H). Anal. ($C_{24}H_{28}N_4O_2\cdot{}^1/_2H_2O$) C, H, N.

Biological Methods: Inhibition of Platelet Aggregation in Vitro. Platelet aggregation studies were done by the method of Born.[9] Blood was collected in 3.8% sodium citrate (1 vol/9 vol of blood) by cardiac puncture from male New Zealand rabbits (2−2.5 kg body weight). Platelet-rich plasma (PRP) was prepared by centrifuging the blood at 250*g* for 10 min at 4 °C. The PRP was diluted with platelet-poor plasma obtained by further centrifuging at 3000*g* for 10 min. The platelet number was adjusted to 3.5×10^5 cells/mm^3. Platelet aggregation was induced by C-18-PAF (1.5×10^{-8} M) and measured with a dual-channel aggregometer Chrono-log 560 instrument. Activity is expressed as the IC_{50} value, i.e., the concentration required to inhibit platelet aggregatory response by 50%. The values shown in the tables were calculated by linear regression from a single experimental curve with no less than four data points, each point being the mean of the percentage inhibition at a given concentration obtained from one to three independent experiments.

Inhibition of PAF-Induced Hypotension in Normotensive Rats.[10,1] Male Sprague−Dawley rats, weighing 180−220 g, were anesthetized with sodium pentobarbital (50 mg/kg ip). Blood pressure was recorded from the left carotid artery using a Statham pressure transducer coupled to a Beckman R611 recorder. Right and left femoral veins were catheterized to inject the test compound and PAF (0.5 μg/kg). Test compounds were administered by intravenous injection (1 mL/kg, dissolved in saline) 3 min before PAF injection. Blood pressure was monitored, and percentage inhibition of PAF-induced hypotension with respect to controls was calculated. The results are expressed as ID_{50} values, i.e., the dose of test compound required to inhibit hypotension by 50%, or as percentage inhibition at a given dose of test compound. The ID_{50} values were calculated by linear regression from a single experimental curve with no less than four points, each point being the mean of the percentage inhibition at a given dose obtained from two or more independent experiments.

Inhibition of PAF-Induced Mortality in Mice.[11] Groups of 10 male Swiss mice weighing 22−26 g were used; 100 μg/kg C-18-PAF plus 1 mg/kg propanolol was administered through a lateral tail vein 5 min after iv or 60 min after po administration of the test compounds (10 mL/kg iv or 20 mL/kg po) or vehicle in control groups (saline iv or 1% Tween 80 po). The animals were observed 2 h after the PAF injection. Following this protocol, we obtained a consistent mortality of 70−100% in the control group. Percentage inhibition of mortality due to treatment in comparison with the control group was calculated. Results are given as ID_{50} values, i.e., the dose required to inhibit PAF-induced mortality by 50%. The results were calculated by linear regression from a single experimental curve with at least four data points. For duration of activity studies, test compounds were given at a single dose of 1 mg/kg iv at time 0. C-18-PAF plus propanolol was administered at different times (10−40 mice/time), and percentage inhibition at each time was recorded.

Inhibition of PAF-Induced Platelet Aggregation in Dog Whole Blood. Blood was collected by venipuncture from male Beagle dogs (8−12 kg body weight) before and 4 and 6 h after the administration of a single dose of 1 mg/kg iv of the test compounds; 3.8% sodium citrate (1 vol/9 vol of blood) was used as the anticoagulant. Blood was further diluted 1:1 (v/v) with saline. Platelet aggregation was induced by C-18-PAF (7.5×10^{-9} M) and measured by an impedance method[12] with a dual-channel aggregometer Chrono-log 560 instrument. Percentage inhibition of platelet aggregation at 4 and 6 h was calculated by comparison with the platelet response in the same animal before the administration of the test compound. Results are the mean percentage inhibition obtained from one to three dogs.

Statistics. Statistical analyses of pharmacological data were done with a standard pharmacology program.[15]

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